Victor R. Preedy
Ronald Ross Watson
Colin R. Martin

Editors

Handbook of Behavior, Food and Nutrition

Volume 1 · Parts 1–5

Springer

Handbook of Behavior, Food and Nutrition

Victor R. Preedy • Ronald Ross Watson
Colin R. Martin
Editors

Handbook of Behavior, Food and Nutrition

Springer

Editors
Prof. Victor R. Preedy
King's College London
Department Nutrition & Dietetics
150 Stamford St.
London SE1 9NH
UK

Prof. Ronald Ross Watson
University of Arizona
Health Sciences Center
Department of Health Promotion Sciences
1295 N. Martin Ave.
Tucson, AZ 85724-5155
USA

Prof. Colin R. Martin
University of the West of Scotland
Ayr Campus
KA8 0SR Ayr
UK

Printed on acid-free paper

This book is dedicated to Miss Caragh Brien, my wonderful daughter.

Colin R. Martin

Foreword

The Editors are to be commended for bringing together what is arguably the best and most comprehensive text book on the complex interrelationships between the brain, behaviour, food selection and choice. There are more than 200 chapters describing not only how behaviour affects our food selection but also how what we eat affects how we behave. Content covers genetics, sensory factors, endocrine and neuro-endocrine processes, neurology, behaviour, psychology, physiology, the act of eating, food choice, selection, preferences, appetite, pregnancy, human development, children and adolescents, ageing, anorexia nervosa, bulimia nervosa, obesity, nutrient excess and toxicity, alcoholism, quality of life, body image and much more. The authors have helpfully included chapters on changing eating behaviour and attitudes. The International Handbook of Behavior, Food and Nutrition can truly be said to be research based, theoretical, factual, scientific, academic and practical.

The International Handbook of Behavior, Food and Nutrition is without doubt a quality text attractive to the wide range of practitioners and intelligent readers with an interest in these areas. These contributions are a testament not only to the skills of the authors, but the Editorial attributes of Professor Preedy, Watson and Martin. They have marshalled together a truly international team of experts. I especially like the structuring of the chapters. Each contribution has a mini-dictionary, "key facts" and "summary points" to facilitation the navigation across fields of interest.

This is a cross-disciplinary book of tremendous importance to the health of individuals and society at large and deserves wide dissemination.

The Editors and all the authors are to be congratulated.

Prof Betty Kershaw DBE FRCN
Emeritus Dean
The School of Nursing and Midwifery
The University of Sheffield
United Kingdom

Preface

In this book the Editors aims to disseminate important data pertaining to the modulatory effects of foods and nutritional substances on behavior and neurological pathways and visa versa. This ranges from the neuroendocrine control of feeding to the effects of disease on the brain. The importance of this book pertains to the fact that food is an essential component of cultural heritage but the effects of perturbations in the food-cognitive axis can be quite profound. The complex inter-relationship between neuropsychological processing, diet and behavioural outcome is explored within the context of the most contemporary psychobiological research in the area. This comprehensive psychobiologically and pathology-themed text examines the broad spectrum of diet, behavioural and neuropsychological interactions from normative function to occurrences of severe and enduring psychopathology. The Editors have taken a scientific and objective stand and included chapters that scrutinize the relationships between the brain, behaviour, food and nutrition in a scientific and rational way.

In very simple terms this books addresses limitations in other works that may individually look at the one-way-traffic of either food and behavior. This book examines via two-way-traffic at multiple levels. For example, it examines at both preclinical and clinical levels, genes and populations, and how (a) components in food will affect our sensory responses and (b) how our behavior and sensory responses affect what foods we eat, their pattern of consumption and so on. This book consists of over 200 chapters, and is conveniently divided into 5 main sections to represent the various specialty areas, namely:

General, normative aspects and overviews
Pathological and abnormal aspects
Specific conditions and diseases
Changing eating behaviour and attitudes
Selective methods

The Editors recognize the difficulty in assigning chapters to specific sections. For example in order to describe normative features, abnormal aspects of diet and behavior may also be described. Chapters on food choice may have coverage on the developing brain, behavior and neuroendocrinology. Thus, some chapters can potentially be assigned to several sections. However, this is resolved with the excellent indexing systems that Springer is renowned for. The chapters are well illustrated with numerous tables and figures.

This book represents a multidisciplinary "one-stop-shop" of information with suitable indexing of the various pathways and processes. The chapters are written by

national or international experts or specialists in their field. The Editors recognize that very often experts in one field may be novices in another. To bridge this knowledge-divide the authors have incorporated sections on "Applications to other areas health and disease", "Key Facts or Features" and "Summary Points" This reference book is for nutritionists, dietitians, food scientists, behavioral scientists, psychologists, doctors, nurses, physiologists, health workers and practitioners, college and university teachers and lecturers, undergraduates and graduates.

Contents

Volume 1

Volume 2

Volume 3

Volume 4

Volume 5

Contributors

Gian Franco Adami, M.D.
Department of Surgery, University of Genova, Largo Rosanna Benzi 8,
Genova 16132, Italy

W. Stewart Agras, M.D.
Department of Psychiatry and Behavioral Sciences, Stanford University,
School of Medicine, Stanford, CA, USA

Rexford S. Ahima, M.D., Ph.D.
Institute for Diabetes, Obesity and Metabolism, School of Medicine, University
of Pennsylvania School of Medicine, 712A Clinical Research Building, 415 Curie
Boulevard, Philadelphia, PA 19104

Jennie C. Ahrén
Center for Health Equity Studies, CHESS, Karolinska Institutet/Stockholm
University, Sveavagen 160, 106 91, Stockholm, Sweden

Akira Akabayashi
Graduate School of Medicine, Department of Stress Sciences and Psychosomatic
Medicine, The University of Tokyo, Tokyo, Japan

Takashi Akamizu
Translational Research Center, Kyoto University Hospital, Kyoto University
School of Medicine, 54 Shogoin-Kawaharacho, Sakyo-ku, Kyoto 606-8507, Japan

Samir Al-Adawi, M.Sc., Ph.D.
Department of Behavioral Medicine, College of Medicine and Health Sciences,
Sultan Qaboos University, Al-Khoudh 123, Muscat, Sultanate of Oman

Abdulmajid Ali
General Surgery Department, Ayr Hospital, Ayr, UK

J. Alaghband-Zadeh
Department of Clinical Biochemistry, King's College Hospital, London, UK

Thomas R. Alley
Department of Psychology, 418 Brackett Hall, Clemson University, Clemson,
SC 29634-1355, USA

Kelly C. Allison, Ph.D.
Department of Psychiatry, Center for Weight and Eating Disorders,
University of Pennsylvania School of Medicine, Philadelphia, PA, USA

Ibrahim Al-Zakwani, Ph.D.
Department of Pharmacy College of Medicine and Health Sciences, Sultan Qaboos
University, Muscat, Sultanate of Oman

Oliver Amft, Ph.D.
ACTLab, Signal Processing Systems, Faculty of Electrical Engineering,
Eindhoven University of Technology, NL-5600 MB Eindhoven, The Netherlands

Joel G. Anderson
Department of Nutrition, University of North Carolina at Greensboro, Greensboro,
NC, USA

Helma Antony
School of Medical Science, Griffith University, Gold Coast Campus, Southport,
Queensland, Australia

Gastón Ares
Sección Evaluación Sensorial, Departamento de Ciencia y Tecnología de Alimentos,
Facultad de Química. Universidad de la República (UdelaR),
Gral. Flores 2124. C.P. 11800, Montevideo, Uruguay

Akihiro Asakawa
Department of Psychosomatic Internal Medicine, Kagoshima University Graduate
School of Medical and Dental Sciences, Kagoshima, Japan

Rheanna N. Ata, B.A.
Department of Psychology, University of South Florida, 4202 E. Fowler Avenue,
PCD 4118G, Tampa, FL 33620-8200

John Atkinson   [AU1]
West of Scotland University, Paisley, UK

Nicole M. Avena, Ph.D.
Department of Psychiatry, University of Florida, Gainesville, FL 32608, USA
and
Department of Psychology and Program in Neuroscience, Princeton University,
Princeton, NJ 08540, USA

Mary Ballard, Ph.D.
Department of Psychology, Appalachian State University, Boone, NC 28608, USA

Pauline Banks
School of Health, Nursing and Midwifery, University of the West of Scotland,
Beech Grove, Ayr, UK

Tom Baranowski, Ph.D.
Children's Nutrition Research Center, Department of Pediatrics,
Baylor College of Medicine, 1100 Bates Street, Houston TX 77030, USA

Stephanie Bauer
Center for Psychotherapy Research, University Hospital Heidelberg, Heidelberg,
Germany

Louise A. Baur, B.Sc.(Med), M.B.B.S. (Hons), Ph.D., FRACP
Discipline of Paediatrics and Child Health, University of Sydney, Sydney, NSW 2006, Australia
and
Weight Management Services, The Children's Hospital at Westmead, Westmead, NSW 2145, Australia

Christian Beaulieu
Department of Biomedical Engineering, 1098 Research Transition Facility, University of Alberta, Edmonton, Alberta T6G 2V2, Canada

Stephen C. Benoitm, Ph.D.
Department of Psychiatry, University of Cincinnati, Cincinnati, OH, USA

David Benton
Department of Psychology, University of Wales Swansea, Swansea SA2 8PP, Wales, UK

Pere Berbel
Instituto de Neurociencias, Universidad Miguel Hernández and Consejo Superior de Investigaciones Científicas, Campus de Sant Joan, Apartado de Correos 18, Sant Joan d'Alacant, 03550 Alicante, Spain

Lynda Bergsma, Ph.D.
Mel & Enid Zuckerman College of Public Health, University of Arizona, P.O. Box 245209, Tucson, Arizona 85724

Daniel M. Bernstein
Department of Psychology, Kwantlen Polytechnic University, 12666 – 72nd Avenue, Surrey, BC, Canada

Monelle Bertrand
Unité de Nutrition, CHU Larrey, Toulouse cedex

Carole A. Bisogni
Division of Nutritional Sciences, 183 MVR Hall, Cornell University, Ithaca, NY 14853, USA

Christine E. Blake
Department of Health Promotion, Education, and Behavior, Arnold School of Public Health, University of South Carolina, Columbia, SC, USA

Eva Blomstrand
The Åstrand Labaratory, The Swedish School of Sport and Health Sciences, Box 5626 114 86 Stockholm, Sweden

Miriam E. Bocarsly
Department of Psychology, Princeton University, Princeton, NJ, USA

Sandra D.M. Bot, Ph.D.
Department of General Practice and the EMGO Institute for Health and Care Research, VU University Medical Center, Amsterdam, the Netherlands

Wayne A. Bowers, Ph.D.
Department of Psychiatry, University of Iowa, 2916 John Pappajohn Pavilion, Iowa City, IA 52242

L. Mallory Boylan, Ph.D., RD, LD
Department of Nutrition, Hospitality & Retailing, Texas Tech University, Lubbock, TX, USA

Emma J. Boyland
Kissileff Laboratory for the Study of Human Ingestive Behaviour, School of Psychology, Eleanor Rathbone Building, Bedford Street South, University of Liverpool, Liverpool, L69 7ZA, UK

Christophe Breton
Neurostress (EA4347), Equipe Dénutritions Maternelles Périnatales, Bâtiment SN4, Université des Sciences et Technologies de Lille, France

Marie-Claude Brindisi, M.D.
Endocrinology and Nutrition Department, CHU le Bocage (Dijon University Hospital), BP 77908, 21079 Dijon Cedex

Russell Brown
Department of Obstetrics & Gynaecology, IWK Health Centre, Dalhousie University, Halifax, NS, Canada

Thomas A. Brunner
ETH Zurich, Institute for Environmental Decisions, Consumer Behavior, Universitaetsstrasse, Zurich, Switzerland

Eleanor J. Bryant
Centre for Psychology Studies, Social Sciences and Humanities, Richmond House, University of Bradford, West Yorkshire, BD7 1DP, UK

S. Alexandra Burt, Ph.D.
Department of Psychology, Michigan State University, East Lansing, MI, USA

Pietro Caliandro
Institute of Neurology, Largo F. Vito 1, 00168, Roma, Italy
and
Fondazione Pro Iuventute Don Carlo Gnocchi, Roma, Italy

Maria Valeria Camboni, Bpsych
Department of Psychology, University of Cagliari, Cagliari, Italy

Jameason D. Cameron
Behavioral and Metabolic Research Unit, School of Human Kinetics, University of Ottawa, Ottawa, Ontario, Canada

L. Arthur Campfield, Ph.D.
Department of Food Science and Human Nutrition, College of Applied Human Sciences, Colorado State University, Fort Collins, CO 80523-1571, USA

Lucia Camporese, PsyD
AIDAP Verona, Via Sansovino, Verona, Italy

Mehmet Cansev
Uludag University Medical School, Department of Pharmacology, Gorukle, 16059 Bursa, Turkey

Antonio Capurso, M.D.
Department of Geriatrics, Center for Aging Brain, Memory Unit,
University of Bari, Bari, Italy

Cristiano Capurso
Department of Geriatrics, University of Foggia, Foggia, Italy

Céline Caquineau
Centre for Integrative Physiology, University of Edinburgh, Edinburgh, UK

Daniel P. Cardinali, M.D., Ph.D.
Departamento de Docencia e Investigación, Pontificia Universidad Católica
Argentina, Buenos, Aires, Argentina

Amanda Carson
School of Health, Nursing and Midwifery, University of the West of Scotland,
Beech Grove, Ayr, UK

Natalie A. Ceballos
Department of Psychology, Texas State University, San Marcos, TX, USA

Kim M. Cecil, Ph.D.
Cincinnati Children's Environmental Health Center at the Cincinnati Children's
Hospital Medical Center, Departments of Radiology, Pediatrics,
Neuroscience and Environmental Health, University of Cincinnati
College of Medicine, Cincinnati, OH, USA
and
Cincinnati Children's Hospital Medical Center, Department
of Radiology/Imaging Research Center MLC 5033,
3333 Burnet Avenue, Cincinnati, OH 45229, USA

Hellas Cena, M.D.
Department of Health Sciences, Section of Human Nutrition, University of Pavia,
Pavia, Italy

Elena Centis, Ph.D.
Clinical Dietetics, University of Bologna, Bologna, Italy

Antonio Cepeda-Benito
Department of Psychology, Henderson Hall, Texas A&M University, College
Station, TX, USA

Seung Hun Cha
School of Medicine, Department of Biological Chemistry, The Johns Hopkins
University, Baltimore, MD, USA

Evonne J. Charboneau, M.D.
School of Medicine, Vanderbilt University, Nashville, TN, USA

Christine Charrueau, PharmD, Ph.D.
Laboratoire de Pharmacie Galénique EA 2498, Faculté des Sciences
Pharmaceutiques et Biologiques, Université Paris Descartes,
Paris Cedex, France

Catherine Chaumontet
INRA, CNRH-IdF, UMR914 Nutrition Physiology and Ingestive Behavior, Paris,
France
and
AgroParisTech, CNRH-IdF, UMR914 Nutrition Physiology and Ingestive Behavior,
Paris, France

Anastasia Chellino, B.S.
Health Psychology, Ingestive Behavior Laboratory, Pennington Biomedical
Research Center, Baton Rouge, LA, USA
and
Department of Natural Sciences, University of Education Heidelberg, Heidelberg,
Germany

Hui Chen
Faculty of Science, Department of Medical and Molecular Bioscience, University
of Technology, Sydney, Australia
and
School of Medical Sciences, Department of Pharmacology, University of New
South Wales, Sydney, Australia

Kai-Chun Cheng
Department of Psychosomatic Internal Medicine, Kagoshima University Graduate
School of Medical and Dental Sciences, Kagoshima, Japan

Sergio Chieffi
Department of Experimental Medicine, Section of Human Physiology, and Clinical
Dietetic Service, Second University of Naples, Naples, Italy

W.I. Cho
Department of Food and Animal Biotechnology, College of Agriculture and Life
Sciences, Seoul National University, San 56-1 Sillim-dong, Gwanak-gu,
Seoul 151-921, Korea

Derrick L. Choi, B.S.
Department of Psychiatry, University of Cincinnati, Cincinnati, OH, USA

Chin Moi Chow
Delta Sleep Research Unit, Discipline of Exercise and Sport Science,
The University of Sydney, Lidcombe NSW 1825, Australia

Yvonne Christley
School of Health, Nursing and Midwifery, University of the West of Scotland,
Beech Grove, Ayr, UK

J.K. Chun
Department of Food and Animal Biotechnology, College of Agriculture and Life
sciences, Seoul National University, Seoul, Korea

Cicero G. Coimbra
Laboratory of Clinical and Experimental Pathophysiology, Department of
Neurology and Neurosurgery, Federal University of São Paulo (UNIFESP),
São Paulo SP BRAZIL

Anna M. Colacicco, Ph.D.
Department of Geriatrics, Center for Aging Brain, Memory Unit, University of Bari, Bari, Italy

Nelson Barros Colauto
Laboratório de Biologia Molecular, Universidade Paranaense, Praça Mascarenhas de Moraes, Umuarama-PR, Brazil

Cian E. Collins, FRCSI (Ophth), MRCOphth
Princess Alexandra Eye Pavilion, Chalmers Street, Edinburgh EH3 9HA

Mark Conner
Institute of Psychological Sciences, University of Leeds, Leeds, UK

James R. Connor, Ph.D.
Milton S. Hershey Medical Center, Pennsylvania State University, Hershey, PA, USA

Richard W.I. Cooke
School of Reproductive and Developmental Medicine, University of Liverpool, First Floor, University Department, Liverpool Women's Hospital, Crown Street, Liverpool, L8 7SS, UK

John Correa, B.S.
Health Psychology, Ingestive Behavior Laboratory, Pennington Biomedical Research Center, Baton Rouge, LA, USA

Vassiliki Costarelli, BSc, MSc, Ph.D, R.Nutr.
Human Ecology Laboratory, Department of Home Economics and Ecology, Harokopio University, 70 El. Venizelou Ave, 17671 Kallithea, Athens, Greece

Mihai Covasa
INRA, Écologie et Physiologie du Système Digestif, 78350 Jouy-en-Josas, France

Ronald L. Cowan M.D., Ph.D.
School of Medicine, Vanderbilt University, Nashville, TN, USA

Sabrina Crepin
Service de Toxicologie et Pharmacologie - Pharmacovigilance, Centre Hospitalier Universitaire, F-87042 Limoges, France

Kristen M. Culbert, M.A.
Department of Psychology, Michigan State University, East Lansing, MI, USA

Maria Czyzewska
Department of Psychology, Texas State University, 601 University Drive, San Marcos, TX, USA

Alessia D'Introno, Ph.D.
Department of Geriatrics, Center for Aging Brain, Memory Unit, University of Bari, Bari, Italy

Ippeita Dan
Sensory & Cognitive Food Science Laboratory, National Food Research Institute, Kannondai, Tsukuba, Ibaraki, Japan

Daniel Rigaud, M.D.
Department of Endocrinology and Nutrition, CHU Le Bocage (Dijon University
Hospital), BP 77908, 21079 Dijon Cedex, France

Nicolas Darcel
INRA, CNRH-IdF, UMR914 Nutrition Physiology and Ingestive Behavior, Paris, France
and
AgroParisTech, CNRH-IdF, UMR914 Nutrition Physiology and Ingestive Behavior,
Paris, France

Undurti N. Das, M.D., FAMS
UND Life Sciences 13800 Fairhill Road, #321, Shaker Heights, OH, 44120, USA
Jawaharlal Nehru Technological University, Kakinada- 533 003, Andhra Pradesh,
India

Christopher Davids
Department of Psychology, Cornell College, Mt. Vernon, IA, USA

Fiona Davies, B.A. (Hons), M.Psych. (Applied)
Weight Management Services, The Children's Hospital at Westmead, Westmead,
Australia
and
Gymea Lily Psychotherapy Centre, Sutherland, Australia

Caroline Davis
Department of Psychiatry, University Health Network, Toronto, Ontario, Canada

Jon F. Davis, Ph.D.
Department of Psychiatry, University of Cincinnati, Genome Research Institute
Building E, Lab 334, 2170 East Galbraith Road, 45237 Cincinnati, OH, USA

Gwenaelle Diene
Centre de référence du syndrome de Prader-Willi, Hôpital des Enfants, Toulouse
Cedex, France

Bruno De Luca
Department of Experimental Medicine, Section of Human Physiology, and Clinical
Dietetic Service, Second University of Naples, Naples, Italy

Mary Jane De Souza, Ph.D., FACSM
Women's Health and Exercise Laboratory, Noll Laboratory, Department
of Kinesiology, Penn State University, University Park, PA 16802, USA

Fabien Delahaye
Neurostress (EA4347), Equipe Dénutritions Maternelles Périnatales, Bâtiment SN4,
Université des Sciences et Technologies de Lille, France

Sylvie Deloof
Neurostress (EA4347), Equipe Dénutritions Maternelles Périnatales, Bâtiment SN4,
Université des Sciences et Technologies de Lille, France

Jean-Claude Desport
Université de Limoges, Institut de Neuroépidémiologie et de Neurologie Tropicale,
EA 3174 NeuroEpidémiologie Tropicale et Comparée, Limoges, France
and
Service de Gastro-Hépato-Entérologie, Unité de Nutrition, Centre Hospitalier
Universitaire, Limoges, France

Silvia Di Domizio, R.D.
Clinical Dietetics, University of Bologna, Bologna, Italy

D.A.J. Dijck-Brouwe
University Medical Center Groningen, Groningen, the Netherlands

Atsu S.S. Dorvlo, Ph.D.
Department of Mathematics and Statistics, Sultan Qaboos University, Muscat,
Sultanate of Oman

Éric Doucet
Behavioral and Metabolic Research Unit, School of Human Kinetics,
University of Ottawa, Ontario, Ottawa, Canada, K1N 6N5

Alison J. Douglas
Centre for Integrative Physiology, University of Edinburgh, Hugh Robson Building,
George Square, Edinburgh, EH8 9XD, UK

Ronald G. Downey, Ph.D.
Kansas State University, Manhattan, KS, USA

Vicky Drapeau
Department of physical education, Laval University, Quebec City, Canada

Robert Drewett
Science Laboratories, Durham University, South Road, Durham, DH1 3LE, UK

Tim Duffy
School of Health, Nursing and Midwifery, University of the West of Scotland,
Beech Grove, Ayr, UK

Audrey DunnGalvin, Ph.D., Reg.Psychol.Ps.S.I.
Clinical Investigations Unit, Department of Paediatrics and Child Health,
Cork University Hospital, University College Cork (UCC), Wilton, Cork, Ireland

Holiday Durham, Ph.D., RD
Pennington Biomedical Research Center, Louisiana State University, Baton Rouge,
LA, USA

Isabelle Dutriez-Casteloot
Neurostress (EA4347), Equipe Dénutritions Maternelles Périnatales, Bâtiment SN4,
Université des Sciences et Technologies de Lille, France

Louise Dye
Human Appetite Research Unit, Institute of Psychological Sciences,
University of Leeds, LS2 9JT, UK

Nina Eikelis, Ph.D.
Human Neurotransmitters Laboratory, Vascular and Hypertension Division, Baker
IDI Heart and Diabetes Institute, Melbourne, Victoria 8008, Australia

Mark Ellrichmann, M.D.
Department of Medicine I, University Hospital Schleswig Holstein, Campus Kiel,
Schittenhelmstr 12, 24105 Kiel, Germany

Enzo Emanuele, M.D.
Department of Health Sciences, Section of Psychiatry, University of Pavia, Pavia, Italy

Keith M. Erikson
Department of Nutrition, University of North Carolina at Greensboro, Greensboro,
NC 27402-6170, USA

Charlotte Erlanson-Albertsson, M.D., Ph.D.
Appetite Control Unit, Division of Diabetes, Endocrinology and Metabolism,
Department of Experimental Medical Science, Lund University, BMC B11,
SE-221 84, Lund, Sweden

Gabriella Morreale de Escobar
Instituto de Investigaciones Biomédicas Alberto Sols, CSIC and Universidad
Autónoma de Madrid, and Center for Biomedical Research on Rare Diseases
(CIBERER), Madrid, Spain

Ana I. Esquifino, Ph.D.
Departamento de Bioquímica y Biología Molecular III, Universidad Complutense,
28040 Madrid, Spain

Christine Feinle-Bisset
Discipline of Medicine, Royal Adelaide Hospital, Adelaide, South Australia, Australia

Dorianne Feldman, M.D., MSPT
Department of Physical Medicine and Rehabilitation, School of Medicine, Johns
Hopkins University, Baltimore, MD

Marlís González Fernández, M.D., Ph.D.
Department of Physical Medicine and Rehabilitation, School of Medicine,
Johns Hopkins University, Baltimore, MD

M. Carmen Fernández
Departamento de Personalidad, Evaluación y Tratamiento Psicológico, Facultad de
Psicología, Universidad de Granada, Granada, Spain

Elizabeth Ferris
University of Arizona, Mel & Enid Zuckerman College of Public Health, Tucson,
AZ, USA
and
Department of Psychiatry, Center for Weight and Eating Disorders,
University of Pennsylvania School of Medicine, Philadelphia, PA, USA

Mick P. Fleming
School of Health, Nursing and Midwifery, University of the West of Scotland,
Beech Grove, Ayr, UK

Eduardo Fonseca-Pedrero
Department of Psychology, University of Oviedo, Centro de Investigación
Biomédica en Red de Salud Mental, CIBERSAM, Plaza Feijoo, s/n, Oviedo, 33003,
Spain

Georg Förster
Department of Psychology, University of Würzburg, Würzburg, Germany

Joanna S. Fowler, Ph.D.
Medical Department, Brookhaven National Laboratory, Upton, New York, USA

Vincenza Frisardi, M.D.
Department of Geriatrics, Center for Aging Brain, Memory Unit, University of
Bari, Bristol, UK

Gilles Fromentin
INRA, CNRH-IdF, UMR914 Nutrition Physiology
and Ingestive Behavior, F-75005 Paris, France
and
AgroParisTech, CNRH-IdF, UMR914 Nutrition Physiology
and Ingestive Behavior, F-75005 Paris, France
and
UMR 914 INRA/AgroParisTech, 16 rue Claude Bernard,
75231 Paris Cedex 05, France

Toshikatsu Fujii
Department of Behavioural Neurology and Cognitive Neuroscience, Tohoku
University Graduate School of Medicine, Sendai, Japan

Tahany M. Gadalla, Ph.D., M.Sc., MMath
Factor-Inwentash Faculty of Social Work, University of Toronto, 246 Bloor Street
West, Toronto, Ontario, Canada, M5S 1V4

Salah Gariballa, M.D., FRCP
Department of Internal Medicine, Faculty of Medicine and Health Sciences, UAE
University, Al-Ain, United Arab Emirates

Michael K. Georgieff, M.D.   [AU2]
Department of Pediatrics, Neonatology Division & Center for Neurobehavioral
Development, School of Medicine, University of Minnesota, 420 Delaware St. SE,
MMC 39 (for mail), D-136 Mayo Building (for courier), Minneapolis,
MN 55455, USA

E.L. Gibson
Clinical and Health Psychology Research Centre, Department of Psychology,
Whitelands College, Roehampton University, Holybourne Avenue,
London SW15 4JD, UK

Giuseppe Derosa, M.D., Ph.D.
Department of Internal Medicine and Therapeutics, University of Pavia, Pavia, Italy

Cheryl Glover
School of Health, Nursing and Midwifery, University of the West of Scotland,
Ayr Campus, Beech Grove, Ayr, UK

Bertrand Godet
Service de Neurologie, Centre Hospitalier Universitaire, Limoges, France

Dina Gohar
Department of Psychology, University of Pennsylvania, Philadelphia, PA, USA

Iratxe Gonzalez

Oscar Gonzalez-Perez, M.D., Ph.D
Laboratory of Neuroscience, School of Psychology, University of Colima,
Av. Universidad 333, Colima, Col 28040, México
and
Neuroscience Department, Centro Universitario de Ciencias de la Salud,
University of Guadalajara, Guadalajara, Jal 44340, México

E. González-Reimers
Servicio de Medicina Interna, Hospital Universitario de Canarias, Ofra s/n 38320,
La Laguna, Tenerife, Canary Islands, Spain

S.A. van Goor
University Medical Center Groningen, Nijlandspark 26, 9301 Bz Roden,
The Netherlands

Amy A. Gorin, Ph.D.
Department of Psychology, Center for Health, Intervention, and Prevention,
University of Connecticut, 2006 Hillside Road, Storrs, CT 06269-1248, USA

Alja Gössler
Department of Pediatric and Adolescent Surgery, General Hospital Klagenfurt,
St.Veiter Str. 47, 9020 Klagenfurt, Austria

Reiko Graham
Department of Psychology, Texas State University, San Marcos, TX, USA

Riccardo Dalle Grave, M.D.
Department of Eating and Weight Disorder, Villa Garda Hospital,
Via Montebaldo 89, I-37016 Garda (VR), Italy

Michael W. Green
Nutrition and Behaviour Laboratory, Psychology Department, School of Life and
Health Sciences, Aston University, Birmingham, UK, B4 7ET

Melinda A. Green
Department of Psychology, Cornell College, 106E Law Hall,
600 First Street West, Mt. Vernon, IA 52314

G. Grugni
Department of Auxology, IRCCS 'S. Giuseppe Hospital'-Verbania, Roma, Italy

Rubem Carlos Araújo Guedes, M.D., Ph.D.
Departamento de Nutrição, Universidade Federal de Pernambuco,
BR-50670901, Recife, PE, Brazil

Matthieu J. Guitton, Ph.D.
Centre de Recherche Université Laval Robert-Giffard (CRULRG), 2601
Chemin de la Canardière F-6517, Québec, QC, G1J 2G3, Canada
and
Faculty of Pharmacy, Laval University, Quebec City, QC, Canada

Alissa A. Haedt, M.A.
Department of Psychiatry, University of Iowa, Iowa City, IA, USA

Jason C.G. Halford
Kissileff Laboratory for the Study of Human Ingestive Behaviour,
School of Psychology, University of Liverpool, Liverpool, UK

John Hall, Ph.D.
Deakin Business School, Deakin University, Melbourne, Victoria, Australia

Hélène Hanaire
Unité de Nutrition, CHU Larrey, Toulouse cedex

Rhona M. Hanning, Ph.D., RD
Department of Health Studies and Gerontology, University of Waterloo, Waterloo,
Ontario, Canada

Joanne A. Harrold
Kissileff Laboratory for the Study of Human Ingestive Behavior, School
of Psychology, University of Liverpool, Liverpool, UK

Sybil L. Hart, Ph.D.
Texas Tech University, Department of Human Development and Family Studies,
Lubbock, TX 79409-1230

Jenni Harvey
Division of Medical Sciences, Centre for Neuroscience, Ninewells Hospital
and Medical School, University of Dundee, Dundee DD1 9SY, UK

Kenji Hashimoto
Division of Clinical Neuroscience, Chiba University Center for Forensic
Mental Health, 1-8-1 Inohana, Chiba 260-8670, Japan

Michio Hashimoto
Department of Environmental Physiology, Shimane University Faculty of Medicine,
Izumo, Shimane 693–8501, Japan

Remco C. Havermans
Department of Clinical Psychological Science, Maastricht University, Maastricht,
6200 MD, The Netherlands

Narasimha Hegde, Ph.D.
Department of Nutritional Sciences, Pennsylvania State University, University Park,
PA, USA

Christopher Herrera
Delta Sleep Research Unit, Discipline of Exercise and Sport Science,
The University of Sydney, Lidcombe, Australia

Marion Hetherington
Institute of Psychological Sciences, University of Leeds, Leeds,
West Yorkshire, UK

Takashi Higuchi
Department of Integrative Physiology, University of Fukui, Eiheij-cho, Matsuoka,
Fukui, 910-1193, Japan

Anke Hinney
Klinik für Psychiatrie und Psychotherapie des Kindes- und Jugendalters, LVR-
Klinikum Essen, Kliniken und Institut der Unisitat Duisburg-Essen, Essen, Germany

Angelica Lindén Hirschberg, M.D., Ph.D.
Department of Obstetrics and Gynaecology, Karolinska University Hospital,
Stockholm, Sweden

Claude Marcel Hladik
UMR CNRS/MNHN 7206, Eco-Anthropologie et Ethnobiologie, Brunoy, France

Bartley G. Hoebel
Department of Psychology, Princeton University, Princeton, NJ, USA

Wilhelm Hofmann
University of Chicago, Booth School of Business,
5807 South Woodlawn Avenue, Chicago, IL 60615

Pleunie Hogenkamp
Division of Human Nutrition, TI Food and Nutrition, Wageningen University
and Research Centre, Wageningen, the Netherlands

Eef Hogervorst, Ph.D.
School of Sport, Exercise and Health Sciences, Loughborough University,
Ashby Road, Loughborough, Leicestershire, United Kingdom

R.H. Holloway, B.Sc. (Med), M.B.B.S., M.D., FRACP
Discipline of Medicine, University of Adelaide, Adelaide, Australia

Chang Hyung Hong
Department of Psychiatry and Ajou Institute of Aging, Ajou University School
of Medicine, San 5, Wonchun-dong, Youngtong-gu, Suwon-si, 443-749, Korea

Mary Hostler
Program Secretary, Cancer Research Center Hawaii, Prevention and
Control Program, University of Hawaii at Manoa, Honolulu, HI, USA

Jonathan O'B. Hourihane, M.B., D.M., MRCPI, FRCPCH
Clinical Investigations Unit, Department of Paediatrics and Child Health, Cork
University Hospital, University College Cork (UCC), Wilton, Cork, Ireland

Alexa Hoyland
Human Appetite Research Unit, Institute of Psychological Sciences, University
of Leeds, Leeds, UK

Wallace Huffman, Ph.D.
Department of Economics, Iowa State University, Ames, IA 50011, USA

Ethan E. Hull, Ph.D.
Children's Hospital of Pittsburgh, Pittsburgh, PA

Michael Huncharek, MD, MPH
Meta-Analysis Research Group, 10 Sasanqua Circle, Columbia, SC 29209, USA

Teresa Iannaccone
Department of Experimental Medicine, Section of Human Physiology, and Clinical Dietetic Service, Second University of Naples, Naples, Italy

Melinda J. Ickes, Ph.D.
Health Promotion & Education, University of Cincinnati, Cincinnati, OH, USA

Bruno P. Imbimbo, Ph.D.
Research and Development Department, Chiesi Farmaceutici, Parma, Italy
and
Department of Geriatrics, University of Foggia, Foggia, Italy

Syed A. Imran
Department of Physiology & Biophysics, Dalhousie University, Halifax, NS, Canada

Sheila M. Innis
Department of Paediatrics, Child and Family Research Institute, University of British Columbia, 950 West 28th Avenue, Vancouver, BC V5Z 4H4, Canada

Akio Inui
Department of Psychosomatic Internal Medicine, Kagoshima University Graduate School of Medical and Dental Sciences 8-35-1 Sakuragaoka, Kagoshima 890-8520, Japan

Shera C. Jackson, M.S., CLC
Department of Human Development and Family Studies, Texas Tech University, Lubbock, TX, USA

Sanjay Jaju, M.D. M.Phil.
Directorate of Research & Studies, DG Planning, Ministry of Health (HQ), Muscat, Sultanate of Oman

Anita Jansen
Department of Clinical Psychological Science, Maastricht University, P.O. Box 616, 6200 MD Maastricht, The Netherlands

Margaret Jastran
Division of Nutritional Sciences, Cornell University, Ithaca, NY, USA

Aminah Jatoi, M.D.
Department of Oncology, Mayo Clinic, 200 First Street SW, Rochester, Minnesota, USA

Vickii B. Jenvey
School of Psychology, Psychiatry, Monash University, Building 17, Clayton, Victoria 3800, Australia

Amanda Jepson
Department of Psychology, Cornell College, Mt. Vernon, IA, USA
and
Neuroscience Department, Centro Universitario de Ciencias de la Salud, University
of Guadalajara, Guadalajara, Jal, México

Amy R. Johnson
Department of Nutrition, University of North Carolina at Chapel Hill, Chapel Hill,
NC, USA

Fiona Jones
Department of Psychology, University of Bedfordshire, Luton, LU1 3JU, UK

Michelle P. Judge, Ph.D., RD
School of Nursing, University of Connecticut, 231 Glenbrook Rd, Unit 2026,
Mansfield, CT, USA

Alexei B. Kampov-Polevoy, M.D., Ph.D.
Department of Psychiatry, University of North Carolina at Chapel Hill, 237 Medical
School Wing B, Campus Box 7160, Chapel Hill, NC 27599-7160

Natalie Kanakam
Institute of Psychiatry, King's College London, London, UK
and
Department of Academic Psychiatry, Eating, Disorder Research Unit,
Guy's Hospital, London, UK

Masanori Katakura
Department of Environmental Physiology, Shimane University Faculty
of Medicine, Izumo, Shimane, Japan
and
Meta-Analysis Research Group, Columbia, SC, USA

Patrick G. Kehoe, Ph.D.
Dementia Research Group, Institute of Clinical Neurosciences, The John James
Building, Frenchay Hospital, University of Bristol, Bristol, UK

A.R. Kelles, Ph.D.
Department of Nutrition, New York Chiropractic College, Seneca Falls,
New York, USA

Eva Kemps
School of Psychology, Flinders University, GPO, Adelaide, SA 5001, Australia

Alexandra P.F. Key, Ph.D.
Vanderbilt Kennedy Center for Research on Human Development, 230 Appleton
Place, Peabody Box 74, Vanderbilt University, Nashville, TN 37203

Joan Khoo
Discipline of Medicine, Royal Adelaide Hospital, Adelaide, South Australia,
Australia

Hiroe Kikuchi
Educational Physiology Laboratory, Graduate School of Education, The University
of Tokyo, Tokyo, Japan

Atsushi Kimura
Sensory & Cognitive Food Science Laboratory, National Food Research Institute, Kannondai, Tsukuba, Ibaraki, Japan

Neil King
Human Movement Studies & Institute of Health and Biomedical Innovation, Queensland University of Technology, Brisbane, Queensland, Australia

Kelly L. Klump, Ph.D.
Department of Psychology, Michigan State University, East Lansing, MI, USA

Y. Kodra
National Centre for Rare Diseases, Istituto Superiore di Sanità, Roma, Italy

Anna Kokavec, Ph.D.
School of Psychological Science, La Trobe University, Bendigo, Australia, 3552

Hitoshi Komuro
Department of Neurosciences/NC30, Lerner Research Institute, The Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, OH 44195, USA

Yutaro Komuro
Department of Neurosciences/NC30, Lerner Research Institute, The Cleveland Clinic Foundation, Cleveland, OH, USA

Takashi Kondoh, Ph.D.
Institute of Life Sciences, Ajinomoto Co., Inc., Kawasaki, Japan
and
AJINOMOTO Integrative Research for Advanced Dieting, Graduate School of Agriculture, Kyoto University, Kyoto, Japan
and
Institute of Psychiatry, King's College London, London, UK
and
Department of Academic Psychiatry, Eating Disorders Research Unit, Guy's Hospital, London, UK

Karel Krafka
Department of Pediatric and Adolescent Surgery, General Hospital Klagenfurt, Klagenfurt, Austria

David Kugler
Department of Psychology, Cornell College, Mt. Vernon, IA, USA

Jyrki T. Kuikka
Imaging Center, Kuopio University Hospital, FIN-70211 Kuopio, Finland

Tatsuro Kumada
Department of Neurosciences/NC30, Lerner Research Institute, The Cleveland Clinic Foundation, Cleveland, OH, USA

Angela B. Kydd
School of Health Nursing and Midwifery, University of the West of Scotland, Hamilton Campus, Almada Street, Hamilton, Lanarkshire, ML3 0JB, UK

Christine Laborie
Neurostress (EA4347), Equipe Dénutritions Maternelles Périnatales,
Bâtiment SN4, Université des Sciences et Technologies de Lille, France

Virginie F. Labrousse
Psynugen, Université Bordeaux 2, INRA, UMR1286, CNRS, UMR5226, Bâtiment
UFR Pharmacie – 2ème Tranche – 2ème Etage, Case courrier 34, 33076
BORDEAUX Cedex

Jeroen Lakerveld
Department of General Practice and the EMGO Institute for Health and Care
Research, VU University Medical Center, van der Boechorststraat 7, 1081 BT,
Amsterdam, The Netherlands

Sylvia M.S. Chung Chun Lam
Riddet Institute, Massey University, Private Bag 11-222, Palmerston North,
New Zealand

Gavin Lambert, Ph.D.
Human Neurotransmitters Laboratory, Vascular and Hypertension Division,
Baker IDI Heart and Diabetes Institute, Melbourne, Australia

Carol J. Lammi-Keefe, Ph.D., RD
Human Nutrition and Food, School of Human Ecology, Louisiana State University,
Baton Rouge, LA, USA

Daniel Lamport
Human Appetite Research Unit, Institute of Psychological Sciences,
University of Leeds, Leeds, UK

M. Daniel Lane
Department of Biological Chemistry, School of Medicine, The Johns Hopkins
University, Baltimore, Maryland 21205

Brenda Larson, M.D.
Department of Oncology, Mayo Clinic, 200 First street SW, Rochester, Minnesota,
USA

Antonio Laverde
Laboratório de Química de Produtos Naturais, Universidade Paranaense, Praça
Mascarenhas de Moraes, Umuarama-PR, Brazil

Clare Lawton
Human Appetite Research Unit, Institute of Psychological Sciences, University of
Leeds, Leeds, UK

Sophie Laye, Ph.D.
Psychoneuroimmunology, nutrition and genetics (Psynugen), Université Bordeaux 2,
INRA, UMR1286, CNRS, UMR5226, Bâtiment UFR Pharmacie – 2ème Tranche –
2ème Etage, Case courrier 34, 146 rue Léo Saignat, 33076 BORDEAUX, Cedex

Catherine Lebel
Department of Biomedical Engineering, 1098 Research Transition Facility,
University of Alberta, Edmonton, Alberta

Edward B. Lee, M.D., Ph.D.
Institute for Diabetes, Obesity and Metabolism, School of Medicine, University of
Pennsylvania, Philadelphia, PA, USA

Kang Soo Lee
Department of Psychiatry, Bundang Cha hospital, CHA University, Bundang-gu,
Seongnam-si, Kyounggi-do, Korea

Louis Lefebvre
Department of Biology, McGill University, Montreal, Quebec, Canada

David S. Leland, Ph.D.
Department of Psychology, University of Wisconsin - Eau Claire, 105 Garfield Ave,
Eau Claire, WI 54702, USA

Serafín Lemos-Giráldez
Department of Psychology, Centro de Investigación Biomédica en Red de Salud
Mental (CIBERSAM), University of Oviedo, Oviedo, Spain

Gareth Leng
Centre for Integrative Physiology, University of Edinburgh, George Square,
Hugh Robson Building, EH8 9XD Edinburgh, UK

William R. Leonard
Department of Anthropology, Northwestern University, 1810 Hinman Avenue,
Evanston, IL 60208, USA

Jean Lesage
Neurostress (EA4347), Equipe Dénutritions Maternelles Périnatales, Bâtiment SN4,
Université des Sciences et Technologies de Lille, France

Moira S. Lewitt
Faculty of Science & Technology, University of the West of Scotland,
Paisley Campus, PA1 2BE, Paisley, Scotland, UK

Ying Li
Department of Neurosciences/NC30, Lerner Research Institute, The Cleveland
Clinic Foundation, Cleveland, OH, USA

Ying-Xiao Li
Department of Psychosomatic Internal Medicine, Kagoshima University Graduate
School of Medical and Dental Sciences, Kagoshima, Japan

S.W. Lim
Department of Biological System Engineering, University of Wisconsin-Madison,
Madison, WI, USA

Giani Andrea Linde
Laboratório de Biologia Molecular, Universidade Paranaense, Praça Mascarenhas
de Moraes, 4282, CEP 87.502-210, Umuarama-PR, Brazil

Katajun Lindenberg
Center for Psychotherapy Research, University Hospital Heidelberg, Bergheimer
Straße 54, 69115 Heidelberg, Germany

Diana M. Lindquist, Ph.D.
Department of Radiology/Imaging Research, Cincinnati Children's Hospital
Medical Center, Cincinnati, OH, USA

Yoav Littner
Department of Neonatology, Cleveland Clinic Children's Hospital, The Cleveland
Clinic Foundation, Cleveland, OH, USA

Elizabeth F. Loftus
Department of Psychology, University of California at Irvine, Irvine, CA, USA

Antonio Carlos Lopes
Department of Medicine, Federal University of São Paulo (UNIFESP), São Paulo, Brazil

Alison Bryant Ludden, Ph.D.
Psychology Department, College of the Holy Cross, Worcester, MA, USA

D. A. de Luis
Institute of Endocrinology and Nutrition, Medicine School and
Unit of Investigation, Hospital Rio Hortega. Hospital Clinico,
University of Valladolid, Valladolid, Spain

Marie-Amélie Lukaszewsk
Neurostress (EA4347), Equipe Dénutritions Maternelles Périnatales, Bâtiment SN4,
Université des Sciences et Technologies de Lille, France

Colleen Taylor Lukens, Ph.D.
Pediatric Feeding and Swallowing Center, The Children's Hospital of Philadelphia,
34th Street & Civic Center Boulevard, Philadelphia, PA 19104, USA

Jennifer D. Lundgren, Ph.D.
Department of Psychology, University of Missouri-Kansas City, 4825 Troost
Avenue, Ste. 124, Kansas City, Missouri, 64110, USA

Christine-Johanna Macare
Institute of Psychiatry, King's College London, London, UK
and
Department of Academic Psychiatry, Eating, Disorder Research Unit,
Guy's Hospital, London, UK

Ian G. Macreadie
Bio21 Institute, University of Melbourne, 30 Flemington Road,
Melbourne, VIC 3010, Australia

Sandra Maestro
Division of Child Neuropsichiatry, Stella Maris Scientific Institute, University of
Pisa, Italy

Mario Maj
Department of Psychiatry, University of Naples SUN, Naples, Italy

Alexandros Makriyannis
Center for Drug Discovery, Northeastern University, Boston, MA, USA

Izaskun Marañon
Navarra Health Service (Osasunbidea), Itsasargi 11-3, 20280 Hondarribia, Spain

Glenn R. Marland
School of Health, Nursing and Midwifery, University of the West of Scotland,
Dumfries Campus, Dudgeon House, Bankend Road, Dumfries, DG1 4ZN, UK

Monica Mars
Division of Human Nutrition, TI Food and Nutrition/Wageningen University and
Research Centre, Wageningen, the Netherlands

Corby K. Martin, Ph.D.
Ingestive Behavior Laboratory, Pennington Biomedical Research Center,
6400 Perkins Rd., Baton Rouge, LA, USA

Colin R. Martin
School of Health, Nursing and Midwifery, University of the West of Scotland,
Ayr Campus, Beech Grove, Ayr, KA8 0SR, UK

Catia Martins
Department of Cancer Research and Molecular Medicine, Faculty of Medicine,
Norwegian University of Science and Technology, Trondheim, Norway

Giulio Marchesini, M.D.
Unit of Metabolic Diseases & Clinical Dietetics, "Alma Mater Studiorum"
University, University of Bologna, Policlinico S. Orsola, Via Massarenti 9,
I-40138, Bologna, Italy

Rebecca Marzocchi, M.D.
Clinical Dietetics, University of Bologna, Bologna, Italy

Alessandra Mauri
Nutrition, Metabolism and Diabetes Unit, Ospedale Ca' Foncello,Treviso, Italy

Sylvain Mayeur
Neurostress (EA4347), Equipe Dénutritions Maternelles Périnatales, Bâtiment SN4,
Université des Sciences et Technologies de Lille, France

F. Joseph McClernon, Ph.D.
Health Behavior Neuroscience Research Program, Investigator, Center for Nicotine
and Smoking Cessation Research, Duke University Medical Center, Durham,
NC, USA

Patrick O. McGowan
Department of Psychiatry, McGill University, Montreal, QC, Canada

Peter J. McLaughlin
Department of Psychology, University of Connecticut, Storrs, CT, USA
and
Department of Psychology, Edinboro University of Pennsylvania, Edinboro, PA, USA

James S. McTaggart
Department of Physiology, Anatomy and Genetics, University of Oxford, Oxford, UK

Michael J. Meaney
Sackler Program for Epigenetics and Psychobiology, Douglas Institute – Research, Montreal, QC, Canada

Giovanni Messina
Department of Experimental Medicine, Section of Human Physiology, and Clinical Dietetic Service, Second University of Naples, Naples, Italy

Jessie L. Miller
Department of Psychiatry and Behavioural Neurosciences, Offord Centre for Child Studies, McMaster University, Chedoke Site, Central Building, 3rd Floor, 1200 Main Street West, Hamilton, Ontario, Canada, L8N 3Z5

Robert R. Miller, Jr.
Biology Department, Hillsdale College, 278 N. West St., Dow Science 213, Hillsdale, MI 49242-1205, USA

Emmanuelle Mimoun
Centre de référence du syndrome de Prader-Willi/Hôpital des Enfants/ 330 av de Grande Bretagne/TSA 70034/31059 Toulouse Cedex 9/France

Paola Miotto, M.D.
Eating Disorders Unit, Department of Psychiatry, Conegliano, TV, Italy

Katsumi Mizuno, M.D., Ph.D.
Department of Pediatrics, Showa University of Medicine, 1-5-8 Hatanodai, Shinagawa-ku, Tokyo, 142-8666, Japan

Markus Moessner
Center for Psychotherapy Research, University Hospital Heidelberg, Heidelberg, Germany

Christophe Moinard, Ph.D.
Laboratoire de Biologie de la Nutrition EA 4466, Faculté des Sciences Pharmaceutiques et Biologiques, Université Paris Descartes, 4 avenue de l'Observatoire 75270 Paris Cedex 06, France

Marcellino Monda, M.D.
Department of Experimental Medicine, Section of Human Physiology, and Clinical Dietetic Service, Second University of Naples, Via Costantinopoli 16, 80138 Naples, Italy

Naresh Mondraty
Wesley Eating Disorders Centre, Wesley Hospital, 85 Milton Street, Ashfield, Sydney NSW, 2131 Australia

Marie-Odile Monneuse
Centre National de la Recherche Scientifique, UMR CNRS/MNHN 7206: Eco-Anthropologie et Ethnobiologie, Musée National d'Histoire Naturelle Département HNS - CP135, 57 rue Cuvier, 75231 Paris Cedex 05, France

Chiara Montalto
Division of Child Neuropsichiatry, Stella Maris Scientific Institute, University of Pisa, Italy

Palmiero Monteleone
Department of Psychiatry, University of Naples SUN, Largo Madonna delle Grazie, 80138 Naples, Italy

Carmen C. Moran
School of Psychology & National Wine and Grape Industry Centre, Charles Sturt University, Wagga Wagga, NSW, Australia

Silvia Moreno
Departamento de Psicología, Facultad de Humanidades y Ciencias de la Educación, Universidad de Jaén, Jaén, Spain

Linda Morgan
Division of Nutritional Sciences, Faculty of Health and Medical Sciences, University of Surrey, Guildford, UK

Etsuro Mori
Department of Behavioural Neurology and Cognitive Neuroscience, Tohoku University Graduate School of Medicine, Sendai, Japan

Béatrice Morio, Ph.D.
UMR1019 Nutrition Humaine, INRA, 63120 Saint Genès Champanelle, France
and
Université Clermont 1, UFR Médecine, 63000 Clermont-Ferrand, France

Margaret J. Morris
Department of Pharmacology, School of Medical Sciences, University of New South Wales, Sydney, NSW 2052, Australia

Paul J. Moughan
Riddet Institute, Massey University, Palmerston North, New Zealand

Leonardo Munari
Dipartimento di Farmacologia Preclinica e Clinica, Universita' di Firenze, Florence, Italy

Filippo Muratori
Division of Child Neuropsichiatry, Stella Maris Scientific Institute, University of Pisa, IRCCS Stella Maris, Via dei Giacinti, 2-56018 Calambrone, Pisa, Italy

F.A.J. Muskiet
University Medical Center Groningen, Groningen, the Netherlands

Sabine Naessén, M.D., Ph.D.
Department of Obstetrics and Gynaecology, Karolinska University Hospital, SE-171 76 Stockholm, Sweden

Naoko Narita, M.D., Ph.D.
Institute of Education, Bunkyo University, 3337 Minamiogishima, Koshigaya-City, Saitama, 343-8511, Japan

Masaaki Narita, M.D., Ph.D.
Developmental and Regenerative Medicine, Mie University, Tsu, Mie, Japan

Chantal Nederkoorn
Department of Clinical Psychological Science, Maastricht University, Maastricht,
the Netherlands

N.Q. Nguyen, M.B.B.S., FRACP, Ph.D.
Department of Gastroenterology and Hepatology, Royal Adelaide Hospital,
North Terrace, Adelaide, SA, 5000, Australia

Heather M. Niemeier, Ph.D.
Department of Psychology, University of Wisconsin Whitewater, Whitewater, WI, USA

Giel Nijpels, M.D., Ph.D.
Department of General Practice and the EMGO Institute for Health and Care
Research, VU University Medical Center, Amsterdam, the Netherlands

Chiara Nuccitelli, Ph.D.
Clinical Dietetics, University of Bologna, Bologna, Italy

Daryl B. O'Connor
Institute of Psychological Sciences, University of Leeds, LS2 9JT, UK

Teresia O'Connor, M.D., MPH
Children's Nutrition Research Center, Department of Pediatrics, Baylor College of
Medicine, Houston, TX, USA

Barry O'Mahony, Ph.D.
School of Hospitality, Tourism and Marketing, Victoria University, Melbourne City,
Vic 8001, Australia

Kaeko Ogura
Department of Pediatrics, National Rehabilitation Center for Persons with
Disabilities, 1, Namiki 4-chome, Tokorozawa, Saitama 359-8555, Japan
and
Department of Behavioural Neurology and Cognitive Neuroscience, Tohoku
University Graduate School of Medicine, Sendai, Japan

Ken Ohashi
Graduate School of Medicine, Department of Metabolic Diseases, The University of
Tokyo, Tokyo, Japan

Chuma O. Okere
Department of Biological Sciences, Clark Atlanta University, Atlanta, GA, USA

Leonardo A. Ortega
Department of Psychology, Texas Christian University, Fort Worth, TX, USA

Sarah E. Overington, Ph.D.
Department of Biology, McGill University, 1205 Avenue Docteur Penfield,
Montreal, Quebec, Canada H3A 1B1

Agostino Paccagnella
Nutrition, Metabolism and Diabetes Unit, Ospedale Ca' Foncello,
31100 Treviso, Italy

L. Padua
Institute of Neurology, Università Cattolica, Roma, Italy
and
Fondazione Pro Iuventute Don Carlo Gnocchi- Roma, Italy

Mercedes Paíno
Department of Psychology, Centro de Investigación Biomédica en Red de Salud
Mental (CIBERSAM), University of Oviedo, Oviedo, Spain

Francesco Panza, M.D., Ph.D.
Department of Geriatrics, Center for Aging Brain, Memory Unit,
University of Bari, Policlinico, Piazza Giulio Cesare, 11, 70124 Bari, Italy

Mauricio R. Papini
Department of Psychology, Texas Christian University, Fort Worth, TX 76129

Timo Partonen, M.D., Ph.D.
Mood, Depression and Suicidal Behaviour Unit, Department of Mental Health and
Substance Abuse Services, National Institute for Health and Welfare, Helsinki, Finland

Elettra Pasqualoni, R.D.
Department of Eating and Weight Disorder, Villa Garda Hospital, Garda, Italy

Elettra Pasqualoni, R.D.
AIDAP Verona, Via Sansovino, Verona, Italy

Patrick Pasquet
UMR CNRS/MNHN 7206: Eco-Anthropologie et Ethnobiologie, Brunoy, France

Maria Beatrice Passani
Dipartimento di Farmacologia Preclinica e Clinica, Universita' di Firenze, Viale
Pieraccini 6, Florence, Italy

Kendra Patrick
Michigan State University, East Lansing, MI, USA

Karen Patte
Faculty of Health, York University, Toronto, Ontario, Canada

Nicole L.M. Pernat
Department of Psychology, Kwantlen Polytechnic University, Surrey, BC, Canada

Jennifer E. Phillips, Jaime A. Pineda, Ph.D.
Department of Cognitive Science and Group in Neuroscience, University of
California, San Diego, CA, USA

J. Pinkney, M.D., FRCP
Department of Diabetes and Endocrinology, Royal Cornwall Hospital, Peninsula
College of Medicine and Dentistry, Truro, Cornwall, UK

Pierluigi Politi
Department of Health Sciences, Section of human nutrition and dietetics,
University of Pavia, Via Bassi 21, I-27100 Pavia, Italy

Kathleen A. Potter
Department of Biochemistry and Molecular Biology, Medical University of South
Carolina, Charleston, SC, USA

Michael L. Power, Ph.D.
Research Department, American College of Obstetricians and Gynecologists,
Washington, DC 20090–6920
and
Nutrition Laboratory, Conservation Ecology Center, Smithsonian
National Zoological Park, MRC 5503 Washington, DC 20013-7012

Antonio Preti, M.D.
Department of Psychology, University of Cagliari, via is Mirrionis 1, 09123
Cagliari, Italy
and
Centro Medico Genneruxi, Via Costantinopoli 42, 09129 Cagliari, Italy

Pierre-Marie Preux
Université de Limoges, Institut de Neuroépidémiologie et de Neurologie Tropicale,
EA 3174 NeuroEpidémiologie Tropicale et Comparée, Limoges, France

Kathryn Proulx, Ph.D., PMHCNS-BC
Mental Health Services, University of Massachusetts, Hills North,
Amherst, MA 01103

Sarah E. Racine, M.A.
Department of Psychology, Michigan State University, East Lansing, MI, USA

Tri Budi W. Rahardjo, Ph.D.
Center for Health Research, University of Indonesia, Jakarta, Indonesia

Sayali C. Ranade
National Brain Research Centre, National Highway-8, Near NSG Campus,
Nainwal Mode, Manesar, Haryana 122050, India

Patrick A. Randall
Department of Psychology, University of Connecticut, Storrs, CT, USA

Christoph Randler
Biology, Department of Natural Sciences, University of Education Heidelberg,
Im Neuenheimer Feld 561–2, D-69120 Heidelberg, Germany

L.R. Ranganath, FRCPE, FRCPath, Ph.D.
Department of Clinical Chemistry, Royal Liverpool University Hospital,
Prescot Street, Liverpool, L7 8XP, UK

Mohammad Tariqur Rahman
Department of Biomedical Science, Kulliyyah of Science,
International Islamic University Malaysia (IIUM), Jalan Istana,
Bandar Indera Mahkota, 25200 Kuantan, Malaysia

Carmen Rasmussen
Department of Pediatrics, Glenrose Rehabilitation Hospital, Edmonton, Alberta

Christopher K. Rayner
Discipline of Medicine, Royal Adelaide Hospital, Adelaide, South Australia, Australia

Katherine Read
Department of Psychology, Cornell College, Mt. Vernon, IA, USA

Caroline Reid
Centre for Addiction and Mental Health, University of Toronto, Toronto, Ontario, Canada

Thomas Reinehr
Department of Paediatric Nutrition Medicine, Vestische Hospital for Children and Adolescents, University of Witten/Herdecke, Dr. F. Steiner Str. 5, 45711 Datteln, Germany

Britta Renner
Department of Psychology, University of Konstanz, Konstanz, Germany

Jared Edward Reser
University of Southern California, Psychology Department, SGM 501, 3620 South McClintock Ave., Los Angeles, CA 90089-1061, USA

Caroline Reverdy
AUXIME - ODOROSMÊ, Les Grandes Roches, 69490, Saint Romain de Popey, France
and
PANCOSMA, R&D Department, 6 Voie des Traz, 1218 Le Grand Saconnex, Switzerland

Paul Richardson
Brain, Behaviour & Cognition Research Group, Psychology, Sheffield Hallam University, Collegiate Campus, Sheffield, UK S10 2BP

A. Rinehart
New York Chiropractic College, Seneca Falls, New York, USA

Reeta Rintamäki, M.D., Ph.D.
National Institute for Health and Welfare, Department of Mental Health and Substance Abuse Services, Mood, Depression and Suicidal Behaviour Unit, 30 (Mannerheimintie 166), FI-00271 Helsinki, Finland

Patrick Ritz, M.D., Ph.D.
Unité de Nutrition, CHU Larrey, TSA 30030, F-31059 Toulouse cedex 9, France

Rachel E. Roberts
Discipline of Medicine, School of Medicine, King's College London, 2nd Floor, Henriette Raphael House, Guy's Campus, London Bridge, London, SE1 1UL, UK

Marcia L. Robertson
Department of Anthropology, Northwestern University, Evanston, IL, USA

Denise Robertson
Division of Nutritional Sciences, Faculty of Health and Medical Sciences, University of Surrey, Guildford, UK

Athena Robinson, Ph.D.
Department of Psychiatry and Behavioral Sciences, Stanford University, School of
Medicine, 401 Quarry Road, Stanford, CA 94305-5722

Sonia Rodríguez-Ruiz
Departamento de Personalidad, Evaluación y Tratamiento Psicológico, Facultad de
Psicología, Universidad de Granada, Campus de la Cartuja s/n, 18071, Granada, Spain

Dana L. Rofey, Ph.D.
Children's Hospital of Pittsburgh, 3414 Fifth Avenue, Room 128, Pgh, PA 15213, USA

Ariz Rojas, M.A.
Department of Psychology, University of South Florida, Tampa, FL, USA

Susanne de Rooij, Ph.D.
Department of Clinical Epidemiology and Biostatistics, Room J1b 210.1,
Academic Medical Centre, University of Amsterdam, Meibergdreef 9,
1100 DD, Amsterdam, The Netherlands

Matthew Rousu, Ph.D.
Department of Economics, Susquehanna University, Selinsgrove, PA, USA

C.W. le Roux
Department of Metabolic Medicine, Imperial College Faculty of Medicine, London, UK

Paul Rozin
Department of Psychology, University of Pennsylvania, 3720 Walnut St,
Philadelphia, PA 19104-6241, USA

J.A. Rycroft
Unilever Research and Development, Colworth House, Sharnbrook, Bedford, UK
and
Department of Experimental Medicine, Section of Human Physiology, and Clinical
Dietetic Service, Second University of Naples, Naples, Italy

Perminder Sachdev
University of New South Wales, Neuropsychiatric Institute, The Prince of Wales
Hospital, Randwick, NSW, Australia

John D. Salamone
Department of Psychology, University of Connecticut, 406 Babbidge Road,
Storrs, CT 06269-1020, USA

Anthony J. Saliba
National Wine and Grape Industry Centre, Charles Sturt University,
Locked Bag 588, Wagga Wagga, NSW, 2678, Australia

F. Santolaria-Fernández
Servicio de Medicina Interna, Hospital Universitario de Canarias, Tenerife, Canary
Islands, Spain

Fumiyo Sato
Corporate Research & Development Group, SHARP Corporation

Nūn Sava-Siva Amen-Ra, M.A., Ph.D.
Amenta Academy of Theoretical Sciences (AATS), 25101Chimney-House Court,
Damascus, MD, USA

Donna Scarborough, Ph.D., CCC-SLP
Department of Speech Pathology and Audiology, Miami University, 26 Bachelor Hall,
Oxford, OH 45056, USA

Sigfrido Scarpa
Dip. di Chirurgia "P. Valdoni", Centro di Ricerca in Neurobiologia "Daniel Bovet"
CriN, Sapienza Università di Roma, via Antonio Scarpa, 14, 00161 Roma, Italy

Jennifer L. Scheide
Women's Health and Exercise Laboratory, Noll Laboratory, Department of
Kinesiology, Penn State University, University Park, PA, USA

Susan M. Schembre, Ph.D., RD
Cancer Research Center Hawaii, Prevention and Control Program, University
of Hawaii, Manoa, 677 Ala Moana Blvd. Suite 200, Honolulu, Hawaii 96813

Anna Schierberl Scherr, B.A.
Center for Health, Intervention, and Prevention, Department of Psychology,
University of Connecticut, Storrs, CT, USA

Gessica Schiavo
Nutrition, Metabolism and Diabetes Unit, Ospedale Ca' Foncello, Treviso, Italy

Jay Schulkin
Nutrition Laboratory, Conservation Ecology Center, Smithsonian National
Zoological Park, Washington DC

Harald T. Schupp
Department of Psychology, University of Konstanz, 78457 Konstanz, Germany

C.M. Schweitzer, M.D., Ph.D.
Department of Internal Medicine, TweeSteden Ziekenhuis, Tilburg

Christina L. Scott, Ph.D.
Whittier College, 13406 E. Philadelphia St. Whittier, CA 90608, USA

Kristen N. Segovia
Department of Psychology, University of Connecticut, Storrs, CT, USA

Claudio A. Serfaty
Laboratory of Neural Plasticity, Fluminense Federal University, 100180,
Niterói, RJ, 24001-970, Brazil

Justine Joan Sheppard, Ph.D.
Department of Biobehavioral Sciences, Teachers College, Columbia University,
525 W. 120th Street, New York, NY 10027

Hossain Md Shahdat
Department of Environmental Physiology, Shimane University Faculty of Medicine,
Izumo, Shimane, Japan
and
Department of Biochemistry and Molecular Biology, Jahangirnagar University,
Savar, Dhaka, Bangladesh

Manoj Sharma, M.B.B.S, Ph.D.
Health Promotion & Education, University of Cincinnati, Cincinnati,
OH 45221-0068, USA

Jason Shogren, Ph.D.
Department of Economics and Finance, University of Wyoming, Laramie, WY, USA

Lauren B. Shomaker, Ph.D.
Department of Medical and Clinical Psychology, Uniformed Services University of
the Health Sciences, Bethesda, MD, USA
and
Unit on Growth and Obesity, Program in Developmental Endocrinology and
Genetics, Eunice Kennedy Shriver National Institute of Child Health and Human
Development, National Institutes of Health Department of Health and Human
Services, Bethesda, MD, USA

M. Shroff, Ph.D.
Department of Health Promotion, Education, and Behavior, University of South
Carolina, Columbia, SC, USA

Susana Sierra-Baigrie
Department of Psychology, University of Oviedo, Plaza Feijoo, s/n, Oviedo
33003 Spain

Kelly Siglin
Department of Psychology, Cornell College, Mt. Vernon, IA, USA

Bruno Simmen
UMR CNRS/MNHN 7206, Eco-Anthropologie et Ethnobiologie, Brunoy, France
and
Department of Biochemistry and Molecular Biology, Jahangirnagar University,
Savar, Dhaka, Bangladesh

Julia Simner
School of Philosophy, Psychology and Language Sciences, University
of Edinburgh, 7 George Square, Edinburgh, EH8 9JZ, UK

Rita Sinigaglia-Coimbra
Electron Microscopy Center, Federal University of São Paulo (UNIFESP),
São Paulo, Brazil
and
Laboratory of Clinical and Experimental Pathophysiology,
Department of Neurology and Neurosurgery, Federal University of São Paulo
(UNIFESP), São Paulo, Brazil

Kelly Sink
Department of Psychology, University of Connecticut, Storrs, CT, USA

Gudrun V. Skuladottir
Department of Physiology, Faculty of Medicine, School of Health Sciences,
University of Iceland, Vatnsmyrarvegi 16, IS-101 Reykjavik, Iceland

Alexandra C. Smith
Department of Food Science and Human Nutrition, College of Applied Human
Sciences, Colorado State University, Fort Collins, CO, USA

Veronique de Smedt-Peyrusse
Psynugen, Université Bordeaux 2, INRA, UMR1286, CNRS, UMR5226, Bâtiment
UFR Pharmacie – 2ème Tranche – 2ème Etage, Case courrier 34, 33076
BORDEAUX Cedex

Françoise J. Smith
Department of Food Science and Human Nutrition, College of Applied Human
Sciences, Colorado State University, Fort Collins, CO, USA

Marek Smulczyk
The Maria Grzegorzewska Academy of Special Education, Institute of Applied
Psychology, 40 Szczesliwicka Street, 02-353 Warsaw, Poland

J. Josh Snodgrass
Department of Anthropology, University of Oregon, Eugene, OR, USA

Harriëtte M. Snoek
Behavioural Science Institute, Radboud University Nijmegen,
The Netherlands
and
Agricultural Economics Research Institute, Wageningen University and Research
Center, P.O. Box 8130, 6700 EW Wageningen, The Netherlands

Vincenzo Solfrizzi, M.D., Ph.D.
Department of Geriatrics, Center for Aging Brain, Memory Unit, University
of Bari, Policlinico, Piazza Giulio Cesare, 11, 70124 Bari, Italy

Annette Stafleu
TI Food and Nutrition/TNO Quality of Life, 3700 AJ Zeist, The Netherlands

J.E.R. Staddon
Department of Psychology and Neuroscience, Duke University, Durham, NC, USA
and
Department of Psychology, University of York, York, UK

Malgorzata Starzomska
The Maria Grzegorzewska Academy of Special Education, Institute of Applied
Psychology, 40 Szczesliwicka Street, 02-353 Warsaw, Poland

Andreas Stengel, M.D.
CURE: Digestive Diseases Research Center, David Geffen School of Medicine,
University of California, Los Angeles, Building 115, Room 117, Los Angeles,
CA, USA

Ashley Stillman
Department of Psychology, Cornell College, Mt. Vernon, IA, USA

Wolfgang Stroebe
Department of Social and Organizational Psychology, Utrecht University, Utrecht,
the Netherlands

James Stubbs
Slimming World, Alfreton, Derbyshire, UK

Albert J. Stunkard, M.D.
Center for Weight and Eating Disorders, Department of Psychiatry, School
of Medicine, University of Pennsylvania, 3535 Market Street, Philadelphia, PA,
19104-3309, USA

Shiro Suda, M.D., Ph.D.
Research Center for Child Mental Development, Hamamatsu University School of
Medicine, Hamamatsu, Shizuoka, Japan

Alessandro Suppini, Ph.D.
Clinical Dietetics, University of Bologna, Bologna, Italy

Nan M. Sussman, Ph.D.
Department of Psychology, College of Staten Island, City University of New York,
Staten Island, New York

Timothy Swartz
INRA, Écologie et Physiologie du Système Digestif, 78350 Jouy-en-Josas, France

Moshe Szyf
Sackler Program for Epigenetics and Psychobiology,
and
Department of Pharmacology and Therapeutics, McGill University, 3655 Sir
William Osler Promenade, room 1309, Montreal, QC, Canada H3G 1Y6

Yvette Taché, Ph.D.
CURE: Digestive Diseases Research Center and Center for Neurovisceral Sciences
& Women's Health, Digestive Diseases Division, David Geffen School of Medicine
at UCLA and VA Greater Los Angeles Healthcare System, Los Angeles, CA, USA

Domenico Tafuri
Department Studies of Institutions and Territorial Systems, Faculty of Movement
Science, University of Naples "Parthenope", Naples, Italy
and
Faculty of Movement Science, University of Naples "Parthenope", Naples, Italy

Nori Takei, M.D., M.Sc., Ph.D.
Research Center for Child Mental Development and United Graduate School of
Child Development, Hamamatsu University School of Medicine, 1-20-1
Handayama, Higashi-ku Hamamatsu Shizuoka, 431-3192 Japan
and
Division of Psychological Medicine, Institute of Psychiatry, London, SE5 8AF, UK

Masato Takii
Department of Psychosomatic Medicine, Graduate School of Medical Sciences, Kyushu University, 3-1-1 Maidashi, Higashi-ku, Fukuoka, 812-8582, Japan

Yoshiyuki Takimoto
Graduate School of Medicine, Department of Stress Sciences and Psychosomatic Medicine, The University of Tokyo, Tokyo, Japan

Marian Tanofsky-Kraff, Ph.D.
Department of Medical and Clinical Psychology, Uniformed Services University of the Health Sciences, Bethesda, MD, USA
and
Unit on Growth and Obesity, Program in Developmental Endocrinology and Genetics, Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Department of Health and Human Services, Bethesda, MD, USA

D. Taruscio
National Centre for Rare Diseases, Istituto Superiore di Sanità, Roma, Italy
and
Fondazione Pro Iuventute Don Carlo Gnocchi, Roma, Italy

Maithe Tauber
Centre de référence du syndrome de Prader-Willi, Hôpital des Enfants, 330 av de Grande Bretagne, TSA 70034, 31059 Toulouse Cedex 9, France

Raed Tayyem
General surgery department, Ayr Hospital, Ayr, UK

Mami Tazoe, M.S.
The Department of Clinical Psychology, Japan Lutheran College, Mitaka, Tokyo, Japan

Ababyue Tegene
US Department of Agriculture, Economic Research Service, Washington DC

Frank Telang, M.D.
Neuroimaging Laboratory, National Institute on Alcohol Abuse and Alcoholism, Upton, New York, USA

Salvadeo Sibilla Anna Teresa, M.D.
Department of Internal Medicine and Therapeutics, University of Pavia, Pavia, Italy

Panayotis K. Thanos, Ph.D.
Behavioral Neuropharmacology & Neuroimaging Laboratory, National Institute on Alcohol Abuse and Alcoholism, Upton, New York, USA
and
Medical Department, Brookhaven National Laboratory, Upton, New York, USA

David R. Thompson
Department of Health Sciences and Department of Cardiovascular Sciences, University of Leicester, Leicester, UK

J. Kevin Thompson, Ph.D.
Department of Psychology, University of South Florida, Tampa, FL, USA

Marika Tiggemann
School of Psychology, Flinders University, Adelaide, Australia

Daniel Tomé
INRA, CNRH-IdF, UMR914 Nutrition Physiology and Ingestive Behavior, Paris,
France
and
AgroParisTech, CNRH-IdF, UMR914 Nutrition Physiology and Ingestive Behavior,
Paris, France

Kunio Torii
Institute of Life Sciences, Ajinomoto Co., Inc., Suzuki-cho 1-1, Kawasaki-ku,
Kawasaki 210-8681, Japan

Phu V. Tran, Ph.D.
Center for Neurobehavioral Development, Neonatology Division & Center for
Neurobehavioral Development, School of Medicine, Department of Pediatrics,
University of Minnesota, MN, USA

Janet Treasure
Institute of Psychiatry, King's College London, London, United Kingdom
and
Department of Academic Psychiatry, Eating Disorder Research Unit, Guy's
Hospital, Bermondsey Wing, SE1 9RT, London, United Kingdom

Angelo Tremblay
Division of Kinesiology, Laval University, Quebec City, QC, Canada

Nhan Truong, Ph.D.
Ismail H. Ulus
Department of Pharmacology, Acibadem University Medical School, Gulsuyu
Mahallesi, Maltepe, Istanbul, Turkey

Erica L. Unger, Ph.D.
Department of Nutritional Sciences, Pennsylvania State University,
University Park, PA 16802

Tracy Vaillancourt
Faculty of Education and School of Psychology, University of Ottawa, Ottawa,
Ontario, Canada
and
Department of Psychology, Neuroscience, & Behaviour, McMaster University,
Hamilton, Ontario, Canada

Olga van den Akker
Department of Psychology, Middlesex University, The Town Hall, The Burroughs,
Hendon, London, NW4 4BT, UK

Koert van Ittersum, Ph.D.
Georgia Institute of Technology, Atlanta, GA, USA

V. Kiran Vemuri
Center for Drug Discovery, Northeastern University, Boston, MA, USA

Gianluigi Vendemiale
Department of Geriatrics, University of Foggia, Foggia, Italy
and
Internal Medicine Unit, IRCSS Casa Sollievo dalla Sofferenza, San Giovanni Rotondo, Puglia, Italy.

R.H. Verheesen, M.D.
Regionaal Reuma Centrum Z.O. Brabant, Máxima Medisch Centrum,
Ds. Th. Fliednerstraat 1, 5631 BM Eindhoven, The Netherlands

Claudia Vicidomini
Department of Experimental Medicine, Section of Human Physiology, and Clinical Dietetic Service, Second University of Naples, Naples, Italy

Didier Vieau
Environment Périnatal et Croissance (EA4489), Equipe Dénutritions Maternelles Périnatales, Bâtiment SN4, 2ème étage, Université des Sciences et Technologies de Lille, 59655 Villeneuve d'Ascq, France

Andrea Viggiano
Department Studies of Institutions and Territorial Systems, Faculty of Movement Science, University of Naples "Parthenope", Naples, Italy
and
Faculty of Movement Science, University of Naples "Parthenope", via Medina, Naples, Italy

Valentina Viglione
Division of Child Neuropsichiatry, Stella Maris Scientific Institute, University of Pisa, Italy

Jaime Vila
Departamento de Personalidad, Evaluación y Tratamiento Psicológico, Facultad de Psicología, Universidad de Granada, Granada, Spain

Piergiuseppe Vinai, M.D.
"GNOSIS" No Profit Research Group, V Langhe 64, 12060, Magliano Alpi,
CN, Italy

Vivianne H.M. Visschers
ETH Zurich, Institute for Environmental Decisions, Consumer Behavior,
Universitaetstrasse 22 CHN J75.2, 8092 Zurich, Switzerland

Nora D. Volkow, M.D.
Office of Director, National Institute on Drug Abuse, Rockville, MD, USA

Yuji Wada
Sensory & Cognitive Food Science Laboratory, National Food Research Institute,
2-1-12, Kannondai, Tsukuba, Ibaraki 305-8642, Japan

Bai-Ren Wang
Institute of Neuroscience, Fourth Military Medical University, Xi'an, China

Gene-Jack Wang, M.D.
Medical Department, Building 490, Brookhaven National Laboratory, Upton,
New York, 11973 USA

Brian Wansink, Ph.D.
Cornell University, 110 Warren Hall, Ithaca, NY 14853-7801, USA

Carolina Werle, Ph.D.
Grenoble Ecole de Management CERAG, Grenoble, France

Stephen Whybrow
Faculty of Health and Medical Sciences, University of Surrey, Guildford, GU2 7XH, UK

Reinout W. Wiers
Department of Psychology, University of Amsterdam, Amsterdam, the Netherlands

Karen Wight
Faculty of Health, York University, 223 Bethune College, 4700 Keele Street, Toronto, Canada
and
Centre for Addiction and Mental Health, University of Toronto, Toronto, Canada

Michael Wilkinson
Department of Obstetrics & Gynaecology, IWK Health Centre, Dalhousie University,
University Avenue, Halifax, NS, Canada, B3K 6R8
and
Department of Physiology & Biophysics, Dalhousie University, Halifax, NS, Canada, B3H 1X5
and
Division of Endocrinology and Metabolism, Victoria General Hospital, Department of Medicine,
Dalhousie University, Halifax, NS, Canada, B3H 2Y9

Gary Wittert
Discipline of Medicine, Royal Adelaide Hospital, Adelaide, South Australia, Australia

Sarah J. Woodruff, Ph.D., CEP
Department of Kinesiology, University of Windsor, 401 Sunset Avenue, Windsor,
Ontario N9B 3P4, Canada

Li-Ze Xiong
Department of Anesthesiology, Xijing Hospital, Fourth Military Medical University,
15 West Changle Rd, Xi'an, 710032, P.R. China

Yajun Xu
Department of Nutrition and Food Hygiene, School of Public Health, Peking University Health
Science Center, No. 38 Xue Yuan Road, Hai Dian District, Beijing 100191, China

Yoshiharu Yamamoto
Educational Physiology Laboratory, Graduate School of Education,
The University of Tokyo

Jack A. Yanovski, M.D., Ph.D.
Section on Growth and Obesity, Program in Developmental Endocrinology and Genetics,
Eunice Kennedy Shriver National Institute of Child Health and Human Development,
National Institutes of Health, Department of Health and Human Services, 9000 Rockvile Pike,
MSC 1103, Hatfield CRC, room IE-3330, Bethesda, Maryland 20892-1103, USA

Amina Yesufu-Udechuku, Ph.D.
CORE, Clinical Health Psychology, University College London, London, UK

Kazuhiro Yoshiuchi
Graduate School of Medicine, Department of Stress Sciences and Psychosomatic Medicine, The
University of Tokyo, Tokyo, Japan

B.S. Zanutto
IIBM-Universidad de Buenos Aires, and IBYME-CONICET, Argentina

Steven H. Zeisel, M.D., Ph.D.
University of North Carolina at Chapel Hill, Nutrition Research Institute,
500 Laureate Way, Kannapolis, North Carolina 28081

Jie Zhao
Department of Nutrition and Food Hygiene, School of Public Health, Peking University Health
Science Center, Beijing, China

Zheng-Hua Zhu
Department of Anesthesiology, Xijing Hospital, Fourth Military Medical University, Xi'an, China
and
Centro Medico Genneruxi, Cagliari, Italy

Nicolien Zijlstra
Division of Human Nutrition, TI Food and Nutrition/Wageningen University and Research Centre,
Wageningen, the Netherlands

Part I
General and Normative Aspects: Evolutionary and Genetic

Chapter 1
Diet and Brain Evolution: Nutritional Implications of Large Human Brain Size

William R. Leonard, J. Josh Snodgrass, and Marcia L. Robertson

Abbreviations

AA	Arachidonic acid
DHA	Docosahexaenoic acid
DQ	Dietary quality
IGF-1	Insulin-like growth factor I
LC-PUFA	Long-chain polyunsaturated fatty acid
MYA	Million years ago
RMR	Resting metabolic rate
RQ	Respiratory quotient

1.1 Introduction

The evolution of the human nutritional requirements is now receiving ever-greater attention among scientists from a variety of different fields, including nutritional science, anthropology and exercise science (Crawford 1992; Leonard et al. 1992, Leonard and Robertson 1994; Aiello and Wheeler 1995; Cordain et al. 2005). We are increasingly coming to realize that many of the key features that distinguish humans from other primates have important implications for our distinctive nutritional needs (Leonard 2002). The most notable of these features is our relatively large brain sizes, which are ~3 times the size our nearest primate relatives, the great apes (Martin 1989; McHenry and Coffing 2000).

Because neural tissue has very high energy demands (~16 times that of muscle tissue; Kety 1957), our large brains exact a high metabolic cost. On average, adult humans spend some 350–400 kcal/day on brain metabolism (Holliday 1986). Yet, despite the fact that humans have much larger brains per body weight than other primates or terrestrial mammals, the resting energy demands for the human body are no more than for any other mammal of the same size (Leonard and Robertson 1994). As a consequence, humans expend a much larger share of their resting metabolic rate (RMR) to "feed their brains" than other primates or non-primate mammals (Leonard et al. 2003).

W.R. Leonard (✉)
Department of Anthropology, Northwestern University, 1810 Hinman Avenue, Evanston, IL 60208, USA
e-mail: w-leonard1@northwestern.edu

To support the high metabolic demands of our large brains, humans have diets of much higher quality – more dense in calories and nutrients – than other primates (Leonard and Robertson 1994). On average, we consume higher levels of dietary fat than other primates (Popovich et al. 1997), and much higher levels of key long-chain polyunsatured fatty acids (LC-PUFAs) that are critical to brain development (Cordain et al. 2001; Crawford et al. 1999). Moreover, humans also appear to be distinctive in their developmental changes in body composition. We have higher levels of body fatness than other primate species, and these differences are particularly evident in early in life.

This chapter draws on both analyses of living primate species and the human fossil record to explore the influence of brain evolution on human nutritional needs. We begin by examining comparative dietary data for modern human groups and other primate species to evaluate the influence that variation in relative brain size has on dietary patterns among modern primates. We then turn to an examination of the human fossil record to examine when and under what conditions in our evolutionary past key changes in brain size and diet likely took place. Finally, we explore how the evolution of large human brains was likely accommodated by distinctive aspects of human growth and development that promote increased levels of body fatness from early in life.

1.2 Comparative Perspectives on Primate Dietary Quality

The high energy costs of large human brains are evident in Fig. 1.1 which shows the allometric (scaling) relationship between brain weight (g) and RMR (kcal/day) for humans, 36 other primate species, and 22 non-primate mammalian species. The solid line denotes the best-fit regression for nonhuman
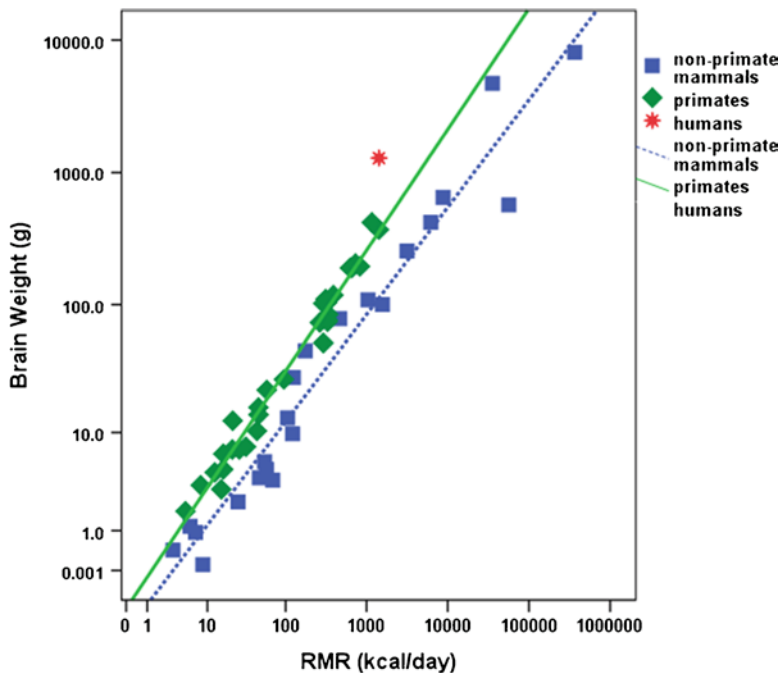
Fig. 1.1 Log-log plot of brain weight (*BW*;g) versus resting metabolic rate (*RMR*; kcal/day) for humans, 36 other primate species, and 22 non-primate mammalian species. The primate regression line is systematically and significantly elevated above the non-primate mammal regression. For a given RMR, primates have brain sizes that are three times those of other mammals, and humans have brains that are three times those of other primates

primate species, and the dashed line denotes the best-fit regression for the non-primate mammals. The data point for humans is denoted with a star.

The slopes of the primate and non-primate mammalian log-log regressions are comparable (0.93 vs 0.90, respectively), whereas the Y-intercept of the primate regression is significantly greater than that of the non-primate mammals (−0.38 vs −0.83; $P<0.001$). These differences imply that for a given RMR, primates have systematically larger brains than other mammals. Humans, in turn, are outliers on the primate regression, having markedly larger brains than expected for their RMRs. In caloric terms, this means that brain metabolism accounts for ~20–25% of RMR in adult humans, as compared to about 8–10% in other primate species, and roughly 3–5% for non-primate mammals.

To accommodate the metabolic demands of our large brains, humans consume diets that are more dense in energy and nutrients than other primates of similar size.

Figure 1.2 shows the association between dietary quality and body weight in living primates, including modern human foragers. The diet quality (DQ) index is derived from Sailer et al. (1985), and reflects the relative proportions (percentage by volume) of (1) structural plant parts (*s*; e.g., leaves, stems, bark), (2) reproductive plant parts (*r*; e.g., fruits, flowers), and (3) animal foods (*a*; including invertebrates):

$$DQ\ index = s + 2(r) + 35(a)$$

The index ranges from a minimum of 100 (a diet of all leaves and/or structural plant parts) to 350 (a diet of all animal material).
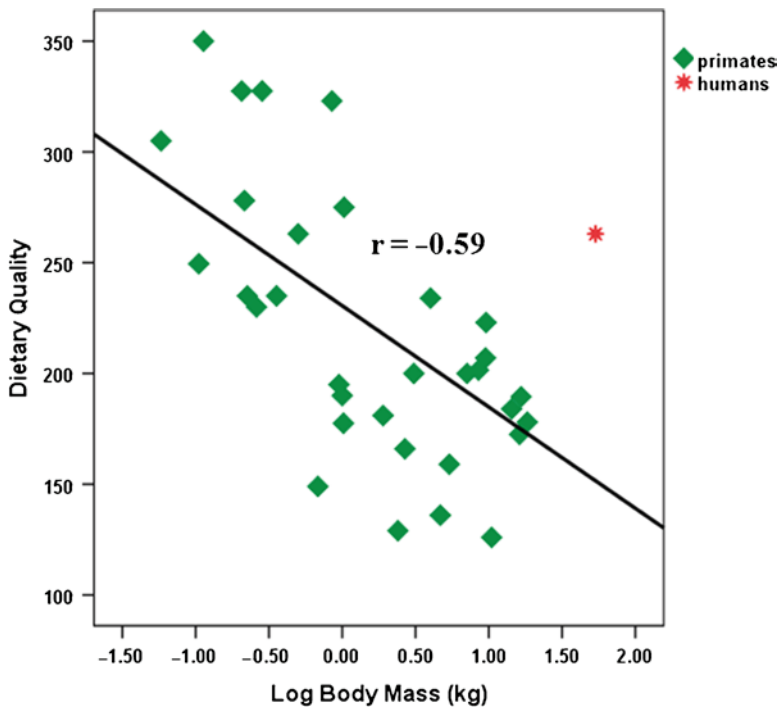
Fig. 1.2 Plot of diet quality (*DQ*) versus log-body mass for 33 primate species. DQ is inversely related to body mass (*r*=−0.59 [total sample]; −0.68 [nonhuman primates only]; *P*<0.001), indicating that smaller primates consume relatively higher quality diets. Humans have systematically higher quality diets than predicted for their size (Adapted from Leonard et al. 2003)

Table 1.1 Macronutrient composition of the diets of humans and modern apes

Species/group	Fat	Protein	CHO	References
Humans (*Homo sapiens*):				
United States (2000)	33	14	53	Briefel and Johnson (2004)
Modern foragers	28–58	19–35	22–40	Cordain et al. (2000)
Chimpanzees (*Pan troglodytes*)	6	21	73[a]	Richard (1985)
				Tutin and Fernandez (1992, 1993)
				Popovich et al. (1997)
Gorilla (*Gorilla gorilla*)	3	24	73[a]	Popovich et al. (1997)

Percent (%) of dietary energy intake derived from fat, protein, and carbohydrates (CHO) in selected human populations, chimpanzees (*Pan troglodytes*), and gorillas (*Gorilla gorilla*)

[a]Includes estimated energy derived from fermentation of dietary fiber

There is a strong inverse relationship between DQ and body mass across primates, with smaller primates relying on energy rich food such as insects, saps, and gums, whereas large-bodied primates rely on low-quality plant foods, such as foliage. Note that the diets of modern human foragers fall substantially above the regression line in Fig. 1.2, implying that humans have systematically higher DQs than expected for a primate of our size. In fact, the staple foods for all human societies are much more nutritionally dense than those of other large-bodied primates. Although there is considerable variation in the diets of modern human foraging groups, recent analyses by Cordain and colleagues (2000) have shown that modern human foragers derive fully 45–65% of their dietary energy intake from animal foods. In comparison, modern great apes obtain the bulk of their diet from low-quality plant foods. Gorillas derive over 80% of their diet from fibrous foods such as leaves and bark (Richard 1985). Even among common chimpanzees (*Pan troglodytes*), only about 5–10% of their calories are derived from animal foods, including insects (Stanford 1996). This higher quality diet means that we need to eat less volume of food to get the energy and nutrients we require.

Table 1.1 presents comparative data on macronutrient intakes of selected human groups, compared to those of chimpanzees and gorillas living in the wild. The dietary information for human populations were derived from the US NHANES data (Briefel and Johnson 2004) and from a recent review of the diets of contemporary hunter-gatherers (foragers) by Cordain et al. (2000). Data for chimpanzees and gorillas were derived from foraging studies in the wild (Tutin and Fernandez 1992, 1993; Richards 1985; Popovich et al. 1997) and compositional analysis of commonly consumed food items (Popovich et al. 1997). Contemporary foraging societies derive between 28% and 58% of their daily energy intakes from dietary fat. Those groups living in more northern climes (e.g., the Inuit) derive a larger share of their diet from animal foods, and thus have higher daily fat intakes. Conversely, tropical foraging populations generally have lower fat intakes because they obtain more of their diet from plant foods. In comparison, Americans and other populations of the industrialized world fall within the range seen for hunter-gatherers, deriving about a third of their daily energy intake from fat (Briefel and Johnson 2004).

In contrast to the levels seen in human populations, the great apes obtain only a small share of calories from dietary fat. Popovich and colleagues (1997) estimate that Western lowland gorillas derive approximately 3% of their energy from dietary fats. Chimpanzees appear to have higher fat intakes than gorillas (about 6% of dietary energy), but they are still well below the low end of the modern forager range. Thus, the higher consumption of meat and other animal foods among human hunter-gatherers is associated with diets that are higher in fat and more dense in energy.

The link between brain size and dietary quality is evident in Fig. 1.3, which shows relative brain size versus relative dietary quality for the 33 different primate species for which we have metabolic, brain size and dietary data. Relative brain size for each species is measured as the standardized residual (z-score) from the primate brain versus body mass regression, and relative DQ is measured
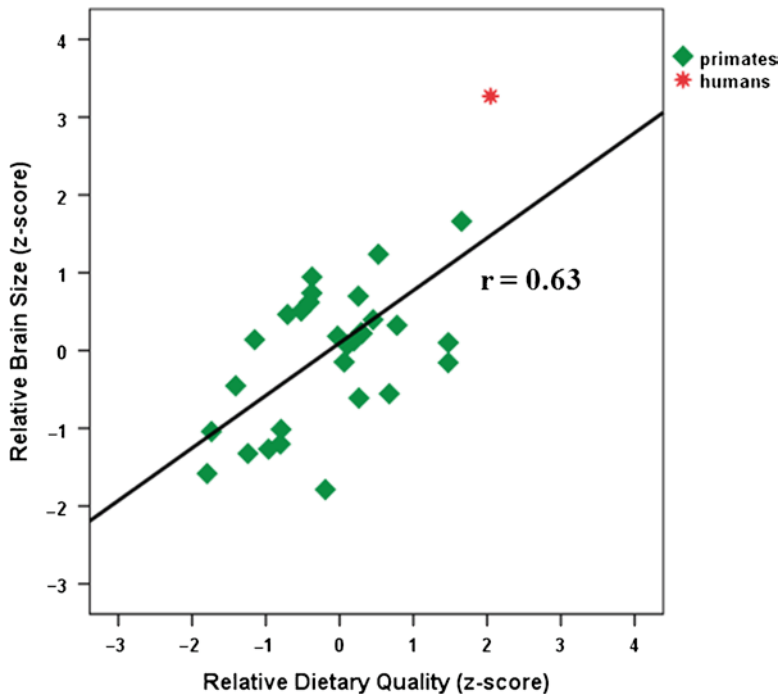
Fig. 1.3 Plot of relative brain size versus relative diet quality for 31 primate species (including humans). Primates with higher quality diets for their size have relatively larger brain size ($r=0.63$; $P<0.001$). Humans represent the positive extremes for both measures, having large brain to body size ratio and a substantially higher quality diet than expected for their size (Adapted from Leonard et al. 2003)

as the residual from the DQ versus body mass regression. There is a strong positive relationship ($r=0.63$; $P<0.001$) between the amount of energy allocated to the brain and the caloric density of the diet. Across all primates, larger brains require higher quality diets. Humans fall at the positive extremes for both parameters, having the largest relative brain size and the highest quality diet.

Thus, the high costs of the large, metabolically expensive human brain is partially offset by the consumption of a diet that is more dense in energy and fat than those of other primates of similar size. This relationship implies that the evolution of larger hominin brains would have necessitated the adoption of a sufficiently high-quality diet (including meat and energy-rich fruits) to support the increased metabolic demands of greater encephalization.

1.3 Evolutionary Trends in Diet, Brain Size, and Body Size

When we look at the human fossil record, we find that the first major burst of evolutionary change in hominin brain size occurs at about 2.0–1.7 million years ago, associated with the emergence and evolution of early members of the genus *Homo* (see Table 1.2). Prior to this, our earlier hominin ancestors, the australopithecines, showed only modest brain size evolution from an average of 400–510 cm³ over a 2 million year span from 4 to 2 million years ago. With the evolution of the genus *Homo*, there is rapid change, with brain sizes of, on average, ~600 cm³ in *Homo habilis* (at 2.4–1.6 mya) and 800–900 cm³ in early members of *H. erectus* (at 1.8–1.5 mya). Although the relative

Table 1.2 Brain size, body weight, and tooth size for selected prehistoric hominin species

| Species | Geological age (mya) | Brain size (cm³) | Body weight | | Postcanine tooth surface area (mm²) |
			Male (kg)	Female (kg)	
A. afarensis	3.9–3.0	438	45	29	460
A. africanus	3.0–2.4	452	41	30	516
A. boisei	2.3–1.4	521	49	34	756
A. robustus	1.9–1.4	530	40	32	588
Homo habilis (*sensu strictu*)	1.9–1.6	612	37	32	478
H. erectus (early)	1.8–1.5	863	66	54	377
Homo erectus (late)	0.5–0.3	980	60	55	390
H. sapiens	0.4–0.0	1,350	58	49	334

Geological ages (millions of years ago), brain size (cm³), estimated male and female body weights (kg), and postcanine tooth surface areas (mm²) for selected fossil hominin species (Data are derived from Leonard et al. 2003)

brain size of *H. erectus* has not yet reached the size of modern humans, it is outside of the range seen among other living primate species.

The evolution of *H. erectus* in Africa is widely viewed as a *major adaptive shift* in human evolution (Antón et al. 2002; Wolpoff 1999). Indeed, what is remarkable about the emergence of *H. erectus* in East Africa at 1.8 million years is that we find marked increases in both brain and body size, and the evolution of human-like body proportions at the same time that we see major reductions of posterior tooth size and craniofacial robusticity (McHenry and Coffing 2000; Ruff et al. 1997). These trends clearly suggest major energetic and dietary shifts: (a) the large body sizes necessitating greater daily energy needs; (b) bigger brains suggesting the need for a higher quality diet; and (c) the craniofacial changes suggesting that they were consuming a different mix of foods than their australopithecine ancestors.

The ultimate driving factors responsible for the rapid evolution of brain size, body size, and craniodental anatomy at this stage of human evolution appear to have been major environmental changes that promoted shifts in diet and foraging behavior. The environment in East Africa at the Plio-Peistocene boundary (2.0–1.8 mya) was becoming much drier, resulting in declines in forested areas and an expansion of open woodlands and grasslands (Bobe and Behrensmeyer 2002; Wynn 2004). Such changes in the African landscape likely made animal foods an increasingly attractive resource for our hominin ancestors (Behrensmeyer et al. 1997; Harris and Capaldo 1993; Plummer 2004).

The archeological record provides evidence that this occurred with *H. erectus*, as this species is associated with stone tools and the development of the first rudimentary hunting and gathering economy. Meat does appear to have been more common in the diet of *H. erectus* than it was in the australopithecines, with mammalian carcasses likely being acquired through both hunting and confrontational scavenging (Bunn 2006; Plummer 2004). In addition, the archeological evidence indicates that butchered animals were transported back to a central location (home base) where the resources were shared within foraging groups (Bunn 2006; Harris and Capaldo 1993; Potts 1998). Increasingly sophisticated stone tools (i.e., the Acheulean industry) emerged around 1.6–1.4 million years ago, improving the ability of these hominins to process animal and plant materials (Asfaw et al. 1992). These changes in diet and foraging behavior would not have turned our hominin ancestors into carnivores; however, the addition of even modest amounts of meat to the diet (10–20% of dietary energy) combined with the sharing of resources that is typical of hunter-gatherer groups would have significantly increased the quality and stability of the diet of *H. erectus*.

Beyond the energetic benefits associated with greater meat consumption, it appears that such a dietary shift would have also provided increased levels of key fatty acids that would have been

necessary for supporting the rapid hominin brain evolution (Cordain et al. 2001). Mammalian brain growth is dependent upon sufficient amounts of two long-chain polyunsaturated fatty acids (PUFAs): docosahexaenoic acid (DHA) and arachidonic acid (AA) (Cordain et al. 2001; Crawford et al. 1999). Species with relatively larger brain sizes have greater requirements for DHA and AA (Crawford et al. 1999). Since mammals have a limited capacity to synthesize these fatty acids, dietary sources of DHA and AA appear to be limiting nutrients that constrained the evolution of larger brain size in many mammalian lineages (Crawford 1992; Crawford et al. 1999).

Cordain and colleagues (2001) have shown that wild plant foods available on the African savanna (e.g., tubers, nuts) contain little or no AA and DHA, whereas muscle tissue and organ meat of wild African ruminants provide moderate to high levels of these fatty acids. As shown in Table 1.3, brain tissue is a rich source of both AA and DHA, whereas liver and muscle tissues are good sources of AA and moderate sources of DHA.

In addition to changes in diet composition, Wrangham and colleagues (1999; Wrangham 2009) have suggested that the development of cooking also helped to increase diet quality and promote brain evolution in early *Homo*. These authors argue that the controlled use of fire for cooking allowed early *Homo* to improve the nutritional density of their diet. They note that the cooking of savanna tubers and other plant foods would have served to both soften them and increase their energy content. In their raw form, the starch in roots and tubers is not absorbed in the small intestine and is passed through the body as non-digestible carbohydrate (Englyst and Englyst 2005). However, when heated, the starch granules swell and are disrupted from the cell walls. This process, known as gelatinization, makes the starch much more accessible to breakdown by digestive enzymes (García-Al.onso and Goñi 2000). Thus, cooking increases the nutritional quality of tubers by making more of the carbo-hydrate energy available for biological processes.

While it is clear that cooking is an innovation in hominin evolution that served to increase dietary digestibility and quality, there is very limited evidence for the controlled use of fire by hominins before 1.5 million years ago (Bellomo 1994; Pennisi 1999). The more widely held view is that the use of fire and cooking did not occur until later in human evolution, at 200–250,000 years ago (Weiner et al. 1998). In addition, compositional analyses of wild tubers consumed by contemporary hunting and gathering populations indicates that the energy content of these resources is markedly lower than that of animal foods, even after cooking (e.g., Schoeninger et al. 2001). In contrast to animal foods, tubers are also devoid of both DHA and AA (see Table 1.3). Consequently, there remain major questions about whether cooking and the heavy reliance on roots and tubers were important forces for promoting rapid brain evolution with the emergence of early *Homo*.

Overall, the available evidence seems to best support a mixed dietary strategy in early *Homo* that involved the consumption of larger amounts of animal foods than with the australopithecines. Greater

Table 1.3 Nutritional composition of selected wild plant and animal foods from Africa (Data are derived from Cordain et al. 2000)

Food item	Energy (kcal)	Fat (g)	Protein (g)	AA (mg)	DHA (mg)
African ruminant (brain)	126	9.3	9.8	533	861
African ruminant (liver)	159	7.1	22.6	192	41
African ruminant (muscle)	113	2.1	22.7	152	10
African ruminant (fat)	745	82.3	1.0	20-180	trace
African fish	119	4.5	18.8	270	549
Wild tuber/roots	96	0.5	2.0	0	0
Mixed wild plants	129	2.8	4.1	0	0

Energy (kcal), fat (g) protein (g), arachidonic acid (AA) and docosahexaenoic acid (DHA) contents of African ruminant, fish and wild plant foods per 100 g

consumption of animal foods would have increased total dietary fat consumption in early *Homo*, and markedly increased the levels of key fatty acids (AA and DHA) necessary for brain development. Together, the nutritional stability provided a critical foundation for fueling the energy demands of larger brain sizes.

1.4 Applications to Other Areas of Health

The high metabolic costs of our large brains also appear to have important implications for patterns of growth and development of human infants. During the human life course, the energy demands of our large brains are highest during infancy and early childhood, when brain to body weight ratios are largest and when brain growth is most rapid. Whereas brain metabolism accounts for 20–25% of resting needs in adults, in an infant of under 10 kg, it is using upward of 60% (Holliday 1986)! Table 1.4 shows changes in the percent of RMR allocated to the brain over the course of human growth and development.

To accommodate the extraordinary energy demands of the developing infant brain, human infants are born with high levels of body fat (Kuzawa 1998; Leonard et al. 2003). Human infants have the highest body fat levels of any mammalian species, and continue to gain fat during their early postnatal life (c.f., Dewey et al. 1993; Kuzawa 1998; Table 1.4). These high levels of adiposity in early life thus coincide with the periods of greatest metabolic demand of the brain.

For young children growing up in impoverished conditions in the developing world, getting sufficient energy and nutrients to sustain rapid rates of growth in both the brain and body can be challenging. This is particularly true during the weaning period, when children are exposed to both higher infectious disease loads and reduced dietary quality. To adapt to these stressors, human infants and toddlers show metabolic responses to preserve body fat reserves.

Research on children of the developing world suggests that chronic, mild-moderate undernutrition has a relatively small impact on a child's fatness. Instead of taking away the fat reserves, nutritional needs appear to be downregulated by substantially reducing rates of growth in height/ length – producing the common problem of infant/childhood "growth stunting" or growth failure that is ubiquitous among impoverished populations of the developing world (Martorell and Habitch 1986).

Figure 1.4 shows an example of this process based on growth data collected from young girls of the indigenous Tsimane' farming and foraging population of lowland Bolivia (from Foster et al. 2005).

Table 1.4 Changes in brain size, body weight, percent body fat, resting metabolic rate, and percent of energy allocated to the brain from birth to adulthood (All data are from Holliday (1986), except for percent body fat data for children 18 months and younger, which are from Dewey et al. (1993))

Age	Body weight (kg)	Brain weight (g)	Body fat (%)	RMR (kcal/day)	BrMet (%)
New born	3.5	475	16	161	87
3 months	5.5	650	22	300	64
18 months	11.0	1,045	25	590	53
5 years	19.0	1,235	15	830	44
10 years	31.0	1,350	15	1,160	34
Adult male	70.0	1,400	11	1,800	23
Adult female	50.0	1,360	20	1,480	27

Body weight (kg), brain weight (g), percent body fat (%), resting metabolic rate (RMR; kcal/day), and percent of RMR allocated to brain metabolism (BrMet; %) for humans from birth to adulthood
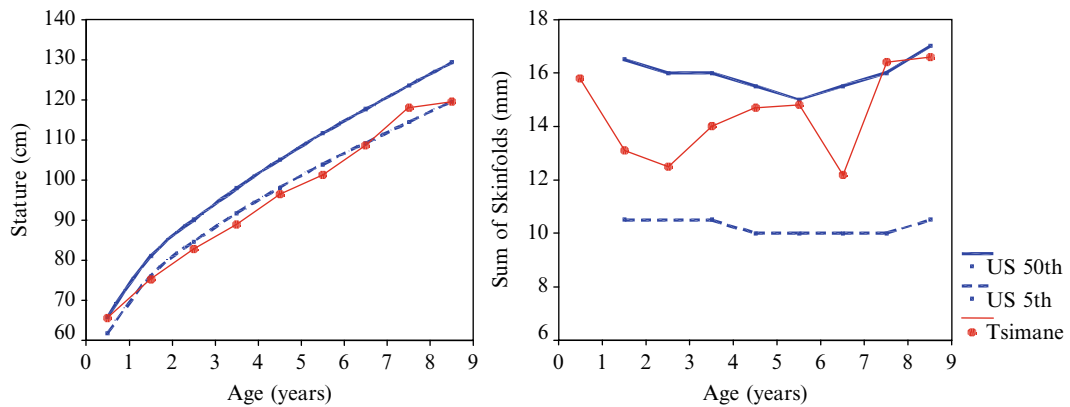
Fig. 1.4 Patterns of physical growth in stature (cm) and body fatness (as sum of triceps and subscapular skinfolds, mm) in girls of the Tsimane' of lowland Bolivia. Growth of Tsimane' girls is characterized by marked linear growth stunting, whereas body fatness compares more favorably to US norms (Data from Foster et al. 2005)

Table 1.5 Body size and metabolic measures for "stunted" and non-stunted children from São Paulo, Brazil (All values are presented as mean ± SEM)

Measure	Non-tunted (*n* = 30)	Stunted (*n* = 28)
Age (mo)	120 ± 3	122 ± 3
Stature (cm)	136 ± 3	126 ± 2[**]
Weight (kg)	32 ± 1	26 ± 1[**]
RMR (kcal/day)	1,179 ± 28	1,044 ± 22[**]
CHO oxidation (% of RMR)	66 ± 2	75 ± 2[*]
Fat oxidation (% of RMR)	34 ± 2	25 ± 2[*]

Age, stature (cm), weight (kg), resting metabolic rate (RMR; kcal/day), carbohydrate (CHO) and fat oxidation (% of RMR) in stunted and non-stunted children (8–11 years) from São Paulo, Brazil. Results are derived from Hoffman et al. (2000)

Differences between stunted and non-stunted groups are significant at: *$P < 0.01$; **$P < 0.001$

Note that early in life the stature of Tsimane' girls closely approximates the US median, but by age 3–4 it has dropped below the 5th centile, where it will track for the rest of life. In contrast, body fatness (as measured by the sum of the triceps and subscapular skinfolds) compares more favorably to US norms, tracking between the 15th and 50th US centiles. The problem of early childhood growth failure is the product of both increased infectious disease loads and reduced dietary quality.

Research on impoverished children in Brazil provides insights into the mechanisms for preserving body fatness under conditions of growth stunting. Hoffman and colleagues (2000) found that children who were growth stunted had significantly lower rates of fat oxidation than those of their "non-stunted" group. Table 1.5 presents a summary of the results of this study. The authors measured RMR on a sample of 28 stunted and 30 non-stunted (control) children between the ages of 8 and 11 years from the slums of Sao Paulo, Brazil. They used the respiratory quotient (RQ) assess levels of fat and carbohydrate oxidation form.

As shown in Table 1.5, the stunted children have significantly lower RMRs and lower levels of fat oxidation compared to their non-stunted counterparts. Under fasting conditions, the stunted children derived only 25% of the resting energy needs from fat, as compared to 34% in the non-stunted group. These researchers hypothesize that the impaired fat oxidation of the stunted children is associated with reductions in insulin-like growth factor I (IGF-I) that is commonly observed with poor childhood growth (Sawaya et al. 2004; Hoffman et al. 2000). IGF-I has been shown to increase lipolysis

(Hussain et al. 1994); hence, significant reductions in IGF-1 during growth can be expected to result in decreased fat oxidation.

Overall, key aspects of human growth and development of body composition are shaped by the very high metabolic demands of brain metabolism early in life. Human infants are born altricially (relatively underdeveloped for their age), and unlike other primates, continue rapid brain growth into early postnatal life (Martin 1989; Rosenberg 1992). To provide energy reserves for the high metabolic demands of large, rapidly growing brains, human infants are born with high body fat levels, and continue to gain fat during the first year of postnatal life. Further, under conditions of chronic nutritional stress, human infants show the capacity preserve brain metabolism by (1) "downregulating" linear growth, (2) reducing fat oxidation, and (3) increasing fat storage. These adaptive responses are evidenced in the preservation of body fatness among "growth stunted" children, and in the tendency of stunted children to gain weight and body fatness later in life (see Frisancho 2003).

1.5 Conclusions

The evolution of large human brain size has had important implications for the nutritional biology of our species. Humans expend a much larger share of their resting energy budget on brain metabolism than other primates or non-primate mammals. Comparative analyses of primate dietary patterns indicate that the high costs of large human brains are supported, in part, by diets that are relatively rich in energy and fat. Relative to other large bodied apes, modern humans derive a much larger share of their dietary energy from fat. Among living primates, the relative proportion of metabolic energy allocated to the brain is positively correlated with dietary quality. Humans fall at the positive end of this relationship, having both a very high quality diet and a large brain.

High levels of encephalization in humans also appear to have important consequences for early childhood growth and development. Human infants have much higher levels of body fatness than the infants of other mammals. These greater levels of adiposity help to accommodate the high metabolic demands of rapid brain growth by providing a ready supply of stored energy. Under conditions of nutritional stress, human infants and toddlers preserve body fat reserves for brain metabolism by reducing rates of linear growth. This process of "'linear growth stunting" is also associated with reduced rates of fat oxidation and increased rates of fat storage. Thus, humans appear to show important adaptations in fat metabolism to accommodate the high energy demands of the brain early in life.

The human fossil record indicates that major changes in both brain size and diet occurred in association with the emergence of early members of the genus *Homo* between 2.0 and 1.7 million years ago in Africa. With the evolution of early *H. erectus* at 1.8 million years ago, we find evidence of an important adaptive shift – the evolution of the first hunting and gathering economy, characterized by greater consumption of animal foods, transport of food resources to "home bases," and sharing of food within social groups. *H. erectus* was human-like in body size and proportions, and had a brain size beyond that seen in nonhuman primates, approaching the range of modern humans. In addition, the reduced size of the face and grinding teeth of *H. erectus*, coupled with its more sophisticated tool technology suggest that these hominins were consuming a higher quality and more stable diet that would have helped to fuel the increases in brain size. Consequently, while dietary change was not the prime force responsible for the evolution of large human brain size, improvements in dietary quality and increased consumption of dietary fat appear to have been a necessary condition for promoting encephalization in the human lineage. Further research is needed to better understand the nature of the dietary changes that took place with the emergence of early human ancestors.

1.6 Table of Key Points on Diet and Human Brain Evolution

The energy demands of brain tissue are ~16 times those of skeletal muscle.

Human adults spend 20–25% of their resting energy budget on brain metabolism, as compared to 8–10% in other primates, and 3–5% in non-primate mammals

Humans fuel the high energy costs of our brains by consuming diets that are much richer in energy and fat than other primates. Human hunter-gatherers derive about half of their daily energy intake from animal foods, much more than chimpanzees, who obtain less than 10%

Over the last 4–5 million years of human evolution, brain size has more than tripled, going from ~400 cc in our australopithecine ancestors to 1,300–1,500 cc in modern humans.

The rate of human brain evolution has been highly variable over the last 4 million years. From 4 to 2 million years ago, brain evolution was relatively slow. With the evolution of the genus *Homo* at ~2 million years ago, brain sizes evolved quite rapidly, in association with changes in foraging and dietary patterns.

Human infants have distinct nutritional needs and growth patterns that are shaped, in part, by the extraordinary energy costs of large, rapidly growing brains.

Human infants have higher levels of body fatness than those of any other mammal. This high level of adiposity helps to accommodate the energy demands of the brain.

Under conditions of chronic, mild-moderate nutritional stress, human infants substantially reduce rates of growth in length/stature, while preserving levels of body fatness. This pattern of growth stunting – characterized by "low height-for-age" – is commonly observed among impoverished populations of the developing world.

Definitions

Altricial: Being relatively "underdeveloped" for one's chronological age.

Australopithecus: Genus of early hominins that existed in Africa between 4 and 1.2 million years ago.

Acheulean: Stone tool industry of the early and middle Pleistocene characterized by hand axes and cleavers. First evident 1.4–1.6 million years ago, associated with early *Homo*.

Encephalization: Brain size in relation to body size. In general, primates are more encephalized than other mammals.

Hominin: Living humans and our fossil ancestors that lived after the last common ancestor between humans and apes.

Scaling (allometry): The change in size on biological measure with respect to another (often body size).

1.7 Summary Points on Diet and Human Brain Evolution

- Humans expend a much larger share of their resting energy budget on brain metabolism than other species. Adult humans spend 20–25% of the RMR on the brain, as compared to 8–10% in other primates, and 3–5% in non-primate mammals.
- To support the high energy costs of brain metabolism, humans consume diets that are easier to digest and much more dense in energy and fat than other primate species.
- The first major increase in brain size in the human lineage occurred with the evolution of the genus *Homo* at 2.0–1.7 million years ago. During this time, we also have evidence from the fossil and archaeological record for greater consumption of animal foods. This increased dietary quality was likely important for supporting brain evolution.

- The addition of animal foods to the diet of early *Homo* would also have increased the availability of key long-chain polyunsaturated fatty acids that are essential for brain growth and development: DHA and AA.
- For human infants, the energy costs of brain metabolism are extraordinarily high (<60% of RMR) due to high brain to body weight ratios and rapid brain growth. These costs are supported, in part, by very high levels of body fatness. At 15–16% fat, humans have the fattest infants of any mammal.
- Under conditions of chronic nutritional and disease stress, human infants "downregulate" growth in length/stature, while preserving body fatness. This pattern of "linear growth stunting" is widely observed among impoverished populations of the developing world, and appears to be associated with reduced fat oxidation and increased fat storage.
- Ongoing research is attempting to better characterize the dietary patterns of our earliest human ancestors through chemical analyses of hominin bones and analyses of microscopic wear patterns of hominin teeth.

References

Aiello LC, Wheeler P. Curr Anthropol. 1995;36:199–221.
Antón SC, Leonard WR, Robertson ML. J Hum Evol. 2002;43:773–85.
Asfaw B, Beyene Y, Suwa G, Walter RC, White TD, WoldeGabriel G, et al. Nature. 1992;360:732–5.
Behrensmeyer K, Todd NE, Potts R, McBrinn GE. Science. 1997;278:1589–94.
Bellomo RV. J Hum Evol. 1994;27:173–95.
Bobe R, Behrensmeyer AK. J Hum Evol. 2002;42:475–97.
Briefel RR, Johnson CL. Annu Rev Nutr. 2004;24:401–31.
Bunn HT. In: Ungar PS, editor. Evolution of the human diet: the known, the unknown, and the unknowable. New York: Oxford University Press; 2006. p. 191–211.
Cordain L, Brand-Miller J, Eaton SB, Mann N, Holt SHA, Speth JD. Am J Clin Nutr. 2000;71:682–92.
Cordain L, Watkins BA, Mann NJ. World Rev Nutr Diet. 2001;90:144–61.
Cordain L, Eaton SB, Sebastian A, Mann N, Lindberg S, Watkins BA, et al. Am J Clin Nutr. 2005;81:341–54.
Crawford MA. Nutr Rev. 1992;50:3–11.
Crawford MA, Bloom M, Broadhurst CL, Schmidt WF, Cunnane SC, Galli C, et al. Lipids. 1999;34:S39–47.
Dewey KG, Heinig MJ, Nommsen LA, Peerson JM, Lonnerdal B. Am J Clin Nutr. 1993;52:140–5.
Englyst KN, Englyst HN. Br J Nutr. 2005;94:1–11.
Foster Z, Byron E, Reyes-García V, Huanca T, Vadez V, Apaza L, et al. Am J Phys Anthropol. 2005;126:343–51.
Frisancho AR. Am J Hum Biol. 2003;15:35–52.
García-Alonso A, Goñi I. Nahrung. 2000;44:19–22.
Harris JWK, Capaldo S. In: Berthelet A, Chavaillon J, editors. The use of tools by human and nonhuman primates. Oxford: Oxford Science; 1993. p. 196–220.
Hoffman DJ, Sawaya AL, Verreschi I, Tucker KL, Roberts SB. Am J Clin Nutr. 2000;72:702–7.
Holliday MA. In: Falkner F, Tanner JM, editors. Human growth: a comprehensive treatise, vol. 2. 2nd ed. New York: Plenum; 1986. p. 101–17.
Hussain MA, Schmintz O, Mengel, Glatz Y, Christiansen JS, Zapf J, et al. J Clin Invest. 1994;94:1126–33.
Kety SS. In: Richter D, editor. Metabolism of the central nervous system. New York: Pergammon; 1957. p. 221–37.
Kuzawa CW. Yrbk Phys Anthropol. 1998;41:177–209.
Leonard WR. Sci Am. 2002;287(6):106–15.
Leonard WR, Robertson ML. Am J Hum Biol. 1992;4:179–95.
Leonard WR, Robertson ML. Am J Hum Biol. 1994;6:77–88.
Leonard WR, Robertson ML, Snodgrass JJ, Kuzawa CW. Biochem Physiol Part A. 2003;135:5–15.
Martin RD. Primate origins and evolution: a phylogenetic reconstruction. Princeton, NJ: Princeton University Press; 1989.
Martorell R, Habicht J-P. In: Falkner F, Tanner JM, editors. Human growth: a comprehensive treatise, vol. 3. 2nd ed. New York: Plenum; 1986. p. 241–62.
McHenry HM, Coffing K. Ann Rev Anthropol. 2000;29:125–46.
Pennisi E. Science. 1999;283:2004–5.

Plummer T. Yrbk Phys Anthrpol. 2004;47:118–64.

Popovich DG, Jenkins DJA, Kendall CWC, Dierenfeld ES, Carroll RW, Tariq N, et al. J Nutr. 1997;127:2000–5.

Potts R. Yrbk Phys Anthropol. 1998;41:93–136.

Richard AF. Primates in nature. New York: WH Freeman; 1985.

Rosenberg KR. Yrbk Phys Anthropol. 1992;35:89–124.

Ruff CB, Trinkaus E, Holliday TW. Nature. 1997;387:173–6.

Sailer LD, Gaulin SJC, Boster JS, Kurland JA. Primates. 1985;26:14–27.

Sawaya AL, Martins PA, Grillo LP, Florêncio TT. Nutr Rev. 2004;62:S127–33.

Schoeninger MJ, Bunn HT, Murray SS, Marlett JA. J Food Comp Anal. 2001;14:3–13.

Stanford CB. Am Anthropol. 1996;98:96–113.

Tutin CEG, Fernandez M. Am J Primatol. 1992;28:29–40.

Tutin CEG, Fernandez M. Am J Primatol. 1993;30:195–211.

Weiner S, Qunqu X, Goldberg P, Liu J, Bar-Yosef O. Science. 1998;281:251–3.

Wolpoff MH. Paleoanthropology. 2nd ed. Boston, MA: McGraw-Hill; 1999.

Wrangham RW. Catching fire: how cooking made us human. New York: Basic Books; 2009.

Wrangham RW, Jones JH, Laden G, Pilbeam D, Conklin-Brittain NL. Curr Anthropol. 1999;40:567–94.

Wynn JG. Am J Phys Anthropol. 2004;123:106–18.

Chapter 2
Epigenetics, Phenotype, Diet, and Behavior

Patrick O. McGowan, Michael J. Meaney, and Moshe Szyf

Abbreviations

CBP	CREB binding protein
DNMT	DNA methyltransferase
HAT	Histone acetyltransferase
HDAC	Histone deacetylase
HDACi	HDAC inhibitor ()
HMT	Histone methyltransferase ()
LG	Licking/Grooming
MBD2	Methylated domain DNA-binding Protein 2
NGFI-A	Nerve growth factor-inducible protein A
SAM	*S*-adenosyl methionine
TSA	Trichostatin A

2.1 Introduction

Different cell types execute distinctive programs of gene expression, which are highly responsive to developmental, physiological, pathological, and environmental cues. The combinations of mechanisms that confer long-term programming to genes and could bring about a change in gene function without changing gene sequence are termed here as epigenetic changes. We therefore propose here a definition of epigenetics, which includes any long-term change in gene function that does not involve a change in gene sequence or structure. This definition stands in contrast to other classical definitions of epigenetics that emphasize heritability. Epigenetic changes occurring in the germ line would result in heritable and trans-generational transmission of alterations in gene function in the classical sense of epigenetics. In addition, epigenetics changes in dividing cells are heritable from cell to daughter cells but are not inherited through the germ line or in postmitotic cells such as neurons and are therefore

M. Szyf (✉)
Sackler Program for Epigenetics and Psychobiology,
and
Department of Pharmacology and Therapeutics, McGill University, 3655 Sir William Osler Promenade,
room 1309, Montreal, QC, Canada H3G 1Y6
e-mail: moshe.szyf@mcgill.ca

Table 2.1 Key facts about the epigenome

1. Almost all cells in the body have the same genetic information, but the cell's epigenetic state determines what genes it expresses, and thus its specific cell type identity (e.g., blood cell, brain cell, etc.)
2. DNA methylation is believed to mark silent genes, and thus aberrant methylation could have similar consequences as genetic mutations.
3. There are also extensive epigenetic marks on chromatin that define whether genes are active or silent
4. The epigenetic status of DNA and chromatin is thought to regulate gene activity by targeting specific molecules to specific sites in the genome
5. There is thought to be a bilateral relationship between DNA methylation and epigenetic marks on chromatin
6. DNA methylation is an extremely stable chemical modification of the DNA, with important diagnostic potential for human disease
7. Both chromatin modifications and DNA methylation are potentially reversible in response to particular environmental conditions
8. The dietary, social, behavioral, and physiological environment can modify the epigenome, with long-term consequences for gene expression, cell signaling, and thus phenotype

This table delineates the role of the epigenome in cellular function and its response to signals from the environment

not heritable. Such changes could be environmentally driven, may occur in response to triggers at different points in life and are potentially reversible, whereas genetic differences are germ line transmitted, fixed, and irreversible.

Many of the phenotypic variations seen in human populations might be caused by differences in long-term programming of gene function rather than the sequence per se, and any future study of the basis for interindividual phenotypic diversity should consider epigenetic variations in addition to genetic sequence polymorphisms (Meaney and Szyf 2005). In effect, epigenetic silencing and genetic silencing could have similar phenotypic consequences. Therefore, epigenetic mapping is potentially as important as genetic mapping in our quest to understand phenotypic differences in human behavior.

Thus, identifying epigenetic changes that are associated with behavioral pathologies have important implications for human health, because they are potentially reversible and amenable to therapeutic intervention (Szyf 2001). Drugs that target epigenetic mechanisms are currently being tested in clinical trials in psychiatric disorders (Simonini et al. 2006). Once we understand the rules through which different environmental exposures modify the epigenetic processes, we might also be able to design behavioral strategies to prevent and revert deleterious environmentally driven epigenetic alterations. The dynamic nature of epigenetic regulation in difference from the static nature of the gene sequence provides a mechanism for reprogramming gene function in response to changes in life style trajectories, including diet. Thus, epigenetics could provide an explanation for well-documented gene x environment interactions. In this chapter, we will describe the path, which we have taken to delineate the basic mechanisms involved in epigenetic programming by maternal care in rats as a paradigm for unraveling the epigenetic basis of phenotypic differences in behavior in humans. We will also discuss our studies of epigenetic differences associated with early life adversity in humans and potential dietary contributions to epigenetic regulation (Table 2.1).

2.2 The Epigenome

2.2.1 Chromatin and the Histone Code

The epigenome consists of the chromatin, a protein-based structure around which the DNA is wrapped, as well as a covalent modification of the DNA itself by the methylation of cytosine rings found at CG dinucleotides (Razin 1998). The epigenome determines the accessibility of the

transcription machinery – which transcribes the genes into messenger RNA – to the DNA. Inaccessible genes are therefore silent whereas accessible genes are transcribed. Densely packaged chromatin can be visualized microscopically and is termed heterochromatin while open accessible chromatin is termed euchromatin. Recently, another new level of epigenetic regulation by small noncoding RNAs termed microRNA has been discovered (Bergmann and Lane 2003), which could potentially play an important role in behavioral pathologies in humans (Vo et al. 2005).

The basic building block of chromatin is the nucleosome, which is made up of an octamer of histone proteins. The N-terminal tails of these histones are extensively modified by methylation, phosphorylation, acetylation, and ubiquitination. The state of modification of these tails plays an important role in defining the accessibility of the DNA wrapped around the nucleosome core. It was proposed that the amino terminal tails of H3 and H4 histones that are positively charged form tight interactions with the negatively charged DNA backbone, thus blocking the interaction of transcription factors with the DNA. Modifications of the tails neutralize the charge on the tails, thus relaxing the tight grip of the histone tails. Different histone variants, which replace the standard isoforms also play a regulatory role and serve to mark active genes in some instances (Henikoff et al. 2004). The specific pattern of histone modifications was proposed to form a "histone code," that delineates the parts of the genome to be expressed at a given point in time in a given cell type (Jenuwein and Allis 2001).

2.2.2 Histone-Modifying Enzymes and Chromatin Remodeling

The most investigated histone-modifying enzymes are histone acetyltransferases (HAT), which acetylate histone H3 at the K9 residue as well as other residues and H4 tails at a number of residues, and histone deacetylases (HDAC), which deacetylate histone tails (Kuo and Allis 1998). Histone acetylation is believed to be a predominant signal for an active chromatin configuration (Perry and Chalkley 1982; Lee et al. 1993). Deacetylated histones signal inactive chromatin and chromatin associated with inactive genes. Histone tail acetylation is believed to enhance the accessibility of a gene to the transcription machinery whereas deacetylated tails are highly charged and believed to be tightly associated with the DNA backbone and thus limiting accessibility of genes to transcription factors (Kuo and Allis 1998).

Some specific histone methylation events are associated with gene silencing and some with gene activation (Lachner et al. 2001). Particular factors recognize histone modifications and further stabilize an inactive state. Recently described histone demethylases remove the methylation mark causing either activation or repression of gene expression (Shi et al. 2004; Tsukada et al. 2006). Chromatin remodeling complexes, which are ATP dependent, alter the position of nucleosomes around the transcription initiation site and define its accessibility to the transcription machinery. It is becoming clear now that there is an interrelationship between chromatin modification and chromatin remodeling (Bultman et al. 2005).

A basic principle in epigenetic regulation is targeting. Histone-modifying enzymes are generally not gene specific. Specific transcription factors and transcription repressors recruit histone-modifying enzymes to specific genes and thus define the gene-specific profile of histone modification (Jenuwein and Allis 2001). Transcription factors and repressor recognize specific *cis*-acing sequences in genes, bind to these sequences and attract the specific chromatin-modifying enzymes to these genes through protein–protein interactions. Signal transduction pathways, which are activated by cell-surface receptors, could serve as conduits for epigenetic change, linking the environmental trigger at cell surface receptors with gene-specific chromatin alterations and reprogramming of gene activity.

2.2.3 DNA Methylation and Gene Expression Silencing

The DNA molecule itself can be chemically modified by methyl residues at the 5′ position of the cytosine rings in the dinucleotide sequence CG in vertebrates (Razin 1998), thus offering a mode of direct interaction between the environment such as diet and the genome itself (Fig. 2.1). What distinguishes DNA methylation in vertebrate genomes is the fact that not all CGs are methylated in any given cell type (Razin 1998). Distinct CGs are methylated in different cell types, generating cell type–specific patterns of methylation. Thus, the DNA methylation pattern confers upon the genome its cell type identity (Razin 1998). Since DNA methylation is part of the chemical structure of the DNA itself, it is more stable than other epigenetic marks and thus it has extremely important diagnostic potential in humans (Beck et al. 1999).

Recent data supports the idea that similar to chromatin modification, DNA methylation is also potentially reversible (Ramchandani et al. 1999b) even in predominantly post mitotic tissues such as the brain (Weaver et al. 2004a). The DNA methylation pattern is not copied by the DNA replication machinery, but by independent enzymatic machinery, (Razin and Cedar 1977) the DNA methyltransferase(s) (DNMT) (Figs. 2.2 and 2.3). DNA methylation patterns in vertebrates are distinguished by their correlation with chromatin structure. Active regions of the chromatin, which enable gene expression, are associated with hypomethylated DNA whereas hypermethylated DNA is packaged in inactive chromatin (Razin and Cedar 1977; Razin 1998).

DNA methylation in critical regulatory regions serves as a signal to silence gene expression. There are two main mechanisms by which cytosine methylation suppresses gene expression (Fig. 2.3). The first mechanism involves direct interference of the methyl residue with the binding of a transcription factor to its recognition element in the gene. The interaction of transcription factors with genes is required for activation of the gene; lack of binding of a transcription factor would result in the silencing of gene expression. This form of inhibition of transcription by methylation requires that the methylation events occur within the recognition sequence of a transcription factor. A second mechanism is indirect. A certain density of DNA methylation moieties in the region of the gene attracts the binding of methylated-DNA-binding proteins such as MeCP2 (Nan et al. 1997). MeCP2 recruits other proteins such as SIN3A and histone-modifying enzymes, which lead to formation of a "closed" chromatin configuration and silencing of gene expression (Nan et al. 1997). Thus, aberrant methylation will silence a gene resulting in loss of function, which will have a similar consequence to a loss of function by genetic mechanism such as mutation, deletion, or rearrangement (Fig. 2.4).
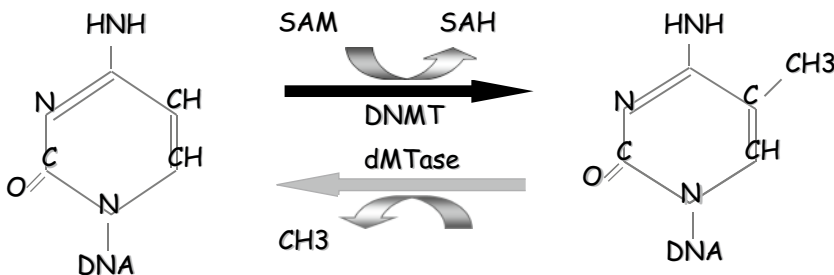
Fig. 2.1 The reversible DNA methylation reaction. DNA methyltransferases (DNMT) catalyze the transfer of methyl groups from the methyl donor *S*-adenosylmethionine to DNA releasing *S*-adenosylhomocysteine. Demethylases release the methyl group from methylated DNA. This is the first mechanism by which the environment can directly interact with the DNA, as levels of *S*-adenosylmethionine are regulated by diet
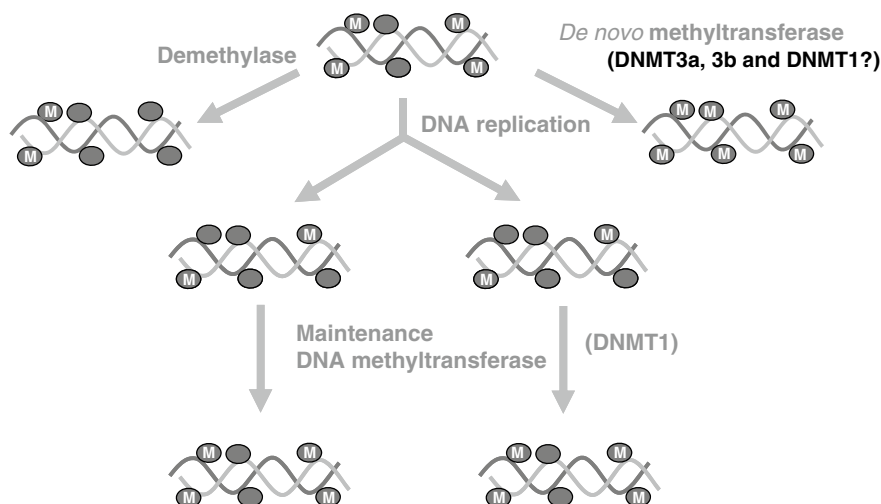
Fig. 2.2 DNA methylation reactions. Early after fertilization many of the methylation marks are removed by demethylases. (methyl groups are indicated by M, potential methylatable sites are indicated by an open circle). De novo DNA methyltransferases (DNMT) add methyl groups. Once a pattern is generated it is inherited by maintenance DNMTs that copy the methylation pattern
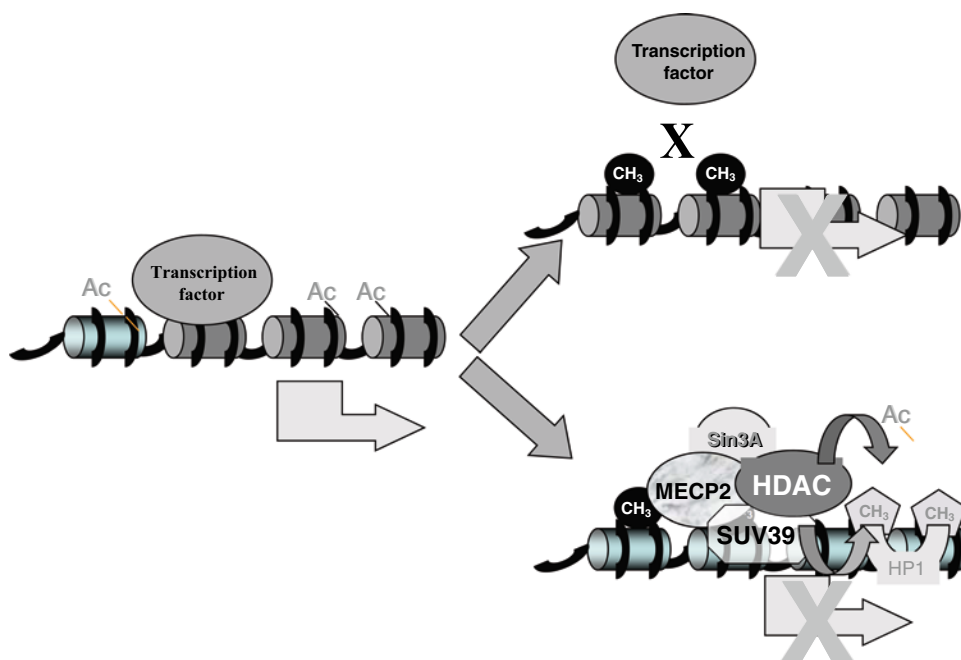
Fig. 2.3 Two mechanisms of silencing gene expression by DNA methylation. An expressed gene (transcription indicated by horizontal arrow) is usually associated with acetylated histones and is unmethylated. An event of methylation would lead to methylation by two different mechanisms. The methyl group (CH_3) interferes with the binding of a transcription factor, which is required for gene expression resulting in blocking of transcription. The second mechanism shown in the bottom right is indirect. Methylated DNA attracts methylated-DNA-binding proteins, which in turn recruit corepressors, histone methyltransferases that methylate histones, and histone deacetylases (HDAC), which remove the acetyl groups from histone tails. Methylated histones recruit heterochromatin proteins, which contribute to a closed chromatin configuration and silencing of the gene
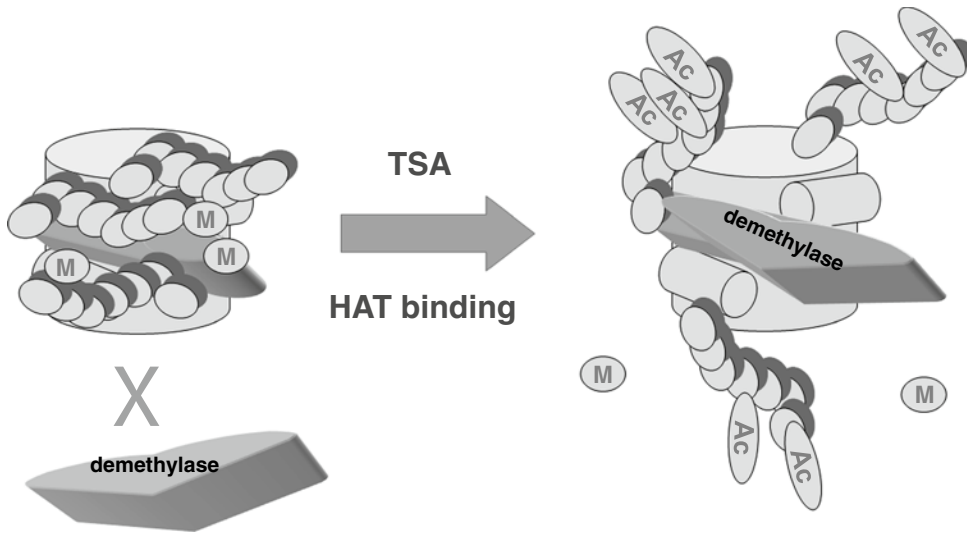
Fig. 2.4 Demethylation is directed by the state of chromatin structure. Histone acetylation (Ac) triggered by a pharmacological inhibitor of histone deacetylase facilitates the interaction of demethylases with methylated DNA allowing for demethylation

2.2.4 The Roles of the DNA Methylation Machinery and the Reversibility of DNA Methylation Patterns

The DNA methylation machinery in vertebrates has two main roles. First, it has to establish new cell-type-specific DNA methylation patterns during development and possibly during adulthood in response to new signals. Second, it has to maintain these patterns during downstream cell divisions and after DNA repair. The different enzymes and proteins of the DNA methylation machinery must address these different tasks. The methylation of DNA occurs immediately after replication by a transfer of a methyl moiety from the donor *S*-adenosyl-l-methionine (AdoMet) in a reaction catalyzed by DNA methyltransferases (DNMT) (Fig. 2.2). In effect, this reaction consists of the first mechanism by which the environment can directly interact with the genome, as levels of AdoMet are regulated by diet. Three distinct phylogenic DNA methyltransferases were identified in mammals. DNMT1 shows preference for hemimethylated DNA in vitro, which is consistent with its role as a maintenance DNMT (Fig. 2.2), whereas DNMT3a and DNMT3b methylate unmethylated and methylated DNA at an equal rate which is consistent with a de novo DNMT role (Okano et al. 1998).

We have proposed that the DNA methylation pattern is a balance of methylation and demethylation reactions that are responsive to physiological and environmental signals and thus forms a platform for gene–environment interactions (Ramchandani et al. 1999a) (Fig. 2.1). There are now convincing examples of active, replication-independent DNA demethylation during development as well as in somatic tissues (Lucarelli et al. 2001; Kersh et al. 2006). One example we will explain in detail is that of the glucocorticoid receptor gene promoter in adult rat brains upon treatment with the HDAC inhibitor TSA (Weaver et al. 2004a). This finding has implications for humans, because drugs and dietary constituents known to be HDAC inhibitors are currently in widespread use.

We also propose that the direction of the DNA methylation reaction is defined by the state of chromatin. The gene specificity of the state of chromatin is defined by sequence-specific *trans*-acting

factors that recruit chromatin-modifying enzymes to specific genes. Chromatin configuration then gates the accessibility of genes to either DNA methylation or demethylation machineries (Cervoni and Szyf 2001; D'Alessio and Szyf 2006) (Fig. 2.4). We propose the following model: Factors that target specific chromatin modification events to genes define the direction of the DNA methylation equilibrium by either recruiting DNA methylation enzymes or by facilitating demethylation. We will illustrate how this might be working using gene expression programming by maternal care as a paradigm for behavioral programming of DNA methylation.

2.3 Mechanisms of Epigenetic Programming by Maternal Care and Diet

2.3.1 Maternal Care Epigenetically Programs Stress Responses in the Offspring

In the rat, the adult offspring of mothers that exhibit increased levels of pup licking/grooming and arched-back nursing (i.e., high-LG mothers) over the first week of life show increased hippocampal GR expression, enhanced glucocorticoid feedback sensitivity, decreased hypothalamic corticotrophin releasing factor (CRF) expression, and more modest HPA stress responses compared to animals reared by low-LG mothers (Liu et al. 1997; Francis et al. 1999). Cross-fostering studies suggest direct effects of maternal care on both gene expression and stress responses (Liu et al. 1997; Francis et al. 1999). We have previously published evidence to support the hypothesis that epigenetic mechanisms mediate the maternal effect on stress response. Increased maternal LG is associated with demethylation that includes a nerve-growth-factor-inducible protein A (NGFI-A) transcription factor response element located within the exon 1_7 GR promoter (Weaver et al. 2004a) (Fig. 2.5). The difference in the methylation status of this CpG site between the offspring of high- and low-LG mothers emerges over the first week of life, is reversed with cross-fostering, persists into adulthood, and is associated with altered histone acetylation and NGFI-A binding to the GR promoter (Weaver et al. 2004a). Thus maternal care affects the chromatin, DNA methylation, and transcription factor binding to the GR exon 1_7 promoter, illustrating the basic principles of epigenetic regulation discussed above. We have also shown that maternal care early in life affected the expression of hundreds of genes in the adult hippocampus (Weaver et al. 2006), thus illustrating the profound effect of the social environment early in life on gene expression programming throughout life.

2.3.2 Epigenetic Programming by Maternal Care is Reversible in the Adult Animal

Although epigenetic programming by maternal care is highly stable and results in long-term changes in gene expression, it is nevertheless reversible. The possibility that certain adverse gene expression programming of behaviorally relevant genes could be reversed by either epigenetic drugs or perhaps even by behavioral intervention has obvious implications. To test this hypothesis we used the well-documented histone deacetylase (HDAC) inhibitor TSA (Yoshida et al. 1990). Since the state of histone acetylation is a balance of histone deacetylation and histone acetylation reactions, inhibition of HDAC activity would tilt the equilibrium toward acetylation and as a consequence bring
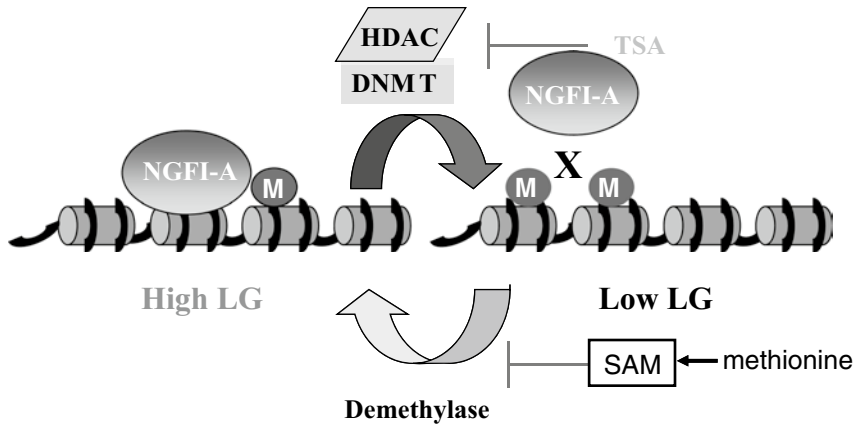
Fig. 2.5 The methylation of the hippocampal glucocorticoid receptor $GR1_7$ promoter blocks the binding of the transcription factor binding NGFI-A. The epigenetic programming of the GR exon 1_7 promoter expression by maternal care is reversible later in life by either the HDAC inhibitor TSA or by the methyl donor SAM

about increased acetylation of histones leading to open chromatin configuration. We have previously proposed as discussed above that chromatin states and DNA methylation states are linked so that opening up of chromatin by increasing histone acetylation would tilt the balance of the DNA methylation equilibrium toward demethylation (Fig. 2.5) (Cervoni et al. 2001; Cervoni and Szyf 2001). Treating adult offspring of low-LG maternal care with TSA reversed the epigenetic marks on the GR exon 1_7 promoter; histone acetylation increased, the gene was demethylated, and there was increased occupancy of the promoter with the transcription factor NGFI-A, resulting in increased GR exon 1_7 promoter expression. The epigenetic reversal was accompanied with a behavioral change so that the stress response of the TSA-treated adult offspring of low LG was indistinguishable from the offspring of high LG (Weaver et al. 2004b). This was the first illustration of reversal of early life behavioral programming by pharmacological modulation of the epigenome during adulthood. TSA is not a DNA methylation inhibitor but nevertheless TSA treatment resulted in demethylation as we predicted. We propose that increased histone acetylation triggered by the HDAC inhibitor facilitated the interaction of a resident demethylase with the GR exon 1_7 promoter (Fig. 2.6). These data illustrate the tight association between the DNA methylation and histone acetylation equilibriums in the adult brain and the potential reversibility of the DNA methylation pattern in the nondividing adult neuron.

If the DNA methylation state remains in equilibrium of methylation–demethylation in adult neurons throughout life, it should be possible also to reverse the DNA methylation in the opposite direction by increasing DNA methylation, including manipulations of methyl donors. We have previously demonstrated that the methyl donor *S*-adenosyl methionine (SAM), and amino acid present in the diet, inhibit the demethylation reaction (Detich et al. 2003). Thus, changing SAM levels would alter the DNA methylation equilibrium by either increasing the rate of the DNA methylation reaction or by inhibiting the demethylation reaction or both (Fig. 2.6). Injection of methionine to the brain led to hypermethylation and reduced expression of the GR exon 1_7 expression in the adult hippocampus of offspring of high LG and reversal of its stress response to a pattern that was indistinguishable from offspring of low LG (Weaver et al. 2005). Thus, maternal epigenetic programming could be reversed later in life in both directions.
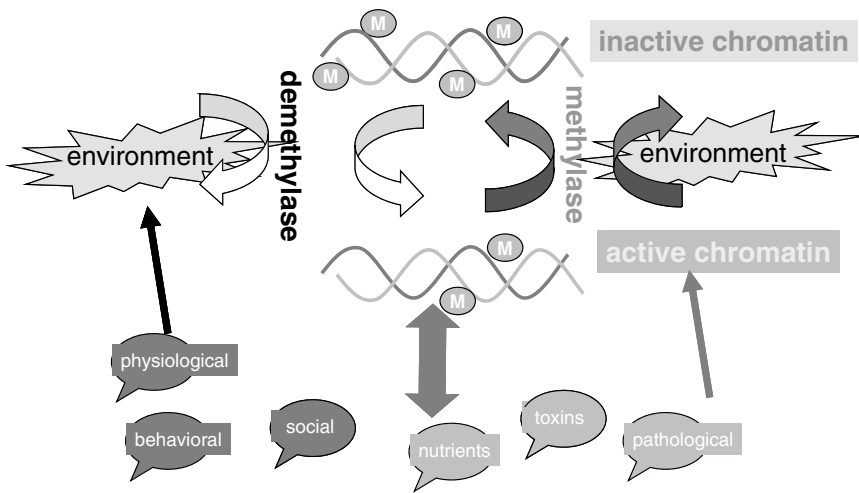
Fig. 2.6 Hypothesis: The steady state methylation pattern is a dynamic equilibrium between methylase and demethylase activities, defined by the state of chromatin. Different environmental exposures could tilt the balance of chromatin state and the DNA methylation state

These studies in rodents offer a model of epigenetic regulation of gene expression in the context of brain, behavior, and nutrition. The data show the regulation of epigenetic mechanisms in the brain (hippocampal glucocorticoid function) by a behavioral mechanism (early life environment) that is susceptible to modulation by l-methionine (a dietary amino acid). The data imply that in animals with a strong parental investment during early development, such as humans, early environment may have a profound effect on later behavioral trajectories. Thus, in humans, it may be expected that analogous mechanisms may exist to those in the animal studies reviewed above, while others may have special relevance in the context of human society.

2.4 Epigenetic Contributions to Mental Health in Humans

2.4.1 Influence of DNA Methylation on Mental Health

Genetic defects in genes encoding the DNA methylation and chromatin machinery exhibit profound effects on mental health in humans. A classic example is RETT syndrome, a progressive neurodevelopmental disorder and one of the most common causes of mental retardation in females, which is caused by mutations in the methylated-DNA-binding protein MeCP2 (Amir et al. 1999). Mutations in MeCP2 and reduced MeCp2 expression were also associated with autism (Nagarajan et al. 2006; Ben Zeev Ghidoni 2007; Herman et al. 2007; Lasalle 2007). ATRX a severe, X-linked form of syndromal mental retardation associated with alpha thalassaemia (ATR-X syndrome) is caused by a mutation in a gene, which encodes a member of the SNF2 subgroup of a superfamily of proteins with similar ATPase and helicase domains, which are involved in chromatin remodeling (Picketts et al. 1996). The ATRX mutation is associated with DNA methylation aberrations (Gibbons et al. 2000). Although these genetic lesions in the methylation machinery were present through development and

are thus fundamentally different from methylation changes after birth, these data nevertheless support the hypothesis that DNA methylation defects could lead to mental pathologies as well. Thus, it is possible that environmental exposuresthat would affect the activity of the methylation machinery would also lead to behavioral and mental pathologies.

There are some data indicating aberrant methylation in late onset mental pathologies, although it is unclear whether these changes in DNA methylation originated during embryogenesis or later in life as a response to an environmental exposure. The gene encoding *REELIN*, a protein involved in neuronal development and synaptogenesis, which is implicated in long-term memory, was found to be hypermethylated in brains of schizophrenia patients. The methylation of *REELIN* was correlated with its reduced expression and increased DNMT1 expression in GABAergic neurons in the prefrontal cortex (Chen et al. 2002; Costa et al. 2002, 2003; Grayson et al. 2005; Veldic et al. 2007).

We have found in our own work that promoters of the genes encoding rRNA are heavily methylated in hippocampi from subjects who committed suicide relative to controls (McGowan et al. 2008). Methylation of rRNA defines the fraction of rRNA molecules that is active in a cell, and the output of rRNA transcription defines to a large extent the protein synthesis capacity of a cell. Protein synthesis is critical for learning and memory. Thus, a reduced capacity for protein synthesis required for learning and memory in the brains of suicide victims could be epigenetically determined. This might be involved in the pathology leading to suicide. Thus, evidence is emerging that aberrant DNA methylation is involved in psychopathologies, and our study was the first published report of aberrant methylation associated with suicide. In our study, however, we found that the sequence of rRNA was identical in all subjects, and there was no difference in methylation between suicide victims and controls in the cerebellum, a brain region not normally associated with psychopathology. These data imply that epigenetic effects that influence psychopathology likely target particular neural pathways. Standardized forensic psychiatry methods had been used to ascertain that all of the suicide victims in our study had a history of severe abuse or neglect during childhood, which is common among suicide victims. Thus, the data suggest that severe adversity during early childhood may have been a contributing factor to the observed epigenetic pathology. It was unclear whether the observed abnormalities were a result of early adversity or whether they had emerged during adulthood as a result of the mental disorders associated with suicide. We undertook another study to address this question, and to examine whether epigenetic alterations analogous to those observed in rodents with differences in maternal care exist in humans.

As in the previous study, we examined the glucocorticoid receptor gene promoter in the hippocampus of human suicide victims and controls (McGowan et al. 2009). All of the suicide victims, and none of the controls, had a history of childhood abuse or severe neglect. A third group comprised suicide victims with a history that was negative for childhood abuse or neglect. We found that, as in the animal model described above, the glucocorticoid receptor was epigenetically regulated in the brain, and associated with altered glucocorticoid receptor gene expression. In humans, hypermethylation of the glucocorticoid receptor gene was found among suicide victims with a history of abuse in childhood, but not among controls or suicide victims with a negative history of childhood abuse. The data are consistent with other data from the literature suggesting that suicide has a developmental origin. They suggest that epigenetic processes might mediate the effects of the social environment during childhood on hippocampal gene expression and that stable epigenetic marks such as DNA methylation might then persist into adulthood and influence the vulnerability for psychopathology through effects on intermediate levels of function, such as HPA activity. However, it remains unclear whether the epigenetic aberrations documented in brain pathologies were present in the germ line, whether they were introduced during embryogenesis, or whether they were truly changes occurring during early childhood.

2.4.2 Chromatin Modification and Its Role in Mental Health

The fact that histone methylation is reversible provides a wide platform for pharmacological and therapeutic manipulations of the state of histone methylation in both directions. Both histone demethylases and histone methyltransferase are excellent candidates for new drug discovery. Understanding the intricate details of their genomic targets will allow the design of targeted and specific therapeutics.

The epigenetic effects of current clinically used monoamine oxidase inhibitors provide leads to further development of therapies targeting the epigenome. For example, H3K4Me2 is a hallmark of active genes and the target of the histone demethylase LSD1, which demethylates H3-K4Me2. Interestingly, certain nonselective monoamine oxidase inhibitors used as antidepressants such as Tranylcypromine that were clinically used for some time and believed to be acting on monoamine oxidases also appear to inhibit LSD1 demethylase (Lee et al. 2006). It is tempting to speculate that the inhibition of LSD1 is part of the mechanism of action of these antidepressants through activation of critical genes suppressed by the H3-K4me2 demethylating activity of LSD1 in the brain (Shi et al. 2004) or by repressing genes activated by the H3-K9Me2 demethylation activity of LSD1 (Metzger et al. 2005). Thus, it is possible that LSD1 inhibition is involved in the mechanism of action of antidepressive agents. It is tempting to speculate that selective inhibitors of LSD1 might be effective as antidepressants. This is an idea that might be pursued in the future.

Valproic acid, a long established antiepileptic and mood stabilizer, is also an HDACi (Phiel et al. 2001), suggesting a possible role for HDACi in treating mental disorders such as schizophrenia and bipolar disorder. Valproic acid has some effect in alleviating psychotic agitation as an adjunct to antipsychotics in schizophrenia (Bowden 2007; Yoshimura et al. 2007). HDACi were shown to improve memory and induce dendritic sprouting in a transgenic mouse model of neurodegeneration, suggesting that HDACi might be of use in treating neurodegeneration and memory loss as well (Fischer et al. 2007). Although biological and behavioral effects of HDACi in the brain are somewhat characterized, the specific gene targets of HDACi in the brain and their function in mental pathologies are not well delineated. Nevertheless, the limited clinical and animal data suggest a potentially important role for HDACi in treatment of mental disorders. Experiments with a novel HDACi from the benzamide class *N*-(2-aminophenyl)-4-[*N*-(pyridin-3-yl-methoxycarbonyl)aminomethyl]benzamide derivative (MS-275) in mice resulted in brain region specific induction of acetylation in the frontal cortex at two genes involved with schizophrenia pathogenesis, *REELIN* and *GAD*(*67*) (Simonini et al. 2006). Valproic acid was shown to induce the expression of *REELIN*, which was silenced by methionine treatment in mice (Dong et al. 2007). These studies raise the possibility that treatment of schizophrenics with HDACi might cause activation of expression of critical genes such as *REELIN* and could reverse the course of this disease (Sharma et al. 2006). Several clinical trials have tested valproate as an adjunctive therapy to antipsychotics in schizophrenia. There are indications that valproate might improve violent episodes in a subset of schizophrenia patients (Basan and Leucht 2004) and might have an effect on euphoric mania in combination with antipsychotics (Bowden 2007), as well as, features of manic symptomatology in bipolar disorders (Bowden 2007). It should be noted that many of these trials were of small size and that further clinical trials are needed with valproate and with more potent and selective HDACi to methodically test the therapeutic potential of HDACi in mental pathologies.

One question that needs to be addressed is whether the observed defects in histone acetylation in mental disease are a consequence of aberrant deregulation of the overall levels of certain HDAC isotypes or HATs, or whether it involves the aberrant targeting of HDAC to a selection of promoters.

The fact that inhibition of a general enzyme such as HDAC results in exquisite positive changes in the brain implies some specificity, even for a general inhibitor of a specific class of HDACs as discussed above. How could such specificity be achieved by treatment with nonselective HDACi? It will be important to delineate the response of the transcriptomes of different brain regions to HDACi and to map the genes that are critically involved in the molecular pathology of the disease. It will also be important to characterize the critical isoforms of HDAC for regulation of these genes. The advent of isotypic-specific HDACi might enhance the efficacy and potency of the treatment and reduce its toxicity.

2.5 Applications to Other Areas of Health and Disease: Role of Dietary Epigenetics in Behavior and Mental Health

The experiments described above involving infusion of methionine into the lateral ventricles of the brain raise the possibility that diet can affect the phenotype being studied. Because intracellular levels of methionine can be affected by both dietary intake and polymorphisms of enzymes involved in methionine metabolism, such as methylenetetrahydrofolate-reductase (Friso et al. 2002), it is tempting to consider the possibility that diet could modify epigenetic programming in the brain not only during early development but also in adult life in humans.

Rodent models have been useful in elucidating the mechanisms involved in epigenetic alterations related to diet during development. Several studies have shown that additional dietary factors, including zinc and alcohol, can influence the availability of methyl groups for SAM formation, and thereby influence CpG methylation (Ross 2003; Davis and Uthus 2004; Pogribny et al. 2006; Ross and Milner 2007). Maternal methyl supplements affect epigenetic variation and DNA methylation and positively affect the health and longevity of the offspring (Wolff et al. 1998; Cooney et al. 2002; Waterland and Jirtle 2003). We hypothesize that reversal of epigenetic states in the brain, such as the remethylation of the exon 1_7 GR promoter, could be triggered not only by pharmacological agents but also by stable variations in environmental conditions.

Other studies have shown that certain dietary components may act as an HDACi, including diallyl disulfide, sulforaphane, and butyrate. For example, broccoli, which contains high levels of sulforaphane, has been associated with H3 and H4 acetylation in peripheral blood mononuclear cells in mice 3–6 h after consumption (Dashwood and Ho 2007). The long-term consequences of such epigenetic effects on human health remain to be studied, however HDACis are an active area of research as anti-inflamatory and neuroprotective agents in autoimmune diseases such as lupus and multiple sclerosis (Gray and Dangond 2006), and sodium butyrate has been shown to have antidepressant effects in mice (Schroeder et al. 2007). Thus, it is conceivable that dietary compounds that influence histone acetylation may affect signaling mechanisms that regulate neural function. In light of the aforementioned link between histone modifications and DNA methylation, future studies are needed to address the possibility that sustained exposure to such compounds may affect DNA methylation at susceptible loci, with implications for mental health in humans. Dietary components could act through cellular signaling pathways, leading from cell surface receptors down to *trans*-acting factors that deliver chromatin-modifying enzymes to specific sequences. The dynamic epigenome has obviously adaptive and physiological roles in the crosstalk between our environment and our inherited genome, but could at the same time serve as a target for dietary components (Figs. 2.6 and 2.7). Thus, unraveling the conduits between our diet and our genomes should have an important impact on our health.

Fig. 2.7 A scheme for environmentally driven epigenetic states and interindividual phenotypic variance in behavior and susceptibility to disease in humans. We propose a reciprocal relationship between phenotype and environmental mechanisms leading to the epigenetic programming of gene expression

environment

↓

epigenetic changes

↓

inter-individual epigenetic variation

↓

gene expression programming

↓

Phenotypic variation
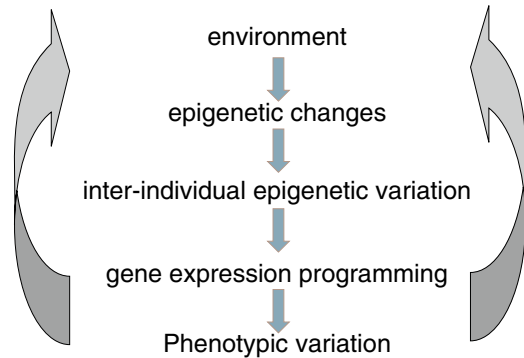
Summary Points

- We propose that the DNA methylation and chromatin structure are found in a dynamic balance through life, which is maintained and defined by sequence-specific factors that deliver histone modification and DNA modification enzymes to genes.
- We propose that the direction of the DNA methylation reaction is defined by the state of chromatin and, as such, factors that target specific chromatin modification events to genes define the direction of the DNA methylation equilibrium by either recruiting DNA methylation enzymes or by facilitating demethylation.
- Epigenetic programming in the brain of rodents by maternal care during the first week of life is a highly stable yet reversible process that results in long-term changes in gene expression.
- In our studies, we found that aberrant DNA methylation of the ribosomal RNA promoter as well as the glucocorticoid receptor promoter lead to decreased transcription of each gene, and that this effect was associated with a history of early childhood abuse or neglect in humans.
- Many of the phenotypic variations seen in human populations might be caused by differences in long-term programming of gene function rather than the sequence per se, and any future study of the basis for interindividual phenotypic diversity should consider epigenetic variations in addition to genetic sequence polymorphisms.
- The fact that histone methylation, histone acetylation, and DNA methylation are potentially reversible processes provides a wide platform for research into pharmacological and therapeutic manipulations with known epigenetic effects from drugs used to treat mental illness such as valproate to dietary supplements such as l-methionine.

Key Terms

Epigenetics: DNA and chromatin modifications that persist from one cell division to the next, despite a lack of change in the underlying DNA sequence.

Epigenome: The overall epigenetic state of a cell that serves as an interface between the environment and the genome.

DNA methylation/demethylation: A biochemical modification of the DNA involving the transfer of a methyl group (CH_3), typically to the 5′ position of the cytosine ring in the dinucleotide combination CG in mammals. In plants and other species DNA methyation may affect other nucleotide pairs.

Histone code: The specific pattern of histone protein modifications that delineate the parts of the genome to be expressed at a given point in time in a given cell type.

Chromatin: Histone proteins associated with the cell's DNA that regulate its accessibility to gene transcription machinery. Chromatin comes in two forms: Heterochromatin, where the DNA is tightly coiled and therefore inaccessible to the transcriptional machinery and euchromatin, where the DNA is more loosely associated with histone proteins.

Phenotype: Any observable characteristic of an organism, including its behavior. An organism's phenotype is a product of its genetics and its environment.

Methyltransferase: Enzymes involved in the transfer of a methyl donor from *S*-Adenosyl Methionine to histone proteins (histone methyltransferases) or DNA (DNA methyltransferases). Epigenetic regulation by histone methyltransferases tends to inhibit transcription.

Histone deacetylase inhibitor (HDACi): A class of chemicals that inhibits the acetylation of histones, leading to a chromatin structure that is more accessible to the transcriptional machinery. A variety of therapeutic chemicals (e.g., valproic acid) and dietary constituents (e.g., sulforaphane) have known HDACi properties.

Psychopathology: The manifestation of mental illness in the form of phenotype, including abnormal behavior and physiology.

References

Amir RE, Van den Veyver IB, Wan M, Tran CQ, Francke U, Zoghbi HY. Nat Genet. 1999;23(2):185–8.
Basan A, Leucht S. Cochrane Database Syst Rev. 2004;1:CD004028.
Beck S, Olek A, Walter J. Nat Biotechnol. 1999;17(12):1144.
Ben Zeev Ghidoni B. Child Adolesc Psychiatr Clin N Am. 2007;16(3):723–43.
Bergmann A, Lane ME. Trends Biochem Sci. 2003;28(9):461–3.
Bowden CL. Expert Rev Neurother. 2007;7(1):9–16.
Bultman SJ, Gebuhr TC, Magnuson T. Genes Dev. 2005;19(23):2849–61.
Cervoni N, Szyf M. J Biol Chem. 2001;276(44):40778–87.
Cervoni N, Sang-beom S, Chakravarti D, Szyf M. 2001; submitted for publication
Chen Y, Sharma RP, Costa RH, Costa E, Grayson DR. Nucleic Acids Res. 2002;30(13):2930–9.
Cooney CA, Dave AA, Wolff GL. J Nutr. 2002;132(8):2393S–400.
Costa E, Chen Y, Davis J, Dong E, Noh JS, Tremolizzo L, et al. Mol Interv. 2002;2(1):47–57.
Costa E, Grayson DR, Mitchell CP, Tremolizzo L, Veldic M, Guidotti A. Crit Rev Neurobiol. 2003;15(2):121–42.
D'Alessio AC, Szyf M. Biochem Cell Biol. 2006;84(4):463–76.
Dashwood RH, Ho E. Semin Cancer Biol. 2007;17(5):363–9.
Davis CD, Uthus EO. Exp Biol Med (Maywood). 2004;229(10):988–95.
Detich N, Hamm S, Just G, Knox JD, Szyf M. J Biol Chem. 2003;278(23):20812–20.
Dong E, Guidotti A, Grayson DR, Costa E. Proc Natl Acad Sci USA. 2007;104(11):4676–81.
Fischer A, Sananbenesi F, Wang X, Dobbin M, Tsai LH. Nature. 2007;447(7141):178–82.
Francis D, Diorio J, Liu D, Meaney MJ. Science. 1999;286(5442):1155–8.
Friso S, Choi SW, Girelli D, Mason JB, Dolnikowski GG, Bagley PJ, et al. Proc Natl Acad Sci USA. 2002;99(8):5606–11.
Gibbons RJ, McDowell TL, Raman S, O'Rourke DM, Garrick D, Ayyub H, et al. Nat Genet. 2000;24(4):368–71.
Gray SG, Dangond F. Epigenetics. 2006;1(2):67–75.
Grayson DR, Jia X, Chen Y, Sharma RP, Mitchell CP, Guidotti A, et al. Proc Natl Acad Sci USA. 2005;102(26):9341–6.

Henikoff S, McKittrick E, Ahmad K. Cold Spring Harb Symp Quant Biol. 2004;69:235–43.

Herman GE, Henninger N, Ratliff-Schaub K, Pastore M, Fitzgerald S, McBride KL. Genet Med. 2007;9(5):268–74.

Jenuwein T, Allis CD. Science. 2001;293(5532):1074–80.

Kersh EN, Fitzpatrick DR, Murali-Krishna K, Shires J, Speck SH, Boss JM, et al. J Immunol. 2006;176(7):4083–93.

Kuo MH, Allis CD. Bioessays. 1998;20(8):615–26.

Lachner M, O'Carroll D, Rea S, Mechtler K, Jenuwein T. Nature. 2001;410(6824):116–20.

Lasalle JM. Epigenetics. 2007;2(1):5–10.

Lee DY, Hayes JJ, Pruss D, Wolffe AP. Cell. 1993;72(1):73–84.

Lee MG, Wynder C, Schmidt DM, McCafferty DG, Shiekhattar R. Chem Biol. 2006;13(6):563–7.

Liu D, Diorio J, Tannenbaum B, Caldji C, Francis D, Freedman A, et al. Science. 1997;277(5332):1659–62.

Lucarelli M, Fuso A, Strom R, Scarpa S. J Biol Chem. 2001;276(10):7500–6.

McGowan PO, Sasaki A, Huang TC, Unterberger A, Suderman M, Ernst C, et al. PLoS ONE. 2008;3(5):e2085.

McGowan PO, Sasaki A, D'Alessio AC, Dymov S, Labonte B, Szyf M, et al. Nat Neurosci. 2009;12(3):342–8.

Meaney MJ, Szyf M. Trends Neurosci. 2005;28(9):456–63.

Metzger E, Wissmann M, Yin N, Muller JM, Schneider R, Peters AH, et al. Nature. 2005;437(7057):436–9.

Nagarajan RP, Hogart AR, Gwye Y, Martin MR, Lasalle JM. Epigenetics. 2006;1(4):172–82.

Nan X, Campoy FJ, Bird A. Cell. 1997;88(4):471–81.

Okano M, Xie S, Li E. Nat Genet. 1998;19(3):219–20.

Perry M, Chalkley R. J Biol Chem. 1982;257(13):7336–47.

Phiel CJ, Zhang F, Huang EY, Guenther MG, Lazar MA, Klein PS. J Biol Chem. 2001;276(39):36734–41.

Picketts DJ, Higgs DR, Bachoo S, Blake DJ, Quarrell OW, Gibbons RJ. Hum Mol Genet. 1996;5(12):1899–907.

Pogribny IP, Ross SA, Wise C, Pogribna M, Jones EA, Tryndyak VP, et al. Mutat Res. 2006;593(1–2):80–7.

Ramchandani S, Bhattacharya SK, Cervoni N, Szyf M. Proc Natl Acad Sci USA. 1999a;96(11):6107–12.

Ramchandani S, Bhattacharya SK, Cervoni N, Szyf M. Proc Natl Acad Sci USA. 1999b;96(11):6107–12.

Razin A. EMBO J. 1998;17(17):4905–8.

Razin A, Cedar H. Proc Natl Acad Sci USA. 1977;74(7):2725–8.

Ross SA. Ann NY Acad Sci. 2003;983:197–207.

Ross SA, Milner JA. Am J Clin Nutr. 2007;86(3):s872–7.

Schroeder FA, Lin CL, Crusio WE, Akbarian S. Biol Psychiatry. 2007;62(1):55–64.

Sharma RP, Rosen C, Kartan S, Guidotti A, Costa E, Grayson DR, et al. Schizophr Res. 2006;88(1–3):227–31.

Shi Y, Lan F, Matson C, Mulligan P, Whetstine JR, Cole PA, et al. Cell. 2004;119(7):941–53.

Simonini MV, Camargo LM, Dong E, Maloku E, Veldic M, Costa E, et al. Proc Natl Acad Sci USA. 2006;103(5):1587–92.

Szyf M. Trends Pharmacol Sci. 2001;22(7):350–4.

Tsukada Y, Fang J, Erdjument-Bromage H, Warren ME, Borchers CH, Tempst P, et al. Nature. 2006;439(7078):811–6.

Veldic M, Kadriu B, Maloku E, Agis-Balboa RC, Guidotti A, Davis JM, et al. Schizophr Res. 2007;91(1–3):51–61.

Vo N, Klein ME, Varlamova O, Keller DM, Yamamoto T, Goodman RH, et al. Proc Natl Acad Sci USA. 2005;102(45):16426–31.

Waterland RA, Jirtle RL. Mol Cell Biol. 2003;23(15):5293–300.

Weaver IC, Cervoni N, Champagne FA, D'Alessio AC, Sharma S, Seckl JR, et al. Nat Neurosci. 2004a;7(8):847–54.

Weaver IC, Diorio J, Seckl JR, Szyf M, Meaney MJ. Ann NY Acad Sci. 2004b;1024:182–212.

Weaver IC, Champagne FA, Brown SE, Dymov S, Sharma S, Meaney MJ, et al. J Neurosci. 2005;25(47):11045–54.

Weaver IC, Meaney MJ, Szyf M. Proc Natl Acad Sci USA. 2006;103(9):3480–5.

Wolff GL, Kodell RL, Moore SR, Cooney CA. FASEB J. 1998;12(11):949–57.

Yoshida M, Kijima M, Akita M, Beppu T. J Biol Chem. 1990;265(28):17174–9.

Yoshimura R, Shinkai K, Ueda N, Nakamura J. Pharmacopsychiatry. 2007;40(1):9–13.

Chapter 3
The Michigan State University Twin Registry (MSUTR): Genetic, Environmental, and Neurobiological Influences on Food and Diet-Related Behavior

Sarah E. Racine, Kristen M. Culbert, S. Alexandra Burt, and Kelly L. Klump

Abbreviations

MSUTR   Michigan State University Twin Registry
MZ   Monozygotic
DZ   Dizygotic
MTFS   Minnesota Twin Family Study
BMI   Body mass index

Key Terms

Phenotype: an observed trait or behavior
Prevalence: an estimate of how common a disorder or phenotype is in a given population
Etiology: the cause or origin of a disorder or phenotype
Heritability: the amount of total variation in a population on a given trait that is due to genetic factors
Moderation: a case when the strength or direction of a causal relationship is influenced by a third variable
Masculinization: the development of male typical physiology, morphology, and patterns of behavior

---

3.1 Introduction

The Michigan State University Twin Registry (MSUTR) is a population-based twin registry that recruits twins from across lower Michigan (Klump and Burt 2006). The MSUTR was created to understand changes in genetic, environmental, and neurobiological influences on internalizing and externalizing psychopathology across development as well as sex differences in these effects, and thus consists of male and female twins across a range of ages, including childhood, adolescence,

---

K.L. Klump (✉)
Department of Psychology, Michigan State University,
East Lansing, MI, USA
e-mail: klump@msu.edu

and adulthood. Eating disorders (i.e., anorexia nervosa, bulimia nervosa, and disordered eating attitudes and behaviors) are the main internalizing phenotype of interest for the MSUTR. Research thus far suggests that there are likely two critical periods for the development of disordered eating: puberty and the prenatal period.

Notably, the predominant influences during these two periods appear to differ, such that genetic effects on disordered eating are most important during puberty (Klump et al. 2007b), whereas "environmental" effects (more specifically, the hormonal environment) are critical during the prenatal period (Culbert et al. 2008). In both cases, gonadal hormones are likely to account for these genetic/environmental effects and may also operate to influence sex differences in prevalence (i.e., Ten females to every one male; American Psychiatric Association 2000). Ongoing data collection will continue to aid in understanding how gonadal hormones may influence individual and sex differences in risk for eating pathology.

This chapter will review twin studies from the MSUTR and other twin registries in order to illustrate differences in genetic and environmental effects on disordered eating across development. First, twin studies of eating disorders in adulthood will be briefly reviewed to demonstrate that genetic and non-shared environmental effects predominate during this time. Second, findings from a series of developmental twin studies from the Minnesota Twin Family Study (MTFS) and the MSUTR will be discussed in depth. These findings suggest that there are stark differences in the genetic and environmental influences on disordered eating across puberty, and that ovarian hormones may be critical for the "activation" of genetic effects. Finally, the prenatal period and in utero testosterone exposure will be presented as potentially influential for individual and sex differences in risk for disordered eating.

3.2 Twin Study Method

Twin studies provide a novel design for examining the etiology of phenotypes or behavior. Twins allow us to separate the effect of genes from that of the environment, as both contribute to the similarity of family members reared together. The twin method takes advantage of the fact that monozygotic (MZ) twins share 100% of their genes, whereas dizygotic (DZ) twins share, on average, 50% of their segregating genetic material. Comparing the degree of similarity among MZ and DZ twin pairs accordingly informs us of the relative importance of genetic and environmental influences on a given phenotype. Using statistical modeling, the total variance in a phenotype within a given population is partitioned into additive genetic (i.e., the additive effects of multiple genes), shared environmental (i.e., factors that make members of a twin pair similar to one another), and non-shared environmental influences (i.e., factors that make members of a twin pair different from one another) (Plomin et al. 2001).

3.3 Twin Studies of Disordered Eating

Twin studies of eating disorders and disordered eating date back to the 1980s and have informed us of the genetic and environmental architecture of eating pathology. Heritability estimates for anorexia nervosa and bulimia nervosa have generally been greater than 50% in adulthood (see Figs. 3.1 and 3.2). Similar heritability estimates have been reported for a range of disordered eating attitudes and behaviors, such as weight preoccupation, body dissatisfaction, dietary restraint,
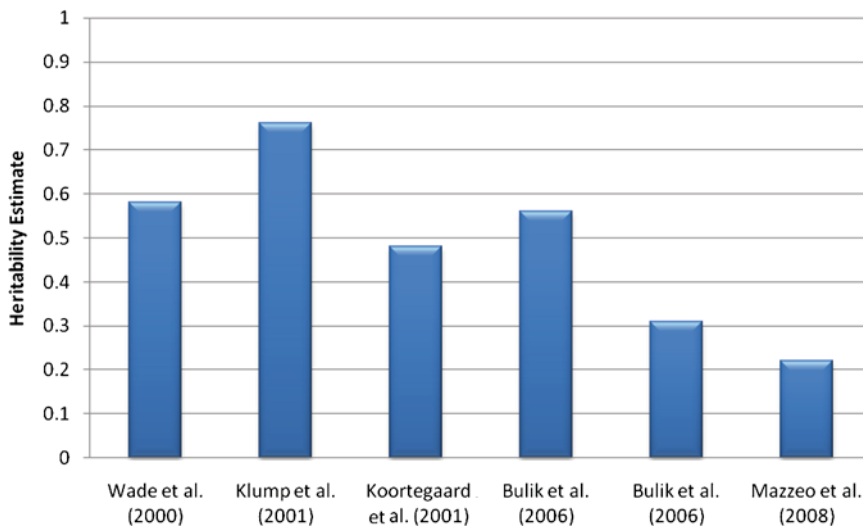
Fig. 3.1 Heritability estimates for anorexia nervosa in adulthood. Twin studies of anorexia nervosa in adulthood indicate that anorexia nervosa is significantly heritable, with heritability estimates ranging from 22% to 76% (Copyright not required)
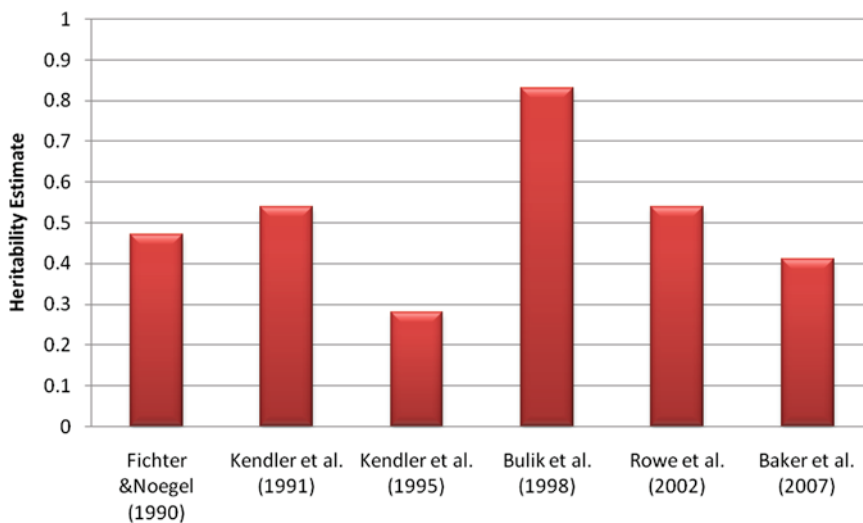
Fig. 3.2 Heritability estimates for bulimia nervosa in adulthood. Twin studies of bulimia nervosa in adulthood indicate that bulimia nervosa is significantly heritable, with heritability estimates ranging from 28% to 83% (Copyright not required)

binge eating, and compensatory behaviors (See Fig. 3.3), thereby indicating that the symptoms that commonly precede the development of anorexia and bulimia nervosa are also highly heritable. With the exception of a few studies (e.g., Kendler et al. 1995; Reichborn-Kjennerud et al. 2004), little to no shared environmental influence has been reported for eating pathology in adulthood (Klump et al. 2009). In general, the remaining variance in disordered eating and eating disorders is accounted for by non-shared environmental influences. These could include factors such as differential parental treatment (e.g., parent(s) are more critical of one twin), different peer group
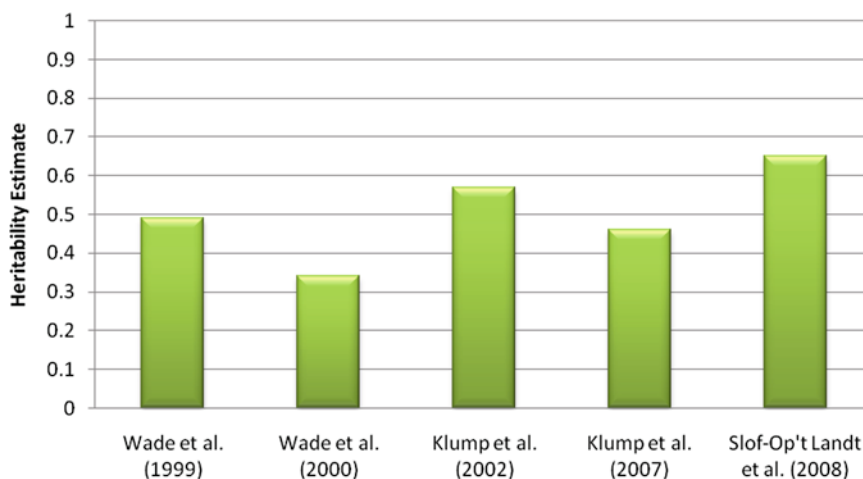
Fig. 3.3 Heritability estimates for overall disordered eating in adulthood. Twin studies of overall disordered eating, measured continuously, in adulthood indicate that disordered eating is significantly heritable, with heritability estimates ranging from 34% to 65% (Copyright not required)

characteristics (e.g., deviant vs. conforming peer groups), and different life experiences (e.g., experience of abuse/trauma), although these possibilities have not been extensively investigated (Klump et al. 2002).

3.4 Developmental Twin Studies of Disordered Eating

Although numerous twin studies have been conducted on disordered eating in adulthood, until recently, little was known about developmental changes in genetic and environmental influences on disordered eating. The first study to empirically examine this question was conducted by Klump et al. (2000) using a large cross-sectional twin sample from the MTFS. The genetic and environmental influences on disordered eating attitudes and behaviors (i.e., overall levels of disordered eating as well as weight preoccupation) differed in an interesting way by age, independent of body mass index (BMI). Specifically, in 11-year-old twins, genetic effects were negligible, as the majority of the variance in disordered eating was accounted for by shared and non-shared environmental factors. In contrast, genetic effects were substantial in 17-year-old twins, with the remaining variance accounted for by non-shared environmental influences. These findings significantly contributed to the literature, as this was the first study to highlight developmental differences in genetic and environmental effects on disordered eating.

Importantly, Klump et al. (2007a) extended these initial cross-sectional results by using longitudinal data to investigate developmental changes in genetic and environmental influences across MTFS twins assessed at ages 11, 14, and 18. Similar to findings from Klump et al. (2000), genetic effects increased with age. Again, minimal genetic influences were found at age 11, yet significant genetic influences were found at age 14 and remained constant through age 18. Thus, this study was able to narrow the time frame for the "activation" of genetic influences on disordered eating by suggesting that the critical period occurs between ages 11 and 14. Taken together, this line of research suggests clear developmental differences in the etiological influences on disordered eating.

Notably, a developmental study that examined unique and common etiological influences on eating, depressive, and anxiety symptoms reported slightly different results. Similar to Klump et al. (2000, 2007a), Silberg and Bulik (2005) found that genes accounted for more variance in eating pathology in adolescent (14–17 years) compared to preadolescent (8–13 years) twins. However, this study also reported that a unique set of genetic factors contributed to the variance in eating disorder symptoms in the 8–13-year-old group. It is possible that differences in the measures used to assess disordered eating could have contributed to these conflicting results. In addition, the preadolescent group in Silberg and Bulik (2005) included twins whose ages overlapped with both the 11 (10–12 years) and 14 (13–15 years) year-old groups from Klump et al. (2007a). Thus, differences in age categorizations could also account for differences in the pattern of results.

3.5 Puberty as a Critical Time Period

Given that our findings suggest that the onset of substantial genetic influences on disordered eating likely occurs between 11 and 14 years, the next line of research aimed to examine the mechanisms responsible for developmental changes in the relative influence of genes and environment. One crucial milestone that occurs between 11 and 14 years for most females is puberty (Herman-Giddens et al. 1997). Puberty is a significant event in a girl's life and is associated with a cascade of biological as well as psychosocial transitions. Research suggests that rates of disordered eating and eating disorders increase across the pubertal period (Killen et al. 1992). Thus, puberty is clearly associated with increases in the incidence of disordered eating and may similarly account for increases in genetic influences on this phenotype.

Indeed, developmental twin studies from the MTFS and MSUTR have suggested that pubertal development moderates the heritability of disordered eating, even after controlling for age. Specifically, there were little to no genetic influences on disordered eating in prepubertal 11-year-old twins from the MTFS, but genetic effects accounted for approximately 50% of the variance in 11-year-old twins who were in mid to late puberty (Klump et al. 2003). Interestingly, 11-year-old twins who had begun puberty closely resembled adult twins in the magnitude of genetic effects; indeed, the best-fitting biometric model constrained genetic influences to be equal in pubertal 11-year-old twins and adult twins. These findings suggest that puberty accounts entirely for changes in genetic effects on disordered eating that occur with age (Klump et al. 2007a).

A series of studies have now replicated these results. Using data from the MTFS, Klump et al. (2007b) demonstrated that genetic influences on disordered eating increase linearly with increasing pubertal development (see Fig. 3.4). These findings were replicated in an independent sample of twins from the MSUTR (Culbert et al. 2009). Again, nominal genetic influences on disordered eating were present in prepubertal young adolescent twins, but substantial and equal genetic influences were found in twins during puberty and into young adulthood. Importantly, this study indicated that the shift in etiological influences may be missed if late markers of pubertal development are used. For example, when menarcheal status is used to categorize pubertal development (see Rowe et al., 2002), no differences in genetic effects are observed in pre-menarche versus post-menarche groups (Culbert et al. 2009; Rowe et al. 2002). By contrast, when categorizations are made using mid-puberty, differences in genetic effects are observed (Culbert et al. 2009; Klump et al. 2003). These findings continue to highlight puberty as the critical period for developmental changes in the genetic and environmental influences on disordered eating.
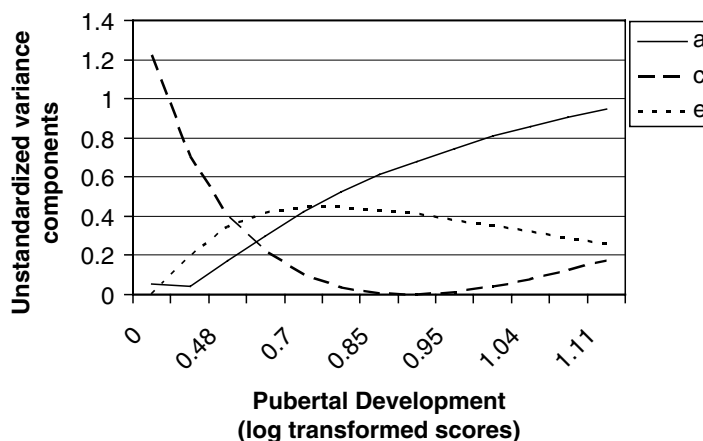
Fig. 3.4 Contributions of genes, shared environment, and non-shared environment to disordered eating across pubertal development. Using gene–environment interaction models, we have shown that the heritability of disordered eating increases from 0% to 44% across pubertal development. In contrast, shared environmental influences sharply decline during this time. Abbreviations include *a* additive genetic effects, *c* shared environment, *e* non-shared environment (From Klump et al. 2007b. Reprinted with the permission of Cambridge University Press, © 2007 Cambridge University Press)

3.6 Ovarian Hormones: Activation of Genetic Influences?

Research examining the mechanisms underlying puberty's effect on the genetic diathesis of disordered eating is still in its infancy. There are numerous possible factors (e.g., hormones, body weight, mood, peer influences) that change at puberty and could influence the increasing genetic influences on disordered eating. While the MSUTR includes assessment of these multiple factors, our research thus far has focused on the role of ovarian hormones. Animal studies suggest that ovarian hormones have direct effects on food intake and body weight (Kemnitz et al. 1989; Wade 1972), and ovarian hormones are important regulators of gene transcription within neurotransmitter systems implicated in eating disorders (Ostlund et al. 2003; Klump and Culbert 2007). Because ovarian hormones appear to have direct genomic effects on behavior, they represent a plausible pubertal mechanism that could influence heritability estimates for disordered eating.

Indeed, data from the MSUTR have supported our hypotheses regarding the role of ovarian hormones in the onset of genetic influences on disordered eating at puberty. One study includes direct assessments of steroid hormone concentrations in 10–15-year-old same-sex female twins. Analyses are ongoing, but initial data suggest that estradiol levels moderate genetic effects on disordered eating, even after controlling for BMI and age (Klump et al. 2010). Specifically, the heritability of disordered eating was greater in twins with high estradiol versus low estradiol levels during puberty. Thus, estrogen's onset at puberty may partially account for the increase in genetic influences on disordered eating with increasing pubertal development.

Moreover, data from the MSUTR suggest that ovarian hormone concentrations show longitudinal associations with disordered eating (Klump et al. 2008). Same-sex female twins were asked to collect daily saliva samples of estradiol and progesterone and daily assessments of binge eating for 65 days. Findings suggested that natural fluctuations in ovarian hormones across the menstrual cycle precede and predict corresponding changes in binge eating, independent of fluctuations in negative affect (see Fig. 3.5). Identical findings have also been reported in women with bulimia nervosa
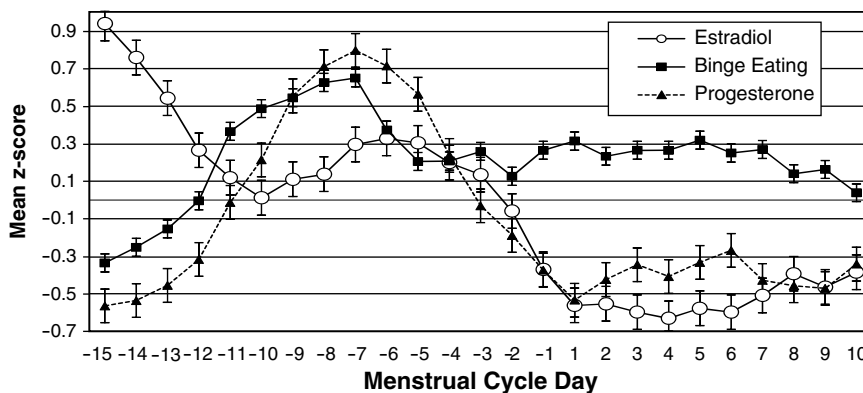
Fig. 3.5 Levels of binge eating, estradiol, and progesterone across the menstrual cycle. Data from female twins across the menstrual cycle have demonstrated that changes in estradiol are negatively correlated with fluctuations in binge eating, whereas changes in progesterone are positively correlated with fluctuations in binge eating (From Klump et al. 2008. Reprinted with the permission of Cambridge University Press, © 2008 Cambridge University Press)

(Edler et al. 2007). Importantly, the MSUTR is currently collecting a larger twin sample to investigate the genetic origins of the associations between ovarian hormones and disordered eating across the menstrual cycle.

3.7 The Prenatal Period as a Critical Time Period

While puberty and ovarian hormones appear to be critical for understanding the emergence of genetic effects on disordered eating, the prenatal period may be important for understanding environmental effects, particularly those that contribute to sex differences in eating disorder prevalence. Animal studies indicate that intrauterine hormones, particularly testosterone, permanently masculinize (i.e., make more male-like) the central nervous system and patterns of behaviors (e.g., increased aggression and food intake). Given the robust sex difference in eating pathology and the effects of prenatal testosterone on sexually dimorphic behaviors, the MSUTR has focused on examining whether variation in testosterone exposure during prenatal development permanently alters levels of disordered eating.

Since prenatal exposure to testosterone cannot be readily examined or manipulated in humans, the MSUTR has used finger-length (2D:4D) ratios and opposite-sex twins as proxies for prenatal testosterone exposure. Specifically, finger length ratios correlate inversely with prenatal testosterone levels (Lutchmaya et al. 2004) and are sexually dimorphic (i.e., lower in males relative to females) (Manning et al. 1998). Data from the MSUTR found significant associations between masculinized/lower 2D:4D finger length ratios and lower levels of disordered eating in adult women (Klump et al. 2006). These findings suggested that prenatal testosterone exposure may exert masculinizing effects on disordered eating in women, and thus, serve as a protective factor against eating disorder development.

Nonetheless, given the inclusion of only females, findings from Klump et al. (2006) could not speak to whether prenatal testosterone influences sex differences in disordered eating. Consequently, the MSUTR used opposite-sex twins to investigate whether prenatal testosterone exposure explains sex differences in eating pathology. Females from opposite-sex twin pairs

develop in utero with a male co-twin and are thus thought to be exposed to increased levels of prenatal testosterone (Ryan and Vandenbergh 2002). Indeed, adult opposite-sex female twins displayed lower levels of disordered eating compared to same-sex female twins from the MSUTR (Culbert et al. 2008). The magnitude of masculinization appeared to depend on the level of testosterone exposure, as same-sex male twins were most masculinized on eating pathology, followed by opposite-sex male twins, opposite-sex female twins, and same-sex female twins. Importantly, these effects were not accounted for by the masculinization of anxiety symptoms or by socialization of being raised with a male sibling. Together, these findings underscore the likely role of prenatal testosterone in explaining lower levels of disordered eating in opposite-sex female twins (Culbert et al. 2008).

However, results from two other twin registries suggested more modest effects than those described above. No significant differences in disordered eating were found between females from opposite-sex versus same-sex twin pairs (Baker et al. 2009; Raevuori et al. 2008), although trends (p's 0.06–0.10) were observed for lower rates of intentional weight loss and anorexia nervosa in opposite-sex female twins (Raevuori et al. 2008). Additional replications are needed, but findings thus far suggest that elevated prenatal testosterone exposure may exert small masculinizing/protective effects on disordered eating and provide a biological mechanism underlying the sex disparity in eating disorder prevalence.

3.8 Combined Influences of Puberty and the Prenatal Period

If elevated exposure to prenatal testosterone does exert masculinizing effects, it will be important to understand the mechanisms underlying such effects. One possible mechanism, currently under investigation within the MSUTR, is that prenatal testosterone alters sex-specific sensitivity to gonadal hormones during puberty. Animal studies have demonstrated that lower exposure to testosterone early in life permits the brain to respond to the female-typical effects of ovarian hormones on food intake at puberty (Gentry and Wade 1976; Madrid et al. 1993). Since ovarian hormones directly influence disordered eating (Edler et al. 2007; Klump et al. 2008), lower rates of disordered eating in opposite-sex female twins may result from decreased sensitivity to the activating effects of ovarian hormones on disordered eating during puberty. Understanding the combined role of prenatal and pubertal effects of gonadal hormones may provide further insight into the etiology of eating pathology and individual and sex differences in risk.

3.9 Applications to Other Areas of Health and Disease

In addition to a focus on disordered eating, the MSUTR assesses a wide range of other phenotypes. This is important given that developmental changes in genetic and environmental influences have been reported for phenotypes in addition to disordered eating, such as anxiety and depressive symptoms, externalizing behaviors, and intelligence (Bergen et al. 2007). Continued exploration of mechanisms underlying these shifts will be important for future research.

The MSUTR is poised to contribute to this future research. The MSUTR is unique in its developmentally informed approach and collection of molecular genetic and neurobiological data. Currently,

the MSUTR is implementing a large-scale, population-based recruitment of approximately 30,000 twins born in Michigan who are between the ages of 3–17-years-old. Once complete, the MSUTR will be one of the largest and most diverse twin registries in the United States. Importantly, all families are asked to complete a comprehensive health questionnaire that assesses a range of internalizing and externalizing psychopathology in the twins (e.g., depression, anxiety, inattention, hyperactivity, conduct problems), twin pubertal development, and family history of numerous medical and psychiatric illnesses (see Table 3.1). Therefore, twin analyses can be conducted to examine differences in the etiology of these phenotypes across a wide range of age groups. Moreover, a database of twins interested in participating in future research will be compiled and will allow researchers the option to select twins with a particular disorder or a specific family history for follow-up studies. The MSUTR will be an invaluable resource for examining developmentally relevant mechanisms underlying potential changes in etiology for a wide range of psychiatric and medical phenotypes.

Table 3.1 Psychiatric and medical illnesses assessed in the Michigan State University Twin Registry (MSUTR) via the family health checklist

Psychiatric conditions	Medical conditions
Eating disorders	Allergies
Anorexia nervosa	Asthma
Binge eating disorder	Blindness
Bulimia nervosa	Cancer
EDNOS	Cerebral palsy
Mood disorders	Cystic fibrosis
Bipolar disorder	Diabetes
Major depressive disorder	Head injury
Anxiety disorders	Hearing problems
Agoraphobia	Heart problems
OCD	Overweight/obesity
Panic disorder	Polycystic ovary syndrome
PTSD	Sleeping problems
Separation anxiety disorder	Smoking
Externalizing disorders	Snoring
ADHD	Stroke
Alcohol abuse	"Other" chronic illnesses
Conduct disorder	
Drug abuse	
Oppositional defiant disorder	
Developmental disorders	
Autism	
Asperger's disorder	
Personality disorders	
Antisocial personality disorder	
Borderline personality disorder	
Other	
Schizophrenia	
Learning disabilities	
Reading problems	

This table provides a comprehensive list of conditions assessed in the MSUTR. Research examining differences in the genetic and environmental influences on these conditions across development is possible using data from the MSUTR (Copyright not required)

Table 3.2 Key features and findings of the Michigan State University Twin Registry (MSUTR)

Key features
- Focus on developmental differences in genetic, environmental, and neurobiological influences
- Focus on sex differences in psychopathology
- Main internalizing phenotype of the MSUTR: disordered eating
- Direct assessment of some key genetic and environmental variables
- Candidate genes
- Hormone concentrations
- Parent–child interactions

Key findings
- Substantial increases in genetic influences on disordered eating during puberty
- Ovarian hormone activation at puberty may account for these effects
- Prenatal testosterone exposure masculinizes the brain and leads to lower levels of disordered eating that may underlie sex differences in eating pathology

This table summarizes the unique features of the MSUTR and the most important empirical findings thus far with regard to biological influences on disordered eating across development (Copyright not required)

3.10 Conclusions

The MSUTR is a new twin registry that is interested in examining critical developmental periods for genetic and environmental influences on disordered eating. Research from the MSUTR suggests that puberty is likely a critical period for the development of disordered eating. Specifically, genetic influences on eating pathology appear to increase across the pubertal period, and one hypothesis is that ovarian hormones moderate genetic risk for disordered eating during this time. In addition, the prenatal period may also be relevant for individual and sex differences in eating pathology, such that prenatal exposure to testosterone may be protective against development of disordered eating. These hypotheses must continue to be investigated, as research into the role of gonadal hormones on disordered eating is early in its development.

Summary Points

- One main focus of the MSUTR is to examine genetic, environmental, and neurobiological influences on disordered eating across development.
- Twin studies of eating disorders and disordered eating in adulthood consistently implicate genetic factors and non-shared environmental factors in the etiology of eating pathology.
- Disordered eating during preadolescence does not show significant genetic effects; shared and non-shared environmental influences predominate during this developmental stage.
- The pubertal period appears to be a critical time for the activation of genetic influences on disordered eating.
- One possibility is that the onset of ovarian hormones at puberty is responsible for the onset of genetic effects for disordered eating.
- The prenatal period is also important for disordered eating development, as environmental exposure to prenatal testosterone may masculinize the brain and lead to lower levels of disordered eating.
- Thus, gonadal hormones appear to be relevant for the development of disordered eating and may act primarily through genetic mechanisms during puberty and environmental mechanisms prenatally.

References

American Psychiatric Association. Diagnostic and Statistical Manual, Text Revision. 4th ed. Washington: American Psychiatric Association; 2000.

Baker JH, Lichtenstein P, Kendler KS. Br J Psychiatry. 2009;194:375–6.

Bergen SE, Garder CO, Kenlder KS. Twin Res Hum Genet. 2007;10:423–33.

Culbert KC, Breedlove M, Burt SA, Klump KL. Arch Gen Psychiatry. 2008;65:329–36.

Culbert KC, Burt SA, McGue M, Iacono WG, Klump KL. Puberty and the genetic diathesis of disordered eating attitudes and behaviors. J. Abnor. Psychol. 2009;118:788–796.

Edler C, Lipson SF, Keel PK. Psychol Med. 2007;37:131–41.

Gentry RT, Wade GN. J Comp Physiol Psychol. 1976;90:747–54.

Herman-Giddens ME, Slora EJ, Wasserman RC, Bourdony CJ, Bhapkar MV, Koch GC, et al. Pediatrics. 1997;99:505–12.

Kemnitz JW, Gibber JR, Lindsay KA, Eisele SG. Horm Behav. 1989;23:235–50.

Kendler KS, Walters EE, Neale MC, Kessler RC, Heath AC, Evans LJ. Arch Gen Psychiatry. 1995;52:374–83.

Killen J, Hayward C, Hammer L, Wilson D, Miner B, Taylor CB, et al. Am J Disord Child. 1992;146:323–5.

Klump KL, Burt SA, Sisk CL, Keel PK. Psychol Med. 2010;40:1745–1753.

Klump KL, Burt SA. Twin Res Hum Genet. 2006;9:971–7.

Klump KL, Culbert KC. Curr Dir Psychol Sci. 2007;16:37–41.

Klump KL, McGue M, Iacono WG. J Abnorm Psychol. 2000;109:239–51.

Klump KL, Wonderlich S, Lehoux P, Lilenfeld LRR, Bulik CM. Int J Eat Disord. 2002;31:118–35.

Klump KL, McGue M, Iacono WG. Int J Eat Disord. 2003;33:287–92.

Klump KL, Gobbrogge KL, Perkins PS, Thorne D, Sisk CL, Breedlove SM. Psychol Med. 2006;36:539–46.

Klump KL, Burt SA, McGue M, Iacono WG. Arch Gen Psychiatry. 2007a;64:1409–15.

Klump KL, Perkins PS, Burt SA, McGue M, Iacono WG. Psychol Med. 2007b;37:627–34.

Klump KL, Keel PK, Culbert KM, Edler C. Psychol Med. 2008;38:1749–57.

Klump KL, Suisman JS, Burt SA, McGue M, Iacono WG. J. Abnorm. Psychol. 2009;118:797–805.

Lutchmaya S, Baron-Cohem S, Raggat P, Knickmeyer R, Manning J. Early Hum Dev. 2004;77:23–8.

Madrid JA, Lopez-Bote C, Martin E. Physiol Behav. 1993;53:329–35.

Manning JT, Scutt D, Wilson J, Lewis-Jones DI. Hum Reprod. 1998;13:3000–4.

Ostlund H, Keller E, Hund YL. Ann NY Acad Sci. 2003;1007:54–63.

Plomin R, DeFries JC, McClearn GE, McGuffin P. Behavioral Genetics. 4th ed. New York: Worth; 2001.

Raevuori A, Kapiro J, Hoek HW, Sihvola E, Rissanen A, Keski-Rahkonen A. Am J Psychiatry. 2008;165:1604–1610.

Reichborn-Kjennerud T, Bulik CM, Kendler KS, Roysamb E, Tambs K, Torgersen S, et al. Int J Eat Disord. 2004;35:123–32.

Rowe R, Pickles A, Simonoff E, Bulik CM, Silberg JL. Biol Psychiatry. 2002;51:172–82.

Ryan BC, Vandenbergh JG. Neurosci Biobehav Rev. 2002;26:665–78.

Silberg JL, Bulik CM. J Child Psychol Psychiatry. 2005;46:1317–26.

Wade GN. Physiol Behav. 1972;8:523–34.

Part II
General and Normative Aspects: Sensory

Chapter 4
Cerebral Activity to Visual Presentation of Food

Jyrki T. Kuikka

Keywords Attention • Block design • Eating disorder • fMRI • Food • Statistical parametric mapping

Abbreviations

ACC	Anterior cingulate cortex
BMI	Body mass index
BOLD	Blood oxygen level-dependent. Changes in BOLD contrast originate from changes in the amount of deoxyhemoglobin present in tissue. These changes are measured by means of an MR scanner.
CBF	Cerebral blood flow
CBV	Cerebral blood volume
$CMRO_2$	Cerebral metabolic rate of oxygen
EEG	Electroencephalography
FDR	False discovery rate. FDR is a thresholding method to correct the amount of false positive areas (voxels) in the region of interest.
fMRI	Functional magnetic resonance imaging
FWHM	Full width half maximum. FWHM is a measure of the spatial resolution.
MEG	Magnetoencephalography. MEG is closely related to EEG in which the magnetic signals are generated by electric current with neurons. MEG offers millisecond temporal resolution but the spatial localization may be ambiguous
MNI	Montreal Neurological Institute
PCC	Posterior cingulate cortex
PET	Positron emission tomography
ROI	Region of interest
SPECT	Single-photon emission tomography
SPM	Statistical parametric mapping. A statistical method to increase reliability and reproducibility of fMRI image findings
T	Tesla. Tesla is the unit of the strength of magnetic field

J.T. Kuikka (✉)
Imaging Center, Kuopio University Hospital, FIN-70211 Kuopio, Finland
e-mail: jkuikka@uku.fi

4.1 Introduction

Food intake is fundamental for survival, and efficient brain processing of information related to this vital function is essential. Potential food sources are perceived through multiple sensory systems and are evaluated based on associative learning (Kringelbach 2004). Food-related disorders, especially obesity, have become common and worldwide problems today. World Health Organization has named obesity as one of the most important preventable health problems in the world today. Research on the central mechanisms regulating food intake can provide new insight to the understanding of mechanisms regulating eating and thereby contribute to the prevention and treatment of eating related disorders.

Positron emission tomography (PET) (Del Pagiri et al. 2002) and single-photon emission computer tomography (SPECT) (Karhunen et al. 1997) can be used for assessing blood flow changes and molecular level connectivity within the brain and body related to obesity and regulation of food intake but their temporal and spatial resolution for activation studies is poorer than that of fMRI (Ogawa et al. 1990; Belliveau et al. 1991; Kuikka et al. 1996; Frank and Kaye 2005; Riera et al. 2008). Moreover, repeated studies increase rapidly subject's radiation exposure. Next, we discuss fMRI studies only.

During recent years, there has been a growing interest to investigate the mechanisms related to regulation of food intake in humans (Kilgore and Yurgelun-Todd 2006; Cornier et al. 2007; Kaurijoki et al. 2008; Stoeckesl et al. 2008; Schienle et al. 2009). These studies have identified several cortical and limbic brain regions with apparent food-related functions in humans. Visual food stimuli have been shown to activate the prefrontal, orbitofrontal, and temporal cortices, cingulate, insula, striatum, and amygdala in the healthy human brain (Morris and Dolan 2001; Killgore et al. 2003; Uher et al. 2004; Kaurijoki et al. 2008; Stice et al. 2008; Siep et al. 2009).

However, it is not in all cases known whether the cerebral activations, observed so far, are specific for processing of food-related information, or whether they are also related, for example, to the complexity of the visual stimuli used in the experiments. Moreover, food is a motivational stimulus and closely related to emotions (Kringelbach 2004). The observed activations might thus have also been associated with emotional processing.

4.2 Functional Magnetic Resonance Imaging (fMRI)

4.2.1 Blood Oxygen Level-Dependent Imaging

Functional magnetic resonance imaging (fMRI) has advanced to be the major tool for the assessment of brain function such as blood flow and blood volume changes using the venous blood oxygenation level-dependent (BOLD) magnetic resonance contrast (Ogawa et al. 1990; Norris 2006) (Table 4.1). Since its initial introduction in 1990 for fMRI about 87,000 studies have been published during the first 20 years to record brain activation in both humans and animals.

Changes in BOLD contrast originate from changes in the amount of deoxyhemoglobin, which act as an endogenous paramagnetic contrast agent (Pauling and Coruell 1936; Ogawa et al. 1990). BOLD signal is generally measured by means of T2*-weighted MRI sequence (Norris 2006). The amount of deoxyhemoglobin present depends on three physiological parameters:

1. The local rate of metabolic consumption of oxygen ($rCMRO_2$)
2. The regional cerebral blood volume (rCBV)
3. The regional cerebral blood flow (rCBF)

Table 4.1 Key features of blood oxygenation level-dependent (BOLD) functional magnetic resonance imaging (fMRI)

1. The subject performs a task in the MR scanner while BOLD images of the whole brain are acquired every 1–3 s and hundreds of images are accumulated
2. A complete fMRI scan lasts around 2–10 min depending on the paradigm
3. fMRI has a spatial resolution as low as 1 mm
4. The images show small changes in the brightness (signal intensity) levels of certain brain areas during the task
5. These brightness changes are compared to another moment when that task is not executed or another condition
6. A subtraction principle is applied between the images of two conditions and any BOLD signal difference above the statistical level chosen represents the brain region involved in the performance of that task
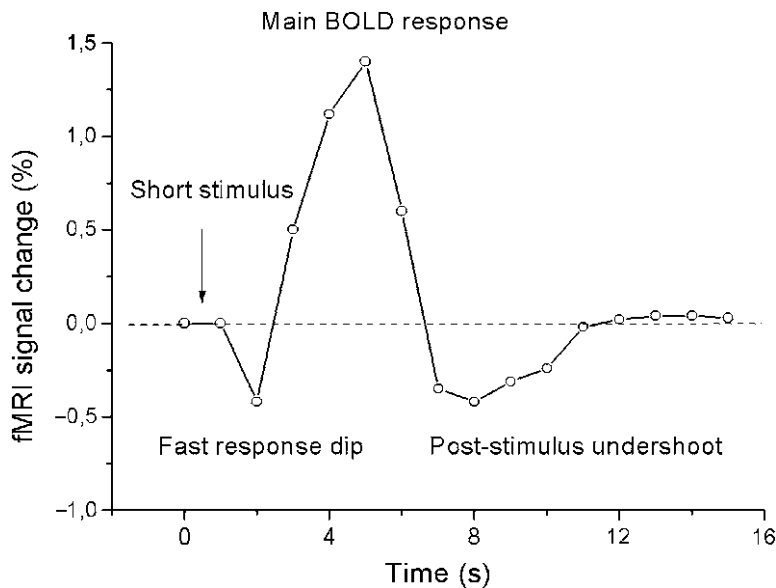
Fig. 4.1 Time course of the blood oxygenation level-dependent (BOLD) response to a haemodynamic short duration stimulus. The BOLD effect peaks 3–4 s after the stimulus and signal takes almost a minute to return to baseline

An increase in neural activity will lead to an increase in all three of these parameters (Fig. 4.1). The current hypothesis is that activation-induced blood flow changes are driven by synaptic input to a brain region. The increase in rCBF is to satisfy an increased demand for oxygen, and that the increase in rCBV is driven by the increase in rCBF. However, we must realize that observed fMRI signal intensity changes are only indirect consequences of synaptic inputs to the regions of interest (ROIs).

Popularity of BOLD studies is based on both wide availability of MRI scanners and safety of the studies in healthy subjects since they can be performed without harmful side effects and without radiation exposure, making repeated studies of the same subjects readily feasible (Norris 2006). The spatial resolution of BOLD fMRI is limited to about 3 mm. The sensitivity of BOLD fMRI depends on main magnetic field strength being order of 1–5% when measured in a scanner of 1.5 T and 2–10% in a scanner of 3.0 T. The temporal resolution is in second scale (1–3 s), as a comparison electroencephalography (EEG) and magnetoencephalography (MEG) enable one to study the living cortical areas within a millisecond (ms) scale but with much poorer spatial resolution (in cm-scale) than fMRI (in mm-scale).

4.2.2 Motion and Movement

A major potential confound for all imaging studies is the object's motion due to the subject's involuntary movement, eyes motion as well as respiratory and cardiac changes during the scan. Motion can introduce a number of artifacts and image blurring of varying degrees and severity. Most current methods rely on realignment to correct for motion, which is capable of correcting interscan motion at the subvoxel level (Norris 2006). There are several freely available programs for motion correction (Statistical parametric mapping, SPM; prospective acquisition correction, PACE; automatic image registration, AIR) (Norris 2006).

Artifacts, image blurring, and pitfalls can arise at any step in the activation fMRI study and can be grouped into issues related to the study design, the subjects, the fMRI protocol, and the statistical analysis (Amaro and Barker 2006).

4.3 Procedure

4.3.1 Subject's Preparation for fMRI

All subjects have to have normal or corrected-to-normal vision (with contact lenses) and no magnetic material in their body. Depending on the aim of the study, the background information, e.g., weight, body mass index (BMI), handiness, eating history, psychiatric diagnosis (including claustrophobia, panic disorder), neurological illnesses, and medication of the subjects should be known. The subjects are usually prohibited from consuming any food, cigarettes, coffee, tea, and cola drinks at least for 2 h before the fMRI session. Whenever possible, all scans should be conducted at about the same time of the day for the all subjects. Avoid all shortcomings between and among the study groups. The size of the study groups depends on many things but for the statistical analysis each group should have at least 12 subjects. The study protocol and scanning process should be carefully explained to the subjects or even trained before the study.

4.3.2 Tasks and Paradigms

It is not known whether the cerebral activations, observed so far, are specific for processing of food-related information, or whether they are also related, for example, to the complexity of the visual stimuli used in the experiments. Moreover, food is a motivational stimulus and closely related to emotions (Kringelbach 2004). The observed activations might thus have also been associated with emotional processing. Therefore, to investigate cerebral responses to visual food stimuli relative to responses evoked by nonfood, stimuli have to be matched with respect to their visual complexity. In addition, the subjects could be presented emotionally different pictures to examine whether the responses evoked by the food stimuli were specific to food or were influenced by the emotional content of the stimuli.

The experiment typically consists of the presentation of several visual activation conditions such as: food, nonfood, and emotionally different conditions (e.g., neutral, pleasant, and unpleasant) (Fig. 4.2). A low-level baseline, a blank gray screen, should be included in the experiment in case direct comparisons of different conditions would not yield specific activations. All pictures
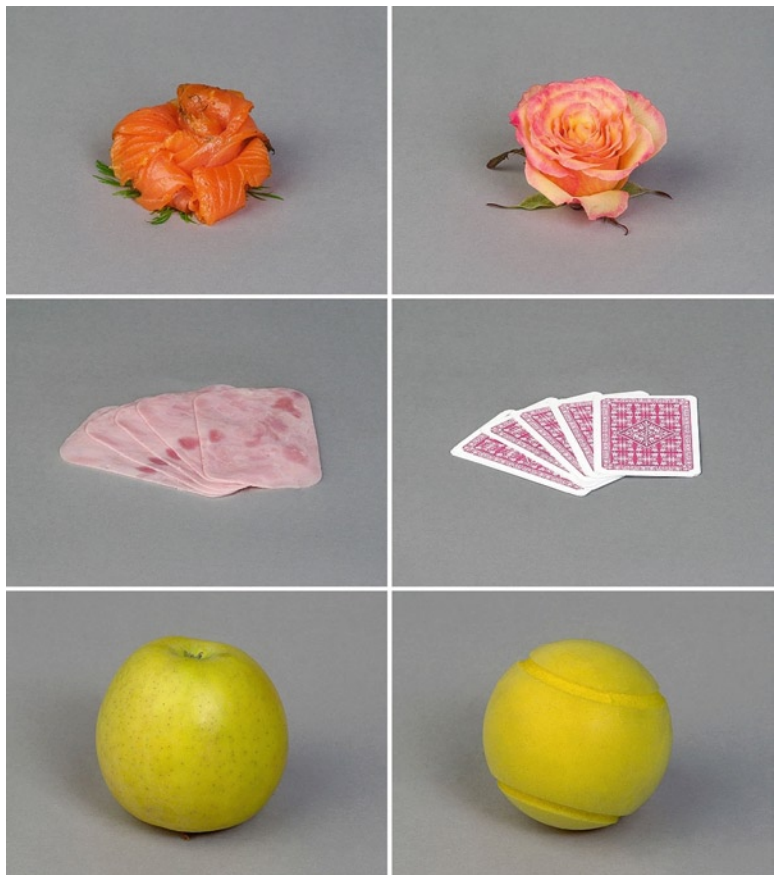
Fig. 4.2 Examples of food and nonfood picture pairs. *Top*: cold smoked salmon versus a rose, centre: slices of ham versus playing cards and bottom: an apple versus a tennis ball. The photograph of each object was presented on a gray background and nonfood items were matched for color, luminance, and visual complexity with the food items (Reprinted from Kaurijoki et al. (2008). With permission of Wiley-Blackwell)

Table 4.2   Key features of food and nonfood pictures

1.   The most important topic here is that the food and nonfood images are similar in texture, color, background, and visual complexity.

should present familiar and well-known items on a neutral, e.g., gray background (Table 4.2). The motivational salience of the pictures, e.g., the caloric content of food pictures, can also be manipulated.

The neutral, pleasant, and unpleasant pictures can be selected, for example, from the International Affective Picture System (IAPS) (Lang et al. 2001). To confirm that the pictures have the expected emotional valence, volunteers of the same age and gender as the study subjects should evaluate these pictures. The food and nonfood pictures should also be pre-evaluated by the volunteers to confirm that the pictures are recognized accordingly. To minimize activation related to eye-movements, the subjects are instructed to visually fixate a central cross on the screen.

4.3.3 Block Design

In our study (Kaurijoki et al. 2008), a two-conditions block design (Friston et al. 1999) was used (Table 4.3) in which each condition (food, nonfood, neutral, pleasant, unpleasant, and control) was shown in six blocks of nine pictures in the central visual field (horizontal visual angle 9.7°, vertical 7.7°). Each condition consisted thus of 54 pictures and each picture was shown only once (Fig. 4.3). Each image was shown for 1 s, followed by a blank gray screen for 2 s. The order of the blocks was counterbalanced. The interval between the blocks was 12 s to allow recovery of the cerebral blood flow from the effects of the previous block. Using Presentation 0.05 software (Neurobehavioral Systems, Inc., San Francisco, CA, USA), the stimuli are displayed on a rear-projection screen placed at the foot of the MR scanner bed. Subjects view this screen from within the bore of the magnet in a mirror placed on the head coil. The computer that controls the stimulus display is triggered by the scanning sequence.

Before the experiment, subjects were informed that various types of pictures would be shown during the scan. The pictures were, however, not specified in more detail. In addition, subjects were shown two examples of the visual stimuli not used in the experiment, as well as a baseline and target

Table 4.3 Key features of two conditions block design

1. The block design is the most efficient paradigm for studying activated areas, for blocks of stimulation allows more time to the BOLD signal to build up
2. The use of this block design has lead to much criticism related to the neuropsychological drawbacks but its increased statistical power still makes it a most valuable technique
3. BOLD-based fMRI can never match the temporal resolution (ms) of EEG or MEG

Fig. 4.3 An example of a block design to show pictures during functional magnetic resonance imaging (fMRI) scan. The order of the blocks is counterbalanced. Each stimulus condition is shown in six blocks of nine pictures, so that each condition consists of 54 images (Unpublished data of Kaurijoki et al. (2008))
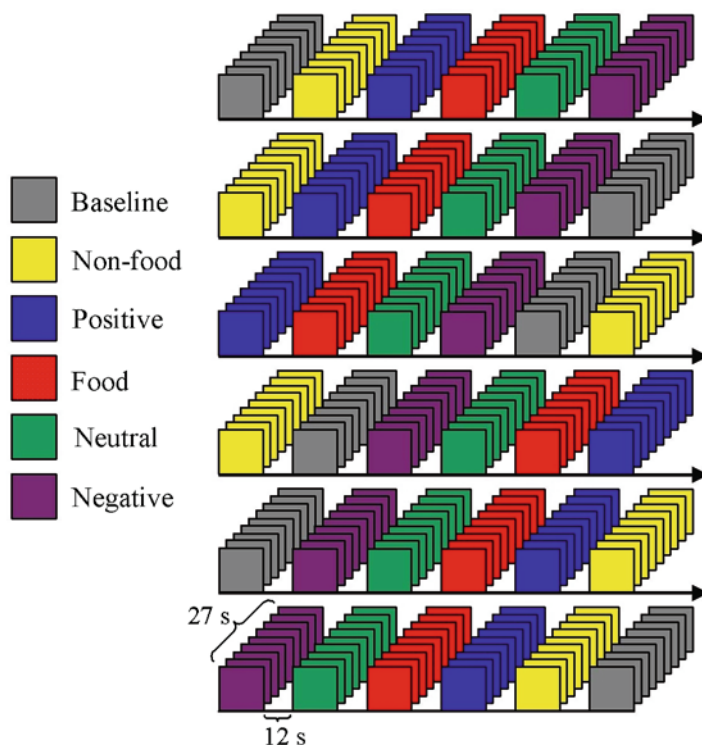
picture. The target which was shown six times over the whole experiment was a neutral picture from the IAPS, and was included into the experiment for monitoring that subjects were awake during the scan. The presentation of the target picture was randomized and located between the blocks so that one block of each condition is followed by the target picture. Subjects were instructed to attend to all stimuli, avoid head movements, focus on the fixation cross in each picture, and press a button when detecting the target picture.

4.3.4 Assessment of Affect

Positive and negative effects have different effects on activation of specific brain areas while undergoing fMRI study. Therefore, post-scanning ratings of the pictures used in stimuli should be done to measure the subject's experience of the emotional content of the picture. This could be performed, e.g., memory and intensity rating test by showing the fMRI stimuli pictures one by one on a computer monitor and to ask the subjects to judge the emotional valence of each picture by, e.g., on a 7-point scale (1 = very pleasant, 2 = pleasant, 3 = slightly pleasant, 4 = neutral, 5 = slightly unpleasant, 6 = unpleasant, 7 = very unpleasant) (Kaurijoki et al. 2008). If also new previously unshown pictures are presented, the test can also be used as an indirect measurement of the subjects' ability to recognize the objects. Subjects judge then whether or not they have seen the presented picture during the scan, e.g., by reporting if their judgment is based on a distinct recollection of having seen the picture, a less certain feeling of familiarity, or on a distinct certainty of not having seen the picture.

4.4 Data Analysis

In our study (Kaurijoki et al. 2008) data was analyzed using Statistical Parametric Mapping software (SPM; Wellcome Department of Cognitive Neurology, London, UK; http://www.fil.ion.ucl. ac.uk) running on MATLAB (The Mathworks, Inc., Natick, MA, USA). Movement-related artifacts were removed by realigning the scans to the middle scan of the time series and resliced using sinc interpolation. Differences in acquisition time of slices were corrected to make the data on each slice correspond to the same point in time. Functional images were then co-registered to structural T1-images. In order to spatially normalize images, thus facilitating intersubject averaging, the data from different subjects have to be transformed into a standard anatomic space. Therefore, the functional images were normalized using the MNI template supplied with SPM to the standard stereotactic space. Finally, to conform to the Gaussian field theory, and to increase the signal-to-noise ratio data were smoothed with an isotropic Gaussian kernel with full width at half maximum (FWHM) of 8 mm.

The hemodynamic response was modeled with a fixed-response box-car function with additional temporal derivates. Low-frequency confounds were excluded from the model with a high-pass filter of twice the experimental run's length. Variations in global signal intensity were not removed. The six realignment parameters for each run were included in the model as covariates, to account for undesired effects of head movement.

In the analysis at single subject level, the following linear contrasts were specified and t-contrasts were calculated: (1) food > nonfood and (2) nonfood > food. In the group level analysis, the relevant contrasts of parameter estimates from the single subjects were entered into a one-sided *t*-test to analyze the mean of group observations using a random-effects approach. A correction of multiple

comparisons was based on the false discovery rate (FDR) (Genovese et al. 2002) at the significance level of $P \leq 0.01$.

Clusters smaller than ten contiguous voxels ($10 \times 2 \times 2 \times 2$ mm $= 80$ mm³) in the combined group image were excluded from the analysis. The SPM (Bellgowan et al. 2003) maps were displayed on an average template brain in the standardized coordinate space [x, y, z in space of Montreal Neurological Institute (MNI) template] within SPM. Active brain regions were specified using the Talairach and Tournoux (1988) after adjustment (www.mrc-cbu.cam.ac.uk/Imaging/mnispace.html) for differences between MNI and Talairach coordinates. Posthoc analysis was performed using a region-of-interest (ROI) approach.

4.5 Cerebral Activity to Visual Presentation of Food in Humans

4.5.1 Food > Nonfood Visual Stimuli and Visualization of Genotypes

The neuroanatomical sites affected by food versus nonfood stimuli depends on several aspects such as genetic, eating behavior, hunger, satiety, study design, etc., and so far results are often spread and partly controversial.

Some examples of recent studies about the cerebral activity to the visual presentation of food in humans are summarized next (Table 4.4).

The main interest in the study of Kaurijoki et al. (2008) was the cerebral reactivity to pictures of food versus nonfood and their links to certain well-known, potentially food-related genetic polymorphisms. Therefore, only the food-related comparisons between the various conditions are presented. In addition, to rule out the possible contribution of differences in the visual complexity among the different conditions, the same comparisons are also presented for the visually matched nonfood stimuli. As a result, the comparison between the food and nonfood stimuli conditions (food>nonfood; Fig. 4.4) showed a significant activation in the left posterior cingulate (PCC), left anterior cingulate (ACC) cortices, and left supramarginal gyrus. No significantly activated areas were found in the comparison of nonfood>food.

The individual analysis of the results of this study also suggests a possible genetically driven variation in the cerebral activity to visual presentation of food (Kaurijoki et al. 2008). In the comparison between food and nonfood conditions, the genotype groups of the serotonin transporter regulatory region polymorphism (5-HTTLPR) showed different mean signal intensities of the left PCC activity ($P < 0.01$). This region probably mediates interactions of food-related emotional and memory processes. Subjects homozygous for the long allele (L/L-genotype) exhibited greater left PCC activity in comparison to food>nonfood compared with short allele (L/S and S/S-genotype; Fig. 4.5). These preliminary data suggest that vulnerability for overeating and obesity may even be enhanced by the presence of L/L genotype.

Table 4.4 Key features of data analysis

1. A major component of the noise in fMRI studies is physiological in origin
2. Group studies should be smoothed with a filter of about 10 mm in width to allow for intersubject variations in the anatomy
3. Both a region of interest (ROI) and a whole-brain voxel-based analysis with individual ratings of appetite, arousal, etc. should be included
4. Activated regions are generally presented in Talairach x-, y-, and z-coordinates
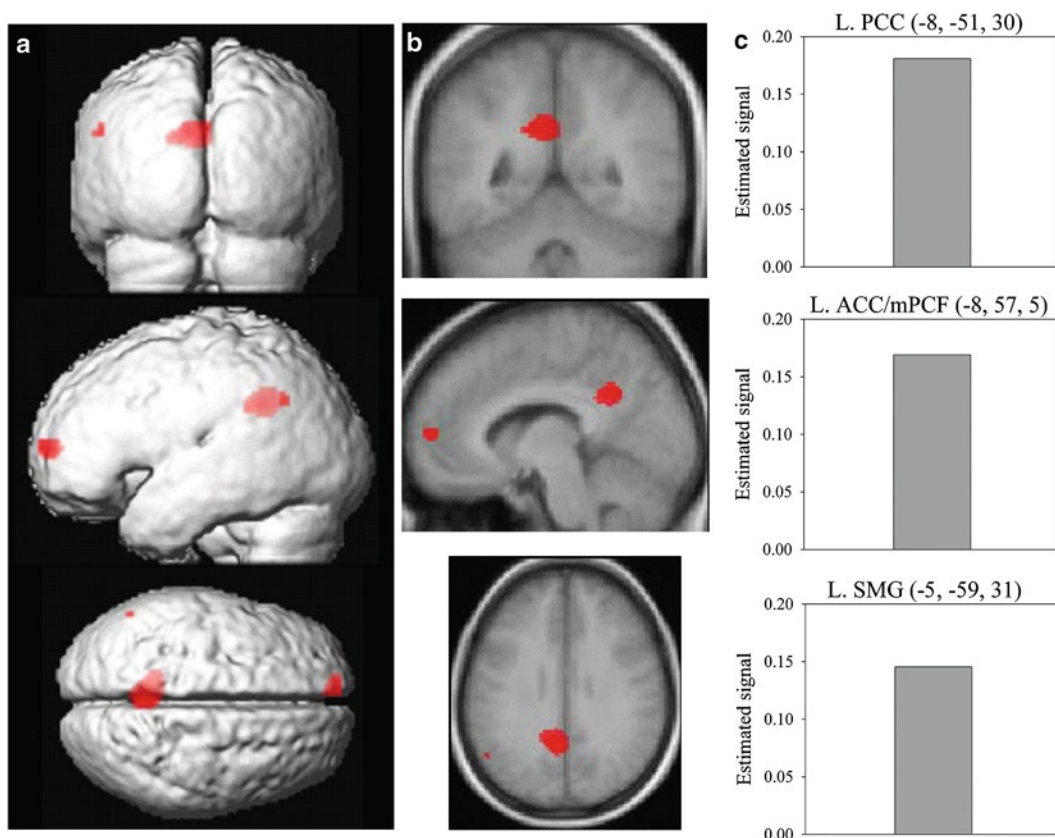
Fig. 4.4 Brain regions activated during the food when compared with nonfood pictures. (**a**) Render images of the coronal view (*top*), left hemisphere (*center*), and transaxial view (*bottom*), and (**b**) coronal, sagittal, and transaxial slices showing the location of increased activation superimposed on a mean anatomical image of the 28 subjects. (**c**) Parameter estimates for the local maxima of the left posterior cingulate (PCC) and left anterior cingulate cortices/ medial prefrontal cortices (ACC/mPCF) and the left supramarginal gyrus (SMG) activations in the food > nonfood comparison (Reprinted from Kaurijoki et al. (2008). With permission of Wiley-Blackwell)

4.5.2 High- and Low-calorie Food > Nonfood Visual Stimuli

Killgore and Yurgulun-Todd (2006) examined whether affect ratings predicted regional cerebral responses to high- and low-calorie food pictures among normal-weight adult women. Positive and negative affect had different effects on appetite-related regions depending on the calorie content of the food images. When viewing high-calorie images, positive affect was associated with increased activity in satiety-related regions (lateral orbitofrontal cortex), but when viewing low-calorie food, affect was associated with increased activity in hunger-related regions (medial orbitofrontal cortex and insular cortex).

4.5.3 Food > Nonfood Visual Stimuli While Fasting > 12 h

St-Onge et al. (2005) employed fMRI to isolate cortical sites involved in the appreciation of food and nonfood pictures in healthy, normal-weight, and fasting individuals. Food, and nonfood images were presented to subjects both visually and tactilely. Brain regions that were significantly activated to a

Fig. 4.5 Association between genotype and brain activation. Effects of serotonin transporter promoter regulatory region polymorphism (5-HTTLPR) variation on the response for the fMRI signal intensity change food > nonfood in the left posterior cingulate cortex (PCC). The subjects with two copies of the long allele variant have the strongest activation (Reprinted from Kaurijoki et al. (2008). With permission of Wiley-Blackwell)
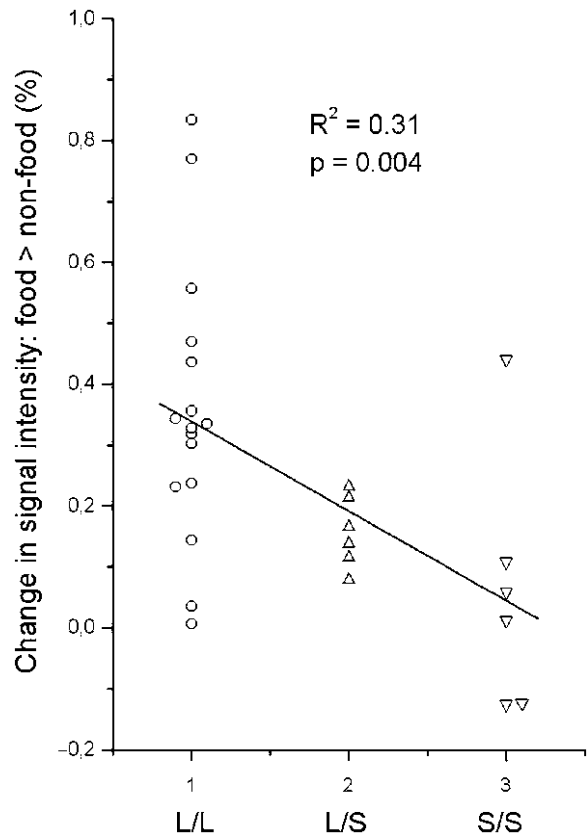
greater extent during the presentation of foods compared with nonfood items included the anterior cingulate cortex, superior temporal gyrus, parahippocampal gyrus, hippocampus, and the insula. This study as well as many others, suffer that in a group analysis alone, all findings are not necessarily observed in all subjects.

4.5.4 Cerebral Activity in Hunger and Satiety

Führer et al. (2008) explored brain activity during hunger versus satiety using visual simulation. During the hunger condition, significantly enhanced brain activity was found in the left striatum and extrastriatal cortex, the inferior parietal lobe, and the orbitofrontal cortex. Stimulation with food images was associated with increased activity in insula, the left striatum, and extrastriatal cortex, and the anterior midprefrontal cortex. A significant interaction in activation pattern between the states of hunger and satiety and stimulation with food and nonfood images was found for the left anterior cingulate cortex, the superior occipital sulcus, and in the vicinity of the right amygdala.

They emphasized that central nervous system activation is not only altered with hunger and satiety but that food and nonfood images have also specific effects on regional cerebral activity if exposure takes place in different states of satiety (Führer et al. 2008; Chechlacz et al. 2009).

4.6 Applications to Other Areas of Health and Disease

The primary field of fMRI applications remains the cognitive neurosciences, but several applications are also found in surgical treatment planning (Vlieger et al. 2004), vascular diseases (Sharma et al. 2009) and preclinical studies (Marota et al. 2000).

4.7 Conclusions

The imaging methods (fMRI, MEG, PET, and SPECT) for evaluating cerebral activity to visual presentation of food have been in use for a decade. The versatility of fMRI makes it a powerful tool and BOLD imaging has proven to have the capacity to objectively measure the response changes, despite the fact that the underlying mechanisms are still not fully understood. The increased sensitivity and specificity of higher-field (≥ 3 T) MRI systems will improve our understanding of the underlying mechanisms related to the regulation of food intake and that way also on the pathophysiology of eating disorders. Further studies on regional activation and connectivity, coupled with psychological observations of the particular affective processes involved, will improve our understanding of food-related disorders.

Summary Points

- The block design is the most efficient paradigm for studying activated areas. Blocks of stimulation allow more time to the BOLD signal to build up and thus statistical certainty between the task minus another condition increases.
- In healthy subjects, a stronger focus locates on the left hemisphere (such as anterior cingulate cortex, insula, medial prefrontal cortex, orbitofrontal cortex, and posterior cingulate cortex).
- The subjects with eating disorder exhibit greater activation in response to food pictures in a large number and usually bilateral regions than controls.
- The present results suggest the possible genetically driven variation in the response of the certain brain regions to visual presentation of food.
- However, the results are still very preliminary and heterogeneous due to the several confounding factors such as subjects' selection, their nutritional and hormonal status, study protocol, statistical settings, etc.

References

Amaro Jr E, Barker GJ. Brain Cogn. 2006;60:220–32.

Bellgowan PS, Saad ZS, Bandettini PA. Proc Natl Acad Sci USA. 2003;100:1415–9.

Belliveau JW, Kennedy Jr DN, McKinstry RC, Buchbinder BR, Weiskoff RM, Cohen MS, et al. Science. 1991;254:716–9.

Chechlacz M, Rotshtein P, Klamer S, Porubská K, Higgs S, Booth D, et al. Diabetologia. 2009;52:524–33.

Cornier AM, von Kaenel SS, Bessesen DH, Tregellus JR. Am J Clin Nutr. 2007;86:965–71.

Del Pagiri A, Gautier JF, Chen K, Salbe AD, Ravussin E, Reiman E, et al. Ann NY Acad Sci. 2002;967:389–97.

Frank GK, Kaye WH. Nucl Med Biol. 2005;32:755–61.

Friston KJ, Zarahn E, Josephs O, Henson RN, Dale AM. Neuroimage. 1999;10:607–19.

Führer D, Zysset S, Stumvoll M. Obesity. 2008;16:945–50.

Genovese CR, Lazar NA, Nichols T. Neuroimage. 2002;15:870–8.

Karhunen LJ, Lappalainen RI, Vanninen EJ, Kuikka JT, Uusitupa MI. Brain. 1997;120:1675–84.

Kaurijoki S, Kuikka JT, Niskanen E, Carlson S, Pietiläinen KH, Pesonen U, et al. Clin Physiol Funct Imaging. 2008;28:270–6.

Killgore WDS, Yurgelun-Todd DA. Int J Eat Disord. 2006;39:357–63.

Killgore WD, Young AD, Femia LA, Bogorodzki P, Rogowska J, Yurgelun-Todd DA. Neuroimage. 2003;19:1381–94.

Kringelbach ML. Neuroscience. 2004;126:807–19.

Kuikka JT, Belliveau JW, Hari R. Eur J Nucl Med. 1996;23:737–40.

Lang PJ, Bradley MM, Cuthbert, BN. International affective picture system (IAPS): instruction manual and affective ratings. In: The center for research in psychopathology. Gainesville: University of Florida; 2001.

Marota JJA, Mandeville JB, Weisskoff RM, Moskowitz MA, Rosen BR, Kosofsky BE. Neuroimage. 2000;11:13–23.

Morris JS, Dolan RJ. J Neurosci. 2001;21:5304–10.

Norris DG. J Magn Reson Imaging. 2006;23:794–807.

Ogawa S, Lee TM, Kay AR, Tank DW. Proc Natl Acad Sci USA. 1990;87:9868–72.

Pauling L, Coryell CD. Proc Natl Acad Sci USA. 1936;22:210–6.

Riera JJ, Schousboe A, Waagepetersen HS, Howarth C, Hyder F. Neuroimage. 2008;40:1436–59.

Schienle A, Schäfer A, Hermann A, Vaitl D. Biol Psychiatry. 2009;65:654–61.

Sharma N, Simmons LH, Jones PS, Day DJ, Carpenter TA, Pomeroy VM, et al. Stroke. 2009;40:1315–24.

Siep N, Roefs A, Roebroeck A, Havermans R, Bonte ML, Jansen A, Behav Brain Res. 2009;198:149–58.

Stice E, Spoor S, Bohon C, Small DM. Science. 2008;322:449–52.

Stoeckesl LE, Weller RE, Cook III EW, Twieg DB, Knowlton RC, Cox JE. Neuroimage. 2008;41:636–47.

St-Onge MP, Sy M, Heymsfield SB, Hirsch J. J Nutr. 2005;135:1014–8.

Talairach J, Tournoux P. Co-planar stereotaxic atlas of the human brain. Stuttgart, New York: Georg Thieme Verlag; 1988.

Uher R, Murphy T, Brammer MJ, Dalgleish T, Phillips ML, Ng VW, et al. Am J Psychiatry. 2004;161:1238–46.

Vlieger EJ, Majoie CB, Leenstra S, Den Heeten GJ. Eur Radiol. 2004;14:1143–53.

Chapter 5
Infant Visual Acuity and Relationships with Diet and Nutrition

Michelle P. Judge, Carol J. Lammi-Keefe, and Holiday Durham

Abbreviations

ACP	Acuity card procedure
ARASCO	Arachidonic acid single-cell oil
DHA	Docosahexaenoic acid
DHASCO	Docosahexaenoic acid single-cell oil
ERG	Electroretinogram
FPL	Forced-choice preferential looking
GPCR	G-protein coupled reaction
Kg	Kilogram
LCPUFA	Long chain polyunsaturated fatty acid
Mg	Milligrams
SCO	Single-cell oil
VEP	Visual evoked potential

5.1 Introduction

The visual system comprises a complex signaling system involving the retina, thalamus and primary visual cortex. In addition, other cortical regions are involved in the cognitive integration of visual information. Researchers have assessed the impact of long-chain polyunsaturated fatty acids (LCPUFA) on infant visual development by evaluating two main aspects of the infant's visual system; retinal development using electroretinogram (ERG) and visual processing at the level of the primary visual cortex. Cortical measures of grated visual acuity include sweep visual evoked potential (VEP) and behavioral assessments such as the forced-choice preferential looking (FPL). Of the grated acuity measures, VEP measures cortical response directly and has less inherent variability. However, behavioral acuity measures provide the most direct measure of what an infant actually perceives and normative data are well established for these procedures (Neuringer 2000).

M.P. Judge (✉)
School of Nursing, University of Connecticut, 231 Glenbrook Rd, Unit 2026, Mansfield, CT, USA
e-mail: Michelle.Judge@uconn.edu

Compared to other cells in the body, the retinal photoreceptors are known to have the highest content of the LCPUFA docosahexaenoic acid (DHA, 22:6 n-3) (Neuringer 2000). The gray matter in the visual cortex and multiple other cortical regions also have high levels of DHA. In rhesus monkeys, a diet deficient in LCPUFA during pregnancy impeded the accumulation of DHA in these tissues in the offspring. A 50% reduction of DHA in retinal tissue and 25% reduction in cerebral cortex DHA were reported for the offspring of rhesus monkeys fed a diet deficient in α-linonenic acid (18:3, n-3) during pregnancy compared to controls (Neuringer et al. 1986). Linolenic acid is the precursor to along the biosynthetic pathway. Neuringer and colleagues also demonstrated that these deficient animals had lower visual acuity measured using preferential looking and a prolonged recovery time of the dark-adapted ERG after a saturating flash.

Behavioral methods for assessment of visual acuity have repeatedly shown that human infants have better visual function with the provision of DHA during the postnatal period (Birch et al. 1993a; Makrides et al. 1993, 1995; Carlson et al. 1996; Jorgensen et al. 1996; Hoffman et al. 2003). To date, there is one report (Judge et al. 2007) of improved infant visual acuity (assessed using the Acuity Card Procedure, ACP) related to maternal dietary DHA intake during pregnancy. Malcolm et al. used VEP (Malcolm et al. 2003a) and ERG (Malcolm et al. 2003b) to assess visual acuity related to maternal DHA supplementation, but no relationship was apparent. There was no significant treatment effect for ERG in the first postnatal week (Malcolm et al. 2003a) or VEP at 2.5 or 6.5 months of age (Malcolm et al. 2003b).

Pregnant women in the USA and Canada have DHA intakes below the current recommended amount of 200 mg/day for optimal fetal development (Koletzko et al. 2008; Lewis et al. 1995; Innis and Elias 2003; Loosemore et al. 2004; Denomme et al. 2005). As the developing fetus has extremely limited capacity for deriving DHA from the 18 carbon precursor, the fetus is clearly at risk for DHA deficiency when maternal DHA intake is low. Given this risk for deficiency, marine, egg-phospholipid, and single-cell oils (SCO) have been developed and explored for maternal and infant supplementation. Increased efforts toward community-based educational programs targeting women of child-bearing age with the goal of increasing DHA intake are recommended. Interruptions in visual development can delay the achievement of other developmental milestones with important long-term implications. This chapter will outline the contemporary research related to infant visual development, contrast assessment methodologies of visual acuity, and explore dietary factors that are fundamental to neurodevelopment.

5.2 Neuroanatomy of the Visual System

The cerebral cortex is comprised of two distinct tissue layers, gray and white matter. The cortex surrounds the entire perimeter of the brain and comprises approximately 80% of the volume of the human brain (Kolb and Whishaw 2003). Neuronal cell bodies are found primarily in the gray matter. The white matter of the brain is comprised primarily of the myelinated nerve axons. Different areas of the cortex are responsible for receiving and processing stimuli. The four functional areas of the cerebral cortex include: motor, sensory, visual and auditory. The primary functional areas of the cerebral cortex receive initial sensory information and the secondary and tertiary areas are responsible for association and processing. Visual information goes to the primary visual cortex and processing related to assessment of shape, color and categorization occur in secondary and tertiary visual areas. These secondary and tertiary areas, include, motor, sensory and auditory cortical areas; all communicate with central brain structures for further processing.

5.3 The Visual System

Vision and behavioral responses to visual stimuli rely on a complex system of communication between the retina, thalamus and multiple regions of the cerebral cortex. Visual processing is initiated when the photoreceptors of the retina receive a visual stimulus that triggers signal transduction. The impulse travels down the optic tract where signal transductions are sent to the opposite cerebral hemisphere after crossing at the optic chiasm (Fig. 5.1). After passing the optic chiasm, the optic tract sends the signal to the lateral geniculate nucleus of the thalamus, which relays visual signaling to the primary visual cortex. When visual information is sent to the primary visual cortex it is disseminated to various cortical areas by two main pathways, the dorsal and ventral streams, for higher cortical processing. The dorsal stream projections are sent to the parietal lobe to process information pertaining to location and movement (Zigmond et al. 1999). The ventral stream projects to the temporal lobe where more integrative processing occurs, e.g., object and facial recognition (Fig. 5.2). The process of facial recognition relating to memory is conducted primarily by the limbic system which involves the entorhinal cortex, hippocampus and amygdala.

At the level of the membrane, G protein-coupled receptor (GPCR) signal transduction occurs in the retina, brain, and nervous system and has been attributed to signaling pathways leading to visual and cognitive function (Salem et al. 2001; Nui et al. 2004). G proteins are binding proteins that use neurotransmitters to collectively activate receptors (referred to as coupled activation) (Zigmond et al. 1999). Action of the neurotransmitter utilizes a second messenger system for the regulation of the
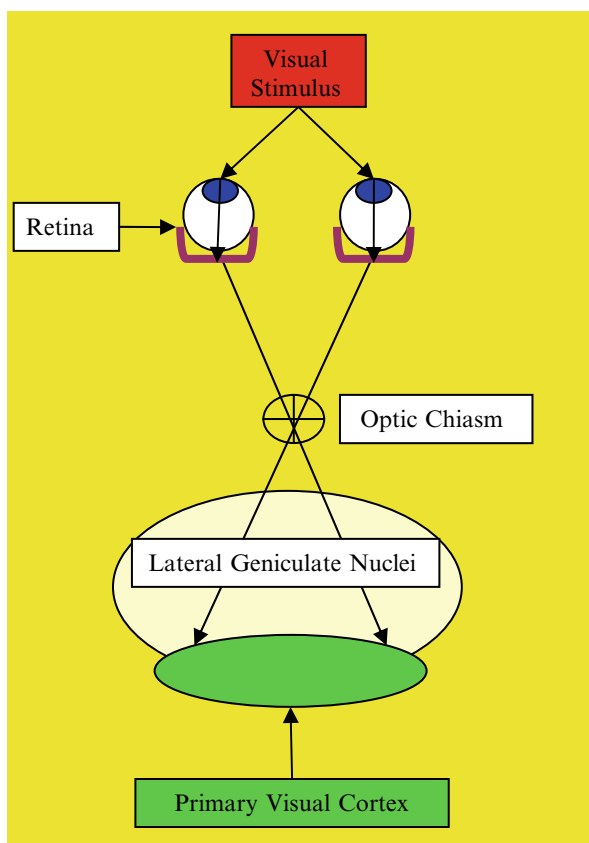
Fig. 5.1 Visual processing is initiated when the photoreceptors of the retina receive a visual stimulus that triggers signal transduction. The impulse travels down the optic tract where signal transductions are sent to the opposite cerebral hemisphere after crossing at the optic chiasm. After passing the optic chiasm, the optic tract sends the signal to the lateral geniculate nucleus of the thalamus, which relays visual signaling to the primary visual cortex
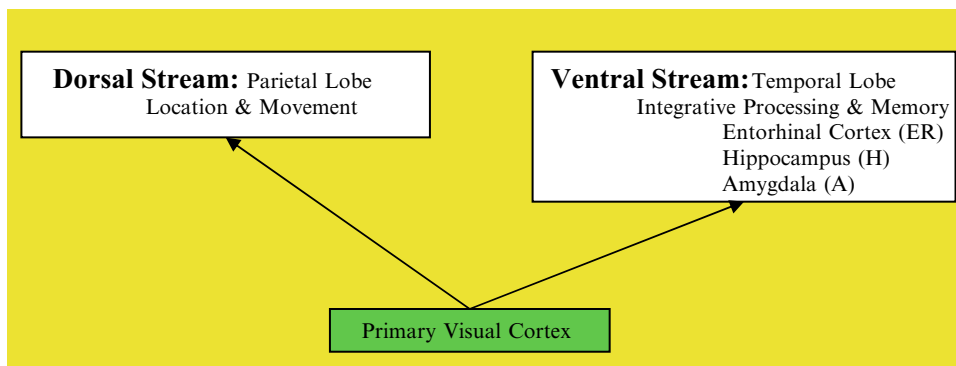
Fig. 5.2 When visual information is sent to the primary visual cortex it is disseminated to various cortical areas by two main pathways, the dorsal and ventral streams. The dorsal stream projections are sent to the parietal lobe to process information pertaining to location and movement. The ventral stream projects to the temporal lobe where more integrative processing occurs, e.g., object and facial recognition involving the entorhinal cortex (*ER*), hippocampus (*H*) and amygdale (*A*)

synthesis of protein kinases. The protein kinase produced as a result of the GPCR depends upon the neurotransmitter coupling the reaction (Zigmond et al. 1999). The specific type of protein kinase generated will initiate a phosphorylation reaction at the site of the ion channel causing excitation or inhibition. In the visual system, the rod photoreceptor is stimulated or hyperpolarized due to the GPCR involving the receptor metarhodopsin II (triggered by rhodopsin) coupled with transducin (the visual G protein) activating the production of the protein kinase phosphodiesterase (Nui et al. 2004). Fatty acid composition of the membrane bilayer has been shown to alter the rate of GPCR coupling (Niu et al. 2001; Mitchell et al. 2003; Nui et al. 2004). In those investigations GPCR coupling was reduced in the absence of DHA.

5.4 Testing and Assessment of the Visual System in Infants and Toddlers

A robust area of research with regard to nutrition and infant development is in the area of visual processing. The majority of the visual research linked to cognitive functioning has been reported during the past three decades (Kellman and Banks 1998). ERG, FLP and VEP are the three main techniques employed for the assessment of infant visual function. The consideration of visual acuity is important to the assessment of cognitive development. There is a need for good vision in order to perform optimally on other developmental tests. If an infant scores poorly on a given developmental test, results could be clouded by poor vision and be mistakenly classified as poor mental processing.

Measures of infant visual development have focused on two main aspects of the visual system; retinal development using ERG and visual processing at the level of the primary visual cortex. Cortical measures of grated visual acuity include sweep VEP and behavioral assessments such as FLP (Fig. 5.3). Of the grated acuity measures, VEP measures cortical response directly and has less inherent variability. However, behavioral acuity measures provide the most direct measure of what an infant actually perceives.

Fig. 5.3 Visual acuity measures. Outline of methodologies measuring cerebral response to visual stimuli: Central response as in visual evoked potential is a direct measure of cortical activity. Behavioral response methodologies like forced-choice preferential looking rely on movement or behavior associated with the cortical stimuli
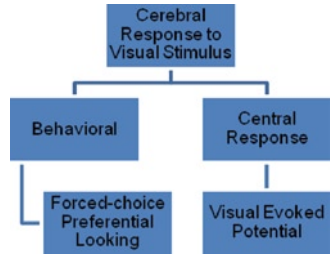
5.4.1 Electroretinogram

The ERG is a direct measure of the retinal response to a visual stimulus prior to reaching any of the cortical areas. In this procedure, electrodes placed on the cornea and surrounding eye tissue measure cellular electrical reactivity related to visual stimulus. ERG measurements therefore do not provide information regarding higher-level (i.e., cortical) visual processing (Table 5.1).

The work of Malcolm et al. (2003a) was focused on maternal DHA supplementation and infant ERG. These investigators supplemented pregnant women with fish oil from 15 weeks gestation to delivery. ERG assessments were performed in the early postnatal period circumventing the potential impact of infant feeding method or other socioeconomic variables. There were no significant differences in retinal reactivity between infants of mothers who were supplemented compared to controls. Maternal DHA concentrations were higher in the experimental group when compared to control, however the relationship between infant DHA status (umbilical cord blood) and maternal status was not significant. The finding that maternal supplementation of DHA was not related to infant status is contrary to the view that a relationship exists and may be related to the dose (200 mg DHA daily) chosen for the investigation. Wijendran et al. (2000) demonstrated a strong relationship between maternal and infant DHA status in pregnancies not complicated with gestational diabetes mellitus (GDM). In that investigation, in which control subjects were compared to women with GDM, the cord vein erythrocyte phospholipid DHA and arachidonic acid (wt%) were higher than the maternal phospholipid DHA and arachidonic acid in the control group with significantly positive correlations between maternal and fetal erythrocyte phospholipid for arachidonic acid and DHA ($r = 0.83$, $P = 0.003$; $r = 0.62$, $P = 0.04$, respectively) (Tables 5.2).

5.4.2 Forced-Choice Preferential Looking (FPL)

Assessment of visual acuity in infancy is complicated by the need for gathering nonverbal information. For this reason, forced-choice preferential looking procedures were developed in the area of visual acuity assessment to better understand and quantify the behavioral cues of infants. Preferential looking procedures use black and white stripes that are grated in a series of frequencies that correspond with the number of stripes per visual angle (commonly termed as cycles/degree) (Fig. 5.4).

Table 5.1 Key features of the electroretinogram

1. Electroretinogram measures retinal response to a visual stimulus.
2. Electrodes are placed directly on the cornea and surrounding eye tissue.
3. The eye is exposed to a visual stimulus, i.e. light.
4. Electrical reactivity of the eye cells is recorded and quantified.

This table lists the key facts of electroretinogram

Table 5.2 Key points on the role of DHA in maternal and infant nutrition

1. The essential fatty acid DHA has a central role in membrane fluidity and synaptic signaling impacting retinal reactivity and visual processing. DHA accumulates in high concentrations in specific regions of the brain, including cerebral cortex, synapses and retinal rod photoreceptors in mice, rats, baboons, and other mammals (Bazan and Scott 1990; Bowen and Clandinin 2002; Sarkadi-Nagy et al. 2003). DHA deficiency induced during the gestational period in rats significantly impact the amount of DHA that was incorporated into the neuronal growth cone (Auestad and Innis 2000).

2. The current recommendation for DHA intake during pregnancy that stemmed from an expert panel is 200 mg/day (Koletzko et al. 2008).

3. Single-cell oils (SCO) and marine sources are safe and can adequately provide DHA supplementation to both the mother and infant to prevent deficiencies. DHA deficiency can interfere with optimal infant visual and cognitive development.

This table lists key points relating to the role of DHA in maternal and infant health including adverse developmental outcomes associated with DHA deficiency during the gestational period, current intake recommendations for pregnant women, and safe supplementation sources
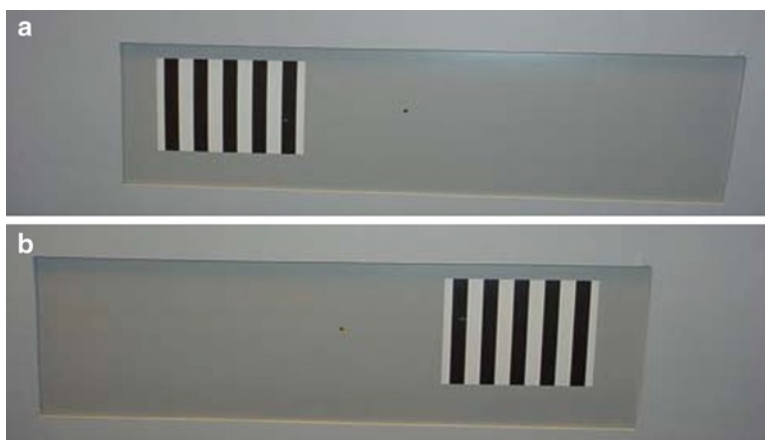
Fig. 5.4 Forced-choice preferential looking. In the Teller Acuity Card procedure, stripes are flipped from right (**a**) to left (**b**) with the location of the stripe unknown to the tester. Tester looks for a behavioral response (i.e., head movement toward the striped patch) (MPJ Original)

The point at which an infant is unable to resolve or see the contrasting stripes in a grated acuity procedure is considered the visual threshold. The term "forced choice" refers to the fact that the observer must choose or assess if the infant is looking to the left or right corresponding with the visual stimulus. The Teller Acuity Card Procedure (ACP) is a FPL procedure that has been standardized for use in a U.S. population. The ACP is portable and easily administered making it ideal in the research setting. As with any measure that relies on the interpretation of behavioral responses, there are a number of confounding variables that could skew findings. For example, a sleepy or fussy infant may lack interest in the visual stimulus and therefore alter results.

There are multiple published studies utilizing ACP/FPL procedures for the investigation of the relationship between DHA status and visual development in term infants (Innis et al. 1994, 1996, 1997; Carlson et al. 1996; Jorgensen et al. 1996; Auestad et al. 1997, 2001; Birch et al. 2000; O'Connor et al. 2001). Carlson et al. (1996) investigated term infants fed formula with varying levels of DHA. Using FPL, the supplemented group performed similarly to the group of infants fed human milk, which contains variable amounts of DHA depending upon the maternal diet and/or supplementation. Three of the studies in term infants relating to DHA status have shown statistically significant differences using ACP/FPL procedures (Birch et al. 1993a, b; Carlson et al. 1996; Jorgensen et al. 1996). Contrary to the findings of

Carlson et al., Auestad et al. (1997, 2001) reported no differences between supplemented and control groups using the ACP procedure. It is noteworthy to mention that the amount of DHA in these studies (Auestad et al. 1997, 2001) was considerably lower than those used in other studies (Birch et al. 1993a, b; Carlson and Werkman 1996; Jorgensen et al. 1996).

Only one investigation has reported on the impact of maternal DHA supplementation during pregnancy and infant visual acuity measured using the ACP. Judge et al. (2007) investigated the role of a DHA-functional food consumed during pregnancy on infant visual acuity at 4 and 6 months of age measured behaviorally using the ACP. In this randomized, longitudinal, double-blinded, and placebo-controlled trial, 30 pregnant women received either the DHA-functional food ($n = 16$) or the placebo ($n = 14$). There were significant main effects for visual acuity at 4 months of age ($P = 0.018$). The mean acuity score were, 3.8 ± 1.1 cycles/degree in the DHA group versus 3.2 ± 0.7 cycles/degree in the placebo group. At 6 months there was no group difference (Judge et al. 2007). Based on these results, it was concluded that DHA supplemented during pregnancy plays a role in the maturation of the visual system. This finding combined with evidence from studies conducted evaluating DHA supplementation during the postnatal period provide compelling evidence that DHA supplementation during pregnancy can have a profound impact on infant visual acuity development.

5.4.3 Visual Evoked Potential

VEP is a direct measure of cortical response and has less inherent subjectivity than the behavioral methods of visual acuity assessment. In this procedure, the infant is given an electroencephalogram by placing electrodes on the scalp to measure neural cell reactivity related to a visual stimulus. The majority of the studies performed using VEP have shown a positive relationship between DHA status and visual development (Makrides et al. 1993, 1995; O'Connor et al. 2001; Hoffman et al. 2003). Hoffman et al. (2003) investigated term infants who fed human milk for 4–6 months then fed either formula supplemented with DHA and arachidonic acid or control formula. Infants in the supplemented group had significantly better VEP than the control group. Makrides et al. (1995) also investigated the impact of DHA supplementation on visual processing in term infants and found that the supplemented and human milk–fed groups performed similarly on VEP measures and better than the group of infants who did not receive DHA. Similar findings have been reported for preterm infants. O'Connor et al. (2001) investigated preterm infants and reported significantly better VEP in DHA supplemented groups. In summary, the majority of studies to assess vision in term and preterm infants have demonstrated a positive association between processing and DHA status.

With regard to fetal development, Malcolm and coworkers (Malcolm et al. 2003a) examined maternal DHA supplementation and infant VEP. They supplemented pregnant women with fish oil from 15 weeks gestation to delivery. VEP assessments were performed at 2.5 and 6.5 months of age and there were no significant differences between infants of mothers who were supplemented compared to controls. This finding is in contrast to the study of visual acuity carried out by Judge et al. (2007).

5.5 Dietary Factors Influencing Visual Development

The last trimester of pregnancy is a critical interval for fetal neurological development. During this time DHA accumulates in neural tissue at an accelerated rate (Fox 1998). Reports of maternal DHA intake during pregnancy suggest that intakes are generally far below the recommended level of intake
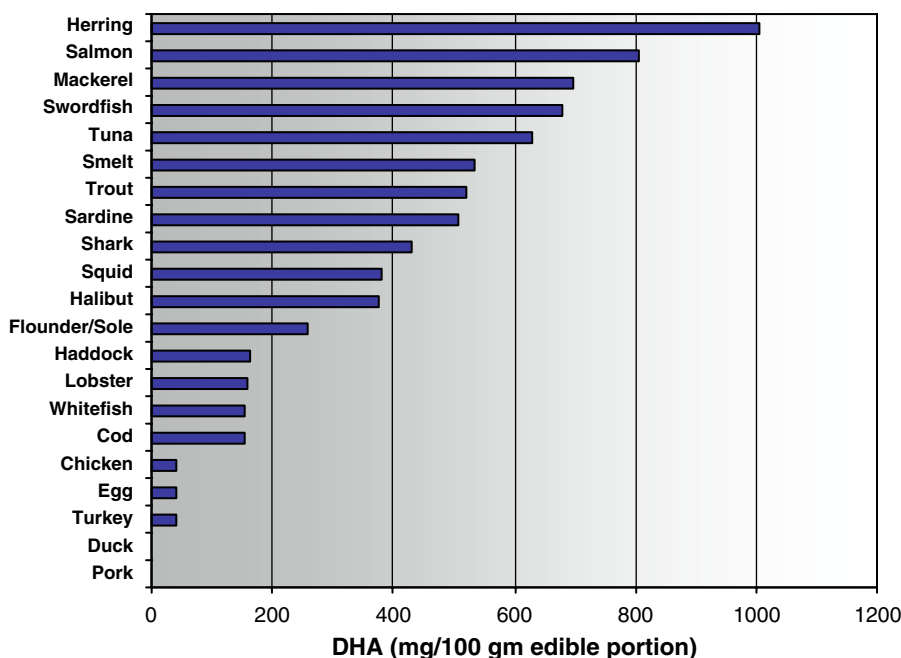
Fig. 5.5 Dietary sources of docosahexaenoic acid (mg DHA/100 g edible portion). Herring, salmon and mackerel are examples of cold-water marine fish that are a rich dietary source of DHA. Source: U.S.D.A., Human Nutrition Information Service

which suggests that many infants are at risk for associated impairments in development (Cheruku et al. 2002; Olsen and Secher 2002; Loosemore et al. 2004). Figure 5.5 outlines common food sources of DHA and points to cold water marine fish as the best dietary sources. It is unknown how concerns about contaminants in fish relate to low DHA intake during pregnancy (Cheruku et al. 2002; Olsen and Secher 2002; Loosemore et al. 2004).

Compounding the problem of reduced maternal intake of DHA, the overall intake of fatty acids in the n-6 family is typically high in western industrialized countries such as the U.S. High intake of n-6 fatty acids is related to an abundance of processed and fried foods containing plant oils with linoleic acid. Linolenic and linoleic both compete for the Δ-6 desaturase and high intake of linoleic acid can inhibit conversion of linolenic acid to DHA (Simopoulos et al. 2000). In 2008 a panel of experts led by Koletzko et al. (2008) concluded that the optimal level of DHA intake during pregnancy is 200 mg/day.

DHA has a central role in membrane fluidity and synaptic signaling in neural tissue and DHA accumulates in high concentrations in specific regions of the brain, including the cerebral cortex, synapses, and retinal rod photoreceptors in mice, rats, baboons, and other mammals (Bazan and Scott 1990; Bowen and Clandinin 2002; Sarkadi-Nagy et al. 2003). DHA deficiency induced during the gestational period in rats significantly reduce the amount of DHA that was incorporated into the neuronal growth cone (Auestad and Innis 2000).

In humans, autopsy studies have demonstrated the importance of DHA in brain tissue. Clandinin et al. (1980) investigated fatty acid components of the fetal brain during the third trimester. Brain tissue fat content was analyzed upon autopsy at varying stages of gestation to determine the pattern of fatty acid accretion during pregnancy. That study demonstrated that the accretion of the essential

fatty acids linolenic acid and linoleic acid (the metabolic precursors for DHA and arachidonic acid, respectively) were low during the last trimester and that there is a substantial accretion of DHA and arachidonic acid. Evidence shows the importance of DHA intake for both maternal and infant health (Table 5.2).

5.5.1 Dietary Sources of DHA for Supplementation

Three main sources of DHA and arachidonic acid oil that have been considered for use in infant formulas are: marine, egg phospholipid, and SCO. Commercially available maternal supplements contain either marine or SCO. There are potential drawbacks associated with the use of marine and egg phospholipid oils in infant formulas.

5.5.1.1 Marine Oil

Early studies focused on the addition of DHA and arachidonic acid to human infants via marine oil which indicated a potential negative impact on growth. This adverse outcome was attributed to the eicosapentaenoic acid content of the oil and a possible competitive inhibition of the n-6 pathway responsible for the production of arachidonic acid (Carlson et al. 1992a, b, 1993). Makrides et al. investigated DHA vis-a-vis marine oil supplementation in term infants and reported a significantly lower DHA erythrocyte concentration in the experimental group receiving marine oil compared to the breast milk or placebo group (Makrides et al. 1995).

An additional safety concern for marine oil supplementation is increased bleeding time related to the eicosapentaenoic acid, a reflection of cyclooxygenase production. Cyclooxygenase inhibits platelet aggregation and causes vasodilatation. Impaired platelet aggregation decreases blood clotting and resulting in increased bleeding time.

Scientific evidence exists that lends credence to the notion that marine oil supplementation does not have a negative impact on growth or bleeding time. In a series of studies, Carlson et al. investigated the safety and efficacy of supplementation with marine oils in preterm infants (Carlson et al. 1992a, b). In study I, infants were given a nasogastric bolus of marine oil in the dose of 750 mg/kg/day for 4 weeks. In study II, the marine oil was mixed into the formula at doses of 116 mg/kg/day (0.2% DHA and 0.3% eicosapentaenoic acid) and 290 mg/kg/day (0.5% DHA and 0.75% eicosapentaenoic acid) of marine oil for a 2-week period. In study III, the dose of 116 mg/kg/day of marine oil was investigated for a 9-month period. The bolus dose of marine oil in study I resulted in poor fatty acid absorption. In studies I and II phosphatidylethanolamine arachidonic acid, a primary phospholipid component of the cell membrane, declined significantly over time for all infants (Carlson et al. 1992a, b). In study II, the infants in the marine oil group had significantly lower phosphatidylethanolamine arachidonic acid than the controls; however, the marine oil groups also had lower baseline arachidonic acid levels, which likely contributed to these findings. Conversely, eicosapentaenoic acid and DHA increased in the marine oil groups and decreased in the control groups. The infants receiving 290 mg/kg/day of marine oil had significantly lower phosphatidylcholine, a primary phospholipid component of the cell membrane also commonly known as lecithin, than the control and lower dose groups (i.e., 116 mg/kg/day). In study III, there were positive correlations between arachidonic acid and DHA in the marine oil group through 9 months of age.

Uauy et al. (1994) compared four groups of very low birth weight infants given human milk (control), formula with corn oil, formula with soy oil, and formula with soy and marine oil. In this study bleeding times were evaluated and no significant differences in bleeding time were reported for any of the groups and bleeding times were within normal ranges for all groups. Additionally, Uauy et al. considered anthropometric data for each of the groups. Anthropometric data included weight, length, head circumference, triceps skinfold, and subscapular skinfold. Measurements were collected at birth, 34, 40, 48, and 57 weeks' gestational age. There were no differences among any of the study groups, i.e., weight gain and growth were similar for all four groups.

Based on the few studies carried out in human infants, there are no associated adverse impacts on growth or bleeding time in a dose of fish oil below 116 mg/kg/d. It appears that DHA absorption is better with marine oil if mixed into the formula compared to a bolus dose. Likewise, multiple large studies have been conducted that provided marine oil during the gestational period and no negative pregnancy outcomes were reported. In fact, marine oil supplemented during pregnancy has been demonstrated to increase the average length of gestation resulting in significantly higher birth weight (Olsen et al. 1995).

5.5.1.2 Egg Yolk Phospholipid

Egg yolk phospholipid is composed primarily of phosphatidlycholine. A drawback of egg-derived oils is that it contains relatively low amounts of DHA and arachidonic acid. Therefore, large amounts need to be added to infant formula to reach the desired DHA and arachidonic acid levels. Given the limitations of supplementation, egg-derived phospholipid has not been studied for commercial use in pregnancy. Consuming large quantities of egg phospholipids cause concern because of the exposure to large doses of sterols and egg-related allergens. In the context of this review, few research groups have used egg-derived phospholipids as DHA and arachidonic acid sources. Of the studies that have been reported, none have reported adverse outcomes with regard to toxicity or growth (Carlson et al. 1996; Auestad et al. 1997, 2001).

5.5.1.3 Single-Cell Oils

DHA and arachidonic acid oils, single-cell oils (SCO), are produced via the fermentation, extraction, and purification of microalgae and microfungus (Boswell et al. 1996). These oils are used as a maternal supplement during pregnancy and in infant formulas. The marine alga used for the production of DHA is Crypthecodinium cohinii and the oil is 40–50% DHA with no Eicosapentaenoic acid. This DHA single-cell oil is commonly referred to as DHASCO (Boswell et al. 1996). Arachidonic acid is formed from the unicellular fungus strain Mortierella alpina and is 40–50% arachidonic acid. This arachidonic acid single-cell oil is commonly referred to as ARASCO (Boswell et al. 1996). The microorganisms used to produce SCO had never before been used in food products and therefore required Food and Drug Administration approval for use in infant formulas. The natural toxins inherent in the two microorganisms were of concern with regard to use in food. Sufficient evidence exists regarding the safety of SCO as these have been investigated extensively for use in infant formulas (Boswell et al. 1996).

In summary, SCO and marine oil are both considered safe and efficacious for consumption during pregnancy; however, research points to the efficacy of a low eicosapentaenoic acid formulation for this group (Carlson et al. 1992a, b, 1993). Single-cell oils have been investigated extensively for use in infant formulas and provide the best alternative to marine and egg-derived sources.

5.6 Summary

In summary, visual signaling involves a complex interaction between the retina, thalamus, and primary visual cortex. Other cortical regions of the brain as well as central brain structures are involved in processing visual stimuli. Measures of visual development in infancy assess retinal reactivity or cortical processing of the visual stimulus. Behavioral measures of visual acuity give insight on the processing of visual information. Retinal photoreceptors have a high DHA concentration and deficiency during fetal development and the postnatal period have been associated with interruptions in visual development.

Maternal intake of DHA during pregnancy is significantly below the recommended 200 mg/day for healthy pregnancy outcomes. In turn, the developing fetus is at risk for negative outcomes. Optimal visual development enables the infant to move toward more integrative cognitive processing and the achievement of established developmental milestones. Additional community-based efforts are necessary to educate communities regarding the important role of DHA for optimal developmental outcomes during both the prenatal and postnatal periods. Future work should focus on the evaluation of maternal DHA status and its relationship to visual development in older children and associations with other cognitive processes.

5.7 Applications to Other Areas of Health and Disease

The consideration of visual acuity is very important to the assessment of cognitive development for a number of reasons. First, there is a need for good vision in order to perform optimally on other developmental tests. If an infant scores poorly on a given developmental test, results could be clouded by poor vision and mistakenly classified as poor mental processing. Additionally, early visual perception probably guides the development of action systems to promote learning about the infant's physical and social worlds (Von Hofsten 1980; Bertenthal 1996). For example, the development of infant reaching is prompted by the visual stimulus of an object that an infant is interested in exploring.

Future work should focus on (1) the evaluation of maternal DHA status and the infant's ability to integrate visual stimuli, as in face and object recognition, and (2) the relationship of acuity assessed during infancy with later vision and other cognitive processes (Neuringer and Jeffrey 2003). Focused community-based programs are necessary for promoting adequate intake of DHA during pregnancy and ensuring optimal infant visual and cognitive development.

Summary Points

- Visual signaling involves the retina, thalamus, and primary visual cortex.
- Other cortical regions of the brain as well as central brain structures are involved in processing visual stimuli.
- Measures of visual development assess retinal stimulation (ERG) or cortical processing (VEP and FPL).
- Forced-choice preferential looking procedures are behavioral measures of visual acuity and lend insight to the integration of visual information.
- Retinal photoreceptors and neural cell bodies are comprised predominantly of the essential fatty acid docosahexaenoic acid.

- Deficiencies of docosahexaenoic acid during fetal and infant development have been associated with interruptions in normal visual processing.
- Alterations in G protein coupled signal transduction related to docosahexaenoic acid provides a plausible mechanism for observations of alterations in visual functioning.
- Maternal docosahexaenoic acid during pregnancy is significantly below recommendations (200 mg/day) for optimal pregnancy outcomes placing the developing fetus at risk.
- Dietary sources of docosahexaenoic acid for the purpose of supplementation include: Marine and single-cell oils.
- Poor visual processing can impede infant attainment of later developmental milestones that rely on integrative processing.
- Additional educational efforts are necessary to educate the community regarding the important role of docosahexaenoic acid in infant development during both the prenatal and postnatal periods.

Definitions of Key Terms

Photoreceptors: A neural cell that is specific to the retina with specificity for visual stimuli.

Visual cortex: The portion of the brain's cortex where visual information is sent for further processing.

Electroretinogram: A direct measure of the retinal response to a visual stimulus prior to reaching any of the cortical areas.

Forced-choice preferential looking: Preferential looking procedures use black and white stripes that are grated in a series of frequencies that correspond with the number of stripes per visual angle (commonly termed as cycles/degree). The point at which an infant is unable to resolve or see the contrasting stripes in a grated acuity procedure is considered the visual threshold.

Visual evoked potential: A direct measure of cortical response to a visual stimulus.

Docosahexaenoic acid: An essential long-chain polyunsaturated fatty acid, which is a metabolic end product of the omega-3 fatty acid biosynthetic pathway.

Marine oil: Oil derived from edible fish sources for the purpose of supplementation.

Egg yolk phospholipid: Phospholipid derived from egg yolk.

Single-cell oils: Oils that are produced from single-cell sources including microalgae and microfungus.

References

Auestad N, Innis SM. Am J Clin Nutr. 2000;71:312S–4.
Auestad N, Montalto MB, Hall RT, Fitzgerald KM, Wheeler RE, Connor WE, et al. Pediatr Res. 1997;41:1–10.
Auestad N, Halter R, Hall RT, Blatter M, Bogle ML, Burks W, et al. J Pediatr. 2001;108:372–81.
Bazan NG, Scott BL. J Med Sci. 1990;48:97–107.
Bertenthal BI. Annu Rev Psychol. 1996;47:431–59.
Birch E, Birch DG, Hoffman D. J Pediatr Opthalmol Strabismus. 1993a;30:33–8.
Birch E, Birch DG, Hoffman D, Everett M, Uauy R. J Pediatr Ophthalmol Strabismus. 1993b;30:33–8.
Birch EE, Garfield S, Hoffman DR, Uauy R, Birch DG. Dev Med Child Neurol. 2000;42:174–81.
Boswell K, Koskelo EK, Carl L, Glaza S, Hensen DJ, Williams KD, et al. Food Chem Toxicol. 1996;34:585–93.
Bowen RA, Clandinin MT. J Neurochem. 2002;83:764–74.
Carlson SE, Werkman SH. Lipids. 1996;31:85–90.
Carlson SE, Cooke R, Werkman S, Tolley EA. Lipids. 1992a;27:901–7.

Carlson SE, Cooke RJ, Rhodes JM, Peeples J, Werkman SH. J Pediatr. 1992b;120:159–67.

Carlson SE, Werkman S, Peeples JM, Cooke RJ, Tolley EA. Proc Natl Acad Sci. 1993;90:1073–7.

Carlson SE, Ford AJ, Werkman SH, Peeples JM, Koo WK. Pediatr Res. 1996;39:882–8.

Cheruku SR, Montgomery-Downs HE, Farkas SL, Thoman EB, Lammi-Keefe CJ. Am J Clin Nutr. 2002;76:608–13.

Clandinin MT, CJ LS, Heim T, Sawyer PR, Chance GW. Early Hum Dev. 1980;4:121–9.

Denomme J, Stark KD, Holub BJ. J Nutr. 2005;135(2):206–11.

Fox P. Fetal and neonatal physiology, vol 1. Philadelphia: W.B. Saunders Company; 1998. p. 489–504.

Hoffman DR, Birch EE, Castaneda YS, Fawcett SL, Wheaton DH, Birch DG, et al. J Pediatr. 2003;142:669–77.

Innis SM, Elias SL. Am J Clin Nutr. 2003;77:473–8.

Innis SM, Nelson CM, Rioux FM, King JD. Am J Clin Nutr. 1994;60:347–52.

Innis SM, Nelson CM, Lwanga D, Rioux FM, Walsen P. Am J Clin Nutr. 1996;64:40–6.

Innis SM, Akrabawi SS, Diersen-Schade DA, Dobson VM, Guy DG. Lipids. 1997;32:63–72.

Jorgensen HM, Hernell O, Lund P, Holmer G, Michaelsen KF. Lipids. 1996;31:99–105.

Judge MP, Harel O, Lammi-Keefe CJ. Lipids. 2007;42:117–22.

Kellman PJ, Banks MS. Infant visual perception. In: Kuhn D, Siegler RS, editors. Handbook of child psychology: cognition, perception, and language, vol 2. New York: Wiley; 1998. p. 103–46.

Kolb B, Whishaw IQ. Organization of the nervous system. In: Atkinson RC, Lindzey G, Thompson RF, editors. Fundamentals of human neuropsychology. New York: Worth Publishers; 2003. p. 46–74.

Koletzko B, Lien E, Agostoni C, Böhles H, Compoy C, Cetin I, et al. J Perinat Med. 2008;36:5–14.

Lewis NM, Widga AC, Buck JS, Frederick AM. J Agromedicine. 1995;2:49–56.

Loosemore ED, Judge MP, Lammi-Keefe CJ. Lipids. 2004;39:421–4.

Makrides M, Simmer K, Goggin M, Gibson RA. Pediatr Res. 1993;33:425–7.

Makrides M, Neumann M, Simmer K, Pater J, Gibson R. Lancet. 1995;345:1463–8.

Malcolm CA, Hamilton R, McCulloch DL, Montgomery C, Weaver LT. Invest Opthalmol Vis Sci. 2003a;44:3685–91.

Malcolm CA, McCulloch DL, Montgomery C, Shepherd A, Weaver LT. Arch Dis Child Fetal Neonatal Ed. 2003b;88:F383–90.

Mitchell DC, Niu SL, Litman BJ. J Pediatr. 2003;143:880–6.

Neuringer M. Am J Clin Nutr. 2000;71:256S–67.

Neuringer M, Jeffrey BG. J Pediatr. 2003;143:S87–95.

Neuringer M, Connor WE, Barstad L, Luck S. Proc Natl Acad Sci. 1986;83:4021–5.

Niu SL, Mitchell DC, Litman BJ. J Biol Chem. 2001;276:42807–11.

Nui SL, Mitchell DC, Lim SY, Wen ZM, Kim HY, Salem N, et al. J Biol Chem. 2004;279:31098–104.

O'Connor DL, Hall R, Adamkin D, Auestad N, Castillo M, Connor WE, et al. J Pediatr. 2001;108:359–71.

Olsen SF, Secher NJ. Br Med J. 2002;324:447–50.

Olsen SF, Hansen HS, Secher NJ, Jensen B, Sandstrom B. Br. J Nutr. 1995;73:397–404.

Salem Jr N, Litman B, Kim HY, Gawrisch K. Lipids. 2001;36:945–59.

Sarkadi-Nagy E, Wijendran V, Diau GY, Chao AC, Hsieh AT, Turpeinen A, et al. Pediatr Res. 2003;54:244–52.

Simopoulos AP, Leaf A, Salem N. Prostaglandins Leukot Essent Fatty Acids. 2000;83:119–21.

Uauy R, Hoffman DR, Birch EE, Birch DG, Jameson DM, Tyson J. J Pediatr. 1994;124:612–20.

Von Hofsten C. J Exp Child Psychol. 1980;30:369–82.

Wijendran V, Bendel RB, Couch SC, Philipson EH, Cheruku S, Lammi-Keefe CJ. Lipids. 2000;35:927–31.

Zigmond MJ, Bloom FE, Landis SC, Roberts JL, Squire LR. Fundamental Neuroscience. San Diego: Academic; 1999.

Chapter 6
Acquired Tastes: Establishing Food (Dis-)Likes by Flavour–Flavour Learning

Remco C. Havermans and Anita Jansen

Abbreviations

ANC   Amygdalar nuclear complex
BMI   Body mass index
CS   Conditioned stimulus
OFC   Orbitofrontal cortex
PDD   Pervasive developmental disorder
UCS   Unconditioned stimulus

6.1 Introduction

It is a truism that eating behaviour (i.e. food choice and food intake) is determined by many different factors. Nonetheless, within the normal physiological boundaries of satiety and hunger one may argue that people simply eat what they like and avoid foods they do not like (Eertmans et al. 2001). Such hedonic eating behaviour is particularly apparent in children. For example, in the early twentieth century, most Dutch children (in addition to children in many other countries) still received a daily spoonful of cod liver oil before bedtime. Many of these individuals, now adults, still shiver at the memory of the often rancid taste of cod liver oil. However, there was good reason to subject children to this cod liver oil ordeal, as this oil was known to somehow prevent rickets (or rachitis; the softening of bones misshaping knees, wrists, and ankles). It wasn't until the 1930s that it was recognised that rickets is caused by vitamin D deficiency and that cod liver oil is rich in such vitamin D. This knowledge eventually allowed for the development of vitamin D supplementation and with it the standard practise of administering children cod liver oil dissipated. One will cease the consumption of aversive tastes when there is no pressing need for the consumption of such tastes.

People are born with a preference for sweet tastes and an aversion against bitter tastes, but more specific flavour preferences are developed during later childhood. Specific food likes and dislikes can differ between individuals and this suggests that these preferences are acquired through personal experience with certain flavours. In other words, one acquires a (dis)taste for certain foods by trying out these foods (Capaldi and Vandenbos 1991). How then does this work exactly? A prominent form

R.C. Havermans (✉)

Department of Clinical Psychological Science, Maastricht University, Maastricht, 6200 MD, The Netherlands
e-mail: r.havermans@maastrichtuniversity.nl

of such purported experiential learning involves Pavlovian conditioning, the learning of an association between a neutral conditioned stimulus (CS) (e.g. a flavour) and a biologically relevant unconditioned stimulus (UCS). In the case of conditioned taste aversion learning, the UCS usually comprises some degree of gastrointestinal discomfort. By pairing a specific flavour with such discomfort, one comes to associate the flavour with the discomfort and this then leads to future avoidance of the flavour (Pelchat and Rozin 1982). Pavlovian conditioning has then endowed the flavour CS a signalling function, it 'predicts' internal malaise (the UCS). Likewise, it was found in animals that a taste preference is conditioned for flavours paired with the recovery of illness (Green and Garcia 1971).

Another way of conditioning a food preference was demonstrated by Holman (1975). In one of his experiments, he gave rats on alternate days either a banana- or almond-flavoured mash. To this mash, he added saccharin to make it taste sweet. Rats, like humans, have an innate preference for sweet tastes. Holman varied the concentration of the saccharin of the different mashes. Rats were divided into two groups: A and B. Group A received 60 min access to the almond paired with concentrated saccharin and banana paired with diluted saccharin solution. For group B, the flavour to saccharin concentration (concentrated versus diluted) assignment was reversed. At test, the rats received 30 min access to 40 mL of both flavours now with an equal saccharin concentration. The rats showed a clear preference for the flavour previously paired with the concentrated saccharin. Figure 6.1 displays an illustration of the procedure, design, and results of this experiment. On the basis of these and similar findings, Holman concluded that the apparent reinforcing effect of saccharin is the hedonic quality of its sweet flavour. This form of learning has thus been termed flavour–flavour learning as the apparent
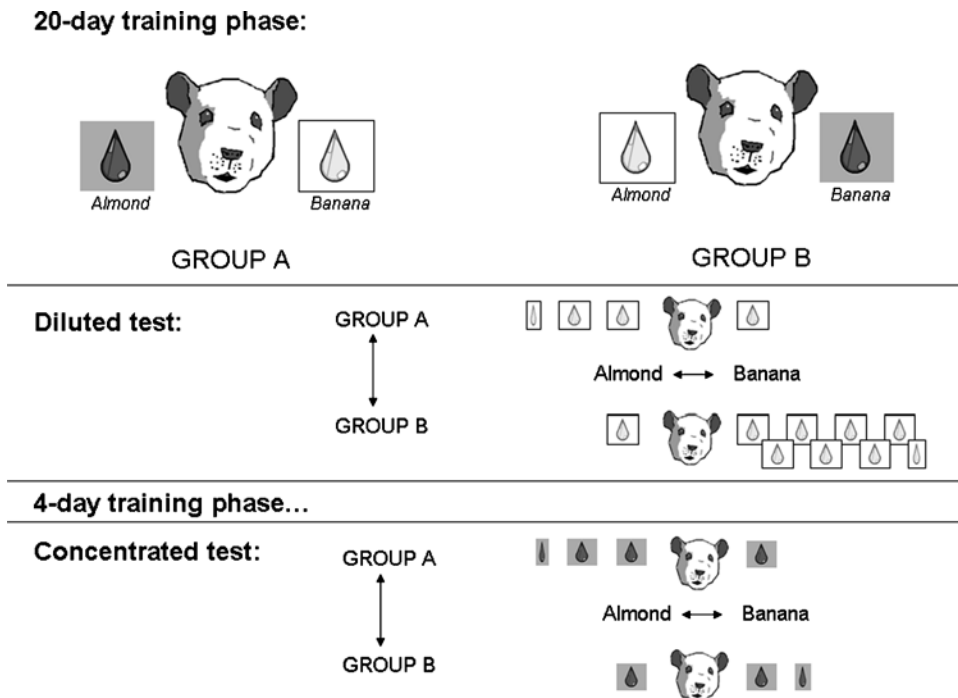
Fig. 6.1 Design, procedure and results of Eric Holman's (1975) experiment on flavour–flavour learning. Eric Holman (1975; Experiment 2) gave rats during a 20-day training period one flavour paired with concentrated saccharin on even days and another flavour paired with diluted saccharin on uneven days. On a first test, rats were given simultaneous access to both flavours, now both with diluted saccharin. Rats drank much more of the flavour previously paired with the concentrated saccharin. On a second test, after another 4-day period of training, the same pattern of results was obtained when both flavours were now presented with concentrated saccharin

Table 6.1   Key facts concerning flavour–flavour learning and its applications

A neutral flavour becomes more liked or less liked after having been paired with, respectively, an already liked or disliked flavour
Children can come to better like the flavour of fruits and vegetables through flavour–flavour learning

shift in flavour preference arises from the acquisition of an association between two flavours: a neutral flavour (e.g. almond) and an already liked flavour (e.g. the sweet taste of concentrated saccharin) (Fanselow and Birk 1982; Myers and Sclafani 2006).

Some researchers argue that a flavour–flavour association is qualitatively different from a preference arising from flavour–consequence learning. As the latter form of association is recognised as the result of Pavlovian conditioning, this implies that flavour–flavour learning may not be considered as a form of Pavlovian associative learning (Hermans et al. 2002) and this gives rise to the question what mechanism then underlies flavour–flavour learning. Other questions raised and discussed in the present chapter concern the generality of flavour–flavour learning, its neurological underpinnings and its application to promoting the development of healthy dietary habits in children (Table 6.1).

6.2   What is Flavour–Flavour learning?

Flavour–flavour learning comprises the transfer of affect to a neutral flavour CS by pairing that particular flavour with another already liked or disliked flavour UCS. The established shift in liking is always in the direction of the affective value of the evaluative UCS. This is why flavour–flavour learning is generally regarded as a form of evaluative conditioning. But what exactly is evaluative conditioning?

6.2.1   Evaluative Conditioning

In a particular study, Levey and Martin (1975) had participants categorise pictures of paintings as liked, neutral, or disliked. Subsequently, the participants received exposure to several neutral pictures paired with other liked pictures, or neutral pictures, or disliked pictures. At test, participants had to evaluate all pictures and it was found that they now rated the neutral pictures that had previously been paired with the disliked pictures more negatively and the neutral pictures that had been paired with the liked pictures as more positive. Martin and Levey (1978) termed this transfer of affect to an originally neutral stimulus due to pairings of this stimulus with another affective (positive or negative) stimulus evaluative conditioning.

Procedurally, evaluative conditioning is very similar to Pavlovian conditioning. With evaluative conditioning, the neutral stimulus is usually referred to as the CS and the affective stimulus as the UCS. Pairing these stimuli should then lead to the formation of an association between these two stimuli, allowing for the transfer of affect from the UCS to the CS. Despite the procedural similarity there are notable discrepancies between evaluative conditioning and other more typical Pavlovian conditioning paradigms such as fear conditioning. In the case of fear conditioning, the CS, a neutral stimulus (e.g. a tone or a picture), is paired with aversive stimulation, such as the administration of an electric shock or a very loud noise. Hermans et al. (2002) exposed participants to such a procedure, pairing pictures of faces (the CSs) with electrocutaneous stimulation (the UCS; i.e. an aversive electric shock). The participant learned to anticipate this adverse stimulation that was reflected by a strong expectation of the UCS when presented with the CS previously paired with the UCS. Hermans and colleagues also showed that participants came to dislike the CSs that had been paired with the

UCS, indicating evaluative conditioning. UCS expectations extinguish easily with non-reinforced exposures to the CS (Dibbets et al. 2008), but an acquired evaluative shift is highly resistant to such an extinction treatment (De Houwer et al. 2000).

Pavlovian conditioning can be described in terms of signal learning; one learns to recognise the CS as a signal for the UCS, and hence, when exposed to the CS, one expects the UCS. No such learning is required in case of evaluative conditioning; the CS then merely has to refer to the UCS (see also De Houwer et al. 2000).

In line with the reasoning that evaluative conditioning reflects some form of referential learning, Havermans and Jansen (2007a) argue that evaluative conditioning more specifically reflects a stimulus generalisation process. Within Pavlovian conditioning, it is well known that an acquired associative strength can generalise from one CS to other CSs. The extent of transfer of associative value is determined by the degree of similarity between the CS and the novel stimulus (Pearce 2002). According to Havermans and Jansen, such transfer is probably not limited to associative value. Indeed, it may also comprise the transfer of other relevant stimulus characteristics, such as affective value. This then means that pairing a neutral CS with an evaluative UCS merely provides one the opportunity for determining (or just passively experiencing) the similarity between the two stimuli. If there is some degree of stimulus similarity, and if this similarity is somehow noted, this may be enough to induce the transfer of affect from the UCS to the CS (Davey 1994; Field and Davey 1999). Figure 6.2 represents the stimulus generalisation model of evaluative conditioning as outlined by Havermans and Jansen.

6.2.2 The Flavour–Flavour Paradigm

Evaluative conditioning is not limited to the transfer of affect between visual stimuli such as the pictures of paintings. Indeed, it was soon recognised that flavour–flavour learning can also be understood in terms of evaluative conditioning. In fact the flavour–flavour paradigm is recognised as one of the more robust forms of evaluative conditioning (Field et al. 2008).
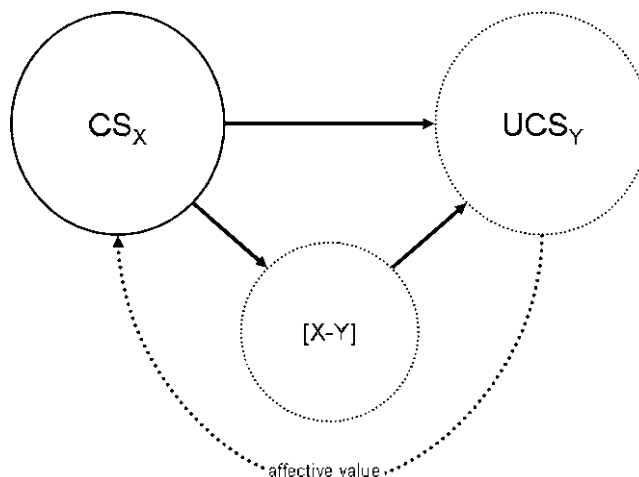
Fig. 6.2 A stimulus generalisation model of evaluative conditioning. Havermans and Jansen (2007a) argue that when a neutral CS X is paired with an affective UCS Y a configural X-Y representation is formed in memory. When subsequently X is presented, the representation of the UCS Y will be activated directly through its similarity with X and indirectly through the X-Y configural representation. The degree to which the representation of Y is activated determines the extent of affective value being transferred from Y to CS X

As described above, Eric Holman (1975) tested whether a rat's flavour preference could be influenced by the sweetness of saccharin associated with the flavour. It could and such flavour–flavour learning is not limited to rats; it has also been demonstrated in humans. Baeyens et al. (1995) found that pairing a flavour with the aversive taste of polysorbate-20 (the emulsifier Tween) led to decreased liking of that particular flavour (see also Baeyens et al. 1990, 1996, 1998a, b). These researchers, however, did not find evidence of positive flavour–flavour learning with pairings of a specific neutral flavour with a sweet taste. This may mean that negative flavour–flavour learning is more easily established than positive flavour–flavour learning, but the failure to induce positive flavour–flavour learning could also be attributed to the fact that the participants only moderately liked the sweet taste. It was already shown that it certainly is not impossible to induce positive flavour–flavour learning. Zellner et al. (1983) had students drink different flavours of tea. Some of these teas had to be tasted several times with sweet-tasting sucrose. At test, all participants again had to taste and evaluate the different teas, now left unsweetened, and the participants clearly and specifically liked the previously sweetened teas better. Yeomans et al. (2008) similarly found evidence of positive flavour–flavour learning when a specific flavour of dessert was paired with the sweet taste of either sucrose or aspartame. To ensure that the sweet taste (the flavour UCS) was well liked, Yeomans took care to only select self-identified sweet likers for participation in their study.

Interestingly, Brunstrom et al. (2001) found that unrestrained eaters showed enhanced preference for drinks most often paired with a sweet reward (e.g. chocolate chips, puffed rice or raisins), but this was not found among restrained eaters, suggesting that dietary restraint somehow devalues the sweet reward. This is precisely what Brunstrom et al. (2005) found in a series of two experiments. In one of these experiments, Brunstrom and colleagues paired different fruit juices of with a sweet reward (i.e. chocolate chips). One of the juices was paired on just 10% of trials with the sweet and another juice was paired 90% of the trials with the sweet reward. Unrestrained eaters came to prefer the 90% paired picture, but the restrained eaters came to prefer the less-often paired pictures. Brunstrom and colleagues thus argued that negative beliefs and attitudes regarding the UCS devalue the UCS and within restrained eaters may in fact function as an aversive stimulus, thus promoting the acquisition of a dislike. In a more recent study, however, Brunstrom and Fletcher (2008) failed to replicate this effect of dietary restraint on flavour–flavour learning, but instead found an effect of hunger state. When pairing tea with a non-caloric sweetener, only hungry participants came to like the flavour of this particular tea relative to other unsweetened teas. Similarly, Mobini et al. (2007) found that pairing a peach-flavoured tea with another sucrose drink, increased liking for the tea particularly when participants had been trained and tested hungry. Further, Yeomans and Mobini (2006) demonstrated that increased liking for odours paired with a sweet sucrose UCS was apparent only when participants were hungry. One may argue that hunger increases attention and liking for caloric cues, such as a sweet taste that generally signals carbohydrate energy (e.g. as in the case of sucrose, fructose and glucose), hence increasing the salience of the flavour UCS allowing for larger transfer of affective value to the CS flavour (see Fig. 6.3).

6.2.3 Neural Correlates of Flavour–Flavour Learning

Cues associated with a certain food UCS can come to affect subsequent food choice and food intake. The brain structures known to be involved in the expression of cue-induced food selection and acceptance, such as the hypothalamus, amygdala and OFC probably also play a role in the associative acquisition of food likes and dislikes (see Holland and Petrovich 2005). Indeed, although many brain areas are activated with exposure to the sight, smell and taste of food, studies on the evaluation of food stimuli ubiquitously point to the specific involvement of the amygdala, the OFC and the insula.

hunger

Neutral flavour X

Liked flavour Y

[X-Y]

positive value
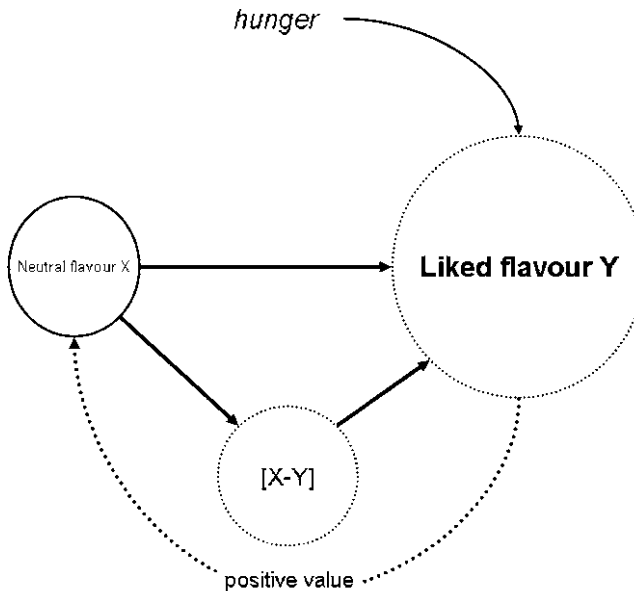
Fig. 6.3 Flavour–flavour learning as stimulus generalisationIn terms of the stimulus generalisation model of evaluative conditioning as put forward by Havermans and Jansen (2007a), pairing a neutral flavour X with an already liked flavour Y, leads to the formation of a configural X-Y representation in memory. Subsequent presentation of X alone then leads to the activation of the configural X-Y unit and the representation of flavour Y. If one is hungry, the salience of the representation of Y is hypothetically bigger and allows for more transfer of affective value to flavour X

With oral taste neurons projecting directly to the insula, activation of this area has been associated with representations of taste intensity and quality (e.g. texture, taste intensity, bitterness, sweetness, sourness or saltiness) and is thus referred to as the primary gustatory cortex (Small et al. 1999; De Araujo and Rolls 2004). Adjacent to this area, the OFC is involved in representations of the purported *acquired* valence of food cues (e.g. the pleasure derived from the sight, smell and taste of food). This region, therefore, has been termed the secondary taste cortex. Rolls and colleagues showed that decreasing the subjective pleasure derived from eating a specific food item through repeated exposure to that food leads to a corresponding decrease in the activation within the OFC when presented with that specific food item (see Rolls 2000).

The amygdala is recognised to be activated by both pleasurable and aversive food cues (O'Doherty et al. 2001) and thus appears to respond nonspecifically to any valenced food stimulus. Recent research suggests that such activation of the amygdala requires deliberate and attentive processing of the presented food stimulus (Siep et al. 2009).

Considering the presumed involvement of the amygdala in the conditioning of likes and dislikes, Coppens et al. (2006) examined whether patients with a unilateral section of the temporal lobe (which includes the amygdala) exhibit impaired flavour–flavour learning as compared to a control. Participants received two flavours, one of which was served with the addition of Tween. The researchers hypothesised that given the fact that even unilateral damage to the amygdala (i.e. the ANC) attenuates fear conditioning; such damage would also disturb evaluative conditioning. However, all participants demonstrated clear negative flavour–flavour learning, acquiring a dislike for the Tween-paired flavour CS relative to the unpaired CS. The authors correctly point out that this does not mean that the amygdala does not play any role in the acquisition of food likes and dislikes as all the patients included in the study had only unilateral damage to the ANC. Clearly, more research is needed to determine the exact neurological underpinnings of flavour–flavour learning.

6.3 Applying Flavour–Flavour Learning to Increase Liking for Vegetables

Overweight (BMI > 25 kg/m²) is a rapidly increasing worldwide health problem. Especially obesity (i.e. severe overweight; BMI > 30) poses several health risks, such as coronary heart diseases and type II diabetes. It is estimated that currently in the USA approximately 25% of total health care costs are associated with obesity, a percentage representing billions of dollars (Levi et al. 2009). Currently, more than two-thirds of the US population is overweight or obese. Table 6.2 displays the present top five states with the highest obesity rates of the USA.

The number of overweight children has also increased dramatically in the past few decades. The health risks associated with obesity at a young age are less dire, but it is more difficult to attain a normal weight if one has been obese since childhood. Moreover, the health risks for obese adults who have been obese since their childhood are greater than for people who became obese in later adulthood (see e.g. Visscher et al. 2002).

Overweight and obesity are the result of a positive energy balance; more energy is consumed than expended. Particularly excessive caloric intake is now thought to have contributed to the steep rise in the incidence of obesity (Swinburn et al. 2009). Healthier eating, that is, consuming less high-calorie products should lower the prevalence of overweight. Indeed, Raynor and Epstein (2001) demonstrated that whereas consuming many different snacks is related to obesity, the consumption of a large variety of fruits and vegetables is associated with lean body weight. Therefore, getting people (especially children) to eat ample amounts of fruits and vegetables may prove to be an effective strategy in curbing the present obesity epidemic.

Recently, we reasoned that flavour–flavour learning might be a powerful technique to increase children's liking of vegetables, and hence their consumption of vegetables. To test whether such flavour–flavour learning actually increases children's liking of vegetables, we conducted an experiment. In this experiment 4- to 6-year-old children evaluated and rank ordered six different vegetables. Next, they were instructed to repeatedly consume small amounts of two of the six specific vegetables. These two flavours served as the flavour CSs and one of the two vegetables was now sweetened with glucose. After this repeated exposure procedure, all children again were instructed to evaluate and rank order the six vegetables. At this posttest, the children now specifically ranked the previously sweetened vegetable as better liked than before (Havermans and Jansen 2007b; see Fig. 6.4).

This positive flavour–flavour learning effect was also demonstrated in a more recent study by Capaldi and Privitera (2008). In a first experiment they had 2- to 5-year-old children repeatedly taste grapefruit juice mixed with the sweet taste of sucrose. This led to increased liking of unsweetened grapefruit juice. Moreover, this positive shift in liking proved stable for weeks. In a second experiment, undergraduate students were presented with several occasions in which they were instructed to consume one small stalk of cauliflower and another stalk of broccoli. One of the two vegetables

Table 6.2 Current obesity rates in the USA

	State	Obesity rate (%)
1	Mississippi	32.5
2	Alabama	31.2
3	West Virginia	31.1
4	Tennessee	30.2
5	South Carolina	29.7

Top five states with the most obese people in the USA, as reported by the Trust for America's Health in their sixth annual issue report (Levi et al. 2009) on the obesity epidemic in the USA
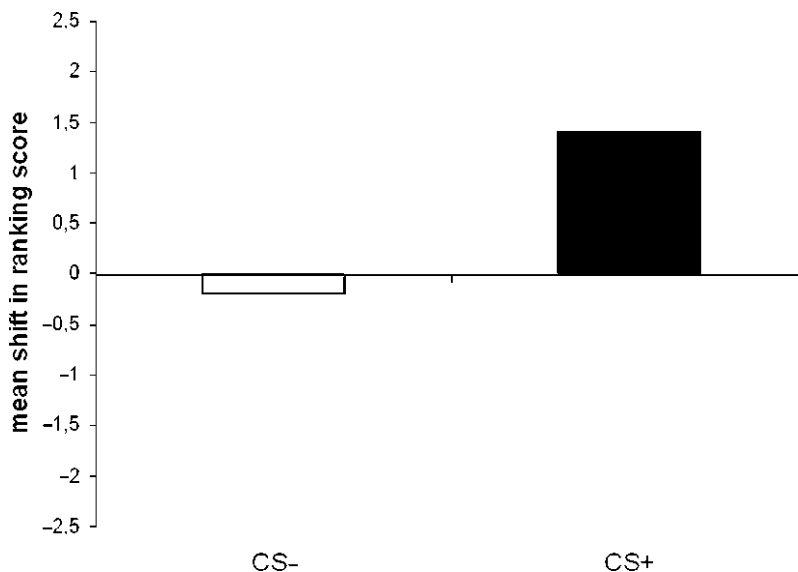
Fig. 6.4 Children's changes in hedonic ranking of vegetables as the result of flavour–flavour learning. Mean shift in ranking score (from pretest to posttest) for the CS paired with glucose (CS+) compared with the shift in ranking for the unpaired CS (CS−), as demonstrated by Havermans and Jansen (2007b) in the conditioning of vegetable flavour preferences in children

would be sweetened by having it dipped in sugar water. The assignment of vegetable to sugar water was counterbalanced between participants. Capaldi and Privitera found that the pairings of either cauliflower or broccoli with sugar increased liking of the taste of these vegetables.

In sum, the results from the studies discussed above suggest that the flavour–flavour learning paradigm can be applied to increase children's liking of fruits and vegetables. Importantly, this can be achieved even when the taste of the CS is initially disliked (e.g. the bitter taste of grapefruit), plus the achieved hedonic shift appears to be stable over a longer term.

6.4 Applications to Other Areas of Health and Disease

Children can develop strong food preferences and as a result may be particularly finicky about having to eat certain foods (Dovey et al. 2008). When such picky eating becomes a longer term habit of eating a very limited variety of food items, this food selectivity can form a serious health risk. One way to treat such food selectivity is through mere exposure. Williams et al. (2008), for example, used this method in six children being treated for extreme food selectivity. One case concerned a young girl diagnosed with autism who during treatment was exposed regularly to foods presented in meals and taste sessions. Meals would contain three table spoons of about three different foods (fruits, vegetables, meat, starch or dairy product), and taste sessions were used to introduce the child to a specific novel food. This mere exposure worked very well. She learned to accept and eat many different foods. Of the 49 different novel foods she learned to eat, she still ate 47 at 3 months after treatment.

Mere exposure thus seems to be a viable method to treat food selectivity. However, flavour–flavour learning may be even more powerful in the treatment of such food selectivity. Compared with a mere

exposure procedure, flavour–flavour learning requires relatively few learning trials. Such flavour–flavour learning may involve the pairing of a novel or nonpreferred food with an already liked food. Furthermore, this pairing should be simultaneous, that is, the two foods (liked and disliked) should be presented together, rather than sequentially, as was shown by Holman (1975) in his rat studies. In one experiment, Holman found that pairing a flavour CS (CS+; cinnamon or wintergreen) with saccharin induced a flavour preference relative to another unpaired flavour (CS−; cinnamon when CS+ was wintergreen, and vice versa). Holman, however, failed to induce a flavour preference for the CS+ in a following experiment when he inserted a 30 min interval between the consumption of the CS+ and the ingestion of a saccharin solution. The procedure, design and results of these experiments are illustrated in Fig. 6.5.

Piazza et al. (2002) compared simultaneous and sequential pairings of non-preferred foods with preferred foods in three children treated for food selectivity. One 11-year-old girl diagnosed with PDD ate lettuce with salad dressing and a few other creamy foods, but not much else. She received exposure to foods from different food groups (fruits and vegetables, starches and protein-rich foods) and these foods were paired with salad dressing. One group of foods (A) was always presented simultaneously with the salad dressing. Another group of foods (B) was paired sequentially with the dressing. The girl would only come to eat the foods from group A, not the foods from group B, corroborating the notion and previous findings that simultaneous pairings are superior in inducing an evaluative shift. Similar findings were reported for the other two cases in this study. It thus seems that food selectivity can be treated by means of evaluative conditioning, but note that the researchers did
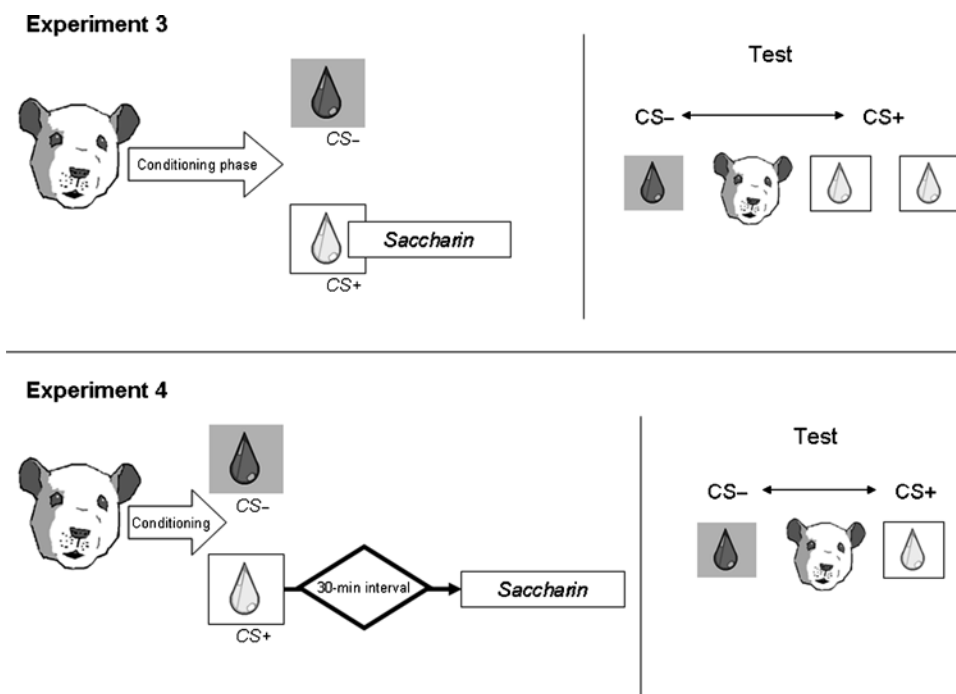
Fig. 6.5 Holman experiments indicating that only simultaneous CS−UCS pairings induce a shift in CS flavour preference. An illustration of the procedure, design and main results of two experiments by Holman (1975; Experiments 3 and 4). Both experiments comprised comparing a shift in liking/preference between a CS+ paired with saccharin (the UCS) and another explicitly unpaired CS flavour (i.e. CS−). At test, the animals received the opportunity to drink from both (now unsweetened) flavours. The tests results from both experiments taken together clearly demonstrate that simultaneous (Experiment 3) but not sequential pairing (Experiment 4) of the CS+ with saccharin induces a flavour preference relative to CS−

not present the 'non-preferred' foods separately without the unconditioned flavour after the repeated pairings. This makes it impossible to assess any positive shift in liking of the flavour of the non-preferred food itself. Furthermore, as the authors themselves note, they did not conduct a follow-up test. Whether flavour–flavour learning is indeed beneficial and perhaps even superior to a mere exposure procedure in the treatment of food selectivity thus requires further empirical validation.

6.5 Conclusion

Evaluative conditioning is the transfer of affective value from an affective stimulus to another stimulus, due to pairing of the latter stimulus with the affective stimulus. As such, flavour–flavour learning – the transfer of affective value to a flavour being paired with an already liked/disliked flavour – can be regarded as a specific instance of evaluative conditioning.

Flavour–flavour learning is a robust form of evaluative conditioning and has been demonstrated in both animals and humans. Humans appear especially sensitive to the reinforcing sweet taste of sugar (Yeomans et al. 2008). The reason for this is unknown, but recent research suggests that humans possess orosensory receptors that specifically function to detect the presence of carbohydrates (apart from sweet taste). Oral maltodextrin (not sweet) and glucose (sweet) both directly activated brain regions known to be involved in the processing of the reward value of food, such as the insula, OFC and striatum (Chambers et al. 2009). One may hypothesise then that flavour–flavour learning in humans is probably much more effective when using some form of sugar and may even be evident when using non-sweet carbohydrates as UCS.

Flavour–flavour learning has proven to be a powerful technique to change someone's preference for a flavour and hence food. It is rapid and requires relatively little experience with the flavours themselves. In terms of nutrition and health, it has been shown that it can be applied to increase children's liking of fruits and vegetables even when the foods are initially disliked (Capaldi and Privitera 2008). However, whether the established positive change in hedonics also leads to a corresponding positive change in behaviour is an effect that is predicted but as of yet has not been examined empirically. The full benefits of flavour–flavour learning to nutrition thus still wait to be examined.

Summary Points

- Food choice and intake can be understood in terms of hedonic behaviour; that is, one prefers consuming foods one likes and tries to avoid having to eat foods one does not like.
- Food likes and dislikes are mostly acquired through direct experience with food.
- Flavour–flavour learning, a form of evaluative conditioning, comprises the transfer of affect (positive or negative) to a flavour by pairing that particular flavour with another already liked or disliked flavour.
- In humans, positive flavour–flavour learning seems to be mediated by hunger state.
- The amygdala is thought to play a critical role in the acquisition of flavour (dis)likes through flavour–flavour learning.
- Flavour–flavour learning can be applied to increase children's liking of fruits and vegetables and may be a beneficial technique in the treatment of severe cases of food selectivity.

Key Terms

Evaluative conditioning: A learning paradigm in which pairing a CS with a positive UCS results in a positive shift in liking for the initially neutral CS, whereas conversely, pairing such a stimulus with a negative UCS results in a negative shift in liking.

Flavour–flavour learning: A form of evaluative conditioning that allows for the learning of flavour preferences by pairing a flavour with an already liked flavour, such as the sweet taste of saccharin or sugar.

Food selectivity: Feeding disorder diagnosed in infants or children when the child is not eating adequately and the insufficient food intake cannot be attributed to any specific medical condition.

Hedonic eating behaviour: The principle that anticipated and derived pleasure guide food choice and food intake, respectively.

Pavlovian conditioning: The learning of a response to a CS due to its pairings with a biologically relevant UCS. This conditioned response typically reflects the anticipation of the UCS.

Stimulus generalisation: Transfer of prominent qualities of one stimulus – such as its associative and affective value – to another stimulus.

References

Baeyens F, Eelen P, Van den Bergh O, Crombez G. Learn Motiv. 1990;21:434–55.
Baeyens F, Crombez G, Hendrickx H, Eelen P. Learn Motiv. 1995;26:141–60.
Baeyens F, Crombez G, De Houwer J, Eelen P. Learn Motiv. 1996;27:200–41.
Baeyens F, Hendrickx H, Crombez G, Hermans D. Appetite. 1998a;31:185–204.
Baeyens F, Vanhouche W, Crombez G, Eelen P. Psychologica Belgica. 1998b;38:83–108.
Brunstrom JM, Fletcher HZ. Physiol Behav. 2008;93:13–9.
Brunstrom JM, Downes CR, Higgs S. Appetite. 2001;37:197–206.
Brunstrom JM, Higgs S, Mitchell GL. Physiol Behav. 2005;85:524–35.
Capaldi ED, Privitera GJ. Appetite. 2008;50:139–45.
Capaldi ED, VandenBos GR. Hosp Community Psychiatry. 1991;42:787–9.
Chambers ES, Bridge MW, Jones DA. J Physiol. 2009;587:1779–94.
Coppens E, Vansteenwegen D, Baeyens F, Vandenbulcke M, van Paesschen W, Eelen P. Neuropsychologia. 2006;44:840–3.
Davey GCL. A reply to Martin and Levey (1994). Behav Res Ther. 1994;32:307–10.
De Araujo IE, Rolls ET. J Neurosci. 2004;24:3086–93.
De Houwer J, Thomas S, Baeyens F. Psych Bull. 2000;127:853–69.
Dibbets P, Havermans R, Arntz A. Behav Res Ther. 2008;46:1070–7.
Dovey TM, Staples PA, Gibson EL, Halford JCG. Appetite. 2008;50:181–93.
Eertmans A, Baeyens F, Van den Bergh O. Health Educ Res. 2001;16:443–56.
Fanselow MS, Birk J. Anim Learn Behav. 1982;10:223–8.
Field AP, Davey GCL. J Exp Psychol Anim Behav Proc. 1999;25:211–24.
Field AP, Lascelles KRR, Lester KJ, Askew C, Davey GCL. Neth J Psychol. 2008;64:46–64.
Green KF, Garcia J. Science. 1971;173:749–51.
Havermans RC, Jansen A. Neth J Psychol. 2007a;63:38–49.
Havermans RC, Jansen A. Appetite. 2007b;48:259–62.
Hermans D, Vansteenwegen D, Crombez G, Baeyens F, Eelen P. Behav Res Ther. 2002;40:217–34.
Holland PC, Petrovich GD. Physiol Behav. 2005;86:747–61.
Holman EW. Learn Motiv. 1975;6:91–100.
Levey AB, Martin I. Behav Res Ther. 1975;4:205–7.
Levi J, Vinter S, Richardson L, St Laurent R, Segal L. Trust for America's Health & Robert Wood Johnson Foundation; 2009.

Martin I, Levey AB. Adv Behav Res Ther. 1978;1:57–102.

Mobini S, Chambers LC, Yeomans MR. Appetite. 2007;48:20–8.

Myers KP, Sclafani A. Dev Psychobiol. 2006;48:380–8.

O'Doherty J, Rolls ET, Francis S, Bowtell R, McGlone F. J Neurophysiol. 2001;85:1315–21.

Pearce JM. Anim Learn Behav. 2002;30:73–95.

Pelchat ML, Rozin P. Appetite. 1982;3:341–51.

Piazza CC, Patel MR, Santana CM, Goh HL, Delia MD, Lancaster BM. J Appl Behav Anal. 2002;35:259–70.

Raynor HA, Epstein LH. Psychol Bull. 2001;127:325–41.

Rolls ET. Cereb Cortex. 2000;10:284–94.

Siep N, Roefs A, Roebroeck A, Havermans R, Bonte M, Jansen A. Behav Brain Res. 2009;198:149–58.

Small DM, Zald DH, Jones-Gotman M, Zatorre RJ, Pardo JV, Frey S, et al. NeuroReport. 1999;10:7–14.

Swinburn BA, Sacks G, Lo SK, Westerterp KR, Rush EC, Rosenbaum M, et al. Am J Clin Nutr. 2009;89:1723–8.

Visscher TLS, Kromhout D, Seidell JC. Int J Obes. 2002;26:1218–24.

Williams KE, Paul C, Pizzo B, Riegel K. Appetite. 2008;51:739–42.

Yeomans MR, Mobini S. J Exp Psychol Anim Behav Process. 2006;32:460–6.

Yeomans MR, Leitch M, Gould NJ, Mobini S. Physiol Behav. 2008;93:798–806.

Zellner DA, Rozin P, Aron M, Kulish C. Learn Motiv. 1983;14:338–50.

Chapter 7
Personality Traits in the Context of Sensory Preference: A Focus on Sweetness

Paul Richardson and Anthony Saliba

Definitions

Agreeableness: Degree toward being considerate, cooperative, and accommodating

Character: A combination of traits that are learned (e.g., responsibility)

Conscientiousness: Degree of self-discipline, persistence, and perfectionism

Disposition: The predominant tendency or pattern

Empathy: Capacity to recognize and share the feelings and emotions of others

Extraversion: Outgoing and highly sociable personality dimension

Harm Avoidance: Anticipatory worry and fear of uncertainty – similar to neuroticism

Impulsiveness: Inclination to act on the spur of the moment without considering long-term implications

Neuroticism: Propensity to experience emotional events negatively; linked with levels of anxiety and stress

Novelty Seeking: Sensation seeking – similar to venturesomeness and impulsivity

Openness: Willingness to explore new and unfamiliar experiences

Personality: An enduring pattern of a person's psychological and behavioral characteristics

Temperament: The collection of unconscious dispositions

Trait: A distinguishing characteristic of someone's personality

Venturesomeness: Thrill-seeking behavior, particularly for high-risk and potentially hazardous situations

P. Richardson (✉)

Brain, Behaviour & Cognition Research Group, Psychology, Sheffield Hallam University, Collegiate Campus, Sheffield, UK S10 2BP

e-mail: p.richardson@shu.ac.uk

7.1 Introduction

The consumption of food and drink is necessary to maintain life. However, there is widespread variation not only in the amount of food eaten, but also in the types of food consumed; the presence of preferences lies behind the mixed patterns of consumption. Certain tastes may be disliked by the vast majority of the population (e.g., bitter-tasting foods) while others (particularly sweet tasting), may be actively preferred (Mennella et al. 2005). The processes associated with these preferences are complex; multifactorial models have been developed in order to delineate the influences underlying the preferences but these can be broadly defined as *food effects*, that is, the physical and sensory properties of food and *non-food effects*, for example, person-specific reasons.

7.2 Sensory Properties of Food

The food-related effects (the sensory properties of food such as texture, appearance, and taste) have been of prime interest in choice behavior research; intuitively, any food perceived to be unpleasant along these dimensions is unlikely to be consumed. The texture of an edible substance (e.g., its viscosity, crispness, or grittiness) is known to relate directly to food selection in both primates and humans (Araujo and Rolls 2004). Similarly, the color and appearance of food has been demonstrated to interfere with judgments of flavor intensity and is known to influence the pleasantness and acceptability of foods. Children seem to be particularly sensitive to these effects, often refusing to consume a particular food if it *has bits in it* (De Moura 2007) or happens to be *green* (see later section on "Sweet Taste Preference"). However, it is how a food product tastes that has been the main focus of the food-choice research.

7.3 The Basic Tastes

The human tongue has receptors for what have been described as sweet, sour, salty, and bitter tastes. These are classically described as the four basic food tastes, and each have been associated with variable levels of like/dislike among the general population. Umami (savoriness) and fat both have a growing recognition in the literature as basic tastes that have corresponding receptors on the tongue and unique neural responses (Bachmanov and Beauchamp 2007). Other "tastes" such as spiciness are not unique, and what may be (erroneously) perceived as taste (the burning irritation) can then be construed as a pleasant or unpleasant sensation.

7.4 Individual Differences in Taste Preference

The sensation of taste arises from chemical stimulation of specialized cells, taste receptors, which are grouped in small clusters called taste buds. Although located throughout the oral cavity, taste buds are in the highest concentration on the human tongue in structures called papillae (see Fig. 7.1 below).
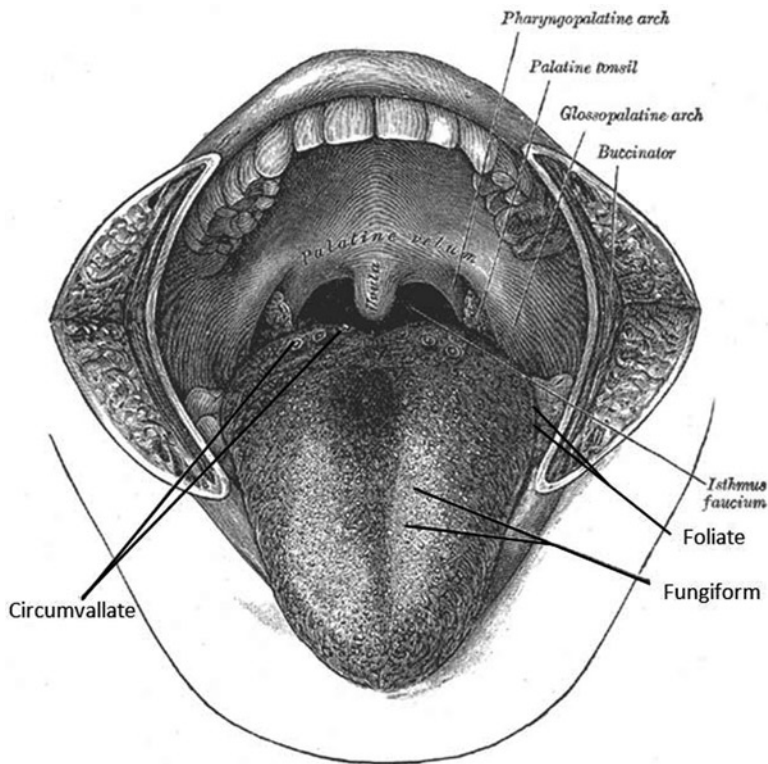
Fig. 7.1 A diagram of the human tongue. The location of the circumvallate, foliate, and fungiform papillae are indicated in bold (Amended from Gray 2000. Reproduced with permission)

Individual differences exist for the exact number present on the tongue and intuitively, taste intensity perception is correlated with the number of papillae present (Miller and Reedy 1990). This biological basis for individual difference in taste preference has thus far been difficult to study; however, with recent advancements in genetic research, it is now becoming clear that genetic differences account for some individual difference in taste preference (Drewnowski et al. 2001). This research thrust is exciting because a genetic basis for preference would transcend cultural boundaries, however it will be several decades before results can be used for any serious applied outcome.

Individual differences could also potentially stem from idiosyncratic likes and dislikes, demographics, psychological, and personality traits. It is entirely plausible that such individual differences could predict taste preferences, however in many published articles these individual differences are often considered "*annoying sources of variance in research…*" and "*referred to as nuisance variables…*" (Stevens 1996 p.303). Obvious differences such as gender and age tend to be included in research, but the less-obvious individual differences, particularly along the psychological dimensions are not. Yet, in other research fields such as health psychology, the opposite pattern is found and individual differences are taught and studied. The emphasis is one of inclusion, and variables such as personality are regarded as potentially important distal determinants of health behavior. They can provide "*useful evidence about the nature of mechanisms underlying sensory phenomena and thus are important in the generation of research hypotheses*" (Stevens 1996, pp. 303).

7.5 Gender Differences

Sex differences have been established in various food-related investigations such as cravings for particular food types, proportion of fruit and vegetables consumed, and avoidance of fats from meat (Goldberg and Strycker 2002). These effects appear to exist as early as primary school (Caine-Bish and Scheule 2009). In relation to sweetness, women do tend to rate sweeter tasting products as more pleasant than men are reported to do (e.g., Laeng 1993); in a study investigating sweet taste preference in obesity, nearly 32% of the female participants rated themselves as having a strong sweet taste preference in comparison to less than 13% of the male participants (Elfhag and Erlanson-Albertsson 2006). However, this apparent gender preference for sweet tasting products does not translate to females consuming greater quantities of sweet snacks (Grogan et al. 1997). This same study reported that women were more ambivalent toward eating sweet snacks than men (perceiving them to be significantly less healthy) and were also more influenced by social pressures than men (Grogan et al. 1997). It is not uncommon for research studies to employ single-sex studies to avoid such entanglements: in a recent study investigating sweet intake, liking, and the urge to eat, in relation to alcohol dependence, the authors decided not to recruit female participants due to the social ambivalence regarding sweet snacks (Krahn et al. 2006). We would recommend against this type of subject selection where it can be avoided, instead, we recommend examining the potential determinants of variation.

Males tend to be less sensitive to bitter and sour tastes than females. Acidity is a natural preservative and is an important ingredient in a range of products; bitterness tends to be minimized but is nevertheless a natural flavor in some foods (e.g., the important antioxidant activity in olive oil is related to polyphenols that elicit a bitter taste). Sweetness may be used to mask certain levels of sour and bitter tastes. It follows that females may seek higher levels of sweetness, firstly because of a natural preference and secondly to mask perceived acidity and bitterness given higher acuity than reported for males.

7.6 Personality

Personality can be described as the relatively enduring pattern of an individual's unique psychological and behavioral characteristics, which can exert some degree of influence over the thoughts and behavior of the individual (e.g., Dworetzky 1999). Different models of personality abound, but those based on trait theory suggest that these dispositions are relatively stable, enabling a high degree of predictability in a person's behavioral repertoire. Secondary traits (or states) tend to be more transient or only appear under certain conditions and can relate to attitudes and preferences. Biological models argue that particular aspects of personality are heritable (see Fig. 7.2) and that these can map onto specific neurotransmitters in the brain with predictable behavioral responses.

One theory of personality that is commonly reported in research is Cloninger's temperament and character model (Table 7.1), based on his work with people who possessed "extreme" personality profiles (Cloninger 1987). Temperament is depicted as a collection of unconscious dispositions that can differentiate people quantitatively. The four constructs of "temperament" include novelty seeking, harm avoidance, reward dependence, and persistence. In contrast, "character" refers to constructs that demonstrate an acquired or learnt component, such as the degree of self-directedness, co-cooperativeness, and self-transcendence (Cloninger 1993, 1994). See Table 7.2 for an explanation of these terms.
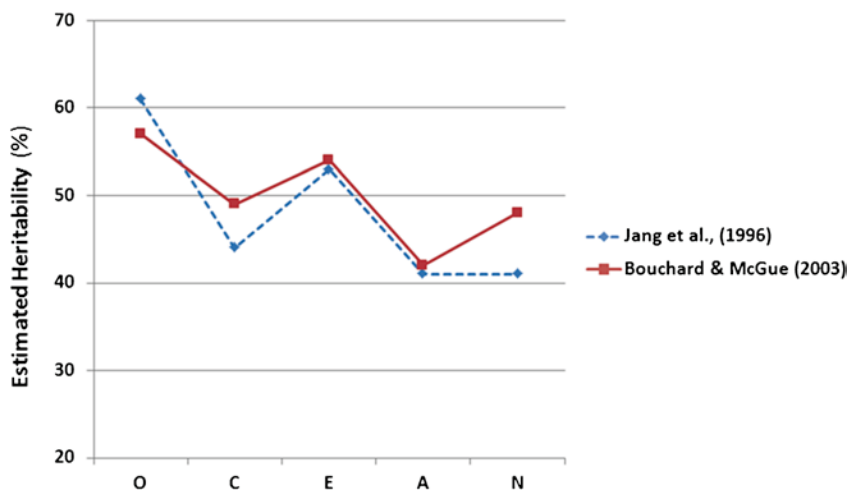
Fig. 7.2 Estimated heritability of personality factors from the Big five questionnaire. Similar data from two independent studies indicate a high degree of consistency in this estimation. Key: *O* openness, *C* conscientiousness, *E* extraversion, *A* agreeableness, *N* neuroticism

7.7 Temperament and Eating Behavior

It is the constellation of temperament qualities that has received most attention in research due to the forging of a direct link between personality and biological mechanisms. Temperament is assumed to have a constitutional or biological basis strongly influenced by heredity. Three strands of Cloninger's theory of temperament have been linked to neurotransmitter functioning in the brain, and are known to modulate eating behavior and the regulation of feeding. Specifically these are: dopamine (novelty seeking), serotonin (harm avoidance), and noradrenalin (reward dependence).

Cloninger posits that high novelty seeking is a proxy measure of dopamine activity within the mesolimbic regions of the brain (Cloninger 1994). Dopamine is a neurotransmitter thought to modulate the rewarding aspects of "motivating" stimuli, particularly during the learning of new likes and dislikes, the seeking out of new and novel experiences. Animal studies indicate that dopamine activity is linked more to the anticipatory desire and motivation (the *wanting*) rather than pleasure derived from consummation (the *liking*) (Robinson et al. 2005). Increases in dopamine activity in the mesolimbic and orbitofrontal regions of the brain have been associated with response to pleasant tastes and these same regions show a higher degree of activity when hungry compared to satiated (Tataranni et al. 1999). As such, dopamine is a primary candidate for involvement in food reinforcement, and by extension, in mediating taste preference.

Low levels of serotonin are typically reported in patients with clinical levels of anxiety and depression. Subscales of harm avoidance include anticipatory worry, fear of uncertainty, and shyness, all of which can be considered prototypical features of clinical anxiety (Cloninger 1993). Those with high levels of harm avoidance may actively avoid novel situations or those that may involve confrontation or punishment. More specifically, raising serotonin levels has been demonstrated to suppress appetite, lower food intake, and lower fat intake (for a review see Lam et al. (in press)).

Classical and operant conditioning are two processes that underpin the ability to learn, essentially the pairing of conditioned stimuli/cues with responses. The acquisition of paired associations is thought to be modulated by noradrenaline. Atypical noradrenaline functioning has

Table 7.1 Key terms of Cloninger's temperament and character theory of personality (Cloninger 1998)

	Descriptors of extreme variants	
Temperament dimension	High	Low
Harm avoidance	Pessimistic	Optimistic
	Fearful	Daring
	Shy	Outgoing
	Fatigable	Energetic
Novelty seeking	Exploratory	Reserved
	Impulsive	Rigid
	Extravagant	Frugal
	Irritable	Stoic
Reward dependence	Sentimental	Critical
	Open	Aloof
	Warm	Detached
	Sympathetic	Independent
	Industrious	Lazy
	Determined	Spoiled
	Ambitious	Underachieving
	Perfectionistic	Pragmatic
Character dimension		
Self-directedness	Responsible	Blaming
	Purposeful	Aimless
	Resourceful	Inept
	Self-accepting	Vain
	Disciplined	Undisciplined
Cooperative	Tenderhearted	Intolerant
	Empathic	Insensitive
	Helpful	Hostile
	Compassionate	Revengeful
	Principled	Opportunistic
Self-transcendent	Self-forgetful	Unimaginative
	Transpersonal	Controlling
	Spiritual	Materialistic
	Enlightened	Possessive
	Idealistic	Practical

been demonstrated in patients with posttraumatic stress disorder, who are overly sensitive to trauma-related cues (for review, see Yehuda 2002). Typically, it is thought of as governing the body's "fight or flight" response in times of acute stress, and on the TCI, its subscales are sentimentality, attachment, and dependence. Low levels of reward dependence are associated with being aloof, withdrawn, and detached; high levels are synonymous with being open, revealing, and dedicated (Cloninger 1993). Drugs that target noradrenaline receptors have been demonstrated to promote weight loss by suppressing appetite and producing early satiety.

7.8 Sweet Taste Preference

Sweetness has been referred to as an innate or naturally preferred taste, even in very young children, while salty, sour, and bitter are acquired tastes that need some perseverance, often extending into late childhood before being liked. Foods that are rated as pleasant and consumed in great quantities by

Table 7.2 Temperament personality constructs indicated with neurotransmitter systems and associated subsequent behavioral response (Amended from Cloninger 1998. The Genetics and Psychobiology of the Seven-Factor Model of Personality pp.68). In Kenneth R. Silk (1998) Biology of Personality Disorders

Temperament construct	Principal neurotransmitter	Relevant stimuli	Behavioral response
Novelty seeking	Dopamine	Novelty	Exploratory pursuit
		CS of reward	Appetitive approach
		CS or UCS of relief of monotony or punishment	Active avoidance, escape
Harm avoidance	Serotonin	Conditioned signals for punishment, novelty, or frustrative nonreward	Passive avoidance, extinction
Reward dependence	Noradrenaline	Reward conditioning (pairing CS and UCS)	Formation of appetitive CS

CS conditioned stimulus, *UCS* unconditioned stimulus

children in most western countries are those with a high sugar and fat content, while vegetables are regarded as universally disliked. This pattern of taste preferences appears to be universal and transcends cultures (Prescott et al. 1992).

Additional evidence for the innate preference of sweet tastes comes from studies involving neonates. A common methodology has been adopted by several studies – neonates are given solutions containing the basic tastants and facial expressions are observed immediately after ingestion (see Fig. 7.3). By observing positive facial expressions, sweet tastes were found to be universally accepted, while sour and bitter tastes were associated with tell-tale facial responses indicating an aversion (e.g., Steiner 1977). Recent research suggests this innate preference for sweet tastes may have a partial genetic basis (Mennella et al. 2005), and this regulates the consumption of sweet foods (Reed et al. 1997). Keskitalo and colleagues (2007) found a relationship between the frequency of consuming sweet foods and a genetic marker on chromosome 16. They had participants rate the pleasantness of various tastants, and reported preference for the extremely sweet solution, reporting an estimated heritability factor of 40% (Keskitalo et al. 2007). However, two caveats to this study are (1) the unequal gender split in favor of women (68% vs. 32%), and (2) the age range of participants (18–78 years). No data was published describing the demographics, but demographic variables were used as covariates in the analysis.

The innate tendency for a sweet preference might confer an adaptive advantage – a sweet taste signals the presence of sugars and thus of immediate high calorific value. In contrast, sour and bitter tastes are perhaps indicative of noxious substances and the decomposition of food and thus best avoided. Infants and older children often appear to be picky with food, particularly if they have not tasted it before. This mild neophobia illustrates the process of children learning what is safe to eat and what is not.

Neophobia has been identified in adults and can predict behavior pertaining to ingestion of novel vs. familiar foods and willingness to eat novel foods (Pliner and Hobden 1992). The authors categorized neophobia as a personality trait, and report that it correlates positively with measures of trait anxiety but negatively with novelty/sensation seeking (Pliner and Hobden 1992). Both of these traits have genetic links, suggesting that neophobia is also heritable. Indeed, one twin study estimated the heritability of neophobia at 67%, though this was only with female participants (Knaapila et al. 2007). This evidence is supportive for the notion that likes and dislikes of specific tastes and foods can be mediated by personality traits.

Fig. 7.3 Neonates displaying variable facial responses to basic tastes (Reproduced from Steiner 1997. With permission). Key: *1* rest, *2* water, *3* sweet, *4* sour, *5* bitter

One early study to investigate personality traits and taste preferences was completed in India by Venkatramaiah and Baby Devaki (1990). They asked 38 female postgraduate students to self-report food preferences via checklist, and measured personality traits with the Indian Personality Inventory (unpublished measure created by the same authors in 1980). The personality traits were derived from the Indian philosophy of Samkhya. They reported main effects for personality and food types, speculating that sweet foods were preferred most by those with high "tamas" scores (a trait that maps onto Cloninger's harm-avoidance trait). However, no post hoc analyses were ran to assess group differences for any tastes.

A recent study investigated the purported influence of trait anxiety on food taste preferences in Japan (Kato et al. 2006) (Fig. 7.4). The authors divided 73 university students into 2 groups according to the trait scores from the State-Trait Anxiety Inventory, and then tested for sensitivity to sweet, salty, and sour tastes. Of prime interest was the finding that the trait-anxiety group had a higher sensitivity to sweet tastes but not salty or sour. Kato and colleagues (2006) posited that people with high trait anxiety experience more stress on a daily basis, and that this was instrumental in causing the change to eating habits. However, the research was based on young university undergraduate students with no breakdown of gender. Given that the study did not employ a longitudinal design and no premorbid dietary measures were taken, it may be speculative to conclude that trait anxiety *caused* any changes to eating habits.

The link between trait anxiety and sweet preference is supported by an earlier study investigating personality and dietary habits (Kikuchi and Watanabe 2000). They tested 470 university undergraduate students who were required to keep daily records of their dietary habits recorded over a 2-year period, designed to capture the frequency and amount of 40 pre-specified food types consumed. Personality was measured using a modified version of the NEO Five Factor Inventory (Costa and McRae 1992). This provided scores on the "big five" factors of personality: openness, conscientiousness, extraversion, agreeableness, and neuroticism. High scores on each of the five personality factors

Fig. 7.4 A taste preference experiment in progress. This may usually take place in a partially secluded booth, in which the participant is able to make judgments on preferred food or drink tastes by sampling the products; this permits a fine degree of control and manipulation of several variables – in contrast to interview-based research, which relies on participants recollecting taste preferences in the absence of any actual tasting

had characteristic features; of specific interest was the finding that those with high neuroticism had a pronounced sweet taste preference irrespective of gender (Kikuchi and Watanabe 2000).

This finding was supported by Elfhag and Erlanson-Albertsson (2006) in a study of 60 clinically obese patients awaiting treatment at a clinic. Sweet (and fat) taste preference was assessed via structured interviews; on this basis, patients were assigned to one of four groups: strong sweet preference, strong fat preference, strong preference for sweet and fat, and no strong taste preference. Personality was measured with the Swedish University Scales of Personality. The Three Factor Eating Questionnaire was also used to provide measures of cognitive restraint (attempts to limit food intake), disinhibition (difficulties in limiting food intake), and hunger experience (subjective feelings of hunger). The results indicated that those who demonstrated a strong preference for sweet tastes (as opposed to no strong taste preference) showed higher levels of neuroticism; in particular, the neuroticism subscales that were critical for this distinction were lack of assertiveness and embitterment. Sweet taste preference bore no relation to any of the three eating characteristics (Elfhag and Erlanson-Albertsson 2006). The authors suggest these imply low self-confidence and self-esteem, and an externalized locus of control for difficulties. However, one earlier study (Stone and Pangborn 1990) instead found that preference for sweetness was higher in university students with an "outgoing" personality style, a trait that Elfhag and Erlanson-Albertsson conceded was the "*opposite of neuroticism and rather implies being more unconcerned and carefree*" (p. 64). However, the authors commented that the relation between the outgoing trait and liking for sweetness was not straightforward, as participants who did prefer sweeter drinks did not differ on personality measures from those who did not prefer the sweeter drinks (Stone and Pangborn 1990).

Overall, these recent studies all indicate that those with high levels of trait anxiety and neuroticism exhibit a sweet taste preference. It has been proposed that this may be characterized by "comfort eating," indicative of some reward deficiency syndrome (Wang et al. 2003) or possibly reflective of some "*self-medicating purpose that exceeds basic energy requirements*" (Davis et al. 2004 p. 132). There are indications that the opioid neurotransmitters may be involved in the rating of sweet tastes as pleasant and in reducing observed behavioral measures of stress after eating sweet tasting foods

(Dallman et al. 2003). Dallman and colleagues (2003) proposed that symptoms of chronic stress could be attenuated by the consumption of sucrose (a sweet tasting sugar) by way of dampening sympathetic activity in the hypothalamo–pituitary–adrenal (HPA) axis, a feedback system known to be dysfunctional in anxiety disorders (e.g., Yehuda 2002); it is thought that this is mediated through opioidergic pathways (Dallman et al. 2003).

We recently published a study investigating personality traits associated with a preference for a sweet white wine (Saliba, Wragg and Richardson 2009). Forty-five participants (with a near-equal gender split) were categorized as preferring either a base or sweet taste on the basis of their hedonic response to a dry white wine and another sample with fructose added at 20 g/L. Personality traits were assessed with the big five personality inventory and the Impulsiveness Venturesomeness and Empathy Scale (IVE - Eysenck and Eysenck 1991). We found that the sweet preference group had significantly lower levels of the openness to experiences trait but higher levels of impulsivity (see Fig. 7.5). Openness to experience has been portrayed as a proxy measure of the willingness to explore new and unfamiliar experiences, ideas, and feelings (Costa and McCrae 1992) and may be akin to the novelty-seeking trait in Cloninger's measure of temperament (Cloninger 1993). Previous studies suggest that those with high openness report healthier dietary practices (Goldberg and Strycker 2002). We speculated that infants with a preference for non-sweet taste do not receive sufficient dietary stimulation and so are open to new experiences in order to fulfill this. The finding that sweet taste was preferred by those with high levels of impulsivity is consistent with previous research (Davis et al. 2004).

Animal studies have reported a positive association between preference for sweet solutions and the subsequent intake of alcohol (Sinclair et al. 1992). In a study conducted in patients with alcohol dependency, Kampov-Polevoy and colleagues reported a preference for a solution containing the
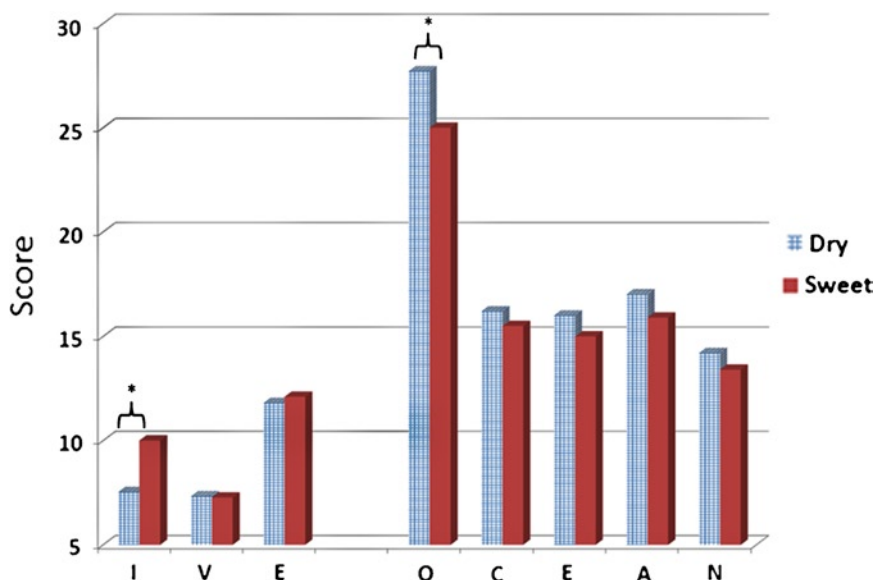
Fig. 7.5 Graph depicting mean average scores of the dry vs. sweet wine taste preference groups on the Impulsiveness, Venturesomeness and Empathy (*IVE*) and Big five (OCEAN) personality questionnaires (data from Saliba et al. 2009). Note: the scores from the two personality tests are not comparable with each other, and are shown for illustrative purposes only. Key: *denotes significance at $p < 0.05$, $N = 45$

highest sucrose concentration (Kampov-Polevoy et al. 1998). They report that the nonalcoholic group preference for sweet tastes was associated with low novelty seeking, and conversely, sweet-disliking participants had high novelty-seeking scores. In stark contrast, the sweet-liking alcoholics showed high novelty-seeking scores as well as high harm-avoidance scores.

A study by Krahn et al. (2006) reported that alcohol-dependent patients reported a preference for the sweetest tastant during the first month of abstinence. Patients who reported abstinence at 6 months were less likely to prefer the sweetest tastant than those who did not maintain abstinence. The authors suggest sweet preferences could be a marker for future abstinence. Garbutt and colleagues suggest this "sweet-liking/sweet-disliking" phenotype can be considered a marker for cerebral opioid functioning (Garbutt et al. 2009). This hypothesis was tested in alcohol-dependent patients during a 12-week treatment program with naltrexone (an opioid receptor antagonist, which arguably blocks the pleasurable effects of alcohol). Patients were dichotomized into sweet-liking or sweet-disliking groups via a taste test given prior to treatment ($n = 15:25$ respectively), and had their responses and compliance to the naltrexone program recorded. Both groups had similar craving levels prior to treatment and similar retention levels following the study, though the sweet-liking group took longer to achieve the necessary 3-abstinent days prior to onset of treatment and were less likely to achieve two consecutive dry days during treatment. The sweet-disliking group also had significantly more abstinent days throughout. Interestingly, the authors also reported that sweet-liking patients with high cravings had a higher percentage of abstinent days compared to sweet-disliking patients also with high craving. However, Kranzler and colleagues (2001) argued that since children of alcoholic parents are at a greater risk of developing alcohol dependency, then preference for sweet taste must be a phenotypic marker for risk of alcoholism. They found no such pattern, and suggest that the effect published by Kampov-Polevoy and colleagues may be instead due to chronic drinking, as opposed to an underlying genetic predisposition.

7.9 Applications to Other Areas of Health and Disease

The World Health Organization has predicted that by 2015, over 700 million people worldwide will be obese (WHO 2006), a prevalence rate of almost 10%. Research investigating the factors associated with poor dietary lifestyle has been ongoing, such as knowledge of the effects of consuming too much food. Research suggests that although 95% of US adults believe that balance, variety, and moderation are the keys to healthy eating (Lachance 1992) and 83% are aware that what they eat can affect their future health, there is a discrepancy between dietary knowledge and actual intake (Shepherd and Stockley 1987). The fact that nutritional knowledge alone may be insufficient to promote changes in eating behavior suggests that psychological factors may be paramount in setting the stage for dietary change. The underlying drivers of consumption, particularly related to personality and taste preferences, are a current focus. Our own work (Saliba et al. 2009) showing a link between personality and taste preference highlights the need for a whole of modeling approach, one that takes into account underlying taste preference, personality type, as well as other variables such as food attitudes and cultural norms.

Of particular concern is the fact that high impulsivity (specifically, sensitivity to reward) has been linked to overeating (Davis, Strachan and Berkson 2004) and along with food preferences strongly predict an individual's body mass index (Davis et al. 2007). An individual who presents high in impulsivity and also has taste preferences that predispose them to overeating is at particular risk. Impulsivity has been linked to sweet taste preference (Saliba et al. 2009) and obesity (Fassino et al. 2002), although recent evidence has questioned whether sweet taste preference actually leads to

higher levels of obesity (Hayes and Duffy 2008). The same research suggests that fat preference may be more predictive of obesity, albeit along with sweet preference (Hayes and Duffy 2008); future research needs to determine the link between personality type, fat taste preference, and subsequent obesity levels.

Summary Points

- Individual taste preferences cause a widespread variation not only in the amount of food eaten, but also in the types of food consumed.
- Individual differences in the concentration of taste buds on the tongue affect taste acuity, which influences taste preferences. This research is exciting because a biological basis for preference would transcend cultural boundaries; however applied outcomes may be some decades away.
- It is entirely plausible that individual differences could predict taste preferences; however in many published articles these individual differences are often not examined. Yet in other research fields such as health psychology the opposite pattern is found and individual differences are taught and studied; variables such as personality are regarded as potentially important distal determinants of health behaviors.
- Women tend to rate sweeter tasting products as more pleasant, whereas males are more tolerant of higher levels of sourness. Although gender differences exist in the types of foods consumed, this does not appear to translate to clearly poorer dietary choices by either gender.
- Different models of personality abound, but those based on trait theory suggest that dispositions are relatively stable, enabling a high degree of predictability in a person's behavioral repertoire. Secondary traits (or states) tend to be more transient or only appear under certain conditions and can relate to attitudes and preferences.
- Sweetness has been referred to as an innate or naturally preferred taste, even in very young children, while salty, sour, and bitter are acquired tastes that need some perseverance, often extending into late childhood before being liked.
- Individuals with high levels of trait anxiety and neuroticism exhibit a sweet taste preference. This may be characterized as "comfort eating."
- Impulsivity is a personality dimension known to be associated with overuse syndromes. Individuals with a sweet taste preference report higher on impulsivity, which may be a concern if future research shows that overeating is linked to sweet taste preference.
- Preference for fatty tastes may be the strongest of all taste preferences in predicting obesity. Further research needs to establish the link between personality and fat taste preference.

References

Bachmanov AA, Beauchamp GK. Annu Rev Nutr. 2007;27:389–414.
Caine-Bish NL, Scheule B. J Sch Hea. 2009;79:532–40.
Cloninger R. Arch Gen Psychiatry. 1987;44:573–88.
Cloninger R. Curr Opin Neurobiol. 1994;4:266–73.
Cloninger CR, Svrakic DM, Przybeck TR. Arch Gen Psychiatry. 1993;50:977–91.
Cloninger R. In: Silk KR (Ed) Biology of Personality Disorders. American Psychiatric Press, Inc; 1998.
Costa PT, McCrae RR. NEO PI-R professional manual. Odessa, FL: PAR Inc.; 1992.
Dallman MF, Akana SF, Laugero KD, Gomez F, Manalo S, et al. Physiol Behav. 2003;79:3–12.
Davis C, Strachan S, Berkson M. Appetite. 2004;42:131–8.
Davis C, Patte K, Levitan RD, Reid C, Tweed S, Curtis C. Appetite. 2007;48:12–9.

de Araujo IE, Rolls ET. J Neurosci. 2004;24:3086–93.

de Moura SL. Appetite. 2007;49:716–9.

Drewnowski A, Henderson SA, Barratt-Fornell A. Drug Metab Disp. 2001;29:535–8.

Elfhag K, Erlanson-Albertsson C. Physiol Behav. 2006;88:61–6.

Eysenck HJ, Eysenck S. Adult impulsiveness venturesomeness and empathy scale. London: Hodder & Stoughton; 1991.

Fassino S, Leombruni P, Piero A, Daga GA, Amianto F, Rovera G. Compr Psychiatry. 2002;43:431–7.

Garbutt JC, Osborne M, Gallop R, Barkenbus J, Grace K, et al. Alc Alcsm. 2009;44:293–300.

Goldberg LR, Strycker LA. Personal Individ Differ. 2002;32:49–65.

Gray H (2000) Anatomy of the Human Body. Philadelphia: Lea & Febiger, 1918; www.bartleby.com/107/ [January 2010].

Grogan SC, Bell R, Conner M. Appetite. 1997;28:19–31.

Hayes JE, Duffy VB. Physiol Behav. 2008;95:77–87.

Kampov-Polevoy AB, Garbutt JC, Davis CE, Janowsky DS. Alcohol Clin Exp Res. 1998;22:610–4.

Kato M, Ito Y, Naga S, Shimizu J. J Int Study Diet Hab. 2006;17:44–8. Google Translation.

Keskitalo K, Knaapila A, Kallela M, Palotie A, Wessman M, et al. Am J Clin Nutr. 2007;86:55–63.

Kikuchi Y, Watanabe S. J Epidemiol. 2000;10:191–8.

Knaapila A, Tuorila H, Silventoinen K, Keskitalo K, Kallela M, et al. Physiol Behav. 2007;91:573–8.

Krahn D, Grossman J, Henk H, Mussey M, Crosby R, Gosnell B. Addict Behav. 2006;31:622–31.

Kranzler HR, Sandstrom KA, Van Kirk J. Am J Psychiatry. 2001;158:813–5.

Lachance PA. In: Finley JW, Robinson SF, Armstrong DJ, editors. Food safety assessment (ACS symposium series 484) (pp. 278–296). Washington, DC: American Chemical Society; 1992.

Laeng B, Berridge KC, Butter CM. Appetite. 1993; 21:247–254.

Mennella JA, Johnson A, Beauchamp GK. Chem Senses. 1995;20:207–10.

Mennella JA, Yanina Pepino M, Reed DR. Pediatrics. 2005;115:216–22.

Miller IJ, Reedy FE. Physiol Behav. 1990;47:1213–9.

Pliner P, Hobden K. Appetite. 1992;19:105–20.

Prescott J, Laing D, Bell G, Yoshida M, Gillmore R, et al. Chem Senses. 1992;17:801–9.

Reed DR, Bachmanov AA, Beauchamp GK, Tordoff MG, Price RA. Behav Genet. 1997;27:373–87.

Robinson S, Sandstrom SM, Denenberg VH, Palmiter RD. Behav Neurosci. 2005;119:5–15.

Saliba AJ, Wragg K, Richardson P. Food Qual Pref. 2009;20:572–5.

Shepherd R, Stockley L. J Am Diet Assoc. 1987;87:615–9.

Sinclair JD, Kampov-Polevoy AB, Stewart R, Li TK. Alcohol. 1992;9:155–60.

Steiner JE. In: Weiffenbach JM, editor. Taste and development: the genesis of sweet preference. Washington DC: US Government Printing Office; 1977.

Steiner JE. Pure Appl Chem. 1997;69:721–7.

Stevens DA. Food Chem. 1996;56:303–11.

Stone LJ, Pangborn RM. Appetite. 1990;15:63–79.

Tataranni PA, Gautier JF, Chen K, Uecker A, Bandy D, et al. PNAS. 1999;96:4569–74.

The World Health Report (WHO). Working together for health. 2006.

Venkatramaiah SR, Baby Devaki P. J Pers Clin Study. 1990;6:1–5.

Wang GJ, Volkow ND, Thanos PK, Fowler JS. Psych Annals. 2003;33:104–11.

Wise RA. Phil Trans R Soc: Biol Sci. 2006;361:1149–58.

Yehuda R. N Engl J Med. 2002;346:108–14.

Chapter 8
Changes to Taste Perception in the Food Industry: Use of Cyclodextrins*

Giani Andrea Linde, Antonio Laverde Jr, and Nelson Barros Colauto

Abbreviations

2HPβCD	2-Hydroxypropyl-β-cyclodextrin
2HPγCD	2-Hydroxypropyl-γ-cyclodextrin
3HPβCD	3-Hydroxypropyl-β-cyclodextrin
ADI	Acceptable daily intake
CD	Cyclodextrin
CGTase	Cyclodextrin glycosyltransferase
DHPβCD	2,3-Dihydroxypropyl-β-cyclodextrin
DMβCD	Ditrimethyl-β-cyclodextrin
DOSY	Diffusion-ordered spectroscopy
DSC	Differential scanning calorimetry
FAO	Food and Agriculture Organization
FDA	Food and Drug Administration
FTIR	Fourier transform infrared
G	Guest
G1βCD	Glucosyl-β-cyclodextrin
G2βCD	Maltosyl-β-cyclodextrin
GRAS	Generally recognized as safe
HEβCD	Hydroxyethyl-β-cyclodextrin
HIBβCD	2-Hydroxyisobutyl-β-cyclodextrin
HPβCD	Hydroxypropyl-β-cyclodextrin
NMR	Nuclear magnetic resonance
NOE	Nuclear Overhauser effect
RMβCD	Methylated-β-cyclodextrin
ROESY	Rotating-frame Overhauser spectroscopy
SBEβCD	Sulphobutylether-β-cyclodextrin

TGA   Thermogravimetric analysis
TMβCD   Trimethyl-β-cyclodextrin
UV   Ultraviolet
WHO   World Health Organization

Definition and Explanations of Key Terms or Words

Controlled release: Release of an ingredient gradually to produce a sustained effect
Cyclodextrin: Cyclical oligosaccharides with variable number of units of α-D-(+)-glucopyranoside bonded by α(1→4)
Equilibrium constant: In a chemical reaction is the quotient between the molar concentration of product and reagents after the reaction reached equilibrium and at a given temperature
Food color: An aspect of food caused by differing qualities of light that is absorbed, reflected, or emitted by food compounds.
Food coloring: A colorant, water soluble or insoluble, permitted by the Food and Drug Administration for use in foods.
Functional food: A food having components that provide a potential benefit to health, well-being, or disease-resistance beyond the benefit expected from its main nutritional components.
Inclusion complex: In host–guest chemistry, an inclusion compound is a complex in which one chemical compound (the "host") forms a cavity in which molecules of a second "guest" compound with chemical affinity can fit.
Sensory characteristics: A group of food characteristics such as color, flavor, odor, texture, and taste that produces a different level of pleasant sensations during food consumption.
Smart food packages: Packages that work as a reservoir of active ingredients that can be used to control the release of active components like antimicrobials, flavors, pigments, and antioxidants.

8.1 Introduction

Sensorial demands, like color, taste, flavor, as well as cost and convenience, are major determinants of food selection. Foods that are bitter, acrid, or astringent tend to be rejected by the consumer and this instinctive rejection may not be modified because it is a key mechanism for survival, developed along species evolution. In addition, alimentary behavior has been altered over time because of women's participation in the formal working market and lifestyle changes with less time availability. This has resulted in an increase of industrialized food consumption. The food industry has been responding to this demand by developing a variety of inexpensive and ready-to-consume products that meet the consumers' primary needs. However, there are few industrialized foods that still remain as functional foods.

Environmental and genetic variables provide several modifications in the sensory characteristics of foods. Therefore, in order to obtain food with standard sensory characteristics, the industry uses the addition of sugar, salt, fat, pigments, and flavors, to name a few, or removes unpleasant-tasting compounds. Various unpleasant tastes are related to bioactive molecules that are necessary to the regulation of metabolism and immune system, like phenols, flavonoids, isoflavones, terpenes,

glucosinolates, minerals, vitamins, and peptides. The reduction of these components in food and stressing sedentary lifestyles have been associated to the increase of obesity, diabetes, circulatory diseases, depression, and disorders of sleeping, learning, memory, pain, sexual behavior, appetite, and stress. In order to compensate this unbalance, the food industry has tried to provide functional foods that act on specific targets in the body, affecting positively consumer's health and nutrition. However, there is a dilemma for the consumer and the industry, which is the consumption and the offering of healthy food with pleasant taste.

This chapter introduces CD and its capacity to form inclusion complexes, reviewing the main application of these cyclic oligosaccharides to improve sensory characteristics like flavor, odor, taste, rheology, color, and food functionality. Also, CD safety and its potential use in "smart" packages to improve sensorial and functional quality and food safety are discussed. Although CDs are still minimally used in food, they are one of the best tools to help the food industry solve the dilemma between the demands of taste versus health foods.

8.2   Cyclodextrins: Characteristics and Mechanisms of Complex Formation

CDs are cyclical oligosaccharides (Table 8.1) with variable number of units of α-D-(+)-glucopyranoside bonded by α(1→4). The most common ones are α-, β-, and γ-CD with six, seven, or eight units, respectively; however, CDs with 9, 10, 11, or more units of α-D-(+)-glucopyranose are also known. These macrocycles are produced by the enzymatic conversion of starch through the action of CD glycosyltransferase (CGTase) (Szejtli 2004). Either as a solid crystal or in solution CDs have a toroidal shape. The toroid upper base, also known as secondary base, is surrounded by secondary hydroxyls bounded to C-2 and C-3 carbons of glucopyranose, while the inferior or primary base is surrounded by primary hydroxyls bounded to C-6 of glucopyranoses. A ring of hydrogen bonds is also formed intramolecularly between the 2-hydroxyl and the 3-hydroxyl groups of adjacent glucose units. This hydrogen bonding ring gives the CD a remarkably rigid structure (Szejtli 2004) and is responsible for the toroidal shape and the rigid structure of CDs. The hydrogen-bond network also affects the CD water solubility. The α-, β-, and γ-CD solubilities at ambient conditions are approximately 13, 2, and 26% (mass by mass), respectively. The lower solubility of β-CD compared with α-CD is due to a stronger hydrogen-bond network giving a higher rigid structure to β-CD and lower water solubility. The disruption of hydrogen bonding via molecular manipulation increases water solubility as for hydroxypropyl-β-CD (HPβCD), which increases 60% of the β-CD aqueous solubility (Davis and Brewster 2004). The CD cavity is surrounded by the H-3 and H-5 hydrogens of glucopyranoses and glucosidic oxygens, with the free electrons directed toward the cavity interior. This high electronic density from glucosidic oxygens, the arrangement of hydrogens, and the lack of free hydroxyls toward the cavity make it less hydrophilic than aqueous environment. Thus, hydrophobic molecules in aqueous solution can increase the chemical stability entering the CD cavity. The CD external area is surrounded by hydroxyls with hydrophilic characteristic (Fig. 8.1), which is responsible for CD aqueous solubility.

For inclusion complex formation, the geometry of the guest molecule is very important because it must fit in the CD cavity. CD inclusion is a stoichiometric molecular phenomenon in which usually only one guest molecule interacts with the cavity of the CD. In some low molecular mass molecules, more than one guest molecule may fit into the cavity, and in the case of some high molecular mass molecules, more than one CD molecule may bind to the guest. As a result, one-to-one molar ratios are not always achieved, especially with high or low molecular mass guests (Fig. 8.2). α-CD typically

Table 8.1 Key features of cyclodextrins

1. CDs are cyclic oligosaccharides of different sizes.
2. The most common CDs are α-, β-, and γ-CD with six, seven, and eight glucose units, respectively.
3. They are produced by bacterial enzymatic conversion of starch.
4. CD structure has a toroidal shape with a hydrophilic exterior and a hydrophobic interior.
5. The hydrophobic interior (host or cavity) may receive hydrophobic molecules (guests) to form an inclusion complex.
6. The host protects the guest, reducing contact with heat, oxygen, light, solvents, and other external factors.
7. The physical–chemical characteristics of the guest are modified after inclusion complex formation.
8. CDs mask sensory characteristics, reduce oxidation, stabilize flavor, convert liquid in powder, and enhance solubility, bioavailability, and control release of guests.
9. CDs are widely used in the food and drug industries to encapsulate many different guests.

This table shows the key features of CDs including molecular structure and shape, hydrophobic and hydrophilic characteristics, inclusion complex formation with CD and guest, and also function and applications of CDs. *CD* cyclodextrin
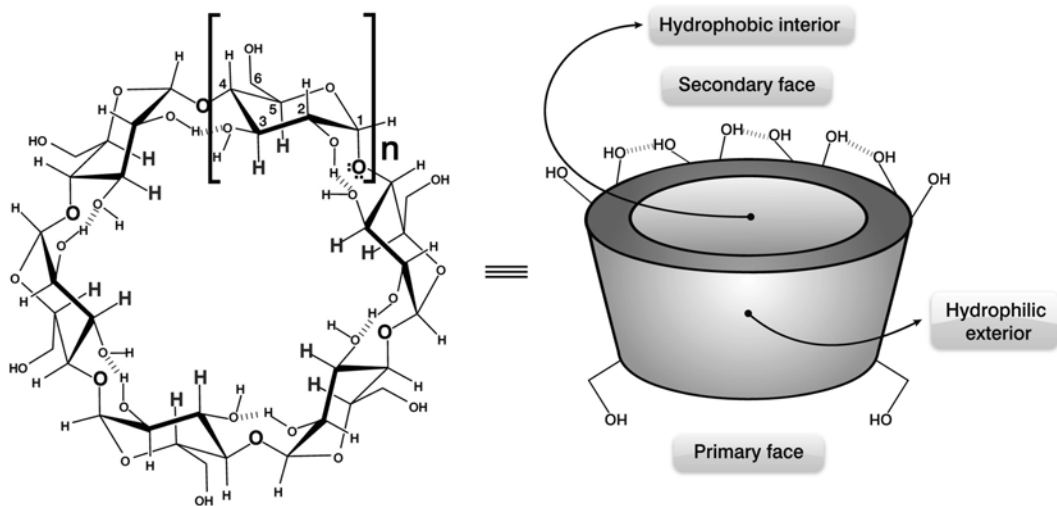
Fig. 8.1 Schematic representations of cyclodextrin. This figure shows the structures of the most used CDs, α-, β-, and γ-CDs (defined by $n = 1$, 2, and 3, respectively), evidencing the arrangement of α-D-(+)-glucopyranoside (glucose) bonded by $\alpha(1 \rightarrow 4)$, and the toroidal structure of CD with hydrophobic cavity and hydrophilic exterior. The secondary face diameter of the interior ring of CD is 0.47–0.53, 0.60–0.65, and 0.75–0.83 nm for α-, β-, and γ-CD, respectively, and that of the exterior ring is 1.46 ± 0.04, 1.54 ± 0.04, and 1.75 ± 0.04 nm for α-, β-, and γ-CD, respectively. *CD* cyclodextrin

complexes low molecular mass molecules with aliphatic side chains, β-CD works well for aromatics and heterocycles, and γ-CD can accommodate macrocycles and steroids (Del Valle 2004).

A second critical factor is the thermodynamic interactions among the different components of the system (CD, guest, solvent); it must have a favorable net energetic driving force that pulls the guest into the CD (Del Valle 2004). The driving forces for complex formation are Van der Waals forces, hydrophobic interactions, changes in solvation energy for both components and, to a lesser extent, hydrogen bonding. The highest stability of the complex occurs with higher hydrophobic guests, whereas polar or ionic guests are less stable (Szejtli 2004). The complex formation and dissociation are a dynamic equilibrium (Fig. 8.3), and the complexation is governed by driving forces expressed
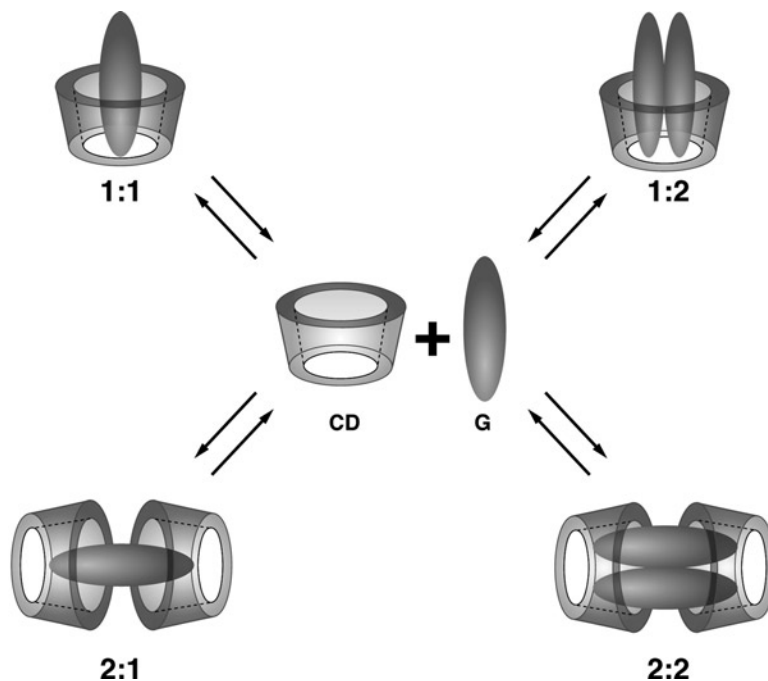
Fig. 8.2 Free cyclodextrin (*CD*) and guest (*G*) to form CD–G complexes. This figure shows the CD–guest complex on a dynamic equilibrium and the formation of inclusion complexes with the entire molecule or only a portion of it and the dependency of the guest size and hydrophobicity in different molar ratios (1:1, 1:2, 2:1, 2:2) to form the CD–guest complex. *CD* cyclodextrin
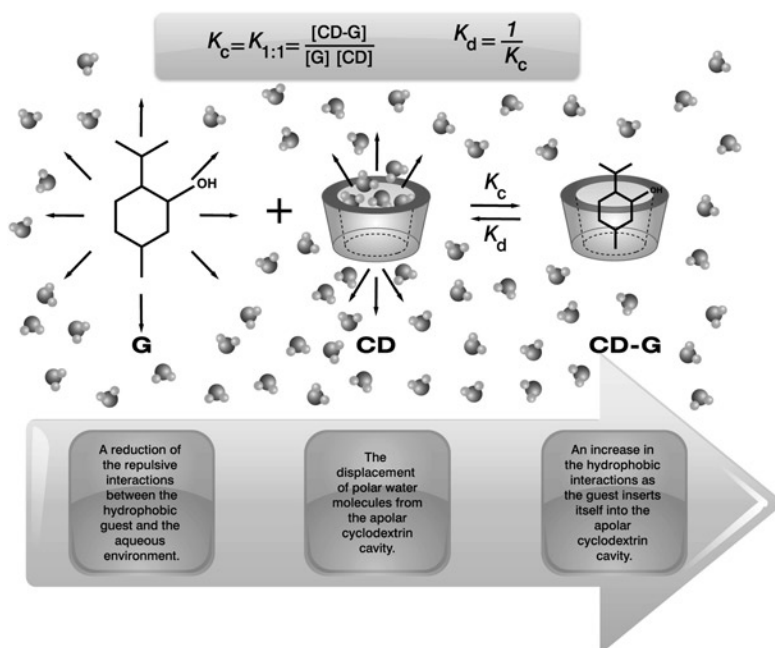
Fig. 8.3 Driving forces to promote the inclusion complex formation of cyclodextrin (*CD*) with guest (*G*). This figure shows the inclusion complex formation with CD and guest, including the dimensional fit between host cavity and guest molecule, as well as the driving forces that push the guest into the CD cavity and the complex formation **Fig. 8.3** dynamic process expressed by an equilibrium constant, K_C. The numerical value of the equilibrium constant can be obtained from measuring the guest and CD concentrations, and this value indicates how the reaction is dislocated. *CD* cyclodextrin

by an equilibrium constant, K_C (Szejtli 2004). The numerical value of the equilibrium constant can be obtained from measuring the guest and CD concentrations.

In the crystalline form, only the surface of CD is available for complexation, but in solutions more CDs molecules are available and it increases the probability of complex formation. As the amount of solvent is increased, the CD and the guest may be so diluted that they do not get in contact as easily as they do in a more concentrated solution. Moreover, water is the most used solvent and it is desirable to keep just enough water to ensure complexation in a sufficiently fast rate. Besides, not all guests are readily solubilized in water, making complexation either very slow or impossible to happen in solution. Some high molecular mass components like oils must be vigorously mixed to allow better dispersion to contact with the CD. Temperature is another important factor to CD–guest formation. The increase of temperature increases molecular shocks which are positive for CD–guest formation; at the same time it increases the molecular vibration that destabilizes CD–guest complex and the guest could be released. Thus, moisture content and temperature are the most important factors to control CD–guest formation or release. A summary of the factors that affect CD inclusion complex formation is presented in Fig. 8.4.

A great technological effort made in the last years, with a lot of investment in research, enabled important cost reductions in the production of CDs, making their industrial use possible (Szejtli 2004). Besides natural CDs, new promising semi-synthetic derivative CDs are expanding new applications of CDs in the food industry (Davis and Brewster 2004).
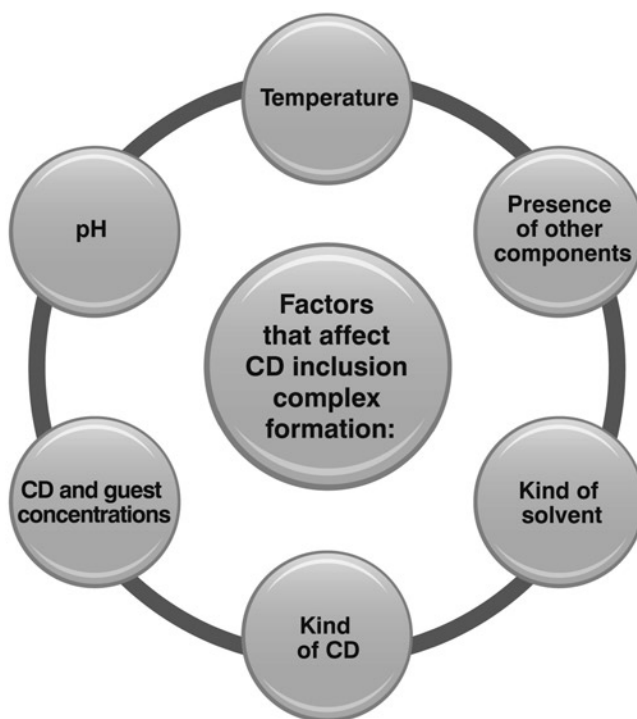
Fig. 8.4 Variables that affect cyclodextrin inclusion complex formation. This figure shows the factors affecting CD inclusion complex formation. For inclusion complex formation, it is necessary that the driving forces push the guest to CD cavity and that CDs and guest get in touch. Thus, any variable that affects driving forces such as pH, kind of CD, and presence of other components affects the molecular shocks as temperature and kind of solvent could affect strongly the inclusion complex formation process. As many variables affect the inclusion complex formation, each CD inclusion complex formation must be evaluated case by case. *CD* cyclodextrin

8.3 Methods of Complex Preparation

CD complexes can be formed by different techniques that are selected according to guest properties such as solubility (Fig. 8.5), equilibrium kinetics, presence of other components, and final guest applications. The commonly used techniques are coprecipitation, slurry, paste, dry mixing, and supercritical carbon dioxide methods; all of them depend on a small amount of water to start the complexation thermodynamics (Hedges 1998; Del Valle 2004).

In coprecipitation, the guest is slowly added to a CD solution and, when the complex solubility is exceeded, it precipitates and can be separated. This method is used when the CD-complex has reduced solubility. Due to the limited solubility of CDs, high water volumes are necessary, limiting the use of coprecipitation for industrial scales (Hedges 1998). Slurry and paste (kneader) methods are similar, because the guest is added in molar proportions to a saturated solution containing 40–50% of CD for the first method and just water to moisten the CD for the latter. After CD-complex formation the mixtures are dried and ground to homogenize particle sizes (Del Valle 2004). Variations of the paste technique using extruders or melt granulators are reported (Suzuki et al. 1993). Due to simplicity, high productivity and easy scale up, the paste technique is more used in food industry (Del Valle 2004).

The dry mixing method is based on simple mixture of components without water addition. In general, it is a slow and inefficient method, restrict to liquid and/or volatile guests that work as solvent like essential oils (Hedges 1998). The supercritical carbon dioxide method consists of obtaining solid complexes and it is considered one of the most promising methods because a unique CD–guest molecular configuration could be obtained. Although it is a fast atoxic chemically stable method with low maintenance cost and promising results described in literature, it is still an experimental technique that has a very high initial cost (Palakodaty and York 1999).
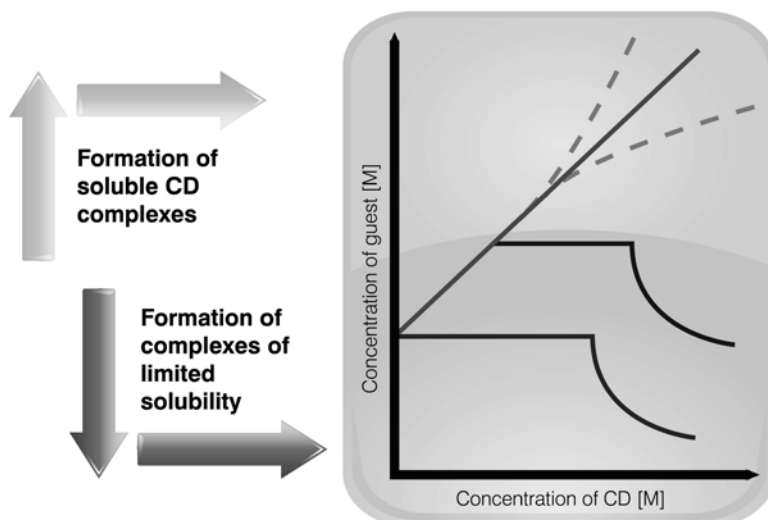
Fig. 8.5 Solubility of cyclodextrin–guest complex. This figure shows how CD concentration affects guest solubility in water. An illustrated number of solubility profiles are presented. The complexes are usually classified as an A-type profile which represents the formation of soluble CD complexes and B-type which indicates the formation of complexes of limited solubility. *CD* cyclodextrin

8.4 Methods of Complex Determination

Most of the determination methods for inclusion complex are based on physical and chemical differences among the CD, the guest, and the inclusion complex CD-guest. Different techniques can measure these differences and have been used to evaluate the CD-complex formation. The differential scanning calorimetry (DSC) or thermogravimetric analysis (TGA) are very used, only if the guest has a melting point below the CD decomposition temperature (300°C). The inclusion complex formation is indicated by an increase of about 10°C in the guest boiling temperature (Hedges 1998). The spectrophotometric methods (UV–visible, fluorescence, and phosphorescence), Fourier transform infrared (FTIR) spectroscopy and Raman spectroscopy have also been used for analyses of complexes. Changes in the guest spectrum occur upon CD–guest formation because the guest is surrounded by the CD and does not interact with other guest molecules, and there is no crystalline guest structure to absorb energy. However there are interferences in the spectra from the CD, and some of the guest spectrum changes are very subtle and require careful interpretation (Li and Purdy 1992). Optical rotary dispersion, circular dichroism, mass spectroscopy, and X-ray crystallography have also been used to characterize complexes. The selection of some specialized techniques frequently depends on available equipment and the guest properties that make the particular technique more sensitive or reliable for the particular complex (Li and Purdy 1992).

Although it is possible to use several techniques to investigate the inclusion process, only analyses through nuclear magnetic resonance (NMR) spectroscopy can confirm the complex formation, determining the association constant and both stoichiometry and topology of the complex (Li and Purdy 1992; Schneider et al. 1998). The topology of the CD-complex can be obtained using a 2D rotating-frame Overhauser spectroscopy (ROESY). The presence of intermolecular nuclear Overhauser effect (NOE) between CD protons (H-3 and H-5) with guest hydrogen proves that the guest is inside the CD cavity for the reason that NOE cross peaks are observed when the protons are closer than 0.4 nm (Schneider et al. 1998). The association constants can be calculated by diffusion-ordered spectroscopy (DOSY) method, based on diffusion coefficient measurements of free guest and CD (Johnson 1999). Several researchers of the field do not use conclusive NMR techniques due to the difficulties to access equipment. However, the other mentioned techniques provide strong indications of complex formation and can be used with restrictions, when CD application does not need confirmation of inclusion complex formation.

Evaluation and characterization of complexes by molecular computational modeling is limited by the size and flexibility of CD and the numerous interactions in aqueous solution, which introduce restrictions to mathematical models (Lipkowitz, 1998). In general, computational modeling allows reasoning and complementing experimental observation.

8.5 Cyclodextrins to Improve Food Color

The food color is the first quality parameter evaluated by consumers before food flavor, taste, and texture. Thus, color intensity and brightness are key parameters to food quality control. The color in food is formed mainly by a group of nonpolar, and chemically and enzymatically unstable pigments. In order to restore color in food, it is usual to add natural or synthetic coloring pigments. The former are less chemically stable than the latter, but some doubts about the safety of synthetic pigments still remain. Therefore, natural coloring pigments are more indicated for good health, but they have low solubility and high rate of degradation, which limit their use as food coloring pigments.

Regarding this, CDs are very important as food color modulators due to both increased solubility and chemical stability of coloring components. The natural pigments curcumin, paprika (Tønnesen et al. 2002), and lycopene (Blanch et al. 2007) have an increase of water solubility and reduction of oxidation rate when included in CDs. In foods with natural coloring such as tomato ketchup, the addition of CDs (0.2%) protected the natural pigments even after heating at 100°C for 2 h (Kawashima 1980).

CDs have the advantage of being directly added to food to protect natural pigments as well to control coloring components produced during food processing. Furthermore, empty CDs can control the Maillard's reaction speed and stabilize the preformed cooked cured-meat pigment derived from red blood cells (Shahidi and Pegg 1991).

CDs can also be used to inhibit the probrowning polyphenol-oxidase reaction, by including substrates and cofactors such as chlorogenic acid, polyphenols, cinnamic acid, and Cu^{+2}. The polyphenol-oxidase reaction converts the colorless polyphenols to colored components and it occurs just after vegetable damage and during juice production (Irwin et al. 1994). An example is the addition of CDs (1–4%) to chopped ginger root, which stabilizes enzymatic browning during vacuum storage for 4 weeks at 5°C. In the case of apple juice and pear juice, the maltosyl-β-CD prevents ascorbic acid oxidation, a strong inhibitor of enzymatic browning. The secondary antioxidant effect of maltosyl-β-CD retains the color and the food antioxidant capacity (Del Valle 2004). However, the efficiency of CDs for polyphenol-oxidase control depends on the fruit. For peach juice, β-CD was incapable of inhibiting juice enzymatic browning, while α-CD and maltosyl-β-CD presented strong inhibition. For banana juice, the CD was a probrowning agent, leading to changes in color parameters (Sojo et al. 1999).

Although enzymatic browning can be controlled by CD addition, it is normally stopped by thermal shock in water. This technique extracts important components from foods like minerals, pigments, volatile components, and polyphenols. These components have important functions in the organism as cofactors and catalyzers of enzymatic reactions, antioxidants, chemical mediators, and electron transporters, among others. Thus, elimination or reduction of food thermal shock in water retains the natural healthy value of vegetables, improving the quality of industrialized food.

8.6 Cyclodextrins to Improve Food Flavor

Odor has an important role in the perception of food quality and it is one of the principal sensory factors for satiety during a meal. Reduced olfactory satiety caused by lack of natural food odors can enhance food intake (Rolls and Rolls 1997). The food aroma compounds are highly volatile, and heat and light unstable. Also, it can change with variations in the food after cultivation, processing, storage, packaging, and preparation (Szente and Szejtli 2004).

Controlling flavor retention and releases in food is an important goal for food industries. The use of encapsulated flavor is well-established and CDs are one of the simplest encapsulating systems for different flavors (Reineccius et al. 2003). CDs can protect chemical and sensorial characteristics of components because the aroma molecule fits in the CD cavity. Encapsulation effects are mainly the reduction of: evaporation, oxidation by light, heat, or pH attack, and transformation of oils into easily manipulated powder for addition to food. Encapsulation can also control aroma release by slow guest liberation, mask off-notes of aromatic molecules by affinity with CD cavity, and increase food flavor by water dissociation of aroma due to polar external part of CD (Reineccius et al. 2003). Even with aroma losses by temperature, there is a great potential for using CD to maintain food flavors during pasteurization and extrusion processes (Kollengode and Hanna 1997). Another interesting

application of CD is in frying oils, because it can remove free fatty acids and reduce smoke formation, foaming, browning, and deposition of oil residues on surfaces (Astray et al. 2009).

The specific nature of the interactions between CD and the aroma components is the CD's major strengths. They are also a weakness, in that only molecules with the right size, geometry, and polarity can fit inside the CD cavity and form a stable complex (Stella and He 2008). The retention of aromatic components inside the CDs is a complex phenomenon in which many factors take part, making the encapsulation method an important step for economical viability of the process. A main reason to choose the encapsulation method is the amount of water involved in the process because it must be removed during the drying process. Slurry and solid mixture are cited as best methods to large-scale production of aroma encapsulation. Proteins, carbohydrates, and emulsifier additions could also improve aroma retention inside the CD (Jouquand et al. 2004). Another important point is the drying process because it involves the energy addition that could destabilize the complex. Bhandari et al. (1999) listed several methods to dry β-CD lemon oil complex and showed that the spray-drying system was simpler and quicker, and achieved an easy-to-use fine powder that is the most indicated to scale up production.

The release of an aromatic component inside the CD depends on the guest affinity to the CD, pH, and food composition. However, the most important points are temperature and moisture content. Temperature affects molecular vibration and reduces the CD–guest affinity, increasing the guest dissociation speed (Kollengode and Hanna 1997). Dry mixtures of oils and CDs have retained 38–100% of their aromatic potential after 14 years (Szente and Szejtli 2004) whereas the presence of water speeds up the release of included aroma because of the complex dissociation (Labows et al. 1996). The main applications of CDs in aroma maintenance in food are shown in Table 8.2.

Although CDs have a great potential to protect aromas, there are some limitations of this technology for the food industry. The principal challenge is the standardization of encapsulated aroma. Aromas are generally a mixture of molecules with different affinities to the CD cavity and consequently with different dissociation speeds in the food. As a consequence, a mixture of aromatic components included in the CD can have a different final aroma than the original (Astray et al. 2009). Therefore, CDs are appropriate for protection and controlled release of aromas compounded of few components and with similar structure and polarity so that the affinity to the cavity does not significantly affect the complex dissociation. Because of the specific characteristics of each aromatic mixture and the intrinsic characteristics of the food, such as composition and pH, the use of CDs for protection and controlled release of aromas in food cannot be generalized, but needs to be analyzed on a case-to-case basis starting from food processing until the food reaches the final consumer.

Table 8.2 Application of cyclodextrin (CD) for food flavor improvement

Compound	Aroma	CD	Improvement	Source
Cyclic sulfur compounds	Shiitake mushroom flavor	α-CD–maltodextrin	Flavor retention	Yoshii et al. (2005)
Eugenol	Clove odor	β	79% odor retention during extrusion	Kollengode and Hanna (1997)
Five ester types	Pear aroma	α	Heat protection at 120 °C for 60 min	Tobitsuka et al. (2006)
Goat's milk	Goaty odor	β	Reduce goaty flavor	Meier et al. (2001)
l-menthol	Menthol odor	β	100% of odor remained in long-term storage and heat protection	Reineccius et al. (2004)
Rice flavor oil	Rice odor	α-CD–dextrin	Odor retention and conversion of oil to powder	Kawakami et al. (2009)

This table presents the main use of CDs in food formulations for flavor protection, delivery, or masking. *CD* cyclodextrin

8.7 Cyclodextrins to Improve Food Taste

The consumer's first criterion to choose food is its good taste and the second one is food with high calories at low cost (Drewnowski and Gomez-Carneros 2000). Considering that obesity has been treated as a public health issue, some industries have been developing healthier foods by reducing sugar, fat, and sodium, and adding polyphenols, phytosterols, vitamins, minerals, and soy products; this addition generally intensifies the bitter and astringent taste in foods (Ley 2008) and consequently decreases their appreciation and demand by consumers.

CDs can reduce the bitter taste in foods by CD inclusion complex formation that surrounds the bitter molecules that pass by the tongue, without signaling the taste. As the complexation occurs through a non-covalent interaction between the bitter molecule and the CD cavity, the guest is normally well liberated along the digestive system; therefore, CD addition in foods seems to be the best method to mask unpleasant taste and keep foods healthier. Furthermore, CDs can neither be considered tasteless nor only slightly sweet because a 0.5% β-CD solution is as sweet as sucrose (Szejtli and Szente 2005). Thus, the natural sweet taste of CDs might also mask bad tastes in food; however, it is not used for this purpose. Another method to eliminate bitter taste is removing bitter molecules from foods through retention in columns filled with CDs. In that case, healthier bitter compounds are removed from foods and the healthy food quality is reduced.

In soybean products, CDs can reduce up to 90% of the grassy smell, bitterness, and astringent taste from hydrolyzed soybean, in the presence of 10% of α-CD (Linde et al. 2009) or 5% of β-CD (Linde et al. 2010). In this case, nonpolar amino acids responsible for bitter taste are included in the CD cavity and pass by the tongue without signaling the taste. Several techniques were suggested to reduce or mask the bitterness of hydrolyzed proteins, but all of them presented disadvantages like loss of essential amino acids and bioactive peptides, osmolarity increase, high cost and industrial inviability of some enzymatic reactions, toxicity of organic solvents, and production of effluents. The use of CDs reduces the bitter taste of hydrolyzed proteins and retains amino acids and bioactive peptides in food, providing a use for healthier proteins that would be otherwise useless for alimentary purposes.

Another application of CDs is to reduce the bitter taste of citric juice like navel orange and grapefruit juices because CDs can form a strong inclusion complex with limonin and naringin. Limonin and naringin, when in low concentration, are important flavor components, but when there is a high concentration of these components due to fruit variety and/or harvest time, a strong bitter taste is present. Moreover, fresh citrus juice is not bitter but becomes so during storage and its rate depends on the pH and storage temperature. Due to the great volumes of produced juice, it is less costly to remove limonin and naringin using columns filled with α- or β-CD, which are recovered by the treatment with diluted alkali or ethanol. The polymer also reduces naringenin-7-β-rutinoside, coumarins, and flavonoids, but the total acidity and ascorbic acid content remain unchanged (Astray et al. 2009). In Table 8.3, the main applications of CDs to improve food taste are shown.

The success of molecular complexation process with bad taste molecules in CDs depends on the value of the association constant that is generally between 10^1 and 10^4 mol^{-1}. The temperature strongly affects the CDs success to remove unpleasant tastes. In cold foods, the equilibrium force causes the inclusion complex formation and CD–guest crystallization, whereas in hot mixtures, it leads to the guest release. Therefore, the use of CDs has succeeded for taste improvement when used in cold foods (Szejtli and Szente 2005).

β-CD is still the most versatile molecule to encapsulate substances. However, an important tool to be exploited by the food industry is the chemically modified CDs like di- and trimethyl-β-CD (DMβCD and TMβCD), randomly methylated-β-CD (RMβCD), hydroxyethyl-β-CD (HEβCD), 2- and 3-hydroxypropyl-β-CD (2HPβCD and 3HPβCD), 2,3-dihydroxypropyl-β-CD (DHPβCD), 2-hydroxyisobutyl-β-CD (HIBβCD), sulphobutylether-β-CD (SBEβCD), glucosyl-β-CD (G1βCD),

Table 8.3 Cyclodextrin (CD) use to improve food taste

Food	CD	Result	Source
Canned citrus and citrus juice	β	Reduce bitter taste of naringin, limonin, and hesperidin and prevent precipitation	Hedges (1998)
Coffee and tea	β	Reduce or eliminate disgusting taste by overbrewing or overlong steeping	Hamilton et al. (1970)
Extracts of artichoke leaves, aloe, and gentian	Chitosan–CD adducts	Mask bitter taste	Binello et al. (2004)
Fish oil	β	Eliminate unpleasant taste, smell, and stabilization against oxidation	Choi et al. (2009)
Ginseng	γ	Reduce bitter taste	Lee et al. (2008)
Hydrolyzed soy protein	α	Reduce bitter taste	Linde et al. (2009)
Hydrolyzed soy protein	β	Reduce bitter taste	Linde et al. (2010)
Naringin, limonin, and caffeine	β-CD–carboxymethyl chitosan	Reduce bitter taste	Binello et al. (2008)
Cooked rice	β	Improvement of odor and flavor after long storage	Kuwabara et al. (1988)
Skim milk hydrolysates	β	Reduce bitter taste	Helbig et al. (1980)

This table presents the main use of CDs in food formulations to mask or reduce unpleasant tastes as well to improve pleasant tastes and flavors. *CD* cyclodextrin

and maltosyl-β-CD (G2βCD) (Davis and Brewster 2004). Other important CD derivatives are sugammadex in which the 6-hydroxyl groups on γ-CD have been replaced by carboxythio acetate ether linkages and hydroxybutenyl-β-CD. Finally, there is a renewed interest in γ-CD itself and modified γ-CDs (Stella and He 2008), and also in macromolecules, which are linked to CDs like CD–maleyl chitosan, CD–carboxymethyl cellulose, CD–carboxymethyl chitosan, and CD–chitosan adducts (Binello et al. 2004). However, they have a potential use to improve the consumption of unpleasant taste healthier food; the use of these modified CDs in the food industry depends on the approval of regulatory organizations.

8.8 Cyclodextrins to Improve Food Rheology

Gelatinization is one of the most important characteristics of some carbohydrates and proteins. It reduces water activity in the food by linking the water to carbohydrates and proteins, modifying food rheology and extending shelf life. As a consequence of the gelatinization, exudation and evaporation of water is reduced in food and that is essential for the quality of the industrialized food.

Highly branched CDs are used in flour-based items like noodles, pie dough, pizza sheets, and rice cakes to impart elasticity and flexibility to dough. The texture of food gelatinization such as in wheat flour was modified by the addition of β-CD, which increases the solubility and swelling power of wheat starch granules. Furthermore, the addition of 1.5% β-CD increased the viscosity of the pastes fourfold, probably by disrupting starch–lipid complexes (Kim and Hill 1984). In meat products, ice cream, beverages, salad dressing, yogurt, mayonnaise, margarine, or butter creams, CDs can be used to stabilize emulsions due to their hydrophilic outer surface and hydrophobic cavity (Del Valle 2004).

CDs are still little used in the alteration of food rheology because the cost-benefit relation is not favorable. In foods in which CDs are used to change flavor or control flavor release, a secondary

positive effect is the improvement of food rheology. Even though the effect of CDs in food rheology is minimal, there is a potential use of this molecule in package biofilms with an effect in both rheology and controlled release of antimicrobial and/or antioxidant compounds in food.

8.9 Cyclodextrins to Improve Food Packages

Packages are essential elements to guarantee food quality from its production, transportation, processing, commercialization, and up to its consumption. Thus, packages are required to maintain food integrity, sensorial qualities and safety, besides being atoxic and biodegradable. Also, the food packages should work as a reservoir of active components like antimicrobials, flavors, pigments, and antioxidants that can be slowly released. Besides that, CDs can include off-flavors and improve the elasticity and barrier properties of food packages.

The controlled release of active compounds throughout shelf life is important because high concentrations of free bioactive components like antimicrobials, pigments, flavors, and antioxidants represent a risk for food quality and safety. The active-component release of food packages must have zero-order kinetics to keep the component concentration constant throughout shelf life (Baker 1987). CDs are able to reduce the diffusion kinetics of one order with the controlled release of guest. Thus, complexation is a potential key to a long-lasting active-component effect of such active packaging.

There are many examples of food packages with CDs to control the release control of active components such as iodine, used to preserve fish paste; ethanol and benzoic acid, used to prevent fungus growth (Szente and Szejtli 2004; Astray et al. 2009); allyl isothiocyanate, used to avoid mold growth on the surface of packaged cheese (Plackett et al. 2006); and the antifungal volatile hexanal, to reduce post-harvest berry diseases (Almenar et al. 2007). The release of flavors like d-limonene, natural pigments, and antioxidants, such as α-tocopherol, have also been reported (Siró et al. 2006).

In packages, CDs are generally used to control the guest release, but empty CDs can be added to encapsulate unwanted components produced along storage. In irradiated food, CDs prevent off-taste of cyclic monoterpene or are used as an interior coating of beer containers to encapsulate aldehydes and ketones (Bobo 1993).

The release of active compounds in packages works well with the increase of relative humidity along storage time, like in fresh-cut fruits or vegetables packages because of the natural water release from food that displace the equilibrium to guest release (Ayala-Zavala et al. 2008). Conversely, if the objective is the inclusion of unwanted components in food, CDs will trap better those components in food with reduced moisture content.

The addition of CDs in packaging films has improved sensory properties while maintaining food quality and safety. There is a potential use of CDs in edible films, from renewable carbon sources like alcohols and carbohydrates, but it is still underutilized and this could result in the creation of new packages in the food industry.

8.10 Cyclodextrins in Health Foods: Potential Use

The increase of obesity and the problems related to an unbalanced diet has led consumers to look for healthier food options. However, consumers in general buy food because of its taste instead of its nutrition or health values; furthermore, this instinctive rejection of disgusting tastes may not be changed because it is a key mechanism for survival (Rouseff 1990). Therefore, the industry has offered light and

functional foods to consumers, but the maintenance of pleasant taste has become the main challenge to broaden industrialization and consumption of healthy foods. Thus, bitterness in food products has been described as a sensory defect and demands for good taste and good health seem to be incompatible.

Also, reduction of sugar, fat, and sodium in the industrialization of light food, intensifies bitter and astringent tastes (Ley 2008). Vegetal components like phenols, flavonoids, isoflavones, terpenes, glucosinolates, and hydrolyzed proteins that have important antioxidant, anticarcinogenic, and a wide spectrum of tumor-blocking activities, are bitter, acrid, or astringent (Drewnowski and Gomez-Carneros 2000). Then, in order to avoid consumers' refusal of food, the bad taste components are generally removed to improve and homogenize taste. It creates some paradoxes, for example, whereas there are proposals of enhancement of glucosinolates in broccoli sprouts for health's sake, the industry has removed them for better taste (Drewnowski and Gomez-Carneros 2000).

Another way to reduce undesirable tastes is the use of recombinant DNA to produce transgenic cultivars with less bitter tastes such as transgenic citrus fruit free of limonin. However, plant varieties that have been selected for palatability by humans are usually more susceptible to diseases, leading to an increased use of synthetic pesticides, creating another paradox to produce good quality food (Benavente-Garcia et al. 1997).

CDs have an important potential in the development of good taste food and its health components. A summary of the main applications of CDs in food is presented in the Fig. 8.6. CDs can complex flavonoids and terpenoids and mask the bitter taste of citrus juice, for example, without changing the
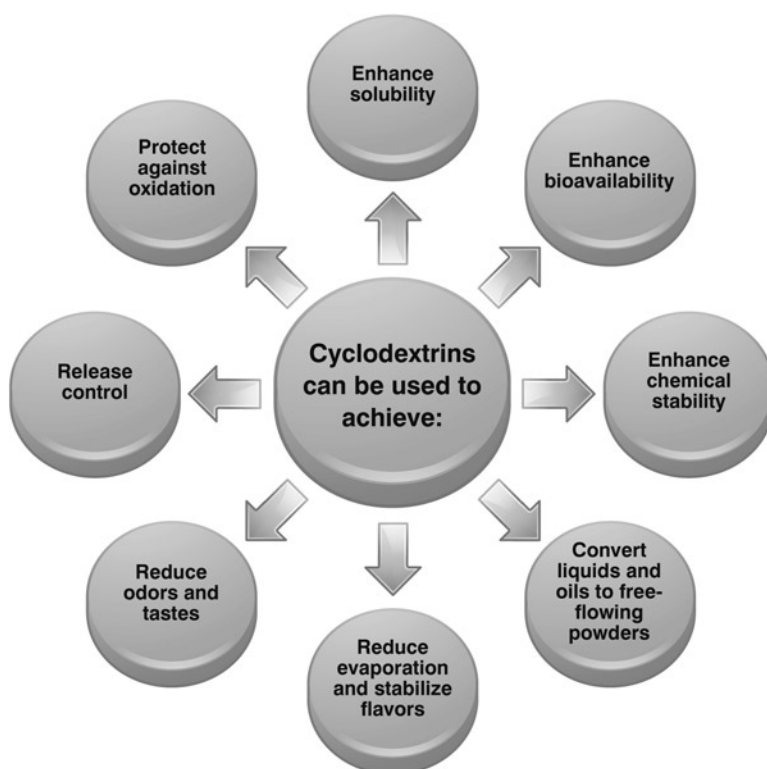
Fig. 8.6 Food applications of cyclodextrins. This figure shows the applications of CDs. The lipophilic cavity of CD provides protection that reduces the contact of the guest with heat, oxygen, light, solvents, among others. Based on these characteristics, the CDs are widely used to encapsulate many different guests with applications in the food and drug industries. *CD* cyclodextrin

bioactive potential of those substances. Del Valle (2004) reported the improvement of health component properties with CD complexation for apple juice and medicinal mushrooms. Linde et al. (2009, 2010) reported that natural α- and β-CDs reduced the bitter taste of hydrolyzed soy protein upto 90%, which represents a potential solution for masking the bitter taste of foods with soybean and bioactive health peptides that are used to prevent diseases.

CDs are also used to remove fat and cholesterol from dairy products such as milk, cheese, yogurt, and whipping cream, fat from egg yolks and lard, and to add components such as phytosterol in mayonnaise, and phytosterol and evening primrose oil in butter (Astray et al. 2009). CDs can produce hardening fats and oils without both hydrogenation and trans fats, resulting in an emulsion with high content of polyunsaturated fatty acids derived from fish and vegetal oils. Plus the emulsion produced by CD presented better sensory characteristics and increased storage stability by delaying acidity (Choi et al. 2009). CDs can be used to increase water solubility and reduce oxidation of thyme oil, an important component that maintains higher polyunsaturated fatty acids levels in cell membranes and with potential use as an antileishmanial drug or a component of a functional food (Mourtzinos et al. 2008).

Another important application of CDs for the development of healthy foods is the improvement of solubility and bioavailability of Coenzyme Q10 (ubiquinone) that plays a fundamental role in converting energy from carbohydrates and fatty acids, and it is also a very effective antioxidant (Madhavi and Kagan 2006). CDs can also be added to potato starch, improving the satiating, glycemic, and insulimemic properties of a meal, suggesting that either gastric emptying is delayed or some of the glucose is absorbed more distally in the small intestine reducing insulin secretion (Raben et al. 1997).

The idea that food must taste good and should prevent diseases introduces a dilemma for the food industry because it has to meet the demands of taste and health without hindering any of them. That is why the development of functional foods presents several challenges and CDs represent new possibilities for the food industry regarding the expansion of the functional food consumption.

8.11 Cyclodextrin Toxicity

Orally administered CDs are practically non toxic, due to lack of absorption in the gastrointestinal tract. Furthermore, a number of safety evaluations have shown that γ-CD, 2-hydroxypropyl-β-CD, sulphobutylether-β-CD, sulphated-β-CD, and maltosyl β-CD appear to be safe even when administered parenterally (Del Valle 2004). However, parenteral and intravenous use of CDs, specifically β-CD, has to be done carefully because it may cause nephrotoxicity due to the formation of a low solubility CD–cholesterol complex, which blocks glomerular filtrations in the kidney; in high doses, CDs may cause hemolysis of human erythrocytes.

In the United States, CDs are generally recognized as safe (GRAS) by the Food and Drug Administration (FDA), in Japan, they are considered natural products when used in foods, whereas in Australia and New Zealand, CDs are classified as novel foods (Cravotto et al. 2006). The acceptable daily intake (ADI) recommended by the Food and Agriculture Organization/World Health Organization (FAO/WHO) for β-CDs is 5 mg kg^{-1} day^{-1}, but for α- and γ-CDs, no ADI has been defined because of their favorable toxicological profiles. But adversely, the United States Environmental Protection Agency has established a maximum permissible level for residues of α-, β- and γ-CDs in various food commodities (Astray et al. 2009).

CDs are resistant to α-amylases and partially resistant to β-amylases, hydrolyzed by the colon microbiota where insignificant amounts are absorbed by the digestive system (Antenucci and Palmer 1984).

The absorbed CDs are essentially excreted in the urine without undergoing metabolism. The absorption of α-, β-, and γ-CDs by oral administration in rats is 1.0, 0.6, and 0.02%, and LD_{50} in mg kg^{-1} is 10,000, 5,000, and 8,000, respectively (Stella and He 2008). Natural and hydrophilic and lipophilic derivative CDs have low permeation capacity and low toxicity when orally administered (Irie and Uekama 1997).

The remarkable effects of oral administration of CDs in rats were soft feces or diarrhea and cecal enlargement. These effects were observed with HP-β-CD, SBE-β-CD, and α-CD, β-CD, and γ-CD in high doses (10–20 g kg^{-1}) (Lina and Bar 2004), but α-CD caused membrane irritation (Del Valle 2004). The effects of CDs on the gastrointestinal tract are similar to those of low digestible carbohydrates such as lactose, and these effects represent physiologically adaptive responses to a large load of poorly digestible carbohydrates and other osmotically active nutrients with minimal relevance to humans (Grice and Goldsmith 2000).

As reported by Del Valle (2004), there is still skepticism within the regulatory agencies regarding the use of CDs, although this seems to be a bigger issue in the FDA than in other agencies. The quantity applied in food has quite lower concentrations of CDs than those that cause toxicological problems. The simple fact that there are now numerous approved products containing CDs (Szente and Szejtli 2004) is a good sign for its future use. The more the products containing CDs and modified CDs undergo rigorous evaluation, the more the agencies will trust CD addition to food better.

8.12 Applications to Other Areas of Health and Disease

8.12.1 Cyclodextrins in Pharmaceutical Applications

Bioavailability and controlled release of drugs are especially important in the pharmaceutical industry and both of them depend on water solubility in active principle. Efficient modern drugs usually present higher molecular mass and lipophilicity, and lower water solubility making bioavailability and controlled release more difficult (Lipinski et al. 1997; Lipinski 2001; Davis and Brewster 2004). Thus, bioavailability difficulties have been more common, and the use of drug delivery formulators has been necessary in order to accomplish drug delivery. In drug formulation, the active principle must be absorbed through the gastrointestinal tract or membranes in order to reach a pharmacologically desired action. Retrospective studies show that more than 40% of drugs fail because they have poor water dissolution or poor permeability (Prentis et al. 1988; Davis and Brewster 2004).
CDs are useful pharmaceutical delivery formulators because they can interact with drug molecules to form highly stable and water-soluble inclusion complexes and could control the drug release (Stella and He 2008). CDs can be used in pharmaceutical formulations to enhance solubility, bioavailability, and stability. They can also convert liquids and oils to free-flowing powders, preventing admixture incompatibilities and reducing drug evaporation and hemolysis (Davis and Brewster 2004). In oral administration, only insignificant amounts of intact CDs are absorbed in the gastrointestinal tract because of their bulky and hydrophilic nature. The absorbed CDs are essentially excreted in the urine without undergoing metabolism, thus, the elimination of CDs strongly depends on renal clearance (Stella and He 2008). The hemolytic effect of CDs has been reported in vitro studies; however, the toxicological implication in vivo is considered negligible. The hemolytic activity of CDs correlates well with their ability to solubilize cellular membrane lipids (Stella et al. 1999). In addition, due to the reduced CD toxicity, mainly in oral drug formulations, CDs are largely used in the pharmaceutical industry. The main drugs with CDs are presented in Table 8.4.

Table 8.4 Approved and marketed drug–CD formulations

Drug–CD	Administration route	Trade name	Country/continent
Chlordiazepoxide–β[c]	Oral	Transillium	Argentine
Meloxicam–β[c]	Rectal	Mobitil	Egypt
Chloramphenicol–randomly methylated-β[a]	Eye drops	Clorocil	Europe
Cisapride–β[c]	Rectal	Propulsid	Europe
Dextromethorphan–β[c]	Oral	Rynathisol	Europe
Hydrocortisone–2-hydroxypropyl-β[a]	Buccal	Dexocort	Europe
Indomethacin–2-hydroxypropyl-β[c]	Eye drops	Indocid	Europe
Nimesulide–β[a]	Oral	Nimedex, Mesulid	Europe
Omeprazole–β[a]	Oral	Omebeta	Europe
Tiaprofenic acid–β[a]	Oral	Surgamyl	Europe
Piroxicam–β[a,b]	Oral	Brexin, Flogene	Europe, Brazil
Alprostadil–α[a,b]	Intravenous	Prostavasin, Caverject, Edex	Europe, Brazil, Japan, United States
Voriconazole–sulphobutylether-β[a]	Intravenous	Vfend	Europe, United States
Flunazine–β[c]	Oral	Fluner	India
Benexate–β[a]	Oral	Ulgut, Lonmiel	Japan
Cefotiam hexetil HCl–α[a]	Oral	Pansporin T	Japan
Cephalosporin–β[c]	Oral	Meiact	Japan
Dexamethasone–β[a]	Dermal	Glymesason	Japan
Iodine–β[a]	Topical	Mena-Gargle	Japan
Nitroglycerin–β[a]	Sublingual	Nitropen	Japan
Mitomycin–2-hydroxypropyl-β[a]	Intravenous	Mitozytrex	United States
Tc-99m Teboroxime–2-hydroxypropyl-γ[c]	Intravenous	Cardiotec	United States

This table presents the main use of CDs in pharmaceutical formulations to achieve better drug performance such as enhance solubility, bioavailability, and stability; convert liquids and oils to free-flowing powders; reduce evaporation and stabilize flavors, odors, and tastes; and reduce hemolysis and prevent admixture incompatibilities. *CD* cyclodextrin

[a]Davis and Brewster (2004)

[b]Agência Nacional de Vigilância Sanitária (2009)

[c]CycloLab (2010)

8.13 Conclusion

Food purchase and choice behavior directly influences consumers' lifestyle and health. Most foods, considered healthy or functional because they prevent or help the treatment of diseases, have low acceptability due to the presence of bioactive components with unpleasant tastes such as fibers, phenols, flavonoids, isoflavones, terpenes, glucosinolates, and others. Furthermore, functional foods have a high concentration of bioactive components and also a higher degradation and oxidation speed, which reduce their shelf life.

Because of their capacity of inclusion complex formation, CDs can help the maintenance and protection of bioactive components in foods. Moreover, these cyclical oligosaccharides can be used to improve the sensory characteristics of functional foods with bioactive components and unpleasant taste. CDs are widely used for increasing solubility and controlled release of flavors in foods as well as to enhance taste, mainly for drinks. But these compounds are very minimally used to control

off-flavor and off-taste encapsulation along shelf life. The cost of CD addition to modify food rheology is not yet worthwhile. However, CDs have a great potential in the improvement of rheology of bio-degradable films for "smart" food packages production with controlled release. They also increase the solubility and chemical stability of healthy compounds such as pigments and antioxidants. CD toxicity is low when ingested orally and their addition to food and drugs is accepted in several countries.

A greater amount of functional foods offered by food industries, which depends on the demand for these products, have grown but it is still small in the traditional industrialized food market world-wide. Healthy foods have a higher production cost either because of the technological development needed for their production, the use of higher cost ingredients, shorter shelf life, or smaller production scale. Thus, while the food industry has to solve the dilemma between the demands of tasty versus healthy foods, society has the dilemma of paying or not for healthier foods. In addition, few countries have educational and nutritional policy and laws to give fiscal incentives to functional food production while overtaxing unhealthy foods. Presently, changes in eating habits and awareness of the need for healthier food intake are necessary.

Summary Points

- A lot of healthy bioactive substances present in functional foods have the capacity to reduce the risk of illness.
- Healthy bioactive substances in general have unpleasant sensory characteristics.
- Pleasant sensory characteristics versus healthy food is a dilemma between consumers' and industries' demands.
- Cyclodextrin may form inclusion complexes with many healthy bioactive substances.
- Molecules encapsulated by cyclodextrin can enhance solubility, bioavailability, and stability; reduce flavor evaporation and mask both odors and tastes; and convert oils into free-flowing powders.
- Cyclodextrins are widely used in the pharmaceutical area and have low toxicity when orally ingested.
- Cyclodextrins are utilized to encapsulate flavors and pigments, protecting against evaporation and oxidation and also to control the release of guest molecules.
- Cyclodextrins can be added to foods to encapsulate unpleasant taste molecules and have a potential application in inclusion of unpleasant taste bioactive compounds in health foods.
- Cyclodextrins can be used to create "smart" food packages with the release of healthy compounds plus the possibility to extend food shelf life.
- Cyclodextrins improve gel rheology and can potentially improve biodegradable film rheology used for "smart" food packages production.
- Cyclodextrins are an excellent tool to help the food industry introduce new solutions for the dilemma of pleasant sensory characteristics in foods versus healthy foods.
- The increase in the society's demand for healthy foods and their willingness to pay for them will allow new commercial application of new techniques such as use of cyclodextrins.

References

Agência Nacional de Vigilância Sanitári. Ministério da Saúde – Medicamentos – Bulas de Medicamentos – Bulário Eletrônico [Brazil]. 2009. Available in http://www.anvisa.gov.br/bularioeletronico/. Accessed 20 Dec 2009.

Almenar E, Auras R, Rubino M, Harte B. Int J Food Microbiol. 2007;118:164–72.

Antenucci RN, Palmer JK. J Agric Food Chem. 1984;32:1316–21.

Astray G, Gonzalez-Barreiro C, Mejuto JC, Rial-Otero R, Simal-Gándara J. Food Hydrocolloids. 2009;23:1631–40.

Ayala-Zavala JF, Del-Toro-Sánchez L, Álvarez-Parrilla E, González-Aguilar GA. J Food Sci. 2008;73:R41–7.

Baker RW. Controlled release of biologically active agents. New York: Wiley; 1987.

Benavente-Garcia O, Castillo J, Marin FR, Ortuño A, Del Rio JA. J Agric Food Chem. 1997;45:4505–15.

Bhandari BR, D'Arcy BR, Padukka I. J Agric Food Chem. 1999;47:5194–7.

Binello A, Cravotto G, Nano GM, Spagliardi P. Flavour Fragr J. 2004;19:394–400.

Binello A, Robaldo B, Barge A, Cavalli R, Cravotto G. J Appl Polym Sci. 2008;107:2549–57.

Blanch GP, Del Castillo MLR, Del Mar Caja M, Perez-Mendez M, Sanchez-Cortes S. Food Chem. 2007;105:1335–41.

Bobo WS Jr. Interior can coating compositions containing cyclodextrins. United States Patent 5177129. 1993

Choi MJ, Ruktanonchai U, Min SG, Chen JY, Soottitantawat A. Food Res Int. 2009;42:989–97.

Cravotto G, Binello A, Baranelli E, Carraro P, Trotta F. Curr Nutr Food Sci. 2006;2:343–50.

CycloLab. General introduction and technology presentation for pharmaceuticals. 2010. Available in http://cyclolab.hu/pict/presentation_for_pharmaceuticals.pdf. Accessed 18 Jan 2010.

Davis ME, Brewster ME. Nat Rev Drug Discov. 2004;3:1023–35.

Del Valle EMM. Process Biochem. 2004;39:1033–46.

Drewnowski A, Gomez-Carneros C. Am J Clin Nutr. 2000;72:1424–35.

Grice HC, Goldsmith LA. Food Chem Toxicol. 2000;38:S1–6.

Hamilton RM, Park LG, Heady RE. Eliminating undesirable taste from coffee and tea extracts and products. United States Patent 3528819. 1970.

Hedges AR. Chem Rev. 1998;98:2035–44.

Helbig NB, Ho L, Christy GE, Nakai S. J Food Sci. 1980;45:331–5.

Irie T, Uekama K. J Pharm Sci. 1997;86:62–78.

Irwin PL, Pfeffer PE, Doner LW, Sapers GM, Brewster JD, Nagahashi G, et al. Carbohydr Res. 1994;256:13–27.

Johnson Jr CS. Prog Nucl Magn Reson Spectrosc. 1999;34:203–56.

Jouquand C, Ducruet V, Giampaoli P. Food Chem. 2004;85:467–74.

Kawakami K, Fujita A, Mikami T, Yoshii H, Paramita V, Neoh TL, et al. Eur Food Res Technol. 2009;229:239–45.

Kawashima K. Prevention of discoloration of food colorants. Jpn Kokai JP 8071464. 1980

Kim HO, Hill RD. Cereal Chem. 1984;61:406–9.

Kollengode ANR, Hanna MA. J Food Sci. 1997;61:985–90.

Kuwabara N, Takaku H, Oku S, Kopure Y. Japan Kokai Patent JP88267246. 1988.

Labows JN, Brahms JC, Cagan RH. Solubilisation of flavors. In: Pickenhagen W, Ho CT, Spanier AM, editors. Carol Stream: Allured; 1996. p. 125–35.

Lee SH, Yu HJ, Cho NS, Park JH, Kim TH, Kim KH, Lee SK. A method for preparing the inclusion complex of ginseng extract with gamma-cyclodextrin, and the composition comprising the same. International Patent Classification IPC A23L 1/212 (2006.01). (2008).

Ley JP. Chemosens Percept. 2008;1:58–77.

Li S, Purdy WC. Chem Rev. 1992;92:1457–70.

Lina BA, Bar A. Regul Toxicol Pharmacol. 2004;39:S14–26.

Linde GA, Laverde Jr A, Faria EV, Colauto NB, Moraes FF, Zanin GM. Food Res Int. 2009;42:814–8.

Linde GA, Laverde Jr A, Faria EV, Colauto NB, Moraes FF, Zanin GM. Food Res Int. 2010;43:187–92.

Lipinski CA. Curr Drug Discov. 2001;1:17–9.

Lipinski CA, Lombardo F, Dominy BW, Feeney PJ. Adv Drug Deliv Rev. 1997;23:3–25.

Lipkowitz KB. Chem Rev. 1998;98:1829–74.

Madhavi DL, Kagan DI. Highly bioavailable coenzyme Q-10 cyclodextrin complex. United States Patent 7030102B1. 2006.

Meier MM, Drunkler DA, Luiz MTB, Fett R, Szpoganicz B. Br Food J. 2001;103:281–90.

Mourtzinos I, Kalogeropoulos N, Papadakis SE, Konstantinou K, Karathanos VT. J Food Sci. 2008;73:S89–94.

Palakodaty S, York P. Pharm Res. 1999;16:976–85.

Plackett DV, Holm VK, Johansen P, Ndoni S, Nielsen PV, Sipilainen-Malm T, et al. Packag Technol Sci. 2006;19:1–24.

Prentis RA, Lis Y, Walker SR. Br J Clin Pharmacol. 1988;25:387–96.

Raben A, Andersen K, Karberg MA, Holst JJ, Astrup A. Am J Clin Nutr. 1997;66:304–14.

Reineccius TA, Reineccius GA, Peppard TL. J Food Sci. 2003;68:1234–9.

Reineccius TA, Reineccius GA, Peppard TL. J Food Sci. 2004;69:FCT58–62.

Rolls ET, Rolls JH. Physiol Behav. 1997;61:461–73.

Rouseff RL. Bitterness in food products: an overview. Amsterdam: Elsevier; 1990. p. 1–14.

Schneider HJ, Hacket F, Rüdiger V. Chem Rev. 1998;98:1755–86.

Shahidi F, Pegg RB. J Food Sci. 1991;56:1500–4.

Siró I, Fenyvesi E, Szente L, de Meulenaer B, Devlieghere F, Orgoványi J, et al. Food Addit Contam. 2006;23:845–53.

Sojo MM, Nuñez-Delicado E, García-Carmona F, Sánchez-Ferrer A. J Agric Food Chem. 1999;47:518–23.

Stella VJ, He Q. Toxicol Pathol. 2008;36:30–42.

Stella VJ, Rao VM, Zannou EA, Zia V. Adv Drug Deliv Rev. 1999;36:3–16.

Suzuki Y, Ogura T, Takagishi Y. Pharm Technol Jpn. 1993;9:999–1008.

Szejtli J. Pure Appl Chem. 2004;76:1825–45.

Szejtli J, Szente L. Eur J Pharm Biopharm. 2005;61:115–25.

Szente L, Szejtli J. Trends Food Sci Technol. 2004;15:137–42.

Tobitsuka K, Miura M, Kobayashi S. J Agric Food Chem. 2006;54:5069–76.

Tønnesen HH, Másson M, Loftsson T. Int J Pharm. 2002;244:127–35.

Yoshii H, Yasuda M, Furuta T, Kuwahara H, Ohkawara M, Linko P. Drying Technol. 2005;23:1205–15.

Chapter 9
Infantile Olfactory Learning

Katsumi Mizuno

9.1 Introduction

In this chapter, I review how infants acquire olfactory preferences, how they discriminate their own mothers, and how olfactory learning benefits both mothers and neonates. I also examine how favorable olfactory stimuli/exposure affords smooth adaptation to this world to neonates. Since a strong bond between the mother and the infant is the key to the neonate's survival, individual olfactory recognition is essential for the development of mother–infant attachment (Table 9.1). During the early neonatal period, infants acquire individual olfactory recognition in three ways: (1) general preference for the odor of own mother's amniotic fluid and breastmilk, which is obtained genetically or in utero; (2) olfactory learning immediately after delivery, which is a critical time period in olfactory learning; and (3) classical conditioning as well as mere exposure to mother's odor, which are enough to allow infants to learn their mother's odor. I shall explore these three categories in detail herein.

9.2 Olfactory Learning in Utero

9.2.1 Olfactory Memory in Utero

Memory begins prenatally and the period of birth merely marks a transition from memory functioning in utero to memory functioning ex utero. Prenatal learning is thought to account for the preference of human neonates for their own mother's voice (DeCasper and Fifer 1980). The olfactory organs are functional at 12 weeks' gestation (de Vries et al. 1985), earlier than the auditory system. Bartocci et al. (2001) found that cortical hemodynamic modifications occur in preterm infants born at a mean of 33.7 weeks after exposure to preparations commonly used in the NICU (a disinfectant and an adhesive remover). Even in these premature infants, the odors of these solutions elicited a significant decrease in blood oxygenation in the orbitofrontal olfactory area. This change was different from that caused by exposure to colostrum and vanilla, which elicited an increase in blood oxygenation in the same region (Bartocci et al. 2000). In general, pleasant odors elicit approach behavior whereas unpleasant odors induce avoidance behavior. The change in brain blood volume to these olfactory stimuli likely relates to the infant's behavior.

K. Mizuno (✉)
Department of Pediatrics, Showa University of Medicine, 1-5-8 Hatanodai, Shinagawa-ku,
Tokyo 142-8666, Japan
e-mail: katsuorobi@med.showa-u.ac.jp; katsuorobi@aol.com

Table 9.1 Key features of infantile olfactory learning

1. Human fetus is capable of leaning odor of amniotic fluid
2. Human neonate has a olfactory preference which is acquired in utero, or genetically determined
3. The odor of amniotic fluid plays roles in soothing the neonate and in preparatory response for oral feeding
4. Maternal discrimination is acquired through olfactory stimuli during the first couple of days after birth
5. Olfactory learning immediately after birth is important in successful breastfeeding
6. The odor of amniotic fluid/colostrums and breast milk is mainly determined by maternal diet
7. Neonates' preferences change from amniotic fluid/colostrum to mature milk over time
8. Maternal diet during pregnancy and lactation affects the weaning process and later dietary preferences of children

This table lists the key facts of infantile olfactory learning including the beneficial aspects of olfactory learning in mother–infant bonding, successful breastfeeding, and later healthier diet

Memory is essential for normal functioning and it is not surprising that such an important psychological function is established in some form before birth. Fetal memory may serve a number of specific functions, dependent upon the learning of particular stimuli prenatally. Human neonates recognize the odor of substances that were introduced into the amniotic fluid or ingested by their pregnant mother (Smotherman and Robinson 1982). Prenatal memory may be important in the development of attachment and maternal recognition. During pregnancy, the mother's Montgomery glands tend to enlarge; these glands provide olfactory stimuli for the infant after birth by emitting flavored secretions composed of milk mingled with sebum. Thus it is clear that, during pregnancy, the mother's body physically prepares for the olfactory interaction that follows the delivery of her infant.

9.2.2 Olfactory Memory Helps Neonates Adapt to Outside of the Womb

Odor cues from lactating women affect the behavior of infants in many ways, ranging from arousal modulation to the fine-tuning of interactions with the mother. The newborn young of several mammalian species are attracted to the odor of amniotic fluid; these chemical cues also appear to calm neonates and help them adapt to their new postnatal environment. For example, the odor of the lactating breast reduces arousal states in active newborns (Schaal et al. 1980; Schaal 1986; Sullivan and Toubas 1998) and increases them in somnolent newborns (Russell 1976; Soussignan et al. 1997; Sullivan and Toubas 1998). Such cues elicit positive head (nose) orientation (Macfarlane 1975) and increase oral activity (Russell 1976; Soussignan et al. 1997). Odor cues may stimulate active approach behavior such as directional crawling (Varendi and Porter 2001), which may be involved in the neonatal ability to reach a nipple (Widström et al. 1987; Righard and Alade 1990). The odor of amniotic fluid is an attractant and helps the infant locate an object to suck. Immediately after birth, neonates display a clear preference for an unwashed breast that retains its biological odor. Significantly more infants select such a breast rather than the odorless alternative for their initial sucking bout (Fig. 9.1). An olfactory memory acquired in utero may be important for the establishment of breastfeeding and later diet.

Two natural sources of potentially odorous substrates have received empirical attention. The first is amniotic fluid and the second is colostrum/milk, both of which are emitted from the main milk ducts that open at the tip of the nipple. Accumulating evidence shows that odor cues carried in human colostrum and milk are attractive to neonates (Marlier and Schaal 1997; Mizuno and Ueda 2004; Mizuno et al. 2004). Interestingly, neonatal responsiveness to these milk cues does not seem to depend on breastfeeding experience as infants that are exclusively fed cow's milk–based formulas react to them as strongly as breastfed infants (Marlier and Schaal 2005). Another potential
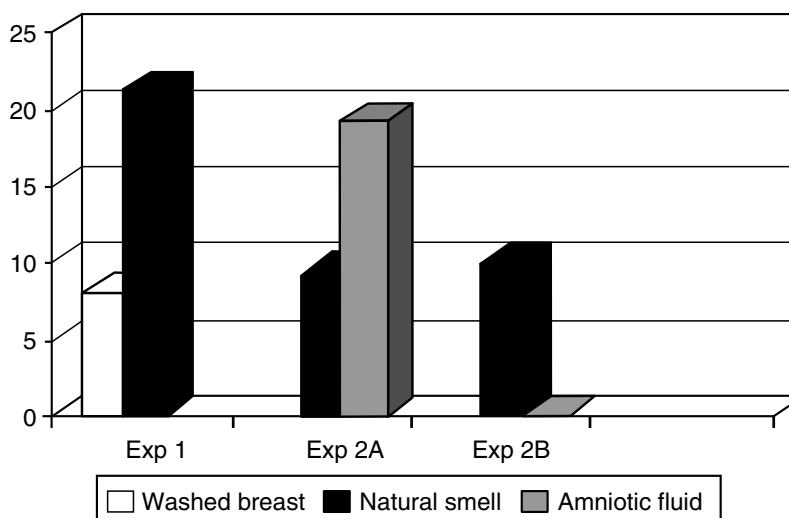
Fig. 9.1 Babies' preference of breast for sucking (Varendi et al. 1997). Comparison of breast choice for sucking is shown. *Y* axis indicates the number of babies who chose the washed breast, naturally smelling breast, and amniotic fluid treated breast. *Left column*: Unwashed breast is preferred over washed breast for infants at a mean postnatal age of 67±10 h. *Middle column*: Amniotic fluid–treated breast is preferred over natural odor breast for infants at a mean postnatal age of 68±15 h. *Right column*: Natural odor breast is preferred over amniotic fluid–treated breast for infants at a mean postnatal age of 165±26 h

source of mammary odor cues are distributed around the areola in the form of small skin protuberances, called Montgomery's glands. These result from the coalescence of sebaceous glands and miniature lactiferous acini (Smith et al. 1982). These glands enlarge during pregnancy and lactation and become more visible on the areolar surface. After delivery, they begin to secrete a milklike fluid (Schaal et al. 2006). The resulting blend may have a positive effect on the perceptual impact of the secretions. The surface temperature of lactating breasts is elevated; as such, evaporation of the secretions increases. This enables the odor to effectively stimulate the neonatal olfactory system. If such an effect exists, it might distinctively affect neonatal response speed and rate. In most lactating women, the number of visible Montgomerian glands ranges from a low of 1 to a high of 40-plus. Their functional involvement has recently been examined in breastfeeding interactions, based on the evidence that the number of areolar glands correlates positively with neonatal weight gain and with maternally reported perception of infant sucking activity (Schaal 1988). Taken together, the above findings suggest that milk and areolar secretions may be significant sources of behaviorally active cues for neonates.

9.2.3 *Origin of the Odor of Amniotic Fluid*

The odor of amniotic fluid is determined by fetal excretion as well as the mother's food. The ingestion of garlic or spicy food by pregnant women significantly alters the odor of their amniotic fluid (Hauser et al. 1984; Mennella et al. 1995). The spices are absorbed from the maternal gastrointestinal tract and transferred to the amniotic fluid (Hauser et al. 1984). Animal and human data indicate that the fetus emits odorous materials into the amniotic fluid as well and that these are externalized into the pregnant mother's excretions. This fetal odor generation and externalization may also explain

why mothers and fathers can detect similarities between their own infant's amniotic fluid odor and maternal body and urine odors (Beauchamp et al. 1994; Varendi et al. 1996).

9.2.4 Neonates Are Attracted to the Odor of Amniotic Fluid

9.2.4.1 Preference to Own Amniotic Fluid Odor

The individually unique quality of amniotic fluid is evidenced by the fact that newborn infants are selectively responsive to the odor of amniotic fluid. When an infant is simultaneously exposed to the odors of his/her own amniotic fluid and the amniotic fluid of another infant, the infant will orient his/her head more quickly and for a longer duration to the former stimulus than to the latter (Schaal et al. 1998). Varendi et al. (1998) presented different odors to neonates for 90 min after their birth and found that neonates exposed to amniotic fluid odor cried significantly less than neonates exposed to control odor (Fig. 9.2). Prenatal familiarization with amniotic fluid odors that are likely to continue to be encountered immediately after birth may help the baby adapt to the otherwise new postnatal environment (Varendi et al. 1996; Schaal and Marlier 1998). This similarity between amniotic fluid and colostrum helps neonates to move toward the breast and locate the mother's nipple.

9.2.4.2 Amniotic Fluid Plays an Important Role in Locating an Object to Suck

When newborn infants are placed in the prone position between their mother's breasts immediately after delivery, they display a consistent sequence of activity, namely, crawling movement, which brings the infants into contact with one of the nipples, and then active sucking, which eventually occurs within about 1 h after delivery (Widström et al. 1987; Varendi et al. 1994). If amniotic fluid is applied to
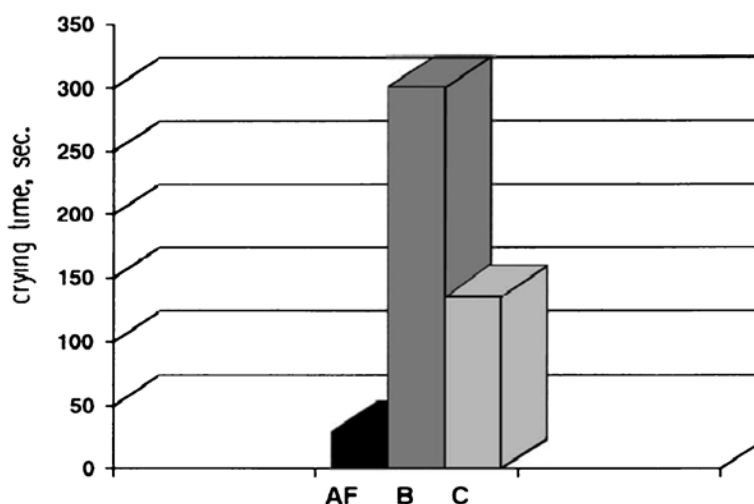
Fig. 9.2 Median crying time with amniotic fluid odor, breast odor, and no odor (Varendii et al. 1998). Median crying time (s) during postnatal 31–90 min in infants assigned to amniotic fluid odor (AF), breast odor (B), and unexposed group (C) used as control. Paired comparison: AF versus B: $p=0.02$, AF versus C: $p=0.02$, B versus C: $p=0.27$. *Y* axis indicates crying time; *X* axis indicates AF, B, and C odor exposure groups

only one breast, the infant will orient to that breast. In other words, if the mother's nipple/areola is washed thoroughly, it would be difficult for a neonate to orient to the mother's breasts effectively. Within the first hour after birth, significantly more neonates spontaneously select a breast treated with amniotic fluid than an untreated breast (Marlier et al. 1998). Varendi et al. (1998) demonstrated that just after birth, more neonates suck their hands if they are not washed. If they are washed, less than half put their hands to their mouth. If the hands smell of amniotic fluid, neonates exhibit searching movements when their hands come close to their nostrils. Based on these observations, it can be said that the odor of amniotic fluid is attractive and helps the baby locate objects to suck.

9.2.5 Similarity of Olfactory Cues Between Amniotic Fluid and Colostrum

There is a distinct similarity between the amniotic fluid and the colostrum of the same woman – these odors are treated as similar by neonates (Marlier et al. 1998). When offered breast for the first time, neonates recognize the colostrum as it has a similar taste to the amniotic fluid. Marlier et al. (1998) found that 2-day-old, breastfed infants demonstrate a similar response to amniotic fluid and colostrum. Her group demonstrated that these infants preferentially orient to gauze pads bearing the odor of amniotic fluid (Schaal et al. 1995). The attractiveness of amniotic fluid and breast odor is thought to be acquired in the prenatal period or genetically. The individually unique quality of amniotic fluid is evidenced by the fact that newborn infants are selectively responsive to the odor of their own amniotic fluid. When an infant is simultaneously exposed to the odors of his/her own amniotic fluid and of the amniotic fluid of another, the infant will orient his/her head more quickly and for a longer duration to the former stimulus than to the latter (Schaal et al. 1998). It is thus evident that the human fetus can detect and store the unique chemosensory information available in the prenatal environment.

It is of interest that bottle-fed infants manifest a greater motivation than breastfed infants to orient to their own amniotic fluid odor than to the unfamiliar amniotic fluid odor. This may result from the decreased opportunity to smell his/her preferred colostrum/amniotic fluid odors. It is evident that neonates demonstrate strong attraction to amniotic fluid odor. This preference remains until an average of 3.3 days after birth.

9.2.6 Alteration of Olfactory Preferences

Neonates' preferences change from amniotic fluid/colostrum to mature milk over time (Fig. 9.1). Bartocci et al. (2000) found that the smell of colostrum increased the blood flow in the orbito-frontal cortex, but that the changes in blood oxygen saturation decreased after 5 days of age. As long as mothers do not change their diet abruptly, there is a consistency in the odor of colostrum and mature milk. Mothers who experience the greatest change in diet before and after birth have the greatest difficulty in establishing breastfeeding. It is thus evident that neonates retain their olfactory memories even if they do not have the opportunity to taste colostrum. In animal studies, rabbit kits raised by mothers fed different diets during pregnancy and lactation show a clear preference for the diet of their mother upon weaning (Bilkó et al. 1994). Litters of rat pups were exposed in utero to taste/odor stimulation through the injection of an apple juice solution into the amniotic fluid. The offspring exposed to the apple juice solution in utero showed an increased preference for apple postnatally (Smotherman 1982).

The mother's diet affects both the amniotic fluid and her breastmilk. More than 20 years ago, Hauser et al. reported the case of an infant that smelled of spices. The spices were absorbed from the maternal gastrointestinal tract and transferred to the amniotic fluid, where they were swallowed by the fetus (Hauser et al. 1984). Prenatal familiarization with the flavor of colostrum contributes to the establishment of breastfeeding. If mothers abruptly change their diet after delivery, infants experience difficulty in establishing breastfeeding due to the reduced degree of prenatal–postnatal olfactory continuity (Hepper 1996).

9.2.7 The Role of Odor of Amniotic Fluid in Parent–Neonate Attachment

Infant–mother bodily contact is believed to be the species-typical pattern of immediate postpartum child care. Mothers and newborns engage in mutually beneficial interactions. As described above, skin-to-skin contact and exposure to maternal odors facilitate infant adaptation to the early postnatal environment. Individual recognition is essential for the development of mother–infant attachment and olfactory cues play an important role in the development of this attachment. When infants touch or lick the areola and nipple shortly after delivery, their mothers make more of an effort not to leave their infants and they talk to them more than mothers whose infants did not initiate this areola or nipple touching or licking (Widström et al. 1987). The amniotic odor that diffuses in the delivery setting has not been explored as a part of the intimate experience of parturition, although it is often noted as being remarkable by midwives and obstetricians. Schaal and Marlier (1998) found that human parents are able to distinguish among the odors of amniotic fluid samples associated with different infants. The parents are also able to recognize the odor of their infant's amniotic fluid. Both parents are not only aware of an amniotic scent that diffuses into the delivery room, but they can accurately identify the olfactory signature carried in their own infant's amniotic fluids.

The similarity of the infant's amniotic fluid odor to their mother's odor is interesting and may be related to several determinants involving either environmental or genetic processes, or probably the interaction of both processes.

Various functional consequences of the perception of amniotic fluid odor may be hypothesized in human parenting: potential impact on the formation of the mother's first impression of the actual newborn; conscious or unconscious recognition of a kin odor from the very beginning, through either maternal recognition of self-odor cues on the infant or paternal recognition of maternal cues in the infant's odor; and promotion of rapid individualization of the infant and the resulting amplification of the parents' nurturing tendencies. The infant's amniotic fluid odor, together with all the other cues they emit, may contribute to the initial steps of the developmental dynamics of feelings of maternal and paternal attachment.

9.2.8 Preference to Breast Odor Is Genetically Obtained

The attractiveness of breast odor is also thought to be obtained in the prenatal period or genetically. Mizuno and Ueda (2004) examined full-term, healthy babies who had been completely separated from their mothers for a certain period postpartum. In this situation, it is possible to separate postnatal olfactory learning from genetically determined (or in utero acquired) preferences. They concluded that preferences for maternal odors acquired independently from postnatal experience have a

greater effect than postnatal olfactory learning on sucking activity even in the absence of triggering signals. Although the infants had been fed exclusively with formula before the study, they sucked more frequently and with higher expression pressure when exposed to their own mother's milk odor (Fig. 9.3). Sucking pressure did not change with the exposure, probably because the suction movement itself is to some extent determined involuntarily. The olfactory preference acquired in utero may persist for a longer time period. Porter and Winberg (1991) reported that 2-week-old, bottle-fed infants responded preferentially to a breast pad from an unfamiliar lactating woman when paired with a pad treated with their familiar formula. These infants displayed a preference for an odor to which they had no obvious postnatal exposure over an odor that they had encountered numerous times in the reinforcing context of feeding. Such attraction to maternal breast odors is presumably acquired independently from postnatal experience.
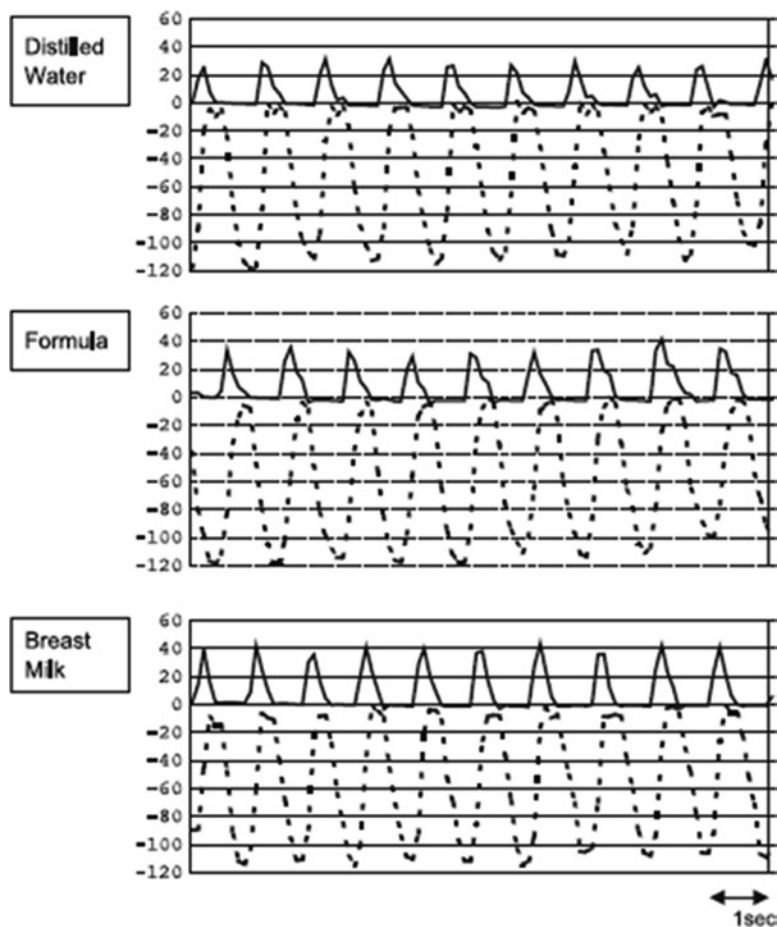
Fig. 9.3 Difference in sucking pressure waves between own mother's milk odor, formula odor, and no odor (Mizuno and Ueda 2004). Traces of sucking pressure waves obtained from the same infants. The solid line indicates expression pressure and the broken line indicates sucking pressure. With own mother's milk odor (lower trace), expression pressure and sucking frequency are higher compared to the formula (*middle*) or control (*upper trace*). Sucking pressure: negative intra-oral pressure which is generated during sucking behavior. Expression pressure: positive intra-oral pressure which is generated by compression between tongue and upper palate

9.3 Olfactory Learning Immediately After Birth

Recent physiological research suggests that norepinephrine plays an important role in early olfactory learning (Brennan et al. 1990; Sullivan 1992). Norepinephrine neurons in the locus coeruleus synapse with the olfactory bulbs and are, at least in rats and sheep, a prerequisite for learning specific odor cues. During the first hour after human birth, plasma levels of catecholamines are increased 20–30-fold as compared to measures from older infants (Lagercrantz 1996). Olfactory learning resulting from a brief period of exposure shortly after birth could be an important process through which neonates become acquainted with the salient features of their postnatal environment. Varendi et al. (2002) exposed infants to an odor (cherry or passion fruit) for 30 min shortly after birth. During tests conducted at 80 h of age, infants were exposed to the familiar odor and the novel odor. The infants spent more time turned toward the familiar odor than the novel one. From this result, it can be said that brief exposure immediately after birth appears to be sufficient for olfactory learning. Romanshik et al. (2007) recently demonstrated that neonates exposed to an odorant for 30 min beginning 4–37 min after birth rapidly became familiar with that olfactory stimulus and retained a memory trace of it over an interval of a couple days. Neonates exposed to the same odor at 12 h after birth, however, did not become familiar with the odor (Fig. 9.4). Newborn babies might be physiologically prepared to learn to recognize the olfactory signature of their mother while interacting with her during the first postnatal hours. Mother–infant skin-to-skin contact immediately after delivery could play an important role in infant learning of maternal odor.

Neonates' sucking behavior and physical stimulation of the breasts within the first hour after birth induce short-term hormonal responses in the mother, including an increase in oxytocin levels (Widstrom et al. 1990; Matthiesen et al. 2001). Given the role of oxytocin in the onset of maternal behavior in nonhuman mammals such as ewes and rats (Pedersen 1997), various authors have speculated that this same hormone (and perhaps other endocrine substances) might also be implicated in the control of maternal responsiveness in humans (Uvnas-Moberg 1998; Numan and Insel 2003). Close contact between the mother and her newborn infant is the biological norm that has evolved in our species. When human birth takes place in a "natural" setting, the mother's odor is arguably the first biologically meaningful odor that confronts the newborn. Enhanced olfactory learning immediately after delivery could have a positive effect on attachment and on early mother–infant interactions and may thereby contribute to the infant's continued well-being.
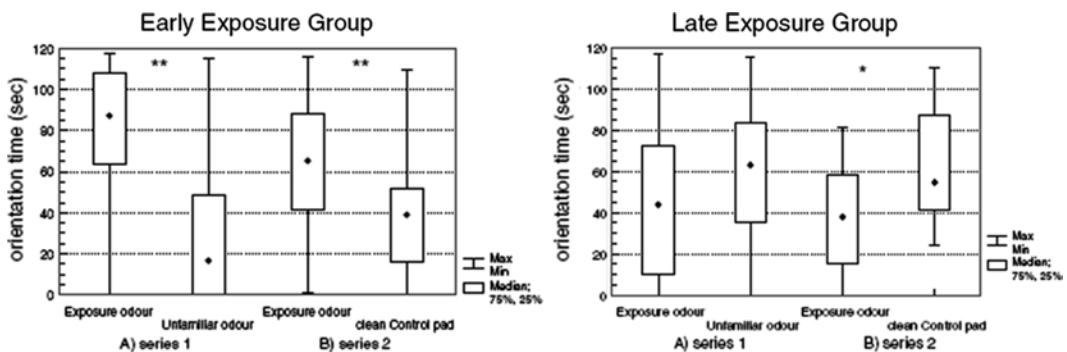
Fig. 9.4 Duration of orientation to odor – early exposure and late exposure – (Romantshik et al. 2007). Early exposure group (*left column*): Duration of orientation to each of the paired stimulus odors by neonates exposed to the odor within 30 min. Late exposure group (*right column*): Duration of orientation to each of the paired stimulus odors by neonates exposed to the odor at 12 h postpartum. Behavioral evidence of efficient olfactory learning and memory was only found when exposure occurred immediately after birth

9.4 Olfactory Learning and Successful Breastfeeding

Skin-to-skin mother–infant contact immediately after birth is known to be beneficial to the neonate as it stabilizes body temperature, decreases stress and the risk of hypoglycemia, and is soothing. In addition, skin-to-skin contact for more than 30 min immediately after delivery results in the early identification of own mother's milk odor (Mizuno et al. 2004), which could lead to early individual discrimination. Enhanced discrimination between own mother's and another mother's milk odor leads to longer breastfeeding duration (Fig. 9.4), partly because individual discrimination plays a major role in creating a strong bond. Infants who experience mother–infant skin-to-skin contact are able to better identify their mother's breastmilk odor. Even for this short period, early infant touching of the mother's areola and nipple could enhance the mother–infant bond, although this short action does not result in longer breastfeeding duration (Fig. 9.5).

What length of time should we recommend that mothers hold their infants immediately after birth in order to extend breastfeeding duration? Mikiel-Kostyra et al. (2002) reported that the duration of skin-to-skin contact is important in the elongation of breastfeeding duration. Effective sucking may be a critical component of this intervention in regards to long-term breastfeeding success. Timing may be critical as most healthy full-term infants will spontaneously grasp the nipple and begin to suck by approximately 55 min post birth (Syfrett and Anderson 1996). In addition, breastfeeding while maintaining skin-to-skin contact stimulates hormones such as oxytocin, which promotes maternal attachment, and prolactin, which promotes lactation and maternal behavior. Extensive skin-to-skin contact immediately after birth promotes early mother–infant interaction and bonding (Kennell and Klaus 1998).
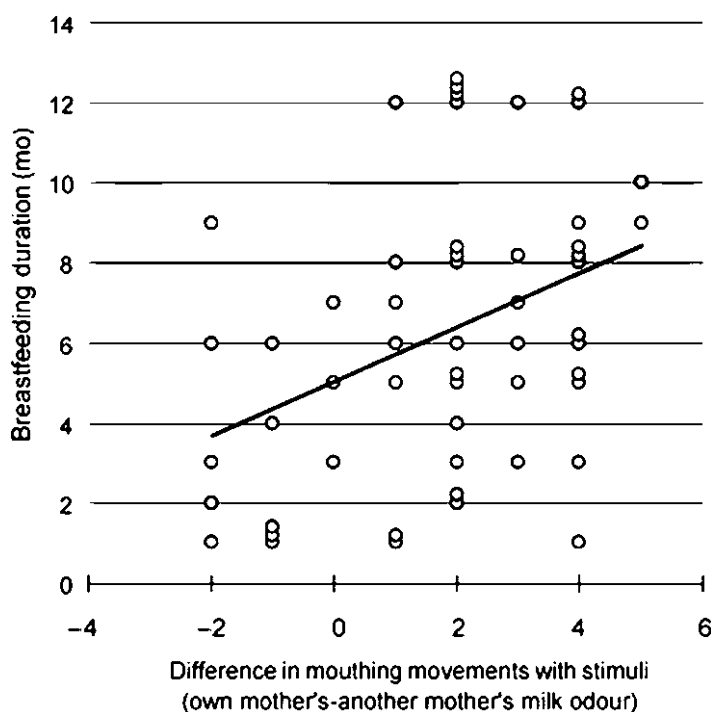
Fig. 9.5 Odor discrimination and breastfeeding duration (Mizuno et al. 2004). The relationship between odor discrimination and breastfeeding duration is shown. *Y* axis indicates breastfeeding duration (months); *X* axis indicates differences in mouthing movement while exposed to own mother's milk odor and another mother's milk odor
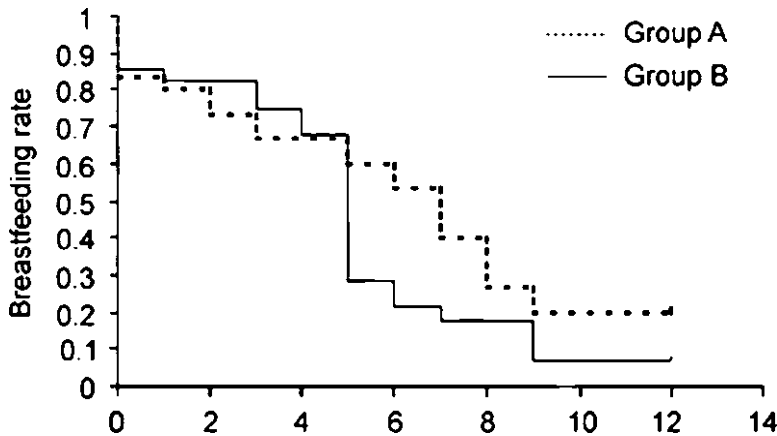
Fig. 9.6 Breastfeeding rate of infants with and without extensive skin-to-skin contact immediately after birth (Mizuno et al. 2004). The breastfeeding rate in groups is shown as a Kaplan–Meier curve. Group A comprises infants who experienced extensive skin-to-skin contact immediately after birth. Group B comprises infants who did not have skin-to-skin contact after birth. *X* axis indicates infant age (mo); *Y* axis indicates percentage of mothers who breastfeed their infants

The early identification of own mother's milk odor from another woman's milk odor may partially explain the early mother–infant interaction.

Schaal et al. reported that neonates can identify their own mother's odor at 3 days of age (Schaal et al. 1980). Mizuno et al. (2004) reported that infants can identify their own mother's breastmilk odor at 4 days of age. These findings could be explained by postnatal odor entrainment. Skin-to-skin contact with the mother immediately after birth creates an optimal environment for the adaptation of newborn infants to extrauterine life. During the early postpartum period, mothers may be especially open to improving their interactions with their infants, which can affect their later parenting (Curry 1982). Some studies indicate that it can also have a long-lasting effect on the duration of breastfeeding. There have been a few studies with a 1-year period of observation. de Château et al. (1984) followed 20 mothers who had extra contact with their infants during the first hour postpartum. They breastfed on average for 2.5 months longer than mothers in the control group. Mikiel-Kostyra et al. studied a group of 1,250 Polish children by the questionnaire method at 3 years of age and concluded that skin-to-skin contact and maternal education were two independent variables that positively influenced the duration of exclusive breastfeeding (Mikiel-Kostyra et al. 2002). In conclusion, prolonged skin-to-skin mother–infant contact immediately after birth is beneficial as it aids in the early identification of mother's odor and leads to a longer breastfeeding duration (Fig. 9.6).

9.5 After Birth: Classical Conditioning – Olfactory Learning of a Novel odor

In animals, in addition to the natural body odor of the mother, artificial odors have been shown to operate as olfactory signals. In addition to classical conditioning, the mere exposure of mother's odor is sufficient for infants to learn their mother's identifying odor.

Sullivan et al. (1991) studied an olfactory classical conditioning procedure in 1-day-old neonates. They gave ten 30-s pairings of a novel olfactory conditioned stimulus (a citrus odor) and tactile stimulation in the form of stroking as the reinforcing unconditioned stimulus. Infants who received

the forward pairings of the odor and stroking exhibited conditioned responses to the citrus odor. From these findings, they concluded that complex associative olfactory learning is seen in neonates within the first 48 h of life.

Engen and Lipsitt (1963) demonstrated that neonates respond to artificial odors presented to them with changes in activity and respiration.

Balogh and Porter (1986) perfumed the beds of newborn for 24 h and were able to show that girls preferred this odor in a choice test given an hour after they were removed from the perfumed bed.

Schleidt and Genzel (1990) found that neonates are able to recognize their own mother's body odors and orient toward them. Infants recognize perfume applied to their own mother's bodies. In this study, breastfeeding mothers perfumed their breasts for 2 weeks and their infants were then tested in a choice test situation. At the age of 1 week, infants oriented their heads significantly more often to the side where they smelled their mother's perfume than to the side where they smelled a control odor.

Davis and Porter (1991) exposed an artificial odorant for 22 h to neonates within the first 2 days after birth. When tested on days 16–18 postpartum, these infants displayed preferential orientation to the exposure odor when paired with a novel odorant. It is thus evident that the effects of early exposure of the stimulus properties of odors can endure over a 2-week interval, indicating that infants retain a memory trace of the exposure odor throughout that time period.

Infants evidently learn very quickly to associate odors with other stimuli if both are experienced in important situations – the most important infant situation of all being close body contact with the mother.

9.6 Olfactory Learning Through the Odor of Breastmilk

Human milk is more than just a complex mixture of substances that best meets the nutritional requirements of the infant. It is a food that varies in flavor because selected volatiles from the mother's diet are transmitted to her milk. Mennella et al. have conducted very interesting research in this area. When human milk is flavored with garlic, infants breastfeed longer and suck more overall than when this flavor is absent, at least under conditions in which the mothers have been ingesting bland diets for several days (Mennella and Beauchamp 1991). Several hypotheses can be put forth to account for this increased responsiveness. The change to garlic-flavored milk may act as a sucking stimulant, a phenomenon similar to that observed in adults when a change in the type and flavor of available foods stimulates intake.

Mennella et al. then examined how infants who had experienced the odor of garlic previously reacted to the odor. Prior and repeated consumption of garlic by nursing mothers modified infant behavior during breastfeeding when the mothers again consumed garlic (Mennella and Beauchamp 1993). Infants of mothers who had repeatedly consumed garlic capsules during the experimental period breastfed for similar periods of time during the 4-h test session in which their mothers consumed garlic (d 11) compared with the session in which their mothers ingested the placebo (d 4). In contrast, infants who had no or minimal exposure to garlic volatiles in their mother's milk during the experimental period spent more time breastfeeding when their mothers ingested garlic than when their mothers ingested the placebo. The garlic flavor became unstimulating to infants who were repeatedly exposed to it in mother's milk. Continued or repeated exposure to an odor results in a relatively rapid suppression of its perceived intensity, presumably because the olfactory receptors have fatigued (Rovee 1972; Todrank et al. 1991).

Studies on other animals (Capretta et al. 1975) suggest that experience with a variety of flavors during breastfeeding, in contrast to the invariant flavor experience of formula feeding, could increase infant willingness to accept a variety of flavors. Breastfed infants consume more of a novel vegetable than formula-fed infants (Sullivan 1992). Besides garlic, a wide variety of flavors (e.g., alcohol, mint, and cheese) ingested by the lactating mother are transmitted to her milk. Whether exposure to these flavors in mother's milk affects the infant's later preferences, development of food habits, and willingness to accept new foods at weaning or thereafter remains an important research area.

The amount of alcohol ingested by a breastfed infant is a small fraction of that consumed by the mother, but even this small amount may have an effect on the infant. The ingestion of alcohol by a lactating woman alters the odor of her milk (Mennella and Beauchamp 1991) Infants suck more frequently during the first minute of feeding after their mothers consume alcohol. The changes in the odor over time are consistent with the changing concentrations of ethanol in the milk. From this finding, it is evident that the breastfed infant may be receiving sensory information about the mother's dietary choices. In nonhuman animals, early and long-term exposure to flavors in the mother's milk affects later flavor preferences (Galef and Henderson 1972, Galef and Sherry 1973; Capretta et al. 1975; Campbell 1976), including that for alcohol (Mainardi et al. 1989).

9.7 Applications to Other Areas of Diet and Behavior

One possibility is to use favorable odors as a treatment for neonates. Marlier et al. demonstrated that the introduction of a pleasant odor in the incubator is of therapeutic value in the treatment of apneas in preterm infants (Marlier et al. 2005).

The human infant, like other mammalian young, has the opportunity to learn about the food choices of the mother because a variety of flavors from her diet are transmitted to human milk (Sullivan 1992). Studies on other animals indicate that this early exposure to characteristics of the mother's diet influences the weanling's responses to flavors and foods. Similar effects have been postulated but not proven for humans. Currently, many researchers are examining dietary factors in the hopes of preventing children from becoming overweight or having metabolic syndrome (Beauchamp and Mennella 2009). Determining if maternal diet during pregnancy and lactation affects the weaning process and later dietary preferences of children should be a priority. I expect that one of keys to decreasing pediatric obesity and metabolic syndrome is a healthy maternal diet, extended breastfeeding, and strong maternal–infant attachment resulting from olfactory learning.

Summary Points

- Fetuses have olfactory memory.
- Maternal diet influences the odor of the amniotic fluid and breastmilk.
- Amniotic fluid supports the neonate in adapting to the world.
- Olfactory preferences change over time after birth.
- Olfactory learning immediately after birth results in earlier discrimination of mother's odor.
- Olfactory learning immediately after birth results in longer breastfeeding duration.
- Neonates/infants become accustomed to different kinds of odors through breastmilk.

Definition of Key Terms

Amniotic fluid: Liquid surrounding the fetus in the womb.

Colostrum: Breastmilk secreted up to 3 days postpartum.

Montgomery glands: Sebaceous glands on the areola of the nipple that emit secretions composed of milk mingled with sebum

Oxytocin: A hormone that plays a key role in milk ejection and promotes maternal attachment.

Olfaction: The sense of smell.

Skin-to-skin contact: Here, refers to mother–neonate skin-to-skin contact immediately after birth.

References

Balogh RD, Porter RH. Infant Behav Dev. 1986;9:395–401.
Bartocci M, Winberg J, Ruggiero C, Bergqvist LL, Serra G, Lagercrantz H. Pediatr Res. 2000;48:18–23.
Bartocci M, Winberg J, Papendieck G, Mustica T, Serra G, Largercrantz H. Pediatr Res. 2001;50:324–30.
Beauchamp GK, Mennella JA. J Pediatr Gastroenterol Nutr. 2009;48:S25–30.
Beauchamp GK, Yamazaki K, Currant M, et al. Immunogenetics. 1994;39:109–13.
Bilkó A, Altbācker V, Hudson R. Physiol Behav. 1994;56:907–12.
Brennan P, Kaba H, Keverne EB. Science. 1990;250:1223–6.
Campbell RG. Anim Prod. 1976;23:417–9.
Capretta PJ, Petersik JT, Stewart DJ. Nature. 1975;254:689–91.
Curry MA. Nursing Res. 1982;31:73–8.
Davis LB, Porter RH. Chem Senses. 1991;16:169–74.
de Vries JIP, Visser GHA, Prechtl HFR. Early Hum Dev. 1985;12:99–120.
DeCasper AJ, Fifer WP. Science. 1980;208:1174–6.
de Château P, Winberg B. Scand J Soc Med. 1984;12:91–103.
Engen T, Lipsitt LP. J Comp Physiol Psychol. 1963;56:73–7.
Galef Jr BG, Henderson PW. J Comp Physiol Psychiatrics. 1972;78:213–9.
Galef Jr BG, Sherry DF. J Comp Physiol Psychiatrics. 1973;83:374–8.
Hauser GJ, Chitayat D, Berns L, Braver D, Muhlbauer B. Eur J Pediatrics. 1984;144:403.
Hepper PG. Acta Paediatr. 1996;416(suppl):16–20.
Kennell JH, Klaus MH. Pediatr Rev. 1998;19:4–12.
Lagercrantz H. News Physiol Sci. 1996;11:214–8.
Macfarlane A. Olfaction in the development of social preferences in the human neonate. In: Porter R, editor. Parent-infant interaction. Amsterdam: Elsevier; 1975. p. 103–13.
Mainardi M, Poli M, Valsecchi P. Biol Behav. 1989;14:185–94.
Marlier L, Schaal B. Dev Psychobiol. 1997;33:133–45.
Marlier L, Schaal B. Child Dev. 2005;76:155–68.
Marlier L, Gaugler C, Messer J. Pediatrics. 2005;115:83–8.
Marlier L, Schaal B, Soussignan R. Child Dev. 1998;69:611–23.
Matthiesen A-S, Ransjo-Arvidson A-B, Nissen E, Uvnas-Moberg K. Birth. 2001;28:13–9.
Mennella JA, Beauchamp GK. Pediatrics. 1991;88:737–44.
Mennella JA, Beauchamp GK. Pediatr Res. 1993;34:805–5.
Mennella JA, Johnson A, Beauchamp GK. Chem Senses. 1995;20:207–9.
Mikiel-Kostyra K, Mazur J, Boltruszko I. Acta Paediatr. 2002;91:1301–6.
Mizuno K, Ueda A. Early Hum Dev. 2004;76:83–90.
Mizuno K, Mizuno N, Shinohara T, Noda M. Acta Paediatr. 2004;93:1640–5.
Numan M, Insel TR. The neurobiology of parental behavior. New York: Springer-Verlag; 2003.
Pedersen CA. Ann NY Acad Sci. 1997;807:126–45.
Porter RH, Winberg J. Neurosci Biobehav Rev. 1999;23:439–49.
Porter RH, Makin JW, Davis LB. Physiol Behav. 1991;50:907–11.
Righard L, Alade MO. Lancet. 1990;336:1105–70.
Romantshik O, Porter R, Tillmann V, Varendii H. Acta Paediatr. 2007;96:372–6.

Rovee CK. J Exp Child Psychol. 1972;13:368–81.

Russell MJ. Nature. 1976;260:520–2.

Schaal B. Presumed olfactory exchanges between mother and neonate in humans. In: LeCamus J, Cosnier J, editors. Ethology and psychology. Toulouse: Privat-IEC; 1986. p. 101–10.

Schaal B. Chem Senses. 1988;13:145–90.

Schaal B, Marlier L. Biol Neonate. 1998;74:266–73.

Schaal B, Marlier L, Hertling E, Bolzoni D, Moyse A, Quichon R. Reprod Nutr Dev. 1980;20:843–58.

Schaal B, Marlier L, Soussignan R. Biol Neonate. 1995;67:397–406.

Schaal B, Marlier L, Soussignan R. Behav Neurosci. 1998;112:1438–49.

Schaal B, Doucet S, Sagot P, Hertling E, Soussignan R Human breast areolae as scent organs: morphological data and possible involvement in maternal-neonatal coadaptation. Dev Psychobiol. 2006;48:100–10.

Schleidt M, Genzel C. Ethol Sociobiol. 1990;11:145–54.

Smith Jr DM, Peters TG, Donegan WL. Arch Pathol Lab Med. 1982;106:60–3.

Smotherman WP. Behav Neural Biol. 1982;36:61–8.

Smotherman WP, Robinson SR. Psychobiology of fetal experience in the rat. In: Kransnegor NA, Blass EM, Hofer MA, Smotherman WP, editors. Perinatal development: a psychobiological perspective. Orlando: Academic Press; 1982. p. 39–60.

Soussignan R, Schaal B, Marlier L, Jiang T. Physiol Behav. 1997;62:745–58.

Sullivan SA. Infant experience and acceptance of solid foods. PhD dissertation, University of Illinois at Urbana-Champaign, 1992.

Sullivan RM, Toubas P. Biol Neonate. 1998;74:402–8.

Sullivan RM, Taborsky-Barba S, Mendoza R, Itano A, Leon M, Cotman CW, et al. Pediatrics. 1991;87:511–8.

Sullivan RM, Zyzak DR, Skierkowski P, Wilson DA. Dev Brain Res. 1992;70:279–82.

Syfrett EB, Anderson GC. Very early kangaroo care beginning at birth for healthy preterm infants and mothers who choose to breastfeed: effect on outcome. Workshop on the Kangaroo-mother method for low birthweight infants. Trieste, Italy: World Health Organisation; October 1996.

Todrank J, Wysocki CJ, Beauchamp GK. Chem Senses. 1991;16:467–82.

Uvnas-Moberg K. Psychoneuroendocrin. 1998;23:819–35.

Varendi H, Porter RH. Acta Paediatr. 2001;90:372–5.

Varendi H, Porter RH, Winberg J. Lancet. 1994;344:989–90.

Varendi H, Porter RH, Winberg J. Acta Paediatr. 1996;85:1223–7.

Varendi H, Porter RH, Winberg J. Acta Paediatr. 1997 Sep:86(9):985–90.

Varendi H, Christensson K, Porter RH, Winberg J. Early Hum Dev. 1998;51:47–55.

Varendi H, Porter RH, Winberg J. Behav Neurosci. 2002;116:206–11.

Widstrom A-M, Wahlberg V, Matthiesen A-S, Eneroth P, Uvnas-Moberg K, Werner S, et al. Early Hum Dev. 1990;21:153–63.

Widström AM, Ransjö-Arvidson AB, Christensson K, Mathiesen AS, Winberg J, Uvnäs-Moberg K. Acta Paediatr Scand. 1987;76:566–72.

Chapter 10
Texture and Diet Related Behavior: A Focus on Satiation and Satiety

Annette Stafleu, Nicolien Zijlstra, Pleunie Hogenkamp, and Monica Mars

Abbreviations

CCK   Cholecystokinin
GLP-1   Glucagon-like peptide 1
PYY   Peptide YY

10.1 Introduction

Overweight and obesity are caused by an imbalance between energy intake and energy expenditure. Some of the food factors associated with this imbalance are energy-dense diets (Rolls 2009) and an increased consumption of energy-yielding beverages (Mattes 2006). Therefore, insight in factors influencing food intake is warranted. Food intake is regulated by cognitive, sensory, post-ingestive, and post-absorptive processes. Blundell and coworkers (see, e.g., Blundell et al. 1994) refer to these processes as the satiety cascade (Fig. 10.1). The terms "satiation" and "satiety" mentioned in this cascade will be explained later.

There is a need for food products that help to lower or maintain body weight. Food properties that increase the process of satiation (meal termination) and/or induce longer-term feelings of satiety (increase the intermeal interval) may help to control weight. The satiating capacity of a certain food depends on food properties like macronutrient composition, energy density, fiber, and volume. This chapter focuses on the role of food texture in food intake regulation. Texture is one of the food characteristics that is supposed to play mainly a sensory or cognitive role.

10.2 Texture Perception

Szczesniak (2002) defines texture as "the sensory and functional manifestation of the structural, mechanical, and surface properties of foods detected through the senses of vision, hearing, touch, and kinesthetics." Texture is an essential part of the whole spectrum of sensory properties of a food.

A. Stafleu (✉)
TI Food and Nutrition/TNO Quality of Life, 3700 AJ Zeist, The Netherlands
e-mail: annette.stafleu@tno.nl
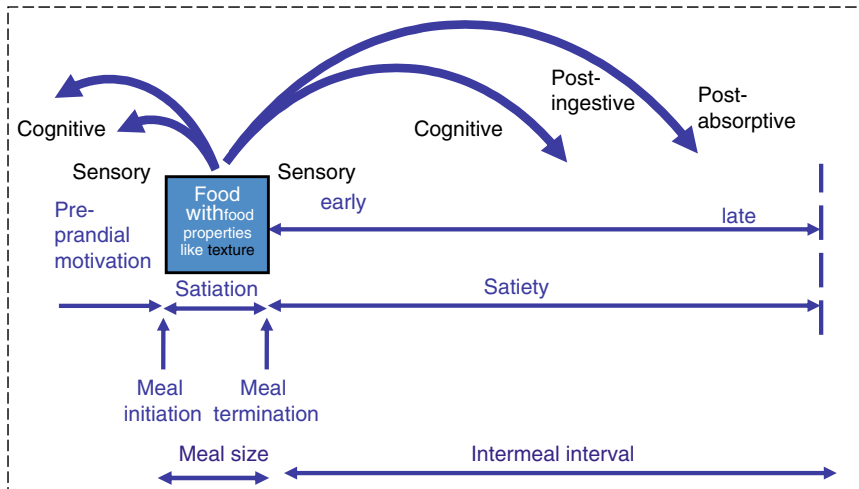
Fig. 10.1 Satiety cascade (Adapted from Blundell et al. 1994). The satiety cascade of Blundell is used often to illustrate processes involved in food intake regulation

During sensory perception of food, people use all their senses of which vision, hearing, touch, smell, and taste are the most important (Van Vliet et al. 2009). During eating, texture plays a role in: (1) initial perception during the first bite, (2) masticating factors during chewing, and (3) changes induced during mastication and swallowing, such as rate of breakdown of the food, moisture absorption, and oral coating (Van Vliet et al. 2009).

10.3 Mastication

Mastication can be defined as the process by which food taken into the mouth is converted into a form suitable for swallowing (Szczesniak 2002). During this process, the food is also assessed for palatability and a decision is made as to whether to swallow or reject it. There are basic biomechanical constraints that determine the duration and amount of oral processing prior to swallowing. In the oral cavity, food is subjected to several mechanical and chemical processes. Solid food is fragmented by the teeth, diluted and broken down by saliva, heated or cooled by the temperature of the mouth, formed into a soft, coherent bolus, and finally swallowed (Hutchings and Lillford 1988; Prinz and Lucas 1997; Van der Bilt et al. 2006). Hardness is known to influence the masticatory process. Dry and hard products require more chewing cycles and therefore more time is needed to break down the food and to add enough saliva to form a bolus suitable for swallowing (Van der Bilt et al. 2006). Low-viscosity liquids are already in a form suitable for swallowing and require minimal processing.

10.4 Satiation and Satiety

In order to understand the effects of texture on food intake, it is important to distinguish between satiation and satiety (see Rogers and Blundell 1979 Blundell et al. 1994) and how they are measured (see Table 10.1). Apart from other reasons such as eating out of boredom or specific social contexts, we start eating when we get hungry and stop when we are full. Satiation is the process that determines

when we stop eating, and therefore determines meal size. Satiation is mainly driven by early processes (<20 min), such as sensory, cognitive, and early pre-absorptive factors. Satiation may be measured by ad libitum food intake of a meal. Satiety is the process which suppresses the internal drive to eat (appetite). Satiety can be quantified by measuring the intermeal-interval. In both satiety and satiation studies rating scales are used to assess appetite. Most investigators use the terminology developed by Rogers and Blundell (1979): hunger, desire to eat, prospective consumption, and fullness (Fig. 10.2). Further, gastric emptying and level of gastrointestinal hormones (such as Ghrelin, CCK, PYY, GLP-1) are used in food intake regulation studies to study the mechanism (gastrointestinal processing) behind the effect (De Graaf et al. 2004). To study the effect of texture on satiation and satiety different approaches have been used. Most studies used a preload-test meal design (see Fig. 10.3). In these kinds of studies, a fixed amount of foods different in texture is given and the amount eaten in the test meal is the primary outcome measurement. Other studies are primarily interested in meal termination. In these studies, foods different in texture are offered in abundance and ad libitum intake of these foods (meal size) is the primary outcome measurement (see Fig. 10.4).

Table 10.1 Key points or features of satiety and satiation

	Features	Measurements
Satiation	Meal termination	Ad libitum intake
		Appetite ratings
		Stomach distension
		CCK, GLP-1
Satiety	Intermeal interval	Preload-test meal
		Appetite ratings
		Spontaneous next eating event
		Stomach emptying
		Glucose, Insulin
		Ghrelin

This table describes the features of satiation and satiety and the measurements used in satiation and satiety research *CCK* cholecystokinin; *GLP-1* glucagon-like peptide 1; *PYY* peptide YYFor biomarkers of satiation and satiety, see De Graaf et al. (2004)

How hungry are you?

Not hungry
at all   Extremely
                                                                                     hungry
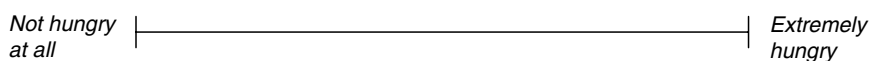
Fig. 10.2 In both satiety and satiation studies rating scales are used to assess appetite (hunger, desire to eat, prospective consumption and fullness (Rogers and Blundell 1979)). This is an example of a visual analogue scale: subjects are asked to indicate their feeling of hunger by placing a vertical line on the scale

Preload-test meal design	Appetite ratings	Fixed amount of foods with different textures (*preload*)	*Ad libitum* test meal *(test meal)*	Appetite ratings

Fig. 10.3 Example of a design in which textures differences were tested in a preload-test meal design

Ad libitum intake design	Appetite ratings	*Ad libitum* consumption of foods with different textures	Appetite ratings

Fig. 10.4 Example of a design in which foods with different textures were offered *ad libitum*

10.5 Liquids

Beverages have become a significant source of dietary energy (Bleich et al. 2009). Several studies showed that liquid foods elicit weaker suppressive appetite responses (Haber et al. 1977; Hulshof et al. 1993; Mattes and Rothacker 2001; Tsuchiya et al. 2006) and a weaker compensatory response in energy intake than solid or semisolid foods (Tournier and Louis-Sylvestre 1991; Mattes 1996; DiMeglio and Mattes 2000; Mourao et al. 2007). This effect is not only apparent in short-term preloads studies, but is also observed in longer-term intervention studies (De Castro 1993; Tordoff and Alleva 1990). Soups seem to be an exception: for example in a study by Mattes (2005) soups led to reductions of hunger and increases of fullness that were comparable to solid foods.

The evidence of a weak satiety value of energy-yielding beverages is strongest for clear beverages (Mattes 2006). Rolls (2009) hypothesized that beverages composed of few nutrients, such as sugary drinks, fail to engage hunger mechanisms and are recognized as beverages that influence thirst. In a 7-day period observational study McKiernan et al. (2009) could not find an association between thirst or hunger and the ingestion of energy-yielding beverages. Perhaps the human appetite system is not well equipped to sense liquid calories (Zijlstra et al. 2008; Wolf et al. 2008).

10.6 Viscosity

Viscosity refers to the thickness of a food.

10.6.1 Ad Libitum Intake

Zijlstra et al. (2008) showed that chocolate-flavored milk-based foods differing in viscosity (starch modification) led to clear differences in ad libitum intake, both in a realistic setting in a cinema and in a laboratory setting. Ad libitum intake decreased as viscosity increased. This effect of viscosity on intake could not be attributed to palatability, macronutrient composition, and energy density or volume. However, it was possible that eating rate or effort needed to consume the product influences meal termination. In the laboratory setting effort and eating rate were controlled for by means of a peristaltic pump. The difference in intake could be partially explained by the higher eating rate of liquids, while effort did not have an effect (for more details see Fig. 10.5). The effect of viscosity on ad libitum intake was replicated in several other studies (De Wijk et al. 2008; Mars et al. 2009).
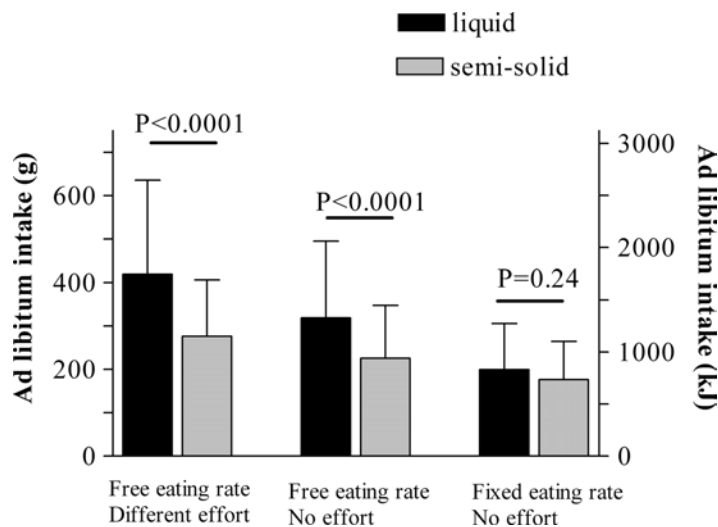
Fig. 10.5 The tested products in this study were chocolate dairy products with different viscosities: a liquid product (milk like) and a semi-solid product (custard like). The products were equal with respect to liking, energy density and nutrient composition. Difference in mean intake of the liquid and semi-solid food was comparable to that of another study in a realistic setting (cinema) (~34%). This difference was hardly affected by controlling for effort (~29%). However, the difference in mean intake of the liquid and semi-solid food was much lower when controlled for eating rate (~14%). Zijlstra et al. (Inter J Obes 2008;32:676–683)

10.6.2 Fixed Preload

Mattes and Rothacker (2001) studied the influence of viscosity on appetitive responses. The used shakes differed in viscosity, but were similar in weight, volume, temperature, energy, and macronutrient content, energy density, rate of consumption, cognitive expectations, palatability, appearance, and requirements for mechanical processing. Significantly greater and more prolonged reductions of hunger scores were observed with the thicker shakes. No differences were found in the size or time to first meal or 24-h energy intake. Russell and Delahunty (2004) did not find an effect of viscosity of a fixed amount of rice milk on hunger scores and time to lunch.

Zijlstra et al. (2009a) explored the effect of viscosity of chocolate-flavored liquid and semi-solid milk-based products on the gastrointestinal hormones ghrelin, CCK, and GLP-1. Subjects were offered a fixed amount of these products and several blood samples were drawn. After 90 min subjects were offered a chocolate cake to consume ad libitum. Although the appetite ratings showed that the semisolid product was apparently more satiating than the liquid product, no clear effects of viscosity on the gastrointestinal hormones or on the ad libitum intake of the cake were found.

Vuksan et al. (2009) showed that a highly viscous polysaccharide preload led to a reduced intake of pizza 90 min later, compared to a medium- and low-viscosity fiber preload. No differences were found in appetite scores and 24-h intake. The drinks were identical in taste, appearance, caloric, and macronutrient content. The only difference was the viscosity of the fiber, which developed in different viscosities in the gastrointestinal tract. Therefore, effects seem to occur beyond the mouth and therefore sensory (texture) perception does not seem to play an important role in this study.

Juvonen et al. (2009) examined the effects of modified oat bran on sensations of appetite and satiety-related gastrointestinal hormone responses. The oat bran beverage with low viscosity induced a greater postprandial increase in satiety and plasma glucose, insulin, CCK, GLP-1, and PYY, and a greater decrease in postprandial ghrelin than the beverage with high-viscosity oat bran. This does not fit in the hypothesis that satiety increases when viscosity increases. An explanation might be the earlier availability of fiber in the gastrointestinal tract due to a faster gastric emptying after the low-viscosity oat bran beverage consumption.

10.7 Food Form

In an early study of Haber et al. (1977), subjects had to consume a fixed amount of apples, apple purée, or apple juice. The apple juice was consumed more than ten times faster than the apple and nearly three times faster than the purée. In a study of Mattes and Cambell (2009) subjects consumed 300 kcal loads of apple (solid), applesauce (semisolid), and apple juice (beverage) at a meal or as a snack. The apple juice showed the weakest appetitive response, followed by the applesauce, while the apples (solid) elicited the highest appetitive response. The interval between test food consumption and the spontaneous next eating event of more than 100 kcal was shortest for the beverage. Also Flood-Obbagy and Rolls (2009) studied the effect of apples in different forms and their results suggested also that solid fruits affect satiety more than pureed fruit or juice. The consumption of the apples was followed by an ad libitum lunch. Fullness rating differed after the preload consumption in the order: apple > applesauce > juices > control. Total lunch energy intake (including the preload) was reduced after eating the apple (solid) as preload.

Mourao et al. (2007) studied the effect of food form on appetite and energy intake in matched beverage and solid food forms. They compared watermelon and watermelon juice (high carbohydrate), cheese and milk (high protein), and coconut meat and coconut milk (high fat). In all cases, the beverage food form elicited a weaker compensatory dietary response than the matched solid food form. Total energy intake was 12–19% higher on the beverage days compared to the solid food days, which was due more to a weak effect on satiety than on satiation.

Not all studies showed an effect in the same direction. Santangelo et al. (1998) reported that meal consistency influences both gastric emptying rate and satiety sensation. In their study a homogenized vegetable-rich meal was found to be more satiating than when the meal was offered in clearly separated solid and liquid components. The overall gastric emptying rate was slowed after the homogenized meal (followed by a CCK peak later).

Flood and Rolls (2007) investigated meal intake after consuming preloads of different soups with the same energy density: broth and vegetables served separately, chunky vegetable soup, chunky-pureed vegetable soup, and pureed vegetable soup. Subjects consumed less of the test food after eating the soup compared to no soup, but the type of soup did not significantly influence test meal intake.

10.8 Mechanism

The mechanisms underlying the effect of texture on satiety are not well understood. Physical properties such as viscosity and texture could affect chewing, oro-gastric handling of foods, and absorption (Rolls 2009).

Chewing solid foods may give a satiety signal, which is not induced by swallowing a liquid (Haber et al. 1977; Mattes 1996; Rolls 2009). From a recent paper by Cassady et al. (2009) it was concluded that masticating nuts, and likely other foods and nutrients, results in important differences in appetitive and physiologic responses.

10.8.1 Cognitive and Sensory Factors

Cognitive and sensory factors could play a role in the effect of food form on satiety. People might have different beliefs about the satiating capacity of solid foods compared to beverages. Expected satiation might influence portion sizes (Brunstrom and Shakeshaft 2009). It may be that the mechanisms through which texture affects food intake work through differences in perception due to differences in oral processing. Also the satiating capacity of soups is thought to be in part cognitive: a soup is believed to be nutritive and impacts appetite more than thirst (Mattes 2006).

Eating rates of liquid foods are higher than eating rates of (semi-)solid foods (Haber et al. 1977; Kissileff et al. 1980; Zijlstra et al. 2008). Based on the study of Zijlstra et al. (2008) it may be hypothesized that the mechanisms through which texture affects food intake works through a higher/ longer sensory exposure time and/or a longer transit time of the product in the oral cavity. A liquid remains a short period in the mouth, while a semisolid product is eaten more slowly and thus stays longer in the mouth. This increases the exposure time to sensory receptors in the oral cavity and therefore there is more opportunity for exposure to taste, smell, texture, and so on (Zijlstra et al. 2008). It is shown that bite size and oral processing indeed affect ad libitum food intake of a semi-solid product (Zijlstra et al. 2009b). Also, smaller food sizes (nibbles versus bars) resulted in lower intake (Weijzen et al. 2008) and small sip sizes reduced the ad libitum intake of soft drinks compared to large sip sizes (Weijzen et al. 2009).

A factor that plays a role in the termination of food intake is the degree of sensory-specific satiety for that food. This refers to a decrease in the reward derived from consumption for the food eaten compared to a not eaten food (see, e.g., Rolls et al. 1981). For example, after consumption of a plate of macaroni, one's pleasure for macaroni is decreased, while the pleasure of custard remains the same or increases. Foods may differ in their degree of sensory-specific satiety. For some foods, the pleasure derived from consumption will decline sooner than for others. Texture-specific satiety might play a role in meal termination. Guinard and Brun (1998) showed that pleasantness of texture, and desire to eat hard test foods decreased after eating a hard lunch food. This might also have played a role in the study of Weenen et al. (2005). They suggested that eating cheese biscuits might have given rise to a higher degree of boredom than eating pears in light syrup, caused by the dryness and thus amount of saliva required to form a bolus that can be swallowed.

10.8.2 Gastrointestinal Processes

Gastrointestinal processing can partly explain the effect of viscosity on intake. Soluble dietary fiber may alter viscosity of gastrointestinal contents and this may result in effects on satiety and food intake (Dikeman and Fahey 2006). Juvonen et al. (2009) did find an effect of bran viscosity on gastric empty-ing and an effect on satiety hormones. Also Santangelo et al. (1998) found effects of physical state of a meal on gastric emptying and CCK release. An effect of viscosity on satiety hormones could not be found in the study of Zijlstra et al. (2009a). An explanation might be that the starch used by Zijlstra et al. (2009a) was already broken down to glucose by enzymes in saliva before it reached the stomach. The mechanism of how viscosity, gastric emptying, and satiety interact is not clear yet. Tieken et al. (2007) examined whether solid meal-replacement products differed from liquid meal-replacement products in appetite and appetite-regulating hormones. They did find differences in appetitive responses, insulin and ghrelin, but not in CCK and leptin, between the products. However, as the authors mentioned, although the products had a similar energy content, the macronutrient composi-tions differed, which might have affected the appetite and hormonal responses.

10.8.3 Learned Associations

Zijlstra et al. (2008) suggest that differences in satiety responses between liquids and solids are partly based on learned behavior during infancy. Since the viscosity and caloric density of human breast milk appear to vary together, breast feeding may provide an important initial exposure to a general rule that thicker substances contain more calories than thinner substances (McDaniel et al. 1989; Davidson and Swithers 2004). This indicates that the mouth feel of a product already could have an effect on the relationship between viscosity and intake. Mars et al. (2009) indicated that the higher viscosity of a food, and thus the longer orosensory stimulation, may facilitate the learned association between sensory signals and metabolic consequences. However, current trends in eating patterns and food supply (high energy drinks and low-energy solids) may alter learned associations between hunger or thirst and the post-ingestive consequences of eating and drinking (McKiernan et al. 2008).

10.9 Conclusions

Most studies on the effect of food form on satiety compared liquids with a solid form. From these studies it appeared that liquids are less satiating than solids. In addition, there seems to be an independent role of viscosity on satiation. More research is necessary to study textures with less pronounced differences than liquid versus solid foods, for example, the effects of texture differences within solid products. Also, the gastric role in food texture warrants further investigation.

10.10 Applications to Other Areas of Health and Disease

Several studies showed that viscosity and texture differences influence satiation (meal termination) and to a lesser extent satiety. Consumption of an energy-yielding beverage poses a greater risk for consuming more energy than a semisolid or solid food. From a review of Malik et al. (2006) it appeared that both short-term and long-term studies have shown that energy ingested from sugar-sweetened beverages add to the total energy intake during the day. Liquid calories may lead to a positive energy balance and subsequent weight gain (DiMeglio and Mattes 2000). This knowledge can be applied both in the underweight and overweight situation.

Summary Points

- Food properties that increase the process of satiation (meal termination) and/or induce longer-term feelings of satiety (increase the intermeal interval) may help to control weight.
- Liquid foods elicit weaker suppressive appetite responses and a weaker compensatory response in energy intake than semisolid foods or solid foods.
- Ad libitum intake of foods decreases as viscosity increases.
- The mechanisms underlying the effect of texture on satiation and satiety are not well understood.
- It may be hypothesized that the mechanisms through which texture affects food intake work through a higher/longer sensory exposure time and/or a longer transit time of the product in the oral cavity.

Definitions of Key Terms

Mastication: The process by which food taken into the mouth is converted into a form suitable for swallowing.

Satiation: The process that determines when we stop eating, and therefore determines meal size.

Satiety: The process that suppresses the internal drive to eat (appetite).

Sensory-specific satiety: The decrease in pleasantness of a product after eating that product to satiety, compared to the pleasantness of selected uneaten control products.

Texture: The sensory and functional manifestation of the structural, mechanical, and surface properties of foods detected through the senses of vision, hearing, touch, and kinesthetics.

For definitions see Rogers and Blundell (1979), Rolls et al. (1981), Szczesniak (2002).

References

Bleich SN, Wang YC, Wang Y, Gortmaker SL. Am J Clin Nutr. 2009;89:372–81.

Blundell JE, Green S, Burley V. Am J Clin Nutr. 1994;59:728S–34.

Brunstrom JM, Shakeshaft NG. Appetite. 2009;52:108–14.

Cassady BA, Hollis JH, Fulford AD, Considine RV, Mattes RD. Am J Clin Nutr. 2009;89:794–800.

Davidson TL, Swithers SE. Int J Obes Relat Metab Disord. 2004;28:933–5.

De Castro JM. Physiol Behav. 1993;53:1133–44.

De Graaf C, Blom WAM, Smeets PAM, Stafleu A, Hendriks HFJ. Am J Clin Nutr. 2004;79:946–61.

De Wijk RA, Zijlstra N, Mars M, de Graaf C, Prinz JF. Physiol Behav. 2008;95:527–32.

Dikeman CL, Fahey GC. Crit Rev Food Sci Nutr. 2006;46:649–63.

DiMeglio DP, Mattes RD. Int J Obes. 2000;24:794–800.

Flood JE, Rolls BJ. Appetite. 2007;49:626–34.

Flood-Obbagy JE, Rolls BJ. Appetite. 2009;52:416–22.

Guinard JX, Brun P. Appetite. 1998;31:141–57.

Haber GB, Heaton KW, Murphy D, Burroughs LF. Lancet. 1977;2:679–82.

Hulshof T, De Graaf C, Westrate JA. Appetite. 1993;21:273–86.

Hutchings JB, Lillford P. J Texture Stud. 1988;19:103–15.

Juvonen KR, Purhonen AK, Salmenkallio-Marttila M, Lähteenmäki L, Laaksonen DE, Herzig KH, et al. J Nutr. 2009;139:461–6.

Kissileff HR, Klingsberg G, Van Itallie TB. Am J Physiol. 1980;238:R14–22.

Malik VS, Schulze MB, Hu FB. Am J Clin Nutr. 2006;84:274–88.

Mars M, Hogenkamp PS, Gosses AM, Stafleu A, de Graaf C. Physiol Behav. 2009;98:60–6.

Mattes RD. Physiol Behav. 1996;59:179–87.

Mattes R. Physiol Behav. 2005;83:739–47.

Mattes R. Physiol Behav. 2006;89:66–70.

Mattes RD, Cambell WW. J Am Diet Assoc 2009;109:430–437.

Mattes RD, Rothacker D. Physiol Behav. 2001;74:551–7.

McDaniel MR, Barker E, Lederer CL. J Dairy Sci. 1989;72:1149–58.

McKiernan F, Houchins JA, Mattes RD. Physiol Behav. 2008;94:700–8.

McKiernan F, Hollis JH, McCabe GP, Mattes RD. J Am Diet Assoc. 2009;109:486–90.

Mourao DM, Bressan J, Campbell WW, Mattes RD. Int J Obes. 2007;31:1688–95.

Prinz JF, Lucas PW. Proc R Soc Lond B. 1997;264:1715–21.

Rogers PJ, Blundell JE. Psychopharmacology. 1979;66:159–65.

Rolls BJ. Physiol Behav. 2009;97:609–15.

Rolls BJ, Rolls ET, Rowe EA, Sweeney K. Physiol Behav. 1981;27:137–42.

Russell K, Delahunty C. Food Qual Prefer. 2004;15:743–50.

Santangelo A, Peracchi M, Conte D, Fraquelli M, Porrini M. Br J Nutr. 1998;80:521–7.

Szczesniak AS. Food Qual Prefer. 2002;13:215–25.

Tieken SM, Leidy HJ, Stull AJ, Mattes RD, Schuster RA, Campbell WW. Horm Metab Res. 2007;39:389–94.

Tordoff MG, Alleva AM. Am J Clin Nutr. 1990;51:963–9.

Tournier A, Louis-Sylvestre J. Appetite. 1991;16:17–24.

Tsuchiya A, Almiron-Roig E, Lluch A, Guyonnet D, Drewnowski A. J Am Diet Assoc. 2006;106:550–7.

Van der Bilt A, Engelen L, Pereira HW, van der Glas HW, Abbink JH. Physiol Behav. 2006;89:22–7.

Van Vliet T, van Aken GA, de Jongh HHJ, Hamer RJ. Adv Colloid Interface Sci. 2009;150:27–40.

Vuksan V, Panahi S, Lyon M, Rogovik AL, Jenkins AL, Leiter LA. Nutr Metab Cardiovasc Dis. 2009;19:498–503.

Weenen H, Stafleu A, de Graaf C. Food Qual Prefer. 2005;16:528–35.

Weijzen PLG, Liem DG, Zandstra EH, De Graaf C. Appetite. 2008;50:435–42.

Weijzen PLG, Smeets PA, de Graaf C. Br J Nutr. 2009;102:1091–7.

Wolf A, Bray GA, Popkin BM. Obes Rev. 2008;9:151–64.

Zijlstra N, Mars M, de Wijk RA, Westerterp-Plantenga MS, De Graaf C. Int J Obes. 2008;32:676–83.

Zijlstra N, Mars M, de Wijk RA, Westerterp-Plantenga MS, Holst JJ, De Graaf C. Physiol Behav. 2009a;97:68–75.

Zijlstra N, de Wijk RA, Mars M, Stafleu A, de Graaf C. Am J Clin Nutr. 2009b;90:269–75.

Chapter 11
Sensory Education: French Perspectives

Caroline Reverdy

Abbreviations

EPODE   *Ensemble Prévenons l'Obésité des Enfants*: Preventing Childhood Obesity Together
PNNS   *Programme National Nutrition Santé*: French national diet and health program

☐ **Effects in children food preferences and behaviours via EXPOSURE to food**

▤ **Effects in children food preferences and behaviours via INFORMATION on food**

◯ : children
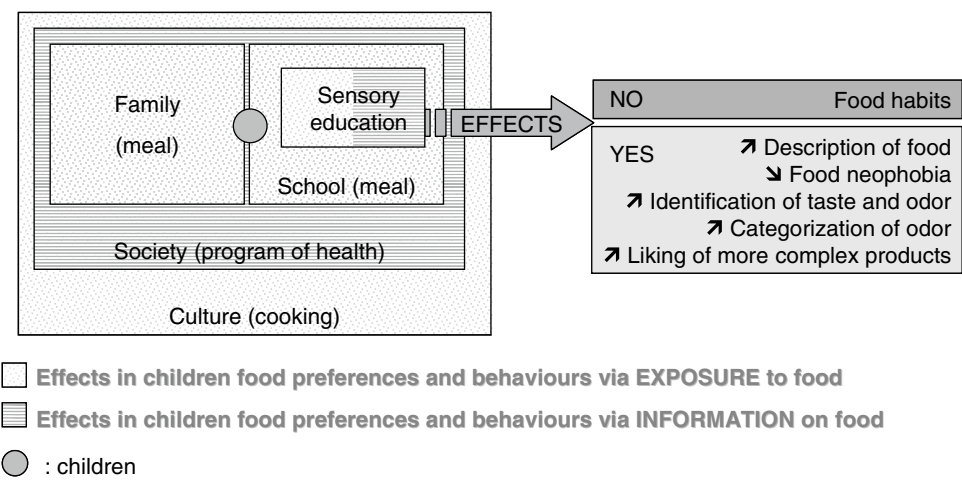
11.1 Introduction

Eating is one of the most common actions in everyday life. What about tasting food? Is there any such thing as sensory education or educating the sense of taste? We shall take the example of one country, France – well known for its culinary culture – to see what factors implicitly or explicitly

C. Reverdy (✉)
AUXIME - ODOROSMÊ, Les Grandes Roches, 69490, Saint Romain de Popey, France
and
PANCOSMA, R&D Department, 6 Voie des Traz, 1218
Le Grand Saconnex, Switzerland
e-mail: caroreverdy@hotmail.com

construct our sense of taste. Then we shall see how explicit sensory education at school could change eating preferences and behavior. And finally, we shall compare sensory education to other forms of education and lay out the prospects of this method.

11.2 Can the Sense of Taste Be Educated?

11.2.1 Learning in Life

As with other omnivores, human eating preferences and habits are mainly learned. Learning varies with the particular food culture, but the general mechanisms are comparable.

Children's tastes are influenced by their mother's feeding habits, first of all by straightforward conditioning in the womb (Schaal et al. 2000), and then via the mother's milk and gradual diversification of diet (Maier et al. 2006). Later, they are shaped by what is eaten at family meals, then in playgroups and at school meals. To pure conditioning are thus added mechanisms such as incident and non-intentional learning by simple exposure to new foodstuffs (Zajonc 1968; Pliner et al. 1993), parental teaching, whether to encourage or to discourage (Birch 1980; Hanse 1994), and imitation of peer behavior (Birch 1980). With the exception of parental teaching, these mechanisms influence behavior in an implicit way, without reaching the cognitive level and without the child being conscious of them. Thus the variety of culinary experience stimulates the development of preferences more or less positively depending on the atmosphere of the feeding situation and on the individual's own olfacto-gustatory sensitivity.

This process develops and enriches sensory experience in terms of what flavors are known. The range of sensory experiences thus depends on circumstances, but also on individual personality (Pliner and Salvy 2006), as in neophobia – where the individual is afraid to try foods that are new to him or her (Loewen and Pliner 1999).

Children are dependent on what foodstuffs they happen to be given; teenagers, on the other hand, become more independent and make their own choices. They can get past their neophobia and extend their sensory experience. This then stabilizes in adulthood, in the encounter with the partner's eating habits, and then those adopted by the couple (Köster 1990).

Simple exposure (Zajonc 1968) to traditional foodstuffs and learning mechanisms (i.e., culture) strongly influence the development of preferences; other mechanisms determine the orientation and dynamics of preference. These influences are the subject of the psychology of exploratory behavior and motivation (Dember and Earl 1957; Berlyne 1970; Walker 1980) and are shown schematically in Fig. 11.1.

Berlyne (1970) explained how a stimulated organism expresses maximal preference for an optimal stimulus activation level, preference being lesser for any other stimulus level. Dember and Earl (1957) further showed how the optimal level changes after exposure to stimuli that are more stimulating than the individual's previous optimum level (pacer): the optimum shifts toward the level of the more stimulating stimuli. Exposure to stimuli that are less stimulating than the optimal level, on the other hand, do not alter the optimum but rather lead to boredom, as predicted by Walker (1980). These theories, based on visual stimuli, have been confirmed using olfacto-gustatory stimuli (fruity drinks) (Lévy et al. 2006). Walker (1980) showed that stimulus complexity as perceived by the subject decreases with exposure – which would explain why novelties at first seem too complex but then come to be more appreciated with time; with yet more exposure, they begin to lose their perceived complexity and may become commonplace.
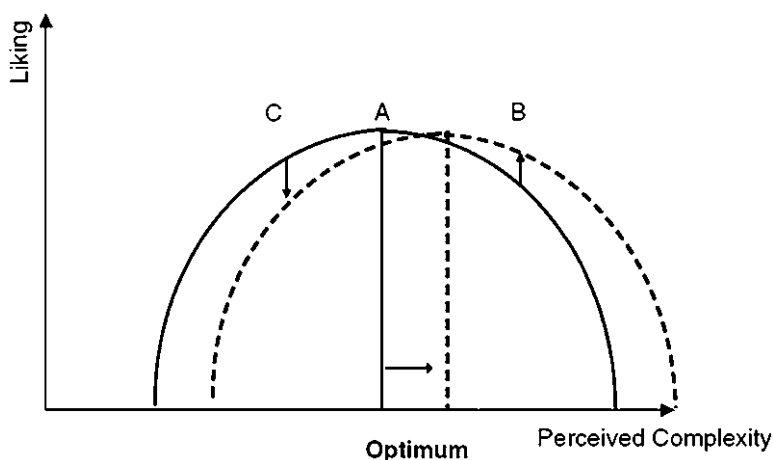
Fig. 11.1 Inverted-U relationship between liking and the arousal potential of a stimulus, as suggested by Berlyne's (1967) arousal theory (*solid curve*), and the shift (*broken curve*) of the original inverted-U curve and the optimal individual level of psychological complexity upon exposure to a "Pacer" (B), as suggested by the arousal theories of Dember and Earl (1957) and Berlyne (1967) (From Lévy et al. 2006). Liking changes with perceived complexity depending on the optimum of the individual

This phenomenon, known as *product boredom*, is well known in marketing (Köster and Mojet 2007).

Thus, taste can evolve under various mechanisms and according to experience. Food preferences are flexible and subject to mainly implicit learning. The question therefore arises as to whether food preferences might also be modifiable over a shorter term by explicit learning such as sensory education.

11.2.2   What Is Sensory Education?

11.2.2.1   Definition

Sensory education develops the senses by focusing attention on them.
The sense of taste is developed by information regarding taste perception (which involves all five senses: taste, smell, touch, sight, and hearing) and by practical training to enhance sensory acuity.

Sensory education is to be distinguished from sensory training. The former concerns the sense of taste in general and is intended for nonexpert consumers, whereas the latter applies to a particular type of foodstuff and is intended for expert analysts.

11.2.2.2   Examples of Sensory Education

Encouraging children to explore their bodies is not a new idea. As early as 1930, Rampillon & Gruyer-Wantrin already explained that "young children should learn to use their senses, just as they need to learn to acquire other skills".

In France, many nonprofit organizations, such as *Agropolis-Museum*, *Pomme et Sens*, and (the oldest) the *Institut du Gout*, work in schools and playgroups, running taste education sessions, with a hedonistic approach, developing the pleasure associated with tasting.

The *Institut du Goût* (*Taste Institute*) introduces teachers to the *Classes du Goût* (*Taste Classes*) method developed in France by Jacques Puisais in the 1970s. This learning method, aimed at children around the age of 9, seeks to develop food curiosity, refine taste, and enrich food vocabulary. In 2001, Daviet explained the three main lines of this method: the first is "knowledge of the senses, balanced diet, production of some foods, and vocabulary enrichment"; the second is "know-how – for example, how to compose meals and menus"; the third is "self-awareness of the body and of sensations". The first version of the module, in 10 sessions, came out in 1984, after more than 10 years of trials and prototypes run in schools in Tours and Paris (Puisais and Pierre 1987; Puisais 1999). It was then applied in schools in many regions of France, for more than 20 years. For example, the method is used by the association *Les Sens du Goût* (*Senses of Taste*), from the Avesnois region, which runs a comprehensive, permanent, and extensive program of developing and education of taste in the local area. In particular, the association runs information, education, and training campaigns for the population as a whole, to raise awareness of local identity and the sense of belonging to a specific area (Pautrel 2002). Subsequently, the creation of the *Institut du Goût* in 1999 gave the method a new lease of life, while respecting its original nature. Thus, in 2002, a CD-ROM[1] (Puisais et al. 2002) presented a second version, in 12 sessions. Transmission to teachers is based not only on the CD-ROM, but also by training courses run by the *Institut du Goût*. In recent years, this French teaching method has been translated and adapted for other European countries (Sweden, The Netherlands, Finland).

Thus, the transmission of taste education is now developing in research programs such as Sapere. This program, set up in 1994, is based in Brussels. Sapere – from the Latin for both knowledge and taste – began as an international association and went on to become an international non-profit-making foundation. It brings together experts from the human sciences, research, industry, and the education and communication sectors. Its partners include many celebrities, scientific institutes, corporations, and associations such as EPODE (*Ensemble Prevenons l'Obésité Des Enfants*: Preventing Childhood Obesity Together). Since its inception, Sapere has promoted Jacques Puisais's method throughout Europe – for instance, in the Scandinavian countries (Jonsson et al. 2005). In other countries (The Netherlands, Switzerland), the focus has been on implicit methods for 6–9 year olds.

This type of sensory education for healthy children is quite recent. Sensory education also exists as a form of therapy.

11.2.3 Application to Other Areas of Health and Disease

11.2.3.1 Obesity and Sensoriality

Sensory education of taste can further be expected to improve food habits and therefore help to limit overweight and the prevalence of obesity. The new generation of dietary education (e.g., EPODE) encourages adding a sensory dimension in their programs, with tastings and cooking. Nevertheless, it must be stressed that the effect of sensoriality on limiting overweight and obesity is quite indirect and needs further investigation to be proven.

---

[1] This program is only available in the form of a compact disc – read only memory.

11.2.3.2 Disability and Sensoriality

General sensory education, not specifically targeting taste, has been extended to work with disabled (blind, deaf) children. In France, Patty Canac, a perfume specialist, runs rehabilitation for cranial trauma, cerebral hemorrhage, and prolonged coma victims. She helps these patients find a taste for life again, using olfactory stimulation to awaken memory by the pleasure of playful learning (Canac et al. 2008).

11.3 What Factors Educate Our Sense of Taste?

11.3.1 Culture

It is well known that food preferences are linked to exposure to a given foodstuff (Wardle et al. 2003) and that we tend to consume the food that is part of our particular culinary culture. We are thus conditioned to appreciate more highly the foodstuffs of our own culture.

11.3.2 Family

Food education within the family involves exposure to foods: children are encouraged to *taste*. The parents play a role and may reinforce neophobia to a greater or lesser extent, whether directly or by showing a strong emotional reaction to their children's not eating (Hanse, l994). Such parental pressure and restriction regarding food are measurable on the Kids' Child Feeding Questionnaire (KCFQ) (Carper et al. 2000).

11.3.3 School Meals

Half of French children take lunch at school (Stratégies 2006). This plays a role in their food education. However, it amounts to only a small number of their annual meals and cannot in itself ensure balanced diet. The elementary taste education provided at school is regulated by the French Education Ministry's *Le Bulletin Officiel* (2001), which encouraged diversity of diet and the development of taste. It is also suggested the following main lines of activities around the issue of food (see Table 11.1).

These recommendations advise providing children with explicit information, but also enriching their implicit experience via tastings and education concerning odors and spices.

Table 11.1 Key points of the main lines suggested by the French Ministry of Education (2001) for activities around the issue of food

1. "Educating pupils' taste and promoting culinary heritage and products of good gustatory and nutritional quality
2. Highlighting precise vocabulary concerning flavors, especially for children who confuse terms, so that they are able to define their sensations clearly
3. Explaining the secrets of the production and composition of foods
4. Tasting local specialties
5. Discovering odors, spices, and essences"

The French Ministry of Education suggested five main lines for activities around the issue of food from food vocabulary to culture of food

Even so, food education as provided by the family and school meals may prove insufficient to ensure healthy eating; dietary education programs have therefore been set up by the authorities.

11.3.4 French Ministry of Health

Taste education and dietary education are often associated. At the present time – in France as in other industrial countries – there is a worrying increase in the prevalence of childhood overweight and obesity in the 5–12-year-old age group from 3% in 1965 to 16% in 2000 (Rolland-Cachera et al. 2001).

Daniel Thomas (2003) stressed the importance of changing behavior with respect to obesity-related cardiovascular risk. It was with this in mind that the French authorities set up the PNNS in 2001, to improve public health by acting on the main determinants of diet. Information and education for young people is one strategic axis of the PNNS (*Programme National Nutrition Santé*: French national diet and health program), stressing the importance of early and lasting dietary education, concerning both food and physical exercise. The Ministry of Health and the Ministry of Education are working together on this. One of the priorities of the circular on *School children's health: 5-year prevention and education program* (dated December 1st, 2003) was dietary education and the prevention of overweight and obesity. For this, dietary education and taste and consumption education are to be included in curricula as of primary school, as supports for teaching and in conjunction with school activities in general. Several programs are already being implemented in schools. Information documents and PNNS-approved intervention tools have been made available (Kerneur et al., information on the Internet). Each guide contains simple and accessible information and practical advice adapted to the individual's habits so as to combine health, pleasure, and the requirements of day-to-day living in meeting the objectives of the PNNS. The guide to children's diet is called *Health comes by eating and moving: a child and teens diet guide for all parents*.

Traditional dietary education also seeks to provide information, but often in terms of *good* and *bad*, which is liable to give rise to feelings of guilt.

The environmental factors influencing food preference are summarized in Fig. 11.2.
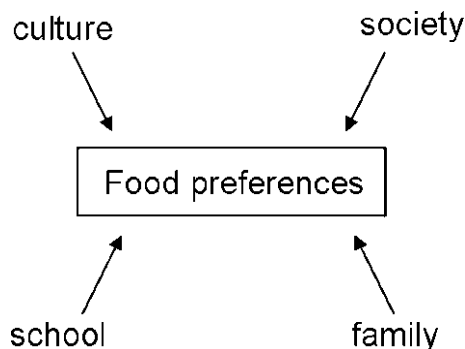
Fig. 11.2 Environmental factors impacting food preference. Culture, society, school, and family have influences on the food preferences

11.3.5 School: *Classes Du Goût*

As described above, *Classes du Goût* modules can be run in schools. We shall now detail their principles and content.

The teaching approach in each session is structured according to the following model. First, there is a questions phase, helping the children explore the theme of the day; then, a tasting phase, which provides information and enables the children to reach a practical understanding of how the gustatory system works; finally, the children's various responses and answers are brought together, with complementary input on the initial questions. The module comprises 12 sessions of 90 min, on the following topics: "the five senses"; "taste"; "vision"; "olfaction"; "touch and hearing"; "aroma"; "flavor"; "preparation of a dish"; "food preferences"; "regional specialties"; "recapitulation"; and "the festive meal". Table 11.2 presents the program of this sensory education module.

Table 11.2 Key points of the description of the sensory education program (Reverdy et al. 2008)

	Title and aim of the session	Organization of the session	Conclusion and/or contribution of the session
Lesson 1	"The five senses" This session evokes the pupils' understanding of the way in which one makes contact with foods.	The teacher presents a 3-step tasting procedure (before, during, and after) using the five senses to describe a food. This session allows children to enrich their vocabulary on what they feel sensorially and emotionally.	– All five senses are necessary to establish contact with the world of foods. – This contact always comes about in three phases (before, during, and after the tasting).
Lesson 2	"Taste" This session lets the pupils discover the basic tastes (sweet, salty, sour, bitter, and umami) and other mouth sensations (prickling, burning, and astringency).	The teacher presents varied tastings to let pupils discover their own taste perception and to find out that the answers they give are similar to others', yet still very personal.	– Food offer a wide variety of tastes and chemical sensations in the mouth. – Knowing how to express different tastes and sensations. – Showing the diversity between individuals in gustative perception.
Lesson 3	"Vision" This session lets the pupils understand how vision creates expectations that allow them to anticipate food taste.	Tasting making use of colorants, to show how visual perception creates expectations that can modify other perceptions.	– Colors have an impact on other sensory perceptions. – Establishment of precise vocabulary for visual perception.
Lesson 4	"Olfaction" This session shows pupils how difficult it is to recognize odors.	Odor bottles (more or less familiar odors, fruity odors, etc.) are presented to evoke pupils' memories and lead to identification.	– Showing the relationship between an odor and the evocation of its source and associated memories. – Identifying certain familiar odors.
Lesson 5	"Touch and hearing" This session aims to enrich vocabulary for touch and to show how touch and hearing complement each other.	Samples of different materials (silk, wool, velvet, etc.) are presented. Foods of varying hardness, crispness, and crumbliness are tasted.	– Various sensations are linked to touch during tasting: tactile, auditory, and thermal perception. – Enriching vocabulary on touch and hearing. – Linking together food texture, consistence, and temperature.

Table 11.2 (continued)

	Title and aim of the session	Organization of the session	Conclusion and/or contribution of the session
Lesson 6	"Aroma" This session shows how aromas in mouth are perceived by retro-nasal olfaction and how the same food eaten cold or warm gives off different aromas.	Various highly aromatic foods are tasted, and the teacher explains how one can get rid of the aromatic sensations by using ortho- or retro-nasal routes.	– Distinction between direct (odor) and indirect (aroma) olfaction. – The temperature of food modifies sensation.
Lesson 7	"Flavor" This session studies the sensations of sessions 2, 4, and 6 simultaneously.	The pupils learn to identify these different sensations when simultaneously present in complex foods, and to identify their development over time.	– Definition of flavor. – Forms of interaction between the senses involved. – Synthesis of all themes dealt with so for (important information and vocabulary).
Lesson 8	"Preparing a dish" In this session, with the help of a professional, the pupils prepare food from a recipe.	This cooking workshop takes place with a professional.	– Experiencing the pleasure of preparing a dish. – Understanding the variety of possible ways to eat a given food. – Discussion of eating habits.
Lesson 9	"Food preferences" The pupils are asked to argue for their preferences and to stimulate their curiosity for new foods.	Tasting unfamiliar food: each group is required to search for taste information about one fruit and then to encourage the others to taste it.	– Individual food preferences differ a lot. – Talking about your preferences and arguing for them. – Accepting the taste of new foods.
Lesson 10	"Regional specialties" The pupils note differences in local and international specialties and how cultural history may explain them.	The teacher and pupils bring in local specialties for tasting.	– Presenting regional culinary specialties brought in by the pupils, and thinking about their origin. – Enlarging knowledge by tasting specialties from other regions and cultures.
Lesson 11	"Recapitulation" In this session, the pupils have to remember the knowledge built up during the previous lessons.	Quiz, synthesizing acquired knowledge.	– Remembering acquired knowledge that can be of help in assessing food.
Lesson 12	"The festive meal" This last session is an opportunity for the pupils to transfer the things they have learned during the previous lessons by evaluating a meal prepared for them.	The pupils eat a meal at a restaurant.	– Applying acquired knowledge. – Taking part in a relaxing experience: the pleasure of eating together. – Developing skills linked to table manners and *savoir-vivre*. – Assessing the effect of preservation on the taste of food.

The sensory education program of *Classes du goût* contains 12 lessons with theoretical knowledge and practical activities

Our cultural, family, social, and school environments can implicitly influence food behavior. How can explicit sensory education at school alter food preferences and behavior?

11.4 How Far Can Sensory or Dietary Education Change Food Preferences and Behavior?

11.4.1 Edusens in France

A program over a period of years to assess the benefits of sensory education has been set up by the European Center of Taste Science in Dijon, France.

The first part of the study focused on young adults, while the rest concerned 8–11 year olds.

11.4.1.1 Assessment of Sensory Education in Young Adults

The aim of the study was to run a sensory education program for young adults and then to assess its impact on their consumer behavior, complexity perception, and preferences. The assumption was that educating *attention to taste* would shift preferences from simple to more complex versions of food, due on the one hand to improved sensory performance (sensitivity, identification, discrimination, and description) and on the other hand to a reduction in the perceived complexity of complex variants, making them less *unsure* and more pleasant (in line with the theories of Berlyne (1970) and Walker (1980)). In the first step, a panel of 67 consumers assessed perceived complexity and stated their preferences for sets of chocolate, coffee, and tea of varying aromatic complexity. Sensory acuity was measured on a battery of tests developed for the study. Then, in the second step, the subjects were divided into two groups of equal size. One of the groups underwent 12 sessions of sensory education, with practical exercises and theoretical data, while the other group did not. At the end of the module, the two groups returned to the laboratory to do the same tests as in the first step. The results confirmed the initial hypotheses that complexity defined a priori by the formulae corresponded to perceived complexity for all the foodstuffs, and that initial preferences correlated negatively with aromatic complexity.

Evolution following sensory education showed a change in the experimental group's assessments. Their descriptive performance was improved. The perceived complexity of the two most complex variants decreased, particularly with regard to variables that were *hard to describe and identify*. These changes led to increased preference for these two items, whereas no change was observed in the control group (Reverdy et al. 2004).

11.4.1.2 Evaluation of Sensory Education in Children

This study was run with a panel comprising an experimental group of 100 children and a control group of the same size. The experimental group took part in 12 one-and-a-half-hour sessions of taste education in class (J. Puisais's *Classes du Goût*) during the primary school year. The entire panel took part in three measurement sessions comprising three laboratory assessments each, before the sensory education module (T0), just after it (T1), and in the following school year, some 9 or 10 months after the module (T2), in order to test durability of impact.

The results showed increased liking in both groups for the more aromatic and intense variants at T1, with this increase persisting in time (T2) only in the experimental group. Thus, repeat assessment

(or exposure) had a stronger effect than education initially (T1), the education effect appearing only later (T2) in the form of a consolidation of the exposure effect (Reverdy et al. 2010a). Education increased children's neophilia, but only temporarily (Reverdy et al. 2008). Education improved description of tasting experience toward more objective rather than subjective criteria, and this improvement was lasting. Finally, education shifted the categorization strategy for unknown odors toward a strategy based on less hedonic criteria (Reverdy et al. 2010b, c).

A new method for measuring food choice was set up for the study, but showed no sensory education effect on choice behavior.

In conclusion, sensory education as carried out here showed some impact on food preference and behavior, but not durably, and mainly affected description of tasting experience (Reverdy 2008).

Some of these conclusions were anticipated by Ton Nu (1996), who assessed the first version of the *Classes du Goût* in France. In 144 9–12 year olds, 69 of whom had had *Classes du Goût*, she found a positive education impact on verbalization of sensation and on attention to food quality, but none on the desire to taste new foods or on consumption patterns for unfamiliar and familiar items. Even so, the children who had been in the *Classes du Goût* claimed to be more tempted to taste new foods and were interested in the history of foodstuffs. These findings put the validity of declarative assessment in doubt when not followed by congruent behavior. The validity of Ton Nu's results is moreover limited by the lack of any pretest to enable intra-subject comparison before and after education.

11.4.2 *Classes Du Goût* in Finland

A second study, conducted in Finland (Mustonen et al. 2009), evaluated the effect of sensory education on taste and odor awareness and food ratings in school children. Two hundred and forty-four school children, aged 7–11 years, from two schools in Helsinki area, were involved. In each school, two distinct treatments – educated (96 children) and uneducated (79 children) – were applied for a 2-year period. The sensory education contained ten lessons of the *Classes du Goût* and five lessons familiarizing the children with different food categories. During the 2-year period, the two groups were assessed four times each on the following parameters: free odor naming, taste identification of six solutions, descriptive characterization of two breads, rating attention paid to the sensory properties of food, willingness-to-try rating for unfamiliar vs. familiar foods, and aided odor naming (5 odors, 10 verbal labels). During the test period, the "educated" children improved their skills to identify tastes and odors and to characterize foods, while the control group exhibited no evolution. However, "education" effects were mainly to be found in younger children, and were small and not always consistent over the 2-year period. However, children activated their odor and taste perceptions and improved their ability to describe sensory properties of food after sensory education.

Finally, *Classes du Goût* sensory education can influence food preferences and behavior, whether in France or in Finland, as summarized in Fig. 11.3.

11.4.3 Dietary Education

The effects of dietary education were measured in a French study conducted in the towns of Fleurbaix and Laventie, and called *Fleurbaix – Laventie Ville Santé*. This epidemiological study started in 1992 in these two towns in the Nord-Pas-de-Calais region of France, with the initial objective of assessing dietary education in young children. The first phase consisted in a dietary survey in the region, which had been chosen due to the high local prevalence of overweight. Children were then
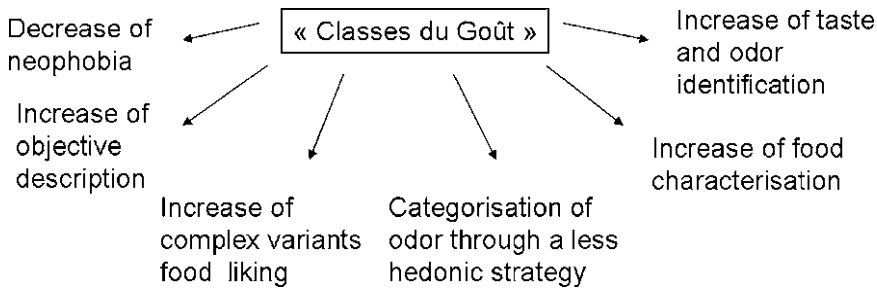
Fig. 11.3 Measured effects of the *Classes du Goût*. The effects of *Classes du Goût* were measured on neophobia, description, liking of complex food, odor categorization, food characterization, and taste and odor identifications

given dietary information. Subsequent change in food behavior in the entire family was observed, validating the hypothesis that children who received dietary education at school would encourage the whole family to adopt better food consumption behavior (Borys et al. 1993; Borys and Lafay 2000; Borys 2003). A positive approach, based on the pleasure of eating, was found to have more effect on families' food behavior than the restrictive approach of other dietary interventions.

This first phase (1992–1997) was followed up by a second, of 5 more years (1997–2002), to explore the determinants of weight gain and the respective impacts of diet, hormones, biological and genetic factors, and physical activity.

In phase 3 (2002–2007), the population was offered the possibility of health coaching. Twice-yearly follow-up of a cohort extended to all age groups assessed dietary and behavioral status in the population in comparison with dietary recommendations (Borys et al. 1993; Basdevant et al. 1999; Brouet 2003).

Moreover, initial results showed the EPODE approach to have a positive influence, reducing childhood obesity in the local areas involved, compared to increasing obesity in control areas.

In the pre-EPODE era, traditional dietary education was mainly based on restriction and avoidance. Unfortunately, it failed to include sufficiently the sensory pleasure associated with mealtimes. This may explain the poorer effectiveness of dietary campaigns in the UK, based almost exclusively on restriction and the analysis of dietary risk.

11.5 Conclusion and Perspectives

11.5.1 Comparison Between Sensory Education at School and Other Forms of Education (Dietary and Family)

11.5.1.1 Comparison with Dietary Education

The explicit information and implicit experience provided by *Classes du Goût* have a more or less lasting effect on children depending on the particular behavior being studied. This teaching method is particularly rich in sensory experience, with attention to each child's individual differences. It is nuanced, unlike dietary education which tends to involve a dualistic approach in terms of *good* and *bad* behavior. Moreover, dietary education is often limited to simple information transmission, divorced from any sensory experience.

Classes du Goût offer implicit sensory experience in a positive context enriched with explicit information as in dietary education.

11.5.1.2 Comparison with Family Education

Within the family, children are often encouraged to extend their range by tasting new foods, which they learn, by repetition, to like over time. Such exposure to foods, however, does not always come with a positive feeling, if it involves parental pressure. *Classes du Goût* offer *tastings*, introduced by prior information. Moreover, they take place in a context of playful, peer-group learning.

Like at home, children extend their food experience in *Classes du Goût*. However, the method associates implicit experience to explicit information. Moreover, how a food is perceived in the context of an exchange with the parents may be very different from how it is experienced in an exchange with the teacher in the presence of the other children.

The comparison of food education types are described in Table 11.3.

Table 11.3 Key points of the comparison between types of food education: sensory, dietary, and parental

Characteristics of the education type	Sensory education at school	Dietary education	Parental education
Sensory experience	Yes	No	Yes
Tasting introduced by prior information	Yes	No	No
Information without tasting	No	Yes	No
Highlighting individual differences	Yes	No	No
Exchange	Peer groups and teachers	Nutritionists	Parents
Dualistic approach (good, bad)	No	Yes	Yes/no
Parental pressure	No	No	Yes

Sensory education at school focus on experience and information; dietary education focus on information; parental education focus on experience

11.5.2 Advantages and Limits of Sensory Education at School

11.5.2.1 Advantages of the Method

This teaching method has the interest of focusing the children's attention on their own sensations, finding their own responses rather than some preestablished or conventional response. Its originality compared to other school subjects (such as mathematics) enables children who are doing badly at school to find a space for expression and success, as Öström and Annett (2008) reported in Swedish children.

Classes du Goût may not really change food behavior, but do provide general knowledge of the raw materials of food and food education including how dishes are cooked. Given the contemporary food system which encourages consumption of processed foods, this approach seeks to promote healthier eating, closer to the natural products. In this way, it helps combat the fast-food culture.

Advertising for processed foods targeting children, such as biscuits, has an impact on the type of consumption. The *Classes du Goût* culture favors a counterculture. However, as we have seen, its impact is slight in comparison with the effectiveness of implicit learning by food exposure.

11.5.2.2 Limits of the Method

The great effectiveness of exposure puts into perspective the effects of explicit education of the *Classes du Goût* type, which finally provides mainly a gastronomic culture for the children without actually changing their eating habits.

Moreover, while the *Classes du Goût* approach stresses a combination of the pleasure of eating and explicit learning, it must be said that implicit learning by exposure also involves the post-ingestion effects of food, which are probably more important than explicit information for the formation of eating habits and the development of food appreciation. Aversion subsequent to bad post-ingestion experiences is much more persistent than attraction caused by good experience, as the avoidance reaction provoked by aversion reduces the chances of correction by new experience, whereas attraction increases the chance of coming up against a bad experience.

11.5.3 Action!

The findings of EduSens, showing increased appreciation of complex food items following a small exposure (just three times is enough), should encourage the authorities to seek to change eating behavior by means of exposure to healthy food. A method focusing on the effects of exposure to varied and complex flavors and odors has the advantage over the *Classes du Goût* approach of being applicable in young children whose language development is incomplete. School meal campaigns, such as the traditional *Taste Week* in October, are to be encouraged, even if the benefit has yet to be properly assessed.

Finally, in the light of the success of the session in which the children got actively involved in preparing a dish and learned to adjust the quantities of ingredients according to their preferences, it would seem that food education should involve active participation in learning to cook, especially as the capability and pleasure of cooking well will be essential when the child reaches adulthood, in order to be able to prepare enjoyable and balanced meals. The kitchen is surely a wonderful place to discover and transmit the pleasure of eating well, as Marie-Claire Thareau Dupire (2006) suggests. This finding was further confirmed in the *Let's make a meal together* session in phase 3 of the EduSens project, which got the families involved. This is why we strongly encourage any cooking activity that enables children to put different ingredients together so as to make a dish adjusted to their own tastes.

Key Point

- **Sensory education:** context, courses of action, and effects

---

Definitions

Classes du Goût: (*Taste Class*) is a method developed in France by Jacques Puisais in the 1970s. This learning method, aimed at children around the age of 9, seeks to develop food curiosity, to refine taste, and enrich food vocabulary

Food preferences: Preferences for food are obtained by comparison, whereas *liking* is absolute information. Thus, preferences can be used to compare several variants of a range, as in the EduSens project.

Neophobia: The fear to try foods that are new to the subject

Sensory education: Develops the senses by focusing attention on them. The sense of taste is developed by information regarding taste perception (which involves all five senses: taste, smell, touch, sight, and hearing) and by practical training to enhance sensory acuity. It is general and intended for nonexpert consumers.

Sensory training: Is training with food, odor, or solutions in order to improve taste ability and is intended for expert analysts in sensory analysis.

Summary Points

- The content of sensory education of taste at school is information regarding taste perception and food processes, and practical training to enhance sensory acuity and to enrich food vocabulary.
- Scientific studies showed the following effects of sensory education in children:
  - Improved description and characterization of food
  - Improved identification of odor and taste
  - Temporary decrease in neophobia
  - Increased liking for more complex food products
  - More expert odor categorization
- The advantages of sensory education at school are to focus on children's own sensations and responses and provide knowledge concerning food.
- Sensory education at school does not really change food habits and its explicit information seems less important than the post-ingestive effects of food.
- An alternative to sensory education could be cooking lessons to encourage better food habits.

References

Basdevant A, Boute D, Borys JM. Int J Obes. 1999;23(4):10–3.
Berlyne DE. In: Nebraska symposium on motivation. Arousal and reinforcement. University of Nebraska Press; 1967. p.1-100.
Berlyne DE. Percept Psychophys. 1970;8:279–86.
Birch LL. Child Dev. 1980;51:489–96.
Borys JM. Nutr Services, Jan 2003:1–2
Borys JM, Lafay L. Rev Méd Suisse Romande. 2000;120:207–9.
Borys JM, Boute D, Thomas F, Fontbonne A, Eschwege E. Cahiers Nutri Diet. 1993;28(3):177–80.
Brouet I. Imp Médec, 16 May 2003
Canac P, Samuel C, Socquet-Juglard S. InterEditions; 2008.
Carper JL, Orlet Fisher J, Birch LL. Appetite. 2000;35:121–9.
Daviet C. La Santé de l'Homme. 2001 March-April: 352
Dember WN, Earl RW. Psychol Rev. 1957;64(2):91–6.
Hanse L (1994) Unpublished Ph.D. thesis. Paris X-Nanterre University, Paris, France.
Jonsson IM, Ekström MP, Gustafsson IB. Int J Consumer Stud. 2005;29:78–85.
Kerneur C, Duchène C, Noirot L http://www.mangerbouger.fr/pro/education/enseignants/intro.html
Köster EP. Food ingredients Europe conference proceedings 1990. The Netherlands: Expoconsult, Maarssen; 1990. p. 32–7.
Köster EP, Mojet J. In: MacFie HJH, editor. Consumer-led food product development. Abington, Cambridge: Woodhead Publishing; 2007. p. 262–80.
Lévy CM, MacRae A, Köster EP. Acta Psychol (Amst). 2006;123:394–413.
Loewen R, Pliner P. Appetite. 1999;32(3):351–66.
Maier AS, Leathwood P, Chabanet C, Issanchou S, Schaal B. Chem Senses. 2006;31:E5.
Ministère de l'éducation nationale (2001) BO spécial n°9, 28 June 2001: 6
Mustonen S, Rantanen R, Tuorila H. Food Qual Prefer. 2009;20(3):230–40.

Öström A, Annett J. A sense of innovation, 3rd European conference on sensory and consumer research, Hamburg, Germany; 7–10 September 2008.

Pautrel D. Cahier Espaces. December 2002;76:27–30.

Pliner P, Salvy SJ. In: Shepherd R, Raats M, editors. The psychology of food choice. Wallingford, Oxon: CABI; 2006. p. 75–92.

Pliner P, Pelchat M, Grabski M. Appetite. 1993;20:111–23.

Puisais J. Le goût chez l'enfant, l'apprentissage en famille. Flammarion; 1999.

Puisais J, Pierre C. Le goût et l'enfant. Flammarion; 1987

Puisais J, Mac Leod P, Politzer N. Le Goût et les 5 Sens, Compact disc – read only memory, Odile Jacob Multimédia-SCEREN; 2002.

Rampillon L, Gruyer-Watrin J. Jeux et exercices en vue de l'éducation sensorielle et mentale des jeunes enfants et qui est destiné aux institutrices maternelles et aux mères de famille. Librairie de l'enfance, Paris, 2nd edition; 1930.

Reverdy C. Unpublished Ph.D. thesis, Université de Bourgogne, Dijon, France; 2008.

Reverdy C, Schlich P, Köster EP, Ginon E, Lange C. Food Qual Prefer. 2010a;21:794-804.

Reverdy C, Lange C, Thibaut A, Schlich P, Köster EP. 32nd Achems Annual Meeting, 21–25 April 2010, St. Pete Beach, USA; 2010b.

Reverdy C, Lange C, Thibaut A, Schlich P, Köster EP. 20th ECRO Congress, 14–19 September 2010, Avignon, France; 2010c.

Reverdy C, Lange C, Schlich P. A sense of identity, 1st European conference on sensory science of food and beverages, 26–29 September 2004, Florence, Italy; 2004.

Reverdy C, Chesnel F, Schlich P, Köster EP, Lange C. Appetite. 2008;51:156–65.

Rolland-Cachera MF, Bellisle F. In: Burniat W, Lissau I, Cole TJ, editors. The obese and overweight child. Cambridge: Cambridge University Press; 2001. p. 69–92.

Schaal B, Marlier L, Soussignan R. Chem Senses. 2000;25:729–37.

Stratégies. 1428, 5 Oct. 10, 2006:24.

Thareau Dupire MC. Mon enfant mange de tout. Paris: Leduc S Editions; 2006.

Thomas D. Pano Méd. 2003;4874:40.

Ton Nu C. Unpublished Ph.D. thesis, ENGREF, Paris, France; 1996.

Walker EL. Enduring effects of occurrence of psychological events, psychological complexity and preference: a hedgehog theory of behavior. Monterey: Brook/Cole; 1980. p. 129–96.

Wardle J, Cooke LJ, Gibson EL, Sapochnik M, Sheiman A, Lawson M. Appetite. 2003;40:155–62.

Zajonc RB. J Personality Social Psychol Monogr Suppl. 1968;9(2):1–27.

Part III
General and Normative: Endocrine and Neuroendocrine

Chapter 12
The Role of Cholecystokinin (CCK) in Eating Behavior

Mihai Covasa and Timothy Swartz

Abbreviations

AP	Area postrema
CCK	Cholecystokinin
CCK–1R	Cholecystokinin 1 receptor
CCK–2R	Cholecystokinin 2 receptor
CCK-8	Cholecystokinin octapeptide
DIO	Diet-induced obesity
DR	Diet-induced obesity resistant
DVC	Dorsal vagal complex
Fos-Li	Fos-like immunoreactivity
GI	Gastrointestinal
HF	High-fat
ICV	Intraventricular
IP	Intraperitoneal
LETO	Long-Evans Tokushima Otuska
LF	Low-fat
mRNA	messenger RNA
NTS	Nucleus tractus solitarius
OLETF	Otsuka Long-Evans Tokushima Fatty

12.1 Introduction

A growing number of humoral factors are released from the gut during feeding and they play a prominent role in the cascade of events bringing a meal to an end. The chief among them is cholecystokinin (CCK), the first gastrointestinal peptide implicated in the control of food intake and subsequently coined "satiation signal." Detected for the first time in 1928 by Ivy and Oldberg and later characterized by Mutt and Jorpes (Jorpes and Mutt 1956), it was not until 36 years ago when Gibbs et al. published the landmark paper showing that the biologically active, synthetic, CCK octapeptide (CCK-8) reduced food intake in the rat (Gibbs et al. 1973). Since then, the

M. Covasa (✉)
INRA, Écologie et Physiologie du Système Digestif, 78350 Jouy-en-Josas, France
e-mail: mcovasa@jouy.inra.fr

investigation into the role of CCK on food intake continued unabated making CCK one of the most intensely studied gut peptide. Consequently, its suppressive effects on food intake have been demonstrated in several species including humans (see Ritter 2004a, b). CCK controls food intake by coordinating visceral functions to optimize digestion and absorption and by interacting with other short- and long-term meal-related signals. CCK may also contribute to satiation by reducing caloric consumption, thus exerting its role in the control or regulation of other systems, such as body adiposity. This chapter addresses: (1) the role of CCK on alimentary organs that participate in control of food intake, (2) mechanisms by which CCK controls meal size, (3) interactions of CCK and other hormones that control food intake, and (4) disruptions in CCK signaling pathways leading to disordered phagia.

12.2 CCK Controls Gastrointestinal Functions to Optimize Digestion

In addition to its role in controlling food intake, CCK elicits multiple effects on the GI tract including stimulation of pancreatic secretion and gallbladder contraction, bile secretion into the duodenum, inhibition of gastric secretion and emptying, as well as motor functions like lower oesophageal sphincter relaxation and intestinal and colonic motility (see Little et al. (2005)). Together, these actions promote reducing the rate of passage of nutrients in the interest of efficient and complete digestion. That is, CCK may control food intake, particularly protein and fats solely in the interest of GI functions. For a list of main functions of CCK, see Table 12.1.

12.3 CCK Controls Food Intake via Vagal Afferents

Vagal sensory afferents synapsing from the gastric, celiac, and intestinal branches of the vagus to the hindbrain are the pathway both endogenous and exogenous CCK use to reduce food intake (Smith et al. 1981; Yox and Ritter 1988). Evidence for this comes from the fact that vagal afferent fibers express CCK receptors and CCK application to vagal afferent preparations results in vagal discharge (Ritter et al. 1989; Raybould and Lloyd 1994). Additionally, sensory fiber removal either by surgical or chemical means attenuates CCK and intestinal nutrient-induced suppression of food intake (Ritter 2004a, b). Finally, vagal sensory fibers innervating gastric and intestinal mucosa are sensitive to CCK (Ritter et al. 1989). These effects are largely due to a paracrine action of CCK on peripheral,

Table 12.1 Key features of CCK in eating behavior

1. CCK is released from the duodenal enteroendocrine I-cells of the small intestine.
2. All three macronutrient classes stimulate release of CCK in humans; however in rodents, only fats and protein cause CCK secretion.
3. CCK's primary pathway to induce satiation is through a paracrine mode of action through CCK-1Rs.
4. CCK elicits physiological effects on a variety of digestive organs including the stomach, intestine, colon, gallbladder, and pancreas.
5. CCK activates hindbrain neurons through vagal afferent sensory nerve fibers.
6. CCK serves as a satiation signal to limit short-term food intake; however its synergistic effects with other long-term homeostatic energy signals implicate it in reducing bodyweight.

Table illustrating the key points of CCK in controlling eating behavior summarizing stimulation of secretion, release, and effects of the hormone

capsaicin-sensitive vagal afferent fibers. However, CCK-producing cells are strategically positioned in very close proximity with vagal afferent terminals in lamina propria, and few synapses-like appositions between them have been reported. Therefore, a neural mode of action has been suggested (Reidelberger et al. 2004) although the largely held view is that locally released CCK diffuses to its action sites through a paracrine mechanism.

In addition to a vagally mediated pathway, CCK sites acting through non-vagal mechanisms may also serve to decrease food intake (Reidelberger 1992; Blevins et al. 2000). CCK localized in the central nervous system also has been reported to decrease food intake (Blevins et al. 2000). Released by neurons from the spinal cord to forebrain, CCK is a potent neuropeptide (Hokfelt et al. 2002). CCK-1 and CCK-2 receptors also are highly expressed in many brain regions, including areas known to control food intake and regulate energy balance. Intraventricular (ICV) or parenchimal administration of CCK into several hypothalamic and hindbrain areas decreases food intake (Blevins et al. 2000) while central infusion of CCK receptor antagonists (Corp et al. 1997; Dorre and Smith 1998) or CCK antisera (Della-Fera et al. 1981) increases food intake. Also, mechanical and chemical stimulation of the GI tract induces release of CCK from brain regions controlling food intake (Schick et al. 1989). Further, reduction of intake by infusion of carbohydrates or feeding of diets that do not result in substantial CCK release can be attenuated or reversed by antagonists of CCK receptors (Brenner and Ritter 1996). Finally, whereas vagal afferents mediate CCK-induced suppression of food intake, they are not required for the increased food intake following systemic administration of CCK-1R antagonists (Reidelberger 1992). Therefore, CCK from other sources can reach CCK-1Rs present outside the abdominal vagal terminals and inhibit food intake. Indeed, administration of devazepide, a CCK-1R antagonist that crosses the BBB, results in increased food intake in both vagotomized and non-vagotomized rats, while A-70104 another CCK-1R antagonist that does not penetrate the BBB increased intake only in non-vagotomized rats (Reidelberger et al. 2004). These results suggest that increased food intake is due to an action of the antagonists at CCK receptors located on peripheral sites. However, it also suggests that devazepide increases food intake by acting either on remnant vagal afferents or by accessing other non-vagal CCK receptors (Ritter 2004a, b). It is known that CCK receptors and CCK-containing neurons and terminals are present in the hindbrain that may also participate to CCK's effects on the vagal hindbrain (Hill and Woodruff 1990).

12.4 CCK Controls Food Intake via Intestinal Nutrients

CCK is released from discrete enteroendocrine I-cells concentrated primarily along the proximal duodenal and jejunal mucosa. The apical surface of the CCK cells comes in contact with food components triggering a series of intracellular events resulting in the peptide release from the basolateral cell membrane into the circulation (Liddle 1997) (see Fig. 12.1). Several molecular forms of CCK have been identified and they are derived from the 95 amino acid pro-CCK (CCK-5 to CCK-83) with CCK-8 and CCK-58 being the most biologically potent in suppression of food intake (Glatzle et al. 2008).

Reduction of food intake by intraintestinal nutrient infusions is thought to exercise controls of food intake, which normally are activated when components of a meal enter the duodenum from the stomach. In the rat and other mammals, plasma CCK concentrations are elevated in response to intraintestinal products of fat digestion, unhydrolyzed protein, and inhibitors of pancreatic trypsin (Liddle et al. 1986; Weller et al. 1992; Brenner et al. 1993). Some, but not all, intestinal nutrients stimulate secretion of the gut peptide, cholecystokinin. For example, carbohydrates and amino acids do not release CCK in the rat (Brenner et al. 1993); although in humans, CCK is released in response
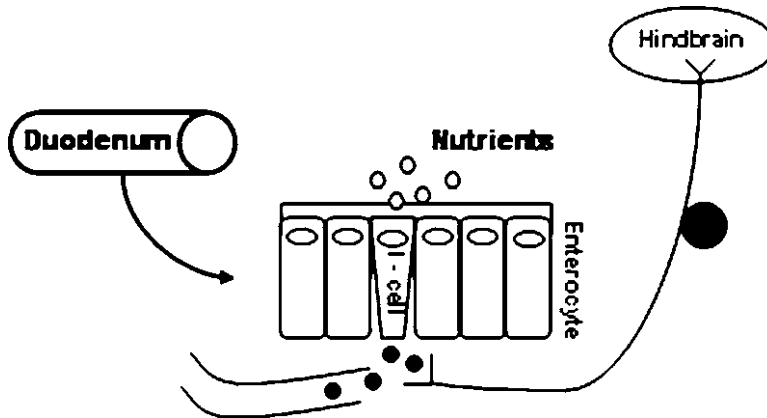
Fig. 12.1 Diagram depicting the stimulation of release of cholecystokinin (*CCK*) (*small black circles*) from a duodenal I-cell by luminal nutrients (*small open circles*) on the apical portion of the cell. CCK is released on the basolateral side of the cell into the circulation or binds to localized CCK-1R on vagal afferent terminals, which activate upstream hindbrain neurons

to both l-phenylalanine (Ballinger and Clark 1994) and glucose (Parker et al. 2005). CCK reduces food intake by acting at CCK-1Rs, located on small unmyelinated vagal sensory neurons (South and Ritter 1988), indicating that the substrate that mediates CCK-induced satiation is similar, if not identical, to that which mediates reduction of food intake by intestinal nutrients. Participation of CCK-1Rs in reduction of food intake by intestinal nutrients is well supported by the fact that CCK-1R antagonists attenuate or abolish reduction of food intake by intraintestinally infused triglycerides (Woltman et al. 1995), long chain fatty acids (Yox et al. 1992), oligosaccharides (Brenner and Ritter 1996), and protein (Woltman and Reidelberger 1999). In addition to reversing the reduction of food intake observed following exogenous CCK (Brenner and Ritter 1995) injection or intestinal nutrient infusion, CCK-1R antagonists increase food intake when they are administered alone (Moran et al. 1992; Brenner and Ritter 1995). Taken together, these results suggest a direct relationship between CCK-1Rs and control of food intake by intestinal nutrients.

There is accumulating convincing evidence indicating that CCK mediates nutrient-suppression of food intake mainly through a paracrine rather than an endocrine mode of action. For example, both suppression of food intake and inhibition of gastric emptying by intraintestinal carbohydrate infusions, which do not elevate plasma CCK, are attenuated by a CCK-1R antagonist (Brenner et al. 1993). On the other hand, infusions of proteins that markedly increase plasma CCK concentrations have a marginal effect on reduction of sham feeding (Brenner et al. 1993). Furthermore, administration of a peptide CCK-1R antagonist impermeable to the BBB attenuated the satiating effects of CCK and intestinal nutrients (Brenner and Ritter 1995) and increased food intake when given alone (Brenner and Ritter 1995). Finally, the endocrine source of CCK must undergo hepatic portal degradation, which renders most of the biologically active CCK ineffective in suppressing food intake (Reeve et al. 2003). Consistent with this, very low concentrations of CCK (1–5 picomolar range) is detectable in the blood circulation and the only endocrine form of CCK found in the rat is CCK-58 (Reeve et al. 2003). Together, these data overwhelmingly point to a peripheral site of action whereby a local source of CCK acting in proximity of vagal afferent fibers may be sufficient to mediate reduction of food intake. This is also supported by studies showing that low doses of intraperitoneal (IP) which likely mimic the paracrine mode of action on vagal afferents (Canova and Geary 1991), or near-arterial administration of CCK-8 reduces food intake more than higher doses when administered intravenously (Cox et al. 1995). Whether sufficient amounts of systemically administered CCK

are able to penetrate the lamina propria and elicit a physiological and behavioral effect is unknown. Thus, the exact identity of this source of CCK outside "I" cell remains to be located. Studies examining receptor affinity indicate a relationship between local concentrations of CCK in the GI tract and CCK-1R affinity. It is thought that low affinity receptors are localized near areas with high CCK concentration while high affinity receptors are in areas with low CCK levels (Pandya et al. 1994; Talkad et al. 1994). For example, administration of an agonist of high affinity CCK-1Rs does not decrease food intake (Weatherford et al. 1993). Additionally, work done in vagal afferent preparations shows the majority of CCK-1Rs expressed on vagal afferent neurons are thought to be low affinity CCK-1Rs (Simasko et al. 2002). Together, these data suggest that gastrointestinal CCK acting locally on vagal afferent sensory fibers is responsible for nutrient induced satiation.

Although the paracrine effects of CCK on peripheral vagal afferents are well documented, a direct action of CCK on the nucleus tractus solitarius (NTS) neurons have been reported. This source of CCK could originate either from CCK-producing neurons located in the hindbrain or from the systemic circulation through the leaky portion of the BBB, including NTS (Baptista et al. 2007).

12.5   CCK Reduces Food Intake via CCK-1 Receptors

The targets of CCK action, CCK-1 and CCK-2 receptors (formerly CCK-A and CCK-B), belong to the G-protein coupled transmembrane classification (Kopin et al. 1992; de Weerth et al. 1993). Several studies have identified and cloned the genes encoding these receptors (Kopin et al. 1992; Wank et al. 1994). For a list of sites where CCK-1Rs are located, see Table 12.2. Selective CCK-1 and CCK-2 receptor antagonist studies indicate that reductions of food intake by systemic injections of CCK are mediated primarily via CCK-1Rs (Melville et al. 1992; Moran et al. 1992). Accordingly, reductions in food intake by systemic CCK administration can be significantly attenuated or abolished by administration of a selective CCK-1R antagonist [for review see Ritter et al. (1999)]. Activation of these receptors is mediated via vagal sensory neurons primarily innervating the proximal duodenum and the stomach (Moran et al. 1990, 1997). In addition, independent administration of CCK-1R antagonists increase food intake, supporting CCK as a physiological satiety signal. At the cellular level, binding sites for CCK receptors are identified on vagal sensory neurons, and 30–40% of vagal sensory neurons express CCK-1R mRNA. Furthermore, use of isolated vagal sensory neuron preparations demonstrates that calcium influx occurs after CCK application and is attenuated by CCK-1R antagonist (Simasko et al. 2002). Finally, electrophysiological data show that CCK-1Rs also mediate activation of vagal afferent fibers by intestinal stimuli (Eastwood et al. 1998).

Table 12.2   Distribution of CCK-1R

- Peripheral
  - ◦ Gallbladder
  - ◦ Pancreas
  - ◦ Pylorus of stomach
  - ◦ Vagal afferents
- Central
  - ◦ Area postrema (AP)
  - ◦ Dorsal medial hypothalamus (DMH)
  - ◦ Median raphe nucleus
  - ◦ Nucleus accumbens
  - ◦ Nucleus tractus solitarius (NTS)

Peripheral and central locations where CCK-1Rs have been detected

Together, these findings are strong evidence that CCK-1Rs are necessary for suppression of food intake by CCK. Indeed, the fact that exogenous administration of CCK is ineffective in animal models lacking CCK-1Rs has demonstrated unequivocally the contribution of CCK-1R in control of food intake by CCK and nutrients.

12.6 Changes in CCK Sensitivity by Nutrients

Responses to gastrointestinal satiation signals are not fixed. Rather they appear to vary widely with changes in the dietary and endocrine milieu. For example, studies in both rats and mice adapted to a high-fat (HF) diet become less sensitive to both exogenous (Covasa and Ritter 1998; Nefti et al. 2009) (Fig. 12.4), and endogenous CCK via intestinal infusion of oleate (Covasa et al. 2000). Similarly, human subjects adapted to a HF diet have increased plasma CCK following a standard meal compared to control subjects and reported greater hunger following intestinal lipid infusion (Boyd et al. 2003). These effects were associated with an increase in the average daily food consumption and body weight.

The exact mechanisms by which maintenance of a HF diet leads to a reduction in sensitivity to satiation signals such as CCK and nutrients are not known. However, similarly, reduction in sensitivity to the anorectic effects of acute CCK injection was also demonstrated in rats receiving chronic infusion of CCK via osmotic minipump (Covasa et al. 2001). This persistent elevated plasma CCK, accompanying long-term exposure to a diet rich in fat leads to several adaptive changes in nutrient- and CCK-signaling pathways. For example, relative to rats fed a low-fat (LF) diet, rats fed a HF diet exhibit increase pancreatic secretory and plasma CCK responses to intestinal fat. They also secrete reduced amounts of pancreatic amylase in response to CCK (Chowdhury et al. 2000) and increased amounts of pancreatic lipase (Gidez 1973).

In normal Sprague-Dawley rats, chronic HF feeding selectively reduces vagal and enteric neuronal sensitivity to intestinal oleic acid or CCK injection (Covasa et al. 2000). Because fat is a potent stimulus for CCK release, it may be that modifications at the level of CCK-1Rs play an important physiologic role. This is supported by evidence that continuous CCK infusion leads to downregulation of the receptor gene expression in rat pancreatic acinar cells (Ohlsson et al. 2000) and hypothalamo–pituitary–adrenal axis (Malendowicz et al. 2003). Indeed, mice maintained on a HF diet for 15 days have a decreased Fos expression in the NTS in response to CCK or nutrient load and a decreased mRNA level of CCK-1R transcripts in nodose ganglia (Nefti et al. 2009). However, in the rat, Broberger and colleagues (Broberger et al. 2001), using in situ hybridization techniques, reported that feeding an HF diet does not appear to alter vagal CCK-1R mRNA expression in the nodose ganglia. It remains to be determined whether alterations in CCK-1Rs in other tissues accompany the diminished sensitivity of endogenous satiety mechanisms resulting from chronic consumption of dietary fat. CCK-1R affinity and capacity are also reduced in rats adapted to an energy-restricted diet (Kawano et al.). Also, rat pancreatic acinar tumor AR42J cells express the CCK-1R subtype, and CCK-8 reduced CCK-1R mRNA expression to 56% after exposure (Kawano et al. 1992).

It is also possible that reducing the number of binding sites at the neuronal membrane surface downregulates vagal sensitivity. In addition to the abnormalities in the binding of CCK to its receptors in genetically obese rats, there are also CCK neuronal changes associated with dietary-induced obesity. For example, early signs of obesity in neonatal overfed weanling rats are associated with a significant decreased number of CCK-positive neurons in the paraventricular hypothalamic nuclei (Plagemann et al. 1998). Studies of CCK-receptor function in pancreatic acini and Chinese hamster ovary cells (Rao et al. 1997) indicate that receptor internalization and

phosphorylation are important mechanisms for CCK-induced desensitization in vitro. Therefore, reduced sensitivity to CCK could be mediated either by altered receptor protein translation or increased sequestration of previously translated receptors. Downregulation of transduction cascades has also been associated with CCK-induced desensitization of pancreatic amylase secretion (Otsuki and Williams 1983). Therefore, a change in postreceptor transduction is yet another potential mechanism for reduced vagal sensory response to CCK. The current data suggests that modifications at the level of the CCK-1Rs plays an important physiological role in the adaptation of feeding behavior; however, the relationship between decreased sensitivity to CCK or nutrient infusion in animals adapted to a HF diet and the functional characteristic changes occurring in the peripheral CCK-1Rs has not been elucidated.

12.7   CCK Interacts with Other Hormones to Control Food Intake

CCK-induced satiation is enhanced when combined with other anorectic signals. For example, serotonin or 5-hydroxytryptamine (5-HT) released from the enterochromaffin (EC) cells in response to carbohydrates serves to terminate a meal in coordination with CCK. While cholecystokinergic and serotonergic systems independently control meal size, when both systems are concomitantly activated, it results in an enhanced suppression of food intake (Burton-Freeman et al. 1999; Helm et al. 2003; Hayes et al. 2004a, b). This enhanced suppression of intake is reversed by simultaneous blockade of CCK-1 and 5HT3R (Hayes et al. 2004a, b; Hayes and Covasa 2005). Further, concomitant blockade of CCK-1 and 5HT3R synergistically enhances food intake and suppression of food intake by CCK is attenuated following blockade of peripheral or central 5-HT3 receptor antagonists (Hayes and Covasa 2006a, b) (Fig. 12.2). These findings demonstrate that CCK and 5-HT systems cooperate interdependently to control food intake. 5HT3 receptor mediated CCK-induced satiation is thought to occur through indirect mechanisms as part of a feedback cascade via inhibition of gastric emptying. Evidence of this comes from the inability of 5-HT receptor antagonists to attenuate CCK-induced reduction of sham feeding. Further, 5-HT receptor antagonism attenuates CCK-induced gastric distention and inhibition of gastric emptying (Hayes and Covasa 2006a, b). Finally, mice that lack specific subtypes of 5-HT receptors, which are localized only in the CNS, have a decreased responsiveness to exogenously administered CCK (Asarian 2009). The interactions between CCK and 5-HT are vagally mediated, which is based on the following evidence: (1) both CCK and 5-HT cause a profound activation of proximal small intestine afferent fibers, which is blocked by vagotomy or capsaicin; (2) 5 out of 9 nodose ganglion neurons that were activated by CCK-8 respond to intraluminal perfusion of 5-HT; (3) a subthreshold dose of CCK-8 that produced no measurable responses augmented the neuronal response to luminal 5-HT perfusion. This potentiation effect was eliminated by a CCK-1R antagonist.

In addition to the interaction between CCK and 5-HT, CCK and mechanical stimuli, such as gastric distension, exert synergistic or cooperative effects on the control of food intake in a variety of species, including rats, monkeys, and humans (Moran and McHugh 1982; Feinle et al. 1996). For example, intake after either a gastric distention, a test meal, or a preload is reduced when combined with lower doses of CCK (Moran and McHugh 1982; van de Wall et al. 2005). These effects are mediated by vagal CCK-1Rs. Furthermore, gastric distension enhances CCK-induced hindbrain c-Fos expression, and vagal excitation (Wang et al. 2007). Thus, CCK-1Rs may act by enhancing responses to gastric detention. Given the interaction between leptin and CCK discussed above and that all leptin-responsive gastric vagal afferents are responsive to CCK, leptin may enhance the responses of gastric afferents to distension or CCK.

Other anorexigenic and orexigenic factors involved in the control of food intake and bodyweight also interact with CCK either to enhance or inhibit its satiating effects. First, apolipoprotein A-IV
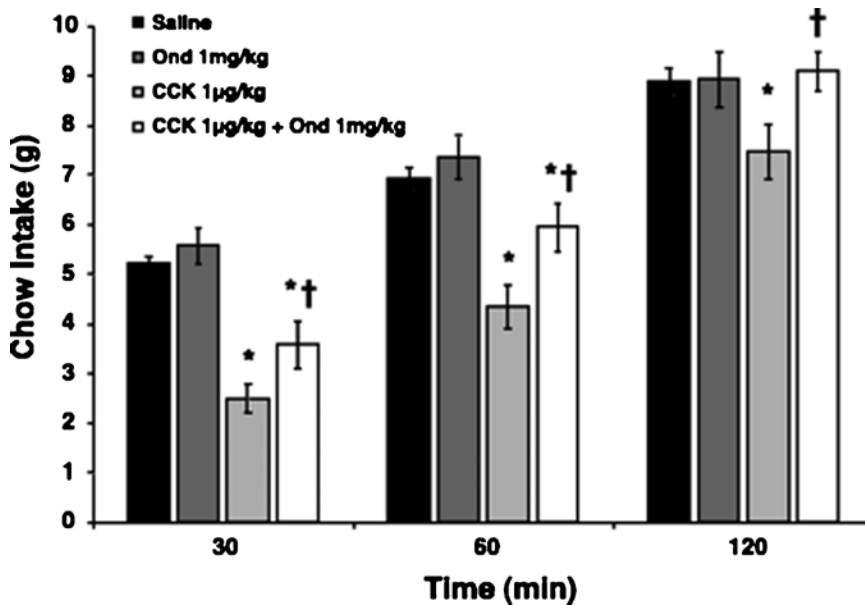
Fig. 12.2 5-HT3 receptor antagonism attenuates cholecystokinin (*CCK*)-induced satiation. Intraperitoneal administration of cholecystokinin (CCK, 1.0 μg/kg) significantly reduced rat chow intake at 30, 60, and 120 min compared with control in food-deprived rats. Concomitant administration of ondansetron, a 5-HT3 receptor antagonist (Ond; 1.0 mg/kg ip) and CCK significantly attenuated CCK-induced reduction of 30-, 60-, and 120-min rat chow intake. *$P<0.05$ versus saline at given time. †$P < 0.05$ versus corresponding CCK at given time (Reprinted from Hayes et al. 2004a, b)

(APO A-IV), a satiety factor secreted from small intestine epithelium in response to chylomicron formation, requires CCK and the CCK-1R for inducing satiation (Lo et al. 2007). Extracts from chylous lymph applied to vagal afferent preparations activates vagal neurons via a CCK-1R-dependent mechanism (Glatzle et al. 2003). Further, while subthreshold doses of either APO A-IV or CCK do not decrease food intake, combination of the two significantly reduces food intake (Lo et al. 2007).

Second, ghrelin, the potent orexigenic hormone released from the stomach is modulated by peripheral CCK. There is a functional relationship between ghrelin and CCK in short-term control of food intake. For example, the stimulation of food intake and neuronal activity in the hypothalamus induced by ghrelin is abolished by intraperitoneal CCK. Vagal afferent neurons express the ghrelin receptor, GHS-1, and peripheral administration of ghrelin resulting in increased food intake is attenuated by surgical and chemical ablation of the vagus. Also, in vitro, ghrelin inhibits the stimulatory effect of CCK on vagal afferent neurons (Date et al. 2002). Third, there is a significant amount of evidence, demonstrating that gonadal hormones such as estradiol decreases eating, at least in rats, by increasing the satiating action of CCK (Asarian and Geary 1999).

12.8 Participation of CCK in Long-Term Energy Balance and Body Weight Regulation

Although CCK is clearly involved in the control of ingestion and individual meals, how these actions translate into the roles for CCK in overall meal-to-meal regulation or energy balance has not been obvious. Recent work examining potential interactions between CCK and adiposity signals such as insulin or leptin suggest a role for CCK in overall energy balance. Figlewicz et al. (1995) first showed that ICV
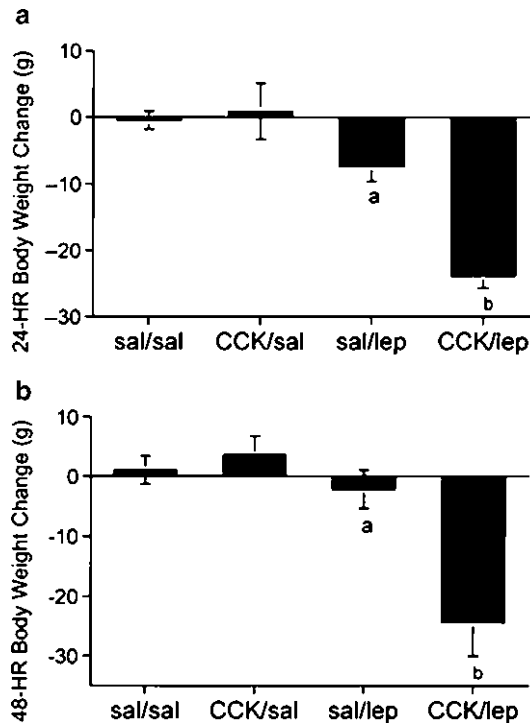
Fig. 12.3 Synergistic action of cholecystokinin (*CCK*) and leptin to reduce bodyweight. CCK-leptin (lep) treatment reduces body weight significantly more than does saline (sal)-lep at 24 (**a**) and 48 h (**b**) after treatment. CCK (1 μg/kg) was given intraperitoneally and leptin (5 μg) was given into the lateral ventricle. [a]Sal-lep-treated rats lost significantly more body weight (compared with baseline day before treatment) than sal- or CCK-treated rats (*P*<0.01 for both); [b]CCK-lep-treated rats lost significantly more weight than sal-lep-treated rats (*P*<0.01) (Reprinted from Matson and Ritter 1999)

infusion of insulin enhances the satiety response to CCK in baboons. Data from a number of studies have indicated that leptin's actions in food intake may depend in part on its ability to modulate the efficacy of within-meal satiety signals such as CCK. Leptin potentiates the satiety actions of CCK in short-term tests (Emond et al. 1999). For example, a subthreshold dose of intraventricular leptin significantly increases the magnitude of feeding suppression produced by peripherally administered CCK. Leptin/CCK combinations also result in elevated levels of c-Fos expression in the hypothalamic paraventricular nucleus (Wang et al. 1998) and within the nucleus of the solitary tract (Wang et al. 2000), beyond those produced by either stimulus alone. Combinations of leptin and CCK have feeding inhibitory effects over the long term, beyond those produced by leptin alone (Fig. 12.3) (Matson and Ritter 1999). Furthermore, CCK/leptin combinations result in greater decreases in body weight over 24 h than does leptin alone (Matson et al. 2002). These findings demonstrate that communication between hypothalamic circuits that respond to changes in adiposity signals and those that respond to meal-generated signals are essential for long-term regulation of energy homeostasis and adipose tissue mass.

12.9 Disordered Satiation and the Role of CCK

A growing number of reports indicate that obese subjects, including humans, exhibit disruptions in their responses to satiation signals. For example, obese humans reported feeling less hungry than lean controls (French et al. 1993), and they were less sensitive to infusion of gastrointestinal peptides such

as bombesin (Fig. 12.4) (Lieverse et al. 1994). Rats made obese by overfeeding were less sensitive to the satiating effects of CCK (Voits et al. 1996; Covasa and Ritter 1998; Covasa et al. 2001), but see also (Torregrossa and Smith 2003).

Animal models of obesity such as obese Zucker, OLETF, and Osborne-Mendel rats have all been reported to be less sensitive to reduction of food intake by fats suggesting that obesity may be associated with a reduced responsiveness to intraintestinal stimuli such as CCK and fats. For example, the Zucker rat, homozygous for the *fa* gene, and heavily used as a model of genetic obesity exhibits reduced sensitivity to intraperitoneal and ICV administration of CCK (McLaughlin and Baile 1979). CCK-stimulated amylase secretion from pancreatic acini and binding capacity of 125I-labelled CCK-8 were decreased in obese versus lean Zucker rats (Niederau et al. 1997), suggesting the differences in CCK's satiety effect between lean and obese rats may be due to differences in CCK-receptor binding and action at peripheral vagal sites. However, recent studies in dietary-induced obese (DIO) mice showed an increase in expression of CCK-1R in the nodose neurons (Paulino et al. 2009), which do not correlate with functional data showing reduced neuronal vagal sensitivity in mice and rats maintained on a HF diet (Nefti et al. 2009). The reason for this discrepancy is not known although altered coupling between receptor and intracellular signaling pathways or changes in synaptic activity at the NTS level have been suggested (Paulino et al. 2009).

Similarly, the OLETF rat, an outbred strain of Long Evans rats, which lacks functional CCK-1Rs, is hyperphagic, and becomes obese and diabetic (Moran and Bi 2006). Consistent with this mutation, little or no CCK-1R mRNA is detected in the pancreas of the OLETF rat (Funakoshi et al. 1994). Furthermore, pancreatic acini from OLETF rats are completely insensitive to
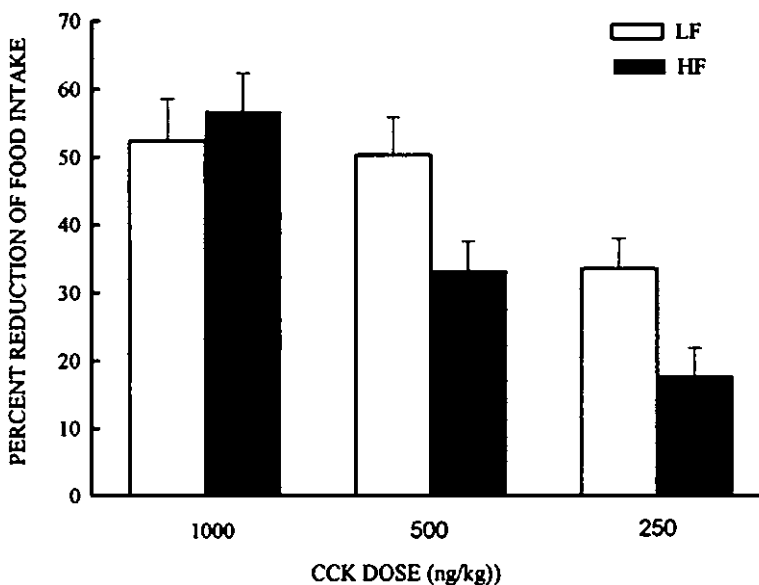
Fig. 12.4 High-fat diet attenuates *CCK*-induced reduction of food intakefatCCK-induced reduction of food intake in rats adapted to low-fat (*LF*) and high-fat (*HF*) diets. Data shown are percent reduction of 30 min food intake following 17 h food deprivation. CCK caused significantly greater reduction of intake at 0.5 and 0.25 μg/kg dose in low-fat adapted rats than in high-fat adapted rats ($P < 0.01$) (Reprinted from Covasa and Ritter 1998)

stimulation of enzyme secretion by CCK (Otsuki et al. 1995). This absence of CCK sensitivity is specific in that OLETF acinar cells do secrete amylase in response to bombesin, carbamylcholine, and secretin. Also, pancreatic CCK binding in OLETF rat is completely absent (Otsuki et al. 1995).

OLETF rats exhibit accelerated rates of weight gain compared to control rats beginning at 5 weeks of age, and results in body weights, which are ~40% higher than the control Long Evans Tokushima strain. They are less sensitive to within-meal satiety signals and this has been attributed to their lack of CCK-1Rs. For example, systemic administration of CCK has no suppressive effect on food intake (Moran et al. 1998) or gastric emptying (Shoji et al. 1997) in OLETF rats. OLETF rats ingest larger meals and are less sensitive to inhibition of food intake by some intraintestinal nutrients (Covasa and Ritter 2001) and gastric distention than LETO control rats (De Jonghe et al. 2006). Therefore, OLETF rats exhibit a broad range of satiation deficits that are controlled by CCK-1Rs. However, not all OLETF satiation deficits are directly related to the absence of CCK receptors (Moran 2008) and genetic ablation of the CCK-1Rs in Fisher 344 rats was not associated with overeating and obesity (Blevins et al. 2009).

12.10 Applications to Other Areas of Health and Disease

Although predominantly viewed as a short-term satiation signal, there is also evidence that CCK plays a role in the pathogenesis of obesity in humans. For example, genetic studies show that CCK-1R gene promoter polymorphism is associated with body fat suggesting a major functional role of CCK-1Rs in the development of obesity (Arya et al. 2004). Similarly, using genotype associations, recent studies revealed that obese carriers of variants in the CCK gene have an increased risk of eating large portion sizes, with a 60% increased risk for carriers of the CCK_H3 haplotype (de Krom et al. 2007). However, the frequency of single gene mutations, in general, and in the CCK-1R in particular, reported in humans, are relatively small and therefore, unlikely to play a major role in the current obesity epidemic.

Studies examining changes in circulating CCK concentrations in obese individuals after various dietary manipulations as well as studies using CCK-1Rs agonists to curb appetite and reduce energy intake have yielded mixed results. For example, compared to lean controls, moderately and morbidly obese women have significant lower fasting plasma CCK concentrations and exhibit a blunt postprandial CCK response (Baranowska et al. 2000; Zwirska-Korczala et al. 2007). This corresponds with an increase in fasting CCK concentrations and diminished feelings of hunger reported in elderly subjects (Sturm et al. 2003). However, plasma CCK concentration in obese subjects remains elevated following consumption of a fatty meal (French et al. 1993). Manipulation of endogenous CCK levels either through diet (e.g., addition of long chain fatty acids), by inhibiting CCK degradation, or through chronic exogenous administration of CCK have all been shown to decrease caloric intake and/or bodyweight. However, whether these approaches can lead to sustained changes in CCK responses without development of tolerance effects, resulting in consistent reduction in appetite in obese subjects require further investigation. Pharmacological studies employing CCK-1R agonists have been promising, with, at least, initial studies showing a significant weight loss (Roses 2004). Uncovering the most effective strategy of manipulating the CCK system either alone or in combination with other anorexigenic peptides in treating obesity remains an area of intense investigation.

Key Terms

CCK: Peptide satiation signal cleaved from the pre-cholecystokinin precursor and released from the proximal duodenum of the small intestine in response to nutrients.

Endocrine: Entry of peptide or hormone into the bloodstream to exert effects on distant tissues

Enteroendocrine cells: Specialized intestinal cells that release peptides and hormones in response to nutrients. The apical portion of the cell faces the lumen of the intestine to sense nutrients while the basolateral portion is responsible for hormone secretion.

Fos: Protein that is a product of the immediate-early c-fos gene. Used in immunohistochemical experiments as a marker of neuronal activation

Paracrine: Action of a peptide or hormone on local or nearby cells without entering the circulatory system.

Summary Points

- CCK is released by the "I" type enteroendocrine cells localized predominantly in the proximal small intestine.
- CCK release is stimulated by the presence of nutrients, especially digestion products of fats and proteins, in the intestinal lumen.
- CCK coordinates digestion and absorption of nutrients and exerts a variety of biological functions within the gastrointestinal tract including stimulation of gallbladder contraction, stimulation of intestinal motor activity and inhibition of gastric emptying, and stimulation of bile and pancreatic enzyme secretion.
- CCK is one of the most potent satiation signals, inhibiting food intake in multiple species including humans.
- CCK exerts its physiological actions via CCK-1 and CCK-2 receptors; however, CCK reduction of food intake is primarily mediated by CCK-1R located on vagal sensory neurons.
- CCK acts to reduce food intake mainly through a paracrine mode of action, though a direct action of CCK on hindbrain neurons has also been suggested.
- Chronic exposure to diets, particularly rich in fats, results in decreased behavioral and neuronal responses to CCK.
- CCK interacts with short-term anorexigenic signals as well as long-term adiposity signals to enhance suppression of food intake and body weight.
- CCK still remains a potential target for use in curbing appetite and treatment of obesity, either alone or in combination with other peptides involved in the control of food intake and energy balance.

References

Arya R, Duggirala R, et al. Am J Hum Genet. 2004;74(2):272–82.
Asarian L. Am J Physiol Regul Integr Comp Physiol. 2009;296(1):R51–6.
Asarian L, Geary N. Peptides. 1999;20(4):445–50.
Ballinger AB, Clark ML. Metabolism. 1994;43(6):735–8.
Baptista V, Browning KN, et al. Am J Physiol Regul Integr Comp Physiol. 2007;292(3):R1092–100.
Baranowska B, Radzikowska M, et al. Diabetes Obes Metab. 2000;2(2):99–103.
Blevins JE, Stanley BG, et al. Brain Res. 2000;860(1–2):1–10.
Blevins JE, Overduin J, et al. Brain Res. 2009;1255:98–112.

Boyd KA, óDonovan DG, et al. Am J Physiol Gastrointest Liver Physiol. 2003;284(2):G188–96.
Brenner L, Ritter RC. Appetite. 1995;24(1):1–9.
Brenner LA, Ritter RC. Pharmacol Biochem Behav. 1996;54(3):625–31.
Brenner L, Yox DP, et al. Am J Physiol. 1993;264(5 Pt 2):R972–6.
Broberger C, Holmberg K, et al. Brain Res. 2001;903(1–2):128–40.
Burton-Freeman B, Gietzen DW, et al. Am J Physiol. 1999;276(2 Pt 2):R429–34.
Canova A, Geary N. Appetite. 1991;17(3):221–7.
Chowdhury P, Nishikawa M, et al. Proc Soc Exp Biol Med. 2000;223(3):310–5.
Corp ES, Curcio M, et al. Physiol Behav. 1997;61(6):823–7.
Covasa M, Ritter RC. Peptides. 1998;19(8):1407–15.
Covasa M, Ritter RC. Peptides. 2001;22(8):1339–48.
Covasa M, Grahn J, et al. Auton Neurosci. 2000;84(1–2):8–18.
Covasa M, Marcuson JK, et al. Am J Physiol Regul Integr Comp Physiol. 2001;280(2):R331–7.
Cox JE, Perdue GS, et al. Am J Physiol. 1995;268(1 Pt 2):R150–5.
Date Y, Murakami N, et al. Gastroenterology. 2002;123(4):1120–8.
De Jonghe BC, Hajnal A, et al. Am J Physiol Gastrointest Liver Physiol. 2006;291(4):G640–9.
de Krom M, van der Schouw YT, et al. Diabetes. 2007;56(1):276–80.
de Weerth A, Pisegna JR, et al. Biochem Biophys Res Commun. 1993;194(2):811–8.
Della-Fera MA, Baile CA, et al. Science. 1981;212(4495):687–9.
Dorre D, Smith GP. Physiol Behav. 1998;65(1):11–4.
Eastwood C, Maubach K, et al. Neurosci Lett. 1998;254(3):145–8.
Emond M, Schwartz GJ, et al. Am J Physiol. 1999;276(5 Pt 2):R1545–9.
Feinle C, D'Amato M, et al. Gastroenterology. 1996;110(5):1379–85.
Figlewicz DP, Sipols AJ, et al. Behav Neurosci. 1995;109(3):567–9.
French SJ, Murray B, et al. Int J Obes Relat Metab Disord. 1993;17(5):295–300.
Funakoshi A, Miyasaka K, et al. Biochem Biophys Res Commun. 1994;199(2):482–8.
Gibbs J, Young RC, et al. J Comp Physiol Psychol. 1973;84(3):488–95.
Gidez LI. J Lipid Res. 1973;14(2):169–77.
Glatzle J, Wang Y, et al. J Physiol. 2003;550(Pt 2):657–64.
Glatzle J, Raybould HE, et al. Nutr Neurosci. 2008;11(2):69–74.
Hayes MR, Covasa M. Peptides. 2005;26(11):2322–30.
Hayes MR, Covasa M. Brain Res. 2006a;1103(1):99–107.
Hayes MR, Covasa M. Brain Res. 2006b;1088(1):120–30.
Hayes MR, Moore RL, et al. Am J Physiol Regul Integr Comp Physiol. 2004a;287(4):R817–23.
Hayes MR, Savastano DM, et al. Physiol Behav. 2004b;82(4):663–9.
Helm KA, Rada P, et al. Brain Res. 2003;963(1–2):290–7.
Hill DR, Woodruff GN. Brain Res. 1990;526(2):276–83.
Hokfelt T, Blacker D, et al. Pharmacol Toxicol. 2002;91(6):382–6.
Jorpes E, Mutt V. Nord Med. 1956;56(42):1511–7.
Kawano K, Hirashima T, et al. Diabetes. 1992;41(11):1422–8.
Kopin AS, Lee YM, et al. Proc Natl Acad Sci USA. 1992;89(8):3605–9.
Liddle RA. Annu Rev Physiol. 1997;59:221–42.
Liddle RA, Green GM, et al. Am J Physiol. 1986;251(2 Pt 1):G243–8.
Lieverse RJ, Jansen JB, et al. Int J Obes Relat Metab Disord. 1994;18(8):579–83.
Little TJ, Horowitz M, et al. Obes Rev. 2005;6(4):297–306.
Lo CM, Zhang DM, et al. Am J Physiol Regul Integr Comp Physiol. 2007;293(4):R1490–4.
Malendowicz LK, Spinazzi R, et al. Int J Mol Med. 2003;12(6):903–9.
Matson CA, Ritter RC. Am J Physiol. 1999;276(4 Pt 2):R1038–45.
Matson CA, Reid DF, et al. Am J Physiol Regul Integr Comp Physiol. 2002;282(5):R1368–73.
McLaughlin CL, Baile CA. Pharmacol Biochem Behav. 1979;10(1):87–93.
Melville LD, Smith GP, et al. Pharmacol Biochem Behav. 1992;43(3):975–7.
Moran TH. Physiol Behav. 2008;94(1):71–8.
Moran TH, Bi S. Philos Trans R Soc Lond B Biol Sci. 2006;361(1471):1211–8.
Moran TH, McHugh PR. Am J Physiol. 1982;242(5):R491–7.
Moran TH, Norgren R, et al. Brain Res. 1990;526(1):95–102.
Moran TH, Ameglio PJ, et al. Am J Physiol. 1992;262(1 Pt 2):R46–50.
Moran TH, Field DG, et al. Peptides. 1997;18(4):547–50.
Moran TH, Katz LF, et al. Am J Physiol. 1998;274(3 Pt 2):R618–25.
Nefti W, Chaumontet C, et al. Am J Physiol Regul Integr Comp Physiol. 2009;296(6):R1681–6.
Niederau C, Meereis-Schwanke K, et al. Regul Pept. 1997;70(2–3):97–104.

Ohlsson B, Borg K, et al. Scand J Gastroenterol. 2000;35(6):612–8.

Otsuki M, Williams JA. Am J Physiol. 1983;244(6):G683–8.

Otsuki M, Akiyama T, et al. Am J Physiol. 1995;268(3 Pt 1):E531–6.

Pandya PK, Huang SC, et al. Biochim Biophys Acta. 1994;1224(1):117–26.

Parker BA, Doran S, et al. Clin Endocrinol (Oxf). 2005;62(5):539–46.

Paulino G, Barbier de la Serre C, et al. Am J Physiol Endocrinol Metab. 2009;296(4):E898–903.

Plagemann A, Rake A, et al. Neurosci Lett. 1998;258(1):13–6.

Rao RV, Hadac EM, et al. J Neurochem. 1997;68(6):2356–62.

Raybould HE, Lloyd KC. Ann NY Acad Sci. 1994;713:143–56.

Reeve Jr JR, Green GM, et al. Am J Physiol Gastrointest Liver Physiol. 2003;285(2):G255–65.

Reidelberger RD. Am J Physiol. 1992;263(6 Pt 2):R1354–8.

Reidelberger RD, Hernandez J, et al. Am J Physiol Regul Integr Comp Physiol. 2004;286(6):R1005–12.

Ritter RC. Physiol Behav. 2004a;81(2):249–73.

Ritter RC. Am J Physiol Regul Integr Comp Physiol. 2004b;286(6):R991–3.

Ritter RC, Ritter S, et al. Am J Physiol. 1989;257(5 Pt 2):R1162–8.

Ritter RC, Covasa M, et al. Neuropeptides. 1999;33(5):387–99.

Roses AD. Nat Rev Genet. 2004;5(9):645–56.

Schick RR, Yaksh TL, et al. Am J Physiol. 1989;256(1 Pt 2):R248–54.

Shoji E, Okumura T, et al. Dig Dis Sci. 1997;42(5):915–9.

Simasko SM, Wiens J, et al. Am J Physiol Regul Integr Comp Physiol. 2002;283(6):R1303–13.

Smith GP, Jerome C, et al. Science. 1981;213(4511):1036–7.

South EH, Ritter RC. Peptides. 1988;9(3):601–12.

Sturm K, MacIntosh CG, et al. J Clin Endocrinol Metab. 2003;88(8):3747–55.

Talkad VD, Patto RJ, et al. Biochim Biophys Acta. 1994;1224(1):103–16.

Torregrossa AM, Smith GP. Physiol Behav. 2003;78(1):19–25.

van de Wall EH, Duffy P, et al. Am J Physiol Regul Integr Comp Physiol. 2005;289(3):R695–703.

Voits M, Forster S, et al. Naunyn Schmiedebergs Arch Pharmacol. 1996;354(3):374–8.

Wang L, Martinez V, et al. Brain Res. 1998;791(1–2):157–66.

Wang L, Barachina MD, et al. Regul Pept. 2000;92(1–3):79–85.

Wang C, Zhou DF, et al. World J Gastroenterol. 2007;13(36):4873–80.

Wank SA, Pisegna JR, et al. Ann NY Acad Sci. 1994;713:49–66.

Weatherford SC, Laughton WB, et al. Am J Physiol. 1993;264(2 Pt 2):R244–9.

Weller A, Corp ES, et al. Peptides. 1992;13(5):939–41.

Woltman T, Reidelberger R. Am J Physiol. 1999;276(6 Pt 2):R1701–9.

Woltman T, Castellanos D, et al. Am J Physiol. 1995;269(6 Pt 2):R1420–33.

Yox DP, Ritter RC. Am J Physiol. 1988;255(4 Pt 2):R569–74.

Yox DP, Brenner L, et al. Am J Physiol. 1992;262(4 Pt 2):R554–61.

Zwirska-Korczala K, Konturek SJ, et al. J Physiol Pharmacol. 2007;58 Suppl 1:13–35.

Chapter 13
The Role of Ghrelin in Eating Behavior

Mihai Covasa and Timothy Swartz

Abbreviations

AP	Area postrema
ARC	Arcuate nucleus
CCK	Cholecystokinin
CNS	Central nervous system
DMH	Dorsomedial hypothalamus
DVC	Dorsal vagal complex
Fos-Li	Fos-like immunoreactivity
GH	Growth hormone
GHS-1Ra	Growth hormone secretagogue
GI	Gastrointestinal
GLP-1	Glucagon-like peptide-1
GOAT	Gastric O-acyl transferase
HF	High-fat
ICV	Intraventricular
IP	Intraperitoneal
IV	Intravenous
mRNA	messenger RNA
NTS	Nucleus tractus solitarius
PVN	Paraventricular nucleus
PYY	Peptide tyrosine-tyrosine
VMH	Ventromedial hypothalamus

13.1 Introduction

Of all hormones and peptides secreted from the gastrointestinal (GI) tract, only one discovered thus far has been shown to promote food consumption. Discovered in 1999, ghrelin, the potent orexigen, is a 28 amino acid peptide released mainly from specialized endocrine cells of the mucosal layer in the stomach. It exerts its physiological effects on stimulating eating and growth hormone (GH)

M. Covasa (✉)
INRA, Écologie et Physiologie du Système Digestif, 78350 Jouy-en-Josas, France
e-mail: mcovasa@jouy.inra.fr

secretion by binding to the GH secretagogue receptor-1a (GHS-R1a). Compared to other peptides released from the GI tract, ghrelin is unique due to its increased circulating levels during fasting, which together with its ability to increase food intake indicates the possibility of a role in initiating a meal. To increase food intake, ghrelin activates neurons of hindbrain and hypothalamic nuclei heavily involved in the short- and long-term control of food intake and energy balance. In addition to its direct effects of stimulating food intake, ghrelin also decreases energy expenditure and promotes the storage of fatty acids in adipocytes, denoting its potential importance in pathological conditions, such as obesity. Furthermore, ghrelin is implicated in other disease states characterized by loss of body mass, such as age-related and pathological anorexia. This chapter will focus on (1) factors regulating ghrelin secretion and circulating levels, (2) mechanisms underlying ghrelin-induced hyperphagia, (3) interaction of ghrelin with other signals that control food intake, and (4) the role of ghrelin on long-term energy homeostasis in pathological conditions.

13.2 Ghrelin Modulates Gastrointestinal Functions

Ghrelin exerts several physiological effects on the gastrointestinal system to decrease the time of transit for ingested nutrients through the GI tract. Most notably, ghrelin has a significant effect on accelerating gastric emptying and enhancing motility of the distal small intestine and colon (Asakawa et al. 2001). In addition to these motility effects on the GI tract, ghrelin also stimulates gastric acid secretion as well as enzymatic secretion from alimentary organs (Masuda et al. 2000; Sato 2003). Thus, ghrelin enhances the digestion of bolus in the stomach and propulsion of chyme through the GI tract in preparation for the next meal. Also, by decreasing the transit time of nutrients in the intestine, ghrelin limits post-ingestive feedback from GI satiety signals that serve to terminate a meal. To increase motility and enzymatic secretions of the GI tract, ghrelin arising from two sources, central and peripheral tissues, controls these mechanisms.

13.3 Ghrelin Is Distributed Through Both Central and Peripheral Tissues

Ghrelin is the endogenous ligand for the GHS-R1a receptor (now referred to as "the ghrelin receptor"). Both ghrelin and its receptor are located in peripheral and central tissues. Within the central nervous system (CNS), ghrelin is localized in hypothalamic and pituitary nuclei of the forebrain that are heavily implicated in the control of food intake or GH secretion. Despite the initial finding that ghrelin stimulates GH secretion (Kojima et al. 1999), the most potent biological function of the peptide is stimulation of food intake through a GH-independent mechanism (Wren et al. 2000). The arcuate nucleus (ARC) of the hypothalamus, which is involved in controlling food intake, expresses the highest concentration of centrally distributed ghrelin (Lu et al. 2002). Although ghrelin is distributed throughout the central nervous system, peripheral ghrelin from the GI tract, most notably the stomach, is thought to be the primary site for ghrelin secretion (Hosoda et al. 2000). In support of this, partial or complete, gastrectomy (removal of the stomach) markedly reduces circulating ghrelin levels by approximately 70% (Jeon et al. 2004). Ghrelin is produced in the mucosal layer of the stomach by the endocrine X/A-type cells (Date et al. 2000), which are distributed throughout the stomach, but are highly concentrated in the fundic area (Yabuki et al. 2004). Gastric X/A-type cells increase in number throughout fetal period, reaching a maximum during infancy. Likewise, ghrelin levels in the stomach are low during development. One month following birth, however, ghrelin

concentrations reach a peak and show no further increase. While the stomach is the main site of ghrelin secretion, ghrelin is detected throughout all layers of the GI tract, salivary glands, and alimentary organs, such as the pancreas (van der Lely et al. 2004), all of which contribute to circulating levels of the peptide. In the circulation, ghrelin is represented by two forms: des-acyl ghrelin and acyl ghrelin (*n*-octanoyl-modified ghrelin) (Hosoda et al. 2003). The former version is five to ten times more abundant in plasma than the latter; however, the less common acyl-peptide is thought to be the active form in nearly all physiological, behavioral, and endocrine processes, including food intake. To yield the biologically active acyl-ghrelin, the enzyme gastric O-acyl transferase (GOAT) must cleave the pre-proghrelin peptide (Yang et al. 2008). While the finding of two forms or ghrelin as well as the enzyme responsible for yielding the active form of ghrelin have been recent in respect to the discovery of ghrelin, both total ghrelin and active ghrelin plasma concentrations have been shown to be highly correlative following experimental manipulations (Yokota et al. 2005). A variety of factors control ghrelin secretion from the stomach into the peripheral circulation, with energy and macronutrient content of a meal being the main ones.

13.4 Ghrelin Secretion Is Regulated by Energy Status and Nutrients

Remarkably, measurable ghrelin levels are consistent between sexes and across age groups; however, age-related anorexic rats' plasma ghrelin levels fail to increase after 72 h fasting (Wolden-Hanson 2006). While this implicates age as a factor in modulating ghrelin levels, it more likely underscores the importance of food components regulating secretion of the peptide. As such, during periods of food deprivation, across a large range of ages, plasma ghrelin is substantially elevated while refeeding or recovery from the deprivation rapidly blunts elevated circulating levels (Ariyasu et al. 2001; Tschop et al. 2000) (Fig. 13.1). The increased levels of plasma ghrelin during these deprivation challenges are associated with up-regulation of ghrelin receptors leading to increased food intake (Tups et al. 2004).

Ghrelin levels are also influenced by the timing of a meal. In schedule-fed rats, rising ghrelin levels coincide with preprandial period or onset of a meal (Drazen et al. 2006). Similarly, in humans, ghrelin levels substantially increase before the onset of a meal and adjust according to meal times
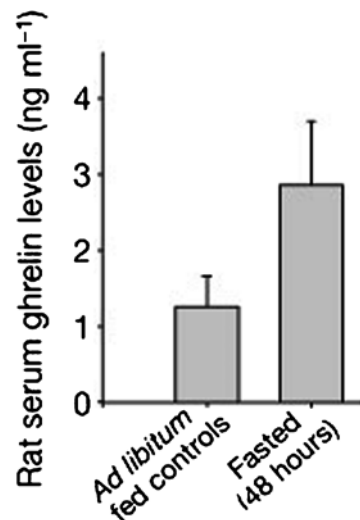
Fig. 13.1 Total serum ghrelin levels in rats either fed or after a 48-h fast. Food deprivation induces increased ghrelin secretion as evidenced by increased serum levels following fasting (Adapted from Tschöp et al. 2000)

(Cummings et al. 2001). Long-term markers of altered energy homeostasis, such as adiposity, also correlate with circulating ghrelin concentrations. Obesity, a pathological state characterized by increased body mass, is characterized by an alteration of secretion and circulating ghrelin concentrations. Specifically, an increased body mass index (BMI) directly correlates with decreased plasma ghrelin levels (Ariyasu et al. 2001). Because obesity is associated with suppressed ghrelin levels, it is not surprising then that anorexic patients with significantly lower BMIs exhibit chronically elevated circulating ghrelin concentrations (Otto et al. 2001). The decreased concentration of circulating ghrelin in obese individuals is thought to be due to excess energy intake; whereas in anorexic patients, a constant caloric deficit causes elevated plasma ghrelin concentrations, in attempt to restore proper energy balance. In both pathological states, however, ghrelin levels begin to return to normal concentrations when the individual is nearing normal body weight (Cummings et al. 2002). Furthermore, in addition to food intake and energy balance, the composition of an ingested meal is an important regulator of ghrelin secretion.

Despite ghrelin being released from the stomach, an organ sensitive to mechanical rather than chemical signals (volume vs. specific nutrients of a meal), and macronutrient content of the meal has a significant effect on modulating ghrelin release. Nutrients from all three major macronutrient classes suppress ghrelin secretion; however, carbohydrates and proteins are most potent inhibitors. Specifically, in humans, a carbohydrate solution significantly decreases ghrelin secretion in a biphasic manner, while protein suppresses circulating ghrelin significantly more 40-min postprandially than an equicaloric and equivolumetric lipid drink (Foster-Schubert et al. 2008) (Fig. 13.2). In rodents, gastric
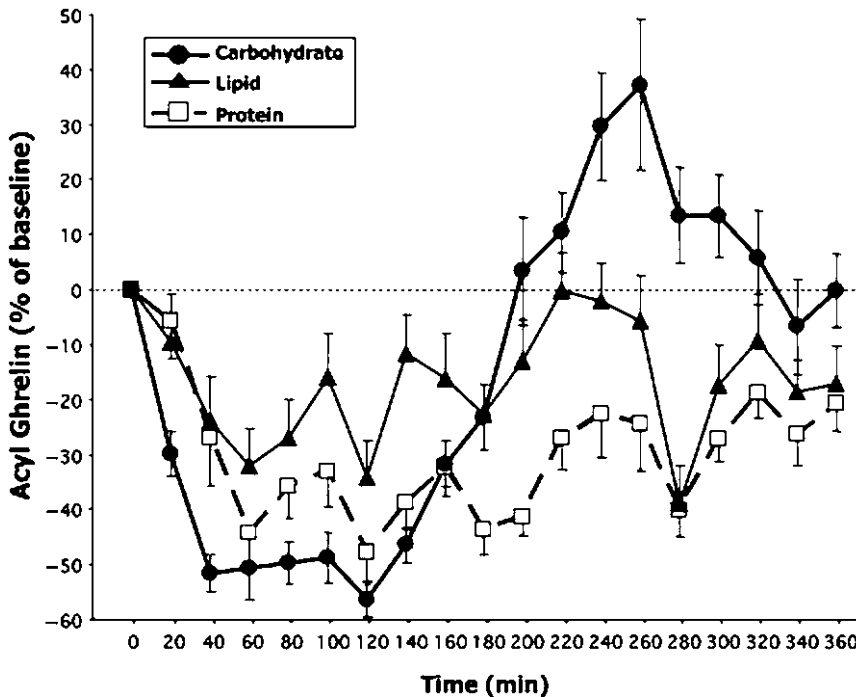
Fig. 13.2 Effects of macronutrients on suppression of circulating plasma acyl-ghrelin concentrations. Both carbohydrate and protein inhibit ghrelin secretion more effectively than lipid (Reprinted from Foster-Schubert et al. 2008)

infusions of glucose more potently inhibit ghrelin secretion than infusions of fatty acids and amino acids. These effects, however, are dependent upon intestinal absorption of nutrients as gastrically infused glucose solutions fail to suppress circulating ghrelin concentrations when the gastric pylorus is occluded (Williams et al. 2003). Furthermore, treatment with orlistat, a potent lipase inhibitor, abolishes long-chain fatty acid–induced reduction of plasma ghrelin levels (Feinle-Bisset et al. 2005). Together, these pieces of evidence demonstrate the importance of short- and long-term food intake as well as macronutrient content of a meal to regulate ghrelin secretion. Because circulating levels of the peptide are largely affected by the timing of a meal, it appears that ghrelin may have a physiological role in meal initiation.

13.5 Ghrelin Increases Food Intake

Ghrelin is the only known potent peripheral peptide hormone that is an orexigenic. This is supported by several pieces of evidence. First, both central and peripheral administration of ghrelin results in increased food intake and associated appetitive ratings (Tschop et al. 2000; Wren et al. 2001a, b) (Table 13.2). In rodents, exogenous ghrelin induces food intake during the light cycle, a period associated with minimal food consumption (Wren et al. 2001b). Second, administration of either a ghrelin receptor antagonist or an anti-ghrelin immunoglobulin (IgG), which inactivates biologically active ghrelin, causes a decrease in food intake in several feeding paradigms (Asakawa et al. 2003; Nakazato et al. 2001). Furthermore, ghrelin decreases latency to eat and increases meal number. Interestingly, both humans and rodent models retain sensitivity to the peptide and repeated administration results in exponential increase in cumulative food intake leading to increased bodyweight and adiposity (Druce et al. 2005; Tschop et al. 2000; Wren et al. 2001b) (Table 13.3). Altogether, these findings support the hypothesis that ghrelin is an orexigenic signal controlling food intake. Currently, two routes of action, endocrine and paracrine, thought to underlie peripheral ghrelin-induced hyperphagia (Fig. 13.3).

Table 13.1 Key features of ghrelin in eating behavior

1. Ghrelin is the endogenous ligand for the growth hormone (GH) secretagogue receptor-1a (GHS-1Ra), now named "the ghrelin receptor."
2. Ghrelin is released from the X/A-type cells in the mucosal layer of the stomach.
3. Currently, ghrelin is the only known endogenous peripheral peptide hormone that potently increases food intake.
4. All three macronutrient classes inhibit release of ghrelin; however, products of carbohydrate and protein digestion are more potent inhibitors than fats.
5. Ghrelin utilizes endocrine and paracrine pathways to induce hyperphagia by activating neurons involved in the control of food intake. Specifically, ghrelin activates downstream neurons that produce orexigenic central neuropeptides.
6. Ghrelin elicits physiological effects on a variety of digestive organs including the stomach, intestine, and pancreas.
7. Circulating ghrelin is considered to be an inverse adiposity signal. That is, ghrelin levels are significantly suppressed in obese individuals and markedly elevated in individuals with a low body mass index.

Key points illustrating the role of ghrelin in controlling eating behavior. It summarizes stimulation of ghrelin secretion, release, and main effects of the hormone

Table 13.2 Food intake following peripheral administration of ghrelin in rats

Ghrelin dose (nmol)	Food intake (g)
0	0.5
1	1.2
3	1.5
10	2

Source: Data adapted from Wren et al. (2001b)

Ghrelin increases food intake significantly more than saline and in a dose-responsive manner

Table 13.3 Effects of chronic ghrelin administration on cumulative body weight gain in rodents

Treatment	7-Day weight gain (g)
Saline	10
Ghrelin	22

Source: Data adapted from Wren et al. (2001b)

Ghrelin increases bodyweight gain compared to saline treatment

Fig. 13.3 Pathways through which peripheral ghrelin activates CNS nuclei and promotes food consumption. Ghrelin binds locally to the ghrelin receptor on vagal afferents innervating the stomach and relays information to the hindbrain, which activates hypothalamic nuclei. Ghrelin also can enter the circulatory system, diffuse into hypothalamic nuclei, and activate neurons producing NPY and AgRP
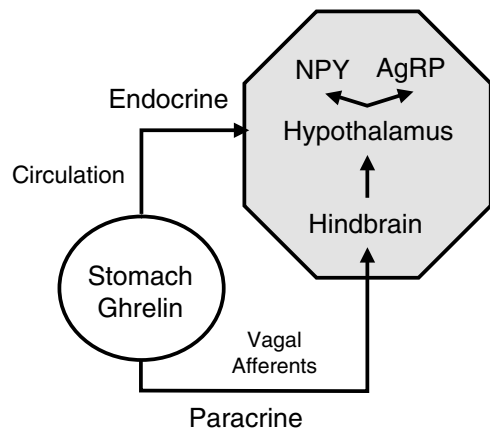
13.6 Ghrelin Controls Food Intake via Endocrine and Paracrine Mechanisms

Administration of ghrelin intravenously (IV) that results in physiological circulating levels in both animals and humans increases food intake (Hashimoto et al. 2007; Wren et al. 2001a) in both fasted or fed conditions (Hashimoto et al. 2007). In addition, IV administration of either ghrelin or a ghrelin receptor agonist stimulates neuronal activation in brain nuclei involved in the control of food intake as evidenced by Fos-like immunoreactivity (Fos-Li, a marker of neural activation) (Lawrence et al. 2002). This evidence, together with the fact that ghrelin producing gastric oxyntic cells are situated in close proximity to vascular capillaries (Date et al. 2000), lend support to the fact that endogenous ghrelin increases food intake through an endocrine route of action. However, there is also substantial evidence demonstrating a paracrine pathway, involving vagal afferents. The vagus cranial

nerve relays information from visceral organs to the hindbrain that integrates sensory and motor information. Many of the gut peptides released from the intestine bind to their receptors on the vagus to transmit information and exert physiological, endocrine, and behavioral effects. In support of a vagally-mediated pathway underlying ghrelin-induced food intake is the presence of the ghrelin receptor on gastric vagal afferents and ghrelin receptor mRNA in nodose ganglion cell bodies of the vagus (Date et al. 2002). Ghrelin administered in the peritoneal cavity also increases food intake by approximately 500% of baseline and is effective in increasing food intake for at least 1-h post injection (Wren et al. 2001b). It is largely thought that IP administration simulates the high concentrations of the gut peptide released by the stomach near local vagal afferents. Direct support of a vagally mediated mechanism of action is that vagotomy attenuates ghrelin-induced stimulation of food intake in humans as well as in rodents (Date et al. 2002; le Roux et al. 2005). The specific afferents responsible for the behavioral effects of ghrelin are thought to be vagal sensory afferents as application of the potent neurotoxin, capsaicin, which destroys a majority of vagal sensory fibers, attenuates increases of food intake stimulated by ghrelin administration (Date et al. 2002). While these data show that peripheral ghrelin increases food intake through two mechanisms of action, the downstream neurons that receive and mediate ghrelin-induced hyperphagia are located in the hypothalamus and hindbrain nuclei.

13.7 Ghrelin Increases Food Intake Through the CNS

The precise mechanisms by which peripheral ghrelin gains access to brain nuclei expressing the receptor are not completely known. Evidence shows that the blood–brain barrier is slightly permeable to the peptide and ghrelin is able to freely diffuse into hypothalamic nuclei involved in the control of food intake. As such, ghrelin acts on the hypothalamus to increase food intake. This is based on the following: (1) acute or chronic administration of ghrelin into either the lateral or third ventricle, which allows access to hypothalamic nuclei, results in a robust increase of meal size (Kinzig et al. 2006) or increases meal frequency (Faulconbridge et al. 2003) followed by substantial body weight gain (Tschop et al. 2000); (2) ICV administration of a ghrelin immunoglobulin attenuates food-deprivation–induced feeding, a time when ghrelin is typically most potent (Bagnasco et al. 2003); and (3) central administration of ghrelin induces neuronal activation (Lawrence et al. 2002). These data clearly demonstrate a role for the hypothalamus in ghrelin-induced increase of food intake. Among the four hypothalamic nuclei – the dorsomedial (DMH), the ventromedial (VMH), the paraventricular (PVN), and the arcuate (ARC) – that display immunoreactivity for ghrelin or the ghrelin receptor (Cowley et al. 2003) and mediate ghrelin's actions (Wren et al. 2001b), it is believed the ARC and PVN are the primary nuclei involved in ghrelin-induced increases of food intake. Compared to other hypothalamic nuclei, the ARC exhibits significantly higher ghrelin immunoreactivity and increased neural activation after exogenous ghrelin (Hewson et al. 2002). Furthermore, rats with ARC neuronal ablation do not increase their intake in response to ghrelin and do not compensate for caloric deficit (Tamura et al. 2002) demonstrating the influence of ghrelin signaling within ARC in maintaining energy balance. Similarly, administration of ghrelin directly into the PVN increases food intake equally to that of ICV infusion (Currie et al. 2005). This suggests that the ARC mediates short-term increases while the PVN is responsible for mediating long-term increases of food intake stimulated by ghrelin (Bagnasco et al. 2003). From these data, the hypothalamus is undoubtedly a mediator of ghrelin-induced hyperphagia.

Ghrelin can also access ghrelin receptors located in the hindbrain, an area heavily involved in food intake, including the nucleus tractus solitarius (NTS), area postrema (AP), and dorsal motor

nucleus of the vagus (DMV) (Guan et al. 1997) either via vagal afferents or through porous blood–brain barrier structures. Indeed, both central and peripheral administration of ghrelin or ghrelin receptor agonists significantly increase neuronal activation in the NTS, AP, and DMV (Lawrence et al. 2002; Takayama et al. 2007). Furthermore, ICV administration into the fourth ventricle, which perfuses the hindbrain, increases food intake in similar magnitudes to third ventricle administration that accesses forebrain hypothalamic nuclei (Kinzig et al. 2006). The effective dose that stimulates food intake in the DVC (10 pmol) is significantly lower than threshold orexigenic dose of ghrelin for the ARC (30 pmol) as well (Faulconbridge et al. 2003). Finally, destruction of the AP also results in decreased sensitivity to exogenous ghrelin (Gilg and Lutz 2006). Together, these data indicate the importance of the hindbrain in mediating ghrelin-induced hyperphagia

While the hindbrain, as well as the hypothalamus, is important in regulating ghrelin-induced increases in food intake, they are not considered to mediate this phenomenon independently. Peripheral satiety signals acting through the hindbrain are integrated at the level of the hypothalamus which modulates intake. As such, destruction of hindbrain–forebrain neuronal circuits results in an attenuation of sensitivity to ghrelin-induced hyperphagia. Additionally, ablation of these relays causes a substantial decrease in neuronal activation in the ARC induced by ghrelin (Date et al. 2006). Thus, ghrelin released from the stomach utilizes a vagally- and hindbrain-mediated pathway to signal hypothalamic nuclei to increase food intake. While ghrelin profoundly stimulates food intake through a hindbrain–hypothalamic pathway, its magnitude of increased consumption is remarkably similar to that caused by other orexigenic agents in the hypothalamus, specifically, Neuropeptide Y (NPY) and Agouti-Related Peptide (AgRP) (Wren et al. 2000, 2001b).

13.8 Ghrelin Interacts with Central Neuropeptides to Increase Food Intake

The majority of neurons expressing NPY are located in the ARC, and approximately half of these neurons co-express AgRP. Both peptides are potent orexigenic signals, but differ in the duration of their effects. Specifically, NPY stimulates short-term increases of food intake while AgRP increases long-term feeding (Tang-Christensen et al. 2004). A wealth of data consisting of both neuroanatomical and behavioral evidences lends support to the interaction between ghrelin and these peptides. Ghrelin producing neurons in the forebrain synapse directly with the somatic or dendritic portion of NPY neurons in the ARC and ghrelin receptor is localized on presynaptic terminals of NPY neurons (Cowley et al. 2003). Together, these data suggest indirectly that ghrelin may modulate feeding behavior through NPY and AgRP neurons.

Studies examining neuronal activation provide direct evidence for the interaction between ghrelin and neurons producing these peptides. For example, ghrelin induces significant increases of intracellular calcium in NPY expressing neurons (Cowley et al. 2003) and ICV administration of an effective orexigenic dose of ghrelin activates ARC neurons expressing NPY as evidenced by Fos-Li (Lu et al. 2002; Wang et al. 2002). Further support of the interaction between these peptides is that in vitro studies examining hypothalamic tissues show increased expression of NPY and AgRP when incubated with a ghrelin receptor agonist (Goto et al. 2006). Similarly, in vivo, NPY and AgRP expression is up-regulated following either acute or chronic central administration of an effective dose of ghrelin (Kamegai et al. 2001). Therefore, ghrelin is able to activate neurons producing NPY and AgRP as well as modulate expression of these potent central orexigens. Conversely, endogenous NPY and AgRP modulate ghrelin-induced hyperphagia. For example, the absence of ARC NPY/AgRP signaling results in an abolished or attenuated sensitivity to ghrelin (Tamura et al. 2002). Additionally, central application of antibodies for NPY or AgRP or antagonists for NPY or AgRP

receptors results in an attenuation of ghrelin-induced hyperphagia (Nakazato et al. 2001; Shintani et al. 2001). Finally, mice engineered with a null gene for NPY and AgRP have a completely abolished response to both central and peripheral ghrelin administration as well (Chen et al. 2004). Collectively, these data support the hypothesis that NPY and AgRP are mediators of ghrelin-induced stimulation of food intake. In addition to the interaction between ghrelin and these central orexigenic peptides, there are antagonistic interactions between ghrelin and peripheral satiety peptides secreted from the GI tract.

13.9 Ghrelin Interacts with Peripheral Satiety Signals

Several studies have shown that ghrelin interacts at various levels with other gut signals to control food intake. For example, vagal afferent neurons that contain the ghrelin receptor also co-express receptors for satiety signals, such as cholecystokinin (CCK), glucagon-like peptide-1 (GLP-1), and peptide tyrosine-tyrosine (PYY) receptors. Additionally, administration of ghrelin down-regulates expression of these peptide receptors (Burdyga et al. 2006; de Lartigue et al. 2007). Ghrelin and CCK have opposing effects. While CCK causes vagal activation, ghrelin potently inhibits activation of the vagus (Date et al. 2002), and ghrelin administered to vagal afferent tissue blocks upstream anorexigenic peptide expression induced by CCK (de Lartigue et al. 2007). Furthermore, ghrelin-induced activation of neurons in the hypothalamus is potently suppressed by administration of CCK. As a result of these opposing effects, administration of CCK prior to ghrelin treatment abolishes ghrelin-induced increase of food intake (Date et al. 2005).

The interaction of ghrelin is not limited to CCK. Administration of ghrelin IV prior to GLP-1 attenuates GLP-1–induced satiation. Additionally, infusion of ghrelin at a level that has no effect on gastric emptying attenuates delayed gastric emptying induced by GLP-1, supporting the powerful action of ghrelin to reduce satiation by affecting GI motility. Finally, ghrelin interacts with PYY. Ghrelin infusion preceding administration of PYY attenuates PYY-induced inhibition of food intake even at a dose of ghrelin that does not stimulate food intake alone. Similarly to GLP-1, PYY-induced delayed gastric emptying also is attenuated by a sub-threshold dose of ghrelin (Chelikani et al. 2006). This evidence shows that ghrelin is a major player in interacting with other gastrointestinal peptides to influence gut functions and food intake.

13.10 Ghrelin Increases Intake of Palatable Foods

While it has been established that hindbrain and forebrain nuclei underlie ghrelin-induced hyper-phagia, brain nuclei that are associated with overconsumption of palatable foods also express the ghrelin receptor. Therefore, it is possible that ghrelin may increase the preference or consumption of palatable foods. The two nuclei involved in palatable food intake that predominantly express the receptor for ghrelin are the ventral tegmental area (VTA) and nucleus accumbens (NAcc) (Guan et al. 1997). Akin to direct injections of ghrelin into hindbrain or hypothalamic nuclei, administration of ghrelin directly into the VTA stimulates food intake in freely fed rats (Naleid et al. 2005). Furthermore, central administration of ghrelin during preference tests with isocaloric high-fat (HF) and low-fat (LF) diets also increases consumption of a usually highly preferred HF meal compared to an LF meal. Surprisingly, the preference of the HF meal after ghrelin injection is established even in rats that normally prefer the LF meal (Shimbara et al. 2004). In contrast to this finding, use of a

synthetic ghrelin receptor agonist in carbohydrate preferring S5B rats increases consumption of carbohydrates while ghrelin increases consumption of fat in Osborne-Mendel rats, which normally prefer fat (Liu et al. 2004). Studies examining intake of energy-dense chow and a highly diluted sucrose solution following ghrelin administration have shown that rodents increase intake of both nutrient sources; however, intake of the energy-dense chow increases to a greater magnitude than that of the dilute sucrose solution (Bomberg et al. 2007). In light of these findings, it appears that ghrelin may stimulate intake of palatable foods, regardless of the preferred nutrient. Additionally, energy density appears to be an important determinant in food intake induced by ghrelin as it increases consumption of fat and highly energy dense chow. Further experiments controlling both palatability and energy density are needed to elucidate whether one or both properties of ingested foods plays a role in ghrelin-induced intake of palatable foods. Moreover, knockout models encoding a null gene for the ghrelin receptor gain weight, but are not susceptible to obesity induced by a highly palatable, HF diet (Zigman et al. 2005). Whether this is due to a decreased preference for the diet or absence of appetite due to inefficient ghrelin signaling has not been determined. Nevertheless, these data collectively show that ghrelin has a role in increased intake of palatable foods. In addition to ghrelin increasing both normal and palatable food intake, it also has a role in increasing adiposity.

13.11 Ghrelin Increases Body Adiposity

While ghrelin increases bodyweight through the initiation of meals or increase of meal size, it also causes increases in body adiposity independently of increased food intake (Theander-Carrillo et al. 2006). To accomplish this, it is thought that ghrelin causes a shift in energy metabolism away from fats to other fuel sources, most likely carbohydrates. In this regard, administration of ghrelin decreases respiratory quotient of animals, which denotes a decrease in lipid metabolism (Asakawa et al. 2001). Also, ghrelin activates the expression of triglyceride storing enzymes that shuttle circulating fatty acids into white adipose tissue, promoting increased body fat. At the same time, the increase in fatty acid storage enzymes is accompanied by decreases in thermogenic enzymes that are active in brown adipose tissue and muscle. Thus, by increasing anabolic pathways of energy storage factors and decreasing catabolic enzyme activity, ghrelin exerts a net effect of increasing adiposity through two routes of action. Therefore, ghrelin allows freely circulating fatty acids in the circulation to be more efficiently stored in adipocytic tissue (Theander-Carrillo et al. 2006). From these findings, it is plausible that chronically increased endogenous levels of ghrelin increase food intake and decrease energy expenditure, creating a scenario with proneness for weight gain and subsequent obesity. Indeed, there is a correlative relationship between obesity and ghrelin. Thus, it may be that ghrelin has implications in treating the current obesity epidemic.

13.12 Applications to Other Areas of Health and Disease

While the worldwide population is becoming increasingly obese, only few mutations in the ghrelin pathway have been reported. In individuals with Prader–Willi syndrome, a disorder characterized by overconsumption of food and obesity during adolescence, ghrelin may be one of the underlying contributors to the exhibited hyperphagia as circulating levels are substantially elevated in these individuals. In general, however, despite the fact that ghrelin levels are decreased in obese

individuals without consistent meal-related preprandial increases and postprandial decreases in plasma concentrations, ghrelin therapeutics may be effective in treating obesity. The finding that ghrelin levels increase with the reduction of weight in obese individuals may denote that ghrelin contributes to the subsequent rebound in weight after diet-induced weight loss. Additionally, the unusually low levels in obese individuals may signify an enhanced sensitivity to the peptide. Together, these findings suggest that antagonists or antibodies for the ghrelin receptor or ghrelin may be useful in treating obesity. Indeed, ghrelin receptor antagonists reduce food intake and weight gain in both lean and obese rodent models (Asakawa et al. 2003; Salome et al. 2009); however, use of these drugs in humans, ironically, results in increased food intake and weight gain (Halem et al. 2004). Furthermore, ghrelin vaccines, which are potent antisera reducing endogenous levels of the peptide, reduce food intake and body weight in lean and obese rodents similarly to ghrelin receptor antagonists (Zorrilla et al. 2006). In humans, ghrelin vaccines result in no noticeable changes in body weight. Thus, current treatments are ineffective in treating obesity in humans, and further investigation into new ghrelin vaccines may reveal other feasible options in the treatment of obesity through ghrelin signaling.

Currently, gastric bypass is the most effective intervention to ameliorate obesity. Initial findings pointed to ghrelin secretion being nearly abolished in individuals with the bypass procedure accompanied by significant weight loss (Cummings et al. 2002) (Fig. 13.4). However, it has been subsequently shown that ghrelin levels normalize or increase after postoperative weight-loss is regained (Holdstock et al. 2003). Decreased circulating ghrelin levels have been associated with decreases in appetitive ratings as well (Cummings and Shannon 2003). Similarly, less invasive surgical interventions, such as
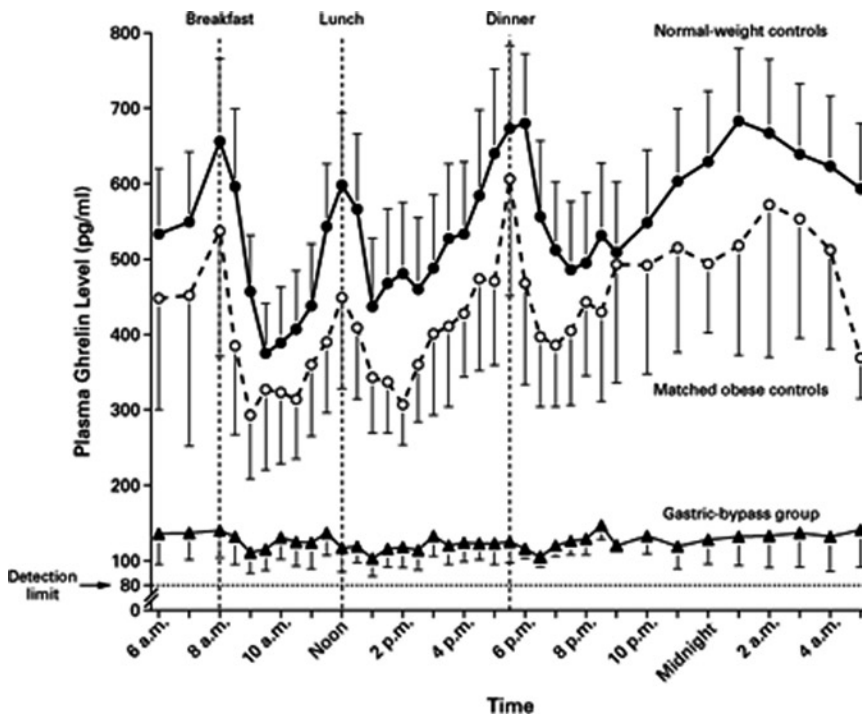
Fig. 13.4 Gastric-bypass modulates circulating ghrelin levels. In obese individuals, circulating ghrelin concentrations are decreased compared to normal-weight individuals; however, after surgical intervention, plasma ghrelin levels are almost completely abolished, nearing undetectable concentrations (Reprinted from Cummings et al. 2002)

gastric bands and intestinal sleeves, which limit exposure of nutrients to the stomach or intestine, result in decreased circulating ghrelin levels or attenuation of weight-loss induced increases in plasma ghrelin concentrations (Aguirre et al. 2008). However, further research is needed to elucidate the specific mechanisms that underlie the decreased ghrelin levels observed in these individuals. In addition to obesity, ghrelin is a targeted therapeutic intervention in disease states characterized by loss of appetite and bodyweight, such as cancer, anorexia, and cardiac cachexia. In these patients, therapy with exogenous ghrelin is very efficacious as it typically increases food intake, associated appetitive scores, as well as bodyweight (Nagaya et al. 2005; Neary et al. 2004).

Summary Points

- Ghrelin is a 28 amino acid peptide hormone that is the endogenous ligand for the growth hormone (GH) secretagouge receptor-1a (GHS-R1a) now referred to as "the ghrelin receptor."
- Ghrelin is produced and secreted by the X/A-type cells in the mucosal layer of the stomach. It is currently the only known peripheral peptide hormone that increases food intake. The biologically active form of ghrelin in the circulation that increases food intake is acyl-ghrelin.
- Both short- and long-term food intake modulate circulating ghrelin levels. Specifically, ghrelin increases during preprandial and decreases during postprandial periods. Chronic food deprivation significantly elevates plasma ghrelin concentrations.
- All three macronutrient classes suppress ghrelin secretion, but carbohydrates and proteins are significantly more effective than fat in inhibiting ghrelin secretion.
- Ghrelin is thought to be an adiposity signal as circulating ghrelin concentrations correlate inversely with body mass index (BMI).
- Peripheral ghrelin increases food intake through an endocrine as well as a paracrine mechanism of action. The two regions of the central nervous system that are thought to underlie ghrelin-induced increase of food intake are the hypothalamus and hindbrain.
- Two potent hypothalamic orexigenic signals, Neuropeptide Y (NPY) and Agouti-Related Peptide (AgRP), are mediators of ghrelin-induced hyperphagia.
- Ghrelin increases consumption of palatable foods regardless of macronutrient preferred.
- Ghrelin increases adiposity independent of increased food intake by inhibiting catabolic and activating anabolic metabolic pathways.

Definitions

Ghrelin: The only known potent peripheral signal that induces hyperphagia as well as inducing adiposity.

Endocrine: Entry of peptide or hormone into the bloodstream to exert effects on distant tissues

X/A-type cells: Specialized gastric cells in the mucosal layer that produce and release ghrelin. The basolateral portion of the cell is responsible for hormone secretion and is positioned next to capillaries.

Fos: Protein that is a product of the immediate-onset c-fos gene. Used in immunohistochemical experiments as a marker of neuronal activation

Paracrine: Action of a peptide or hormone on local or nearby cells without entering the circulatory system.

References

Aguirre V, Stylopoulos N, et al. Obesity (Silver Spring). 2008;16:2585–92.
Ariyasu H, Takaya K, et al. J Clin Endocrinol Metab. 2001;86:4753–8.
Asakawa A, Inui A, et al. Gut. 2003;52:947–52.
Asakawa A, Inui A, et al. Gastroenterology. 2001;120:337–45.
Bagnasco M, Tulipano G, et al. Regul Pept. 2003;111:161–7.
Bomberg EM, Grace MK, et al. Neuroreport. 2007;18:591–5.
Burdyga G, Varro A, et al. Am J Physiol Gastrointest Liver Physiol. 2006;290:G1289–97.
Chelikani PK, Haver AC, et al. Diabetes. 2006;55:3038–46.
Chen HY, Trumbauer ME, et al. Endocrinology. 2004;145:2607–12.
Cowley MA, Smith RG, et al. Neuron. 2003;37:649–61.
Cummings DE, Shannon MH. Arch Surg. 2003;138:389–96.
Cummings DE, Purnell JQ, et al. Diabetes. 2001;50:1714–9.
Cummings DE, Weigle DS, et al. N Engl J Med. 2002;346:1623–30.
Currie PJ, Mirza A, et al. Am J Physiol Regul Integr Comp Physiol. 2005;289:R353–8.
Date Y, Murakami N, et al. Gastroenterology. 2002;123:1120–8.
Date Y, Kojima M, et al. Endocrinology. 2000;141:4255–61.
Date Y, Toshinai K, et al. Endocrinology. 2005;146:3518–25.
Date Y, Shimbara T, et al. Cell Metab. 2006;4:323–31.
de Lartigue G, Dimaline R, et al. J Neurosci. 2007;27:2876–82.
Drazen DL, Vahl TP, et al. Endocrinology. 2006;147:23–30.
Druce MR, Wren AM, et al. Int J Obes (Lond). 2005;29:1130–6.
Faulconbridge LF, Cummings DE, et al. Diabetes. 2003;52:2260–5.
Feinle-Bisset C, Patterson M, et al. Am J Physiol Endocrinol Metab. 2005;289:E948–53.
Foster-Schubert KE, Overduin J, et al. J Clin Endocrinol Metab. 2008;93:1971–9.
Gilg S, Lutz TA. Physiol Behav. 2006;87:353–9.
Goto M, Arima H, et al. Endocrinology. 2006;147:5102–9.
Guan XM, Yu H, et al. Brain Res Mol Brain Res. 1997;48:23–9.
Halem HA, Taylor JE, et al. Eur J Endocrinol. 2004;151 Suppl 1:S71–5.
Hashimoto H, Fujihara H, et al. Endocrinology. 2007;148:1638–47.
Hewson AK, Tung LY, et al. Diabetes. 2002;51:3412–9.
Holdstock C, Engstrom BE, et al. J Clin Endocrinol Metab. 2003;88:3177–83.
Hosoda H, Kojima M, et al. Biochem Biophys Res Commun. 2000;279:909–13.
Hosoda H, Kojima M, et al. J Biol Chem. 2003;278:64–70.
Jeon TY, Lee S, et al. J Clin Endocrinol Metab. 2004;89:5392–6.
Kamegai J, Tamura H, et al. Diabetes. 2001;50:2438–43.
Kinzig KP, Scott KA, et al. Am J Physiol Regul Integr Comp Physiol. 2006;290:R1565–9.
Kojima M, Hosoda H, et al. Nature. 1999;402:656–60.
Lawrence CB, Snape AC, et al. Endocrinology. 2002;143:155–62.
le Roux CW, Neary NM, et al. J Clin Endocrinol Metab. 2005;90:4521–4.
Liu X, York DA, et al. Peptides. 2004;25:2171–7.
Lu S, Guan JL, et al. Neurosci Lett. 2002;321:157–60.
Masuda Y, Tanaka T, et al. Biochem Biophys Res Commun. 2000;276:905–8.
Nagaya N, Itoh T, et al. Chest. 2005;128:1187–93.
Nakazato M, Murakami N, et al. Nature. 2001;409:194–8.
Naleid AM, Grace MK, et al. Peptides. 2005;26:2274–9.
Neary NM, Small CJ, et al. J Clin Endocrinol Metab. 2004;89:2832–6.
Otto B, Cuntz U, et al. Eur J Endocrinol. 2001;145:669–73.
Salome N, Hansson C, et al. J Neuroendocrinol. 2009.
Sato N, Kanai S, et al. Jpn J Physiol. 2003;53:443–9.
Shimbara T, Mondal MS, et al. Neurosci Lett. 2004;369:75–9.
Shintani M, Ogawa Y, et al. Diabetes. 2001;50:227–32.
Takayama K, Johno Y, et al. Neurosci Lett. 2007;417:292–6.
Tamura H, Kamegai J, et al. Endocrinology. 2002;143:3268–75.
Tang-Christensen M, Vrang N, et al. Endocrinology. 2004;145:4645–52.
Theander-Carrillo C, Wiedmer P, et al. J Clin Invest. 2006;116:1983–93.
Tschop M, Smiley DL, et al. Nature. 2000;407:908–13.
Tups A, Helwig M, et al. J Neuroendocrinol. 2004;16:922–8.

van der Lely AJ, Tschop M, et al. Endocr Rev. 2004;25:426–57.

Wang L, Saint-Pierre DH, et al. Neurosci Lett. 2002;325:47–51.

Williams DL, Cummings DE, et al. Endocrinology. 2003;144:2765–7.

Wolden-Hanson T. Physiol Behav. 2006;88:267–76.

Wren AM, Seal LJ, et al. J Clin Endocrinol Metab. 2001a;86:5992.

Wren AM, Small CJ, et al. Endocrinology. 2000;141:4325–8.

Wren AM, Small CJ, et al. Diabetes. 2001b;50:2540–7.

Yabuki A, Ojima T, et al. J Anat. 2004;205:239–46.

Yang J, Brown MS, et al. Cell. 2008;132:387–96.

Yokota I, Kitamura S, et al. Endocr J. 2005;52:271–6.

Zigman JM, Nakano Y, et al. J Clin Invest. 2005;115:3564–72.

Zorrilla EP, Iwasaki S, et al. Proc Natl Acad Sci USA. 2006;103:13226–31.

Chapter 14
The Role of Glucagon-Like Peptide-1 (Glp-1) in Eating Behavior

Mihai Covasa and Timothy Swartz

Keywords: Diffusion tensor imaging • Fetal alcohol spectrum disorder • Brain • Fetal alcohol syndrome • MRI • DTI

Abbreviations

AP	Area Postrema
ARC	Arcuate nucleus
CNS	Central Nervous System
DMV	Dorsal Motor Nucleus of the Vagus
DPP-IV	Dipeptidyl peptidase IV
GI	Gastrointestinal
GLP-1	Glucagon-like peptide-1
GLP-1R	Glucagon-like peptide-1 receptor
HF	High-fat
ICV	Intracerebroventricular
IP	Intraperitoneal
IV	Intravenous
mRNA	Messenger RNA
NTS	Nucleus Tractus Solitarius
PVN	Paraventricular nucleus
PYY	Peptide tyrosine-tyrosine

14.1 Introduction

Numerous peptides are produced and released from the enteroendocrine L-cells lining the distal small intestine and colon. Among these are peptides from the proglucagon family, which are derived from expression of the proglucagon gene. A number of other glucagon-like peptides have also been identified with similar biological activities that are representative of the proglucagon family. These

M. Covasa (✉)

INRA, Écologie et Physiologie du Système Digestif, 78350 Jouy-en-Josas, France

e-mail: mcovasa@jouy.inra.fr

Table 14.1 Key features of GLP-1 in eating behavior

1. GLP-1 is mainly released from the enteroendocrine L-cells of the ileum and colon
2. All three macronutrient classes stimulate release of GLP-1
3. GLP-1 has potent regulatory effects on gastrointestinal functions
4. GLP-1 induces satiation through both central and peripheral pathways, which mediate different gastrointestinal stimuli
5. GLP-1 activates hindbrain neurons through vagal afferent sensory nerve fibers and is also locally produced by hindbrain neurons
6. GLP-1 potentiates nutrient-induced insulin secretion, which classifies it as an incretin
7. GLP-1 analogs are effective in normalizing blood glucose levels in diabetics and reduce body weight in obese individuals

Table illustrating the features of GLP-1 in controlling eating behavior summarizing stimulation of secretion, release, and effects of the hormone

peptides have a profound role in gastrointestinal (GI) functions including secretion and motility, gut proliferation, potentiation of insulin secretion, and inhibition of food intake. One such peptide is glucagon-like peptide-1 (GLP-1). GLP-1 exerts physiological and behavioral effects by binding to the GLP-1 receptor (GLP-1R), which is expressed by central and peripheral nervous systems as well as alimentary organs, such as the pancreas. In addition to the L-cells of the GI tract, neurons of the central nervous system (CNS) produce GLP-1. To decrease food intake, GLP-1 acts through paracrine and endocrine pathways, which stimulate neuronal nuclei involved in the control of food intake. Furthermore, locally produced GLP-1 in the brain also serves to control food intake. The finding that GLP-1 potentiates insulin secretion denotes its role in pathological disease states, such as obesity, which is often accompanied by insulin resistance, and diabetes mellitus. This chapter focuses on (1) distribution of GLP-1 and factors regulating GLP-1 secretion, (2) mechanisms underlying GLP-1 induced satiation, (3) the interaction of GLP-1 with other signals controlling food intake, and (4) the role of GLP-1 in pathological conditions (Table 14.1).

14.2 GLP-1 Is Distributed Throughout Central and Peripheral Tissues

GLP-1 is the posttranslational product of pre-proglucagon gene expressed in the pancreatic α-cells, intestinal L-cells, as well as the CNS. It is synthesized by intestinal L-cells in two forms: GLP-1$_{1-37}$ and GLP-1$_{1-36}$ and undergoes further cleavage to produce the biological active fragments: GLP-1$_{7-36}$ and GLP-1$_{7-37}$ (Holst et al. 1987; Mojsov et al. 1987). Both peptide isoforms are equally potent in their biological activities; however, the GLP-1$_{7-36}$ amide is the major circulating form (Orskov et al. 1994). The two forms of GLP-1 are rapidly inactivated by the dipeptidyl peptidase-4 (DPP-IV) enzyme leaving approximately 10–15% of active GLP-1 in the systemic circulation, which is further degraded by DPP-IV. Thus, GLP-1 has a very short half-life in the circulation (~1–2 min) (Deacon et al. 1996). To exert endocrine, physiological, and behavioral effects, GLP-1 binds to the GLP-1R. The GLP-1R is a G-protein transmembrane-bound receptor and is coupled to a stimulatory G-protein to exert its downstream cellular cascade of events. The GLP-1R was first identified and cloned from rat pancreatic islets followed by the cloning of the human variant (Dillon et al. 1993; Thorens et al. 1992). Since its discovery, two exogenous ligands derived from the venom of the Gila monster, a reptilian species native to the Southwestern United States, have been discovered for the GLP-1R (Parker et al. 1984). The first is exendin-4, which is an agonist for the receptor and the second is exendin-9 that serves as an inverse agonist, but typically referred to as an antagonist for GLP-1Rs.

Both GLP-1 and its receptor are distributed throughout both central and peripheral tissues. In the CNS, the peptide and its receptor are widely distributed throughout hindbrain, midbrain, and forebrain nuclei. Because of the dichotomous nature of some of these nuclei, GLP-1 appears to play a role in many physiological and neurological functions. Although the brain may be a vast supply of the peptide, the major source is thought to be the GI tract. Because of this, GLP-1 is widely recognized as one of the predominant distal gut satiety signals released from the ileum of the small intestine as well as the large intestine. Enteroendocrine L-cells largely localized in these regions of the GI tract are the major source of GLP-1, with two predominant factors regulating its secretion: a neuro-humoral reflex and nutrients in the lumen of the intestine.

14.3 Regulation of GLP-1 Secretion

Intestinal L-cells located mainly in the distal ileum and colon secrete GLP-1 in response to a variety of nutrient, neural, and endocrine factors. Initially, due to the kinetics of meal-induced GLP-1 release, the primary mechanism of GLP-1 secretion was thought to be through an indirect, neuro-humoral reflex. Specifically, GLP-1 secretion is highest 10 min post meal ingestion when nutrients are not yet thought to make contact with GLP-1 secreting L-cells (Roberge and Brubaker 1991). While this mechanism induces secretion of GLP-1, nutrients are also thought to directly regulate release of the peptide (Dube and Brubaker 2004). Two pieces of indirect evidence support this. First, infusion of glucose directly into the proximal small intestine results in elevated circulatory GLP-1 levels comparable to distal small intestine infusion of glucose (Holst 2004). Second, recent advances in the ability to tag and detect L-cells throughout the GI tract have identified large populations of GLP-1 secreting cells that are also present in the proximal intestinal tissues that most likely mediate this rapid release of the peptide (Theodorakis et al. 2006).

The L-cells of the GI tract are open-type endocrine cells, with the apical surface strategically positioned to sense intraluminal intestinal nutrients. Binding of nutrients to apical surface membrane proteins is thought to stimulate release of GLP-1. Some of the candidate receptors thought to induce GLP-1 release are gustducin and T1R family receptor subtypes (Rozengurt and Sternini 2007). Inside the cells, a vesicular transport system shuttles GLP-1 to the basolateral portion of the cell and releases the peptide into the circulation or lymph. Thus, GLP-1-secreting cells are in an excellent position to release the hormone in response to mixed meals or single nutrients. Indeed, ingested nutrients cause secretion of GLP-1 from the GI tract. Specifically, peptone or products of protein digestion, such as amino-acids, result in secretion of GLP-1 both in vitro and in vivo (Cordier-Bussat et al. 1998; Layer et al. 1995). Fatty acids, triglycerides, and carbohydrates are also potent stimuli for GLP-1 secretion (Chu et al. 2008). GLP-1 is secreted from cell models via mechanisms that are normally dependent on glucose, including sodium-glucose transporters, and potassium-ATP sensitive pumps (Tolhurst et al. 2009). The increase of circulatory GLP-1 is prolonged in response to complex carbohydrates and fiber as well, which can be attributed to the slow digestion of these nutrients allowing for greater intestinal transit time, and increasing exposure of nutrients to GLP-1 secreting L-cells. While fasting typically results in low levels of GLP-1, blockade of enzymatic GLP-1 degradation results in increased circulatory levels, denoting some constitutive release of the peptide (Mari et al. 2005). Altogether, these data show that nutrients stimulate GLP-1 secretion, thus demonstrating the role of GLP-1 in control of food intake.
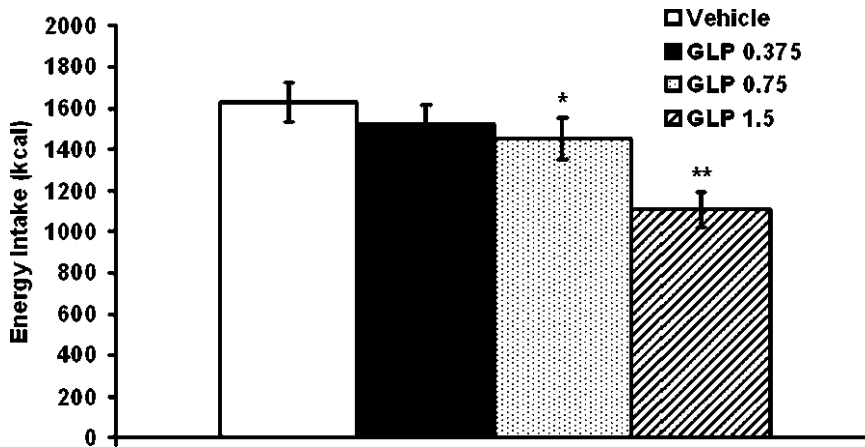
Fig. 14.1 Effect of IV infusion of GLP-1 at increasing rates on food intake in humans. At a free buffet meal, GLP-1 infusion dose-dependently decreased energy intake. *$P < 0.05$, **$P < 0.001$ (Adapted from Gutzwiller et al. (1999))

14.4 GLP-1 Decreases Food Intake

Administration of GLP-1 into either the periphery or central tissues results in a subsequent dose-dependent decrease of food intake in several species (Flint et al. 1998; Gutzwiller et al. 1999; Turton et al. 1996) (Fig. 14.1). Similar to injections of other peripheral satiety agents, such as CCK, GLP-1 limits food intake by decreasing meal size; however, at high doses, GLP-1 also decreases meal number. Furthermore, chronic administration of the GLP-1R agonist, exendin-4, results in reduced body-weight gain and adiposity (Larsen et al. 2001; Mack et al. 2006). Conversely, blockade by exendin-9 in fed rats increases food intake (Williams et al. 2009). In humans, peripheral administration of GLP-1 reduces food intake and gastric emptying. However, the role of endogenous GLP-1 in control of food intake in humans is not entirely clear since no studies thus far examined the effect of exendin-9 on energy intake. In contrast, mice lacking the GLP-1R exhibit normal eating behavior and are of normal body weight (Scrocchi et al. 1996). This has been attributed to compensatory up-regulation of other satiation signals derived from the gastrointestinal tract, especially hormones co-secreted with GLP-1 from the intestinal L-cells. Together, these data provide strong support that GLP-1 has an important role in energy balance.

14.5 GLP-1 Controls Gastrointestinal Functions

GLP-1 has potent regulatory effects on the GI tract, including gastrointestinal emptying, motility, and enzymatic secretion, thus controlling postprandial metabolical effects. Administration of GLP-1 slows gastric emptying, an effect analogous to the effects of nutrients on gastrointestinal motor functions. This is associated with the relaxation of the proximal stomach (Schirra et al. 2000), increased meal retention in the distal stomach (Little et al. 2006), the suppression of antral and duodenal pressure waves and stimulation of tonic and phasic pyloric pressures (Brennan et al. 2005; Schirra et al. 2000). Treatment with the GLP-1-specific receptor antagonist, exendin-9, blocks the effects of

GLP-1 on gastric emptying in rats (Tolessa et al. 1998) and attenuates the effects of intraduodenal glucose on the stimulation of tonic and phasic pyloric motility and the suppression of antral and duodenal pressure waves in humans (Schirra et al. 2006), suggesting that endogenous GLP-1 plays a physiological role in mediating the effects of nutrients on gastrointestinal motility. The main effect of GLP-1 on GI motility is through the "ileal brake" mechanism, which serves to slow gastric emptying. GLP-1 also decreases gastrin-stimulated gastric acid secretion, allowing more time for digestion of food (Schjoldager et al. 1989). In addition to its effects on the stomach, GLP-1 potently inhibits distal intestinal and colonic motility, and inhibits pancreatic exocrine enzymatic secretions. These actions result in increased transit time for ingesta and delays the process of digestion and absorption of nutrients. The effects of GLP-1 on GI motility and enzymatic secretions are mediated by vagal afferents since vagal deafferentation results in attenuation of GLP-1-induced delay of gastric emptying and inhibition of pancreatic enzymatic secretions (Imeryuz et al. 1997). Collectively, these findings demonstrate that GLP-1 modulates GI functions, which are accompanied by changes in food intake and metabolical profile.

14.6   GLP-1 Controls Food Intake via Vagal and Endocrine Pathways

The enteroendocrine L-cells secreting GLP-1 are situated in juxtaposition to capillaries, thus it is reasonable to assume that some of the peptide from this source makes its way into the circulation. This suggests that GLP-1 may reduce food intake by acting through an endocrine mechanism. Indeed, after a meal, circulatory levels of the peptide are substantially increased. The hepatic portal vein, which receives incoming venous blood from the GI tract as well as the intestinal epithelium, however, contains high concentrations of DPP-IV, ready to quickly degrade GLP-1 and yield an inactive form of the peptide. Thus, GLP-1 must first pass through an intermediate pathway before reaching the circulation. One such route is the lymphatic system. By circulating through the chylous lymph from the GI tract, GLP-1 enters the circulatory system at the level of the subclavian vein, an area with extremely low levels of DPP-IV, thus avoiding immediate degradation (D'Alessio et al. 2007). Once in the circulation, the active form of GLP-1 exerts its effects on the gut. For example, intravenous (IV) infusions of the peptide that result in physiological circulating levels reduces food intake in rodent models (Ruttimann et al. 2009). Similarly, infusion of GLP-1 in humans results in a dose-dependent decrease of food intake and a concomitant enhancement of satiety (Verdich et al. 2001). Together, these data clearly support an endocrine role of the peptide in controlling food intake. In addition to this route of action, GLP-1 also utilizes a paracrine pathway to decrease food intake.

Vagal afferents from the hepatic and intestinal branches of the vagus innervating the GI tract mediate the effects of GLP-1 on food intake. This is supported by research demonstrating that nodose ganglion cell bodies of the vagal afferents express immunoreactivity for the GLP-1R and application of GLP-1 to in vitro vagal afferent preparations results in activation of vagal nerve fibers (Nakabayashi et al. 1996; Nakagawa et al. 2004). Additionally, vagotomy or selective vagal deafferentation attenuates suppression of food intake and gastric emptying by intraperitoneal administration of GLP-1 (Abbott et al. 2005). Furthermore, sensory fibers are thought to be responsible for this pathway as capsaicin treatment, which selectively destroys most of these fibers, attenuates exendin-4 suppression of food intake (Talsania et al. 2005). Evidence for an endogenous role of GLP-1 to control food intake is that intraperitoneal administration of the GLP-1R antagonist, exendin-9, in rodents results in increased food intake during various feeding paradigms. Specifically, in fully sated rodents, GLP-1 antagonism results in an almost 100% increase of food intake. Additionally, while peripheral

administration of GLP-1 decreases food intake, peripheral, but not central blockade of GLP-1R using exedin-9 results in attenuation of GLP-1-induced satiation (Williams et al. 2009). Collectively, these findings point toward a local physiological role of GLP-1 secreted from peripheral organs. While peripheral GLP-1 undoubtedly is effective acting through endocrine and paracrine modes of action, several brain nuclei appear to be involved in GLP-1-induced satiation as well.

14.7 GLP-1 Decreases Food Intake via the CNS

GLP-1 is able to access CNS nuclei that control food intake. The blood-brain barrier is permeable to GLP-1 and the peptide freely diffuses into hypothalamic nuclei involved in the control of food intake that lack a structural barrier. However, the likelihood that a relevant physiological amount of the peptide evading the DPP-IV degradation reaches the brain to elicit an effect is rather low. It is more likely that brain-derived GLP-1 acts directly on hindbrain and hypothalamic neurons to control appetite. For example, intracerebroventricular (ICV) administration of GLP-1 into the forebrain or direct administration into the paraventricular nucleus (PVN) of the hypothalamus results in suppression of food intake (Kinzig et al. 2002; McMahon and Wellman 1998; Schick et al. 2003). Similarly, destruction of arcuate (ARC) hypothalamic neurons results in abolishment of GLP-1-induced satiation (Tang-Christensen et al. 2000). While the hypothalamus certainly mediates GLP-1 to control food intake, some data elude that the peptide in the forebrain may decrease food intake by inducing aversive effects. As such, ICV administration, which may lead to diffusion into the amygdala as well as site-specific injections into this nucleus, leads to aversive effects; however, direct administration into the PVN reduces food intake without nonspecific effects or any associated illness (Kinzig et al. 2002). Therefore, the hypothalamus is indeed responsible for GLP-1-induced satiation, without aversive effects. Furthermore, other brain nuclei, localized in the hindbrain are thought to participate in GLP-1-induced suppression of food intake.

GLP-1 also acts on GLP-1Rs located in the hindbrain nuclei that control food intake, such as the nucleus tractus solitarius (NTS), area postrema (AP), and dorsal motor nucleus of the vagus (DMV) via either vagal afferents or through the leaky blood-brain barrier. In this regard, fourth ventricle administration of GLP-1 causes a significant suppression of food intake (Hayes et al. 2008, 2009; Hayes et al. 2008; Kinzig et al. 2002). After acute blockade of hindbrain GLP-1Rs, the effect on food intake is quite pronounced with intake remaining elevated for 24 h following injection. Within the hindbrain, the NTS seems to mediate the actions of GLP-1 since direct administration of exendin-9 at subthreshold ICV doses into this nucleus results in increased food intake (Hayes et al. 2009). These findings strongly support the role of central GLP signaling pathways in control of food intake. Indeed, GLP-1 is a potent neurotransmitter that is produced in the hindbrain. Specifically, neurons of the NTS are a rich source of GLP-1 and they synapse directly with neurons in the hypothalamus that express GLP-1R (Tang-Christensen et al. 2001). Thus, two sources of GLP-1, one arising from periphery and one produced locally in the brain participate in GLP-1-induced satiation. Recently, the functions of the GLP-1 coming from these two sources have been examined. Specifically, peripheral, gut-derived GLP-1 has been shown to mediate nutrient-induced satiation while central GLP-1 controls distention-induced satiation signals arising from the stomach (Hayes et al. 2009; Williams et al. 2009) (Fig. 14.2). Altogether, GLP acting in brain nuclei either produced locally or from the periphery has a profound effect on inducing satiation. Interestingly, the extent to which GLP-1 reduces food intake is similar to the reported effects of antagonists for potent orexigens in the hypothalamus.

Fig. 14.2 Effect of hindbrain GLP-1R antagonism on gastric balloon distention-induced satiation. Hindbrain administration of GLP-1R antagonist, Ex-9, reduces gastric distention-induced suppression of food intake in overnight-food deprived rats. *P<0.05 (Adapted from Hayes et al. (2009))
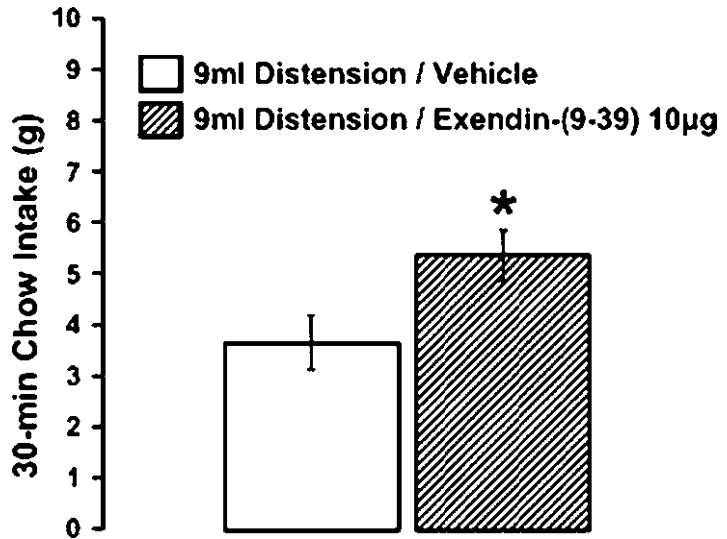
14.8 GLP-1 Reduces Food Intake via Central Neuropeptides

Regulation of energy homeostasis involves interaction with multiple neuropeptides produced in the brain. The hypothalamus produces both orexigenic and anorexigenic signals governing food intake. While these peptides directly affect food intake, they are normally modulated by peripheral signals arising from endocrine organs, such as the GI tract. For example, production of two hypothalamic orexigenic peptides, NPY and AgRP that are heavily involved in regulation of energy intake and expenditure are modulated by GLP-1 signaling. The inhibitory effects of GLP-1 are associated with hypothalamic mRNA expression of NPY and AgRP (Seo et al. 2008). Hypothalamic anorectic signals appear to be modulated by GLP-1 as well. As such, GLP-1 administration increases gene expression of pro-opiomelanocortin (POMC) as well as induces secretion of the peptide (Ma et al. 2007; Seo et al. 2008). Similar to POMC, GLP-1 attenuates deprivation-induced suppression of cocaine amphetamine regulated transcription (CART) expression in hypothalamic nuclei (Seo et al. 2008). Furthermore, GLP-1R antagonism via central exendin-9 administration results in attenuation of CART-induced suppression of food intake (Aja et al. 2006). Together, these data provide compelling evidence for GLP-1 and GLP-1Rs modulating the actions of central neuropeptides, suggesting that the anorectic effects of GLP-1 are mediated through hypothalamic peptides. These interactions between GLP-1 and signals controlling food intake are not limited to central neuropeptides. Many signals arising from peripheral organs interact with GLP-1 to control food intake as well.

14.9 GLP-1 Interacts with Other Peripheral Satiety Signals to Control Food Intake

Most peptides released from the gut in response to meal related stimuli interact with each other at various levels to control physiological determinants of food intake. For example, another gut peptide, peptide tyrosine-tyrosine (PYY) also produced by the intestinal L-cells in response to the presence of nutrients, particularly fats, in the intestinal lumen, decreases intestinal motility and causes a

significant reduction in food intake. These peptides share similar physiological and behavioral effects; however, they suppress food intake independently, but act in a synergistic manner to control meal size. In the rat, administration of either PYY or GLP-1 at doses that are inefficient in reducing food intake when given alone, results in a significant suppression of food intake when given in combination (Neary et al. 2005). Likewise, in healthy lean patients, infusion of subthreshold doses of both GLP-1 and PYY results in significantly reduced intake of a free buffet meal (Neary et al. 2005). While both of these signals are relayed on vagal afferents and neurons of the hindbrain express receptors for PYY and GLP-1R, the mechanism by which these peptides decrease food intake is thought to involve two separate pathways. Specifically, GLP-1 decreases food intake through a vagal sensory mechanism as capsaicin treatment, which destroys vagal sensory fibers, results in attenuation of exendin-4-induced suppression of food intake. The same treatment, however, does not affect suppression of food intake following PYY administration (Talsania et al. 2005). Other neurotransmitters secreted from the GI tract, notably 5-hydroxytryptamine (5-HT), also coordinate GLP-1-induced suppression of food intake. In a mouse model lacking the 5-HT2C receptor, the anorectic effects of GLP-1 are abolished (Asarian 2009).

In addition to interacting with short-term satiety signals and neurotransmitters secreted from the GI tract, GLP-1 also interacts with long-term energy homeostatic signals, such as the adiposity hormone leptin, to decrease food intake. When subthreshold doses of GLP-1 or exendin-4 are combined with subthreshold doses of leptin, the result is a significant reduction of food intake over 24 h in rodents (Bojanowska and Nowak 2007). Despite both peptides being secreted by peripheral endocrine organs, molecular data suggests that central pathways involving both hypothalamic or hindbrain nuclei are involved in this synergistic interaction. For example, in cultured brain tissue slices from the hypothalamic nuclei, application of leptin results in increased expression of GLP-1R (Sanz et al. 2008). Furthermore, the leptin receptor is expressed in the NTS on GLP-1-producing neurons. Thus, leptin may regulate the secretion or the effectiveness of GLP-1 signaling. Indeed, application of leptin to GLP-1-producing cells results in secretion of the peptide. Likewise application of the GLP-1R antagonist, exendin-9, results in attenuation of leptin-induced reduction of food intake and body weight (Nowak and Bojanowska 2008). Together, these findings demonstrate the importance of the interaction between leptin and GLP-1 in controlling food intake and body weight.

One of the most widely studied functions of GLP-1 is the effect it has on modulating secretion of insulin and counterregulatory hormones. The incretins are a family of peptides or hormones that stimulate insulin secretion. Data from both animal models and humans show that GLP-1 potentiates nutrient-induced insulin secretion (Kreymann et al. 1987; Mojsov et al. 1987), an action mediated by GLP-1Rs located on pancreatic β-cells. In addition to insulin, GLP-1 controls the release of the counterregulatory hormone, glucagon, which is responsible for activating catabolic pathways to increase blood glucose levels in times of deprivation. As such, administration of GLP-1 or GLP-1R agonists results in decrease of plasma glucagon (Orskov et al. 1988). Together, stimulation of insulin secretion and inhibition of glucagon release serves to decrease blood glucose levels. Given the ability of GLP-1 to regulate anabolic and catabolic pathways and its interaction with the homeostatic regulatory hormone, leptin, GLP-1 may be an important signal in long-term energy balance. Indeed, pathological states characterized by a dysregulation of energy homeostasis alter GLP-1 signaling pathways from secretion to receptor binding.
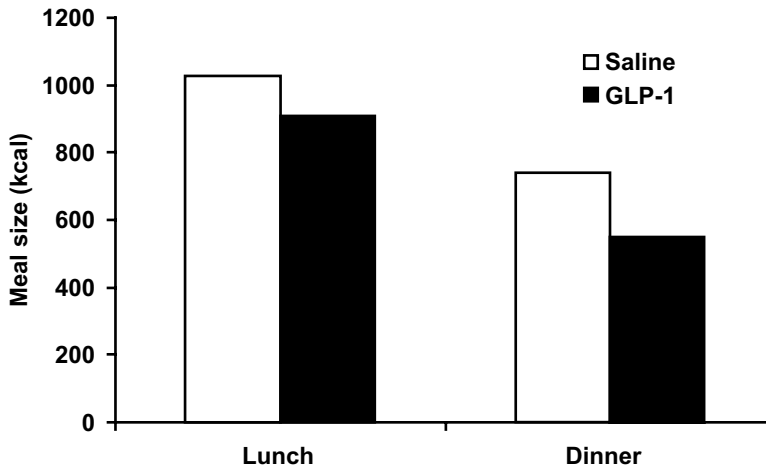
Fig. 14.3 Effect of intravenous (IV) infusion of GLP-1 on food intake in obese patients. After a fixed breakfast, IV GLP-1 decreases energy intake significantly more than saline during both lunch and dinner (Adapted from Naslund et al. (1999))

14.10 Pathological States Alter GLP-1 Signaling

Two major pathologies are associated with alteration in GLP-1 signaling: obesity and diabetes. In morbid obese patients, baseline circulatory concentrations of the peptide are dramatically reduced (Holst et al. 1983). Furthermore, prandial and postprandial increases in circulatory GLP-1 are almost abolished in obese patients (Naslund et al. 1998). Despite this, IV infusion of the peptide decreases the size of subsequent meals (Fig. 14.3). In these individuals, this compromised secretion is thought to be controlled by body weight. As such, when an obese individual is nearing normal body weight, GLP-1 secretion markedly increases (Verdich et al. 2001). Due to the fact that postprandial circulating levels of GLP-1 are partially restored during periods of weight loss, body weight may regulate L-cell sensitivity. The mechanism for this phenomenon is not clear; however, two hypotheses have been put forward that are not mutually exclusive. First, it is possible that loss of bodyweight restores sensitivity to luminal nutrients. Secondly, obesity is a disease often associated with insulin resistance. Normally, L-cells are responsive to insulin. Thus, loss of bodyweight, which is usually associated with increased insulin sensitivity, may restore GLP-1 secretion as well (Rask et al. 2001). Together, these data suggest that the pathological state of obesity not only correlates, but also results in suppressed secretion of GLP-1 from L-cells.

Similarly, diabetes is associated with impaired secretion and function of GLP-1. Non-insulin-dependent diabetes mellitus (NIDDM), also known as type 2 diabetes, is characterized by reduced insulin sensitivity to normally insulin-responsive tissues (predominantly muscle and adipose tissue) and hyperinsulinemia. In NIDDM, there is a gradual decrease in the mass of insulin-producing B-cells and later stages of the disease are characterized by complete loss of insulin secretion. In these patients, glucagon levels are typically elevated as well. More recently, NIDDM has also been associated with absence of the incretin effect, which may contribute to impaired insulin secretion and increased glucagon levels (Nauck et al. 1986). As a result, in majority of diabetic patients, secretion of GLP-1 is decreased, as is the sensitivity to the peptide at normal physiological levels that potentiates insulin secretion (Rask et al. 2001). At supraphysiological levels, however, diabetic individuals retain some sensitivity to the incretin effects of peptide as seen by normalization of

glucose-induced secretion following GLP-1 infusion (Nauck et al. 1997). Similar to obesity, the impairment in GLP-1 secretion may be secondary to the diabetic state. Data collected from individuals genetically at risk for NIDDM support this hypothesis. First, first-degree relatives of individuals with diabetes and individuals with glucose intolerance have normal secretory profiles of GLP-1 following an oral load or IV infusion of glucose (Nyholm et al. 1999). Furthermore, examination of identical twins discordant for NIDDM reveals that only the diabetic individual has an impaired GLP-1 secretion whereas the healthy twin maintains otherwise normal postprandial peptide secretion (Vaag et al. 1996). Altogether, these data implicate GLP-1 as an important player in this very intricate puzzle characterized by metabolic dysregulation manifested in pathological states such as obesity and diabetes.

14.11 Applications to Other Areas of Health and Disease

The findings that two disease states currently plaguing individuals worldwide may be caused by or result in reduced secretion or sensitivity to GLP-1 gives promise to the use of treatments that directly or indirectly manipulate GLP-1 signaling and alleviate these pathologies. Numerous clinical trials are being performed to evaluate strategies to enhance the understanding of how this peptide may be used to decrease the incidence of obesity and diabetes. For example, one of the primary treatments for diabetes, alpha-glycosidase inhibitors, such as acarbose, markedly reduces proximal intestinal absorption of nutrients, thus, allowing greater exposure of nutrients to the distal intestine leading to increase GLP-1 secretion and normalization of blood glucose levels (Qualmann et al. 1995). Presently, however, the most effective treatment for individuals suffering from both obesity as well as diabetes is surgical intervention. Following operation, gastric bypass patients show complete reversal of diabetic complications and rapidly lose weight. Additionally, GLP-1 levels are markedly elevated due to diversion of nutrients directly from the stomach into resected areas of the distal small intestine and increased L-cell sensitivity due to weight loss (Patti et al. 2005). Because plasma concentrations of the peptide increase, GLP-1 becomes again effective in stimulating insulin secretion in these individuals.
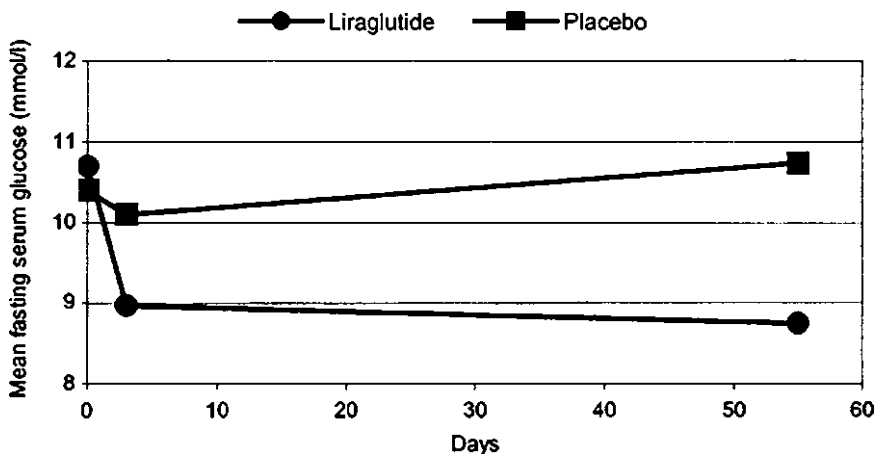
Fig. 14.4 Effect of Liraglutide treatment on fasting serum glucose levels in diabetic patients. Compared to placebo treatment, Liraglutide (0.6 mg/kg) significantly improves impaired fasting serum glucose levels in patients with non-insulin dependent diabetes mellitus (NIDDM) (Reprinted from Harder et al. (2004))
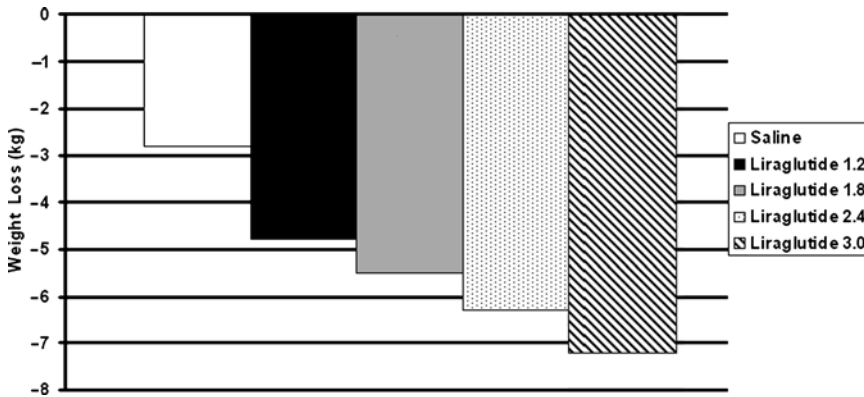
Fig. 14.5 Effect of Liraglutide treatment on body weight loss in obese individuals. Once daily subcutaneous injection of the GLP-1 agonist, Liraglutide, decreases body weight more than placebo control over 20 weeks in obese patients (Adapted from Astrup et al. (2009))

In addition to indirectly manipulating GLP-1 secretion, other treatments focus on utilizing the GLP-1 pathway directly in treating diabetes and obesity. Two main drugs are used as GLP-1R agonists and marketed for diabetic patients: exenatide and liraglutide. They are synthetic analogs of GLP-1 and are relatively resistant to enzymatic degradation by DPP-IV, maintaining prolonged circulatory levels of the peptides between 6 and 12 h post administration (Degn et al. 2004; Kolterman et al. 2005). GLP-1 analogs have been effective either alone or in coordination with other diabetes treatments, effectively normalizing blood glucose and other associated measures (Buse et al. 2009) (Fig. 14.4). In addition, they cause delayed gastric emptying in diabetics with increased gastric emptying rates, allowing for a more sustained delivery of nutrients to the intestine to aid severely fluctuating blood glucose concentrations (Kendall et al. 2006). The same drugs cause a significant reduction in body weight in obese, nondiabetic patients (Astrup et al. 2009) (Fig. 14.5). In addition to GLP-1 analogs, the finding that most GLP-1 is enzymatically degraded rapidly following entry into the portal vein has spurred interest in inhibitors of the DPP-IV enzyme. Clinical trials have shown that DPP-IV inhibitors used as either co- or monotherapeutic agents normalize or decrease plasma blood glucose levels (Deacon and Holst 2006). One problem plaguing this therapeutic strategy, however, is that DPP-IV is ubiquitous and plays a role in important immune-related functions, such as production of cytokines. Thus, the use of DPP-IV inhibitors have resulted in a range of side effects, including elevated blood pressure. Despite this, currently two drugs acting on DPP-IV are used for diabetes treatment. Collectively, these data provide substantial evidence for GLP-1 pathways as an effective target in the treatment of diabetes, and other metabolic diseases characterized by insulin resistance.

Summary Points

- GLP-1 is a member of the proglucagon peptide family. It is a satiation signal released from the enteroendocrine L-cells of the distal gastrointestinal tract
- GLP-1 release is stimulated by a neural-humoral reflex as well as the presence of nutrients in the intestinal lumen.
- GLP-1 exerts a variety of biological functions within the gastrointestinal tract including intestinal motility, gastric emptying, and pancreatic enzymatic secretion.
- GLP-1 is a potentiator of nutrient-induced insulin secretion.

- GLP-1 exerts its physiological actions as well as satiation via GLP-1 receptors.
- GLP-1 reduces food intake via peripheral and central mechanisms of action.
- Peripheral GLP-1 reduces food intake through both endocrine and paracrine pathways while GLP-1 produced in the brain acts on neurons that are synapsed with GLP-1ergic neurons.
- GLP-1 regulates expression and production of centrally produced neuropeptides to reduce food intake.
- GLP-1 interacts with short-term anorexigenic signals and long-term adiposity signals to enhance suppression of food intake and body weight.
- GLP-1 secretion is significantly decreased in pathological states, such as obesity and diabetes. However, a majority of its function is retained in these individuals.
- Currently, GLP-1, and GLP-1Rs are targets in ameliorating metabolic diseases, such as diabetes and obesity, as GLP-1 analog administration normalizes blood glucose and reduces body weight.

Key Definitions

Apical: Portion of cell that faces the lumen of the gastrointestinal (GI) tract.

Basolateral: Portion of the cell that is opposite the apical side of the cell. Typically faces capillaries or maintains connections with the nervous system.

GLP-1: Peptide hormone that is a posttranslational product derived from the proglucagon gene. Major functions include decreasing GI motility, food intake, and potentiating nutrient-induced insulin secretion.

Endocrine: Entry of peptide or hormone into the bloodstream to exert effects on distant tissues

L-cells: Cells of the small intestine and colon that are responsible for secreting GLP-1 and other peptide hormones. The apical portion of the cell senses nutrients while the basolateral portion of the cell is responsible for hormone secretion.

Paracrine: Action of a peptide or hormone on local or nearby cells without entering the circulatory system.

Potentiate: The ability of a molecule to enhance the actions of another molecule.

References

Abbott CR, Monteiro M, et al. Brain Res. 2005;1044:127–31.

Aja S, Ewing C, et al. Peptides. 2006;27:157–64.

Asarian L. Am J Physiol Regul Integr Comp Physiol. 2009;296:R51–6.

Astrup A, Rossner S, et al. Lancet. 2009;374:1606–16.

Bojanowska E, Nowak A. J Physiol Pharmacol. 2007;58:349–60.

Brennan IM, Feltrin KL, et al. Am J Physiol Regul Integr Comp Physiol. 2005;288:R1477–85.

Buse JB, Rosenstock J, et al. Lancet. 2009;374:39–47.

Chu ZL, Carroll C, et al. Endocrinology. 2008;149:2038–47.

Cordier-Bussat M, Bernard C, et al. Diabetes. 1998;47:1038–45.

D'Alessio D, Lu W, et al. Am J Physiol Regul Integr Comp Physiol. 2007;293:R2163–9.

Deacon CF, Holst JJ. Int J Biochem Cell Biol. 2006;38:831–44.

Deacon CF, Pridal L, et al. Am J Physiol. 1996;271:E458–64.

Degn KB, Juhl CB, et al. Diabetes. 2004;53:1187–94.

Dillon JS, Tanizawa Y, et al. Endocrinology. 1993;133:1907–10.

Dube PE, Brubaker PL. Horm Metab Res. 2004;36:755–60.

Flint A, Raben A, et al. J Clin Invest. 1998;101:515–20.

Gutzwiller JP, Goke B, et al. Gut. 1999;44:81–6.
Harder H, Nielsen L, et al. Diabetes Care. 2004;27:1915–21.
Hayes MR, Skibicka KP, et al. Endocrinology. 2008;149:4059–68.
Hayes MR, Bradley L, et al. Endocrinology. 2009;150:2654–9.
Holst JJ. Horm Metab Res. 2004;36:747–54.
Holst JJ, Orskov C, et al. FEBS Lett. 1987;211:169–74.
Holst JJ, Schwartz TW, et al. Int J Obes. 1983;7:529–38.
Imeryuz N, Yegen BC, et al. Am J Physiol. 1997;273:G920–7.
Kendall DM, Kim D, et al. Diabetes Technol Ther. 2006;8:385–96.
Kinzig KP, D'Alessio DA, et al. J Neurosci. 2002;22:10470–6.
Kolterman OG, Kim DD, et al. Am J Health Syst Pharm. 2005;62:173–81.
Kreymann B, Williams G, et al. Lancet. 1987;2:1300–4.
Larsen PJ, Fledelius C, et al. Diabetes. 2001;50:2530–9.
Layer P, Holst JJ, et al. Dig Dis Sci. 1995;40:1074–82.
Little TJ, Doran S, et al. Am J Physiol Endocrinol Metab. 2006;291:E647–55.
Ma X, Bruning J, et al. J Neurosci. 2007;27:7125–9.
Mack CM, Moore CX, et al. Int J Obes (Lond). 2006;30:1332–40.
Mari A, Sallas WM, et al. J Clin Endocrinol Metab. 2005;90:4888–94.
McMahon LR, Wellman PJ. Am J Physiol. 1998;274:R23–9.
Mojsov S, Weir GC, et al. J Clin Invest. 1987;79:616–9.
Nakabayashi H, Nishizawa M, et al. Am J Physiol. 1996;271:E808–13.
Nakagawa A, Satake H, et al. Auton Neurosci. 2004;110:36–43.
Naslund E, Gryback P, et al. Dig Dis Sci. 1998;43:945–52.
Naslund E, Barkeling B, et al. Int J Obes Relat Metab Disord. 1999;23:304–11.
Nauck M, Stockmann F, et al. Diabetologia. 1986;29:46–52.
Nauck MA, Holst JJ, et al. Horm Metab Res. 1997;29:411–6.
Neary NM, Small CJ, et al. Endocrinology. 2005;146:5120–7.
Nowak A, Bojanowska E. J Physiol Pharmacol. 2008;59:501–10.
Nyholm B, Walker M, et al. Diabetologia. 1999;42:1314–23.
Orskov C, Holst JJ, et al. Endocrinology. 1988;123:2009–13.
Orskov C, Rabenhoj L, et al. Diabetes. 1994;43:535–9.
Parker DS, Raufman JP, et al. J Biol Chem. 1984;259:11751–5.
Patti ME, McMahon G, et al. Diabetologia. 2005;48:2236–40.
Qualmann C, Nauck MA, et al. Scand J Gastroenterol. 1995;30:892–6.
Rask E, Olsson T, et al. Diab Care. 2001;24:1640–5.
Roberge JN, Brubaker PL. Endocrinology. 1991;128:3169–74.
Rozengurt E, Sternini C. Curr Opin Pharmacol. 2007;7:557–62.
Ruttimann EB, Arnold M, et al. Endocrinology. 2009;150:1174–81.
Sanz C, Vazquez P, et al. Metabolism. 2008;57:40–8.
Schick RR, Zimmermann JP, et al. Am J Physiol Regul Integr Comp Physiol. 2003;284:R1427–35.
Schirra J, Houck P, et al. Gut. 2000;46:622–31.
Schirra J, Nicolaus M, et al. Gut. 2006;55:243–51.
Schjoldager BT, Mortensen PE, et al. Dig Dis Sci. 1989;34:703–8.
Scrocchi LA, Brown TJ, et al. Nat Med. 1996;2:1254–8.
Seo S, Ju S, et al. Endocr J. 2008;55:867–74.
Talsania T, Anini Y, et al. Endocrinology. 2005;146:3748–56.
Tang-Christensen M, Vrang N, et al. Int J Obes Relat Metab Disord. 2001;25 Suppl 5:S42–7.
Tang-Christensen M, Larsen PJ, et al. Nat Med. 2000;6:802–7.
Theodorakis MJ, Carlson O, et al. Am J Physiol Endocrinol Metab. 2006;290:E550–9.
Thorens B, Wu YJ, et al. J Clin Invest. 1992;90:77–85.
Tolessa T, Gutniak M, et al. J Clin Invest. 1998;102:764–74.
Tolhurst G, Reimann F, et al. J Physiol. 2009;587:27–32.
Turton MD, O'Shea D, et al. Nature. 1996;379:69–72.
Vaag AA, Holst JJ, et al. Eur J Endocrinol. 1996;135:425–32.
Verdich C, Toubro S, et al. Int J Obes Relat Metab Disord. 2001a;25:1206–14.
Verdich C, Flint A, et al. J Clin Endocrinol Metab. 2001b;86:4382–9.
Williams DL, Baskin DG, et al. Endocrinology. 2009;150:1680–7.

Chapter 15
The Role of PYY in Eating Behavior and Diet

Jennifer L. Scheid and Mary Jane De Souza

Abbreviations

AgRP	Agouti-related protein
BMI	Body mass index
CART	Cocaine- and amphetamine-regulate
DPP-IV	Dipeptidly peptidease IV
FHA	Function hypothalamic amenorrhea
NPY	Neuropeptide Y
PYY	Peptide PYY
POMC	Pro-opiomelanocortin

15.1 Introduction

Food intake and eating behavior are controlled by many gastrointestinal hormones that are secreted from the gut region including the stomach and the intestine. These hormones have unique roles in the digestive process, but also interact with the vagus nerve and/or can cross the blood brain barrier and act as signals to the brain to initiate hunger. Gut hormones, such as peptide YY (PYY), control food intake by signaling satiety to the brain, and since PYY can control food intake, this hormone has a pivotal role in eating behavior and may also play a role in the clinical consequences of over or under eating as observed in clinical models of obesity and anorexia nervosa (Table 15.1).

M.J. De Souza (✉)
Women's Health and Exercise Laboratory, Noll Laboratory, Department of Kinesiology, Penn State University, University Park, PA 16802, USA
e-mail: mjd34@psu.edu

Table 15.1 Key features of PYY

1. The primary function of PYY is to act as satiety signal and control food intake.
2. PYY is secreted in response to food intake.
3. PYY is secreted from the endocrine L cells of the intestine.
4. PYY concentrations are elevated in women with anorexia nervosa.
5. PYY concentrations are elevated in women with functional hypothalamic amenorrhea.
6. PYY concentrations are suppressed in obese patients.

This table lists the key facts of Peptide YY (PYY) including basic physiology of PYY and the specific populations that have altered concentrations of PYY

15.2 General Physiology of PYY

15.2.1 Secretion and Meal Responses

PYY is a gastrointestinal peptide secreted from the endocrine L cells of the intestine in response to food intake (Batterham et al. 2003; Huda et al. 2006; Adrian et al. 1985; Kim et al. 2005). The two forms of circulating PYY are PYY_{1-36} and PYY_{3-36}. PYY_{3-36} is the major form of circulating PYY after a meal, while PYY_{1-36} is the main form of circulating PYY during a fasted state (Grandt et al. 1994). An enzyme, dipeptidyl peptidase IV (DPP-IV) is an important regulator of the expression of PYY_{3-36}; PYY_{1-36} is released from the L cell in the lumen of the intestine and then DPP-IV removes tyrosine-proline (Ballantyne 2006) from PYY_{1-36} to create the active form of PYY, PYY_{3-36} (Grandt et al. 1992). PYY_{3-36} is highly selective for the Y2 receptor and acts as an agonist for the Y2 receptor (Grandt et al. 1992). PYY, once released peripherally, can cross the blood brain barrier and act centrally at the level of the arcuate nucleus in the hypothalamus to contribute to eating behavior. PYY_{3-36} activates the Y2 receptors to inhibit neuropeptide Y (NPY) and agouti-related protein (AgRP), as well as pro-opiomelanocortin (POMC) and cocaine- and amphetamine-regulate (CART), also in the arcuate nucleus, to decrease food intake (Batterham et al. 2003). The ability of PYY_{3-36} to bind to the Y2 receptor indicates the key pivotal role of this peptide in body weight regulation. Hypothalamic Y2 receptors are involved in both food intake and body weight regulation at the level of the hypothalamus (Sainsbury et al. 2002).

Circulating PYY is an anorexigenic hormone involved in short-term energy homeostasis, i.e., PYY signals satiety following food intake. PYY concentrations rise in response to a caloric load after a meal (Huda et al. 2006; Korner et al. 2005; Kim et al. 2005) and stay elevated for several hours (Adrian et al. 1985). PYY starts to rise a few minutes after the calories are ingested and peak PYY concentrations occur 30 min after caloric intake (Degen et al. 2005) (Fig. 15.1). After a meal, PYY is elevated, while after short-term fasting (2–3 days), total PYY concentrations are suppressed 40–60% below baseline in lean men and women (Chan et al. 2006). Peak PYY concentrations are achieved in proportion to the amount of calories ingested (Huda et al. 2006; Degen et al. 2005). While PYY is a short-term satiety signal involved in the regulation of caloric intake following a caloric load and subsequent meals following a caloric load, PYY is also a signal for long-term energy homeostasis, i.e., during conditions such as anorexia nervosa (Misra et al. 2006; Pfluger et al. 2007; Nakahara et al. 2007) and obesity (le Roux et al. 2006; Stock et al. 2005; Batterham et al. 2003).

The rise in plasma PYY concentrations after a meal is also influenced by the macronutrient content of the meal (Batterham et al. 2006). PYY concentrations are released from the intestine in response to specific macronutrients as evidenced by the higher increase in PYY following high- versus normal-protein meals (Batterham et al. 2006). Lipids also modulate the release of PYY from the
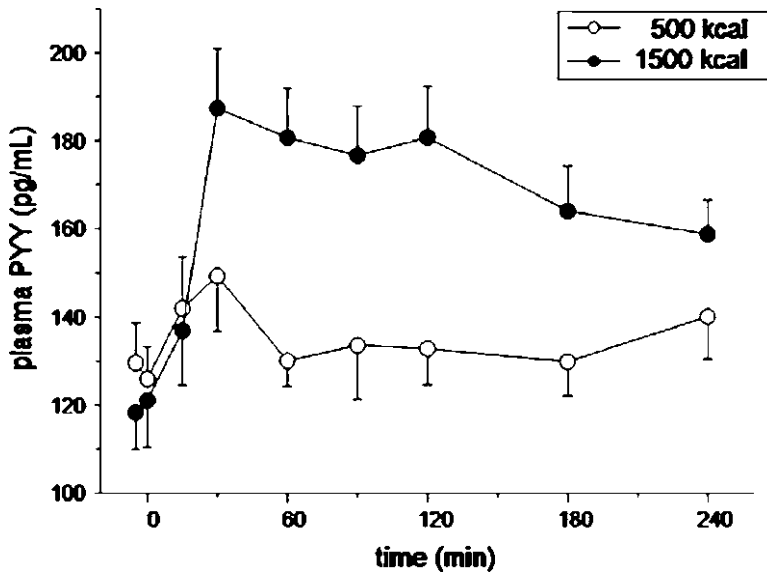
Fig. 15.1 Total PYY concentrations following a small meal and a large meal. Total plasma PYY ($PYY_{3-36} + PYY_{1-36}$) concentrations achieved during two meals with different caloric contents. The larger meal (1,500 kcal) induced a greater total PYY response compared to the smaller meal (500 kcal). Results are expressed as mean ± SEM, $n = 12$ (Reprinted from Degen et al. (2005). With permission)

intestine (Lin and Chey 2003; Feinle-Bisset et al. 2005). In normal-weight subjects, a high-protein (65% protein, 17% fat, and 17% carbohydrate) meal elicted the greatest increase in total PYY and PYY_{3-36} compared to high-fat (17% protein, 66% fat, and 17% carbohydrate) and high-carbohydrate (17% protein, 18% fat, and 65% carbohydrate) meals, while the high-fat meal still had a greater increase in total PYY and PYY_{3-36} compared to the high-carbohydrate meal (Fig. 15.2) (Batterham et al. 2006).

Pharmacological administration of PYY_{3-36} supports a role for PYY in altering eating behavior in both animal (Chelikani et al. 2005) and human models (Sloth et al. 2007; Batterham et al. 2003; Degen et al. 2005; le Roux et al. 2006; Batterham et al. 2002). Peripherally administered PYY_{3-36} has been shown to decrease appetite and 24-h food intake by 33% in humans (Batterham et al. 2002) (Fig. 15.3). In another study, PYY_{3-36} infusion in both lean and obese individuals decreased caloric intake by 30% during a buffet meal (Batterham et al. 2003).

15.2.2 Fasting Measures Versus Meal Responses

Baseline PYY concentrations are typically measured following an overnight fast. Two to three days of fasting will suppress total PYY 40–60% below baseline concentrations (Chan et al. 2006). The meal responses of PYY_{3-36} and total PYY concentrations have been investigated following the intake of a caloric load. Both PYY_{3-36} and total PYY concentrations rise following a caloric load (Degen et al. 2005; Pfluger et al. 2007; Batterham et al. 2003). Total PYY concentration increased 208% compared to fasting concentrations of total PYY following a heavy breakfast of approximately 1,000 kcal, while PYY_{3-36} concentration increased 125% compared to fasting PYY_{3-36} concentration following the same heavy
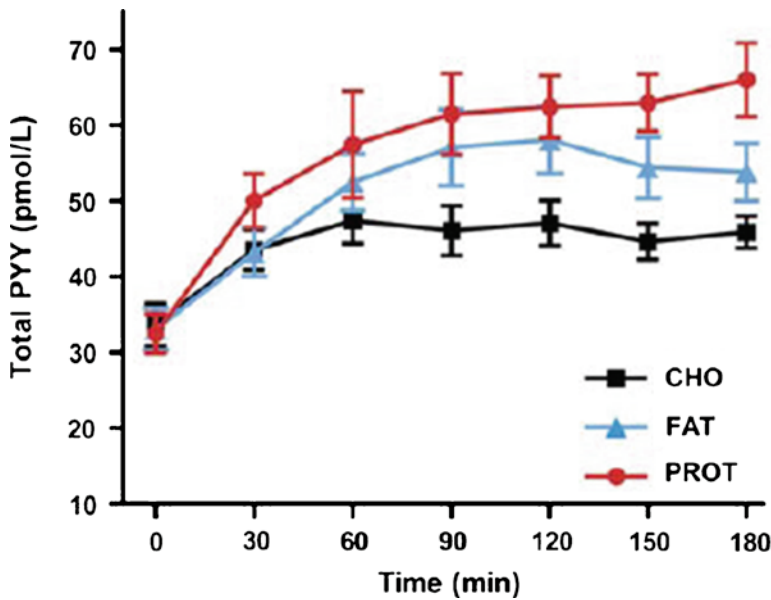
Fig. 15.2 Total PYY concentrations following meals with different macronutrient compositions. Total plasma PYY ($PYY_{3–36}$ + $PYY_{1–36}$) concentrations in normal weight individuals following high-protein (PROT), high-fat (FAT), and high-carbohydrate (CHO) meals. The high-protein meal elicited the greatest increase in total PYY compared to high-fat and high-carbohydrate meals, while the high-fat meal still had a greater increase in total PYY compared to the high-carbohydrate meal. Results are expressed as mean ± SEM, $n = 10$ (Reprinted from Batterham et al. (2006). With permission)

Fig. 15.3 The effects of $PYY_{3–36}$ infusion on food intake and appetite. (**a**) Caloric intake during a buffet meal following either saline or $PYY_{3–36}$ infusion. The lines represent individual subject data. (**b**) Caloric intake during the 24 h periods following either saline or $PYY_{3–36}$ infusion. ***$p < 0.0001$ versus saline. Results are expressed as mean ± SEM, $n = 12$. (**c**) Appetite scores expressed as percentage change from baseline following either saline or $PYY_{3–36}$ infusion. *$p < 0.05$ versus saline, **$p < 0.01$ versus saline. Results are expressed as mean ± SEM, $n = 12$ (Reprinted from Batterham et al. (2002). With permission)
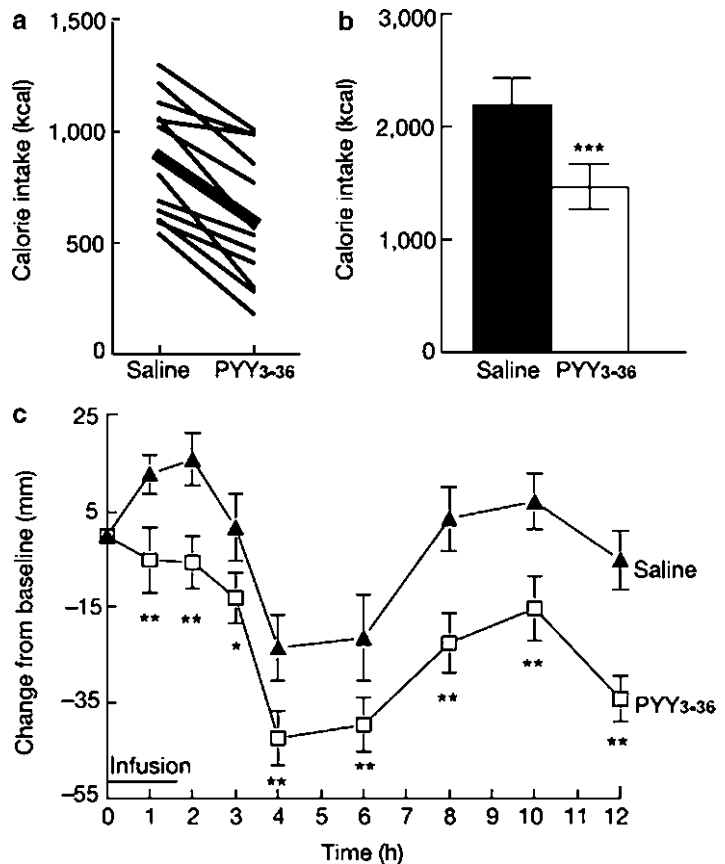
breakfast (Pfluger et al. 2007). The rise in PYY concentrations compared to fasting is clearly related to the amount of calories ingested; total PYY concentrations were measured following a light lunch of 500 kcal and a heavy lunch of 1,500 kcal and, although total PYY increased significantly compared to fasting concentrations of PYY following the light lunch, the increase in PYY was small compared to the increase in total PYY concentrations following a heavy lunch of 1,500 kcal (Degen et al. 2005) (Fig. 15.1).

15.2.3 Assays and Measurement Concerns

Total PYY and PYY_{3-36} concentrations can be measured in plasma. When measuring total PYY, an antibody is used that recognizes both PYY_{1-36} and PYY_{3-36}. For research purposes, scientists are also interested in measuring PYY_{3-36} because of the peptide's direct ability to activate the Y2 receptor and influence food intake and eating behavior. When measuring PYY_{3-36}, an antibody is used that only has cross-reactivity for the active form of PYY, PYY_{3-36}. When measuring PYY_{3-36}, a DPP-IV inhibitor needs to be used to stop DPP-IV from cleaving PYY_{1-36} into PYY_{3-36}. The addition of the DPP-IV inhibitor needs to occur immediately after the blood is drawn for the most accurate results. The effects of long-term storage on total PYY and PYY_{3-36} concentrations are unknown; however, if total PYY breaks down during long-term storage of samples, then the relative concentrations of PYY_{1-36} and PYY_{3-36} would likely be compromised.

15.3 Clinical Populations: PYY and Anorexia Nervosa

15.3.1 Fasting PYY in Anorexia Nervosa and Functional Hypothalamic Amenorrhea

Anorexia nervosa is related to the cognitive suppression of food intake, i.e., starvation and undernutrition, that leads to a chronic energy deficiency (De Souza and Metzger 1991). Interestingly, the etiology of exercise-associated functional hypothalamic amenorrhea (FHA) is also related to energy deficiency and in these women and in women with anorexia nervosa the energy deficiency involves a decrease in resting energy expenditure, and suppression of triiodothyronine, insulin-like growth factor-1 and leptin concentrations and elevated ghrelin and cortisol concentrations (De Souza et al. 2007b; De Souza and Williams 2004). Evidence is accumulating that fasting and post-prandial PYY concentrations are chronically elevated in populations of energy-deficient women, including women with anorexia nervosa and FHA (Misra et al. 2006; Pfluger et al. 2007; Nakahara et al. 2007; Scheid et al. 2009; Russell et al. 2009). Patients with anorexia nervosa, i.e., a population exhibiting chronic energy deficiency, have consistently been observed to exhibit elevated fasting PYY concentrations (Misra et al. 2006; Pfluger et al. 2007; Nakahara et al. 2007). Exercising women with FHA, secondary to an energy deficit, also demonstrate elevations in fasting PYY concentrations (Scheid et al. 2009; Russell et al. 2009).

15.3.2 PYY Meal Responses in Anorexia Nervosa

Investigators have consistently observed that women with anorexia nervosa have an elevated total PYY and PYY_{3-36} in response to a meal (Nakahara et al. 2007; Otto et al. 2007). Nakahara et al. (2007) have shown that PYY_{3-36} concentrations are elevated at baseline and following intake of a 400 kcal standard

meal (20% protein, 22% fat, and 58% carbohydrate) in women with anorexia nervosa compared to normal weight controls (Fig. 15.4). Since PYY is an anorexigenic hormone, elevated PYY may play a role in reduced food intake in both women with anorexia nervosa and exercising women with FHA, such that circulating elevated PYY may cause a decrease in hunger and total caloric intake and may contribute to the energy deficiency in these populations of women.

15.3.3 PYY Responses to Weight Gain in Anorexia Nervosa

Although PYY_{3-36} concentrations are elevated in women with anorexia nervosa, weight gain in women with anorexia nervosa after treatment for the disease causes decreases fasting and postprandial PYY_{3-36} concentrations compared to before treatment, but this weight gain in women with anorexia nervosa following treatment does not normalize fasting or postprandial PYY_{3-36} concentrations compared to healthy controls (Nakahara et al. 2007) (Fig. 15.4).

Notably, elevated PYY concentrations have been hypothesized to be more than just a marker of energy deficiency but rather may play an important role in modulating eating behavior in women with anorexia nervosa. Misra et al. (2006), who observed elevated PYY concentrations in a population of adolescent girls with anorexia nervosa, suggested that elevated PYY may be involved in the pathogenesis of anorexia nervosa by way of reducing food intake. PYY is an anorexigenic hormone
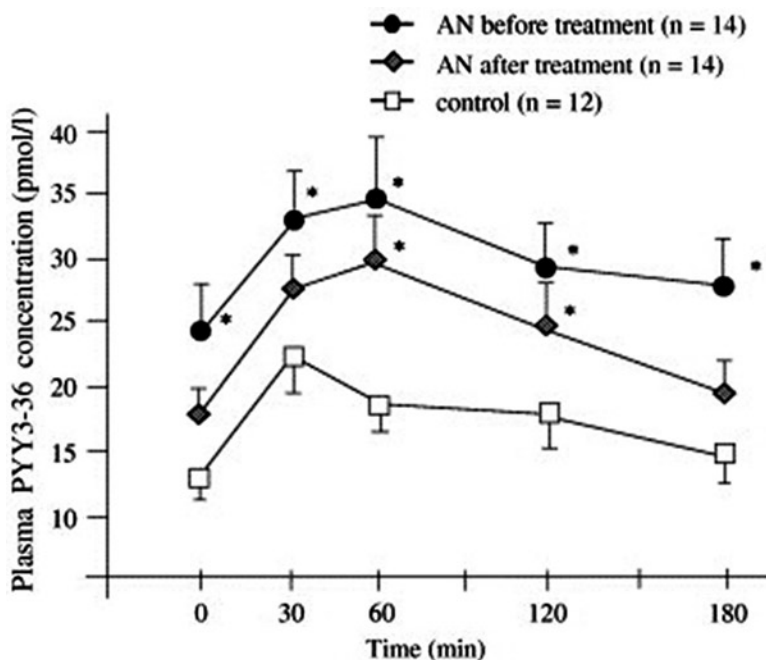
Fig. 15.4 PYY_{3-36} concentrations following a meal in women with anorexia nervosa before treatment and after treatment. Plasma PYY_{3-36} concentrations in women with anorexia nervosa before treatment following intake of a standard meal compared to controls. After treatment, women with anorexia nervosa decrease their PYY concentrations after a meal, but women with anorexia nervosa after treatment still have elevated circulating plasma PYY_{3-36} concentrations after a standard meal compared to controls. *$p < 0.05$ versus controls. Results are expressed as mean ± SEM, $n = 40$ (Reprinted from Nakahara et al. (2007). With permission)
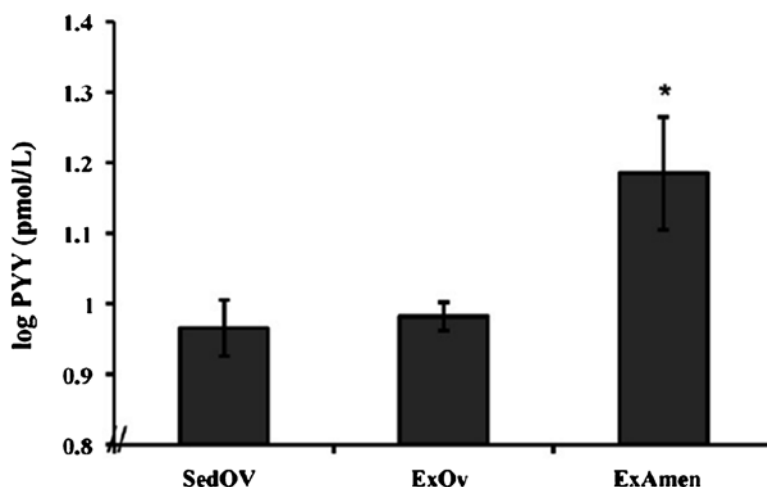
Fig. 15.5 Fasting total PYY concentrations in exercising women with functional hypothalamic amenorrhea. Fasting total PYY concentrations in women who are sedentary and have ovulatory menstrual cycles (SedOv) and exercising women, who have ovulatory menstrual cycles (ExOv), compared to exercising women with amenorrhea (ExAmen). ExAmen women had higher fasting total PYY compared to SedOv and ExOv women. *$p<0.05$ SedOv and ExOv. Results are expressed as mean±SEM, $n=48$ (Reprinted from Scheid et al. (2009). With permission)

and elevated PYY reduces food intake in lean individuals (Batterham et al. 2003). Exercising women with FHA are also an undernourished clinical population in an energy deficit. Similar to women with anorexia nervosa, exercising women with FHA demonstrate elevations in fasting PYY concentrations (Scheid et al. 2009; Russell et al. 2009) (Fig. 15.5). This finding suggests that elevated PYY may cause a decrease in relative caloric intake and may compound the psychological struggle in women attempting to recover from anorexia nervosa and consume food for the purpose of weight gain. Thus, in general, elevated PYY in women with anorexia nervosa and exercising women with FHA may contribute to energy deficiency by way of causing a compensatory decrease in food intake and may represent a component of the underlying mechanism involved in suppressed food intake in these women.

15.3.4 PYY and Eating Behaviors in Anorexia Nervosa and FHA

PYY may play a role in modulating eating behaviors and suppressing food intake by interfacing with other gastrointerestinal peptides at the level of the hypothalamus. Interestingly, ghrelin concentrations are also elevated in women with anorexia nervosa (Germain et al. 2007; Nakahara et al. 2007; Monteleone et al. 2008; Germain et al. 2009; Harada et al. 2008) and in exercising women with FHA (Scheid et al. 2009; De Souza et al. 2004, 2007b). Elevated ghrelin concentrations in energy-deficient populations, such as women with anorexia nervosa or FHA are, in part, the body's attempt to increase food intake; and an increase in food intake would then, presumably, help to reverse energy deficiency. Ghrelin is an orexigenic hormone and infusions during a buffet meal are associated with an increase in food intake (Wren et al. 2001). Elevated PYY in the presence of elevated ghrelin may cause a relative ghrelin resistance in women with anorexia nervosa (Misra et al. 2006), i.e., in spite of chronically elevated ghrelin there is no compensatory increase in food intake. Ghrelin resistance may represent the

underlying mechanism explaining why undernourished women with elevated ghrelin concentrations are not increasing food intake. Interestingly, PYY has been shown to inhibit ghrelin neurons (Riediger et al. 2004) and may represent a physiological mechanism explaining ghrelin resistance. Women with elevated PYY concentrations such as women with anorexia nervosa consistently express behaviors including restricting food intake even in the presence of elevated physiological signals, like ghrelin, to increase food intake. Elevated PYY may be disrupting food intake signals in the uncoupled relationship between elevated ghrelin and food intake in women with anorexia nervosa.

Although there is no direct evidence to date to demonstrate that PYY is involved in the etiology of anorexia or exercise-associated FHA, Scheid et al. (2009) found an association between fasting PYY concentrations and drive for thinness. High drive for thinness includes disordered eating behaviors that encompass a fear of gaining weight and a preoccupation with body weight and body shape (Cobb et al. 2003; Otis et al. 1997). High drive for thinness has been physiologically linked to an energy deficiency in exercising women (De Souza et al. 2007a), and it is therefore not surprising that PYY is also associated with a high drive for thinness. However, if PYY is indeed a physiological signal that is suppressing food intake, this signal may be compounding disordered eating behaviors in women with anorexia and exercising women with FHA.

15.4 Clinical Populations: PYY and Obesity

15.4.1 Fasting PYY in Obesity

PYY concentrations are suppressed in some (Batterham et al. 2003; le Roux et al. 2006; Roth et al. 2005; Alvarez Bartolome et al. 2002), but not all studies of (Pfluger et al. 2007) obese patients, a population exhibiting a long-term positive energy imbalance. Fasting PYY is negatively correlated with body mass index (BMI) demonstrating that individuals with suppressed fasting PYY concentrations have elevated BMIs and may be overweight/obese (Guo et al. 2006). Suppressed PYY in obesity may play a role in increased food intake in this population given PYY's important role in promoting satiety. Indeed, Batterham et al. (2003) suggest that suppressed PYY concentrations may be involved in the pathogenesis of obesity, suggesting that obese individuals may be predisposed to low circulating PYY concentrations, leading to an increase in food intake and weight gain.

15.4.2 PYY Meal Responses in Obesity

Obese patients demonstrate an attenuated total PYY response to a caloric load (le Roux et al. 2006; Stock et al. 2005; Batterham et al. 2003). Total circulating PYY concentrations are consistently suppressed in obese individuals compared to lean individuals prior to, during, and following a buffet lunch (Fig. 15.6). The attenuated PYY response to a caloric load during obesity leads to an increase in food intake and is one of the factors that make weight control difficult in obese populations (Batterham et al. 2003). le Roux et al. (2006) investigated the meal response in both obese and lean subjects and found that the obese group had a consistently attenuated PYY response during a 1,000 kcal liquid meal and also during a liquid meal that totaled almost 3,000 kcal. They found that the obese group needed to consume almost double the caloric load to achieve the same PYY concentration as the lean group, potentially demonstrating that an attenuated PYY response to a caloric load may lead to overeating and weight gain in obese individuals.
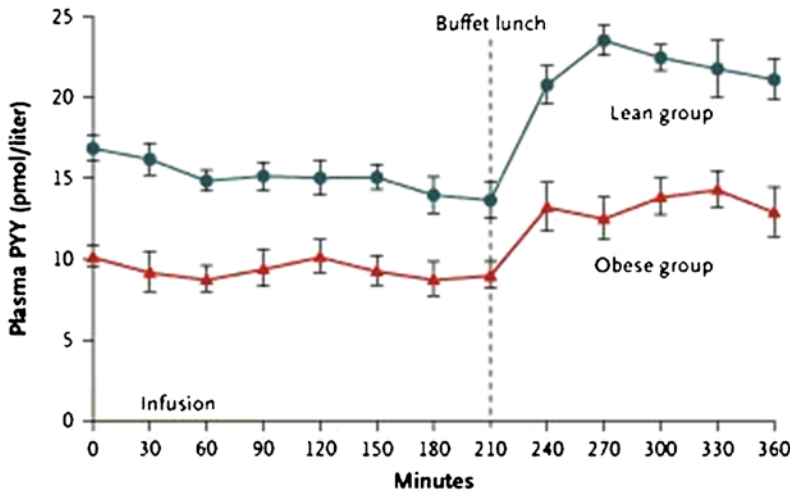
Fig. 15.6 Total PYY concentrations following a meal in obese and lean individuals. Total circulating PYY concentrations in an obese group (*triangles*) compared to a lean group (*circles*) during infusion of saline and after a buffet lunch. Total circulating PYY concentrations are consistently suppressed in the obese group compared to the lean group during infusion of saline and after a buffet lunch. Results are expressed as mean ± SEM, $n = 24$ (Reprinted from Batterham et al. (2003). With permission)

15.4.3 PYY Responses to Weight Loss in Obesity

Prospective studies that utilize weight loss interventions to create an energy deficit offer valuable insights into the role of PYY in long-term energy homeostasis, but results have been inconsistent and thus difficult to interpret. Consistent with the concept that fasting PYY concentrations are elevated in situations following long-term energy deficiency, fasting PYY concentrations are elevated in obese children after weight loss (Roth et al. 2005) and adolescents (Jones et al. 2009) after exercise training. Roth et al. (2005) investigated the effects of a 1-year outpatient program that included exercise, nutrition education, and individual counseling on fasting total PYY concentrations in obese children. Roth and colleagues demonstrated that in the quartile of children with the greatest BMI reduction the greatest percentage increase in total PYY concentrations was observed. Jones et al. (Jones et al. 2009) investigated the effects of a 32-week exercise training program on PYY concentrations in obese adolescents and demonstrated that total PYY concentrations were increased following the training compared to baseline PYY concentrations, indicating that exercise training in the absence of weight loss may affect circulating PYY concentrations, however the mechanism behind this increase in PYY is unknown.

Unfortunately, the weight loss literature regarding PYY is very inconsistent and while obese children who lose weight have an increase in circulating PYY concentrations (Roth et al. 2005), other studies in obese adults have reported that PYY concentrations decrease after weight loss (Pfluger et al. 2007; Lien et al. 2009), indicating that PYY concentrations may be regulated differently in adults and children. The inconsistencies in the literature regarding PYY concentrations following weight loss may also be due to the notion that some obese individuals may be predisposed to low circulating PYY concentrations (Batterham et al. 2003), meaning that they already have low PYY concentrations and that these low PYY concentrations may respond differently to weight loss.

An additional complication in the weight loss literature is that fasting PYY concentrations may not be sensitive to smaller changes in weight, particularly in normal weight populations. For example, in

our laboratory (Leidy et al. 2004; Scheid et al. 2010 unpublished) we implemented a well-controlled and intensive 3-month exercise and diet intervention that produced weight loss (2–4 kg) in normal weight women 18–30 years old. The weight loss produced was associated with changes in energy balance evident by elevated ghrelin concentrations and suppressed resting metabolic rate (Leidy et al. 2004). However, we (Scheid et al. 2010 unpublished) observed that total PYY concentrations were not altered by diet and exercise-induced weight loss in these women. Future research will need to investigate the relationship of weight loss and initial PYY concentrations and if changes in PYY concentrations following weight loss impact eating behavior and weight maintenance.

15.4.4 PYY Infusion Studies in Obesity

Since PYY is a peripherally circulating hormone that signals satiety, pharmacological administration of PYY has reportedly been referred to as having a potential application as a weight loss drug. Pharmacological administration of PYY_{3-36} has been shown to decrease food intake in both animal (Chelikani et al. 2005) and human models (Sloth et al. 2007; Batterham et al. 2003; Degen et al. 2005; le Roux et al. 2006; Batterham et al. 2002). Peripherally administered PYY_{3-36} has been shown to decrease appetite and 24-h food intake by 33% in humans (Batterham et al. 2002) (Fig. 15.3). Batterham et al. (2003) investigated the effects of PYY_{3-36} infusion in both lean and obese individuals and found that PYY infusion decreased caloric intake by approximately 30% in both the lean and obese individuals during a buffet meal. The authors suggest that these data indicate that obese subjects may in fact not be PYY resistant, but rather that they may simply be PYY deficient. These studies also suggest that the administration of PYY_{3-36} may be a future weight loss aid by potentially decreasing caloric intake during meals (Batterham et al. 2003).

15.4.5 PYY and Eating Behaviors in Obesity

Suppressed PYY in obesity may play a role in increased food intake in this population given PYY's important role in promoting satiety. Indeed, fasting total PYY concentrations are suppressed in obese patients, and of greater concern, obese patients demonstrate an attenuated total PYY response to a caloric load (le Roux et al. 2006; Stock et al. 2005; Batterham et al. 2003). Since obese individuals have an attenuated response during food intake, obese individuals likely do not experience the same satiety signals as lean individuals. Obese individuals may need to consume almost double the caloric load to achieve the same PYY concentration associated satiety as the lean group (le Roux et al. 2006). Suppressed PYY may therefore represent a physiological factor that leads to increased food intake in obese individuals and may make weight loss difficult for these people.

Macronutrient meal composition can also affect PYY_{3-36} secretion in obese populations and lead to alterations in food intake. The rise in plasma PYY_{3-36} concentrations after a meal is influenced by the macronutrient content of the meal; however the PYY_{3-36} response to macronutrients differs between lean and obese individuals. A high-protein meal is associated with the greatest increase in total PYY and PYY_{3-36} compared to high-fat and high-carbohydrate meals in both lean and obese individuals (Batterham et al. 2006). On the other hand, a high-fat meal is associated

with a greater increase in total PYY and PYY$_{3-36}$ compared to a high-carbohydrate meal only in the lean group, suggesting that a high-protein diet would be beneficial for obese individuals, potentially increase satiety, and may assist with weight control or weight loss (Batterham et al. 2006). Misra et al. (2009) fed obese and lean adolescent girls high-fat, high-carbohydrate, and high-protein meals and measured the % change in PYY$_{3-36}$ and active ghrelin concentrations. The investigators reported suppressed PYY$_{3-36}$ concentrations in the obese girls after the high-fat meal, but no difference between the lean girls after the high-carbohydrate and high-protein meals. Interestingly, food intake following the high-fat meal was increased in the obese girls, suggesting that suppressed PYY$_{3-36}$ concentrations in obese girls' influences subsequent food intake. The findings of Misra and colleagues (Misra et al. 2009) further indicated that a high carbohydrate meal caused an increase in ghrelin concentrations in obese girls also leading to an increase in food intake and that high-protein meals did not alter PYY$_{3-36}$ secretion or ghrelin secretion in the obese girls and did not increase food intake compared to the controls. These findings suggest that macronutrient composition of meals such as high-protein meals could increase satiety in obese populations and contribute to weight control.

15.4.6   PYY and Genetic Obesity

While elevated PYY has been suggested to play a role in the pathogenesis of anorexia nervosa, Batterham et al. (2003) suggest that suppressed PYY concentrations may be involved in the pathogenesis of obesity. Boey et al. (2006) investigated the relationship between suppressed total PYY and a genetic predisposition toward obesity and diabetes and suggested that suppressed fasting PYY concentrations may indeed indicate a genetic predisposition that is associated with obesity and type 2 diabetes. Suppressed fasting PYY concentrations are also observed in females with first-degree relatives who have type 2 diabetes (Boey et al. 2006) further supporting the idea that obesity may be linked to a PYY deficiency.

15.5   Applications to Other Areas of Health and Disease

15.5.1   PYY and Reproduction Suppression

Women with anorexia and FHA both experience suppressed reproductive function and elevated PYY concentrations (Misra et al. 2006; Russell et al. 2009; Scheid et al. 2009). Many metabolic and gastrointestinal hormones are hypothesized to cross the blood brain barrier and interact with NPY in the arcuate nucleus and POMC in the paraventricular nucleus to effect the hypothalamic-pituitary-ovarian axis as well as appetite (Budak et al. 2006). There is evidence that PYY may be directly participating in the downregulation of reproductive function. Animal models in Syrian hamsters have shown that infusions of PYY inhibit estrous (Keene et al. 2003). Human studies have shown that the human placenta contains PYY (Xiao et al. 1998). There is a plausible role for PYY to be one of the metabolic and gastrointestinal hormones involved in the suppression of reproductive function. More research is needed to explore the extent of PYY's role in modulating female reproductive function.

15.5.2 PYY and Suppressed Bone Health

Women with anorexia and FHA both demonstrate a decrease in bone mineral density (Cobb et al. 2003; Utz et al. 2008; De Souza et al. 2008; Drinkwater et al. 1984; Salisbury and Mitchell 1991). Women with amenorrhea experience increased bone resorption related to estrogen deficiency and a decrease in bone formation related to an energy deficiency (De Souza et al. 2008). Elevated PYY is associated with suppressed bone mineral density (Utz et al. 2008; Misra et al. 2007) and suppressed markers of bone formation (Misra et al. 2006). An elevation in PYY associated with an energy deficiency may be directly participating in a central mechanism to suppress bone formation and decrease bone mineral density in energy-deficient populations. Utz et al. (2008) investigated women with anorexia nervosa and found a negative correlation between mean PYY concentrations (samples over 12 h) and bone mineral density. A plausible mechanism explaining the relationship between elevated PYY concentrations and a decrease in bone mineral density comes from the animal literature. Y2 deficient mice have shown that hypothalamic Y2 receptors regulate bone formation and suppression in Y2 receptor activation increases bone volume (Baldock et al. 2002). PYY_{3-36} activates the hypothalamic Y2 receptor and downregulates NPY release and through this central mechanisms related to a downregulation of NPY, PYY appears to be decreasing bone mineral density (Utz et al. 2008).

15.6 Conclusions

PYY is a satiety hormone involved in short-term food intake highlighted by the rise in PYY_{3-36} following a meal, as well as pharmacological administration of PYY_{3-36} causing a decrease in caloric intake. PYY concentrations are altered in conditions reflecting long-term disturbances in energy homeostasis such as anorexia nervosa and obesity. Elevated PYY may be involved in the pathogenesis of anorexia nervosa and elevated PYY concentrations may play a role in preventing compensatory increases in food intake, while suppressed PYY concentrations may be involved in the pathogenesis of obesity and may play a role in preventing weight control.

Summary Points

- Peptide YY (PYY) is a gastrointestinal peptide secreted from the endocrine L cells of the intestine in response to food intake.
- PYY_{3-36} is the major form of circulating PYY after a meal.
- PYY_{3-36}'s ability to bind to the Y2 receptor indicates the key pivotal role of this peptide in body weight regulation.
- Peak PYY concentrations are achieved in proportion to the amount of calories ingested.
- Peripherally administered PYY_{3-36} has been shown to decrease appetite.
- Fasting and post-prandial PYY concentrations are chronically elevated in women with anorexia nervosa.
- Fasting PYY concentrations are elevated in exercising women with functional hypothalamic amenorrhea (FHA).
- Elevated PYY in the presence of elevated ghrelin may cause a relative ghrelin resistance in women with anorexia nervosa or FHA.
- Fasting PYY concentrations are suppressed in most studies of obese patients.

- PYY concentrations are consistently suppressed in obese individuals compared to lean individuals after a meal.
- A high-protein diet would be beneficial for obese individuals, potentially increase satiety, and assist with weight control or weight loss.

Key Terms

Anorexia nervosa: A psychological disorder that leads to a chronic suppression of food intake and severe undernutrition.

Body Mass Index (BMI): An estimate of body composition by using the formula, body mass/height.

Dipeptidyl peptidase IV (DPP-IV): An enzyme that removes tyrosine-proline from PYY_{1-36} to create the active from of PYY, PYY_{3-36}.

Function hypothalamic amenorrhea: No menses for more than 90 days, caused by a decrease in the hypothalamic hormone regulating reproduction, gonadotrophin-releasing hormone.

Ghrelin: A gastrointestinal, orexigenic hormone, secreted from the stomach that causes an increase in food intake.

Peptide YY: A gastrointestinal, anorexigenic hormone, secreted from the intestine in response to food intake.

Postprandial: A term used for "after a meal."

References

Adrian TE, Ferri GL, Bacarese-Hamilton AJ, Fuessl HS, Polak JM, Bloom SR. Gastroenterology. 1985;89:1070–7.

Alvarez Bartolome M, Borque M, Martinez-Sarmiento J, Aparicio E, Hernandez C, Cabrerizo L, et al. Obes Surg. 2002;12:324–7.

Baldock PA, Sainsbury A, Couzens M, Enriquez RF, Thomas GP, Gardiner EM, et al. J Clin Invest. 2002;109:915–21.

Ballantyne GH. Obes Surg. 2006;16:651–8.

Batterham RL, Cowley MA, Small CJ, Herzog H, Cohen MA, Dakin CL, et al. Nature. 2002;418:650–4.

Batterham RL, Cohen MA, Ellis SM, Le Roux CW, Withers DJ, Frost GS, et al. N Engl J Med. 2003;349:941–8.

Batterham RL, Heffron H, Kapoor S, Chivers JE, Chandarana K, Herzog H, et al. Cell Metab. 2006;4:223–33.

Boey D, Heilbronn L, Sainsbury A, Laybutt R, Kriketos A, Herzog H, et al. Neuropeptides. 2006;40:317–24.

Budak E, Fernandez Sanchez M, Bellver J, Cervero A, Simon C, Pellicer A. Fertil Steril. 2006;85:1563–81.

Chan JL, Stoyneva V, Kelesidis T, Raciti P, Mantzoros CS. Diabetologia. 2006;49:169–73.

Chelikani PK, Haver AC, Reidelberger RD. Endocrinology. 2005;146:879–88.

Cobb KL, Bachrach LK, Greendale G, Marcus R, Neer R, Nieves J, et al. Med Sci Sports Exerc. 2003;35:711–9.

De Souza MJ, Metzger DA. Med Sci Sports Exerc. 1991;23:995–1007.

De Souza MJ, Williams NI. Hum Reprod Update. 2004;10:433–48.

De Souza MJ, Leidy HJ, O'Donnell E, Lasley B, Williams NI. J Clin Endocrinol Metab. 2004;89:3536–42.

De Souza MJ, Hontscharuk R, Olmsted M, Kerr G, Williams NI. Appetite. 2007a;48:359–67.

De Souza MJ, Lee DK, Vanheest JL, Scheid JL, West SL, Williams NI. Fertil Steril. 2007b;88:971–5.

De Souza MJ, West Sl, Jamal SA, Hawker GA, Gundberg CM, Williams NI. Bone. 2008;43:140–8.

Degen L, Oesch S, Casanova M, Graf S, Ketterer S, Drewe J, et al. Gastroenterology. 2005;129:1430.

Drinkwater BL, Nilson K, Chesnut 3rd CH, Bremner WJ, Shainholtz S, Southworth MB. N Engl J Med. 1984;311:277–81.

Feinle-Bisset C, Patterson M, Ghatei MA, Bloom SR, Horowitz M. Am J Physiol Endocrinol Metab. 2005;289:E948–53.

Germain N, Galusca B, Le Roux CW, Bossu C, Ghatei MA, Lang F, et al. Am J Clin Nutr. 2007;85:967–71.

Germain N, Galusca B, Grouselle D, Frere D, Tolle V, Zizzari P, et al. Psychoneuroendocrinology. 2009;34:413–9.

Grandt D, Teyssen S, Schimiczek M, Reeve Jr JR, Feth F, Rascher W, et al. Biochem Biophys Res Commun. 1992;186:1299–306.

Grandt D, Schimiczek M, Beglinger C, Layer P, Goebell H, Eysselein VE, et al. Regul Pept. 1994;51:151–9.

Guo Y, Ma L, Enriori PJ, Koska J, Franks PW, Brookshire T, et al. Obesity. 2006;14:1562–70.

Harada T, Nakahara T, Yasuhara D, Kojima S, Sagiyama K, Amitani H, et al. Biol Psychiatry. 2008;63:245–7.

Huda MS, Wilding JP, Pinkney JH. Obes Rev. 2006;7:163–82.

Jones TE, Basilio JL, Brophy PM, McCammon MR, Hickner RC. Obesity. 2009;17:1189–95.

Keene AC, Jones JE, Wade GN, Corp ES. Physiol Behav. 2003;78:711–6.

Kim BJ, Carlson OD, Jang HJ, Elahi D, Berry C, Egan JM. J Clin Endocrinol Metab. 2005;90:6665–71.

Korner J, Bessler M, Cirilo LJ, Conwell IM, Daud A, Restuccia NL, et al. J Clin Endocrinol Metab. 2005;90:359–65.

le Roux CW, Batterham RL, Aylwin SJ, Patterson M, Borg CM, Wynne KJ, et al. Endocrinology. 2006;147:3–8.

Leidy HJ, Gardner JK, Frye BR, Snook ML, Schuchert MK, Richard EL, et al. J Clin Endocrinol Metab. 2004;89:2659–64.

Lien LF, Haqq AM, Arlotto M, Slentz CA, Muehlbauer MJ, McMahon RL, et al. OMICS. 2009;13:21–35.

Lin HC, Chey WY. Regul Pept. 2003;114:131–5.

Misra M, Miller KK, Tsai P, Gallagher K, Lin A, Lee N, et al. J Clin Endocrinol Metab. 2006;91:1027–33.

Misra M, Miller KK, Cord J, Prabhakaran R, Herzog DB, Goldstein M, et al. J Clin Endocrinol Metab. 2007;92:2046–52.

Misra M, Tsai PM, Mendes N, Miller KK, Klibanski A. Obesity. 2009;17:1689–95.

Monteleone P, Serritella C, Martiadis V, Scognamiglio P, Maj M. J Clin Endocrinol Metab. 2008;93:4418–21.

Nakahara T, Kojima S, Tanaka M, Yasuhara D, Harada T, Sagiyama K, et al. J Psychiatr Res. 2007;41:814–20.

Otis CL, Drinkwater B, Johnson M, Loucks A, Wilmore J. Med Sci Sports Exerc. 1997;29:i–ix.

Otto B, Cuntz U, Otto C, Heldwein W, Riepl RL, Tschop MH. Appetite. 2007;48:301–4.

Pfluger PT, Kampe J, Castaneda TR, Vahl T, D'Alessio DA, Kruthaupt T, et al. J Clin Endocrinol Metab. 2007;92:583–8.

Riediger T, Bothe C, Becskei C, Lutz TA. Neuroendocrinology. 2004;79:317–26.

Roth CL, Enriori PJ, Harz K, Woelfle J, Cowley MA, Reinehr T. J Clin Endocrinol Metab. 2005;90:6386–91.

Russell M, Stark J, Nayak S, Miller KK, Herzog DB, Klibanski A, et al. Bone. 2009;45:104–9.

Sainsbury A, Schwarzer C, Couzens M, Fetissov S, Furtinger S, Jenkins A, et al. Proc Natl Acad Sci USA. 2002;99:8938–43.

Salisbury JJ, Mitchell JE. Am J Psychiatry. 1991;148:768–74.

Scheid JL, De Souza MJ, Leidy HJ, Williams NI. 2010, unpublished.

Scheid JL, Williams NI, West SL, VanHeest JL, De Souza MJ. Appetite. 2009;52:184–92.

Sloth B, Holst JJ, Flint A, Gregersen NT, Astrup A. Am J Physiol Endocrinol Metab. 2007;292:E1062–8.

Stock S, Leichner P, Wong AC, Ghatei MA, Kieffer TJ, Bloom SR, et al. J Clin Endocrinol Metab. 2005;90:2161–8.

Utz AL, Lawson EA, Misra M, Mickley D, Gleysteen S, Herzog DB, et al. Bone. 2008;43:135–9.

Wren AM, Seal LJ, Cohen MA, Brynes AE, Frost GS, Murphy KG, et al. J Clin Endocrinol Metab. 2001;86:5992.

Xiao Q, Han X, Arany E, Hill D, Challis JR, McDonald TJ. J Endocrinol. 1998;156:485–92.

Chapter 16
The Role of Enterostatin in Eating Behavior and Diet

Charlotte Erlanson-Albertsson

Keywords Fat intake • Satiety • Blood cholesterol • Serotonin • Cholecystokinin • F1-ATPase

Abbreviations

α-MSH	α-melanocyte-stimulating hormone
ACTH	Adrenocorticotropic hormone
AgRP	Agouti-related protein
AMP	Adenosine monophosphate
AMPK	AMPkinase
ADP	Adenosine diphosphate
ARC	Arcuate nucleus
ATP	Adenosine triphosphate
cAMP	Cyclic adenosine monophosphate
CCK	Cholecystokinin
CNS	Central nervous system
CRH	Corticotropin releasing hormone
CSF	Cerebrospinal fluid
ERK	Extracellular regulated kinase
GLP-1	Glucagon-like peptide 1
GIP	Gastrin inhibitory peptide
5-HT	Serotonin
MAP	Kinase Mitogen activated protein kinase
MCR	Melanocortin receptor
NMRI	Naval Medical Research Institute
NPY	Neuropeptide Y
PVN	Paraventricular nucleus
UCP	Uncoupling protein
VEGF	Vascular endothelial growth factor

C. Erlanson-Albertsson (✉)
Appetite Control Unit, Division of Diabetes, Endocrinology and Metabolism, Department
of Experimental Medical Science, Lund University, BMC B11, SE-221 84, Lund, Sweden
e-mail: charlotte.erlanson-albertsson@med.lu.se

A number of peptides and aminergic compounds have been suggested to have selective effects on the ingestion of macronutrients. Thus protein intake will be stimulated by growth hormone (Dickson and Vaccarino 1994), whereas neuropeptide Y (NPY) will stimulate carbohydrate intake (Stanley and Leibowitz 1985). For stimulation of fat intake at least two different peptides have been described, galanin (Leibowitz 1994) and agouti-related peptide (AgRP) (Hagan et al. 2001) (Table 16.1). As opposed to these stimulating effects on food intake a couple of peptides have been suggested to inhibit macronutrient intake. Cholecystokinin (CCK) has been described to decrease intake of carbohydrate during the first 30 min after injection, but during the following 1–5 h suppress protein intake as well as fat intake in a three-choice macronutrient diet (McCoy et al. 1990). Thus CCK has a more complex role in promoting satiety.

We have identified enterostatin as a peptide that specifically inhibits fat intake (Erlanson-Albertsson et al. 1991a). Enterostatin is released from pancreatic procolipase during fat digestion (Erlanson-Albertsson 1992a); it is therefore important to know that satiety for fat is observed only after hydrolysis of dietary fat in the intestine (Degen et al. 2007). This suggests that fat hydrolysis is coupled to satiety for fat. The following article describes the properties of enterostatin and the conditions that are essential to promote satiety for fat. A number of reviews have been written about enterostatin, among others (Erlanson-Albertsson and York 1997). The key features of enterostatin are listed in Table 16.2.

Table 16.1 Regulation of fat intake and interaction with enterostatin

Hormone	Effect	Interaction with enterostatin	Reference
Galanin	Stimulates fat intake	Effect inhibited by enterostatin	Nagase et al. (1997)
Agouti-related peptide	Stimulates fat intake	Expression suppressed by enterostatin	Lin et al. (2007)
Beta-casomorphin	Stimulates fat intake	Effect inhibited by enterostatin by competition	Berger et al. (2004); Lin et al. (1998)
Kappa-opiate agonist	Stimulates fat intake	Effect inhibited by enterostatin	Barton et al. (1995); Ookuma et al. (1997)
Mu-opiate agonist	Stimulates fat intake	Effect of enterostatin unknown	Kelley et al. (2002)
Serotonin	Inhibits fat intake	Released by enterostatin	Blundell et al. (1995); Koizumi and Kimura (2002)
CCK	Inhibits fat intake	Releasor of enterostatin	Mei et al. (1993a)
NPY	Inhibits fat intake	No interaction with enterostatin	Lin et al. (1993a)

This table lists the hormones that are responsible for regulation of fat intake, both stimulating and inhibiting and how enterostatin interacts with these hormones

Table 16.2 Key features of enterostatin

1. Enterostatin is a pentapeptide that promotes satiety for fat intake
2. Enterostatin is released from pancreatic procolipase during fat digestion in the intestine
3. The satiety occurs through the release of the reward signal serotonin and by suppression of the hunger signal AgRP
4. The receptor for enterostatin is the beta-subunit of F1-ATPase
5. Both enterostatin expression and the receptor are increased by high-fat diet
6. Sucrose impairs the effect and expression of enterostatin
7. Enterostatin is important to promote satiety using strict high-fat diets without sucrose
8. Enterostatin lowers blood cholesterol and insulin levels
9. Enterostatin stimulates fatty acid oxidation in myocytes, hence promoting the utilization of fat as energy substrate
10. Dietary protein stimulates enterostatin expression
11. Diets with fat and protein from green plants stimulate the expression of enterostatin and are satiating in human

AgRP agouti-related peptide
This table lists the key properties of enterostatin including its effects on appetite regulation, the regulation by various diets, the effect on metabolism, and mechanism of action

16.1 The Discovery of Enterostatin

The first discovery of enterostatin as a feeding-related peptide was in 1988 when during immunization of rabbits with enterostatin, the animals lost their appetite. The basis for immunization of rabbits with enterostatin was the fact that we had found that all colipase molecules produced by pancreas were secreted in the form of procolipase molecules. This was strange with the knowledge that colipase is not an enzyme that needs to be protected as the other enzymes of exocrine pancreas like trypsin or phospholipase. We therefore wondered if enterostatin was indeed released in vivo as we had found in vitro. With the knowledge that the rabbits did not want to eat we started systematic feeding studies in rat and found that enterostatin decreased food intake after intraperitoneal administration (Erlanson-Albertsson and Larsson 1988a). It was very difficult to get this article published but I was lucky to be invited to write a chapter in the French Journal *Biochimie*, in an issue devoted to professor Pierre Desnuelle, a grand French scientist who died in 1985 and whom I worked together with during my postdoctoral scholarship in Marseille during 1972–1973.This was the first publication on the effect of enterostatin, which was named procolipase activation peptide (Erlanson-Albertsson and Larsson 1988a). Shortly afterward a very similar article repeated and verified the findings of a suppressed food intake in rat after peripheral injection of enterostatin in a dose dependent way (Erlanson-Albertsson and Larsson 1988b).

16.2 Central Effect of Enterostatin – The Start of a Lifelong Cooperation

Under the circumstances, I was lucky to attend a conference on obesity in Stockholm, where Professor George Bray, USA, was invited to give a plenary lecture. I found the opportunity to ask him if he was interested to go further with this peptide. George Bray became immediately interested – he had just got a position in Baton Rouge as head of the Pennington Biomedical Research Centre; another coworker was on his way to Baton Rouge for a research position – David York. This was how the story of enterostatin continued.

The first experiment performed in USA was the administration of enterostatin centrally in rat and also by this way of administration there was a suppressive effect on food intake (Shargill et al. 1991). If the food intake had been stimulated with clonidine, an alpha 2-adrenergic agonist, there was no inhibitory effect, suggesting that the anorectic effect was not mediated through the alpha 2-adrenergic system. This publication was the first to name the procolipase activation peptide *enterostatin* (Shargill et al. 1991).

16.3 Enterostatin as a Specific Modulator of Fat Intake

As mentioned above, enterostatin is a pentapeptide released from the N-terminal end of pancreatic procolipase by proteolytic cleavage (Fig. 16.1). The residual product called pancreatic colipase is a protein cofactor for pancreatic lipase during intraduodenal hydrolysis of fat (Erlanson-Albertsson 1992b). Since enterostatin and colipase are released more specifically during the intake of fat, the idea that enterostatin might specifically regulate the intake of fat as opposed to carbohydrate and protein was forwarded by Bray and his colleagues. Experiments were thus performed to elucidate whether enterostatin had any specific effect on fat intake. And this was really so.

a   The formation of enterostatin

b   The structure of enterostatin
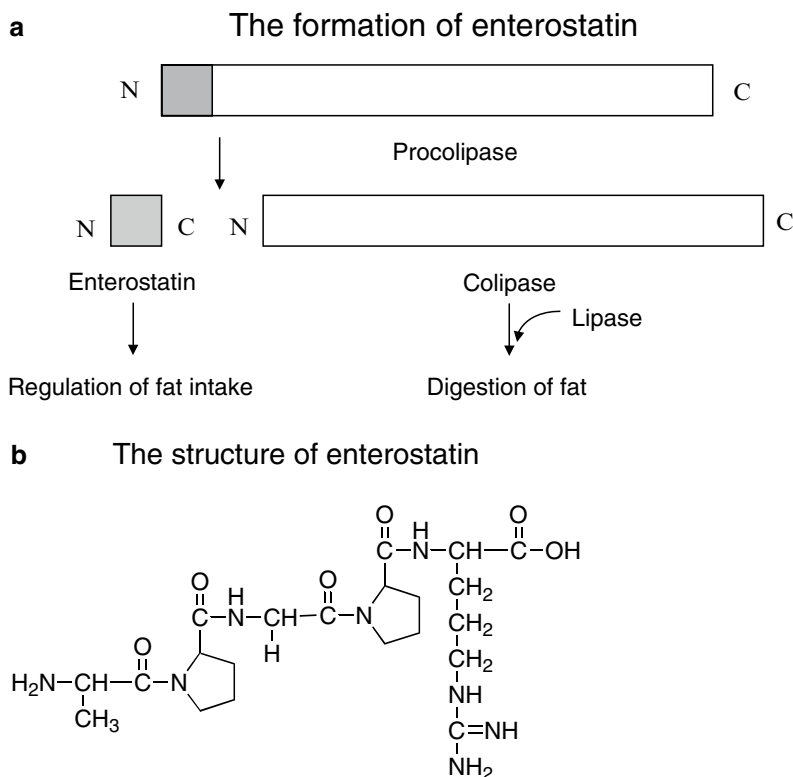
Fig. 16.1 (**a**) Enterostatin is a pentapeptide that is cleaved from the amino terminus of pancreatic procolipase. While colipase acts as protein cofactor for pancreatic lipase during fat digestion, enterostatin promotes satiety for fat in a feedback system. (**b**) The amino acid sequence of human enterostatin, Ala-Pro-Gly-Pro-Arg, a sequence highly conserved among different animal species. The two proline ring structures make the peptide a very stable compound

In the first experiment, Osborne-Mendel rats, rats that are specifically prone to eat fat, were offered a three-choice diet between fat, protein, and carbohydrate (Okada et al. 1991). After fasting overnight the rats were subsequently injected with enterostatin intraperitoneally. A dose-dependent reduction was observed for fat intake, but not with either protein or carbohydrate intake. In another regimen, the rats were given a two-choice diet between high-fat diet and low-fat diet; after enterostatin injection, there was a reduction of food intake only in the high-fat-fed rats (Okada et al. 1991). The experiments suggested that enterostatin could act as a feedback signal to regulate the intake of fat (Fig. 16.1).

In another setup, Sprague-Dawley rats were given a free choice of a low-fat diet (5.2% fat by weight; 14.1% by energy) and a high-fat diet (17.8% fat by weight; 32.8% by energy) in separate containers. After injection of enterostatin into the lateral ventricle, the rats selectively decreased the intake of the high-fat diet by 45% ($p < 0.05$), while the intake of the low-fat diet was unaffected compared to saline injection. A fragment of enterostatin after intracerebroventricular injection had totally lost the selective effect on the consumption of a high-fat and a low-fat diet (Erlanson-Albertsson et al. 1991a). It was concluded that the effect of enterostatin to selectively inhibit fat intake was observed both after central administration and after peripheral administration. Furthermore, it was not specific to any special strain of rat (Fig. 16.2).

Fig. 16.2 Enterostatin specifically reduces high-fat food intake in Sprague-Dawley rat with a two-choice diet between a high-fat (32.8 % by energy) and a low-fat diet (14.1% by energy). The animals were fasted overnight and then injected icv with enterostatin at a dose of 200 ng. Food intake was measured after 30 min. The animals receiving enterostatin had a significantly reduced food intake compared to control when eating high-fat diet ($p < 0.05$) but not when eating low-fat diet). Deviations are SEM

The effect of enterostatin on food intake
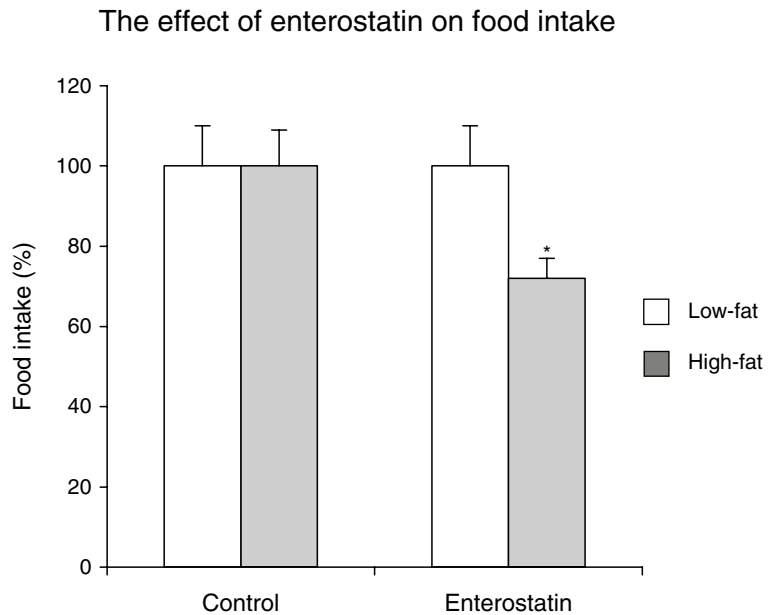
16.4 Long-Term Effects of Enterostatin

It was important to find out if enterostatin could be given repeatedly without any development of tolerance. Enterostatin was thus infused chronically into the lateral ventricle of Osborne-Mendel rats for 11 days (Okada et al. 1993a). A lowered food intake was observed in the treated animals compared to the vehicle-treated controls, in turn leading to a significantly reduced body weight gain (Okada et al. 1993a). This suggested that there was no long-term tolerance effect as has been observed for other appetite-regulating peptides such as CCK (Crawley and Beinfeld 1983; Duncan et al. 2005). Another important finding was a significant reduction of serum insulin levels in the enterostatin-treated animals (Okada et al. 1993a). The reduced insulin levels might be a consequence of a reduced body weight or a direct effect of enterostatin on insulin secretion as demonstrated (Erlanson-Albertsson et al. 1994). The endocrine changes observed at the end of the experiment supported the argument that enterostatin remained effective throughout the infusion period.

The studies also demonstrated that corticosterone was significantly increased in rats receiving chronic infusions of enterostatin into the lateral ventricle and that the level of hepatic glucocorticoid receptor was decreased in these animals as measured by Western blot (Okada et al. 1993a). The elevation of serum corticosterone levels by enterostatin suggests that the hypothalamic-pituitary-adrenal axis has been activated. The CRH peptide is known to reduce fat intake, but experiments with a CRH-antagonist, which failed to block the feeding response of enterostatin suggests that this peptide is not involved in the mechanism of action of enterostatin.

In another type of long-term treatment, rats were given a two-choice diet between high-fat diet and low-fat diet. After adaptation, the animals were chronically infused with enterostatin for 9 days (0.5 μg/h) or artificial cerebrospinal fluid (CSF) into the lateral ventricle of rats. Enterostatin reduced intake of the high-fat diet with the maximum depression at day 4, without any compensatory increase in low-fat food intake (Lin et al. 1997). The body weight of enterostatin-infused rats declined significantly

and was associated with a reduction in fat pad as well as liver weight compared to the CSF-infused control rats (Lin et al. 1997). Serum triglycerides and insulin were likewise decreased, whereas corticosterone was elevated in enterostatin-infused rats. These studies thus demonstrated that enterostatin reduced fat intake in long-term studies and that there was no overeating of low-fat diet to compensate for the reduced food intake (Lin et al. 1997).

16.5 Long-Term Effects of Enterostatin When Added to Food

In the first publication of enterostatin, it was noted that enterostatin when added to food decreased food intake in rat (Erlanson-Albertsson and Larsson 1988b). A similar approach was done in long-term studies in mouse (Rippe et al. 2000). Thus high-fat food was prepared, containing 63% fat, 24% protein, and 13% carbohydrate, in the absence of enterostatin (control) and in the presence of enterostatin (116 ug added per gram food). Female NMRI mice were fed during 25 days a high-fat diet with and without enterostatin during which body weight and food intake was measured (Rippe et al. 2000). It was found that food intake was significantly reduced as well as body weight in the animals receiving enterostatin added to food. In these experiments, brown adipose uncoupling protein expression was measured and found to be elevated in the enterostatin-treated animals. This suggests that the decreased body weight was not only a consequence of a decreased food intake but also an increased diet-induced thermogenesis (Rippe et al. 2000). A long-term feeding experiment is demonstrated in Fig. 16.3, where enterostatin was added to the diet for 55 days in NMRI mice.

The effect of enterostatin on body weight
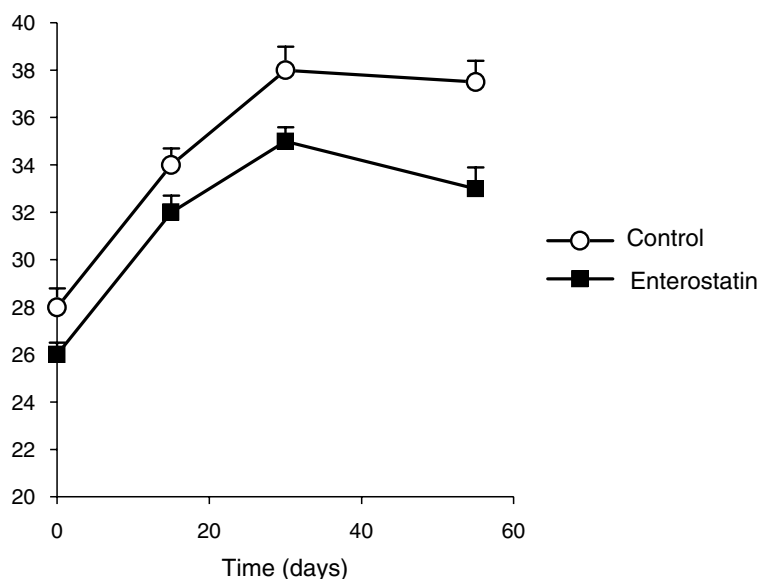
Fig. 16.3 Effect of enterostatin on body weight in female NMRI mice fed a high-fat diet during 55 days. The high-fat diet contained 63% fat, 24% protein, and 13% carbohydrate. Enterostatin was added to the high-fat food dissolved in the lipid phase at a concentration of 166 μg enterostatin per gram food. A significant decrease in body weight was observed in the enterostatin-fed mice compared to control mice ($p < 0.01$). The staples are SEM

16.6 Enterostatin Induces a Normal Feeding Reaction

When identifying a peptide that suppresses appetite it is always important to find out if the suppression is natural and that there is no aversion. In a study to investigate eating behavior, enterostatin was found to induce an early satiety (Lin et al. 1993b). The time course of feeding, grooming, exploration, and sleeping behaviors was measured following injection of enterostatin prior to presenting food. The observation time was 1 h. It was found that enterostatin shortened the time spent eating (21%) compared to saline-injected controls (27%) without any delay in the onset of feeding. Grooming activity appeared earlier following enterostatin, whereas physical activity was reduced (18% vs 27%). Resting time was prolonged (47% vs 27%). There was no change in the drinking behavior. These studies support the concept that enterostatin decreases food intake by producing early satiety (Lin et al. 1993b).

To know if the reduced food intake following injection of enterostatin was related to any aversion reaction, a two-bottle conditioned aversion test was performed (Mei and Erlanson-Albertsson1992), where the effect of enterostatin when injected at such doses that inhibited fat intake was compared with lithium chloride, which is known to produce an aversion reaction. It was found that enterostatin produced no aversion, the animals behaving like the saline-injected animals, while lithium chloride produced a clear aversion reaction (Mei and Erlanson-Albertsson 1992). It was concluded that the inhibition of food intake exerted by enterostatin is not due to malaise.

16.7 The Occurrence of Enterostatin

An important goal was to find and develop antibodies that could be used for a specific assay of enterostatin. To our luck, an assay for measuring pancreatic procolipase activation peptide was published in 1991 with the goal to have an early and sensitive method for measuring acute pancreatitis (Bowyer et al. 1991). Dr. Hermon-Taylor and his group demonstrated through their method the release of immunoreactive enterostatin from human pancreatic juice upon addition of trypsin, while there was no immune reactivity from human pancreatic procolipase prior to the trypsin treatment. One problem with assaying serum enterostatin was the rapid loss of immune reactivity with a half life of 5 min. The loss of reactivity was however significantly slowed by the addition of 20 mmol/L Zinc ions (Zn^{2+}), while ethylenediaminetetra-acetic acid (EDTA) and other protease inhibitors were ineffective (Bowyer et al. 1991).

16.8 Enterostatin in Serum

With the immunoreactive method serum enterostatin was identified and measured in normal and morbidly obese human subjects (Bowyer et al. 1993). It was found that normal subjects displayed a biphasic release of enterostatin in the circulation postprandially, whereas the morbidly obese patients had a weaker response (Bowyer et al. 1993). Enterostatin was also identified in the urine, suggesting that enterostatin reaches the circulation shortly after feeding in human and is thereafter excreted in the urine. In postmenopausal women, the levels of enterostatin was elevated compared to lean control, but were not raised after a meal, suggesting a lack of responsiveness in the obese subjects. This supports earlier observations of a weak response in obese subjects to enterostatin (Prasad et al. 1999).

Fig. 16.4 Fasting levels of plasma enterostatin in Sprague-Dawley rat fed a low-fat diet (14.1% fat by energy), a high-fat diet (32.8% fat by energy), and a high-fat/sucrose diet (added with 23% sucrose) at the start and at the end of the 7-day regimen. Whereas high-fat diet for 7 days induced a significant increased level of enterostatin ($p < 0.05$), this increase was abolished and not observed in the high-fat/ sucrose fed animals. Deviations are SEM and six animals in each group

Effect of fat and sucrose diets on enterostatin
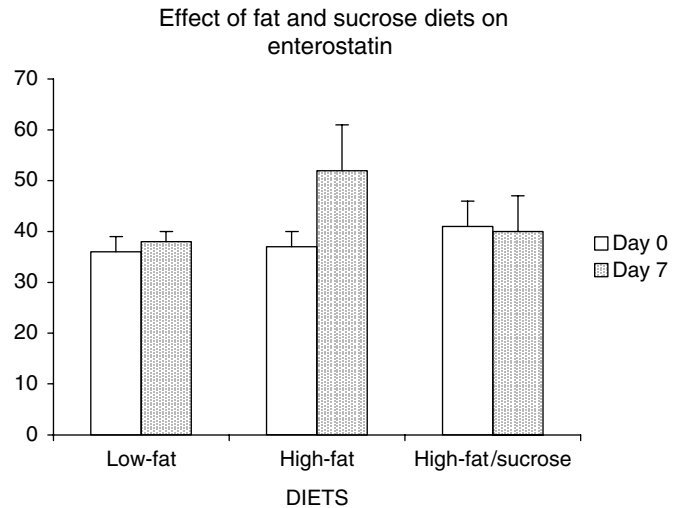
Studies have been performed to investigate if enterostatin binds to any protein in the circulation. At least three different proteins were found to bind enterostatin with a molecular size of 300, 205, and 60 kDa, albumin being one possible binding protein (Wu et al. 2002). The presence of enterostatin-binding protein(s) in the circulation retards the uptake of enterostatin into the brain or other local target tissues and also prevents a rapid degradation.

In rat, enterostatin was demonstrated to increase postprandially after a meal (Mei et al. 2002). The magnitude of response was dependent on the type of meal given. With high-fat and high-fat/high-sucrose meals, the response was greater in magnitude and duration than that consuming a low-fat meal (Mei et al. 2002). Plasma enterostatin levels after high-fat feeding were found to be similar to those after intravenous administration of exogenous enterostatin known to inhibit high-fat food intake. After 7 days of feeding, the enterostatin levels were however reduced in the high-fat sucrose group compared with the high-fat-fed animals (Fig. 16.4). The lowering of enterostatin response in the presence of sucrose may be one important factor for the overeating occurring when fat is combined with sugar. The reduced enterostatin response in the presence of sucrose is probably due to higher insulin levels known to suppress enterostatin synthesis (Duan and Erlanson-Albertsson 1990).

Gel chromatography of pooled postprandial plasma extracts followed by high-performance liquid chromatography analysis showed that plasma enterostatin was identical to synthetic enterostatin. Affinity cross-linking of plasma proteins with ^{125}I-enterostatin on sodium dodecyl sulfate-polyacrylamide gel electrophoresis, followed by autoradiography, revealed a single band with a molecular weight of about 66 kDa, indicating the presence of a potential enterostatin-binding protein in plasma.

16.9 Enterostatin in Intestinal Content

After learning this method, we identified enterostatin immunoreactivity in rat intestinal content (Mei et al. 1993a). Following intravenous infusion of cholecystokinin the concentration of intestinal enterostatin increased from a basal level of 2.0 µM to around 6.0 µM within 60 min. The release of

Table 16.3 Regulation of enterostatin synthesis and release

Factor	Effect	Site of effect	References
Hormones			
GIP	Increased synthesis	Pancreas	Duan and Erlanson-Albertsson (1992)
CCK	Increased release	Intestinal content	Mei et al. (1993a)
Leptin	No effect		
Insulin	Decreased synthesis	Pancreas	Duan and Erlanson-Albertsson (1990)
Corticosterone	Decreased release	Pancreas	Mei and Erlanson-Albertsson (1996a); Okada et al. (1993b)
Diets			
High-fat diet	Increased synthesis	Pancreas	Mei et al. (1993a)
	Decreased synthesis	Stomach	Winzell et al. (1998)
	Increased synthesis	Brain	Rippe et al. (2007)
	Increased release	Blood	Mei et al. (2002)
High-fat/sucrose	No effect	Blood	Mei et al. (2002)
Sucrose	No effect	Brain	Rippe et al. (2007)
Protein	Increased synthesis	Pancreas	Ouagued et al. (1980)
Plant proteins (thylakoids)	Increased synthesis	Pancreas	Albertsson et al. (2007); Kohnke et al. (2009b)
Medicaments			
Orlistat	No effect	Pancreas	Mei et al. (2006)

This table demonstrates the regulation of enterostatin synthesis by various hormones, by different diets, and by treatment with Orlistat, a medicament that is used as an antiobesity drug that inhibits fat digestion and absorption

enterostatin into the intestinal content was parallel to the release of pancreatic lipase and colipase (Mei et al. 1993a). We also found that high-fat diet significantly raised the level of enterostatin in the intestine (Table 16.3). This increase occurred already 24 h after the start of a high-fat diet regimen, indicating a rapid response of enterostatin release and high-fat feeding. There was also a parallel increase in pancreatic lipase and colipase activities following the start of the high-fat feeding, suggesting a close link between fat intake, fat digestion, and satiety for fat.

In the intestinal lumen enterostatin is degraded within 30 min by epithelial brush border peptidases, mainly eliminating the C-terminal arginine residue (Huneau et al. 1994). Another powerful degrading enzyme is dipeptidylaminopeptidase IV, which readily cleaves dipeptides containing proline as second residue, as occurs in enterostatin. Through the use of enzyme inhibitors the survival of enterostatin was significantly prolonged (Bouras et al. 1996), in a similar way as has been demonstrated and used therapeutically for glucagon-like peptide. In spite of peptide degradation during normal conditions an intact trans-epithelial passage of enterostatin was demonstrated (Bouras et al. 1995) in a similar way as has been demonstrated and used therapeutically for glucagon-like peptide. In spite of peptide degradation during normal conditions an intact trans-epithelial passage of enterostatin was demonstrated (Huneau et al. 1994). It was concluded that although immunoreactive enterostatin exhibits a low apparent permeability coefficient in rabbit ileum, the high luminal concentration of enterostatin may be sufficient for production of biological effects after absorption into the serum.

Also in human, enterostatin immunoreactivity has been identified, being present in equimolar concentration to colipase, i.e. around 1 μM (Erlanson-Albertsson and York 1997).

16.10 Enterostatin in Intestinal Cells

In the gastrointestinal tract, enterostatin was found to be present in the gastric mucosa, secreted by chief cells (Okada et al. 1993c; Sorhede et al. 1996b). Cloning of gastric procolipase revealed that this molecule is identical to the pancreatic procolipase (Winzell et al. 1998). Strangely enough high-fat diet decreased the expression of gastric procolipase, which is in contrast to pancreatic procolipase that is increased by high-fat feeding (Table 16.3). Enterostatin was present in the gastric juice, pepsin, and acid being responsible for the cleavage of gastric procolipase into enterostatin and colipase. The role of gastric colipase is unknown, but may be important to prepare lipase-catalyzed fat digestion already in the stomach. The released gastric enterostatin may be involved in the onset of early satiety (Winzell et al. 1998).

Enterostatin was also identified in endocrine cells in the antral part of the stomach and in the small intestine of rat (Sorhede et al. 1996a). The immunoreactive cells were more frequent in the antrum and duodenum and became gradually fewer toward the distal small intestine. In some of the labeled endocrine cells, a coexistence of enterostatin with serotonin was revealed by immunocytochemical double staining, implying that the cells were enterochromaffin cells (Sorhede et al. 1996a). Serotonin is another satiety-promoting signal specific for fat (Blundell et al. 1995; Halford et al. 2004). Whether enterostatin and serotonin are simultaneously released by fat intake is not known but certainly deserves to be measured. Serotonin has is released after central administration of enterostatin; thus there are multiple interactions between enterostatin and serotonin.

16.11 Enterostatin in the Brain

Enterostatin has been identified in the brain in the form of procolipase (York et al. 2006; Rippe et al. 2007). Procolipase and enterostatin immuno-reactivity was demonstrated in PVN, ARC, supraoptic nuclei, amygdala, and dorsal median thalamus (York et al. 2006). These regions are associated with the regulation of food intake and energy expenditure. Procolipase was seen as dense particles in the cytoplasm, whereas enterostatin immune reactivity was observed in nerve fibers. This suggests that procolipase is produced and processed in the neuronal cell body, whereas enterostatin is transported down the nerve fiber to be released at the nerve terminal (York et al. 2006).

Since enterostatin is particularly active when injected into the amygdala, the endogenous production of enterostatin in this nucleus suggests that this might be important for regulation of fat intake. Enterostatin was also present in cells lining the third ventricle, where it could be secreted into the cerebrospinal fluid, as confirmed by Imamura et al. (1998). Thus, the procolipase gene is expressed in the brain, translated to protein, and cleaved to release enterostatin.

In further studies, the hypothalamic procolipase expression was found to be stimulated by a high-fat diet in a similar fashion as the pancreatic procolipase (Rippe et al. 2007) (Table 16.3). Since diets rich in fat are energy-dense, the stimulation of hypothalamic procolipase seems to be an adequate event to induce satiety and energy balance during fat intake. Other palatable food like mono- and disaccharides (glucose, fructose, and sucrose) had no significant effect on the expression of hypothalamic procolipase, indicating that the procolipase expression is unresponsive to sugars (Table 16.3). Fasting overnight caused a threefold down-regulation of hypothalamic procolipase, which is in agreement with the activity of a satiating agent. There was no expression of classical lipase in the hypothalamus, supporting a role of procolipase in the hypothalamus in the production of enterostatin (Rippe et al. 2007).

The presence of enterostatin and its precursor procolipase in the pancreas, the stomach, and in the central nervous system tells us that enterostatin is a typical gut–brain peptide regulating food intake both in the gut and in the brain.

16.12 Feeding Effects after Peripheral and Central Administration of Enterostatin

Dietary fat intake was reduced after intragastric (White et al. 2000), intraduodenal (Mei and Erlanson-Albertsson 1996b) and intraperitoneal (Okada et al. 1992) administration of enterostatin (Table 16.4). These administrations are close to the main production site of enterostatin in the gastrointestinal tract and gave a response with a short delay. The response in the gastrointestinal tract is dependent on vagal afferent signaling pathways, as demonstrated by several studies (Fig. 16.5). This explains why the response to enterostatin occurred fairly rapidly after intraintestinal administration (Table 16.4). After intravenous administration of enterostatin, a delayed effect on food intake was observed (Mei and Erlanson-Albertsson 1992), indicating that the targeting of enterostatin to its receptor protein is not an immediate process in this situation. Enterostatin binds to plasma proteins in the circulating blood, which reduces the rate of uptake into the brain. The administration of enterostatin near the celiac artery (Lin et al. 2000) or intra-cariotic (Lin et al. 2000) gave an immediate effect on feeding and at low doses of enterostatin. The enterostatin effect after intra-cariotic injection was independent of vagal afferent nerves consistent with a central site of action for enterostatin (Lin et al. 2000).

Reduction of fat intake after intracerebroventricular administration of enterostatin was demonstrated in rat, sheep, and baboon (Lin et al. 1994). The low dose required compared to peripheral administration and the early response suggests a direct mode of action of enterostatin (Table 16.3). Investigations of the various nuclei in hypothalamus demonstrated that PVN (Lin and York 1998a) and amygdala (Lin and York 1998a) were the most sensitive nuclei to give an enterostatin response. In these nuclei, enterostatin was demonstrated to decrease meal size and to reduce meal duration. The local production of procolipase (Rippe et al. 2007; York et al. 2006) in these regions may produce enterostatin that acts centrally. Enterostatin may also be taken up by the blood-brain barrier to reach these target nuclei (Koizumi et al. 2002).

Table 16.4 Inhibition of fat intake by enterostatin and onset of action

Administration	Dose (nmol)	Onset of action (min)	Reference
Food additive	200	<30	Rippe et al. (2000)
Intragastric	100	<30	White et al. (2000)
Intraduodenal	11	<30	Mei and Erlanson-Albertsson (1996b)
Intraperitoneal	40	15	Okada et al. (1992)
Intravenous	13	60–120	Mei and Erlanson-Albertsson (1992)
Intracarotid arterial	2	<5	Lin et al. (2000)
Near celiac arterial	2	<5	Lin et al. (2000)
Intracerebroventricular	0.3	<30	Lin et al. (1994)
Paraventricular nucleus	0.1	<10	Lin and York (1998a)
Amygdala	0.01	<5	Lin and York (1998a)

This table demonstrates the onset time of action for enterostatin after injection at various sites in the body. The intraintestinal site of action is around 30 min and the most likely time span for enterostatin to act

A scheme of enterostatin action
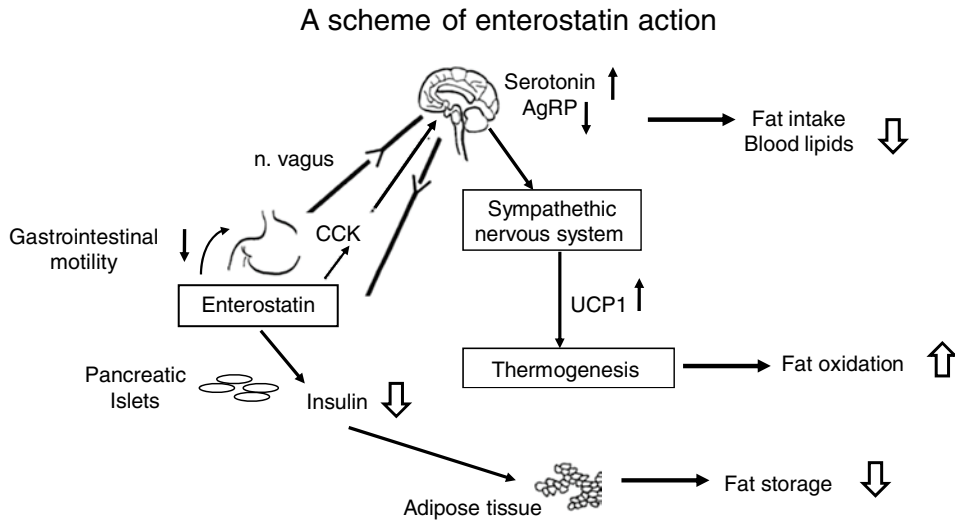
Fig. 16.5 A schematic picture on the effects of enterostatin. Enterostatin is released from the intestine, where it activates CCK-dependent pathways to promote satiety, acting both peripherally to decrease gastric emptying and centrally to release serotonin. In this pathway, the vagal afferent nerves from the intestine to the brain is crucial. Suppression of fat intake by enterostatin also involves a melanocortin pathway, suppressing AgRP. In the islets enterostatin inhibits insulin secretion, which is important to decrease fat storage in the adipose tissue. At the same time, enterostatin stimulates thermogenesis through the activation of the sympathetic system and induction of UCP1, important for stimulation of fat oxidation. Low blood lipids occur through a CCK-dependent pathway. Enterostatin is induced by high-fat feeding and therefore adapts the organism to regulate fat intake and promote utilization of fat as energy source

16.13 Metabolic Effects of Enterostatin

In addition to its effect on feeding behavior, enterostatin has metabolic effects, directly promoting fatty acid oxidation in muscle (Lin et al. 2006), inhibiting insulin secretion (Ookuma and York 1998), lowering serum cholesterol (Takenaka et al. 2003, 2008a) and promoting corticosterone release (Okada et al. 1993a; Takenaka et al. 2003). These effects are closely coupled to the feeding behavior effect of enterostatin. In addition, enterostatin has been found to display various inhibitory gastrointestinal effects linked to satiety (Erlanson-Albertsson et al. 1991b; Lin and York 1997). Finally, a couple of general effects on physiology has been documented such as stimulation of memory (Ohinata et al. 2007; Takenaka et al. 2001), suppression of analgesia (Takenaka et al. 2001, 2003) and inhibition of angiogenesis (Park et al. 2008). The effects are summarized in Table 16.5.

16.13.1 Inhibition of Insulin Secretion

Inhibition of insulin secretion by enterostatin was first observed in isolated islets, where a dose-dependent inhibition of insulin secretion was observed (Mei et al. 1993b; Erlanson-Albertsson et al. 1994; Ookuma and York 1998) (Fig. 16.5). Enterostatin inhibited insulin secretion from islets incubated in the presence of glucose in a dose-dependent manner. Enterostatin also inhibited insulin

Table 16.5 Metabolic and gastrointestinal effects of enterostatin

Effect	Species	References
Inhibiton of insulin secretion	Rat	Mei et al. (1997)
Inhibiton of insulin secretion	Rat islets	Erlanson-Albertsson et al. (1994); Ookuma and York (1998); Rodriguez-Gallardo et al. (1999)
Lowering of blood cholesterol	Mouse	Takenaka et al. (2003, 2008a)
Lowering of blood triglyceride	Rat	Lin et al. (1997)
Release of blood corticosterone	Rat	Okada et al. (1993a)
Inhibition of gastric motility	Pig	Erlanson-Albertsson et al. (1991b)
Inhibiton of gastric emptying	Rat	Lin and York (1997)
Stimulation of thermogenesis	Mouse	Rippe et al. (2000)
Stimulation of fatty acid oxidation	Rat	Lin et al. (2006)
Stimulation of memory	Mouse	Ohinata et al. (2007); Takenaka et al. (2001)
Suppression of analgesia	Mouse	Takenaka et al. (2008b)
Inhibiton of angiogenesis	Human	Park et al. (2008)
Suppression of AgRP expression	Mouse	Lin et al. (2007)
Stimulation of α-MSH neurons	Rat	Lin et al. (2007)
Release of serotonin	Rat	Koizumi and Kimura (2002)
Release of amylin	Rat	Arsenijevic et al. (2005)

This table lists the metabolic and gastrointestinal effects of enterostatin, in which species the effects have been demonstrated and the key references

Table 16.6 Cellular effects of enterostatin

Effect	Cell type	Mechanism	Reference
Inhibition of insulin secretion	INS-1 cells	ATP decrease	Berger et al. (2002)
Inhibiton of insulin secretion	Islets	cAMP decrease	Ookuma and York (1998)
Increase of plasma membrane F1-ATPase	INS-1 cells	Increased expression	Lindqvist et al. (2008)
Stimulation of fatty acid oxidation	Human primary myocyte cultures	AMPK activation	Lin et al. (2006)
Suppression of AgRP expression	GT1-7 cells SH-SY5Y neuroblastoma cells	cAMP increase MAP kinase activation	Park et al. (2009)
Inhibition of angiogenesis	HepG2 cells	AMPK decrease VEGF decrease	Park et al. (2008)

This table lists the mechanism of action of enterostatin during its various effects as demonstrated in various cell systems including the intracellular messengers and the key references

secretion stimulated by phorbol acetate (TPA) and the kappa-opioid agonist U50,488 (Ookuma and York 1998). The enterostatin inhibition of insulin secretion was blocked by 8-Br-cAMP, suggesting that enterostatin may suppress insulin secretion through the reduction of cAMP, but other mechanisms may also be possible (Ookuma and York 1998). In insulin-producing cells (INS-1 cells) enterostatin targeted the F_1-ATPase β-subunit with a simultaneous perturbation of ATP production, a raised thermogenesis and a reduced insulin secretion (Berger et al. 2002) (Table 16.6).

A lowering of insulin levels were observed in short-term as well as in long-term experiments after administration of enterostatin in vivo (Okada et al. 1993a; Mei and Erlanson-Albertsson 1996a; Mei et al. 1997). This inhibition occurred also after stimulation of insulin release with intestinal incretins like GLP-1 and GIP (Rodriguez-Gallardo et al. 1999).

16.13.2 Lowering of Blood Cholesterol

A hypocholesterolemic effect of enterostatin was demonstrated in mice after oral administration of enterostatin (Takenaka et al. 2003). In further studies, it was demonstrated that this reduction in cholesterol levels occurred independent of the food suppressive effect of enterostatin and that this effect was dependent on cholecystokinin action (Takenaka et al. 2008a). Since enterostatin was found to increase the excretion of bile salt into the feces, it was suggested that the hypocholesterolemic effect of enterostatin could be due to an increased secretion of bile. There may however be other explanations for the lowering of cholesterol levels by enterostatin, related to reduced insulin levels and increased fatty acid oxidation. The endogenous role of enterostatin in lowering cholesterol levels is evident from enterostatin knockout mice, who demonstrate significantly increased serum cholesterol levels (Miller et al. 2009).

16.13.3 Promotion of Corticosterone

Corticosterone is a hormone that promotes utilization of fat as energy substrate sparing glucose. Several studies have indicated enterostatin to promote corticosterone release and that the effect of enterostatin to promote satiety for fat is dependent on corticosterone (Mei and Erlanson-Albertsson 1996a; Lin et al. 1997). The anti-analgesic effect of enterostatin was also mediated through corticosterone release from the adrenal cortex in mice (Takenaka et al. 2001; 2003), suggesting the importance of corticosterone release in some enterostatin-induced effects.

16.13.4 Inhibition of Gastric Motility and Gastric Emptying

Since hunger and satiety are strongly correlated with changes in gastrointestinal motility, the effects of enterostatin were investigated on gastric emptying and intestinal motility. Enterostatin was found to inhibit pancreatic secretion as well as to inhibit intestinal motility when administered intraintestinally in pig (Erlanson-Albertsson et al. 1991b) (Fig.16.5). These effects were observed only after intestinal administration and not after intravenous injection of enterostatin. It is thus clear that certain effects of enterostatin are observed only after local administration and may need a direct interaction with a receptor on the cellular level. The inhibition of motility may be linked to a CCK receptor-dependent pathway.

In rat enterostatin was shown to reduce gastric emptying (Lin and York 1997), which is an essential target mechanism for gastrointestinal satiety peptides. The inhibition of gastric emptying may be mediated through vagal afferent fibers or be explained by the release of amylin, a pancreatic islet hormone released by enterostatin (Arsenijevic et al. 2005) and known to strongly inhibit gastric emptying (Table 16.5).

16.13.5 Stimulation of Memory

Several gastrointestinal peptides have memory-enhancing effects, for instance CCK. This was found to be the case also for enterostatin. Using passive avoidance test enterostatin was found to improve step-through latency after oral and central administration in normal mice (Ohinata et al. 2007),

suggesting that enterostatin enhances memory consolidation. Two signaling pathways of orally administered enterostatin to the CNS were hypothesized. One way is through afferent vagal pathways as has been demonstrated for regulation of fat intake (Lin et al. 2000). Another pathway is a direct uptake of enterostatin into the brain as has been demonstrated (Koizumi et al. 2002). At present, it is not clear whether the memory-enhancing effect of orally administered enterostatin is mediated by the vagal pathway or by a direct passage of enterostatin across the blood-brain barrier. The memory enhancing effect of enterostatin was completely abolished through a CCK-receptor antagonist, indicating the CCK-signaling system to be obligatory for the memory-enhancing effect of enterostatin.

16.13.6 Suppression of Analgesia

Feeding promotes release of reward molecules, among them opiates, serotonin, and dopamine. It is not surprising that a peptide that stops eating also stops analgesia. In an experiment using morphine to induce analgesia during tail-pinch studies in mice, it was found that enterostatin inhibited the analgesia (Takenaka et al. 2001). The mechanism for this inhibiting effect of enterostatin was not due to an antagonistic effect of opiates on the receptor level, but instead was found to be dependent on CCK signaling (Takenaka et al. 2008b). Cholecystokinin is known to antagonize morphine analgesia in rat via a CCK-B-receptor (Pu et al. 1994).The effect of enterostatin to reduce fat intake thus may involve a decrease in analgesia. We must be aware of these facts!

16.13.7 Inhibition of Angiogenesis

In order to develop an adipose tissue angiogenesis is an important event. Adipose tissue is a highly vascularized tissue that has the capacity to expand throughout life. A network of capillaries surrounds each adipocyte and in order for an expansion of new adipose tissue mass the vasculature has to develop. Some studies suggest that blocking of angiogenesis in the adipose tissue can help to induce loss of fat mass. By the use of angiogenic blockers in obese mice loss of body fat has been induced (Rupnick et al. 2002). In human obesity, a number of angiogenic factors are increased in the circulation, including VEGF A, C, and D, as well as the inflammatory cytokine interleukin-6 and insulin. With this background, the effect of enterostatin on angiogenesis was studied. Using liver cells (Hep G2 cells) it was demonstrated that enterostatin inhibited angiogenesis and that this occurred through suppression of angiogenic factors like VEGF (Park et al. 2008). It is possible hence that this anti-angiogenic effect of enterostatin may contribute to the loss of adipose tissue that is observed following enterostatin administration. The release of fatty acids increases the availability for fatty acids to be oxidized (Fig. 16.5).

16.14 Mechanism of Action of Enterostatin

Enterostatin acts through both direct and indirect pathways. The direct pathway involves the interaction of enterostatin with its receptor, the β subunit of F_1-ATPase (Berger et al. 2002; Park et al. 2004), while the indirect pathways involve serotonin, CCK, and melanocortin pathways.

16.14.1 The β-Subunit of F1-ATPase as a Receptor for Enterostatin

Using purified rat membranes Berger et al. (2002) was able to demonstrate a specific binding of enterostatin to a 60 kDa protein, which was sequenced through Malditof analysis and found to be the β-subunit of F_1-ATPase (Fig. 16.6). There was also a change in intracellular ATP/ADP concentrations by enterostatin, which may be important to modulate intracellular signaling in response to enterostatin. The identification of the β-subunit of F_1-ATPase as a receptor for enterostatin was confirmed by Park et al. (2004) who established the binding constant to be 1.7×10^{-7} M using surface plasmon resonance technique. Using an aqueous two-phase system, the binding between enterostatin and its receptor was found to be equal to 1.5×10^{-7}M (Berger et al. 2004). The identification of the enterostatin receptor (β-subunit of F_1-ATPase) in the plasma membranes of liver cells as well as in amygdala was an important finding (Park et al. 2004). The enterostatin receptor was also localized in INS-1 cells, where enterostatin caused a threefold upregulation of the expression of the receptor (β-subunit of F_1-ATPase) in the plasma membrane (Lindqvist et al. 2008) (Fig. 16.6). Likewise, fatty acids were found to stimulate the expression of the β-subunit of F_1-ATPase in the plasma membrane (Lindqvist et al. 2008). The fact that fat components like fatty acids cause an increased expression of the enterostatin receptor may explain the need to feed animals high-fat diets before they respond to enterostatin (Lin and York 1998b). High-fat diets are known to increase the expression of procolipase/enterostatin. Thus high-fat diets cause an increased expression, both of enterostatin and its receptor (Fig. 16.6).
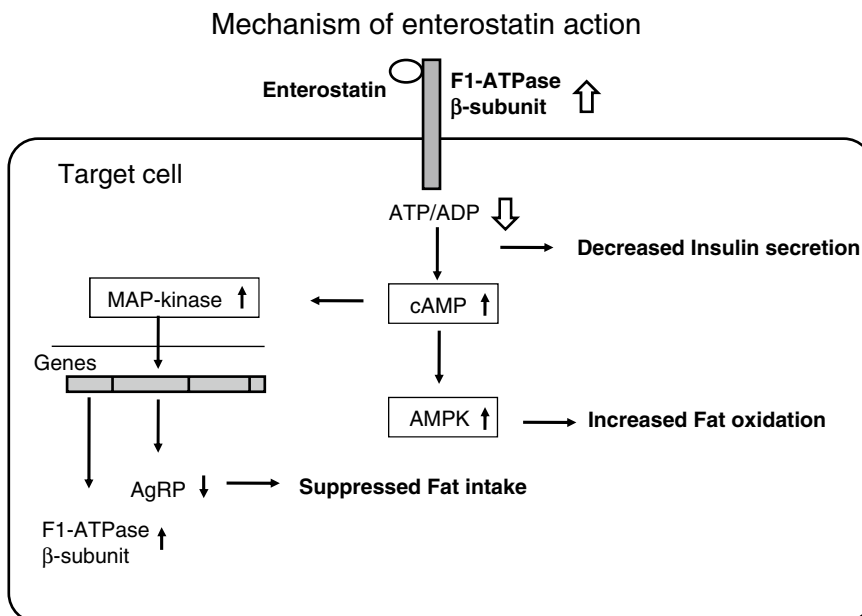
Fig. 16.6 The intracellular mechanisms for enterostatin. Enterostatin binds to its receptor, the β-subunit of F_1-ATPase. This causes a perturbation of ATP/ADP formation, which in turn activates cAMP, AMPkinase, and MAPkinase. The inhibition of insulin secretion occurs following a reduced ATP or cAMP, whereas an increased AMPkinase is responsible for the increased fat oxidation. Activation of MAPkinase suppresses the expression of the hunger hormone AgRP, leading to suppressed fat intake. Enterostatin induces the expression of its own receptor, the β-subunit of F_1-ATPase in the plasma membrane. High-fat diet induces both enterostatin and its receptor to express satiety

The identity and targeting of F1-ATPase β-subunit in the plasma membrane and not as expected in the mitochondria as part of the ATPsynthase complex is not a unique phenomenon of enterostatin action. There are in fact several reports on the presence of the F1-ATPase β-subunit in the plasma membranes of a variety of cell types, including adipocytes, hepatocytes, and various tumor cell lines (Champagne et al. 2006) and the targeting of various signals to this protein. In the plasma membrane, the F1-ATPase β-subunit is probably complexed with other subunits than when present in the mitochondria. Different functions have been described. The targeting of enterostatin to the F1-ATPase β-subunit in the plasma membrane seems a possible mechanism for enterostatin to affect various cellular processes (Fig. 16.6).

16.14.2 The Interaction with the Serotonin System

Serotonin has been described as a signal specifically related to satiety for fat (Halford and Blundell 2000).With the construction of a three-choice diet of fat–carbohydrate–protein, it was demonstrated that fenfluramine, which raises serotonin levels, reduced fat intake from 61% to 47% compared to saline treatment. This reduction occurred both in fat- and carbohydrate-preferring rats, thus independent of the mechanism involved in dietary preferences (Smith et al. 1998). Thus serotonin signaling was investigated for its possible role in transmission of the enterostatin effect.

Enterostatin was infused into the amygdala to reduce fat intake (Lin and York 2004). In the presence of a serotonin receptor antagonist (5HT1b), the response of enterostatin was completely abolished (Lin and York 2004). Since enterostatin does not interact directly with a serotonin receptor, the mechanism of action could involve the ability of enterostatin to release serotonin (Koizumi and Kimura 2002) (Fig.16.5). Serotonin was released after enterostatin infusion into the lateral hypothalamic area, reaching a maximum 40 min after enterostatin administration.

16.14.3 The Interaction with the CCK-System

Another component that is important for the enterostatin response is the presence of CCK-A receptors (Lin et al. 2003) (Fig. 16.5). CCK is released by dietary fat reaching the intestine and reduces food intake through a CCK-A receptor. CCK causes a reduction in meal size and is dependent on afferent vagal nerves from the gastrointestinal tract to hypothalamic and extrahypothalamic forebrain regions to reduce food intake in a similar way as enterostatin. The interaction of enterostatin with the CCK-induced signaling is based on studies using the OLEFTA rat, which lacks CCK-A receptors (Lin et al. 2003). This rat was found to be unresponsive to enterostatin in contrast to the control LETO rat, where fat intake was reduced by 23% after enterostatin administration. Further support for the involvement of CCK-A receptor was the observation that lorglumide, a receptor antagonist specific for CCK-A receptor, totally abolished the enterostatin effect (Lin et al. 2003). There was however no binding of enterostatin to the CCK-A receptor, neither peripherally nor centrally. There are therefore several possibilities for the explanation of the enterostatin dependence on the CCK-system.

Since enterostatin is released and localized to mucosal layers in the intestine, one possible scenario is the influence of enterostatin on CCK-A-receptors present on vagal afferent neurons from the gastrointestinal tract to the brain and higher centers. This is further supported by the fact that vagal afferent neurons are necessary for the mediation of the reduction in fat intake by enterostatin (Tian et al. 1994).

Another possibility is the release of CCK by enterostatin. There are many similarities between the peripheral action of CCK and enterostatin; they both work through vagal afferent nerves, they both inhibit gastric emptying, they both decrease meal size, they are both fat-specific. The effect of enterostatin to suppress food intake during a longer period than CCK could be explained by a continued release of CCK in response to enterostatin. In Sprague-Dawley rat, where procolipase levels were raised through administration of plant thylakoids (Albertsson et al. 2007), there was also a strong release of CCK suggesting a parallel release between CCK and enterostatin, although the order of release is not known.

16.14.4 The Interaction with the Melanocortin System

The third pathway for enterostatin is the melanocortin pathway. The melanocortin system consists of the hunger hormone agouti-related peptide (AgRP) and the satiety signal melanocyte-stimulating hormone (α-MSH), both of which interact with the melanocortin receptors 3 and 4 to affect food intake. Several lines of evidence support AgRP as a hunger signal specifically stimulating fat intake. In a two-choice paradigm between high-fat and low-fat food, AgRP significantly enhanced high-fat (41 energy percent) food intake during the 4 h following an injection into the third ventricle, whereas low-fat (11 energy percent) food intake was not affected (Hagan et al. 2001). The fact that such a preference for fat also occurred in animals with chronic overexpression of agouti-protein was supported by the finding that the agouti mice (Ay/a), when given a three-choice diet between fat, protein, and carbohydrates, chose to eat fat thus inducing an important weight gain (Koegler et al. 1999). With this background information, experiments were carried out to find out if the melanocortin pathway was involved in mediating the action of enterostatin (Lin et al. 2007).

A first discovery was that food intake was not affected by intracerebroventricular injection of enterostatin into melanocortin receptor 4 (MC4R) knock-out mice, whereas food intake was reduced in wild-type mice by approximately 25% (Lin et al. 2007). Following this result, the receptor antagonist SHU9119 was injected to wild-type mice and essentially abolished the inhibitory effect of enterostatin on food intake. Thus it was concluded that the melanocortin pathway is involved in the mechanism of enterostatin in suppressing fat intake (Lin et al. 2007). Further experiments demonstrated that enterostatin decreased the expression of AgRP in the amygdala and in the hypothalamus (Lin et al. 2007). Since AgRP stimulates fat intake, this inhibition could explain a decreased fat intake by enterostatin. However, the immediate suppression of food intake by enterostatin cannot be explained by a changed gene expression. A likely hypothesis is the release of serotonin, which in turn can activate or release the melanocyte-stimulating hormone (α-MSH) to suppress food intake. It was indeed found that enterostatin caused an increased expression of the satiety hormone melanocyte-stimulating hormone (α-MSH) and an increased release in the arcuate nucleus (Lin et al. 2007). Thus, one possible mechanism for the suppression of fat intake by enterostatin is the release of melanocyte-stimulating hormone (α-MSH), which centrally interacts with its receptor to promote satiety.

16.15 Intracellular Mechanisms Mediating the Enterostatin Effect

Intracellular enterostatin has been found to activate different pathways depending on cell type and intracellular events (Table 16.6).

Regarding the inhibition of insulin secretion enterostatin was found to act through cyclic AMP (cAMP). Thus enterostatin caused a decreased production of intracellular cyclic AMP, after the islet

cells had been stimulated with an opiate kappa agonist (U50 488) (Ookuma and York 1998). The changes in cAMP content of the cells were parallel with changes in insulin release. Berger et al. (2002) suggested that the inhibition of insulin secretion observed in INS-1 cells was due to a perturbed ATP production and increased thermogenesis, ATP being important to stimulate insulin secretion. The expression of the F1-ATPase receptor in the plasma membrane of INS-1 cells was induced by enterostatin, suggesting a feed-forward type of modulation (Lindqvist et al. 2008) (Fig. 16.6).

Regarding the stimulation of fatty acid oxidation in myocytes enterostatin was demonstrated to act through AMP-activated kinase (AMPK) (Fig. 16.6) (Lin et al. 2006). AMPK is recognized to have a central role in regulating energy balance between anabolic and catabolic pathways (Ruderman and Prentki 2004). When activated, AMPK leads to increased fatty acid oxidation and glucose transport in muscle as well as decreased fatty acid synthesis and gluconeogenesis. Enterostatin caused a phosphorylation and subsequent activation of AMPK, which is in agreement with an activation of energy metabolism to recruit energy from energy stores while food intake is suppressed (Lin et al. 2006) (Fig. 16.5).

The regulation of AgRP expression by enterostatin was studied in GT1-7 murine hypothalamic neuronal cells in culture, where enterostatin caused a reduced expression after 1 h of incubation (Park et al. 2009). The mechanism for this effect was found to be under the control of cyclic AMP and MAP kinase ERK pathways (Park et al. 2009). Enterostatin was found to initially increase cAMP levels, the downstream intracellular event being an increased activation of MAPkinase pERK pathway. The activation of the MAPkinase way was found to correlate to a decreased expression of AgRP expression (Fig. 16.6). The GT1-7 cells were shown to possess the F1-ATPase ß subunit protein, the enterostatin receptor, in the plasma membrane, where it was associated with lipid rafts. It was hence suggested that a perturbation of the ATP/ADP could be responsible for the raised cAMP concentration and the following intracellular events.

In the study to understand the mechanism for the anti-angiogenic effect of enterostatin, HepG2 cells were incubated in the absence of glucose, which induced an activation of AMP kinase (Park et al. 2008). In this situation, enterostatin reduced the levels of AMPkinase (Park et al. 2008). This reduction of AMPkinase in turn caused a down-regulation of angiogenic factors like the VEGF (vascular endothelial growth factor), hence explaining the anti-angiogenic effect of enterostatin. Thus enterostatin could either stimulate or reduce the activity of AMPkinase, depending on the energy state of the cell, suggesting enterostatin to have a modulatory role.

16.16 Enterostatin Stimulates Energy Expenditure

Several satiety hormones raise energy expenditure and thermogenesis of which enterostatin is one example (Table 16.5). Chronic injection of enterostatin either intracerebroventricularly (icv) or peripherally caused a greater weight loss than could be accounted for by the reduction of food intake (Lin et al. 1997; Berger et al. 2002). Additionally, enterostatin was found to enhance sympathetic activation of brown adipose tissue (Nagase et al. 1997). One explanation for the increased thermogenesis was an enhanced expression of uncoupling protein 1 in brown adipose tissue in mice fed a high-fat diet, leading to increased heat production (Rippe et al. 2000). The increased energy expenditure served to achieve energy balance during high-fat feeding. The increased expression of uncoupling protein 2 in the stomach by enterostatin (Rippe et al. 2000) probably does not produce heat, but may regulate oxidative stress.

In INS-1 cells enterostatin was found to increase heat production as well as oxygen consumption (Berger et al. 2002), an effect believed to occur through an interaction with the β-subunit of F1-ATPase. The stimulation of energy expenditure by enterostatin could occur through a central or a peripheral pathway.

16.17 Enterostatin as an Endogenous Regulator of Fat Intake

The question of whether enterostatin is an endogenous regulator of fat intake is answered by the fact that the receptor antagonist beta-casomorphin has the ability to increase fat intake (Lin et al. 1998; Berger et al. 2002). There are also studies demonstrating an increased food intake after intracerebroventricular administration of enterostatin antibodies (D.A. York, unpublished). Voluntary fat intake in rodents was demonstrated to be inversely related to the amount of procolipase/enterostatin (Okada et al. 1992) suggesting that endogenous enterostatin regulates fat intake. There are hence various arguments for the statement that enterostatin is an endogenous regulator or modulator of fat intake under normal conditions.

16.18 Regulation of Enterostatin Synthesis and Release

The regulation of enterostatin synthesis and release is summarized in Table 16.3. A couple of hormones like the gastric inhibitory stimulating peptide (GIP) specifically stimulate the synthesis of the pancreatic procolipase, the precursor for enterostatin. This may be one factor mediating the high-fat-diet-induced synthesis of enterostatin, since GIP is released by dietary fat. Another powerful releaser of pancreatic lipase and procolipase and hence of enterostatin is CCK, which stimulates both synthesis and secretion. Leptin has however no effect on enterostatin release. A couple of important metabolic hormones inhibit the synthesis or release of enterostatin/procolipase, like insulin and glucocorticoid hormone. Peripheral insulin acts to promote energy storage and the utilization of carbohydrate as energy substrate, whereas enterostatin is more involved in the utilization of fat as energy substrate. It is therefore not surprising that enterostatin and insulin mutually inhibit each other. The glucocorticoid hormone has a complex role of stimulating the use of carbohydrate as energy substrate and translocating fat as energy store from peripheral adipose tissue to central adipose tissue. The suppression of colipase/enterostatin expression by glucocorticoids may promote such a fat redistribution.

High-fat diets have in several studies been shown to increase the synthesis of procolipase/enterostatin (Table 16.3). It is important to note that sucrose alone and sucrose/high-fat diets fail to simulate enterostatin production (Table 16.3). This may be the consequence of an increased release of insulin, which acts to suppress procolipase synthesis. The stimulated expression of enterostatin by high-fat diets may explain why "pure" high-fat diets are satiating, whereas high-fat/sucrose diets promote overeating. That dietary protein stimulates procolipase/enterostatin synthesis may appear surprising (Table 16.3). One interpretation is that high-fat and high-protein diets often are linked, whereas low-fat diets more often are combined with high-carbohydrate diets.

16.19 Enterostatin Effects in Man

Since the discovery of enterostatin there have been a couple of human studies on the effect of enterostatin on appetite regulation (Rossner et al. 1995; Kovacs et al. 2003). In these experiments, enterostatin were injected as single shots, either intravenously or orally. There has been no visible effect on eating but a documented suppressed hunger.

We have recently performed experiments where the endogenous levels of enterostatin/colipase were found to be elevated through the administration of thylakoids in the food (Albertsson et al. 2007;

Kohnke et al. 2009b) (Table 16.3). Thylakoids are membranes from green leaves that interact with fat digestion by binding both to the fat droplets as well as to the lipase/colipase complex in this way reducing the rate of fat digestion (Albertsson et al. 2007). In humans, the addition of thylakoids to a meal promoted satiety signaling with a release of CCK during 6 h after eating, whereas a control meal induced a CCK signaling only during 3–4 h (Kohnke et al. 2009a). At the same time, insulin levels were reduced (Kohnke et al. 2009a). These experiments hence indicate that endogenous levels of enterostatin are important for the suppression of appetite and the promotion of satiety and that induction of elevated *endogenous* levels of enterostatin is a better way of achieving appetite control than infusion of the peptide. It is important to note that enterostatin targets both appetite-regulating sites to promote satiety and metabolic sites to reduce insulin levels, blood cholesterol, and blood tria-cylglycerol levels. Targeting pancreatic lipase by Xenical to reduce fat digestion fails to promote CCK-signaling and enterostatin/procolipase expression (Mei et al. 2006) (Table 16.3).

16.20   Applications to Other Areas of Health and Disease

Appetite regulation regarding fat intake is important to know in the face of the obesity epidemia, which is linked to a high dietary fat intake in combination with sucrose. Since the satiety for fat is impaired by the presence of sucrose as evidences by the study of enterostatin, diet programs should be careful to restrict fat and sucrose intake, and in particular to separate these two macronutrients to different meals and occasions. The importance of a memory-enhancing effect by enterostatin suggests that areas of aging and mental health are closely related to this field.

Summary Points

- Enterostatin is a pentapeptide
- Is released from pancreatic procolipase during fat digestion
- Suppresses fat intake
- Acts both peripherally and centrally
- Acts in short-term and long-term treatment
- Enterostatin is a gut–brain peptide
- Is produced in the stomach, small intestine, and brain
- Is present in the circulating blood postprandially
- Passes blood–brain-barrier
- Is produced in hypothalamic nuclei and amygdala
- Enterostatin synthesis/release is increased by high-fat food
- Is stimulated by dietary protein
- Is inhibited by dietary sucrose even in the presence of high-fat food
- Is stimulated by the gastrointestinal hormone GIP
- Is inhibited by insulin
- Enterostatin receptor is the β-subunit of F_1-ATPase
- The receptor is localized in the plasma membrane of various cells
- The receptor expression is stimulated by enterostatin and by fatty acids
- Intracellular targets are cAMP, AMPkinase, and MAPkinase

- Gene expression of the hunger hormone AgRP is suppressed
- Enterostatin reduces insulin secretion
- Reduces plasma cholesterol levels
- Stimulates fatty acid oxidation in myocytes
- Increases thermogenesis
- Stimulates memory
- Enterostatin releases serotonin
- Acts through CCK-dependent pathways
- Acts through vagal afferents
- Acts as an opiate-antagonist
- Enterostatin knockout mice have increased serum cholesterol levels
- Induction of enterostatin production produces body weight control in rodents
- Induction of enterostatin production in human produces satiety signals
- Endogenous release of enterostatin – a necessary strategy to produce satiety

---

Key terms

Enterostatin: Peptide which promotes satiety for fat and the utilization of fat as energy substrate.
Procolipase: The precursor from of enterostatin and colipase.
Colipase: A pancreatic protein that acts together with pancreatic lipase to hydrolyze dietary fat especially triacylglycerol in the intestine.
Amygdala: A nucleus in the brain that expresses reward.
Hypothalamus: A brain region where homeostatic mechanisms are expressed to give balance. This includes appetite, body weight, and body temperature.
Melanocortin pathways: Intracellular pathways that express hunger and satiety linked to the melanocortin system, containing two key hormones, AgRP, a hunger hormone, and MSH, a satiety hormone.
Thermogenesis: Production of heat during metabolic events.
F1-ATPase β subunit: Receptor for enterostatin located in the plasma membrane of liver cells, insulin-producing cells, and cells in amygdala that mediates the effects of enterostatin.
AMPkinase: Intracellular enzyme that is activated by enterostatin through its receptor to stimulate the utilization of energy, for instance fat oxidation.
Serotonin: A reward molecule produced centrally and in the gastrointestinal tract to promote stability and satiety.

References

Albertsson PA, Kohnke R, Emek SC, Mei J, Rehfeld JF, Akerlund HE, et al. Biochem J. 2007;401:727–33.
Arsenijevic D, Gallmann E, Moses W, Lutz T, Erlanson-Albertsson C, Langhans W. Am J Physiol. 2005;298:E40–5.
Barton C, Lin L, York DA, Bray GA. Brain Res. 1995;702:55–60.

Berger K, Sivars U, Winzell MS, Johansson P, Hellman U, Rippe C, et al. Nutr Neurosci. 2009;297:E856–65.

Berger K, Winzell MS, Mei J, Erlanson-Albertsson C. Physiol Behav. 2004;83:623–30.

Blundell JE, Lawton CL, Halford JC. Obes Res. 1995;3 Suppl 4:471S–6.

Bouras M, Huneau JF, Luengo C, Erlanson-Albertsson C, Tome D. Peptides. 1995;16:399–405.

Bouras M, Huneau JF, Tome D. Life Sci. 1996;59:2147–55.

Bowyer RC, Jehanli AM, Patel G, Hermon-Taylor J. Clin Chim Acta. 1991;200:137–52.

Bowyer RC, Rowston WM, Jehanli AM, Lacey JH, Hermon-Taylor J. Gut. 1993;34:1520–5.

Champagne E, Martinez LO, Collet X, Barbaras R. Curr Opin Lipidol. 2006;17:279–84.

Crawley JN, Beinfeld MC. Nature. 1983;302:703–6.

Degen L, Drewe J, Piccoli F, Grani K, Oesch S, Bunea R, et al. Am J Physiol. 2007;292:R1391–9.

Dickson PR, Vaccarino F. Peptides. 1994;15:1343–52.

Duan RD, Erlanson-Albertsson C. Int J Pancreatol. 1990;6:271–9.

Duan RD, Erlanson-Albertsson C. Am J Physiol. 1992;262:G779–84.

Duncan EA, Davita G, Woods SC. Physiol Behav. 2005;85:387–93.

Erlanson-Albertsson C. Nutr Rev. 1992a;50:307–10.

Erlanson-Albertsson C. Biochim Biophys Acta. 1992b;1125:1–7.

Erlanson-Albertsson C, Hering B, Bretzel RG, Federlin K. Acta Diabetol. 1994;31:160–3.

Erlanson-Albertsson C, Larsson A. Biochimie 1988a;70:1245–50.

Erlanson-Albertsson C, Larsson A. Regulatory peptides 1988b;22:325–31.

Erlanson-Albertsson C, Mei J, Okada S, York D, Bray GA. Physiol Behav. 1991a;49:1191–4.

Erlanson-Albertsson C, Westrom B, Pierzynowski S, Karlsson S, Ahren B. Pancreas. 1991b;6:619–24.

Erlanson-Albertsson C, York D. Obes Res. 1997;5:360–72.

Hagan MM, Rushing PA, Benoit SC, Woods SC, Seeley RJ. Am J Physiol. 2001;280:R814–21.

Halford JC, Blundell JE. Ann Med. 2000;32:222–32.

Halford JC, Cooper GD, Dovey TM. The pharmacology of human appetite expression. Curr Drug Targets. 2004;5:221–40.

Huneau JF, Erlanson-Albertsson C, Beauvallet C, Tome D. Regul Pept. 1994;54:495–503.

Imamura M, Sumar N, Hermon-Taylor J, Robertson HJ, Prasad C. Peptides. 1998;19:1385–91.

Kelley AE, Bakshi VP, Haber SN, Steininger TL, Will MJ, Zhang M. Physiol Behav. 2002;76:365–77.

Koegler FH, Schaffhauser RO, Mynatt RL, York DA, Bray GA. Physiol Behav. 1999;67:809–12.

Kohnke R, Lindbo A, Larsson T, Lindqvist A, Rayner M, Emek SC, et al. Scand J Gastroenterol. 2009a;44:712–9.

Kohnke R, Lindqvist A, Göransson N, Emek SC, Albertsson PA, Rehfeld JF, Hultgårdh-Nilsson A, Erlanson-Albertsson C. Phytother Res. 2009b;23:1778–83.

Koizumi M, Kimura S. Neurosci Lett. 2002;320:96–8.

Koizumi M, Nakanishi Y, Sato H, Morinaga Y, Ido T, Kimura S. Physiol Behav. 2002;77:5–10.

Kovacs EM, Lejeune MP, Westerterp-Plantenga MS. Br J Nutr. 2003;90:207–14.

Leibowitz SF. Ann NY Acad Sci. 1994;739:12–35.

Lin L, Bray G, York DA. Am J Physiol. 2000;278:R1346–51.

Lin L, Chen J, York DA. Peptides. 1997;18:657–61.

Lin L, Gehlert DR, York DA, Bray GA. Obes Res. 1993a;1:186–92.

Lin L, McClanahan S, York DA, Bray GA. Physiol Behav. 1993b;53:789–94.

Lin L, Okada S, York DA, Bray GA. Peptides. 1994;15:849–54.

Lin L, Park M, Hulver M, York DA. Am J Physiol. 2006;290:R909–15.

Lin L, Park M, York DA. Peptides. 2007;28:643–9.

Lin L, Thomas SR, Kilroy G, Schwartz GJ, York DA. Am J Physiol. 2003;285:R321–8.

Lin L, Umahara M, York DA, Bray GA. Peptides. 1998;19:325–31.

Lin L, York DA. Brain Res. 1997;745:205–9.

Lin L, York DA. Peptides. 1998a;19:557–62.

Lin L, York DA. Am J Physiol. 1998b;275:R619–23.

Lin L, York DA. Brain Res. 2004;1020:147–53.

Lindqvist A, Berger K, Erlanson-Albertsson C. Nutr Neurosci. 2008;11:55–60.

McCoy JG, Stump B, Avery DD. Peptides. 1990;11:221–5.

Mei J, Bouras M, Erlanson-Albertsson C. Peptides. 1997;18:651–5.

Mei J, Bowyer RC, Jehanli AM, Patel G, Erlanson-Albertsson C. Pancreas. 1993a;8:488–93.

Mei J, Cheng Y, Erlanson-Albertsson C. Int J Obes Relat Metab Disord. 1993b;17:701–4.

Mei J, Erlanson-Albertsson C. Regul Pept. 1992;41:209–18.

Mei J, Erlanson-Albertsson C. Obes Res. 1996a;4:513–9.

Mei J, Erlanson-Albertsson C. Obes Res. 1996b;4:161–5.

Mei J, Lindqvist A, Krabisch L, Rehfeld JF, Erlanson-Albertsson C. Physiol Behav. 2006;89:563–8.

Mei J, Sorhede-Winzell M, Erlanson-Albertsson C. Obes Res. 2002;10:688–94.

Miller R, DÀgostino D, Erlanson-Albertsson C, Lowe ME. Am J Physiol. 2009;297:E856–65.

Nagase H, Bray GA, York DA. Brain Res. 1997;709:44–50.

Ohinata K, Sonoda S, Shimano T, Yoshikawa M. Peptides. 2007;28:719–21.

Okada S, Lin L, York DA, Bray GA. Physiol Behav. 1993a;54:325–9.

Okada S, Onai T, Kilroy G, York DA, Bray GA. Am J Physiol. 1993b;265:R21–7.

Okada S, York DA, Bray GA. Biochem J. 1993c;292:787–9.

Okada S, York DA, Bray GA, Erlanson-Albertsson C. Physiol Behav. 1991;49:1185–9.

Okada S, York DA, Bray GA, Mei J, Erlanson-Albertsson C. Am J Physiol. 1992;262:R1111–6.

Ookuma K, Barton C, York DA, Bray GA. Peptides. 1997;18:785–91.

Ookuma M, York DA. Int J Obes Relat Metab Disord. 1998;22:800–5.

Ouagued M, Saraux B, Girard-Globa A, Bourdel G. J Nutr. 1980;110:2302–9.

Park M, Lin L, Thomas S, Braymer HD, Smith PM, Harrison DH, et al. Peptides. 2004;25:2127–33.

Park M, Lyons J, Oh H, Yu Y, Woltering EA, Greenway F, et al. Int J Obes (Lond). 2008;32:922–9.

Park M, Oh H, York DA. Peptides. 2009;30:181–90.

Prasad C, Imamura M, Debata C, Svec F, Sumar N, Hermon-Taylor J. J Clin Endocrinol Metab. 1999;84:937–41.

Pu SF, Zhuang HX, Han JS. Brain Res. 1994;657:159–64.

Rippe C, Berger K, Boiers C, Ricquier D, Erlanson-Albertsson C. Am J Physiol. 2000;279:E293–300.

Rippe C, Erlanson-Albertsson C, Lindqvist A. Brain Res. 2007;1185:152–7.

Rodriguez-Gallardo J, Silvestre RA, Marco J. Int J Obes Relat Metab Disord. 1999;23:787–92.

Rossner S, Barkeling B, Erlanson-Albertsson C, Larsson P, Wahlin-Boll E. Appetite. 1995;24:37–42.

Ruderman N, Prentki M. Nat Rev Drug Discov. 2004;3:340–51.

Rupnick MA, Panigrahy D, Zhang CY, Dallabrida SM, Lowell BB, Langer R, et al. Proc Natl Acad Sci USA. 2002;99:10730–5.

Shargill NS, Tsujii S, Bray GA, Erlanson-Albertsson C. Brain Res. 1991;544:137–40.

Smith BK, York DA, Bray GA. Pharmacol Biochem Behav. 1998;60:105–14.

Sorhede M, Erlanson-Albertsson C, Mei J, Nevalainen T, Aho A, Sundler F. Peptides. 1996a;17:609–14.

Sorhede M, Mulder H, Mei J, Sundler F, Erlanson-Albertsson C. Biochim Biophys Acta. 1996b;1301:207–12.

Stanley BG, Leibowitz SF. Proc Natl Acad Sci USA. 1985;82:3940–3.

Takenaka Y, Nakamura F, Jinsmaa Y, Lipkowski AW, Yoshikawa M. Biosci Biotechnol Biochem. 2001;65:236–8.

Takenaka Y, Nakamura F, Yamamoto T, Yoshikawa M. Biosci Biotechnol Biochem. 2003;67:1620–2.

Takenaka Y, Shimano T, Mori T, Hou IC, Ohinata K, Yoshikawa M. Peptides. 2008a;29:2175–8.

Takenaka Y, Shimano T, Yamada Y, Yoshida M, Ohinata K, Yoshikawa M. Peptides. 2008b;29:559–63.

Tian Q, Nagase H, York DA, Bray GA. Obes Res. 1994;2:527–34.

White CL, Bray GA, York DA. Peptides. 2000;21:1377–81.

Winzell MS, Lowe ME, Erlanson-Albertsson C. Gastroenterology. 1998;115:1179–85.

Wu YJ, Hughes D, Lin L, Braymer DH, York DA. Peptides. 2002;23:537–44.

York DA, Lin L, Thomas SR, Braymer HD, Park M. Brain Res. 2006;1087:52–9.

Chapter 17
The Paradoxical Role of Glucose-Dependent Insulinotropic Polypeptide (GIP) in Diet and Eating Behaviour in Health and Disease

L.R. Ranganath and J. Pinkney

Abbreviations

GIP	Gastric inhibitory polypeptide or glucose-dependent insulinotropic polypeptide
GIPR	Glucose-dependent insulinotropic polypeptide receptor
B-cell	Pancreatic insulin secreting cell
GIT	Gastro-intestinal tract
GLP-1	Glucagon-like peptide-1
T2D	Type 2 diabetes mellitus
K-cell	GIP secreting intestinal cell
DPP IV	Dipeptidyl peptidase IV
MUFA	Monounsaturated fatty acid
SFA	Saturated fatty acid
PUFA	Polyunstaturated fatty acid
EE	Energy expenditure
A-cell	Pancreatic glucagon secreting cell
D-cell	Pancreatic somatostatin secreting cell
SGLT 1 transporters	Sodium-dependent glucose transporter 1
GIPR-/-mice	GIP receptor gene knockout mice

17.1 Introduction

The gastrointestinal tract (GIT) is the organ responsible for the digestion and absorption of ingested nutrients prior to metabolism and storage. Enzymes and hormones produced in the gut enable these processes to occur efficiently. Obesity and diabetes, twin disorders of nutrient intake and metabolism, have assumed major importance, and the role of the GIT in these processes is being re-examined. In particular, two intestinal hormones known as "incretins", glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide 1 (GLP-1), have become important areas of research. Although GIP was the first incretin to be discovered, there has been greater progress in the understanding

L.R. Ranganath (✉)
Department of Clinical Chemistry, Royal Liverpool University Hospital,
Prescot Street, Liverpool, L7 8XP UK
e-mail: lrang@liv.ac.uk; clare.molyneux@rlbuht.nhs.uk

of GLP-1 leading to its therapeutic application in type 2 diabetes mellitus (T2D) (Meier et al. 2002). Therefore, the present chapter will instead address the basic and clinical science of GIP and its potential role in human health and disease. The focus of this brief review is on its most important clinical application – the treatment of obesity and T2D, conditions brought about by an imbalance between energy intake and energy expenditure and characterised by insulin resistance and progressive failure of insulin secretion.

17.2 History of GIP

A rise in glucose concentrations in arterial blood perfusing pancreatic B-cell leads to insulin release that in turn restores euglycaemia. The observation that oral rather than intravenous glucose administration resulted in greater insulin secretion confirmed the existence of a connection between the intestinal tract and endocrine pancreas (McIntyre et al. 1964). These studies established that although the arterial blood glucose concentration was a stimulus for insulin secretion, factors that were termed "incretins" released from the gut in response to glucose absorption, which were found subsequently to include GIP and GLP-1 (Brown & Dryburgh, 1971), sensitised the pancreatic B-cell to glucose, and reduced the threshold for release of insulin. The concept of the 'entero-insular' axis was thus born (Fig. 17.1). The first incretin to be discovered was GIP but its significance in gut biology has been overshadowed by rapid advances in the understanding of GLP-1. There continues to be debate about the relative importance of the insulinotropic and other physiological effects of these two incretin hormones.

17.2.1 Incretin concept

The recognition that insulin secretion is different when the same amount of glucose is given orally or intravenously led to the description of the 'incretin' effect (Fig. 17.2). The incretin effect can be calculated under conditions where similar plasma glucose concentrations are produced by oral and controlled intravenous glucose administration (Fig.17.3). Using this approach, it has been estimated that the incretin effect accounts for 70% of insulin secretion in health and half that in T2D (Nauck et al. 1986). Several criteria have to be fulfilled for a hormone to be called an incretin: (a) The hormone should be
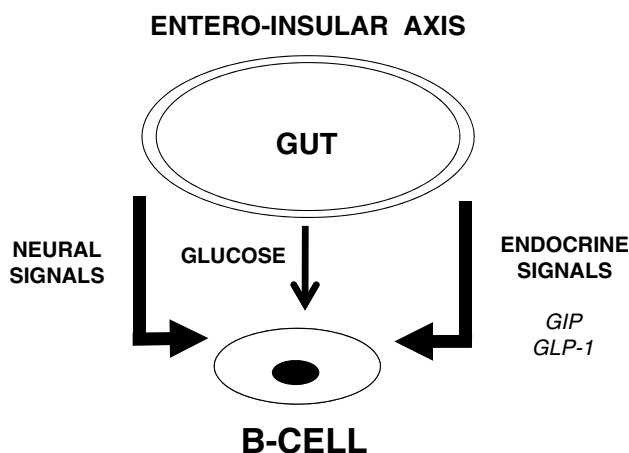
Fig. 17.1 The entero-insular axis Ingested nutrients, especially carbohydrates, lead to secretion of insulin from the B-cell by a combination of direct nutrient stimulation as well as neural and endocrine mechanisms (Brown & Dryburgh, 1971)
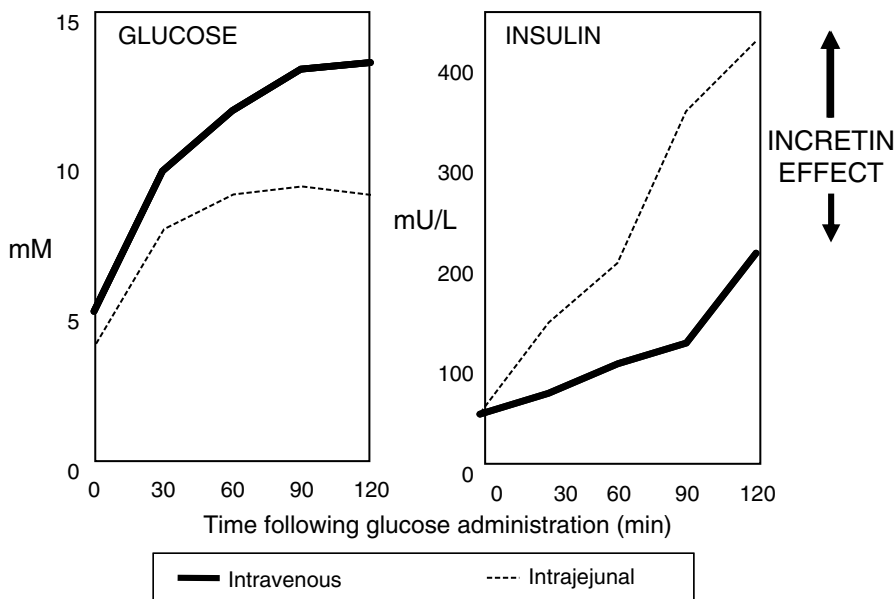
Fig. 17.2 The incretin effectWhen glucose is administered orally or intravenously, the difference in insulin responses evoked was described as the incretin effect as indicated by the figure (McIntyre et al. 1964)

Insulin
Incremental Area Under the curve
(Intravenous)
_____ **X 100**
Insulin
Incremental Area Under the curve
(Oral)

Fig. 17.3 The quantitation of incretin effect (as %)When glucose is administered orally or intravenously to produce quantitatively similar plasma glucose concentrations, the insulin responses evoked can be used to calculate the incretin effect as indicated by the figure (Nauck et al. 1986)

released in response to oral nutrient ingestion, especially glucose, and (b) it should reach physiological concentrations in vivo that cause insulin release. GLP-1 and GIP are the only currently known incretins. A further property of these incretins that make them attractive as potential therapeutic agents in diabetes is that insulin secretion in response to these peptide hormones ceases when euglycaemia is achieved, thereby minimising the risk of hypoglycaemia. Lastly, the incretin effect appears not only to be due to increased secretion but also decreased hepatic insulin extraction in humans (Shuster et al. 1988).

17.3 Biology of GIP (Table 17.1)

17.3.1 GIP producing cells

GIP is secreted by enterochromaffin K-cells of the proximal intestine (Fehmann et al. 1995). K-cells, which are 'open' to the lumen, are found in greatest density in the proximal intestine. GIP is secreted in response to activation of adenylate cyclase, potassium-mediated membrane depolarisation and

Table 17.1 GIP versus GLP-1 basic science

	GIP	GLP-1
Structure	42 Aminoacids MW 4984	30/31 aminoacids MW 3298
Cell of origin	K cell	L cell
	Duodenum	lleum
	Jejunum	Colon
Circulating half-life (minutes)	<5	<5
Degradation	DPP IV enzyme	DPP IV enzyme
Insulin secretion to hormone in health	Increased	Increased
Insulin secretion to hormone in T2D	Impaired	Retained to nearly normal
Effect on B-Cell mass	Increased	Increased
Gastric emptying	No effect	Delayed
Secretion in T2D	Decreased	Decreased
Insulin sensitivity	Unchanged	Probably Improved
Food intake	?Increased	Decreased

This table lists key facts of GIP including how they relate to carbohydrate and lipid metabolism in health and disease. A comparison with the other major incretin GLP-1 is shown. GLP-1: glucagon-like peptide-1. GIP:glucose-dependent insulinotropic polypepide. T2D: type 2 diabetes mellitus.

rise in intracellular calcium concentrations in the K-cell. In addition to GIP, some K-cells produce additional hormones such as xenin (Althage et al. 2008). K-cells are known to be glucose-sensing cells but much remains to be learned about their physiology. A better understanding of K-cell biology could open the way to the development of new treatments to augment endogenous incretin secretion (Gribble, 2008).

17.3.2 GIP Gene and peptide

The GIP gene is located on chromosome 17, and has 6 exons and 5 introns spanning 10 kb. The gene codes for a pro-GIP protein of 153 amino acids (Fehmann et al. 1995), and this is processed by pro-hormone convertase 1/3 resulting in the production of one main product - active GIP (1–42). Although GIP was initially described as being present in a range of different molecular sizes, there is so far no evidence for the existence of more than one physiologically active form of GIP. The amino-acid sequence of GIP is shown in Fig. 17.4. Both the N-terminus and the central region of the molecule are required for the biological activity of GIP (Fehmann et al. 1995).

17.3.3 Assays for GIP

Most assays for GIP are not specific for the biologically active form since they detect all circulating GIP immunoreactivity. This has given rise to contradictory results in the GIP literature and investigators need to be aware of this issue. Furthermore, the relative amounts of 1–42 and 3–42 forms vary in the fasting and postprandial states, although the 1–42 biologically active form accounts for around 35% of measured immunoreactivity.
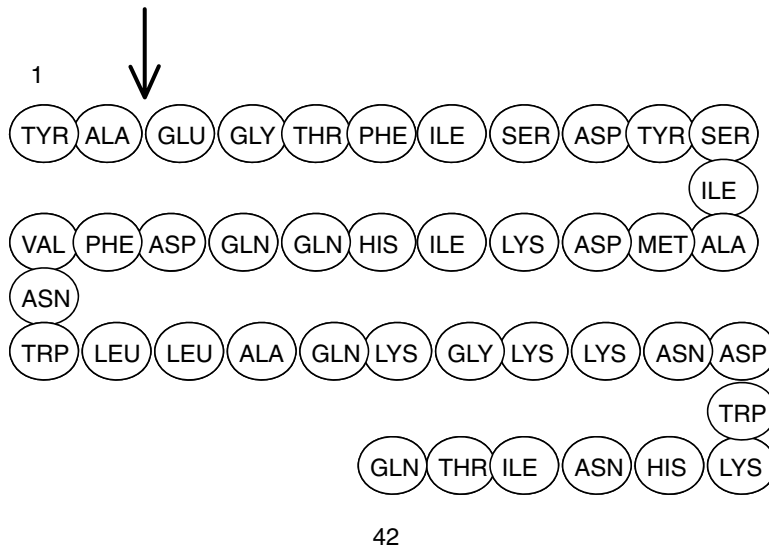
Fig. 17.4 Amino acid sequences of GIPAmino acid sequences of active GIP (1–42) is shown in the accompanying cartoon. The site of cleavage by enzyme DPP IV is shown by an arrow (Fehmann et al. 1995)

17.3.4 GIP receptors

The GIP receptor (GIPR) is a member of the B-family of G protein-coupled receptors, possessing seven membrane-spanning domains, and that also includes receptors for VIP, glucagon and secretin. The post-receptor pathways in the B-cell include modulation of adenyl cyclase, Ca(2+)-independent phospholipase A2, protein kinase (PK) A and PKB, as well as the Mek1/2-Erk1/2 and p38 MAP kinase (McIntosh et al. 2009). The GIP receptor in the rat is a 455 amino acid protein with molecular weight 52,000 daltons. Other than in pancreatic B-cells, GIP receptors are found on gastric parietal cells, in the duodenum, jejunum, adrenal glands, adipose tissue, pituitary gland and in the brain (Fehmann et al. 1995). The biological function of GIP receptors has been established in some but not all of these tissues. A GIP receptor knockout mouse has been produced (GIPR-/-), which exhibits higher blood glucose levels and impaired initial insulin response after oral glucose load. This suggests that a defect of GIP signalling might contribute to the pathogenesis of diabetes (Miyawaki et al. 1999). Interestingly, high-fat diets in GIPR-/- worsen glycaemic responses after mixed meals, further suggesting that a defect in GIP might contribute to the onset of diabetes.

17.3.5 Kinetics of GIP secretion

Circulating GIP concentrations rise within 15 minutes of ingestion of nutrients, as a result of direct nutrient stimulation of proximally situated K-cells. The plasma concentration of GIP peaks at around 250 pM within 30–45 minutes of ingestion of nutrients, and returns to basal values by 2–4 hours (Fig. 17.5) (Ranganath et al. 2001). Circulating GIP concentrations are at their lowest in the fasting state, but once feeding begins during daytime, concentrations of GIP do not return to fasting levels late until midnight (Elliott et al. 1993). Various luminal and non-luminal factors modulate GIP secretion. Serum triglycerides tend to parallel GIP levels throughout the day, suggesting that lipid rather than carbohydrate has the dominant influence on GIP secretion.
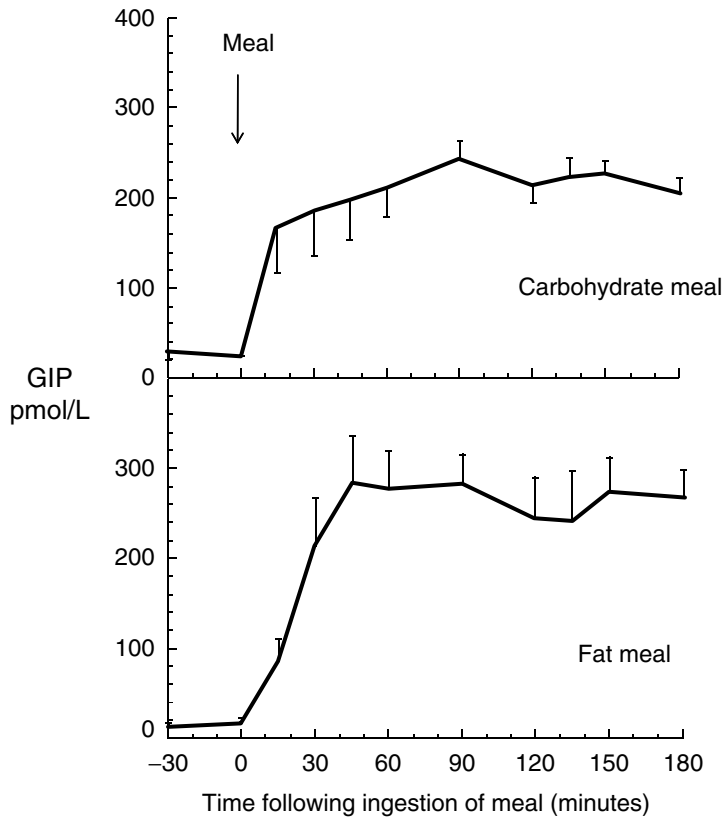
Fig. 17.5 Single meal GIP responses to oral carbohydrate and fat in 6 lean subjects (Mean ± SEM). Circulating GIP concentrations are low in the fasting state increasing rapidly upon ingestion of liquid carbohydrate or fat reaching near-peak concentrations by 30 to 60 minutes. Little difference is seen in GIP responses between carbohydrate and fat meal in lean subjects (Ranganath et al. 2001)

17.3.6 Degradation of GIP

The aminopeptidase, dipeptidyl peptidase IV (DPP IV), found in the endothelium of the local capillary bed within the intestinal wall, is important for the initial inactivation of GIP. Cleavage by DPP IV generates an inactive N-terminally truncated metabolite, GIP (3–42), which is a major circulating form. Subsequently, the peptides may be degraded by other enzymes and extracted in an organ-specific manner. Intact GIP, initially carried in the portal blood, is inactivated by hepatic DPP IV before further degradation by peripheral tissues. The kidney is important for the final elimination of these metabolites (McIntosh et al. 2009; Deacon, 2004). There is uncertainty whether GIP metabolites affect the action of intact GIP. An antagonistic role at the GIP receptor was initially proposed for (3–42) form but has not been convincingly demonstrated (Deacon, 2004).

17.3.7 Regulation of GIP secretion

Ingestion of nutrients leads to release of GIP from K-cells; carbohydrate and fat macronutrients are the main stimuli and appear nearly equal in their ability to stimulate GIP secretion. Only carbohydrate-mediated GIP secretion leads to insulin secretion whereas this is not the case for fat- and

protein-mediated GIP secretion. Actual absorption of nutrient, and not merely its presence within the intestinal lumen, is required for release of GIP from the K-cell. The GIP secretory response is abolished by the blockade of glucose absorption by phlorizin or chylomicron formation with pluronic L81 (Marks V. GIP – The obesity hormone. In: Current Approaches Obesity et al. 1988; Shimotoyodome et al. 2009). Other nutrient-derived extracellular substances such as meat hydrolysate, glyceraldehyde, and methylpyruvate increase GIP release from a cell line (Li & Wice, 2005). The rate of nutrient entry into the small intestine determined by gastric emptying may further modulate secretion of GIP. Rapid gastric emptying as occurs in post-gastrectomy dumping syndrome causes marked increase in GIP secretion (Gebhard et al. 2001). The physical state of the meal may also play an important role in modulating endocrine and metabolic responses to food since homogenised meals induced a higher GIP response (Peracchi et al. 2000). Functional foods containing cyclodextrin starch, guar gum and xanthan gum that decreased the glycaemic response and delayed gastric emptying also decreased the postprandial GIP responses (Nunes & Malmlof 1992). The influence of the individual nutrient factors is considered in greater detail in the next section.

A series of local and systemic neuroendocrine factors also influence GIP secretion. Enteric neurons stimulate GIP release in vivo through the action of neuropeptides such as bombesin (Li & Wice, 2005), although there continues to be debate about the importance of the neural regulation of GIP secretion. It has been observed that increased GIP secretion occurs in GLP-1 -/- mice (Pederson et al. 1998), raising the possibility that insulin or GLP-1 may influence GIP secretion. Apart from intestinal luminal factors, systemic factors also modulate GIP secretion. Pancreatic glucagon (Ranganath et al. 1999), predominantly present during the fasting state, suppresses the secretion of GIP.

17.3.8 Dietary carbohydrate

Actively absorbed sugars such as glucose and galactose stimulate GIP secretion (Marks V. GIP – The obesity hormone. In: Current Approaches Obesity et al. 1988). Phlorizin blocks active transport of glucose across the intestine and prevents GIP secretion. Food deprivation causes a decrease in GIP synthesis and secretion (Higashimoto et al. 1995). The effect of sucrose on GIP secretion is uncertain, with some suggesting no increase (Flatt et al. 1990) and others reporting a substantial increase (Mazzaferri et al. 1984). Inhibition of sucrose breakdown by alpha-glucosidase inhibitors decreased meal-related GIP secretion (Ranganath et al. 1998). Preventing breakdown of complex carbohydrates by amylase inhibition also decreased GIP secretion (Boivin et al. 1988). Modest variations in the initial rate of duodenal glucose entry may have profound effects on subsequent glycemic, insulin, and incretin responses (O'Donovan et al. 2004). Overall the indications are that normal carbohydrate digestion and absorption of glucose in the gut are required for GIP secretion.

17.3.9 Dietary fat

The role of fat ingestion in the regulation of postprandial blood glucose and insulin levels has received far less attention than carbohydrate intake, which has been assumed to be the dominant influence (Shimotoyodome et al. 2009). Long, but not short or medium chain fatty acids are at least as powerful stimuli of GIP secretion than equimolar amounts of carbohydrate. Triglycerides are normally converted to long chain fatty acids and monoglycerides prior to absorption in the bowel, and are also a powerful stimulus for GIP release (Marks V. GIP – The obesity hormone. In: Current Approaches Obesity et al. 1988). There is evidence, at least in animals, that dietary triglyceride augments glucose-induced insulin secretion via gut-derived GIP, while diacylglycerol reduces GIP

secretion, and therefore the insulin response (Shimotoyodome et al. 2009). Pluronic L-81, which inhibits chylomicron formation in the small intestine, reduces GIP secretion. Similarly, fat malabsorption, either due to pancreatic exocrine failure or action of the lipase inhibitor (Orlistat), is associated with impaired GIP secretion. Altogether, this evidence suggests that digestion and absorption of dietary triglycerides are required for normal GIP secretion.

The influence of different types of dietary triglyceride on GIP secretion has received much attention. Diets rich in MUFA improve glucose tolerance, and this might involve increased GIP secretion (Thomsen et al. 1999). Diets enriched with polyunsaturated fatty acids (PUFA) also augment insulin secretion and post-heparin LPL activity, but these effects appear to be independent of changes in GIP (Lardinois et al. 1987). GIP concentrations have been shown to be relatively lower in response to ingestion of fish oil, compared to other fats such as cocoa butter (SFA), olive oil (MUFA) or corn oil (PUFA). The dietary ratio of PUFA/SFA may therefore influence the postprandial GIP response (Musso et al. 2009). In another study, similar GIP responses were observed with MUFA (olive oil) and PUFA (corn oil), but lower responses were observed with SFA (cocoa butter) (Lardinois et al. 1988). These findings suggest that both the degree of saturation of fatty acids in triglycerides and source of the individual triglyceride has different effects on GIP secretion. Lastly, bile is important in the absorption of dietary fat and it is no surprise that intraluminal bile acid administration in dogs influences fat-stimulated GIP release (Takahashi et al. 1996).

17.3.10 Dietary protein and amino acids

In contrast to the influences of carbohydrate and fat, most studies suggest that dietary protein appears to have only a minor effect on GIP secretion. After protein ingestion, the early GIP response correlates with the insulin but not glucagon response, suggesting that early GIP secretion after protein ingestion may be have a role in islet hormone secretion. Postprandial increase in amino acid concentrations interact with increased glucose during mixed meal consumption and leads to GIP-mediated insulin secretion.

There are differences between individual aminoacids in their ability to increase GIP secretion. Tryptophan administration results in increased secretion of GIP and glucagon (Tsiolakis & Marks, 1984). In animals, the aminoacids arginine, cysteine, and histidine increased secretion of GIP and insulin. In contrast, threonine had no effect , while alanine, hydroxyproline and lysine all increased GIP but not insulin secretion (Flatt et al. 1991). These results suggest that a range of essential and nonessential neutral and basic amino acids can stimulate the release of GIP. However, as with protein consumption, GIP made only a modest contribution to the stimulation of insulin secretion following administration of amino acids in the presence of glucose (Flatt et al. 1991).

17.3.11 Miscellaneous influences on GIP secretion

When consumed with a mixed meal ethanol decreases the incretin levels in the early postprandial period and aggravates postprandial lipemia in type 2 diabetic patients (Dalgaard et al. 2004). There are contradictory reports with regard to fasting, some studies suggesting no change in GIP secretion while others observed increased responses. Insulin-induced hypoglycemia has been shown to result in a modest increase in GIP secretion (Jorde et al. 1981).

Geographical differences in GIP has been described since Southern Europeans show higher dietary GIP and insulin responses that may provide an explanation for attenuated postprandial triacylglycerol and apolipoprotein B-48 responses in this group (Jackson et al. 2000).

17.3.12 Eating behaviour

Humans are periodic feeders and energy consumption usually occurs in a social context. Therefore eating behaviour, influenced by the social context, is important in health and disease. It has been suggested that smaller and more frequent meals may be associated with better health, whereas large and more erratic meals increase the risks of obesity and diabetes. Fewer but larger daily meals have been shown to result in increased levels of GIP (Jones et al. 1995) and conversely more frequent meals was associated with decreased GIP levels (Jones et al. 1993). It has been suggested that larger meal sizes and meals with high caloric value that are associated with exaggerated GIP responses and increased rates of gastric emptying, may partly account for the apparent associations of health with meal size and frequency (Ebert & Creutzfeldt, 1989). The association between meal size and GIP response suggests the existence of rapid mechanisms of adaptation of the GIP-producing cells to the incoming load (Beck et al. 1984). It has been suggested that the incretin defect in type 2 diabetes might be overcome by ingesting a larger meal; however, in practice this is not a realistic option since calorie restriction and weight loss are major priorities in patient management.

17.3.13 Satiety/hunger

Food intake in humans is influenced by a complex interaction of biological factors and social context. Satiety and hunger are influenced by short and long term afferent information about ingested and stored nutrients received from the gastrointestinal tract, liver and adipose tissue. This information reaches the brain through both neural and blood borne routes – and is mediated by nutrient and endocrine signals. Control of energy intake is tightly coupled to control of energy expenditure such that there is usually a reciprocal relationship between energy intake and energy expenditure (EE). Since GIP concentrations increase rapidly following food intake it has been suggested that the postprandial GIP response may be an important regulator of short-term appetite. However, there is little information on the effect of GIP on human energy balance (Daousi et al. 2009). In a recent study involving infusion of synthetic GIP, we observed a trend for healthy subjects to report higher hunger scores and a reduction in EE, whereas these parameters remained unchanged in people with T2DM (Daousi et al. 2009). If confirmed, these findings could suggest that resistance to GIP in T2D may be more widespread and not merely confined to the pancreatic B-cell. It may also suggest, if confirmed, that such GIP resistance by decreasing hunger may limit food intake and protect against obesity and diabetes.

17.4 Effects of GIP (Fig. 17.6)

Insulin secretion: An important physiological property of GIP is its ability to promote insulin secretion in a glucose-dependent manner, without inducing hypoglycaemia (Byrne et al. 1998; Wideman & Kieffer, 2004). Glucose entry into B-cell results in formation of ATP which phosphorylates potassium (K)-channels in the cell membrane leading to their closure, in turn triggering calcium entry into cell and exocytosis of vesicular insulin. GIP acts on the pancreatic B-cell by binding to a specific receptor that is coupled to glucose entry and metabolism. c-AMP mediated GIP post receptor events either potentiate the phosphorylation of K-channels and therefore cellular calcium influx and/or directly increase intracellular calcium concentrations leading to insulin release (Fig. 17.7). A GIP
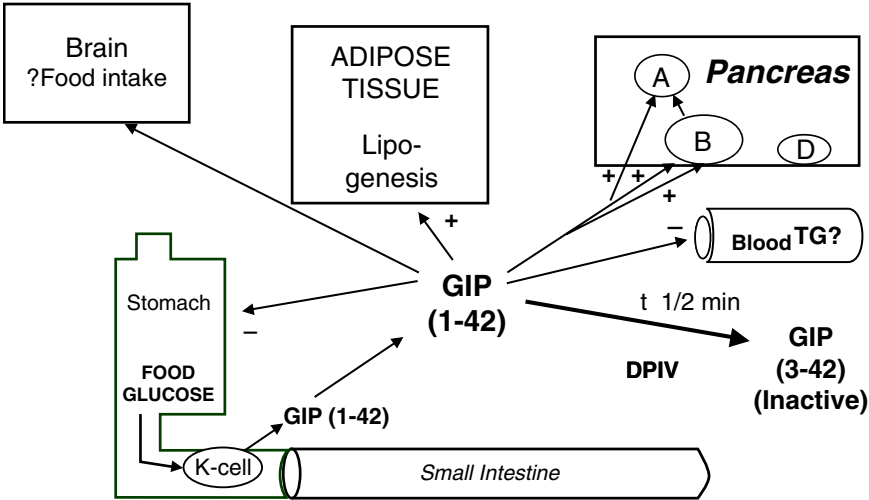
Fig. 17.6 Pancreatic and Extra-pancreatic effects of circulating GIP. GIP after secretion has a number of biological effects in health that are shown in this cartoon (+ = increase; - = decrease)
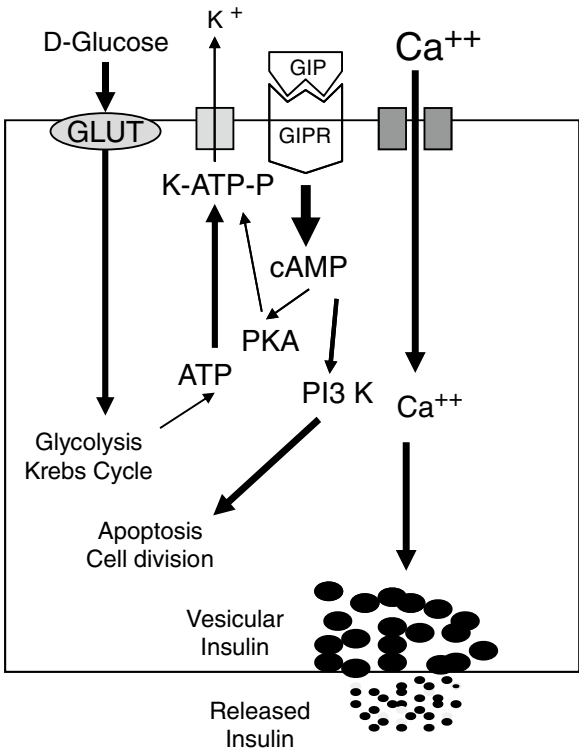
Fig. 17.7 Interplay of glucose and incretins (here GIP is depicted) on the pancreatic B-cell.The entry and metabolism of glucose generates ATP. Phosphorylation of K-channels by ATP is potentiated by GIP mediated c-AMP protein kinases allows increased calcium entry and subsequent insulin release. C-AMP dependent phopsphoinostiol pathways appear to be involved in maintaining B-cell mass by effects on apoptosis and cell division (Byrne et al. 1998; Wideman & Kieffer, 2004)

knockout mouse was found to exhibit impaired glucose tolerance (Miyawaki et al. 1999), consistent with the idea that GIP signalling is required for optimal prandial insulin secretion.

B-cells mass: GIP has a trophic effect on B-cells both in terms of enhancing the magnitude of insulin secretion as well as increasing their number. GIP regulates cell proliferation and survival and in the pancreatic islets leads to expansion of cell mass by stimulating B-cell proliferation and induction of islet neogenesis as well as by inhibiting apoptosis (Wideman & Kieffer, 2004). GIP also promotes cell differentiation, from exocrine ductal cells or immature islet progenitors, toward a more differentiated B-cell phenotype (Wideman & Kieffer, 2004; McIntosh et al. 2009).

Glucagon secretion: It is currently unclear whether GIP influences glucagon secretion or action. There are no receptors for GIP on the A-cell in the pancreatic islets, and.glucagon secretion has been found to be both increased (Meier et al. 2003) and unchanged (Ahrén et al. 1991) in response to GIP. Although GIP receptors have been found on D-cells, their function is unclear. Given that the insulin/glucagon ratio is an important determinant of glucose and fat metabolism, it is plausible that GIP interacts directly or indirectly with all the major endocrine cells of the islets, to influence glucose and lipid metabolism.

Stomach: The binding of GIP to gastric parietal cells inhibits H+ production at supra-physiological concentrations in humans. In fact, this was the first property of GIP to be recognized, giving rise to its initial name - gastric inhibitory polypeptide - before the more important insulinotropic property was identified (Brown & Dryburgh, 1971). There is no evidence that GIP affects gastric emptying. However, in animal studies, acid instillation into the stomach increases GIP expression in duodenal mucosa (Wolfe et al. 2000).

Liver: There is no evidence for expression of GIP receptors in the liver or that GIP alters hepatic metabolism directly. The evidence that GIP alters the hepatic extraction of insulin is mixed, some observing (Hanks et al. 1984) and others failing to observe such an effect (Rudovich et al. 2004). Unlike GLP-1, which increases insulin and decreases glucagon secretion, affecting hepatic carbohydrate metabolism, GIP secretion appears to have less of a beneficial effect on the insulin/glucagon ratio.

Intestine: The intestine not only produces and secretes GIP but is also subjected to the effects of GIP. Recently, GIP has been shown to increase absorption of glucose in the small intestine by stimulating SGLT 1 transporters (Singh et al. 2008). Physiological concentrations of GIP do not alter gut motility. Enterocyte insulin resistance have been noted in insulin resistant diabetic states and altered lipid metabolism has been described in the enterocyte under these conditions; an altered enterocyte lipid handling including chylomicron assembly and secretion has been postulated. The role of GIP in small intestine metabolism, an area that is clearly important, is currently not fully understood (Hsieh et al. 2008).

Adipose tissue: In vivo, the release of insulin by GIP and the consequent suppression of free fatty acid release is probably an important action for adipose tissue. GIP has been found to be associated with circulating lipoprotein levels, and it also stimulates lipoprotein lipase, thus promoting triglyceride deposition in adipose tissue. In animals, exogenous and endogenous GIP is able to lower the plasma triglyceride response to a fat load (Ebert et al. 1991). An overactive enteroinsular axis has been suggested to play a key role in the accretion of fat (Marks V. GIP – The obesity hormone. In: Current Approaches Obesity et al. 1988) since GIP has been reported to (a) stimulate fatty acid synthesis, (b) enhance insulin-stimulated incorporation of fatty acids into triglycerides, (c) increase insulin receptor affinity, and (d) increase sensitivity of insulin-stimulated glucose transport. The mechanism of action of GIP-induced effects on adipocytes may have an indirect component through insulin, although the presence of GIP receptors on adipocytes suggests there may also be direct effects (Fehmann et al. 1995). Biological effects of adipocyte GIPR stimulation include an alteration in adipokine secretion, including changes in resistin and adiponectin (Naitoh et al. 2008).

Brain: GIP is a member of the VIP/PACAP/secretin family and is also synthesised in the brain (Nyberg et al. 2005). GIP immunoreactivity has been observed in and around neurones in several areas such as the olfactory bulb, hippocampus, cerebellum, cerebral cortex, amygdala, substantia nigra, and lateral septal nucleus as well as in several nuclei in the thalamus, hypothalamus and brainstem suggesting a function either as a neurotransmitter or neuromodulator (Nyberg et al. 2007). In addition to local brain synthesis, the VIP/PACAP/secretin family members are also released into blood from peripheral sites, especially the gut, circulating in the bloodstream and accessing the brain through the blood brain barrier at several sites (Dogrukol-Ak et al. 2004). Therefore, GIP produced peripherally can access and bind to various regions of the brain.

Receptors for GIP are also present in the brain (Ding et al. 2006) allowing specific interaction and biological effects. This therefore suggests that conditions exist for GIP to modulate brain structure and function. Although very little is known about the effect of GIP on the brain in humans at the moment, in rat brain GIP has been shown to modulate neuronal proliferation (Nyberg et al. 2005), reverse the effects of beta-amyloid fragments on synaptic plasticity (Gault & Hölscher, 2008), and increase locomotor behaviour (Ding et al. 2006).

Interestingly, type 2 diabetes has been identified as a risk factor for Alzheimer's disease and incretin biology is altered in this disease. GIP may therefore be capable of protecting and reversing the detrimental effects that beta-amyloid fragments have on synaptic plasticity (Gault & Hölscher, 2008). The use of GIP and its enzyme-resistant analogues show potential as novel treatment for preventing neurodegenerative disease including those secondary to diabetes.

Eyes: Eyes are developmentally derived from the forebrain. GIP peptide and receptor are also expressed in the eyes (Cho et al. 2002). In animal studies GIP expression has been shown to be strongly up regulated in the epithelial cells of the lens in experimental cataract models (Nakajima et al. 2002). In animal studies there has been a demonstration of GIP and GIP receptor in the retina and their up-regulation in streptozotocin-induced diabetes model (Cho et al. 2002), suggesting a possible role in diabetic retinopathy.

17.5 Application of GIP to disease states (Table 17.2)

Diabetes mellitus: The possible role of GLP-1 in the treatment of type 2 diabetes is being investigated by clinical trials. GIP secretion in T2D has had variable reports, some suggesting no change, some suggesting an increase and others a decrease. Administration of GIP did not augment insulin secretion or restore euglycaemia in type 2 diabetes, providing evidence for resistance to the peptide (Nauck et al. 1986). However, inhibition of the K(ATP) channels of the diabetic B-cell using sulphonylureas appears to restore insulin response to GIP thus overcoming the B-cell resistance to GIP

Table 17.2 Summary of role of GIP in Diabetes and Obesity

1. GIP is an important incretin hormone to maintain euglycaemia in health
2. Resistance to GIP occurs in T2D at the B-cell and may play a part in insulin secretion failure in T2D
3. Current thinking suggests that GIP may be more important in lipid storage and metabolism
4. Antagonists to GIPR in animals such as mice decreases lipid storage, body fat stores and also paradoxically improves glucose tolerance preventing diabetes
5. Both pro-GIP and anti-GIP strategies have been proposed in the treatment of obesity and diabetes

This table lists key facts of GIP including how they relate to carbohydrate and lipid metabolism in obesity and diabetes. GIP:glucose-dependent insulinotropic polypepide. T2D: type 2 diabetes mellitus

(Aaboe et al. 2009). GIP, like GLP-1, cannot be given orally due to degradation in the gut; interest in GIP as a treatment of type 2 diabetes has therefore been slow to develop. Inhibitors of the enzyme that degrades GIP, DPPIV enzyme, are increasingly being used in the treatment of type 2 diabetes and have the virtue of oral administration. Significant increase in postprandial GIP concentrations, along with GLP-1, occurs after DPP IV inhibition along with improvement in insulin secretion and glycaemic control; how much of the beneficial effect of DPP IV inhibition is due to GIP is unclear. The long term safety of DPP IV inhibition is unknown since it is not only bioactive GIP and GLP-1 which circulate for longer but a number of other endogenous peptides as well (Doupis & Veves, 2008).

Studies on alteration in GIP secretion in prediabetic states show a mixed picture, some suggesting no change such as those with low birth weight , and others showing a decrease such as in first-degree relatives of patients with T2D pointing to an early, possibly genetic defect . A reduced hepatic insulin extraction in response to GIP may compensate for reduced insulin secretion in normal-weight and normal glucose tolerant first-degree relatives of T2D patients (Rudovich et al. 2004). The foregoing discussion would appear to suggest that re-establishing the biological actions of GIP is beneficial and should be goal of therapy in T2D. Indeed some long acting analogues of GIP enhance insulin release and decrease glucose in vivo in a commonly used animal model of T2D (O'Harte et al. 2000). Also, GIPR-/- mice have higher blood glucose levels with impaired initial insulin response after oral glucose load, suggesting that a defect of GIP in the entero-insular axis may contribute to the pathogenesis of diabetes (Miyawaki et al. 1999). High-fat diets in GIPR-/- worsen glycaemic responses after mixed meals further suggesting that a defect in GIP may contribute to the pathogenesis of diabetes .

In view of the foregoing discussions of the phenotypes of the GIP-/- and GIPR-/- mice, which appear to be more diabetes prone, it is paradoxical that there is evidence suggesting that abolishing the effect of GIP might be beneficial in T2D. For example, active immunisation against GIP has been shown to improve blood glucose control in an animal model of obesity/diabetes (Irwin et al. 2009). Since GIP appears to play a role in lipid physiology, and elevated levels of GIP have been associated with obesity (Marks V. GIP – The obesity hormone. In: Current Approaches Obesity et al. 1988), antagonising GIP action has been proposed as a therapeutic strategy for obesity. This concept has recently been reinforced by the observation that GIP receptor knock-out mice are protected from high-fat diet-induced obesity (Miyawaki et al. 2002). However, eliminating the effect of endogenous GIP may at the same time impair postprandial insulin secretion, thereby disturbing glucose homeostasis. Therefore, therapeutic strategies based on either augmenting or antagonising GIP action are far from being established alternatives for the future therapy of T2D or obesity.

Bariatric surgery: Bariatric surgery is associated with a rapid improvement in glucose tolerance long before weight changes occur. It is hypothesized that endocrine and metabolic factors are altered by the surgery leading to the observed beneficial effects. Laparoscopic gastric banding leads to weight loss and metabolic improvement but does not change GIP responses (Shak et al. 2008).

However when the proximal bowel is excluded by Roux-en-Y gastric bypass and the biliopancreatic diversion leading to the early arrival of a meal in the terminal ileum, GIP and GLP-1 responses are increased and has been postulated to account for the metabolic benefits post-surgery (Patriti et al. 2004; Laferrere et al. 2008); such improvement is very early after surgery (Laferrere et al. 2008). The place of GIP in obesity surgery remains to be clarified.

Obesity: Obesity occurs as a mismatch between energy intake and energy expenditure. Excess calorie intake, easier to achieve by consuming more calorie dense fatty foods, is clearly an important factor in obesity. Since we are experiencing an epidemic of obesity (and consequently diabetes), a better understanding of pathophysiology of obesity, including the role of food intake and appetite,

and the development of effective treatments are urgently needed. Appetite signals including those arising in the brain may be important in modulating food intake. There are few studies that have examined the effect of GIP originating in the periphery, such as the gut, on the brain and appetite (Daousi et al. 2009). Unlike GLP-1 administration that has been associated with long term weight loss, no such studies have been undertaken with GIP or a GIP antagonist.

Experimental obesity can be produced in animals by feeding them 'confectionary style' or 'cafeteria' diets; such diets differ in composition (high fat) but not total energy (Marks V. GIP – The obesity hormone. In: Current Approaches Obesity et al. 1988). Such high-fat diet induced obesity has become an important investigative model. GIP production and secretion are induced by high fat diets in such models. Human studies employing high fat intake also show hypersecretion of GIP or hypergGIPaemia and the loss of normal inhibitory effect of insulin upon fat-stimulated GIP release (Marks V. GIP – The obesity hormone. In: Current Approaches Obesity et al. 1988). This led investigators to postulate a model of obesity due to excess GIP action more than 20 years ago (Marks V. GIP – The obesity hormone. In: Current Approaches Obesity et al. 1988). Experiments using knockout mice suggest that the lack of the GIP receptor prevents diet-induced and high-fat induced obesity, preserves insulin sensitivity, lowered respiratory quotient (by burning fat as the preferred energy substrate) and increased energy expenditure due to increased locomotor activity (Miyawaki et al. 2002; Hansotia et al. 2007). Aging is associated with increased fat mass and decreased lean mass, and knocking out GIP receptor in mice can prevent the development of aging-associated insulin resistance through body composition changes (Yamada et al. 2007). Obesity and its metabolic consequences, induced by ovariectomy in mice, can be prevented by GIP-receptor knockout (Isken et al. 2008). The evidence presented so far has lead to an intriguing hypothesis that ablation of GIP receptor actions may prevent obesity and therefore diabetes. In this regard several groups but especially Flatt and colleagues (Green & Flatt, 2007) have generated a number of GIP analogues that can be tested and is shown in Table 17.3. In the ob/ob mouse early administration of the GIP receptor antagonist (Pro3)GIP prevented the development of diabetes and related abnormalities, thus suggesting that sustained GIP receptor antagonism is a viable approach (Irwin et al. 2007). Even in non-genetic obesity such as high-fat and cafeteria diets fed mice, GIP receptor antagonism both using (Pro(3))GIP and longer acting (Pro(3))GIP[mPEG] decreased body weight, circulating plasma insulin levels and improved glucose tolerance (Gault et al. 2007).

Paradoxically, there is evidence however that GIP *agonists* are beneficial in glucose and lipid metabolism. In mice N-AcGIP(LysPAL37), a longer acting agonist of GIPR, improved glucose tolerance due to enhancement of pancreatic beta cell glucose responsiveness and insulin

Table 17.3 GIP modulation – approaches in therapy

K-Cell secretogogues	Experimental; under development
DPP IV Inhibitors	Sitaliptin, Vildaliptin, ?others
GIP Agonist analogues N-terminal modified	N-AcGIP
Mid-acylated GIP	N-AcGIP(Lys[37]PAL) GIP(Lys[37]PAL)
C-terminal modified	(GIP[mPEG]) D- Ala(2)-GIP or DA-GIP
GIP Antagonist analogues	(Pro3)GIP (Pro3)GIPLys16PAL

This table lists key facts of approaches to GIP therapy in obesity and T2D. For details of analogues consult references in accompanying bibliography (Green & Flatt, 2007; Irwin et al. 2007; Gault et al. 2007; Irwin et al. 2006a; Irwin et al. 2006b; Kerr et al. 2009)

secretion by long term activation of GIPR (Irwin et al. 2006a). Other GIPR agonists such as N-AcGIP (N-terminal modified GIP), as well as mid-GIP acylated molecules such as GIP(Lys(37)PAL) and N-AcGIP(Lys(37)PAL), induced insulin release, improved insulin sensitivity, showed no evidence of GIP-receptor desensitization, increased islet number and islet size; upon administration to diabetic ob/ob mice, body weight, food intake and circulating glucagon were unaltered (Irwin et al. 2006b). In mice prolonged activation of the GIP receptor with GIP[mPEG] counters aspects of impaired beta-cell function and age-related glucose intolerance (Kerr et al. 2009).

We cannot fully know at the moment whether a clinical approach to obesity and therefore to diabetes should focus on pro-GIP or anti-GIP strategies. Whether these paradoxically opposite properties of GIP analogues are due to differences in duration of action at the GIPR is not clear. This is not a unique situation since chronically elevated parathyroid hormone in primary hyperparathyroidism leads to bone destruction while intermittent PTH administration leads to bone formation. There are also well known examples of major species differences in endocrine regulators, and so it is by no means assured that the physiology of GIP in humans is the same as in mice.

Summary

- GIP is an intestinal hormone with an important role in maintenance of B-cell function and mass in health
- In type 2 diabetes, resistance to GIP at the B-cell appears to hinder a therapeutic role for the peptide
- GIP promotes triacylyglycerol accumulation is adipose tissue and behaves as an obesity hormone
- Blockade of GIP receptor has been shown in animals has been shown to decrease and prevent high-fat induced obesity and it's complications
- Further research is urgently required to clarify whether pro-GIP or anti-GIP approaches should be employed in obesity and diabetes

---

Key Terms

GIP: A hormone secreted by small intestinal cells having multiple biological effects in the body

GIPR: The receptor that mediates the biological actions of glucose-dependent insulinotropic polypeptide receptor

K-cell: The small intestinal GIP secreting cell present in greatest density in proximal small bowel

DPP IV: The enzyme that degrades incretins including GIP as well as a host of other biological molecules and is mainly responsible for the very short half life

GIP-/- mice: A mouse model where the gene for GIP has been deleted to allow a study of the consequences of lack of biological GIP hormone

GIPR -/- mice: A mouse where the gene for GIP receptor has been deleted to allow a study of the consequences of lack of biological GIP activity

References

Aaboe K, Knop FK, Vilsboll T, Volund A, Simonsen U, Deacon CF, et al. J Clin Endocrinol Metab. 2009;94:603–8.

Ahrén B, Pettersson M, Uvnäs-Moberg K, Gutniak M, Efendic S. Diabetes Res Clin Pract. 1991;13:153–61.

Althage MC, Ford EL, Wang S, Tso P, Polonsky KS, Wice BM. J Biol Chem. 2008;283:18365–76.

Beck B, Villaume C, Chayvialle JA, Gariot P, Ulmer M, Desalme A, et al. Peptides. 1984;5:403–6.

Boivin M, Flourie B, Rizza RA, Go VL, DiMagno EP. Gastroenterol. 1988;94:387–94.

Brown JC, Dryburgh JR. Can J Biochem. 1971;49:867–72.

Byrne MM, Gliem K, Wank U, Arnold R, Katschinski M, Polonsky KS, et al. Diabetes. 1998;47:1259–65.

Cho GJ, Ryu S, Kim YH, Kim YS, Cheon EW, Park JM, et al. Curr Eye Res. 2002;25:381–8.

Dalgaard M, Thomsen C, Rasmussen BM, Holst JJ, Hermansen K. Metabol. 2004;53:77–83.

Daousi C, Wilding JP, Aditya S, Durham BH, Cleator J, Pinkney JH, et al. Clin Endocrinol (Oxf). 2009;71:195–201.

Deacon CF. Horm Metab Res. 2004;36:761–5.

Ding KH, Zhong Q, Xie D, Chen HX, Della-Fera MA, Bollag RJ, et al. Peptides. 2006;27:2750–5.

Dogrukol-Ak D, Tore F, Tuncel N. Curr Pharm Des. 2004;10:1325–40.

Doupis J, Veves A. Adv Ther. 2008;25:627–43.

Ebert R, Creutzfeldt W. Acta Diabetol Lat. 1989;26:1–15.

Ebert R, Nauck M, Creutzfeldt W. Horm Metab Res. 1991;23:517–21.

Elliott RM, Morgan LM, Tredger JA, Deacon S, Wright J, Marks V. J Endocrinol. 1993;138:159–66.

Fehmann HC, Goke R, Goke B. Endocr Rev. 1995;16:390–410.

Flatt PR, Bailey CJ, Kwasowski P, Swanston-Flatt SK. Diabetes Res. 1990;13:23–8.

Flatt PR, Kwasowski P, Howland RJ, Bailey CJ. J Nutr. 1991;121:1123–8.

Gault VA, McClean PL, Cassidy RS, Irwin N, Flatt PR. Diabetol. 2007;50:1752–62.

Gault VA, Hölscher C. J Neurophysiol. 2008;99:1590–5.

Gebhard B, Holst JJ, Biegelmayer C, Miholic J. Dig Dis Sci. 2001;46:1915–23.

Green BD, Flatt PR. Best Pract Res Clin Endocrinol Metabol. 2007;21:497–516.

Gribble FM. Diabet Med. 2008;25:889–94.

Hanks JB, Andersen DK, Wise JE, Putnam WS, Meyers WC, Jones RS. Endocrinol. 1984;115:1011–8.

Hansotia T, Maida A, Flock G, Yamada Y, Tsukiyama K, Seino Y, et al. J Clin Invest. 2007;117:143–52.

Higashimoto Y, Opara EC, Liddle RA. Comp Biochem Physiol Part C Pharmacol, Toxicol, Endocrinol. 1995;110:207–14.

Hsieh J, Hayashi AA, Webb J, Adeli K. Atheroscler Suppl. 2008;9:7–13.

Irwin N, Green BD, Gault VA, Cassidy RS, O'Harte FP, Harriott P, et al. Peptides. 2006a;27:893–900.

Irwin N, Clarke GC, Green BD, Greer B, Harriott P, Gault VA, et al. Biochem Pharmacol. 2006b;72:719–28.

Irwin N, McClean PL, O'Harte FP, Gault VA, Harriott P, Flatt PR. Diabetol. 2007;50:1532–40.

Irwin N, McClean PL, Patterson S, Hunter K, Flatt PR. Biol Chem. 2009;390:75–80.

Isken F, Pfeiffer AF, Nogueiras R, Osterhoff MA, Ristow M, Thorens B, et al. Am J Physiol Endocrinol Metab. 2008;295:E350–5.

Jackson KG, Zampelas A, Knapper JM, Roche HM, Gibney MJ, Kafatos A, et al. Am J Clin Nutr. 2000;71:13–20.

Jones PJ, Leitch CA, Pederson RA. Am J Clin Nutr. 1993;57:868–74.

Jorde R, Waldum HL, Burhol PG. Scand J Gastroenterol. 1981;16:219–23.

Jones PJ, Namchuk GL, Pederson RA. Metab: Clin & Experim. 1995;44:218–23.

Kerr BD, Irwin N, Flatt PR, Gault VA. Peptides. 2009;30:219–25.

Laferrere B, Teixeira J, McGinty J, Tran H, Egger JR, Colarusso A, et al. J Clin Endocrinol Metab. 2008;93:2479–85.

Lardinois CK, Starich GH, Mazzaferri EL, DeLett A. J Am Coll Nutr. 1987;6:507–15.

Lardinois CK, Starich GH, Mazzaferri EL. J Am Coll Nutr. 1988;7:241–7.

Li L, Wice BM. Am J Physiology – Endocrinol & Metab. 2005;288:E208–15.

Marks V. Current Approaches Obesity, Eds James WPT & Parker SW, Duphar Medical Relations, 1988, pp 13–20.

Mazzaferri EL, Starich GH, St Jeor ST. J Clin Endocrinol Metab. 1984;58:640–5.

McIntyre N, Holdsworth CD, Turner DS. Lancet. 1964;2:20–1.

McIntosh CH, Widenmaier S, Kim SJ. Vitam Horm. 2009;80:409–71.

Meier JJ, Nauck MA, Schmidt WE, Gallwitz B. Regul Pept. 2002;107:1–13.

Meier JJ, Gallwitz B, Siepmann N, Holst JJ, Deacon CF, Schmidt WE, et al. Diabetolog. 2003;46:798–801.

Miyawaki K, Yamada Y, Ban N, Ihara Y, Tsukiyama K, Zhou H, et al. Nat Med. 2002;8:738–42.

Miyawaki K, Yamada Y, Yano H, Niwa H, Ban N, Ihara Y, et al. Proc Nat Acad Sci USA. 1999;96:14843–7.

Musso G, Gambino R, Pacini G, De Michieli F, Cassader M. Am J Clin Nutr. 2009;89:558–67.

Naitoh R, Miyawaki K, Harada N, Mizunoya W, Toyoda K, Fushiki T, et al. Biochem Biophys Res Comm. 2008;376:21–5.

Nakajima T, Nakajima E, Fukiage C, Azuma M, Shearer TR. Exp Eye Res. 2002;74:231–6.

Nauck M, Stockmann F, Ebert R, Creutzfeldt W. Diabetologia. 1986;29:46–52.

Nunes C, Malmlof K. Br J Nutr. 1992;68:693–700.

Nyberg J, Anderson MF, Meister B, Alborn AM, Strom AK, Brederlau A, et al. J Neurosci Res. 2005;25:1816–25.

Nyberg J, Jacobsson C, Anderson MF, Eriksson PS. J Neurosci Res. 2007;85:2099–119.

O'Donovan DG, Doran S, Feinle-Bisset C, Jones KL, Meyer JH, Wishart JM, et al. J Clin Endocrinol Metab. 2004;89: 3431–5.

O'Harte FP, Mooney MH, Kelly CM, Flatt PR. J Endocrinol. 2000;165:639–48.

Patriti A, Facchiano E, Sanna A, Gullà N, Donini A. Obes Surg. 2004;14:840–8. 121.

Pederson RA, Satkunarajah M, McIntosh CH, Scrocchi LA, Flamez D, Schuit F, et al. Diabetes. 1998;47:1046–52.

Peracchi M, Santangelo A, Conte D, et al. Br J Nutr. 2000;83:623–8.

Ranganath L, Norris F, Morgan L, Wright J, Marks V. Diabetes Med. 1998;15:120–4.

Ranganath L, Schaper F, Gama R, Morgan L, Wright J, Teale D, et al. Diabetes Metab Res Rev. 1999;15:390–4.

Ranganath LR, Beety JM, Wright J, Morgan LM. Horm Metab Res. 2001;33:57–61.

Rudovich NN, Rochlitz HJ, Pfeiffer AF. Diabetes. 2004;53:2359–65.

Shak JR, Roper J, Perez-Perez GI, Tseng CH, Francois F, Gamagaris Z, et al. Obes Surg. 2008;18:1089–96.

Shimotoyodome A, Fukuoka D, Suzuki J, Fujii Y, Mizuno T, Meguro S, Tokimitsu I, Hase T. Endocrinol 2009 Jan 29 [Epub].

Shuster LT, Go VL, Rizza RA, O'Brien PC, Service FJ. Diabetes. 1988;37:200–3.

Singh SK, Bartoo AC, Krishnan S, MO Schwartz JH, Michael Wolfe M. Obesity (Silver Spring). 2008;16:2412–6.

Takahashi M, Sasaki I, Naito H, Funayama Y, Shibata C, Matsuno S. Tohoku J Exp Med. 1996;178:151–62.

Thomsen C, Rasmussen O, Lousen T, Holst JJ, Fenselau S, Schrezenmeir J, et al. Am J Clin Nutr. 1999;69:1135–43.

Tsiolakis D, Marks V. Horm Metab Res. 1984;16:226–9.

Wideman RD, Kieffer TJ. Horm Metab Res. 2004;36:782–6.

Wolfe MM, Zhao KB, Glazier KD, Jarboe LA, Tseng CC. Am J Physiol Gastrointest Liver Physiol. 2000;279: G561–6.

Yamada C, Yamada Y, Tsukiyama K, Yamada K, Yamane S, Harada N, et al. Biochem Biophys Res Commun. 2007; 364:175–80.

Chapter 18
The Relationship between the IGF System, Nutrition, and Behavior

Moira S. Lewitt

Abbreviations

IGF	Insulin-like growth factor
IGF1R	Type 1 insulin-like growth factor receptor
IGFBP	Insulin-like growth factor-binding protein
GH	Growth hormone
GHR	Growth hormone receptor
ALS	Acid-labile subunit of the IGFBP-3 ternary complex
kDa	kilodalton
TNF-α	Tumor necrosis factor-alpha

Key Terms

Insulin-like growth factors: IGF-I and IGF-II are ~7 kDa proteins that are ubiquitously expressed, have widespread tissue actions that are regulated by the IGFBPs.

IGFBPs: Family of six proteins with high affinity for IGF-I and IGF-II that have stimulatory or inhibitory effects on IGF actions, depending on the cell milieu, e.g., limited proteolysis by IGFBP proteases, interaction with other proteins in the cell matrix, or on the cell surface.

"Free" IGFs: Those IGFs that are unbound or readily released from binary complexes with IGFBPs, and therefore available to act on target cells.

Endocrine actions of IGFs: IGF effects on cells in tissues distant to where the IGF was produced, with transport via the circulation.

Paracrine/autocrine actions of IGFs: IGF effects in the local tissue environment on cells of the same or different type to those producing the IGFs.

Proinflammatory cytokines: Cytokines produced by activated immune cells and involved in mediating inflammatory effects, e.g., TNF-α.

Plasticity: Ability of brain structure and/or function to adapt to environmental change.

M.S. Lewitt (✉)
Faculty of Science & Technology, University of the West of Scotland, Paisley Campus, PA1 2BE, Paisley, Scotland, UK
e-mail: Moira.Lewitt@uws.ac.uk

18.1 Introduction

Although the insulin-like growth factor (IGF) system appears overwhelming in its complexity, its relationship to nutrition has emerged as a key to understanding its role in health and disease. The responses of this system to acute and chronic changes in nutrient availability in turn have a metabolic impact on many cell types. The actions of this system on specific areas of brain, and the changes observed in a variety of cognitive disorders, suggest an important role for the IGF system in learning, memory, and behavior.

This chapter will describe the IGF system, with a particular focus on its relationship to nutrition, and its functional role in brain. Evidence of a central role for IGFs and nutrition in the cognitive dysfunction of aging and cytokine-induced sickness behavior will be highlighted, and the potential contribution to other areas of health and disease will also be addressed. In the concluding remarks, challenges and recommendations for future research will be made.

18.2 The IGF System and Nutrition

The IGFs (IGF-I and IGF-II) are members of an evolutionarily ancient superfamily of proteins that include insulin and relaxin (Claeys et al. 2002). Ubiquitously expressed, IGFs have paracrine/autocrine actions, in addition to endocrine roles on cell growth and metabolism which are distinct from and complement those of insulin (Le Roith et al. 2001; Clemmons 2006). The spectrum of activity is dependent on the tissue distribution and level of expression of their receptors (the type 1 IGF receptor (IGF1R), insulin receptor, and hybrids of these receptors), on postreceptor signaling, including cross talk with other growth factor signaling pathways, and on interactions with a family of six high affinity IGF-binding proteins (IGFBPs). Differences in receptor affinity and signaling, and the ability of IGFs to bind to IGFBPs distinguishes their metabolic roles from those of insulin.

An overview of the IGF system in the circulation and peripheral tissues is illustrated in Fig. 18.1. IGFs in the circulation exist mainly in a ternary complex with two other proteins, IGFBP-3, and the acid-labile subunit (ALS). This form has a high molecular mass (150 kDa) which is retained in the circulation, thereby limiting the availability of the IGFs (~7 kDa) to the peripheral tissues. The unbound fraction of IGFs and binary complexes with IGFBP-1 to -6 in the circulation are readily available to the peripheral tissues, where IGFs and IGFBPs are also secreted locally. In this review, those IGFs that are unbound or readily released from binary complexes and therefore available to target cells are collectively referred to as "free" IGFs. IGFBPs are key regulators of the activity of IGFs at the tissue level, with both inhibitory and stimulatory effects observed depending on the cell milieu (Firth and Baxter 2002). A number of IGFBP proteases have been described which generate IGFBP fragments with reduced IGF affinity.

Growth hormone (GH) stimulates IGF-I expression peripherally, and IGF-I reaching the pituitary has an inhibitory effect on GH secretion (Fig. 18.2). Nutrition, in the form of total energy and protein consumption, is also an important regulator of serum IGF-I, directly and through stimulation of insulin production. The other proteins of the ternary complex, IGFBP-3 and ALS, are also increased by GH and nutrition, thus stabilizing IGF-I in the circulation and making it a useful clinical marker of GH secretion and nutritional status. GH also has direct, IGF-I-independent, effects on tissue. For example, GH has a direct effect to increase peripheral insulin resistance, while IGF-I has an insulin-sensitizing role (Clemmons 2006). Less is known about the regulation and roles of IGF-II; however, its higher affinity for insulin receptors than IGF-I (Pandini et al. 2002) suggests that it may have a special role in nutrition.
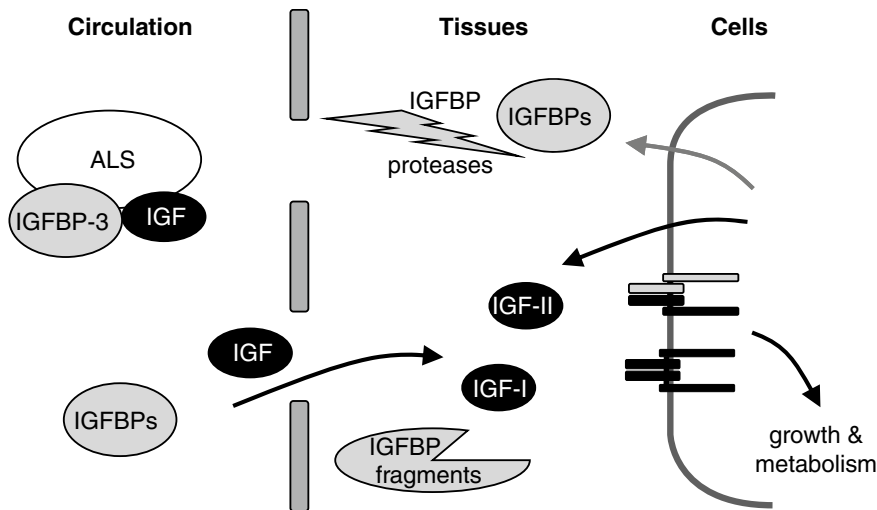
Fig. 18.1 Overview of the IGF system in the circulation and peripheral tissues. The figure illustrates the major proteins involved in the IGF system, including IGF-I and IGF-II, six IGF-binding proteins (*IGFBPs*), the high molecular mass ternary complex of IGFs, IGFBP-3 and the acid-labile subunit (*ALS*) which is retained in the circulation, and IGFBP proteases which have effects in the tissues. IGFs regulate cellular growth and metabolism by interacting with specific receptors on the cell surface
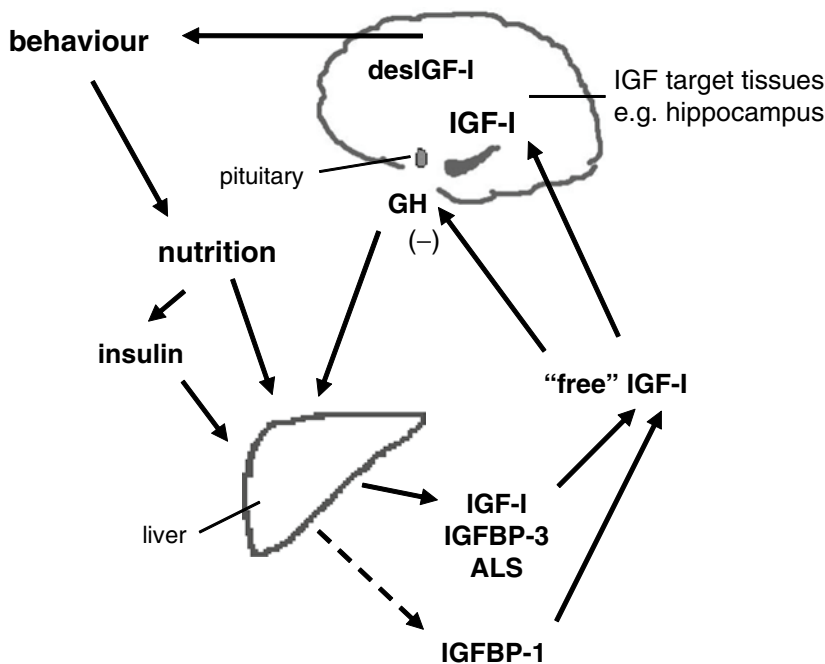
Fig. 18.2 The endocrine IGF system and brain under conditions of normal nutritional intake. The liver has a central role in producing the IGF-I that reaches the circulation, along with IGFBP-3 and the acid-labile subunit (*ALS*), under the stimulation of GH and nutrition. Insulin also stimulates IGF-I, IGFBP-3 and ALS, but inhibits IGFBP-1 production. Under these conditions, appropriate concentrations of IGFs are available to the peripheral tissues, including the brain, where IGF-I activity is known to influence cognitive function and behavior
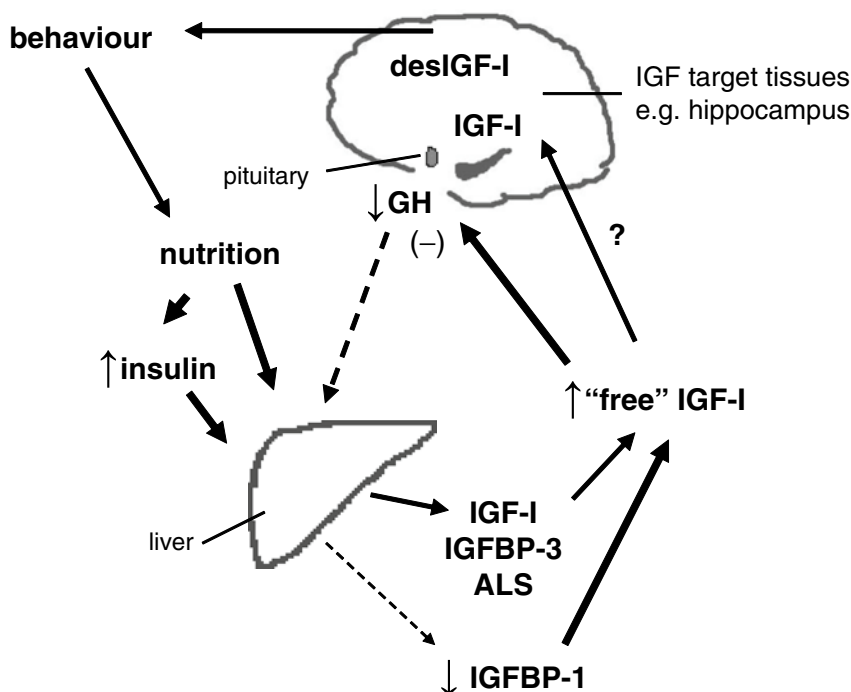
Fig. 18.3 The endocrine IGF system and brain under conditions of excessive food consumption. In obesity, increased portal insulin concentrations suppress IGFBP-1 levels, which increase "free" IGF availability to the peripheral tissues, including the pituitary, where there is feedback inhibition of GH secretion. In the metabolic syndrome, there are many other factors, including chronic inflammation, which may have an impact on the activity of IGF-I in brain

In contrast to the IGFBP-3 ternary complex, which acts as a long-term storage pool of IGFs in the circulation, IGFBP-1 has a short-term nutritional role. Also produced in liver, IGFBP-1 is inhibited by insulin and stimulated by several factors including glucagon and cytokines. The patterns of regulation in the circulation together with its effect, to increase blood glucose, suggest that it indeed has a dynamic role to counter-regulate the availability of IGFs for glucose homeostasis (Lewitt and Baxter 1991; Lewitt et al. 1991). It has been proposed that low IGFBP-1 concentrations are responsible for the increase in "free" IGF-I levels in obesity (Frystyk et al. 1995), which in turn have a negative feedback effect on GH secretion in this condition (Attia et al. 1998). This is illustrated in Fig. 18.3. In contrast, under conditions of reduced calorie and protein intake, shown in Fig. 18.4, decreases in the complex of IGF-I, IGFBP-3, and ALS, along with increases in IGFBP-1, result in reduced "free" IGF-I and increases in pituitary GH production. Under these conditions of malnutrition there is resistance to GH action in peripheral tissues that further reduces production of IGF-I. Total IGF-I and fasting IGFBP-1 concentrations are useful clinical markers of nutritional status (Lewitt and Baxter 1991).

18.3 The IGF System in Brain

The IGF system has a well-established role in the growth and development of the central nervous system (Russo et al. 2005; Åberg et al. 2006) and there is evidence that it continues to have important effects throughout life. Adult brain can regenerate following injury to various regions, including the
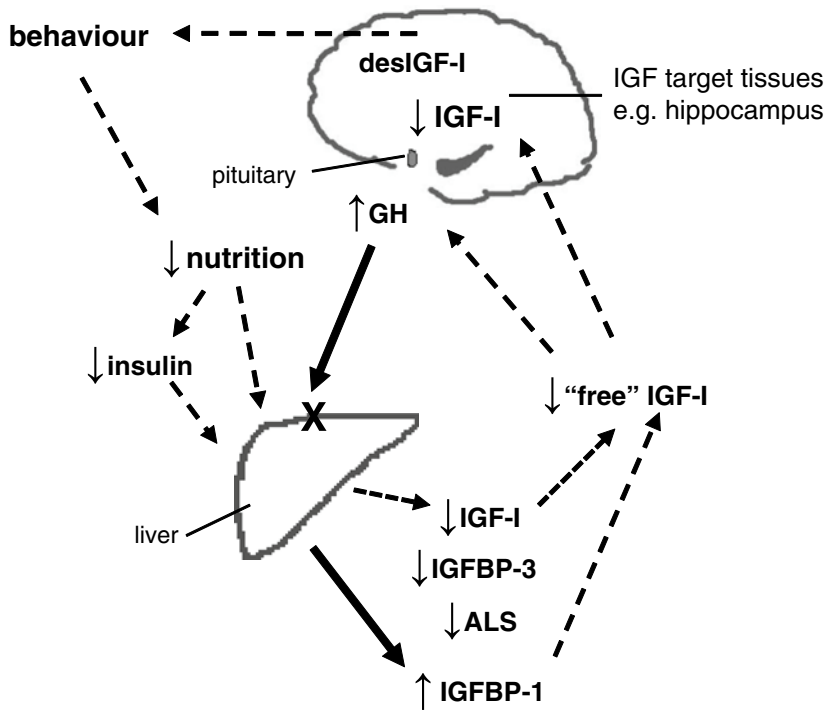
Fig. 18.4 The endocrine IGF system and brain under conditions of reduced nutritional intake. In starvation or malnutrition, decreased portal insulin and increased IGFBP-1 secretion, along with GH resistance and reduced total production of IGF-I, result in reduced "free" IGF-I and increases in pituitary GH production. One can speculate that reduced IGF-I activity in brain may have an impact on cognitive function and behavior

cerebral cortex, and IGFs are of particular therapeutic interest in this context (Russo et al. 2005). It is now emerging that the IGF system is involved in normal cognition. Growth hormone receptors, IGF-I and IGF1R are expressed in the proliferative zones of the adult brain, and IGF-I can stimulate adult hippocampal neurogenesis and may be involved in synaptic plasticity (Åberg et al. 2006; Fernandez et al. 2007; Llorens-Martin et al. 2009). IGFs also maintain normal brain function through effects on nonneuronal cells, such as glial cells and blood vessel endothelial cells. It has been shown that IGF-I is involved in regulating the transport of proteins across the blood-brain barrier (Carro et al. 2002).

The relative roles of the brain paracrine/autocrine IGF system and of systemically derived (endocrine) IGFs, which can cross the blood-brain barrier (Reinhardt and Bondy 1994), are yet to be established. Ames dwarf mice, despite being deficient in endocrine IGF-I, have increased hippocampal neurogenesis and local IGF-I expression (Sun et al. 2006), suggesting that the paracrine/autocrine IGF system is of primary importance. Mice with a forebrain-specific IGF-I deletion, however, are reported to have few brain changes (Davila et al. 2007); while mice with a liver-specific IGF-I deletion and markedly low circulating IGF-I levels have reduced adult hippocampal neurogenesis, which is restored by systemic IGF-I administration (Trejo et al. 2008). Increasing the complexity of the brain IGF system, a variant of IGF-I, which is truncated by three amino acids (des(1-3)IGF-I), has been purified from brain tissue (Sara et al. 1993). While its role is not yet clear, this variant has reduced affinity for IGFBPs and is likely to have higher biological activity than normal IGF-I. The cleaved *N*-terminal tripeptide may have its own neuroprotective actions (Sizonenko et al. 2001). The role of IGFBPs also needs to be considered, and these are differentially expressed in brain, with IGFBP-5 being selectively expressed near IGF-I producing neurons (Bondy and Lee 1993).

18.4 IGFs and Behavior

There is now a body of evidence supporting a role for peripheral IGF-I in behavior in humans and in animals (Table 18.1). Patients with GH deficiency, and therefore reduced IGF-I levels, have reduced cognitive performance, which may be ameliorated during GH replacement (Falleti et al. 2006). A meta-analysis in the "healthy elderly" supports the conclusion that there is a relationship between IGF-I levels and cognitive function (Arwert et al. 2005). Unfortunately, there was no correction for the confounding of age in this study. However another study which made an adjustment for age, reported an association between "free" IGF-I levels and cognitive performance in older individuals living in the community (Landi et al. 2007). In younger adults, aged 20–44 years, a relationship between IGF-I and factors representing psychological well-being has been demonstrated (Undén et al. 2002). A correlation between the increases in IGF-I levels in response to a

Table 18.1 Studies of the relationship between the GH/IGF system and behavior or cognitive function

	Study population	Aspect of GH/IGF system	Outcome	Reference
Human				
	Meta-analyses of studies in the healthy elderly	Serum IGF-I levels	Relationship with cognitive function	Arwert et al. 2005
	Meta-analyses of studies of adults with GH deficiency	GH-deficient, compared to controls	Associated with reduced cognitive function	Falleti et al. 2006
	Older community-living adults	Serum "free" IGF-I and IGFBP-3	Relationship with cognitive function	Landi et al. 2007
	Centenarians	Serum IGF-I levels	Lower IGF-I associated with higher prevalence of dementia	Arai et al. 2001
	Younger adults	Serum IGF-I levels	Relationship with well-being	Undén et al. 2002
	Older adults	IGF-I response to nutritional supplement	Relationship with mood and memory	Arwert et al. 2003
	Postmenopausal women	IGF-I treatment	No effect on cognitive function	Friedlander et al. 2001
Rodent				
	Mice	Treatment with IGF-I or IGFBP inhibitor	Antidepressant and anxiolytic behavior	Malberg et al. 2007
	Exercising mice	Low circulating IGF-I levels (liver-specific IGF-I knockout)	Resistance to effect of exercise on learning and anxiety	Trejo et al. 2008
	Exercising rats	IGF-I treatment	Antidepressant-like behavior	Duman et al. 2009
	Aging rats	IGF-I treatment	Some reversal of emotional reactivity	Markowska et al. 1998
	Diabetic rats	IGF-I treatment	Prevention of deficit in learning/memory	Lupien et al. 2003
	Mice given cytokines centrally	IGF-I treatment	Attenuation of sickness behavior	Bluthé et al. 2006

This table presents human and rodent studies that address the role of the IGF system in behavior or cognitive function. The study population, the main aspect of the IGF system studied, and relevant outcomes in terms of behavior or cognitive function are summarized

nutritional supplement, and mood and memory parameters has been reported (Arwert et al. 2003). There has been one study of the effect of exogenous IGF-I on normal cognitive functioning in humans, showing no effect on memory in healthy postmenopausal women (Friedlander et al. 2001). Several studies have reported the effects of IGF-I treatment in rodents and reported antidepressant-like or anxiolytic effects (see Table 18.1).

18.5   The Role of IGFs and Nutrition in the Cognitive Dysfunction of Aging

A fall in IGF-I and a decline in cognitive function are both part of the normal aging process. Although the fall in IGF-I with age reflects the decline in GH concentrations, there may be an additional effect of reduced nutritional intake (Arai et al. 2001; Lewitt and Hall 2005). To what extent is the IGF system directly responsible for coincident age-related cognitive decline? In rats, IGF-I ameliorates age-related behavioral deficits (Markowska et al. 1998) and the decline in hippocampal neurogenesis (Lichtenwalner et al. 2001). Alzheimer's disease occurs on this background of normal aging, and it is now recognized that impaired insulin and IGF signaling play a central role in the pathophysiology of that disease (de la Monte 2009). Changes in expression of IGFs as well as insulin, IGF1R and insulin receptors, and intracellular signaling molecules are seen in Alzheimer's disease (Rivera et al. 2005; Steen et al. 2005). The recognition that brain insulin deficiency and resistance may be the cause of neuronal cell death has resulted in the terms "type 3 diabetes" and "brain diabetes" being coined (Hoyer 2004; Steen et al. 2005; de la Monte 2009). Centenarians with lower serum IGF-I levels have higher prevalence of dementia (Arai et al. 2001). The observation that IGF-I reduces brain amyloid-β levels raises the possibility that targeting this system may be a therapeutic approach in Alzheimer's disease (Carro et al. 2002). It is well established that reduced IGF-I signaling and dietary restriction are intricately connected and are associated with longevity (Narasimhan et al. 2009), highlighting that the benefits of increasing IGF-I activity to improve cognitive function needs to be weighed against the potential risks. Many tumor cell types express IGF1R and there is interest in targeting this receptor in the management of cancer (Clemmons 2007). Thus, the risk of increased tumor growth should also be considered if endocrine IGF activity is increased to improve brain function.

18.6   Role of IGFs in Cytokine-Induced Disturbances in Behavior and Cognition

Chronic activation of the immune system may be involved in the pathophysiology of altered mental function in a number of disorders (Elenkov et al. 2005). The syndrome of cytokine-induced sickness behavior, with its attendant symptoms of loss of appetite and fatigue, is a common manifestation of infection and malignancy (O'Connor et al. 2008). The IGF and cytokine signaling pathways represent an interface of the endocrine and immune systems. Cytokines are implicated in causing IGF resistance in peripheral tissues by a variety of mechanisms, and it has been proposed that the central effects of inflammation may also act in part by abrogating IGF function. Treatment with IGF-I attenuates the sickness behavior of mice given intracerebroventricular injections of TNF-α (Bluthé et al. 2006). In that study, IGF-I was delivered centrally, along with the cytokine. Peripheral IGF-I administration in mice also reduces the sickness behavior induced by activated immune responses with peripheral lipopolysaccharide (O'Connor et al. 2008).

18.7 Applications to Other Areas of Health and Disease

The observation that the inflammatory mediators can induce IGF resistance and that IGF-I may reduce cytokine-induced behavioral changes has implications for other diseases that are associated with an increased prevalence of depression. There are a variety of such disorders which are now recognized to have underlying chronic inflammation, including obesity and diabetes (Elenkov et al. 2005). Nutritional factors and insulin resistance and/or deficiency also contribute to reduced IGF-I concentrations that are seen in obesity and diabetes. Treatment with IGF-I has been shown to prevent cognitive impairment in diabetic rats (Lupien et al. 2003).

It has been suggested that depressive syndromes should themselves be considered neuroinflammatory in type and relabeled metabolic syndrome type II (McIntyre et al. 2007). It has been shown that antidepressant treatment is associated with a twofold increase in IGF-I protein expression in rat hippocampus (Khawaja et al. 2004) and that antidepressant-induced neural plasticity depends on peripheral IGF-I uptake (Chen and Russo-Neustadt 2007). Nervous pointer dogs, which are a model of panic disorder and severe anxiety, have lower IGF concentrations than normal pointer dogs, and the degree of fearfulness correlates inversely with the IGF-I levels (Uhde et al. 1992). The role of IGFBPs is yet to be fully explored. One study has shown that subjects with bipolar disorders have reduced IGFBP-2 expression in the prefrontal cortex (Bezchlibnyk et al. 2007).

It is now recognized that physical activity has an important influence on brain plasticity (Llorens-Martin et al. 2009). Exercise improves depression in humans and in animal models, and there is a growing body of evidence that this effect on the brain is mediated at least in part by uptake of peripheral IGF-I (Chen and Russo-Neustadt 2007; Trejo et al. 2008; Duman et al. 2009).

Individuals with anorexia nervosa have decreased IGF-I and increased IGFBP-1 levels in the circulation. Although this is expected to decrease brain IGF availability, in this situation it is difficult to unravel the relative roles of nutrition and the IGF system on the behavior disturbance. The observation that the IGF system changes are reversible with refeeding (Counts et al. 1992) suggests that they are markers of the nutritional state and are not involved in the etiology of the disease.

18.8 Conclusions, Challenges, and Recommendations

The IGF system and insulin have distinct but complementary roles in growth and metabolism. There is a growing evidence base supporting a role for both in brain, in neurogenesis, and in functional plasticity, with effects on cognitive function and behavior. Human and rodent studies that address these roles of the IGF system are summarized in Table 18.1, the multiplicity of factors regulating IGF availability in brain is illustrated in Fig. 18.5, and the key features of the IGF system underpinning its relationship to nutrition and behavior are shown in Table 18.2. Further knowledge of the IGF system and nutrition in relation to behavior is a key to understanding how the body integrates somatic and cognitive functioning.

IGF-I is a pleiotropic signal; it modulates cell growth and survival, metabolism, cerebral blood flow, transport of proteins across the blood-brain barrier, and the action of other growth factors and neurotransmitters. One of the research challenges is to fully characterize these pathways, to determine the unique roles of truncated des(1–3)IGF-I and its *N*-terminal tripeptide, and the IGFBPs, and to define the relative importance of the endocrine versus paracrine/autocrine in brain function. In undertaking this, it is impossible to separate a study of the role of nutrition, with its impact on regulation of the IGF system and because of the important effects of IGFs on metabolism.
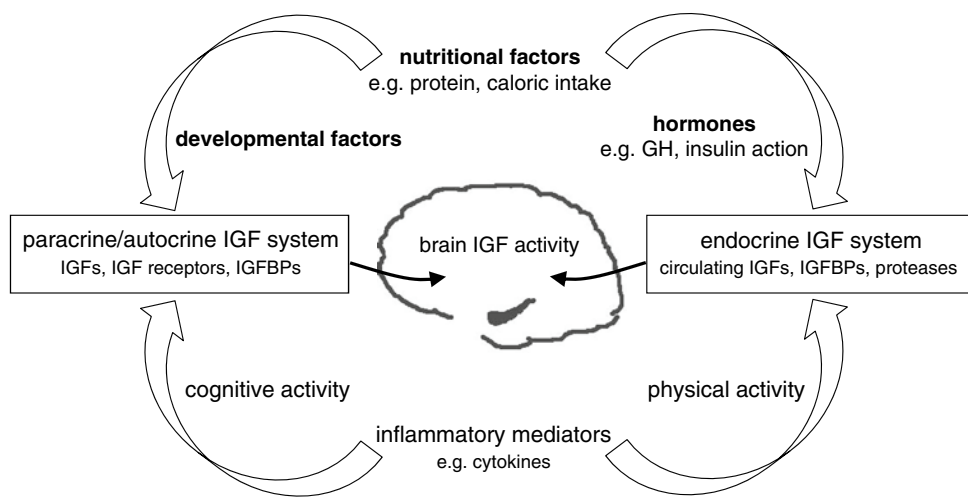
Fig. 18.5 Factors which may impact brain IGF availability for cognitive function and behavior.The figure summarizes some of the factors influencing IGF activity in brain. Some, such as developmental factors and cognitive activity, have the greatest impact on the paracrine/autocrine IGF system. Inflammatory cytokines have effects both centrally and peripherally. The effects of nutrition and hormonal factors on the endocrine IGF system are well established, but these may also have direct on the brain IGFs and receptors signaling that are yet to be documented. Similarly, there may be a central effect of physical activity in addition to its well-documented action to increase availability of peripheral IGF-I to brain

Table 18.2 Key features of the IGF system

1. The insulin-like growth factors (IGF-I and IGF-II) are proteins that are structurally and functionally related to insulin. In addition to insulin-like, metabolic roles, they have effects on cell growth and survival.
2. The IGFs are widely expressed and have effects on cells in the local environment (paracrine/autocrine actions), as well as in distant tissues after transport via the circulation (endocrine actions).
3. The endocrine IGF system is growth hormone-dependent.
4. A family of six high affinity IGF-binding proteins (IGFBPs) are key regulators of the IGF actions on cells. One of these, IGFBP-1, has an important role in nutrition, by inhibiting the effect of IGFs on glucose homeostasis.
5. Good nutrition and physical activity are important for normal function of the IGF system.
6. The IGF system (paracrine/autocrine and endocrine IGFs and IGFBPs) is involved in normal brain development and function throughout life.
7. There is a fall in IGF-I with age which reflects the decline in growth hormone, with an additional effect of reduced nutritional intake.
8. The IGF system mediates some of the effects of disease on learning, memory and behavior.
9. When considering the use of IGF-I as a therapy, the positive effects of the IGF system on metabolism need to be weighed against the potential effects to promote abnormal cell growth (e.g., cancer).

This table lists the key features of the IGF system that underpin its relationship with nutrition and behavior

A sedentary lifestyle underlies the pandemic of obesity, diabetes, and depression, and it is now known that the impact of exercise on cognitive function is linked to its effect on peripheral IGF-I availability. It is well established that serum IGF-I and IGFBP-1 are useful markers of general nutritional status. Future work should focus on the best type of exercise and on the specific nutritional requirements for an appropriate concentration of each of these at each stage of life, in order to develop guidelines for health promotion and disease prevention. It is now recognized that this may have also an impact on the health of offspring and future generations (Pembrey 2002). High IGF activity is associated with reduced longevity and with progression of some tumors. While exogenous

IGF-I is therefore not recommended in otherwise healthy individuals, the challenge for the future is to target relevant tissues for treating disorders of learning, memory, and behavior, such as those associated with aging and depression.

Summary Points

- IGFs have paracrine/autocrine and endocrine roles in growth and metabolism.
- IGFBPs are key regulators of tissue IGF activity, and may inhibit or stimulate IGF action depending on the IGFBP and the cell milieu.
- Serum IGF-I and IGFBP-1 are useful markers of metabolic status, with low total IGF-I and high fasting IGFBP-1 concentrations indicating poor nutrition.
- IGFs are neuroprotective; and also stimulate hippocampal neurogenesis and plasticity, and have important effects on learning, memory, and behavior throughout life in health and disease.
- The relative roles of the paracrine/autocrine and endocrine IGF system in brain are yet to be established.
- The fall in IGF-I may contribute to the decline in cognitive function with aging and is a background for the development of Alzheimer's disease in predisposed individuals.
- Proinflammatory cytokines cause IGF resistance, which may contribute to disturbances in behavior and cognition.
- The effects of physical activity on cognitive function are mediated in part by endocrine IGF-I.
- Further knowledge of the IGF system and nutrition in relation to behavior may be a key to understanding the integration of somatic and cognitive functioning.

References

Åberg ND, Brywe KG, Isgaard J. TheScientificWorldJOURNAL. 2006;6:53–80.
Arai Y, Hirose N, Yamamura K, Shimizu K, Takayama M, Ebihara Y, et al. J Gerontol A Biol Sci Med Sci. 2001;56A:M79–82.
Arwert LI, Deijen JB, Drent ML. Nutr Neurosci. 2003;6:269–75.
Arwert LI, Deijen JB, Drent ML. Growth Horm IGF Res. 2005;15:416–22.
Attia N, Tamborlane WV, Heptulla R, Maggs D, Grozman A, Sherwin RS, et al. J Clin Endocrinol Metab. 1998;83:1467–71.
Bezchlibnyk YB, Xu L, Wang J-F, Young LT. Brain Res. 2007;1147:213–7.
Bluthé R-M, Kelley KW, Dantzer R. Brain Behav Immun. 2006;20:57–63.
Bondy C, Lee WH. J Neurosci. 1993;13:5092–104.
Carro E, Trejo JL, Gomez-Isla T, LeRoith D, Torres-Aleman I. Nat Med. 2002;8:1390–7.
Chen MJ, Russo-Neustadt AA. Growth Factors. 2007;25:118–31.
Claeys I, Simonet G, Poels J, Van Loy T, Vercammen L, De Loof A, et al. Peptides. 2002;23:807–16.
Clemmons DR. Curr Opin Pharmacol. 2006;6:620–5.
Clemmons DR. Nat Rev Drug Discov. 2007;6:821–33.
Counts DR, Gwirtsman H, Carlsson LMS, Lesem M, Cutler GB. J Clin Endocrinol Metab. 1992;75:762–7.
Davila N, Piriz J, Trejo JL, Torres-Aleman I. Front Biosci. 2007;12:3194–202.
de la Monte SM. BMB Rep. 2009;42:475–81.
Duman CH, Schlesinger L, Terwilliger R, Russell DS, Newton SS, Duman RS. Behav Brain Res. 2009;198:366–71.
Elenkov IJ, Iezzoni DG, Daly A, Harris AG, Chrousos GP. Cytokine dysregulation, inflammation and well-being. Neuroimmunomodulation. 2005;12(5):255–69.
Falleti MG, Maruff P, Burman P, Harris A. Psychoneuroendocrinology. 2006;31:681–91.
Fernandez S, Fernandez AM, Lopez-Lopez C, Torres-Aleman I. Growth Horm IGF Res. 2007;17:89–95.
Firth SM, Baxter RC. Endocr Rev. 2002;23:824–54.
Friedlander AL, Butterfield GE, Moynihan S, Grillo J, Pollack M, Holloway L, et al. J Clin Endocrinol Metab. 2001;86:1496–503.

Frystyk J, Vestbo E, Skjaerbaek C, Mogensen CE, Ørskov H. Metabolism. 1995;10 Suppl 4:37–44.

Hoyer S. Eur J Pharmacol. 2004;490:115–25.

Khawaja X, Xu J, Liang J-J, Barrett JE. J Neurosci Res. 2004;75:451–60.

Landi F, Capoluongo E, Russo A, Onder G, Cesari M, Lulli P, et al. Growth Horm IGF Res. 2007;17:58–66.

Le Roith D, Bondy C, Yakar S, Liu JL, Butler A. Endocr Rev. 2001;22:53–74.

Lewitt MS, Baxter RC. Mol Cell Endocrinol. 1991;79:C147–52.

Lewitt MS, Hall K (2005). The insulin-like growth factor system and nutrition in adulthood and aging. In: IGF and Nutrition in Health and Disease. Houston MS, Holly J, Feldman E (eds) Humana Press, pp. 157–74.

Lewitt MS, Denyer GS, Cooney GJ, Baxter RC. Endocrinology. 1991;129:2254–6.

Lichtenwalner RJ, Forbes ME, Bennet SA, Lynch CD, Sonntag WE, Riddle DR. Neuroscience. 2001;107:603–13.

Llorens-Martin M, Torres-Aleman I, Trejo JL. Neuroscientist. 2009;15:134–48.

Lupien SB, Bluhm EJ, Ishii DN. J Neurosci Res. 2003;74:512–23.

Malberg JE, Platt B, Rizzo SJ, Ring RH, Lucki I, Schechter LE, et al. Neuropsychopharmacol. 2007;32:2360–8.

Markowska AL, Mooney M, Sonntag WE. Neuroscience. 1998;87:559–69.

McIntyre RS, Soczynska JK, Konarski JZ, Woldeyohannes HO, Law CWY, Miranda A, et al. J Clin Psychiatry. 2007;18:257–64.

Narasimhan SD, Yen K, Tissenbaum HA. Curr Biol. 2009;19:R657–66.

O'Connor JC, McCusker RH, Strle K, Johnson RW, Dantzer R, Kelley KW. Cell Immunol. 2008;252(1–2):91–110

Pandini G, Frasca F, Mineo R, Sciacca L, Vigneri R, Belfiore A. J Biol Chem. 2002;22:22.

Pembrey ME. Eur J Hum Genet. 2002;10:669–71.

Reinhardt RR, Bondy CA. Endocrinology. 1994;135:1753–61.

Rivera EJ, Goldin A, Fulmer N, Tavares R, Wands JR, de la Monte SM. J Alzheimers Dis. 2005;8:247–68.

Russo VC, Gluckman PD, Feldman EL, Werther GA. Endocr Rev. 2005;26:916–43.

Sara V, Carlsson-Skwirut C, Drakenberg K, Giacobini M, Håkansson L, Mirmiran M, et al. Ann NY Acad Sci. 1993;692:183–91.

Sizonenko SV, Sirimanne ES, Williams CE, Gluckman PD. Brain Res. 2001;922:42–50.

Steen E, Terry BM, Rivera EJ, Cannon JL, Neely TR, Tavares R, et al. J Alzheimers Dis. 2005;7:63–80.

Sun LY. Steven Evans M, Hsieh J, Panici J, Bartke A. Endocrinology. 2006;146:1138–44.

Trejo JL, Llorens-Martin MV, Torres-Aleman I. Mol Cell Neurosci. 2008;37:402–11.

Uhde TW, Malloy LC, Slate SO. Pharmacol Biochem Behav. 1992;43:263–9.

Undén A-L, Elofsson S, Knox S, Lewitt MS, Brismar K. Clin Endocrinol. 2002;57:793–803.

Chapter 19
Leptin and the CNS

Jenni Harvey

Abbreviations

4-AP	4-Aminopyridine
β-amyloid	Beta amyloid
AD	Alzheimer's disease.
AMPA	α-Amino-3-hydroxy-5-methylisoxazole-4-propionic acid
ARC	Arcuate nucleus
BK	Large conductance Ca^{2+}-activated K^+ channel.
CNS	Central nervous system
CSF	Cerebrospinal fluid
D-AP5	D-Amino-5-phosphonopentanoic acid
DMH	Dorsomedial nucleus
ERK	Extracellular signal regulated kinase
EPSC	Excitatory postsynaptic current
GABA	Gamma-aminobutyric acid
ICV	Intracerebroventricular
IPSC	Inhibitory postsynaptic current.
IRS	Insulin receptor substrate
JAK	Janus tyrosine kinase
K_{ATP}	ATP-sensitive K^+ channel
LTD	Long-term depression
LTP	Long-term potentiation
MAPK	Mitogen-activated protein kinase.
NMDA	N-methyl-d-aspartate
NPY	Neuropeptide Y
ObR	Leptin receptor
PI 3-kinase	Phosphoinositide 3-kinase
PKC	Protein kinase C
POMC	Proopiomelanocortin
$PtdIns(4,5)P_2$	Phosphatidylinositol-4,5-bisphosphate.
$PtdIns(3,4,5,)P_3$	Phosphatidylinositol-3,4,5-trisphosphate

J. Harvey (✉)
Division of Medical Sciences, Centre for Neuroscience, Ninewells Hospital and Medical School,
University of Dundee, Dundee DD1 9SY, UK
e-mail: j.z.harvey@dundee.ac.uk

Sos	Son-of-sevenless
STAT	Signal transducer and activator of transcription
STP	Short-term potentiation
TEA	Tetraethylammonia
VMH	Ventromedial nucleus

19.1 Introduction

It is known that a physiological system exists that homeostatically regulates body weight. Kennedy first proposed that the amount of energy stored in adipose mass was a balance between calorie intake and energy expenditure. Later, Hervey (1958) formulated the idea of a circulating satiety factor. This concept was supported by parabiosis studies he carried out and the discovery of natural recessive mutations in the obese (*ob*) and diabetes (*db*) genes, which resulted in obesity in mice (Ingalls et al. 1950). The subsequent cloning of the *ob* and *db* genes confirmed the role of these genetic loci in the regulation of energy balance. Injection of leptin into leptin-deficient or wild-type mice was shown to evoke a significant reduction in food intake and body weight (Halaas et al. 1995). Thus, the product of the *ob* gene was given the name leptin (from the Greek, *leptos* meaning thin).

19.2 Leptin

Leptin, the product of the obese (*ob*) gene, is made predominantly by white adipose tissue and once released it circulates in the plasma as a 16 kDa protein in amounts proportional to body fat (Maffei et al. 1995). The obese gene product displays a high degree of homology amongst different species. Leptin also displays a very similar structure to other cytokines and it contains an intra-chain disulphide bond that is pivotal for biological activity.

In mice, mutations in the *ob* gene result in early onset obesity. In leptin-deficient *ob/ob* mice, the substitution of a cysteine with a threonine residue causes synthesis of a truncated leptin protein that is not secreted. In another leptin-deficient mouse strain (*ob²ʲ/ob²ʲ*) synthesis of ob mRNA is stopped by insertion of a transposon in the first intron of the *ob* gene. As well as displaying leptin deficiency, both these mutant mice have morbid obesity, hypothermia and hyperphagia. In contrast, mutations in the *ob* gene are extremely rare in humans. Morbid obesity due to *ob* gene mutations was first reported in two children from a Pakistani family. In these cases, a truncated form of leptin that is targeted for proteosomal degradation was synthesized after deletion of a single guanine nucleotide in codon 133. Members of a Turkish family have also been identified as having morbid obesity associated with a missense mutation in codon 105, which results in the production of an abnormal nonsecretory form of leptin. The rarity of *ob* gene mutations in humans indicates that genetic abnormalities are unlikely to be the major cause of obesity in humans (Table 19.1).

19.2.1 Sites of Leptin Expression

It was initially thought that adipose tissue was the only site of leptin expression. However numerous studies have demonstrated that leptin is widely expressed in many other peripheral tissues including skeletal muscle, gastric mucosa as well as placental and mammary tissues. The expression of leptin

Table 19.1 Key facts of leptin

1. Leptin is a hormone, consisting of 167 amino acids that circulates in the blood and can enter the brain
2. Leptin and its receptors are expressed widely in the brain, suggesting that leptin is a pleiotropic hormone that regulates numerous CNS functions
3. Leptin is an important regulator of food intake and body weight via its actions in the hypothalamus
4. Leptin is a potential cognitive enhancer as it facilitates the cellular events underlying hippocampal-dependent learning and memory
5. Leptin is implicated is various CNS-driven disease as dysfunctions in the leptin system have been linked to neurodegenerative disorders and neuropsychological diseases

in the periphery is influenced by various external factors. For instance, in placenta, glucocorticoids and insulin stimulate expression of leptin (Mise et al. 1998). In the CNS, leptin mRNA, *ob* protein and leptin immunoreactivity have been detected in many brain regions including hippocampus, cortex, and cerebellum (Morash et al. 1999). In addition, the subcellular localization of leptin varies between different neuronal populations. One example of this occurs in the hippocampus as leptin labeling is evident in nuclear and perinuclear regions in the dentate gyrus, whereas labeling is restricted to the nucleus in the CA2 region (Ur et al. 2002). It is also feasible that leptin may be released or made from specific neurons. Indeed, recent studies have demonstrated net efflux of leptin into the internal jugular vein indicating that there is substantial production and secretion of leptin from the brain (Eikelis et al. 2006).

19.3 Leptin Receptor

The leptin receptor (ObR) was first isolated from the choroid plexus by expression cloning techniques (Tartaglia et al. 1995). ObR is encoded by the diabetes (*db*) gene and at least six isoforms (termed ObRa-f) are generated by alternate splicing of the *db* gene. All the isoforms, except ObRe, are membrane spanning receptors that have either short (30–40 residues) or long (302 residues) intracellular domains. ObRb is the main signaling isoform, whereas the short isoforms have limited signaling capacity. ObRe is a distinct isoform as it lacks a transmembrane region and it is thought to bind and transport leptin in the plasma.

In rodents, mutations in the leptin receptor result in leptin insensitivity, early onset obesity, hyperphagia and various neuroendocrine abnormalities (Halaas et al. 1995). In *db/db* mice, a truncated form of ObRb that is unable to stimulate JAK-STAT signaling is produced, whereas there is normal expression of the other splice variants. In fa/fa rats, a single-point mutation in the extracellular domain of all six leptin receptor isoforms occurs, resulting in reduced affinity of the receptor for leptin and attenuated leptin-driven signaling capacity (da Silva et al. 1998). Leptin receptor mutations have been identified in humans, but these are extremely rare. Three sisters from a Kabilian family were the first reported human cases with leptin receptor mutations (Clément et al. 1998). In these individuals, a point mutation in the splice donor site of exon 16 resulted in truncated leptin receptors that lacked both transmembrane and intracellular domains (Fig. 19.1).

19.3.1 Leptin Receptor Expression in the CNS

The hypothalamus is the main target for leptin in the CNS, with respect to regulating food intake and body weight. In rodents, high levels of leptin receptor mRNA and protein are expressed in various hypothalamic nuclei associated with energy homeostasis including the ventromedial hypothalamus
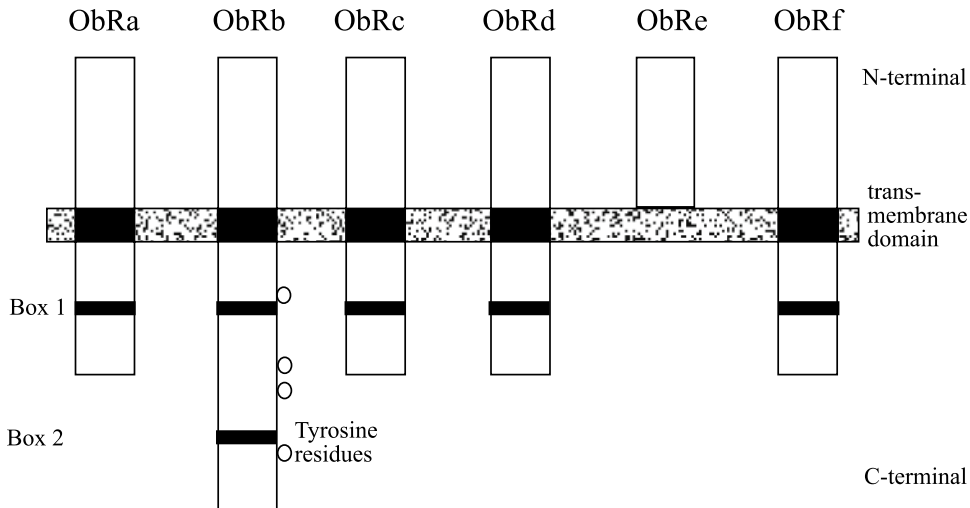
Fig. 19.1 Leptin receptor isoforms. Schematic representation of the six leptin receptor isoforms. ObRb, the long isoform, has an extended C-terminal region that contains the various tyrosine residues required for leptin-driven signaling. The short isoforms, ObRa, ObRc, ObRd, and ObRf, have shorter C-terminal regions, which are thought to limit their signaling capacity. ObRe is a distinct leptin receptor isoform that has no transmembrane region. It is thought to act as a carrier for leptin in the plasma

(VMH), arcuate nucleus (ARC) and dorsomedial hypothalamus (DMH) (Schwartz et al. 1996; Hâkansson et al. 1998). High levels of leptin receptor expression also occur in the hypothalamus of humans (Savioz et al. 1997). In addition to the hypothalamus, high levels of leptin receptor immunoreactivity and mRNA have been detected in numerous other brain regions including the hippocampus, cortex, thalamus, cerebellum, and brain stem (Harvey 2007b). The CA1/CA3 and dentate gyrus regions of the hippocampus display widespread expression of leptin receptor mRNA and immunoreactivity. Expression of leptin receptor mRNA in the hippocampal formation is influenced by fasting (Lin and Huang 1997). The expression of leptin receptors outwith hypothalamic brain regions suggests that in addition to regulating energy balance, leptin plays a more fundamental modulatory role in the CNS. In support of this, leptin mRNA and protein are also highly expressed in numerous brain regions, suggesting that leptin may be made and released locally within the CNS. It is not yet known if centrally derived leptin fulfills the criteria of being a neurotransmitter (or a co-transmitter); however, leptin originating from peripheral sources can still function in the brain. Indeed, intraperitoneal injection of leptin influences glucocorticoid expression in the hippocampus (Proulx et al. 2001).

19.4 Leptin Receptor Signaling

Leptin receptors are members of the class I cytokine receptor superfamily, which includes interleukin 6 and leukemia-inhibitory factor receptors. Like other cytokines, leptin binding to ObR results in the activation of janus tyrosine kinases (JAKs), in particular JAK2 (Baumann et al. 1996). The activation of JAK2 results in its association with specific domains within the C-terminal region of the receptor which in turn promotes trans-phosphorylation of JAK2 and subsequent phosphorylation of tyrosine residues on ObR. This series of events enables recruitment and activation of various
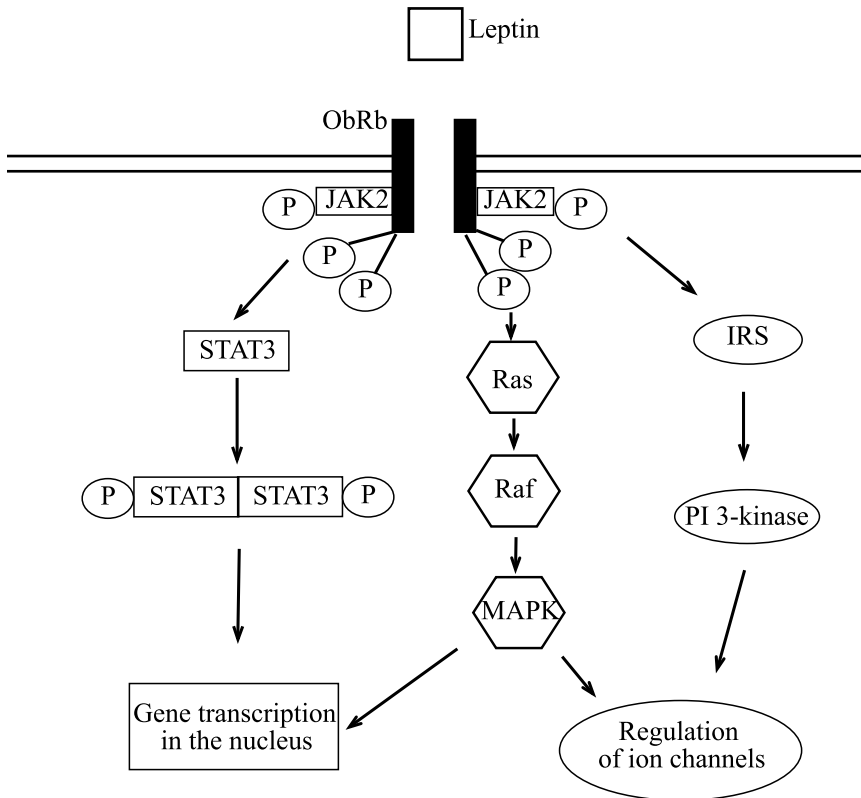
Fig. 19.2 Leptin receptor signaling in neurons. Schematic representation of the key signaling pathways activated by the long leptin receptor isoform in neurons. Following leptin binding to ObRb, tyrosine residues are phosphorylated which results in the association with and activation of JAK2. Subsequently activated JAK2 recruits various signaling molecules including STAT3, IRS proteins and PI 3-kinase and the MAPK signaling cascade. Leptin receptor activation of these pathways results in gene transcriptional changes as well as the regulation of various ion channels

downstream signaling pathways including the STAT (signal transduction and activators of transcription) family of transcription factors, insulin receptor substrate (IRS) proteins, phospho-inositide 3-kinase (PI 3-kinase) and mitogen-activated protein kinase (MAPK) (Fig. 19.2).

19.4.1 STAT3

ObRb is the only isoform that contains the various motifs within its intracellular domain required for activation of STATs. It has been shown that one tyrosine residue (Y1138) in particular enables STAT3 binding, which results in STAT3 dimerization and translocation to the nucleus. Although ObRb activation leads to tyrosine phosphorylation of STAT1, STAT3, and STAT5 in vitro systems, activation of only STAT3 occurs in the hypothalamus following intravenous administration of leptin in vivo. Following STAT3 activation a number of immediate early genes are stimulated such as c-fos and c-jun (Bjorbaek et al. 1998). Furthermore, STAT3 signaling is required for leptin regulation of energy balance as gene-targeted disruption of ObRb-STAT3 signaling in mice results in hyperphagia and obesity (Bates et al. 2003).

19.4.2 PI 3-Kinase

As well as promoting gene transcriptional changes via the JAK-STAT pathway, leptin can also evoke more rapid biological effects by stimulating divergent signaling pathways. In hypothalamic glucose-responsive neurons and insulinoma cells, leptin activates ATP-sensitive K^+ (K_{ATP}) channels via rapid activation of a PI 3-kinase-driven signaling cascade (Spanswick et al. 1997; Harvey et al. 2000a). PI 3-kinase is also implicated in leptin-driven attenuation of food intake as PI 3-kinase inhibitors prevent the anorectic effects of leptin (Niswender et al. 2001). In hippocampal neurons, PI 3-kinase is also a key component of leptin receptor–dependent signaling (Harvey 2007a). One of the main functions of PI 3-kinase is to promote phosphorylation of phosphoinositides on the 3-position, resulting primarily in $PtdIns(3,4,5,)P_3$. Numerous studies have shown a link between the actin cytoskeleton and the lipid products of PI 3-kinase, as the activity of many cytoskeletal proteins is dependent on the levels of $PtdIns(4,5)P_2$ or $PtdIns(3,4,5,)P_3$. The ability of leptin to activate K_{ATP} channels in insulinoma cells is prevented by actin filament stabilization, thereby indicating a functional role for the actin cytoskeleton in the actions of leptin (Harvey et al. 2000a). Leptin application also evokes rapid disassembly of actin filaments, via stimulation of a PI 3-kinase-driven pathway in insulinoma cells. It is known that PI 3-kinase also possesses serine kinase activity and PI 3-kinase has been shown to interact with AGC serine kinases, Tec tyrosine kinases and Rho GTPases. In pancreatic beta cells and hepatocytes leptin activates cyclic nucleotide phosphodiesterase 3B downstream of PI 3-kinase. Furthermore, the PI 3-kinase-cyclic nucleotide phosphodiesterase 3B pathway is implicated in the regulation of food intake and body weight by leptin as ICV administration of selective inhibitors of cyclic nucleotide phosphodiesterase 3B prevent the anorexigenic effects of leptin (Zhao et al. 2002).

19.4.3 Ras-Raf-MAPK

Leptin is also capable of rapidly stimulating the Ras-Raf-MAPK signaling cascade. Leptin receptor–driven activation of this pathway involves tyrosine phosphorylation of Src homology collagen (Shc), an adapter protein, which interacts with Grb2 and subsequently recruits Sos (son-of-sevenless) exchange protein to the plasma membrane. This in turn enables activation of Ras, which then stimulates the step-wise activation of Raf, MEK, and ERK. Leptin receptor activation of this pathway has been observed in many peripheral cell types including rat peradipocytes, porcine chromaffin, and insulinoma cell lines. There is also growing evidence of leptin receptor coupling to MAPK signaling in neurons (Shanley et al. 2001; Morikawa et al. 2004).

19.5 Leptin Transport to the Brain

It is now well established that leptin enters the brain via saturable transport across the blood brain barrier (Banks et al. 1996). Brain microvessels express high levels of the short leptin receptor isoforms, which are capable of binding and internalizing leptin. Impairments in the transport of leptin across the blood brain barrier develop at the same time as obesity in rodents and this can be reversed by modest reductions in weight (Banks and Farrell 2003). The blood-to-brain transport of leptin is also regulated by numerous factors including triglycerides and epinephrine. There is also evidence that leptin transport to the brain may occur via the cerebrospinal fluid (CSF). Indeed, the key site for CSF production, the choroid plexus, expresses high levels of the short leptin receptor isoform, ObRa, which could mediate leptin transport from the blood to the CSF. Leptin may also reach hypothalamic sites via diffusion

as the predominant leptin-target neurons in the hypothalamus are situated extremely close to the median eminence. It is also feasible that leptin is made and released locally in the CNS as there is widespread expression of leptin mRNA and immunoreactivity in the CNS (Morash et al. 1999; Ur et al. 2002).

19.6 Modulation of Hippocampal Function by Leptin

19.6.1 Leptin Regulation of Hippocampal Excitability

19.6.1.1 Leptin Activates BK Channels

A number of studies have shown that leptin inhibits peripheral insulinoma cells (Harvey et al. 1997) and central hypothalamic, nucleus solitarius dorsal motor nucleus neurons ((Spanswick et al. 1997); Williams et al. 2007) via activation of ATP-sensitive potassium (K_{ATP}) channels. In contrast, however, the ability of leptin to inhibit hippocampal CA1 neurons is mediated by the activation of large conductance calcium activated potassium (BK) and not K_{ATP}, channels (Shanley et al. 2002a). Indeed, the leptin-dependent membrane hyperpolarization and increased K^+ conductance in hippocampal neurons were blocked by TEA, but not the sulphonylurea, tolbutamide. Additionally, leptin increased the activity of native BK single channels in hippocampal cultures; an effect that was prevented by the selective BK channel inhibitor, charybdotoxin. BK channels are known to consist of a pore-forming α subunit (*Slo*) either with or without a modulatory β subunit (Toro et al. 1998). Studies in HEK29 cells expressing recombinant BK channels (either h*Slo* or h*Slo*β1) together with the leptin receptor demonstrated that the application of leptin resulted in a rapid increase in BK channel activity. This suggested that expression of β subunits was not required for the effects of leptin. Moreover, the effects of leptin were blocked by charybdotoxin at concentrations that preferentially inhibit BK channels consisting of only α subunits (Fig. 19.3).

19.6.1.2 Role of PI 3-Kinase

In a manner similar to its effects on hypothalamic K_{ATP} channels, leptin-dependent activation of hippocampal BK channels is mediated by a PI 3-kinase-driven process (Shanley et al. 2002b). Recent studies have examined further the nature of the signaling events occurring downstream of PI 3-kinase, that couple leptin receptors to stimulation of BK channels. Agents that promote actin filament stablization inhibit BK channel activation by leptin indicating that disruption of the actin cytoskeleton plays a key role in this process (O'Malley et al. 2005). Indeed, actin filament disrupters such as cytochalasin D mimicked the effects of leptin on single hippocampal BK channels. Leptin receptor activation also results in a rapid and localized PI 3-kinase-dependent increase in the synaptic levels of phosphatidylinositol-3,4,5-trisphosphate (PtdIns(3,4,5)P$_3$), which in turn promotes actin filament depolymerization. Ultimately this series of events causes BK channel activation and subsequent clustering at hippocampal synapses.

19.6.1.3 Leptin Has Anticonvulsant Activity

Neuronal BK channel activity is known to be tightly regulated by voltage and the levels of intracellular Ca^{2+} (Latorre 1989). Hippocampal BK channels also underlie the fast after hyperpolarization which is responsible for action potential repolarization. Thus, BK channels are thought to play an
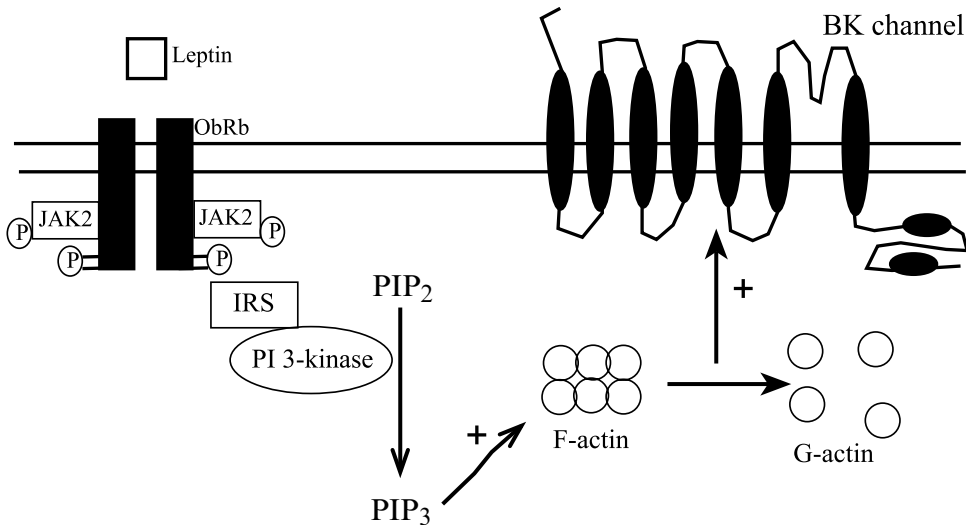
Fig. 19.3 Activation of BK channels on hippocampal neurons by leptin. Binding of leptin to its receptor (ObRb) promotes the activation of PI 3-kinase, which leads to the conversion of PtdIns(4,5)P_2 into PtdIns(3,4,5)P_3. This lipid intermediate induces alterations in the actin cytoskeletal architecture such that actin filaments (F-actin) are disassembled into globular actin (G-actin). Leptin-driven disruption of actin filaments provokes BK channel opening and also translocation of BK channel to hippocampal synapses

important role in regulating action potential firing rates and the patterns of burst firing. Thus it is conceivable that leptin, by regulating BK channel activity, influences hippocampal excitability. Indeed, leptin significantly attenuates epileptiform-like activity in two distinct models of epilepsy, via a process involving BK channel activation (Shanley et al. 2002b). Thus, in an Mg^{2+}-free hippocampal culture model of epilepsy, leptin reduced the enhanced global levels of intracellular Ca^{2+}, in a rapid and reversible manner. The effects of leptin were mirrored by application of NS 1619, a specific BK channel activator and prevented by exposure to BK channel antagonists, indicating the involvement of BK channels. Leptin also reduced the frequency of interictal firing in hippocampal slices exposed to Mg^{2+}-free conditions. The antiepileptic effects of leptin were absent in Zucker *fa/fa*, but not Zucker lean, rats indicating that leptin receptor activation was required for this process (Shanley et al. 2002b). Recent studies indicate that leptin has antiepileptic properties in other hippocampal models of epilepsy (4-AP, pentylenetetrazole; Xu et al. 2008). Moreover, pentylenetetrazole is reported to induce more severe seizures than normal in leptin-deficient (*ob/ob*) mice (Erbayat-Altay et al. 2008). The ability of leptin to regulate neuronal excitability is not confined to the hippocampus as direct administration of leptin reduces the frequency of spikes in hypothalamic neurons (Takahashi and Cone 2005). Contrastingly, leptin is reported to have pro-convulsant activity as this hormone increases the frequency of epileptic discharges in a penicillin model of epilepsy in the somatomoter cortex. This suggests that there may be regional differences in the regulation of neuronal excitability by leptin.

In addition to regulating hippocampal excitability via modulation of neuronal potassium channel function, recent studies indicate that under hyper-excitable conditions, leptin evokes a novel form of NMDA receptor–dependent long-term depression (LTD; (Durakoglugil et al. 2005); This aspect will be discussed in greater detail in Sect. 19.6.2.2). The capacity of leptin to persistently alter the strength of hippocampal excitatory synaptic transmission under such conditions indicates that both synaptic and non-synaptic mechanisms contribute to the regulation of hippocampal excitability by leptin.
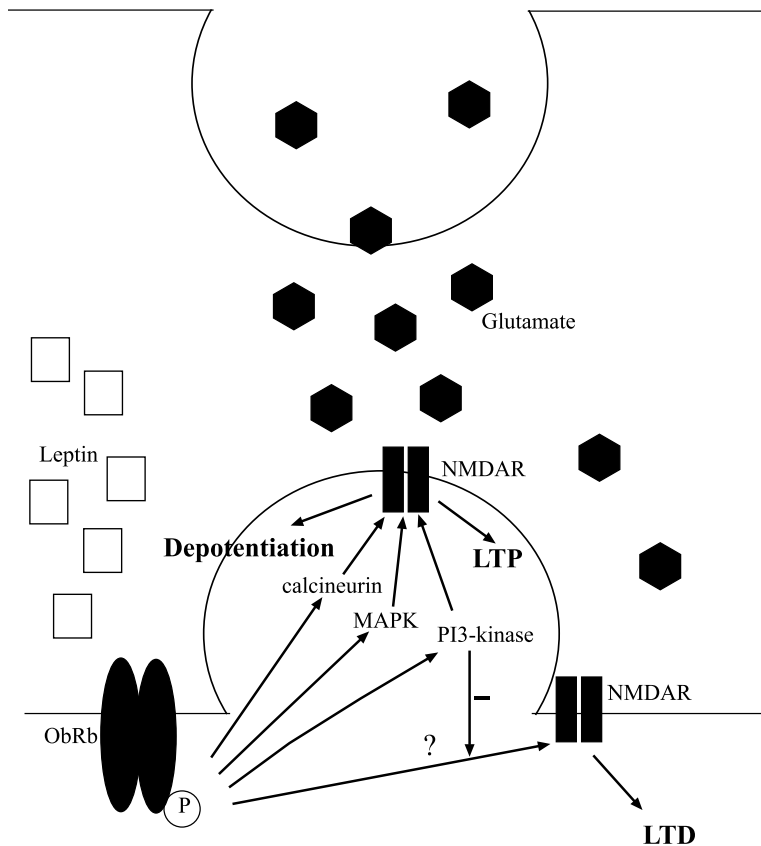
Fig. 19.4 Leptin modulates various forms of activity-dependent hippocampal synaptic plasticity. Schematic representation of the different forms of hippocampal synaptic transmission that are regulated by leptin. Following binding of leptin to the leptin receptor divergent signaling cascades are activated. Activation of MAPK and PI 3-kinase-driven signaling leads to facilitation of NMDA receptor-mediated synaptic transmission, which in turn promotes facilitation of hippocampal LTP. Under conditions of enhanced excitability leptin evokes a novel form of NMDA receptor-dependent de novo LTD. In contrast to leptin-driven facilitation of LTP, leptin-induced LTD is negatively regulated by PI 3-kinase. Activation of leptin receptors in the CA1 region of the hippocampus, also results in the reversal of established LTP (depotentiation); a process that is also NMDA receptor dependent and is mediated by calcineurin

Interestingly, divergent signaling pathways underlie these processes as a PI 3-kinase-dependent event mediates leptin activation of BK channels, whereas leptin-induced LTD is negatively regulated by PI 3-kinase (Fig. 19.4).

19.6.2 *Leptin Modulation of Hippocampal Excitatory Synaptic Function*

19.6.2.1 Leptin Facilitates NMDA Receptor–Dependent LTP

It is well documented that the hippocampal formation plays a key role in learning and memory processes and one form of synaptic plasticity, long-term potentiation (LTP) is thought to be a cellular correlate of certain forms of learning and memory and habituation. In the CA1 region of the hippocampus, activity-dependent NMDA receptor–dependent LTP contributes to spatial learning and memory.

Evidence is growing that hippocampal synaptic plasticity can be modulated by various hormones, including leptin. Indeed, rodents that are insensitive to leptin (*db/db* mice; *fa/fa* rats) display significant impairments in hippocampal LTP and LTD as well as impaired spatial memory (Li et al. 2002). Administration of leptin directly into the hippocampus results in the facilitation of synaptic plasticity (Wayner et al. 2004) and it enhances performance in specific hippocampal-dependent learning tasks (Farr et al. 2006). At hippocampal CA1 synapses, leptin promotes conversion of short-term potentiation (STP) into LTP, via enhancing NMDA receptor function (Shanley et al. 2001). Studies in acute hippocampal slices and cultured neurons demonstrated that activation of PI 3-kinase and MAPK (ERK) was required for facilitation of NMDA receptor function by leptin (Shanley et al. 2001). Leptin also enhanced the amplitude, but not the kinetics of NMDA-evoked currents in *Xenopus* oocytes expressing recombinant NMDA (NR1A, NR2A) receptors. This effect of leptin was observed following application of maximal, as well as submaximal concentrations of NMDA suggesting that leptin increased the numbers of NMDA receptors expressed at the cell membrane (Harvey et al. 2008).

19.6.2.2 Leptin Induces a Novel Form of Hippocampal De Novo LTD

It is well established that hippocampal synapses can, in addition to LTP, support activity-dependent reductions in the strength of excitatory synaptic transmission. Long-term depression (LTD) of excitatory synaptic transmission is a persistent weakening of synaptic strength that is involved in learning and memory processes. Moreover, heterosynaptic forms of de novo LTD and depotentiation are thought to enhance the computational flexibility of synaptic networks, which in turn is likely to increase network storage capacity. Two main forms of LTD exist in the mammalian CNS, which are evoked by the synaptic activation of NMDA and metabotropic receptors, respectively (Massey and Bashir 2007). However recent studies have shown that a number of hormones and growth factors have the ability to induce distinct forms of hippocampal LTD. For instance insulin can induce an NMDA receptor–dependent form of LTD at CA1 synapses that is mediated by activation of a PI 3-kinase/PKC coupled pathway (Huang et al. 2004). Under conditions of enhanced excitability (evoked by removal of Mg^{2+} or blockade of $GABA_A$ receptors), leptin can also induce a persistent reduction in the efficacy of excitatory synaptic transmission (LTD; Durakoglugil et al. 2005). Like insulin-induced LTD, the ability of leptin to induced LTD requires the synaptic activation of NMDA receptors as leptin-induced LTD was inhibited by the competitive NMDA receptor antagonist, D-AP5. Contrastingly, metabotropic glutamate receptor antagonists failed to influence the induction or maintenance phases of leptin-induced LTD, indicating that this form of LTD is independent of metabotropic glutamate receptor activation. However, leptin-induced LTD does involve similar expression mechanisms to activity-dependent LTD, as low-frequency stimulation (LFS)-induced LTD occluded leptin-induced LTD, whereas LFS depressed synaptic transmission even after leptin-induced LTD (Durakoglugil et al. 2005). Indeed, like LFS-induced LTD, leptin-induced LTD has a postsynaptic locus of expression as the persistent synaptic depression induced by leptin was not associated with any change in the paired pulse facilitation ratio. In addition, the signaling pathways mediating leptin-induced LTD have been examined. In contrast to the ability of leptin to facilitate hippocampal LTP (Shanley et al. 2001), PI 3-kinase inhibitors enhanced the level of synaptic depression induced by leptin, suggesting that this process is negatively regulated by PI 3-kinase. Protein phosphatases also appear to negatively regulate leptin-induced LTD as inhibition of protein phosphatases 1/2A, but not protein phosphatase 2B, enhanced the magnitude of leptin-induced LTD (Durakoglugil et al. 2005). Several lines of evidence indicate that internalization of AMPA receptors play a pivotal role in mediating activity-dependent forms of hippocampal LTD (Collingridge et al. 2004). Indeed, LFS-induced LTD is associated with endocytosis of GluR2-containing AMPA receptor subunits (Ahmadian et al. 2004). Insulin-induced

LTD is also accompanied by a reduction in the cell surface expression of GluR2 subunits (Ahmadian et al. 2004). However, it still remains to be determined if changes in AMPA receptor trafficking underlie leptin-induced LTD.

19.6.2.3   Leptin Depotentiates Hippocampal CA1 Synapses

Characteristics of Leptin-induced Depotentiation

Recent studies indicate that leptin can also reverse (depotentiate) LTP at hippocampal CA1 synapses (Moult et al. 2009). Thus, application of leptin to hippocampal slices 10–30 min after the induction of LTP resulted in a depression of synaptic transmission to baseline levels (pre-LTP). In contrast, when leptin was applied at later time points after LTP induction, it failed to influence the magnitude of potentiated synapses. This suggests that the ability of leptin to depotentiate hippocampal CA1 synapses occurs within a specific time window. It is known that synaptic plasticity is greatly influenced by prior synaptic activity (known as metaplasticity). Thus, the inability of leptin to depress synaptic transmission when applied 50 min after LTP induction suggests that physiological or biochemical alterations have occurred at the potentiated synapses that have rendered them leptin-insensitive. However the nature of such changes remains to be determined. The ability of leptin to depotentiate hippocampal synapses is concentration-dependent as at 25 and 50 nM concentrations leptin readily reversed LTP, whereas application of 10 nM leptin failed to influence LTP. Leptin-induced depotentiation is also expressed postsynaptically as leptin-induced depotentiation was not accompanied by any change in the paired pulse facilitation ratio or on the coefficient of variation. In a manner analogous to leptin' effects on other forms of synaptic plasticity, leptin-induced depotentiation was NMDA receptor–dependent as exposure to the competitive NMDA receptor antagonist, D-AP5, blocked the effects of leptin. Previous studies have demonstrated that LFS-induced depotentiation involves internalization of AMPA receptors. Endocytosis of synaptic AMPA receptors also underlies depotentiation of hippocampal synapses by metabotropic glutamate receptors or neuregulin. Similarly, the ability of leptin to depotentiate synapses was associated with internalization of GluR2-containing AMPA receptors. Thus, the reversal of potentiated synapses by leptin was accompanied by a reduction in the rectification of synaptic AMPA receptors. Moreover, application of the selective inhibitor of GluR2-lacking AMPA receptor, philanthotoxin, to potentiated synapses mirrored leptin-induced depotentiation. This indicates that leptin-induced depotentiation involves a reduction in the density of GluR2-lacking AMPA receptors at hippocampal CA1 synapses.

Role of NMDA Receptors

Several lines of evidence indicate that de novo LTD and depotentiation are distinct forms of hippocampal synaptic plasticity. For instance, robust NMDA receptor–dependent de novo LTD is observed in calcineurin Aα-knockout mice, whereas activity-dependent depotentiation is absent (Zhuo et al. 1999). Leptin-induced depotentiation and leptin-induced de novo LTD also appear to be a distinct phenomenon as these processes involve the activation of divergent signaling cascades. Thus, inhibitors of calcineurin prevented leptin-induced depotentiation, whereas calcineurin plays no role in leptin-induced LTD (Moult et al. 2009). Evidence is growing that molecularly distinct NMDA receptors underlie different forms of hippocampal synaptic plasticity. Thus NR2B-containing NMDA receptors are implicated in de novo LTD and NR2A-containing NMDA receptors underlie LFS-induced depotentiation. It is also known that depotentiation and de novo LTD results in the

activation of divergent signaling cascades, which in turn leads to dephosphorylation of different sites on GluR1. Thus it has been proposed that the activation of molecularly distinct NMDA receptors triggers the activation of divergent signaling molecules, which in turn underlies different forms of activity-dependent hippocampal synaptic plasticity. In view of this, it is possible that leptin is capable of inducing depotentiation and de novo LTD by activating molecularly distinct NMDA receptors. It is thought that depotentiation of synapses is a process that leads to resetting of potentiated synapses, which is likely to enhance the probability of subsequent generation of LTP. Thus the ability of leptin to depotentiate synapses may indirectly increase the likelihood of LTP induction, which would in turn enhance the effectiveness of information storage in the network.

19.6.2.4 Leptin Promotes Structural Plasticity of Hippocampal Dendrites

Numerous studies support the idea that structural changes contribute to activity-dependent synaptic plasticity in the mammalian CNS. Indeed it is well documented that alterations in dendritic morphology as well as changes in spine density occur following hippocampal LTP (Yuste and Bonhoeffer 2001). Several reports have indicated that growth factors and hormones can promote structural changes in dendrites and spines that enable additional refining of synapses during activity-dependent synaptic plasticity. Similarly, application of leptin to cultured hippocampal neurons evokes rapid (within minutes) changes in the motility and density of dendritic filopodia (O'Malley et al. 2005). This process requires ongoing synaptic transmission as it is blocked by inhibition of action potential driven synaptic transmission with tetrodotoxin. Additionally, the synaptic activation of NMDA receptors is likely to be pivotal for leptin-induced dendritic morphogenesis as the effects of leptin were prevented by blockade of NMDA receptors, but not following inhibition of either AMPA receptors or NR2B-containing NMDA receptors. The leptin-induced alterations in dendritic morphology were associated with the formation of new synapses as increases in synaptic labeling were apparent around 15 min after dendritic morphogenesis (O'Malley et al. 2007). Previous studies have shown that MAPK activation plays an important role in the structural plasticity changes. For example activation of NMDA receptors in hippocampal neurons leads to increases in both MAPK activity and the density of dendritic spines (Goldin and Segal 2003). Similarly, the leptin-driven structural changes involve a MAPK (ERK)-dependent process as inhibitors of MAPK, but not PI 3-kinase block the effects of leptin.

19.6.3 Modulation of Fast Inhibitory Synaptic Transmission by Leptin

In addition to regulating excitatory synaptic transmission, recent studies have shown that leptin also has the capacity to regulate fast inhibitory synaptic transmission mediated by $GABA_A$ receptors in the mammalian CNS. Indeed, application of leptin results in attenuation of $GABA_A$ receptor-mediated synaptic transmission onto proopiomelanocortin (POMC) but not neuropeptide Y (NPY) neurons in the hypothalamus (Cowley et al. 2001; Munzberg et al. 2007). This suggests that leptin is likely to act on presynaptic terminals to reduce the release of GABA onto POMC neurons. Consistent with this possibility, GABAergic inhibitory tone onto POMC neurons is significantly enhanced in leptin-deficient *ob/ob* mice (Pinto et al. 2004). But there is limited information about cellular and molecular basis for the regulation of fast inhibitory synaptic transmission by leptin. However, a recent study by (Solovyova et al. 2009) examined the effects of leptin on $GABA_A$ receptor–mediated inhibitory postsynaptic potentials (IPSCs) onto hippocampal CA1 pyramidal cells. In this study, application of

leptin resulted in a rapid increase in the amplitude of evoked IPSCs and this effect was readily reversed on washout of leptin. Furthermore on prolonged washout of leptin a further reduction in IPSC amplitude was observed that persisted for the duration of recordings. The leptin-dependent enhancement of evoked IPSCs was not associated with any change in the paired pulse ratio or coefficient of variation, but it was paralleled by increases in both the frequency and amplitude of miniature IPSCs (mIPSCs). Furthermore, leptin enhanced postsynaptic currents induced by the $GABA_A$ receptor agonist, muscimol. Together these data indicate that facilitation of fast inhibitory synaptic transmission by leptin involves a postsynaptic mechanism. In support of this, postsynaptic dialysis with inhibitors of PI 3-kinase or Akt prevented the increase in eIPSC amplitude by leptin, indicating mediation by a PI 3-kinase/Akt-dependent process. In contrast the persistent depression induced by leptin (I-LTD) was unaffected by postsynaptic inhibition of PI 3-kinase/Akt indicating that the cellular mechanisms underlying this process are distinct from those responsible for the rapid facilitation of fast inhibitory synaptic transmission induced by leptin. However, leptin-induced I-LTD is also expressed postsynaptically as this effect of leptin was not accompanied by any change in paired pulse ratio or coefficient of variation.

Our previous studies have demonstrated that leptin regulates hippocampal neuron excitability by direct activation of BK channels expressed on pyramidal neurons (Shanley et al. 2002a, b). It is also well established that fast inhibitory synaptic transmission in the CNS plays an important role in regulating neuronal excitability. Thus, leptin is also likely to regulate hippocampal neuron excitability indirectly by modulating the inhibitory drive onto hippocampal CA1 pyramidal neurons. In addition to directly influencing neuronal excitability, alterations in GABAergine tone can also indirectly regulate the induction of synaptic plasticity at excitatory synapses. Thus hippocampal LTP induction is facilitated by $GABA_A$ receptor antagonists (Wigstrom and Gustafsson 1985); an action attributed to $GABA_A$ receptor-mediated regulation of postsynaptic depolarization. Changes in neuronal excitability also accompany hippocampal LTP as there is an increase in the ability of excitatory postsynaptic potentials to fire an action potential after LTP. This phenomenon is known as the E-S coupling component of LTP. Moreover, E-S coupling involves persistent reductions in $GABA_A$ receptor-mediated inhibitory drive (Abraham et al. 1987). Thus, leptin, via its ability to evoke a persistent attenuation of inhibitory tone onto CA1 pyramidal cells, may in turn facilitate the induction of LTP at this synapse (Fig. 19.5).

19.7 The Role of Leptin in Other Areas of Health and Disease

19.7.1 Leptin and its Role in Neurodegeneration

In western societies, life expectancy in steadily increasing and as a consequence more people are suffering from age-related neurodegenerative disorders such as Alzheimer's disease (AD). Evidence is growing that diet and lifestyle are key factors influencing the risk of developing neurodegenerative disorders. Moreover metabolic imbalance is a common feature of such diseases. Numerous studies indicate that dysregulation of metabolic systems are associated with AD. Indeed, dysfunctional neuronal insulin-driven signaling is linked to AD pathology. Recent studies have linked leptin to neurodegeneration as AD patients display markedly reduced levels of circulating leptin (Power et al. 2001). In transgenic murine models of AD that have enhanced levels of β-amyloid, leptin levels are also reduced. Moreover administration of leptin to these murine AD models leads to reductions in the CNS levels of β-amyloid (Fewlass et al. 2004). Furthermore, leptin improves memory in a

Hippocampus
* Neuronal excitability
* learning and memory
* depression
* neurodegenerative disorders
* neuroprotection

Cortex
* Neuronal excitability
* Neuroprotection

VTA
* food intake
* reward behaviour

Hypothalamus
* Appetite
* Reproduction
* Thermogensis
* Neuronal excitability

Cerebellum
* NMDAR function
* Neuroprotection

NTS
* Food intake
* neuronal excitability

Leptin

adipocytes

Fig. 19.5 Leptin modulates diverse neuronal functions. Schematic representation of the predominant neuronal functions that are regulated by leptin. Leptin derived from adipocytes enters the brain by saturable transport across the blood brain barrier. Within the hypothalamus, leptin acts in the arcuate nucleus to signal satiety. Leptin also plays an important role in regulating thermogenesis and reproductive function via its actions in the hypothalamus. Leptin is also capable of reaching other brain regions at physiologically relevant concentrations. In the hippocampal CA1 region, leptin plays a role in learning and memory processes by enhancing NMDA receptor function and modulating various forms of activity-dependent synaptic plasticity. Defects in the leptin system have also recently been linked to neurodegenerative disorders such as Alzheimer's disease. Leptin also regulates hippocampal neuron excitability by modulating BK channel activity; a process that may play a role in the antiepileptic properties of leptin. The excitability of other neuronal populations including cortical, hypothalamic and nucleus tractus solitarius are also controlled by this hormone. Leptin has also been shown to protect cerebellar, cortical, and hippocampal neurons from various toxic insults. Other brain regions have been shown to play a role in controlling feeding behavior including nucleus tractus solitarius (NTS) and ventral tegmental area (VTA). Leptin receptors have been detected in these regions and leptin influences food intake via its actions in NTS and VTA neurons

murine model of β-amyloid-induced toxicity, and recent studies indicate that leptin reduces tau hyperphosphorylation in neuronal cells. These findings suggest not only that leptin dysfunction contributes to AD pathology but also that leptin may be a potential therapeutic target in the treatment of AD. However, a greater understanding of the cellular and molecular basis for leptin dysfunction in the pathology of AD is still required for progression in this field.

19.7.2 Leptin is a Novel Antidepressant

Depression is currently the most prevalent mental illness with around 20% of the population suffering from this condition worldwide. However a significant proportion of depressed patients are unresponsive to currently available antidepressant therapies that are predominantly monoamine-based drugs. However recent studies indicate that the hormone leptin may be a novel antidepressant (Lu 2007) and the leptin system may offer a possible alternative target for the generation of novel antidepressant therapies in the future. Indeed, rats exposed to chronic stress display significant reductions in circulating leptin levels (Lu et al. 2006), and this occurs independently of alterations in body weight. Systemic administration of leptin mimics the effects of antidepressant agents such that in chronically stressed rats, leptin reversed the deficits in rewarding behavior. The antidepressant effects of leptin are likely to be mediated by leptin receptors located in the hippocampal formation as direct administration of leptin into the hippocampus resulted in antidepressant effects in the forced swim test. In contrast administration of leptin into the hypothalamus failed to influence forced swim behavior. Thus these findings indicate that leptin is a potent antidepressant agent in a number of rodent models that mirror certain behavioral aspects of human depression. However, there is limited information about the role of leptin in human depression. Two studies have reported raised circulating leptin levels in depressed patients, whereas other studies have linked attenuated plasma leptin levels to patients with major depression (Lu 2007). Although the efficacy of leptin as an antidepressant has not been assessed clinically, it is tempting to speculate that depressed patients displaying low leptin levels may be a suitable target group for leptin therapy.

Summary Points

- Leptin, the product of the ob gene is a circulating hormone.
- Leptin mediates its biological actions by activating leptin receptors.
- Leptin receptors are widely expressed in the brain.
- Leptin plays a key role in the hypothalamic regulation of energy homeostasis.
- Leptin modulates hippocampal synaptic transmission and synaptic plasticity.
- Leptin regulates hippocampal neuron excitability.
- Leptin is implicated in CNS-driven disease including neurodegenerative and neuropsychological disorders.

Definitions

Synaptic plasticity: A persistent, activity-driven alteration in the strength of synaptic transmission that is thought to be the cellular basis for information storage in the brain.
Long-term potentiation; A persistent activity-dependent increase in the efficacy of synaptic transmission.
Long-term depression: A long-lasting and activity-dependent reduction in the strength of synaptic transmission.
Structural plasticity: Dynamic modifications that occur in brain structures such as dendrites and synapses, that are thought to contribute to activity-dependent changes in synaptic efficacy.
Metaplasticity: A persistent change in the physiological or biochemical characteristics of a chemical synapse that in turn alters the plastic properties of that synapse.

References

Abraham WC, Gustafsson B, Wigström H. J Physiol. 1987;394:367–80.

Ahmadian G, Ju W, Liu L, Wyszynski M, Lee SH, Dunah AW, et al. EMBO J. 2004;23:1040–50.

Banks WA, Farrell CL. Am J Physiol Endocrinol Metab. 2003;285:E10–5.

Banks WA, Kastin AJ, Huang W, Jaspan JB, Maness LM. Peptides. 1996;17:305–11.

Bates SH, Stearns WH, Dundon TA, Schubert M, Tso AW, Wang Y, et al. Nature. 2003;421:856–9.

Baumann H, Morella KK, White DW, Dembski M, Bailon PS, Kim H, et al. Proc Natl Acad Sci USA. 1996;93:8374–8.

Bjørbaek C, Elmquist JK, Michl P, Ahima RS, Van Bueren A, McCall AL, Flier JS. Endocrinology. 1998;139(8):3485–91.

Clément K, Vaisse C, Lahlou N, Cabrol S, Pelloux V, Cassuto D, et al. Nature. 1998;392:398–401.

Collingridge GL, Isaac JT, Wang YT. Nat Rev Neurosci. 2004;5:952–62.

Cowley MA, Smart JL, Rubinstein M, Cerdán MG, Diano S, Horvath TL, Cone RD, Low MJ. Nature. 2001;411(6836):480–4.

da Silva BA, Bjørbaek C, Uotani S, Flier JS. Endocrinology. 1998;139:3681–90.

Durakoglugil M, Irving AJ, Harvey J. J Neurochem. 2005;95:396–405.

Eikelis N, Esler M, Barton D, Dawood T, Wiesner G, Lambert G. Mol Psychiatry. 2006;11:800–1.

Erbayat-Altay E, Yamada KA, Wong M, Thio LL. Neurosci Lett. 2008;433(2):82–6.

Farr SA, Banks WA, Morley JE. Peptides. 2006;27(6):1420–5.

Fewlass DC, Noboa K, Pi-Sunyer FX, Johnston JM, Yan SD, Tezapsidis N, FASEB J. 2004;18(15):1870–8.

Goldin M, Segal M. Eur J Neurosci. 2003;17:2529–39.

Hâkansson ML, Brown H, Ghilardi N, Skoda RC, Meister B. J Neurosci. 1998;18:559–72.

Halaas JL, Gajiwala KS, Maffei M, Cohen SL, Chait BT, Rabinowitz D, et al. Science. 1995;269:543–6.

Harvey J. J Neurochem. 2007a;100:307–13.

Harvey J. Curr Opin Pharmacol. 2007b;7:643–7.

Harvey J, Hardy SC, Irving AJ, Ashford ML. J Physiol. 2000a;527(Pt 1):95–107.

Harvey J, McKay NG, Walker KS, Van der Kaay J, Downes CP, Ashford ML. J Biol Chem. 2000b;275:4660–9.

Harvey J, Shanley LJ, O'Malley D, Irving AJ. Biochem Soc Trans. 2005;33(Pt5):1029–32.

Hervey GR. J Physiol. 1958;145:336–52.

Huang CC, Lee CC, Hsu KS. J Neurochem. 2004;89:217–31.

Ingalls AM, Dicckie MM, Snell GD. J Hered. 1950;41:317–8.

Latorre R. Acta Physiol Scand Suppl. 1989;582:13.

Li XL, Aou S, Oomura Y, Hori N, Fukunaga K, Hori T. Neuroscience. 2002;113(3):607–15.

Lin S, Huang XF. NeuroReport. 1997;8:3625–9.

Lu X-Y. Curr Opin Pharmacol. 2007;7:648–52.

Lu XY, Kim CS, Frazer A, Zhang W. Proc Natl Acad Sci USA. 2006 Jan 31;103(5):1593–8.

Maffei M, Halaas J, Ravussin E, Pratley RE, Lee GH, Zhang Y, et al. Nat Med. 1995;1(11):1155–61.

Massey PV, Bashir ZI. Trends Neurosci. 2007;30:176–84.

Mise H, Sagawa N, Matsumoto T, Yura S, Nanno H, Itoh H, et al. J Clin Endocrinol Metab. 1998;83(9):3225–9.

Morash B, Li A, Murphy PR, Wilkinson M, Ur E. Endocrinology. 1999;140(12):5995–8.

Morikawa Y, Ueyama E, Senba E. J Neuroendocrinol. 2004;16:105–12.

Moult PR, Milojkovic B, Harvey J. J Neurochem. 2009;108:685–96.

Münzberg H, Jobst EE, Bates SH, Jones J, Villanueva E, Leshan R, Björnholm M, Elmquist J, Sleeman M, Cowley MA, Myres MG Jr. J Neurosci. 2007;27(1):69–74.

Niswender KD, Morton GJ, Stearns WH, Rhodes CJ, Myers Jr MG, Schwartz MW. Nature. 2001;413:794–5.

O'Malley D, Irving AJ, Harvey J. FASEB J. 2005;19(13):1917–9.

O'Malley D, MacDonald N, Mizielinska S, Connolly CN, Irving AJ, Harvey J. Mol Cell Neurosci. 2007;35(4):559–72.

Pinto S, Roseberry AG, Liu H, Diano S, Shanabrough M, Cai X, Cai X, Friedman JM, Horvath TL. Science. 2004;304(5667):110–5.

Power DA, Noel J, Collins R, O'Neill D. Dement Geriatr Cogn Disord. 2001;12(2):167–70.

Proulx K, Clavel S, Nault G, Richard D, Walker CD. Endocrinology. 2001;142:4607–16.

Savioz A, Charnay Y, Huguenin C, Graviou C, Greggio B, Bouras C. NeuroReport. 1997;8:3123–6.

Schwartz MW, Seeley RJ, Campfield LA, Burn P, Baskin DG. J Clin Invest. 1996;98:1101–6.

Shanley LJ, Irving AJ, Harvey J. J Neurosci. 2001;21:RC186.

Shanley LJ, Irving AJ, Rae MG, Ashford ML, Harvey J. Nat Neurosci. 2002a;5(4):299–300.

Shanley LJ, Irving AJ, Rae MG, Ashford ML, Harvey J. J Physiol. 2002b;545:933–44.

Solovyova N, Moult PR, Milojkovic B, Lambert JJ, Harvey J. J Neurochem. 2009;108:190–201.

Spanswick D, Smith MA, Groppi VE, Logan SD, Ashford ML. Nature. 1997;390:521–5.

Takahashi KA, Cone RD. Endocrinology. 2005;146(3):1043–7.

Tartaglia LA, Dembski M, Weng X, Deng N, Culpepper J, Devos R, et al. Cell. 1995;83:1263–71.

Toro L, Wallner M, Meera P, Tanaka Y. News Physiol Sci. 1998;13:112–117.

Ur E, Wilkinson DA, Morash BA, Wilkinson M. Neuroendocrinology. 2002;75(4):264–72.

Wayner MJ, Armstrong DL, Phelix CF, Oomura Y. Peptides. 2004;25(6):991–6.

Williams KW, Zsombok A, Smith BN. Endocrinology. 2007;148(4):1868–81.

Xu L, Rensing N, Yang XF, Zhang HX, Thio LL, Rothman SM, Weisenfeld AE, Wong M, Yamada KA. JClin Invest. 2008;118(1):272–80.

Yuste R, Bonhoeffer T. Annu Rev Neurosci. 2001;24:1071–89.

Zhao AZ, Huan JN, Gupta S, Pal R, Sahu A. Nat Neurosci. 2002;5:727–8.

Zhuo M, Zhang W, Son H, Mansuy I, Sobel RA, Seidman J, Kandel ER. Proc Natl Acad Sci USA. 1999 Apr 13;96(8):4650–5.

Chapter 20
Oxytocin and Appetite

Céline Caquineau and Gareth Leng

Abbreviations

AgRP	Agouti-related protein
AP	Area postrema
ARC	Arcuate nucleus
CCK	Cholecystokinin
CNS	Central nervous system
ER	Endoplasmic reticulum
Icv	Intracerebroventicular
Ins (1,4,5)P$_3$	Inositol-1,4,5-triphosphate
InsP$_3$R	Inositol-1,4,5-triphosphate receptor
Ip	Intraperitoneal
Iv	Intravenous
MC4R	Melanocortin receptor 4
α-MSH	Alpha-melanocyte stimulating hormone
NPY	Neuropeptide Y
NTS	Nucleus of the solitary tract
OC	Optic chiasm
OTR	Oxytocin receptor
PLC	Phospholipase C
Ptdlns(4,5)P$_2$	Phosphatidylinositol-4,5-biphosphate
POMC	Proopiomelanocortin
PVN	Paraventricular nucleus
RP	Reserve pool
RPP	Readily releasable pool
Sim1	Single-minded 1
SON	Supraoptic nucleus
VMN	Ventromedial nucleus of the hypothalamus
3V	Third ventricle

G. Leng (✉)
Centre for Integrative Physiology, University of Edinburgh, George Square,
Hugh Robson Building, EH8 9XD Edinburgh, UK
e-mail: gareth.leng@ed.ac.uk

20.1 Anatomy of the Oxytocin Systems

Oxytocin is synthesized in the hypothalamus by neurons of the supraoptic nucleus (SON) and paraventricular nucleus (PVN); the PVN contains both large (magnocellular) and smaller (parvocellular) oxytocin neurons, while the SON contains only magnocellular neurons (Fig. 20.1). Axons from the magnocellular neurons project to the posterior pituitary gland, where oxytocin stored in vesicles within neurosecretory nerve endings. Oxytocin stored in these nerve endings is secreted into the blood circulation following calcium-dependent exocytosis, triggered by neuronal electrical activity. There are small additional sources of systemic oxytocin from peripheral sources, but the concentration of oxytocin in the blood essentially mirrors the electrical activity of magnocellular neurons in the hypothalamus. The blood-brain barrier prevents most of the oxytocin that is secreted into the blood from penetrating into the brain, but oxytocin is also secreted centrally, and acts at numerous
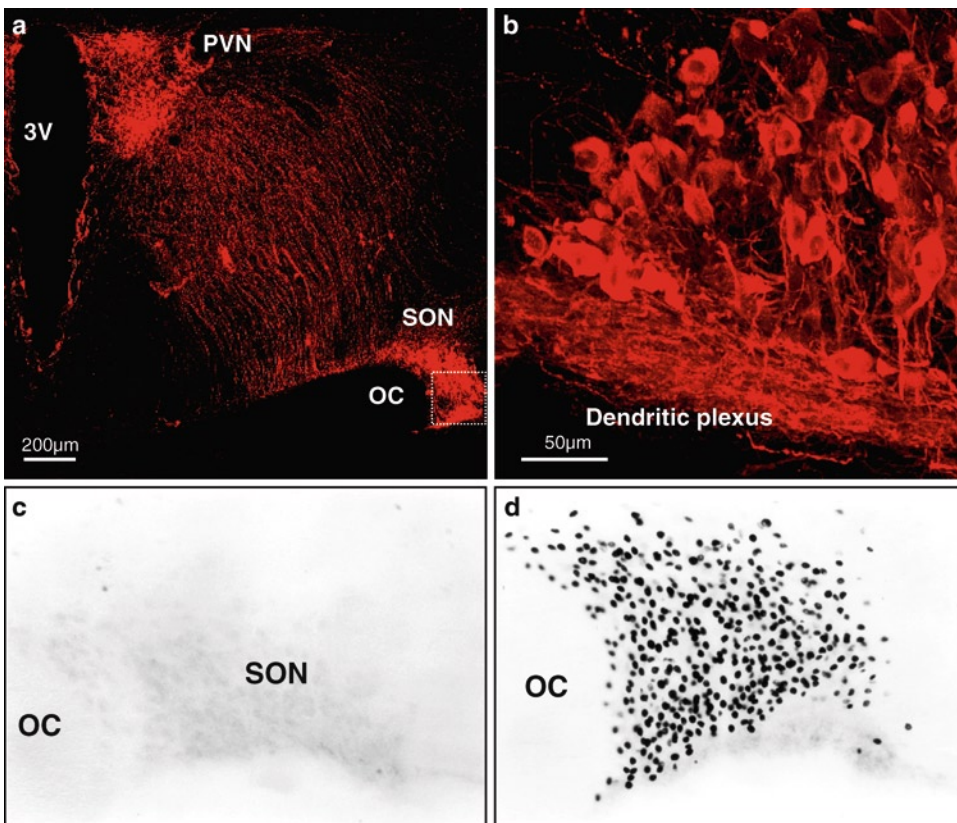
Fig. 20.1 The oxytocin system. (**a, b**) Coronal section of the rat hypothalamus. Oxytocin cells and fibers are immunostained with fluorescent red. Oxytocin is synthesized in the hypothalamus by neurones in the supraoptic nucleus (*SON*) and paraventricular nucleus (*PVN*) (**a**). While the PVN contains magnocellular and parvocellular oxytocin neurons, the SON only contains magnocellular oxytocin neurons (**b**). Axons from magnocellular neurons project to the posterior pituitary gland, where oxytocin stored in vesicles can be secreted into the blood. Axons from parvocellular oxytocin neurons project within the central nervous system (*CNS*) to many areas including the hypothalamus, the brainstem and spinal cord. Oxytocin can also be released centrally from the soma and dendrites of the magnocellular neurons. (**c, d**). Expression of Fos, the protein product of the immediate–early gene c-*fos*, in the SON of a hungry rat (**c**) and of a recently fed rat (**d**). There is very little Fos in the SON in the hungry rat, but after a meal, most SON cells are very active (See Johnstone et al. 2006). *OC* Optic chiasm, *3V* Third ventricle

sites in the brain and spinal cord. Axons from parvocellular oxytocin neurons project extensively to the brainstem and spinal cord, and these neurons are regulated independently of the magnocellular neurons. Oxytocin can also be released centrally from the soma and dendrites of the magnocellular neurons and this release can also be regulated independently of peripheral secretion. Thus oxytocin in the brain derives from two separate sources which can be regulated independently of each other, and independently of peripheral secretion (see Ludwig and Leng 2006).

Oxytocin acts through high affinity G-protein coupled receptors, which are widely distributed both at the periphery and within the brain (see Gimpl et al. 2008). Some of these brain areas that contain oxytocin receptors are densely innervated by parvocellular axon terminals, but others aren't, and there is generally no correlation between the abundance of oxytocin receptors and the density of innervation by oxytocin fibers. The parvocellular oxytocin cells of the PVN project mainly to the caudal brainstem, in particular to the NTS and to the spinal cord. In many other areas, including the ventromedial nucleus of the hypothalamus (VMN), oxytocin receptors are abundant and functional, but there are few, if any, oxytocin-containing fibers (see Leng et al. 2008). Thus the central effects of oxytocin depend more on where its receptors are located rather than where the parvocellular neurons project to. Oxytocin that is released in the brain has a relatively long half-life, meaning that oxytocin released within the brain acts more like a "brain hormone" than like a conventional neurotransmitter, diffusing to sometimes distant sites to exert its effects (see Leng and Ludwig 2006).

20.2 Classical Roles of Oxytocin

Oxytocin is important for parturition in mammals. In the rat, an increase in uterine production of prostaglandins toward the end of pregnancy leads to a fall in the production of ovarian progesterone, and one result of this is that the expression of oxytocin receptors is increased in both the myometrium and endometrium. The uterus thus becomes extremely sensitive to oxytocin, which acts directly on the myometrium to promote uterine contractions and indirectly by stimulating further prostaglandin production. Signals from the contracting uterus and cervix are transmitted via the brainstem back to the oxytocin cells, whose activation leads to a further increase in oxytocin secretion, completing a positive-feedback loop. During parturition, large pulses of oxytocin secretion are superimposed on an elevated background secretion, and each birth is associated with one of these pulses, which are triggered by brief and intense bursts of electrical activity of the oxytocin neurons. Oxytocin is thus important in normal parturition, although oxytocin-deficient transgenic mice ("oxytocin knock-out mice") will still give birth; in these mice, prostaglandins replace oxytocin actions and initiate uterine contractions and parturition (see Russell and Leng. 1998; Russell et al. 2003).

However, the only indispensable physiological role for oxytocin is the milk-ejection reflex (Fig. 20.2). The sucking of a baby at one breast causes milk to be let-down as a reflex, and this reflex is not "local" to the breast being suckled but happens in both; it is mediated by the suckling-induced release of oxytocin from the pituitary gland. Without oxytocin there is no significant milk let-down in any mammal, and pups of oxytocin knock-out mice will starve although milk is available. During suckling, sensory receptors in the skin overlying the mammary gland are activated, leading to the activation of spinal nerves, which project indirectly to the oxytocin neurons to induce oxytocin secretion. This reflex, first described in the rat, is one of the most spectacular of physiological reflexes. When hungry pups suckle at the nipples of their mother, all of the magnocellular oxytocin cells, in near synchrony, discharge a brief burst of action potentials every 5–10 min. This burst, which lasts just a few seconds at most, results in a pulse of oxytocin secretion that causes an abrupt rise in intramammary pressure and milk let-down; when oxytocin reaches the mammary gland,

Electrical activity –the milk-ejection reflex
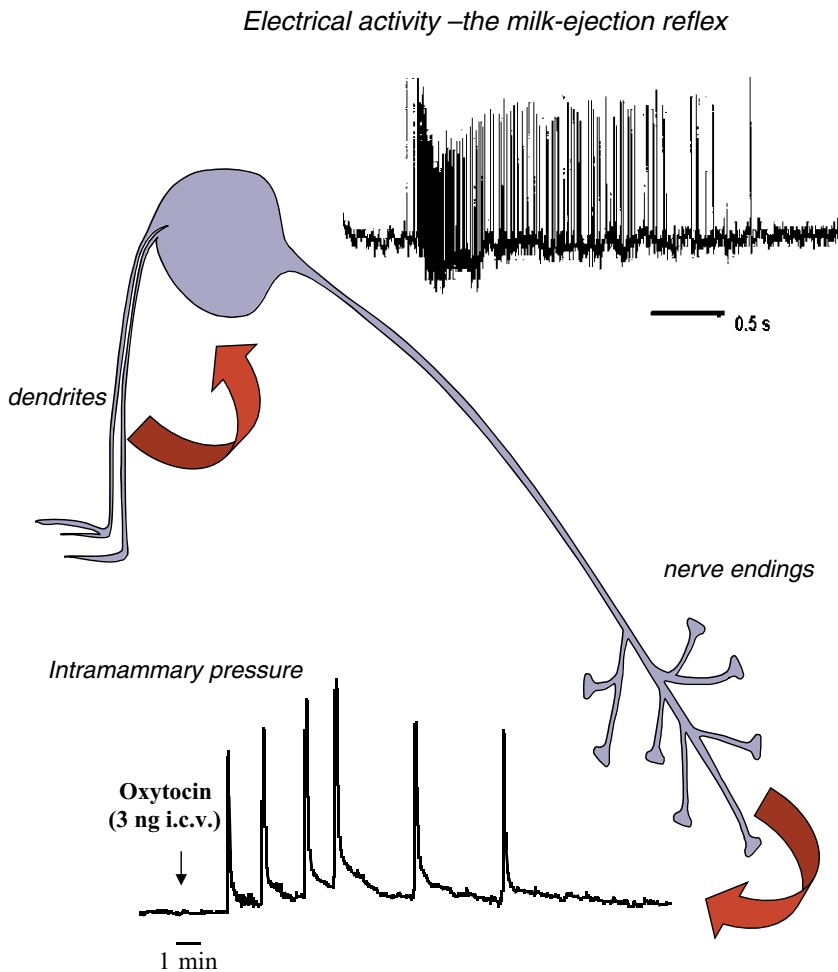
Fig. 20.2 The milk-ejection reflex. During suckling, magnocellular oxytocin neurons in the supraoptic nucleus (*SON*) and paraventricular nucleus (*PVN*) display intense bursts of electrical activity every few minutes; an example of one of these bursts (From Dyball and Leng 1986) is shown at *top right*. These bursts induce oxytocin secretion from both dendrites and axon terminals in the posterior pituitary gland. The dendritic oxytocin release acts back on the oxytocin cells to mobilize intracellular calcium release, an important element in maintaining the reflex. Secretion from the nerve endings enters the blood and reaches the mammary gland, where pulses of oxytocin elicit abrupt rises in intramammary pressure, signaling milk let-down. Oxytocin given centrally in very small amounts will facilitate this reflex, leading to large repeated bursts of activity and subsequent milk let-down. The oxytocin that is released from dendrites subsequently diffuses to act at other brain sites to facilitate maternal behavior

it stimulates the contraction of myoepithelium cells surrounding the alveoli of the mammary gland, inducing milk let-down from these cells to the collecting duct of the mammary gland. Oxytocin released within the brain plays a key role in this reflex; suckling causes large amounts of oxytocin to be released from the dendrites of magnocellular oxytocin neurons, which depolarizes them, and triggers Ca^{2+} release from intracellular stores, and one result of this is to stimulate even more oxytocin release. Very low doses of oxytocin injected directly into the brain (i.c.v.) will facilitate this suckling-induced reflex, milk-ejection bursts are more frequent and more intense; oxytocin antagonists have the opposite effect; they block the reflex (see Leng and Ludwig 2006).

The milk-ejection reflex requires oxytocin secretion to be pulsatile; continuous secretion of oxytocin quickly desensitizes the mammary gland and thus inhibits the milk let-down. The frequency and intensity of milk-ejection bursts in the rat depend on the intensity of suckling – they are proportional to the number of pups suckling. A lactating rat spends many hours of each day nursing her pups, but many other species feed their young only intermittently: rabbits for instance, suckle their young just once a day, and each suckling episode results in just a single milk-ejection reflex. In the pig, the piglets suckle frequently, but for only about 10 min at a time, resulting in a single milk-ejection reflex, after which the piglets detach from the nipples. Thus, in most mammalian species, the reflex comprises a large abrupt pulse of oxytocin release that is triggered with a delay after the onset of suckling. The reflex can also be conditioned – in humans, the cry of a hungry infant can trigger milk let-down, and it can also be easily disrupted by stress and anxiety. In some species, including the rat, the milk-ejection reflex only occurs during periods of slow-wave sleep.

In contrast, many marsupial mammals secrete mesotocin rather than oxytocin from the posterior pituitary gland. Mesotocin differs from oxytocin by only a single amino acid, and appears to be a neutral mutation, as it is fully active at oxytocin receptors. Marsupial mammals display a sophisticated pattern of lactation to allow the nourishment of a neonate that at birth is almost embryonic in form. Milk production is confined to the mammary gland to which the neonate attaches, the volume of milk produced increases and the composition changes during lactation, and evacuation of the pouch leads to the birth of the next young and the development of a second lactation in parallel to the previous one. Thus, at any one time, the kangaroo may support a young neonate permanently attached to one mammary gland in the pouch that receives a dilute milk low in fat and protein but high in carbohydrates, and a lively juvenile intermittently suckling at another, that receives a more concentrated milk higher in protein and fat content (Brennan et al. 2007). The nipples can stretch to an extraordinary degree, allowing the young to feed from almost any position in the pouch and avoiding the danger of accidental detachment of the neonate during maternal grooming or by the activity of the juvenile. In early lactation, the very small pouch young evoke intermittent release of small pulses of mesotocin, enough to induce milk let-down in the gland to which they are attached but not enough to affect the other, less sensitive glands. The juvenile, when it suckles, evokes a much larger reflex secretion which is effective at the "older" gland resulting in a large milk let-down at that gland and, incidentally, giving the neonate an additional meal.

20.3 Oxytocin and Behaviors

In recent years, it became clear that oxytocin receptors are present in many parts of the brain, and that oxytocin acts centrally in the regulation of several behaviors such as pair bonding, maternal care, maternal aggression, stress coping behavior and sexual behavior (see Insel and Young 2001; Ferguson et al. 2002; Carter 2003 for reviews). Oxytocin stimulates maternal motivation toward the offspring and also facilitates the attachment of the infant toward its mother. In rats, oxytocin facilitates the onset of maternal care by overcoming the mother's avoidance behavior toward the neonates and by stimulating nurturing behaviors (Pederson et al. 1982). In sheep, oxytocin is responsible for the selectivity of maternal care that a ewe develops toward her own lamb, leading to rejecting any alien lambs (Keverne and Kendrick 1992). In rats and sheep, these maternal behaviors are initiated by the process of parturition, by the oxytocin that is released within the brain. However, mice are spontaneously maternal, and oxytocin knock-out mice present normal nurturing behaviors. Oxytocin also facilitates the learning processes that allow the pups to recognize its mother olfactory cues and influences the vocalization that a pup produces to signal its isolation to its mother. The involvement of oxytocin in pair bonding has been elegantly described using the prairie and montane voles. Prairie voles are monogamous and

form pair bonds after mating. In female prairie voles, central oxytocin facilitates the formation of pair bonds even in the absence of mating. By contrast, montane voles are polygamous and oxytocin fails to induce pair bonding. This species difference reflects a difference in receptor expression; oxytocin receptors in the prairie vole are densely expressed in brain areas associated with reward such as the nucleus accumbens and caudate putamen, but are almost absent from the same areas in the montane vole (Lim et al. 2004).

The plasma concentration of oxytocin increases during mating in rats and during orgasm in humans. Systemic injections of oxytocin facilitate male sexual behavior by reducing the number of intromissions required to reach ejaculation in rats and rabbits, but oxytocin also has a role in the central regulation of sexual behaviors. When injected into the hypothalamus, oxytocin potently induces penile erection in rats, rabbits, and monkeys, and it increases sexual receptivity and facilitate lordosis in female rats in an estrogen–progesterone-dependent manner (Schumacher et al. 1989). Oxytocin cells in the SON and PVN are activated during penile erection, and expression of the immediate–early gene c-*fos* (a marker of neuronal activity) in oxytocin neurons in the PVN is increased during mating (Witt and Insel 1994). Oxytocin is released in the PVN of male rats during mating and also in the presence of an inaccessible receptive female, suggesting that it has a role in sexual motivation as well as performance (Waldherr and Neumann 2007)

20.3.1 Oxytocin and Feeding Behavior

Central oxytocin is a potent satiety factor; peripheral injections of oxytocin do not affect feeding in rats, but central injections of oxytocin or oxytocin agonists inhibit feeding, including in fasted rats; and these effects can be prevented by an oxytocin antagonist. In mice, the expression of oxytocin mRNA in the hypothalamus is reduced after fasting and restored after refeeding (Kublaoui et al. 2008).

The parvocellular oxytocin neurons of the PVN have a clear role in feeding (see Douglas et al. 2007; Leng et al. 2007). Many of these neurons densely project to the NTS, and conversely, the NTS is the source of dense projections to the SON and PVN. The NTS receives inputs from gastric vagal afferents; these mediate signals from the gut arising as a result of gastric distension and of the effects of peptides released during feeding, including especially the gut peptide cholecystokinin (CCK). Conversely, the NTS is the source of a descending efferent vagal regulation of gastric reflexes that control the flow of food through the gut. In rats, stimuli that increase oxytocin release peripherally are generally accompanied by a reduction in food intake – dehydration, for example, which is a potent stimulus for oxytocin secretion as well as for vasopressin secretion, is accompanied by a profound depression of appetite. Such dehydration-induced anorexia is attenuated in oxytocin knock-out mice, while consumption of solutions that contain NaCl is enhanced. This is not solely attributable to any specific effect on sodium appetite, as oxytocin-deficient mice will also overconsume palatable sucrose solutions, and both sweet and non-sweet carbohydrate solutions (see Leng et al. 2007 for references).

While mice lacking oxytocin appear generally normal in body weight, male (but not female) mice lacking the oxytocin receptor (OTR-KO) mice) have an overt, though mild, late-onset obesity, being slightly heavier than wild-type mice; OTR-KO mice eat significantly more at each meal than wild-type mice, although the meal frequency per day is not significantly different (Takayanagi et al. 2008). As some parvocellular oxytocin neurons in the PVN project polysynaptically to brown adipose tissue, it is possible that oxytocin is involved in peripheral regulation of energy metabolism. When OTR-KO mice are placed in a cold environment (5°C), their body temperature decreases by more than wild-type mice, so a reduced energy consumption might contribute to the late-onset obesity.

Oxytocin deficiency also contributes to the hyperphagia seen in *Sim1*$^{+/-}$ mice. Single-minded 1 (*Sim1*) is one of the six genes implicated in human monogenic obesity and encodes for nuclear

transcription factors (Hung et al. 2007), and is expressed in the PVN and SON and at other sites in the hypothalamus. *Sim1* knock-out mice die shortly after birth and present developmental malfunction of the neurons in the SON, PVN, and anterior periventricular nucleus. Heterozygous *Sim1*^{+/−} mice present a phenotype of hyperphagic obesity, increased linear growth and enhanced sensitivity to diet-induced obesity (Holder 2004; Michaud et al. 2001). Oxytocin mRNA expression is reduced in the hypothalamus of *Sim1*^{+/−} mice in both magnocellular and parvocellular oxytocin neurons (Kublaoui et al. 2008). Central injection of oxytocin receptor antagonist amplified the hyperphagia seen in *Sim1*^{+/−} mice whereas repeated central injections of oxytocin led to a reduction in weight gain in *Sim1*^{+/−} mice.

20.4 Oxytocin and Satiety Signaling

The regulation of food intake depends upon a dynamic balance between "hunger" signals and "satiety" signals arising from the periphery. During feeding, gastric distension and factors released in the stomach mediate satiety by activating afferent vagal neurons that project to the caudal brainstem (Fig. 20.3). Cholecytokinin (CCK) is one important satiety factor that regulates the amount
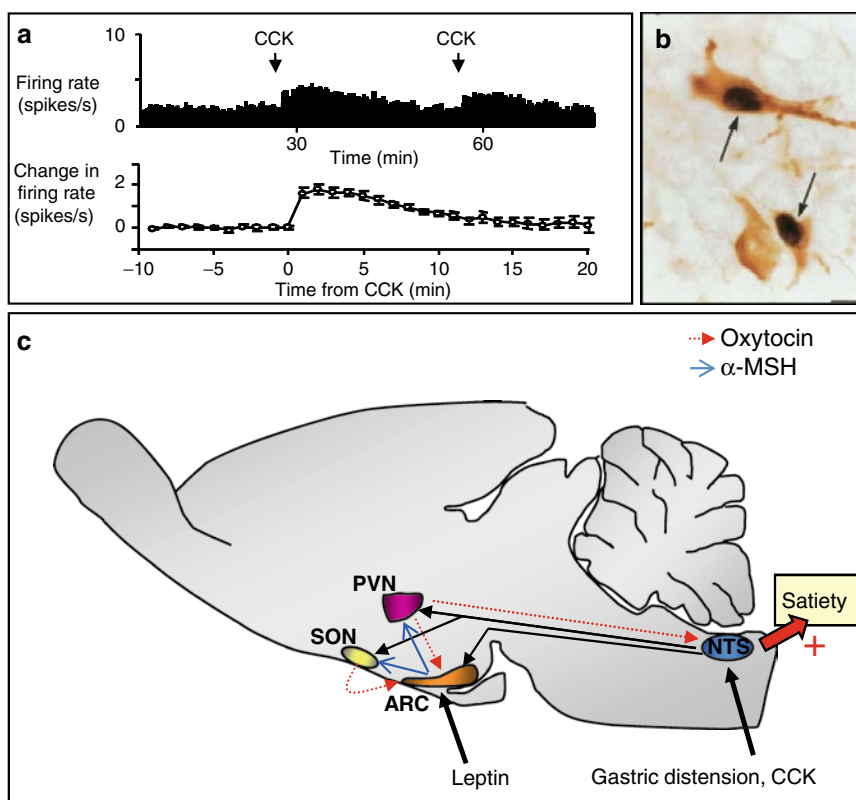
Fig. 20.3 Oxytocin satiety signaling pathways. (**a**) Cholecystokinin (*CCK*) increases the firing rate of oxytocin cells. (**b**) Oxytocin fibers in the nucleus tractus solitarii (*NTS*), immunostained in fluorescent red. (**c**) Oxytocin is involved in the complex neural network that regulates food intake. Gastric distension and satiety signals such as CCK and leptin activate the release of oxytocin into the brain which then enhances the mediation of satiety. *ARC* arcuate nucleus, *AP* area postrema

of food consumed during a meal. CCK released from the gut during eating acts via CCK-A receptors that are located on the nerve endings of gastric vagal afferent nerves. Via this pathway, peripheral injections of CCK activate neurons in the NTS in the causal brainstem, which project to the SON and PVN, activating both parvocellular and magnocellular oxytocin neurons. As a result of the activation of the magnocellular oxytocin neurons, CCK causes a large amount of oxytocin to be secreted from the posterior pituitary into the systemic circulation. This oxytocin acts on the heart to induce the secretion of atrial natriuretic peptide, which in turn acts at the kidney to promote natriuresis (sodium excretion) as a homeostatic regulatory response to compensate for salt intake that accompanies feeding (Gutkowska et al. 1997); in some species, including the rat, this indirect natriuretic action of oxytocin is supplemented by a direct natriuretic action mediated by oxytocin receptors expressed in the kidney. The parvocellular oxytocin neurons of the PVN that are activated during food intake project back to the NTS; oxytocin released from these parvocellular nerve endings acts on oxytocin receptors, which are present at a high density in the NTS, to activate a descending vagal efferent pathway, which regulates the passage of food through the gut (Blevins et al. 2003). Oxytocin may also have a direct effect on gastric motility, and reduced postprandial secretion of oxytocin has been reported in patients with delayed gastric emptying (Borg et al. 2009). Oxytocin antagonists have also been reported to slow gastric emptying in healthy humans (Ohlsson et al. 2006).

The sensitivity of the hypothalamus and brainstem to signals derived from the gut is modulated by peripheral signals reflecting the status of the body's energy stores, and especially by leptin. Leptin is an anorectic hormone secreted mainly from adipocytes; its plasma concentration increases with feeding and decreases with fasting. When injected centrally, leptin reduces food intake and increases the number of NTS neurons that express c-*fos* after peripheral administration of CCK, and during fasting, leptin deficiency reduces the satiety effect of CCK. There is evidence that oxytocin contributes to the effects of leptin. Leptin induces an increase in c-*fos* expression in the parvocellular oxytocin neurons that project to the NTS. Furthermore, a central injection of an oxytocin receptor antagonist followed by a central leptin and a peripheral CCK injection reduces the potentiating effect of leptin on the satiety action of CCK. This suggests that parvocellular oxytocin neurons activated by leptin act as a relay between the hypothalamus and the NTS to enhance NTS neurons sensitivity to increase their sensitivity to meal-related satiety signals (Blevins et al. 2004). Leptin not only influence oxytocin releases, it also modulates oxytocin expression. This has been supported by an elegant study using laser microdissection and microarray hybridization that showed that the reduction of oxytocin gene expression in the PVN seen in fasted rats can be reversed by peripheral injection of leptin (Tung et al. 2008).

Although considerable evidence supports the role of central oxytocin as a potent satiety factor, the precise neuronal source of oxytocin is still uncertain. Because axons from magnocellular neurons project to the posterior pituitary, the possible central role of these neurons was disregarded in favor of the centrally projecting parvocellular oxytocin neurons. Oxytocin released from parvocellular neurons is undoubtedly involved in the regulation of food intake, by providing a local source of oxytocin in the NTS. However, the major source of oxytocin in the hypothalamus is the magnocellular neurons (Ludwig and Leng 2006). Magnocellular oxytocin neurons are clearly strongly activated during feeding; c-*fos* expression in the SON is markedly increased after food intake in rats (Johnstone et al. 2006) and in the ewe (Chaillou et al. 2000). Gastric distension and systemic injection of CCK both increase c-*fos* expression in magnocellular neurons and induce oxytocin secretion into the bloodstream. Magnocellular oxytocin neurons are also affected by many other factors regulating appetite; for example, they densely express leptin receptors (Håkansson and Meister 1998), and they are powerfully regulated by alpha-melanocyte-stimulating hormone (α-MSH), one of the most potent satiety factors known (Sabatier et al. 2003).

20.5 Magnocellular Oxytocin Neurons and α-MSH

The anorexigenic factor α-MSH is a peptide product of the proopiomelanocortin (POMC) prohormone. Centrally, it is produced in neurons in the dorsomedial hypothalamus and in the arcuate nucleus (ARC) of the hypothalamus. α-MSH actions are primarily mediated via MC4 receptors which are widely distributed throughout the CNS. Central injections of α-MSH inhibit food intake, and mutations in the POMC gene or in the MC4 receptor gene lead to obesity associated with hyperphagia; in humans, mutations of the MC4 receptor gene are the most common monogenic identified cause of early-onset of obesity, suggesting that α-MSH is critical in the regulation of food intake. Within the arcuate nucleus, POMC neurons are innervated by neurons-secreting neuropeptide Y (NPY), a potent orexigenic factor. NPY neurons also produce an endogenous antagonist of the MC4 receptors, the agouti-related protein (AgRP), whose overexpression in the hypothalamus leads to hyperphagia, reduced energy expenditure and obesity (Lu et al. 1994). POMC neurons are also inhibited by the "hunger" signal ghrelin (a large peptide secreted from the empty stomach) both directly and indirectly via the NPY neurons that ghrelin has been shown to excite. Leptin stimulates POMC neurons to release α-MSH directly and indirectly via inhibiting NPY neurons; it also modulates the expression of the processing enzymes responsible for the cleavage of POMC into α-MSH, thus regulating α-MSH synthesis and availability for release.

Oxytocin and α-MSH have remarkably similar behavioral effects. They are both potent satiety factors and they are also both potent stimulator of sexual motivation and performance in rats and humans (Wessells et al. 2000). When injected into the PVN or NTS, α-MSH, and MC4 receptors agonist strongly inhibit food intake, just as oxytocin does. Magnocellular oxytocin neurons express MC4 receptors, and α-MSH-containing fibers innervate both the SON and PVN (Mountjoy et al. 1994). Like for oxytocin, hypothalamic melanocortin signaling is impaired in *Sim1*^{+/−} mice (Wisse and Schwartz 2003). It has been suggested that Sim1 intervenes in the regulation of body weight by modulating MC4 receptors signaling in the PVN (Holder 2004). A subset of PVN *Sim1* neurons expresses oxytocin but also MC4 receptors, suggesting that α-MSH signaling is mediated via oxytocin whose expression depends upon Sim1 (Kublaoui et al. 2008).

Central injection of α-MSH induces strong expression of c-*fos* in both the PVN and SON, but more in magnocellular oxytocin neurons than in parvocellular oxytocin neurons (Caquineau et al. 2006). While central injection of α-MSH or MC4 receptor agonist inhibits the electrical activity of magnocellular oxytocin neurons and does not stimulate oxytocin release into the blood circulation, it potently stimulates release of oxytocin from neuronal dendrites. Thus, α-MSH stimulates *central* release of oxytocin rather than peripheral secretion, and this central release originates from dendrites of magnocellular oxytocin neurons rather than the axon terminals of parvocellular neurons (see Sabatier 2006 for review).

20.6 Dendritic Oxytocin Release and Its Significance in the Regulation of Food Intake

The dendrites are those processes of a neuron that receive most of a neuron's synaptic input, and until recently were assumed to have a merely passive role in collating these signals. The only output of a neuron was equally assumed to be neurotransmitters released at axonal nerve endings as a result of electrical activity in the form of action potentials transmitted along the axons. As far as neuropeptides are concerned, however, both of these assumptions are false. Many neurons make and release

one or more neuropeptides as well as conventional neurotransmitters, but the peptides are not packaged in the same vesicles as the neurotransmitters are. Conventional neurotransmitters, like glutamate and GABA, are packaged in small synaptic vesicles that are targeted specifically to synapses. Peptides are packaged in much larger vesicles that are, in generally uniformly distributed throughout the cytosol of a neuron; accordingly, because the dendrites of most neurons comprise 80–90% of the cytosolic volume, most peptides in the brain are packaged in large dense core vesicles that are mainly located within dendrites, and this is true in particular of oxytocin in the hypothalamus.

The secretion of oxytocin from axon terminals is regulated by neuronal electrical activity: depolarization induced by an action potential cause an increase in voltage-gated calcium entry into the nerve terminals, leading to exocytosis of oxytocin-containing vesicles. By contrast, vesicle exocytosis in dendrites of magnocellular neurons is not only triggered by the entry of extracellular calcium but can also be triggered by a mobilization of calcium from endoplasmic reticulum (ER) stores. The mobilization of calcium from ER stores results from the activation of G protein–coupled receptors and related second messenger Phospholipase C (PLC)-inositol-triphosphate pathways, and these pathways can be activated independently from electrical activity – in particular, α-MSH stimulates dendritic oxytocin release by mobilizing intracellular calcium stores while at the same time inhibiting neuronal electrical activity (see Ludwig and Leng 2006). In parallel with stimulating exocytosis, the increase in intracellular calcium can also induce a redistribution of the remaining vesicles in the dendrite into a readily releasable pool; this very important mechanism enhances the availability of oxytocin-containing vesicles to future putative electrical triggers. This preparation for future release of oxytocin, or "priming," lasts for at least 90 min, and so engenders a reconfiguration of the local oxytocin circuitry, opening new routes of communication between neurons (see Ludwig and Leng 2006)

In many brain areas, the content of oxytocin in extracellular fluid is much higher than would be expected by local release from the sparse axon terminals, so it is likely that oxytocin acts as a neurohormone by diffusing through the extracellular fluid from the magnocellular neurons that release it in abundance from their dendrites (Leng and Ludwig 2006).

20.7 The Ventromedial Nucleus of the Hypothalamus

The VMN is one important target for central oxytocin release; it expresses oxytocin receptors densely, but contains few if any oxytocin-containing fibers. The VMN is a large heterogeneous nucleus that can be subdivided into dorsomedial, central, and ventrolateral regions based on the expression of transcription factors, receptors, and neuropeptides (Fig. 20.4). The ventrolateral region is mainly responsible for the facilitation of lordosis behavior in female rats, whereas the dorsal VMN has been known as a satiety center since 1940, when it was first reported that rats with lesions of the VMN display a "voracious" appetite. One interesting subpopulation of VMN neurons, which delineates the more dorsal and central regions, expresses the nuclear receptor steroidogenic factor-1 (SF1); mutations of SF1 are linked to obesity and type-2 diabetes in humans. Leptin excites SF1 neurons in vitro, and the actions of leptin in the VMN help to resist diet-induced obesity. Another population of VMN neurons is involved in glucose homeostasis, and these glucoreceptor neurons are also activated by leptin in vivo. The dorsomedial VMN projects to the bed nucleus of the stria terminalis, the nucleus accumbens, and the medial prefrontal cortex, and also sends strong excitatory inputs to POMC neurons in the arcuate nucleus; this connection is dynamically regulated by nutritional state, as it is weakened by fasting (see Leng et al. 2007 for references).

In the rat brain, the VMN is one of the regions that contain the highest densities of oxytocin-binding sites and oxytocin receptor mRNA expression, with particularly intense labeling in the
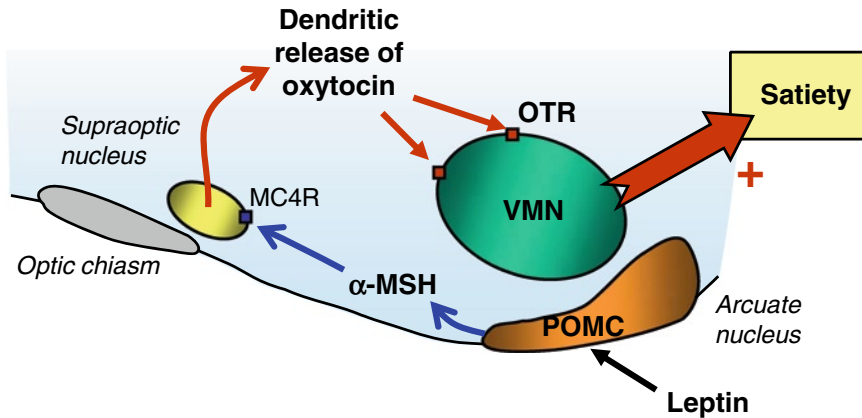
Fig. 20.4 The ventromedial nucleus of the hypothalamus (*VMN*) and oxytocin. (**a**, **b**) Oxytocin fibers immunostained with fluorescent red in coronal section of a rat brain. Although the VMN is rich in oxytocin receptors it is barely innervated by oxytocin fibers (**b**). (**c**) Leptin released from the body's fat stores activates the release of alpha-melanocyte stimulating hormone (*α-MSH*) from POMC neurons in the arcuate nucleus (*ARC*) these neurons project densely to the supraoptic nucleus (*SON*) and paraventricular nucleus (*PVN*). In the SON and PVN, α-MSH acts on magnocellular oxytocin neurons via MC4 receptors to stimulate the dendritic release of oxytocin. Oxytocin then diffuses to the satiety center VMN, which expresses oxytocin receptors in great abundance, to reduce appetite. *MC4R* melanocortin receptor 4, *OC* optic chiasm, *OTR* oxytocin receptor, *POMC* proopiomelanocortin neurones. Scale bar:200μm

ventrolateral VMN, and these receptors have been confirmed as functional by electrophysiological studies. The abundance of functional oxytocin receptors on VMN neurons contrasts strikingly with the absence there of oxytocin-containing fibers. The VMN contains very few fibers that show any immunoreactivity for oxytocin (Fig. 20.2), and it is not known whether the few oxytocin fibers there are "stray" axons or dendrites of magnocellular neurons, or come from parvocellular neurons of the PVN. By marked contrast, the region ventrolateral to the VMN is densely permeated by oxytocin-containing axons of magnocellular neurons on their way from the PVN and SON to the neurohypophysis. The magnocellular neuronal axons do not have any collateral branches in this region, so give rise to no conventional nerve endings and synapses. This does not however mean that no oxytocin is released from these axons; oxytocin vesicles can be released from any part of a neuron in which they are present, even including undilated axons; the likelihood of a vesicle being released appears to depend solely on how close it is to the cell plasma membrane. Axons contain relatively few vesicles that are close to the plasma membrane, and far fewer in total than are contained in dendrites, but nevertheless, might be a functionally significant source of oxytocin in the region adjacent to the VMN. So far, there is no evidence of any synaptic innervation of VMN neurons by parvocellular oxytocin neurons of the PVN. Thus it is not clear whether the most important source of oxytocin for the VMN is the nearby axons of magnocellular neurons, from which small amounts are released in response to electrical activity propagated down the axons, or the more distant dendrites, from which more oxytocin is released by stimuli that can be independent of electrical activity.

20.7.1 Interactions Between Appetite for Food and Appetite for Sex

Feeding behavior and sexual behavior are mutually exclusive goal-orientated behaviors: they are both initiated with a drive, a drive to find food or to seek sexual contact. Their regulation involves a complex network of hormonal and neuronal actions to ensure the display of appropriate behavior

Table 20.1 Key features of oxytocin

1. Oxytocin is a peptide hormone secreted from the posterior pituitary gland
2. It is secreted into the systemic circulation from the nerve endings of large neurons whose cell bodies lie in the hypothalamus
3. Oxytocin is secreted into the blood in response to suckling, and is *essential* for milk let-down
4. It is also secreted during parturition, when it promotes the progress of parturition, and it is secreted during sexual activity
5. Oxytocin is also released in the brain, where it affects many behaviors. This central release is governed independently of peripheral secretion
6. Oxytocin release in the brain promotes maternal, social and sexual behaviors, while inhibiting feeding behaviors
7. Oxytocin does not cross the blood-brain barrier, so peripheral administration of oxytocin does not have these behavioral effects

This table lists the key features of oxytocin

according to the physiological needs of each individual. Many factors that regulate feeding also affect sexual behavior and reciprocally, many factors that regulate sexual behavior also regulate feeding. For instance: orexins, neuropeptides that stimulate food intake, also increase sexual arousal and performance in male rats (Gulia et al. 2003); NPY, a potent appetite stimulator, inhibits sexual behavior in sexually experienced male rats (Poggioli et al. 1990); central injection of leptin restores copulatory behavior in streptozotocin-induced diabetic male rats (Saito et al. 2004); dopamine, a crucial factor in the regulation of sexual behavior involved in both sexual motivation and sexual performance (e.g., Hull et al. 1995), also plays a role in the drive for food (e.g., Wang et al. 2002); and analogs of the satiety factor α-MSH induce penile erection in rats and in men with psychogenic erectile dysfunction (e.g., Wessells et al. 2000; Martin et al. 2002).

When male rats are hungry, their sexual behavior is impaired; they are slower to mate than normal; the drive for sex competes with the drive for food in hungry rats, and is thus responsive to the animal's nutritional status. Central injections of MC4 receptor antagonist also impair sexual behavior in male rats, and this action is accompanied by a reduction in c-*fos* expression in magnocellular oxytocin neurons, suggesting that the effects of the antagonist on sexual behavior involve a suppression of oxytocin release in the brain (Caquineau et al. 2006). The need for a coherent organization of feeding and sexual behaviors implies that the competing drives for food and for a sexual partner must be reciprocally regulated. This is likely to involve central mechanisms coordinating a switch in motivation, or a transfer from one drive to another according to physiological and nutritional needs. In part, this fundamental switch in motivational behaviors seems to be regulated by the hypothalamic actions of α-MSH, mediated in part by oxytocin (Table 20.1).

20.7.2 Applications to Other Areas in Health and Disease

As oxytocin in mammals is indispensable for successful reproduction in mammals by virtue of its essential role in nurture of the young, it is unsurprising that few genetic defects of oxytocin systems have been recognized in human populations, One exception is Prader–Willi syndrome, a rare genetic disorder arising from the loss of paternally inherited genes on chromosome 15q11–13, leading to life-threatening insatiable hunger and obesity from early childhood, through developmental hypothalamic defects. The PVN from humans with this syndrome shows a 42% reduction in the number of parvocellular oxytocin neurons (see Goldstone 2006).

There has been recent speculation that autism may be linked to dysregulation of central oxytocin release, but this has yet to be clearly established. Oxytocin is used clinically to promote the progress of labor, and antagonists are used in some cases to prevent threatened preterm labor (Zingg and Laporte 2003).

Summary Points

- Oxytocin secreted from the posterior pituitary gland is essential for milk let-down in response to suckling.
- Oxytocin released in the brain is important for maternal behaviors essential for nurturing the offspring.
- Oxytocin released in the brain is also a potent satiety factor.
- Both parvocellular and magnocellular oxytocin neurones are involved in the regulation of feeding behavior.
- Oxytocin neurons are regulated by signals from the gut and from fat stores, and they interact with the central neuropeptide signaling pathways that regulate food intake.
- Oxytocin acts as a neurohormone. Oxytocin released from dendrites of magnocellular oxytocin neurones diffuses to distant targets areas such as the VMN to inhibit food intake and modulate behaviors.

Definitions

Dendrite: A branched projection of a neuron where synaptic inputs are integrated and processed to generate action potentials. Dendrites can also release neuroactive substances including neurotransmitters and neuropeptides that regulate the cell of origin as well as neighboring cells.

Magnocellular neuron: A large neuroendocrine neuron of the supraoptic nuclei and paraventricular nuclei of the hypothalamus that projects to the posterior pituitary gland.

Parvocellular neuron: A centrally projecting neuron of the paraventricular nucleus.

c-*fos*: An immediate–early gene encoding a transcription factor (Fos) whose expression is stimulated by a variety of cellular stimuli. It is commonly used as a marker of neuronal activation.

Neurohormone: A chemical messenger secreted from one group of neurons that acts on another distant group of neurons.

"knock-out" mice: Transgenic mice with an engineered inactivation of a particular gene; oxytocin knock-out mice do not synthesize oxytocin.

Hypothalamus: Complex brain area that regulates many important homeostatic neuroendocrine functions; different regions of the hypothalamus regulate, among many things, body temperature, hunger, plasma volume and electrolyte balance, stress responses, metabolism and growth, release of hormones from many glands, especially the pituitary gland, sex drive, sleep, circadian rhythms, and thirst

---

References

Blevins JE, Eakin TJ, Murphy JA, Schwartz MW, Baskin DG. Brain Res. 2003;993:30–41.
Blevins JE, Schartz MW, Baskin DG. Am J Physiol. 2004;287:87–96.
Borg J, Melander O, Johansson L, Uvnäs-Moberg K, Rehfeld JF, Ohlsson B. BMC Gastroenterol. 2009;9:17.
Brennan AJ, Sharp JA, Lefevre C, Topcic D, Auguste A, Digby M, et al. J Dairy Sci. 2007;90 Suppl 1:E66–75.
Caquineau C, Leng G, Guan XM, Jiang M, Van der Ploeg L, Douglas AJ. J Neuroendocrinol. 2006;18:685–91.
Carter CS. Physiol Behav. 2003;79:383–97.
Chaillou E, Baumont R, Tramu G, Tillet Y. Eur J Neurosci. 2000;12:4515–24.
Douglas AJ, Johnstone LE, Leng G. Physiol Behav. 2007;91:352–65.
Dyball REJ, Leng G. J Physiol. 1986;380:239–56.
Ferguson JN, Young LJ, Insel TR. Front Neuroendocrinol. 2002;23:200–24.
Gimpl G, Reitz J, Brauer S, Trossen C. Prog Brain Res. 2008;170:193–204.
Goldstone AP. Prog Brain Res. 2006;153:57–73.
Gulia KK, Mallick HN, Kumar VM. Neuroscience. 2003;116:921–3.
Gutkowska J, Antunes-Rodrigues J, McCann SM. Physiol Rev. 1997;77:465–515.
Håkansson ML, Meister B. Neuroendocrinology. 1998;6:420–7.
Holder JR. Am J Endocrinol Metab. 2004;287:E105–13.
Hull EM, Du J, Lorrain DS, Matuszewich L. J Neurosci. 1995;15:7465–71.
Hung CC, Luan J, Sims M, Keopgh JM, Hall C, Wareham NJ, et al. Int J Obes. 2007;31:429–34.
Insel TR, Young L. Nat Rev Neurosci. 2001;2:129–36.
Johnstone LE, Fong TM, Leng G. Cell Metab. 2006;4:313–21.
Keverne EB, Kendrick KM. Ann NY Acad Sci. 1992;652:83–101.
Kublaoui BM, Gemelli T, Tolson KP, Wang Y, Zinn AR. Mol Endocrinol. 2008;22:1723–34.
Leng G, Ludwig M. J Neuroendocrinol. 2006;18:379–92.
Ludwig M, Leng G. Nat Rev Neurosci. 2006;7:126–36.
Leng G, Onaka T, Caquineau C, Sabatier N, Tobin V, Takayangi Y. Prog Brain Res. 2007;170:137–51.
Leng G, Onaka T, Caquineau C, Sabatier N, Tobin V, Takayangi Y. Prog Brain Res. 2008;170:137–51.
Lim MM, Wang Z, Olazabal DE, Ren X, Terwilliger EF, Young LJ. Nature. 2004;429:754–7.
Lu D, Willard D, Patel IR, Kadwell S, Overton L, Kost T, et al. Nature. 1994;371:799–802.
Martin WJ, McGowan E, Cashen DE, Gantert LT, Drisko JE, Hom GJ, et al. Eur J Pharmacol. 2002;454:71–9.
Michaud JL, Boucher F, Melnyk A, Gauthier F, Goshu E, Levy E, et al. Hum Mol Genet. 2001;10:1465–73.
Mountjoy KG, Mortrud MT, Low MJ, Simerly RB, Cone RD. Mol Endocrinol. 1994;8:1298–308.
Ohlsson B, Björgell O, Ekberg O, Darwiche G. BMC Gastroenterol. 2006;6:11.
Pederson CA, Asher JA, Monroe YL, Prange AJ. Science. 1982;216:648–50.
Poggioli R, Vergoni AV, Marrama D, Giuliani D, Bertolini A. Neuropeptides. 1990;16:169–72.
Russell JA, Leng G, Douglas AJ. Front Neuroendocrinol. 2003;24:27–61.
Russell JA, Leng G. J Endocrinol. 1998;157:343–59.
Sabatier N. J Neuroendocrinol. 2006;18:703–10.
Sabatier N, Caquineau C, Dayanithi G, Bull P, Douglas AJ, Guan X, et al. J Neurosci. 2003;23:10351–8.
Saito TR, Tatsuno T, Takeda A, Hashimoto H, Suzuki M, Terada M, et al. Exp Anim. 2004;53:445–51.
Schumacher M, Coirini H, Frankfurt M, McEwen BS. Proc Natl Acad Sci USA. 1989;86:6798–67801.
Takayanagi Y, Kasahara Y, Onaka T, Takahashi N, Kawada T, Nishimori K. NeuroReport. 2008;19:951–5.
Tung YCL, Ma M, Piper S, Coll A, O'Rahilly S, Yeo GSH. J Neurosci. 2008;28:12419–26.
Waldherr M, Neumann ID. Proc Natl Acad Sci USA. 2007;104:16681–4.
Wang GJ, Volkow ND, Fowler JS. Expert Opin Ther Targets. 2002;6:601–9.
Wessells H, Gralnek D, Dorr R, Hruby VJ, Hadley ME, Levine N. Urology. 2000;56:641–6.
Wisse BE, Schwartz MW. Nat Neurosci. 2003;6:655–6.
Zingg HH, Laporte SA. Trends Endocrinol Metab. 2003;14:222–7.
Witt DM, Insel TR. J Neuroendocrinol. 1994;6:13–8.

Chapter 21
The Role of Apolipoprotein APO A-IV in Eating Behavior and Diet

Giuseppe Derosa and Sibilla Anna Teresa Salvadeo

Abbreviations

TC	Total cholesterol
HDL	High-density lipoproteins
LDL	Low-density lipoproteins
Tg	Triglyceride; triglycerides
Apo A-IV	Apolipoprotein A-IV
PYY	Peptide Y
NPY	Neuropeptide Y
HNF-4	Hepatocyte nuclear factor 4
PGC-1	Peroxisome proliferator-activated receptor gamma co-activator 1
BMI	Body mass index
CCK	Cholecystokinin
LCAT	Cholesterol acyl transferase
OFLT	Oral fat load test
AUC	Area under curve
POMC	Pro-opiomelanocortin
ABCA 1	ATP binding cassette transporter 1
CETP	Cholesteryl ester transfer protein

21.1 Introduction

Apolipoprotein A-IV was discovered over 22 years ago, but its physiological features were not clearly defined until recently (Table 21.1). Apolipoprotein A-IV has been studied both in rodents and humans, even if the major part of information comes from experiments in animals. In animals, apo A-IV is secreted both in the intestine and the liver, the former being the major organ responsible of circulating apo A-IV. In humans, apo A-IV is produced in the small intestine only. The first data about a relation between apo A-IV and lipid metabolism were published between late 1970s and 1980s (Dvorin et al. 1988).

G. Derosa (✉)

Department of Internal Medicine and Therapeutics, University of Pavia, Pavia, Italy
e-mail: giuseppe.derosa@unipv.it

Table 21.1 Apolipoprotein A-IV: update of physiological functions

Authors	Actions	Mechanisms
Chen et al. (1985)	Stimulates activity of lecithin:cholesterol acyl transferase (LCAT)	
Dvorin et al. (1986)	Favor cellular cholesterol efflux	Interaction with ABCA 1 transporter
Barter et al. (1988) Lagrost et al. (1990)	Participate in HDL3 particles conversion into new population of particles	Action on CEPT
Goldberg et al. (1990) Sato et al. (2002)	Modulates activity of lipoprotein lipase	Facilitates the transfer of apo C-II to Tg-rich lipoproteins
		Stimulates V_{max} of lipoprotein lipase in triacylglycerol emulsions containing apo B and apo C-II.
Goldberg et al. (1990)	Enhances the clearance of Tg-lipoproteins	Action on lipoprotein lipase
Goldberg et al. (1990)	Increases HDL formation	Action on lipoprotein lipase
Guyard et al. (1994)	Transfer of cholesteryl ester between HDL and LDL fractions	Action on CEPT

ABCA 1 ATP binding cassette transporter 1, *Tg* triglycerides, *HDL* high density lipoproteins, *LCAT* cholesterol acyl transferase, *CEPT* cholesteryl ester transfer protein. See also Fig. 21.1

Fig. 21.1 Proteins associated with chylomicrons in rats and humans. *ARP* Apolipoprotein E (Reproduced from Bisgaier et al. 1987)
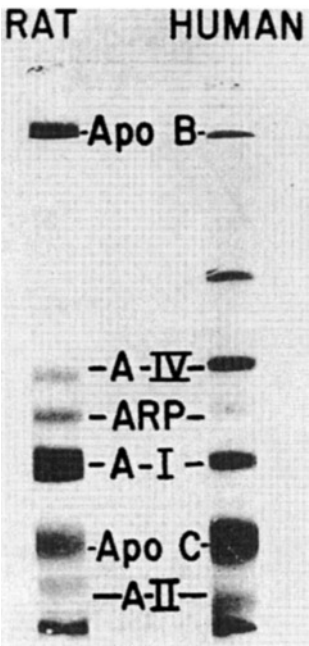
In 1990 Hayashi et al. demonstrated that stimulation of apo A-IV production, induced by lipid feeding, is followed by formation of chylomicrons (Hayashi et al. 1990).

Subsequently, many studies were conducted sustaining a role of apo A-IV in lipoproteins metabolism (Goldberg et al. 1990; Stein et al. 1986) even if no direct evidences are available about similar effects of apolipoproteins in vivo. Recent studies have evaluated the genetic expression of apo A-IV and its effects on other lipoproteins metabolism (Li et al. 2008).

There are evidences that apo A-IV exerts a protective action against atherosclerosis in mice (Vergnes et al. 2000). These effects are more evident when highly atherogenic conditions, such as hyperlipidemia and high-fat diet, are present, while no significant results have been observed in the few studies that examined apo A-IV antiatherogenic actions under physiological conditions.

The main purpose of this chapter is to elucidate the role of apo A-IV in food intake regulation and diet according to recent findings. Moreover, recent studies have shown a protective action of apo A-IV against atherosclerosis in humans (Kronenberg et al. 2000) and this has stimulated increasing interest of researchers in this field.

So far, a series of physiological studies supporting the role of apo A-IV in the regulation of food intake in animals and humans have been published (Fujimoto et al. 1992) and new evidences are available about the role of apo A-IV on the regulation of food intake in particular populations, such as diabetic patients.

21.2 Apolipoprotein A-IV

21.2.1 Biochemical Features

Apolipoprotein A-IV is a 46-kDa glycoprotein containing 6% carbohydrate and 376 amino acid residues. It is coded by a gene located on chromosome 11q and clustered with apo A-I and apo C-III. Apo A-IV contains a 14 peptide repeat with the potential of forming amphipathic α-helices and is primarily incorporated into the surface of nascent chylomicrons and high-density lipoproteins (HDL), with a small percentage of very-low-density lipoproteins (VLDL). In circulating blood, active exchange occurs between chylomicrons and HDL particles, the former providing apo A-IV and the latter donating apo C-II and apo E (Ghiselli et al. 1986). Moreover, apo A-IV has been found in the lipoprotein-free plasma fraction. Some studies have demonstrated that apo A-IV α-helices are not amphipathic enough to penetrate lipid monolayers, so that the interaction between apo A-IV and lipoproteins results very labile (Saito et al. 2004). Apo A-IV is secreted by enterocytes in association with Tg-rich lipoproteins (chylomicrons). In humans, apo A-IV is synthesized by small intestine only (Gordon et al. 1984) (Fig. 21.1).

Many genetic variants of apo A-IV have been identified (Table 21.2): two common, apo A-IV-1 and apo A-IV-2, and two rare alleles are characteristic of Caucasian populations. Population screening

Table 21.2 Alleles of apolipoprotein A-IV

Alleles	Populations
Apo A-IV-1	Common in Caucasian populations (0.91)
Apo A-IV-2	Common in Western Countries populations, completely absent in Japanese population (0.07–0.09)
Apo A-IV-0	Rare
Apo A-IV-3	Rare
Apo A-IV-5	Rare, found in US Black population
Apo A-IV-6	Rare
Apo A-IV-7	Common in Nigerian populations

According to these data, apo A-IV-2 allele is a Caucasian marker and the different phenotypes observed are is due to variable degrees of Caucasian admixture. The detection of the apo A-IV-5 allele in Black People from Nigeria and the USA indicates that this is a marker unique to blacks, since no example of this variant allele has been reported in other population groups. If these differences are able to explain different metabolic features between races is still unknown (Sepehrnia et al. 1988)

has estimated that an allele frequency of 0.91 features the major allele apo A-IV-1. One in seven Americans seems heterozygous for the apo A-IV-2 allele, which is completely absent in Japanese population. Data from many studies report a relationship between apo A-IV polymorphism and interindividual variability in plasma lipid concentrations, glucose levels, and body mass index (BMI) (Ehnholm et al. 1994; Hanis et al. 1991).

Recent observations demonstrated that apo A-IV-2 allele delays the postprandial clearance of Tg-rich lipoproteins (Hockey et al. 2001). Discrepancies between results of the different studies in this field are still unexplained, even if an interaction between apo A-IV gene and different diets has been hypothesized.

21.2.2 Regulation of Apolipoprotein A-IV

21.2.2.1 Nutritional Status

Both in animal models and humans, apo A-IV concentration increases following fat-feeding. Malabsorption studies confirm the role of intestinal Tg in regulating apo A-IV concentration. Low levels of apo A-IV have been detected in a variety of pathological states of malabsorption, such as abetalipoproteinemia, hypobetalipoproteinemia, chronic pancreatitis, malabsorptive syndromes, and in total parenteral nutrition (Bisgaier et al 1983; Weinberg et al 1983; Koga et al. 1985; Sherman et al 1988).

Few and controversial data are available about the effects of short- and medium-chain fatty acids on apo A-IV, while long-chain fatty acids have been demonstrated to elicit significant effect on apo A-IV. Furthermore, little attention has been paid to the possible effects of cholesterol on intestinal apo A-IV biogenesis in humans. Up to date, the hypothesis retained is that cholesterol consumption increases hepatic apo A-IV mRNA in the postprandial state, and some authors suggest a chronic fat-induced adaptation of apo A-IV (Kalogeris et al 2001).

Apo A-IV has been found to be associated to Tg-rich lipoproteins and HDL particles in plasma (Lagrost et al. 1989). Moreover, apo A-IV plays a role in the metabolism of both Tg-rich lipoproteins and HDL and modulates the activation of lipoprotein lipase in the presence of apo C-II (Goldberg et al. 1990). A recent study has shown that a dietary intervention occurring later in life is able to prevent cardiovascular decline by affecting apo A-IV and apo C-III levels in rats (Araki et al 2004). Apo A-IV has been clearly demonstrated to play a potentially important role in reverse cholesterol transport, by stimulating the activity of cholesterol acyl transferase (LCAT), a regulatory enzyme of HDL (Duverger et al. 1994).

Furthermore, apo A-IV increases cholesterol efflux from adipose cells (Steinmetz et al. 1990) and participates in HDL particles conversion by cholesteryl ester transfer protein (CETP) (Barter et al. 1988). Apo A-IV can modulate CETP-mediated transfer of cholesteryl esters between HDL and low-density lipoproteins (LDL) fractions, exhibits labile reversible binding to HDL 3 (Weinberg et al. 1992; Gambert et al. 1988) and helps to maintain optimal surface pressure for CETP activity (Weinberg et al. 1992) (Table 21.3 and Fig. 21.2).

Apolipoprotein A-IV gene polymorphism is supposed to be involved in the response to change in the percentage of dietary fats. To our knowledge, only three studies have examined this problem. In a study by Waggemans et al. the polymorphism by itself seemed to produce no effects on response to dietary intervention (Weggemans et al. 2000).

In a second study by Ostos et al., Apo A-IV-2 allele was associated with hyperresponsivity to fat during the postprandial period. Other investigators approached the role of apo A-IV polymorphism

Table 21.3 Main factors with regulatory effects on apo A-IV

Regulation	Hypothalamus	Intestine	Unsolved issues
Lipid absorption	↑ synthesis ↑ secretion	↑ synthesis ↑ secretion	Stimulation by different type of Tg; Mechanism underlying apo A-IV expression in hypothalamus
Circadian rhythms	–	Secretion increased just before feeding and peaked midway through the dark period. Integrity of enterohepatic circulation is necessary for circadian rhythm.	More studies are needed to understand relation between this pattern, lymphatic Tg, cholesterol, and phospholipids output
Leptin	–	↓ apo A-IV transcript levels	Apparent auto-regulation of apo A-IV may be related to elevation in circulating leptin levels
Pancreatic polypeptide family	NPY: ICV infusion increases apo A-IV	PYY: simulates jejunal apo A-IV synthesis and secretion, probably acting via vagus nerve NPY: ICV infusion does not provide increase of jejunal apo A-IV.	NPY effects of jejunal synthesis of apo A-IV
Diet	Apo A-IV ↓ by food deprivation ↑ by lipid feeding	Apo A-IV synthesis and secretion become less responsive to lipid feeding following the chronic consumption of high-fat diet.	Mechanisms that induce this "chronic adaptation" to lipid ingestion are still unexplained.
Apolipoproetin A-IV antibodies	ICV infusion ↑ lipid feeding ↓ hypothalamic apo A-IV mRNA levels	–	Mechanism that induce reduction of apo A-IV mRNA after local infusion of antiserum are still unexplained

ICV intra-cerebroventricular, *PPY* peptide YY, *NPY* neuropeptide Y

in the interindividual variability in reduction of blood lipids, body weight, and cardiovascular risk. Heilborn et al. assessed the effects of an energy-restricted diet for 12 weeks on weight loss and plasma lipids according to apo A-IV genotype in 186 overweight/obese patients. Among participants, a significant increase in HDL was observed in apo A-IV-1/1 subjects, while apo A-IV-2 was associated to increase in HDL. In this study, apo A-IV genotype was not associated to changes in total cholesterol (TC), Tg, and LDL. The authors concluded that apo A-IV genotype might be related to the efficacy of body weight control in reduction of CV (Heilbronn et al. 2000).

Furthermore, the apolipoprotein gene cluster APOA1/C3/A4/A5 probably plays a role in the development of abnormalities in Tg and HDL in nondiabetic population. Recent data indicate that the variability in APOA1/C3/A4/A5 gene cluster may affect Tg and HDL levels in women with type 2 diabetes (Qi et al. 2007). Few studies are available that provide direct demonstration of a relation between Tg concentrations and apo A-IV in humans (Fig. 21.3).
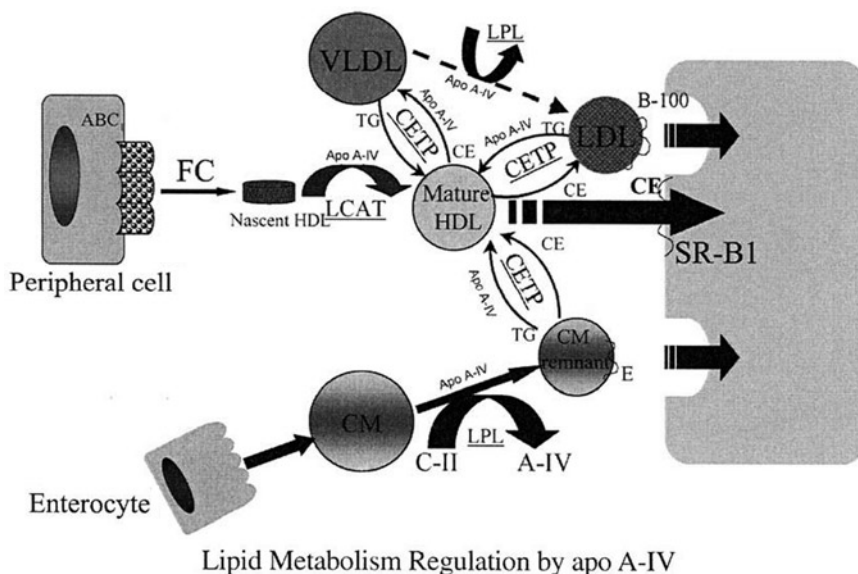
Fig. 21.2 Interactions between apo A-IV and other lipoproteins in lipid metabolism. *ABC1* ATP binding cassette transporter 1, *HDL* high density lipoproteins, *LCAT* cholesterol acyl transferase, *CETP* cholesteryl ester transfer protein, *CE* cholesteryl ester; The activation of LCAT by apo A-IV promotes esterification of cholesterol, which converts discoidal particles to spherical HDL. Apolipoprotein A-IV stimulates lipoprotein lipase activity. Apolipoprotein A-IV enhances the transfer of Tg and CE between lipoproteins by CETP (Reproduced from Stan et al. 2003)

Fig. 21.3 Plasma Tg and apo A-IV during OFLT in humans. Plasma apo A-IV increased after OFLT. After 8 h, apo A-IV levels were significantly higher than basal values ($p < 0.0001$), while Tg had returned nearly to basal values (Verges et al. 2001)
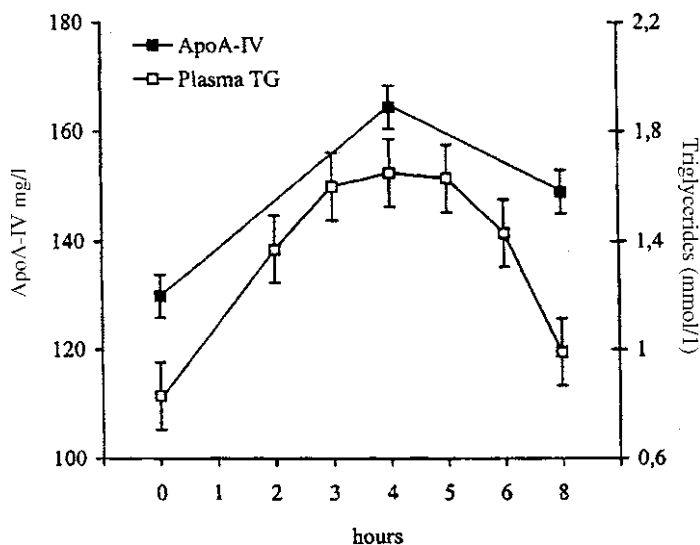
The influence of a high-glucose diet on apo A-IV has been examined in a study by Strobl et al. who determined the effects of a fish oil-rich and a sucrose-rich diet on apo A-IV gene transcription and nuclear and total cellular apo A-IV mRNA abundance in the liver of genetically obese, hyperlipoproteinemic *Zucker rats* and their lean littermates. The sucrose-rich diet increased apo A-IV gene expression twofold in both lean and obese rats. According to results obtained in this study, genetic obesity probably alters the response of hepatic apo A-IV gene expression to a lipid-lowering diet, rich in fish oil, by a mechanism affecting transcriptional regulation (Strobl et al. 1993).

Recent data indicate a modulation of apo A-IV levels by glycemic status. Higher apo A-IV levels have been found in insulin-dependent diabetic patients (independently of Tg or HDL levels) and were closely related to glycemic control (Attia et al. 1997). In addition, there is demonstration that mRNA levels of apo A-IV increase in the liver of rats treated with insulin (Evert et al. 2003).

Results obtained by Hanniman et al. suggest that hepatic and ileal apo A-IV gene expression are induced by fasting in a glucocorticoid-dependent manner. In this study, apo A-IV concentration increase was induced in two established mouse models of diabetes. Despite the requirement for glucocorticoids, analysis of the mouse and human apo A-IV promoters indicated a direct regulatory role of Hepatocyte Nuclear Factor 4 (HNF-4) and peroxisome proliferator-activated receptor gamma coactivator 1 (PGC-1). Although HNF-4 and PGC-1 are necessary for the induction of apo A-IV during fasting and diabetes, these data suggest a more complex and highly conserved in vivo mechanism for regulation of apo A-IV during times of nutritional and/or metabolic stress (Hanniman et al. 2006).

21.2.2.2 Pancreatobiliary Secretion

Studies in animals show that variation of the intestinal availability of bile acids may affect the regulation of apo A-IV synthesis (Sonoyama et al. 1994). Some authors assume that apo A-IV gene expression requires participation of pancreatic output in addition to biliary secretion (Felgines et al. 1994).

The mechanisms underlying the coordinate effects of bile and pancreatic exogenous secretion on apo A-IV regulation remain to be determined.

21.2.2.3 Hormones

Evidences of the existence of hormonal regulation of apo A-IV come from studies in animals. A particular relation between apo A-IV concentration and development has been observed. In rats, apo A-IV is higher in the neonatal period, while, during the adulthood, rat liver apo A-IV mRNA might be stimulated by thyroid hormones and hydrocortisone and suppressed by ethinyl estradiol and *n*-proptylthiouracil, which interfere with the endogenous synthesis of thyroid hormone. Interestingly, the same treatments have no effects on apo A-IV gene expression in the intestine, thus supporting the hypothesis of a different regulation of apo A-IV in the liver and the intestine. In cultured rat hepatocytes, insulin and glucagon inhibit the production of apo A-IV in a dose-dependent manner and dexamethasone stimulates its synthesis and secretion into the media (Huchida et al. 1991).

Another strong hormonal modulator of apo A-IV synthesis is peptide tyrosine, produced by the endocrine cells and released in the ileum and the colon after nutrients ingestion (Table 21.3) (Hill et al. 1991).

21.3 The Role of Apo A-IV in Regulation of Food Intake

Apoliporpotein A-IV was first described in the 1970s and since 1990s amounting data have been collected sustaining a role of this protein in satiety regulation and food intake behavior.

In 1993, Fujimoto et al. showed that intra-cerebrovascular administration of apo A-IV significantly inhibited food intake in a dose-dependent manner and stopped the action of endogenous apo A-IV locally (Fujimoto et al. 1993a).

In 2001, Liu et al. demonstrated that apo A-IV is synthesized also in hypothalamus, which is the organ that regulates satiety and food intake in rats, and postulated that apo A-IV gene expression might be modulated by food deprivation and lipid refeeding (Liu et al. 2001).

Recently, Shen et al. elegantly described, for the first time, a detailed distribution of apo A-IV-containing cells in rat brain areas, which are involved in the regulation of energy homeostasis (Table 21.4 and Figs. 21.4 and 21.5).

Interestingly, apo A-IV immunoreactive cells were found in the arcuate and ventromedial hypothalamic nuclei with less staining in cells of paraventricular and dorsomedial nuclei. Arcuate nucleus cells release a number of neuropeptides, such as NPY and pro-opiomelanocortin (POMC), and are a primary target for leptin, a food-intake regulatory hormone produced by adipose tissue. In a recent study, apo A-IV in the arcuate nucleus is mainly localized in neurons and apo A-IV was found in around 23% of neurons containing POMC. In the same study, injection of apo A-IV in 48-h fasted rats reversed reduction of POMC induced by fasting (Shen et al. 2008).

Apolipoprotein A-IV probably exerts an anorexic effect through interaction with arcuate nucleus. Intravenous administration of apo A-IV affects POMC mRNA expression only in fasted rats and not

Table 21.4 Characterization of apolipoprotein A-IV in brain areas involved in energy homeostasis (Shen et al. 2008)

Previous evidences	• Apo A-IV is synthesized in the hypothalamus
	• Apo A-IV plays an important role in the control of food intake
	• ICV administration of apo A-IV significantly inhibits food intake in a dose-dependent manner and blocks the action of endogenous apo A-IV locally
	• Hypothalamus expresses the Apo A-IV gene and expression is reduced by food deprivation and restored by lipid refeeding
Materials and methods	• Animals: adult male Sprague-Dawley rats divided into four groups (ad libitum fed and 46 h fasting).
	• Double staining of immunohistochemistry
	• Intravenously administration of 125I-labeled recombinant rat apo A-IV and subsequent determination of its uptake in the brain
Statistical analysis	• Two-way ANOVA followed by Turkey's test was used for analysis of gene mRNA levels
	• Multiple time regression analysis was used for calculation of unidirection influx constant from blood to brain
Purpose	• To describe distribution of apo A-IV in the brain areas involved in energy homeostasis;
	• To asses if apo A-IV in the brain comes from blood circulation.
Results	• Apo A-IV immunoreactivity:
	ARC[a]
	PVN[b]
	DMH[c]
	VMH[a]
	LHA[c]
	NTS[d]
	• Circulating apo A-IV does not cross the brain barrier.
Conclusions	• Apo A-IV is produced by neuronal cells and probably exerts its anorexic function by interacting with catabolic regulatory neuropeptides

ICV intra-cerebroventricular, *ARC* arcuate nucleus, *PVN* paraventricular nucleus, *DMH* dorsomedial nucleus, *LHA* lateral hypothalamic area, *nts* nucleus of solitary tract
[a]High density
[b]Moderate density
[c]No nuclear signal
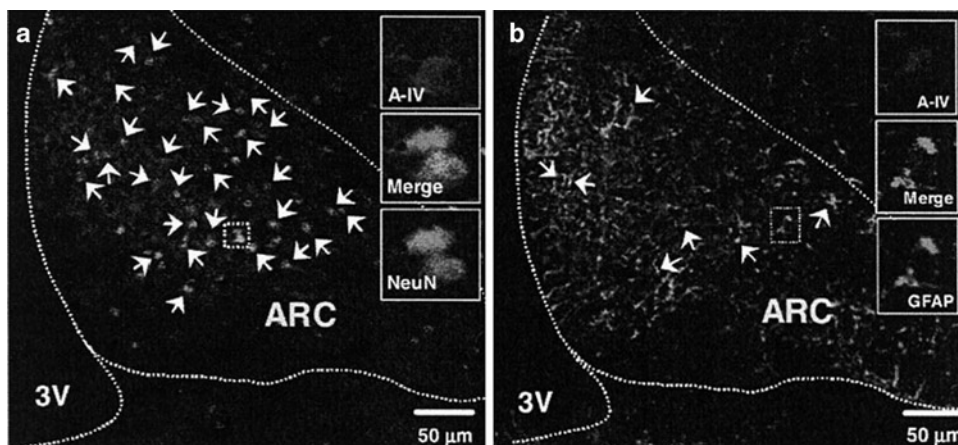
Fig. 21.4 Distribution of apo A-IV in ARC of rats. *ARC* arcuate nucleus, *3V* third ventricule (Reproduced from Shen et al. 2008)
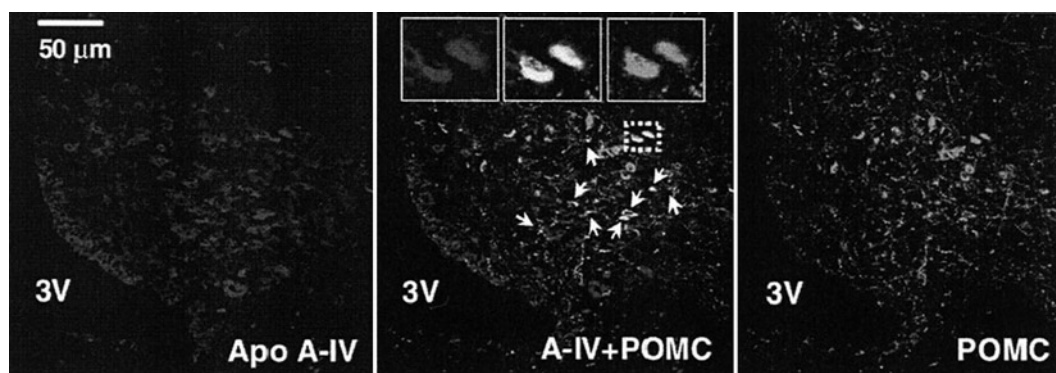
Fig. 21.5 Apolipoprotein A-IV is partially co-localized with POMC in the ARC. Co-localization of apo A-IV and POMC in ARC (Reproduced from Shen et al. 2008)

in ad libitum fed rats. Even if the anorexic effect of apo A-IV is still unclear, these results provide a morphological support to the hypothesis of a direct effect of apo A-IV on melanocortin signaling, which plays a key role in animals' ingestive behavior (Woods et al. 1998) regulation in hypothalamus (Shen et al. 2008) (Fig. 21.6).

Results of this study appear consistent with previous data sustaining a regulation of apo A-IV gene expression by NPY and lipids in rats and a synergistic interaction between apo A-IV and melanocortin system. All these observations strongly support a role of this apolipoprotein in arcuate nucleus and its associated neural circuits (Liu et al. 2003; Gotoh et al. 2006).

A still unsolved issue concerns the possible effect of circulating apo A-IV, produced in the intestine and in the liver, on nutritional behavior. No studies exist that directly demonstrated that apo A-IV is able to cross the blood-brain barrier, even if Fujimoto et al. have reported an increase in cerebrospinal fluid concentration of apo A-IV after lipid administration in rats (Fujimoto et al. 1993b). According to available evidences, apo A-IV in the brain appears locally synthesized (Liu et al. 2001). Again, in Shen et al.'s study, leptin, which had been demonstrated to stimulate apo A-IV synthesis and secretion from neurons in hypothalamus, appeared able to cross the blood-brain barrier (Shen et al. 2007) (Fig. 21.7).

Fig. 21.6 Apolipoprotein A-IV reverses the reduction of POMC mRNA induced by fasting in animals. After 48-h fasting POMC levels were significantly reduced, but this reduction was reversed by iv administration of apo A-IV (Reproduced from Shen et al. 2008). Saline: control solution; *POMC* pro-opi-omelanocortin, *iv* intravenous
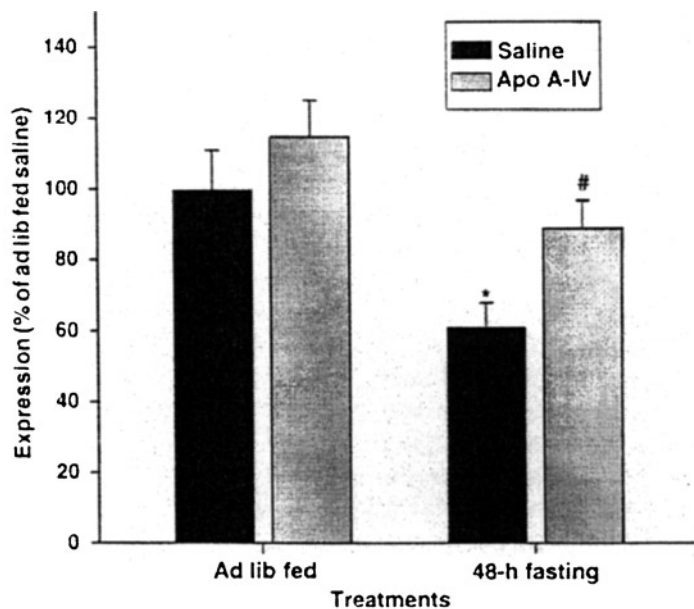
Fig. 21.7 Circulating apo A-IV does not cross the brain barrier. On *x* axis: time of exposure of animals. On *y* axis: the ratio of brain to serum over time for recombinant ^{125}I-labeled apo A-IV and ^{99}Tc-albumin. The slope of lines reflects the rate of entry which was not significantly different between apo A-IV and albumin. This was the first experimental demonstration that apo A-IV found in the brain does not come from circulating blood (Reproduced from Shen et al. 2008)
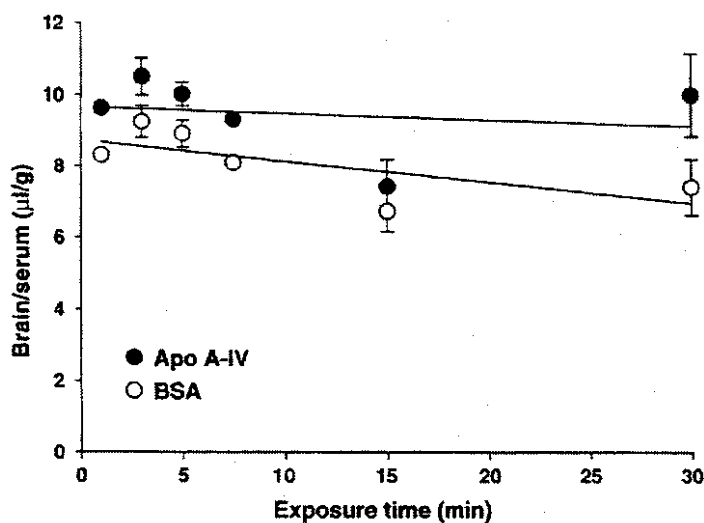
Among the different apolipoproteins assembled in gastrointestinal tract, only apo A-IV synthesis and secretion in highly stimulated, till two- to threefold, by fat absorption (Fukagawa et al. 1994). Synthesis and secretion of this apolipoprotein in intestine is regulated by circadian rhythm, bile secretion, and peptides produced in the distal tract of small intestine (Kalogeris et al. 1998).

Fujimoto et al. firstly suggested that apo A-IV might be a circulating signal released by the small intestine in response to fat feeding, and a mediator of the anorexic effect of a lipid meal (Fujimoto et al. 1992).

Further studies confirmed these findings and better described the physiological effects of acute administration of fat: according to results obtained by Rodriguez et al. in 1997, increase in plasma

Table 21.5 Increase of plasma apo A-IV levels is a marker of abnormal postprandial lipemia: a study in normoponderal and obese subjects (Verges et al. 2001)

Previous evidences	Apo A-IV is elevated in hypetriglyceridemic patients
Materials and methods	Subjects: 16 normotriglyceridemic, normally glucose tolerant android obese subjects and 30 normal weight controls
Statistical analysis	• The AUC was calculated by trapezoidal methods
	• Means were compared between two groups by Student's unpaired *t*-test and between several groups by ANOVA
	• nonparametric Mann-Whitney *U*-test when men and women were analyzed separately
	• χ^2 was used to compare frequency between controls and obese subjects
	• Multiple linear regression analyses were performed for significant independent predictors of postprandial lipemia parameters and independent predictors of fasting plasma apo A-IV levels
Purposes	To determine plasma apo A-IV and postprandial Tg levels after an OFLT
Results	• Obese patients showed increased apo A-IV levels both at fast ($p < 0.05$) and during OFLT ($p < 0.05$)
	• Fasting plasma apo A-IV significantly correlated with AUC of plasma Tg ($p < 0.001$), AUC of chylomicron Tg ($p < 0.01$) and AUC of non-chylomicron Tg ($p < 0.001$)
Conclusions	A strong link exists between fasting apo A-IV and postprandial Tg metabolism

OFLT oral fat load test, *Tg* triglycerides, *AUC* area under curve

levels of apo A-IV in response to a lipid meal was sufficiently quick and extended to produce satiety (Table 21.5) (Rodriguez et al. 1997).

The role of apo A-IV in long-term food intake control is supported by several evidences: first, intravenous administration of apo A-IV decreases food intake in rats (Fujimoto et al. 1993b); second, a link exists between food assumption and circadian rhythms of serum and lymph apo A-IV levels (Fukagawa et al. 1994), that appear independent of dietary restriction; third, intestinal production of apo A-IV is regulated by leptin and insulin (Woods et al. 1998), two hormones that play a key role in energy homeostasis.

Chronic consumption of a high-fat diet induces stimulation of apo A-IV synthesis and increases expression of apo A-IV mRNA levels in the jejunum. Probably, apo A-IV affects gastrointestinal motility and gastric acid secretion (Glatzle et al. 2004).

In humans, chronic consumption of a high-fat diet increases apo A-IV levels, but only at the beginning (i.e., during the first week) of dietary modification. These results also appear consistent with the hypothesis that apo A-IV might be subjected to a rapidly acting auto-regulatory mechanism (Weinberg et al. 1990).

Recent findings in rodents show that chronic consumption of a high-fat diet significantly reduces apo A-IV mRNA levels and the response of apo A-IV gene expression to dietary lipids in the hypothalamus (Liu et al. 2004).

21.4 Apolipoprotein A-IV and Obesity

Plasma apo A-IV levels are increased in human obesity and apo A-IV polymorphism appears associated to the extent of obesity. Lingenhel et al. have determined the effects of weight loss on plasma apo A-IV in obese adolescents and examined the relation of apo A-IV with the degree of obesity in

a longitudinal intervention study of a low-fat hypocaloric diet conducted in a dietary camp. Apolipoprotein A-IV levels before and after weight reduction and changes in plasma apo A-IV were not independently related to relative BMI, weight loss, or plasma leptin levels. Plasma apo A-IV concentration markedly decreased in overweight adolescents undergoing short-term weight reduction. The decrease was not directly related to the degree of weight loss and the mechanisms of this reduction remain to be clarified (Lingenhel et al. 2004).

In experimental studies, leptin-deficient obese (ob/ob) had reduced hypothalamic apo A-IV mRNA levels while intra-gastric infusion of a lipid emulsion significantly stimulated hypothalamic apo A-IV gene expression in lean controls, but not in obese mice with leptin deficiency. Centrally administered leptin raised the reduced apo A-IV gene expression induced by fasting. These results suggest that leptin and apo A-IV might have synergistic effects in reducing food intake. More studies are needed to investigate the mechanisms underlying obesity and/or augmented calories consumption, the differential influence of central and peripheral apo A-IV expression in animals and the relation between leptin and the responsivity of brain cells to apo A-IV (Shen et al. 2007).

With most of the required reagents available, e.g., the apo A-IV knockout and transgenic animals and apo A-IV antibodies, the next few years should bring considerable new information on the function of apo A-IV. Apolipoprotein A-IV and cholecystokinin (CCK) are peptides that act both peripherally and centrally to reduce food intake. Lo et al. examined the effects of intraperitoneal administered bolus doses of recombinant apo A-IV, CCK-8, and a combination of subthreshold doses of apo AIV and CCK on 4-h food intake in rats that were fasted overnight. Subthreshold single doses of apo A-IV (50 μg/kg) or CCK (0.06 μg/kg) alone had no effect on food intake. However, when the same doses of apo A-IV and CCK were administered together, the combination produced a significant inhibition of food intake and duration of the effect was longer than that caused by the administration of either apo A-IV or CCK alone. The satiation effect produced by CCK-8 + apo A-IV resulted attenuated by lorglumide, a CCK-1 receptor antagonist. Authors concluded that, whereas the intraperitoneal administration of doses of either recombinant apo A-IV or CCK, at or above threshold levels, reduces food intake, the coadministration of subthreshold doses of the two peptides induces significant effect on satiety probably acting via CCK-1 receptor (Lo et al. 2007).

Systemic or central administration of apo A-IV reduces food intake and body weight of rats and administration of apo A-IV antibodies has the opposite effect. Because both intestinal and hypothalamic apo A-IV are regulated by absorption of lipid but not by carbohydrate, this peptide may be an important link between short- and long-term regulators of body fat (Fujimoto et al. 1993b.)

21.5 Apolipoprotein A-IV: Applications to Other Areas of Health

21.5.1 Apolipoprotein A-IV as a Target for Pharmacological Therapy in Obesity

Actually, few studies have examined a possible role of apo A-IV as a marker of efficacy of pharmacological treatment of obesity. In a recent study by Guo et al., 17 Chinese medicinal herbs, traditionally used to treat obesity, have been tested for their potential effect on apo A-IV expression and Tg formation on intestinal cell line Caco-2/TC7 (Guo et al. 2009).

Among apolipoproteins, apo A-IV resulted as the most affected by gastric by-pass as demonstrated in a recent study by Culnan et al. This interesting observation is consistent with the effects of

Table 21.6 Apolipoprotein A-IV and pharmacological therapies that affect metabolism

Drugs	Authors	Results
Fibrates	Liu et al. (2009)	Apolipoprotein A-IV has been proposed as a possible marker of individual response to fibrates
Herbal medications	Guo et al. (2009)	17 traditional Chinese medical herbs were tested for their potentiality to increase apo A-IV and Tg
Thiazolidinediones	–	No data available
Metformin	–	No data available
Sibutramine	–	No data available
Orlistat	–	No data available
Rimonabant	–	No data available

apo A-IV on satiety and with the fact that patients undergoing bariatric surgery commonly experience an augmented sensation of satiety. Since apo A-IV is mainly expressed in the duodenum and in the first tract of the small intestine, which are by-passed by this surgical procedure, other factors were examined by authors. In this field, many open issues are still unsolved, and more studies are needed to define the role of changes in apo A-IV after surgery (Culnan et al. 2008).

To our knowledge, no studies are available that directly examined changes in apo A-IV levels after administration of commonly used antiobesity drugs such as orlistat and sibutramine.

There are recent findings sustaining a direct relation between apo A-IV and postprandial hypertriglyceridemia, that is an established cardiovascular risk factor in humans (Verges et al. 2001). Apolipoprotein A-IV expression is one of the mechanisms underlying decrease of Tg and elevation of HDL observed with PPAR-α agonist treatment (Nagasawa et al. 2009). Some authors suggest that genetic variants of APOA1/C3/A4/A5 gene cluster may be useful markers to predict response to a lipid-lowering therapy with fenofibrate. Further studies to replicate and to confirm these results are warranted (Liu et al. 2009) (Table 21.6).

Key Points

- Apolipoprotein A-IV is produced in the small intestine and the liver in rodents and only in the small intestine in humans. Recently apo A-IV has been detected also in the hypothalamus of experimental animals, and its concentration in brain cells is influenced by food deprivation.
- Apolipoprotein A-IV is involved in lipid metabolism.
- Apolipoprotein A-IV plays a role in lipoproteins metabolism even if this issue has been better studied in experimental animals.
- Apolipoprotein A-IV secretion and concentration are regulated by hormones, circadian rhythms, food, and particularly by lipids intake.
- Amounting evidences are available sustaining a key role of apo A-IV in regulation of food intake and satiety.
- An anti-atherogenic role of apo A-IV has been suggested according to the results of recent experimental studies.

References

Araki S, Goto S. Biogerontology. 2004;5:445–50.

Attia NA, Touzani M, Lahrichi A, Balafrej O, Kabbaj, Girard-Globa A. Diabet Med. 1997;14:242–7.

Barter PJ, Rajaram OV, Chang LB, Rye KA, Gambert P, Lagrost L, et al. Isolation of a high-density-lipoprotein conversion factor from human plasma. A possible role of apolipoprotein A-IV as its activator. Biochem J. 1988;254:179–84.

Bisgaier CL, Sachdev OP, Lee ES, Williams KL, Blum CB, Glickman RM. J Lipid Res. 1987;28(6):693-03.

Bisgaier CL, Glickman RM. Annu Rev Physiol. 1983;45:625–36.

Chen CH and Albers JJ. Biochimica et Biophysica Acta (BBA) - Lipids and Lipid Metabolism. 1985; 836(3): 279–85.

Culnan DM, Cooney RN, Stanley B, Lynch CJ. Obesity. 2008;17:46–52.

Duverger N, Ghalim N, Theret N, Fruchart JC, Castro G. Biochim Biophys Acta. 1994;1211:23–8.

Dvorin E, Gorder Nl, Benson DM, Gotto AM (1988). J. Biol. Chem. 261: 15714-18.

Dvorin E, Gorder NL, Benson DM, Gotto AM. J Biol Chem. 1988;261:15714–8.

Ehnholm C, Tenkanen P, de Knijff L, Havekes L, Rosseneu M, Menzel HJ, et al. Atherosclerosis. 1994;107:229–38.

Evert M, Schneider-Stock R, Dombrowski F. Pathol Res Pract. 2003;199:373–9.

Felgines C, Mazur A, Rayssiguier Y. Life Sci. 1994;55:1053–60.

Fukagawa K, Gou HM, Wolf R, Tso P. Am J Physiol Regul Integr Comp Physiol. 1994;267:R1385–90.

Fujimoto K, Cardelli JA, Tso P. Am J Physiol. 1992;262(6 Pt 1):G1002–6.

Fujimoto K, Fukagawa K, Sakata T, Tso P. J Clin Invest. 1993a;91:1830–3.

Fujimoto K, Machidori H, Iwakiri R, Yamamoto K, Fujisaki J, Sakata T, et al. Brain Res. 1993b;608:233–7.

Gambert P, Lagrost L, Athias A, Bastiras S, Lallemant C. Adv Exp Med Biol. 1988;243:263–9.

Ghiselli G, Krishnan S, Beigel Y, Gotto Jr AM. J Lipid Res. 1986;27:813–27.

Glatzle J, Darcel N, Rechs AJ, Kalogeris TJ, Tso P, Raybould HE. Am J Physiol Regul Integr Comp Physiol. 2004;287:R354–9.

Goldberg IJ, Scheraldi CA, Yacoub LK, Saxena U, Bisgaier CL. J Biol Chem. 1990;265:4266–72.

Gotoh K, Liu M, Benoit SC, Clegg DJ, Davidson WS, D'Alessio D, et al. Am J Physiol Regul Integr Comp Physiol. 2006;290:R202–7.

Guo AJ, Choi RC, Cheung AW, Li J, Chen IX, Dong TT, et al. Chin Med. 2009;4:5.

Guyard-Dangremont V, Lagrost L, Gambert P. J Lipid Res. 1994; 35: 982–92.

Hanniman EA, Lambert G, Inoue Y, Frank J, Gonzalez FJ, Sinall CJ. J Lipid Res. 2006;47:2503–11.

Heilbronn LK, Noakes M, Morris AM, Kind KL, Clifton PM. Atherosclerosis. 2000;150:187–92.

Hill FL, Zhang T, Gomez G, Greeley Jr GH. Peptide YY, a new gut hormone (mini-review). Steroids. 1991;56:77–82.

Hockey KJ, Anderson RA, Cook VR, Hantgan RR, Weinberg RB. J Lipid Res. 2001;42:211–7.

Huchida E, Masumoto A, Sakamoto S, Koga S, Nawata H. Atherosclerosis. 1991;87:195–202.

Kalogeris TJ, Qin X, Chey WY, Tso P. Am J Physiol. 1998;275(4 Pt 1):G668–74.

Kalogeris TJ, Painter RG. Am J Physiol Regul Integr Comp Physiol. 2001;280:R1155–61.

Koga S, Miyata Y, Funakoshi A, Ibayashi H. Digestion. 1985;32:19–24.

Kronenberg F, Stühlinger M, Trenkwalder E, Geethanjali FS, Pachinger O, Von Eckardstein A, et al. J Am Coll Cardiol. 2000;36:751–7.

Lagrost, L, Gambert P, Boquillon M, and Lallemant C (1989) J. Lipid. Res. 30: 1525-34.

Lagrost L, Gambert P, Boquillon M, Lallemant C. J Lipid Res. 1989;30:1525–34.

Li YJ, Wei YS, Fu XH, Hao DL, Xue Z, Gong H, et al. J Biol Chem. 2008;17(283):28436–44.

Lingenhel A, Eder C, Zwiauer K, Stangl H, Kronenberg F, Patsch W, et al. Int J Obes Relat Metab Disord. 2004;28(11):1509–13.

Liu M, Doi T, Shen L, Woods SC, Seeley RJ, Zheng S, et al. Am J Physiol Regul Integr Comp Physiol. 2001;280:1382–7.

Liu Y, Ordovas JM, Gao G, Province M, Straka RJ, Tsai MY, et al. Pharmacogenet Genomics. 2009;19(2):161–9.

Liu M, Shen L, Doi T, Woods SC, Seeley RJ, Tso P. Brain Res. 2003;971:232–8.

Liu M, Shen L, Liu Y, Woods SC, Seeley RJ, D'Alessio D, et al. Am J Physiol Endocrinol Metab. 2004;287(2):E366–70.

Lo CM, Zhang DM, Pearson K, Ma L, Sun W, Sakai RR, et al. Am J Physiol Regul Integr Comp Physiol. 2007;293:R1490–4.

Nagasawa M, Hara T, Kashino A, Akasaka Y, Ide T, Murakami K. Biochem Pharmacol. 2009;78:523–30.

Qi L, Liu S, Rifai N, Hunter D, Hu FB. Atherosclerosis. 2007;192:204–10.

Rodriguez MD, Kalogeris TJ, Wang XL, Wolf R, Tso P. Am J Physiol. 1997;272(4 Pt 2):R1170–7.

Saito H, Lund-Katz S, Phillips MC. Prog Lipid Res. 2004;43(4):350–80.

Sato K, Takahashi Y, Takahashi T, Katoh N, Akiba Y. J Nutri Biochem. 2002; 13(9):528.

Sepehrnia B, Kamboh MI, Adams-Campbell LL, Nwankwo M, Ferrell RE RE. Am J Hum Genet. 1988;43:847–53.

Shen L, Tso P, Woods SC, Sakai RR, Davidson WS, Liu M. Endocrinology. 2007;148:2681–9.

Shen L, Pearson KJ, Xiong Y, Lo CM, Tso P, Woods SC, et al. Physiol Behav. 2008;95:161–7.

Sherman JR, Weinberg RB. Gastroenerology. 1988;95:394–401.

Sonoyama K, Nishikawa H, Kiriyama S, Niki R. J Nutr. 1994;124:621–7.

Stan S, Delvin E, Lambert M, Seidman E, Levy E. Biochimica et Biophysica Acta (BBA) - Molecular and Cell Biology of Lipids, 2003;1631(2):177-87.

Steinmetz AR, Barbaras N, Ghalim V, Clavey JC, Fruchart, Ailhaud G. J Biol Chem. 1990;265:7859–63.

Strobl W, Knerer B, Gratzl R, Arbeiter K, Lin-Lee YC, Patsch W. J Clin Invest. 1993;92:1766–73.

Vergnes L, Baroukh N, Ostos MA, Castro G, Duverger N, Nanjee MN, et al. Arterioscler Thromb Vasc Biol. 2000;20:2267–74.

Verges B, Guerci B, Durlach V, Galland-Jos C, Paul JL, Lagrost L, and P. Gambert. J. Lipid Res. 2001;42:2021–29.

Weggemans RM, Zock PL, Meyboom S, Funke H, Katan MB. J Lipid Res. 2000;41:1623–8.

Weinberg RB, Scanu AM. J Lipid Res. 1983;24:52–9.

Weinberg RB, Ibdah JA, Phillips MC. J Biol Chem. 1992;267:8977–83.

Woods SC, Seeley RJ, Porte Jr D, Schwartz MW. Science. 1998;280:1378–83.

Chapter 22
Brain Histamine Affects Eating and Drinking Behaviours

Leonardo Munari and Maria Beatrice Passani

Abbreviations

2-AG	2-Arachidonoylglicerol
ADH	Antidiuretic hormone
BAT	Brown adipose tissue
cGMP	Cyclic guanosine monophosphate
CNS	Central nervous system
FEO	Food-entrainable oscillator
GABA	Gamma-aminobutyric acid
GLP-1	Glucagon-like peptide 1
LH	Lateral hypothalamus
NAcc	Nucleus accumbens
PVN	Paraventricular nucleus
TMN	Tuberomammillary nucleus
TRH	Thyrotropin releasing hormon
Ucp-1	Uncoupling protein 1
VLPO	Ventrolateral preoptic area
VMH	Ventromedial hypothalamus

22.1 Introduction

In the early 1980s two major discoveries convinced the scientific community of the existence of a central histaminergic system and contributed to the understanding of its many functions. Immunohistochemical studies demonstrated the localization of histaminergic neurones in the tubero-mammillary nuclei of the posterior hypothalamus with projections to almost all parts of the brain (Panula et al. 1984; Watanabe et al. 1984), and pharmacological studies proved the existence of a novel histaminergic autoreceptor, the H_3 receptor (Arrang et al. 1983). A plethora of neuro-pharmacological and behavioural studies ensued and it soon became clear that brain histamine affects a variety of homeostatic regulatory functions such as circadian rhythms, neuroendocrine secretion,

M.B. Passani (✉)

Dipartimento di Farmacologia Preclinica e Clinica, Universita' di Firenze, Viale Pieraccini 6, Florence, Italy
e-mail: beatrice.passani@unifi.it

food intake, body weight and drinking. Furthermore, it was soon proven that histamine-containing neurones constitute a major wake-promoting system because their terminals influence neuronal excitability in distinct brain regions. Wakefulness is a prerequisite for learning and memorising salient events, but there is ample evidence that the histaminergic system affects cognitive functions per se. These observations are relevant for feeding behaviour, both for food searching and food consumption, as the ability to remember the context associated with food availability or the palatability of the food eaten provides a clear adaptive advantage to animal foraging. Hence, brain histamine does not only provide a satiety signal released during eating that might integrate postprandial messages conveyed from peripheral tissues (e.g. leptin), but it is important in setting up circadian homeostatic functions that create the expectations for a meal and coordinate food searching strategies. In other words, evidence indicates that histaminergic neurones control both the appetitive, or food searching, behaviour and the consummatory phases of feeding. However, very few experiments have dealt with this issue. The association of histamine with feeding behaviour became clear when it was observed that antidepressants and antipsychotics stimulate appetite and induce weight gain and that these drugs are potent H_1 receptor blockers. Indeed, early studies showed that intracerebral injections of histamine depressed the feeding behaviour of rats (Clineschmidt and Lotti 1973), while microinjections of the histaminergic H_1 receptor antagonists in the ventromedial hypothalamus (VMH) elicit feeding. Recent observations, though, indicate that histamine release during feeding is better interpreted in the context of appetitive rather than the consummatory phase of feeding behaviour (Meynard et al. 2005).

We now know that brain histamine is involved in feeding physiology by modulating the release of neurotransmitters and hormones that drive or inhibit feeding (Toftegaard et al. 2003). In addition, to exert their orexigenic or anorexigenic effects, hormones and peptides require an intact histaminergic system. Hence, in addition to having an effect on food intake, brain histamine regulates body weight by modulating peripheral energy metabolism in rodents. Also, compulsive eating in *anorexia nervosa*, bulimia, or binge-eating syndrome likely relates to histamine effects on brain reward systems and learning circuits and their dysfunction in addiction.

22.2 Histamine as a Central Neurotransmitter

Like the other biogenic amine neurotransmitter systems (noradrenaline, dopamine and serotonin), the somata of histamine-containing neurones are localised in a discrete brain region in the posterior hypothalamus, the tuberomammillary nuclei (TMN; Fig. 22.1). Histaminergic neurones project throughout the brain, including the VMH and the infralimbic cortex, two brain regions involved in different aspects of feeding behaviour. Histaminergic neurones appear a rather homogenous cell group and for a long time they have been thought of as a regulatory network for whole brain activity through diffuse and overlapping projections (Kohler et al. 1985) (Inagaki et al. 1990). Recent evidence, though, shows that histaminergic neurones are not homogenous, as only subgroups respond to different types of stress (Miklos and Kovacs 2003) or *hypercapnic* loading (Haxhiu et al. 2001). Neuroanatomical studies have shown differences in size and shape, in the complement of intracellular components such as histamine vescicular monoamine transporter, neurotransmitters like gamma-aminobutyric acid (GABA) or galanin (Kukko-Lukjanov and Panula 2003), and in their sensitivity to GABA (Sergeeva et al. 2002). Anatomical experiments did not demonstrate a topographical mapping of histaminergic projections as it is the case, for instance, for the dopaminergic system, but recent findings demonstrated that the histaminergic system is organized into distinct functional circuits that may contribute to the diverse roles played by brain histamine in feeding homeostasis, arousal and procognitive effects (Giannoni et al. 2009).
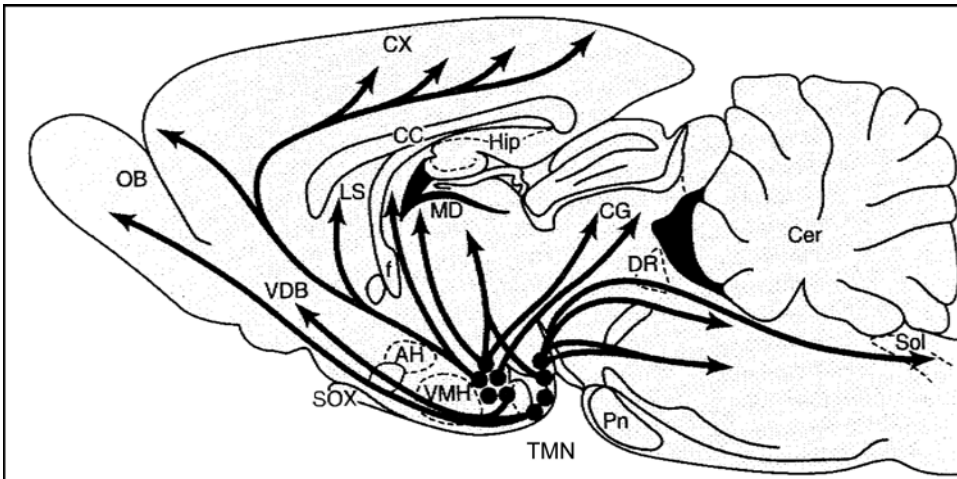
Fig. 22.1 Sagittal, schematic representation of the rat histaminergic systems. The somata of histaminergic neurons are located in the posterior hypothalamus, in the tuberomammillary nucleus (*TMN*). Histaminergic fibers project to the whole brain. *CX* cerebral cortex, *OB* olfactory bulb, *LS* lateral sulcus, *VDB* ventral diagonal band, *MD* mediodorsal nucleus, *AH* amygdalo-hippocampal area, *SOX* supraoptic chiasm, *VMH* ventral medial hypothalamus, *CG* cingulate gyrus, *DR* dorsal raphe, *Cer* cerebellum, *Pn* peduncular nucleus, *CC* corpus callosum, *Hip* hippocampus

Hypothalamic histamine neurones receive inputs from the cortex, the septum and other hypothalamic areas. The infralimbic, frontal cortex provides the principle cortical input to the TMN (Wouterlood et al. 1987) and lesion studies demonstrated that the activation of this pathway is important to determine the behavioural arousal that accompanies the appetitive behaviour in rats (Valdés et al. 2006).

22.3 Histamine and Wakefulness

The histaminergic neurones in the TMN are *pacemakers*, they fire at a slow regular rate that can vary depending on the behavioural state (Haas and Panula 2003). Direct recordings of these neurones in freely moving cats indicate that their activity is high during waking and attention, and low or absent during sleep (Lin et al. 1994). The inhibition during sleep is thought to be mediated mainly by GABA innervation from the ventrolateral preoptic area (VLPO) a brain region that shows high activity during slow-wave sleep. Indeed, the histaminergic system is part of a neuronal organization that regulates biological rhythms, integrating the inputs and the activity of wake-promoting systems (reviewed in Haas et al. 2008). Together with the cholinergic, serotonergic, adrenergic and orexinergic cells, histaminergic neurones form a wake-promoting system named the ascending arousal system, where each cell group contributes in a unique way to the onset or maintenance of wakefulness. Histamine regulates the sleep-wake cycle through projections to the suprachiasmatic nucleus, the centre of the biological clock and contributes to cortical activation and wakefulness by activating cholinergic corticopetal neurones originating in the basal forebrain (Lin et al. 1994). TMN neurones also excite cholinergic cells in the mesopontine tegmentum that project to the thalamus and hypothalamus, which in turn affect cortical excitability (Lin et al. 1996). More precisely, the activity of histaminergic neurones plays an important role, not so much in the induction of wakefulness *per se*, but in the maintenance of the high level of vigilance necessary for cognitive processes. Conversely, cessation of their activity seems to be important in both the initiation and maintenance of sleep (Takahashi et al. 2006) (Table 22.3).

The importance of histaminergic neurones in maintaining the brain in a wake state when challenged by environmental demands was demonstrated in mice lacking either histidine decarboxylase (the histamine synthesizing enzyme) (Parmentier et al. 2002) or the histamine H_1 receptor (Parmentier et al. 2006). Indeed, the abolition of histamine synthesis or one of its effector mechanisms impairs the cortical electroencephalogram and deteriorates both sleep and waking quality, thus causing somnolence and behavioural deficits. Histamine is also involved in regulating the maintenance of the circadian rhythm. Histamine deficiency leads to a lowered activity level, disrupts circadian rhythm of the clock genes *mPer1* and *mPer2* expression in the neocortex and striatum, but not in the circadian pacemaker suprachiasmatic nucleus, suggesting that histamine modulates the output behaviour of the circadian pacemaker (Abe et al. 2004). Furthermore, the activity of histaminergic cells is important for maintaining a high level of arousal during demanding tasks such as food searching (Meynard et al. 2005). Thus, the histaminergic system is a good candidate to link the sleep-wake cycle and feeding habits. Indeed, reversible depletion of brain histamine enhances food-associated locomotor activity only in the circadian phase during which histamine is high (reviewed in Haas et al. 2008). These observations are relevant to understanding feeding disorders in humans, as several studies demonstrated that disruption of the circadian rhythm of feeding behaviour often accompanies obesity in animal models and in patients.

22.4 Histamine and Cognition

It is known that manipulation of the histaminergic central system during several learning paradigms modifies animal behaviour; however, the results are often contradictory, as both facilitatory and inhibitory effects of histamine on memory have been described (Passani et al. 2004). This is not too surprising, as memory is a complex process that consists of related, but dissociable events, involving distinct brain regions activated to different degrees and at different times to elaborate disparate learning situations. The specificity of action of histamine depends on the localization of histaminergic receptor subtypes, the brain region and the nature of the cognitive task involved, and the activation of specific intracellular pathways. Hence, activation of selected histaminergic circuits may be important to consolidate temporal and spatial information associated with food availability and consumption and to coordinate appetitive and consummatory behaviours.

22.5 Histamine in Feeding and Energy Metabolism

The participation of the histaminergic system in regulating food intake has been known for many years (Fig. 22.2). Early studies showed that treatments increasing histamine availability in the central nervous system (CNS) of rats and mice suppressed food intake, in contrast administration of compounds that decreased central histamine increased food consumption. Brain histamine not only affects food intake, but studies in rodents showed that it apparently regulates body weight and adiposity by modulating peripheral energy. One of the markers of energy expenditure is *Uncoupling protein 1* (Ucp1) in brown adipose tissue (BAT), the expression of which is regulated by humoral and neuronal factors. The central administration of histamine or H_1 receptor agonist increases the expression levels of BAT Ucp1 mRNA in rodents, the central administration of histamine or the H_3
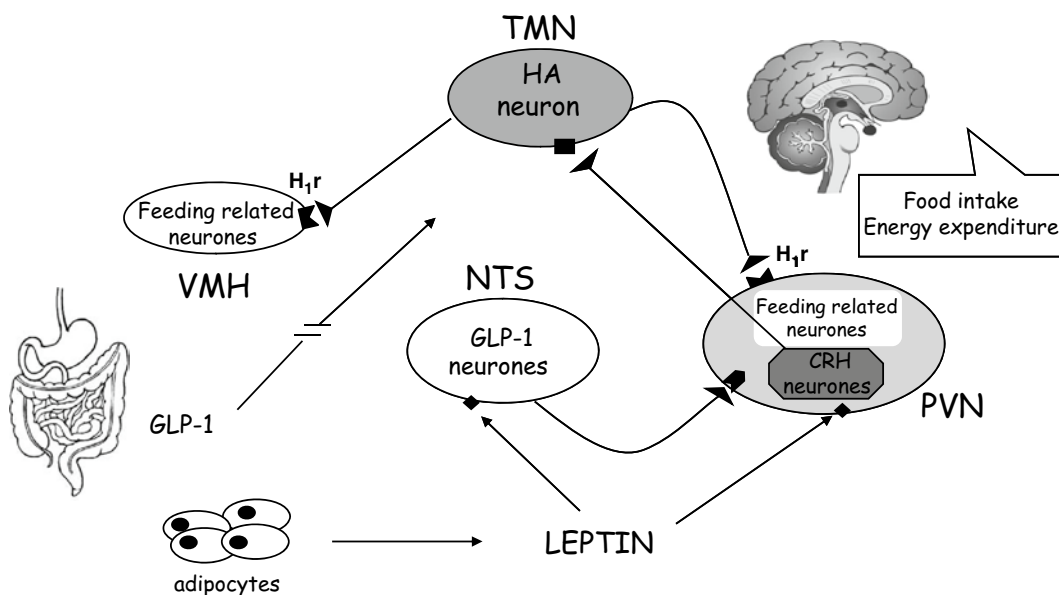
Fig. 22.2 Schematic drawing of the hypothesized action of hypothalamic histamine neurons in feeding behaviour. Glucagon-like protein-1 (*GLP-1*) regulates histamine neurons in the TMN via GLP-1 receptors expressed on CRH neurons and histamine suppresses food intake via H1-receptors expressed on feeding-related neurones in the PVN and the VMH. Leptin stimulates histamine neurons via leptin receptors (Ob-Rs) expressed on GLP-1 and CRH neurons. *HA* histamine, *H1r* histamine H1 receptor, *NTS* nucleus of the solitary tract, *PVN* paraventricular nucleus, *TMN* tuberomammilary nucleus, *VMH* ventromedial hypothalamic nucleus

receptor antagonist thioperamide increases the lipolytic response in rodents white adipose tissue and pretreatment with a β-receptor antagonist, blocks the thioperamide-induced response suggesting that the effect is mediated by sympathetic nerves that innervate white adipose tissue (reviewed in Masaki and Yoshimatsu 2006). Brain histamine also inhibits the development of obesity in both diet-induced and *db*/*db* obese mice (Masaki and Yoshimatsu 2006). These mice are hyperleptinemic, develop obesity and severe type 2 diabetes partly due to a functional defect in a leptin receptor. Hence, all these findings support the notion that the histaminergic system regulates adiposity by affecting both food intake and energy expenditure in rodents. Another site implicated in food intake is the mesencephalic trigeminal nucleus, as mastication activates histaminergic neurones (Sakata et al. 2003) that in turn suppress food intake through H_1 receptor activation in the paraventricular nucleus (PVN) and VMH.

22.6 Histaminergic Receptors

As a neurotransmitter, histamine interacts with four known receptor subtypes each of which has been sequentially cloned (Fig. 22.3). Histamine receptors H_1, H_2, H_3, are densely expressed in the brain. The expression of the fourth histaminergic receptor (H_4, which was initially described only in peripheral tissues such as the bone marrow and leukocytes) is restricted to some regions in the rat brain, such as the cerebellum (Strakhova et al. 2009). The histaminergic receptors differ in their signal transduction pathways, CNS distribution, and function and pharmacological properties of their
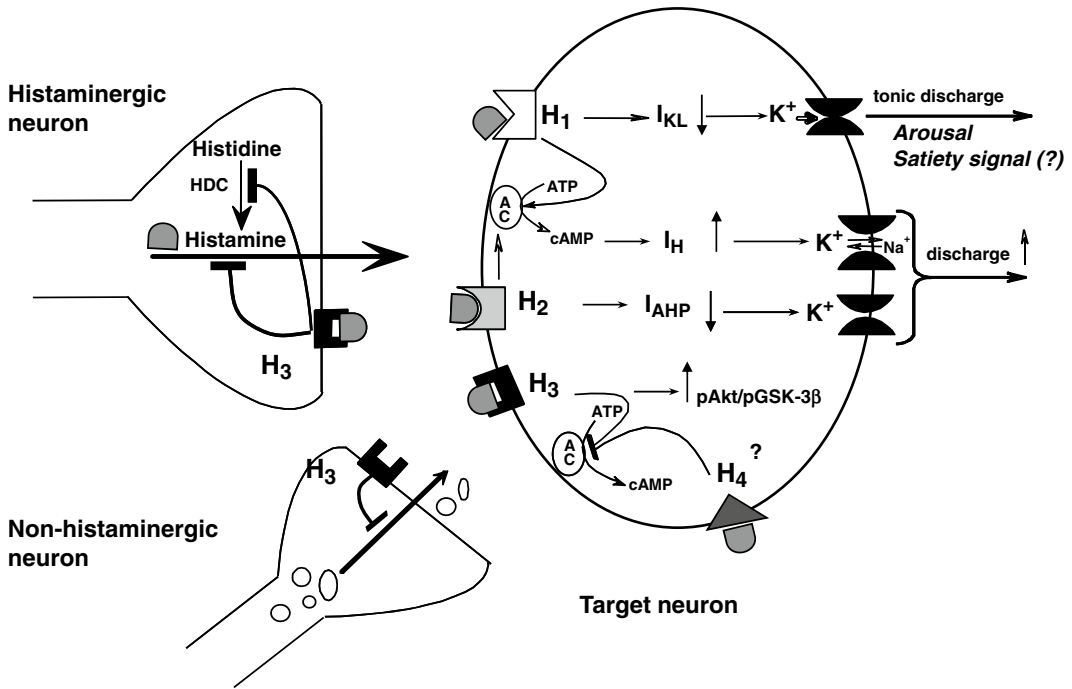
Fig. 22.3 Histamine-mediated transmission and cellular mechanisms involved in arousal and feeding behaviour. Activation of histamine H1 or H2 receptors increases cell activity and excitability by decreasing the background K+ leakage current (IKL) or the after hyperpolarization current (IAHP) or by increasing the hyperpolarization-activated cation current (IH). H3 auto- and heteroreceptors are involved in arousal and feeding behaviour regulation by modulating the release or synthesis of histamine and other neurotransmitters. Histamine also interacts with the H4 receptor that was recently found to be expressed in the brain. *AC* adenylyl cyclase, *HDC* histidine decaborxylase (Modified from Passani et al. 2004)

agonists and antagonists. Histamine excites neurones in most brain regions through H_1 receptors and selective H_1 agonists stimulate vigilance and alertness, in contrast to the all-too-well-known sedative effects of centrally acting H_1 receptor antagonists.

The H_1 and H_3 receptors are important for regulating feeding, whereas the H_2 receptor does not have any effect. The H_1 receptor transduction signal is typical of and convergent with that of other $G\alpha q/11$ protein-coupled receptors including activation of phospholipase C. Other effector pathways of the H_1 receptor include production of arachidonic acid, nitric oxide, and cyclic guanosine monophosphate (cGMP) via pertussis toxin–sensitive Gi/Go protein-mediated activation of phospholipase A2, $[Ca^{2+}]_i$-dependent nitric oxide synthase, and nitric oxide–dependent guanylate cyclase, respectively. The H_1 receptor activates AMP-kinase, a checkpoint in the control of energy metabolism and food intake (reviewed in Haas et al. 2008). When postsynaptic H_1 receptors are activated within the VMH, food intake is inhibited, whereas H_1 receptor antagonists block this effect. Indeed, orexigenic atypical antipsychotic drugs stimulate hypothalamic AMP-kinase pathways potently, reverse the action of the anorexigenic hormone leptin and these effects require the activation of H_1 receptors (Kim et al. 2007). Hence the weight gain induced by atypical neuroleptics requires the integrity of the brain histaminergic system. Unfortunately, no CNS penetrating nor CNS selective H_1 receptors agonists are currently available, that would have anti-obesity effects. Infact, from a therapeutic perspective, the challenge exists of identifying potent H_1 receptor agonists to be delivered selectively to the CNS without activating peripheral H_1 sites that could lead to severe cardiovascular, respiratory, or gastrointestinal side effects.

H_3 receptors are located on histaminergic and other cell somata, dendrites and axons, where they provide negative feedback to restrict histamine synthesis and release, and the release of other transmitters, such as serotonin, acetylcholine and noradrenaline, some of which have important roles in appetite or mood (e.g. serotonin). Blockade of H_3 autoreceptors enhances CNS histamine release from histaminergic neurones and several preclinical studies indicate that H_3 receptor antagonists causes changes in food consumption and body weight (Hancock and Brune 2005). Hence, a proposed alternative strategy to H_1 activation to treat obesity is afforded by the blockade of H_3 receptors, provided the effects of presynaptic, H_3 heteroreceptor activation and ensuing enhancement of various neurotransmitters do not interfere (but see below). The cloning and functional expression of the H_3 receptor paved the way to the discovery of several splice variants and signal transduction mechanisms, and a variety of H_3 *receptor isoforms* from several species that show differential CNS expression has been reported (Drutel et al. 2001). Stimulation of the H_3 receptor activates several intracellular pathways including $G_{i/o}$-dependent inhibition of adenylate cyclase, activation of the antiapoptotic Akt/GSK-3β pathway (Mariottini et al. 2009), activation of phospholipase A_2, as well as inhibition of the Na^+/H^+ exchanger, and of K^+-induced Ca^{2+} mobilization (Leurs et al. 2005). Splice variants of the H_3 receptor may couple preferentially to different signal transduction pathways and have varying distribution within the CNS (Drutel et al. 2001). H_3 receptors are constitutively active, which implies that antagonists of H_3 receptors may also function as inverse agonists to alter the basal state of the receptor and uncouple constitutive receptor-G-protein interactions. To add to their complexity, H_3 receptors exhibit different pharmacological characteristics at multiple levels.

22.7 Is Hypothalamic H_1 Receptor Activation a Satiety Signal?

Remarkably consistent evidence supports a role of brain histamine in food intake and energy metabolism. In rodents' CNS, activation of H_1 receptors regulates the diurnal rhythm of feeding and modulates peripheral energy metabolism (Table 22.1). The preferential site of histamine-mediated suppression of food intake in the mammalian brain is likely the VMH, a prominent satiety centre. When postsynaptic H_1 receptors are activated within the VMH food intake is inhibited and H_1 receptor antagonists block this effect. On the other hand, microinfusions of H_1 antihistamines into the VMH, but not other hypothalamic nuclei such as the PVN or lateral hypothalamus (LH), elicit feeding responses and increases both meal size and duration (Fukagawa et al. 1989). In accordance to pharmacological manipulation of the H_1 receptors, genetically modified mice that do not express H_1 receptors exhibit an increase in daily food consumption and visceral adiposity (Masaki et al. 2004). In humans, atypical antipsychotics such as olanzapine stimulate appetite most probably through H_1 receptor signalling, although relatively few studies in humans have been carried out to unequivocally establish a relationship between food consumption and H_1 receptors activation.

22.8 H_3 Receptors and Feeding Behaviour: Controversial Findings

The growing interest in the histaminergic H_3 receptor as a potential target to develop anti-obesity drugs, stems from the unavailability of selective H_1 receptor agonists devoid of peripheral action. As already mentioned, the use of compounds that enhance histamine release from nerve terminals such as H_3 receptor antagonists, may afford an effective therapeutic alternative. The role of H_3

Table 22.1 Activation of histaminergic receptors regulates the diurnal rhythm of feeding and modulates peripheral energy metabolism

Drug	Class	Effect	Reference
Histamine and H_1 agonist	HA agonist	Increases expression levels of BAT *Ucp 1* mRNA in rodents (marker of energy expenditure)	Masaki and Yoshimatsu (2006)
Mepyramine	H_1 antagonist	Increases food intake and decreases water intake	Magrani et al. (2004)
Chlorpheniramine	H_1 antagonist	Increases food intake and decreases water intake (light phase)	
Chlorpheniramine	H_1 antagonist	Elicites feeding behaviour, increases deambulation. No effect on water intake	Fukagawa et al. (1989)
Prometazine		Elicites feeding behaviour	
Mepyramine		Elicites feeding behaviour	
Chlorpheniramine	H_1 antagonist	Bilateral injections into VMH elicit feeding behaviour; Bilateral injection into LH; no effect; Bilateral injection into PVN; no effect	Sakata et al. (1988)
Thioperamide	H_3 antagonist	Decreases food intake and does not affect water intake (dark phase)	Doi et al. (1994)
Immepip	H_3 agonist	Elicits feeding behaviour	Chiba et al. (2009)

The brain histaminergic system modulates food consumption and energy metabolism. The table lists some of the seminal papers that demonstrated the role of brain histamine controlling food intake and drinking

receptor ligands in the treatment of metabolic diseases, though, is still unclear as results from different studies are inconsistent, which is understandable in sight of the above mentioned complexity of the H_3 receptor.

Most experimental observations in rodents seem to agree that blockade of brain H_3 receptors is beneficial in decreasing energy intake, body weight and plasma triglycerides (Hancock and Brune 2005) (Table 22.1). Indeed, several studies have shown that H_3 receptor antagonists increase histamine release from the hypothalamus and reduce energy intake in normal and leptin-resistant mice with diet induced obesity (Ishizuka et al. 2008). In addition, the administration of H_1 receptor antagonists attenuates the feeding suppression induced by H_3 antagonists (Hancock and Brune 2005).

Not all data, though, support an appetite-suppressant effect of H_3 receptor blockade. A recent report showed that in diet-induced obese mice, an H_3 receptor agonist suppresses food intake and decreases body weight, presumably with a mechanism independent of histamine release modulation (Yoshimoto et al. 2006). Also, H_3-receptor-deficient mice manifest disrupted regulation of body weight, energy expenditure and food intake. H_3 receptor deletion produced obese hyperphagic mice with reduced energy expenditure, which resembles the phenotype of H_1-receptor-deficient mice (Takahashi et al. 2002). Why then, does deletion of the H_3 receptor induce hyperphagia with reduced energy expenditure in mice? One possible explanation hypothesised by the authors is that a concomitant downregulation of the H_1 receptor in the hypothalamus of H_3-receptor-deficient mice leads to hyperphagia and obesity. It is clear that the effects of H_3 receptors modulators on food consumption and metabolism are more complex and not only mediated by histamine release, but they are regulated

through a variety of receptors and neurotransmitters and may be responsible for the discrepancies described above.

Given the substantial differences of the preclinical outcome, considerable experimental effort remains necessary to prove the so far unclear concept of H_3 receptor antagonists in the treatment of obesity and weight gain. Certainly, the general profile of the more recently synthesized H_3 receptor ligands suggest that they may offer clinical advantages over currently used drugs or those used in the past for treating obesity. Considering the abuse and addiction of amphetamines for instance, H_3 receptor antagonists lack stimulant and sensitization properties (Fox et al. 2003) and tend to show a gradual and prolonged decrease in body weight in contrast to the rapid and often quickly waning effect of other anti-obesity drugs. In this regard, clinical trials phase II with H_3 receptor antagonists are underway for the treatment of other neurological pathologies, namely, narcolepsy and photo-induced epilepsy.

22.9 The Relationship Between Histamine and Some Peptides That Control Feeding Behaviour

Several peptides function as satiety or hunger signalling molecules in the hypothalamus. These hypothalamic systems that regulate energy balance and food intake have a prominent role in the development of obesity. Peptides such as orexin/hypocretin, leptin, glucagon-like peptide 1 (GLP-1) and thyrotropin releasing hormone (TRH), exert their orexigenic or anorexigenic effect through, at least in part, the histaminergic system (Table 22.2).

Orexin/hypocretin-containing neurones intermingle partially with histaminergic neurones in the posterior hypothalamus and together they represent a functional entity. Orexinergic neurones maintain wakefulness, particularly in the context of metabolic challenges, and presumably are responsible for preventing unwanted frequent transitions between behavioural states (Saper et al. 2005). There is a close and reciprocal anatomical connection between histaminergic and orexin neurones and orexin strongly excites TMN neurones (Eriksson et al. 2001). Perfusion of orexin A into rats TMN increases wakefulness (Huang et al. 2001) and stimulates food intake (Jørgensen et al. 2005), effects that depend on an intact histaminergic neuronal system and seems to involve a mechanism mediated by

Table 22.2 The relationship between histamine and some peptides that control feeding behaviour

Peptide	Class	Effect	Reference
TRH (thyrotropin-releasing hormone)	Anorexigenic hormone	Decreases food intake	Gotoh et al. (2007)
Orexin-A	Orexigenic peptide	Increases histamine release	Huang et al. (2001) and Jørgensen et al. (2005)
Ghrelin	Orexigenic peptide	Increases food intake Stimulates food intake	
Glucagon-like peptide-1 (GLP-1)	Anorexigenic peptide	i.c.v. injection of GLP-1 decreases food intake and increases histamine content into TMN	Gotoh et al. (2005)
Leptin	Adipocyte-derived peptide	Decreases food intake and decreases hypothalamic histamine content	Toftegaard et al. (2003)

The table lists some of the seminal papers that demonstrated the role of brain histamine in mediating the orexigenic and anorexigenic effect of some hormones

Table 22.3 Key features of histamine

1. Brain histamine regulates the circadian wake-sleep cycle in concert with other neurotransmitter systems, maintains the brain in a vigilant state, controls feeding homeostasis and cognitive processes.
2. As a neurotransmitter, histamine interacts with four known receptor subtypes each of which has been sequentially cloned and is expressed in the brain.
3. Activation of the histaminergic H_1 receptor subtype regulates the diurnal rhythm of feeding and modulates peripheral energy metabolism.
4. In humans, antihistamine drugs used to treat allergies block the H_1 receptors and have a sedative effect.
5. Atypical antipsychotics have sedative effects and stimulate appetite most probably through H_1 receptor signalling.
6. Brain histamine also regulates diuresis with mechanisms independent of food intake regulation.
7. Currently, no histaminergic compounds have entered clinical trials to regulate feeding disorders. Preclinical studies though are providing promising results that may soon lead to the therapeutic applications of brain penetrating histaminergic ligands.

This table lists the key facts of brain histamine and its relevance in controlling homeostatic functions such as sleep, arousal, feeding and drinking behaviours

Table 22.4 Key features of circadian rhythms

1. A circadian rhythm is defined as the cyclical 24-h period of animal biological activity.
2. The circadian cycle is controlled by a region of the brain known as the hypothalamus, which is the master centre for integrating rhythmic information and establishing sleep patterns.
3. A hypothalamic region receives signals about light and dark from the eye.
4. During the wakeful hours, mental and physical functions are most active.
5. During sleep, voluntary muscle activities almost disappear and there is a decrease in metabolic rate, respiration, heart rate, body temperature and blood pressure.
6. The circadian cycle can alter the effectiveness of some drugs. The administration of hormonal drugs, for instance, must follow the natural circadian rhythm of hormone production.

This table lists the key facts of circadian rhythms

H_1-receptor. In contrast to various other genetically modified mice, H_1 receptor knock-out mice have lower orexin levels (Table 22.4).

The interaction between the histaminergic and orexinergic systems is of clinical relevance, as orexin deficiency causes *narcolepsy*, which combines sudden loss of muscle tone with maintenance of environmental awareness. In this pathological condition, histamine neurones are the only monoaminergic cells of the ascending arousal system to remain active during cataplegic attacks in narcoleptic orexin-2 receptor-deficient dogs, suggesting that activity in histamine cell groups is strongly linked to forebrain arousal, rather than motoractivity (John et al. 2004).

Leptin provides a satiety signal linking peripheral adiposity levels to the regulation of energy homeostasis in the brain. Leptin affects feeding behaviour partially by activating histamine-containing neurones and H_1 receptors. Indeed, the administration of α-fluoromethylhistidine, an inhibitor of histidine decarboxylase, the histamine synthesising enzyme, in rats and mice decreases the leptin-induced suppression of food intake (Yoshimatsu et al. 1999). Also, in H_1 receptor–deficient mice leptin-induced hypofagia is diminished, and leptin deficient, *ob/ob* mice have lower histamine turn over (Yoshimatsu et al. 1999).

TRH is secreted by neurones in the PVN, it suppresses food intake, directly activates the majority of TMN neurones (Parmentier et al. 2009) and increases histamine turnover (Gotoh et al. 2007). In food-deprived, H_1-receptor knock-out mice and histamine-depleted rats, TRH-induced suppression of feeding is significantly attenuated (Gotoh et al. 2007).

Glucagon-like peptide 1 is produced by and released from intestinal L-cells in response to dietary fat and carbohydrate and is also expressed in the nucleus of solitary tract and ventrolateral medulla

of the brainstem. GLP-1 reduces food intake by inhibiting gastric emptying, increasing satiety through central actions and by suppressing glucagon release. Hypothalamic neuronal histamine partially mediates the GLP-1-induced suppression of feeding behaviour, as its anorexigenic effects are blunted by pharmacological or genetic loss of H_1 receptors function (Gotoh et al. 2005).

All together, these observations further prove the intricacy of the histaminergic system as a regulator of food intake, and energy metabolism, as both orexigenic and anorexigenic effects of endogenous molecules appear to necessitate the integrity of the histaminergic system.

22.10 Histamine, Endocannabinoids and Feeding Behaviour

There is convincing evidence that both exogenous and endogenous cannabinoids such as anandamide and 2-arachidonoylglicerol (2-AG) stimulate feeding. Their action is mediated by activation of CB1 receptors distributed in all brain areas and peripheral tissues involved in the control of energy intake, including the hypothalamus and nucleus accumbens (NAcc; reviewed in Matias et al. 2006). This effect is of therapeutic relevance, as cannabinoid agonists are currently used to alleviate anorexia and nausea in AIDS patients.

It has been suggested that brain endocannabinoids control energy balance both in the appetitive phase, increasing the incentive to find food, and during the consummatory phase, increasing appetite, but the mechanisms involved remain to be elucidated. Recent evidence indicates that both the *mesolimbic reward* mechanism and the homeostatic hypothalamic nuclei are involved in these two aspects of feeding behaviour. Endocannabinoid levels vary in the hypothalamus and limbic forebrain with different nutritional manipulations, with levels being the highest with food deprivation and lowest during food consumption (Kirkham et al. 2002). Furthermore, either 2-AG injections in the shell of the NAcc (Kirkham et al. 2002), or anandamide administration into the VMH-induce hyperfagia (Jamshidi and Taylor 2001). In some aspect, the histaminergic and endocannabinoid systems seem to be regulated in an opposing fashion: for instance, systemic administration of leptin that signals to the hypothalamus the nutritional state and reduces food intake, facilitates histamine release from the hypothalamus (Morimoto et al. 1999), whereas it downregulates endocannabinoids levels in the same region (DiMarzo et al. 2001). Furthermore, concentrations of hypothalamic histamine and tele-methylhistamine, a major histamine metabolite, are significantly lower in obese (*ob*/*ob*) and diabetic (*db*/*db*) mice, and fatty (*fa*/*fa*) rats, leptin-deficient and leptin-receptor-defective animals, respectively, relative to lean littermates (Itateyama et al. 2003). On the other hand, defective leptin signalling is associated with elevated hypothalamic levels of enocannabinoids in obese *db*/*db* and *ob*/*ob* mice and Zucker rats. In conclusion, for both histamine and endocannabinoids the mechanisms involved in regulating food intake are not fully understood and nothing is known about the temporal and causal relationship between these two systems in controlling feeding behaviour. We recently began to address these questions studying the effect of systemic and intra-hypothalamic administration of selective CB1 receptor agonists on histamine release from several brain regions of the rat brain, with the double-probe microdialysis technique in freely moving rats (Cenni et al. 2006). Unexpectedly, CB1 receptor agonists increase histamine release in some, but not all areas tested (Fig. 22.4). The question arises then, if and where in the brain the endocannabinoids and the histaminergic system interact and whether these interactions are involved in feeding behaviour. Understanding in what circumstances endocannabinoids are released and activate histaminergic cells may provide interesting hints to develop new therapeutic strategies in the treatment, for instance, of food intake disorders.
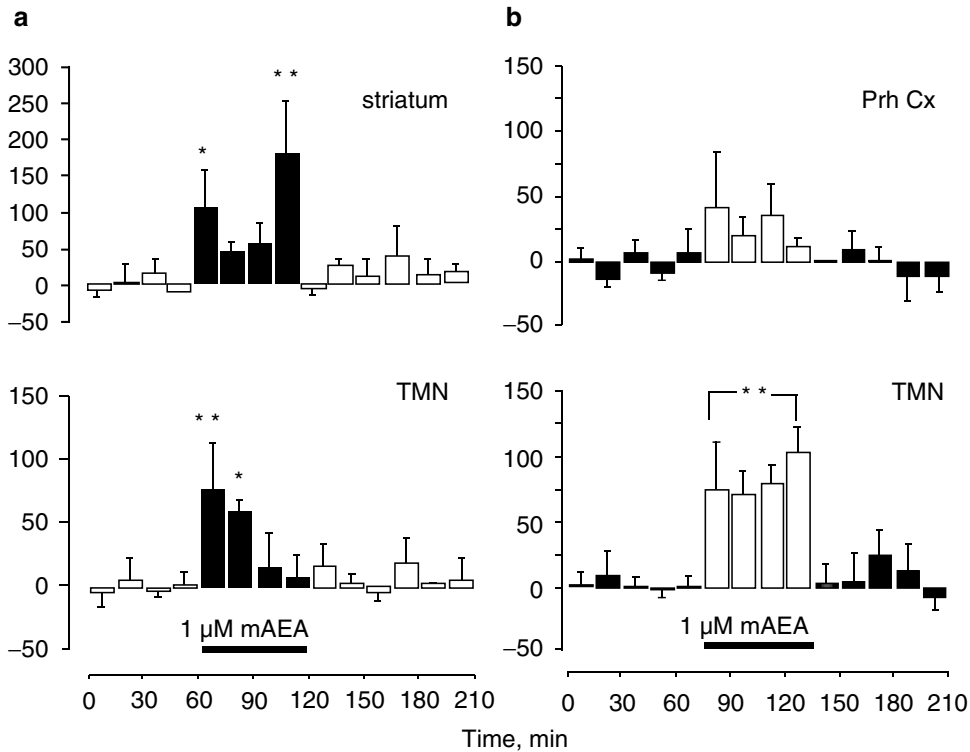
Fig. 22.4 Effect of intra TMN administration of the CB1 receptor agonist mAEA in different brain regions of freely moving animals. Results obtained from double-probe microdialysis experiments in freely moving rats. (**a**) Administration of the CB1 receptor agonist mAEA into TMN significantly increased histamine content in both the TMN and the striatum. In contrast (**b**), mAEA perfused into TMN increased the local release of histamine, but did not histamine release in the Prh Cx. ** $p < 0.01$, *p < 0.05 relative to basal level; ANOVA and Dunnett's post hoc test. *mAEA* R(+)-methanandamide, *Prh Cx* perirhinal cortex, *TMN* tuberomammilary nucleus (Modified from Passani et al. 2007)

22.11 Anticipatory and Consummatory Phases of Feeding Behaviour

The observations presented so far make it clear that histamine controls heterogeneous aspects of feeding and, presumably, histamine drives food intake by increasing the arousal state of the animal (Valdés et al. 2005). Secondary to arousing the animal, brain histamine seems to coordinate satiety and the consolidation of temporal information associated with food consumption. Infact, nowadays it is generally accepted that histamine does more than only mediating satiety. Recently, it has become clear that food-anticipatory activity exhibits the characteristics of a circadian rhythm, although determining the anatomic location of the food-entrainable oscillator (FEO) has been very difficult.

Histamine drives feeding anticipating arousal, an important actor in the FEO, and is probably involved in numerous other feeding-related processes such as temperature and locomotion changes. In fact, while the effects of the histaminergic system in the modulation of the consummatory phase of feeding have been shown to be robust although sometimes contradictory, the role of histamine in the appetitive phase and underlying behavioural mechanisms remains unclear. The appetitive phase of motivated behaviours has distinctive preparatory physiological changes, such as increases in behavioural arousal (Pfaff et al. 2002) and core temperature (Valdés et al. 2005). Therefore, the histaminergic system is a good candidate to promote arousal during the appetitive state. Indeed, histamine-containing neurones are the only aminergic cells related to arousal that become active in

anticipation of an upcoming meal, as rats rendered motivated for food by 24-h fasting and enticed with food that they cannot obtain, show a significant increase in the early gene marker of activated neurones *c-Fos* immunoreactivity in the TMN, much earlier than in other brain regions (Meynard et al. 2005). Recent reports demonstrated that the infralimbic cortex that receives visceral information and coordinates motivated behaviour (Hok et al. 2005), and the TMN are activated in a coordinated temporal way during the appetitive responses to food enticing (Valdés et al. 2006).

Histamine neurones may participate in the appetitive aspects of feeding also modulating reward processes involved in the motivation to feed. The shell of the nucleus NAcc (a reward related brain area) receives a dense histaminergic innervation and local administration of histamine into the NAcc enhances dopamine release (Galosi et al. 2001). The role of histamine in reward-related processes, though, is controversial, as both inhibitory and facilitatory effects have been described (Hasenöhrl et al. 2001; Wagner et al. 1993), and nothing is known on the role of this pathway during feeding behaviour.

22.12 Histamine and Fluid Intake

The role of histamine in diuresis has been extensively studied with mechanisms independent of food intake regulation and has been reviewed extensively elsewhere (Haas et al. 2008). Injection of histamine into the cerebral ventricles or into several hypothalamic sites elicits drinking in rats and evokes antidiuresis (Leibowitz 1973). This effect is mediated by activation of H_1 receptors that stimulates neurones in the supraoptic nucleus to release the antidiuretic hormone (ADH) (Knigge et al. 1999). The release of ADH causes antidiuresis and renal sympathetic activation. In addition, AVP release is stimulated indirectly via histamine-induced local release of norepinephrine (Bealer and Abell 1995). Prolonged (24 or 48 h) dehydration increases synthesis and release of histamine in the hypothalamus (Kjaer et al. 1995). Pharmacological blockade of histamine synthesis, activation of presynaptic H_3 autoreceptors, or antagonism of postsynaptic H_1 receptors and H_2 receptors strongly depress dehydration-induced vasopressin release (Kjaer et al. 1995). Indeed, acute functional blockade of central H_3 receptors is often demonstrated by blocking the *dipsogenia* response to selective H_3 receptors agonists (Fox et al. 2005).

22.13 Concluding Remarks

Our knowledge of the functional roles of brain histamine is far from complete. It is clear that the hypothalamic histamine neurones are involved in basic brain and body functions linking behavioural state and biological rhythms with vegetative and endocrine control of body weight and temperature. For as much as it may seem that the role of the histaminergic system is redundant in modulating the sleep–wake cycle, it is becoming clear that histamine in the brain finely orchestrates diverse aspects of behavioural responses that require an aroused state. Histamine plays a major not only in many homoeostatic mechanisms, among which the regulation of energy expenditure, but also in higher integrative brain functions. Novelty-induced attention and arousal are of major importance for adaptation to changing environments by comparing new information with the recollection of past events. This has a major impact on feeding behaviour, as histamine supposedly drives food intake by increasing the arousal state of the animal, and secondary to arousing the animal, it coordinates satiety and the consolidation of temporal information associated with food consumption. Augmented

histamine release is also an indicator of stress and disrupting the spatiotemporal specificity of histamine release may contribute to maladaptive behavioural responses.

In conclusion, the all-too-long-neglected histaminergic system is raising interest in the scientific community in light of its role in enabling the organism to cope with environmental challenges and novelty, and in the physiology and pathophysiology of central nervous disorders, among which dysfunctions of metabolism and feeding behaviour.

22.14 Applications to Other Areas of Health and Disease

The control that histamine exerts on appetite, feeding rhythms and energy metabolism may be relevant in eating disorders and metabolic syndromes. Compulsive eating, anorexia, bulimia may relate to maladaptive effects of the histaminergic system on brain reward systems and learning circuits that may lead to addictive behaviour.

Changes in brain histamine release may also accompany cardiovascular dysfunction and hypertension linked to metabolic syndromes or obesity, as brain histamine regulates fluid balance, adiposity and energy metabolism.

Summary Points

- Histamine as a central neurotransmitter
- Histamine is a neurotransmitter that alters central nervous system functions in both behavioural and homeostatic contexts through activation of four receptor subtypes. Histaminergic neurones are organized into distinct functional circuits that may contribute to the diverse roles played by brain histamine in feeding homeostasis, arousal and procognitive effects.
- Histamine and wakefulness
- The histaminergic system is part of a wake-promoting system named ascending arousal system. The activity of histaminergic neurones plays an important role, not so much in the induction of wakefulness per se, but in the maintenance of the high level of vigilance necessary for cognitive processes and feeding behaviour.
- Histamine and cognition
- Manipulation of the histaminergic system during several learning paradigms modifies animal behaviour. Activation of selected histaminergic circuits may be important to consolidate temporal and spatial information associated with food availability and consumption and to coordinate appetitive and consummatory behaviours.
- Histamine in feeding and energy metabolism
- Plenty and consistent evidence supports a role of brain histamine in controls food intake and appetite. Activation of H_1 receptors in the ventral hypothalamus provides a satiety signal, whereas compounds that decrease central histamine increase food consumption. Brain histamine also regulates body weight and adiposity and energy expenditure.
- H_3 receptors and feeding behaviour: controversial findings
- The role of H3 receptor ligands in the treatment of metabolic diseases is still unclear and results from different studies are inconsistent. The growing interest in the H_3 receptor as a potential target to develop anti-obesity drugs stems from observations that H_3 receptor antagonists lack stimulant

and sensitization properties and tend to show a gradual and prolonged decrease in body weight in contrast to the rapid and often quickly waning effect of other anti-obesity drugs.
- The relationship between histamine and peptides that control feeding behaviour
- Several peptides function as satiety or hunger signalling molecules in the hypothalamus. Peptides such as orexin/hypocretin, leptin, glucagon-like peptide 1 (GLP-1), thyrotropin releasing hormone (TRH), exert their orexigenic or anorexigenic effect through, at least in part, the histaminergic system.
- Histamine, endocannabinoids and feeding behaviour
- The histaminergic and endocannabinoid systems seem regulated food intake in opposing fashion, but the mechanisms involved in regulating food intake are not fully understood. Understanding the relationship between histaminergic and endocannabinoid systems may provide interesting hints to develop new therapeutic strategies in the treatment of food intake disorders.
- Histamine regulates both anticipatory and consummatory phases of feeding behaviour
- Histamine controls heterogeneous aspects of feeding. Presumably, histamine drives food intake by increasing the arousal state of the animal -and coordinates satiety and the consolidation of temporal information associated with food consumption. This may be relevant to understand dysfunctions of metabolism and feeding behaviour.
- Histamine and fluid intake and balance
- The role of histamine in diuresis has been extensively studied with mechanisms independent of food intake regulation.

Key Terms

Dipsogenia: A metabolic disorder characterized by intense thirst and excessive urination.

Hypercapnia: (from the Greek *hyper* = 'above' and *kapnos* = 'smoke'), also known as hyper-carbia, is a condition of above-normal carbon dioxide (CO_2) in the blood.

Mesolimbic system: Is one of the dopaminergic pathways in the brain. Dopaminergic fibers originate in the ventral tegmental area of the midbrain and project to the limbic system. It is known to be involved in modulating behavioural responses to stimuli that activate feelings of reward (motivation) and reinforcement.

Narcolepsy: Is a chronic sleep disorder. The condition is characterized by excessive daytime sleepiness in which a person experiences extreme fatigue and may fall asleep at inappropriate times, such as whilst at work or at school. A narcoleptic will most probably experience disturbed nocturnal sleep and also abnormal daytime sleep pattern, which is often confused with insomnia.

Pacemakers: 'natural pacemakers' are cells that create rhythmical impulses. A classical example is the cardiac cells that directly control the heart rate.

Receptor isoform: Any of several different forms of the same receptor. Different forms of a protein may be produced from related genes, or may arise from the same gene by alternative splicing.

Uncoupling protein 1 (Ucp-1): Also called thermogenin, is an uncoupling protein found in the mitochondria of brown adipose tissue (BAT). It is used to generate heat by non-shivering thermogenesis. Non-shivering thermogenesis is the primary means of heat generation in hibernating mammals and in human infants.

References

Abe H, Honma S, Ohtsu H, Honma K. Circadian rhythms in behavior and clock gene expressions in the brain of mice lacking histidine decarboxylase. Brain Res Mol Brain Res. 2004;124:178–87.

Arrang JM, Garbarg M, Schwartz JC. Auto-inhibition of brain histamine release mediated by a novel class (H_3) of histamine receptors. Nature. 1983;302:832–7.

Bealer SL, Abell SO. Paraventricular nucleus histamine increases blood pressure by adrenoreceptor stimulation of vasopressin release. Am J Physiol Heart Circ Physiol. 1995;269:H80–5.

Cenni G, Blandina P, Mackie K, Nosi D, Formigli L, Giannoni P, et al. Differential effect of cannabinoid agonists and endocannabinoids on histamine release from distinct regions of the rat brain. Eur J Neurosci. 2006;24:1633–44.

Chipa S, Itateyama E, Sakata T, Yoshimatsu H, Acute central administration of immepip, a histamine H3 receptor agonist, suppresses hypothalamic histamine release and elicits feeding behavior in rats. Brain Res Bull. 2009;79:37–40.

Clineschmidt BV, Lotti VJ. Histamine: intraventricular injection suppresses ingestive behavior of the cat. Arch Int Pharmacodyn Ther. 1973;206:288–98.

DiMarzo V, Goparaju S, Wang L, Liu J, Batkai S, Jarai Z, et al. Leptin-regulated endocannabinoids are involved in maintaining food intake. Nature. 2001;410:822–5.

Doi T, Sakata T, Yoshimatsu H, Machidori H, Kurokawa M, Jayasekara LA, et al. Hypothalamic neuronal histamine regulates feeding circadian rhythm in rats. Brain Res. 1994;64:311–8.

Drutel G, Peitsaro N, Karlstedt K, Wieland K, Smit M, Timmerman H, et al. Identification of rat H3 receptor isoforms with different brain expression and signaling properties. Mol Pharmacol. 2001;59:1–8.

Eriksson K, Sergeeva O, Brown R, Haas H. Orexin/hypocretin excites the histaminergic neurons of the tuberomammillary nucleus. J Neurosci. 2001;21:9273–9.

Fox GB, Pan JB, Radek RJ, Lewis AM, Bitner RS, Esbenshade TA, et al. Two novel and selective nonimidazole H_3 receptor antagonists A-304121 and A-317920: II In vivo behavioral and neurophysiological characterization. J Pharmacol Exp Ther. 2003;305:897–908.

Fox GB, Esbenshade TA, Pan JB, Radek RJ, Krueger KM, Yao BB, et al. Pharmacological properties of ABT-239 [4-(2-{2-[(2R)-2-methylpyrrolidinyl]ethyl}-benzofuran-5-yl)benzonitrile]: II. Neurophysiological characterization and broad preclinical efficacy in cognition and schizophrenia of a potent and selective histamine H3 receptor antagonist. J Pharmacol Exp Ther. 2005;313:176–90.

Fukagawa K, Sakata T, Shiraishi T, Yoshimatsu H, Fujimoto K, Ookuma K, et al. Neuronal histamine modulates feeding behavior through H1-receptor in rat hypothalamus. Am J Physiol Regul Integr Comp Physiol. 1989;256:R605–11.

Galosi R, Lenard L, Knoche A, Haas H, Huston J, Schwarting R. Dopaminergic effects of histamine administration in the nucleus accumbens and the impact of H1-receptor blockade. Neuropharmacology. 2001;40:624–33.

Giannoni P, Passani MB, Nosi D, Chazot PL, Shenton FC, Medhurst AD, et al. Heterogeneity of histaminergic neurons in the tuberomammillary nucleus of the rat. Eur J Neurosci. 2009;29:2363–74.

Gotoh K, Fukagawa K, Fukagawa T, Noguchi H, Kakuma T, Sakata T, et al. Glucagon-like peptide-1, corticotropin-releasing hormone, hypothalamic neuronal histamine interact in the leptin-signaling pathway to regulate feeding behavior. FASEB J. 2005;19:1131–3.

Gotoh K, Fukagawa K, Fukagawa T, Noguchi H, Kakuma T, Sakata T, et al. Hypothalamic neuronal histamine mediates the thyrotropin-releasing hormone-induced suppression of food intake. J Neurochem. 2007;103:1102–10.

Haas HL, Panula P. The role of histamine and the tuberomammillary nucleus in the nervous system. Nat Neurosci Rev. 2003;4:121–30.

Haas HL, Sergeeva OA, Selbach O. Histamine in the nervous system. Physiol Rev. 2008;88:1183–241.

Hancock AA, Brune ME. Assessment of pharmacology and potential anti-obesity properties of H3 receptor antagonists/inverse agonists. Expert Opin Invest Drugs. 2005;14:223–41.

Hasenöhrl R, Kuhlen A, Frisch C, Galosi R, Brandao M, Huston H. Comparison of intra-accumbens injection of histamine with histamine H1-receptor antagonist chlorpheniramine in effects on reinforcement and memory parameters. Behav Brain Res. 2001;124:203–11.

Haxhiu MA, Tolentino-Silva F, Pete G, Kc P, Mack SO. Monoaminergic neurons, chemosensation and arousal. Respir Physiol. 2001;129:191–209.

Hok V, Save E, Lenck-Santini P, Poucet B. Coding for spatial goals in the prelimbic/infralimbic area of the rat frontal cortex. Proc Natl Acad Sci USA. 2005;102:4602–7.

Huang Z-L, Qu W-M, Li W-D, Mochizuki T, Eguchi N, Watanabe T, et al. Arousal effect of orexin A depends on activation of the histaminergic system. Proc Natl Acad Sci USA. 2001;98:9965–70.

Inagaki N, Toda K, Taniuchi I, Panula P, Yamatodani A, Tohyama M, et al. An analysis of histaminergic efferents of the tuberomammillary nucleus to the medial preoptic area and inferior colliculus of the rat. Exp Brain Res. 1990;80:374–80.

Ishizuka T, Hatano K, Murotani T, Yamatodani A. Comparison of the effect of an H(3)-inverse agonist on energy intake and hypothalamic histamine release in normal mice and leptin resistant mice with high fat diet-induced obesity. Behav Brain Res. 2008;188:250–4.

Itateyama E, Chiba S, Sakata T, Yoshimatsu H. Hypothalamic neuronal histamine in genetically obese animals: its implication of leptin action in the brain. Exp Biol Med. 2003;228:1132–7.

Jamshidi N, Taylor D. Anandamide administration into the ventromedial hypothalamus stimulates appetite in rats. Br J Pharmacol. 2001;134:1151–4.

John J, Wu MF, Boehmer LN, Siegel JM. Cataplexy-active neurons in the hypothalamus: implications for the role of histamine in sleep and waking behavior. Neuron. 2004;42:619–34.

Jørgensen EA, Knigge U, Watanabe T, Warberg J, Kjaer A. Histaminergic neurons are involved in the orexigenic effect of orexin-A. Neuroendocrinology. 2005;82:70–7.

Kim SF, Huang AS, Snowman AM, Teuscher C, Snyder SH. Antipsychotic drug-induced weight gain mediated by histamine H1 receptor-linked activation of hypothalamic AMP-kinase. Proc Natl Acad Sci USA. 2007;104:3456–9.

Kirkham TC, Williams CM, Fezza F, Marzo VD. Endocannabinoid levels in rat limbic forebrain and hypothalamus in relation to fasting, feeding and satiation: stimulation of eating by 2-arachidonoyl glycerol. Br J Pharmacol. 2002;136:550–7.

Kjaer A, Larsen PJ, Knigge U, Warberg J. Dehydration stimulates hypothalamic gene expression of histamine synthesis enzyme: importance for neuroendocrine regulation of vasopressin and oxytocin secretion. Endocrinology. 1995;136:2189–97.

Knigge U, Willems E, Kjaer A, Jorgensen H, Warberg J. Histaminergic and catecholaminergic interactions in the central regulation of vasopressin and oxytocin secretion. Endocrinology. 1999;140:3713–9.

Kohler C, Swanson L, Haglund L, Wu JY. The cytoarchitecture, histochemistry and projections of the tuberomammillary nucleus in the rat. Neuroscience. 1985;16:85–110.

Kukko-Lukjanov TK, Panula P. Subcellular distribution of histamine, GABA and galanin in tuberomamillary neurons in vitro. J Chem Neuroanat. 2003;25:279–92.

Leibowitz SF. Histamine: a stimulatory effect on drinking behavior in the rat. Brain Res. 1973;63:440–4.

Leurs R, Bakker RA, Timmerman H, Esch IJd. The histamine H3 receptor: from gene cloning to H3 receptor drugs. Nat Rev Drug Discov. 2005;4:107–20.

Lin J, Sakai K, Jouvet M. Hypothalamo-preoptic histaminergic projections in sleep-wake control in the cat. Eur J Neurosci. 1994;6:618–25.

Lin JS, Hou Y, Sakai K, Jouvet M. Histaminergic descending inputs to the mesopontine tegmentum and their role in the control of cortical activation and wakefulness in the cat. J Neurosci. 1996;16:1523–37.

Magrani J, de Castro e Silva E, Varjão B, Duarte G, Ramos AC, Athanazio R, et al. Histaminergic H1 and H2 receptors located within the ventromedial hypothalamus regulate food and water intake in rats. Pharmacol Biochem Behav. 2004;79:189–98.

Mariottini C, Scartabelli T, Bongers G, Arrigucci S, Nosi D, Leurs R, et al. Activation of the histaminergic H3 receptor induces phosphorylation of the Akt/GSK-3 beta pathway in cultured cortical neurons and protects against neurotoxic insults. J Neurochem. 2009;110:1469–78.

Masaki T, Yoshimatsu H. The hypothalamic H1 receptor: a novel therapeutic target for disrupting diurnal feeding rhythm and obesity. Trends Pharmacol Sci. 2006;5:279–84.

Masaki T, Chiba S, Yasuda T, Noguchi H, Kakuma T, Watanabe T, et al. Involvement of hypothalamic histamine H1 receptor in the regulation of feeding rhythm and obesity. Diabetes. 2004;53:2250–60.

Matias I, Bisogno T, Marzo VD. Endogenous cannabinoids in the brain and peripheral tissues: regulation of their levels and control of food intake. Int J Obes. 2006;Suppl 1:S7–12.

Meynard MM, Valdes JL, Recabarren M, Seron-Ferre M, Torrealba F. Specific activation of histaminergic neurons during daily feeding anticipatory behavior in rats. Behav Brain Res. 2005;158:311–9.

Miklos I, Kovacs K. Functional heterogeneity of the responses of histaminergic neuron subpopulations to various stress challenges. Eur J Neurosci. 2003;18:3069–79.

Morimoto T, Yamamoto Y, Mobarakeh IJ, Yanai K, Watanabe T, Yamatodani A. Involvement of the histaminergic system in leptin-induced suppression of food intake. Physiol Behav. 1999;67:679–83.

Panula P, Yang HY, Costa E. Histamine-containing neurons in the rat hypothalamus. Proc Natl Acad Sci USA. 1984;81:2572–6.

Parmentier R, Ohtsu H, Djebarra-Hannas Z, Valtx J-L, Watanabe T, Lin J-S. Anatomical, physiological and pharmacological characteristics of histidine decarboxylase knock-out mice: evidence for the role of brain histamine in behavioral and sleep-wake control. J Neurosci. 2002;22:7695–711.

Parmentier R, Anaclet C, Watanabe T, Lin J-S. Characteristics of cortical EEG and sleep-wake cycle in histamine H1-receptor knock out mice. In: Athens MSotUo, editor, European Histamine Research Society, Delphi, 2006.

Parmentier R, Kolbaev S, Klyuch BP, Vandael D, Lin JS, Selbach O, et al. Excitation of histaminergic tuberomamillary neurons by thyrotropin-releasing hormone. J Neurosci. 2009;29:4471–83.

Passani M, Lin J-S, Hancock A, Crochet S, Blandina P. The histamine H3 receptor as a novel therapeutic target for cognitive and sleep disorders. Trends Pharmacol Sci. 2004;25:618–25.

Passani MB, Giannoni P, Bucherelli C, Baldi E, Blandina P. Histamine in the brain: beyond sleep and memory. Biochem Pharmacol. 2007;73:1113–22.

Pfaff D, Frohlich J, Morgan M. Hormonal and genetic influences on arousal–sexual and otherwise. Trends Neurosci. 2002;25:45–50.

Sakata T, Ookuma K, Fukagawa K, Fujimoto K, Yoshimatsu H, Shiraishi T, et al. Blockade of the histamine H1-receptor in the rat ventromedial hypothalamus and feeding elicitation. Brain Res. 1988;441:403–7.

Sakata T, Yoshimatsu H, Masaki T, Tsuda K. Anti-obesity actions of mastication driven by histamine neurons in rats. Exp Biol Med. 2003;228:1106–10.

Saper CB, Scammell TE, Lu J. Hypothalamic regulation of sleep and circadian rhythms. Nature. 2005;437:1257–63.

Sergeeva OA, Eriksson KS, Sharonova IN, Vorobjev VS, Haas HL. GABA(A) receptor heterogeneity in histaminergic neurons. Eur J Neurosci. 2002;16:1472–82.

Strakhova MI, Nikkel AL, Manelli AM, Hsieh GC, Esbenshade TA, Brioni JD, et al. Localization of histamine H4 receptors in the central nervous system of human and rat. Brain Res. 2009;1250:41–8.

Takahashi K, Suwa H, Ishikawa T, Kotani H. Targeted disruption of H3 receptors results in changes in brain histamine tone leading to an obese phenotype. J Clin Invest. 2002;110:1791–9.

Takahashi K, Lin JS, Sakai K. Neuronal activity of histaminergic tuberomammillary neurons during wake-sleep states in the mouse. J Neurosci. 2006;26:10292–8.

Toftegaard CL, Knigge U, Kjaer A, Warberg J. The role of hypothalamic histamine in leptin-induced suppression of short-term food intake in fasted rats. Regul Pept. 2003;111:83–90.

Valdés J, Farías P, Ocampo-Garce A, Cortes N, Seron-Ferre M, Torrealba F. Arousal and differential Fos expression in histaminergic neurons of the ascending arousal system during a feeding-related motivated behaviour. Eur J Neurosci. 2005;21:1931–42.

Valdés J, Maldonado P, Recabarren M, Fuentes R, Torrealba F. The infralimbic cortical area commands the behavioral and vegetative arousal during appetitive behavior in the rat. Eur J Neurosci. 2006;23:1352–64.

Wagner U, Segura-Torres P, Weiler T, Huston J. The tuberomammillary nucleus region as a reinforcement inhibiting substrate: facilitation of ipsihypothalamic self-stimulation by unilateral ibotenic acid lesions. Brain Res. 1993;613:269–74.

Watanabe T, Taguchi Y, Shiosaka S, Tanaka J, Kubota H, Terano Y, et al. Distribution of the histaminergic neuron system in the central nervous system of rats: a fluorescent immunohistochemical analysis with histidine decarboxylase as a marker. Brain Res. 1984;295:13–25.

Wouterlood FG, Steinbusch HW, Luiten PG, Bol JG. Projection from the prefrontal cortex to histaminergic cell groups in the posterior hypothalamic region of the rat Anterograde tracing with Phaseolus vulgaris leucoagglutinin combined with immunocytochemistry of histidine decarboxylase. Brain Res. 1987;406:330–6.

Yoshimatsu H, Itateyama E, Kondou S, Hidaka S, Tajima D, Kurokawa M. Hypothalamic neuronal histamine as a target of leptin action on feeding behavior in the central nervous system. Diabetes. 1999;48:1342–6.

Yoshimoto R, Miyamoto Y, Shimamura K, Ishihara A, Takahashi K, Kotani H, et al. Therapeutic potential of histamine H3 receptor agonist for the treatment of obesity and diabetes mellitus. Proc Nat Acad Sci USA. 2006;103:13866–71.

Chapter 23
Ectopic Brain Peptides Posing as Adipokines: Fat as a Novel Site of *kiss1* Expression

Russell Brown, Syed A. Imran, and Michael Wilkinson

Abbreviations

ACTH	Adrenocorticotropin hormone
AT1	Angiotensin II receptor 1
BMI	Body mass index
cAMP	Cyclic adenosine monophosphate
CART	Cocaine and amphetamine regulated transcript
cDNA	Complementary deoxyribonucleic acid
cGMP	Cyclic guanosine monophosphate
CRF	Corticotrophin releasing factor
D2R	Dopamine receptor 2
FIAF	Fasting-induced adipose factor
GPR54	G protein coupled receptor 54
IGF-1	Insulin like growth factor 1
mRNA	Messenger ribonucleic acid
NGF	Nerve growth factor
NPY	Neuropeptide Y
NPYR	Neuropeptide Y receptor
PCOS	Polycystic ovarian syndrome
PPARγ	Peroxisome proliferator-activated receptor gamma
RT-PCR	Reverse transcriptase-polymerase chain reaction
TGF-β	Transforming growth factor beta
TNF-α	Tumor necrosis factor alpha
TrkA	Tyrosine kinase receptor A

M. Wilkinson (✉)

Department of Obstetrics & Gynaecology, IWK Health Centre, Dalhousie University, University Avenue, Halifax, NS, Canada, B3K 6R8
and
Department of Physiology & Biophysics, Dalhousie University, Halifax, NS, Canada, B3H 1X5
and
Division of Endocrinology and Metabolism, Victoria General Hospital, Department of Medicine, Dalhousie University, Halifax, NS, Canada, B3H 2Y9
e-mail: mwilk@dal.ca

23.1 Introduction

Adipose tissue is an endocrine organ affecting a wide variety of functions, including the regulation, and dysregulation, of metabolism, and reproduction (Ahima and Lazar 2008; Catalan et al. 2009). The prototypical adipose-tissue-derived hormone remains leptin, but proteomic analysis of the adipocyte secretome revealed almost 100 proteins, or *adipokines*, that behave as secretory molecules released from adipose tissue (Trayhurn and Wood 2004; Halberg et al. 2008). Further evidence for the adipocyte's complexity comes from a recent in-depth analysis of the *total* adipocyte proteome, using mass spectrometry and bioinformatics, that identified 3,287 proteins (Adachi et al. 2007). It remains unclear whether the adipocyte is the primary site of production of adipokines, or whether other adipose cell types act in concert with adipocytes. Nevertheless, adipokines function as hormones as well as autocrine/paracrine factors in a complex signaling network (Breitling 2009) that includes the immune response (e.g., interleukins, tumor necrosis factor alpha (TNF-α)); control of metabolism (e.g., leptin, resistin, visfatin); regulation of the extracellular matrix (e.g., cathepsin S, matrix metalloproteases); and various other complex pathways via, for example, nerve growth factor (NGF), angiotensinogen, and fibroblast growth factor. Also, because fat deposits are interspersed with many tissues throughout the body (e.g., liver, muscle, heart, bone marrrow) they may function as "miniorgans" with specific paracrine effects (Halberg et al. 2008). Also, given the overwhelming complexity of the adipocyte proteome, it remains possible that these different sites might employ distinct signaling arrays.

For leptin at least, the brain is perhaps the most studied target system (Ahima and Antwi 2008). Leptin receptors are widely distributed in the rodent and human brain, and this led us to hypothesize that many of these – with the exception of those in the basal hypothalamus – would be accessible *only* to a brain-derived ligand, if not leptin of brain origin. We subsequently demonstrated that leptin mRNA was detectable within the rat brain, and leptin immunoreactivity could be co-localized to neurons. Further studies revealed that leptin mRNA was also readily detectable in human, guinea pig, hamster, sheep, pig, and fish brain, and in human neuroblastoma and rat glioblastoma cells (Wilkinson et al. 2007). In the mouse, Lim et al. reported a marked induction of leptin mRNA in injured spinal cord (Lim et al. 2009). Investigations in vivo demonstrated that leptin was also secreted from the human brain (Eikelis and Esler 2005). Several other adipokines, such as resistin, adiponectin, and fasting-induced adipose factor (FIAF), are also expressed in the central nervous system where they function as *cephalokines*. We believe that they exist as components of a unique circuitry able to fine tune the feedback effects of peripherally derived adipokines via their cognate receptors not only in the control of energy balance (Wilkinson et al. 2007) but perhaps in cognitive function as well (see Harvey; this volume, Sect. 1.3).

We have now extended our original hypothesis – *that adipokines would be expressed in brain cells* – to include the possibility that the converse is also true, i.e., *peptides previously assumed to be brain- or hypothalamic-specific should be expressed in adipose tissue*. In fact, gene expression profiling of human fat revealed several transcripts that are associated with hypothalamic function, including those for neuropeptide Y (NPY), corticotrophin releasing factor (CRF), melanin concentrating hormone (MCH), and orexin (Yang et al. 2003; Gomez-Ambrosi et al. 2004). There is also evidence that adipose tissue expresses receptors for NPY, angiotensin II, and orexin, implicating local (autocrine) or paracrine feedback loops (Yang et al. 2003). This chapter will outline the evidence that adipose tissue should be considered as a local source of neuropeptides, which may also function as adipokines.

In the first section, we focus on *kiss1* expression and outline our evidence that this gene, currently a worldwide research focus in the hypothalamic control of reproduction, is expressed and regulated in rodent and human adipose tissue. We will then describe other neuropeptide/adipokine candidates, including NGF, NPY, prolactin, and a product of the renin-angiotensin system, angiotensin II.

23.2 *Kiss1* Gene Expression in Adipose Tissue

Kiss1, originally identified as a metastasis suppressor gene, encodes a 145 amino acid precursor that is cleaved to a family of peptides known as kisspeptins. Kisspeptins appear to be the natural ligands of the orphan G-protein coupled receptor 54 (GPR54), and the *kiss1*/kisspeptin network is a fundamental gatekeeper of the reproductive system (Roa et al. 2008). For example, loss-of-function mutations in human *gpr54* are associated with absence of puberty and hypogonadotrophic hypogonadism. Further, hypothalamic *kiss1* expression is regulated by sex hormones and decreased by food restriction (Smith 2008; Castellano et al. 2009). Since the hypothalamic-pituitary-gonadal axis is crucially dependent on sufficient energy stores such as adipose tissue (Wade et al. 1996), the sensitivity of *kiss1* expression to food restriction provides a plausible link between negative energy balance and infertility. This observation led us to speculate that kisspeptins may also exert biological effects outside of the brain. *Kiss1* and *gpr54* mRNA were detected in several peripheral sites, including pituitary, pancreas, ovary, and placenta (Horikoshi et al. 2003; Castellano et al. 2006; Hauge-Evans et al. 2006; Brown et al. 2008; Richard et al. 2009), and was recently demonstrated in hypothalamic GT1–7 neurons in tissue culture (Quaynor et al. 2007). Therefore, kisspeptins could act as autocrine/paracrine signals in these peripheral sites.

Using hypothalamic tissue as a positive control, we demonstrated that a *kiss1* gene transcript was readily detectable in rat adipose tissue (Brown et al. 2008). Previous work by Muir et al. confirmed the presence of *gpr 54* mRNA in human fat tissue (Muir et al. 2001), and we determined that rat adipose tissue also expresses this gene (Brown et al. unpublished data). In subsequent experiments we showed that adipose *kiss1* mRNA levels were *increased* severalfold by food restriction (Fig. 23.1). Additional studies in obese rat models also revealed abnormal adipose *kiss1* expression and regulation. For example, *kiss1* mRNA levels were significantly *reduced* in fat tissue from rats fed a high-fat diet, and in fat from the obese *fa/fa* rat (Brown et al. 2008). In contrast, in rats made obese with dihydrotestosterone treatment (Manneras et al. 2007), adipose *kiss1* expression was e*levated* 8-fold (Fig. 23.2). Note that *kiss1* mRNA levels were significantly *reduced* in hypothalamic tissue from the same rats, suggesting that *kiss1* expression is differentially regulated in these two tissue sites.

Our data indicate that *kiss1* gene expression in rat fat tissue is under metabolic and hormonal control, and raise several questions regarding a physiological or pathological role for adipose-derived kisspeptins. For example: (a) are kisspeptins secreted from adipose tissue? (b) in which adipose tissue cell type(s) is the gene expressed? (c) how is *kiss1* expression regulated ? (d) how do adipose tissue cells respond to stimulation with kisspeptins via the GPR54 receptor? (e) is *kiss1* expressed in human adipose tissue? (f) given that high levels of kisspeptins were detected in the circulation (Horikoshi et al. 2003; Katagiri et al. 2009), what would be the purpose of adipose tissue GPR54 receptors being exposed to both circulating (e.g., from the placenta) and locally produced, kisspeptin?

We have made some progress in answering question (e): is *kiss1* expressed in human fat? *Kiss1* mRNA was detectable in female omental fat tissue, and particularly in women with high body mass indices (BMI) (see Fig. 23.3). This observation is not consistent with our data from obese rats, where *kiss1* mRNA levels were reduced in fat, and suggests that an important avenue of investigation should be the possible influence of leptin and insulin on adipose *kiss1* expression. Leptin is known to increase *kiss1* mRNA in murine hypothalamus (Luque et al. 2007). The answers to questions (a)–(d) should be forthcoming from current investigations, but question (f) remains a difficult one. We posed a similar question with respect to circulating leptin, which is expressed in the pituitary gland even though the pituitary is normally exposed to blood-borne leptin (Wilkinson et al. 2007). We speculated that pituitary-derived leptin could tune the local leptin-signaling pathway to maintain

Effect of fasting/refeeding on adipose *Kiss1* expression
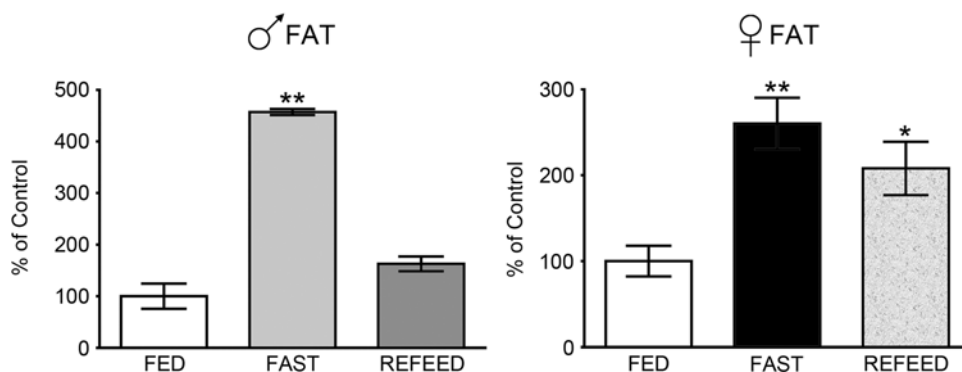
Fig. 23.1 Effects of fasting (18 h) and then refeeding (6 h) on *Kiss1* mRNA in visceral fat from male and female rats. *Kiss1* mRNA values were determined by realtime RT-PCR and are expressed as percentage changes compared to control rats fed *ad lib* (mean ± SEM). *$p < 0.05$; **$p < 0.01$ versus fed control values ($n = 5$–6 per group)

The effects of dihydrotestosterone on *Kiss1* expression
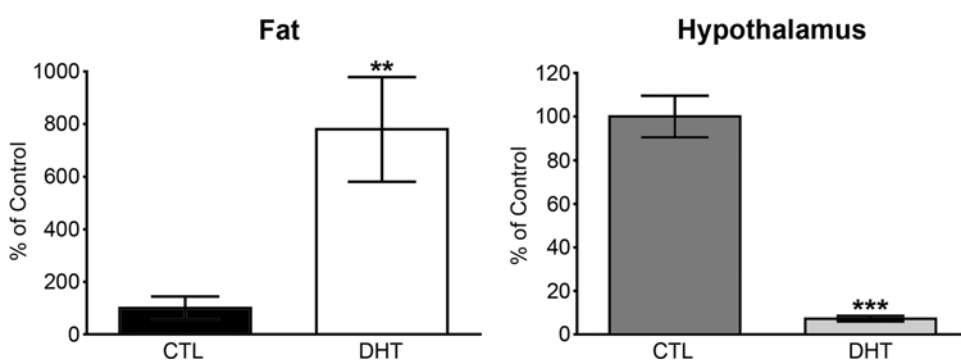
Fig. 23.2 *Kiss1* mRNA in adipose and hypothalamic tissue of female rats treated with dihydrotestosterone. Rats were exposed to dihydrotestosterone for 26 days released from subcutaneous pellets according to the method of Manneras et al. (2007). *Kiss1* mRNA values were determined by realtime RT-PCR and are expressed as percentage changes compared to untreated control rats. Values are mean ± SEM ($n = 4$–6 per group). **$p < 0.01$; ***$p < 0.001$

responsiveness, particularly when circulating levels of fat-derived leptin are reduced, for example, during food restriction. A similar concept has been proposed for localized renin-angiotensin systems (see below) and we will illustrate several other examples in this review.

23.3 A Renin-Angiotensin System in Adipose Tissue

Angiotensin II is derived from the proteolytic cleavage of angiotensinogen and is a prototypical *ectopic* neuropeptide. Originally regarded as the effector peptide of a peripheral hormonal system involved in the maintenance of volume and blood pressure homeostasis, organ-based sites of production are now well described (Paul et al. 2006). Brain renin-angiotensin systems, now considered as a model neuro-peptide system particularly in the hypothalamus, may potentially be involved in several pathologies such as stress and depression (Phillips and de Oliveira 2008). Other so-called *tissue renin-angiotensin*
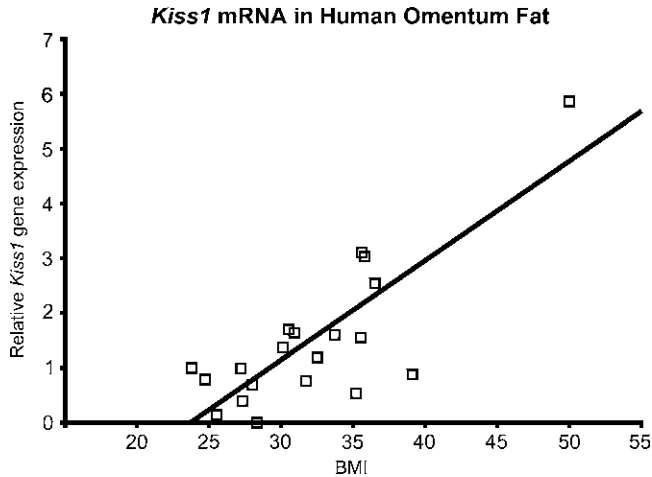
Fig. 23.3 *KISS1* mRNA levels in omental fat obtained from women. *KISS1* mRNA values were determined by real-time RT-PCR and are expressed relative to the value obtained at the lowest BMI (23.8). There is a highly significant correlation ($p < 0.0001$) between *KISS1* expression and BMI. This correlation was not seen in subcutaneous adipose tissue obtained from the same patients (Cockwell, Wilkinson, Bouzayen, Imran and Wilkinson; unpublished data)

systems are reported for adrenal, kidney, and heart (Bader and Ganten 2008), and there is good evidence for a local renin-angiotensin system in adipose tissue that appears to regulate fat growth, metabolism, and adipocyte differentiation (Fowler et al. 2009). Local adipose production of renin occurs independently of circulating renin, and gene expression of all components of the renin-angiotensin system, namely, renin, angiotensin converting enzyme, and the peptide products angiotensinogen and angiotensin I and II, have been identified in adipocytes (Paul et al. 2006). Angiotensinogen gene expression (*agt* mRNA) was also reported to be significantly reduced in adipose tissue from obese rodents (Jones et al. 1997), but increased in obese men (Van Harmelen et al. 2000). Expression of angiotensin II receptor types I and 2 (AT1 and AT2) were also detected in human and rodent adipocytes (Schling et al. 1999; Mallow et al. 2000), suggesting the possibility of autocrine/paracrine interactions. Recent studies by Cassis et al. revealed a differential effect of local angiotensin II production (stimulatory) compared to an *inhibitory* influence of *systemic* angiotensin II (Cassis et al. 2004). This relates directly to the question posed in Sect. 23.2, i.e., what would be the purpose of adipose tissue angiotensin II receptors exposed to both locally produced and circulating, angiotensin II? Cassis et al. (2004) provide one reasonable answer that low, physiological, concentrations of angiotensin II, produced locally by adipocytes, *stimulate* leptin expression and secretion whereas high circulating levels of angiotensin II are inhibitory. An adipose renin-angiotensin system may therefore be a necessary functional component of adipocytes in the presence of low levels of systemic angiotensin II.

Significant progress has been made in confirming the importance of the adipose renin-angiotensin system using transgenic mice in which *agt* expression was specifically modified in adipose tissue (Kim et al. 2006). Figure 23.4 illustrates that a complete knockout of the *angiotensinogen* gene decreased fat mass and lowered blood pressure, whereas *overexpression* of *agt* specifically in adipose tissue in wild-type mice did the opposite, i.e., fat mass and blood pressure were both increased. However, when *agt* was reexpressed *only* in adipose tissue in the *agt* knockouts, fat levels were substantially restored and blood pressure was normalized. Adipokine secretion was also affected; restoration of *agt* expression specifically in adipose tissue increased leptin and resistin secretion, but decreased adiponectin release, when compared to *agt* knockouts. These data imply that locally produced angiotensin II has direct effects on fat mass and adipokine secretion, but also influences blood pressure presumably via secretion into general circulation. Note also that *overexpression* of *agt* in adipose tissue induced hyperinsulinemia and greatly increased leptin secretion. In keeping with these

Effects of *agt* expression on adipose tissue
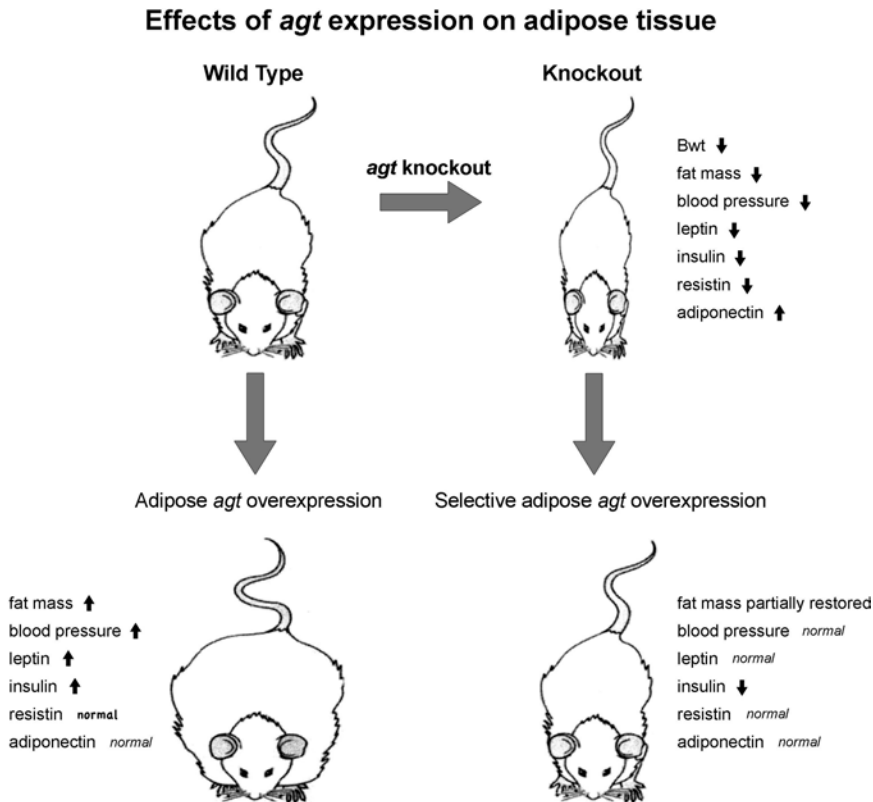
Fig. 23.4 Adipose-specific and endocrine effects of targeted angiotensinogen (*agt*) gene expression. Overexpression of adipose *agt* in wild-type mice produced obesity and increases in blood pressure and insulin levels, whereas in *agt* knockouts the effects were in the opposite direction. Note that targeted expression of *agt* in adipose tissue of *agt* knockouts largely restored these changes to normal (adapted from Massiera et al. 2001)

data, Engeli et al. (2003) suggested a role for the adipose renin-angiotensin system in the development of the metabolic syndrome (Engeli et al. 2003). Also, In attempts to implicate the adipose renin-angiotensin system in the onset of type 2 diabetes, Kohlstedt et al. (2009) reported that angiotensin converting enzyme inhibitors upregulated adiponectin expression in isolated human adipocytes (Kohlstedt et al. 2009). This strongly implicates the involvement of an endogenous, adipose-specific formation of angiotensin II that may contribute to the beneficial effects of angiotensin converting enzyme inhibition in the development of type 2 diabetes.

In summary angiotensin II, a peptide product of an adipose tissue renin-angiotensin system, is a component of adipocyte function that might operate separately, or in conjunction with, the systemic renin-angiotensin system. The evidence obtained so far indicates that this system may be a useful therapeutic target in the treatment of obesity and diabetes.

23.4 Neuropeptide Y as an Adipokine

Neuropeptide Y (NPY) is widely distributed in the central and peripheral nervous systems and is known primarily for its appetite-stimulating effects (Morris 1989), particularly in the arcuate nucleus of the hypothalamus (Kalra and Kalra 2004). The role of NPY in appetite regulation is the subject of

intensive study where it is emerging as a promising target for the development of new anti-obesity drugs (Kamiji and Inui 2007). For instance, centrally injected NPY stimulates food intake whereas NPY inhibition reduces appetite (Kalra et al. 1999). NPY also activates the hypothalamic-pituitary-adrenal axis, another crucial system implicated in the regulation of metabolism and energy balance (Kakui and Kitamura 2007).

Direct effects of NPY on adipocyte function are also well described. Treatment of human subcutaneous adipocytes with recombinant human NPY downregulates leptin expression (Kos et al. 2007), exerts an anti-lipolytic effect (Valet et al. 1990), and promotes the proliferation of pre-adipocytes (Kuo et al. 2007; Yang et al. 2008a). These data led to the hypothesis that NPY would also be expressed in adipose tissue. Supporting evidence for this idea came from gene expression profiling of human omental (visceral) adipose tissue obtained from non-obese female subjects (Yang et al. 2003). Several appetite-regulating genes including melanin concentrating hormone, corticotrophin releasing factor, cholecystokinin and NPY, as well as their corresponding receptors, were expressed in visceral adipose tissue. Kos et al. subsequently reported that NPY was not only expressed, but was also secreted by human adipose tissue (Kos et al. 2007). The coexistence of locally produced NPY and its receptors, implicates an NPY autocrine/paracrine system in adipose tissue function. Kuo et al. (2007) confirmed this view and demonstrated that a combination of stress and a high-fat/sucrose diet induced a marked upregulation of *Npy* and *Npyr2* gene expression in mouse adipose tissue (Kuo et al. 2007). They also showed that in obese *ob/ob* mice, characterized by high glucocorticoid secretion (Edwardson and Hough 1975), subcutaneous fat tissue had very high levels of *Npy* gene expression. The adipogenic NPY/NPYR2 system also exists in nonhuman primate adipose tissue (Kuo et al. 2007).

Polycystic ovary syndrome (PCOS) is also associated with obesity and insulin resistance, and in a recent study Manneras et al. (2007) demonstrated that mesenteric (visceral) adipose tissue expression of NPY in a rat model of PCOS, is higher than that in control rats. Exercise reduced adiposity and normalized ovarian cyclicity and adipose NPY expression. The increase in NPY expression in the obese PCOS rats is consistent with the data of Kuo et al. (2007). However, it is unlikely that stress-induced increases in blood corticosterone levels were responsible since Manneras et al. (2007) reported a decrease in corticosterone in blood. Thus, unlike the model described by Kuo et al. (2007), stress may not be important in elevating adipose NPY expression.

As we have outlined in other sections, a key question is why should adipose tissue produce NPY in the face of systemic and sympathetic neural sources of NPY? Kuo et al. (2007) propose that under stressful and high-fat dietary conditions circulating glucocorticoids enhance local adipose NPY production, which in turn drives the expression of NPYR2 receptors. Such an enhancement of autocrine signaling leads directly to increases in adipogenesis and angiogenesis, producing further growth of adipose tissue. These authors argue that targeting the local NPY/NPYR2 system may be a therapeutic route to drug-induced *liporemodelling*, but this requires further investigation.

23.5 Is Nerve Growth Factor an Adipokine?

Early structural analysis revealed profound similarities between nerve growth factor (NGF) and pro-insulin, and like insulin, NGF was also found to influence cellular metabolism in sympathetic neurons as well as in isolated rat adipocytes (Mukherjee and Mukherjee 1982; Ng and Wong 1985). Thus NGF stimulated lipogenesis and glucose metabolism in isolated rat adipocytes, while simultaneously inhibiting lipolysis, although its effects were less potent than those of insulin (Mukherjee and Mukherjee 1982; Ng and Wong 1985). NGF also induced the expression of vascular endothelial growth factor in 3T3-L1 adipocytes, as well as in brown adipose tissue from transgenic mice

overexpressing NGF (Hansen-Algenstaedt et al. 2006). As expected, the expression of both low-affinity (p75) and high-affinity (Trk A) NGF receptors were also detected in a range of adipose tissue depots as well as in isolated adipocytes and adipocyte cell line models (Nisoli et al. 1996; Peeraully et al. 2004). Thus NGF has the capacity to directly modulate adipocyte gene expression and metabolism. NGF is also expressed and released from adipose tissue, where it appears to modify local adipocyte metabolism and the innervation of adipose tissue by sympathetic nerves, raising important questions about its putative role as an adipokine (Peeraully et al. 2004; Trayhurn and Wood 2004).

NGF mRNA and protein secretion have been detected in a variety of white and brown adipose tissue depots from several species including mice, rats, canines, and humans (Nisoli et al. 1996; Peeraully et al. 2004; Ryan et al. 2008). NGF mRNA was found to be enriched in isolated adipocytes suggesting that fat cells are a major source of adipose tissue-derived NGF (Nisoli et al. 1996; Peeraully et al. 2004). Further, NGF expression was highest in epididymal and peri-renal fat depots, but was also readily detected in subcutaneous and omental depots isolated from mice (Peeraully et al. 2004). Although this tissue-dependent pattern of distribution was not replicated in canines, limited data suggested that NGF gene expression was also higher in omental, rather than subcutaneous, human adipose tissues (Peeraully et al. 2004; Ryan et al. 2008). This tissue-dependent pattern of NGF distribution may account for the varying degree of sympathetic nervous system innervation within the various fat tissue depots (Peeraully et al. 2004). Murine, canine, and human cell cultures also confirmed the direct expression and secretion of NGF from adipocytes. However it was found that NGF regulation was dependent on the degree of differentiation such that NGF expression and secretion was greatest in preadipocytes (Nisoli et al. 1996; Peeraully et al. 2004; Wang et al. 2005; Ryan et al. 2008). Although one of the major roles predicted for adipose-derived NGF is to direct the sympathetic nervous system-dependent innervation of fat (Peeraully et al. 2004), we should not preclude other possible functions, such as mediating local energy metabolism and gene expression. Regulatory studies suggest that NGF may also be involved with the inflammatory processes associated with obesity (Nisoli et al. 1996, 1998; Peeraully et al. 2004; Bullo et al. 2007). Various inflammatory molecules were shown to stimulate the expression of NGF, including tumor necrosis factor alpha and lipopolysaccharide, whereas anti-inflammatory compounds such as rosiglitazone, a peroxisome proliferator-activated receptor gamma (PPARγ) ligand, or dexamethasone were found to have an inhibitory effect on adipocyte NGF mRNA levels (Peeraully et al. 2004; Wang et al. 2005; Ryan et al. 2008). Thus it was not surprising that NGF levels were increased in obese subjects given the recent correlations drawn between obesity and inflammation (Nisoli et al. 1996; Bullo et al. 2007). However other factors may influence the regulation and secretion of NGF, including age and gender. For example, NGF levels increase markedly after birth until around 3 months of age, and decrease thereafter in rats (Nisoli et al. 1998). Although data from humans failed to detect any correlation with age in adults, we do not know what the pattern is like in early life when the sympathetic nervous system is developing (Bullo et al. 2007). However the major question that remains is what is the purpose(s) and role(s) of adipose-derived NGF in all these various processes?

Although it is now evident that adipocytes express NGF, as well as the low (p75) and high-affinity tyrosine kinase receptor A (TrkA) NGF receptors, the precise role(s) of adipose-derived NGF within fat tissue, and within the whole body, remains unknown. Current evidence suggests that locally derived NGF plays a critical role in the sympathetic innervation of adipose tissue, but emerging data also implicates NGF in local inflammatory responses associated with obesity. Further, like other adipose-derived brain peptides, NGF may act locally within fat via autocrine/paracrine pathways in order to control gene expression and adipocyte metabolism, in addition to impacting local tissue function. In summary, this remains an interesting avenue of discovery as attempts are made to

uncover the role(s) of adipose-derived NGF that may ultimately prove to be a unique modulator of adipocyte function, or even bodyweight regulation.

23.6 Prolactin as an Adipokine

Prolactin is a multifunctional pituitary peptide hormone implicated in numerous hormonal, immune, and metabolic functions (Goffin et al. 2002; Ben-Jonathan et al. 2008), and is also expressed, and secreted, in the hypothalamus as a neuropeptide (Torner et al. 2004; Roselli et al. 2008). Ben-Jonathan and coworkers have provided persuasive evidence that prolactin is also an adipokine (Brandebourg et al. 2007). These data are of particular interest because prolactin gene expression in rodent adipose tissue is thought to be negligible, whereas production in human fat and adipocytes is well described (Hugo et al. 2008). It is clear that prolactin is secreted from adipocytes and that pituitary and adipose prolactin proteins are identical. Prolactin receptors were also identified in adipose tissue and considerable evidence exists that circulating prolactin, of *pituitary* origin, participates in adipose tissue function through prolactin receptor signaling. For example, prolactin affects adipogenesis, lipolysis, and release of adipokines such as leptin and interleukin 6 (Hugo et al. 2008). Thus it seems highly likely that locally produced adipose prolactin could serve as an autocrine and/or paracrine factor (Ben-Jonathan et al. 2008).

Explants of visceral, but not subcutaneous, adipose tissue obtained from obese patients secreted high levels of prolactin over several days (Hugo et al. 2008). This was not the case in non-obese explants where elevated secretion from both depots was essentially the same. Adipocyte cultures, derived from mature, non-obese, subcutaneous adipose tissue, also released high levels of prolactin. This suggests that adipocytes might be the primary source of prolactin expression, though this would not exclude contributions from other cell types (e.g., preadipocytes, fibroblasts) which themselves could provide other factors capable of regulating prolactin secretion.

A critical development in these studies followed the establishment of a human adipocyte cell line, LS14, that secretes prolactin along with other prototypical adipokines such as leptin and adiponectin (Hugo et al. 2006). LS14 cells also expressed the prolactin receptor and angiotensinogen (see Sect. 23.3). In general, gene expression profiles appeared similar to those seen in primary adipocytes with the exception of tumor necrosis factor α and interleukin 6, which were markedly downregulated following differentiation. In fact, interleukin 6 mRNA was dose-dependently inhibited by exogenous prolactin. In addition, insulin, but not IGF-1, dose-dependently inhibited both prolactin release and expression. Similar results were obtained from human differentiated primary subcutaneous adipocytes (Hugo et al. 2008). Further investigations into the control of prolactin expression in LS14 cells, especially following treatment with tumor necrosis factor α and β, and forskolin, revealed differences between differentiated and non-differentiated adipocytes. Several drugs that normally increase cyclic adenosine monophosphate (cAMP) levels, such as isoproterenol and epinephrine, successfully elevated prolactin gene expression and prolactin release from preadipocytes (McFarland Mancini et al. 2006). Of particular interest is the recent demonstration that adipocyte prolactin release is regulated by dopamine, just as in the anterior pituitary (Borcherding et al. 2009). These authors demonstrated the presence of dopamine receptor mRNAs in human visceral, subcutaneous and breast adipose tissues, and in mature adipocytes. Moreover, prolactin secretion from adipose explants and differentiated adipocytes was inhibited by dopamine receptor 2 (D2R) and 4 agonists.

In summary, prolactin appears to be an adipokine and its expression and release from adipocytes is regulated by obesity, insulin, and biogenic amines. Prolactin production by adipose tissue might also be depot specific. Progress has been made in delineating some of the signaling pathways, and the role of the prolactin gene promoter, in controlling adipose tissue prolactin release. A fundamental question

remains to be answered: What is the purpose of local prolactin release from adipocytes when adipose tissue is already exposed to high levels of pituitary-derived prolactin in the circulation? Hugo et al. (2008) estimated that adipocyte secretion of prolactin was 4–5 orders of magnitude *lower* than that seen from pituitary gland, implying that adipose contribution to *circulating* prolactin is probably negligible. They also speculated that low levels of prolactin released from adipocytes are likely to be bound by connective tissue heparin sulphate proteoglycans and held in the vicinity of adipocyte prolactin receptors, increasing local concentrations and the likelihood that prolactin acts in a paracrine/autocrine fashion. Further studies are needed to examine possible interactions between adipocyte prolactin expression and other hormones, such as glucocorticoids, that are known to influence glucose metabolism, lipogenesis and lipolysis. Local homeostatic control of adipose prolactin may be important in conditions where pituitary prolactin secretion is low. This would, in turn, imply that pituitary prolactin secretion should be regulated differently to prolactin release from adipocytes. Indeed, at least one notable difference lies in the response to estrogen and progesterone. As noted by Zinger et al., the superdistal prolactin promoter in adipose tissue is unaffected by estrogen and progesterone whereas the proximal promoter in pituitary is stimulated by estrogens (Zinger et al. 2003). On the other hand, dopamine agonists *inhibit* prolactin secretion from adipose tissue just as it is from pituitary gland. The possibility that adipocyte prolactin expression might be specifically targeted for therapeutic purposes in the treatment of obesity and diabetes exists.

23.7 Expression of Atrial Natriuretic Peptide in Adipose Tissue

Atrial natriuretic peptide is another prototypical *ectopic* peptide. Originally discovered as a polypeptide secreted from cardiac muscle cells, it is implicated not only in the control of cardiovascular, renal, endocrine, and skeletal homeostasis (McGrath et al. 2005; Gardner et al. 2007), but is also expressed in several brain sites including cortex and hypothalamus (Wiggins et al. 2003). It is now clear that atrial natriuretic peptide is a physiological regulator of human and primate, but not rodent, adipocyte lipolysis (Sengenes et al. 2002; Lafontan et al. 2008), acting through the atrial natriuretic peptide receptor type A and the guanylyl cyclase/cGMP system (Nishikimi et al. 2009). Garruti and coworkers postulated the presence of atrial natriuretic peptide expression in human fat cells and employed several tissue preparations to confirm this hypothesis. Atrial natriuretic peptide gene expression was observed in visceral and subcutaneous samples of fat tissue obtained from obese patients (Garruti et al. 2007). In addition, they determined that primary human preadipocytes, and an immortal human preadipocyte cell line (*Chub-S7*; derived from human subcutaneous fat tissue), also expressed atrial natriuretic peptide. Immunofluorescence studies employing a specific antiserum for pro-atrial natriuretic peptide revealed the presence of atrial natriuretic peptide-like immunoreactivity in Chub-S7 cells, thus confirming the expression and production of atrial natriuretic peptide protein. Further, using a highly sensitive radioimmunoassay, they demonstrated that Chub-S7 and primary preadipocytes also secreted pro-atrial natriuretic peptide/atrial natriuretic peptide into the culture medium at concentrations similar to those found in the circulation. Since the authors demonstrated the presence of the protease necessary for conversion of pro-atrial natriuretic peptide to atrial natriuretic peptide, they speculated that the secreted protein was probably atrial natriuretic peptide. In preliminary experiments to investigate possible atrial natriuretic peptide-mediated signaling pathways, the PPAR-γ agonist rosiglitazone increased atrial natriuretic peptide secretion from both types of preadipocyte cultures.

As intimated elsewhere for other hormones in this chapter, adipocytes possess an autocrine/paracrine regulatory system involving atrial natriuretic peptide. Further exploration into the significance of this phenomenon is required, and especially to seek an answer to why atrial natriuretic peptide receptors

on adipose cells should be exposed to both systemic and locally produced atrial natriuretic peptide. Intuitively one might suppose that the local atrial natriuretic peptide system could be especially important in situations where cardiac atrial natriuretic peptide secretion is minimal or nonexistent. Also, as described for prolactin (Sect. 23.6), the control of atrial natriuretic peptide gene expression may be different in adipose and cardiac tissue, i.e., in situations where cardiac atrial natriuretic peptide expression is inhibited, the adipose atrial natriuretic peptide gene may be unaffected, so as to preserve local production of atrial natriuretic peptide. Whether this might be therapeutically valuable remains to be determined. This is especially relevant given the known involvement of atrial natriuretic peptide in angiogenesis, an important process that also occurs in adipose tissue (Casco et al. 2002).

23.8 Additional Neuropeptide Gene Transcripts Identified in Adipose Tissue

Table 23.1 lists further examples of neuropeptide gene transcripts in adipose tissue. In general, gene expression was detected by microarray technology or by reverse transcriptase-polymerase chain reaction (RT-PCR). Yang et al. (2003) identified numerous unusual transcripts in adipose tissue, including expression of several peptides normally considered to be hypothalamic neuropeptides, and their receptors. Although these data suggest the existence of additional adipose-derived neuropeptides, a word of caution has been offered by Trayhurn and Wood (2004). These authors, using conventional RT-PCR, were unsuccessful in their search for some of these transcripts. This discrepancy might reflect the different techniques used (i.e., microarray vs RT-PCR) or could be due to different experimental preparations (cultured cells vs rodent tissue). Moreover, Yang et al. (2003) performed additional experiments with in situ hybridization to confirm some of their microarray results. Nevertheless, all of these potential new adipokines require further study in terms of protein identification and whether they are expressed and secreted by adipocytes.

Solid evidence is also available for nesfatin-1 and IGF-1 as potential adipokines. Nesfatin-1 was originally identified as a satiety molecule in rat hypothalamus (Oh et al. 2006) and the protein found in many brain regions (Foo et al. 2008). However, recent studies by Ramanjaneya et al. (2009) provided firm evidence, using RT-PCR and Western blotting, that nesfatin-1 is highly expressed in human and rodent adipose tissue, and nesfatin-1 is secreted from mouse adipocytes in culture during the differentiation of preadipocytes (Ramanjaneya et al. 2009). Adipose gene expression is also upregulated in mouse models of obesity and in mice given a high-fat diet. There is also some evidence that expression of nesfatin-1 is regulated by insulin, dexamethasone, and tumor necrosis factor α, strongly suggesting that nesfatin-1 is a new adipokine.

Insulin-like growth factor 1 (IGF-1) is also a prototypical *ectopic* peptide. Thought of as an endocrine hormone, IGF-1 is secreted predominantly by the liver. However, it is a well-described

Table 23.1 Additional neuropeptide gene transcripts in adipose tissue

Galanin, Orexin, Neurotensin	
MCH, CCK, CART, Urocortin	
Ghrelin	Yang et al. (2003)
Nesfatin-1	Ramanjaneya et al. (2009)
Chemerin	MacDougald and Burant (2007)
IGF-1	Fischer-Posovszky et al. (2004)

MCH melanin concentrating hormone, *CCK* cholecystokinin, *CART* cocaine and amphetamine regulated transcript, *IGF-1* insulin like growth factor 1

brain-derived neurotrophin that acts on central IGF-1 receptors (Aguado et al. 1993; Sonntag et al. 1999). In addition, IGF-1 promotes survival of adipocytes in culture by inhibiting apoptosis, but it is now evident that human adipocytes express and secrete IGF-1 (Fischer-Posovszky et al. 2004). These authors demonstrated that inhibition of the autocrine/paracrine action of IGF-1 dramatically sensitized human fat cells to ligand-induced apoptosis. Thus human adipocytes protect themselves from cell death through an autocrine/paracrine effect of IGF-1. This knowledge offers a potential therapeutic route to a reduction of fat mass.

Chemerin is a newly described adipokine that is also widely expressed in the brain, including the hypothalamus (Goralski et al. 2007; KB Goralski, Personal Communication). The involvement of chemerin in adipocyte function seems to be complex, involving adipogenesis, lipolysis and the inflammatory response that accompanies metabolic stress (MacDougald and Burant 2007).

23.9 Conclusions and Speculations

In little more than a decade, the perceived biological role of adipose tissue has grown in stature from a mere energy storage system to its current acceptance as a complex multifunctional endocrine organ, and fat is now known to secrete multiple adipokines. The present review provides evidence that certain brain and pituitary peptides, such as NPY, NGF, prolactin, and atrial natriuretic peptide, are also expressed and released by adipose tissue. In their paper on adipokines, Trayhurn and Woods (2004) speculated that if such neuropeptides were confirmed as adipokines, then: "the adipocyte is even more remarkable as a secretory cell than currently envisaged; indeed, it would be a veritable powerhouse of neuroendocrine signals." Gene microarray and proteomic analyses indicate that there are likely to be many more adipokines waiting to be discovered. The amazing complexity of cell signaling within adipose tissue suggests that a high degree of redundancy is likely to exist. At present, we can only speculate that the signaling cascades and communication networks present in adipose tissue are required to be sufficiently robust that the loss of individual entities can readily be accommodated. The application of this knowledge to an understanding of adipose physiology, and especially to pathophysiology, might only be achieved through a systems biology approach (Breitling 2009). We can also assume that the integration of multilayered signaling components in adipose tissue, with local and endocrine feedback loops, might constitute site-specific functions of various adipose tissue depots. There is no doubt that there are adipose depot-specific differences in gene expression profiles and that these are modified by, for example, type 2 diabetes (Vidal 2001; Yang et al. 2008b). The *ectopic neuropeptides* discussed in this review could represent an additional signaling device that reflects, or responds to, neuroendocrine activity in the hypothalamic/pituitary system. Schäffler and colleagues have already proposed the existence of "adipotropins"; i.e., circulating pituitary and hypothalamic hormones that act directly on adipocytes via a hypothalamic-pituitary-adipose axis (see Fig. 23.5) (Schaffler et al. 2006). Given that the pituitary hormone prolactin – described by Schaffler et al. (2006) as an adipotropin – is released from adipose tissue (Sect. 23.6), it is possible that other adipotropins, such as growth hormone and vasopressin, could also be expressed there.

A fundamental issue that this review has not satisfactorily confronted is why adipose tissue should possess autocrine signaling devices for secretory products that are already present in the circulation. Put another way, what could be the purpose of prolactin secreted from adipose tissue when this hormone is already present in high concentration in the blood? We posed a similar question with respect to circulating leptin, which is expressed in the pituitary gland even though the
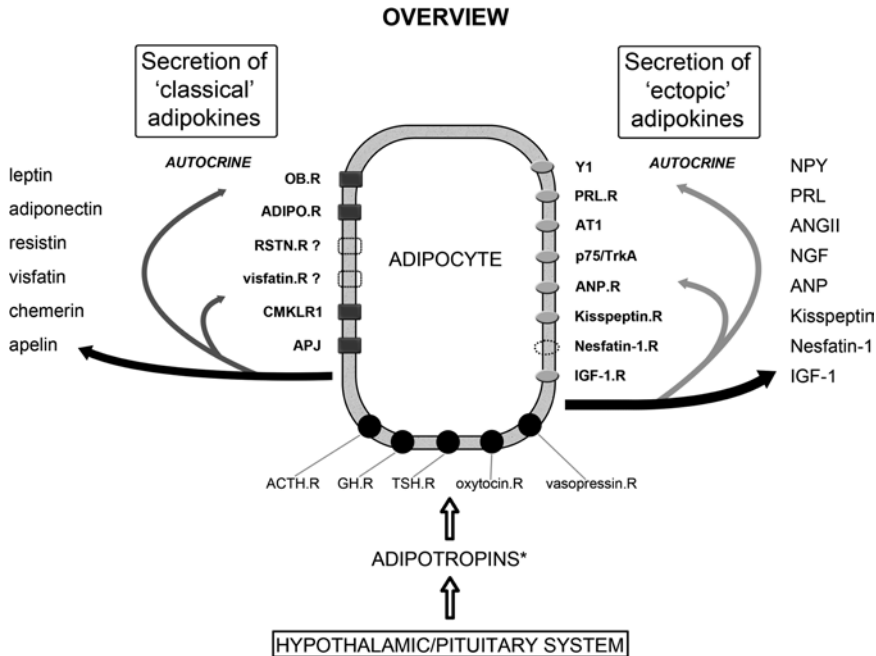
Fig. 23.5 Overview of the possible major contributions of locally derived neuropeptides to adipocyte function. On the *left* of the figure is a partial list of *adipokines*, such as leptin and resistin, that we have termed "classical." These adipokines are secreted into the systemic circulation but may also exert autocrine activity. On the right are some neuropeptides, and their receptors, now found to be produced by adipose tissue, that are commonly regarded to be of brain, or non-adipose, origin. We provide evidence that this latter group has profound autocrine effects on adipocytes, though they are unlikely to contribute to blood levels. *We also illustrate peptide hormone input from several circulating pituitary hormones (*Adipotropins*), as described by Schaffler et al. (2006). At present, there is no evidence that these pituitary hormones are also expressed in adipose tissue

pituitary is normally exposed to systemic leptin (Wilkinson et al. 2007). We speculated that pituitary-derived leptin could "tune" the pituitary-specific leptin signaling pathway to maintain responsiveness, particularly when circulating levels of fat-derived leptin are reduced, for example, during food restriction. A similar concept has been proposed for localized renin-angiotensin systems (see Sect. 23.3), and for adipose *kiss1*/kisspeptin (Sect. 23.2). In the latter case, we noted that *kiss1* gene expression is regulated differently in adipose tissue compared to the hypothalamus, i.e., following food restriction we demonstrated that *kiss1* mRNA was reduced in hypothalamic tissue but increased in fat (Fig. 23.1). Prolactin gene expression is also regulated differently in adipose tissue versus pituitary gland (Sect. 23.6). Finally, we note that there is a logical parallel between what we have termed *ectopic neuropeptides* and the well-described synthesis of steroid hormones in traditional "target" tissues (Schmidt et al. 2008). For example, glucocorticoids, the accepted signaling products of the hypothalamic pituitary adrenal axis, are also synthesized in the immune system where they are hypothesized to play an important role in thymic homeostasis (Pazirandeh et al. 2005). Analogous to the local renin-angiotensin system described in Sect. 23.3, the thymus employs a complete CRF – adrenocorticotropin hormone (ACTH) – cortisol system that Schmidt et al. (2008) describe as a miniature hypothalamic pituitary adrenal "homolog." We suggest that this homolog concept can be profitably applied to probing the function of ectopic adipose neuropeptides. The practical means to do this are available and site-specific gene knockouts, or gene silencing techniques, will provide a clearer understanding of the role of neuropeptides in adipose tissue.

23.10 Application to Other Areas of Health and Disease

Although the study of adipose-derived neuropeptides is in its infancy, it seems likely that in the coming years the potential roles for these atypical neuropeptides in adipose tissue will be uncovered. Although it may be premature to speculate as to the exact purpose of each of these genes within adipocytes, and their potential impacts on health and disease, the evidence presently available has clearly demonstrated that many of these peptides are capable of influencing a variety of adipocyte-specific processes including modifications to energy metabolism through the induction of lipogenesis or lipolysis, as well as impacting adipogenesis. Further, many of these neuropeptides also appear to exert an effect on local gene expression, and that their regulation is tightly associated with both inflammatory (e.g., lipopolysaccharide and interleukin 6) and anti-inflammatory (e.g., PPARγ ligands) suggesting that locally produced neuropeptides may offer an even further layer of control in the complex inflammatory processes that have become firmly associated with obesity. We also speculate that neuropeptide expression and release from adipocytes may contribute to the developmental "tuning" of local energy metabolism and could have lifelong effects on adipocyte function.

The discovery of *ectopic neuropeptides* in adipose tissue not only enhances our understanding of the complex neuroendocrine signaling in adipose tissue, but will perhaps lead to the identification of unique targets for new therapies. For example, bromocriptine, which is traditionally used to treat hyperprolactinemia, is now emerging as a novel treatment for the metabolic syndrome. As we noted in Sect. 23.6, dopamine agonists inhibit the release of prolactin from adipocytes and Kok et al. (2006) report that bromocriptine may stimulate lipolysis in obese women (Kok et al. 2006).

The diversity of these adipokines, and their tissue-specific effects, will also offer an exciting area for developing tissue target-based therapies to avoid undesirable side effects. Needless to say, many avenues of discovery have now been opened, and as further progress and discoveries are made, it seems likely that adipose-derived neuropeptides may be found to impact local development and energy metabolism. Perhaps adipose-derived neuropeptides may even prove to be unique targets that can be harnessed to control and prevent some of the devastating consequences that are now known to be associated with obesity, including the development of cardiovascular disease, diabetes, and perhaps even fertility.

Summary Points

- Adipose tissue is now known to secrete a large number of signaling molecules called *adipokines*.
- We have shown, for the first time, that several of these adipokines are also made in the brain and by pituitary cells. Such neuropeptides are more appropriately termed *cephalokines*.
- We now hypothesize that the converse of this would also be true: that some neuropeptides, normally considered to be of specific brain or pituitary origin, should be expressed in adipose tissue.
- In this chapter, we have outlined fairly solid evidence for gene expression of the following peptide systems, and their receptors, in adipose tissue: *Kiss1*/kisspeptin, renin-angiotensin system/angiotensin II, neuropeptide Y (NPY), nerve growth factor (NGF), prolactin, and atrial natriuretic peptide.
- More limited evidence exists for many other peptides, including IGF-1, nesfatin-1, galanin, orexin, neurotensin, cholecystokinin, and ghrelin.
- Using *kiss1* as an example, we have sought answers to the following questions as a means to establish possible physiological/pathological function(s) to these potential new adipokines:
- Are kisspeptins secreted from adipose tissue?
- In which adipose tissue cell type(s) is the gene expressed (i.e., mature adipocytes versus stromal vascular cells versus stem cells)?

- How is adipose *kiss1* expression regulated?
- How do adipose tissue cells respond to *autocrine* stimulation with kisspeptins via the G protein coupled receptor 54 (GPR54) receptor, which is also present in adipose tissue?
- Is *kiss1* expressed in human adipose tissue?

Given that high levels of kisspeptins (e.g., of placental origin) have been detected in the circulation, what is the purpose of adipose tissue GPR54 receptors being exposed to both circulating, and locally produced, kisspeptin? We believe that one answer to the latter question is to propose that kisspeptin receptor signalling in adipose tissue might be critical in situations in which systemic, *circulating* levels of peptides are very low, for example, during fasting. Indeed, we have shown that adipose and hypothalamic *kiss1* expression is regulated in opposite directions following fasting.

- Following the discovery of leptin, adipose tissue swiftly became accepted as probably the largest endocrine gland. The present chapter further establishes that adipose tissue is capable of secreting a bewilderingly complex array of neuroendocrine as well as adipokine signals.

Definitions

Adipokines: Also known as *adipocytokines*. Proteins secreted from adipocytes in humans and rodents. Act as signaling molecules within adipose tissue or as systemic hormones. *Leptin*, for example, is the best known adipokine. We all secrete leptin from our fat cells, particularly when we eat. Leptin is thought to give us the feeling of being "full," so that we do not eat too much. In some people, the leptin does not work and as a result they become obese. It may be possible one day to target this system with drugs so as to reduce body weight.

Cephalokines: Adipokines that are expressed in the brain and pituitary gland.

Adipose secretome: The entire body of molecules released (secreted) by adipose tissue, including hormones, adipokines, and lipids. *Proteomic* analysis of the secretome would reveal the number of *protein* hormones or messengers released by adipose tissue.

Polymerase chain reaction (PCR): A common laboratory technique used to amplify and detect very small amounts of DNA. Widely used in medical and biological research laboratories for a variety of applications, including functional analysis of genes, the diagnosis of hereditary disease, and the identification of genetic fingerprints (used in forensic sciences and paternity testing).

Neuropeptide: Neuropeptides are usually small proteins found in brain or nerve tissue. They are released, and act as messengers, by different populations of neurons in the mammalian brain.

Autocrine/paracrine: Paracrine signaling is a form of cell signaling in which cells send chemical messages over short distances to other cells that are located close by ("para" = near). An important distinction is made between paracrine and autocrine signaling since autocrine signaling occurs when a cell releases a message that then acts on itself, i.e., acts on the releasing cell.

Microarrays: Microarray technology enables scientists to estimate, in a single experiment, the expression levels of hundreds or thousands of genes within a cell or tissue. With the aid of a computer, *microarray* analysis can generate a profile of gene expression in specific tissues such as fat.

Gene knockout: A *knockout* mouse is one that is genetically engineered so that one or more genes have been disrupted and rendered nonfunctional. These knockout mice are very important because they can be used to find out what would happen if a gene of interest, such as *angiotensinogen*, is disabled. Then, if the mouse's behavior or physiology changes, researchers can arrive at conclusions as to that gene's probable function.

Key Points

- Several neuropeptides, and their associated receptors, are now known to be expressed in adipose tissue. These neuropeptides may also function as adipokines (see Overview: Fig. 5). This list includes, but is not limited to: *kiss1,* the renin-angiotensin system, NPY, NGF, prolactin, and atrial natriuretic peptide.
- Regulation of fat-derived neuropeptides is different than that in the central nervous system, suggesting a unique role in local adipose tissue function.
- Also, because deposits of adipose tissue are interspersed with many tissues throughout the body (e.g., liver; muscle; heart; bone marrow) they may function as "miniorgans" with specific paracrine effects.
- The possibility exists to specifically target adipocyte expression of neuropeptides for therapeutic purposes, for example, in the treatment of obesity, diabetes, and infertility.

References

Adachi J, Kumar C, Zhang Y, Mann M. Mol Cell Proteomics. 2007;6:1257–73.

Aguado F, Rodrigo J, Cacicedo L, Mellstrom B. J Mol Endocrinol. 1993;11:231–9.

Ahima RS, Antwi DA. Endocrinol Metab Clin North Am. 2008;37:811–23.

Ahima RS, Lazar MA. Mol Endocrinol. 2008;22:1023–31.

Bader M, Ganten D. J Mol Med. 2008;86:615–21.

Ben-Jonathan N, LaPensee CR, LaPensee EW. Endocr Rev. 2008;29:1–41.

Borcherding DC, Hugo ER, Brandebourg TD, Ben-Jonathan N. Proceedings of the 91st annual meeting endocrine society abstract, Washington, 2009, pp. 3–359.

Brandebourg T, Hugo E, Ben-Jonathan N. Diabetes Obes Metab. 2007;9:464–76.

Breitling R. Trends Endocrinol Metab. 2009;20:1–7.

Brown RE, Imran SA, Ur E, Wilkinson M. Mol Cell Endocrinol. 2008;281:64–72.

Bullo M, Peeraully MR, Trayhurn P, Folch J, Salas-Salvado J. Eur J Endocrinol. 2007;157:303–10.

Casco VH, Veinot JP, Kuroski de Bold ML, Masters RG, Stevenson MM, de Bold AJ. J Histochem Cytochem. 2002;50:799–809.

Cassis LA, English VL, Bharadwaj K, Boustany CM. Endocrinology. 2004;145:169–74.

Castellano JM, Gaytan M, Roa J, Vigo E, Navarro VM, Bellido C, et al. Endocrinology. 2006;147:4852–62.

Castellano JM, Roa J, Luque RM, Dieguez C, Aguilar E, Pinilla L, et al. Peptides. 2009;30:139–45.

Catalan V, Gomez-Ambrosi J, Rodriguez A, Salvador J, Fruhbeck G. Expert Opin Pharmacother. 2009;10:239–54.

Edwardson JA, Hough CA. J Endocrinol. 1975;65:99–107.

Eikelis N, Esler M. Exp Physiol. 2005;90:673–82.

Engeli S, Schling P, Gorzelniak K, Boschmann M, Janke J, Ailhaud G, et al. Int J Biochem Cell Biol. 2003;35:807–25.

Fischer-Posovszky P, Tornqvist H, Debatin KM, Wabitsch M. Endocrinology. 2004;145:1849–59.

Foo KS, Brismar H, Broberger C. Neuroscience. 2008;156:563–79.

Fowler JD, Krueth SB, Bernlohr DA, Katz SA. Am J Physiol Endocrinol Metab. 2009;296:E343–50.

Gardner DG, Chen S, Glenn DJ, Grigsby CL. Hypertension. 2007;49:419–26.

Garruti G, Giusti V, Nussberger J, Darimont C, Verdumo C, Amstutz C, et al. Obesity (Silver Spring). 2007;15:2181–9.

Goffin V, Binart N, Touraine P, Kelly PA. Annu Rev Physiol. 2002;64:47–67.

Gomez-Ambrosi J, Catalan V, Diez-Caballero A, Martinez-Cruz LA, Gil MJ, Garcia-Foncillas J, et al. FASEB J. 2004;18:215–7.

Goralski KB, McCarthy TC, Hanniman EA, Zabel BA, Butcher EC, Parlee SD, et al. J Biol Chem. 2007;282:28175–88.

Halberg N, Wernstedt-Asterholm I, Scherer PE. Endocrinol Metab Clin North Am. 2008;37:753–68. x-xi.

Hansen-Algenstaedt N, Algenstaedt P, Schaefer C, Hamann A, Wolfram L, Cingoz G, et al. Histochem Cell Biol. 2006;125:637–49.

Hauge-Evans AC, Richardson CC, Milne HM, Christie MR, Persaud SJ, Jones PM. Diabetologia. 2006;49:2131–5.

Horikoshi Y, Matsumoto H, Takatsu Y, Ohtaki T, Kitada C, Usuki S, et al. J Clin Endocrinol Metab. 2003;88:914–9.

Hugo ER, Brandebourg TD, Comstock CE, Gersin KS, Sussman JJ, Ben-Jonathan N. Endocrinology. 2006;147:306–13.

Hugo ER, Borcherding DC, Gersin KS, Loftus J, Ben-Jonathan N. J Clin Endocrinol Metab. 2008;93:4006–12.

Jones BH, Standridge MK, Taylor JW, Moustaid N. Am J Physiol. 1997;273:R236–42.

Kakui N, Kitamura K. Endocrinology. 2007;148:2854–62.

Kalra SP, Kalra PS. Neuropeptides. 2004;38:201–11.

Kalra SP, Dube MG, Pu S, Xu B, Horvath TL, Kalra PS. Endocr Rev. 1999;20:68–100.

Kamiji MM, Inui A. Endocr Rev. 2007;28:664–84.

Katagiri F, Nagai K, Kida A, Tomita K, Oishi S, Takeyama M, et al. Oncol Rep. 2009;21:815–9.

Kim S, Soltani-Bejnood M, Quignard-Boulange A, Massiera F, Teboul M, Ailhaud G, et al. J Biomed Biotechnol. 2006;2006:27012.

Kohlstedt K, Gershome C, Trouvain C, Hofmann WK, Fichtlscherer S, Fleming I. Mol Pharmacol. 2009;75:685–92.

Kok P, Roelfsema F, Frolich M, van Pelt J, Stokkel MP, Meinders AE, et al. Am J Physiol Endocrinol Metab. 2006;291:E1038–43.

Kos K, Harte AL, James S, Snead DR, O'Hare JP, McTernan PG, et al. Am J Physiol Endocrinol Metab. 2007;293:E1335–40.

Kuo LE, Kitlinska JB, Tilan JU, Li L, Baker SB, Johnson MD, et al. Nat Med. 2007;13:803–11.

Lafontan M, Moro C, Berlan M, Crampes F, Sengenes C, Galitzky J. Trends Endocrinol Metab. 2008;19:130–7.

Lim G, Wang S, Zhang Y, Tian Y, Mao J. J Clin Invest. 2009;119:295–304.

Luque RM, Kineman RD, Tena-Sempere M. Endocrinology. 2007;148:4601–11.

MacDougald OA, Burant CF. Cell Metab. 2007;6:159–61.

Mallow H, Trindl A, Loffler G. Horm Metab Res. 2000;32:500–3.

Manneras L, Cajander S, Holmang A, Seleskovic Z, Lystig T, Lonn M, et al. Endocrinology. 2007;148:3781–91.

Massiera F, Bloch-Faure M, Ceiler D, Murakami K, Fukamizu A, Gasc JM, et al. FASEB J. 2001;15:2727–9.

McFarland-Mancini M, Hugo E, Loftus J, Ben-Jonathan N. Biochem Biophys Res Commun. 2006;344:9–16.

McGrath MF, de Bold ML, de Bold AJ. Trends Endocrinol Metab. 2005;16:469–77.

Morris BJ. J Comp Neurol. 1989;290:358–68.

Muir AI, Chamberlain L, Elshourbagy NA, Michalovich D, Moore DJ, Calamari A, et al. J Biol Chem. 2001;276:28969–75.

Mukherjee SP, Mukherjee C. Biochem Pharmacol. 1982;31:3163–72.

Ng TB, Wong CM. Comp Biochem Physiol B. 1985;81:687–9.

Nishikimi T, Iemura-Inaba C, Akimoto K, Ishikawa K, Koshikawa S, Matsuoka H. Regul Pept. 2009;153:56–63.

Nisoli E, Tonello C, Benarese M, Liberini P, Carruba MO. Endocrinology. 1996;137:495–503.

Nisoli E, Tonello C, Carruba MO. Neurosci Lett. 1998;246:5–8.

Oh IS, Shimizu H, Satoh T, Okada S, Adachi S, Inoue K, et al. Nature. 2006;443:709–12.

Paul M, Poyan Mehr A, Kreutz R. Physiol Rev. 2006;86:747–803.

Pazirandeh A, Jondal M, Okret S. Endocrinology. 2005;146:2501–7.

Peeraully MR, Jenkins JR, Trayhurn P. Am J Physiol Endocrinol Metab. 2004;287:E331–9.

Phillips MI, de Oliveira EM. J Mol Med. 2008;86:715–22.

Quaynor S, Hu L, Leung PK, Feng H, Mores N, Krsmanovic LZ, et al. Mol Endocrinol. 2007;21:3062–70.

Ramanjaneya M, Chen J, Brown JEP, Tan BK, Patel S, Lehnert H, Randeva HS. Proceedings of the 91st annual meeting of the endocrine society abstract OR09-3, Washington, 2009.

Richard N, Corvaisier S, Camacho E, Kottler ML. Peptides. 2009;30:123–9.

Roa J, Aguilar E, Dieguez C, Pinilla L, Tena-Sempere M. Front Neuroendocrinol. 2008;29:48–69.

Roselli CE, Bocklandt S, Stadelman HL, Wadsworth T, Vilain E, Stormshak F. Neuroendocrinology. 2008;87:206–15.

Ryan VH, German AJ, Wood IS, Hunter L, Morris P, Trayhurn P. Horm Metab Res. 2008;40:861–8.

Schaffler A, Scholmerich J, Buechler C. Nat Clin Pract Endocrinol Metab. 2006;2:374–83.

Schling P, Mallow H, Trindl A, Loffler G. Int J Obes Relat Metab Disord. 1999;23:336–41.

Schmidt KL, Pradhan DS, Shah AH, Charlier TD, Chin EH, Soma KK. Gen Comp Endocrinol. 2008;157:266–74.

Sengenes C, Zakaroff-Girard A, Moulin A, Berlan M, Bouloumie A, Lafontan M, et al. Am J Physiol Regul Integr Comp Physiol. 2002;283:R257–65.

Smith JT. Brain Res Rev. 2008;57:288–98.

Sonntag WE, Lynch CD, Bennett SA, Khan AS, Thornton PL, Cooney PT, et al. Neuroscience. 1999;88:269–79.

Torner L, Maloumby R, Nava G, Aranda J, Clapp C, Neumann ID. Eur J Neurosci. 2004;19:1601–8.

Trayhurn P, Wood IS. Br J Nutr. 2004;92:347–55.

Valet P, Berlan M, Beauville M, Crampes F, Montastruc JL, Lafontan M. J Clin Invest. 1990;85:291–5.

Van Harmelen V, Ariapart P, Hoffstedt J, Lundkvist I, Bringman S, Arner P. Obes Res. 2000;8:337–41.

Vidal H. Ann Med. 2001;33:547–55.

Wade GN, Schneider JE, Li HY. Am J Physiol. 1996;270:E1–19.

Wang B, Jenkins JR, Trayhurn P. Am J Physiol Endocrinol Metab. 2005;288:E731–40.

Wiggins AK, Shen PJ, Gundlach AL. Neuroscience. 2003;118:715–26.

Wilkinson M, Brown R, Imran SA, Ur E. Neuroendocrinology. 2007;86:191–209.

Yang YS, Song HD, Li RY, Zhou LB, Zhu ZD, Hu RM, et al. Biochem Biophys Res Commun. 2003;300:839–46.

Yang K, Guan H, Arany E, Hill DJ, Cao X. FASEB J. 2008a;22:2452–64.

Yang YK, Chen M, Clements RH, Abrams GA, Aprahamian CJ, Harmon CM. Cell Physiol Biochem. 2008b;22:531–8.

Zinger M, McFarland M, Ben-Jonathan N. J Clin Endocrinol Metab. 2003;88:689–96.

Chapter 24
Orexigenic Hypothalamic Peptides Behavior and Feeding

Jon F. Davis, Derrick L. Choi, and Stephen C. Benoit

24.1 Introduction

The primary focus of this chapter is to understand better how peptides produced within hypothalamic nuclei act to influence behavior and feeding. In particular, this chapter will focus on peptides that are "orexigenic" which act to increase feeding behavior.

To date there are two distinct regions within the hypothalamus that produce orexigenic peptides; the Arcuate nucleus (Arc) located in the mediobasal hypothalamus and the lateral hypothalamus (LH) located adjacent to the third ventricle which spans almost the entire length of the hypothalamus. The traditional contention regarding orexigenic peptide function ascribed that peptides produced within the Arc & LH exerted their effects on feeding through acting within local hypothalamic centers, with a major emphasis on the LH. These ideas were borne from observations that administration of orexigenic peptides into the neighboring third ventricle produced robust increases in food intake in addition to altering the activation and gene expression profiles of feeding peptides in the hypothalamus. However, reports over the last decade indicate that orexigenic peptides not only act within hypothalamic centers to regulate food intake but are also capable of affecting feeding through their actions at extra-hypothalamic centers, namely, within the brain's endogenous reward circuitry. This observation not only expanded the complexity of feeding behavior but also indicated that the behavior of feeding itself could be manifested through reward processing. In addition, studies from the field of addiction biology now indicate that orexigenic peptides are also capable of modulating drug taking behavior. Thus, to begin our discussion of how orexigenic peptides regulate behavior and feeding, it is first important to gain an understanding of rewarding behavior and the circuitry which control it.

Rewarding behaviors include three basic functional components: (1) they induce learning, (2) they produce approach and consummatory behavior, and (3) they induce positive emotions regarding the behavior (Dickinson 1994; Shultz 2004). Thus, reward and learning overlap to produce optimal conditions for obtaining a particular goal/reward. In rodents, rewarding behaviors are controlled by the mesocorticolimbic system (Shultz 1998, 2004; Wise 1978), which originates in the ventral mesencepahalon or ventral tegmental area (VTA). Dopaminergic fibers originating in the VTA send dense projections to the nucleus accumbens (Nacc) as well as the medial wall of the Prefrontal

J.F. Davis (✉)
Department of Psychiatry, University of Cincinnati, Genome Research Institute
Building E, Lab 334, 2170 East Galbraith Road, 45237 Cincinnati, OH, USA
e-mail: Jon.Davis@uc.edu
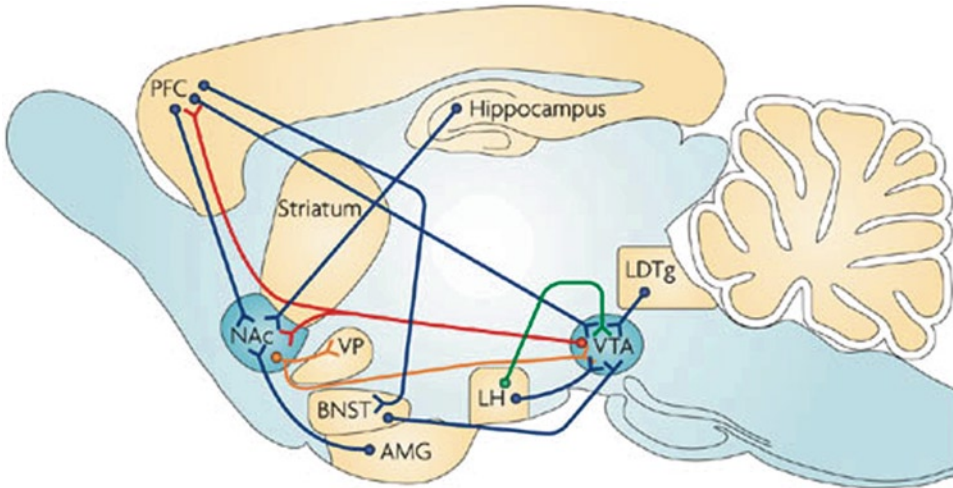
Fig. 24.1 Rat mesolimbic system. Mesolimbic system schematic in the rat adapted from Kauer and Malenka (2007) highlighting the mesolimbic system and its target regions; blue lines indicate glutamatergic projections, red lines indicate dopaminergic projections and green lines indicate orexinergic connections. This figure also highlights the ability of the orexin system, originating in the lateral hypothalamus, to activate ventral tegmental area (*VTA*) neurons and thus activate mesolimbic circuitry

Cortex (mPFC) (Emson and Koob 1978; Fuxe and Hokfelt 1972). The projection of dopamine neurons from the VTA to Nacc comprises the mesolimbic component of this system and the dopamine projection from the VTA to the mPFC make up the mesocortical component of this system. The mPFC along with receiving dopamine input from the VTA sends glutamatergic projections both back to the VTA as well as to the Nacc (Sesack et al. 1989; Sesack and Pickel 1992; Bernedise et al. 1992), thus allowing a cortical interface to be superimposed onto rewarding behaviors. Although it is not the primary focus of this chapter, it should be noted that manipulations of dopamine or glutamate signaling within the mesolimbic system affect many aspects of drug taking including self-administration, relapse, and withdrawal (Fig. 24.1).

Although much of the field of reward neurobiology is focused on unnatural rewards like drugs of abuse, there is now a growing understanding of the novel and shared neural mechanisms involved in natural reward processing like ingestive behaviors (Volkow and Wise 2005). Recently, it was demonstrated that leptin, a well-documented homeostatic regulator of food intake, acts on mesolimbic dopamine neurons in the VTA and regulates reward-related behaviors (Fulton et al. 2006; Hommel et al. 2006). It is believed that the dysregulation of mechanisms like these and the overriding of homeostatic regulators may be significant contributors to the obesity crisis (Berthoud 2004; Volkow and Wise 2005). Food reward behaviors are driven by the hedonic impact and motivational aspects of food intake. On the other hand, they are also very much different from drug reward behaviors in that the reward, food, is a natural necessity for energy homeostasis and survival. The neural mechanisms of food reward are believed to be largely common to those of unnatural rewards, namely, the mesolimbic dopamine pathway (Berridge 1996; Kelley and Berridge 2002; Wise 2004). High-fat food is commonly considered a highly palatable and rewarding food type (Levine et al. 2003) and in many cases, despite metabolic repletion or a state of satiation, animals and humans can still experience high-fat appetite (Zhang et al. 1998; Berthoud et al. 2007). A central hypothesis in addiction biology states that neuroplastic changes as a result of chronic drug use create neuroadaptive changes that further promote the behavior (Nestler 2002). Thus, it is possible that chronic ingestion of high-fat

foods may contribute to adaptations of the central reward pathway to further promote high-fat food reward behaviors and, ultimately, lead to weight gain (Levine et al. 2003). To understand how this might occur, it is important to gain a better understanding of food reward behavior.

24.2 Food Reward

Here we define the term "reward" operationally as behavior reinforced through multiple pairings with rewarding stimuli, i.e. food, or drugs. Food reward in particular can be characterized as a reinforced-learning phenomenon driven by sensory stimulus inputs such that the food elicits positive emotion and is desired independent of homeostatic or metabolic demands (Berthoud 2007). One way reward behavior is modeled in rodents is by using an operant conditioning chamber (Skinner Box) in which a rat can be trained and learn to associate the action of lever-pressing with the acquisition of a reward. The number of lever-presses can be correlated to the animal's motivation or "wanting" of the reward. Evidence to support this correlation in food reward can be seen in the dependence of this behavior on dopamine signaling (Wise and Schwartz 1981). Drug addicts, when attempting to abstain from drug use, often relapse to drug-seeking behavior. This phenomenon is also modeled in a self-administration paradigm, reinstatement following extinction (Shaham et al. 2003), and was first described in Pavlov's original studies, called spontaneous recovery or renewal, using food reinforcements (Pavlov 1928). Recently, studies have "re-adapted" this technique of reinstatement of food reward-seeking in modeling of stress-induced and food-primed relapse to maladaptive eating habits (Nair et al. 2006; Ghitza et al. 2006; 2007). Another model of reward behavior commonly used in studies of reward in drugs of abuse is the conditioned place preference (CPP) paradigm. In this model, a rat is conditioned to associate the environmental cues of its surroundings (unique chamber) with positive reinforcements. A preference to spend more time in a reinforcement-paired chamber is a measure of the rewarding aspects of that reinforcement. Place preference can be acquired in animals conditioned with food rewards (Tzschentke 1998) and is dependent on intact dopamine signaling (Papp 1988). Reinstatement of food-seeking behavior can also be modeled in the CPP procedure (Duarte et al. 2003).

We will now consider, individually, four separate orexigenic hypothalamic peptide systems. Initially, a functional–anatomical description of each neuropeptide system will be discussed. These descriptions will then be followed by a brief description of how each system impacts mesolimbic reward circuitry.

24.3 Neuropeptide Y

Neuropeptide Y (NPY) is a 36 amino acid neuropeptide distributed throughout both the peripheral and central nervous systems. One of the central regions with the highest expression of NPY is the Arcuate nucleus (ARC) of the hypothalamus (Chronwall et al. 1985). NPY is perhaps the best-described anabolic effector peptide in the brain. When injected centrally, NPY is capable of inducing feeding in animals that had been previously sated prior to testing (Clark et al. 1984) suggesting that NPY is a potent meal initiation signal. Although NPY mRNA and peptide are distributed widely throughout the CNS, NPY-containing cell bodies in the ARC are hypothesized to be especially important in the control of food intake (Schwartz et al. 1992). ARC neurons that express NPY directly influence several areas of the brain; however, two major projections to the nearby periventricular nucleus

(PVN) and the lateral hypothalamic area (LHA) have received a significant amount of attention in regard to the regulation of energy balance. For instance, in response to food deprivation, ARC NPYergic neurons respond by synthesizing more NPY mRNA, which is consequently released into the PVN (Kalra et al. 1991; Schwartz et al. 1992) and presumably the LHA as well. Importantly, animals in negative energy balance have low levels of the adiposity hormones insulin and leptin, which normally act to suppress NPY and AgRP expression. Thus, when energy levels are low, this suppression is removed, resulting in elevated NPY mRNA in the ARC. Moreover, local replacement of either insulin or leptin in the vicinity of the ARC normalizes the elevated NPY mRNA in the ARC in fasted animals (Schwartz et al. 1992; Sipols 1992). Hence, the activity of these ARC NPY neurons is under the direct influence of at least two adiposity signals.

Although NPY has been recognized primarily for its ability to influence energy balance, it is also capable of affecting food reinforcement learning. Progressive ratio (PR) responding is one way to measure an animals ability to work for a given reinforcer (Fig. 24.2). In this model, animals are trained to make an operant response (normal to press a lever) in order to achieve a single reinforcer (normally a food pellet of intravenous injection of a drug). Initially, to achieve a reinforcer the animal is required to make a single response; however, using a PR schedule of reinforcement each subsequent reinforcer requires a higher work requirement. When using this model, animals trained to respond for sucrose pellets will respond at significantly greater rates after receiving a central injection of NPY (Brown et al. 1998), suggesting that in addition to initiating feeding behavior, NPY also modulates an animal's motivation to obtain a food reward. The effect of NPY on operant responding is mediated by NPY's action in the perifornical hypothalamus (PFA) as direct application of NPY into the PFA stimulates PR responding (Fig. 24.3) (Brown et al. 1998). Interestingly, NPY positive neurons are also located within brain reward circuits, and these extra-hypothalamic neuronal populations
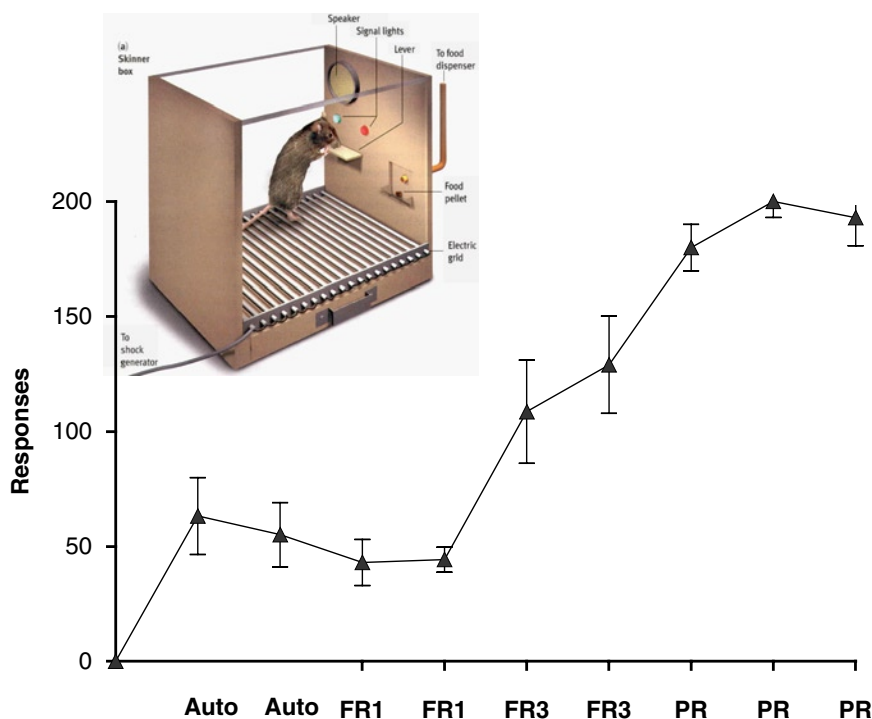
Fig. 24.2 Operant responding in the rat. Figure illustrating instrumental fixed and progressive ratio (*PR*) training across time. Figure also illustrates operant training apparatus with auditory and visual cues

Fig. 24.3 Hypothalamic regulation of food intake. Hypothalamic regulation of food intake figure adapted from Schwartz et al. (1992) illustrating anatomical location of neuropeptide Y/melanocortin neurons, POMC, and orexin neurons. NPY/melanocortin neurons normally promote feeding behavior; however, when energy levels are high, leptin and insulin from the periphery feedback on POMC and melanocortin neurons to negatively regulate feeding behavior
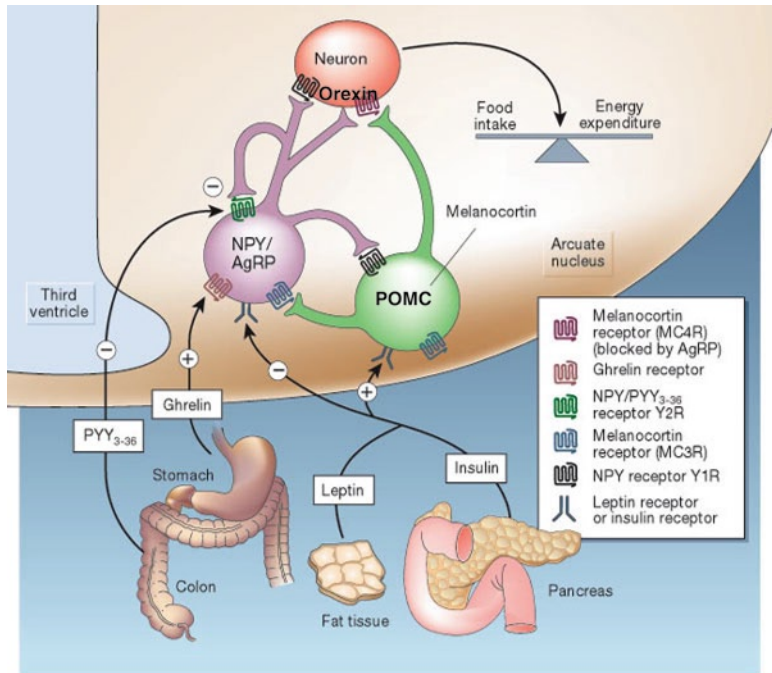
are capable of regulating rewarding behavior. The nucleus accumbens and dorsal striatum are two regions that lie within the brains natural reward circuitry that each contains NPY-positive populations of neurons (Adrian et al. 1993). Importantly, NPY neurons within these regions make neuronal contacts with terminals that express tyrosine hydroxylase (the rate-limiting enzyme for dopamine production) suggesting that once released, NPY may be capable of affecting mesolimbic dopamine tone (Aoki and Pickel 1988). Interestingly, early behavioral pharmacological studies indicated that NPY could impart direct effects on dopaminergic neurocircuitry. For instance, NPY applied directly to the NAcc elicits the formation of a conditioned place preference, an effect that is dependent on intact dopamine signaling (Josselyn and Beninger 1992) suggesting that NPY is capable of effecting rewarding processes through its direct action within mesolimbic neurons. Although it seems plausible that NPY might affect food reinforcement through a similar mechanism, an elegant study by Brown and colleagues (Brown et al. 2000) determined that the effects of NPY on food reinforcement and general reward could be dissociated. In particular, the effect of NPY on food reinforcement is mediated through NPY action on PFA neurons and is dopamine independent, while the effects of NPY on general reward are mediated through both the PFA and NAcc, the later of which is dopamine dependent (Brown et al. 2000). Collectively, these results suggest that NPY is capable of influencing feeding, food-reinforced behavior, and general reward through distinct neural circuits that reside both within and outside the hypothalamus (Fig. 24.4).

24.4 Melanocortins

The hypothalamic melanocortin (MC) system is another central effector system with the ability to exert both positive and negative effects on the control of food intake and energy balance. The evidence for this is multifold: In melanocytes inappropriate expression of agouti-related peptide (AgRP) results in

Fig. 24.4 Regulation of non-homeostatic feeding. This figure adapted from Cota et al. (2006) illustrates the ability of cognitive emotional information processed by the amygdala, hippocampus, and prefrontal cortex as well as reward information processed by the mesolimbic system to interface and override hypothalamic processes that normally mediate homeo-static feeding behavior
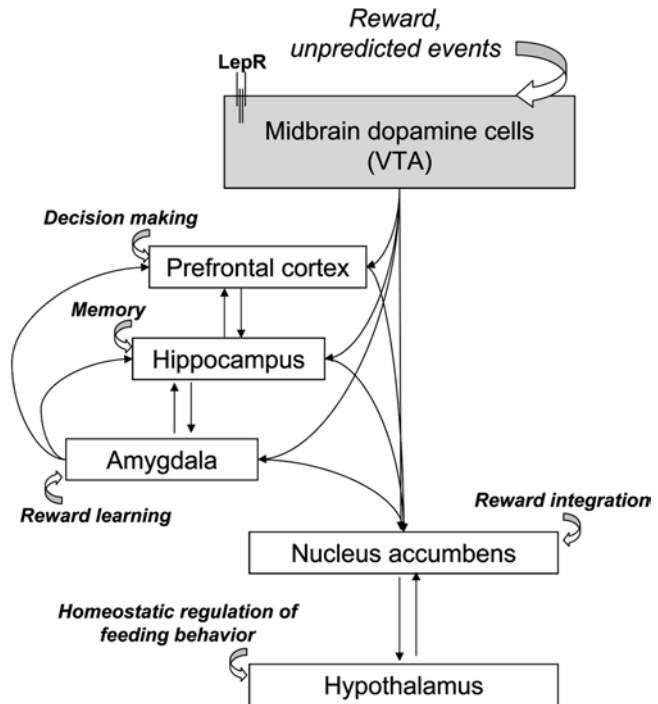
antagonism of alpha-melanocyte-stimulating-hormone (α-MSH) signaling. The resulting phenotype is an obese mouse with a yellow coat. This observation led to the hypothesis that ectopic agouti protein antagonizes central MC receptors involved in food intake. As predicted, agouti is an antagonist of these receptors, which were later reported to be localized to the hypothalamus (Lu et al. 1994). Importantly, an endogenous agouti-related peptide (AgRP) was found to be almost exclusively produced in the ARC and to project to the sites of the hypothalamic MC receptors. Additionally, during periods of negative energy balance, expression of AgRP mRNA is increased while expression of POMC, the precursor molecule to α-MSH, is decreased (Mizuno et al. 1999). During positive energy balance on the other hand, expression of POMC mRNA is increased and AgRP is decreased. Further, POMC-containing neurons also have the ability to respond to the adipocyte hormone, leptin (Cheung et al. 1997; Mountjoy and Wong 1997; Seeley et al. 1997). These findings suggest that the hypothalamic MC system is a likely central target of adipose signals and a mediator of their effects on food intake.

The melanocortin system has been studied extensively for its role in the hypothalamic regulation of food intake. This system is unique in that it possesses both an endogenous agonist and an inverse agonist with opposite effects on feeding behavior. Alpha-melanocyte stimulating hormone (α-MSH) and agouti related peptide (AgRP) are the primary effector peptides of the melanocortin system. Increases in α-MSH serve to decrease food intake while increases in AgRP drive food consumption; under basal conditions, the expression of each peptide is regulated by caloric status as they are down-stream targets of the adiposity hormone leptin (Schwartz et al. 2000). Traditionally, these peptides are thought to mediate their effects by binding specifically to the melanocortin-4 receptor (MC4R) within a distributed set of nuclei in the hypothalamus. However, emerging evidence suggests that this system is capable of mediating effects outside the hypothalamus, specifically within the mesolimbic system (Alvaro et al. 1996; 2003; Hsu et al. 2002, 2005).

The yellow mouse has an autosomally transmitted trait resulting from deletion of DNA 3′ of the coding region of the agouti gene which results in ectopic expression of the agouti protein. In melanocytes, this inappropriate

expression results in antagonism of alpha-melanocyte-stimulating-hormone (α-MSH) signaling. The resulting phenotype is a yellow coat. However, the agouti mouse is obese as well as yellow. This observation led to the hypothesis that ectopic agouti protein antagonizes central MC receptors involved in food intake. Indeed, though melanocortins have been known to influence food intake since the 1980s, it was only during the last decade that their receptors were cloned and localized to the hypothalamus, an important CNS site for the control of energy balance. As predicted, agouti is an antagonist of these receptors. Importantly, an endogenous agouti-related peptide (AgRP) was found to be almost exclusively produced in the ARC and to project to the sites of the hypothalamic MC receptors.

Separate from their expression in hypothalamic nuclei, melanocortin receptors (MC3R and MC4R) are also expressed in brain regions that regulate motivated behaviors (Mountjoy et al. 1994; Alvaro et al. 1996; Adan and Gispen 1997). Importantly, pharmacological studies have outlined functional roles for these receptors in the modulation of drug-taking behavior. Specifically, antagonism of these receptors within nucleus accumbens inhibits operant responding for cocaine, while central agonism of this system augments amphetamine-related behaviors (Cabeza de Vaca and Carr 2002; Hsu et al. 2005). In addition, the expression of the MC4R is increased in the striatum after repeated exposure to psychostimulants and mutant mice lacking this particular receptor fail to display a sensitized locomotor response to repeated cocaine administration (Hsu et al. 2002, 2005). Taken together, these results suggest that the MC system is capable of influencing addictive behaviors.

24.5 Orexin

Orexin, a neurotransmitter produced in small neuronal populations of the LH and perifornical area (PFA), is known to regulate arousal, wakefulness, and feeding behaviors (Sakurai 2007). There are two different orexins: orexin-A (33 amino acids) and orexin-B (28 amino acids). Orexin-A can bind to both orexin-1 receptors and orexin-2 receptors (two orexin G-protein–coupled receptor subtypes) while orexin-B has preferential binding affinity for orexin-2 receptors (Sakurai et al. 1998). Both orexin receptors are widely distributed throughout the central nervous system (Marcus et al. 2001). Due to the lack of an effective and commercially available orexin-2 receptor antagonist, orexin-A signaling on orexin-1 receptors is much better characterized. Intracerebroventricular administration of orexin-A increases food intake (Sakurai et al. 1998) and when given a choice, rats will selectively increase intake of a preferred high-fat diet (Clegg et al. 2002). Furthermore, a selective orexin-1 receptor antagonist, SB-334867, is effective in blocking central orexin-A-induced hyperphagia and behavioral satiety (Rodgers et al. 2001). Orexin neurons receive important orexigenic information from NPY/AgRP neurons of the arcuate nucleus and are thought to be "second order" neurons of a hierarchy in the integration processes involved in regulating food intake (Dube et al. 2000; Yamanaka et al. 2000). However, evidence suggests that orexin neurons may also act as "first order" neurons, sensors of metabolic status, that are modulated by circulating leptin, glucose, and ghrelin levels (Cai et al. 1999; Lopez et al. 2000; Toshinai et al. 2003; Burdakov et al. 2005). Orexin neurons most likely take on both first- and second-order neuron roles in integrating intra- and extra-hypothalamic information to affect consummatory behaviors (Fig. 24.5).

Orexin neurons in the LH have very diverse projections in the CNS, and the VTA is one structure that receives input from these neurons (Peyron et al. 1998; Fadel and Deutch 2002). Additionally, VTA neuron populations express both orexin receptor subtypes (Marcus et al. 2001). It was proposed that plasticity in the VTA could be regulated and enhanced by secondary input neuroadaptations from the orexin system (Scammell and Saper 2005; Carr and Kalivas 2006). Indeed, orexinergic projections to the VTA signal specifically on a majority of dopamine neurons, increase dopaminergic neuron firing rates and activate the mesolimbic pathway (Korotkova et al. 2003; Narita et al. 2006).
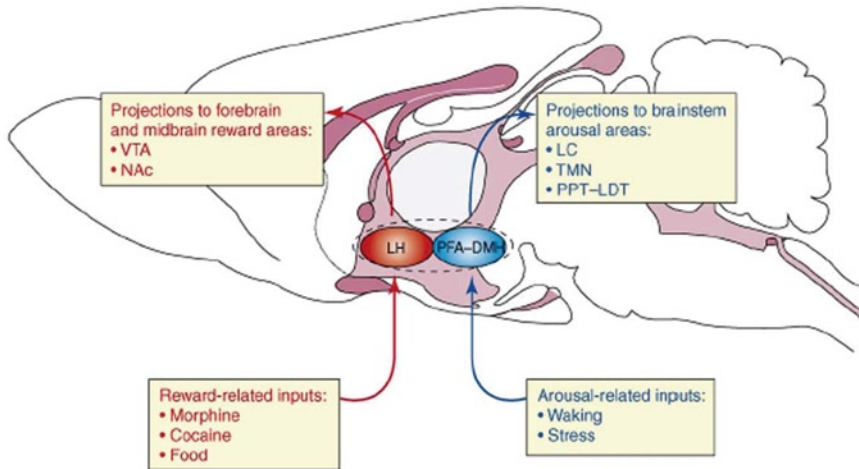
Fig. 24.5 Functional anatomy of the orexin system in rat. This figure adapted from Harris et al., illustrates the functional anatomical connections of the hypothalamic orexin system in the rat brain and its target regions. Orexin-containing neurons in the lateral hypothalamus (*LH*) are activated in response to food- and drug-related cues and project to limbic regions to mediate food and drug reward. Orexin neurons in the perifornical hypothalamus (*PFA*) are activated by general arousal and project to brainstem nuclei important for autonomic responses
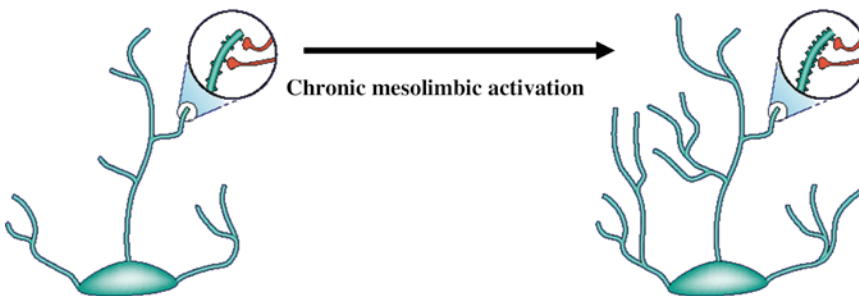
Fig. 24.6 Structural plasticity within a rat mesolimbic neuron. Structural plasticity figure adapted from Nestler (2001) illustrating the ability of mesolimbic neurons to undergo morphological changes in response to repeated activation by abused drugs or food

Importantly, drug-associated cues activate orexin neurons, and central application of orexin-A reinstates drug-seeking behavior (Harris et al. 2005). Similar results were demonstrated using orexin-1 receptor blockade to attenuate operant responding for alcohol and the reinstatement of alcohol- and cocaine-seeking (Boutrel et al. 2005; Lawrence et al. 2006). Moreover, studies in male sexual behavior also suggest a role for orexin in the VTA in natural reward processing (Muschamp et al. 2007). These behavioral implications have set the stage for orexin's role as a functional neuromodulator at the level of the VTA. Furthermore, intra-VTA orexin-1 receptor blockade effectively prevents behavioral sensitization and neurophysiological changes that are typically caused by chronic cocaine use (Borgland et al. 2006). Orexin-A is implicated in lever-pressing for palatable food rewards (Nair et al. 2008; Thorpe et al. 2005) and within the mesolimbic system, is necessary for opioid-induced high fat intake (Zheng et al. 2007). These studies suggest that orexin's effects on reward-related behaviors include not only those of drugs of abuse, but also of natural rewards like food. We hypothesize that orexin neurons may play a critical role in relaying information from the hypothalamus, possibly regarding changes in metabolism and energy status, to extra-hypothalamic areas such as the mesolimbic dopamine pathway to ultimately affect reward-related behaviors (Fig. 24.6).

24.6 Ghrelin

Ghrelin is a 28 amino acid peptide synthesized in both gut and brain that increases food intake (Tschop et al. 2000; Nakazato et al. 2001; Tolle et al. 2002) and gut motility (Masuda et al. 2000). Endogenous ghrelin signals through a seven transmembrane G coupled protein receptor (GHSR) that is present in many brain regions including the hypothalamus, hippocampus, thalamus, and ventral tegmental area (VTA) (Guan et al. 1997; Zigman et al. 2006). Ghrelin is produced in the Arc nucleus of the hypothalamus (Lu et al. 2002) and like other orexigenic hypothalamic peptides, in times of negative energy balance plasma ghrelin levels increase (Tschop et al. 2001) suggesting that ghrelin may act as a meal initiator. Interestingly, plasma ghrelin levels peak before expected meals in both humans and animals (Cummings et al. 2001; Sugino et al. 2002) and drop post prandially (Tschop et al. 2001), suggesting that ghrelin may act as a meal initiation signal. However, one study by Drazen and colleagues suggested that plasma ghrelin increases as a function of meal conditioning rather than being a conditioning factor itself. The implication being pre-prandial rises in plasma ghrelin act to facilitate the consumption, absorption, and metabolism of an expected meal without effecting meal initiation (Drazen et al. 2006). Nevertheless, ghrelin is thought to exert its effects on feeding behavior through activation of NPY and AgRP signaling mechanisms. The evidence for this comes from the observation that NPY/AgRP neurons express ghrelin receptors (Willesen et al. 1999). Furthermore, both NPY and AgRP mRNA levels are increased by ghrelin and NPY/AgRP neurons become activated by central ghrelin administration (Shintani et al. 2001).

However, ghrelin receptors are present in other area of the hypothalamus known to regulate feeding behavior, in particular, the LH. Functional anatomical studies indicate that ghrelin also promotes feeding behavior through activation of LH orexin neurons. A study by Toshinai et al. demonstrated that ghrelin positive axon terminals synapse onto orexin-producing neurons in the LH. In addition, central ghrelin administration induced neuronal activation of LH orexin producing neurons. In the same study, ghrelin-induced feeding was suppressed in animals pretreated with antibodies directed toward orexin A, orexin B, or NPY, suggesting that ghreli's ability to stimulate food intake is achieved through activation of both NPY and orexin signaling (Toshinai et al. 2003).

Apart from its role in stimulating food intake, central ghrelin signaling has also been suggested to act as a "meal preparation" signal. This contention comes from the observation that central ghrelin administration increases glucose utilization in white and brown adipose tissue which resides outside the central nervous system (Theander-Carillo et al. 2006). Additionally, the expression of enzymes associated with fat storage is reduced in ghrelin-deficient mice. When viewed collectively, these data suggest that central ghrelin is capable of modulating peripheral metabolism and that ghrelin may exert these effects on peripheral metabolism prior to meal consumption. Moreover, these data suggest that central ghrelin signaling may be at the top of a neuroendocrine cascade which participates in many aspects of feeding behavior and nutrient storage.

One way in which ghrelin may effect feeding behavior is through its ability to modulate meal anticipation or food-seeking behavior. Ghrelin receptors are present on neurons in the VTA, an area noted for its role in food-seeking behavior. Direct application of ghrlein within the VTA of rodents induces new synapse formation and neuronal activation in dopaminergic neurons. Intra-VTA injection of ghrelin also triggers feeding behavior and increases dopamine turnover in the NAcc (Abizaid et al. 2006). Thus, like many of the other orexigenic peptides discussed in this chapter, ghrelin is also capable of activating brain reward circuitry to promote feeding behavior.

Another way in which ghrelin may affect feeding behavior is through its ability to modulate learned associations after an organism experiences a meal. The primary brain region noted for its ability to modulate memory formation is the hippocampus; ghrelin receptors are present on hippocampal neurons and ghrelin selectively binds its receptors within this region (Diano et al. 2006). Perhaps more importantly, ghrelin acts in the hippocampus to promote new dendritic spine formation, and

prolonged electrical activity. Mutant mice which lack functional ghrelin receptors in the hippocampus display decreased dendritic spines in the CA1 region, a region noted for its role in memory consolidation, as well as spatial learning deficits (Diano et al. 2006). Taken together, these results suggest that ghrelin signaling within the hippocampus is capable of altering learning and potentially the learning associated with meal consumption.

24.7 Applications to Other Areas of Health and Disease

At this point, the ability of orexigenic hypothalamic peptides to affect alternative area of human health will be discussed. This section will focus entirely on the propensity of orexigenic peptides to impact drug addiction, and relapse to addictive drugs.

24.8 Metabolic Status and Drug Intake

For several decades it has been recognized that alterations in metabolic status have dramatic effects on drug taking behavior in animals. In particular, restricting or depriving an animal from feeding augments the reward efficacy as well as the motivation to engage in drug-taking behavior (Bell et al. 1997; Carroll et al. 1984). Since the realization that lateral hypothalamic self-administration (LHSS) was an invaluable model to investigate reward and motivated behaviors, many have speculated that one or more of the peptide systems in the hypothalamus that promote feeding may also impart positive effects on drug taking. Moreover, because many individuals that display disordered eating behavior also abuse drugs, it has been suggested that a common neural mechanism, may contribute to both disordered eating and drug-taking behavior (Kalra et al. 1991). In fact, some have even suggested that a disruption within a hypothalamic neuropeptide system might underlie pathological overfeeding and addictive behaviors (Brown et al. 2000). Over the past decade numerous reports have indicated that apart from promoting feeding behavior, orexigenic hypothalamic neuropeptides can also modulate drug-taking behavior.

24.8.1 NPY and Melanocortins

For example, central replacement of NPY is capable of augmenting the rewarding properties of both opioids and psychostimulants, which are functionally distinct in their method of cellular activation. When delivered into the third ventricle of the brain, NPY increased self-administration of heroin as well as the relapse to heroin in rats that had extinguished heroin taking (Maric et al. 2008). A more recent study from the same group extended these finding by demonstrating that central NPY replacement also augments cocaine self-administration and also the locomotor activating effects of cocaine (Maric et al. 2009). These studies suggest that apart from affecting feeding behavior, and general reward, NPY signaling is also capable of modulating the rewarding properties of recreationally abused drugs. As the NPY and melanocortin system overlap in their anatomical location and both augment feeding behavior, it is perhaps not surprising that melanocortin peptides have also been implicated as regulators of drug-taking behavior.

As mentioned earlier (Sect. 24.4) melanocortin receptors are expressed within mesolimbic circuitry and antagonism of the MC4R within the NAcc with the synthetic antagonist SHU9119 attenuates

self-administration as well as the locomotor activating effects of cocaine (Hsu et al. 2006). Moreover, agonism of the MC system with the synthetic agonist melanotan-II (MTII) augments the rewarding effects of amphetamine (Cabeza de Vaca and Carr 2002) a drug that is very similar to cocaine in regards to its psychostimulant properties. It is important to note here that both antagonism and agonism of the same receptor population seem to have similar effects on psychostimulant taking behavior. This is in contrast to the general notion that peptides that normally stimulate food intake also stimulate drug taking. The synthetic agonist MTII decreases food intake behavior, while the synthetic antagonist/inverse agonist SHU9119 stimulates feeding behavior. It is possible that the differential effects of melanocortin signaling on drug-taking behavior in animals are due to the site of pharmalogical intervention, in this case the NAcc versus central injection which presumably also reaches the NAcc; it is also possible that these effects might be brought about by actions at different receptors (i.e. MC3R vs MC4R). However, at this point, it is unclear how agonism and antagonism of the melanocortin system achieve similar effects in their ability to attenuate drug-taking behavior.

24.8.2 Ghrelin

In the context of metabolic status, the temporal pattern of the hormone ghrelin is unique in that it increases in plasma before scheduled meals but also increases as a result of food deprivation. The ability of ghrelin to increase before a meal, also known as the cephalic response, has been suggested to result from an animals' ability to learn or anticipate their next meal. This "feeding entrainment" is important to consider when investigating the effects of metabolic status on drug taking behavior as it identifies a time in which endogenous levels of orexigenic peptides are elevated. Thus, it is possible that food-entrained hormones such as ghrelin may exert maximal effects on drug-taking behavior when they are naturally elevated before a meal. Although this possibility has not been explored directly, ghrelin has been shown to be capable of altering the rewarding potential of psychostimulants. Systemic administration of ghrelin increases cocaine-induced locomotor activity in rats, and also learned associations with cocaine ingestion as measured by the conditioned place preference model (Wellman et al. 2007; Davis et al. 2007) suggesting that exogenous ghrelin can affect cocaine-related behaviors.

24.8.3 Orexin

As the rate of recidivism is high among drug addicts, gaining a better understanding into the neurobiology of relapse behavior is of utmost importance. Among all of the hypothalamic orexigenic peptides discussed, the orexin system has the potential to make the most significant impact on relapse behavior. In the context of relapse, environmental cues associated with drug-taking behavior are very potent activators of relapse. Although the orexin system was initially recognized for its ability to mediate arousal in animals, orexin neurons in the hypothalamus become activated in response to both food- and drug-related cues. The first evidence of this was reported in 2005 when Harris and colleagues reported that animals trained to expect chocolate and morphine exhibited significant neuronal activation within hypothalamic orexin neurons (Harris et al. 2002). In the same study, exogenous orexin administration reinstated a conditioned place preference for morphine (Harris et al. 2005) suggesting that orexin was capable of mediating both the anticipation and learned associations with opioid drugs. In a more recent report, rats that had previously extinguished operant responding

for cocaine reinstated responding after receiving a direct injection of orexin-2 peptide into the VTA (Wang et al. 2009). A major concept regarding relapse behavior ascribes that the endogenous stress system plays a major role in reinstatement of drug-taking behavior. In this way, the experience of stress or administration of stress hormones (CRH, corticosterone) is sufficient to elicit drug taking in animals that had previously extinguished drug-taking behavior, suggesting that stress alone is a potent activator of relapse behavior. It is important to note here that the ability of orexin to reinstate cocaine-taking behavior is independent from the effects of the stress on reinstatement; the implication of this being that orexin signaling alone within VTA neurons is sufficient to reinstate drug cocaine taking. Collectively, these examples provide evidence that the hypothalamic orexin system is capable of modulating the anticipation of cues associated with previous drug experience as well as the reinstatement of drug-taking behavior.

Summary

In summary, it is apparent that factors originally recognized for their ability to increase feeding behavior are also capable of modulating drug-taking behavior. With the exception of the melanocortin system, most orexigenic peptides impart positive effects on drug ingestion, i.e. they increase the rates of ingestion, or other read outs of drug efficacy such as drug-induced locomotion or conditioning effects of repeated drug exposure. Relapse to drug-taking behavior is a major problem faced by the addiction community and as such factors that affect relapse or reinstatement of drug-taking behavior are useful toward an understanding of the underlying neurobiology contributing to addiction. The orexin system has the capacity to affect anticipation and reinstatement of drug taking behavior, both of which contribute to relapse behavior. In closing, it is possible that metabolic status and the factors that regulate it are more important than ever before in their ability to regulate addictive behaviors.

Definitions

Orexigenic peptides: Peptides that stimulate appetite.
Reward: A specific intuitive drive in animals; utilized in most animal training systems.
Drug relapse: To engage in drug taking after abstinence.
Mesolimbic system: A neural pathway in the brain which links the ventral tegmentum in the midbrain to the nucleus accumbens which is located in the striatum.
Psychostimulant: A stimulant which acts on the nervous system which increases locomotor behavior and in addition to having mood-elevating effects.

References

Abizaid A, Liu ZW, Andrews ZB, Shanabrough M, Borok E, Elsworth JD, et al. Ghrelin modulates the activity and synaptic input organization of midbrain dopamine neurons while promoting appetite. J Clin Invest. 2006;116:3229–39.

Adan RA, Gipsen W. Brain melanocortin receptors: from cloning to function. Peptides. 1997;8:1279–87.

Alvaro JD, Tatro JB, Quillan JM, Fogliano M, Eisenhard M, Lerner MR, et al. Morphine down regulates melanocortin-4 receptor expression in brain regions that mediate opiate addiction. Mol Pharmacol. 1996;3:583–91.

Aoki C, Pickel VM. Neuropeptide Y-containing neurons in the rat striatum: ultrastructure and cellular relations with tyrosine hydroxylase-containing terminals and with astrocytes. Brain Res. 1988;459:205–25.

Bassareo V, Di Chiara G. Modulation of feeding-induced activation of mesolimbic dopamine transmission by appetitive stimuli and its relation to motivational state. Eur J Neurosci. 1999;11:4389–97.

Bassareo V, Di Chiara G. Differential influence of associative and nonassociative learning mechanism on the responsiveness of prefrontal and accumbal dopamine transmission to food stimuli in rats fed ad libitum. J Neurosci. 1997;17:851–61.

Berridge KC. Food reward: brain substrates of wanting and liking. Neurosci Biobehav Rev. 1996;20:1–25.

Berthoud HR. Neural control of appetite: cross-talk between homeostatic and non-homeostatic systems. Appetite. 2004;43:315–7.

Borgland SL, Taha SA, Sarti F, Fields HL, Bonci A. Orexin A in the VTA is critical for the induction of synaptic plasticity and behavioral sensitization to cocaine. Neuron. 2006;49:589–601.

Boutrel B, Kenny PJ, Specio SE, Martin-Fardon R, Markou A, Koob GF, et al. Role for hypocretin in mediating stress-induced reinstatement of cocaine-seeking behavior. Proc Natl Acad Sci USA. 2005;102:19168–73.

Burdakov D, Gerasimenko O, Verkhratsky A. Physiological changes in glucose differentially modulate the excitability of hypothalamic melanin-concentrating hormone and orexin neurons in situ. J Neurosci. 2005;25:2429–33.

Cabeza de Vaca SHJ, Afroz T, Krahnne LL, Carr KD. Feeding, body weight and non-ingestive reward stimuli during and after 12 day continuous central infusions of melanocortin receptor ligands. Peptides. 2005;11:2314–21.

Cabeza de Vaca SKG, Carr KD. The melanocortin receptor agonist MTII augments the rewarding effects of amphet-maines in ad-libitum fed and food restricted rats. Psychopharmacology. 2002;1:77–85.

Cai XJ, Widdowson PS, Harrold J, Wilson S, Buckingham RE, Arch JR, et al. Hypothalamic orexin expression: modulation by blood glucose and feeding. Diabetes. 1999;48:2132–7.

Carr D, Kalivas PW. Orexin: a gatekeeper of addiction. Nat Med. 2006;12:274–6.

Carroll ME, Meisch RA. Increased drug reinforced behavior due to food deprivation. Adv Behav Pharmacol. 1984;4:47–88.

Carroll ME, Stotz DC, Kliner DJ, Meisch RA. Self-administration of orally-delivered methohexital in rhesus monkeys with phencyclidine or pentobarbital histories: effects of food deprivation and satiation. Pharmacol Biochem Behav. 1984;20:145–51.

Clegg DJ, Air EL, Woods SC, Seeley RJ. Eating elicited by orexin-a, but not melanin-concentrating hormone, is opioid mediated. Endocrinology. 2002;143:2995–3000.

Cota D, Barrera JG, Seeley RJ. Leptin in energy balance and reward: two faces of the same coin? Neuron. 2006;51:678–80.

Cummings DE, Purnell JQ, Frayo RS, Schmidova K, Wisse BE, Weigle DS. A preprandial rise in plasma ghrelin levels suggests a role in meal initiation in humans. Diabetes. 2001;50:1714–9.

Di Chiara GAE, Tanda G, Candoni C. Drugs of abuse: biochemical surrogates of specific aspects of natural reward. Biochem Soc Symp. 1993;59:65–81.

Diaz-Munoz M, Vazquez-Martinez O, Aguilar-Roblero R, Escobar C. Anticipatory changes in liver metabolism and entrainment of insulin, glucagon, and corticosterone in food-restricted rats. Am J Physiol Regul Integr Comp Physiol. 2000;279:R2048–56.

Di Chiara G, Imperato A. Drugs abused by humans preferentially increase dopamine concentraions in the mesolimbic system of freely moving rats. Proc Natl Acad Sci. 1988;85:5274–8.

Drazen DL, Vahl TP, D'Alessio DA, Seeley RJ, Woods SC. Effects of a fixed meal pattern on ghrelin secretion: evidence for a learned response independent of nutrient status. Endocrinology. 2006;147:23–30.

Duarte C, Biala G, Le Bihan C, Hamon M, Thiebot MH. Respective roles of dopamine D2 and D3 receptors in food-seeking behaviour in rats. Psychopharmacology (Berlin). 2003;166:19–32.

Dube MG, Horvath TL, Kalra PS, Kalra SP. Evidence of NPY Y5 receptor involvement in food intake elicited by orexin A in sated rats. Peptides. 2000;21:1557–60.

Emson PC, Koob GF. The origin and distribution of dopamine-containing afferents to the rat frontal cortex. Brain Res. 1978;142:249–67.

Fadel J, Deutch AY. Anatomical substrates of orexin-dopamine interactions: lateral hypothalamic projections to the ventral tegmental area. Neuroscience. 2002;111:379–87.

Figlewicz DP, Higgins MS, Ng-Evans SB, Havel PJ, Ng-Evans SB, Havel PJ. Leptin reverses sucrose conditioned place preference in food restricted rats. Physiol Behav. 2001;1–2:229–34.

Fuxe K, Hokfelt T. On the existence of dopaminergic and noradrenergic mechanisms in the control of hormone releasing and inhibitory factor secretion from the median eminence. J Anat. 1972;111:475–6.

Guan XM, Yu H, Palyha OC, McKee KK, Feighner SD, Sirinathsinghji DJ, et al. Distribution of mRNA encoding the growth hormone secretagogue receptor in brain and peripheral tissues. Brain Res Mol Brain Res. 1997;48:23–9.

Hagan MM, Benoit SC, Rushing PA, Pritchard LM, Woods SC, Seeley RJ. Immediate and prolonged patterns of Agouti related peptide-(83-132) induced c-fos activation in hypothalamic and extrahypothalamic sites. Endocrinology. 2001a;3:1050–6.

Hagan MM, Rushing PA, Benoit SC, Woods SC, Seeley RJ. Opioid receptor involvement in the effect of AgRP-(83-132) on food intake and food selection. Am J Physiol Reg Integr Comp Physiol. 2001b;1:R814–21.

Harris GC, Wimmer M, Aston-Jones G. A role for lateral hypothalamic orexin neurons in reward seeking. Nature. 2005;437:556–9.

Harris GC, Wimmer M, Randall-Thompson JF, Aston-Jones G. Lateral hypothalamic orexin neurons are critically involved in learning to associate an environment with morphine reward. Behav Brain Res. 2007;183:43–51.

Holland PC, Petrovich GD. A neural systems analysis of the potentiation of feeding by conditioned stimuli. Physiol Behav. 2005;86:747–61.

Holst B, Schwartz TW. Constitutive ghrelin receptor activity as a signaling set-point in appetite regulation. Trends Pharmacol Sci. 2004;25:113–7.

Holst B, Cygankiewicz A, Jensen TH, Ankersen M, Schwartz TW. High constitutive signaling of the ghrelin receptor – identification of a potent inverse agonist. Mol Endocrinol. 2003;17:2201–10.

Hsu R, Taylor JR, Newton SS, Alvaro JD, Haile C, Han G, et al. Blockade of melanocortin transmission inhibits cocaine reward. Eur J Neurosci. 2005;8:2233–42.

Kalra SP, Dube MG, Sahu A, Phelps CP, Kalra PS. Neuropeptide Y secretion increases in the paraventricular nucleus in association with increased appetite for food. Proc Natl Acad Sci USA. 1991;88:10931–5.

Kelley AE, Berridge KC. The neuroscience of natural rewards: relevance to addictive drugs. J Neurosci. 2002;22:3306–11.

Korotkova TM, Sergeeva OA, Eriksson KS, Haas HL, Brown RE. Excitation of ventral tegmental area dopaminergic and nondopaminergic neurons by orexins/hypocretins. J Neurosci. 2003;23:7–11.

Lawrence AJ, Cowen MS, Yang HJ, Chen F, Oldfield B. The orexin system regulates alcohol-seeking in rats. Br J Pharmacol. 2006;148:752–9.

Lopez M, Seoane L, Garcia MC, Lago F, Casanueva FF, Senaris R, et al. Leptin regulation of prepro-orexin and orexin receptor mRNA levels in the hypothalamus. Biochem Biophys Res Commun. 2000;269:41–5.

Lu D, Willard D, Patel I, et al. Agouti protein is an antagonist of the melanocyte-stimulating-hormone receptor. Nature. 1994;371:799–802.

Marcus JN, Aschkenasi CJ, Lee CE, Chemelli RM, Saper CB, Yanagisawa M, et al. Differential expression of orexin receptors 1 and 2 in the rat brain. J Comp Neurol. 2001;435:6–25.

Masuda Y, Tanaka T, Inomata N, Ohnuma N, Tanaka S, Itoh Z, et al. Ghrelin stimulates gastric acid secretion and motility in rats. Biochem Biophys Res Commun. 2000;276:905–8.

Mendoza J, Angeles-Castellanos M, Escobar C. Entrainment by a palatable meal induces food-anticipatory activity and c-Fos expression in reward-related areas of the brain. Neuroscience. 2005;133:293–303.

Mistlberger RE. Circadian food-anticipatory activity: formal models and physiological mechanisms. Neurosci Biobehav Rev. 1994;18:171–95.

Mizuno TM, Makimura H, Silverstein J, Roberts JL, Lopingco T, Mobbs CV. Fasting regulates hypothalamic neuro-peptide Y, agouti-related peptide, and proopiomelanocortin in diabetic mice independent of changes in leptin or insulin. Endocrinology. 1999;140:4551–7.

Mountjoy MG, Robbins LS, Mortrud M, Cone R. The cloning of a family of genes that encode the melanocortin receptors. Science. 1992;257:1248–51.

Muschamp JW, Dominguez JM, Sato SM, Shen RY, Hull EM. A role for hypocretin (orexin) in male sexual behavior. J Neurosci. 2007;27:2837–45.

Carr KD, Kutchukhidze N. Chronic food restriction increases fos-like immunoreactivity (FLI) induced in rat forebrain by amphetamine. Brain Res. 2000;861:88–96.

Nair SG, Golden SA, Shaham Y. Differential effects of the hypocretin 1 receptor antagonist SB 334867 on high-fat food self-administration and reinstatement of food seeking in rats. Br J Pharmacol. 2008;154:406–16.

Nakazato M, Murakami N, Date Y, Kojima M, Matsuo H, Kangawa K, et al. A role for ghrelin in the central regulation of feeding. Nature. 2001;409:194–8.

Narita M, Nagumo Y, Hashimoto S, Narita M, Khotib J, Miyatake M, et al. Direct involvement of orexinergic systems in the activation of the mesolimbic dopamine pathway and related behaviors induced by morphine. J Neurosci. 2006;26:398–405.

Nestler EJ. Common molecular and cellular substrates of addiction and memory. Neurobiol Learn Mem. 2002;78:637–47.

Panskepp J, Reilly P, Bishop P, Meeker RB, Vilberg TR, Kastin AJ. Effects of alpha-MSH on motivation, vigilance, and brain respiration. Pharmacol Biochem Behav. 1976;1(Suppl):59–64.

Papp M. Different effects of short- and long-term treatment with imipramine on the apomorphine- and food-induced place preference conditioning in rats. Pharmacol Biochem Behav. 1988;30:889–93.

Peyron C, Tighe DK, van den Pol AN, de Lecea L, Heller HC, Sutcliffe JG, et al. Neurons containing hypocretin (orexin) project to multiple neuronal systems. J Neurosci. 1998;18:9996–10015.

Robinson TE, Berridge K. The neural basis of drug craving and incentive-sensitization theory of addiction. Brain Res Brain Res Rev. 1993;18:247–91.

Rodgers RJ, Halford JC, Nunes de Souza RL, Canto de Souza AL, Piper DC, Arch JR, et al. SB-334867, a selective orexin-1 receptor antagonist, enhances behavioural satiety and blocks the hyperphagic effect of orexin-A in rats. Eur J Neurosci. 2001;13:1444–52.

Rogers RD, Ramnani N, Mackay C, Wilson JL, Jezzard P, Carter CS, et al. Distinct portions of anterior cingulate cortex and medial prefrontal cortex are activated by reward processing in separable phases of decision-making cognition. Biol Psychiatry. 2003;55:594–602.

Rossi M, Kim MS, Morgan DG, Small CJ, Edwards CM, Sunter D, et al. A C-terminal fragment of Agouti related protein increases feeding and antagonizes the effect of alpha-melanocyte stimulating hormone in vivo. Endocrinology. 1998;10:4428–31.

Sakurai T. The neural circuit of orexin (hypocretin): maintaining sleep and wakefulness. Nat Rev Neurosci. 2007;8:171–81.

Sakurai T, Amemiya A, Ishii M, Matsuzaki I, Chemelli RM, Tanaka H, et al. Orexins and orexin receptors: a family of hypothalamic neuropeptides and G protein-coupled receptors that regulate feeding behavior. Cell. 1998;92:573–85.

Scammell TE, Saper CB. Orexin, drugs and motivated behaviors. Nat Neurosci. 2005;8:1286–8.

Schroeder BE, Binzak JM, Kelley AE. A common profile of prefrontal cortical activation following exposure to nicotine- or chocolate-associated contextual cues. Neuroscience. 2001;105:535–45.

Schwartz MW, Figlewicz DP, Baskin DG, Woods SC, Porte Jr D. Insulin in the brain: a hormonal regulator of energy balance. Endocr Rev. 1992;13:387–414.

Schwartz MW, Woods SC, Porte Jr D, Seeley RJ, Baskin DG. Central nervous system control of food intake. Nature. 2000;6778:661–71.

Sesack SR, Pickel VM. Prefrontal cortical efferents in the rat synapse on unlabeled neuronal targets of catecholamine terminals in the nucleus accumbens septi and on dopamine neurons in the ventral tegmental area. J Comp Neurol. 1992;320:145–60.

Sesack SR, Deutch AY, Roth RH, Bunney BS. Topographical organization of the efferent projections of the medial prefrontal cortex in the rat: an anterograde tract-tracing study with Phaseolus vulgaris leucoagglutinin. J Comp Neurol. 1989;290:213–42.

Sugino T, Hasegawa Y, Kikkawa Y, Yamaura J, Yamagishi M, Kurose Y, et al. A transient ghrelin surge occurs just before feeding in a scheduled meal-fed sheep. Biochem Biophys Res Commun. 2002;295:255–60.

Sutton GM, Perez-Tilve D, Nogueiras R, Fang J, Kim J, Cone R, et al. The melanocortin-3 receptor is required for entrainment to meal intake. J Neurosci. 2008;48:12946–55.

Thorpe AJ, Cleary JP, Levine AS, Kotz CM. Centrally administered orexin A increases motivation for sweet pellets in rats. Psychopharmacology (Berlin). 2005;182:75–83.

Tolle V, Bassant MH, Zizzari P, Poindessous-Jazat F, Tomasetto C, Epelbaum J, et al. Ultradian rhythmicity of ghrelin secretion in relation with GH, feeding behavior, and sleep-wake patterns in rats. Endocrinology. 2002;143:1353–61.

Toshinai K, Date Y, Murakami N, Shimada M, Mondal MS, Shimbara T, et al. Ghrelin-induced food intake is mediated via the orexin pathway. Endocrinology. 2003;144:1506–12.

Tschop M, Smiley DL, Heiman ML. Ghrelin induces adiposity in rodents. Nature. 2000;407:908–13.

Tschop M, Wawarta R, Riepl RL, Friedrich S, Bidlingmaier M, Landgraf R, et al. Post-prandial decrease of circulating human ghrelin levels. J Endocrinol Invest. 2001;24:RC19–21.

Tzschentke TM. Measuring reward with the conditioned place preference paradigm: a comprehensive review of drug effects, recent progress and new issues. Prog Neurobiol. 1998;56:613–72.

Volkow ND, Wise RA. How can drug addiction help us understand obesity? Nat Neurosci. 2005;8:555–60.

Weingarten HP. Conditioned cues elicit feeding in sated rats: a role for learning in meal initiation. Science. 1983;220:431–3.

Wise RA. Catecholamine theories of reward: a critical review. Brain Res. 1978;152:215–47.

Wise RA. Brain reward circuitry: insights from unsensed incentives. Neuron. 2002;36:229–40.

Wise RA. Dopamine and food reward: back to the elements. Am J Physiol Regul Integr Comp Physiol. 2004;286:R13.

Wise RA, Schwartz HV. Pimozide attenuates acquisition of lever-pressing for food in rats. Pharmacol Biochem Behav. 1981;15:655–6.

Wise RA, Bozarth MA. A psychomotor stimulant theory of addiction. Psychol Rev. 1987;94:469–92.

Xue G, Lu Z, Levin I, Weller J, Li X, Bechara A. Functional dissociations of risk and reward processing in the medial prefrontal cortex. Cereb Cortex. 2009;19:1019–27. Epub 2008.

Yamanaka A, Kunii K, Nambu T, Tsujino N, Sakai A, Matsuzaki I, et al. Orexin-induced food intake involves neuropeptide Y pathway. Brain Res. 2000;859:404–9.

Zheng H, Berthoud HR. Eating for pleasure or calories. Curr Opin Pharmacol. 2007;7:607–12.

Zheng H, Patterson LM, Berthoud HR. Orexin signaling in the ventral tegmental area is required for high-fat appetite induced by opioid stimulation of the nucleus accumbens. J Neurosci. 2007;27:11075–82.

Zigman JM, Nakano Y, Coppari R, Balthasar N, Marcus JN, Lee CE, et al. Mice lacking ghrelin receptors resist the development of diet-induced obesity. J Clin Invest. 2005;115:3564–72.

Chapter 25
Circadian Neuroendocrine-Immune Aspects of Feeding Behavior: Lessons from Calorie-Restricted or High-Fat-Fed Rats

Ana I. Esquifino and Daniel P. Cardinali

Abbreviations

ACTH	Corticotropin
FSH	Follicle-stimulating hormone
GH	Growth hormone
IFN-γ	Interferon-γ
IL	Interleukin
LH	Luteinizing hormone
MCP-1	Monocyte chemoattractant protein-1
PAI-1	Plasminogen activator inhibitor-1
SCN	Suprachiasmatic nucleus
TNF-α	Tumor necrosis factor-α
TSH	Thyroid-stimulating hormone

25.1 Introduction: Relevance of the Circadian Clock for Neuroimmune Organization

Temporal organization is an important feature of the biological systems and its main function is to facilitate adaptation of the organism to the environment. It is known that the mammalian circadian timing system comprises peripheral oscillators located in almost every cell of the body together with a central rhythm generator located in the hypothalamic suprachiasmatic nucleus (SCN) (Hastings et al. 2003). At the cell level, circadian rhythms are driven by the self-regulatory interaction of a set of genes named clock genes and their protein products.

The light–dark cycle, food, ambient temperature, scents, and social cues have been identified as synchronizers (or "Zeitgebers") in rodents. An entraining agent can actually reset, or phase shift, the internal clock. Depending on when an organism is exposed to such an entraining agent, circadian rhythms can be advanced, delayed, or not shifted at all. Therefore, involved in adjusting the daily activity pattern to the appropriate time of day is a rhythmic variation in the influence of the Zeitgeber

A.I. Esquifino (✉)
Departamento de Bioquímica y Biología Molecular III,
Universidad Complutense, 28040 Madrid, Spain
e-mail: pelayos@med.ucm.es

as a resetting factor (Hastings et al. 2003). In humans, light exposure during the first part of the night delays the phase of the cycle; a comparable light change near the end of the night, advances it. At other times during the day light exposure has no phase-shifting influence.

Both the humoral arm and the delayed (cellular) arm of the immune system function in a rhythmic manner. Circadian changes in the circulation of T, B, or natural killer lymphocyte subsets in peripheral blood and in the density of epitope molecules at their surface, which may be related to cell reactivity to antigen exposure, have been reported (Cutolo et al. 2006). Changes in lymphocyte subset populations can depend on the time of day-associated changes in cell proliferation in immunocompetent organs and/or on diurnal modifications in lymphocyte release and traffic among lymphoid organs. Circadian rhythmicity is revealed in circulating cells, lymphocyte metabolism and transformability, circulating hormones and other substances that may exert various actions on different targets of the immune system, cytokines, receptors, and adhesion molecules, cell cycle events in health and cancer, reactions to antigen challenge, and disease etiology and symptoms (Hastings et al. 2003; Cutolo et al. 2006).

It must be noted that the role of SCN in the entrainment of lymphocyte function and in coordinating signals by which circadian information is conveyed to the immune cells remains unsettled. Rhythms in the number of circulating T cells persisted in rats with disrupted circadian output. Similarly, SCN ablation did not affect the 24-h rhythms in cell cycle phase distribution in bone marrow cells (Filipski et al. 2004), suggesting that some rhythms in the immune system are SCN-independent. Rather than a mere rhythm generator for the periphery, the SCN should be envisioned as a transducer for light entrainment. However, there are entrainment signals other than light that may be coordinating the rhythm in natural killer cell function and other immunological parameters like, e.g., feeding.

Several studies have investigated the changes in cytokine levels that occur during the most prominent 24-h cycle in humans, the sleep–wake cycle. Plasma tumor necrosis factor (TNF)-α levels peak during the dark phase of the cycle, and the circadian rhythm of TNF release is disrupted by sleep pathology like obstructive sleep apnea. Plasma interleukin (IL)-1β levels also have a diurnal variation, being highest at the onset of slow sleep. The levels of other cytokines (including IL-2, IL-6, IL-10 and IL-12) and the proliferation of T cells in response to mitogens also change during the 24-h cycle. Although the production of macrophage-related cytokines (such as tumor necrosis factor-α (TNF-α)) increases during sleep (in response to in vitro stimulation), this occurs in parallel with the rise in monocyte numbers in the blood. The production of T-cell-related cytokines (such as IL-2) increases during sleep, independent of migratory changes in T-cell distribution (Pandi-Perumal et al. 2007). All of these observed diurnal changes could be specific to the effects of sleep or associated with the circadian oscillator. To dissociate the effects that result from the sleep–wake cycle from those due to the endogenous circadian oscillator, experimental procedures such as constant routine or forced desynchrony need to be used. At present, there are no reports of studies using these methods to elucidate the effects of sleep on immunity.

Sleep and the immune system share regulatory molecules (Pandi-Perumal et al. 2007). These are involved in both physiological sleep and sleep in the acute-phase response to infection or in chronic inflammation. This supports the view that sleep and the immune system are closely interconnected. It is feasible that sleep influences the immune system through the action of centrally produced cytokines that are regulated during sleep. These endogenous cytokines are known to function through the autonomic nervous system and the neuroendocrine axis, although other pathways might be involved.

In recent years, we examined the circadian disruption of hormone release and immune-related mechanisms in several animal models in which circulating cytokines are increased including calorie restriction and a high-fat diet. Basic rationale for the experimental approach used was that most published studies dealing with hormone or immune changes in the above mentioned situations were performed at single time-points in the 24-h span, an important drawback in view of the circadian

Table 25.1 Summary of changes in circadian rhythms of neuroimmune responses after caloric restriction in rats (Results from Chacon et al. 2004, 2005, 2006; Esquifino et al. 2004b)

24-h rhythms	Amplitude	Acrophase	Mean
Plasma			
Prolactin	Unchanged	Changed	Increased
LH	Decreased	Changed	Decreased
FSH	Unchanged	Unchanged	Unchanged
Testosterone	Decreased	Changed	Decreased
ACTH	Decreased	Changed	Decreased
Corticosterone	Increased	Changed	Increased
GH	Suppression of rhythm	Suppression of rhythm	Decreased
Leptin	Decreased	Changed	Decreased
Submaxillary lymph nodes			
Mitotic response to Con A	Increased	Changed	Increased
Mitotic response to LPS	Decreased	Changed	Unchanged
T cells	Suppression of rhythm	Suppression of rhythm	Increased
B cells	Decreased	Unchanged	Decreased
T/B ratio	Unchanged	Unchanged	Increased
T – B cells	Unchanged	Changed	Unchanged
CD4$^+$ cells	Increased	Changed	Increased
CD8$^+$ cells	Unchanged	Unchanged	Unchanged
CD4$^+$/CD8$^+$ ratio	Increased	Unchanged	Increased
CD4$^+$ – CD8$^+$ cells	Unchanged	Changed	Unchanged
IFN-γ release	Decreased	Changed	Decreased
Glutamine	Decreased	Changed	Decreased
Glutamate	Decreased	Changed	Decreased
Aspartate	Decreased	Changed	Unchanged
Taurine	Suppression of rhythm	Suppression of rhythm	Unchanged
GABA	Decreased	Unchanged	Unchanged
Spleen			
Mitotic response to Con A	Increased	Unchanged	Increased
Mitotic response to LPS	Suppression of rhythm	Suppression of rhythm	Unchanged
T cells	Suppression of rhythm	Suppression of rhythm	Increased
B cells	Suppression of rhythm	Suppression of rhythm	Decreased
T/B cells	Increased	Changed	Increased
CD4$^+$ cells	Suppression of rhythm	Suppression of rhythm	Increased
CD8$^+$ cells	Decreased	Changed	Increased
CD4$^+$/CD8$^+$ cells	Decreased	Changed	Decreased
IFN-γ release	Decreased	Unchanged	Decreased

nature of hormone release and immune function and on the fact that most manipulations employed disrupt circadian rhythmicity. The results obtained are reviewed below and are summarized in Tables 25.1 and 25.2.

25.2 Circadian Neuroimmune Organization after Caloric Restriction

Homeostasis defines the mechanisms that react to maintain a constant, fixed set point of a physiological variable (reactive homeostasis) as well as those that are active in advance to maintain a set point that itself is rhythmic (predictive homeostasis) (Moore-Ede 1986). This last type of homeostasis evolves

Table 25.2 Summary of changes in circadian rhythms of hormones and adipocytokines in rats fed a high-fat diet (Results from Cano et al. 2008, 2009)

24-h rhythms	Amplitude	Acrophase	Mean
Plasma			
Prolactin	Unchanged	Unchanged	Unchanged
LH	Increased	Changed	Unchanged
TSH	Decreased	Changed	Decreased
Testosterone	Decreased	Changed	Decreased
Corticosterone	Suppression of rhythm	Suppression of rhythm	Increased
Insulin	Increased	Changed	Increased
Glucose	Increased	Unchanged	Increased
IL-1	Suppression of rhythm	Suppression of rhythm	Increased
IL-6	Suppression of rhythm	Suppression of rhythm	Increased
TNF-α	Increased	Changed	Increased
Adiponectin	Increased	Changed	Increased
Leptin	Suppression of rhythm	Suppression of rhythm	Increased
Active ghrelin	Decreased	Changed	Decreased
Total ghrelin	Decreased	Changed	Decreased
PAI-1	Unchanged	Unchanged	Unchanged
MCP-1	Increased	Changed	Increased
Pineal gland			
Melatonin	Decreased	Unchanged	Decreased

Table 25.3 Circadian neuroendocrine-immune organization in calorie restriction: key points

- Availability of nutrients affects the mechanisms that modulate the circadian variation of pituitary-gonadal axis
- Reduced availability of nutrients is a stressor that affects the circadian variation of pituitary hormones and leptin
- Malnutrition produced by low or absent proteins in diet is linked to increased susceptibility to infection while calorie restriction of rodents by a diet enriched in proteins and low in fat and carbohydrates significantly increases immune responses

as an adaptation to anticipate predictable changes in the environment, such as light and darkness, food availability, temperature, or predator activity, and is the basis of the circadian clock as discussed above.

One of those environmental predictable changes, the scarcity of food, occurs rhythmically in nature every year and can be reproduced in laboratory conditions by calorie restriction (Table 25.3). Experimental calorie restriction (e.g., 25–50% reduction of caloric intake), without deficiency in essential nutrients have been widely employed in this respect (Roth et al. 1999; Masoro 2000).

Under calorie restriction the use of energy is greatly reduced and the basal plasma levels of several hormones are altered. Among them, the hormones of the hypothalamic–pituitary–gonadal axis have been extensively examined.

In a study analyzing the effect of caloric restriction on the 24-h variation of pituitary–testicular function in young male Wistar rats, we submitted animals to a calorie restriction equivalent to 66% of food restriction for 4 weeks starting on day 35 of life (Chacon et al. 2004). Rats were killed at six time intervals around the clock. Mean secretion of prolactin augmented and that of luteinizing hormone (LH) and testosterone decreased in calorie-restricted rats whereas follicle-stimulating hormone (FSH) release remained unchanged. Significant changes in the 24-h secretory pattern of circulating prolactin, LH, and testosterone levels occurred in calorie-restricted rats. These include the appearance of a second maximum of plasma prolactin, the blunting of LH peak and a phase-delayed of testosterone peak. The significant positive correlation between individual LH and testosterone levels found in controls was not longer observed in calorie-restricted rats (Chacon et al. 2004).

Availability of nutrients presumably affects the mechanisms that modulate the circadian variation of pituitary-gonadal axis in growing male rats.

With the aim to assess whether the chronobiological sequels of calorie restriction could be the consequence of stress, we examined the 24-h variations of plasma corticotropin (ACTH), corticosterone, GH, and leptin, and of adrenal corticosterone content (Chacon et al. 2005). Significantly lower ACTH levels were detected in calorie-restricted rats. Plasma corticosterone levels during the light phase of daily cycle (but not in the whole set of six time points throughout the 24-h cycle) were significantly higher in calorie-restricted rats. Time-of-day variations of plasma ACTH and corticosterone attained significance in calorie-restricted rats only, with a maximum toward the end of the resting phase. The daily pattern of adrenal gland corticosterone mirrored that of circulating corticosterone, calorie restriction reducing its levels. Plasma ACTH and corticosterone correlated significantly in controls only. Calorie restriction decreased plasma GH and leptin and distorted their 24-h rhythmicity (Fig. 25.1). Plasma ACTH levels in calorie-restricted rats were lower, and plasma corticosterone levels were higher than those of pair-fed, isolated controls and grouped caged controls (Chacon et al. 2005). The results indicate that a reduced availability of nutrients is a stressor that affects the circadian variation of pituitary hormones and leptin.

Malnutrition produced by low or absence of proteins in diet is linked to increased susceptibility to infection, often associated with severe marasmus or kwashiorkor. In contrast, calorie restriction of adult rats by a diet enriched in proteins and low in fat and carbohydrates only partially affected weight and significantly increased immune responses (Pahlavani 2004). The immunological status of adult rodents fed a calorie-restricted diet is superior to the immunological status of the nonrestricted animals and through this mechanism caloric restriction may retard immunosenescence. Indeed, experimental calorie restriction (e.g., 25–50% reduction of caloric intake), without deficiency in essential nutrients, is a very unique manipulation in slowing the aging process in rodents. To examine this subject, mitogenic responses, lymphocyte subset populations, and interferon (IFN)-γ release were determined in submaxillary lymph nodes at 6 time intervals during the 24 h span (Esquifino et al. 2004b). After caloric restriction, mean values of concanavalin A (Con A) response, lymph node T and CD4$^+$ cell number and CD4$^+$/CD8$^+$ ratio augmented, whereas those of B cell number, IFN-γ release and glutamine and glutamate concentration decreased. Calorie restriction modified 24-h rhythmicity of lymph node mitogenic responses to Con A and lipopolysaccharide (LPS), and of T, T-B, CD4$^+$, and CD4$^+$–CD8$^+$ lymph node cell subsets. It also changed the 24 h pattern of lymph node IFN-γ release. Availability of nutrients presumably affects the mechanisms that modulate the circadian variation of immune responsiveness in growing rats.

In a subsequent experiment the effect of calorie restriction on splenic immune responses was studied (Cano et al. 2006). Calorie-restricted rats showed increased splenic Con A response with peak activity during the activity span. The highest values of T cells occurred in calorie-restricted rats and mean values of splenic CD4$^+$ and CD8$^+$ cells augmented in these animals. It is of interest that these immunological changes correlate with the efficacy of calorie restriction to prevent experimental allergic encephalomyelitis in rats (Esquifino et al. 2004a, 2007). The changes caused by caloric restriction on circadian organization of the neuroimmune response in rats are summarized in Table 25.1.

25.3 Circadian Neuroimmune Organization after Hyperadiposity in High Fat-Fed-Rats

There is a large body of evidence that links feeding regimens and food components with the circadian system (Froy 2007). A high-fat diet, that contributes to insulin resistance, impaired glucose metabolism, type 2 diabetes mellitus, stroke, and coronary artery disease can feed back to influence the
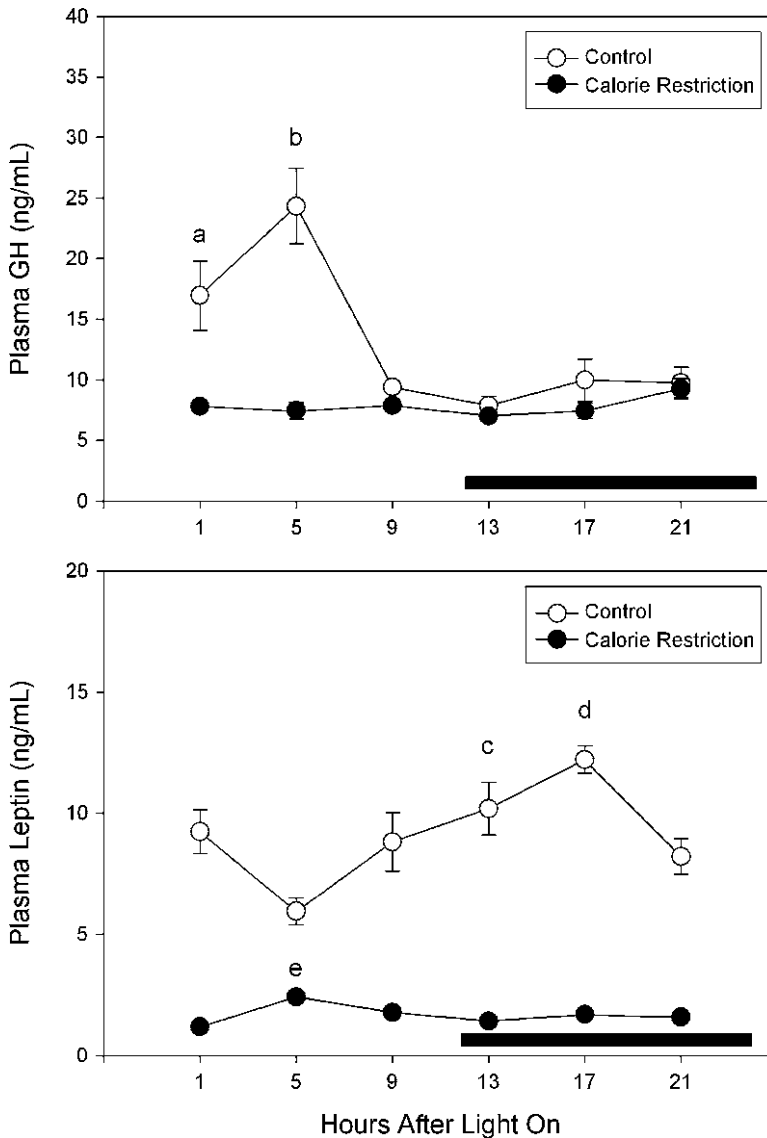
Fig. 25.1 Effect of calorie restriction on 24-h changes in plasma GH and plasma leptin levels in male rats. Calorie-restricted rats had daily access to 7 g of a diet enriched in proteins and low in fat and carbohydrates and water ad libitum for 4 weeks. This calorie restriction was equivalent to a 66% of food restriction. Groups of seven to eight rats were killed by decapitation at six different time intervals throughout a 24-h cycle. Bar indicates scotophase duration. Results are the means ± SEM. Letters indicate the existence of significant differences between time points within each group after a one-way ANOVA followed by Tukey–Kramer´s multiple comparisons test, as follows: [a] $p < 0.05$ versus 13 HALO. [b]$p < 0.01$ versus 9, 13, 17, and 21 HALO. [c]$p < 0.05$ versus 5 HALO. [d]$p < 0.05$ versus 21 HALO, $p < 0.01$ versus 5 HALO. [e]$p < 0.05$ versus 1, 13, 17, and 21 HALO (Reproduced from Chacon et al. 2005. With permission)

biological clock (Yanagihara et al. 2006). This could explain why the circadian oscillation of many hormones involved in metabolism, such as corticosterone, insulin, glucagon, adiponectin, leptin, and ghrelin, becomes disrupted in the development of the metabolic syndrome and obesity (Froy 2007).

In a recent series of studies we have analyzed the effect of a high-fat diet (35% fat) on 24-h changes circulating prolactin, LH, testosterone, corticosterone, thyroid-stimulating hormone (TSH),
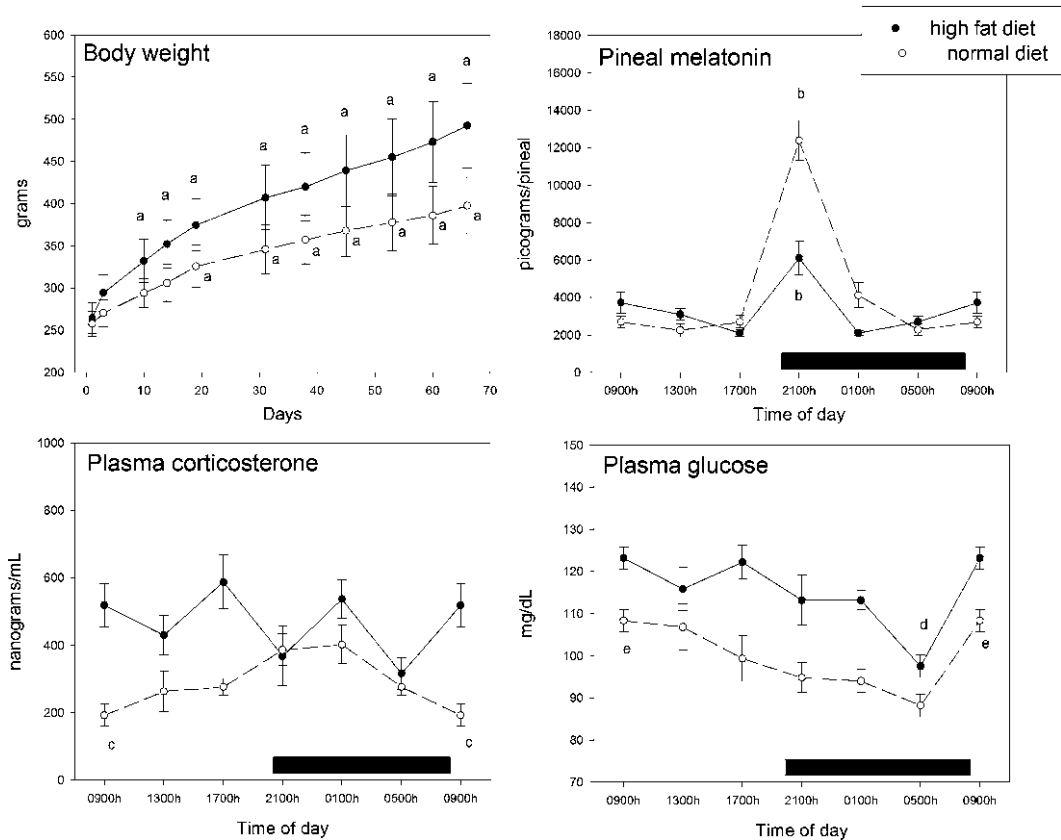
Fig. 25.2 Progression of body weight, and 24-h changes in pineal melatonin content, plasma corticosterone, and glucose levels in Wistar male rats fed with normal or high-fat diet. When body weights of high-fat-fed rats attained values about 20–25% higher than controls (after 66 days of treatment), groups of eight rats were killed by decapitation at six different time intervals throughout a 24-h cycle. Shown are the means ± SEM. [a]$p < 0.01$ versus initial weight; [b]$p < 0.01$ versus the remaining time points; [c]$p < 0.02$ versus 2100 and 0100 h. [d]$p < 0.01$ versus 0900, 1700, and 0100 h, $p < 0.05$ versus 1300 and 2100 h. [e]$p < 0.01$ versus 0100 and 0500 h (one-way ANOVA followed by a Student–Newman–Keuls multiple comparisons test) (Redrawn from Cano et al. 2008. With permission)

and glucose, and pineal melatonin content, in rats fed a high fat diet (Fig. 25.2) (Cano et al. 2008). A significant disruption of the 24-h pattern of plasma TSH, LH and testosterone, and a less prominent disruption of prolactin rhythm were found (Table 25.4). Additionally, high-fat-fed rats showed significantly lower total values of plasma TSH and testosterone and absence of correlation between testosterone and circulating LH levels. Plasma corticosterone levels increased significantly in high-fat-fed rats and their 24-h variation became blunted. In obese animals, a significant hyperglycemia developed, individual plasma glucose values correlating with circulating corticosterone in high-fat-fed rats only. The amplitude of the nocturnal pineal melatonin peak decreased significantly in high-fat fed rats (Fig. 25.2). Altogether the results underlie the significant effects that obesity has on circadian organization of hormone secretion (Cano et al. 2008).

The key involvement of the adrenocortical axis in obesity in animals is well recognized, since most obese animals are hypercorticoid and many of the metabolic and endocrine impairments are normalized or attenuated by adrenalectomy or by preventing glucocorticoid action (Vegiopoulos and Herzig 2007). Indeed, high-fat feeding alters both basal and stress-induced hypothalamic–pituitary–adrenal

Table 25.4 Circadian neuroendocrine-immune organization in hyperadiposity: keypoints

- Circadian oscillation of many hormones involved in metabolism (corticoids, insulin, glucagon, adiponectin, leptin, ghrelin) becomes disrupted in the development of the metabolic syndrome and obesity
- Obese rats show increased circulating levels of leptin and decreased plasma ghrelin, together with signs of insulin resistance
- The increased levels of plasma IL-1, IL-6, TNF-α, and MCP-1 in obese rats indicate the occurrence of a moderate degree of inflammation
- Obesity is associated with a low-grade inflammation of the white adipose tissue that can subsequently lead to insulin resistance, impaired glucose tolerance, and diabetes
- A disruption of the 24-h pattern of TSH, corticosterone, melatonin, LH, and testosterone with absence of correlation between testosterone and circulating LH levels is found in obese rats
- Obesity results in disruption of the inherent transcription, translation, and posttranslational modifications that give the cellular clock its own natural rhythmicity

activity in genetically obese Zucker rats, as well as in other rodent models of obesity (Chen and Wang 2005). A major observation is that the return of ACTH and corticosterone to initial values was delayed, indicating resistance to glucocorticoid feedback. In a study to assess whether dietary fat-induced increase in corticosterone was due to an altered regulation of hypothalamic–pituitary–adrenal axis, rats fed a high-fat diet exhibited significantly elevated levels of plasma ACTH, corticosterone, fatty acid, and glucose before, during, and after the termination of a restraint stress (Tannenbaum et al. 1997).

A high-fat diet contributes to insulin resistance, impaired glucose metabolism, type 2 diabetes mellitus, stroke, and coronary artery disease. As far as glucose metabolism is concerned, dietary fat not only lowers glucose uptake but also stimulates inappropriate glucose production, resulting in elevations in both circulating insulin and glucose (Glueck et al. 1969). High-fat diets decrease the number of insulin receptors in liver, skeletal muscle, and adipose tissue, decrease glucose uptake into skeletal muscle and adipose tissue, and decrease hepatic glycolysis and glycogen synthesis. One of the factors accounting for insulin resistance in high-fat fed animals is the elevation of glucocorticoid production that antagonizes most of insulin's actions. Indeed, the effects of increased glucocorticoid levels mimic those of a high-fat diet, as suggested in our studies by the significant correlation between circulating corticosterone and glucose levels found in high-fat-fed rats only (Cano et al. 2008).

In obese men, sex hormone-binding globulin as well as total testosterone levels are decreased (Winters et al. 2006). The results of Cano et al. (2008) in obese rats indicate a significant decrease of total plasma testosterone levels and a loss of correlation of testosterone with circulating LH levels. Since saturated fatty acid treatment decreases LH-stimulated adenylate cyclase activity and testosterone levels (Gromadzka-Ostrowska et al. 2002) in rat testis, and induces apoptosis of Leydig cells (Lu et al. 2003), the results are compatible with a deleterious effect of high-fat diet on testicular function (Cano et al. 2008). It must be noted, however, that interpretation of the total serum testosterone concentration is problematic because it is related directly to the serum sex hormone-binding globulin concentration. Further studies are needed to assess whether free testosterone are also decreased in high-fat-fed rats. Indeed, an estimate of the serum-free testosterone concentration is frequently advised to better assess the clinical status of the obese patient (Elin and Winters 2004), being decreased in some morbidly obese men only.

Melatonin has a role in energy expenditure and body mass regulation in mammals (Bartness et al. 2002). Daily melatonin administration has been found to inhibit age- and olanzapine-related gain in visceral fat (Rasmussen et al. 2001; Raskind et al. 2006), and to prevent the increase in body fat caused by ovariectomy in rats (Ladizesky et al. 2003; Sanchez-Mateos et al. 2007). In a model of diet-induced obesity, Sprague Dawley rats fed a 39.7% high-fat diet and concomitantly administered with melatonin showed a 50% reduction in body weight increase (Prunet-Marcassus et al. 2003). Melatonin had no effect on plasma insulin level, but it decreased plasma glucose, leptin, and triglyceride

levels significantly. Conversely, in pinealectomized high-fat fed rats, body weight gain and feed efficiency increased, an effect prevented by melatonin treatment (Prunet-Marcassus et al. 2003). These results, together with the significant reduction of melatonin synthesis in high-fat-fed rats described by us (Fig. 25.2), indicate that melatonin can act as a regulator of body weight in this model of obesity and can prevent some of the side effects on glucose homeostasis such as decreased insulin sensitivity.

Reduction in amplitude of circadian rhythms like that reported for melatonin has been attributed to fatness. For example, in rats susceptible to obesity (Osborne-Mendel rats) the amplitude of rhythm of leptin and insulin was about 50% that in rats relatively resistant to obesity (Ishihara et al. 2004). Other 24-h rhythms are affected by high-fat diet in animals. For example, induction of obesity using a high-fat diet in rabbits causes hypertension by suppression of the nocturnal dip in blood pressure and heart rate and elimination of the day–night difference in both parameters (Antic et al. 2001). Diurnal rhythms of blood pressure and heart rate were abolished as early as day 1 of ad libitum high-fat feeding, before significant changes in body weight were evident (Carroll et al. 2005). Thus, food intake by itself appears to be a significant influence on the circadian apparatus (Table 25.2).

Via a number of secreted proteins called adipocytokines including hormones, cytokines, growth factors, complement factors, and matrix proteins, the adipose tissue participates in the regulation of body weight homeostasis, glucose and lipid metabolism, immunity, and inflammation (see for Ref. (Holvoet 2008)). This prompted us to examine whether the significant disruption of 24-h hormonal pattern seen in high-fat fed rats coexists with changes in the daily pattern of several circulating adipocytokines (Cano et al. 2009) (Table 25.2). As expected in high-fat fed rats increased circulating levels of leptin and decreased plasma ghrelin, together with signs of insulin resistance (i.e., hyperglycemia and increased insulin levels). Concomitantly, the increased mean levels of plasma IL-1, IL-6, TNF-α, and MCP-1 suggested the occurrence of a moderate degree of inflammation in high-fat-fed rats. The normal daily pattern of plasma insulin, leptin, ghrelin, adiponectin, TNF-α, and monocyte chemoattractant protein (MCP)-1, and to a lesser extent, that of IL-1 and IL-6, became disrupted in experimentally obese rats (Cano et al. 2009).

There is impressive information indicating that obesity is associated with a low-grade inflammation of the white adipose tissue that can subsequently lead to insulin resistance, impaired glucose tolerance, and diabetes (Waki and Tontonoz 2007; Phillips and Prins 2008). Inflammation in obesity is indicated by increased circulating levels of C-reactive protein and other biological markers of inflammation. The adipose tissue, in obesity, is characterized by an increased production and secretion of inflammatory molecules like TNF-α and IL-6, which may have local and systemic effects. The amounts of TNF-α and IL-6 are positively correlated with body fat and decrease in obese patients after weight loss (Tilg and Moschen 2008). Among the biological actions of TNF-α and IL-6, induction of insulin resistance is paramount; thus, fat cells are both a source of and a target of TNF-α and IL-6. High-fat diets have been shown to produce a significant increase of TNF-α, IL-1, and IL-6 levels (Guest et al. 2008). The increased circulating levels of leptin and insulin and decreased plasma ghrelin reported in high-fat-fed rats (Cano et al. 2009) confirms that excess fat accretion is associated with hyperleptinemia, hyperinsulinemia, and hypoghrelinemia in experimental animals and humans (Guest et al. 2008).

Adiponectin is known to have an important anti-inflammatory and antiatherogenic effect that is apparently mediated by inhibition of inflammatory cytokines, blocking the activation of macrophages and posterior transformation to foam cells Sheng and Yang 2008). Although several studies point out to a decrease in plasma concentration of adiponectin in obesity other results indicate an increase in mean levels of adiponectin in high-fat-fed rats as well as a significant modification in its daily pattern in circulation (Cano et al. 2009) (Table 25.2). Therefore, in dietary-obese rats, a decrease in adiponectin mRNA levels reported in fat does not translate to a parallel decrease in plasma adiponectin concentration.

In the stromovascular (non-adipocyte) fraction of adipose tissue from obese rodents there is an increase in the number of bone marrow–derived macrophages (Weisberg et al. 2003). Indeed, white adipose tissue from obese animals expresses multiple genes usually attributed to macrophages. The mechanism for macrophage recruitment to adipose tissue has not been defined in detail but presumably includes chemotactic molecules like MCP-1, which is synthesized and secreted by preadipocytes and mature adipocytes in diet-induced obese mice (Chen et al. 2005). The results of Cano et al. (2009) indicate that a high-fat diet augments the mean levels of MCP-1 and disrupts its 24-h pattern (Table 25.2). Since MCP-1 impairs insulin-stimulated glucose uptake by cultured adipocytes in vitro (Sartipy and Loskutoff 2003), the increased MCP-1 levels may contribute to the insulin resistance. Collectively, the above discussed observations suggest that a high-fat intake causing insulin resistance and signs of inflammation may disrupt the daily pattern of several hormones and adipocytokines, an indication that obesity has a significant effect on circadian organization of neuroendocrine and immune responses.

That the high-fat diet did interfere with the circadian signaling regulating gene expression of these enzymes was indicated by clock gene expression changes (Figs. 25.3 and 25.4). At a cellular
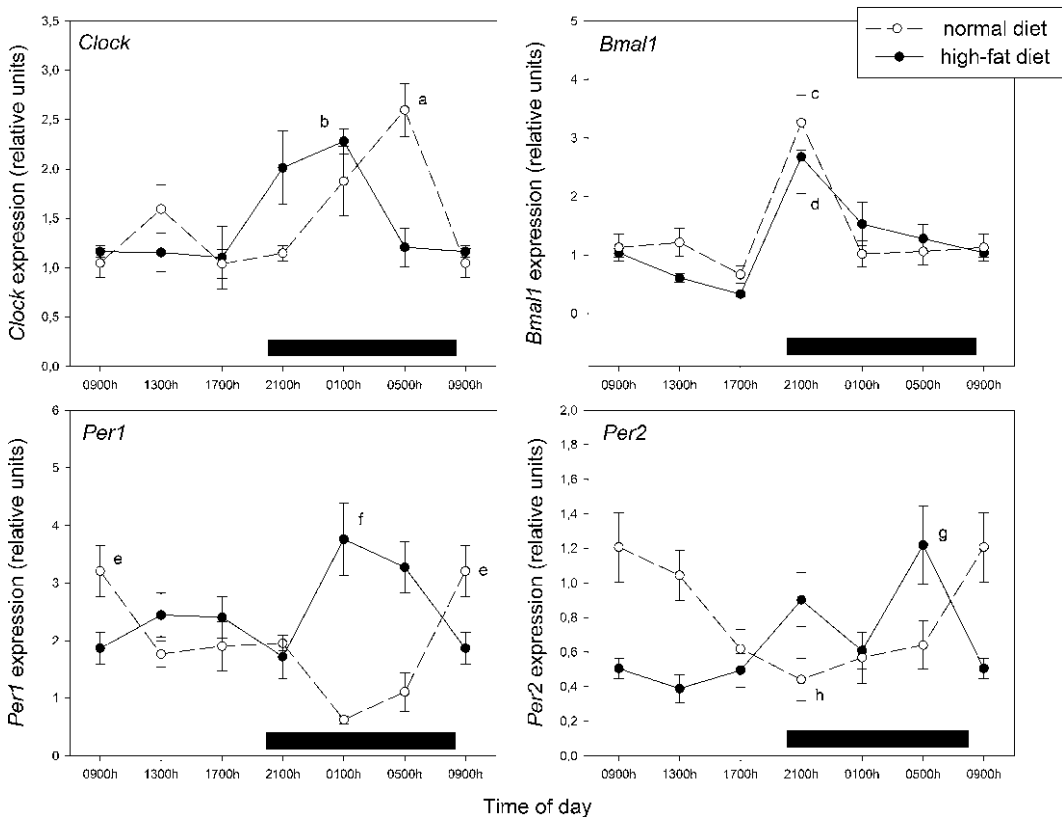
Fig. 25.3 Effect of a high-fat diet on 24-h changes in expression of *Clock*, *Bmal1*, *Per1*, and *Per2* genes in the anterior pituitary of rats. When body weight of high-fat-fed rats attained values about 20–25% higher than controls, groups of six to eight rats were killed by decapitation at six different time intervals throughout a 24-h cycle. mRNA levels encoding circadian clock genes were measured as described elsewhere (Cano et al. 2007). Shown are the means ± SEM of mRNA determination as measured by triplicate real-time PCR analyses of RNA samples. Letters denote significant differences in a one-way ANOVA followed by a Bonferroni's multiple comparison test, as follows: [a]$p < 0.05$ versus 0900, 1700, and 2100 h; [b]$p < 0.05$ versus 0900, 1300, and 2100 h; [c]$p < 0.01$ versus all other time points; [d]$p < 0.01$ versus 0900, 1300, and 1700 h; [e]$p < 0.01$ versus 0100 and 0500 h; [f]$p < 0.05$ versus 0900 h; [g]$p < 0.01$ versus 0100, 0900, 1300, and 1700 h; [h]$p < 0.05$ versus 0900 h (Esquifino et al. unpublished results)

Fig. 25.4 Effect of a high-fat diet on 24-h changes in expression of *Cry1* and *Cry2* in the anterior pituitary of rats. When body weights of high-fat-fed rats attained values about 20–25% higher than controls, groups of six to eight rats were killed by decapitation at six different time intervals throughout a 24-h cycle. mRNA levels encoding circadian clock genes were measured as described elsewhere (Cano et al. 2007). Shown are the means ± SEM of mRNA determination as measured by triplicate real-time PCR analyses of RNA samples. Letters denote significant differences in a one-way ANOVA followed by a Bonferroni's multiple comparison test, as follows: [a]$p < 0.05$ versus 0900 h; [b]$p < 0.01$ versus 1300, 1700, 0100, and 0500 h; [c]$p < 0.05$ versus [d]$p < 0.05$ versus 0900, 0100, and 0500 h (Esquifino et al. unpublished results)
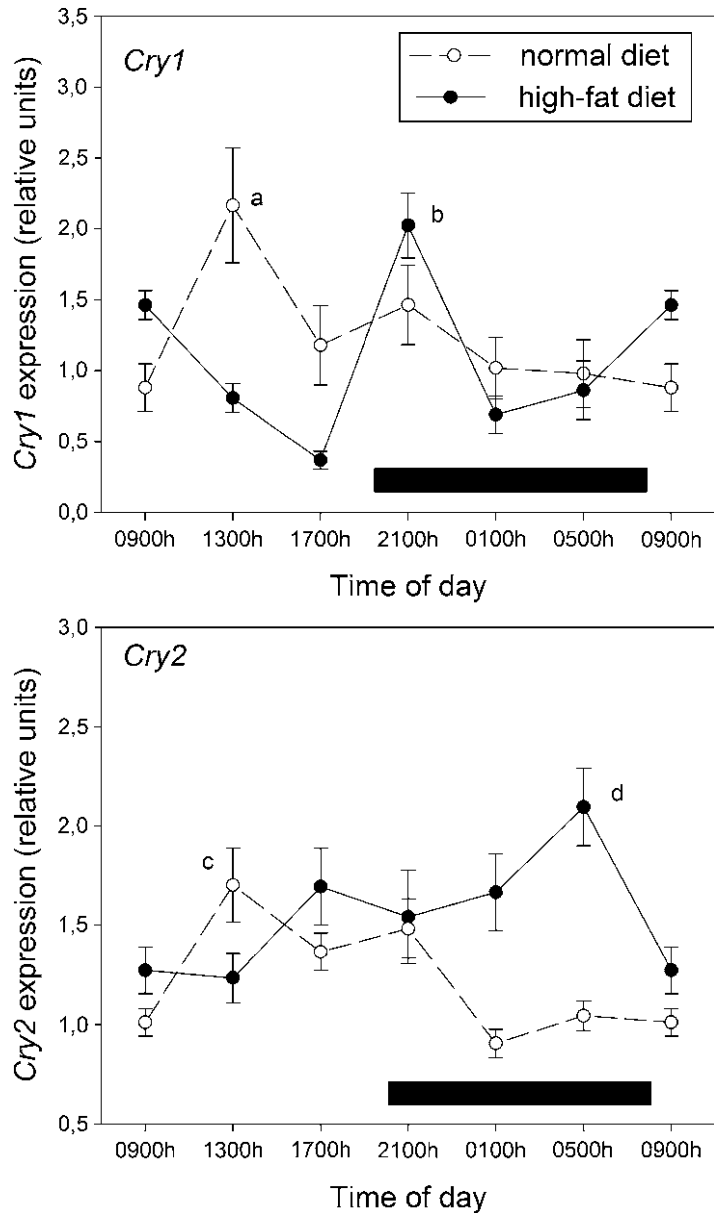
level, circadian rhythms are driven by the self-regulatory interaction of clock genes and their related proteins. Among these *Bmal1*, *Per1*, *Per2*, *Cry1*, *Cry2*, and *Clock* play a major role (Hastings et al. 2003). The heterodimer of the proteins Clock:Bmal1 binds E-box elements at the promoter region of *Per1*, *Per2*, *Cry1*, and *Cry2*, inducing their transcription. Conversely, Per1–2 and Cry1–2 proteins, by interacting with the Clock:Bmal1 heterodimer operate as negative regulators inhibiting their own transcription. Via clock-controlled genes and their downstream effectors, peripheral circadian clock components directly regulate many aspects of cell physiology, such as membrane trafficking, detoxification, nutrient metabolism, and the cell cycle (Hastings et al. 2003).

In the anterior pituitary of rats fed a normal diet the peaks of *Bmal1* and *Per1* and *Per2* expression were in antiphase, *Bmal1* peaking at the beginning of the night and *Per1* and *Per2* peaking about 12 h

later, at the beginning of the light phase. Such a normal relation was reported in several peripheral tissues. Maximal expression of *Cry1* and *Cry2* showed a phase delay of about 4 h as compared to *Per1* or *Per2*.

High-fat-fed rats exhibited a disrupted 24-h rhythmicity of *Clock*, *Per1*, *Per2*, *Cry1*, and *Cry2* expression without affecting the diurnal rhythmicity of *Bmal1*. In particular, *Per1*, *Per2*, *Cry1*, and *Cry2* rhythmicity was almost inverted by the high-fat diet. The results indicate that the inherent transcription, translation, and posttranslational modifications that give the clock its own natural rhythmicity can be severely disrupted in obese rats.

25.4 Conclusions

This review discusses the circadian disruption of hormone release and immune-related mechanisms in the animal models of calorie restriction and hyperadiposity in rats. In every case, the experimental manipulation used perturbed the temporal organization by affecting the shape and amplitude of the rhythm. Further experiments are needed to assess whether the changes in amplitude as well in timing of 24-h rhythms discussed herein can be attributed to an effect on the SCN or to a masking effect on some output(s) of the clock.

25.5 Applications to Other Areas of Health and Disease

Among the innumerable periodic changes that underlie and support the overt circadian physiologic rhythms, the peak values occur in a characteristic sequence over the day ("phase map") in human healthy subjects. Such a sequence and spacing reflects the order and temporal relationships of cause–effect in the normal interactions of the various bodily processes and is very indicative of an organism's health. Most chronic diseases come along with a significant circadian disruption. Medical chronobiology is concerned with the mechanisms of periodic influences on health and disease. Chronopathology is the study of biological rhythms in disease processes and in morbid and mortal events; most medical conditions are affected by circadian rhythms. Chronopharmacology is the discipline that investigates the effects of a drug as a function of biological time. Disruption of amplitude or phase of circadian rhythms by dietary conditions like that discussed in rodents herein can underlie major health problems affecting the developed and the developing world, like the metabolic syndrome.

Summary Points

- Availability of nutrients affects the mechanisms that modulate the circadian variation of pituitary–gonadal axis.
- Malnutrition produced by low or absent proteins in diet is linked to increased susceptibility to infection while calorie restriction of rodents by a diet enriched in proteins and low in fat and carbohydrates significantly increases immune responses.
- Circadian oscillation of many hormones involved in metabolism (corticoids, insulin, glucagon, adiponectin, leptin, ghrelin) as well as of TSH, corticosterone, melatonin, LH, and testosterone becomes disrupted in the development of the metabolic syndrome and obesity.
- Obesity results in disruption of the inherent transcription, translation, and post-translational modifications that give the cellular clock its own natural rhythmicity.

Definitions and Explanations

Circadian: The term "circadian" comes from the Latin circa, "around," and diem or dies, "day," meaning literally "approximately one day."

Zeitgeber: Circadian rhythms are endogenously generated, and can be entrained by external cues, called Zeitgebers, the primary one of which is daylight. An entraining agent can actually reset, or phase shift, the internal clock.

Humoral immunity, delayed (cellular) immunity: Humoral Immunity comprises the aspect of immunity that is mediated by secreted antibodies produced in the cells of the B lymphocyte lineage (B cell). Delayed (cellular) immunity is an immune response that does not involve antibodies or complement but rather involves the activation of macrophages, natural killer cells, antigen-specific cytotoxic T-lymphocytes, and the release of various cytokines in response to an antigen.

Cytokines: Cytokines are a category of signaling molecules that are used extensively in cellular communication. The term cytokine encompasses a large and diverse family of polypeptide regulators that are produced widely throughout the body by cells of diverse embryological origin. Although current terminology refers to cytokines as immunomodulating agents, the differences with hormones are not yet clearly defined.

Adipocytokines: It is a cytokine produced by an adipocyte. The term includes, besides cytokines, hormones like adiponectin, leptin, and resistin.

References

Pandi-Perumal SP, Cardinali DP, Chrousos GP. Neuroimmunology of sleep. New York: Springer Science + Business Media, LLC; 2007.

Antic V, Van Vliet BN, Montani JP. Loss of nocturnal dipping of blood pressure and heart rate in obesity-induced hypertension in rabbits. Auton Neurosci. 2001;90:152–7.

Bartness TJ, Demas GE, Song CK. Seasonal changes in adiposity: the roles of the photoperiod, melatonin and other hormones, and sympathetic nervous system. Exp Biol Med (Maywood). 2002;227:363–76.

Cano P, Cardinali DP, Fernandez P, Reyes Toso C, Esquifino AI. 24-hour rhythms of splenic mitogenic responses, lymphocyte subset populations and interferon ã release after calorie restriction or social isolation of rats. Biol Rhythm Res. 2006;37:255–63.

Cano P, Carreras LO, Ríos-Lugo MP, Fernández-Mateos MP, Reyes MP, Esquifino AI. Effect of a high-fat diet on 24-hour pattern of circulating adipocytokines in rats. Obesity. 2009;17:1866–71.

Cano P, Jimenez-Ortega V, Larrad A, Reyes Toso CF, Cardinali DP, Esquifino AI. Effect of a high-fat diet on 24-hour pattern of circulating levels of prolactin, luteinizing hormone, testosterone, corticosterone, thyroid stimulating hormone and glucose, and pineal melatonin content, in rats. Endocrine. 2008;33:118–25.

Cano P, Poliandri AH, Jimenez V, Cardinali DP, Esquifino AI. Cadmium-induced changes in Per 1 and Per 2 gene expression in rat hypothalamus and anterior pituitary: Effect of melatonin. Toxicol Lett. 2007;172(3):131–6.

Carroll JF, Thaden JJ, Wright AM, Strange T. Loss of diurnal rhythms of blood pressure and heart rate caused by high-fat feeding. Am J Hypertens. 2005;18:1320–6.

Chacon F, Cano P, Jimenez V, Cardinali DP, Marcos A, Esquifino AI. 24-hour changes in circulating prolactin, follicle-stimulating hormone, luteinizing hormone and testosterone in young male rats subjected to calorie restriction. Chronobiol Int. 2004;21:393–404.

Chacon F, Esquifino AI, Perelló M, Cardinali DP, Spinedi E, Alvarez MP. 24-hour changes in ACTH, corticosterone, growth hormone and leptin levels in young male rats subjected to calorie restriction. Chronobiol Int. 2005;22:253–65.

Chen A, Mumick S, Zhang C, Lamb J, Dai H, Weingarth D, et al. Diet induction of monocyte chemoattractant protein-1 and its impact on obesity. Obes Res. 2005;13:1311–20.

Chen D, Wang MW. Development and application of rodent models for type 2 diabetes. Diabetes Obes Metab. 2005;7:307–17.

Cutolo M, Sulli A, Pizzorni C, Secchi ME, Soldano S, Seriolo B, et al. Circadian rhythms: glucocorticoids and arthritis. Ann NY Acad Sci. 2006;1069:289–99.

Elin RJ, Winters SJ. Current controversies in testosterone testing: aging and obesity. Clin Lab Med. 2004;24:119–39.

Esquifino AI, Cano P, Jimenez V, Cutrera RA, Cardinali DP. Experimental allergic encephalomyelitis in male Lewis rats subjected to calorie restriction. J Physiol Biochem. 2004a;60:245–52.

Esquifino AI, Cano P, Jimenez-Ortega V, Fernández-Mateos MP, Cardinali DP. Immune response after experimental allergic encephalomyelitis in rats subjected to calorie restriction. J Neuroinflammation. 2007;4(1):6.

Esquifino AI, Chacon F, Cano P, Marcos A, Cutrera RA, Cardinali DP. 24-hour rhythms of mitogenic responses, lymphocyte subset populations and amino acid content in submaxillary lymph nodes of growin male rats subjected to calorie restriction. J Neuroimmunol. 2004b;156:66–73.

Filipski E, King VM, Etienne MC, Li X, Claustrat B, Granda TG, et al. Persistent twenty-four hour changes in liver and bone marrow despite suprachiasmatic nuclei ablation in mice. Am J Physiol Regul Integr Comp Physiol. 2004;287:R844–51.

Froy O. The relationship between nutrition and circadian rhythms in mammals. Front Neuroendocrinol. 2007;28:61–71.

Glueck CJ, Levy RI, Fredrickson DS. Immunoreactive insulin, glucose tolerance, and carbohydrate inducibility in types II, 3, IV, and V hyperlipoproteinemia. Diabetes. 1969;18:739–47.

Gromadzka-Ostrowska J, Przepiorka M, Romanowicz K. Influence of dietary fatty acids composition, level of dietary fat and feeding period on some parameters of androgen metabolism in male rats. Reprod Biol. 2002;2:277–93.

Guest CB, Park MJ, Johnson DR, Freund GG. The implication of proinflammatory cytokines in type 2 diabetes. Front Biosci. 2008;13:5187–94.

Hastings MH, Reddy AB, Maywood ES. A clockwork web: circadian timing in brain and periphery, in health and disease. Nat Rev Neurosci. 2003;4:649–61.

Holvoet P. Relations between metabolic syndrome, oxidative stress and inflammation and cardiovascular disease. Verh K Acad Geneeskd Belg. 2008;70:193–219.

Ishihara Y, White CL, Kageyama H, Kageyama A, York DA, Bray GA. Effects of diet and time of the day on serum and CSF leptin levels in Osborne-Mendel and S5B/Pl rats. Obes Res. 2004;12:1067–76.

Ladizesky MG, Boggio V, Albornoz LE, Castrillón P, Mautalen CA, Cardinali DP. Melatonin increases oestradiol-induced bone formation in ovariectomized rats. J Pineal Res. 2003;34:143–51.

Lu ZH, Mu YM, Wang BA, Li XL, Lu JM, Li JY, et al. Saturated free fatty acids, palmitic acid and stearic acid, induce apoptosis by stimulation of ceramide generation in rat testicular Leydig cell. Biochem Biophys Res Commun. 2003;303:1002–7.

Masoro EJ. Caloric restriction and aging: an update. Exp Gerontol. 2000;35:299–305.

Moore-Ede MC. Physiology of the circadian timing system: predictive versus reactive homeostasis. Am J Physiol. 1986;250:R737–52.

Pahlavani MA. Influence of caloric restriction on aging immune system. J Nutr Health Aging. 2004;8:38–47.

Phillips LK, Prins JB. The link between abdominal obesity and the metabolic syndrome. Curr Hypertens Rep. 2008;10:156–64.

Prunet-Marcassus B, Desbazeille M, Bros A, Louche K, Delagrange P, Renard P, et al. Melatonin reduces body weight gain in Sprague Dawley rats with diet-induced obesity. Endocrinology. 2003;144:5347–52.

Raskind MA, Burke BL, Crites NJ, Tapp AM, Rasmussen DD. Olanzapine-induced weight gain and increased visceral adiposity is blocked by melatonin replacement therapy in rats. Neuropsychopharmacology. 2006;32:284–8.

Rasmussen DD, Mitton DR, Larsen SA, Yellon SM. Aging-dependent changes in the effect of daily melatonin supplementation on rat metabolic and behavioral responses. J Pineal Res. 2001;31:89–94.

Roth GS, Ingram DK, Lane MA. Calorie restriction in primates: Will it work and how will we know? J Am Geriatr Soc. 1999;47:896–903.

Sanchez-Mateos S, Alonso-Gonzalez C, Gonzalez A, Martinez-Campa CM, Mediavilla MD, Cos S, et al. Melatonin and estradiol effects on food intake, body weight, and leptin in ovariectomized rats. Maturitas. 2007;58:91–101.

Sartipy P, Loskutoff DJ. Monocyte chemoattractant protein 1 in obesity and insulin resistance. Proc Natl Acad Sci USA. 2003;100:7265–70.

Sheng T, Yang K. Adiponectin and its association with insulin resistance and type 2 diabetes. J Genet Genomics. 2008;35:321–6.

Tannenbaum BM, Brindley DN, Tannenbaum GS, Dallman MF, McArthur MD, Meaney MJ. High-fat feeding alters both basal and stress-induced hypothalamic-pituitary-adrenal activity in the rat. Am J Physiol. 1997;273: E1168–77.

Tilg H, Moschen AR. Inflammatory mechanisms in the regulation of insulin resistance. Mol Med. 2008;14:222–31.

Vegiopoulos A, Herzig S. Glucocorticoids, metabolism and metabolic diseases. Mol Cell Endocrinol. 2007;275:43–61.

Waki H, Tontonoz P. Endocrine functions of adipose tissue. Annu Rev Pathol. 2007;2:31–56.

Weisberg SP, McCann D, Desai M, Rosenbaum M, Leibel RL, Ferrante Jr AW. Obesity is associated with macrophage accumulation in adipose tissue. J Clin Invest. 2003;112:1796–808.

Winters SJ, Wang C, Abdelrahaman E, Hadeed V, Dyky MA, Brufsky A. Inhibin-B levels in healthy young adult men and prepubertal boys: is obesity the cause for the contemporary decline in sperm count because of fewer Sertoli cells? J Androl. 2006;27:560–4.

Yanagihara H, Ando H, Hayashi Y, Obi Y, Fujimura A. High-fat feeding exerts minimal effects on rhythmic mRNA expression of clock genes in mouse peripheral tissues. Chronobiol Int. 2006;23:905–14.

Chapter 26
Development of Regulation of Food Intake by the Gut and the Brain: Modeling in Animals

Takashi Higuchi and Chuma O. Okere

Abbreviations

AGRP	Agouti-related protein
ARC	Arcuate nucleus
CART	Cocaine-amphetamine-regulated transcript
CCK	Cholecystokinin
DG	Deoxyglucose
DMH	Dorsomedial hypothalamus
DVC	Dorsal vagal complex
LHA	Lateral hypothalamic area
MA	Mercaptoacetate
MC	Melanocortin
NPY	Neuropeptide Y
NTS	Nucleus of the solitary tract
OLETF	Otsuka Long-Evans Tokushima fatty
POMC	Proopiomelanocortin
PVN	Paraventricular nucleus

26.1 Pups Receive Nutrition from the Mother Through Suckling

26.1.1 Suckling and Weaning

The rat offspring is immature at birth and the pups are born blind and deaf, unable to maintain body temperature, or eliminate wastes without maternal stimulation. During the first 2 weeks of postnatal life, milk supply from the mother is the only food for the young pups. Milk contains 60% fat and provides required fatty acids and ketones that are utilized for routine metabolism by the brain. In addition to dependence on food, the pups depend on their mothers for warmth, urination, and

T. Higuchi (✉)
Department of Integrative Physiology, University of Fukui, Eiheij-cho, Matsuoka, Fukui, 910-1193, Japan
e-mail: higuchit@u-fukui.ac.jp

defecation. During this period, for instance, the thermoregulatory mechanisms present in adults that are responsible for increasing heat production when there is a decline in body temperature are immature in the pups. Thermal homeostatic mechanisms mature between P10 and P20 and the pups begin to nibble on solid matter including bedding, feces, and chow around the P16 or P17 postnatal day. The process of weaning proceeds gradually over the next week. These developmental changes are paralleled by a change in diet from one that is high in fat and low in carbohydrate to one that is low in fat and high in carbohydrates during weaning. Concomitant with the process of weaning, the eyes and ears open on P14, just before the pups commence on a robust avid exploration of their environment.

26.2 Suckling: Interaction Between Mother and Pup

26.2.1 Location and Attachment to the Nipple by the Pups

Generally speaking, behavioral interaction between mothers and pups can be described in three phases. The first phase occurs during the first week after birth with the mother being the exclusive initiator of contact with pups. Typically, the maternal behavior during this first phase includes, but is not limited to, the mother dam retrieving the pups to her nest followed by spending 80–90% of her time hovering over her nestled young during the initial days immediately following parturition. By P15, the pups are well insulated with fur and fat and their eyes have opened and are rarely retrieved by the dam. The second phase is characterized by mutually initiated bouts of contact with the pups often leaving the nest to approach the mother. In the third stage of the nursing–suckling relation, the contact is initiated almost exclusively by the infant (Blass and Teicher, 1980).

26.2.2 Lactation and Nipple Attachment

Once contact with the mother is established, the pups locate and attach to a nipple and suckle. In the rat pup, contact elicits a characteristic "rooting" response through which the infant, using swimming-like motions, moves quickly across the mother's body, scanning the surface by moving its head from side to side until the pup contacts a nipple. The pup probes the nipple area, extending its tongue and vigorously licking the nipple until it becomes erect, whereupon the pup suckles and becomes immediately quiescent (Blass and Teicher, 1980). It appears that physicochemical features of the nipple facilitate the attachment of pups. For instance, washing the nipples essentially eliminate attachment, indicating that some substance must coat the rat's nipples in order for pup attachment to occur. Subsequent application of the perfusate to the nipple reinstated suckling in much the same way that painting an extract of pup saliva on washed nipples resulted in full restoration of suckling. Intriguingly, while rat milk does not constitute an effective stimulus for nipple attachment, maternal saliva and amniotic fluid effectively bring about suckling in much the same way as the extract from washed nipples. The effectiveness of maternal saliva and amniotic fluid in enhancing pup nipple attachment is based on the fact that the parturient rat mother, between the births of pups, cleans and licks each newborn and her anogenital

region, both of which are coated with birth fluids. She also licks the nipple region thereby depositing her saliva, now rich with amniotic fluids and serves as a chemoattractant for the pups (Blass and Teicher, 1980).

26.3 Ontogeny of Hunger

Various internal stimuli (for example, stomach distension) that inhibit feeding in adult rats do not affect milk withdrawal until the pups are about 15 days old; this is the age that also marks the transitional point in nipple-attachment latency. The stretch response that is associated with milk letdown is eliminated only when the pups' stomach become so distended by repeated injections of milk that fills up the esophagus (Fig. 26.1). Another distinction between infants and adult ingestion derives from the influence of nutrient in the stomach, which differentially suppresses intake in adults, but does not exert such an effect in the pups (Fig. 26.2).

26.3.1 Attachment Latency

In early studies, the anesthetized, non-lactating dam model was used to investigate the attachment latency in the suckling test in rat pups deprived of the opportunity to suckle. It is known that olfactory cues of the dam play a significant role in the pup attachment to the nipple depending on the age of the pups (Hall and Cramer, 1977). Hence, during the first 12 days of postnatal life, the mean attachment latency for non-deprived rat pups was virtually identical to that of their deprived siblings (Fig. 26.3). However, at about P12–P14, rat pups deprived of suckling continued to exhibit rapid nipple attachment resulting in a lower mean attachment frequency in comparison with the non-deprived pups. Also, between P15 and P25, suckling was still observed in the non-deprived rats, but attachment of the nipple in addition to occurring with longer latencies, appeared to differ quantitatively. During this latter age limit, attachment to the nipple seemed almost casual in that the rats sniffed about the nipple, or they might lick it and then turn away. This overall behavior in non-deprived pups lacked the excitement characteristic of younger pups or their deprived siblings. It is therefore apparent that after the pups attained 25 days of age, liberation from maternal sensory cues seems complete. Consequently, sensory properties of the mother no longer elicited any suckling in the absence of deprivation. In this regard, suckling takes on the characteristics of adult ingestion behavior (Hall and Cramer, 1977). Suckling-deprived pups showed another age-related difference in suckling behavior. Pups 12 days of age and younger, did not leave non-lactating nipple even after 8 h of nonnutritive suckling. Starting at about P15, they shift from nipple to nipple in the absence of milk letdown. This incidence of shifting increased with deprivation and age, reaching its maximum in 21–24-day-old rat pups (Henning et al., 1979).

Cholecystokinin (CCK) is usually a potent modulator of milk ejection. However, the stretch response and milk intake were not affected by CCK until pups were about 2 weeks old: at this age, a 40-unit dose was effective in reducing milk intake (Blass et al., 1979). On the other hand, at 29 days of age, a 20-unit dose of CCK was effective in reducing milk intake in these young rats as was observed in free-feeding adults. In addition, both suckling and the stretch response were voluntarily terminated in older pups. This may be interpreted as indicating that they exhibited grooming, cage exploration, eventual rest, and sleep behaviors typically observed in adult rats at the end of a

Fig. 26.1 Stretch reaction by a pup at the time of milk letdown. A pup is suckling to an anesthetized mother (**a**), when milk-ejection reflex occurs, the pup exhibits characteristic stretch reaction, it pulls strongly against the nipple with its legs outstretched and its back arched (**b**)

meal. Such a sequence of behavioral patterns associated with satiety usually become evident after 15 days of age.

Thus during the first 2 weeks of postnatal life, pups have a basic tendency to suckle, perhaps due to olfactory cues but do not have hunger signals per se. During this time, the mother plays an active role in pup nutrition by retrieving and crouching over them to encourage suckling. A sense of hunger is not necessary during this early stage and attachment to the nipple may be an end in itself since the behavior of rats that have been suckling almost continuously is virtually indistinguishable from that of rat pups
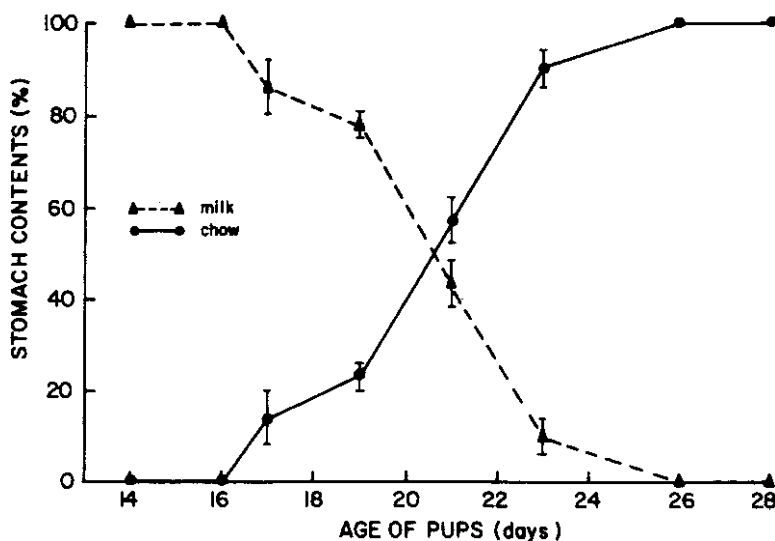
Fig. 26.2 Pattern of weaning as determined by amount of milk and chow present in stomach contents at various developmental ages. Units are percentage by weight of total stomach contents and values are given as means±SE (*n*=5) (Reprinted from Henning et al. 1979. With permission)
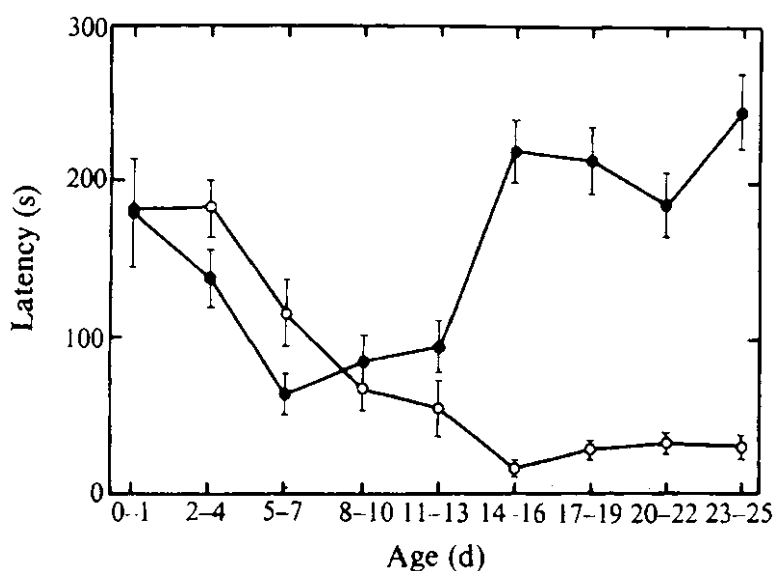
Fig. 26.3 Mean latency (±SE) of non-deprived (●) and 22-h deprived (○) rat pups to attach to nipples of their anesthetized mother. A pup's score was taken as the mean of its three 5-min tests. The number of subjects given varied from 22 to 36 at each data point (Reprinted from Hall et al. 1975. With permission)

deprived of suckling for up to 24 h. Moreover, continued attachment to the nipple is apparently not dependent on letdown or amount of milk in the stomach. However, beyond the second week of postnatal life, the pups begin to roam further from their mothers and also start to nibble solid food. During this and later ages, a sense of hunger assumes a more important role as a stimulus that regulates food intake in contrast to the active role of the mother, which ensures adequate nutrition of pups of younger age.

26.4 Suckling Is Not a Prototype of Food Intake Pattern in Adults

26.4.1 Suckling and Independent Ingestion

In order to distinguish the suckling behavior of rat pups from the behaviors initiated by the mother, Hall (1979b) developed a new experimental paradigm with anesthetized mothers and pups with oral catheters. In this paradigm, a thin, polyethylene tube was implanted in the back of the rat pup's mouth through which a bolus of milk could be injected after pup attachment to a nipple. The injection of milk through this tongue cannula triggered the "stretch" response, which occurs naturally when the milk-ejection reflex occurs intermittently at 3–5 min intervals (Lincoln et al. 1973). Using these intraoral catheters, milk was infused into the mouths of pups in warm, moist, testing chambers on P3. Differential behavioral dispositions result depending on the location of oral cannula placement. For instance, when the catheter was placed on top of the tongue toward the rear to the mouth at the position of the teat during sucking, pups swallowed all of the volume of milk infused. Interestingly, the pups continued to withdraw or accept milk until they were no longer able to retain any more milk in their stomach as evidenced by either esophageal milk reflux or pup inability to maintain an appropriate nipple attachment posture (Cramer and Blass 1983). This behavior is a reflexive swallowing resulting from stimulation of the posterior portion of the oral cavity, the last component of the sensorimotor sequence of ingestion (Hall 1979b).

However, placement of the catheter beneath the tongue on the anterior floor of the mouth resulted in ingestion accompanied by active mouth movements in the pups resembling mastication and mandibulation observed in the adult rat during feeding. One major difference from pups with cannula placement in the top of the tongue toward the back of the mouth is that pups with cannula placement beneath the tongue do not ingest all the infused milk. Rather, these pups controlled their milk intake; essentially eating more after deprivation of suckling and refraining from further ingestion of infused milk when gastric volume was about 5% of body weight. This controlled ingestion observed during anterior catheter infusions is called "independent ingestion" because it occurs away from the dam and its oromotor topography differed from that associated with suckling. Another form of independent ingestion is based on the observation that the pups licked from a puddle of milk on the floor of the test chamber (Hall and Bryan 1980). This eliminates the need for a pup to search for milk while retaining the demand that the pup initiate licking and other oral movements required to move milk to the rear of the mouth to elicit swallowing. However, not until P9–P12 do pups consume milk from a spatially restricted source. Therefore, it is a reasonable proposition that independent ingestion, not suckling, may be a developmentally continuous process with adult feeding.

From a behavioral standpoint, certain distinctions can be made between suckling in pups and adult feeding behavior in terms of the physiological control and motor pattern of ingestion. For example, in the normal mother–litter situation, direct control of milk intake does not depend upon the pups altering their nipple-attachment behavior, regardless of whether suckling occurs or not. Rather, it is presumable that pups indirectly regulate intake by the vigor and rhythm of suckling. Hence, any gross or general change in behavioral vigor would have a significant influence on intake within the limits of milk availability determined by the amount of milk provided by the mother. One functional consequence of this fact is that young rats will literally drown at the nipple if provided with unlimited milk supply because young pups do not control intake when suckling. On the contrary, adult rats directly control food intake when feeding.

26.5 Development of Positive and Negative Feedback Control of Independent Ingestion

26.5.1 Positive and Negative Feedback Control

Observations from several studies indicate that post-ingestive stimulation terminated feeding because sham-fed meals were always larger than real-fed meals. The type of diet, duration of food deprivation, and experience with the diet has been suggested to determine the size of animals with sham-fed meal (Smith 2006). The different feeding patterns are under regulation of specific pathways and stimuli. For instance, olfactory and orosensory stimuli exert positive-feedback control of food intake while post-ingestive stimuli produce negative-feedback control of intake. Both orosensory and post-ingestive stimuli act preabsorptively, and stimulate the mucosal surface of the gut from mouth to the end of small intestine (Smith 2006) and may be segregated into positive and negative influences, respectively. While the positive stimuli are conveyed to the nucleus of the solitary tract (NTS) in the medulla by fibers in the cranial nerves, the negative stimuli are transmitted to the NTS by the abdominal vagus nerves. Functionally, the NTS comprises the dorsal vagal complex (DVC) with the dorsal motor nucleus of the vagus and area postrema (Fig. 26.4). Neurons within the DVC receive direct neural input from neurons in the hypothalamus implicated in the control of food intake including the paraventricular nucleus (PVN), lateral hypothalamic area (LHA), dorsomedial hypothalamus
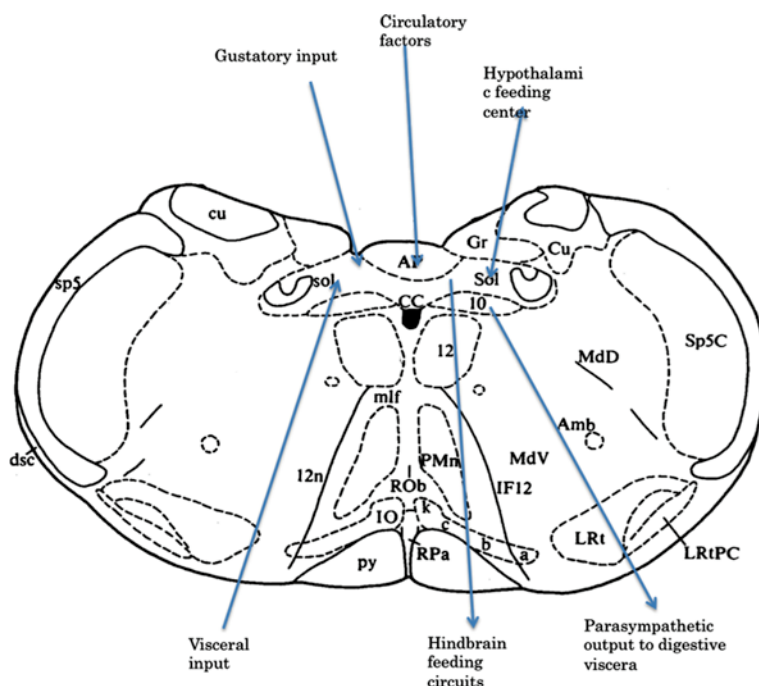
Fig. 26.4 A schematic illustration of the neural connections of the hindbrain dorsal vagal complex (*DVC*) and hormonal inputs to the DVC in the rat. *Ap* area postrema, *Sol* nucleus of the solitary tract (*NTS*); 10 dorsal motor nucleus of the vagus (Reprinted from The Rat Brain in Stereotaxic Coordinates written by Paxinos and Watson 1982 with modification. With permission)

(DMH), and arcuate nucleus (ARC). Several unique features of the DVC make it ideally suited as a brainstem integration and command center for ingestive behavior (Rinaman 2006).

26.5.2 Eating and Drinking

Until the second week of postnatal life, eating and drinking are not differentiated as distinct responses to food and water deprivation. Hence, orosensory stimulation with milk, sucrose, and water are generally adequate orosensory stimuli in the first postnatal week since from P3 to P6, intake of the three respective stimuli are not significantly different after 24 h of deprivation (Hall 1979a). On the contrary, during the later phase of postnatal life, the extent of ingestion is dependent on the duration of nutrient deprivation. Expectedly therefore, more food intake occurs during the independent ingestion phase after 24 h of deprivation than after 1- or 7-h deprivation (Hall 1979b). In terms of functional efficacy to induce ingestion, while dehydration is the critical property that increases food intake during the first postnatal week, adult rats display dehydration anorexia. Similarly, it is hydration, not metabolic or caloric signals, that appears to be the primary modulator of independent intake after a period of deprivation. This preferential efficacy of the influence of hydration on ingestion appears to depend on postnatal evolution given that gastric infusion of isotonic saline or milk during deprivation eliminated the stimulation of intake by deprivation in pups on P6. However, only milk infusions blocked the increased intake in pups on P15 (Phifer et al. 1986). These observations suggest that when deprived of nutrients in early postnatal life, thirst but not hunger is the primary stimulus for increased ingestion by pups.

This conclusion is supported by findings that as early as P2, intracerebroventricular (i.c.v.) injection of angiotensin II induces an intake of both milk and water. It is noteworthy that a preferential intake of a greater amount of water relative to milk, which is the characteristic dipsogenic response to angiotensin II seen in adults, appears on P8. Also, neurochemical modulators of feeding exert different effects during different phases of early postnatal life or development. For example, the orexigenic effect of i.c.v. norepinephrine is believed to appear at P9 and P10; and, at an age when it exerted orexigenic effect in pups feeding away from their dam, norepinephrine had no effects on nipple attachment latencies or on the amount of time spent on the nipple (Ellis et al. 1984). Also, injection of neuropeptide Y (NPY) into the PVN enhanced milk and water intake equally at P2 while at P15, NPY produced a significantly greater enhancement of milk than water intake (Capuano et al., 1993).

In another context, dehydration anorexia does not emerge until after the first 2 weeks of postnatal development (Bruno, 1981), while the inhibitory effect of dehydration on gastric emptying emerges sometime between P11 and P19. This developmental period coincides with that during which plasma hyperosmolality first begins to inhibit independent ingestion (Callahan and Rinaman 1998). Taken together, an early picture of the ontogeny of mechanisms controlling food intake in rat pups suggest that pups possess only rudimentary control over independent ingestions that are related to the hydrational status and not to energy status.

26.5.3 Taste

During the first few days of postnatal life, rat pups can distinguish various chemical solutions and milk from water. Hence, intraoral milk infusions on P1 can serve as a reinforcing stimulus in shaping an operant response (Johanson and Hall, 1980). From P3, pups show discrimination between water and sucrose in their mouthing behavior and general activity, but discrimination of the amount of intake appears from P6. For example, infusions of 5%, 10%, and 20% sucrose during this period of

postnatal life produced equivalent intake in the amounts of the three solutions all of which were significantly more than the intake after water infusion (Hall and Bryan 1981). Later in development by P14, the volume of sucrose ingested was a monotonic linear function of sucrose concentration (Ackerman et al. 1992).

Similarly, intake after infusions of corn oil changed during this period, but these changes occurred later than those in response to sucrose. For instance, by 12–15 days of age, pups responded more to oil emulsions (10% and 30%) than they did to water or emulsifier solution. Interestingly, the corn and mineral oil emulsions were almost as effective as milk but less effective than sucrose (0.3 M) in stimulating ingestion (Ackroff et al., 1990). On P14, emulsions of corn oil produced more intake than infusions of water, but the intake was not a monotonic function of concentration until P21 (Ackerman et al., 1992). The changing potency of corn oil emulsion is due to maturation of the sensitivity of the trigeminal tactile system to texture of viscosity or the maturation and sensitivity of a gustatory system to fatty acids.

26.6 Emergence of the Post-ingestive Inhibition

26.6.1 Gastric Volume

Of all the post-ingestive stimuli that can influence ingestion, gastric volume is sufficient to terminate eating in the first postnatal week, a time when the eating and drinking systems have not been differentiated. For instance, when pyloric noose was open or closed on P6, a gastric preload of milk or saline decreased food intake equally in pups. However, regardless of noose or preload condition, post-ingestive food intake stopped when stomach content reached approximately 6.5% of body weight (Phifer et al. 1986). When gastric fistulas were unplugged after the pups had stopped ingesting milk, additional vigorous ingestion followed with total intakes of up to 20% body weight. Therefore, the signal for termination of intake in young rat pups appears to be controlled exclusively by the level of gastric filling: pregastric signals alone appear insufficient, and postgastric signals appear unnecessary for termination of intake (Phifer et al. 1986).

26.6.2 Hypertonic Preload

In addition to the effect of preload volume, hypertonic preloads of 20% glucose and 20% maltose produce a larger reduction of food intake by pups than isotonic preloads (Weller et al. 1997). This inhibitory effect of 20% glucose on P12 may be unrelated to post-absorptive metabolic effects because a preload of 20% 2-deoxyglucose (2-DG), which is not metabolized, actually decreased glucose utilization and produced equivalent inhibition of intake (Weller et al. 1997). In addition, the magnitude of the reduction of intake by intraperitoneal injection of 20% glucose was much smaller than by gastric preload (Weller et al. 2001). In a separate experiment circumventing intestinal degradation and transport problems, the glucose solution was introduced into the rat's body closer to the circulation; but this route drastically decreased the efficacy of the glucose solution to inhibit intake. This suggests that the nutritive metabolic stimulus of carbohydrate preload may not control post-ingestive intake during preweaning period in the rat. Moreover, hypertonic stimuli in the stomach or small intestine provide inhibitory control of food intake by postnatal day 12.

The mechanism by which the volume of an isotonic preload or hypertonic preload inhibits food intake is unknown, but is most likely through vagal mechanoreceptors transmitting the signal to the

NTS. This derives from findings that CCK1 receptor antagonist devazepide did not inhibit the inhibitory effect of volume and hypertonic preloads (Weller et al. 1997). When the CCK antagonist was administered prior to the test in which no preload was given, food intake did not change in pups tested on P9–P18. This evidence suggests that endogenous CCK does not mediate the post-ingestive negative feedback control of intake of milk in pups of this age.

26.6.3 Nutritive Effect of Fats and Proteins

Compared to a sham-preload treatment, gastric preloads of corn oil inhibited intake on P12 to an equivalent extent as preloads of a similar concentration of nonnutritive mineral oil. Only a few days later, on P15 and P18, corn oil preloads significantly reduced intake more than the mineral oil preloads (Weller et al. 1997). The inhibitory effect of corn oil appeared to be due to its fatty acid components rather than its tactile or textual effects because identical preload of mineral oil produced significantly less inhibition of intake. The gastric preload of corn oil probably inhibited intake by a preabsorptive chemical action related to its component fatty acids. The site of this preabsorptive action is uncertain, but is mediated, at least in part, by the endogenous CCK system. While pretreatment with devazepide did not affect the decreased net intake produced by a nonnutritive fat preload compared to sham preload, this antagonist significantly reduced the intake inhibition of corn oil. This result suggests an attenuation of its differential effect compared to the mineral oil preload (Weller et al. 1997), probably acting at the vagal afferent terminals in the small intestine.

Intragastric or intraduodenal administration of peptones, hydrolysates of proteins, decreases food intake in adult rats. Also, the effects of isotonic or hypertonic gastric preloads of peptones on food intake during an independent ingestion test away from the dam reveal that preloads of isotonic peptone significantly reduced intake more than preloads of isotonic saline on P18, but not on P12 (Weller and Tsitolovskya 2004). Thus, the ability to respond behaviorally to this nutritive stimulus appears to emerge between P12 and P18. This is a similar ontogenic time course as that observed for the inhibition of intake by a preload of corn oil.

26.6.4 CCK

CCK exists in several forms (amino acid chain lengths), all sharing a common identical bioactive C-terminal primary 8-amino-acids long, called CCK-8. Most experiments were performed using this CCK-8. Release of CCK from the upper small intestine by preabsorptive nutrient stimuli is a mechanism for negative feedback control of meal size under physiological conditions. Entry of food into the intestine triggers the release of endogenous CCK by the intestinal mucosa thereby activating CCK-1 receptors located in the abdomen and vagus nerve terminals to transmit satiety signal to the NTS in the hindbrain (Moran and Kinzig, 2004).

It has been reported that CCK reduced the volume of milk ingested during independent feeding as early as P1 without any evidence of aversive behavioral side effects (Robinson et al., 1988). Also CCK inhibited the rate of gastric emptying in P1 and P3 rat pups, and the threshold dosage for this suppression were identical to the threshold for the inhibition of ingestion. Since in P6 rat pups, gastric distention is the only signal inhibiting independent ingestion (Phifer et al. 1986), an aspect of the satiety action of CCK is indirect and derives from the hormone's action on gastric emptying, resulting in gastric distention.

Rinaman and colleagues were the first to investigate the pattern of increased cFos immunoreactivity, an index of neuronal activity, after intraperitoneal CCK injections in neonatal rats. They observed

that CCK increased the numbers of cFos-positive cells in the NTS on P2, but unlike the adult rats, there was no increase in the number of cFos immunoreactive cells in the forebrain (Rinaman et al. 1994). They interpreted the lack of forebrain cFos immunoreactivity in pups on P2 as evidence of immaturity of ascending connections from the hindbrain to the hypothalamus. The caudal brainstem of the adult rat has sufficient neural complexity to process vagal stimulation by peripheral CCK into an inhibitory effect on intake, because peripheral CCK decreased intake in the chronic decerebrated rats (Grill and Smith 1988). That CCK decreased intake on P1 and increased cFos immunoreactive cells in the NTS but not in the forebrain, is evidence that this is also the case in the neonatal rat. On the other hand, CCK did not reduce milk intake by P5 and P10 but was effective in depressing milk intake in P15 and P20 rat pups. Of significant note is that, despite its inhibitory effect on milk intake, CCK never lengthened the latency to attach to the nipple (Blass et al. 1979).

The stimulation of cFos immunoreactive cells in the NTS in pups on P10 and P11 (Blumberg et al. 2006b), and the decrease in food intake produced by the release of endogenous CCK in pups on P9–P12 (Weller et al. 1990) indicate that negative feedback control mechanisms from the small intestine may be functional by the second week by which time the regulatory mechanisms that control nutrient and water intake during independent ingestion have become differentiated. Results from studies using devazepide suggest that CCK-1 receptors appear to mediate a portion of the reduction of food intake produced by corn oil, but not by glucose or peptone in infant rats. However, recent finding that Otsuka Long-Evans Tokushima fatty (OLETF) rats, which do not express CCK-1 receptors, exhibit increased meal size and weight gain as early as P2–P4 (Blumberg et al. 2006a), suggest that the CCK system may have a physiological role in the regulation of food than earlier thought.

26.6.5 Ghrelin

Ghrelin was identified as an endogenous ligand for growth hormone secretogogue receptor, and was later found to have an orexigenic action. Ghrelin is produced mainly in the oxyntic glands of the stomach and is released in response to negative energy balance, such as starvation (Kojima and Kanagawa 2005). Generally, it is accepted that olfactory and orosensory stimuli elicit positive-feedback control of intake while post-ingestive stimuli produce negative-feedback control of intake. Ghrelin is only one endogenous orexigenic substance that is synthesized in the gastrointestinal tract. Similar to the site of action of CCK, the vagus afferent nerve is the major pathway for peripheral signals of ghrelin for starvation (Kojima and Kangawa 2005).

There are not many studies on the role of ghrelin in the control of food intake during preweaning period. It is however known that 8 h of milk restriction significantly decreased and increased the ghrelin concentration in the stomach and the plasma, respectively, in P7 rat pups (Hayashida et al., 2002). It has been reported recently that ghrelin increased independent feeding as early as P10 in pups whereas the increase in milk intake during suckling appeared only after P20. Also, an anti-ghrelin antibody inhibited milk intake on P25 and later, indicating that ghrelin may start regulating food intake from about fourth postnatal week (Piao et al. 2008).

26.7 Development of Controlling Food Intake by Metabolic Signals

Generally speaking, periods of food deprivation result in increased food intake. Among the factors that contribute to this response are cues related to change in energy availability. In adult rats, alterations in the utilization of glucose-derived energy provide a clear stimulus to increase food intake. In P6 pups, nutritive gastric preloads were followed by similar intakes and only changes in hydrational

state caused by distilled water loads appeared to affect food intake. Thus, such young pups appeared to be relatively insensitive to metabolic or caloric signals produced during deprivation. However, by P15, food intake following nutritive preloads was less than intake following nonnutritive preloads (Phifer et al. 1986). Therefore, by P15, behavioral responsiveness to a metabolic signal appears to have emerged or at least began to do so. Studies examining the nature of this metabolic signal first focused on changes in glucose metabolism using 2-DG.

The effects of interfering with glucose utilization or availability using 2-DG, 5-thioglucose, or insulin did not increase independent ingestion until the fourth postnatal week (Houpt and Epstein 1973; Leshem et al. 1990). 2-DG stimulates pups to eat chow but not to suckle (Gisel and Henning 1980). The lack of effect of glucoprivation on independent ingestion in the first 3 weeks of postnatal life is not due to the inability of the preweaning pup to sense glucoprivation, because the hyperglycemic response to glucoprivation occurs as early as P3 (Houpt and Epstein 1973; Leshem et al. 1990). Thus, it is unlikely that the metabolic or caloric signal produced by food deprivation that emerges between P6 and P15 in rat pups is related to changes in availability of glucose utilization.

An alternative possibility is that the signal is related to changes in fat availability or utilization. Changes in fat metabolism were produced by administration of mercaptoacetate (MA), a drug that inhibits mitochondrial acetyl-CoA dehydrogenases resulting in increased food intake over several hours and is accompanied by characteristic changes in circulating energy-related substances such as ketone bodies and free fatty acids in adult rats. In addition, simultaneous blockade of both fat and glucose metabolism produces synergistic effects on food intake, suggesting that these signals are integrated to control food intake.

In tests of consuming diet from the floor of a test container, moderate doses of MA stimulated independent ingestion on P12 and P15. Although MA failed to stimulate independent feeding on P9, its effect to decrease the plasma concentration of beta-hydroxybutyrate (a ketone body) (Swithers 1997), indicates that MA was effective in decreasing fat metabolism at this age. However, results from a recent study appear to contradict this conclusion. For instance, MA failed to stimulate intake of milk on P18 and P21 while higher doses which stimulate intake in adult rats, suppressed milk intake. In addition, MA inhibited chow intake on P18 (Swithers et al. 2004). Hence, it is not clear why MA does not stimulate food intake during preweaning rat pups. This is because by P18, pups initiate food intake independent of the dam and begin to alter the fat composition of their diet from the high-fat milk to a lower fat chow. In adult animals, the effect of MA is influenced by the fat composition of the maintenance diet, with higher fat diets resulting in more profound responses. Thus, while P18 pups still consume a significant percentage of their calories from the mother's milk, the decreasing fat content of the chow may inhibit the response to changes in fatty acid oxidation by MA in preweaning pups.

26.7.1 Leptin

The adipose hormone leptin is an important regulator of energy balance. Leptinergic pathways send signals about nutritional status and energy storage levels to the feeding center in the hypothalamus, through its action on the orexigenic and anorexigenic neuropeptides in the ARC (Schwartz et al. 2000).

There is a surge in plasma levels of leptin during the second postnatal week without a concomitant increase in body fat mass in mice (Ahima et al. 1998). The high level of leptin during the neonatal period is surprising, because this is an important growth phase and it seems counterintuitive to have such a high satiety signal (Fig. 26.5). It is reasonable to conceive the idea that the neonatal pups may be in some form of leptin resistance. This metabolically irrelevant surge of leptin may consequently
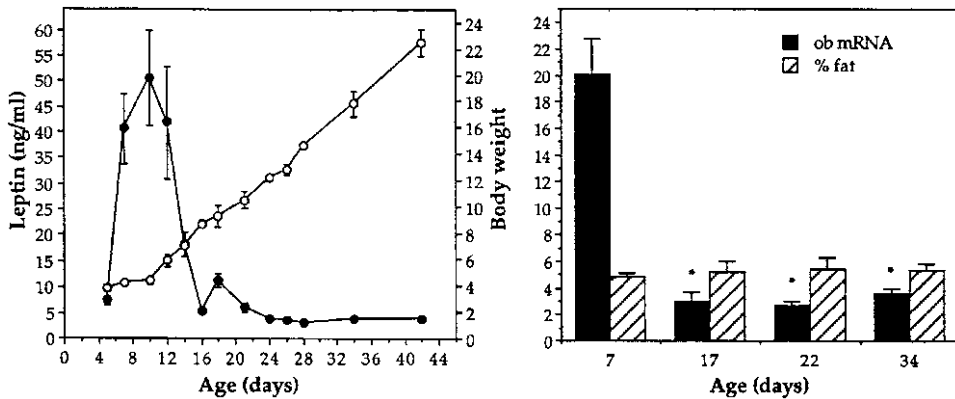
Fig. 26.5 Leptin signaling in neonatal life. The plasma leptin levels (*left*) and leptin (*ob*) mRNA expression (*right*) in female mice. Values represent means $\pm$ SE; $n = 5$–10. For ob (leptin) mRNA, values represent arbitrary densitometric units, $P < 0.05$ compared with day 7 (Reprinted from Ahima et al. 1998. With permission)

act as a developmental signal to promote formation of arcuate pathways (Bouret and Simerly 2004) as discussed later.

There are many reports that show that exogenous leptin treatment does not inhibit growth, ingestion, or energy expenditure during the first 2–3 postnatal weeks (Ahima and Hileman 2000; Proulx et al. 2002). While leptin seems to have little effect on food intake during early postnatal period, it affects neuronal activity in the ARC during this phase. Acute peripheral leptin treatment at P10 increased mRNA expression of suppressor of cytokine signaling 3 (a marker of leptin receptor activity) in the ARC, suggesting that the leptin receptors in the ARC are functional (Proulx et al. 2002). The same treatment increased proopiomelanocortin (POMC) mRNA levels, but decreased NPY mRNA levels in the rostral part of the ARC. Chronic leptin treatment (daily, P3–P10) downregulated leptin receptor mRNAs and NPY mRNAs (Proulx et al., 2002). Although there is a report that daily leptin injections from P10 to P17 did not exhibit any change in hypothalamic expression of mRNAs for NPY, agouti-related protein (AGRP), POMC, or cocaine- and amphetamine-regulated transcript (CART) in mice (Ahima and Hileman, 2000), a recent report confirms leptin's effect on neurons in the ARC as early as P6 (Bouret and Simerly, 2004).

26.8 Development of the Hypothalamic Circuit Controlling Food Intake

26.8.1 NPY Neuron

NPY neurons in the ARC are the target of leptin activity and provide a potent orexigenic drive in the brain, as well as energy expenditure (Gehlert, 1999). The NPY neurons in the ARC synthesize AGRP, an endogenous antagonist of anorexigenic melanocortin 3/4 receptors, and is itself a potent orexigenic peptide (Table 26.1). Thus, NPY/AGRP fibers provide a powerful dual orexigenic drive by activating NPY receptors and antagonizing MC3/4 receptors.

Since microinjection of NPY into the PVN as early as P2 can elicit an increase in independent milk intake (Capuano et al. 1993), there is an intact NPY receptor system within the hypothalamus during early postnatal period when NPY neurons in the ARC have not extended their axons to the targets. NPY mRNA expression has been reported to be present within the ARC throughout

Table 26.1 Key features of AGRP

1. AGRP is a potent orexigenic peptide.
2. AGRP was identified from studies of agouti mouse, an autosomal dominant model of genetic obesity character-ized by a yellow coat color and an obese phenotype.
3. AGRP is synthesized in the NPY neuron that exists in the arcuate nucleus (ARC).
4. AGRP binds to melanocortin 3 (MC3) and melanocortin 4 (MC4) receports.
5. AGRP is an endogenous antagonist of anorexigenic melanocortins such as α-melanocyte-stimulating hormone (α-MSH).
6. AGRP causes hyperphasia when administered into the cerebroventricle.
7. AGRP expression is upregulated together with NPY by fasting and leptin deficiency.

postpartum development, with low levels at P1 followed by rapid, progressive increase that peaks at P16 before returning to levels observed in the adult by P30 (Grove et al. 2005). The physiological significance of this increase in NPY mRNA at P16 is not known but may be associated with a stimulation of the drive to eat solid food, possibly due to a change in dietary needs prior to weaning. Another characteristic feature of NPY expression during early postnatal period is its presence in the regions such as the DMH, perifornical region, PVN, and LHA that are not apparent in the adult rats. The reason for this NPY distribution in the neonatal period is not clear. Also, AGRP mRNA is expressed exclusively in the ARC throughout postnatal development, and that it displays a developmental pattern of expression similar to that seen for NPY mRNA in the ARC, with relatively low levels of gene expression observed as early as P2, and high levels by P12 (Grove et al. 2003).

26.8.2 POMC Neuron

The melanocortin system is also an important regulator of food intake and energy balance. The main populations of melanocortin neurons that contain POMC and CART are located within the ARC. Nearly all of the components of the melanocortin system (POMC, AGRP and MC4 receptor) are present in the hypothalamus throughout the postnatal period (Grove et al. 2003). A nonselective melanocortin receptor agonist melanocortin II (MTII) decreased milk intake and increased energy expenditure at P5–P6, P10–P11, and P15–P16. Also, MT II induced cFos activation in the PVN and VMH, but did not increase NPY mRNA in the ARC (Glavas et al., 2007). MT II can inhibit food intake and stimulate energy expenditure as early as P5–P6, before the full development of hypothalamic feeding neurocircuitry. It is noteworthy that MT II inhibited suckling-mediated milk intake as early as P5–P6, a time when food intake is primarily inhibited by gastric filling (Phifer et al. 1986). At least at this time of development, visceral inhibitory signal is able to stimulate melanocortin system.

26.8.3 Development of Leptin-Sensitive Projection Pathways

Using axonal tracer Dil to label axons of the ARC in mice at various postnatal ages, the ontogeny of projections from the ARC was visualized (Bouret and Simerly 2004). The neurons of the ARC do not extend axons to the majority of their target nuclei until the second week of postnatal life. ARC projections extend through the periventricular zone of the hypothalamus to provide inputs to the DMH by P6, followed by inputs to the PVN between P8 and P10. Projections from the ARC to the

LHA appeared on P12 and the pattern of arcuate projections does not achieve their adult-like distribution until P18 (Bouret and Simerly, 2004). Consistent with this idea, peripheral leptin injection induces cFos immunoreactivity in the ARC as early as P6, whereas leptin-induced cFos is not observed in the PVN before P10, or in the LHA before P16. This suggests that this activation by leptin may be due to transneuronal relay of leptin signals originating from the ARC (Bouret and Simerly, 2004). The inability of leptin to affect independent ingestion during the first 3 postnatal weeks may be attributed to the immaturity of the neural pathways from the ARC to the target areas that play important roles in food intake regulation.

26.8.4 Trophic Action of Leptin on Arcuate Neurons

By comparing projection pathways from the ARC in leptin-deficient (ob/ob) and wild-type mouse pups, leptin deficiency was shown to cause a dramatic reduction in the density of axons emanating from the ARC and innervating the DMH, PVN, and LHA (Fig. 26.6) (Bouret et al. 2004). Both NPY/AgRp and POMC projections are affected. Leptin treatment in adult ob/ob mice is largely ineffective in reversing innervation pathways, whereas supplementation during the neonatal period fully restores the density of arcuate projections to that found in wild-type mice (Bouret et al. 2004).

Mice with intrauterine undernutrition, when fed a high-fat diet, develop pronounced weight gain and adiposity. These mice exhibited a premature onset of neonatal leptin surge compared to offspring with intrauterine normal nutrition (Yura et al. 2005). Both offspring with intrauterine undernutrition and neonatally leptin-treated offspring with intrauterine normal nutrition exhibited an impaired response to leptin administration as well as an increased density of nerve terminals
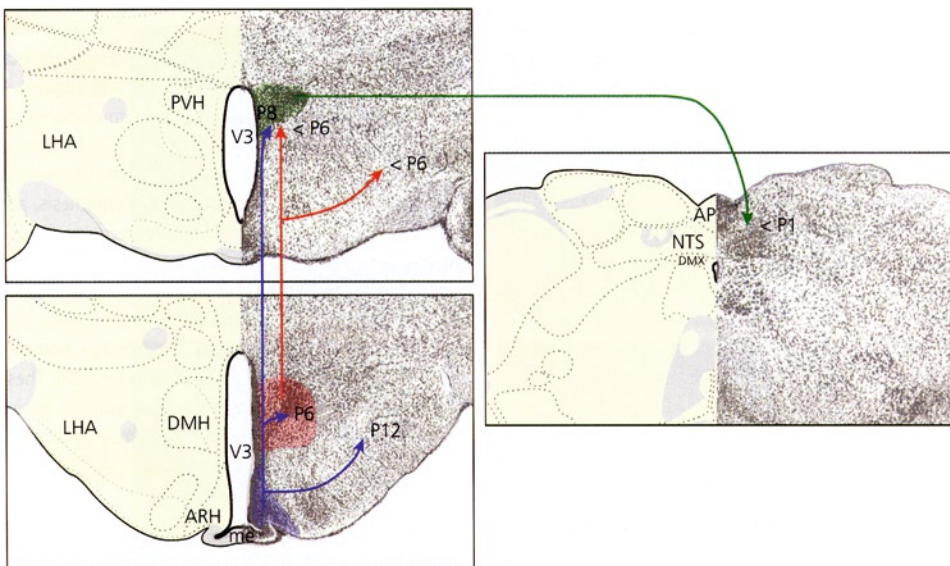
Fig. 26.6 Ontogeny of circuits regulating feeding. Projections from the arcuate nucleus (*ARH*) are immature at birth and appear to innervate the dorsomedial nucleus (*DMH*), paraventricular nucleus (*PVN*), and lateral hypothalamic area (*LHA*) in succession, within distinct temporal domains. The projections from the ARH to the DMH develop rapidly and are established by P6, whereas those to the PVH develop significantly later, with the mature pattern of innervation first apparent between P8 and P10. Projections to the LHA are established by P12. Projections from the brain stem appear developed at birth (Reprinted from Bouret and Simerly 2007. With permission)

containing NPY or CART in the PVN (Yura et al. 2005). These confirmed the importance of the premature leptin surge in the pronounced developmental origins of obesity using ob/ob mice (Yura et al. 2008) and may explain the epidemiological evidence suggesting that intrauterine undernutrition is closely associated with adulthood obesity related to detrimental metabolic sequelae.

26.9 Application to Other Areas of Health and Disease

It is not clear whether there are two types of ingestive behavior (suckling and independent feeding) in human infants. For instance, milk ejection from mother's nipple does not appear to exhibit intermittent bursts of release of milk like that observed in the rat. However, whether a child's suckling is regulated by mechanisms similar to those involved in the development of as drinking behavior in rodents is an interesting question that will await further investigation.

Summary Points

- The volume of milk ingested by rat pups is not under their voluntary regulation, as is the case in adult rats that stop eating when they have had enough food.
- Ingestion of milk by pups independent of the mother's direct influence (independent ingestion) can be experimentally induced in neonatal pups, but this type of feeding behavior naturally does not occur before the weaning begins. Rather, this ingestion is regulated by the pups themselves.
- Eating and drinking are not differentiated in the rat pups in the first postnatal week. During this period, deprivation from their mother stimulates independent ingestion primarily on the basis of dehydration, a shortage of water, which acts to inhibit food intake in adults.
- Hormones secreted from the epithelial cells of the gastrointestinal tract play important roles in the movement of the gastrointestinal tract and secretion of digestive juices. In addition, they also regulate food intake such as CCK and ghrelin discussed in this chapter.
- During the second week after birth, there is dramatic spike in the blood concentration of leptin. This leptin surge may have a role in the facilitation of neuronal development of the hypothalamus, a brain area responsible for food regulation.

Key Terms

Independent injection: This is induced by injecting milk through an implanted cannula into the anterior portion of pup's mouth as early as 1 day after birth and is a good experimental model for studying the development of feeding behavior observed in adult animals.

Milk ejection: Milk secreted from epithelial cells of the mammary gland is expelled by contraction of myoepithelial cells surrounding the alveolus in response to circulating oxytocin.

Arcuate nucleus: A key hypothalamic nucleus responsible for regulating metabolic balance.

Leptin: An important hormone secreted from fat cells and acts within the arcuate nucleus to inhibit appetite.

Preabsorptive inhibition: Ingested food in the stomach or intestine inhibit food intake before being assimilated.

References

Ackerman SH, Albert M, Shindledecker RD, Gayle C, Smith GP. Am J Physiol. 1992;262:R624–7.
Ackroff K, Vigorito M, Sclafani A. Appetite. 1990;15:171–88.
Ahima RS, Hileman SM. Regul Pept. 2000;92:1–7.
Ahima RS, Prabakaran D, Flier JS. J Clin Invest. 1998;101:1020–7.
Blass EM, Beardsley W, Hall WG. Am J Physiol. 1979;236:E567–70.
Blass EM, Teicher MH. Science. 1980;210:15–22.
Blumberg S, Haba D, Schroeder M, Smith GP, Weller A. Am J Physiol Regul Integr Comp Physiol. 2006a;290:R208–18.
Blumberg S, Schroeder M, Haba D, Malkesman O, Torregrossa AM, Weller A, et al. Peptides. 2006b;27:2820–8.
Bouret SG, Draper SJ, Simerly RB. Science. 2004;304:108–10.
Bouret SG, Simerly RB. Endocrinology. 2004;145:2621–6.
Bouret SG, Simerly RB. J Neuroendocrinol. 2007;19:575–82.
Bruno JP. J Comp Physiol Psychol. 1981;95:1016–27.
Callahan JB, Rinaman L. Physiol Behav. 1998;64:683–7.
Capuano CA, Leibowitz SF, Barr GA. Neuropeptides. 1993;24:177–82.
Cramer CP, Blass EM. Am J Physiol. 1983;245:R154–9.
Ellis S, Axt K, Epstein AN. J Neurosci. 1984;4:945–55.
Gehlert DR. Neuropeptides. 1999;33:329–38.
Gisel EG, Henning SJ. Physiol Behav. 1980;24:313–8.
Glavas MM, Joachim SE, Draper SJ, Smith MS, Grove KL. Endocrinology. 2007;148:3279–87.
Grill HJ, Smith GP. Am J Physiol. 1988;254:R853–6.
Grove KL, Allen S, Grayson BE, Smith MS. Neuroscience. 2003;116:393–406.
Grove KL, Grayson BE, Glavas MM, Xiao XQ, Smith MS. Physiol Behav. 2005;86:646–60.
Hall WG. Science. 1979a;205:206–9.
Hall WG. J Comp Physiol Psychol. 1979b;93:977–1000.
Hall WG, Bryan TE. J Comp Physiol Psychol. 1980;94:746–56.
Hall WG, Bryan TE. J Comp Physiol Psychol. 1981;95:240–51.
Hall WG, Cramer CP. J comp Physiol Psychol. 1977;91:1141–55.
Hall WG et al. Nature. 1975;258:318–20.
Hayashida T, Nakahara K, Mondal MS, Date Y, Nakazato M, Kojima M, et al. J Endocrinol. 2002;173:239–45.
Henning SJ, Chang SS, Gisel EG. Am J Physiol. 1979;237:R187–91.
Houpt KA, Epstein AN. Am J Physiol. 1973;225:58–66.
Johanson IB, Hall WG. J Comp Physiol Psychol. 1980;94:977–92.
Kojima M, Kangawa K. Physiol Rev. 2005;85:495–522.
Leshem M, Flynn FW, Epstein AN. Am J Physiol. 1990;258:R365–75.
Lincoln DW, Hill A, Wakerley JB. J Endocrinol. 1973;57:459–76.
Moran TH, Kinzig KP. Am J Physiol Gastrointest Liver Physiol. 2004;286:G183–8.
Paxinos G, Watson C. The rat brain in stereotaxic coordinates. New York: Academic; 1982.
Phifer CB, Sikes CR, Hall WG. Am J Physiol. 1986;250:R807–14.
Piao H, Hosoda H, Kangawa K, Murata T, Narita K, Higuchi T. J Neuroendocrinol. 2008;20:330–4.
Proulx K, Richard D, Walker CD. Endocrinology. 2002;143:4683–92.
Rinaman L. Dev Psychobiol. 2006;48:389–96.
Rinaman L, Hoffman GE, Stricker EM, Verbalis JG. Brain Res Dev Brain Res. 1994;77:140–5.
Robinson PH, Moran TH, McHugh PR. Am J Physiol. 1988;255:R14–20.
Schwartz MW, Woods SC, Porte DJ, Seeley RJ, Baskin DG. Nature. 2000;404:661–71.
Smith GP. Dev Psychobiol. 2006;48:345–59.
Swithers SE. Am J Physiol. 1997;273:R1649–56.
Swithers SE, Doerflinger A, Mowery T. Physiol Behav. 2004;82:3–9.
Weller A, Gispan IH, Smith GP. Physiol Behav. 1997;61:819–22.
Weller A, Smith GP, Gibbs J. Science. 1990;247:1589–91.
Weller A, Tsitolovskya L. Physiol Behav. 2004;82:11–6.
Weller A, Tsitolovskya L, Smith GP. Physiol Behav. 2001;72:199–203.
Yura S, Itoh H, Sagawa N, Yamamoto H, Masuzaki H, Nakao K, et al. Obesity (Silver Spring). 2008;16:1289–95.
Yura S, Itoh H, Sagawa N, Yamamoto H, Masuzaki H, Nakao K, et al. Cell Metab. 2005;1:371–8.

Part IV
General and Normative Aspects: Neurological

Chapter 27
Dietary Proteins and Satiety-Related Neuronal Pathways in the Brain

Gilles Fromentin, Nicolas Darcel, Catherine Chaumontet, and Daniel Tomé

Abbreviations

BDNF	Brain derived neurotrophic factor
CCK	Cholecystokinin (formerly called pancreozymin), a food intake suppressing peptide hormone released by the gastrointestinal tract during digestion
5-HT	Serotonin
HP	High protein
NP	Normal protein
NTS	Nucleus tractus solitarius
ARC	Arcuate nucleus of the hypothalamus
APC	Anterior piriform cortex
I-cells	A type of enteroendocrine cell found in the mucosal epithelium that lines the lumen of the small intestine. I-cells secrete a wide variety of gut hormones, including cholecystokinin.
PYY	Peptide YY
GLP-1	Glucagon-like peptide 1
IAA	Indispensable amino acid
GC	General control
CNS	Central nervous system
CTA	Conditioned taste aversion
PVN	Paraventricular nucleus
VMN	Ventromedial nucleus
DMN	Dorsomedial nucleus
LH	Lateral hypothalamus
POMC	Proopiomelanocortin
NPY	Neuropeptide Y
AgRP	Agouti-related peptide
αMSH	α Melanocyte stimulating hormone
mTOR	Mammalian target of rapamycin

G. Fromentin (✉)
INRA, CNRH-IdF, UMR914 Nutrition Physiology and Ingestive Behavior, F-75005 Paris, France
and
AgroParisTech, CNRH-IdF, UMR914 Nutrition Physiology and Ingestive Behavior, F-75005 Paris, France
and
UMR 914 INRA/AgroParisTech, 16 rue Claude Bernard, 75231 Paris Cedex 05, France
e-mail: gilles.fromentin@agroparistech.fr

AMPK   AMP-activated protein kinase
ICV   Intracerebroventricular
ACC   Acetyl-CoA carboxylase

27.1 Introduction

Proteins appear to be the macronutrient that exerts the greatest satiety effect in rats and humans (Latner and Schwartz 1999; Bensaid et al. 2002), ahead of carbohydrates and lipids (Porrini et al. 1997). Moreover, the macronutrient (Latner and Schwartz 1999) composition of a diet is known to influence energy intake, energy metabolism, and long-term changes to body weight and body composition. High-protein diets have been studied extensively for their ability to reduce total energy intake and body weight, and to limit lipid deposition (Jean et al. 2001). These observations are in line with the idea that in addition to total ingested energy, nutrient-specific mechanisms are also involved in inducing satiety and controlling food intake. Several redundant mechanisms, such as the secretion of gut satiety peptides, an increase in energy expenditure or an increase in plasma amino acid levels, are candidate signals for protein-induced satiety (Potier et al. 2009). Dietary proteins are thought to be closely monitored by the central nervous system (CNS), and especially by central structures such as the nucleus tractus solitarius (NTS), hypothalamus, and anterior piriform cortex (APC), regions that control or influence food intake. Since proteins are likely to be monitored in the same regions where satiety is thought to originate, dietary proteins may therefore influence the onset of satiety.

The purpose of this review is thus to consider some aspects of these neuromechanisms that are associated with peripheral and central signaling processes and concern the effects of protein and amino acids on the control of food intake.

27.2 Protein-induced Satiety (High Protein Preload and High-Protein Diet)

> Protein is considered to be a strong inhibitor of food intake in omnivores, displaying the most marked appetite suppressant effects of the three macronutrients. Eating a high-protein diet does not induce a conditioned food aversion but rather experience-enhanced satiety. Moreover the poor palatability of dietary protein is not the principal mechanism causing a reduction in energy intake.

In the short term, and in the context of the preload paradigm, a test-meal was given to subjects after an interval that followed ingestion of the preload. Dietary protein appeared to be a strong appetite inhibitor and suppressed food intake during subsequent meals beyond that which could be accounted for by its energy content alone, both in rats (Trigazis et al. 1997) and humans (Barkeling et al. 1990). Moreover, dietary proteins cause stronger appetite inhibition than carbohydrates. For instance, a gluten load induced a more pronounced depression of food intake than an isocaloric wheat starch load (Bensaid et al. 2002). However, some discrepancies have been shown to originate from physiological status, the duration of eating, and the method of nutrient administration; i.e., oral, intra-gastric, or intravenous (Reid and Hetherington 1997). Moreover, the type of protein can influence the satiating effect, although the mechanism involved remains unclear, it being unlikely that this originates from the presence of certain specific amino acids as precursors of neuromediators, e.g., tryptophan and serotonin, or tyrosine and dopamine (Anderson et al. 1994). Finally, some interactions have been suspected between the satiating effects of the three macronutrients. In order to analyze the

nature of the food intake depression induced by a high-protein (HP) load, one research group performed a meal pattern analysis (Bensaid et al. 2002) of the meal following the load, which suggested that animals were more satiated by protein (at least when loads contained a high level of protein) than by carbohydrate.

In the longer term, the ingestion of a high-protein diet most frequently promotes satiety, facilitates weight loss, and improves body composition. In rats, the consumption of a high-protein diet (55% of energy supplied by proteins) for several days led to both a reduction in cumulative food intake and less weight gain and adiposity than a normal-protein diet (14% of energy supplied by proteins) (Harper and Peters 1989; Jean et al. 2001; Halton and Hu 2004). However, this effect was modulated by the ratio between carbohydrate and fat and by the protein type (total milk protein, whey protein, or beta-lactoglobulin). Indeed, it has been suggested that different protein sources may differently affect satiety in a context of high-protein diets (Pichon et al. 2008).

In order to determine the respective roles of conditioned food aversion, satiety, and palatability, behavioral responses to an HP diet were compared to those observed with a normal-protein diet (Bensaid et al. 2003; L'Heureux-Bouron et al. 2004). Different paradigms were applied, including meal pattern analysis, two-choice testing, flavor testing, a behavioral satiety sequence, and taste reactivity. Only behavioral and food intake parameters were disturbed during the first day on which the animals ate the HP diet, and most of them returned to the control level as early as the second day of this diet. Rats adapted to an HP diet did not acquire a conditioned taste aversion but exhibited satiety and a normal behavioral satiety sequence.

It is possible that the appetite suppressant effect of dietary protein is partially induced by poor palatability. Indeed, the poor palatability of high-protein diets has been documented (McArthur et al. 1993), but its relative importance remains unclear. L'Heureux-Bouron et al. (2004) measured food intake in rats after modifying the composition of their high-protein diets by varying the carbohydrate composition (sucrose/cornstarch) and protein source (soy, gluten, or total milk protein) of these diets. The orosensory properties of the diets were also modified. However, no differences in food intake were observed between the groups of rats studied during the transition phase or after adaptation. More generally, this issue was studied several decades ago by modifying the orosensory properties of experimental foods by the addition of pleasant flavors (citral), unpleasant flavors (eucalyptol) (Le Magnen 1999), or unpleasant substances (e.g., quinine or sucro octa acetate (Kratz et al. 1978)). After a transient decline that was dependent on the substance used, all groups chronically consuming the poorly palatable diets ad libitum ate as much as the control group. This putative poor palatability of dietary protein is probably not the principal mechanism that reduces energy intake, but an initial decrease in HP diet intake appears to result from the poorer palatability of a food, combined with the satiety effect of an HP diet and the interval required for metabolic adaptation to the HP level.

27.3 Proteins, Amino Acids, and Satiety Signaling to the Brain

> The input signals associated with protein and amino acid ingestion originate from visceral and metabolic mechanisms and involve both indirect (signals originating from different parts of the gut, mainly mediated by vagal afferents) and direct information (plasma levels of nutrients, gut peptides, and hormones), recorded by the central nervous system.

Ingested proteins are believed to generate redundant pre- and post-absorptive signals that contribute to controlling gastric kinetics, pancreatic secretions, and food intake. In the brain, two major
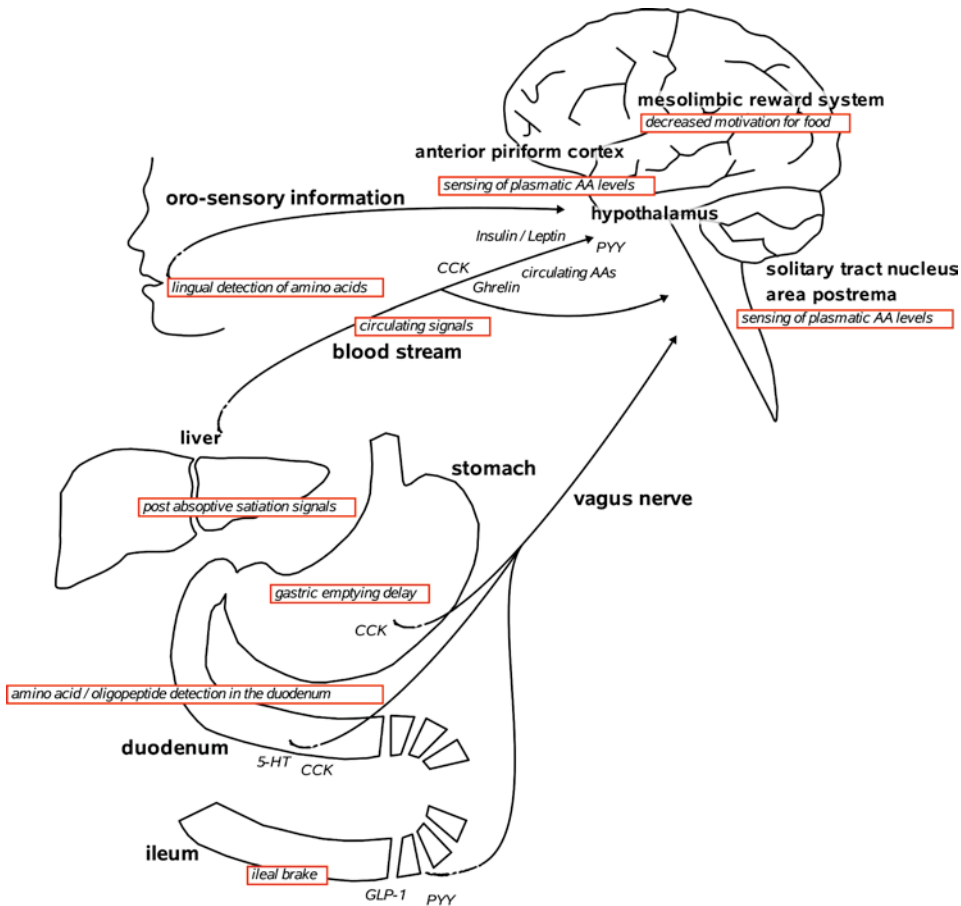
Fig. 27.1 Mechanisms responsible for the protein-induced suppression of food intake. Dietary protein is detected as early as in the mouth, via amino acid sensing by taste cells. Gastrointestinal signals are generated in the stomach, duodenum, and ileum via the release of gut hormones that activate peripheral nerves (particularly the vagus nerve). These gut hormones are also carried by the bloodstream and act directly on brain centers such as the area postrema and hypothalamus to suppress food intake. Post absorptive anorectic signals are also generated by the liver. Finally, protein detection may modulate the reward system and reduce the motivation for food

afferent pathways are involved in monitoring proteins and amino acids: the indirect, neuromediated (vagus-mediated/ileal brake) pathway and the direct blood pathway (Potier et al. 2009). The neuro-mediated pathway communicates pre-absorptive and visceral information which is mainly transferred via the vagus nerve that innervates part of the orosensory zone: stomach, duodenum, and liver. Other information is directly monitored in the blood (Fig. 27.1).

27.3.1 Sensory Information

Orosensory information provides animals with valuable information about the nature and quality of food (Nelson et al. 2002). Mammals can recognize and respond to a wide variety of chemical products, including sugars, salts, acids, and a broad range of toxic substances.

According to Zhao et al. (2003), several amino acids taste sweet or delicious (umami) to humans, and are attractive to rodents and other animals. Umami is one of the five basic taste sensations, induced solely and synergistically by free glutamate and 5-mononucleotides. To sense umami, several receptors such as taste receptors (T1R1/T1R3 heterodimer) and metabotrophic glutamate receptors (mGluR1 and mGluR4) can be found in the taste buds on the tongue.

Nelson et al. (2002) identified and characterized another mammalian amino acid taste receptor, T1R1 + 3, which combines the T1R1 and T1R3 G-protein coupled receptors to function as a broadly tuned L-amino-acid sensor; this responds to most of the 20 standard amino acids.

Gustatory detection via taste receptor cells on the tongue and palate is a key process in protein and amino acid signaling to the brain centers that control ingestion and hunger.

27.3.2 Satiation: The Gastrointestinal Regulation of Food Intake

27.3.2.1 Visceral Vagus-mediated Signals

Vagus Nerve

During digestion, both dietary proteins and other macronutrients are detected in the small intestine (this nutrient-specific information acting as a potent anorexigenic signal). This sensory process is dependent upon the action of gut mediators such as cholecystokinin (CCK) or serotonin (5-HT) on vagal afferents which in turn convey peripheral information to the brain in order to influence the control of food intake. The vagus nerve is thus a key element in the pathways controlling ingestion. Although dietary proteins have been shown to activate vagal afferents (Darcel et al. 2005b), the links between protein detection in the intestine and the control of ingestion have not yet been clarified.

Role of Dietary Proteins in Gastric Volume and Stomach Emptying

Powley and Phillips (2004) stated that the prepotent negative feedback from the stomach regarding short-term ingestion is a volumetric signal that is monitored by mechanoreceptor innervation of the stomach assured by multiple vagal branches. An increase in intake volume may participate in a post-prandial increase in stomach distension, causing activation of the vagal afferent fibers associated with reduced gastric kinetics and food intake (Davis 1999). The increase in gastric volume induced by dietary proteins is probably due to an increase in gastric secretions and/or the amount of water drunk. However, L'Heureux-Bouron et al. (2004) showed that eating an HP diet did not induce a marked increase in stomach volume, which might explain the enhanced satiety and decreased food intake triggered by the activation of vagal afferent fibers.

A variation in the rate of gastric emptying can alter the gut peptide response, but may also modify the hormonal response to feeding and hence the rate of ingested nitrogen. According to Mellinkof et al. (1956), ("The aminostatic hypothesis") such modifications to plasma amino acid kinetics may modulate food intake. Boirie et al. (1997) showed differences in gastric emptying as a function of dietary protein type (thus demonstrating the concept of fast and slow proteins). Hall et al. (2003) tried to correlate the concept of fast and slow proteins and an effect on satiety. However, according to Calbet and Holst (2004), caloric density seems to be the main factor determining the rate of gastric emptying, even if at the isocaloric level, dietary factors (that include the volume, osmolarity, viscosity, pH, and nutrient content of the meal) modulate the physiological control of gastric emptying.

Detection of Protein in the Gastrointestinal Wall

Our current understanding of amino acid detection in the intestinal wall is based on two main detection mechanisms: the first involves specialized cells present throughout the gastrointestinal tract (Conigrave et al. 2000; Xu et al. 2008) which carry amino acid receptors on their luminal membranes. These cells initiate a signaling process that results in the release of gut hormones by enteroendocrine cells in the gastrointestinal tract epithelia which act on the vagus nerve to trigger satiation. The second detection process involves epithelial absorptive cells that are able to sense variations in luminal amino acid concentrations via changes in their cellular metabolism. In the same way, these cells initiate a paracrine signaling process that results in the release of gut mediators by enteroendocrine cells. Both of these detection mechanisms are present in the gut (Bezençon et al. 2007), but their contribution to the positive effects of peptide and amino acid intake on energy intake has not been studied.

The sensing mechanisms underlying the detection of dietary proteins and their hydrolysates in the intestine is not entirely clear; however, it has been found that proteins and amino acids trigger release of the anorexigenic gastrointestinal hormone CCK (Foltz et al. 2008). Whether other mechanisms are also involved (such as reduced production of the "hunger hormone" ghrelin) remains unknown. The precise mechanism by which dietary protein induces CCK release is unclear, but a recent study showed that the transport peptide PepT1 was necessary to enable CCK release from duodenal I-cells (Darcel et al. 2005b) (Fig. 27.2).
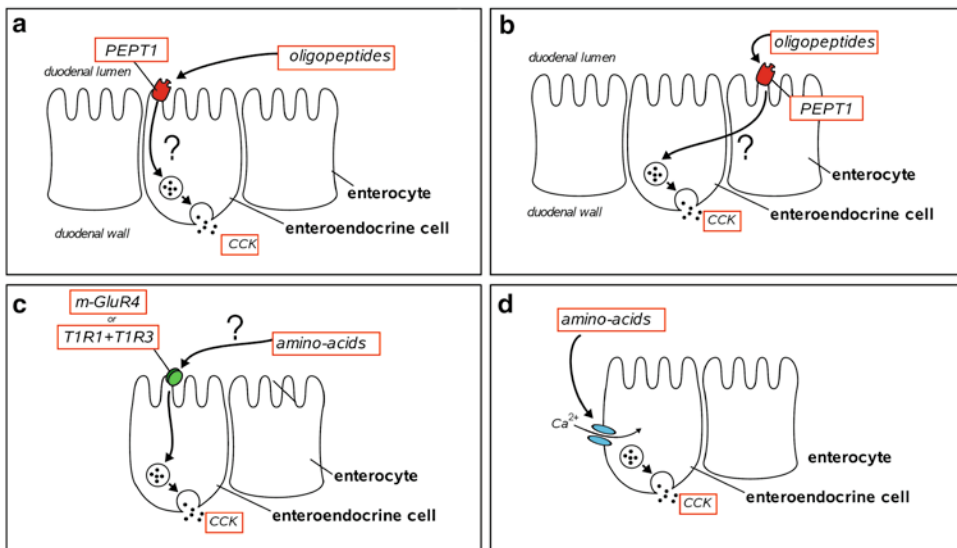
Fig. 27.2 Putative mechanisms for protein detection in the duodenum. Several mechanisms have been proposed regarding the intestinal sensing of dietary proteins. First, it has been shown that the proton-coupled oligopeptide transporter PEPT1 is necessary to detect oligopeptides in the intestinal wall (Darcel et al. 2005a) (**a, b**). However, it is not yet clear whether PEPT1-mediated detection involves cross-talk between enterocytes and enteroendocrine cells (**a**), or whether enteroendocrine cells express PEPT1 and can detect oligopeptides independently of enterocytes. It is also possible that amino acids may be sensed by taste receptors located at the apical side of enteroendocrine cells; e.g., through the heterodimeric T1R1/T1R3 receptor or the mGluR1 or mGluR4 glutamate receptors (Zhao et al. 2003) (**c**). It has also been postulated that amino acids such as phenylalanine may act directly on L-type calcium channels at the basolateral side of the enteroendocrine cells to stimulate the exocytosis of gut hormones (Mangel 1995) (**d**). In addition, recent data have also suggested that additional receptors may be involved in detecting dietary protein, such as the calcium sensing receptor CaSR in the intestine

It is conceivable that other mechanisms are involved, particularly because peptide uptake via PepT1 does not occur in other gastrointestinal compartments such as the stomach. Indeed, it has been hypothesized that protein-induced satiety may be linked to the secretion of gut neuropeptides; candidate mechanisms include either an increased secretion of the anorexigenic gut hormones glucagon-like peptide 1 (GLP-1), CCK, and peptide YY (PYY), or a decreased secretion of the orexigenic gut hormone ghrelin.

27.3.2.2 Ileal Brake

The ileal brake is a feedback mechanism that results in the inhibition of proximal gastrointestinal motility and secretion. Animal and human studies have shown that activation of the ileal brake by local nutrient perfusions increases feelings of satiety and reduces ad libitum food intake (Maljaars et al. 2008). These results point to a potential role for the ileal brake in the regulation of digestion, exerting a direct or indirect impact on eating behavior and satiety. Ileal protein infusions in both humans and animals activate the ileal brake, and differences may exist between different types of protein or amino acids (Meyer et al. 1998).

PYY and GLP-1, two peptide hormones secreted mainly in the lower gut, and particularly the ileum, colon, and rectum, seem to be most relevant to the control of appetite. Interestingly, they are both secreted by the same enteroendocrine cells: L-cells. According to Batterham et al. (2006), a high protein intake induced the greatest release of PYY and the most pronounced satiety in normal-weight and obese human subjects. A long-term augmentation of dietary protein in mice induced elevated plasma PYY levels, and reduced food intake and adiposity. In order to determine directly the role of PYY in mediating the satiating effects of protein, Batterham (Batterham et al. 2006) generated PYY null mice that were selectively resistant to the satiating and weight-reducing effects of protein; these animals developed marked obesity that was reversed by exogenous PYY treatment.

27.3.3 Blood-Mediated Signals of Satiety

Metabolic signals, including an increase in energy expenditure and the production of glucose through gluconeogenesis, have been also hypothesized as signals for protein and amino acids (Potier et al. 2009). It is currently accepted in the literature that in humans, protein stimulates diet-induced thermogenesis to a greater extent than other macronutrients (Westerterp-Plantenga 2008). The de novo synthesis of glucose in the liver from gluconeogenic precursors (including amino acids) is stimulated by an HP diet in the fed state (Azzout-Marniche et al. 2007). This process may be involved in the satiating effect of protein through a modulation of glucose homeostasis and glucose signaling to the brain.

It has been suggested that elevated concentrations of blood or plasma amino acids that cannot be channeled into protein synthesis may serve as a satiety signal for a food intake regulating mechanism and thereby result in depressed food intake (Mellinkoff et al. 1956; Harper and Peters 1989). Elevated plasma amino acid concentrations can be detected directly by a specific area in the hypothalamus. Variations in plasma hormones and free amino acid concentrations can be recorded directly by the central nervous system, mainly through concomitant variations in their intracerebral levels. However, even though histidine and tyrosine are precursors of histamine and dopamine, respectively, Bassil et al. (2007) failed to demonstrate any effect of a diet supplemented with 5% of either histidine or tyrosine on the levels of food intake by Sprague-Dawley rats (Potier et al. 2009).

The neuromediated pathway transfers pre-absorptive and visceral information via the vagus nerve that innervates part of the orosensory zone (stomach, duodenum, and liver). Localized in the brainstem, the NTS is the main projection of the vagus nerve and integrates sensory information from the oropharyngeal, intestinal, and visceral organs. The involvement of vagal afferent pathways in protein sensing and signaling to the brain is supported by results showing that intraduodenal protein activates vagal afferent fibers, and high-protein feeding induces c-Fos expression in neurons within the NTS (Phifer and Berthoud 1998; Darcel et al. 2005a). Faipoux et al. (2008) showed that a reduction in food intake after a high-protein load (versus a normal-protein load) resulted from activation of the noradrenergic neurons related to CCK-induced anorexia. Another study also showed that neurons expressing GLP-1 were not activated, which is consistent with the fact that protein-induced satiety is not associated with aversive behavior or conditioned taste aversion (CTA) (Bensaid et al. 2003).

27.4.2.2 Activation of the Hypothalamus

Peripheral information is further centralized in the hypothalamus, which is critical to the regulation of food intake as it contains a number of discrete neuronal populations or nuclei, including the ARC, the paraventricular nucleus (PVN), the ventromedial nucleus (VMN), the dorsomedial nucleus (DMN), and the lateral hypothalamus area (LH). Energy homeostasis-regulating circuits are found within and connecting these nuclei. In the ARC, proopiomelanocortin (POMC) neuron activation induces a reduction in food intake. These neurons are responsible for the anorectic response induced by circulating leptin (Cowley et al. 2003) through the activation of neurons in the PVN (Balthasar et al. 2005). The activation of POMC neurons is also inseparable from the behavior of another population in the ARC, neuropeptide Y (NPY)/agouti-related peptide (Agrp) neurons, activation of which is potent in increasing food intake and inhibiting POMC neuron activation (Cowley et al. 2001). Indeed, Faipoux et al. (2008) showed that after the ingestion of a high-protein meal, the numbers of double-labeled fos and α-melanocyte stimulating hormone (MSH) (a marker of POMC neuron activation) increased, concomitantly with a reduction in the activation of non-POMC neurons. This result was less pronounced when a high-protein diet had been served for several days (21 days) than in an acute setting. Moreover, because arcuate neurons are mainly POMC or NPY, it could be hypothesized that NPY neurons are less strongly activated after high-protein meals.

27.4.2.3 AMP-Activated Protein Kinase and the Mammalian Target of Rapamycin Are Involved in the Satiety Induced by High-Protein Diets

HP diets, an increase in dietary leucine (Ropelle et al. 2008) or the intra-cerebroventricular (ICV) administration of amino acids (or leucine only) (Cota et al. 2006; Morrison et al. 2007) reduce food intake and body weight. This effect seems to be leucine-specific, because leucine alone exerts the same effect on food intake as a mixture of amino acids (Ropelle et al. 2008). It has been shown that AMP-activated protein kinase (AMPK) and the mammalian target of rapamycin (mTOR) are involved in the satiety induced by high-protein diets (Fig. 27.3).

AMPK is the downstream component of a kinase cascade that acts as a sensor for the cellular energy charge, being activated by an increase in the AMP/ATP ratio. Once activated, AMPK phosphorylates acetyl-CoA carboxylase (ACC) and switches on energy-producing pathways at the expense of energy-depleting processes. Ropelle et al. (2008) showed that both a high-protein
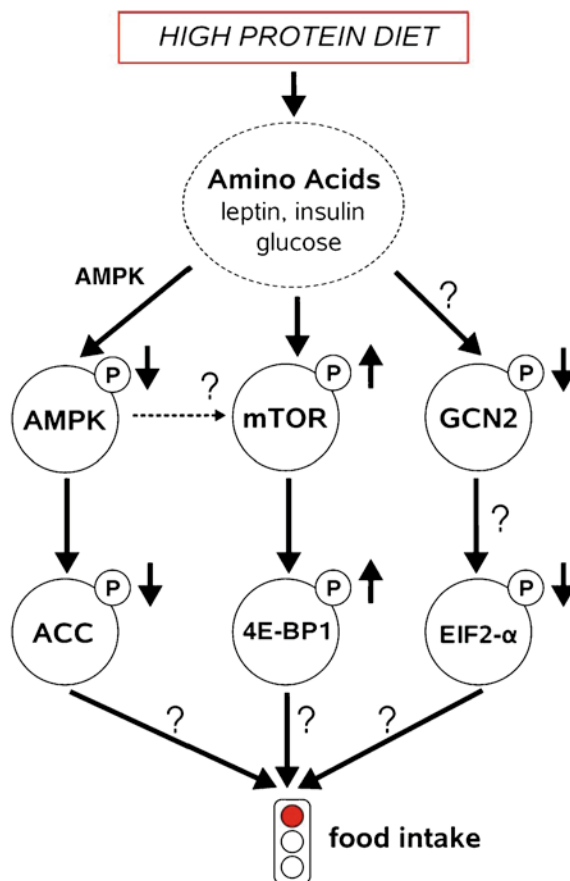
Fig. 27.3 mTOR, AMPK, and GCN2 coordinate adaptation of the metabolic pathways for energy in response to protein intake in the rat. Putative signaling pathways induced in the arcuate nucleus of the hypothalamus by amino acids. The AMP-activated protein kinase (*AMPK*) and the mammalian target of rapamycin (*mTOR*) are involved in the satiety induced by high-protein diets. High-protein diet and ICV leucine administration suppressed AMPK and acetyl-CoA carboxylase (*ACC*) phosphorylations in the rat hypothalamus. In parallel, there has been growing interest in mTOR, an intracellular signaling molecule sensitive to both amino acid and growth factors, which is also described as a metabolic sensor and is able to phosphorylate two regulatory proteins, the p70 ribosomal S6 protein kinase (*p70S6K*) and the eukaryotic initiation factor 4E-binding protein-1 (*4E-BP1*) that stimulates translation initiation. The general control nondepressible 2 kinase (GCN2), which is sensitive to amino acid deprivation, could be also a target for amino-acid signals, GCN2 controls translation via the phosphorylation of eukaryotic initiation factor 2α (*eIF2α*). Nevertheless, there is no evidence that the increase in amino acid concentration decreased the phosphorylation of GCN2 in the hypothalamus. The participation of these pathways on food intake control needs to be clarified

diet and ICV leucine administration suppressed AMPK and ACC phosphorylation in the rat hypothalamus, this being concomitant with a reduced AMP/ATP ratio. In parallel, there has been growing interest in mTOR, an intracellular signaling molecule sensitive to both amino acid and growth factors which is also described as a metabolic sensor. Both a high-protein diet and the ICV administration of free amino acids, or leucine only, led to mTOR activation in the hypothalamus (Cota et al. 2006; Morrison et al. 2007). Moreover, high-protein diets modulate AMPK and

mTOR in the same specific neuronal subsets, the ARC and PVN of the hypothalamus. AMPK and mTOR may have overlapping and reciprocal functions (Cota et al. 2006). Finally, the activation of mTOR and the suppression of AMPK phosphorylation activity seem to modulate hypothalamic neuropeptides: they reduce levels of NPY and Agrp (which are both orexigenic neuropeptides) and increase the expression of POMC, which exerts an anorexigenic effect (Morrison et al. 2007; Ropelle et al. 2008).

27.5 Applications to Other Areas of Health and Disease

The macronutrient composition of a diet is known to influence energy intake, energy metabolism, and long-term changes to body weight and body composition (Potier et al. 2009). Reduced-energy diets are a widely recommended as a noninvasive primary strategy to treat overweight and obese subjects. High-protein diets have been studied extensively for their ability to reduce total energy intake and body weight and to limit lipid deposition. One major criticism advanced regarding evaluations of high-protein, low-carbohydrate, high-fat diets is that their high protein and high fat contents may have adverse effects on health. High-protein diets nevertheless remain popular, suggesting that there are some perceived benefits in the eyes of the public. One such benefit may be the increased satiety arising from the protein in these diets, which aids in ensuring better compliance with a reduced energy diet and/or contributing to a spontaneous reduction in energy intake (Anderson and Moore 2004).

27.6 Conclusion

The protein and amino acid content of a food is a strong determinant of short-term satiety and the amount that will be eaten. Peripheral hormones (CCK, GLP-1, and PYY) have been shown to be involved in the mechanism of short-term protein-induced satiety. Moreover, the fact that the protein source may impact their satiety effect seems to suggest the presence of functional specific peptides that are selectively beneficial. Still at the peripheral level, an increase in energy expenditure and the production of glucose through gluconeogenesis have been also hypothesized as signals for protein-induced satiety. Specific amino acids such as leucine, or other precursors of neuropeptides, can exert an impact on protein-induced satiety thanks to central mechanisms. Several brain regions are indeed involved in the central regulation of food intake, and it has been shown that proteins may affect them by acting in different regions of the brain stem or in the hypothalamus. Other areas that are also involved in the detection of high-protein meals include the area postrema or the lateral hypothalamus with orexin-containing neurons, but their precise roles need to be clarified. Finally, recent findings have suggested that neural components of the gut brain axis display a high potential for neuronal plasticity that is present or could be active in adult subjects. These phenomena may explain the prolonged aspects of diet-induced metabolic and behavioural changes (Table 27.1).

Table 27.1 Key features of neuronal plasticity of the gut brain axis

1. Receptor dynamics
  1.1 Receptor dynamics at the level of the plasma membrane constitute a common modality for neuronal adaptations in response to diet
  1.2 Neurons can down-regulate their activity when subjected to repeated stimulations
  1.3 Chronic stimulation can lead to neuronal desensitization or potentialization via either receptor internalization or changes to de novo receptor expression by vagal afferent neurons
  1.4 Furthermore, receptor profiles (particularly at the level of peripheral sensory terminals) can be influenced by external conditions
2. Neurogenesis
  2.1 Neurogenesis in the brain stem has been shown to occur in adult laboratory animals
  2.2 The presence of neural stem cell progenitors in the brainstem and hypothalamus has been demonstrated, suggesting that newly formed neurons can be included in existing neural networks controlling food intake
  2.3 Very few studies have tried to understand the physiological role of these adult neurogenesis processes, even though they may be of considerable importance to the sustained satiety induced by high-protein diets
3. Neurotrophic factors
  3.1 The brain-derived neurotrophic factor (BDNF) supports the high plasticity potential of the vagus nerve, as this mechanism has been shown to play a role in vagus nerve resection
  3.2 These receptors have been localized in the brainstem at the level of the solitary tract nucleus, but their role in neuronal plasticity remains controversial and has not been studied in detail (Bariohay 2009)

This table lists the key factors of neuronal plasticity including receptor dynamics, neurogenesis, and neurotrophic factors.

Summary Points

- Protein is considered to be a strong inhibitor of food intake in omnivores, displaying the most marked appetite suppressant effects of the three macronutrients.
- Eating a high-protein diet does not induce a conditioned food aversion but rather experience-enhanced satiety.
- The input signals associated with amino acid ingestion originate from visceral and metabolic mechanisms.
- The satiety effect of dietary proteins appears to be mediated by anorexigenic hormones such as CCK, GLP-1, and PYY, there is also evidence that circulating leucine levels may impact food intake.
- In the central nervous system, high-protein diets trigger the activation the nucleus of the solitary tract and the hypothalamus.
- How information arising from the ingestion of dietary protein leads to the control of food intake is a highly complex process that is not yet fully understood.

Definitions and Explanations

Satiety: Satiety is defined as an absence of hunger during the interprandial period, while satiation describes the overall mechanisms that lead to a cessation of eating. It is satiety that delays the start of the next meal and may reduce food consumption the next time there is an opportunity.

Palatability: Palatability is the property of a food product of being acceptable, pleasant to the mouth. Palatability depends to a large extent on food intrinsic properties, in particular on their organoleptic properties or also on macronutrient content.

Conditioned taste aversion (CTA): Conditioned taste aversion is an acquired mechanism allowing a subject to avoid consuming a food when the post-ingestive consequences are remembered as harmful. CTA requires that the subject links one or more orosensory characteristics of the food to unpleasant post-ingestive consequences.

Gut brain axis: Gut brain axis is a multiple signaling system involving the brain and the gastrointestinal tract and playing a key role in metabolic control. The gut brain axis exhibits two major communication modalities: (1) effects may take place directly through action of gut peptide in the brain or (2) through nervous signaling from the gastrointestinal to the brain. The gut-brain axis is involved in a multitude of physiological processes including satiety, food intake, and regulation energy metabolism.

References

Anderson GH, Li ET, Anthony SP, Ng LT, Bialik R. Dissociation between plasma and brain amino acid profiles and short-term food intake in the rat. Am J Physiol. 1994;266:R1675–86.

Anderson GH, Moore SE. Dietary proteins in the regulation of food intake and body weight in humans. J Nutr. 2004;134:974S–9.

Azzout-Marniche D, Gaudichon C, Blouet C, Bos C, Mathe V, Huneau JF, et al. Liver glyconeogenesis: a pathway to cope with postprandial amino acid excess in high-protein fed rats? Am J Physiol Regul Integr Comp Physiol. 2007;292:R1400–7.

Balthasar N, Dalgaard LT, Lee CE, Yu J, Funahashi H, Williams T, et al. Divergence of melanocortin pathways in the control of food intake and energy expenditure. Cell. 2005;123:493–505.

Barkeling B, Rossner S, Bjorvell H. Effects of a high-protein meal (meat) and a high-carbohydrate meal (vegetarian) on satiety measured by automated computerized monitoring of subsequent food intake, motivation to eat and food preferences. Int J Obes. 1990;14:743–51.

Bariohay B, Roux J, Tardivel C, Trouslard J, Jean A, Lebrun B. Brain-derived neurotrophic factor/tropomyosin-related kinase receptor type B signaling is a downstream effector of the brainstem melanocortin system in food intake control. Endocrinolgy, 2009;150:2646–53.

Bassil MS, Hwalla N, Obeid OA. Meal pattern of male rats maintained on histidine-, leucine-, or tyrosine-supplemented diet. Obesity (Silver Spring). 2007;15:616–23.

Batterham RL, Heffron H, Kapoor S, Chivers JE, Chandarana K, Herzog H, et al. Critical role for peptide YY in protein-mediated satiation and body-weight regulation. Cell Metab. 2006;4:223–33.

Bensaid A, Tome D, Gietzen D, Even P, Morens C, Gausseres N, et al. Protein is more potent than carbohydrate for reducing appetite in rats. Physiol Behav. 2002;75:577–82.

Bensaid A, Tome D, L'Heureux-Bourdon D, Even P, Gietzen D, Morens C, et al. A high-protein diet enhances satiety without conditioned taste aversion in the rat. Physiol Behav. 2003;78:311–20.

Bezençon C, le Coutre J, Damak S. Chem Senses. 2007;32:41–9.

Boirie Y, Dangin M, Gachon P, Vasson MP, Maubois JL, Beaufrere B. Slow and fast dietary proteins differently modulate postprandial protein accretion. Proc Natl Acad Sci USA. 1997;94:14930–5.

Calbet JA, Holst JJ. Gastric emptying, gastric secretion and enterogastrone response after administration of milk proteins or their peptide hydrolysates in humans. Eur J Nutr. 2004;43:127–39.

Conigrave AD, Quinn SJ, Brown EM. L-amino acid sensing by the extracellular Ca^{2+}-sensing receptor. Proc Natl Acad Sci USA. 2000;97:4814–9.

Cota D, Proulx K, Smith KA, Kozma SC, Thomas G, Woods SC, et al. Hypothalamic mTOR signaling regulates food intake. Science. 2006;312:927–30.

Cowley MA, Smart JL, Rubinstein M, Cerdan MG, Diano S, Horvath TL, et al. Leptin activates anorexigenic POMC neurons through a neural network in the arcuate nucleus. Nature. 2001;411:480–4.

Cowley MA, Smith RG, Diano S, Tschop M, Pronchuk N, Grove KL, et al. The distribution and mechanism of action of ghrelin in the CNS demonstrates a novel hypothalamic circuit regulating energy homeostasis. Neuron. 2003;37:649–61.

Darcel N, Fromentin G, Raybould HE, Gougis S, Gietzen DW, Tome D. Fos-positive neurons are increased in the nucleus of the solitary tract and decreased in the ventromedial hypothalamus and amygdala by a high-protein diet in rats. J Nutr. 2005a;135:1486–90.

Darcel NP, Liou AP, Tome D, Raybould HE. Activation of vagal afferents in the rat duodenum by protein digests requires PepT1. J Nutr. 2005b;135:1491–5.

Davis JD. Some new developments in the understanding of oropharyngeal and postingestional controls of meal size. Nutrition. 1999;15:32–9.

Faipoux R, Tome D, Gougis S, Darcel N, Fromentin G. Proteins activate satiety-related neuronal pathways in the brainstem and hypothalamus of rats. J Nutr. 2008;138:1172–8.

Foltz M, Ansems P, Schwarz J, Tasker MC, Lourbakos A, Gerhardt CC. Protein hydrolysates induce CCK release from enteroendocrine cells and act as partial agonists of the CCK1 receptor. J Agric Food Chem. 2008;56:837–43.

Fromentin G, Gietzen DW, Nicolaidis S. Aversion-preference patterns in amino acid- or protein-deficient rats: a comparison with previously reported responses to thiamin-deficient diets. Br J Nutr. 1997;77:299–314.

Gietzen DW. Neural mechanisms in the responses to amino acid deficiency. J Nutr. 1993;123:610–25.

Gietzen DW, Rogers QR. Nutritional homeostasis and indispensable amino acid sensing: a new solution to an old puzzle. Trends Neurosci. 2006;29:91–9.

Hall WL, Millward DJ, Long SJ, Morgan LM. Casein and whey exert different effects on plasma amino acid profiles, gastrointestinal hormone secretion and appetite. Br J Nutr. 2003;89:239–48.

Halton TL, Hu FB. The effects of high protein diets on thermogenesis, satiety and weight loss: a critical review. J Am Coll Nutr. 2004;23:373–85.

Hao S, Sharp JW, Ross-Inta CM, McDaniel BJ, Anthony TG, Wek RC, et al. Uncharged tRNA and sensing of amino acid deficiency in mammalian piriform cortex. Science. 2005;307:1776–8.

Harper AE, Peters JC. Protein intake, brain amino acid and serotonin concentrations and protein self-selection. J Nutr. 1989;119:677–89.

Jean C, Rome S, Mathe V, Huneau JF, Aattouri N, Fromentin G, et al. Metabolic evidence for adaptation to a high protein diet in rats. J Nutr. 2001;131:91–8.

Kratz CM, Levitsky DA, Lustick S. Differential effects of quinine and sucrose octa acetate on food intake in the rat. Physiol Behav. 1978;20:665–7.

L'Heureux-Bouron D, Tome D, Bensaid A, Morens C, Lacroix M, Huneau JF, et al. Preabsorptive factors are not the main determinants of intake depression induced by a high-protein diet in the rat. Physiol Behav. 2004;81:499–504.

Latner JD, Schwartz M. The effects of a high-carbohydrate, high-protein or balanced lunch upon later food intake and hunger ratings. Appetite. 1999;33:119–28.

Le Magnen J. Role of dietary odour in the short-term control of intake in the white rat (first published in French in 1956) [classical article]. Appetite. 1999;33:30–2.

Leung PM, Rogers QR. Importance of prepyriform cortex in food-intake response of rats to amino acids. Am J Physiol. 1971;221:929–35.

Maljaars PW, Peters HP, Mela DJ, Masclee AA. Ileal brake: a sensible food target for appetite control. A review. Physiol Behav. 2008;95:271–81.

Mangel AW. Electrophysiology of intestinal cholecystokinin secretion. Regul Pept. 1995;56:121–9.

McArthur LH, Kelly WF, Gietzen DW, Rogers QR. The role of palatability in the food intake response of rats fed high-protein diets. Appetite. 1993;20:181–96.

Mellinkoff SM, Frankland M, Boyle D, Greipel M. Relationship between serum amino acid concentration and fluctuations in appetite. J Appl Physiol. 1956;8:535–8.

Meyer JH, Hlinka M, Tabrizi Y, DiMaso N, Raybould HE. Chemical specificities and intestinal distributions of nutrient-driven satiety. Am J Physiol. 1998;275:R1293–307.

Morrison CD, Xi X, White CL, Ye J, Martin RJ. Amino acids inhibit Agrp gene expression via an mTOR-dependent mechanism. Am J Physiol Endocrinol Metab. 2007;293:E165–71.

Nelson G, Chandrashekar J, Hoon MA, Feng L, Zhao G, Ryba NJ, et al. An amino-acid taste receptor. Nature. 2002;416:199–202.

Phifer CB, Berthoud HR. Duodenal nutrient infusions differentially affect sham feeding and Fos expression in rat brain stem. Am J Physiol. 1998;274:R1725–33.

Pichon L, Potier M, Tome D, Mikogami T, Laplaize B, Martin-Rouas C, et al. High-protein diets containing different milk protein fractions differently influence energy intake and adiposity in the rat. Br J Nutr. 2008;99:739–48.

Porrini M, Santangelo A, Crovetti R, Riso P, Testolin G, Blundell JE. Weight, protein, fat, and timing of preloads affect food intake. Physiol Behav. 1997;62:563–70.

Potier M, Darcel N, Tomé D. Protein, amino acids and the control of food intake. Curr Opin Clin Nutr Metab Care. 2009;12(1):54–8.

Powley TL, Phillips RJ. Gastric satiation is volumetric, intestinal satiation is nutritive. Physiol Behav. 2004;82:69–74.

Reid M, Hetherington M. Relative effects of carbohydrates and protein on satiety – a review of methodology. Neurosci Biobehav Rev. 1997;21:295–308.

Ropelle ER, Pauli JR, Fernandes MF, Rocco SA, Marin RM, Morari J, et al. Diabetes. 2008;57:594–605.

Trigazis L, Orttmann A, Anderson GH. Effect of a cholecystokinin – A receptor blocker on protein-induced food intake suppression in rats. Am J Physiol. 1997;272:R1826–33.

Westerterp-Plantenga MS. Protein intake and energy balance. Regul Pept. 2008;149:67–9.

Xu X, Lei Y, Liu S, Chen JD. Inhibitory effects of gastrointestinal electrical stimulation on rectal tone are both organ-specific and distance-related in dogs. Dis Colon Rectum. 2008;51:467–73.

Zhao GQ, Zhang Y, Hoon MA, Chandrashekar J, Erlenbach I, Ryba NJ, et al. The receptors for mammalian sweet and umami taste. Cell. 2003;115:255–66.

Chapter 28
The Importance of Trace Elements for Neurological Function

Joel G. Anderson and Keith M. Erikson

Keywords Iron • Manganese • Copper • Zinc • Nutritional Deficiency • Neurotransmitters • Neurodegeneration

Abbreviations

Aβ	Amyloid beta protein
AD	Alzheimer's disease
APP	Amyloid precursor protein
BBB	Blood-brain barrier
BCB	Blood cerebral spinal fluid barrier
CNS	Central nervous system
CSF	Cerebrospinal fluid
Ctr-1	Copper transporter-1
DAT	Dopamine transporter
DMT-1	Divalent metal transporter-1
GABA	Gamma-aminobutyric acid
GAT	GABA transporter
ID	Iron deficiency
IRE	Iron response element
IRP	Iron regulatory protein
MNK	Menkes copper ATPase
MRI	Magnetic resonance imaging
NET	Norepinephrine transporter
NMDA	N-methyl-d-aspartate
PD	Parkinson's disease
SOD	Superoxide dismutase
TfR	Transferrin receptor
UTR	Untranslated region
WND	Wilson's copper ATPase
ZnT	Zinc transporter

K.M. Erikson (✉)
Department of Nutrition, University of North Carolina at Greensboro,
Greensboro, NC 27402-6170, USA
e-mail: kmerikso@uncg.edu

28.1 Introduction

The essentiality of micronutrients for proper development and function of biological systems has long been recognized. By participating in oxidation-reduction reactions, trace elements play a role in various cellular metabolic processes. However, the dual nature of dietary metals requires that they must be both available to cells and stringently regulated. Disturbances in the homeostasis of these metals can have deleterious effects, specifically in the central nervous system (CNS), resulting in substantial injury to neurons and glia through oxidative damage, in turn leading to neurodegeneration and neurological dysfunction (see Table 28.1). This chapter will focus on iron, manganese, copper, and zinc, essential metals required for numerous important processes in mammalian systems, particularly the CNS (Aschner et al. 2005; Burhans et al. 2005; Arredondo and Núñez 2005; Donnelly et al. 2007).

Iron plays a crucial role as a component of various enzymes and is required for oxidative phosphorylation, nitric oxide metabolism, and oxygen transport (Donnelly et al. 2007). Found throughout the brain, with the highest concentrations in the basal ganglia and the white matter, iron is involved in the synthesis of neurotransmitters and myelin, playing an essential role in neuronal function (Table 28.2) and as a cofactor for a variety of metalloenzymes (Table 28.3) (Beard et al. 1993). As a critical component in dozens of proteins and enzymes, manganese is present in all mammalian tissues and is active in maintaining normal immune function, regulation of blood sugar, and cellular energy, reproduction, digestion, bone growth, defense against free radicals, and blood clotting in concert with vitamin K (Aschner et al. 2005).

Copper is an essential component for a variety of critical enzymes in metabolism, as outlined in Table 28.3. Required for cellular respiration, iron oxidation, and pigment formation, copper also plays a role in neurotransmitter biosynthesis, antioxidant defense, peptide amidation, and connective tissue formation (Madsen and Gitlin 2007). Almost 100 enzymes in mammalian systems require zinc as a cofactor (Table 28.2) (NAS 2002). Zinc is highly abundant in mammalian tissue second only to iron (McCall et al. 2000), and present predominately in the brain (Szewczyk et al. 2008). A major regulator of synaptic transmission and other neuronal processes, zinc is present in the synapse at millimolar concentrations (Donnelly et al. 2007).

28.2 Uptake and Transport of Metals in the Brain

28.2.1 Iron

Iron is widely distributed throughout the various cell types of the CNS, but is particularly abundant in astrocytes, lending credence to the hypothesis that glial cells function in iron storage and regulation (Madsen and Gitlin 2007). The highest concentrations of iron within the brain occur in the basal

Table 28.1 Key facts about trace elements that are important for normal brain functioning

1. The primary essential trace elements that are important for normal brain functioning are iron, manganese, copper, and zinc
2. These trace elements are critical for normal motor control, appetite regulation, learning, memory, mood, and several other neurological functions
3. Brain cells have multiple mechanisms for ensuring adequate trace element availability
4. A lack of these trace elements will cause devastating neurological problems ranging from behavioral to cognitive deficiencies
5. An overload of these trace elements is linked with neurodegenerative diseases (e.g., Parkinson's disease and Alzheimer's disease)

This table lists the key facts about neurologically relevant essential trace elements

Table 28.2 Key brain functions of selected trace elements

Metal	Function
Iron	• Cofactor essential for synthesis of ATP in the brain • Maintains sufficient oxygen levels in the brain as a component of hemoglobin • Functions as a cofactor in the enzymes responsible for the synthesis of biogenic amine neurotransmitters • Critical role in myelinogenesis • Important for packaging, uptake, and degradation of neurotransmitters
Manganese	• Cofactor essential for production of ATP via gluconeogenesis • Antioxidant functions through the action of Mn-SOD • Regulates brain ammonia levels as a component of glutamine synthetase
Copper	• Antioxidant function through the action of Cu/Zn-SOD • Ferroxidase activity as a component of ceruloplasmin and hephaestin • Critical for production of norepinephrine through the action of dopamine β-hydroxylase • Participates in oxidative phosphorylation as a cofactor of cytochrome c oxidase • Plays role in brain development through synaptogenesis
Zinc	• Trace element with the highest intracellular abundance • Involved in protein synthesis • Cofactor in a myriad of enzymes involved in all aspects of metabolism • Regulates synaptic activity and neuronal processes • Critical role in regulation of gene transcription • Important for synaptogenesis and neuronal growth

This table lists the key brain functions attributed to enzymes or processes that depend on the listed trace element. Many functions are related to neurotransmitter biology and chemistry

Table 28.3 Selected metalloenzymes

Metal	Enzyme	Function	Consequences of loss
Iron	Tyrosine hydroxylase	Dopamine synthesis	Dystonia and movement disorders
	Tryptophan hydroxylase	Serotonin synthesis	Anxiety and pulmonary dysfunction
	Xanthine oxidase	Catabolism of purines	Hematuria
	Ribonucleotide reductase	Rate limiting step in DNA synthesis	Embryonic lethality
	Cytochrome P450s	Various metabolic pathways	Altered metabolism, congenital defects, and embryonic lethality
	Catalase	Antioxidant defense	Oxidative damage
Manganese	Glutamine synthetase	Regulation of ammonia levels	Severe brain malformations
	Phosphoenolpyruvate carboxykinase	Gluconeogenesis	Altered ATP synthesis
	Manganese superoxide dismutase	Antioxidant defense	Oxidative damage
Copper	Lysyl oxidase	Crosslink formation in collagen and elastin	Perinatal death
	Peptidylglycine α-amidating monooxygenase	Activation of peptides with α terminal glycine	Embryonic lethality
	Copper/zinc superoxide dismutase	Antioxidant defense	Oxidative damage
	Ceruloplasmin	Ferroxidase	Iron overload, anemia, diabetes, and neurodegeneration
	Hephaestin	Ferroxidase	Impaired iron absorption, anemia
	Dopamine β-hydroxylase	Norepinephrine synthesis	Impaired sympathetic regulation
	Cytochrome c oxidase	Oxidative phosphorylation	Encephalopathy
Zinc	Copper/zinc superoxide dismutase	Antioxidant defense	Oxidative damage
	Alcohol dehydrogenase	Catabolism of alcohol	Decreased retinol utilization
	Carbonic anhydrase	Conversion of carbon dioxide to carbonate	Osteopetrosis

This table highlights key enzymes that are dependent upon the divalent metals for proper functioning. The role of the enzyme as well as the pathologies associated with its dysfunction are listed by column
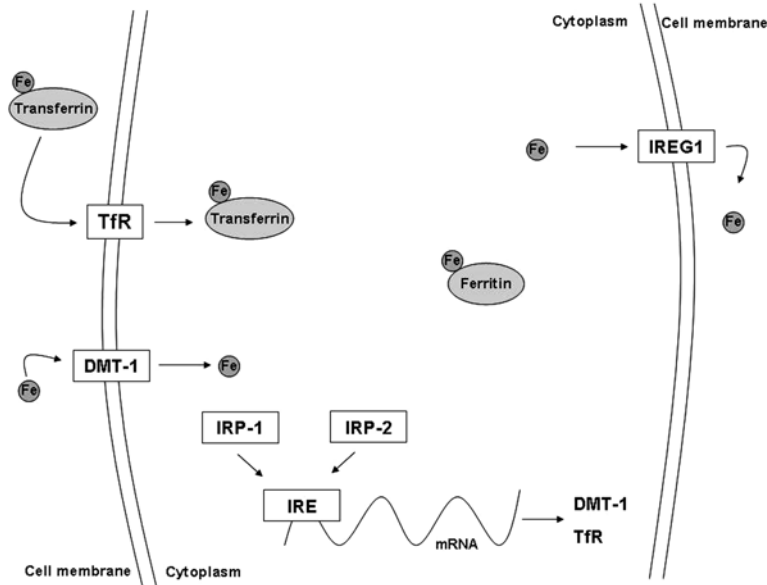
Fig. 28.1 Basic cellular iron transport. Mechanisms of cellular iron transport within the brain are illustrated, including known transport proteins and pathways. Iron may enter cells via transferrin-mediated transport or via the divalent metal transporter (*DMT-1*). Once inside the cell, iron is stored complexed with ferritin. Iron may be excreted from cells by ferroportin, also known as IREG-1. Iron regulatory proteins such as IRP-1 and IRP-2 bind iron responsive elements (*IRE*) in response to changes in iron homeostasis, influences the transcription of iron transport proteins, such as TfR and DMT-1

ganglia at levels equivalent to those observed in the liver, suggesting that the basal ganglia may act as a region of iron storage and distribution within the brain (for a more thorough review, see Beard et al. 1993). Transferrin, a plasma glycoprotein transporting iron in the periphery, is responsible for the shuttling of iron across the blood-brain barrier (BBB) (Madsen and Gitlin 2007) (Fig. 28.1). The highest levels of transferrin in the brain occur in regions containing more myelin, and in the white matter more so than the gray matter. The synthesis of myelin from fatty acids and cholesterol by oligodendroglia is an iron-dependent process (Beard et al. 1993).

One-third of brain iron is stored as ferritin, which is ten-fold more abundant in the brain than transferrin, mostly in oligodendroglia and microglia. Ferritin is comprised of either a heavy chain, which takes up and releases iron more rapidly and is found predominately in neurons, or a light chain, found mostly in glia (Beard et al. 1993). This implies that within the brain, cell populations regulate iron levels in differing ways. The mature brain gains iron through BBB and the brain-cerebral spinal fluid barrier (BCB) via pathways dependent upon transport by transferrin receptor (TfR) and divalent metal transporter-1 (DMT-1), a transporter of divalent metals present in astrocytes (Siddappa et al. 2003). Expression of both TfR and DMT-1 is regulated by the iron regulatory proteins IRP-1 and IRP-2, cytosolic proteins sensitive to decreases in intracellular iron status. These proteins bind to an iron response element (IRE) on 3′ UTR of TfR and DMT-1 mRNA when intracellular iron is low, increasing the stability of the mRNA and increasing protein expression (Fig. 28.1). The brain has two mechanisms to increase iron delivery to neurons: increasing total brain iron delivery from serum via BBB and BCB and/or increasing the percentage of cells expressing TfR and DMT-1 (Siddappa et al. 2003).

28.2.2 Manganese

Most brain manganese is found in the iron-rich regions of the basal ganglia. Transport of manganese into the CNS may occur via the blood at the BBB or via cerebral spinal fluid at the BCB (Aschner et al. 2005), with the entry of manganese into the CNS via the BCB increasing with elevated plasma concentrations of manganese (Normandin et al. 2004). Manganese may also enter the brain following inhalation, bypassing the normal systemic regulatory processes and delivering manganese directly to the CNS. This may occur via the olfactory nerve, the epithelia, or a more systemic route through the mucosa (see Erikson et al. 2007 for review of brain manganese transport). In the brain, manganese can migrate to most regions utilizing a variety of mechanisms. Axonal transport of manganese has been demonstrated, as well as the ability of manganese to cross synapses and travel along secondary and tertiary neurons (Aschner et al. 2005). Manganese may also enter neurons and glial cells through calcium channels (Aschner et al. 2005). To date, the precise mechanism of manganese transport in the brain is still unknown and probably consists of more than one primary route. Facilitated diffusion, active transport, and transferrin-dependent transport are all proposed mechanisms of manganese transport across the BBB (Aschner et al. 2005) (Fig. 28.2). A recent study demonstrated that inhibition of DAT inhibits manganese accumulation in the globus pallidus during chronic exposure, suggesting that the DAT may not play a central role in normal manganese transport in the brain, but may become relevant in a toxicological paradigm in terms of manganese exposure (Anderson et al. 2007). Other transporters recently implicated in the manganese transport include the monocarboxylic acid transporter and the organic anion transporter (Crossgrove et al. 2003), as well as the Zrt/Irt-like proteins (ZIP) (He et al. 2006) (Fig. 28.2).
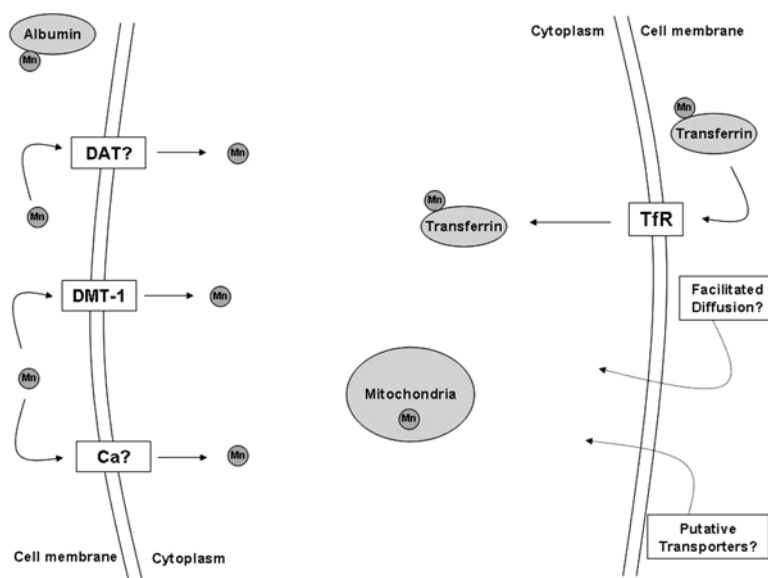
Fig. 28.2 Basic cellular manganese transport. Mechanisms of cellular manganese transport within the brain are illustrated, including known and hypothesized transport proteins and pathways. Manganese may enter cells via transferrin-mediated transport or via the divalent metal transporter DMT-1, though the exact mechanism of manganese absorption is not completely understood and may include facilitated diffusion or other putative transporters, such as the monocarboxylic acid transporter, organic anion transporter, or ZIP transporter. DAT and calcium channels have been shown to allow entry of manganese into the cell. Inside the cell, the mitochondria act as a sink for manganese

28.2.3 Copper

Copper is distributed across most regions of the brain, with the highest levels found in the basal ganglia (Madsen and Gitlin 2007). Transport of copper is dependent upon the oxidation state, with the reduced form of copper being the only form able to be transported (Macreadie 2008). Additionally, metallochaperone proteins, such as Atox1, bind and transport copper to specific locations within the cell in a pathway-specific manner (Fig. 28.3). Since excess and free copper is toxic to cells, sequestration is essential through copper-binding proteins such as metallothionein, a cysteine-rich cytoplasmic protein that chelates copper and is essential to protect against toxicity (Madsen and Gitlin 2007). Two transporting ATPases, Atp7a (MNK) and Atp7b (WND), are the main proteins regulating cellular copper homeostasis (Arredondo and Núñez 2005). MNK excretes copper from most cells when concentrations become too high, while WND performs this function in hepatocytes, excreting copper into the bile. Both transport proteins supply copper for enzymes by shuttling copper into the Golgi (Fig. 28.3). Additionally, in the brain MNK is expressed within specific populations of neurons in several brain regions, including the cerebellum and hippocampus, as well as the BBB endothelium, and facilitates copper movement (Madsen and Gitlin 2007). Copper transporter-1 (Ctr-1) is a plasma membrane protein present on the endothelium of the BBB and essential for early embryonic development (Madsen and Gitlin 2007). Expression of Ctr-1 increases during perinatal copper deficiency (Arredondo and Núñez 2005), suggesting that Ctr-1 transports copper into the brain from the plasma. DMT-1 (Arredondo and Núñez 2005) and amyloid precursor protein (APP) (Macreadie 2008) are also likely copper transporters in the brain (Fig. 28.3).
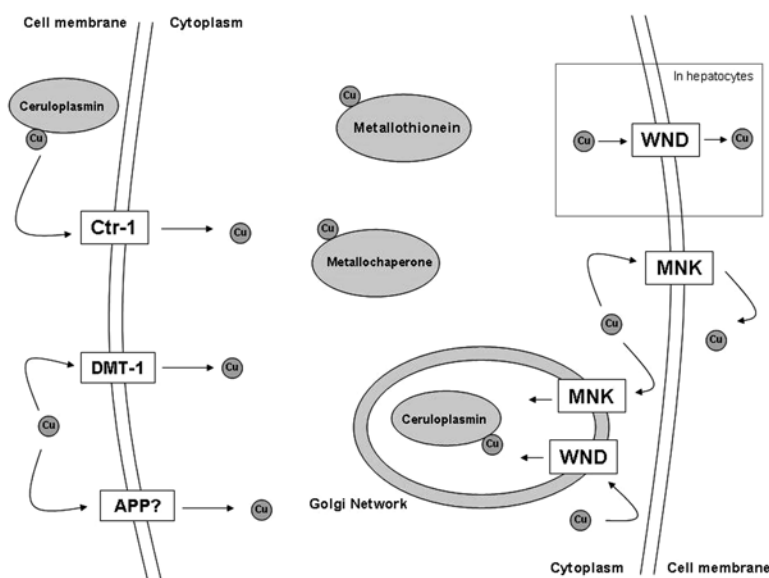
Fig. 28.3 Basic cellular copper transport. Mechanisms of cellular copper transport within the brain are illustrated, including known and hypothesized transport proteins and pathways. Copper may enter the cell through the copper transporter Ctr-1 or DMT-1. The amyloid precursor protein may act as a copper transport protein as well. Inside the cell, copper is bound to metalloproteins such as ceruloplasmin or metallothionein to prevent cytotoxicity of free copper. Metallochaperone proteins direct copper in a pathway-specific manner to organelles for incorporation of copper into metalloenzymes. MNK and WND transport copper into the Golgi network for processing and packaging. MNK can also transport copper out of the cell, with this function being performed by WND in hepatocytes
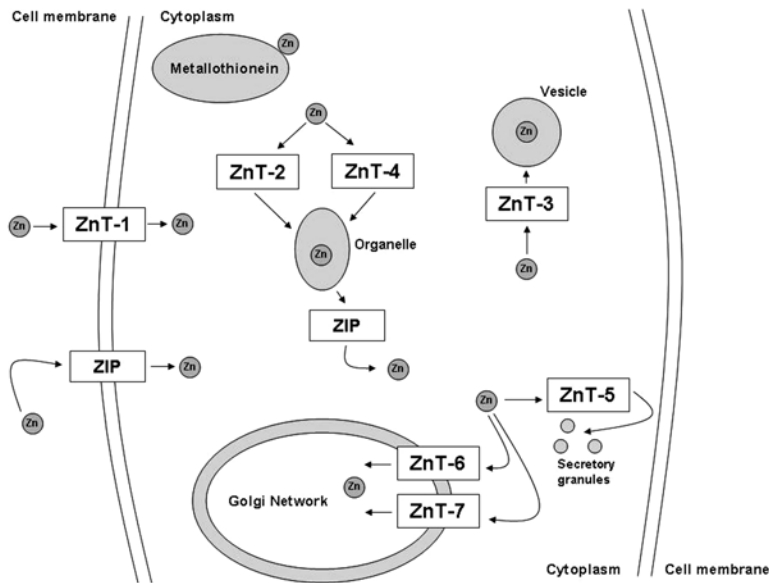
Fig. 28.4 Basic cellular zinc transport. Mechanisms of cellular zinc transport within the brain are illustrated, including known and hypothesized transport proteins and pathways. Zinc may enter the cell via zinc transporter 1 (*ZnT-1*) or through Zn/Irt proteins (*ZIP*). Inside the cell, zinc may be transported via ZnT-2 or ZnT-4 into organelles, ZnT-3 into vesicles, ZnT-5 into secretory granules, or ZnT-6 or ZnT-7 into the Golgi network. Free zinc in the cell is usually bound to a metalloprotein such as metallothionein to prevent toxicity

28.2.4 Zinc

The presence of zinc within the brain, particularly the cerebellum, has been known for the past several decades (Reviewed in: Sandstead et al. 2000). Brain zinc concentrations are highest in the telencephalon, hippocampus, amygdala, and gray matter of the cortex. The vast majority of zinc in the brain is bound to metalloproteins, such as metallothionein, with the rest found in presynaptic vesicles (Szewczyk et al. 2008). Zinc is found highly concentrated within neurons of the CNS (Sandstead et al. 2000). Several zinc transporters (ZnT) have been identified and are crucial for the movement of zinc within mammalian systems (Fig. 28.4). ZnT-1 lowers intracellular zinc, preventing toxicity, since moderate increases in the concentration of intracellular zinc can lead to cytotoxicity. ZnT-2 and ZnT-4 sequester zinc into organelles, with ZnT-6 and ZnT-7 moving zinc into the Golgi and ZnT-5 transporting zinc into secretory granules. ZnT-3 and ZnT-4 are found in the CNS, with ZnT-3 responsible for transporting zinc into vesicles (Sandstead et al. 2000). Zrt/Irt-like proteins (ZIP) transport zinc into the cytoplasm from both the extracellular space and from zinc-containing organelles (Nakashima and Dyck 2009) (Fig. 28.4).

28.3 Role of Metals in Brain Development

28.3.1 Iron

Iron is extremely important to the developing nervous system, with the rate of iron uptake by the brain greatest during fetal life (for review see Madsen and Gitlin 2007), coinciding with a peak in myelinogenesis, with perinatal ID significantly altering myelination of the spinal column and the

white matter of the cerebellum. Iron requirements in the brain far exceed brain iron uptake, suggesting that most of the iron in the brain used daily is recycled behind the BBB, with recycling a major source of iron for brain function following birth. This is analogous to what occurs with regard to iron homeostasis in the periphery (Madsen and Gitlin 2007).

28.3.2 Manganese

Manganese is essential for the functioning and development of the brain and manganese distribution within the brain varies across the life cycle, with concentrations higher in adults than in infants. Alterations in brain Mn levels might be associated with brain maturation and function (Takeda 2003). Manganese is highly concentrated in the hippocampus and pons following birth, structures that may require high levels of manganese, and is found in high concentrations within regions of the basal ganglia in the adult brain, with movement of manganese within the brain likely associated with neuronal activity.

28.3.3 Copper

Copper is essential for CNS development, with studies suggesting a role for MNK and copper in axon extension and synaptogenesis during brain development (Madsen and Gitlin 2007). Disruption of copper homeostasis during fetal life can lead to perinatal mortality, severe growth retardation, and neurodegeneration. Timing of perinatal copper deficiency influences the severity of the neurological outcomes, suggesting a critical period for adequate copper in brain development (Madsen and Gitlin 2007). Rapid growth increases copper demands, with infancy representing the most critical period for copper requirements (Arredondo and Núñez 2005). Diets based on milk provide low amounts of copper and deficiency is of greatest concern during this stage. Also at this stage there is an increased risk of toxic effects due to immature liver functioning unable to handle high copper exposure (Arredondo and Núñez 2005).

28.3.4 Zinc

Zinc plays a role in synaptogenesis and neuronal growth during early brain development, with deficiency during these stages causing malformations and behavioral alterations. Zinc is required for DNA and protein synthesis in the embryo, as well as dendritic growth and motor development. Deficiency of zinc during embryonic development can lead to stunted fetal growth, though concentrations of zinc are higher in adults than in newborns (Sandstead et al. 2000).

28.4 Effects of Metals on Neurotransmitter Systems

28.4.1 Iron

The role of intraneuronal iron includes incorporation of iron into enzymes for oxidation-reduction reactions, electron transport, and synthesis, packaging, uptake, and degradation of neurotransmitters (Beard et al. 1993) (Fig. 28.5). Iron is involved in the synthesis of catecholamines, with iron status
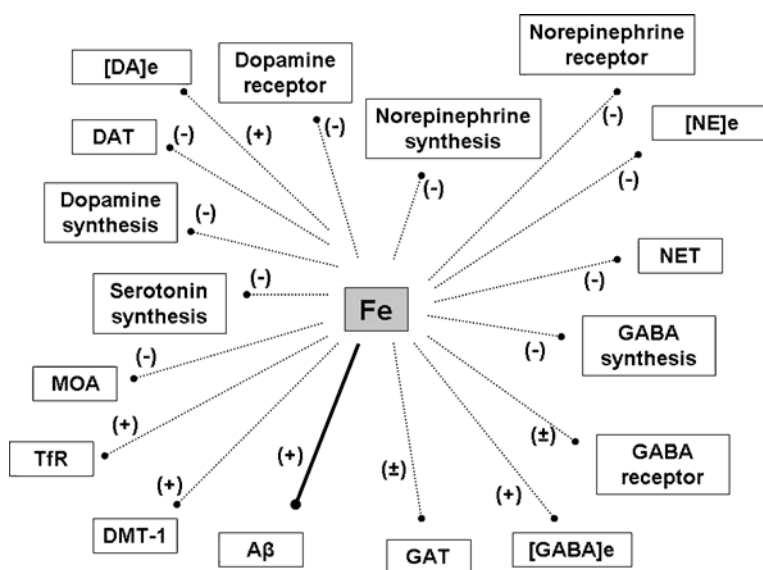
Fig. 28.5 Role of iron in neurotransmitter biology. Increases (+) and decreases (−) in activity resulting from the effects of iron on neurotransmitter biology are illustrated during normal homeostasis, deficiency (*dotted line*), and toxicity (*heavy line*)

hypothesized to affect both monoamine oxidase and aldehyde dehydrogenase, enzymes critical for the catabolism of these biogenic amines. Alterations in iron homeostasis can negatively impact synthesis of γ-aminobutyric acid (GABA) (Beard et al. 1993), as well as expression of GABA transport and receptor proteins (Anderson et al. 2008). Over two decades ago, ID was linked to alterations in dopamine receptor expression (Youdim et al. 1989), with more recent studies observing increased extracellular dopamine and decreased functioning of dopamine receptors (Beard et al. 2006). Studies have found effects of ID on norepinephrine pool size, norepinephrine uptake, and norepinephrine transporter expression both in vitro and in vivo (Beard et al. 2006).

28.4.2 Manganese

Manganese has been shown to block voltage-dependent Ca channels and nerve-evoked neurotransmitter release (Takeda 2003) (Fig. 28.6). Manganese may be released concurrently with glutamate and can decrease the ability of astrocytes to clear glutamate from the synapse, which is likely linked to downregulation of the glutamate:aspartate transporter (Fitsanakis and Aschner 2005). Additionally, manganese has been shown to increase both the frequency and amplitude of spontaneous excitatory post-synaptic potentials in the striatum, leading to increased extracellular glutamate (Fitsanakis and Aschner 2005). Manganese is known to affect GABA by dose-dependently increasing binding at GABA$_B$ receptors (Kerr and Ong 1995), with manganese exposure leading to perturbations in expression of GABA transport and receptor proteins (Anderson et al. 2008). Manganese exposure has also been shown to decrease density of the dopamine transporter (DAT) in rodent models (McDougall et al. 2008). Data from nonhuman primate studies point to a reduction in dopamine receptors post-synaptically in response to manganese exposure (Eriksson et al. 1992). Loss of autoreceptor control of dopamine activity during early stages of manganese poisoning has been demonstrated in mice as
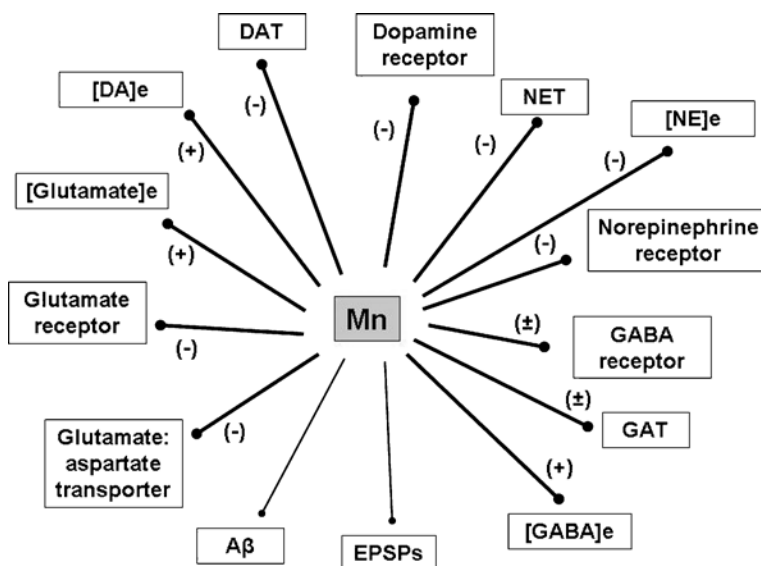
Fig. 28.6 Role of manganese in neurotransmitter biology. Increases (+) and decreases (−) in activity resulting from the effects of manganese on neurotransmitter biology are illustrated during normal homeostasis, deficiency (*dotted line*), and toxicity (*heavy line*)

well (Cuesta de Di Zio et al. 1995), affecting extracellular levels of dopamine and expression of DAT. Struve et al. (2007) found marginal increases in GABA and norepinephrine in response to manganese exposure in primates. A study by Autissier et al. (1982) found alterations in tissue concentrations of norepinephrine in a rodent model, while manganese was found to inhibit uptake of norepinephrine in a dose-dependent manner ex vivo (Lai et al. 1982). Additionally, manganese exposure has been shown to decrease cellular concentrations of serotonin (Reaney and Smith 2005).

28.4.3 Copper

At some neurons, copper may be co-released at the synapse with classical neurotransmitters (Madsen and Gitlin 2007). Copper plays a role in long-term potentiation, modulating activity of calcium-dependent cascades, and synaptic plasticity (Fig. 28.7). Copper is an antagonist at NMDA receptors, leading to rapid and reversible trafficking by MNK, suggesting a mechanism linking copper homeostasis and neuronal activation. The neurotransmitter norepinephrine is a catecholaminergic neuromodulatory neurotransmitter derived from dopamine by dopamine β-hydroxylase, a copper-dependent enzyme (Madsen and Gitlin 2007).

28.4.4 Zinc

Zinc may be co-released at the synapse with classical neurotransmitters and can modulate GABA, NMDA, and glycine receptors at micromolar concentrations (Fig. 28.8). A special class of glutamatergic neurons has zinc-containing vesicles in the axon terminals, releasing zinc into the synaptic cleft and modulating post-synaptic NMDA receptors (Sandstead et al. 2000). All zinc-containing neurons are glutamatergic, but not vice versa (Donnelly et al. 2007), with zinc-containing somata located almost

Fig. 28.7 Role of copper in neurotransmitter biology. Increases (+) and decreases (−) in activity resulting from the effects of copper on neurotransmitter biology are illustrated during normal homeostasis, deficiency (*dotted line*), and toxicity (*heavy line*)
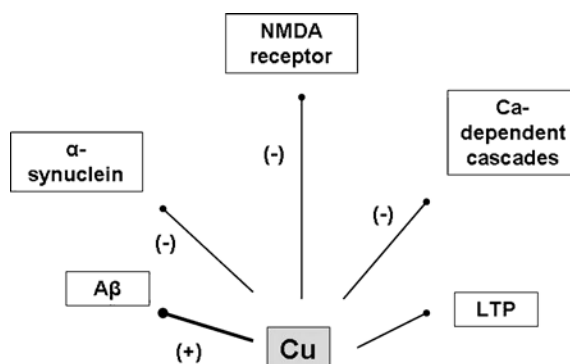
Fig. 28.8 Role of zinc in neurotransmitter biology. Increases (+) and decreases (−) in activity resulting from the effects of zinc on neurotransmitter biology are illustrated during normal homeostasis, deficiency (*dotted line*), and toxicity (*heavy line*)
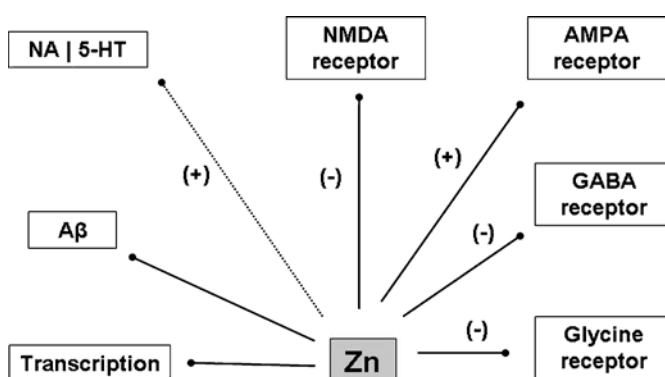
exclusively in cerebral cortex and amygdala. Zinc alters neuronal excitability, plays a role in synaptic plasticity, and can function as a signaling molecule affecting protein function (Szewczyk et al. 2008). Zinc is an inhibitor of GABA receptors, binding to the extracellular domain and allosterically stabilizing the receptor into a shut formation without blocking the channel (Gingrich and Burkat 1998). Zinc also inhibits the GABA transporter (Nakashima and Dyck 2009). Zinc-ATP is necessary for the synthesis of pyridoxal-5-phosphate and flavin adenosine dinucleotide, coenzymes that are essential for the synthesis of biogenic amines and monoamine oxidase metabolism. Severe zinc deficiency has been shown to increase brain concentrations of norepinephrine in rodent models (Sandstead et al. 2000).

28.5 Effects of Altered Metal Homeostasis

28.5.1 *Deficiency*

28.5.1.1 Iron

Iron deficiency is reported as the most prevalent nutritional problem in the world, affecting more than two billion individuals worldwide (WHO/UNICEF/UNU 2006), and is associated with malformation of red blood cells, growth impairment, perturbations in thermoregulation, and deficits in cognitive function (Beard et al. 1993). The neurobiological sequelae of ID in humans include variations in behavior, cognition, and neurotransmitter metabolism, including anemia, reduced immune function, diminished work capacity, and impaired thermoregulation. Disturbances in iron homeostasis

are linked to cognitive dysfunction, neurodegenerative diseases, restless leg syndrome, and Parkinson's disease (Burhans et al. 2005). Iron deficiency in early life may lead to insufficient myelination and dysfunction of dopaminergic tracts (Arredondo and Núñez 2005), as well as neuropsychological effects linked to delayed cognitive development in children and adolescents, delays that may respond to iron therapy (Sandstead et al. 2000). Iron deficiency during late fetal and early postnatal life is associated with cognitive impairments that persist despite repletion, presumably due to alterations in iron-based neuronal cellular processes that occur during the period of rapid brain growth and high iron demand (Siddappa et al. 2003). During the perinatal period, ID results in regionalization of functional brain iron, which may depend on the responsiveness of TfR and DMT-1 and the regulatory proteins IRP-1 and IRP-2 (Siddappa et al. 2003). Studies that have followed children several months after iron repletion suggest that there is an early critical period of brain development during which ID can have a permanent impact (for review, see Youdim 2001).

28.5.1.2 Manganese

Because of its widespread presence in human diets, frank manganese deficiency is generally not clinically recognized in humans. Manganese deficiency has been observed in laboratory animals and has been associated with impaired growth, skeletal defects, reduced reproductive function, birth defects, and abnormal glucose tolerance, as well as altered lipid and carbohydrate metabolism (Aschner et al. 2005). Reduced manganese status may also be observed in individuals with osteoporosis and epilepsy. Blood manganese concentrations are lower in epileptic patients, and alterations in brain manganese homeostasis may be associated with susceptibility to seizures. People with exocrine pancreatic insufficiency, chronic hemodialysis, Perthes' disease, and phenylketonuria may also possess inadequate manganese levels (Aschner et al. 2005).

28.5.1.3 Copper

Frank copper deficiency is rare in humans, though it has been observed in infants fed milk formulas and those recovering from malnutrition, or in adult patients receiving prolonged total parenteral nutrition (Fujita et al. 1989). Symptoms of copper deficiency include anemia, leukopenia, neutropenia, and osteoporosis (Fujita et al. 1989). During severe copper deficiency, iron transport within the body is adversely affected (Arredondo and Núñez 2005), with iron tending to accumulate in many tissues, followed by anemia. Acquired copper deficiency in adults leads to myelopathy, limb spasticity, and sensory ataxia due to neurodegeneration (Madsen and Gitlin 2007).

28.5.1.4 Zinc

Zinc deficiency is not uncommon and may present simultaneously with ID. Both metals are most bioavailable from similar food sources and absorption of both is inhibited by the same dietary substances (Sandstead and Smith 1996). Zinc deficiency causes abnormal development of the nervous system, leading to distinct behavioral effects (Sandstead et al. 2000). Depression and impaired cognitive function are early clinical manifestations of zinc deficiency, with lower serum zinc levels found in depressed individuals, which may be normalized after successful antidepressant therapy (Szewczyk et al. 2008). Zinc deficiency has been reported in Alzheimer's disease (AD) patients and could be a contributing factor in development of this condition (Shcherbatykh and Carpenter 2007).

28.5.2 Overload/Toxicity

28.5.2.1 Iron

Dysregulation of iron homeostasis in the brain leading to increased concentrations of iron result in saturation of iron transport and storage proteins, increased free iron in the cell, production of reactive oxygen species, oxidative damage, and cell death via apoptosis (Beard et al. 1993). Accumulation of iron in the brain occurs with aging, along with an increase in ferritin. This increase may lead to oxidative damage as a result of proxidant-free iron, which may be released from ferritin under acidic condition caused by excess concentrations of SOD or ascorbate, intracerebral hemorrhage, or hypoxic ischemia (Gaasch et al. 2007). High concentrations of brain and dysregulation of iron homeostasis in the brain are associated with Parkinson's disease (PD) and Alzheimer's disease (AD), which will be described further in the Applications to Health and Disease section of this chapter. Interestingly, inherited disorders of iron metabolism such as hemochromatosis do not always correlate with increased brain iron (Gaasch et al. 2007).

28.5.2.2 Manganese

Manganese toxicity resulting from environmental exposure has been documented since the early nineteenth century, when a small group of workers grinding manganese oxide developed an unsteady gait and muscular weakness (Normandin et al. 2004). At present, manganese toxicity is most often associated with occupational exposure of welders, miners, and steel workers to chronic high levels of airborne particulate manganese (Pal et al. 1999). When inhaled, the manganese can lead to inflammation in the lungs and potential respiratory symptoms, including cough, bronchitis, pneumonitis, and impaired pulmonary function (Roels et al. 1987). Cases from drinking contaminated well water have also been reported in several countries, resulting in impaired cognitive function (Sahni et al. 2007). Working memory, concentration, and spatial orientation have all been shown to be affected following toxic manganese exposure (Mergler et al. 1994). Manganese neurotoxicity is characterized by a psychiatric disorder resembling schizophrenia, and eventually manifests as a neurological disorder sharing similarities with several clinical disorders, in particular Parkinson's disease (Pal et al. 1999).

28.5.2.3 Copper

At steady state the amount of copper excreted into the bile is equivalent to that absorbed from the intestine, with excretion increasing promptly in response to elevated dietary copper. Therefore, excess copper does not occur in the absence of an underlying metabolic defect (Madsen and Gitlin 2007). The consequences of these genetic disorders of copper metabolism are discussed in the section, Applications to Health and Disease.

28.5.2.4 Zinc

High intracellular concentrations of zinc are cytotoxic and can lead to neurodegeneration through the production of ROS, resulting in oxidative damage. It is hypothesized that excess zinc leads to cell death by inhibiting synthesis of ATP at various points in cell metabolism. Zinc has been shown to

disrupt glycolysis, the Kreb's cycle, and the electron transport chain through the inhibition of specific enzymes required for these processes. These high levels of intracellular zinc may be achieved through the influx of zinc from the extracellular space through ion channels of glutamate receptors. Moreover, zinc has been implicated as a potential neurotoxin in models of stroke and epilepsy, and high levels of zinc can lead to aggregation of amyloid plaques and dementia in neurodegenerative diseases (Dineley et al. 2003).

28.6 Applications to Health and Disease

Imbalance of trace metals can play a role in the etiology of various neurodegenerative and neurological disease states. Cellular levels of Fe and transferrin are altered around plaques present in multiple sclerosis, with iron contained in sclerotic plaques and MRI data from multiple sclerosis patients showing a general disruption in regulation of iron (Beard et al. 1993). Human prions have been shown to have binding sites for trace metals (Shcherbatykh and Carpenter 2007). Moreover, individuals suffering from a complete deficiency of ceruloplasmin have alterations in iron metabolism and develop dementia later in life (Madsen and Gitlin 2007). Altered brain metal homeostasis has been implicated in Huntington's disease, Freidreich's ataxia, and amyotrophic lateral sclerosis (Aschner et al. 2005; Gaasch et al. 2007). Parkinson's disease (PD) and Alzheimer's disease (AD) are two neurodegenerative conditions in which altered homeostasis of metals is of keen interest. Additionally, genetic disorders of copper metabolism deleteriously impact neurological function.

28.6.1 Parkinson's Disease

Parkinson's disease is one of the most common neurodegenerative conditions among the elderly, affecting a marginal percentage of the worldwide population (Rommelfanger and Weinshenker 2007). Disturbed iron homeostasis has been linked to cognitive dysfunction and PD (Burhans et al. 2005), with the postmortem brain iron content of PD patients significantly higher than that of age-matched controls (Beard et al. 1993). Manganese neurotoxicity shares similarities with PD (Pal et al. 1999), and manganese accumulation in the brain may play a role in the pathology of idiopathic PD (for review, see Aschner et al. 2005). Copper affects oligomerization of α-synuclein, a protein essential for neurotransmission, during PD (Macreadie 2008). Additionally, alterations in norepinephrine biology brought on by perturbations in metal homeostasis may play a role in the etiology of PD given the profound effects of norepinephrine on brain inflammation, oxidative stress, and the function of protein implicated in the condition (Rommelfanger and Weinshenker 2007).

28.6.2 Alzheimer's Disease

Recently, there has been substantial interest in role of copper, zinc, manganese, and iron in the neuropathology of AD, since these metals are known to be concentrated in and around amyloid plaques at concentrations three to five times higher than in age-matched controls (Shcherbatykh and Carpenter 2007).

Additionally, there is an observed imbalance of these metals (decreased copper; increased iron, manganese, and zinc) in the AD brain, with chelators having been shown to enhance resolubilization of plaques (Cornett et al. 1998). However, the exact role of these trace metals in AD pathogenesis remains uncertain (Shcherbatykh and Carpenter 2007).

Iron is a component of senile plaques and iron encrustation of blood vessels is common in AD. Iron mobility decreases and iron levels in the brain are increased during AD, with an associated decrease in metabolic activity and increase in perioxidative damage. IRE is located on the mRNA for the amyloid precursor protein (Beard et al. 1993). Compared to normal aged tissue, the concentration of transferrin decreases, ferritin levels decrease, and iron levels increase in tissues from AD patients, with loss of the transferrin receptor observed the in AD brains (Beard et al. 1993). The amyloid β protein (Aβ), which forms the senile plaques in AD, reduces copper and iron leading to production of hydrogen peroxide and toxicity (Shcherbatykh and Carpenter 2007). Copper can induce Aβ precipitation, with Aβ having selective binding sites for copper, making the copper in Aβ plaques available for reactive oxygen species production (Macreadie 2008). A clear association exists between excess zinc and formation of amyloid plaques, with an imbalance of zinc a hallmark of the AD brain. Zinc promotes aggregation of endogenous Aβ in CSF in low concentrations and inhibits Aβ-mediated hydrogen peroxide production (Shcherbatykh and Carpenter 2007).

28.6.3 Genetic Disorders of Copper Metabolism

28.6.3.1 Menkes Disease

The neurological features of Menkes disease are present in early infancy, with impaired copper transport into and within the developing brain resulting in demyelination and neurodegeneration, revealing the critical role for MNK and copper in neuronal development (Madsen and Gitlin 2007). Menkes disease is an X-linked disorder characterized by growth failure, brittle hair, hypopigmentation, arterial tortuosity, and neuronal degeneration due to a loss-of-function mutation in the gene encoding the copper transporter Atp7a (MNK). Neuropathological exam reveals a focal degeneration of gray matter and neuronal loss most prominent in hippocampus and cerebellum, with decreased myelination with cerebellar and cerebral atrophy as revealed by MRI (Madsen and Gitlin 2007).

28.6.3.2 Wilson Disease

Wilson disease is an autosomal recessive disorder leading to cirrhosis of the liver and progressive neurodegeneration in the basal ganglia as a result of a loss-of-function mutation in the gene encoding the copper transporter Atp7b (WND) (Madsen and Gitlin 2007). Wilson disease is characterized by impairment in the biliary excretion of copper, leading to hepatocyte copper accumulation, copper-mediated liver damage, apoptosis, leakage of copper into plasma, and copper overload in extrahepatic tissues due to excess accumulation from the plasma following liver injury. Half of the patients with Wilson disease present with signs and symptoms of neuropsychiatric illness, with brain copper accumulation during Wilson disease leading to dystonia, dysarthria, and other Parkinsonian symptoms, as well as psychiatric symptoms of depression, cognitive deterioration, personality change, psychosis, and schizophrenia (Madsen and Gitlin 2007).

Summary Points

- Trace elements are required for proper biological functioning, but homeostasis must be strictly regulated to prevent oxidative damage and neurodegeneration.
- Iron is required for oxidative phosphorylation, nitric oxide metabolism, and oxygen transport.
- Manganese is required for normal immune function, regulation of blood sugar and cellular energy, reproduction, digestion, bone growth, defense against free radicals, and blood clotting in concert with vitamin K.
- Copper is required for cellular respiration, iron oxidation, and pigment formation, neurotransmitter biosynthesis, antioxidant defense, peptide amidation, and connective tissue formation.
- Zinc is required for protein synthesis, all stages of metabolism, synaptic activity, and neuronal function.
- Iron, manganese, copper, and zinc play a critical role in brain development, with metal deficiencies or toxicities during embryogenesis deleterious.
- Iron, manganese, copper, and zinc are essential for proper neurotransmitter biology, influencing synaptic function and neurotransmitter receptor and transport proteins.
- Deficiencies of essential trace metals can have deleterious effects of the functioning of central nervous system, leading to learning deficits and neurodegeneration.
- Overload or toxic levels of trace metals can lead to production of reactive oxygen species, oxidative damage, and neural dysfunction.
- Neurodegenerative diseases such as Parkinson's disease and Alzheimer's disease have been linked to altered brain homeostasis of trace metals such as iron, manganese, copper, and zinc.

Key Terms

Biogenic amine: A biologically active neurotransmitter than contains an amine group.

Blood-brain barrier: A selectively permeable barrier formed by the tight junctions of vascular endothelial cell membranes and astrocytes in the brain; this barrier protects the brain from exogenous molecules; most metabolites and molecules require a specific protein transporter for trafficking across the membrane.

Blood-cerebrospinal fluid barrier: A barrier formed in the choroid plexus of the brain between the cerebral capillaries and the extracellular space containing the cerebrospinal fluid; metabolites, molecules, and toxins may enter the brain through this barrier.

Catecholamine: A classical neurotransmitter that contains a catechol group and an amine group; includes dopamine, norepinephrine, and serotonin.

Ceruloplasmin: A copper-containing protein essential for copper transport and regulation of intracellular copper concentrations that act as a ferroxidase in the brain.

Ferritin: An iron-storing protein composed of a heavy and light chain that regulates intracellular iron concentrations.

Glial cell: a cell within the central nervous system that supports the activity and function of neurons; glial cell types include astrocytes, oligodendroglia, and microglia.

Metalloenzyme: A catalytic protein enzyme that contains one or more metal ions or requires metal ions as a cofactor in order to function.

Metallothionein: A cysteine-rich protein that binds and sequesters metal ions in the cell to prevent cytotoxicity and cellular damage.

Transferrin: A glycoprotein that binds iron for transport in the bloodstream and inside cells; may also bind and transport other metals such as manganese.

References

Anderson JG, Cooney PT, Erikson KM. Environ Toxicol Pharmacol. 2007;23:179–84.

Anderson JG, Fordahl SC, Cooney PT, Weaver TL, Colyer CL, Erikson KM. Neurotoxicology. 2008;29:1044–53.

Arredondo M, Núñez MT. Mol Asp Med. 2005;26:313–27.

Aschner M, Erikson KM, Dorman DC. Crit Rev Toxicol. 2005;35:1–32.

Autissier N, Rochette L, Dumas P, Beley A, Loireau A, Bralet J. Toxicology. 1982;24:175–82.

Beard JL, Connor JR, Jones BC. Nutr Rev. 1993;51:157–70.

Beard JL, Wiesinger JA, Jones BC. Brain Res. 2006;1092:47–58.

Burhans MS, Dailey C, Beard Z, Wiesinger J, Murray-Kolb L, Jones BC, et al. Nutr Neurosci. 2005;8:31–8.

Cornett CR, Markesbery WR, Ehmann WD. Neurotoxicology 1998;19:339–345.

Crossgrove J, Allen D, Bukaveckas B, Rhineheimer S, Yokel R. Neurotoxicology. 2003;24:3–13.

Cuesta de Di Zio MC, Gomez G, Bonilla E, Suarez-Roca H. Life Sci. 1995;56:1858–64.

Dineley KE, Votyakova TV, Reynolds IJ. J Neurochem. 2003;85:563–70.

Donnelly PS, Xiao Z, Wedd AG. Curr Opin Chem Biol. 2007;11:128–33.

Erikson KM, Thompson K, Aschner J, Aschner M. Pharmacol Ther. 2007;113:369–77.

Eriksson H, Gillberg PG, Aquilonius SM, Hedström KG, Heilbronn E. Arch Toxicol. 1992;66:359–64.

Fitsanakis VA, Aschner M. Toxicol Appl Pharmacol. 2005;204:343–54.

Fujita M, Itakura T, Takagi Y, Okada A. J Parenter Enteral Nutr. 1989;13:421–5.

Gaasch JA, Lockman PR, Geldenhuys WJ, Allen DD, Van der Schyf CJ. Neurochem Res. 2007;32:1196–208.

Gingrich KJ, Burkat PM. J Physiol. 1998;506:609–25.

He L, Girijashanker K, Dalton TP, Reed J, Li H, Soleimani M, et al. Mol Pharmacol. 2006;70:171–80.

Kerr DIB, Ong J. Pharmacol Ther. 1995;67:187–246.

Lai JCK, Lim L, Davison AN. J Inorg Biochem. 1982;17:215–25.

Macreadie IG. Eur Biophys J. 2008;37:295–300.

Madsen E, Gitlin JD. Annu Rev Neurosci. 2007;30:317–37.

McCall KA, Huang C, Fierke CA. J Nutr 2000;130:1437s–1446s.

McDougall SA, Reichel CM, Farley CM, Flesher MM, Der-Ghazarian T, Cortez AM, et al. Neuroscience. 2008;154:848–60.

Mergler D, Huel G, Bowler R, Iregren A, Belanger S, Baldwin M, et al. Environ Res. 1994;64:151–80.

Nakashima AS, Dyck RH. Brain Res Rev. 2009;59:347–73.

NAS (National Academy of Science), 2002. Dietary Reference Intakes for Vitamin A, Vitamin K, Arsenic, Boron, Chromium, Copper, Iodine, Iron, Manganese, Molybdenum, Nickel, Silicon, Vanadium, Zinc. Available at www.nap.edu/books/0309072794/html/.

Normandin L, Beaupré LA, Salehi F, St. Pierre A, Kennedy G, Mergler D, et al. Neurotoxicology. 2004;25:433–41.

Pal PK, Samii A, Calne DB. Neurotoxicology. 1999;20:227–38.

Reaney SH, Smith DR. Toxicol Appl Pharmacol. 2005;205:271–81.

Roels H, Lauwerys R, Genet P, Sarham MJ, de Fays M, Hanotiau I, et al. Am J Ind Med. 1987;11:297–305.

Rommelfanger KS, Weinshenker D. Biochem Pharmacol. 2007;74:177–90.

Sahni V, Léger Y, Panaro L, Allen M, Giffin S, Fury D, et al. Environ Health Perspect. 2007;115:1176–9.

Sandstead HH, Smith Jr JC. J Nutr. 1996;126:2410s–8.

Sandstead HH, Frederickson CJ, Penland JG. J Nutr. 2000;130:496s–502.

Shcherbatykh I, Carpenter DO. J Alzheimers Dis. 2007;11:191–205.

Siddappa AJM, Rao RB, Wobken JD, Casperson K, Leibold EA, Connor JR, et al. Pediatric Res. 2003;53:800–7.

Struve MF, McManus BE, Wong BA, Dorman DC. Am J Ind Med. 2007;50:772–8.

Szewczyk B, Poleszak E, Sowa-Kucma M, Siwek M, Dudek D, Ryszewska-Pokrasniewicz B, et al. Pharmacol Rep. 2008;60:588–99.

Takeda A. Brain Res Rev. 2003;41:79–87.

WHO/UNICEF/UNU. Iron deficiency anaemia: assessment, prevention and control. A guide for programme managers. Geneva: World Health Organization; 2006.

Youdim MBH, Ben-Shachar D, Yehuda S. Am J Clin Nutr. 1989;50:607–17.

Youdim MB. Nutr Rev. 2001;59:83–7.

Chapter 29
Cannabinoid Cb₁ Receptor Antagonists/Inverse Agonists and Food-Seeking Behavior

John D. Salamone, Kelly Sink, Kristen N. Segovia, Patrick A. Randall,
Peter J. McLaughlin, V. Kiran Vemuri, and Alexandros Makriyannis

Abbreviations

THC	delta-9-tetrahydrocannabinol
DA	dopamine
FR	fixed ratio
c-AMP	cyclic-adenosine monophosphate

29.1 Introduction

Drugs that act upon cannabinoid CB1 receptors can exert a number of physiological and behavioral effects. CB1 agonists, such as delta-9-tetrahydrocannabinol (THC), CP559490, and AM411, affect neural processes related to motor control (Martin et al. 1991; Carriero et al. 1998; McLaughlin et al. 2005a), pain (Martin et al. 1991; McLaughlin et al. 2005a), and cognitive function (Darley et al. 1973; Heishman et al. 1990; Ilan et al. 2004; McLaughlin et al. 2005b). In addition, CB1 agonists have been reported to exert actions related to food intake. Initial findings indicated that consumption of marijuana could be accompanied by feelings of increased hunger and decreased satiety, as well as increases in food intake (Halikas et al. 1985). Laboratory experiments with humans demonstrated that CB1 agonists could increase eating (Foltin et al. 1986, 1988) and increase body weight (Greenberg et al. 1976). Overall, the effects of cannabinoid CB1 agonists on food intake studies conducted in animals appear to depend greatly upon the dose that is used (Giuliani et al. 2000). Some papers have reported that injection of relatively high doses of CB1 agonists that produce catalepsy and suppress locomotion also tend to decrease feeding (e.g., Drewnowski and Grinker 1978). Nevertheless, administration of moderate-to-low doses of CB1 agonists generally has been shown to increase food intake (Giuliani et al. 2000; Johansson et al. 1975; Williams et al. 1998; Koch 2001; Williams and Kirkham 1999, 2002). Because of these actions, CB1 agonists have been investigated for their potential as treatments for anorexia and the wasting syndrome associated with AIDS and cancer chemotherapy (Hao et al. 2000).

With the development of CB1 receptor antagonists such as rimonabant (SR141716A; Rinaldi-Carmona et al. 1994), it was suggested that CB1 receptor blockade could act to reduce food intake.

J.D. Salamone (✉)
Department of Psychology, University of Connecticut, 406 Babbidge Road,
Storrs, CT 06269-1020, USA
e-mail: john.salamone@uconn.edu; JDSalamone@gmail.com

Table 29.1   Key features of the functional significance of cannabinoid receptors

1. There are two subtypes of cannabinoid receptors – CB1 and CB2
2. Delta 9 THC, the active ingredient in marijuana, is a CB1 agonist
3. Several synthetic CB1 agonists and antagonists have been developed
4. There are endogenous ligands for the CB1 receptor, known as anandamide and 2AG, which act as neuromodulators and physiological signaling molecules
5. CB1 antagonists and inverse agonists block the effects of these endogenous ligands, and also block the effects of pharmacological agents that act as CB1 agonists

This table presents some of the key features of the functional significance of cannabinoid receptors, and drugs that act on cannabinoid receptors.

Arnone et al. (1997) reported that rimonabant decreased intake of high-sucrose food pellets. Rimonabant also was shown to decrease intake of food, but not water, during the first few days of repeated administration in rats (Colombo et al. 1998). In this study, tolerance developed rapidly to the appetite suppression effect, although body weight was decreased during the entire period of drug administration, even at the lowest dose (2.5 mg/kg). As well as studying food consumption, researchers also investigated the effects of rimonabant on food-reinforced operant responding. Rimonabant reduced food-reinforced fixed ratio 15 responding in a dose-related manner, an effect that was partially reversed by coadministration of the CB1 agonist WIN55, 212-2 (Freedland et al. 2000).

 Over the last few years, there has been a rapid expansion of research in this area (see Table 29.1), and a number of different behavioral methods have been used to assess the ever increasing number of compounds that act to interfere with cannabinoid CB1 transmission (Simiand et al. 1998; Hildebrandt et al. 2003; McLaughlin et al. 2003, 2005a, b, c, 2006; Shearman et al. 2003; Chen et al. 2004; Wiley et al. 2005). Clinical trials with the CB1 inverse agonists rimonabant and taranabant have shown these drug to be effective at reducing body weight and waist circumference (Curioni and Andre 2006; Despres et al. 2005; Pi-Sunyer et al. 2006; Van Gaal et al. 2005; Addy et al. 2008). However, there also have been major problems related to the clinical utility of CB1 receptor inverse agonists for the treatment of obesity. Clinical trials have provided evidence of nausea and malaise, and also serious psychiatric side effects including depression and anxiety, with administration of rimonabant and taranabant. Nausea was one of the most common adverse effects reported in clinical trials with rimonabant (Pi-Sunyer et al. 2006; Van Gaal et al. 2005). In terms of psychiatric symptoms, a meta-analysis of rimonabant studies conducted by the Food and Drug Administration (FDA) showed that 26% of subjects treated with 20 mg rimonabant reported adverse psychiatric events versus 14% of those treated with placebo (US Food and Drug Administration Advisory Committee 2007). In the FDA-sponsored meta-analysis of clinical trials using rimonabant, the most commonly reported adverse psychiatric event was anxiety (US Food and Drug Administration Advisory Committee 2007). Clinical trials with taranabant, another CB1 inverse agonist, also were marked by the presence of adverse psychiatric events. Onset of psychiatric symptoms occurred early in the clinical trials, and dropouts related to psychiatric adverse events were frequent (Addy et al. 2008). The induction of adverse psychiatric symptoms was a key factor in the decision of the FDA to deny approval of rimonabant for treatment of obesity in the USA. In turn, this decision has led several pharmaceutical companies to abandon their research programs in this area (Le Foll et al. 2009). Nevertheless, research employing cannabinoid antagonists and inverse agonists remains very useful, in that it can provide insights into the neurochemical mechanisms regulating food motivation. Furthermore, alternative research strategies that focus on novel pharmacological agents with unique profiles, such as peripherally acting drugs or neutral antagonists, could yield clinically useful compounds (Salamone et al. 2007a; Le Foll et al. 2009). For those reasons, the present review will provide a brief summary of some of the studies that have focused upon recently synthesized compounds, and also will discuss novel cannabinoid-based strategies for the development of appetite suppressants.

29.2 Effects of CB1 Receptor Inverse Agonists on Food Intake and Food-Reinforced Behavior

Like rimonabant, the more recently developed drugs AM251 and AM1387 can bind with relatively high affinity to CB1 receptors, and they have a moderate level of selectivity for CB1 receptors relative to CB2 receptors. Furthermore, rimonabant, AM251, and AM1387 all act as inverse agonists at the cellular level, and exert actions on signal transduction mechanisms when administered in the absence of CB1 receptor stimulation (i.e., they inhibit GTPγS binding and increase cAMP production; Landsman et al. 1997; Mato et al. 2002; McLaughlin et al. 2006). These drugs have all been assessed under a standard set of conditions that provide measures of food-reinforced behavior and food intake. A series of experiments examined the effects of rimonabant, AM 251, and AM1387 on food-reinforced operant responding, using two different fixed ratio schedules (fixed ratio 1 (FR1) and 5 (FR5)). These particular ratio requirements were employed because previous studies have indicated that FR1 and FR5 schedules can show differential sensitivity depending upon the pharmacological conditions being studied (Solinas et al. 2003; Ishiwari et al. 2004). Rimonabant, AM251, and AM1387, all suppressed responding on both schedules of reinforcement (McLaughlin et al. 2003, 2005a, b, c), with each schedule being affected at roughly the same dose range for a given drug. In addition to being a useful tool for characterizing the effects of CB1 inverse agonists on food-reinforced responding, the suppression of FR5 lever pressing can be used to assess the duration of action for each compound. Rimonabant and AM251 were shown to have a relatively long duration of action ($t_{1/2}$: rimonabant-15.6 h; AM 251–22.0 h), while the half-life AM1387 was considerably shorter ($t_{1/2}$ = 4.87 h; McLaughlin et al. 2006).

Additional experiments were conducted to characterize the effects of rimonabant, AM251, and AM1387 on the consumption of different types of foods. There has been considerable interest in identifying the role that different diets may play in modulating the appetite-related effects of drugs that act on CB1 receptors. Snacking on sweets between meals was reported to increase after administration of cannabinoid agonists in humans, although meal size was not affected (Foltin et al. 1986). In rats, increases in food intake following administration of Δ9-THC were significantly larger for consumption of a high-fat diet compared to standard laboratory chow (Koch 2001). Although some reports have indicated that interference with CB1 transmission suppressed intake of sweet foods such as sucrose to a greater extent than standard laboratory chow (Arnone et al. 1997; Simiand et al. 1998), others have found that intake of standard diets such as laboratory chow also can be affected (Rowland et al. 2001; Verty et al. 2004a). In view of these discrepancies, a series of studies (McLaughlin et al. 2003; 2006) assessed the effects of rimonabant, AM251, and AM1387 on the intake of three different foods: a high-fat diet (HF; Diet # D12451, Research Diets, New Brunswick, NJ, 45% kcal from fat), a high-carbohydrate diet (HC; Diet # D12450B, Research Diets, New Brunswick, New Jersey, 67% kcal from carbohydrate), and standard laboratory chow (LC, 5P00 Prolab RMH 3000, PMI Nutrition International, St. Louis, MO). In these studies, rats were food deprived and trained to eat their assigned diet in test cages; after successive weeks of training, the drug treatment period began (one drug treatment per week following two baseline days). IP injections of rimonabant, AM251, and AM1387 produced a dose-related suppression of intake of all three food types, including the laboratory chow.

An important aspect of studies involving multiple types of foods is that baseline or control levels of consumption can differ dramatically. Indeed, in the studies described above (McLaughlin et al. 2003, 2006), intake was highest for the high-carbohydrate and high-fat diets, and considerably lower for the laboratory chow. For this reason, data were reanalyzed, with food intake being expressed as a percent of the two previous baseline days, in order to correct for differences in baseline levels. With this type of analysis, there were significant dose-related decreases in food intake with all three drugs,

but no significant interactions, and the dose–response curves for consumption of each food overlapped considerably (McLaughlin et al. 2003, 2006). These results indicate that rimonabant, AM251, and AM1387 do not seem to be selectively suppressing feeding upon diets that are high in carbohydrates or fat. Instead, effects of these drugs on intake of different foods may be due to differences in baseline intake or scaling. Furthermore, it may be difficult to show a suppression of lab chow intake if baseline levels of consumption are very low. It appears that as long as the testing conditions generate substantial levels of chow intake, interference with CB1 transmission can reduce intake of this type of food, which is generally considered not to be highly palatable. However, in considering the potential use of these drugs as appetite suppressants, it also is useful to note that the intake of distinct types of foods can show differential patterns of tolerance after repeated administration of CB1 inverse agonists (Arnone et al. 1997).

29.3 Effects of CB1 Inverse Agonists on Nausea and Malaise

As one evaluates the literature on the effects of CB1 receptor inverse agonists on food-related behaviors, it is critical to consider that drugs can affect food intake by altering a number of different behavioral processes. In addition to food motivation or appetite, effects of drugs on motor slowing, incoordination, nausea, or malaise may also occur, and these actions could affect food consumption. Some of the feeding-related effects produced by drugs that act on CB1 receptors may be due to actions on processes such as food avoidance, food aversion, nausea, or malaise. Several studies have shown that CB1 agonists have anti-emetic effects (Gonzalez-Rosales and Walsh 1997; Simoneau et al. 2001; Darmani and Johnson 2004). CB1 receptors that are associated with triggering emetic responses are present in the dorsal vagal complex in the brainstem (Van Sickle et al. 2003). Rimonabant enhanced lithium chloride-induced conditioned rejection in rats (Parker et al. 2003). Furthermore, administration of rimonabant led to the development of conditioned taste avoidance in the rat (De Vry et al. 2004), vomiting in the least shrew (Darmani 2001), and nausea in humans (Despres et al. 2005; Pi-Sunyer et al. 2006). Despite the fact that rats do not vomit, several papers have used measures of conditioned gaping in rats, which is thought to be a selective marker of nausea in that species (Parker et al. 1998; Limebeer et al. 2004). Gaping responses are induced by conditions that produce vomiting in species capable of emesis (Parker et al. 1998), and treatments that reduce toxin-induced vomiting in emetic species also attenuate toxin-induced conditioned gaping in rats (Parker et al. 2003; Limebeer et al. 2004). Consistent with the observation that CB1 receptor inverse agonists can induce nausea in humans, doses of AM251 that attenuate feeding were shown to be accompanied by the induction of conditioned food avoidance and conditioned gaping (McLaughlin et al. 2005a, b, c). These data indicate that drug-induced food aversions, nausea, and malaise may contribute to the reductions in food intake induced by CB1 receptor inverse agonists.

29.4 Studies of the Effects of CB1 Receptor Neutral Antagonists

As stated above, biochemical studies have indicated that rimonabant, AM251, and AM1387 act as inverse agonists, exerting effects on signal transduction mechanisms that are opposite to those induced by CB1 receptor stimulation (inhibition of GTPγS binding and increase c-AMP production, see Fig. 29.1; Landsman et al. 1997; Mato et al. 2002; McLaughlin et al. 2006). However, the

Effects of Drugs on Signal Transduction
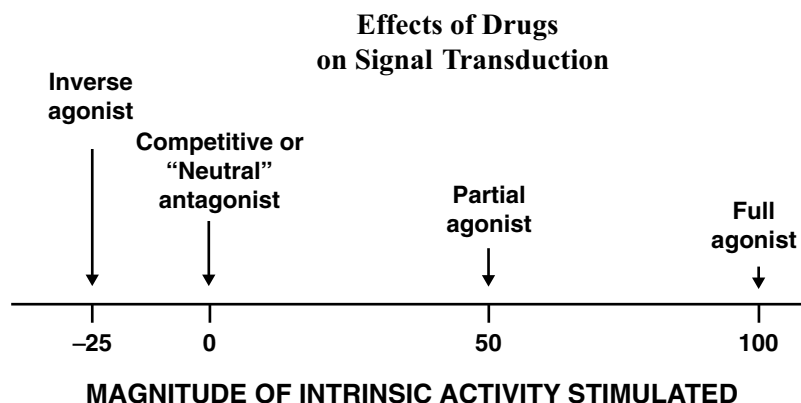
Fig. 29.1 Signal transduction effects of drugs. Signal Transduction Effects of Drugs. This figure depicts the continuum of effects upon intrinsic activity that can be induced by different classes of drugs that act on the same receptor site as the neurotransmitter. Each of these drug classes (i.e., agonists, antagonists, inverse agonists) has affinity for the receptor. Agonists bind to the receptor and stimulate the same intrinsic activity as the endogenous transmitter. Full agonists maximally stimulate intrinsic activity, and partial agonists produce low-to-moderate levels of stimulation of the signal transduction mechanism (e.g., the arbitrary value shown here is 50%). Competitive antagonists (i.e., neutral or "silent" antagonists) bind to the receptor but do not instigate signal transduction effects on their own. In contrast, inverse agonists stimulate signal transduction effects in the opposite direction from those stimulated by the agonist and the transmitter. CB1 receptor agonists inhibit cyclic-AMP production, while inverse agonists stimulate production of this second messenger. In neuropharmacology, the identification of compounds as inverse agonists or neutral antagonists is based upon their signal transduction effects, which are determined at the cellular or tissue levels. Nevertheless, in behavioral pharmacology it also is important to determine if neutral antagonists block the behavioral actions of both inverse agonists and agonists

behavioral significance of these inverse agonist actions is unclear. Compared to wild-type mice, CB1 receptor knockout did not affect progressive ratio responding reinforced by corn oil, while administration of rimonabant to wild-type mice reduced responding (Ward and Dykstra 2005). This pattern of effects indicates that rimonabant may exert inverse agonist effects in addition to simply blocking CB1 receptors. The development of CB1 receptor neutral antagonists, weak partial agonists, or inverse agonists with very low intrinsic activity, would yield important tools for research in this field. The ability of these drugs to decrease feeding would indicate that there is a tonic influence of endogenous cannabinoids on food intake. Perhaps most importantly, it is possible that CB1 receptor neutral antagonists might be able to suppress food intake at doses that do not affect food avoidance, aversion, anxiety, or depression, a pattern of effects that would offer several clinical advantages (Salamone et al. 2007a; Sink et al. 2008a, b; Le Foll et al. 2009).

Within the last few years, investigators have begun to investigate the behavioral effects of drugs that have little in the way of CB1 receptor inverse agonist activity, and may be acting largely as neutral or "silent" antagonists. Gardner and Mallet (2006) reported that O-2050 suppressed food intake in non-deprived rats. Several recent papers have focused upon the effects of AM4113, which is a pyrazole analog that is structurally related to rimonabant and AM251 (Chambers et al. 2007; Sink et al. 2008a, b, 2009a). AM4113 blocked the locomotor suppression and analgesia induced by the CB1 agonist AM411 (Sink et al. 2008a), and also produced many of the food-related effects induced by rimonabant, AM251, and AM1387 (see above). AM4113 reduced food-reinforced FR1 and FR5 responding (Sink et al. 2008a, 2009a), and in fact was more potent at suppressing FR1 lever pressing than it was at reducing FR5 performance. AM4113 reduced intake of high-carbohydrate, high-fat, and laboratory chow diets, and as was the case with the inverse agonists, the degree of suppression

Table 29.2 Key points: effects of the CB1 receptor neutral antagonist AM4113 (Chambers et al. 2007; Sink et al. 2008a, b)

- High Affinity for CB1 receptors
- Can block effects of CB1 antagonists
- Tests of signal transduction show that this drug has no intrinsic activity, i.e., it is not an inverse agonist
- Important for showing behavioral significance of endogenous cannabinoid tone
- Suppresses food intake and food-reinforced behavior at doses that do not induce nausea or food aversion

This table summarizes some of the key points related to the actions of AM4113. See text for details

of intake for each food type relative to baseline was roughly comparable (Sink et al. 2008a). These data demonstrate that CB1 receptor neutral antagonists can suppress feeding and food-reinforced behavior, which suggests that blockade of endogenous tone at CB1 receptors is sufficient to produce a suppression of food-motivated behaviors.

In addition to demonstrating that drugs such as AM4113 can reduce food intake, it also is important to determine whether or not this suppression of feeding is accompanied by signs of nausea, malaise, or food aversion (Limebeer and Parker 2000; Parker and Limebeer 2006). Clinical studies have shown that nausea was one of the most common adverse effects reported in clinical trials with the antagonist/inverse agonist rimonabant (Pi-Sunyer et al. 2006; Van Gaal et al. 2005). AM4113, in contrast to the inverse agonist AM251, did not induce vomiting in ferrets (Chambers et al. 2007). In addition, doses of AM4113 that substantially suppressed food intake did not induce conditioned gaping (Sink et al. 2008a), which is a marker of nausea in rats. Another recent study demonstrated that, unlike the inverse agonist AM251, AM4113 did not produce anxiogenic effects in the elevated plus maze (Sink et al. 2010). Thus, if CB1 receptor neutral antagonists can suppress feeding without producing food aversions or anxiety-related effects in humans, it might mean that neutral antagonists would offer some clinical advantages over drugs that also have inverse agonist properties (Table 29.2).

29.5 Comparisons Between the Effects of CB1 Antagonists and DA Antagonists or Depletion

Rimonabant administration in moderate doses does not lead to obvious signs of sedation or motor slowing. Nevertheless, high doses can produce other effects such as reductions in spontaneous locomotion, and the induction of grooming, scratching, and head twitching (Darmani and Pandya 2000; Jarbe et al. 2002). It has been suggested that drug-induced grooming could be interfering with engagement in feeding behavior (Tallett et al. 2007), however, recent evidence indicates that response competition between grooming and feeding may not provide a sufficient explanation of the feeding suppression produced by AM251 and AM4113 (Hodge et al. 2008). Other motor dysfunctions, such as forepaw incoordination, also could act to interfere with normal feeding behavior. However, in order to evaluate the possible role that various aspects of motor function play in feeding behavior, it is important to emphasize that it is inadequate to obtain measures of gross locomotor activity. As shown in several papers, impairments in locomotion can be easily dissociated from impairments in motor control and food handling during food intake. Dopamine (DA) depletions in the ventrolateral neostriatum do not suppress spontaneous locomotion, but to reduce food intake and impair feeding efficiency and food handling (Jicha and Salamone 1991; Cousins et al. 1993; Salamone et al. 1993). By contrast, DA depletions in nucleus accumbens suppress locomotion but do not impair feeding or food handling (Salamone et al. 1993; Cousins et al. 1993; Correa et al. 2002). Because locomotor impairments

are easily dissociable from deficits in motor patterns related to food intake, direct observations of feeding behavior are necessary to determine if CB1 receptor inverse agonists impair motor functions specifically related to feeding. When these analyses were conducted, it was demonstrated that AM251 failed to suppress feeding rate or disrupt forepaw usage during feeding at doses that substantially suppressed food intake (McLaughlin et al. 2005a, b, c). Thus, CB1 receptor inverse agonists do not appear to reduce food intake simply by disrupting the motor patterns necessary for feeding behavior. Despite the fact that the neostriatum contains a relatively high concentration of CB1 receptors (Herkenham 1992; Egertova and Elphick 2000; Gonzalez-Rosales and Walsh 1997), the effects of CB1 inverse agonists do not closely resemble those produced by neostriatal DA depletions (Salamone et al. 1990).

In fact, it has been suggested that drugs that act on cannabinoid receptors could be modulating DA transmission, particularly in the nucleus accumbens (Cohen et al. 2002; Wenger et al. 2003; Gardner 2005). CB1 receptor stimulation has been shown to increase extracellular DA in nucleus accumbens (Gardner and Lowinson 1991; Tanda et al. 1997; Gardner 2005), and this effect can be blocked by CB1 receptor antagonism (Tanda et al. 1997). Recent evidence indicates that the CB1 receptor inverse agonist rimonabant can reduce the increase in extracellular DA in nucleus accumbens that accompanies consumption of a palatable food (Melis et al. 2007), and it has been suggested that interference with CB1 receptor transmission could reduce feeding by suppressing mesolimbic DA activity (Melis et al. 2007). Nevertheless, there appear to be some difficulties with the idea that drugs that interfere with CB1 transmission act on food-motivated behaviors by decreasing activity of DA systems that are hypothesized to mediate primary food motivation. Considerable evidence has demonstrated that the mesolimbic DA system does not mediate primary food "reward," motivation, or appetite (Salamone et al. 1997, 2003, 2005, 2007b; Salamone and Correa 2002; Kelley et al. 2005). It has been shown repeatedly that nucleus accumbens DA depletion or antagonism does not suppress food intake (Ungerstedt 1971; Koob et al. 1978; Salamone et al. 1993; Baldo et al. 2002). Based upon this evidence, it does not seem highly likely that CB1 antagonists decrease food intake because they reduce accumbens DA release.

Very few studies have offered direct comparisons between the behavioral effects of DA and CB1 antagonists. If CB1 antagonists or inverse agonists are exerting their effects on food motivation by reducing DA transmission, then it is reasonable to suggest that the effects of these CB1-related drugs should closely resemble the effects of DA antagonists. Recent studies were undertaken to assess this possibility. These experiments employed a concurrent lever-pressing/chow-feeding procedure that has frequently been used to assess the effects of dopaminergic manipulations (Salamone et al. 1991, 1997, 2002, 2003, 2007b; Cousins et al. 1993; Cousins and Salamone 1994; Nowend et al. 2001; Farrar et al. 2007). With this task, rats can press a lever to receive a preferred food (Bioserv pellets), or, alternatively, approach and consume a less-preferred lab chow that is concurrently available in the operant chamber (Salamone et al. 1991, 1996, 1997; Cousins et al. 1993, 1994; Cousins and Salamone 1994; Nowend et al. 2001; Farrar et al. 2007). Untreated rats pressing on a fixed-ratio 5 (FR5) schedule will typically obtain most of their food by pressing the lever, and will consume very little of the laboratory chow. Several papers have provided a behavioral and pharmacological characterization of performance on this task. In rats performing this procedure, prefeeding to reduce food motivation suppressed both lever pressing and chow intake (Salamone et al. 1991). In contrast, low-to-moderate doses of DA antagonists, injected systemically or directly into nucleus accumbens, as well as accumbens DA depletions, generally produce a very different pattern of effects. Systemic injections of DA antagonists with varying profiles of selectivity for DA family receptors, including cis-flupenthixol, haloperidol, raclopride, SCH23390, and SKF83566, all decreased lever pressing for food, but substantially *increased* intake of the concurrently available chow (Salamone et al. 1991, 1996, 2002; Cousins et al. 1994; Koch et al. 2000). The low dose of haloperidol that produced this shift in

behavior (0.1 mg/kg) did not alter intake of the preferred or non-preferred foods, and DA antagonism did not affect food preference in free-feeding choice tests (Salamone et al. 1991). The shift from lever pressing to chow intake that is produced by systemic DA antagonists also was induced by accumbens DA depletions and intra-accumbens injections of DA antagonists into core or shell regions (Salamone et al. 1991; Cousins et al. 1993; Cousins and Salamone 1994; Sokolowski and Salamone 1998; Koch et al. 2000; Nowend et al. 2001), while DA depletions in ventrolateral neostriatum produced severe motor dysfunctions that impaired both lever pressing and chow intake (Cousins et al. 1993).

In order to directly compare the effects of DA antagonists with those of CB1 antagonists/inverse agonists, Sink et al. (2008b) used this concurrent lever pressing/chow intake procedure. Rats treated with IP injections of the DA D1 antagonist ecopipam (0.05–0.2 mg/kg) or the D2 antagonist eticlopride (0.025–0.1 mg/kg) showed substantial decreases in lever pressing and concomitant increases
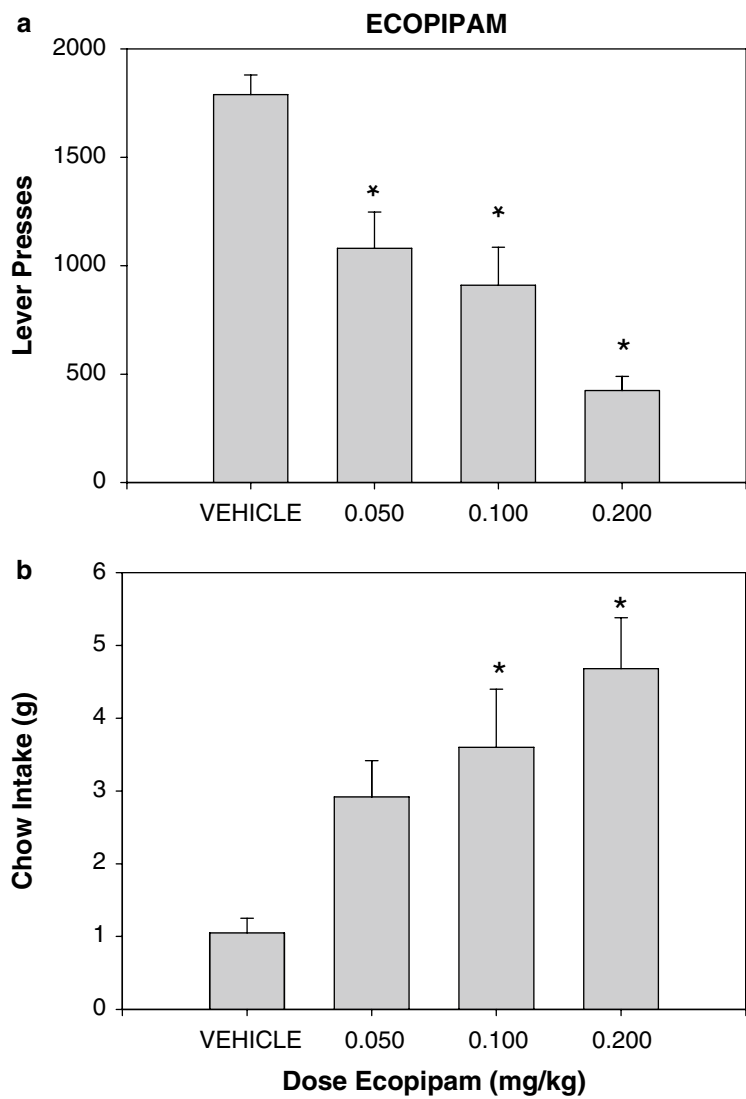
Fig. 29.2 Effects of the DA D1 receptor antagonist SCH 39166 on the concurrent lever-pressing/chow-feeding procedure. Effects of the DA D1 receptor antagonist SCH 39166 on the concurrent lever-pressing/chow-feeding procedure. (**a**) Mean (±SEM) number of lever presses after treatment with vehicle and various doses of SCH 39166. (**b**) Mean (±SEM) intake of lab chow (in grams) after treatment with vehicle and various doses of SCH 39166. $*p < 0.05$, different from vehicle, planned comparison (Data are from Sink et al. (2008b))

Fig. 29.3 Effects of the DA D2 receptor antagonist eticlopride on the concurrent lever-pressing/chow-feeding procedure. Effects of the DA D2 receptor antagonist eticlopride on the concurrent lever-pressing/chow-feeding procedure. (**a**) Mean (± SEM) number of lever presses after treatment with vehicle and various doses of eticlopride. (**b**) Mean (± SEM) intake of lab chow (in grams) after treatment with vehicle and various doses of eticlopride. *$p < 0.05$, different from vehicle, planned comparison (Data are from Sink et al. (2008b))
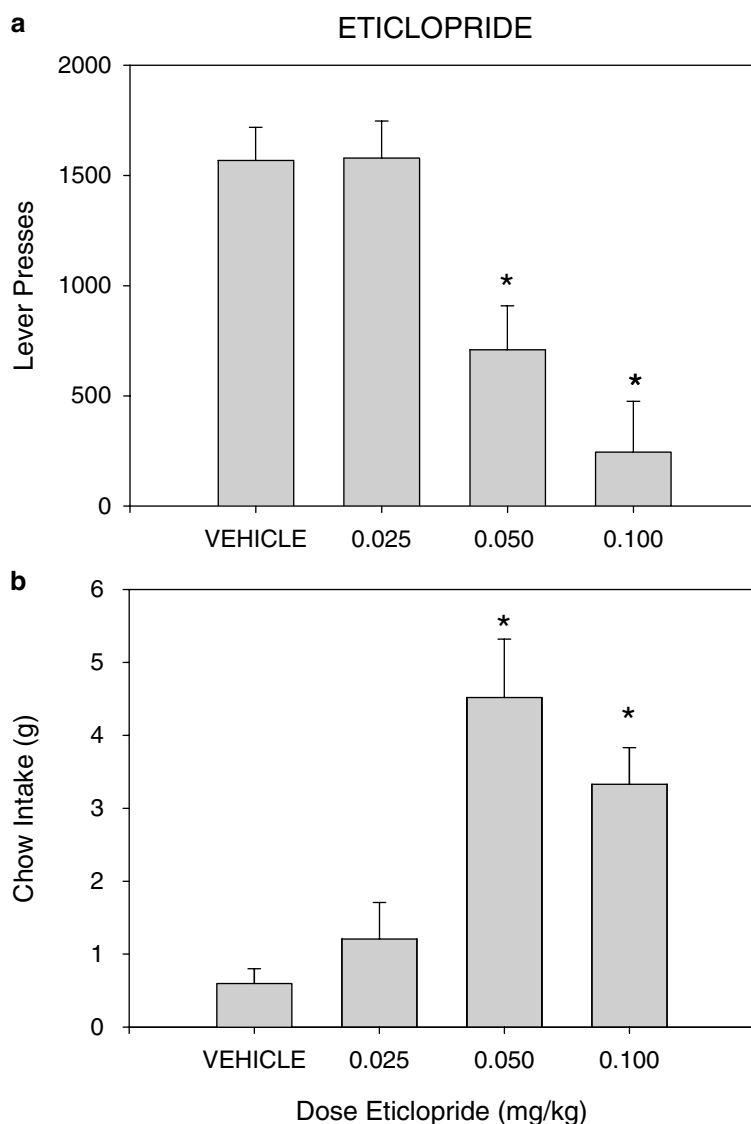
in chow intake (Figs. 29.2 and 29.3). In contrast, IP administration of the CB1 inverse agonist AM251 (2.0–8.0 mg/kg), as well as the CB1 neutral antagonist AM4113 (4.0–16.0 mg/kg), decreased operant responding for pellets, but failed to increase chow intake (Figs. 29.4 and 29.5). These effects of CB1 antagonists/inverse agonists were similar to those produced by the serotonergic appetite suppressant fenfluramine (Salamone et al. 2002). Thus, low doses of DA antagonists leave primary food motivation (i.e., "appetite") intact, but shift behaviors toward food reinforcers that can be obtained with lower effort. In contrast, interference with cannabinoid CB1 receptor transmission appears to suppress food-motivated instrumental behavior because of direct actions on food intake regulation mechanisms. These results demonstrate that the effects of interference with CB1 transmission are easily distinguishable from those of reduced DA transmission (Sink et al. 2008b).

Fig. 29.4 Effects of the cannabinoid CB1 receptor antagonist/inverse agonist AM251 on the concurrent lever-pressing/chow-feeding procedure. Effects of the cannabinoid CB1 receptor antagonist/inverse agonist AM251 on the concurrent lever-pressing/chow-feeding procedure. (**a**) Mean (± SEM) number of lever presses after treatment with vehicle and various doses of AM251. (**b**) Mean (± SEM) intake of lab chow (in grams) after treatment with vehicle and various doses of AM251. *p < 0.05, different from vehicle, planned comparison (Data are from Sink et al. (2008b))
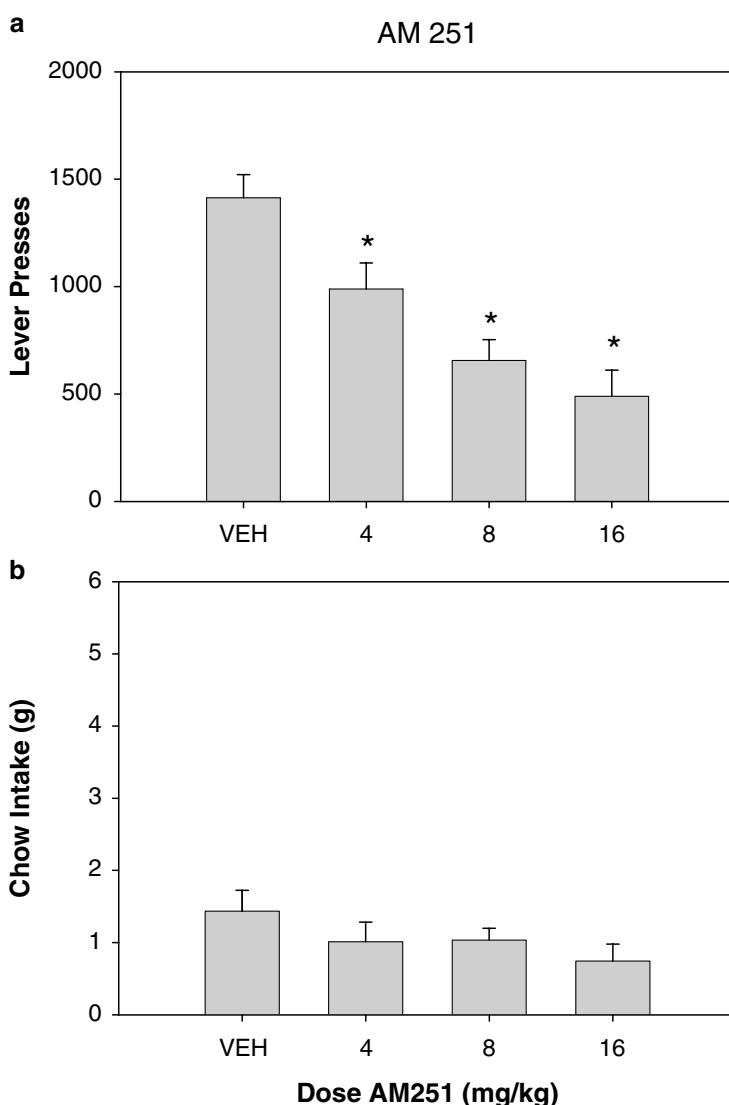
29.6 Possible Importance of Peripheral CB1 Receptors

While it now seems clear that these CB1 antagonists and inverse agonists decrease food intake and food-reinforced behavior, there is still controversy as to the primary locus of action for these effects. CB1 agonists injected directly into hypothalamic nuclei related to feeding, or into nucleus accumbens, which is involved in various aspects of motivated behavior, have been shown to induce hyperphagia (Jamshidi and Taylor 2001; Williams and Kirkham 1999; Verty and Mallet 2005; Soria-Gomez et al. 2007). Moreover, these effects were blocked by administration of CB1 inverse agonists. However, these particular studies did not demonstrate that administration of a CB1 inverse agonist on its own could affect feeding. Although a few papers have demonstrated that forebrain injections of CB1 inverse agonists reduce feeding (Werner and Koch 2003; Verty et al. 2004b, c), it also has been argued that the actions of CB1 inverse agonists on feeding may not depend substantially on

Fig. 29.5 Effects of the cannabinoid CB1 receptor neutral antagonist AM4113 on the concurrent lever-pressing/chow-feeding procedure. Effects of the cannabinoid CB1 receptor neutral antagonist AM4113 on the concurrent lever pressing/chow feeding procedure. (**a**) Mean (± SEM) number of lever presses after treatment with vehicle and various doses of AM4113. (**b**) Mean (± SEM) intake of lab chow (in grams) after treatment with vehicle and various doses of AM4113. *$p < 0.05$, different from vehicle, planned comparison (Data are from Sink et al. (2008b))
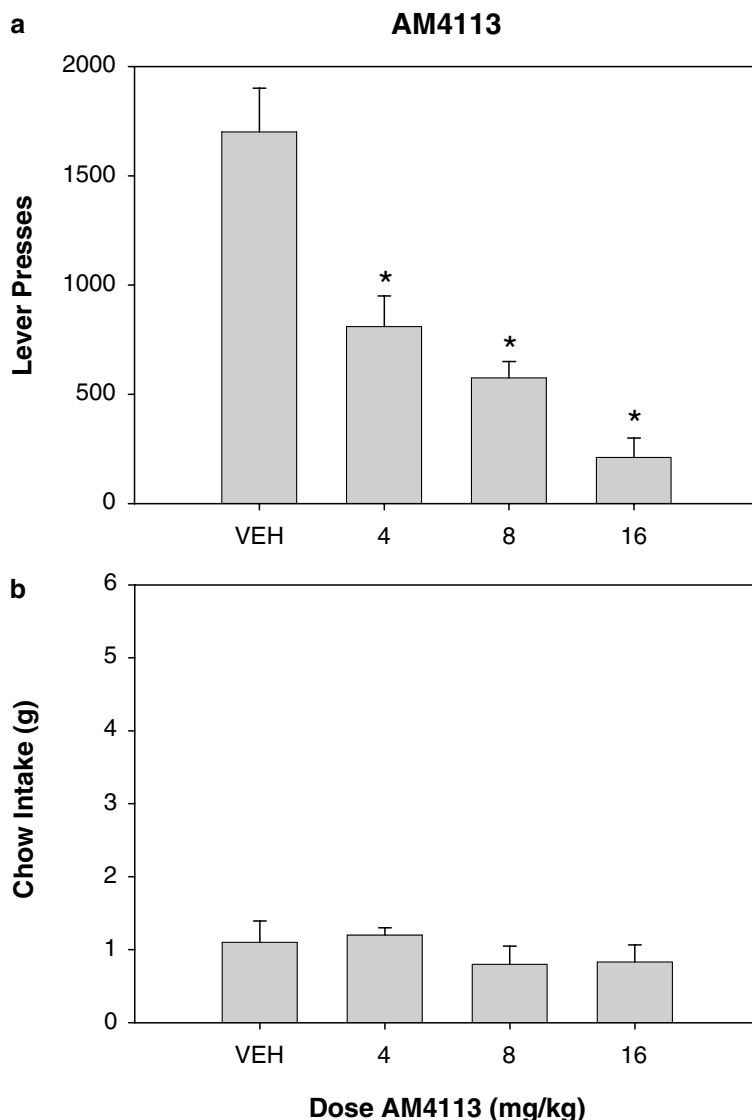
forebrain sites. Gomez et al. (2002) reported that food intake could be suppressed by systemic, but not intraventricular administration of SR141716. Furthermore, capsaicin-induced deafferentation of peripheral vagal nerves eliminated the changes in feeding induced by systemic administration of a CB1 agonist and the inverse agonist SR141716 (Gomez et al. 2002). Therefore, these authors suggested that drugs acting on CB1 receptors may modulate feeding via sites located on these peripheral sensory nerve terminals.

Recent studies were conducted to determine if AM251 and AM4113 could affect food-reinforced behavior after administration into the lateral ventricle (Sink et al. 2009b). Although systemic administration of both drugs has been shown to suppress food-reinforced behavior, neither

AM251 (40, 80, and 160 μg) nor AM4113 (60, 120, and 240 μg) produced any suppression of food-reinforced operant responding in rats tested on an FR5 schedule. Because locomotor effects of drugs that act on CB1 receptors are thought to be dependent upon actions on the forebrain (e.g., basal ganglia and related structures), AM251 and AM4113 also were assessed for their ability to reverse the locomotor suppression produced by the CB1 agonist AM411. Intraventricular administration of either AM251 or AM4113 reversed the locomotor suppression induced by the CB1 agonist AM411 in the same dose range that failed to produce any effects on feeding. This pattern of effects indicated that both AM251 and AM4113, when administered into the lateral ventricle, can interact with forebrain CB1 receptors, and are effective at producing forebrain-mediated functions unrelated to feeding. Taken together, these results suggest that CB1 neutral antagonists or inverse agonists may not be affecting food-reinforced behavior via interactions with forebrain CB1 receptors located in nucleus accumbens or hypothalamus, and indicate that lower brainstem or peripheral receptors may be involved.

An important line of future investigation that could further clarify this issue would be the measurement of food consumption or food-motivated behaviors after systemic administration of a CB1 inverse agonist or antagonist with poor blood-brain barrier penetrability. If the suppression of food intake could be observed following systemic injection of such a compound, this would support the hypothesis that peripheral CB1 receptors are involved in the modulation of feeding. It has been reported that LH-21, a compound that is purported to be a CB1 antagonist with poor blood-brain barrier penetrability, did act to decrease feeding (Pavón et al. 2006, 2008). However, continued pharmacological evaluation of this compound will be necessary in order to determine which of its effects are peripheral and which are central (Chen et al. 2008a; Pavón et al. 2008), and additional compounds need to be evaluated. Recently, a novel CB1 antagonist, AM6545, was developed as a tool for investigating the behavioral actions of peripherally active CB1 antagonists. Although this drug has poor penetrability into the brain compared to AM251 (i.e., sevenfold less penetration in a mouse model), it was shown to suppress feeding and food-reinforced FR5 lever pressing at doses of 4.0–16.0 mg/kg IP (Randall et al. 2010). These results indicate that a peripherally active CB1 neutral antagonist with poor central penetration could be useful as an appetite suppressant, and it is possible that such a drug could avoid side effects related to central actions.

29.7 Applications to Other Areas of Health and Disease

In addition to the suggestion that CB1 antagonists and inverse agonists could be useful for the suppression of appetite and the induction of weight loss, it also has been suggested that these drugs could be employed for treating substance abuse disorders, including smoking, alcoholism, and drug addiction (Fattore et al. 2007; Chen et al. 2008a). In fact, the results of clinical research on the effects of rimonabant for cessation of smoking are rather mixed (Stapleton 2009; Rigotti et al. 2009). In a recently published clinical trial, rimonabant had little efficacy to induce smoking cessation on its own, but combined treatment with rimonabant plus a nicotine patch yielded a stronger effect, and the presence of rimonabant suppressed the weight gain that is commonly seen with smoking cessation (Rigotti et al. 2009). This effect is not trivial for individuals who have gained substantial amounts of weight after successfully quitting smoking. Nevertheless, because of the psychiatric problems described above, the FDA is not currently considering rimonabant as a treatment for smoking (Stapleton 2009).

In some ways, the conception of rimonabant as a "wonder drug" that could treat obesity, smoking, alcoholism, and drug addiction was predicated on the misconception that this drug acted on a

dopaminergic "reward" system that mediates all forms of primary motivation, for both natural reinforcers and drugs of abuse. As reviewed above, this view of DA function has been strongly challenged (e.g., Salamone et al. 1999, 2001, 2006, 2007b, 2009), and the hypothesis that the effects of CB1 antagonism closely resemble those produced by DA antagonism has numerous problems (Sink et al. 2008b). Yet despite these conceptual issues, it remains to be determined if future development of drugs that act on CB1 receptors could generate compounds that are useful for the treatment of substance abuse disorders.

29.8 Conclusions

Considerable evidence indicates that drugs that interfere with cannabinoid CB1 receptor transmission can reduce food intake. These effects are evident across a variety of tasks, and different food types, and can occur under conditions involving food-reinforced behavior as well as feeding. Nevertheless, there also is evidence that cannabinoid inverse agonists can induce signs of nausea, malaise, food aversion, anxiety, and depression. Recent studies have been undertaken to characterize the behavioral effects of CB1 receptor neutral antagonists such as AM4113 to determine if these drugs can reduce feeding and food-reinforced behaviors at doses that do not have deleterious effects on other behavioral processes. AM4113 affects food-motivated behavior in ways that are very similar to the effects of CB1 inverse agonists. Moreover, this drug did not induce conditioned gaping in rats or vomiting in ferrets. These results suggest that CB1 neutral antagonists may decrease appetite by blocking endogenous cannabinoid tone, and that these drugs may be less associated with nausea than CB1 inverse agonists. Future studies should place great emphasis on characterizing the effects of CB1 neutral antagonists that do not easily penetrate the blood-brain barrier, to determine whether the use of these drugs can minimize the occurrence of some of the aversive motivational and psychiatric events. Another useful strategy would be to investigate the effects of combined administration of opiate antagonists along with drugs that interfere with CB1 transmission (e.g., Tallett et al. 2009). Such a combined drug treatment may produce conditions in which food intake is suppressed, but the occurrence of deleterious side effects is reduced.

Summary Points

- Drugs that act to interfere with cannabinoid CB1 receptor transmission can suppress food intake and food-reinforced behavior.
- The effects of interfering with cannabinoid CB1 receptor transmission do not closely resemble the effects of dopamine antagonism.
- Drugs such as rimonabant, which act as CB1 inverse agonists at the cellular level, produce undesirable side effects such as food aversion, nausea, and psychiatric problems.
- It is possible that neutral or "silent" antagonists such as AM4113 can suppress food intake at doses that are lower than those that induce nausea or psychiatric symptoms such as anxiety.
- Although much emphasis has been placed upon the central actions of drugs that act on CB1 receptors, it also is possible that peripheral mechanisms contribute to this effect. Thus, it is possible that a CB1 receptor neutral antagonist that does not penetrate well into the central nervous system could be useful as an appetite suppressant.

Definitions and Explanations of Key Terms

Agonist: A drug that binds to the receptor and stimulates the same intrinsic activity (i.e., signal transduction effect) as the endogenous neurotransmitter.

Full agonist: A drug that stimulates maximal levels of intrinsic activity (i.e., near the level stimulated by the transmitter itself).

Partial agonist: A drug that produces only low-to-moderate levels of stimulation of the signal transduction mechanisms.

Neutral antagonist: A competitive antagonist (i.e., neutral or "silent" antagonist) is a drug that binds to the receptor but does not instigate signal transduction effects on its own. This occupation of the receptor blocks the effect of an agonist or the neurotransmitter.

Inverse agonist: A drug that stimulates intrinsic activity (i.e., signal transduction effects) that is in the opposite direction to that stimulated by the agonist and the transmitter.

References

Addy C, Rothenberg P, Li S, Majumdar A, Agrawal N, Li H, et al. J Clin Pharmacol. 2008;48:734–44.

Arnone M, Maruani J, Chaperon F, Thiebot MH, Poncelet M, Soubrie P, et al. Psychopharmacology (Berl). 1997;132:104–6.

Baldo BA, Sadeghian K, Basso AM, Kelley AE. Behav Brain Res. 2002;137:165–77.

Carriero D, Aberman J, Lin SY, Hill A, Makriyannis A, Salamone JD. Psychopharmacology. 1998;137:147–56.

Chambers AP, Vemuri VK, Peng Y, Wood JT, Olzewska T, Pittman QJ, et al. Am J Physiol Regul Integr Comp Physiol. 2007;293:R2185–93.

Chen RZ, Huang RR, Shen CP, MacNeil DJ, Fong TM. Brain Res. 2004;999:227–30.

Chen RZ, Frassetto A, Lao JZ, Huang RR, Xiao JC, Clements MJ, et al. Eur J Pharmacol. 2008a;584:338–42.

Cohen C, Perrault G, Voltz C, Steinberg R, Soubrie P. Behav Pharmacol. 2002;13:451–63.

Colombo G, Agabio R, Diaz G, Lobina C, Reali R, Gessa GL. Life Sci. 1998;63:PL113–7.

Correa M, Carlson BB, Wisniecki A, Salamone JD. Behav Brain Res. 2002;137:179–87.

Cousins MS, Salamone JD. Pharmacol Biochem Behav. 1994;49:85–91.

Cousins MS, Sokolowski JD, Salamone JD. Pharmacol Biochem Behav. 1993;46:943–51.

Cousins MS, Wei W, Salamone JD. Psychopharmacology. 1994;116:529–37.

Curioni C, Andre C. Cochrane Database Syst Rev. 2006;4:CD006162.

Darley CF, Tinklenberg JR, Hollister TE, Atkinson RC. Psychopharmacologia. 1973;29:231–8.

Darmani NA. Neuropsychopharmacology. 2001;24:198–203.

Darmani NA, Johnson JC. Eur J Pharmacol. 2004;488:201–12.

Darmani NA, Pandya DK. J Neural Transm. 2000;107:931–45.

De Vry J, Schreiber R, Eckel G, Jentzsch KR. Eur J Pharmacol. 2004;483:55–63.

Despres JP, Golay A, Sjostrom L, Rimonabant in Obesity-Lipids Study Group. N Engl J Med. 2005;353:2121–34.

Drewnowski A, Grinker JA. Pharmacol Biochem Behav. 1978;9:619–30.

Egertova M, Elphick MR. J Comp Neurol. 2000;422:159–71.

Farrar AM, Pereira M, Velasco F, Hockemeyer J, Muller CE, Salamone JD. Psychopharmacology. 2007;191:579–86.

Fattore L, Fadda P, Fratta W. Pharmacol Res. 2007;56:418–27.

Foltin RW, Brady JV, Fischman MF. Pharmacol Biochem Behav. 1986;25:577–82.

Foltin RW, Fischman MW, Byrne MF. Appetite. 1988;11:1–14.

Freedland CS, Poston JS, Porrino LJ. Pharmacol Biochem Behav. 2000;67:265–70.

Gardner EL. Pharmacol Biochem Behav. 2005;81:263–84.

Gardner EL, Lowinson JH. Pharmacol Biochem Behav. 1991;40:571–80.

Gardner A, Mallet PE. Eur J Pharmacol. 2006;530:103–6.

Giuliani D, Ottani A, Ferrari F. Eur J Pharmacol. 2000;391:275–9.

Gomez R, Navarro M, Ferrer B, Trigo JM, Bilbao A, Del Arco I, et al. J Neurosci. 2002;22:9612–7.

Gonzalez-Rosales F, Walsh D. J Pain Symptom Manage. 1997;14:311–4.

Greenberg I, Kuehnle J, Mendelson JH, Bernstein JG. Psychopharmacology. 1976;49:79–84.

Halikas JA, Weller RA, Morse CL, Hoffmann RG. Int J Addiction. 1985;20:701–11.

Hao S, Avraham Y, Mechoulam R, Berry EM. Eur J Pharmacol. 2000;392:147–56.

Heishman SJ, Huestis MA, Henningfield JE, Cone EJ. Pharmacol Biochem Behav. 1990;37:561–5.

Herkenham M. Ann NY Acad Sci. 1992;654:19–32.

Hildebrandt AL, Kelly-Sullivan DM, Black SC. Eur J Pharmacol. 2003;462:125–32.

Hodge J, Bow JP, Plyler KS, Vemuri VK, Wisniecki A, Salamone JD, et al. Behav Brain Res. 2008;193:298–305.

Ilan AB, Smith ME, Gevins A. Psychopharmacology (Berl). 2004;176:214–22.

Ishiwari K, Weber SM, Mingote S, Correa M, Salamone JD. Behav Brain Res. 2004;151:83–91.

Jamshidi N, Taylor DA. Br J Pharmacol. 2001;134:1151–4.

Järbe TUC, Andrzejewski ME, DiPatrizio NV. Pharmacol Biochem Behav. 2002;73:911–9.

Jicha GA, Salamone JD. J Neurosci. 1991;11:3822–9.

Johansson JO, Jarbe TU, Henriksson BG. TIT J Life Sci. 1975;5:17–27.

Kelley AE, Baldo BA, Pratt WE, Will MJ. Physiol Behav. 2005;86:773–95.

Koch JE. Pharmacol Biochem Behav. 2001;68:539–43.

Koch M, Schmid A, Scnhnitzler HU. Psychopharmacology. 2000;152:67–73.

Koob GF, Riley SJ, Smith SC, Robbins TW. J Comp Physiol Psychol. 1978;92:917–27.

Landsman RS, Burkey TH, Consroe P, Roeske WR, Yamamura HI. Eur J Pharmacol. 1997;334:R1–2.

Le Foll B, Gorelick DA, Goldberg SR. Psychopharmacology. 2009;205:171–4.

Limebeer CL, Parker LA. J Exp Psychol Anim Behav Process. 2000;26:371–84.

Limebeer CL, Parker LA, Fletcher PJ. Behav Neurosci. 2004;118:1391–9.

Martin BR, Compton DR, Thomas BF, Prescott WR, Little PJ, Razdan RK, et al. Pharmacol Biochem Behav. 1991;40:471–8.

Mato S, Pazos A, Valdizan EM. Eur J Pharmacol. 2002;443:43–6.

McLaughlin PJ, Winston K, Swezey L, Wisniecki A, Aberman J, Tardif DJ, et al. Behav Pharmacol. 2003;14:583–8.

McLaughlin PJ, Lu D, Winston KM, Thakur G, Swezey LA, Makriyannis A, et al. Pharmacol Biochem Behav. 2005a;81:78–88.

McLaughlin PJ, Brown CM, Winston KM, Thakur G, Lu D, Makriyannis A, et al. Behav Pharmacol. 2005b;16:477–86.

McLaughlin PJ, Winston KM, Limebeer CL, Parker LA, Makriyannis A, Salamone JD. Psychopharmacology (Berl). 2005c;180:286–93.

McLaughlin PJ, Qian L, Wood JT, Wisniecki A, Winston KM, Swezey LA, et al. Pharmacol Biochem Behav. 2006;83:396–402.

Melis T, Succu S, Sanna F, Boi A, Argiolas A, Melis MR. Neurosci Lett. 2007;419:231–5.

Nowend KL, Arizzi M, Carlson BB, Salamone JD. Pharmacol Biochem Behav. 2001;69:373–82.

Parker LA, Limebeer CL. Auton Neurosci. 2006;129:36–41.

Parker LA, Limebeer CL, Simpson GR. Pharmacol Biochem Behav. 1998;59:33–7.

Parker LA, Mechoulam R, Schlievert C, Abbott L, Fudge ML, Burton P. Psychopharmacology (Berl). 2003;166:156–62.

Pavón FJ, Bilbao A, Hernandez-Folgado L, Cippitelli A, Jagerovic N, Abellan G, et al. Neuropharmacology. 2006;51:358–66.

Pavón FJ, Serrano A, Pérez-Valero V, Jagerovic N, Hernández-Folgado L, Bermúdez-Silva FJ, et al. J Neuroendocrinol. 2008;20 suppl 1:116–23.

Pi-Sunyer FX, Aronne LJ, Heshmati HM, Devin J, Rosenstock J, RIO-North America Study Group. JAMA. 2006;295:761–75.

Randall PA, Vemuri VK, Segovia KN, Torres EF, Hosmer S, Nunes EJ, Santerre JL, Makriyannis A, Salamone JD. Pharmacol Biochem Behav. 2010;97:179–184.

Rigotti NA, Gonzales D, Dale LC, Lawrence D, Chang Y. Addiction. 2009;104:266–76.

Rinaldi-Carmona M, Barth F, Héaulme M, Shire D, Calandra B, Congy C, et al. FEBS Lett. 1994;350:240–4.

Rowland NE, Mukherjee M, Robertson K. Psychopharmacology. 2001;159:111–6.

Salamone JD, Correa M. Behav Brain Res. 2002;137:3–25.

Salamone JD, Zigmond MJ, Stricker EM. Neuroscience. 1990;39:17–24.

Salamone JD, Steinpreis RE, McCullough LD, Smith P, Grebel D, Mahan K. Psychopharmacology. 1991;104:515–21.

Salamone JD, Mahan K, Rogers S. Pharmacol Biochem Behav. 1993;44:605–10.

Salamone JD, Cousins MS, Bucher S. Behav Brain Res. 1994;65:221–9.

Salamone JD, Cousins MS, Maio C, Champion M, Turski T, Kovach J. Psychopharmacology. 1996;125:105–12.

Salamone JD, Cousins MS, Snyder BJ. Neurosci Biobehav Rev. 1997;21:341–59.

Salamone JD, Aberman JE, Sokolowski JD, Cousins MS. Psychobiology. 1999;27:236–47.

Salamone JD, Wisniecki A, Carlson BB, Correa M. Neuroscience. 2001;105:863–70.

Salamone JD, Arizzi M, Sandoval MD, Cervone KM, Aberman JE. Psychopharmacology. 2002;160:371–80.

Salamone JD, Correa M, Mingote S, Weber SM. J Pharmacol Exp Ther. 2003;305:1–8.

Salamone JD, Correa M, Mingote SM, Weber SM. Curr Opin Pharmacol. 2005;5:34–41.

Salamone JD, Correa M, Mingote SM, Weber SM, Farrar AM. Curr Psychiatry Rev. 2006;2:267–80.

Salamone JD, McLaughlin PJ, Sink K, Makriyannis A, Parker LA. Physiol Behav. 2007a;91:383–8.

Salamone JD, Correa M, Farrar A, Mingote SM. Psychopharmacology. 2007b;191:461–82.

Salamone JD, Randall P, Hosmer S, Sink KS, Segovia KN, Stopper CM, et al. Abstract viewer/itinerary planner. Washington, DC: Society for Neuroscience, 2009; 2009. Online.

Shearman LP, Rosko KM, Fleischer R, Wang J, Xu S, Tong XS, et al. Behav Pharmacol. 2003;14:573–82.

Simiand J, Keane M, Keane PE, Soubrie P. Behav Pharmacol. 1998;9:179–81.

Simoneau II, Hamza MS, Mata HP, Siegel EM, Vanderah TW, Porreca F, et al. Anesthesiology. 2001;94:882–7.

Sink KS, McLaughlin PJ, Wood JA, Brown C, Fan P, Vemuri VK, et al. Neuropsychopharmacology. 2008a;33:946–66.

Sink KS, Segovia KN, Sink J, Randall PA, Collins LE, Correa M, Markus EJ, Vemuri VK, Makriyannis A, Salamone JD. Eur Neuropsychopharmacol. 2010;20:112–122.

Sink KS, Vemuri VK, Olszewska T, Makriyannis A, Salamone JD. Psychopharmacology. 2008b;196:565–74.

Sink KS, Vemuri VK, Wood J, Makriyannis A, Salamone JD. Pharmacol Biochem Behav. 2009;91:303–6.

Sink KS, Segovia KN, Nunes EJ, Collins LE, Vemuri VK, Thakur G, Makriyannis A, Salamone JD. Psychopharmacology. in press.

Sokolowski JD, Salamone JD. Pharmacol Biochem Behav. 1998;59:557–566.

Solinas M, Panlilio LV, Antoniou K, Pappas LA, Goldberg SR. J Pharmacol Exp Ther. 2003;306:93–102.

Soria-Gomez E, Matias I, Rueda-Orozco PE, Cisneros M, Petrosino S, Navarro L, et al. Br J Pharmacol. 2007;151:1109–16.

Stapleton JA. Addiction. 2009;104:277–8.

Tallett AJ, Blundell JE, Rodgers RJ. Psychopharmacology. 2007;195:27–39.

Tallett AJ, Blundell JE, Rodgers RJ. Pharmacol Biochem Behav. 2009;91:358–66.

Tanda G, Pontieri FE, Di Chiara G. Science. 1997;276:2048–50.

Ungerstedt U. Acta Physiol Scand Suppl. 1971;367:95–122.

US Food and Drug Administration Advisory Committee. FDA briefing document: zimulti (rimonabant) Tablets, 20 mg, FDA, Rockville. 2007. [WWW document]. URL (http://www.fda.gov/OHRMS/DOCKETS/AC/07/briefing/2007-4306b1-00-index.htm). Accessed September 2008.

Van Gaal LF, Rissanen AM, Scheen AJ, Ziegler O, Rossner S, RIO-Europe Study Group. Lancet. 2005;365:1389–97.

Van Sickle MD, Oland LD, Mackie K, Davison JS, Sharkey KA. Am J Physiol Gastrointest Liver Physiol. 2003;285:G566–76.

Verty AN, Mallet PE. Neuropharmacology. 2005;49:1101–9.

Verty AN, McGregor IS, Mallet PE. Neurosci Lett. 2004a;354:217–20.

Verty AN, McFarlane JR, McGregor IS, Mallet PE. Neuropharmacology. 2004b;47:593–603.

Verty AN, McFarlane JR, McGregor IS, Mallet PE. Endocrinology. 2004c;145:3224–31.

Ward SJ, Dykstra LA. Behav Pharmacol. 2005;16:381–8.

Wenger T, Moldrich G, Furst S. Brain Res Bull. 2003;61:125–8.

Werner NA, Koch JE. Brain Res. 2003;967:290–2.

Wiley JL, Burston JJ, Leggett DC, Alekseeva OO, Razdan RK, Mahadevan A, et al. Br J Pharmacol. 2005;145:293–300.

Williams CM, Kirkham TC. Psychopharmacology. 1999;143:315–7.

Williams CM, Kirkham TC. Physiol Behav. 2002;76:241–50.

Williams CM, Rogers PJ, Kirkham TC. Physiol Behav. 1998;65:343–6.

Chapter 30
The Nutritional Neurotrophic Neoteny Theory: Evolutionary Interactions Among Diet, Brain, and Behavior

Nūn Sava-Siva Amen-Ra

Abbreviations

AOHP	Amen optimal health protocol
ATP	Adenosine triphosphate
BDNF	Brain-derived neurotrophic factor
CREB	Cyclic adenosine monophosphate (cAMP) response element-binding protein
ETH	Expensive tissue hypothesis
H[3]	Homo hypothalamic hypometabolic
N[3]	Nutritional neurotrophic neoteny

30.1 Introduction

Several prominent phenotypic features distinguish humans from other apes. Humans live longer, develop more slowly, have a temporally reduced reproductive range and exhibit exceptional encephalization – that is, a high brain to body weight ratio. This collection of biological traits I have denominated the *Quadripartite Complex*. Certainly there are other important elements of the human bio-behavioral repertoire, not the least of which include bipedal locomotion and language. What makes the Quadripartite Complex particularly important and interesting is the apparent interrelationship among its components. In a theoretical paper published in the journal *Medical Hypotheses*, it was argued that the Quadripartite Complex arose as a unified response to a single selective force – environmentally imposed dietary restriction (Amen-Ra 2006). Quite tellingly, each of the aforementioned attributes – lengthened lifespan, delayed development, reduced reproductive range, and increased encephalization – are effectuated in animals that are experimentally subjected to chronic caloric restriction. Added to this is compelling evidence indicating that human evolution was heavily influenced by climatic changes – changes that likely reduced the availability of food to our hominin forbears. Furthermore, the phylogenetic generality of the caloric restriction response – the fact that organisms respond physiologically in strikingly similar ways to protracted dietary deficits – makes this experimental protocol a particularly valuable model for evolutionary theorization. To elaborate, because caloric restriction induces almost identical alterations in numerous animal models via similar

Nūn S. Amen-Ra (✉)
Amenta Academy of Theoretical Sciences (AATS),
25101 Chimney-House Court, Damascus, MD, USA
e-mail: AmentaPr@AmentaPress.com

Fig. 30.1 The quadripartite
complex. This figure lists
the components of the
quadripartite complex, the
four phenotypic features that
most markedly distinguish
humans from their hominin
predecessors and other apes
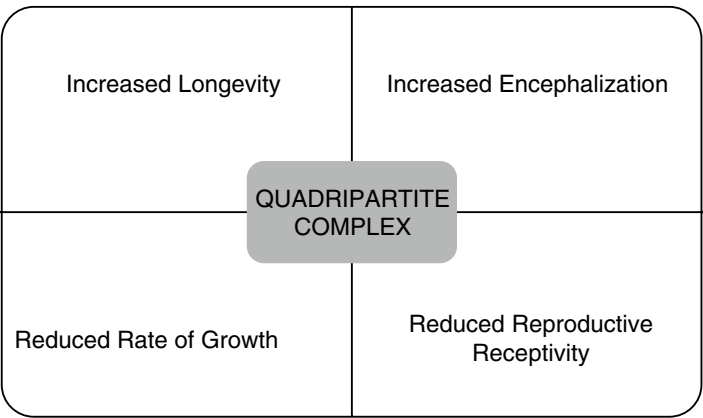
Fig. 30.2 Neuro-endocrine
underpinnings of human
longevity. This figure
illustrates how the
hypothalamic/neuro-endocrine
complex may have responded
to the selective pressure of
environmentally-imposed
dietary restriction by
reducing the rapidity with
which scarce metabolic
resources were used. Given
the established inverse
relationship between
metabolic rate and maximum
species lifespan, increased
human longevity could
plausibly have resulted from
such metabolic suppression
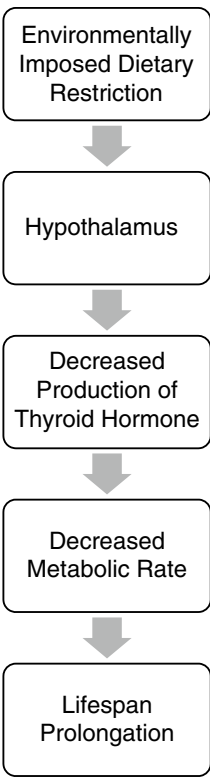
molecular mechanisms, the stereotypic response thereto is suggestive of substantial evolutionary conservation. It is plausible that climatic conditions which curtail dietary resources for prolonged periods can select adaptive traits identical to those influenced by ontogenetic caloric restriction. Thus, we may surmise that the Quadripartite Complex emerged as a consequence of environmentally imposed caloric restriction incurred during a critical stage of human evolution (Figs. 30.1 and 30.2). This theory is developed in greater detail in a book entitled *Evolutionary Nutrition* (Amen-Ra 2003). The purpose of the present exposition is to expatiate upon the evolution of encephalization, undoubtedly the most momentous element of the Quadripartite Complex (Table 30.1).

Table 30.1 Comparative similitude of QC and DR

The Quadripartite Complex	Effects of dietary restriction
1. Encephalization – high brain weight/body weight ratio	1. Encephalization – high brain weight/bodyweight ratio
2. Neoteny – depressed rate of physical development and sexual maturation	2. Neoteny – depressed rate of physical development and sexual maturation
3. Reduced reproductive receptivity	3. Reduced reproductive receptivity during dietary deprivation
4. Enhanced longevity	4. Enhanced longevity

This table lists the hominin evolutionary attributes known as the Quadripartite Complex (QC) in apposition to the effects of ontogenetic dietary restriction (DR) so as to illustrate their similarity

30.2 Discussion

In metabolic terms, the brain is extraordinarily expensive. In view of the fact that hominins evolved under ecological conditions that likely limited their metabolic resources, the excrescence of the encephalon seems paradoxical. The paucity of theories purporting to explain human encephalization may be partly attributable to this seeming paradox. Indeed, one of the few such theories sufficiently coherent to warrant the designation is the Aiello–Wheeler Expensive Tissue Hypothesis (ETH). Advanced by anthropologist Leslie Aiello and biologist Peter Wheeler, this theory posits metabolic compensation as the key to human encephalization. They identify the brain as one of several of the body's "expensive tissues" and opine that evolutionary accretion of brain tissue was offset by evolutionary extirpation of another expensive tissue – namely, the gastrointestinal tract. As to how a reduced alimentary apparatus could extract the requisite resources to support a burgeoning brain, the theorists invoke an inveterate explanation in the anthropological arena – meat. It is their contention that meat is of a "higher" nutritional quality, being more easily digestible than vegetal fare. Subsistence upon meat would, *ex hypothesi*, permit pronounced reduction of gastrointestinal mass and/or volume. Hence, consistent consumption of meat would have facilitated alimentary attenuation and this, in consequence, would have conduced to neural augmentation. The interested reader is referred to their erudite manuscript published in *Current Anthropology* for details and poignant critiques from contributors to the article (Aiello and Wheeler 1995).

Before presenting an alternative theory of human encephalization, let us briefly consider several logical lapses in the ETH. The first flaw is the theory's lack of conservatism. Human encephalization can be conceived as an evolutionary extremum of a continuum. That is, humans are relatively more encephalized than extinct hominins (i.e., bipedal apes such as those of the genus *Australopithecus*); hominins are relatively more encephalized than other hominids (i.e., "great apes" such as gorillas and orangutans); hominids are relatively more encephalized than other hominoids (i.e., "lesser apes" such as gibbons); hominoids are relatively more encephalized than other anthropoids (i.e., monkeys); anthropoids are relatively more encephalized than prosimian primates (i.e., lemurs and lorises); and primates are relatively more encephalized than other mammals. Clearly, members of the Primate Order cannot be collectively characterized as carnivorous inasmuch as most subsist preponderantly on vegetation. If encephalization is an entrenched attribute of the Order and if carnivory cannot be correctly conceived as a contributor to the general trend of increased encephalization among the primates, then something other than meat must be offered as an explanation for the accentuated encephalization of humans. Ostensibly, this something must amount to a dietetic difference of degree and not of kind.

In keeping with the concept of conservatism, there are substantive reasons for doubting the obstinately held notion that meat consumption catalyzed human evolution. As argued in *Evolutionary*

Nutrition, it strains the intellect to assume that humans could have consistently consumed meat before the advent of sophisticated lithic projectile weapons of the sort that appeared in Europe only ~10,000–20,000 years ago. Presumably, humans had been fully modern (anatomically) for over one hundred thousand years before hunting could have been a habitual practice. The period commencing ~20,000 years ago is evidently the surest juncture at which humans began to consume considerable quantities of meat for it coincides with the paleontological record of mass extinctions of mammalian fauna – extinctions that are reasonably interpreted to have been caused by humans (Stanley 1987).

Added to the non-conservative character of the ETH is its logical circuitousness. In terms of strength, speed, and agility, humans are decidedly disadvantaged compared to other apes and especially compared to felid and canid carnivores and scavengers. Human hunting undoubtedly required technical innovations enabled by evolutionarily augmented intelligence. Thus, increased encephalization likely facilitated human hunting and other technology-assisted activities. The theory espoused by Aiello and Wheeler contends the converse – that reliable access to copious quantities of meat enabled encephalization. The ETH affirms that voluminous viscera constrain the evolutionary expansion of the encephalon and that meat – in virtue of its alleged ease of assimilation – enabled alimentary reduction. Meat purportedly permitted the relaxation of a metabolically mediated constraint against encephalization. This asynchronous scenario is untenable – it inverts cause and effect.

It would seem that the designation of meat as a "high-quality" food warrants qualification or indeed castigation. A high-quality food in the context of the ETH, we may surmise, is one that can be digested efficiently enough to enable eventual alimentary reduction. This cannot be the only criterion, however, for a diet that ensures encephalization must support the physiological functioning of the brain. While meat is replete with protein, the major nutrient upon which the brain is dependent is glucose – a nutrient for which meat is a poor precursor. Moreover, when protein intake exceeds nutritional requirements, the excess is metabolized in such a way that removes the constituent nitrogenous moieties from amino acids. A product of this process is ammonia – an agent that is particularly toxic to the brain (Guyton and Hall 2006). Notably, human breast milk – the sole source of sustenance for the developing neonate – reportedly has the lowest protein concentration of any primate, with primates exhibiting lower levels than most mammals (Oftedal 1991). This may reflect the fact that slowly growing infants necessitate less protein provisioning during their protracted developmental period. As with encephalization, humans seem to exhibit an accentuation of this primate attribute.

Finally, Aiello and Wheeler neglect to identify an ontogenetic example of the phylogenetic phenomenon upon which they focus. For example, the theorists in question convincingly catalog correlations between gut size and brain size. They unconvincingly conclude that improved diet quality (i.e., meat) caused visceral contraction which, perforce, facilitated encephalization. They fail to substantiate this claim with corroborative ontogenetic evidence. This deficit in inductive reasoning could be rectified by determining whether in fact liquefied nutrients (an idealized proxy for "high-quality" food), administered enterally or parenterally, effectuate alimentary atrophy. As it were, a sound study published in the *Journal of Parenteral and Enteral Nutrition* found no such causative relationship (Zaloga et al. 1991). Using murine subjects, the authors of the aforesaid study observed the effects of four different isocaloric, isonitrogenous dietary regimens – a standard rodent diet and three liquid diets (enterally administered), the nitrogen sources of which were comprised of whole proteins, peptides, or amino acids, respectively. They assessed proximal, mid, and distal gut dimensions and found no reduction in proximal or mid gut size secondary to any of the liquid nutrients. This study would seem to suggest that improved diet quality does not appreciably alter alimentary magnitude. Such experimental investigations as this can be instructively extrapolated to phylogenetic phenomena. In the case of Aiello and Wheeler's gut/brain correlation, extrapolation indicates that meat (far more crude than the nutrients utilized in the aforementioned study) could not likely have catalyzed visceral contraction. Conversely, dietary deprivation and dietary diminution routinely result in

reduced gut size (Wang et al. 2006; Chappell et al. 2003). What is more, several studies suggest that dietary restriction induces adaptations in intestinal cells, augmenting their ability to absorb nutrients (Casirola et al. 1996, 1997). Increased enteric absorptive ability apparently offsets the effects of alimentary reduction. If this adaptive ontogenetic effect were mirrored evolutionarily, it would have been beneficial to dietetically restricted hominins. Therefore, it is dietary diminution, not dietary enrichment, which plausibly promotes the kind of gut size reduction that the ETH invokes as a critical catalyst of encephalization. While the theory to be presented forthwith does not consider visceral contraction as a key to human encephalization, it can explain this effect as an epiphenomenon of environmentally imposed dietary restriction.

30.3 The Homo Hypothalamic Hypometabolic Theory

The Homo Hypothalamic Hypometabolism (H³) theory posits that the climatic changes that ensued ~4 million years ago were sufficient to alter the ecological environment in which the hominin lineage evolved. Cooler temperatures, increased aridity, and marked oscillations of climatic conditions characterized these changes, which would have reduced the availability of vegetal resources upon which hominins depended for food. Hominins, I hypothesize, responded to this reduction in resources in a manner commensurate with ontogenetic dietary restriction. That is, they experienced a reduction in the rapidity of physical and sexual maturation, a lengthening of lifespan, and – as a concomitant consequence of the aforementioned alterations – an increase in the relative proportions of their brains. The concomitancy of the Quadripartite Complex is an important explanatory element of encephalization inasmuch as the economizing effects of reduced growth and temporally truncated sexual receptivity enable appreciable metabolic resources to be diverted to the brain (and also allocated to preservative processes that maintain the physiologic integrity of the body such that lifespan is lengthened). Interestingly, a single structure in mammals mediates most of the effects of ontogenetic dietary restriction – the hypothalamus and its associated endocrine effectors. Notably, the hypothalamus controls somatic growth by modulating levels of somatotrophic hormones (e.g., growth hormone); it controls sexual receptivity by modulating levels of gonadotrophic hormones such as luteinizing hormone and follicle-stimulating hormone; it likely influences lifespan by modulating metabolic rate (via thyroid hormone) which may determine, in part, the rapidity of aging; and it indirectly influences encephalization by ensuring virtually invariant nutrient allocation to the brain (via corticotrophic control) during bouts of dietary deprivation or diminution.

The centrality of the hypothalamic/neuro-endocrine complex in the mediation of ontogenetic dietary restriction makes it an ideal focus for selective pressure under evolutionary conditions of environmentally imposed dietary restriction. This may explain the uniformity of the metabolic response to caloric restriction exhibited by diverse organisms. Over evolutionary time, animals inevitably experience food shortages and have evolved mechanisms by which to mitigate dietary deficits. These evolutionarily conserved, compensatory mechanisms are activated under conditions of ontogenetic dietary restriction. Having abandoned arboreality for a terrestrial niche, hominin bipeds may have been especially sensitive to ecologically imposed food shortages. Thus, they may have been under increased pressure to adopt accentuated attributes enabling subsistence on marginal dietary resources. Concomitantly, there would have been increased selective pressure for augmented intelligence. Augmented intelligence undoubtedly ensures more successful foraging and recourse to novel methods of food acquisition. Note that, in contradistinction with the Expensive Tissue Hypothesis, the model delineated herein posits dietary diminution, not dietary enrichment, as the critical catalyst for encephalization. Moreover, N³ identifies specific molecular mechanisms that likely mediated neural expansion.

30.4 Molecular Mediators of Encephalization

One of the most striking effects of chronic caloric restriction is body weight reduction (Mattison et al. 2007). Less commonly considered, however, is the simultaneous salvaging of brain mass (Greenberg and Boozer 2000). This ontogenetic encephalization is effectuated by molecular mechanisms which ensure that the brain is provisioned with an adequate amount of energy at the expense of other organs amidst dietary depreciation. Insight into one such mechanism was provided by Gyorgy Bodoky and colleagues in an intriguing study published in the journal *Physiology & Behavior*. The investigators subjected groups of rats to three different dietary dispensations: ad libitum access to food; continuous parenteral infusion of nutrients equivalent to 100% of the daily caloric intake of the freely fed subjects; and complete food deprivation (4 days in duration). They sought to determine the effects of continuous feeding, intermittent feeding, and prolonged fasting on levels of energy (specifically ATP concentration) in the brain relative to the liver. In accordance with their hypothesis of preferential provisionment of nutrients to the brain, they found that while ATP levels in the livers of fasted animals were substantially reduced, levels of ATP in the *brains* of the deprived subjects were comparable to the nutrient-replete groups (Bodoky et al. 1995). Clearly, the energy deficits induced in these experimental subjects were borne by the body to the exclusion of the brain.

Glucose plays a central role in animal metabolism. Moreover, as mentioned previously, glucose is the chief fuel currency of the brain. However, food deprivation induces substantial suppression of circulating glucose concentration. Considering the centrality of glucose in brain metabolism, it is interesting to note that neurotrophins facilitate influx of glucose into neurons (Burkhalter et al. 2003). Thus, neurotrophins ostensibly ensure adequate allocation of glucose to the brain, a function of vital import under conditions of dietary diminution. Of greater interest is the body of research (upon which much of my theorization rests) that caloric restriction increases expression of neurotrophic factors (Mattson et al. 2004; Duan et al. 2001; Lee et al. 2000). Neurotrophins are known to promote proliferation and differentiation of neural precursor cells (Kandel et al. 2000). As to why dietary deprivation should eventuate in accretion or preservation of precursor cells we shall consider shortly. For now, we note with interest that caloric restriction reportedly improves indices of mental acuity by augmenting neurotrophin production and, consequently, promotes the preservation of progenitor neurons in regions of the cerebral cortex that are instrumental in learning and memory (Lee et al. 2000, 2002a, b; Kandel et al. 2000). Teleologically, this makes sense: enhanced memory and learning capacity likely enable more successful foraging. Hunger can be conceived as a psycho-physical stimulus intended to impel acquisitive action. Two momentous studies involving fasting corroborate this contention. The first study, published in the journal *Frontiers in Systems Neuroscience*, subjected rodents to a bout of fasting 18 hours in duration. They subsequently assessed the state of a particular family of transcription factors known to be operative in influencing brain development and various aspects of cognition. Called CREB (cyclic adenosine monophosphate (cAMP) response element-binding protein) they found this substance to be significantly elevated in animals subjected to fasting as compared to fed controls. More specifically, they found that fasting-induced CREB production was particularly prominent in regions of the brain crucial to cognition, such as the hippocampus, piriform cortex, and entorhinal cortex. Additionally, CREB was elevated in the hypothalamus, underscoring the importance of this structure in mediating neuro-behavioral responses to metabolic stressors. Importantly, CREB is known to play a regulatory role in *neurogenesis* – the origination of new neurons (Jagasia et al. 2009; Dworkin et al. 2009). It is interesting to note that cAMP indicates energy depletion – specifically ATP depletion. cAMP therefore abounds in the fasted/food deprived state. The interplay among fasting, cAMP, and CREB and the dependence of neurogenesis, learning, and memory upon the latter provide crucial clues to the relationship between nutrition and cognition.

The second study to which I would like to direct the reader's attention was published in the journal *Nature Neuroscience*. This study found that a peptide called *ghrelin* – released by the gastrointestinal organs in response to fasting – is translocated from the gastric mucosa to the brain (Diano et al. 2006). Ghrelin subsequently binds to receptors in the hippocampus and, by so doing, mediates *synaptogenesis* – the formation of synaptic connections between neurons. Synaptogenesis is known to modulate cognitive processes and the investigators in the said study found that the synapse formation secondary to the action of ghrelin was associated with improved functioning of mice on learning and memory tasks. Like the aforementioned fasting study, this finding offers an explanatory link between dietary deprivation and the augmentation of neurophysiological functioning. Intuitively, I reiterate, it makes sense that hunger should heighten cognition insofar as enhanced cognition conduces to successful food acquisition. More pointedly, increased expression of neurotrophic factors elicited by dietary restriction offers an intriguing explanatory framework for evolutionary encephalization. First, it should be noted that mammals are known to exhibit supernumerary neurons neonatally, such that nearly half those generated during development are eventually eliminated through programmed cell death or *apoptosis* (Kandel et al. 2000). The extent of apoptotic extirpation is determined largely by levels of neurotrophins. Presumably, profuse overproduction of neurons provides for plasticity. Such plasticity could conduce to increased encephalization under certain selective circumstances. Ecological dietary diminution placed a premium on intelligence (and its morphological corollary, encephalization). Selection for increased intelligence/encephalization elicited attenuation of neural apoptosis, a process promoted by enhanced expression of neurotrophins. This resulted in retention of neurons that would otherwise have been expunged. This model – herein termed Nutritional Neurotrophic Neoteny (N^3) – provides a mechanistic basis for the evolutionary induction of encephalization in humans. The term neoteny is intended to convey the notion that humans appear to retain robust expression of neurotrophins at a developmental stage at which they apparently diminish in other mammals. This results in protracted production of progenitor neurons and eventual differentiation of these into mature neurons. The selection of this adaptive trait was arguably effected by environmentally imposed nutritional deprivation (Fig. 30.3).
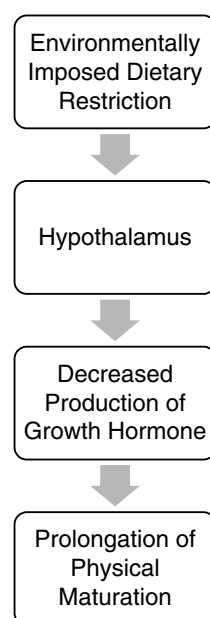
Fig. 30.3 Neuro-endocrine underpinnings of neoteny. This figure illustrates the conjecture that the relative developmental delay that distinguishes humans from other apes may have been mediated by a reduction in the output of growth hormone, control over which is exerted by the hypothalamus

Environmentally Imposed Dietary Restriction

Hypothalamus

Decreased Production of Growth Hormone

Prolongation of Physical Maturation

Fig. 30.4 Neuro-endocrine underpinnings of enceph-alization. This figure illustrates the manner in which encephalization may have been facilitated via preferential provisionment of metabolic resources (i.e. glucose) to the brain at the expense of peripheral tissues. This physiological effect may have been mediated primarily by cortisol, an endocrine hormone whose release is regulated by the hypothalamus
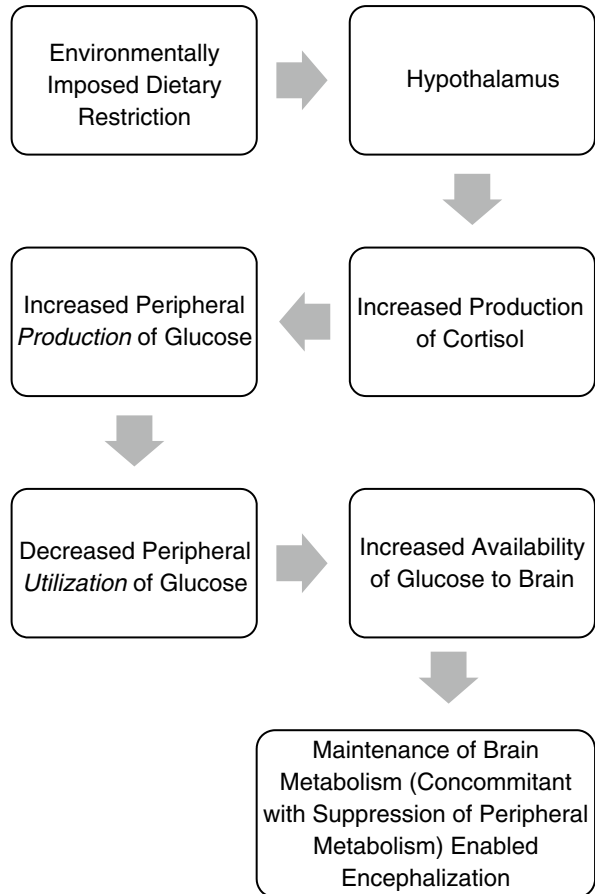
The N^3 theory is a subset of a metatheory of human evolution – H^3. The critical link between the two is that somatic hypometabolism (induced by dietary diminution and mediated by the hypothalamus) enabled energy to be preferentially provided to the brain (Fig. 30.4). The strength of these wedded theories derives, I aver, from their empirical underpinnings. That is, empirical investigations have established the ability of experimentally imposed energy restriction to augment energy efficiency and this improved energy efficiency arguably enables appreciable amounts of energy to be allocated, alternatively, to the brain (Lopez-Lluch et al. 2006; Sanz et al. 2005). Further, empirical evidence indicates that humans and other primates typically respond to chronic caloric restriction by reducing their metabolism (Blanc et al. 2003; Heilbronn et al. 2006). Suppression of somatic metabolic rate facilitates maintenance of brain metabolism which, as it were, is not amenable to much modulation. Somatic metabolic suppression, it would seem, correlates with developmental depression in the human lineage: Reduced rate of development reflects reduced energy expenditure which, in turn, reflects reduced energy availability and intake. Sexual maturation is mitigated by somatic metabolic suppression; developmental depression and the energy salvaged by reproductive repression can commensurately be allocated to neural metabolism; lifespan prolongation proceeded passively in accordance with reduced metabolism and depressed development. This reasoning reinforces the notion that the Quadripartite Complex – lengthened lifespan, depressed development, reduced reproductive range, and increased encephalization – evolved contemporaneously in response to a single selective stressor: Dietary restriction (Fig 30.5).

Fig. 30.5 Neuro-endocrine regulation of reproduction. This figure illustrates how the constricted reproductive range that characterizes humans could have been catalyzed by the neuro-endocrine system through reductions in the circulating concentration of gonadotro-phins (i.e. luteinizing hormone and follicle stimulating hormone)

Environmentally Imposed Dietary Restriction

Hypothalamus

Decreased Production of Gonadotrophins

Reduced Reproductive Receptivity
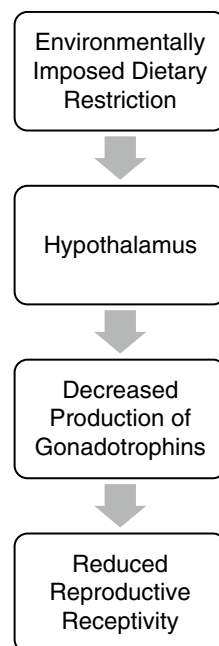
Scientists and scholars are often impelled to evaluate the merits of competing theories invoked to explain identical phenomena. One indication of a theory's explanatory superiority is its encompassment, incorporation, or obviation of competitors. The N^3/H^3 theoretical complex evidently does so. The model presented herein not only provides a plausible, empirically informed explanation of enhanced human encephalization, it explains the logical linchpin of the ETH (i.e., gut reduction) as a minor evolutionary epiphenomenon of environmentally imposed dietary diminution. Moreover, it supersedes the ETH by casting encephalization as a concomitant of a larger, interrelated complex – the Quadripartite Complex. The N^3/H^3 model also comports with the scientific aesthetic of conservatism in that it explains the cardinal phenotypic characteristics of the human lineage as elaborated, accentuated simian traits. Its conservative comportment is further exemplified by its identification of known molecular mechanisms to infer antecedent evolutionary conditions in an effort to explain consequent phenotypic features.

30.5 Applications to Other Areas of Health and Disease

It is evident from the foregoing exposition that humans exhibit adaptations to protracted, pronounced dietary deficits. What is more, it is clear that the human brain is exquisitely suited to self-sustainment under conditions of caloric curtailment. As such, it is of practical interest to consider whether this adaptability of the brain to nutritional deprivation can be advantageously exploited to enhance cognitive acuity or neurophysiological functioning ontogenetically – that is, in the context of a single human lifespan. The available evidence suggests that it can. Indeed, the optimization of cognitive capacity is among the aims I have sought to effectuate in formulating the lifestyle regimen known as the Amen Optimal Health Protocol (AOHP). Details of the AOHP have been delineated elsewhere (Amen-Ra 2007) so we shall concern ourselves with only the general elements thereof. Though the

primary purport of the AOHP is the maximization of human lifespan potential, it is interesting to note that those experimental interventions which have most consistently conduced to lifespan prolongation – caloric restriction and cyclic fasting – have evidenced the most impressive augmentation and preservation of neurocognitive functioning in animals (Fontán-Lozano et al. 2007; Halagappa et al. 2007). I hasten to add at this juncture that the AOHP incorporates both caloric restriction and cyclic fasting. Specifically, the caloric content of the diet (which is thoroughly vegetal, devoid of meat and animal by-products) ranges from 1,000 to 1,500 kcal. The single daily meal is consumed in the nocturnal period over a span of time not exceeding 1 hour. Throughout the 23-hour daily fast, certain non-caloric beverages are imbibed – namely, teas of various sorts. Practitioners of the Amen Protocol (myself included) engage in exercise twice daily, in the morning and evening. Morning exercise is aerobic in nature while evening exercise is resistive in nature.

Underlying the aforementioned elements of the AOHP is the ability of each measure – restrictive feeding, fasting, exercise, and selective supplementation – to influence cognition by modulating the expression of genes and promoting the production of peptides that are known to regulate neurogenesis, synaptogenesis, and other molecular mediators of complex behavior. One molecule in particular plays an important role in this regard: brain-derived neurotrophic factor (BDNF). BDNF is but one of a family of neurotrophic factors that profoundly influence the morphology and physiology of the brain. The formulation and consolidation of memories and the facilitation of learning is dependent upon such neural peptides as BDNF and a host of integral molecules that interact therewith. One such molecule is CREB, the protein mentioned previously in the context of fasting. The reader will recall that fasting (18 hours in the cited study) reportedly increased the concentration of CREB in specific regions of the brain that control complex cognition. The 23-hour fast prescribed by the Amen Protocol is ostensibly sufficient to elevate levels of CREB as well as ghrelin – the gastrointestinal peptide that reportedly strengthens synapses and is augmented under conditions of food deprivation. The tea that is customarily consumed during the fast has a specific effect conducive to cognitive enhancement. The catechins in green and black teas and the ginsenosides in ginseng tea have been found to elevate levels of CREB and BDNF in murine models of memory impairment (Li et al. 2009; Zhao et al. 2009).

The temporal organization of the AOHP is of some practical import. To formulate a protocol that is predicated upon magnifying mental acuity, measures must be taken to ensure that the functioning of the brain is not merely maximized but that it is maximized at precisely those junctures at which productive, purposive activity is most desired. It will be noted that the Amen Protocol prescribes aerobic exercise in the morning, after an overnight fast of approximately 8–10 hours. The effects of these measures should be to stimulate cognition and also to elevate mood by augmenting neurotrophin production (Deslandes et al. 2009; Duman et al. 2008). Fasting ensues for another 10–12 hours, an interval during which only tea is partaken. Both measures – fasting and tea consumption – augment production of peptides that promote cognition. This period – the diurnal phase – is the time at which individuals ideally engage in productive work. It is significant that during this most auspicious interval that several signals converge to heighten cognition – the stimulatory effects of exercise, fasting, and nutraceutical agents in tea. Next, an evening resistance exercise session ensues. Evening exercise is followed by the single daily feeding session. Feeding for an hour or less practically ensures caloric restriction. Sufficient restriction of caloric content is further ensured by the vegetal composition of the diet. Caloric restriction, I reiterate, independently increases expression of neurotrophic factors. Thus, each component of the Amen Protocol – fasting, feeding, exercise, and tea intake – facilitates augmentation of cognitive acuity by advantageously altering the molecular milieu of the brain. What is more, the prolongation of chronological life that is a common characteristic of caloric restriction and cyclic fasting is accompanied by improvements in cognitive function, effectively promoting the extension of healthful mental life in a complementary manner. Humans, we must acknowledge, are
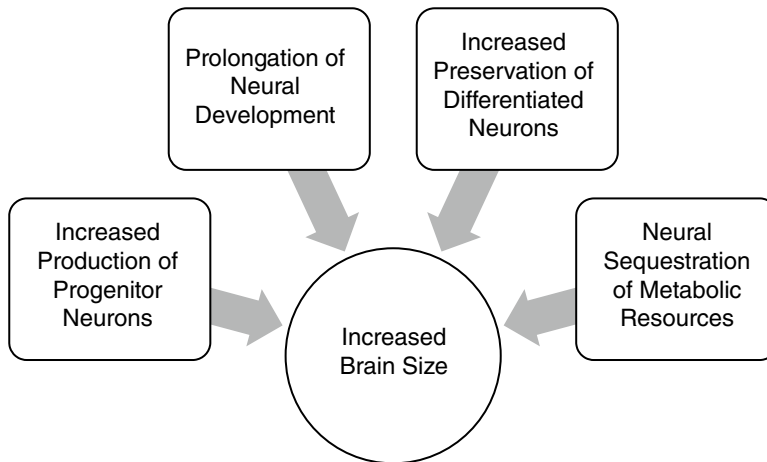
Fig. 30.6 Neuro-endocrine underpinnings of encephalization. This figure illustrates the physiological factors that likely contributed to the augmentation of human encephalization

quintessentially intellectual entities. To heighten intellectual acumen is to heighten the capacity for uniquely human gratification and this, in the vein of utilitarianism, is the *summum bonum* – the highest conceivable good. A protocol that could defensibly make this momentous claim would warrant attention. It is of course controversial whether appreciable numbers of people could consistently comply with such a restrictive regimen. However, having practiced the protocol for nearly a decade, my collaborators and I are confident that whoever deigns to adopt it will experience benefits that far exceed any inconveniences attendant to the daily exercise of dietary discipline. What is more, the mind is capable of such conditioning that the ascetic application of self-restraint can become a source of solace in and of itself. Such an ideal is well worth pursuing in the eyes of this theoretician (Fig. 30.6).

Summary Points

- Any theory of human evolution must explain encephalization—the dramatic increase in human brain size, specifically since the emergence of australopithicines.
- Evolutionary theorization about the underpinnings of encephalization must be reliant upon reasonable extrapolations from empirical data.
- Empirical data indicate that energy restriction induces increased expression of neurotrophic agents that promote the production and preservation of neurons.
- Empirical data indicate that hominins incurred environmental conditions that presumably constrained the availability of food (i.e. imposed energy restriction).
- Hominins faced selective pressure for increased intelligence/ingenuity amidst environmentally-imposed energy restriction.
- Selection for increased intelligence/ingenuity was mediated by increased expression of neurotrophic factors, particularly during neonatal development.
- Increased expression of neurotrophic factors during development eventuated in the expansion of the hominin brain.

Key Terms:

Encephalon [f. Greek (Gr.) *egkephalos* **brain]:** The brain.

Encephalization: Proportional increase in the size of the brain.

Lithic [f. Gr. *lithos* **stone]:** Pertaining to stone.

Murine [f. classical Latin *mūrīnus* **mouse]:** Relating to the Family Muridae, comprising rats and mice.

Neurotrophic [neuro- f. Gr. *neuron* **nerve, tendon +** *troph* **nourishment]:** Relating to neural control over the development, maintenance, or activity of cells, tissues, or organs.

Neoteny [f. Gr. *neos* **young +** *teinein* **to extend]:** The exhibition or retention of juvenescent characteristics suggestive of slow or protracted maturation.

Ontogenetic [f. Gr. *ont-,* **on being +** *genesis* **origin]:** Concerning or occurring within the lifespan of an individual organism.

Phylogenetic [f. Gr. *phylon* **race +** *genesis* **origin]:** Concerning attributes of organisms that develop over evolutionary time.

References

Aiello LC, Wheeler P. Curr Anthropol. 1995;36:199–221.

Amen-Ra N. Evolutionary nutrition. Damascus: Amenta Press; 2003.

Amen-Ra N. Med Hypotheses. 2006;66:978–84.

Amen-Ra N. The optimal human diet: theoretical foundations of the Amen Protocol. In: Willis AP, editor. Dietary therapy research trends. New York: Nova Science; 2007.

Blanc S, Schoeller D, Kemnitz J, Weindruch R, Colman R, Newton W, et al. J Clin Endocrinol Metab. 2003;88:16–23.

Bodoky G, Yang ZJ, Meguid MM, Laviano A, Szeverenyi N. Physiol Behav. 1995;58:521–7.

Burkhalter J, Fiumelli H, Allman I, Chatton JY, Martin JL. J Neurosci. 2003;23:8212–20.

Casirola DM, Rifkin B, Tsai W, Ferraris RP. Am J Physiol. 1996;271:G192–200.

Casirola DM, Lan Y, Ferraris RP. J Gerontol. 1997;A 52:B300–10.

Chappell VL, Thompson MD, Jeschke MG, Chung DH, Thompson JC, Wolf SE. Dig Dis Sci. 2003;48:765–9.

Deslandes A, Moraes H, Ferreira C, Veiga H, Silveira H, Mouta R, et al. Neuropsychobiology. 2009;59:191–8.

Diano S, Farr SA, Benoit SC, McNay EC, da Silva I, Horvath B, et al. Nat Neurosci. 2006;9:381–8.

Duan W, Guo Z, Mattson MP. J Neurochem. 2001;76:619–26.

Duman CH, Schlesinger L, Russell DS, Duman RS. Brain Res. 2008;1199:148–58.

Dworkin S, Malaterre J, Hollande F, Darcy PK, Ramsay RG, Mantamadiotis T. Stem Cells. 2009;27:1347–57.

Fontán-Lozano A, Sáez-Cassanelli Jl, Inda MC, de los Santos-Arteaga M, Sierra-Domínguez SA, López-Lluch G, et al. J Neurosci. 2007;27:10185–95.

Greenberg JA, Boozer CN. Mech Ageing Dev. 2000;113:37–48.

Guyton AC, Hall JE. Textbook of medical physiology. Philadelphia: Elsevier; 2006.

Halagappa VK, Guo Z, Pearson M, Matsuoka Y, Cutler RG, Laferla FM, et al. Neurobiol Dis. 2007;26:212–20.

Heilbronn LK, de Jonge L, Frisard MI, Delany JP, Larson-Meyer DE, Rood J, et al. JAMA. 2006;295:1539–48.

Jagasia R, Steib K, Englberger E, Herold S, Faus-Kessler T, Saxe M, et al. J Neurosci. 2009;29:7966–77.

Kandel ER, Schwartz JH, Jessell TM, editors. Principles of neural science. New York: McGraw-Hill; 2000.

Lee J, Duan W, Long JM, Ingram DK, Mattson MP. J Mol Neurosci. 2000;15:99–108.

Lee J, Duan W, Mattson MP. J Neurochem. 2002a;82:1367–75.

Lee J, Seroogy KB, Mattson MP. J Neurochem. 2002b;80:539–47.

Li Q, Zhao H, Zhang Z, Liu Z, Pei X, Wang J, Li Y. Neuroscience. 2009; Jul 10; 163(3):741–9.

Lopez-Lluch G, Hunt N, Jones B, Zhu M, Jamieson H, Hilmer S, et al. Proc Natl Acad Sci USA. 2006;103:1768–73.

Mattison JA, Roth GS, Lane MA, Ingram DK. Interdiscip Top Gerontol. 2007;35:137–58.

Mattson MP, Duan W, Wan R, Guo Z. NeuroRx. 2004;1:111–6.

Oftedal OT. Philos Trans R Soc Lond B. 1991;334:161–70.

Sanz A, Caro P, Ibanez J, Gomez J, Gredilla R, Barja G. J Bioenerg Biomembr. 2005;37:83–90.

Stanley M. Extinction. New York: Scientific American Books; 1987.

Wang T, Hung CC, Randall DJ. Annu Rev Physiol. 2006;68:223–51.

Zaloga GP, Ward KA, Prielipp RC. JPEN J Parenter Enteral Nutr. 1991;15:42–7.

Chapter 31
Forebrain Activation by Postoral Nutritive Substances

Takashi Kondoh and Kunio Torii

Abbreviations

CS+   Conditioned stimulus paired with test unconditioned stimulus
CS-   Conditioned stimulus paired with control (neutral) unconditioned stimulus
EAAC-1   Excitatory amino acid carrier-1
fMRI   Functional magnetic resonance imaging
GIP   Glucose-dependent insulinotropic polypeptide
GLP-1   Glucagon-like peptide-1
5-HT$_3$R   Serotonin receptor type 3
mGluR   Metabotropic glutamate receptor
MRI   Magnetic resonance imaging
MSG   Monosodium L-glutamate
NOS   Nitric oxide synthase
NST   Nucleus of the solitary tract
TRPM5   Transient receptor potential cation channel M5
TVX   Subdiaphragmatic total vagotomy

To survive and maintain normal physiological functions, all animals need to ingest nutrients. Digestion and nutrient absorption take place in the gut, whereas sensations of hunger and satiety originate in the neuronal circuits in the brain. Nutritional stimuli in the gut elicit hormonal release into the circulation as well as vagal activation, which are key components of the gut-brain crosstalk. Brain regions that regulate homeostasis, such as the brainstem and the hypothalamus, receive inputs from a variety of sources, including forebrain structures involved in reward processes (Chaudhri et al. 2008). Neuroendocrine signals arising from the gastrointestinal tract are also integrated in these brain regions, and contribute to homeostatic regulation. However, the precise mechanisms supporting gut-brain communication remain poorly understood.

L-Glutamate is a multifunctional amino acid involved in perception of umami taste, intermediary metabolism, and excitatory neurotransmission (Table 31.1). In addition, recent studies have uncovered new roles for glutamate in gut-brain axis activation and energy homeostasis. Glutamate receptors

K. Torii (✉)
Institute of Life Sciences, Ajinomoto Co., Inc., Suzuki-cho 1-1, Kawasaki-ku, Kawasaki 210-8681, Japan
e-mail: kunio_torii@ajinomoto.com

Table 31.1 Key features of L-glutamate

1. L-Glutamate is the anionic part of acidic amino acid, L-glutamic acid.
2. There are two distinct forms of glutamate, i.e., free and protein-bound forms. Specific actions of glutamate are mediated via free form.
3. Glutamate is a multifunctional amino acid involved in perception of umami taste, intermediary metabolism, and excitatory neurotransmission.
4. Although glutamate is typically classified as a nonessential amino acid in textbooks, it plays physiologically "essential (indispensable)" roles in our body, especially in the intermediary metabolism.
5. In addition, recent studies have uncovered new roles for dietary glutamate in gut-brain axis activation and energy homeostasis.
6. These glutamate effects are mediated via specific glutamate receptors (ionotropic and metabotropic receptors) located in the mouth, gastrointestinal tract, and central nervous system.
7. Glutamate in the mouth elicits umami taste (one of five basic tastes) via activation of taste nerves. Glutamate also enhances palatability of most foods and hence is used as a flavor enhancer in cuisines.
8. One of the most pronounced features is the synergism of umami taste observed between glutamate and 5′-ribonucleotides.
9. Glutamate in the gut is thought to convey food (protein)-related signals to the brain via activation of vagal afferent fibers.
10. As glutamate is the single largest contributor to energy production in the mucosal cells of the small intestine, most of the glutamate absorbed is metabolized in the gut and hence it does not reflect changes in blood glutamate levels.
11. Glutamate acts as the major excitatory neurotransmitter in the brain, and its activity regulates synaptic plasticity, learning, memory, motor activity, and neural development.
12. Glutamate in the brain is not derived from ingested glutamate but is synthesized within the brain from glucose.
13. Glutamate intake suppresses obesity without changing caloric intake.
14. Therefore, dietary glutamate influences numerous physiological functions, suggesting a broad, integrative role for dietary glutamate in body homeostasis.

This table lists the key facts of glutamate in our body

and their cellular transduction molecules have now been identified in gut epithelial cells (Bezençon et al. 2007; Mace et al. 2007; San Gabriel et al. 2007; Mace et al. 2009), and stimulation of these receptors by luminal monosodium L-glutamate (MSG) activates gut vagal afferent nerve fibers (Niijima 2000; Uneyama et al. 2006). In addition, such activation of gut glutamate receptors is behaviorally relevant, since ingestion of a flavored solution paired with intragastric infusion of MSG enhances preference for the flavored solution (Uematsu et al. 2009). As a consequence the activation of vagal terminals by glutamate, brain regions targeted directly or indirectly by vagal inputs respond to intragastric infusions of MSG (Kondoh and Torii 2008a; Tsurugizawa et al. 2008; Kondoh et al. 2009a, 2009b). In contrast, lesions to the dopaminergic neurons of the ventral tegmental area, a brain area involved in reward processing, interfere with preferences for sucrose, but not umami solutions (Shibata et al. 2009). Therefore, current evidence supports distinct brain-sensing mechanisms for dietary glutamate and carbohydrates, with the former depending on subdiaphragmatic vagal transmission and latter on dopaminergic signaling. These nutrient-specific brain responses to dietary glutamate might underlie some of the beneficial metabolic effects produced by MSG intake. Recently, it has been found that chronic, elective ingestion of a palatable solution of MSG by rats ameliorates obesity as well as the elevated fat deposition and plasma leptin levels induced by high calorie foods (Kondoh and Torii 2008b). Such effects of MSG may be initiated by gut glutamate receptors linked to afferent branches of the vagus nerve, taste glutamate receptors in the oral cavity (Chaudhari et al. 2000; Li et al. 2002; Nelson et al. 2002; San Gabriel et al. 2005), or both. This review focuses primarily on these recent findings concerning postingestive mechanisms of dietary glutamate involved in the gut-brain crosstalk.

31.1 Glutamate Content and Monitoring of Dietary Protein Levels

Glutamate is one of the most abundant molecules in our body. Glutamate content accounts for approximately 10% or more of total animal protein (Giacometti 1979). Therefore, considering that proteins correspond to approximately 20% of the human body composition, glutamate content should account for approximately 2% of the total. Therefore, a person who weights 50 kg should have approximately 1,000 g of glutamate distributed throughout the body (Fig. 31.1a). However, activation of glutamate receptors requires the presence of the free, rather than bound, form of glutamate in the mouth and gastrointestinal tract (Fig. 31.1b). Therefore, by stimulating glutamate receptors, free glutamate can trigger both gustatory and visceral signals. For glutamate absorption, both the glutamate receptors and glutamate transporters are required (*see* next). Being an essential link in intermediary metabolism, the free form of glutamate is in fact found in large quantities in animal and plant tissues (Giacometti 1979).

It has repeatedly been suggested that the sensing of protein ingestion by animals might be linked to the glutamate content in foods (Torii et al. 1987). It is unlikely that such protein "sensing" would depend (exclusively) on glutamate taste in the mouth, since only free, but not to protein-bound, glutamate activate taste receptors; in addition, the free glutamate content of natural foods is not tied to their protein content (e.g., tomatoes are high in free glutamate, but not in protein-bound glutamate; Yamaguchi and Ninomiya 2000; Giacometti 1979). However, the total glutamate content in foods (free + protein-bound forms) might provide a reasonable index of protein ingestion, as glutamate is the most abundant amino acid in almost all dietary proteins (Giacometti 1979).

31.2 Roles of Glutamate in the Intermediary Metabolism and Neurotransmission

In cells, glutamate functions as an interface between amino acid and carbohydrate metabolism, given its key role as a substrate in transamination reactions. Although glutamate is classified as a nonessential amino acid, dietary glutamate has an "essential" functional role, especially in the intestinal
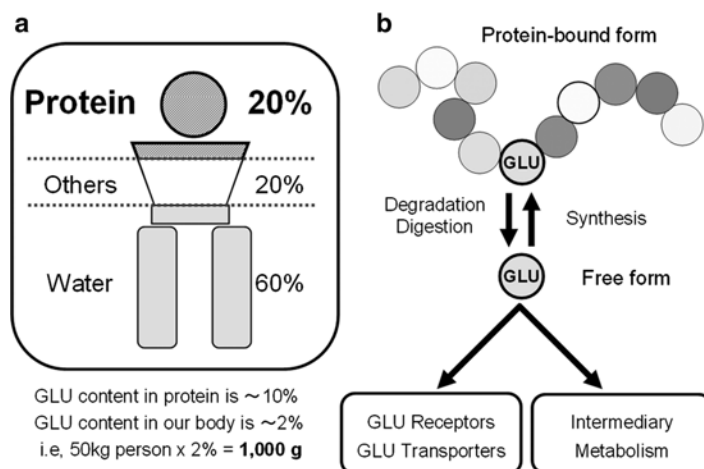
Fig. 31.1 Content of L-glutamate (*GLU*) in human body (**a**) and the importance of free glutamate as a bioactive molecule (**b**). Glutamate content is about 2% of the body weight. Glutamate in free form plays multiple functions through receptor activation, transportation, and intermediary metabolism

mucosa. For example, glutamate is: (1) the single largest contributor to energy production, (2) the specific precursor for the biosynthesis of two conditionally essential amino acids (proline, alanine) and glutathione (an antioxidant), and (3) the essential oxidative substrate in intermediary metabolism (Reeds et al. 2000; Young and Ajami 2000).

Glutamate also acts as the dominant excitatory neurotransmitter in the brain, and its activity regulates synaptic plasticity, learning, memory, motor activity, and neural development. Glutamate also acts as a transmitter outside the brain [e.g., between enteric neurons of the gut (Liu et al. 1997)].

31.3 Detection and Perception of Umami Taste

Umami taste is one of the five basic tastes, and is represented by the characteristic taste of the traditional Japanese soup "dashi" (Yamaguchi and Ninomiya 2000). Glutamate is a prototypical umami substance found in both natural and processed foods such as kelp, cheese, tea, vegetable, meat, fish, and human milk.

Multiple glutamate receptors, expressed in the taste cells of the oral cavity, mediate the transduction of umami taste. Such receptors include the heterodimer T1R1/T1R3 and the truncated forms of metabotropic glutamate receptors 1 and 4 (mGluR1 and mGluR4; Chaudhari et al. 2000; Li et al. 2002; Nelson et al. 2002; San Gabriel et al. 2005). T1R1/T1R3 receptors couple to G-proteins such as α-gustducin and/or transducin and activate phospholipase C β2-dependent pathways to increase intracellular Ca^{2+} concentration (Li et al. 2002; Nelson et al. 2002). T1R1/T1R3 receptors may also activate a cyclic AMP-dependent pathway (Margolskee 2002). In contrast, truncated mGluR4 reduces cyclic AMP levels (Chaudhari et al. 2000). Concerning the truncated mGluR1, signal elements were not identified. The coding of taste modalities is accomplished by the separation of subsets of taste cells expressing modality-specific taste receptors (Chandrashekar et al. 2006).

The excitation of taste cells is then transmitted to the rostral part of the nucleus of the solitary tract (NST) via four taste nerves (Fig. 31.2). Neurons in the NST project to the parabrachial nucleus, and then relay to a variety of forebrain areas via dorsal and ventral routes. In general, it is considered that the taste quality and intensity are represented in the taste cortex, while hedonic aspects are represented in the ventral forebrain regions (Yamamoto 2006).

31.4 Visceral Mechanisms

Intestinal brush cells or solitary chemosensory cells lining the mucosa have a structure similar to lingual taste cells. Recently, several investigators have reported that the gut epithelial cells express receptors for umami, sweet, and bitter substances that are indistinguishable from those found in the oral cavity (Wu et al. 2002; Bezençon et al. 2007; Jang et al. 2007; Mace et al. 2007; Margolskee et al. 2007; San Gabriel et al. 2007; Mace et al. 2009). The downstream elements found to be required for glutamate taste transduction in the oral cavity are also coexpressed in gut cells. What roles might such "taste" receptors play in the gut? Since glutamate receptors are expressed in the gut epithelium (luminal side), would they be involved in physiological responses such as nutrient digestion, absorption, and metabolism? In what follows, we describe the existence of a glutamate-sensing system in the gut linked to glutamate absorption and activation of vagal afferent fibers that transmits food-related signals to the brain.
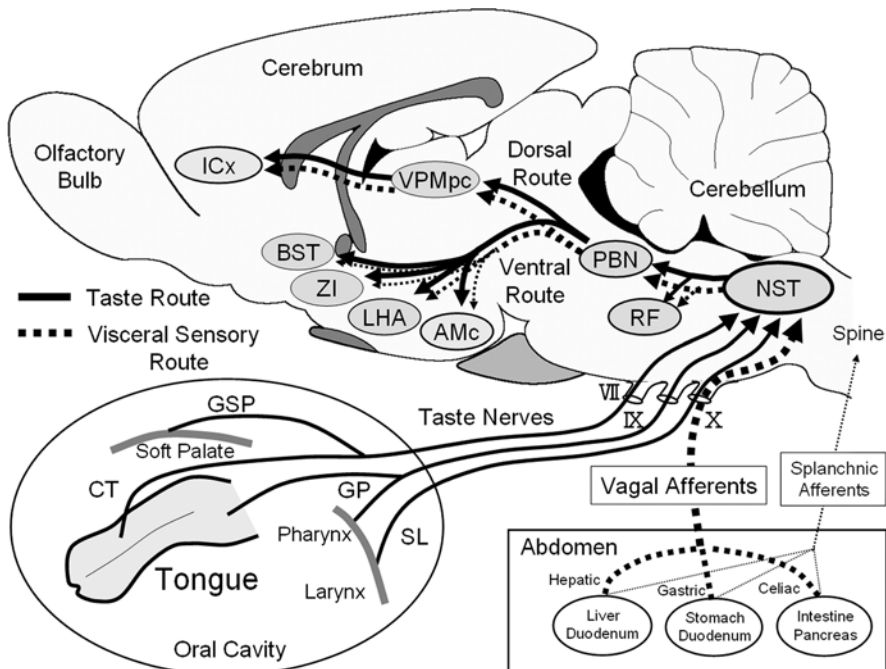
Fig. 31.2 Ascending neural pathways for nutrient-related signals in rats. Taste information is transmitted to the brain via four taste nerves, while visceral sensory information is transmitted via vagal and splanchnic afferents. The first relay in the brain is the nucleus of the solitary tract (*NST*). The neurons in the NST project to the parabrachial nucleus (*PBN*), and then project to a variety of forebrain areas via dorsal and ventral routes. Neurons in the NST also project to the reticular formation (RF) for reflex responses. *CT* chorda tympni nerve; *GSP* greater superficial petrosal nerve; *GP* glossopharyngeal nerve; *SL* superior laryngeal nerve; *VPMpc* ventral posteromedial nucleus of the thalamus, parvicellular part; *ICx* insular cortex; *AMc* central nucleus of the amygdala; *LHA* lateral hypothalamic area; *ZI* zorna incerta; *BST* bed nucleus of the stria terminalis. VII, IX, and X denote the 7th, 9th and 10th cranial nerves, respectively

31.4.1 Glutamate Receptors in the Gut

Currently, two candidate glutamate receptors have been identified in the gut, i.e., mGluR1 and T1R1/ T1R3. The mGluR1 is located in chief cells (pepsinogen-secreting cells) of the stomach (San Gabriel et al. 2007), whereas the T1R1/T1R3 heterodimer is found in epithelial cells of the stomach, small intestine, and colon (Bezençon et al. 2007). The cellular transduction molecules of taste glutamate receptors, including α-gustducin, transducin, phospholipase C β2, protein kinase C βII and transient receptor potential cation channel M5 (TRPM5) are also coexpressed in these cells (Bezençon et al. 2007; Mace et al. 2007, 2009), indicating the presence of the complete receptor transduction machinery. These findings suggest that taste-like gut glutamate receptors might detect ingested glutamate on the luminal side of the gut, and provide this information to adjacent cells and neurons.

31.4.2 Glutamate Transporters and Absorption

The intestinal absorption of glutamate presumably occurs for the most part in the epithelial cells lining the mucosa, namely enterocytes. Glutamate is transported from the intestinal lumen across the apical membrane to cytosol mainly via the high affinity X^-_{AG} system and to a lesser extent by the low

affinity B^0 system (Burrin and Stoll 2009). These systems also transport a second acidic amino acid, aspartate. Studies with pig and mice tissue show that excitatory amino acid carrier-1 (EAAC-1) is the most abundant glutamate transporter among four proteins capable of X^-_{AG} system activity in the intestine (Fan et al. 2004). An important and yet unresolved question is to what extent the gut microflora competes in the process of glutamate absorption (Burrin and Stoll 2009).

In the jejunum of a fed rat, T1R1 and T1R3 are colocalized in enterocytes, solitary chemoreceptor cells, and Paneth cells (Mace et al. 2007). Stimulation of the T1R1/T1R3 receptor activates an intracellular signaling cascade involving α-gustducin, transducin, phospholipase C β2, and protein kinase C βII, which will eventually lead to enhanced expression of EAAC-1 in the apical membrane thereby facilitating glutamate absorption (Fig. 31.3). EAAC-1 levels in the apical membrane are doubled after glutamate stimulation (Mace et al. 2009). As glutamate is the single most important energy source in the intestinal mucosa (Reeds et al. 2000), most of the glutamate absorbed is used for energy production and biosynthesis of amino acids (aspartate, alanine, proline), glutathione, and protein. This is one of the reasons why glutamate levels in the blood and brain remain stable for several hours following food intake (Adibi and Mercer 1973; Young and Ajami 2000; Kondoh and Torii 2008a).

Addition of glutamate to an intestinal perfusate induces rapid internalization of T1R1, T1R3, and transducin (Mace et al. 2009), suggesting the presence of a dynamic regulatory system mediating glutamate absorption. Interestingly, this glutamate absorption system acts to coordinate the regulation of apical transporters for glucose and oligopeptides reciprocally through a common enterocytic pool of protein kinase C βII. This network may be important for the control of energy supply to the body.
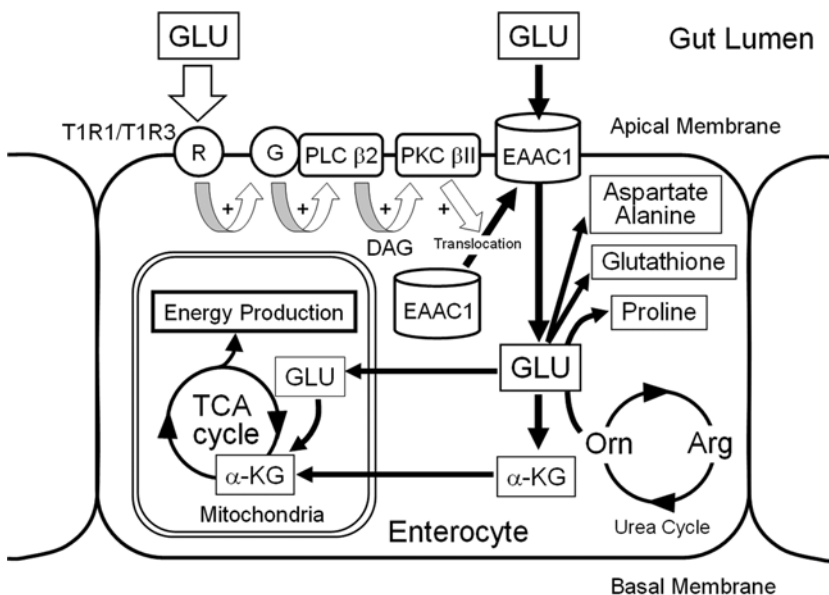
Fig. 31.3 Regulation of L-glutamate (*GLU*) absorption and metabolism in the small intestine. Stimulation of T1R1/T1R3 receptor by luminal glutamate enhances expression of a high affinity glutamate transporter, the excitatory amino acid transporter-1 (*EAAC-1*), in the apical membrane of enterocyte. After absorption, most glutamate is consumed for catabolism and oxidization. *R* glutamate receptor; *G* GTP-binding protein (including α-gustducin and transducin); *PLC* phospholipase C; *PKC* protein kinase C; *DAG* diacylglycerol; *α-KG* α-ketoglutarate; *TCA* tricarboxylic acid; *Orn* ornithine; *Arg* arginine

31.4.3 Hormonal Release

The gastrointestinal tract is the largest endocrine organ of the body. Hormones released into the systemic circulation from the gut in response to nutritional stimuli form a key component of the gut-brain crosstalk (Chaudhri et al. 2008). Gut peptides such as cholecystokinin, glucagon-like peptide-1 (GLP-1), oxyntomodulin, pancreatic polypeptide, and peptide YY_{3-36} reduce food intake and are thought to act as satiety signals and meal terminators. Typically, appetite-modifying actions of most of these peptides are partly reduced or completely abolished after vagotomy, suggesting importance of vagus nerve on appetite control and energy homeostasis.

However, there is no evidence to this day indicating that dietary glutamate stimulates hormonal release from the gut into the circulation. This is in sharp contrast to the case of sweet receptor stimulation, despite the fact that the T1R1/T1R3 umami receptor shares common intracellular signaling pathways to T1R2/T1R3 sweet receptor. For example, stimulation of gut T1R2/T1R3 by sugars and artificial sweeteners causes release of incretins such as glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 (Jang et al. 2007). In addition to the enhancement of glucose-induced insulin release, these hormones act on enterocytes to stimulate the absorption of glucose from the intestinal lumen through upregulation of apical expression of Na^+/glucose cotransporters 1 and 2 (Mace et al. 2007, 2009; Margolskee et al. 2007). GLP-1 exerts additional physiological actions, including stimulation of insulin biosynthesis, inhibition of glucagon secretion, inhibition of gastric emptying and acid secretion, reduction of food intake, and trophic effects on the pancreas (Gautier et al. 2008). Gut sweet receptors thus appear to participate in the coordination of dietary carbohydrate absorption and their release into the circulation. In contrast to this concept, however, there is a contradicting report that artificial sweeteners do not produce incretin release in vivo (Fujita et al. 2009).

Although glutamate stimulates the vagus nerve through the release of bioactive substances such as nitric oxide and serotonin in the stomach (*see* next), it remains to be clarified whether gut peptide release can be triggered by luminal sensing of glutamate.

31.4.4 Activation of Vagal Afferent Fibers

The ascending pathway of abdominal vagal information is parallel to the taste pathway (Yamamoto 2006). Signals detected in the abdominal regions are transmitted to the NST via the hepatic, gastric, and celiac branches of the vagus nerve (Figs. 31.2 and 31.4a). Each branch carries both afferent and efferent fibers. The vagal afferent fibers project to a region of the NST located caudal to the NST area receiving gustatory inputs.

The administration of MSG into the stomach, duodenum, and portal vein activates vagal afferents of the gastric, celiac, and hepatic branches, respectively (Niijima 2000). Such findings suggest the existence of glutamate-sensing mechanisms at these sites (stomach, small intestine, and hepato-portal region). Of the three vagal components, gastric afferents respond specifically to MSG; i.e., *no* response is elicited by infusing *any* of the other amino acids or NaCl into the stomach (Uneyama et al. 2006). The specific response to MSG cannot be explained by activation of T1R1/T1R3 because, at least in rodents, it functions as a broadly tuned L-amino acid receptor (Nelson et al. 2002). In contrast, hepatic afferents respond to all amino acids delivered into the portal vein (Niijima and Meguid 1995). The response of gastric afferents to MSG is concentration-dependent (Uneyama et al. 2006). Moreover, the vagus does not respond to the intravenous administration of MSG (Uneyama et al. 2006), implying that the vagal effects of luminal glutamate administration are restricted to the gastrointestinal tract since any leakage into the circulation would in principle have no effects.
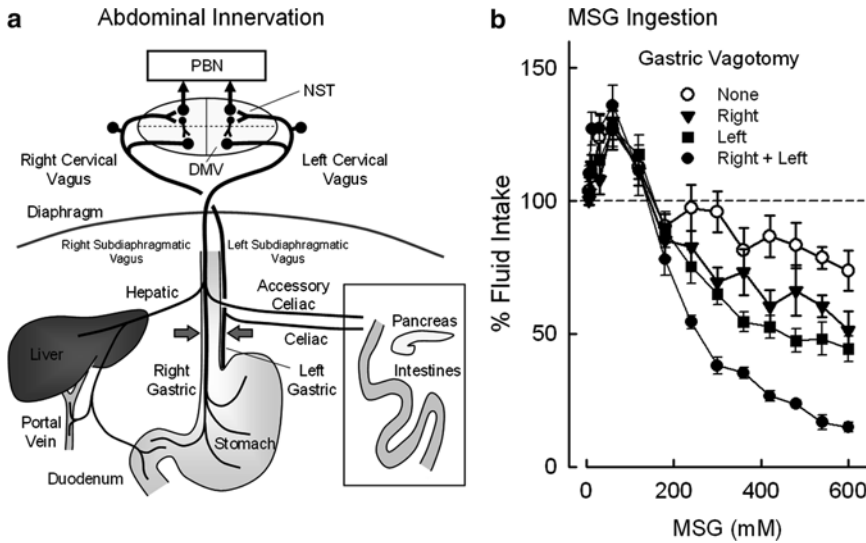
Fig. 31.4 Abdominal innervation of the vagus nerve (**a**) and effects of selective gastric vagotomy on monosodium L-glutamate (*MSG*) ingestive behavior in 30-min one-bottle acceptance test (**b**) in rats. Abdominal vagal branches carry both afferent and efferent fibers. Consumption of MSG solution is reduced by half after the partial vagotomy of gastric branch at the level either in the right gastric or left gastric compared with their combination (*arrows*). Vertical represents percentage fluid intake relative to water intake. *NST* nucleus of the solitary tract; *DMV* dorsal motor nucleus of the vagus; *PBN* parabrachial nucleus. Results are expressed as mean ± SEM, $n = 6$

The afferent endings of the vagus are not in direct contact with gut epithelial cells. Hence, how does the activation of glutamate receptors stimulate vagal nerve endings? We have observed that the activation of gastric vagal afferents by intragastric MSG can be suppressed by either (a) luminal perfusion with lidocaine, a local anesthetic, (b) pretreatment of animals with *p*-chrolophenylalanine, which depletes gut endogenous serotonin stores, (c) administration of granisetron, a selective antagonist at serotonin receptor type 3 (5-HT$_3$R), or (d) administration of N^ω-nitro-L-arginine methyl ester [a nonselective inhibitor of nitric oxide synthase (NOS)] (Uneyama et al. 2006). Moreover, the vagal response to MSG can be mimicked by intragastric administration of sodium nitroprusside (a nitric oxide donor), an effect that is abolished by pretreatment with granisetron (Uneyama et al. 2006). Together, these findings suggest that luminal glutamate activates the vagal nerve indirectly via the production and release of nitric oxide and serotonin.

Anatomical and immunohistochemical evidence reveals that serotonin-immunoreactive cells are found in the stomach, particularly in the superficial part of the mucosal epithelium and at the base of the fundic glands (Iijima et al. 2008). 5-HT$_3$R immunoreactivity is localized to the neck of the fundic glands. NOS1/neuronal NOS-immunoreactive cells of bipolar shape in the stomach are found in the *lamina propria*, where a dense network of neuronal cells is present. These findings suggest that complex cellular events mediate glutamate signaling in the stomach.

31.4.5 Effects of Vagotomy on MSG Ingestive Behavior

Behavioral data obtained from vagotomized rats indicates that gut glutamate signaling via the afferent vagus is an important regulator of food intake. In particular, selective abdominal vagotomy reduces the ingestion of MSG solutions (240–600 mM), as measured by 30-min one-bottle acceptance tests

(Kondoh et al. 2000; Kondoh and Torii 2008a). Importantly, the strength of these effects depended on which vagal branches has been severed, as follows: subdiaphragmatic total vagotomy (TVX) = gastric vagotomy > celiac vagotomy > hepatic vagotomy = intact controls (where the symbol ">" means "lower intake levels than"; Kondoh et al. 2000; Kondoh and Torii 2008a). Since the effects of gastric vagotomy are comparable to those of TVX, the glutamate signal appears to be mediated mainly via the gastric branches. This conclusion is further confirmed by experiments employing partial vagotomy of the gastric branch (Fig. 31.4). Selective transection of either right or left branch of the gastric vagus showed moderate (approximately 50%) reduction of MSG ingestion compared to bilateral transections.

In contrast to MSG, ingestive behavior of proline (a sweet amino acid) is unaffected by TVX (Kondoh et al. 2009a), suggesting that the vagotomy-induced reduction of MSG intake is not related to a local unpleasant sensation in the gut.

If nonvagal neural inputs to the brain have any significant roles, transection of these nerves would alter the behavior. Surprisingly, MSG ingestive behavior was little affected by bilateral transections of taste nerves (chorda tympani, glossopharyngeal nerve, and their combination) or splanchnic nerve (Fig. 31.5). Altogether the results suggest that the vagus nerve, especially the gastric branches, have crucial roles for transmission of glutamate signals to promote MSG ingestion. Splanchnic afferents have least contribution on the glutamate signaling in the gut.

31.4.6 Luminal Glutamate Triggers Reward Signals

Postingestive consequences (nutrition, satiation, and food memories) are important factors determining long-term preferences for foods and fluids. Preference is increased for flavored solutions paired with intragastric infusions of highly caloric substances (carbohydrates, long-chain fatty acids, and
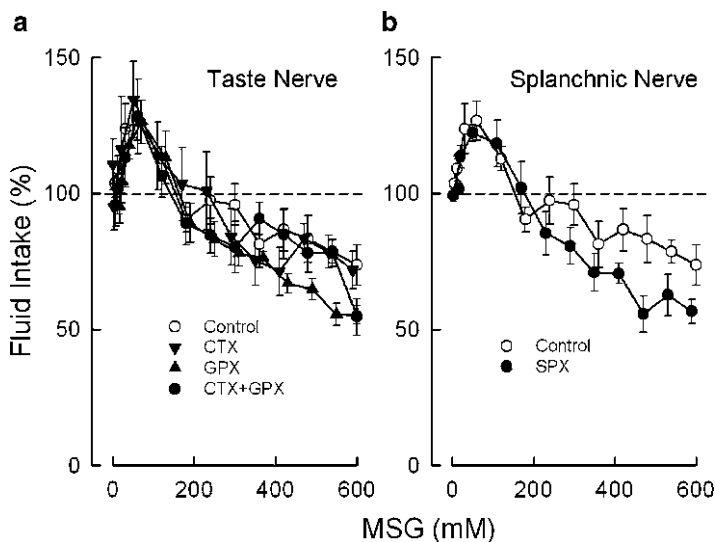
Fig. 31.5 Bilateral transection of the taste nerves (**a**) and splanchnic nerve (**b**) had little influence on monosodium L-glutamate (*MSG*) ingestive behavior in 30-min one-bottle acceptance test in rats. Taste nerves and splanchnic nerve do not play crucial roles for transmission of glutamate signals to the brain to alter ingestive behavior of MSG consumption. Vertical represents percentage fluid intake relative to water intake. *CTX* transection of the chorda tympani nerve; *GPX* transection of the glossopharyngeal nerve; *SPX* transection of the splanchnic nerve. Control represents intact animals. Results are expressed as mean ± SEM, *n* = 6

Conditioned Flavor Preference Learning
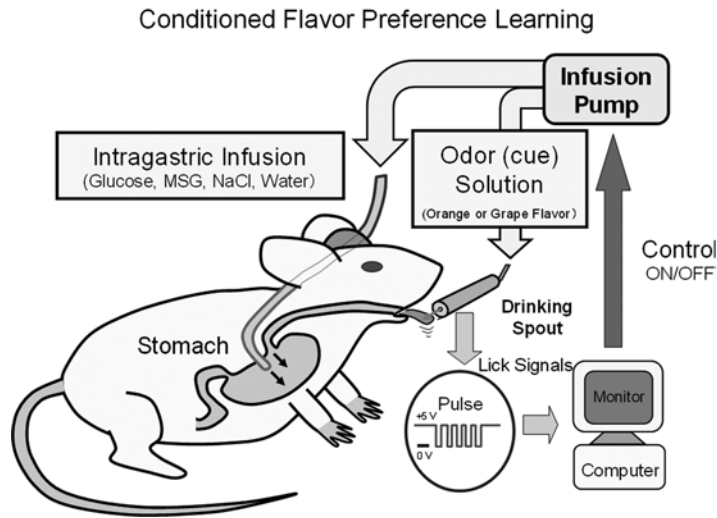
Fig. 31.6 Scheme of conditioned flavor preference learning experiment. Licking of the drinking spout triggers an infusion pump through computer software to deliver a cue solution (an orange- or grape-flavored solution) in the spout and simultaneously a nutrient solution in the stomach via intragastric cannula. The volumes delivered are equal each other. Another flavored solution paired with intragastric water infusion acts as a control. After training (learning), rats are subjected to two-bottle preference tests. *MSG*, monosodium L-glutamate

ethanol), as shown in conditioned flavor preference paradigms (Sclafani 2004). Until recently, however, the influence of postingestive effects produced by umami substances on flavor preference learning had been poorly studied. We set out to investigate flavor preferences conditioned by intragastric infusions of MSG in rats. We hypothesized that MSG intake produces reinforcing postingestive effects that are sufficient to enhance preferences for flavors associated with intragastric MSG infusion.

To test this hypothesis, a conditioned flavor preference paradigm was employed (Fig. 31.6). Rats implanted with chronic intragastric cannulae were trained to drink either a fruit-flavored solution (conditioned stimulus; CS+) paired with intragastric infusions of a test solution (MSG, NaCl, or glucose at 60 mM, so that orosensory receptors for these tastants were not activated) or a second flavored solution (CS−) paired with intragastric infusion of water. CS+ and CS− solutions were presented (along with their respective intragastric infusions) on alternate days. After this conditioning phase, the MSG group showed significantly higher intake and preference for the CS+ over CS− solution during two-bottle preference tests. Neither NaCl nor glucose infusions produces significant increases in preferences (Uematsu et al. 2009). The findings with respect to glucose are intriguing and imply that at this concentration (60 mM) intragastric infusions of glucose produce no reinforcing effects on conditioned flavor preferences. The results clearly suggest that postingestive MSG is rewarding for animals at a low caloric concentration. The MSG effect can be explained neither by Na^+ effect nor by a caloric effect. A glutamate-specific sensing mechanism involving vagal activation following gut glutamate receptor stimulation is a plausible explanation for the behavioral effects observed.

31.5 Brain Mechanisms

As the ingestion of high protein foods (and thus glutamate) does not lead to appreciable changes in plasma glutamate levels (Adibi and Mercer 1973; Young and Ajami 2000; Kondoh and Torii 2008a), the brain is unlikely to monitor protein intake via meal- or diet-related variations in plasma glutamate.

However, luminal glutamate content, which should rise once proteins are digested, may well reflect protein ingestion, and thus might constitute a reliable signal for protein intake. In this case, the stimulation of gut glutamate receptors by luminal glutamate following protein digestion, and the subsequent activation of afferent vagal fibers, might constitute a primary mechanism by which the brain senses protein ingestion.

31.5.1 Forebrain Activation by Intragastric Nutrient Administration

The vagal afferent fibers project to neurons in the caudal part of the NST, from where projections arise that spread to numerous areas in the brain (Berthoud and Neuhuber 2000). Some of these brain areas might be responsive to the activation of the afferent vagus by luminal glutamate. Functional magnetic resonance imaging (functional MRI or fMRI) studies in anesthetized rats indicate that intragastric administration of nutritive substances [glucose (sweet), MSG (umami) and NaCl (salty) at 60 mM, which is the most preferred concentration of MSG by rats (Kondoh et al. 2000; Kondoh and Torii 2008a)] activates a number of brain areas, including the cortex, basal ganglia, limbic system, and hypothalamus (Kondoh and Torii 2008a; Tsurugizawa et al. 2008; Kondoh et al. 2009a, 2009b). All of these regions receive vagal information through the NST (Berthoud and Neuhuber 2000). Notably, three areas of the brain (the medial preoptic area, the dorsomedial nucleus of the hypothalamus, and the habenular nucleus) are activated only by MSG, while the nucleus accumbens is activated only by glucose (Fig. 31.7). The amygdala is activated by both glucose and MSG. Other areas, such as the insular cortex (the primary visceral sensory cortex), anterior cingulate cortex, caudate-putamen, hippocampus, and lateral hypothalamic area are activated by all three substances. The medial preoptic area and dorsomedial nucleus of the hypothalamus have both been proposed to play a role in thermoregulation (Dimicco and Zaretsky 2007; Kumar et al. 2007), while the habenular
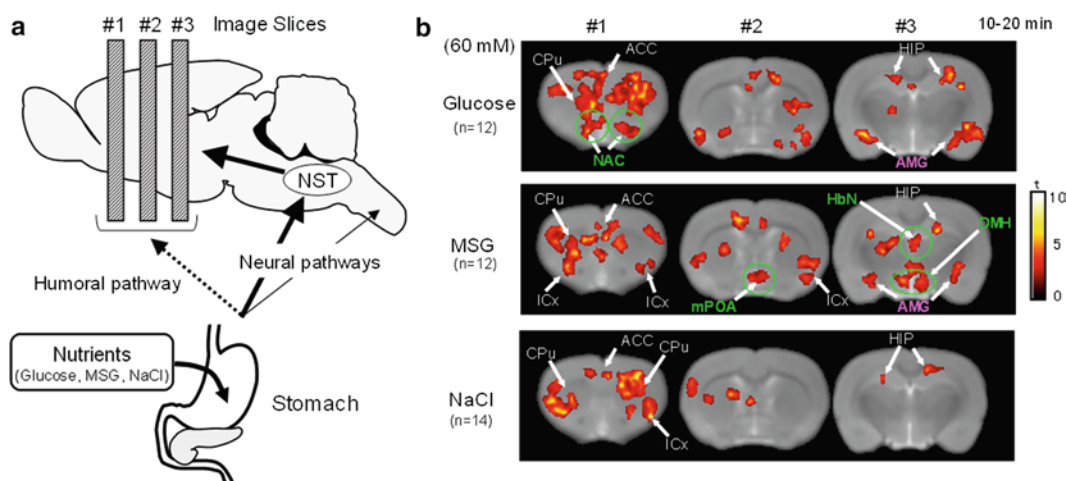
Fig. 31.7 Scheme of functional magnetic resonance imaging (fMRI) experiments (**a**) and typical examples of activated areas in the rat brain at 10–20 min after intragastric administration of nutritive substances (**b**). Fluids of nutritive substances [glucose, monosodium L-glutamate (*MSG*), and NaCl at 60 mM, 1.0 mL/100 g body weight] were delivered directly into the stomach via gastric cannula for 10 min. Three images were taken from the forebrain regions (+2.0, -0.5, and -3.0 mm to bregma, slice thickness = 1.5 mm) by using T_2*-weighted MRI. Results are expressed as mean ± SEM, n = 12–14
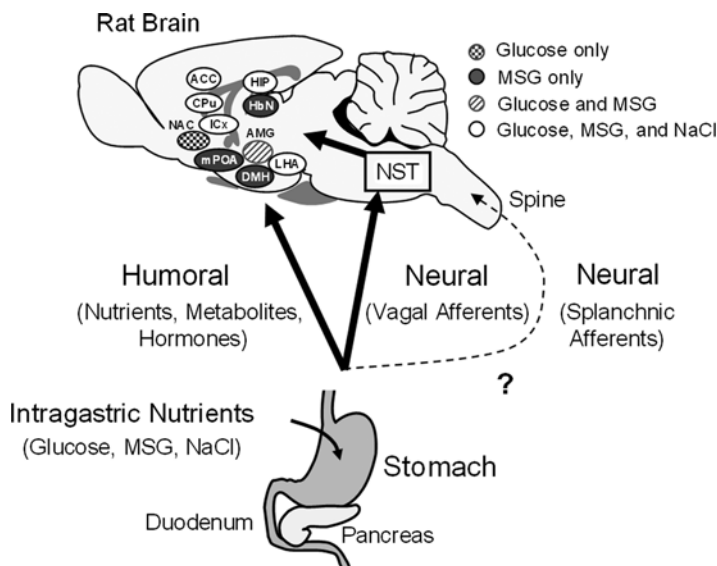
Fig. 31.8 Forebrain activation induced by intragastric administration of nutritive substances. Brain activation is observed in several forebrain regions in the cortex, basal ganglia, limbic system, and hypothalamus. Notably, the medial preoptic area (*mPOA*), dorsomedial nucleus of the hypothalamus (*DMH*), and habenular nucleus (*HbN*) are activated by monosodium L-glutamate (*MSG*) alone. In contrast, the nucleus accumbens (*NAC*) is activated by glucose alone. The amygdala (*AMG*) is activated by both glucose and MSG. *NST* nucleus of the solitary tract; *ICx* insular cortex; *ACC* anterior cingulate cortex; *CPu* caudate-putamen; *HIP* hippocampus; *LHA* lateral hypothalamic area

nucleus, especially the lateral habenula, participates in affective decision-making by influencing the activity of midbrain dopamine and serotonin neurons (Matsumoto and Hikosaka 2007). The amygdala is a key structure in the evaluation of the biological significance of foods (Nishijo et al. 1998). Such findings suggest that luminal glutamate may play a role in thermoregulation, energy homeostasis, reward processing, and emotional behavior. Figure 31.8 is a summary of activated areas in the rat forebrain induced by intragastric administration of typical nutrients.

The temporal patterns of the brain responses were also distinct for each luminal stimulus. The glucose response develops slowly, with the peak at 20–30 min after the beginning of gastric infusion; the response was sustained for up to 60 min (Tsurugizawa et al. 2008). This response pattern parallels changes in blood glucose levels. However, the MSG-induced response develops rapidly, with the peak occurring just at the end of the 10-min infusion period. The response then dropped off to baseline values within the next 15 min. The response to NaCl infusion paralleled (in time) that for MSG, but was much weaker. In another experiment, 150 mM NaCl produces no response (Tsurugizawa et al. 2008), suggesting that the response to 60 mM NaCl is likely a hypotonic effect (Mei and Garnier 1986), as the experimental conditions (gastric expansion, temperature change, and anesthetic) are otherwise the same for each solution tested. An analysis of the response to 60 mM MSG minus that to 60 mM NaCl shows a result for MSG like that to MSG alone (though reduced).

In addition to these findings, the brain activation induced by intragastric glutamate, but not by intragastric glucose, is abolished after the TVX (Tsurugizawa et al. 2009). This result suggests that gut luminal glutamate is "sensed" in the brain by a signal provided by the afferent vagus. Afferent vagus information is critical for the transmission of glutamate signals to the brain, and circulating factors (e.g. direct sensing of blood chemicals by the brain) appear to be the primary pathway for

glucose signals. If this difference holds, it is interesting to note that the mechanism by which the gut handles ingested glucose (relatively little metabolism) and glutamate (almost complete metabolism) is consistent with the signaling pathways used by these compounds to communicate their presence in the gut to the brain.

31.5.2 Cerebral Blood Flow Changes by Intraduodenal Nutrient Administration

Changes in cerebral blood flow are physiological events associated with brain activation (Kwong et al. 1992). Effects of intraduodenal nutrient infusions on cerebral blood flow were investigated by using T_1-weighted MRI in awake and nonfasted rats. Infusion of isotonic MSG solution (150 mM) into the rat duodenum enhances overall cerebral blood flow with the responses peaking at 20–40 min after the start of the infusion, with flow levels decreasing with respect to baseline levels after 60 min of the start of the infusion (Fig. 31.9). In contrast, isotonic glucose (300 mM) infusions reduce blood
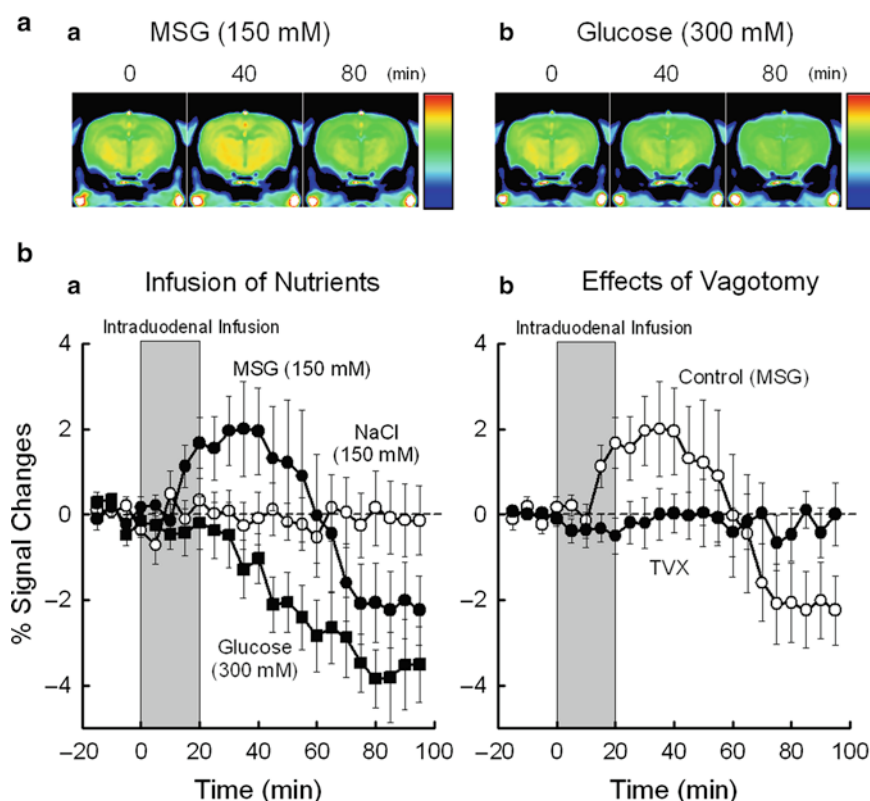
Fig.31.9 Cerebral blood flow responses by intraduodenal infusion of nutrients in awake and nonfasted rats. *A* Examples of flow images after intraduodenal infusions (2.0 mL/100g body weight for 20 min) of 150 mM monosodium L-glutamate (*MSG*) (**a**) and 300 mM glucose (**b**) scanned by T_1-weighted magnetic resonance imaging (*MRI*). *Ba*,changes in cerebral blood flow after infusion of isotonic nutrient solutions (glucose, MSG and NaCl); *Bb* effects of subdiaphragmatic total vagotomy (*TVX*) on MSG (150 mM)-induced cerebral blood flow changes. MSG-induced response was completely blocked after vagotomy. Results are expressed as mean ± SEM, $n = 10$–12

flow only after peaking at 80 min. Neither isotonic NaCl (150 mM) nor water infusions produced significant effects. These results suggest that the MSG response is not ascribed to Na^+ nor caloric component but to glutamate. Importantly, the MSG-induced response is again completely abolished after the TVX, suggesting the crucial role of the vagus nerve on this blood flow response.

31.5.3 Preference for Umami Taste and Reward Circuits

The dopaminergic neurons in the ventral tegmental area have a crucial role in regulating behavioral responses to natural rewards such as sweet solutions, as well as artificial rewards such as drugs of abuse. However, lesions of the ventral tegmental area dopaminergic neurons by microinjection of 6-hydroxydopamine do not interfere with preferences for umami (MSG and 5′-ribonucleotides) or NaCl solutions (Shibata et al. 2009). Interestingly, enhanced preference for lysine (a bitter amino acid) in lysine-deficient rats is also unaffected by ventral tegmental area lesions. These results suggest that preferences for umami (MSG and 5′-ribonucleotides), essential amino acids, and NaCl, but not for sweet, operate through reward circuits that are independent of ventral tegmental area dopaminergic neurons. Contribution of dopaminergic neurons from other brain areas and the identification of the reward circuits regulating preferences for umami substances must be clarified in future experiments.

31.6 Effects of Oral Glutamate on Body Energy Metabolism

Since MSG generally enhances the palatability of food, effects of MSG ingestion on food intake and development of obesity are of growing interest. To verify whether MSG provides protective effects against obesity, rats were given free access to two drinking bottles, one containing a 1% (w/v) MSG solution and the other plain water (Kondoh and Torii 2008b). Rats given free access to MSG and water show a high preference (93–97%) for the MSG solution. Interestingly, rats ingesting the MSG solution show smaller weight gain over the 15-week study, compared to rats ingesting no MSG (water only; Fig. 31.10). In addition, abdominal fat mass and plasma leptin levels are also lower in rats ingesting MSG than in animals ingesting no MSG. Naso-anal length, lean mass, food and caloric intakes, blood pressure, blood glucose, and plasma levels of insulin, triglyceride, total cholesterol, albumin, and glutamate do not differ between the two groups. Taken together, these results suggest that MSG ingestion reduces weight gain, the rise in body fat mass, and plasma leptin levels. These changes are most likely mediated by increased energy expenditure, since food intake is unaffected by MSG ingestion (Kondoh and Torii 2008b; Kondoh et al. 2009a, 2009b). In support of this possibility, ingestion of MSG enhances diet-induced thermogenesis (Viarouge et al. 1992; Smriga et al. 2000). Conceivably, such effects of MSG might include neural links involving the afferent branches of the vagus nerve in the gut, the afferent sensory nerves in the oral cavity, and perhaps activation of the medial preoptic area and dorsomedial nucleus of the hypothalamus, the areas activated by intragastric MSG (Kondoh and Torii 2008a; Tsurugizawa et al. 2008; Kondoh et al. 2009a, 2009b) and known to be involved in thermoregulation (Dimicco and Zaretsky 2007; Kumar et al. 2007).

    In nursing home elderly, addition of 300 mg MSG with or without flavor to the cooked meal for 16 weeks does not lead to a higher overall energy intake at lunch, not does it increase body weight (Essed et al. 2007). Interestingly, both the MSG group and flavor + MSG group show a mean 0.7–0.8 kg reduction in body weight (0.1 kg increase in the control group). The MSG group also shows a mean
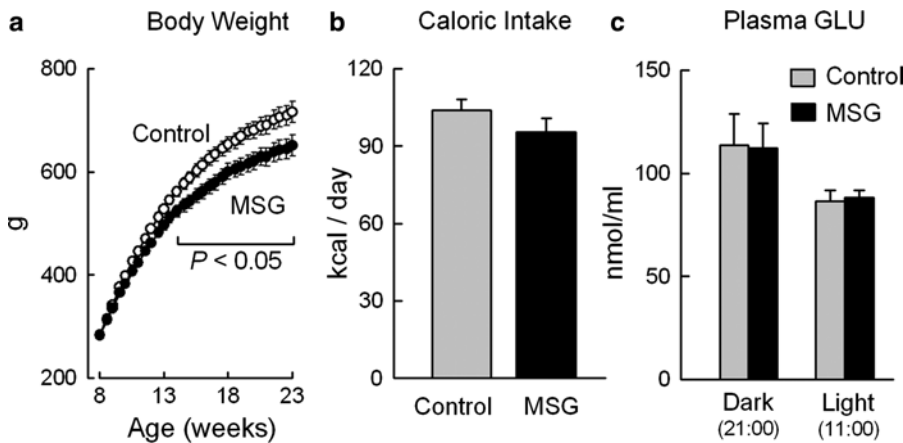
Fig. 31.10 Effects of monosodium L-glutamate (*MSG*) intake on body weight (**a**), daily caloric intake (**b**), and plasma glutamate (*GLU*) levels (**c**). Rats were given free access to high fat diet (45% of total calorie as fat) and water with or without 1% (60 mM) MSG solution. Weight gain was slowed by MSG intake while the caloric intake and plasma glutamate levels both in the light and dark periods were unchanged by MSG intake. Results are expressed as mean ± SEM, *n* = 8–9 (Reprinted from Kondoh and Torii (2008). With permission)
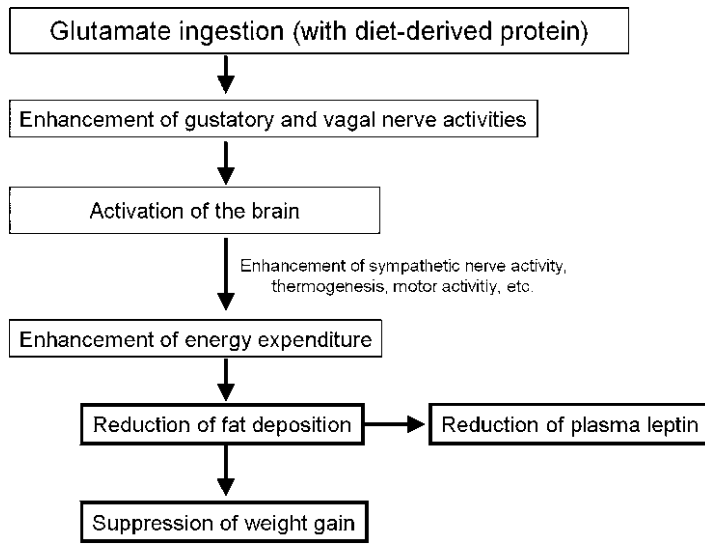
Fig. 31.11 Proposed mechanisms of dietary glutamate on energy expenditure, fat deposition, plasma leptin levels, and weight gain. Ingestion of dietary glutamate reduces weight gain by enhancing energy expenditure. Caloric intake is not modified by glutamate ingestion

0.7 kg reduction in body fat (0.1 kg increase in the control group). Plasma leptin was not measured in this experiment. These results suggest that MSG might also reduce body weight and body fat mass in humans without changing caloric intake. Enhanced thermogenesis may be involved in the MSG effects on energy homeostasis.

Taken together, proposed mechanisms of dietary glutamate on energy expenditure, fat deposition, plasma leptin levels, and weight gain are shown in Fig. 31.11. Such possibilities need to be examined in the future experiments.

31.7 Applications to Other Areas of Health and Disease

Obesity increases a risk of lifestyle-related diseases such as type II diabetes, hypertension, hyperlipidemia, cardiovascular disease, and ischemia. Many people desire an alternative remedy instead of medication and exercise for prevention of body fat accumulation and obesity. Ingestion of functional foods or ingredients is one of the ideal means for their prevention and remedy. Addition of glutamate on cuisines enhances food palatability but suppresses fat deposition and obesity by increasing energy expenditure. Usage of glutamate does not produce overeating (no changes in caloric intake). Therefore, manipulation of glutamate signals arising in the mouth and gut may be an effective strategy for treatment of obesity and metabolic syndrome.

Summary Points

- Glutamate has several physiological functions including perception of umami taste, intermediary metabolism, and excitatory neurotransmission.
- In addition, new functions for dietary glutamate in gut-brain axis activation and energy homeostasis have been found.
- A current hypothesis regarding the physiological function of the glutamate receptor transduction cascade relates to signaling the brain on the amounts of protein ingested by an organism.
- Glutamate levels in both blood and brain remain stable throughout the day.
- Glutamate receptors are expressed in the gut mucosa producing local actions on gut function including apical expression of glutamate transporters (glutamate absorption) and vagal activation (gut-brain communication).
- The gastric vagal afferent fibers respond specifically to glutamate but not to other amino acids or NaCl delivered in the stomach.
- The release of signaling molecules (nitric oxide and serotonin) is involved in the observed increases in afferent vagus nerve activity upon stimulation with glutamate and consequently in a number of different areas of the brain.
- Intragastric infusion of MSG specifically activates three brain areas, i.e., the medial preoptic area, dorsomedial nucleus of the hypothalamus, and habenular nucleus.
- Glutamate activates the brain through vagal route while glucose activates the brain through nonvagal (humoral) route.
- Glutamate in the gut is rewarding.
- Umami preference is unaffected by lesions of dopaminergic neurons in the ventral tegmental area.
- Chronic intake of a palatable MSG solution is effective to reduce weight gain, fat deposition, and plasma leptin levels in rats, most likely through an enhancement of energy expenditure.
- These findings indicate that dietary glutamate influences numerous physiological functions, suggesting a broad, integrative role for dietary glutamate in body homeostasis.

Definitions and Explanations

Dorsomedial nucleus of the hypothalamus: A nucleus in the hypothalamus involved in regulation of feeding, drinking, body weight, energy consumption, and behavioral circadian rhythms.

Functional magnetic resonance imaging (fMRI): A noninvasive MRI approach that measures brain functional changes based on blood oxygenation level-dependent contrast of hemoglobin (an endogenous contrast agent) in blood. Because activation of the brain causes increase in blood flow (oxygen supply) over the oxygen consumption to reduce deoxyhemoglobin levels, signal increases in general can be detected.

ʟ-Glutamate: An acidic and multifunctional amino acid involved in perception of umami taste, intermediary metabolism, and excitatory neurotransmission. In addition, it plays important roles in the activation of gut–brain axis, reward processing, and regulation of energy homeostasis. Several types of glutamate receptors (ionotropic and metabotropic receptors) are expressed in the body.

α-gustducin: A GTP-binding protein expressed in type II taste cells and also in epithelial cells in the gut. In the oral cavity, it transduces sweet, bitter, and umami stimuli into cellular excitation via activation of phospholipase C β2.

Incretin: A concept of peptide hormones released during meals from endocrine cells located in the gut mucosa and stimulate insulin secretion from pancreatic β-cells in a glucose-dependent manner. Glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) are the two major incretin hormones in humans.

Medial preoptic area: A nucleus in the anterior hypothalamus involved in regulation of body temperature, sleep–wakefulness, and male sexual behavior.

Nucleus accumbens: A nucleus involved in regulation of motivation, reward, feeding, pleasure, fear, attention, and drug addiction. Dopaminergic neurons originating in the ventral tegmental area terminate the nucleus accumbens, which is thought to be involved in reward and reinforcement and appears to be implicated in most if not all addictions.

Nucleus of the solitary tract: A nucleus in the medulla oblongata that receives afferent information concerning taste, cardiovascular, respiratory, and visceral sensation via the facial (VII), glossopharyngeal (IX), and vagus (X) cranial nerves.

Splanchnic nerve: A nerve carrying nerve fibers from the lower thoracic paravertebral ganglions to the collateral ganglions. It innervates the viscera, carrying fibers of the autonomic nervous system (visceral efferent fibers) as well as sensory fibers from the organs (which are also known as visceral afferent fibers).

T1R: The receptors belong to class C G protein-coupled receptors for detection of umami and sweet tastes. There are three subunit proteins in T1R: the T1R1/T1R3 heterodimer detects umami taste while the T1R2/T1R3 detects sweet taste. These receptors are expressed in the mouth and gut mucosa.

Umami taste: One of five basic tastes (salty, sweet, sour, bitter, and umami) elicited typically by glutamate, inosine-5′-monophosphate, and guanosine-5′-monophosphate. Umami taste is often described as the meaty, savory, or broth-like taste.

Vagus nerve: The Xth cranial nerve that innervates the larynx, heart, lungs, and visceral organs. It consists of both afferent and efferent fibers at the abdominal levels.

Ventral tegmental area: An area in the midbrain implicated in drug and natural reward circuitry, motivation, cognition, drug addiction, and several psychiatric disorders. Dopaminergic cell bodies originate and their two primary efferent projections are the mesocortical (innervates the prefrontal and insular cortices) and mesolimbic (innervates septum, hippocampus, amygdala, and nucleus accumbens) pathways.

References

Adibi SA, Mercer DW J Clin Invest. 1973;52:1586–94.
Berthoud HR, Neuhuber WL Auton Neurosci. 2000;85:1–17.
Bezençon C, le Coutre J, Damak S Chem Senses. 2007;32:41–9.
Burrin DG, Stoll B. Am J Clin Nutr. 2009;90:850S–6S.
Chaudhari N, Landin AM, Roper SD Nat Neurosci. 2000;3:113–9.
Chaudhri OB, Salem V, Murphy KG, Bloom SR Annu Rev Physiol. 2008;70:239–55.
Chandrashekar J, Hoon MA, Ryba NJ, Zuker CS Nature. 2006;444:288–294.
Dimicco JA, Zaretsky DV Am J Physiol Regul Integr Comp Physiol. 2007;292:R47–R63.
Essed NH, van Staveren WA, Kok FJ, de Graaf C Appetite. 2007;48:29–36.
Fan MZ, Matthews JC, Etienne NM, Stoll B, Lackeyram D, Burrin DG Am J Physiol Gastrointest Liver Physiol. 2004;287:G385–98.
Fujita Y, Wideman RD, Speck M, Asadi A, King DS, Webber TD, Haneda M, Kieffer TJ Am J Physiol Endocrinol Metab. 2009;296:E473–9.
Gautier JF, Choukem SP, Girard J Diabetes Metab. 2008;34:S65–S72.
Giacometti T In: Filer LJ Jr, Garattini MR, Kare MR, Reynolds WA, Wurtman RJ editors. Glutamatetamic acid: advances in biochemistry and physiology. New York: Raven Press; 1979. p. 25–34.
Iijima J, Horie S, Hasegawa R, Yasui H, Takami S Biol Pharm Bull. 2008;31:1838–40.
Jang HJ, Kokrashvili Z, Theodorakis MJ, Carlson OD, Kim BJ, Zhou J, Kim HH, Xu X, Chan SL, Juhaszova M, Bernier M, Mosinger B, Margolskee RF, Egan JM Proc Natl Acad Sci USA. 2007;104:15069–74.
Kondoh T, Mori M, Ono T, Torii K J Nutr. 2000;130:966S–70S.
Kondoh T, Torii K Biol Pharm Bull. 2008a;31:1827–32.
Kondoh T, Torii K Physiol Behav. 2008b;95:135–44.
Kondoh T, Mallick HN, Torii K. Am J Clin Nutr. 2009a;90:832S–7S.
Kondoh T, Tsurugizawa T, Torii K. Ann N Y Acad Sci. 2009b;1170:77–81.
Kumar VM, Vetrivelan R, Mallick HN Neurochem Int. 2007;50:783–90.
Kwong KK, Belliveau JW, Chesler DA, Goldberg IE, Weisskoff RM, Poncelet BP, Kennedy DN, Hoppel BE, Cohen MS, Turner R, Cheng H, Brady TJ, Rosen BR Proc Natl Acad Sci USA. 1992;89:5675–79.
Li X, Staszewski L, Xu H, Durick K, Zoller M, Adler E Proc Natl Acad Sci USA. 2002;99:4692–6.
Liu MT, Rothstein JD, Gershon MD, Kirchgessner AL J Neurosci. 1997;17:4764–84.
Mace OJ, Affleck J, Patel N, Kellett GL J Physiol. 2007;582:379–92.
Mace OJ, Lister N, Morgan E, Shepherd E, Affleck J, Helliwell P, Bronk JR, Kellett GL, Meredith D, Boyd R, Pieri M, Bailey PD, Pettcrew R, Foley D J Physiol. 2009;587:195–210.
Margolskee RF. J Biol Chem. 2002;277:1–4.
Margolskee RF, Dyer J, Kokrashvili Z, Salmon KSH, Ilegems E, Daly K, Maillet EL, Ninomiya Y, Mosinger B, Shirazi-Beechey SP Proc Natl Acad Sci USA. 2007;104:15075–80.
Matsumoto M, Hikosaka O Nature. 2007;447:1111–5.
Mei N, Garnier L J Auton Nerv Syst. 1986;16:159–70.
Nelson G, Chandrashekar J, Hoon MA, Feng L, Zhao G, Ryba NJ, Zuker CS Nature. 2002;416:199–202.
Niijima A. J Nutr. 2000;130:971S–73S.
Niijima A, Meguid MM Obes Res. 1995;3:741S–45S.
Nishijo H, Uwano T, Tamura R, Ono T J Neurophysiol. 1998;79:21–36.
Reeds PJ, Burrin DG, Stoll B, Jahoor F J Nutr. 2000;130:978S–82S.
San Gabriel A, Uneyama H, Yoshie S, Torii K Chem Senses. 2005;30:i25–i26.
San Gabriel AM, Maekawa T, Uneyama H, Yoshie S, Torii K FEBS Lett. 2007;581:1119–23.
Sclafani A. Physiol Behav. 2004;81:773–79.
Shibata R, Kameishi M, Kondoh T, Torii K Physiol Behav. 2009;96:667–74.
Smriga M, Murakami H, Mori M, Torii K Physiol Behav. 2000;71:403–7.
Torii K, Mimura T, Yugari Y In: Kawamura Y, Kare MR editors. Umami: a basic taste. New York: Marcel Dekker; 1987. p. 513–563.
Tsurugizawa T, Kondoh T, Torii K Neuroreport. 2008;19:1111–5.

Tsurugizawa T, Uematsu A, Nakamura E, Hasumura M, Hirota M, Kondoh T, Uneyama H, Torii K Gastroenterology. 2009;137:262–73.

Uematsu A, Tsurugizawa T, Kondoh T, Torii K Neurosci Lett. 2009;451:190–3.

Uneyama H, Niijima A, San Gabriel A, Torii K Am J Physiol Gastrointest Liver Physiol. 2006;291:G1163–70.

Viarouge C, Caulliez R, Nicolaidis S Physiol Behav. 1992;52:879–84.

Wu SV, Rozengurt N, Yang M, Young SH, Sinnett-Smith J, Rozengurt E Proc Natl Acad Sci USA. 2002;99:2392–7.

Yamaguchi S, Ninomiya K J Nutr. 2000;130:921S–6S.

Yamamoto T. Arch Histol Cytol. 2006;69:243–55.

Young VR, Ajami AM J Nutr. 2000;130:892S–900S.

Chapter 32
Oral Administration of Phosphatide Precursors Enhances Learning and Memory by Promoting Synaptogenesis

Mehmet Cansev and Ismail H. Ulus

Abbreviations

PUFA   Polyunsaturated fatty acid
DHA   Docosahexaenoic acid
EPA   Eicosapentaenoic acid
AA   Arachidonic acid
UMP   Uridine-5′-monophosphate
UDP   Uridine-5′-diphosphate
UTP   Uridine-5′-triphosphate
CMP   Cytidine-5′-monophosphate
CDP   Cytidine-5′-diphosphate
CTP   Cytidine-5′-triphosphate
PC   Phosphatidylcholine
PE   Phosphatidylethanolamine
PS   Phosphatidylserine
PI   Phosphatidylinositol
SM   Sphingomyelin
DAG   Diacylglycerol

32.1 Introduction

Phosphatides are major constituents of brain membranes, particularly of synaptic membranes. Synthesis of phosphatidylcholine (PC), the major brain membrane phosphatide, requires uptake into brain of various circulating precursors. These precursors include the pyrimidines uridine and cytidine; polyunsaturated fatty acids (PUFA), particularly the omega-3 PUFA docosahexaenoic acid (DHA); and choline.

Animals exhibit improvements in cognitive behaviors if they are treated for several weeks with food constituents normally present in the blood – uridine, DHA, and choline (Teather and Wurtman 2006; Holguin et al. 2008a, 2008b). These improvements are associated with biochemical and structural

M. Cansev (✉)
Uludag University Medical School, Department of Pharmacology,
Gorukle, 16059 Bursa, Turkey
e-mail: mcansev@uludag.edu.tr

changes in the brain. For example, the amounts of brain phosphatides that are formed from these compounds increase significantly (Wurtman et al. 2006; Cansev and Wurtman 2007). Parallel changes are observed in levels of proteins known to be associated with pre- and postsynaptic membranes (e.g., PSD-95; synapsin-1), but not the amount of a ubiquitous structural protein, beta-tubulin (Wurtman et al. 2006; Cansev and Wurtman 2007). In addition, the brains show such signs of enhanced synaptic activity as increased numbers of dendritic spines (Sakamoto et al. 2007) and increased release of certain neurotransmitters (Wang et al. 2005, 2007). In addition, the treatment has been shown in a recent clinical trial to improve cognitive functions in Alzheimer's disease (Scheltens et al. 2008), a neurodegenerative disease that associates the loss of synapses.

This review considers the behavioral consequences with regard to learning and memory of consuming these food constituents by showing evidence on the involvement of such biochemical mechanisms as increased quantity of synaptic membrane, and perhaps enhanced number of brain synapses. These mechanisms appear to involve an essential kinetic property – poor affinities for their substrates – of some of the brain enzymes that transform the three constituents to biologically active products as well as the activation of neuronal receptors by some of the products of the enzymes (e.g., UDP and UTP, which activate various P2Y receptors).

The review starts with brief descriptions of biosynthesis of membrane phosphatides, enzymes that mediate brain phosphatide synthesis, and the availability of phosphatide precursors to brain cells. It then describes the experimental and human studies of learning and memory in order to provide evidence for the behavioral consequences of administering phosphatide precursors and its relation with biochemical and structural alterations in the brain, such as enhanced levels of phosphatides, synaptic proteins, and dendritic spines in adult gerbils as well as rat pups. As no data yet are available on the effects of this or related biochemical treatments on the actual number of synapses, estimates of such numbers must be extrapolated from surrogate measurements, like numbers of dendritic spines which is generally believed to provide the best correlations with the actual number of synapses (Knott et al. 2006).

32.2 Biosynthesis of Membrane Phosphatides

Mammalian cells utilize DHA and other fatty acids, uridine, and choline to form the phosphatide subunits (e.g., PC) which, when aggregated, constitute the major components of their membranes. PC, the principal such subunit in brain, is synthesized from these precursors by the "Kennedy Cycle" (Fig. 32.1). Phosphatidylethanolamine (PE) likewise is synthesized via this pathway, utilizing ethanolamine instead of choline as a precursor, while phosphatidylserine (PS), the third major structural phosphatide, is generated by exchanging a serine molecule for the choline in PC or the ethanolamine in PE.

The Kennedy cycle involves three sequential enzymatic reactions. In the first, catalyzed by choline kinase (CK), a phosphate is transferred from ATP to the hydroxyl oxygen of the choline, yielding phosphocholine. The second, catalyzed by CTP:phosphocholine cytidylyl transferase (CT), transfers cytidylylmonophosphate (CMP) from cytidine-5′-triphosphate (CTP) to the phosphorus of phosphocholine, yielding cytidylyldiphosphocholine (also known as CDP-choline, or citicoline). As discussed next, much of the CTP that the human brain uses for this reaction derives from circulating uridine. The third and last reaction, catalyzed by CDP-choline:1,2-diacylglycerol choline phosphotransferase (CPT), binds the phosphocholine of CDP-choline to the hydroxyl group on the 3 C of diacylglycerol (DAG; particularly DAG containing DHA), yielding the PC. All three of these PC precursors must be obtained by brain entirely (DHA) or in large part (uridine; choline) from the circulation, and do in fact readily cross the blood–brain barrier (BBB; reviewed in Wurtman et al. 2009). Moreover, because the PC-synthesizing enzymes that act on all three have low affinities for them, treatments that increase blood levels of all three can affect the overall rate of PC synthesis.
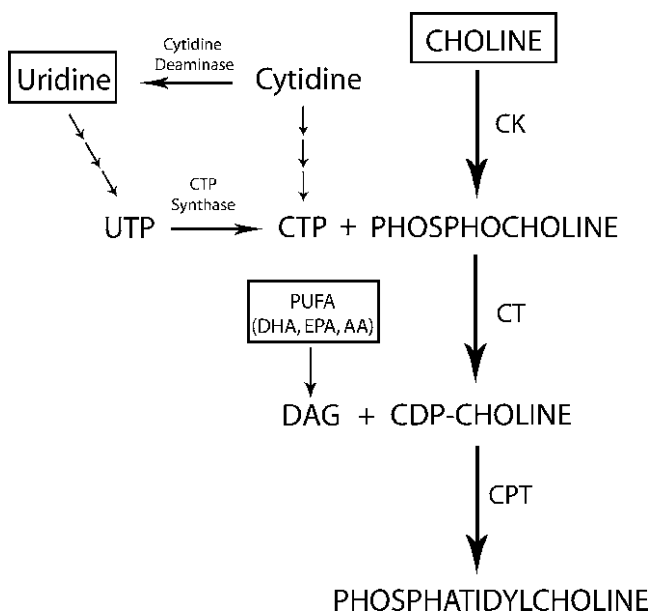
Fig. 32.1 Phosphatidylcholine (PC) biosynthesis via the Kennedy cycle. In rats, plasma cytidine is the major circulating pyrimidine; in gerbils and humans, the primary circulating pyrimidine is uridine. Only small amounts of circulating cytidine are converted to brain CTP, since the blood–brain barrier (BBB) is a high-affinity transporter for pyrimidines (CNT2) and has a very low affinity for cytidine; uridine, in contrast, readily enters the brain via CNT2, yielding UTP which can then be converted to CTP by CTP synthase (Cansev 2006). CTP then reacts with phosphocholine to form endogenous CDP-choline, which combines with diacylglycerol (DAG), preferentially species containing PUFAs like DHA, EPA, or AA to form PC. Boxes indicate the compounds that are obtained from the circulation (From Cansev and Wurtman 2007)

The ability of each of the three circulating phosphatide precursors to affect the rate of phosphatide synthesis results principally from the low affinities of the enzymes for which these nutrients are substrates. CK has a very low affinity for its choline substrate; its *Km* for choline in brain (which, of course, describes the choline concentrations at which the CK operates at only half-maximal velocity) is reportedly 2.6 mM, whereas brain choline levels are only about 30–60 μM (Wurtman et al. 2009). *Km* values of CT for CTP and phosphocholine in brains of laboratory rodents and humans are reportedly 1–1.3 mM and 0.30–0.31 mM, respectively, while brain levels of these compounds are only 70–110 μM and 0.32–0.69 mM, respectively (Wurtman et al. 2009). The choline phosphotransferase reaction catalyzed by CPT also is unsaturated with the enzyme's substrates: its *Km* values for CDP-choline and DAG in rat liver are 200 and 150 μM, respectively, while the concentrations of these compounds in liver are approximately 40 and 300 μM. (A DAG concentration of at least 1,000 μM thus would probably be needed to saturate the enzyme.) Brain CDP-choline and DAG levels are even lower, i.e., about 10–30 and 75 μM, respectively (Wurtman et al. 2009).

32.3 Availability of Phosphatide Precursors to Brain Cells

32.3.1 Choline

Mammalian brains contain choline as the free base; as water-soluble phosphorylated metabolites, phosphocholine and glycerophosphocholine (Nitsch et al. 1992), and as constituents of membrane, phospholipids including PC, sphingomyelin, and lyso-PC. Free choline molecules in the brain derive

from four known sources – uptake from the plasma; liberation from the PC in brain membranes; high affinity uptake from the synaptic cleft after acetylcholine released from a cholinergic terminal has been hydrolyzed; and, probably to a minor extent, the breakdown of newly synthesized PC formed from the methylation of PE.

The brain can obtain circulating choline via two routes: small amounts can pass from the blood to the cerebrospinal fluid through the action of a specific transport protein, organic cation transporter 2 (OCT2), which is present in cells that line the choroid plexus (Sweet et al. 2001). However orders of greater magnitude pass bidirectionally between the blood and the brain's extracellular fluid (ECF) by facilitated diffusion. This process is catalyzed by a different transport protein, not yet cloned, which is localized within the endothelial cells that line the brain's capillaries (Oldendorf and Braun 1976). The protein is unsaturated at physiological plasma choline concentrations, and its net activity is affected by variations in these concentrations. It might constitute a kind of pore through which choline can pass in either direction, based on the gradient between its blood and brain levels. It has been estimated that the plasma choline concentration in rats required in order for the net choline flux to pass from blood to brain is about 15 μM; below this concentration net choline flux presumably is from brain to blood (Klein et al. 1990).

Once circulating choline has entered the brain's ECF it can be taken up into all cells by a low affinity transport protein (Km = 30–100 μM), or into cholinergic nerve terminals by a high affinity uptake protein (Km = 0.1–10 μM; Wurtman et al. 2009).

Besides the uptake from blood, brain free choline is derived from other sources including liberation of choline in membrane PC through the actions of the phospholipase enzymes, phospholipase C and D, which catalyze the hydrolysis of various bonds between PC's three oxygen molecules and fatty acids or its phosphate moiety; rapid hydrolysis of acetylcholine released into synapses to free choline and acetate; and breakdown of newly synthesized PC formed from the methylation of PE.

32.3.2 Uridine and Cytidine

Uridine and cytidine are transported across cell membranes, including the BBB, via two families of transport proteins, i.e., the Na⁺-independent, low affinity, equilibrative transporters (ENT1 and ENT2) and the Na⁺-dependent, high affinity, concentrative (CNT1, CNT2, and CNT3) nucleoside transporters (reviewed in Cansev 2006). Inasmuch as their Km values for the pyrimidines are in the high micromolar range (100–800 μM) they probably mediate BBB pyrimidine uptake only when plasma levels of uridine and cytidine have been elevated experimentally. In contrast, CNT2, which transports both the pyrimidine uridine and purines such as adenosine, probably does mediate uridine transport across the BBB under physiologic conditions (Cansev 2006). CNT2 can also transport cytidine, however with a much lower affinity than that for uridine (Cansev 2006).

It should be noted that, while both uridine and cytidine are present in the blood of laboratory rats, human blood contains unmeasurably low quantities of cytidine even among individuals consuming a cytidine source like oral CDP-choline (Wurtman et al. 2000); the cytidine is quantitatively deaminated to uridine in the human liver. Hence, in humans, circulating uridine, and not cytidine, is the precursor of the brain CTP utilized for phosphatide synthesis. Gerbil blood contains both of the pyrimidines, but proportionately less cytidine than blood of rats; hence, gerbils are often used as a model for studying the effects of uridine sources on the human brain.

Like other circulating compounds, pyrimidines may also be taken up into brain via the epithelium of the choroid plexus (CP) and the ENT1, ENT2, and CNT3 transporters; all of these proteins have

been found in CP epithelial cells of rats and rabbits (Cansev 2006). However, the surface area of BBB is probably 1,000 times that of the CP epithelium (i.e., 21.6 m² vs 0.021 m² in humans); hence, the BBB is the major locus at which circulating uridine enters the brain.

Uridine and cytidine are converted to their respective nucleotides by successive phosphorylations catalyzed by various kinases. Uridine-cytidine kinase (UCK; ATP:uridine 5′-phosphotransferase, EC 2.7.1.48) phosphorylates uridine and cytidine to form UMP and CMP, respectively. UMP-CMP kinase (UMP-CMPK; ATP:CMP phosphotransferase, EC 2.7.4.14) then converts UMP or CMP to UDP or CDP. These nucleotides are further phosphorylated to UTP and CTP by nucleoside diphosphate kinases (NDPK). Various interconversions between uridine and cytidine, and between their respective nucleotides, are known to occur in mammalian cells. Cytidine and CMP can be deaminated to uridine and UMP, while UTP is aminated to CTP by CTP synthase (UTP:ammonia ligase (ADP-forming), EC 6.3.4.2). This enzyme acts by transferring an amide nitrogen from glutamine to the C4 position of UTP, thus forming CTP.

All the enzymes described above apparently are unsaturated with their respective nucleoside or nucleotide substrates in normal brain. For example, the *Km* values for uridine and cytidine of UCK prepared from various tissues varied between 33 and 270 μM, and the *Km* for uridine of recombinant enzyme cloned from mouse brain was 40 μM (Wurtman et al. 2009). Brain uridine and cytidine levels are about 22–46 pmol/mg wet weight and 6–43 pmol/mg wet weight, respectively. Hence, the syntheses of UTP and CTP, and the subsequent syntheses of brain PC and PE via the Kennedy pathway, depend on available levels of their pyrimidine substrates. Indeed, increasing the supply of uridine or cytidine to neuronal cells, in vitro or in vivo, enhanced the phosphorylation of uridine and cytidine, and elevated cell and tissue levels of UTP, CTP, and CDP-choline (Wurtman et al. 2009).

32.3.3 DHA and Other PUFA

The omega-3 polyunsaturated fatty acids DHA and eicosapentaenoic acid (EPA), and the omega-6 fatty acid arachidonic acid (AA) are essential for humans and other animals, and must be obtained from the diet either as such or as their also-essential precursors, alpha-linolenic acid (ALA) and linoleic acid (LA). PUFAs enter the brain probably by both simple diffusion (Kamp et al. 1993) and protein-mediated transport (Abumrad et al. 1984). DHA, EPA, and AA are then transported from the brain's ECF into cells, and can be activated to their corresponding CoA species (e.g., docosahexaenoyl-CoA; eicosapentaenoyl-CoA; arachidonoyl-CoA) and acylated to the sn-2 position of DAG to form PUFA-rich DAG species.

DHA is acylated by a specific acyl-CoA synthetase, Acsl6 (Marszalek et al. 2005) which exhibits a low affinity for this substrate (*Km* = 26 μM); relative to usual brain DHA levels (1.3–1.5 μM). Hence, treatments that raise blood DHA levels rapidly increase its uptake into and retention by brain cells and its availability for incorporation into PC. EPA can also be acylated to DAG by the acyl-CoA synthetase or it can be converted to DHA by brain astrocytes, allowing its effects on brain phosphatides and synaptic proteins to be mediated by DHA itself. Exogenously administered AA, like DHA, is preferentially incorporated into brain phosphatides, as well as into other lipids, e.g., the plasmalogens. AA shares with DHA the ability to activate syntaxin-3 (Darios and Davletov 2006); however, as described next, its oral administration to laboratory rodents apparently does not promote phosphatide or synaptic membrane synthesis (Cansev and Wurtman 2007), the formation of dendritic spines (Sakamoto et al. 2007), nor improve rodent cognitive processes (Sarah Holguin, personal communication).

DHA and AA are major components of brain membrane phospholipids. While AA is widespread throughout the brain and is abundant in phosphatidylinositol (PI) and PC, DHA is concentrated in synaptic regions of gray matter and is especially abundant in PE and PS. EPA is found only in trace amounts in brain phosphatides, mostly in PI.

The ability of orally administered DAG, given daily for several weeks, to increase brain phosphatide levels does not necessarily imply that the quantities of DHA in the phosphatides, relative to those of other fatty acids, also are increased. Indeed this has not been demonstrated. Conceivably, DHA-rich DAG is preferentially utilized for PC synthesis, but once the DAG-containing PC is formed it is rapidly hydrolyzed to form lyso-PC lacking DHA and then reacylated to PC by addition of a different fatty acid.

32.4 Effects of Phosphatide Precursor on Learning and Memory

32.4.1 Experimental Studies

Experimental evidence indicates that chronic administration of phosphatide precursors enhances cognitive function and ameliorates impairments in memory. A UMP-supplemented diet (0.1%) can reverse the memory impairments observed among rats reared under impoverished environmental conditions (Teather and Wurtman 2006). DHA administration ameliorates the impairment of spatial cognition learning ability in β-amyloid-infused rats (Hashimoto et al. 2002, 2005) or in aged rats (Kotani et al. 2006). Giving aging mice a choline-rich diet chronically counteracts the age-associated decline in learning and memory (Golczewski et al. 1982). Perinatal supplementation with choline causes long-lasting improvements in spatial memory (Meck and Williams 1999) and protects memory impairments associated with normal aging (Tees 1999), prenatal alcohol exposure (Thomas et al. 2004), or epileptic seizures (Holmes et al. 2002).

Coadministration of these phosphatide precursors further enhances their effects on memory, learning, and cognitive functions (De Bruin et al. 2003; Teather and Wurtman 2003, 2005; Holguin et al. 2008a, 2008b). Chronic uridine supplementation, combined with choline, normalizes cognitive deficits in spontaneously hypertensive rats (De Bruin et al. 2003). Dietary administration of CDP-choline, a drug which provides both choline and cytidine/uridine (Wurtman et al. 2000), protects against the development of memory deficits in aging (Teather and Wurtman 2003), and prevents memory impairments caused by impoverished environmental conditions (Teather and Wurtman 2005). Among socially impoverished rats chronic (4 weeks) dietary supplementation of uridine (as its monophosphate, UMP; 0.5%) and choline (0.1%) enhances the improvement in learning and memory produced by administering DHA (300 mg/kg/day) in gerbils (Holguin et al. 2008a). UMP plus DHA and choline significantly enhances cognitive function in normal adult gerbils (Holguin et al. 2008b).

32.4.2 Human Studies

CDP-choline improves verbal memory in aging (Spiers et al. 1996) and benefits memory in elderly subjects (Alvarez et al. 1997).

One study has examined effects on humans of daily consumption of a liquid mixture (Souvenaid™) containing UMP, DHA, choline, and additional nutrients that promote endogenous choline synthesis, suppress auto-oxidation, and/or enhance the solubility of other ingredients. This randomized, controlled,

double-blind, parallel group, multicenter, multicountry trial (the Dutch Trial Registry, No: ISRCTN 72254645), involving 212 drug-naïve subjects with mild Alzheimer's disease and directed by Prof. Phillip Scheltens examined the treatment's effects on a delayed verbal memory task and the 13-item modified Alzheimer's Disease Assessment Scale-cognitive subscale at 12 weeks. In the group receiving Souvenaid a significant benefit was found in mild and very mild Alzheimer's disease patients on the delayed verbal memory task (Scheltens et al. 2008).

32.5 Relation of Enhancement in Learning and Memory with Enhanced Synaptogenesis

Learning and memory result from changes in the neural representation of stimuli through plastic events that modify the way neurons communicate with each other. Morphological change events including alterations in the structure, distribution, and number of synapses underlie memory formation. Accumulating evidence suggests that synapse formation is a major factor contributing to cognitive functions like learning and memory (Ramirez-Amaya et al. 2001). On the contrary, loss of synapses is generally believed to underlie the impaired learning and memory in degenerative diseases of the brain like Alzheimer's (Selkoe 2002).

Our previous studies demonstrated that chronic administration of various phosphatide precursors (uridine, DHA, and choline) to experimental animals induced biochemical and morphological changes in pre- and postsynaptic regions. For example, the amounts of brain phosphatides and of proteins (e.g., PSD-95; synapsin-1) known to be associated with pre- and postsynaptic membranes increased significantly (Wurtman et al. 2006). Uridine or UMP treatment also enhanced release of certain neurotransmitters (e.g., acetylcholine, dopamine) in brains of laboratory rodents. In addition, numbers of dendritic spines in CA1 region of the hippocampus were increased by this treatment. Since spine changes are associated with learning and memory (Muller et al. 2000), summarized next, the biochemical and structural alterations observed in the brain after chronic treatment with phosphatide precursors are likely to lead to the abovementioned enhanced cognitive functions in normal and in environmentally impoverished animals and Alzheimer's patients.

32.6 Effects of Phosphatide Precursors on Levels of Brain Phosphatides and Synaptic Proteins in Adult Gerbils and Rat Pups

If adult gerbils are given a standard diet supplemented with choline and uridine (as its monophosphate, UMP) and, also, by gavage, DHA, brain PC synthesis rapidly increases and absolute levels of PC per cell (i.e., DNA) or per mg protein rise substantially (e.g., by 40–50% after several weeks of daily treatment; Wurtman et al. 2006; Cansev and Wurtman 2007; (Table 32.1). Similar increases in levels of membrane phosphatides are observed if DHA in the diet is replaced by another omega-3 PUFA EPA, but not the omega-6 PUFA AA (Table 32.2). This treatment also increases the levels of particular proteins known to be localized within pre- and postsynaptic membranes (e.g., synapsin-1, PSD-95) and syntaxin-3 (Fig. 32.2), but not of β-tubulin, a ubiquitously distributed protein (Wurtman et al. 2006; Cansev and Wurtman 2007). As seen in Fig. 32.2, EPA shares the property of enhancing levels of synaptic proteins with DHA, while AA fails to alter such parameters (Cansev and Wurtman 2007).

Table 32.1 Effects of various PUFA, given with a UMP-supplemented diet, on gerbil brain phosphatide levels. Data are nmol/mg protein (From Cansev and Wurtman 2007)

	Total PL	PC	PE	PS	PI
UMP diet + vehicle	332 ± 7	131 ± 2	70 ± 1	29 ± 1	16 ± 1
UMP diet + AA	379 ± 21	132 ± 3	81 ± 6	31 ± 3	20 ± 2
UMP diet + DHA	384 ± 7*	147 ± 3**, y	88 ± 2**	39 ± 2**	22 ± 1**
UMP diet + EPA	407 ± 7***	148 ± 2**, y	91 ± 1***	41 ± 2**, x	25 ± 1***

Groups of gerbils were given a UMP-containing (0.5%) diet, and received by gavage AA, DHA, or EPA (each 300 mg/kg; in a vehicle of 5% gum Arabic solution) or just its vehicle for 28 days. On the 29th day their brains were assayed for phosphatides. Data are given as means ± SEM

*$P < 0.05$, **$P < 0.01$, and ***$P < 0.001$ compared to Control diet + Vehicle group

[x]$P < 0.05$ and [y]$P < 0.01$ compared to UMP diet + AA group by one-way ANOVA

In addition to the findings in adult animals, if the combination of uridine, DHA, and choline is administered chronically to rat dams from prenatal 10th day (E10) through weanling (postnatal 21st day; P21) levels of phosphatides also are increased in brains of weanling rat pups (Cansev et al. 2009) (Table 32.3). Likewise, levels of synaptic proteins (Synapsin-1, mGluR1, and PSD 95) in weanling rat pups also are increased following treatment of their dams chronically with the combination of uridine, DHA, and choline (Cansev et al. 2009) (Fig. 32.3).

32.7 Effects of Phosphatide Precursors on Dendritic Spine Formation and Synaptogenesis in Adult Gerbils and Rat Pups

Numbers of mature dendritic spines in particular brain regions are highly correlated with numbers of synapses (Knott et al. 2006) and it has been proposed (Toni et al. 1999) that "more than 90% of excitatory synapses occur on dendritic spines." This suggests that processes that damage the spines (e.g., β-amyloid; amyloid plaques or that increase spine number; treatment with uridine, DHA, and choline, discussed next) will cause parallel changes in synapse number. The formation of dendritic spines is induced physiologically by synaptic inputs that induce long-term potentiation in CA1 pyramidal neurons, probably mediated by enhanced calcium influx into the postsynaptic neuron.

The effects of administering the phosphatide precursors DHA (300 mg/kg) and uridine (as UMP, 0.5%) on dendritic spine number (in CA1 pyramidal hippocampal neurons) were examined in adult gerbils treated daily for 1–4 weeks; animals received one or both compounds. DHA alone caused dose-related increases in spine density; its effect was doubled if animals also received UMP (Sakamoto et al. 2007) (Fig. 32.4). In contrast, administration of AA with or without uridine had no effect on spine density like its effects on phosphatide or synaptic protein levels. DHA administration has been described as promoting cognition (Hashimoto et al. 2002, 2005) yet its effects on neurotransmission have been obscure. Perhaps its effect on cognition is mediated in part by the increases it produces in numbers of dendritic spines or synapses.

Similar studies were performed on pregnant rats and their offspring (Cansev et al. 2009). The dams consumed UMP, DHA, or both compounds for 10 days prior to parturition and 21 days while nursing. By day 21, brains of weanlings exhibited significant increases in hippocampal dendritic spine density (Cansev et al. 2009) (Fig. 32.5).
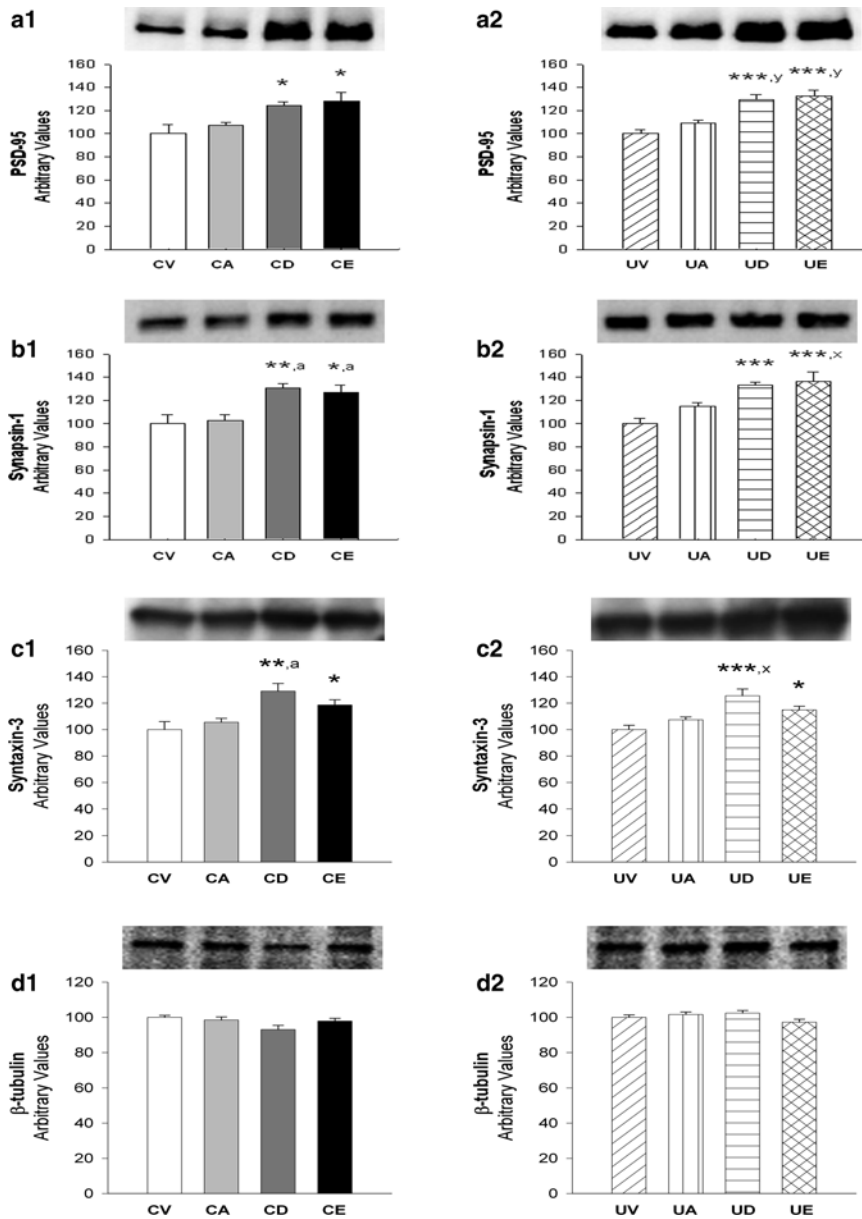
Fig. 32.2 Effects of AA, DHA, or EPA, alone or in combination with a UMP-supplemented diet, on levels of the presynaptic or postsynaptic proteins PSD-95 (a1, a2); synapsin-1 (b1, b2) and syntaxin-3 (c1, c2). CV, control diet + vehicle; CA, control diet + AA; CD, control diet + DHA; CE, control diet + EPA; UV, UMP-supplemented diet + vehicle; UA, UMP-supplemented diet + AA; UD, UMP-supplemented diet + DHA; UE, UMP-supplemented diet + EPA. *$P < 0.05$, **$P < 0.01$, and ***$P < 0.001$ compared with CV, and $^{a}P < 0.05$ compared with CA on the left-sided columns (a1, b1, and c1) using one-way ANOVA. *$P < 0.05$, **$P < 0.01$, and ***$P < 0.001$ compared with UV, and $^{x}P < 0.05$ and $^{y}P < 0.01$ compared with UA on the right-sided columns (a2, b2, and c2) using one-way ANOVA (From Cansev and Wurtman 2007)

Table 32.2 Effects of various PUFA, given with a control diet, on gerbil brain phosphatide levels (Data are nmol/mg protein)

	Total PL	PC	PE	PS	PI
Control diet + Vehicle	322 ± 3	113 ± 3	63 ± 3	25 ± 1	15 ± 1
Control diet + AA	326 ± 5	114 ± 1	65 ± 2	28 ± 1	16 ± 1
Control diet + DHA	344 ± 13	133 ± 6*	77 ± 4*	32 ± 2***	18 ± 1*
Control diet + EPA	347 ± 6	125 ± 8	76 ± 4*	31 ± 1**	19 ± 1**,[a]
[b]UMP diet + Vehicle	332 ± 7	131 ± 2*	70 ± 1	29 ± 1*	16 ± 1

Groups of gerbils were given a control diet, and received by gavage AA, DHA, or EPA (300 mg/kg; in a vehicle of 5% gum Arabic) or just its vehicle for 28 days. On the 29th day their brains were assayed for phosphatides. Data are given as means ± SEM

*$P < 0.05$; **$P < 0.01$; and ***$P < 0.001$ compared to Control diet + Vehicle group

[a]$P < 0.05$ compared to Control diet + AA group by one-way ANOVA

[b]Data from gerbils receiving the UMP diet but no PUFA are included in the table to illustrate that uridine alone also affects phosphatide levels.

Table 32.3 Key features of phosphatide precursors

Precursor	Key features
Choline	Choline is a water-soluble essential nutrient and a natural amine that is found in membrane lipids and is a precursor for the neurotransmitter acetylcholine. Choline is found in blood and in tissues.
Uridine	Uridine is a pyrimidine nucleoside which is involved in syntheses of nucleic acids, glycogen, membrane phosphatides, and is a ligand to various P2Y receptors after being phosphorylated to UDP or UTP. Uridine is the major circulating pyrimidine in humans.
Cytidine	Cytidine is a pyrimidine nucleoside which, after being phosphorylated to CTP within the cell, determines the usual limiting step in phosphatide synthesis. Cytidine is almost undetectable in human blood and its nucleotides have not yet been shown to activate P2Y receptors to an extent that can induce a cellular response.
DHA	DHA is an omega-3 essential fatty acid with a 22-carbon chain and 6 *cis* double bonds (22:6n−3). It is found in fish oil and small amounts can be synthesized from alpha-linolenic acid. DHA is incorporated into sn-2 position of phosphatides thus serving as a phosphatide precursor. It is essential in the development of nervous system and retina and is known to help lower heart disease.
EPA	EPA is an omega-3 essential fatty acid with a 20-carbon chain and 5 *cis* double bonds (20:5n−3). It is found in fish oil and small amounts can be synthesized from alpha-linolenic acid. EPA also serves as a phosphatide precursor by incorporating into sn-2 position of phosphatides.
AA	AA is an omega-6 essential fatty acid that has a 20-carbon chain and 4 *cis* double bonds (20:4n−6). AA can be obtained from dietary animal sources and be synthesized in the body from linoleic acid.

Key facts of phosphatide precursors have been listed

32.8 Effects of Uridine or UMP on Neurotransmitter Release

Consumption by rats of a diet containing uridine (as UMP) and choline can increase dopamine (DA) and ACh levels in, and – as assessed using in vivo microdialysis – their release from, corpus striatum neurons. Dietary supplementation of aged male Fischer 344 rats with 2.5% w/w UMP for 6 weeks, ad libitum, increased the release of striatal DA that was evoked by potassium-induced depolarization from 283 ± 9% in control rats to 341 ± 21% in those receiving the UMP ($P < 0.05$; Wang et al. 2005). Giving both uridine and DHA amplifies uridine's effect on dopamine levels (Cansev et al. 2008).

In general, each animal's DA release correlated with its striatal DA content, measured postmortem. The levels of neurofilament-70 and neurofilament-M proteins, two markers of neurite outgrowth, were also increased after UMP treatment, to 182 ± 25% of control levels for the neurofilament-70 ($P < 0.05$) and to 221 ± 34% ($P < 0.01$) for the neurofilament-M (Wang et al. 2005).

In a similar microdialysis study, ACh release, basally as well as after administration of atropine (a muscarinic antagonist which blocks inhibitory presynaptic cholinergic receptors), was found to be enhanced following UMP consumption. Among aged animals consuming a 2.5% diet for 1 or 6
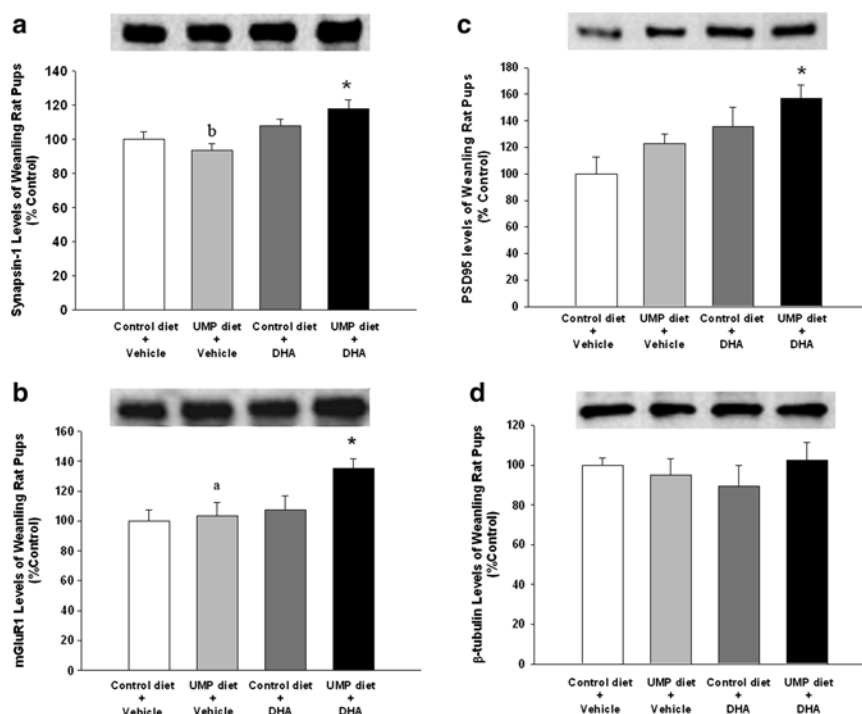
Fig. 32.3 Levels of synaptic proteins in weanling pups (P21). Dams were treated and brains of weanling pups were obtained. Samples were analyzed for (**a**) synapsin-1, (**b**) mGluR1, (**c**) PSD-95, and (**d**) β-tubulin using Western Blotting. $N = 6$ per each group. *$P < 0.05$ compared with "Control" group and [a]$P < 0.05$, [b]$P < 0.01$ versus "UMP diet + DHA" group using one-way ANOVA followed by Tukey's test. (From Cansev et al. 2009)

weeks, baseline ACh levels in striatal microdialysates rose from 73 to 148 fmol/min after 1 week of treatment ($P < 0.05$), and to 197 fmol/min after 6 weeks ($P < 0.05$) (Wang et al. 2007). A lower dose of dietary UMP (0.5%, 1 week) also amplified the increase in ACh release caused by giving atropine (10 μM, via the artificial CSF); atropine alone increased ACh concentrations from 81 to 386 fmol/min in control rats and from 127 to 680 fmol/min in those consuming UMP ($P < 0.05$; Wang et al. 2007). Young rats eating the UMP-containing diet exhibited similar responses. These data suggest that giving a uridine source may enhance some cholinergic functions, perhaps by increasing the amount of synaptic membrane, or the quantities of ACh stored in synaptic vesicles. Apparently, no data are available on effects of UMP plus DHA on neurotransmitter release.

32.9 Possible Involvement of Uridine-Nucleotide-Stimulated P2Y Receptor Activation

Administration of uridine results in increased levels of cellular proteins, specifically of certain pre- and postsynaptic neuronal proteins most likely by a second mechanism in which uridine's phosphorylated products act as ligands for P2Y receptors which then activate protein synthesis and normal neuronal differentiation.

Extracellular nucleotides can serve as ligands for various ionotropic P2X and metabotropic P2Y receptors. While P2X receptors recognize adenine nucleotides, P2Y receptors can recognize both adenine and uridine nucleotides. Members of the P2Y family, G-protein-coupled receptors, are

Fig. 32.4 Dendritic spine formation in adult gerbil hippocampus is enhanced by cosupplementation of DHA with UMP. (**a**) Apical dendrites of CA1 pyramidal neurons. (**b**) DHA supplementation increased spine density (by 19%, *$P = 0.004$ vs Control); both DHA and UMP caused a greater increase (by 36%, **$P < 0.001$ vs Control or by 17%, $P = 0.008$ vs. DHA). $n = 20–25$ neurons from four animals per group. One-way ANOVA followed by Tukey's test. (**c**) The treated groups received both UMP (0.5%) and DHA (300 mg/kg) daily for 1, 2, 3, or 4 weeks; the control groups were given only a regular diet. $n = 12–20$ neurons from two animals per group. Two-way ANOVA followed by Tukey's test. *$P = 0.02$ and **$P < 0.001$ (From Sakamoto et al. 2007)
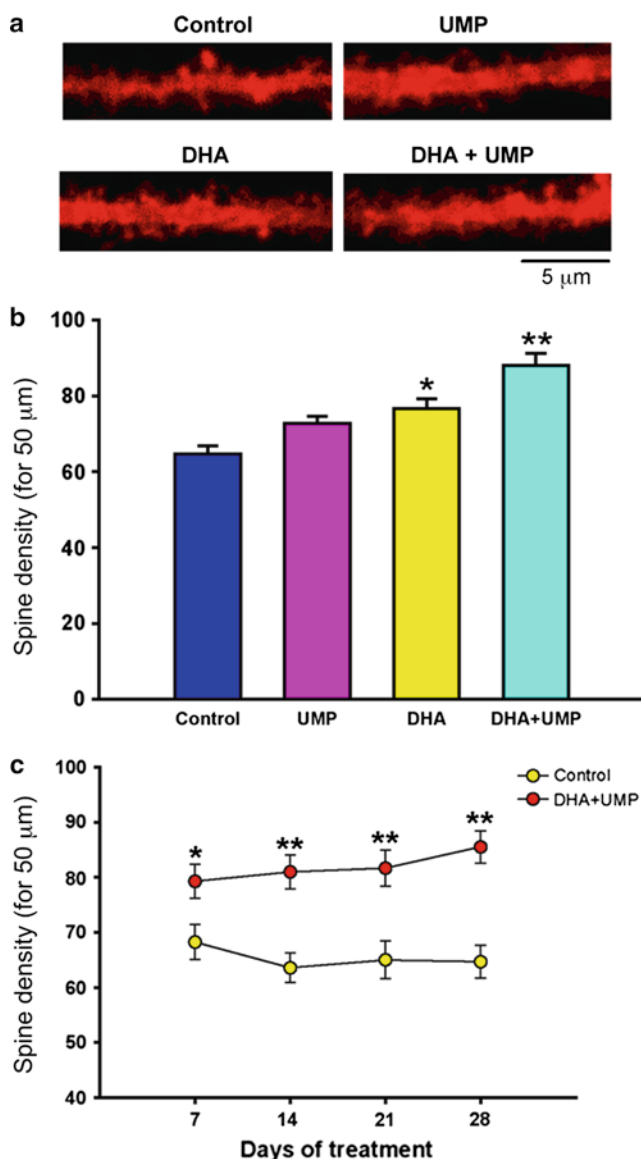
widely distributed throughout the body, including in the brain (Burnstock 2007). To date, eight P2Y receptors of human origin (P2Y1, 2, 4, 6, 11, 12, 13, 14) have been cloned and characterized (Abbracchio et al. 2006).

P2Y receptors that recognize adenine but not uridine nucleotides, and comprising the P2Y1, P2Y11, P2Y12, and P2Y13 subtypes, exist principally outside the brain (Abbracchio et al. 2006). P2Y2 receptors, in contrast, are abundant in brain and are activated by UTP or ATP; P2Y4 receptors are activated by UTP, and P2Y6 receptors by UDP (Abbracchio et al. 2006). Their activation, through coupling to phospholipase C (PLC), increases intracellular concentrations of DAG, IP3, and calcium (Cansev 2007).

That uridine nucleotides affect both neurite outgrowth and neuronal differentiation by stimulating P2Y receptors has been demonstrated mainly by using in vitro assay systems (Cansev 2007). UTP increases neurite outgrowth by Nerve Growth Factor-stimulated PC-12 cells and the expression of some neurofilament proteins (Pooler et al. 2005). The uridine nucleotides also cause receptor-mediated neuronal proliferation and differentiation (e.g., of dopaminergic neurons during development [Milosevic et al. 2006]),
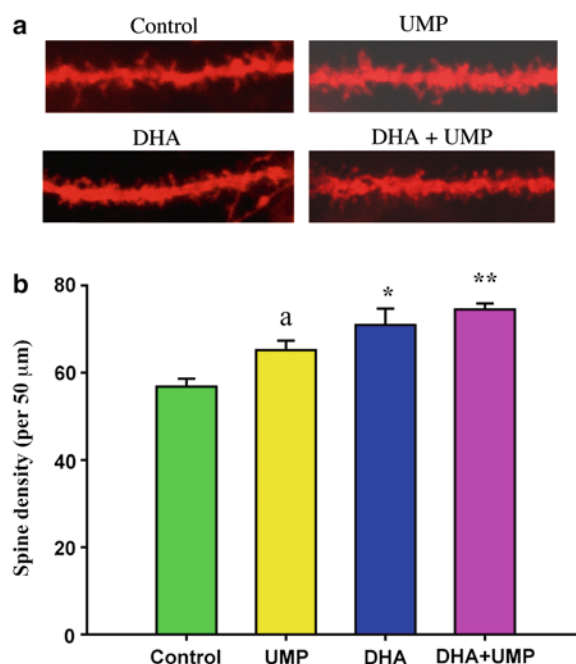
Fig. 32.5 Hippocampal dendritic spine density in weanling pups (P21). Rat dams received UMP (0.5%), DHA (300 mg/kg), or both daily from E10 to P21 (weaning); their pups were examined for CA1 spine density at P21. (**a**) Apical dendrites of CA1 pyramidal neurons. (**b**) Changes in dendritic spine density following UMP and/or DHA administration. $*P < 0.01$ and $**P < 0.001$ compared with the "Control" group and $^aP < 0.05$ versus "UMP diet + DHA" group using one-way ANOVA followed by Tukey's test. $n = 15–21$ neurons from 4 animals per group (From Cansev et al. 2009)

and can mediate signaling events such as release of the neurotransmitters noradrenaline and glutamate (Boehm et al. 1995; Von Kugelgen et al. 1999), long-term potentiation (Price et al. 2003), and neuroprotection (Cansev 2007). Such P2Y-receptor-mediated actions could argue for the possible utility of P2Y agonists in enhancing learning and memory and in treating Alzheimer's disease, especially since P2Y2 receptors are known to be deficient in parietal cortex of Alzheimer's disease brains (Lai et al. 2008).

32.10 Conclusions

Chronic oral administration of membrane phosphatide precursors – uridine, DHA, and choline – enhances learning and memory and improves diminished cognitive performance in both experimental animals as well as patients with Alzheimer's disease. The enhancement in cognitive performance is likely to be resulted from biochemical and structural changes in the brain. The three Kennedy cycle enzymes that catalyze the formation of brain phosphatides from circulating precursors, and the proteins that take up uridine into the brain and convert it to UTP and CTP, all have low affinities for these substrates and are thus unsaturated. Hence administering these substrates can accelerate the biosynthesis, and elevate brain levels of membrane phosphatides. Moreover brain levels of pre- and postsynaptic proteins and, ultimately, the quantity of synaptic membrane and the formation of additional dendritic spines, and, therefore, numbers of synapses are elevated in animals after such treatment. Since this treatment revealed promising improvements in cognitive functions of Alzheimer's patients in a recent clinical trial, it is reasonable to hypothesize that the treatment results in similar biological changes, leading to enhanced learning and memory in human brain as well.

32.11 Applications to Other Areas of Health and Disease

Although this review focused specifically on the role of phosphatide precursors-induced synaptogenesis in the enhancement of learning and memory, stimulation of membrane phospholipid synthesis and promotion of synaptogenesis in the brain could have several applications to other areas of health and disease. Availability of these precursors (i.e., choline, DHA, and uridine/cytidine) in sufficient amounts is particularly important during the prenatal and postnatal period for normal development of the human brain. Human breast milk contains these precursors in high amounts and their supplementation through infant formulas to preterm and term infants may also be beneficial for normal development and in enhancing long-term learning and memory. By increasing membrane synthesis, phosphatide precursors could prevent, slow, and/or restore the decline in several brain functions that occur physiologically in normal aging due to progressive neuronal and synaptic loss. In addition, since most neurodegenerative diseases are associated with membrane breakdown and loss of neurons and synaptic structures, chronic treatment with phosphatide precursors may also be beneficial in treatment of Parkinson's disease, as well as metabolic, toxic, and ischemic/traumatic brain injuries. Phosphatide precursors affect neuroinflammation and immunity by altering the rate and amount of production of phospholipid-derived lipid mediators (i.e., prostaglandins, resolvins, docosatrienes, neuroprotectins, lysophosphatidylcholine) in brain.

Some of these phosphatide precursors, i.e., DHA and choline, also alter inflammation in the periphery and protect organs from metabolic, toxic, ischemic, and traumatic insults. Dietary intake of DHA and/or choline modulates carcinogenesis and development of atherosclerosis. DHA has important roles in health and disease of retina (i.e., increases visual acuity and protects retinal ganglion cells from toxic insults).

Choline, by acting as a precursor of the neurotransmitter acetylcholine, may increase cholinergic neurotransmission in the central and peripheral cholinergic synapses and may help improve cholinergic functions. Choline, by acting as a methyl donor, alters methylation and related epigenetic effects on gene expression and DNA repairs.

Uridine prevents mitochondrial, hepatic, and hemotopoetic toxicity during antiretroviral drug therapy.

Summary Points

- Chronic oral treatment with phosphatide precursors uridine, DHA, and choline enhances learning and memory in experimental animals, as well as humans with Alzheimer's disease.
- The treatment enhances the amount of membranes in brains of adult and developing rodents.
- The treatment enhances the amount of synaptic proteins in brains of adult and developing rodents.
- The treatment also increases the numbers of dendritic spines in brains of adult and developing rodents.
- Treatment with uridine or UMP stimulates the release of certain neurotransmitters in brains of adult rats.
- These observations suggest that such cognitive functions as learning and memory are enhanced via enhanced synaptogenesis in rodent brain.
- Such morphological alterations are likely to occur in human brain since impaired cognitive functions were partly restored in patients with Alzheimer's disease by the treatment.

Key Terms

Phosphatide: Naturally occurring phospholipids that are derivatives of glycerol phosphate and which normally contain a nitrogenous base. Phosphatides include phosphatidylcholine, phosphatidylethanolamine, phosphatidylserine, and phosphatidylinositol Phosphatidylcholine is the most abundant phosphatide in brain membranes.

Polyunsaturated fatty acid: Fatty acids which have more than 2 *cis* double bonds which are separated from each other by a single methylene group. The essential fatty acids are all omega-3- and -6 methylene-interrupted fatty acids. Omega-3 fatty acids have a double bond three carbons away from the methyl carbon, whereas omega-6 fatty acids have a double bond six carbons away from the methyl carbon. Most studied omega-3 or omega-6 polyunsaturated fatty acids include alpha-linolenic acid (ALA; 18:3n−3), eicosapentaenoic acid (EPA; 20:5n−3), and docosahexaenoic acid (DHA; 22:6n−3) or linoleic acid (LA; 18:2n−6) and arachidonic acid (AA; 20:4n−6).

Synapse: Junctions through which neurons signal to each other and to non-neuronal cells such as those in muscles or glands. Synapses allow neurons to form circuits within the central nervous system. They are essential to biological processes that underlie perception, thought, and memory.

Dendritic spine: Postsynaptic structures which are precursors to mature synapses. A dendritic spine is a small membranous protrusion from a dendrite that receives input from a single synapse of an axon. They serve as a site for synaptic strength and help transmit electrical signals to the neuron's cell body.

Synaptogenesis: Formation of synapses. Brain synapses are formed by a presynaptic bouton (i.e., the terminal site of an axon) and a postsynaptic spine (i.e., the dendritic spine).

References

Abbracchio MP, Burnstock G, Boeynaems J-M, Barnard EA, Boyer JL. Pharmacol Rev. 2006;58:281–341.

Abumrad NA, Park JH, Park CR. J Biol Chem. 1984;259:8945–53.

Alvarez XA, Laredo M, Corzo D, Fernandez-Novoa L, Mouzo R, Prea JE, Daniele D, Cacabelos R. Methods Find Exp Clin Pharmacol. 1997;19:201–10.

Boehm S, Huck S, Illes P. Br J Pharmacol. 1995;116:2341–3.

Burnstock G. Cell Mol Life Sci. 2007;64:1471–83.

Cansev M. Brain Res Rev. 2006;52:389–97.

Cansev M. Centr Nerv Syst Agents Med Chem. 2007;7:223–9.

Cansev M, Wurtman RJ. Neuroscience. 2007;148:421–31.

Cansev M, Ulus IH, Wang L, Maher TJ, Wurtman RJ. Neurosci Res. 2008;62:206–9.

Cansev M, Marzloff G, Sakamoto T, Ulus IH, Wurtman RJ. Dev Neurosci. 2009;31:181–92.

Darios F, Davletov B. Nature. 2006;440:813–7.

De Bruin NM, Kiliaan AJ, De Wilde MC, Broersen LM. Neurobiol Learn Mem. 2003;80:63–79.

Golczewski JA, Hiramoto RN, Chanta VK. Neurobiol Aging 1982;3:223–6.

Hashimoto M, Hossain S, Shimada T, Sugioka K, Yamasaki H. J Neurochem. 2002;81:1084–91.

Hashimoto M, Tanabe Y, Fuji Y, Kikuta T, Shibata H, Shido O. J Nutr. 2005;135:549–55.

Holguin S, Huang Y, Liu J, Wurtman RJ. Behav Brain Res. 2008a;191:11–16.

Holguin S, Martinez J, Chow C, Wurtman RJ. FASEB J. 2008b;22:3938–46.

Holmes GL, Yang Y, Liu Z, Cermak JM, Sarkisian MR, Stafstrom CE, Neill JC, Blusztajn JK. Epilepsy Res. 2002;48:3–13.

Kamp F, Westerhoff HV, Hamilton JA. Biochemistry. 1993;32:11074–86.

Klein J, Koppen A, Loffelholz K. J Neurochem. 1990;55:1231–36.

Kotani S, Sakaguchi E, Warashina S, Matsukawa N, Ishikura Y, Kiso Y, Sakakibara M, Yoshimoto T, Guo J, Yamashima T. Neurosci Res. 2006;56:159–64.

Knott GW, Holtmaat A, Wilbrecht L, Welker E, Svoboda K. Nat Neurosci. 2006;9:1117–24.

Lai MK, Tan MG, Kirvell S, Hobbs C, Lee J. J Neural Transm. 2008;115:1165–72.

Marszalek JR, Kitidis C, DiRusso CC, Lodish HF. J Biol Chem. 2005;280: 10817–26.

Meck WM, Williams CL. Brain Res Dev Brain Res. 1999;118:51–9.

Milosevic J, Brandt A, Roemuss U, Arnold A, Wegner F. J Neurochem. 2006;99:913–23.

Muller D, Toni N, Buchs P-A. Hippocampus. 2000;10:596–604.

Nitsch RM, Blusztajn JK, Pittas AG, Slack BE, Growdon JH. Proc Natl Acad Sci USA. 1992;89:1671–5.

Oldendorf WH, Braun LD. Brain Res. 1976;113:219–24.

Pooler AM, Guez, DH, Benedictus R, Wurtman RJ. Neuroscience. 2005;134:207–14.

Price GD, Robertson SJ, Edwards FA. Eur J Neurosci. 2003;17:844–50.

Ramirez-Amaya V, Balderas I, Sandoval J, Escobar ML, Bermudez-Rattoni F. J Neurosci. 2001;21:7340–8.

Sakamoto T, Cansev M, Wurtman RJ. Brain Res. 2007;1182:50–9.

Scheltens P, Verhey FRJ, Olde Rikkert MGM, Kamphuis PJ, Wilkinson D, Kurz A. Alzheimers Dement. 2008;4 Suppl 2:T789.

Selkoe DJ. Science. 2002;298:789–91.

Spiers, PA, Myers D, Hochanadel GS, Lieberman HR, Wurtman RJ. Arch Neurol. 1996;53:441–8.

Sweet DH, Miller DS, Pritchard JB. J Biol Chem. 2001;276:41611–9.

Teather LA, Wurtman RJ. Prog Neuro-Pyschopharmacol Biol Pyschiatry. 2003;27:711–7.

Teather LA, Wurtman RJ. Learn Mem. 2005;12:39–43.

Teather LA, Wurtman RJ. J Nutr. 2006;136:2834–7.

Tees RC. Behav Brain Res. 1999;105:173–8.

Thomas JD, Garrison M, O'Neill TM. Neurotoxicol Teratol. 2004;26:35–45.

Toni N, Buchs PA, Nikonenko I, Bron CR, Muller D. Nature. 1999;402:421–5.

Von Kugelgen I, Norenberg W, Meyer A, Illes P, Starke K. Naunyn-Schimiedeberg's Arch Pharmacol. 1999;359:360–69.

Wang L, Pooler AM, Albrecht MA, Wurtman RJ. J Mol Neurosci. 2005;27:137–45.

Wang L, Albrecht MA, Wurtman RJ. Brain Res. 2007;1133:42–8.

Wurtman RJ, Regan M, Ulus I, Yu L. Biochem Pharmacol. 2000;60:989–92.

Wurtman RJ, Ulus IH, Cansev M, Watkins CJ, Wang L, Marzloff G. Brain Res. 2006;1088:83–92.

Wurtman RJ, Cansev M, Ulus IH (2009) In: Tettamanti G, Goracci G (eds.), Neural Lipids, Hand book of Neurochem Mol Neurobiol. Springer, Berlin-Heidelberg.

Chapter 33
Gender Differences in Brain Activation by Food Stimulation

Gene-Jack Wang, Nora D. Volkow, Frank Telang, Panayotis K. Thanos, and Joanna S. Fowler

Abbreviations

BMI   Body mass index
BOLD   Blood oxygen level dependent
DA   Dopamine
FDG   2-deoxy-2-[^{18}F]fluoro-d-glucose
fMRI   Functional magnetic resonance imaging
PET   Positron emission tomography
SPM   Statistical parameter mapping

33.1 Introduction

Human appetite control and weight regulation are modulated by the nutritional need, hedonic influences over eating, and responses to stress. Obesity can derive from a variety of causes (i.e., genetic, cultural, nutrition intake, physical activity). Of particular relevance is the environment, which has made food not only widely available but also increasingly more varied and palatable. It is likely that a gene–environment interaction(s) (in which genetically susceptible individuals respond differently to an environment with increased availability of palatable energy-dense foods and reduced opportunities for energy expenditure) contribute to the current high prevalence of obesity.

Gender is another contributing factor to obesity. Gender differences in the prevalence of obesity have been reported in the USA and in many countries of the world. In the USA, the last National Health and Nutrition Examination Survey reported overall prevalence rates of obesity in adult women (35.3%) that did not differ from those in men (33.3%) but reported much higher rates in African American (54% vs 34%) and Hispanic (42% vs 32%) women (Ogden et al. 2006). Similarly, reports from the WHO and the International Obese Task Force (IOTF 2008) document significantly higher rates of obesity in women than in men. There are many factors (i.e., hormones, frequent dieting, stress reactivity, socioeconomic status, physical activity; Matheson et al. 2008), which may contribute to the difference. Several studies had previously reported that women, when compared with men, more frequently attempt to lose weight, have significantly higher disinhibition scores (Matheson

---

G.-J. Wang (✉)

Medical Department, Building 490, Brookhaven National Laboratory, Upton, New York, 11973 USA
e-mail: gjwang@bnl.gov

et al. 2008), and report having higher scores on measures of dietary helplessness and disinhibition in weight control programs (Carmody et al. 1995; Provencher et al. 2004). Obesity-related metabolic disorders are much lower in premenopausal women than men; however, there is a dramatic increase following menopause in women (Shi et al. 2009). Understanding the mechanism(s) contributing to overeating behaviors in women can provide a scientific basis for pharmacological and behavioral approaches to its prevention and treatment.

In this chapter we explore and answer the following questions: What gender differences contribute to the desire to eat and to inhibition of the desire to eat? Answers to these questions will be described based on findings from brain imaging experiments and from relevant preclinical studies.

33.2 Gonadal Steroid Hormones and Food Intake

There are very few overt gender differences in eating behavior. Meal size and meal frequency are similar between females and males in both humans and rodents. Body size estimates tend to match total energy intake and energy expenditure in both sexes. However, women display higher rates of morbid obesity (BMI > 40) than men (Ogden et al. 2006; IOTF 2008). Gonadal steroid hormones (i.e., the androgens, estrogens, and progestins) have many actions that might affect body weight and adiposity independent of eating (i.e., energy expenditure, gastrointestinal function, metabolism, growth, body composition; Asarian and Geary 2006). The mechanisms underlying these effects and their relation to eating are unknown. A functional neuroimaging study showed great similarity between men and women in response to fasting and satiety. The study found greater perfusion of subcortical regions in men during fasting and greater perfusion in occipital and parietal sensory associated regions in women during satiety. It has also been reported that total energy intake varies during the menstrual cycle (Del Parigi et al. 2002).

Rodent and human studies reported that females eat less during the peri-ovulatory phase of the ovarian cycle. The highest food intake occurs in the luteal phase, which has been demonstrated both in primate and human studies (Reimer et al. 2005). This pattern was not seen in women using hormone replacement preparations or in those with anovulatory cycles. Women were reported to prefer sweet foods with a higher carbohydrate and a higher fat content; they also appear to eat more sweets during the luteal phase of the cycle than other phases, which has been ascribed to increases in estradiol and progesterone (Fong and Kretsch 1993).

33.3 Food-related Cues and Eating Behavior

Emotional responses to food are important influences on food intake. An increasing proportion of human food consumption appears to be driven by pleasure and not just nutritional needs. Food ingredients such as glucose modulate dopamine (DA) neuronal activity directly in the ventral tegmental area and substantia nigra (Levin 2000). DA is a neurotransmitter that is known to play a major role in motivation and is involved with reward and prediction of reward. Daily bingeing on sugar repeatedly releases DA in the nucleus accumbens (Avena et al. 2009). A human PET study with [^{11}C]raclopride that measured DA release in the striatum following blind intravenous administration of glucose solution (300 mg/kg) showed significant DA release in fasting men but not in women (Haltia et al. 2007).

Sensory processing of food and food-related cues also plays an important role in the motivation for food and it is especially important in the selection of a varied diet. The hedonic reward value of food is

closely linked to the sensory perception of the food. DA in these brain regions is associated with sensory perception of food (Rolls 2007). An imaging study showed that DA release in the striatum follows the consumption of a favorite food and the amount of striatal DA release correlated with the ratings of meal pleasantness (Small et al. 2003). It is likely that the reinforcement related to eating is not only associated with food ingredients (i.e., sugar) but also with other stimuli (i.e., sensory experience of food). The hedonic value of a food is modulated by the motivational state of the individual. Sensory inputs of taste, vision, olfaction, temperature, and texture are first sent to the primary sensory cortices (i.e., insula, primary visual cortex, pyriform, primary somatosensory cortex) and then to the orbitofrontal cortex and amygdala (Rolls 2007). Recently, a preclinical study from our laboratory (Thanos et al. 2008) examined rats under food stimulation with micro-PET and FDG showed activation in the hippocampus, a region involved in memory, the insular cortex, a region involved with interoception (perception of internal sensations), the medial thalamus (region involved in alertness), and in regions involved with sensory perception (olfactory bulb, olfactory nucleus, occipital cortex, superior colliculus, and parietal cortex), which corroborates their relevance in the perception of food.

Food deprivation potentiates the rewarding effects of food (Cameron et al. 2008). During fasting, the role of DA is not selective for food but rather signals the salience for a variety of potential biological rewards and cues that predict rewards (Carr 2007). Chronic food deprivation also potentiates the reinforcing effects of most addictive drugs (Carr 2002). The striatum, orbitofrontal cortex, and amygdala, which are brain regions receiving DA projections are activated during the expectation of food. Using PET and FDG with food-related cue paradigm (visual, olfactory, and gustatory display of food without eating in food deprived subjects) we showed that cues increase DA in dorsal striatum in fasting (14–16 h) normal weight men and women (Volkow et al. 2002). Exposure to food cues increased metabolism in orbitofrontal cortex (Fig. 33.1) and these increases were associated with the perception of hunger (Fig. 33.2) and the desire for food (Wang et al. 2004) in men and women. The enhanced orbitofrontal cortex activation by the food stimulation is likely to reflect downstream dopaminergic effects and is likely to participate in DA's involvement in the drive for food consumption. The orbitofrontal cortex also participates in learning stimulus-reinforcement associations and conditioning including conditioned cues eliciting feeding. Thus, its activation secondary to food-induced DA stimulation could result in an intense motivation to consume food. Dysfunction of the orbitofrontal cortex is associated with compulsive behaviors including overeating. This is relevant because food-induced conditioned responses very likely contribute to overeating irrespective of hunger signals.

Excessive and repeated food intake in obese subjects might lead to a downregulation of DA signaling in the reward circuitry. An fMRI study looking at consumption of anticipated food showed decreased activation in the caudate nucleus in response to food consumption in adolescent obese women (Stice et al. 2008). Thus, hyposensitivity to food stimuli in brain regions modulated by DA in obese individuals could increase their risk of overeating. In fact our (Wang et al. 2001) and other (Haltia et al. 2007) PET studies with [^{11}C]raclopride have previously documented a reduction in striatal D2/D3 receptor availability in obese subjects that was inversely related to BMI.

33.4 Gender Differences in Response to Food Cues

Gender differences in sensory experience of food might contribute to eating behaviors. A study that showed photographs of food revealed that both men and women reported pleasant responses to food that were associated with ratings of hunger in a nonfasting state. However, fasting enhanced the pleasantness of food images to a greater extent in women than in men (Stoeckel et al. 2007). Similar results were reported in an fMRI study; women had greater reactivity to food stimuli in brain regions

Fig. 33.1 PET-FDG brain images of food stimulation. Transaxial PET-FDG brain images of a male subject during food stimulation and during neutral stimulation at levels of orbitofrontal cortex. The metabolic images for both scans are scaled with respect to the maximum absolute metabolic value obtained on the neutral intervention and presented using the rainbow scale where red represents the highest value and dark violet represents the lowest value. (Adapted from NeuroImage (Wang et al. 2004))
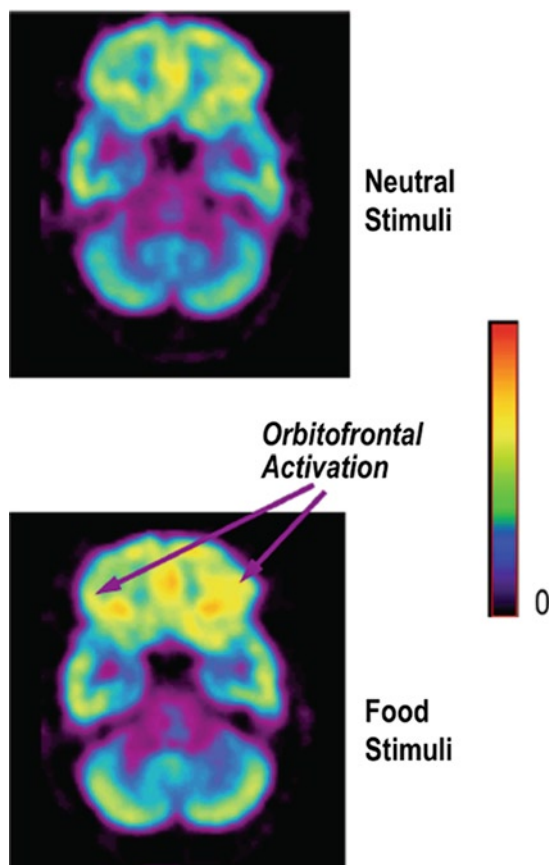
Fig. 33.2 Correlation analysis of food stimulation. Correlation between changes in right orbitofrontal metabolism and self-report rating of hunger was significant ($r = 0.84$, $p = 0.001$) (Adapted from NeuroImage (Wang et al. 2004))
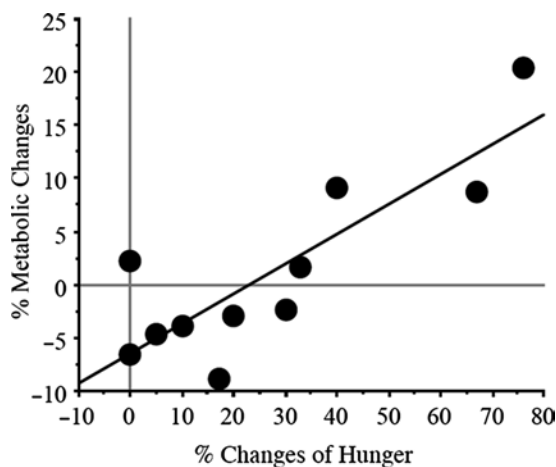
that process visual and taste sensations after 24 h of fasting (Uher et al. 2006). Responses in the occipital visual-related cortex to visual stimuli and in the insula and prefrontal cortex to taste stimuli were stronger in women than in men.

Using our food stimulation paradigm (presentation of palatable food without consumption) with PET-FDG after 14–16-h fasting (Wang et al. 2004), we observed a greater reactivity in the right anterior prefrontal and left orbitofrontal cortex in women than in men (Fig. 33.3) during food stimulation
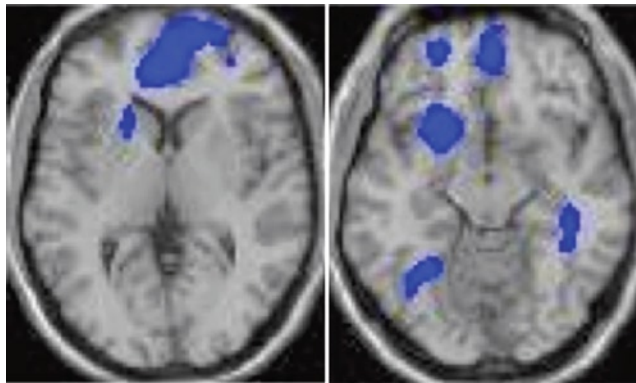
Fig. 33.3 Gender differences in food stimulation. SPM results ($p < 0.05$) for the difference between women and men during food stimulation without cognitive inhibition. Color-coded SPM results are displayed in a transaxial plane superimposed on a structural brain MR image. The results (T value) are presented using the color scale where blue represents deactivation as a result of lesser metabolic activation in men than women (Adapted from PNAS (Wang et al. 2009a))

(Wang et al. 2009a). The prefrontal dorsolateral cortex is associated with attention/alertness, working memory, and with inhibition of intentional actions, whereas the orbitofrontal cortex is associated with salience attribution to reinforcers (e.g., food). The greater activation of the prefrontal cortex and orbitofrontal cortex in the women during food stimulation could reflect the modulation of these brain regions by gonadal steroid hormones. Indeed in women, activation of the frontal cortex during a working memory task is associated with estradiol levels in the menstrual cycle. fMRI studies have also shown that estrogen levels modulate the responses of brain regions that process emotions and reward signals (Dreher et al. 2007). Thus, these findings suggest that estrogen may have contributed to the gender differences in the regional brain responses during food stimulation.

When a certain food is eaten, the pleasant responses to the food item and motivation to eat gradually decrease. One may still motivate to consume other food items, particularly those foods with different sensory characteristics (Rolls 2007). It is likely that highly palatable foods can override internal homeostatic mechanisms through action on brain DA pathways (i.e., orbitofrontal cortex) and lead to overeating and obesity (Batterham et al. 2007). When food is ingested, the feeling of fullness increases and the motivation to eat decreases. The effect of satiation on brain activation has been reported for visual, olfactory, and gustatory stimuli. Brain regions particularly orbitofrontal cortex significantly decreased after satiation (Rolls 2007). An fMRI study assessed gender differences in taste of chocolate before and after eating chocolate until the subjects were satiated (Smeets et al. 2006). When satiated, men had less response to taste activation in the hypothalamus than women. The decreased activation in hypothalamus could reflect the decrease in hunger. Chocolate satiation was associated with a greater decrease in taste activation in orbitofrontal cortex, ventral striatum, and medial prefrontal cortex in men than in women. The study suggests that women are more affected than men by the hedonic value of food.

33.5 Gender Differences in Cognitive Inhibition During Food Stimulation

The decisions to eat are complex and involve higher brain function circuits (i.e., prefrontal cortices). Impaired cognitive function (i.e., inhibitory control) may contribute to behavioral disorders such as addiction and pathological overeating (Goldstein et al. 2009). We evaluated the responses of the

brain when subjects were exposed to highly desirable food either with or without a prior directive to suppress the desire for food (cognitive inhibition) in men and women (Wang et al. 2009a). Regional brain metabolic responses to food stimulation with and without cognitive inhibition were assessed with PET and FDG. Specifically with cognitive inhibition as compared with no inhibition the male subjects showed significant decreases in anterior cingulate, left orbitofrontal cortex, left amygdala, and right striatum (Fig. 33.4a), which are regions involved in emotional regulation, conditioning, and motivation. These regions, which decreased metabolism, had been shown by prior studies to be activated by food stimuli when presented via pictures, smells, taste, recall, or a combination of these. The suppressed activation of the orbitofrontal cortex with inhibition was also associated with decreases in self-reports of hunger (Fig. 33.5a), which corroborates the involvement of this region in processing the conscious awareness of the drive to eat. This finding suggests a mechanism by which cognitive inhibition decreases the desire for food.

Using the same food stimulation paradigm with PET-FDG, we found a significant gender difference (Fig. 33.4) in the regional brain responses to cognitive inhibition (Wang et al. 2009a). In women, different from what was observed in men, the decrease in the self-reports of hunger was not paralleled by deactivation in limbic and paralimbic brain regions (Fig. 33.5b). Our findings of a lack of response to cognitive inhibition in women are consistent with behavioral studies showing significantly higher scores in disinhibition (tendency to overeat in response to food stimuli when presented with palatable food or under emotional distress) in women than in men (Matheson et al. 2008;
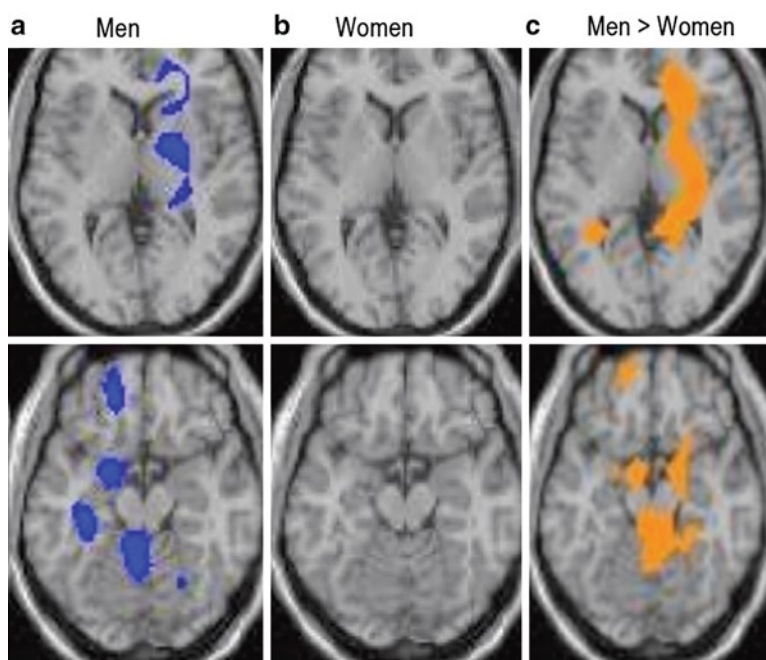
Fig. 33.4 Gender differences in purposeful cognitive inhibition of the desire for food during food stimulation. SPM images ($p < 0.01$) of cognitive inhibition during food stimulation (comparison between food stimulation with and without cognitive inhibition) in women (**b**) and in men (**a**). Color-coded SPM results are displayed in a transaxial plane superimposed on a structural brain MR image. The results (*T* value) are presented using the color scale where blue represents deactivation as a result of cognitive inhibition. (**c**) The SPM results ($p < 0.01$) for the difference between women (**b**) and men (**a**), showing the areas where males showed greater decrements with cognitive inhibition than females. Women did not show showed greater metabolic decrements than men during cognitive inhibition for any of these regions (Adapted from PNAS (Wang et al. 2009a))
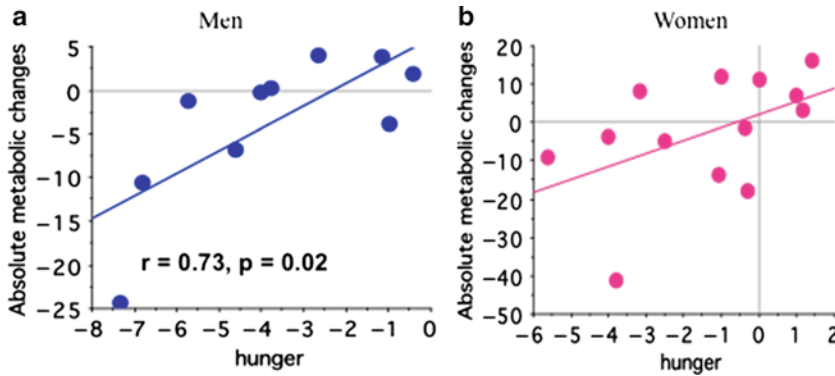
Fig. 33.5 Correlation analysis of cognitive inhibition. Correlation analysis between the differences in the behavioral and regional brain metabolic changes induced by the food stimulation with and without cognitive inhibition revealed that they were significant for the changes in self-reports of hunger and the changes in the orbitofrontal cortex ($r = 0.73$, $p = 0.02$); the greater the suppression in metabolism the greater the decreases in the self-reports of hunger in men (**a**). This correlation did not reach significance in women ($r = 0.49$, $p = 0.09$) probably due to the modest sample size (**b**) (Adapted from PNAS (Wang et al. 2009a))

Provencher et al. 2004). The decreased inhibitory control in women could underlie their lower success in losing weight while dieting when compared with men.

Sex hormones directly influence food intake, body weight and fat distribution, and modulate the signaling of leptin and insulin. Leptin concentrations increased significantly during the luteal phase as compared with the follicular phase (Anim-Nyame et al. 2000). Indeed female rats are more sensitive to the anorexic effects of leptin than male rats. Leptin in the brain enhances the response to satiety signals and decreases perception of food reward during food consumption (Kruge et al. 2003). Leptin also modulates food-related mesolimbic sensitivity to visual food stimulation (Farooqi et al. 2007). Furthermore, gonadal steroid hormones affect neurotransmitter turnover in prefrontal regions and in the ventral tegmental area, where DA cells are located. Female gonadal hormone levels fluctuate during the rat estrous cycle affecting the release and reuptake of neurotransmitters (i.e., DA, serotonin, and norepinephrine) that are involved in satiety and motivation to eat (Thompson and Moss 1997). Several studies have reported increases in appetite and food intake during luteal phase of the menstrual cycle when estrogen and progesterone are high (Reimer et al. 2005).

33.6 Applications to Other Areas of Health and Disease

Obesity is becoming an increasing public health problem. This has triggered the high prevalence rates of dieting seen as an attempt to confront a vast array of highly desirable food products and heavily promoted foods. Obesity is associated with abnormal eating behaviors. Brain imaging studies show that obese individuals have significant deficits in circuits that regulate abnormal eating behaviors (i.e., motivation, reward, emotion, learning, memory, and inhibitory control; Wang et al. 2009b). Women more frequently diet but are less successful in weight control program than men. Brain imaging studies showed that female sex hormones modulate brain regions related to reward response and women had greater reactivity to food stimuli in brain regions that process sensations and salience attribution. Women lacked the ability to inhibit the activation of brain regions involving emotional regulation, conditioning, and motivation during food stimulation even when they attempted to do so (Wang et al. 2009a). This may underlie their inability to control food intake when exposed to highly palatable food.

The regular hormone fluctuations that are associated with the menstrual cycle influence appetite control and eating behavior. These cyclic variations might affect regional brain responses to favorite foods and the ability to exert inhibitory control. The gender differences in eating behaviors are likely to reflect the confluence of peripheral metabolic signals (i.e., leptin, insulin, ghrelin), female sex hormones (i.e., estrogen, progesterone, luteinizing hormone), and reactivity of neuronal circuits. Understanding the relationships between these circuits, their neuromodulation by food stimulation, peripheral metabolic markers, and the overall impact on hunger and desire for food, may be helpful in devising strategies to counteract the overwhelming salience that palatable food has on women to help reduce overeating behaviors.

Summary Points

- Exposure to food cues increased DA in dorsal striatum and increased metabolism in orbitofrontal cortex in normal weight individuals. These increases were associated with the perception of hunger and the desire for food.
- Women had greater activation in brain regions associated with attention/alertness, working memory (i.e., prefrontal cortex), and with salience attribution to food (i.e., orbitofrontal cortex) during food stimulation than men.
- Men when exposed to food cues with cognitive inhibition decreased activation in limbic and paralimbic brain regions involved in emotional regulation, conditioning, and motivation.
- Women when exposed to food cues with cognitive inhibition did not decrease activation in limbic and paralimbic brain regions. The decreased inhibitory control in women could underlie their lower success in losing weight while dieting when compared with men.
- The results of imaging studies have the potential to facilitate understanding the mechanisms underlying obesity and gender-related overeating behaviors as well as the development of strategies for prevention and treatment.

Definitions and Explanations

[^{11}C]raclopride: A dopamine D2/D3 receptor radioligand that measures D2/D3 receptor availability. Since it binds reversibly to D2/D3 receptors, it can be used to measure changes in extracellular dopamine.

Dopamine: A neurotransmitter that is known to play a major role in motivation and is involved with reward and prediction of reward.

FDG (2-deoxy-2-[^{18}F]fluoro-D-glucose): A radiotracer which measures brain glucose metabolism.

Functional magnetic resonance imaging (fMRI): An imaging method that measures changes in neural activity levels in the brain in response to various stimulations. fMRI measures the vascular correlate of neuronal activity via the blood oxygen level-dependent (BOLD) signal.

Positron emission tomography (PET): Imaging method that measures the distribution and movement of radiolabeled compounds in the living human and animal body. With these methods, it is possible to measure the distribution and concentration of many receptors, transporters, and enzymes in the human brain as well as cerebral blood flow and glucose metabolism (Table 33.1).

Statistical parameter mapping (SPM): A statistical method for studying differences in brain activity obtained during functional neuroimaging experiments using fMRI or PET.

Table 33.1 Key features of positron emission tomography

- Positron emission tomography (PET) is an imaging method that measures the distribution and movement of radiolabeled compounds in the living human and animal body.
- PET measures the distribution and concentration of many receptors, transporters and enzymes, and labeled drugs in the human brain as well as cerebral blood flow and glucose metabolism.
- PET with [^{11}C]raclopride has been used to measure brain dopamine D2 receptor availability in obese individuals. The imaging methods with food stimulation paradigms such as consumption of palatable food or food presentation (presentation of palatable food without consumption) are used to assess the association of brain dopamine function and eating behaviors.
- PET with FDG (2-deoxy-2-[^{18}F]fluoro-d-glucose), a radioactive glucose analog, measures brain glucose metabolism. It has been used to assess brain function in obese individuals during fasting state and gender differences in baseline (no stimulation) condition. With food stimulation paradigms, PET-FDG scan measures brain circuits involved during eating behaviors and cognitive function.
- PET with O-15 water measures cerebral blood flow, which was used to assess brain circuits during stimulation paradigms involving food intake (i.e. glucose), eating disorders, and obesity.

This table lists the key features of using PET to investigate effects of food stimulation in humans, including brain dopamine function and brain circuits involved in eating behaviors

References

Anim-Nyame N, Domoney C, Panay N, Jones J, Alaghband-Zadeh J, Studd JW. Hum Reprod. 2000;15: 2329–32.
Asarian L, Geary N. Philos Trans R Soc Lond B Biol Sci. 2006;361:1251–63.
Avena NM, Rada P, Hoebbel BG. J Nutr. 2009;139:623–8.
Batterham RL, Ffytche DH, Rosenthal JM, Zelaya FO, Barker GJ, Withers DJ, Williams SC. Nature. 2007;450:106–9.
Cameron JD, Goldfield GS, Cyr MJ, Doucet E. Physiol Behav. 2008;94:474–80.
Carmody TP, Brunner RL, St Jeor ST. Int J Eat Disord. 1995;18:247–56.
Carr KD. Physiol Behav. 2002;76:353–64.
Carr KD. Physiol Behav. 2007;91:459–72.
Del Parigi A, Chen K, Gautier JF, Salbe AD, Pratley RE, Ravussin E, Reiman EM, Tataranni PA. Am J Clin Nutr. 2002;75:1017–22.
Dreher JC, Schmidt PJ, Kohn P, Furman D, Rubinow D, Berman KF. Proc Natl Acad Sci U S A. 2007;104:2465–70.
Farooqi IS, Bullmore E, Keogh J, Gillard J, O'Rahilly S, Fletcher PC. Science. 2007;317:1355.
Fong AK, Kretsch MJ. Am J Clin Nutr. 1993;57:43–6.
Goldstein RZ, Craig AD, Bechara A, Garavan H, Childress AR, Paulus MP, Volkow ND. Trends Cogn Sci. 2009;13: 372–80.
Haltia LT, Rinne JO, Merisaari H, Maguire RP, Savontaus E, Helin S, Nagren K, Kaasinen V. Synapse. 2007;61:748–56.
IOTF International association for the study of obesity. 2008.
Kruge U, Schraft T, Kittner H, Kiess W, Illes P. Eur J Pharmacol. 2003;482:185–7.
Levin BE. Brain Res. 2000;874:158–64.
Matheson FI, Moineddin R, Glazier RH. Soc Sci Med. 2008;66:675–90.
Ogden CL, Carroll MD, Curtin LR, McDowell MA, Tabak CJ, Flegal LKM. JAMA. 2006;295:1549–55.
Provencher V, Drapeau V, Tremblay A, Despres JP, Bouchard C, Lemieux S. Br J Nutr. 2004;91:997–1004.

Reimer RA, Debert CT, House JL, Poulin MJ. Physiol Behav. 2005;84:303–12.

Rolls ET Proc Nutr Soc. 2007;66:96–112.

Shi H, Seeley RJ, Clegg DJ. Front Neuroendocrinol. 2009;30:396–404.

Small DM, Jones-Gotman M, Dagher A. Neuroimage. 2003;19:1709–15.

Smeets PA, De Graaf C, Stafleu A, Van Osch MJ, Nievelstein RA, Van Der Grond J. Am J Clin Nutr. 2006;83:1297–305.

Stice E, Spoor S, Bohon C, Veldhuizen MG, Small DM J Abnorm Psychol. 2008;117:924–35.

Stoeckel LE, Cox JE, Cook EW, 3rd, Weller RE Appetite. 2007;48:139–44.

Thanos PK, Michaelides IM, Gispert JD, Pascau J, Soto-Montenegro ML, Desco M, Wang R, Wang GJ, Volkow ND. Int J Obes (Lond). 2008;32:1171–9.

Thompson TL, Moss RL. Neurosci Lett. 1997;229:145–8.

Uher R, Treasure J, Heining M, Brammer MJ, Campbell IC. Behav Brain Res. 2006;169:111–9.

Volkow ND, Wang GJ, Fowler JS, Logan J, Jayne M, Franceschi D, Wong C, Gatley SJ, Gifford AN, Ding YS, Pappas N. Synapse. 2002;44:175–80.

Wang GJ, Volkow ND, Logan J, Pappas NR, Wong CT, Zhu W, Netusil N, Fowler JS. Lancet. 2001;357:354–7.

Wang GJ, Volkow ND, Telang F, Jayne M, Ma J, Rao M, ZhuW, Wong CT, Pappas NR, Geliebter A, Fowler JS Neuroimage. 2004;21:1790–7.

Wang GJ, Volkow ND, Telang F, Jayne M, Ma Y, Pradhan K, Zhu W, Wong CT, Thanos PK, GeliebterA, Biegon A, Fowler JS. Proc Natl Acad Sci USA. 2009a;106:1249–54.

Wang GJ, Volkow ND, Thanos PK, Fowler JS J Addict Med. 2009b;3:8–18.

Chapter 34
Food Perception in Adults: Neuroimaging Findings

Alexandra P.F. Key, Evonne J. Charboneau, and Ronald L. Cowan

Abbreviations

BA   Brodmann area
BOLD   Blood oxygen level dependent
EEG   Electroencephalogram
ERP   Event-related potential
fMRI   Functional magnetic resonance imaging
PET   Positron emission tomography
PFC   Prefrontal cortex
PWS   Prader-Willi syndrome

34.1 Introduction

Over the past 20 years, research in the area of diet, nutrition, and general food perception has expanded from relying primarily on behavioral measures to also include brain-based assessments. Examination of brain processes associated with perception of food stimuli provides information about the areas of the brain involved in processing specific food characteristics (e.g., visual appearance, smell, taste) and how these perceptual processes may differ based on internal physiological states as well as personal choices and beliefs. Neurophysiological measures can also help disambiguate the contributions of hunger and appetite, sensory systems (e.g., sensitivity to smell) or higher cognitive functions (e.g., attention, motivation, emotion regulation) to typical and atypical behavioral responses to food. Another important contribution of brain imaging techniques is their ability to provide information about perceptual and other cognitive processes even in the absence of overt verbal or motor responses. These characteristics make neuroimaging methods especially valuable for studying processes that may not be adequately captured by behavioral assessments due to response bias (e.g., tendency to provide socially desirable answers) or insufficient cooperation (e.g., lack of motivation, limited communication skills, or poor comprehension of the instructions).

A.P.F. Key (✉)
Vanderbilt Kennedy Center for Research on Human Development, 230 Appleton Place, Peabody Box 74,
Vanderbilt University, Nashville, TN 37203
e-mail: sasha.key@vanderbilt.edu

Table 34.1 Key features of neuroimaging

1. Neuroimaging refers to a collection of techniques for documenting brain structures and their activity in a live human.
2. Many neuroimaging techniques are noninvasive, can be obtained from persons of any age, and do not require an overt behavioral response.
3. Neuroimaging techniques vary in the type of signal source (e.g., electrical, magnetic, or chemical), temporal resolution, and spatial resolution.
4. Psychophysiological measures (EEG/ERP) reflect electrical activity of groups of neurons firing in temporal synchrony and offer the best temporal resolution (millisecond level) but limited spatial resolution (~2 cm). These measures are best suited for studying the speed and overall time course of sensory and cognitive processes.
4. Functional MRI methods track changes in blood oxygen levels and provide excellent spatial resolution (2–3 mm) but limited temporal resolution (2–6 s). This technique is best suited for identifying specific brain structures involved in performing various tasks.
5. Positron emission tomography (PET) reflects regional metabolic changes and locations and amounts of neurotransmitters and neuroreceptors. PET provides reasonable spatial resolution (2–4 mm) and poor temporal resolution (15–45 s). PET procedures involve brief radiation exposure.

EEG electroencephalogram, *ERP* event-related potential, *MRI* magnetic resonance imaging

This table lists the key features of neuroimaging techniques frequently used to investigate food perception processes in humans, including temporal and spatial resolution, signal type and sources.

While technological advancements gave rise to a number of diverse neuroimaging techniques, electroencephalography (EEG), event-related potentials (ERP), positron emission tomography (PET), and functional magnetic resonance imaging (fMRI) are the most frequently used in research on food-related behaviors (see Table 34.1). In this chapter, we will briefly discuss how each of these methods works and illustrate their use for understanding how typical persons process food-related information. Finally, we will discuss applications of these methods for studies of atypical eating behaviors.

34.2 Techniques for Studying Brain Processes

34.2.1 Electrophysiology

Electroencephalogram (EEG) has long been used as an indicator of ongoing brain activity. The EEG involves placing at least two or as many as 256 sensors on the person's scalp and recording electrical activity of the brain. Such recordings typically span several minutes and are quantified in terms of signal frequencies. They allow one to examine general brain state characteristics, such as level of arousal and degree of connectivity among various brain regions, as well as specific processes underlying among others, attention, perception, and working memory.

A brief temporary change in the EEG in a response to a specific external or internal event (e.g., seeing an image, making a decision) is known as an *event-related potential* (ERP). ERP waveforms are represented as a series of positive and negative peaks following the onset of the eliciting event and varying in amplitude, onset latency, and scalp distribution. Generally, variations in ERP peak characteristics are interpreted to reflect speed (latency) or degree (amplitude) of processing. Shorter latencies are assumed to indicate more rapid processing while larger amplitudes might suggest increased processing (i.e., a greater number of neurons firing in synchrony). Because their millisecond-level resolution is comparable to the speed of many sensory and cognitive processes, ERPs have been widely used to examine both automatic (e.g., sensory) and controlled (e.g., memory, attention, inhibition) stages of stimulus processing (Zani and Proverbio 2003).

One limitation of the EEG/ERP technique is that it does not offer detailed spatial resolution needed to directly link activity recorded on the scalp to specific brain regions. Even with high-density electrode arrays, not all brain electrical activity is captured due to variations in signal strength, distance from various cortical areas to the scalp, and the orientation of cortical columns generating the signal. However, other neuroimaging can offer the needed spatial resolution.

34.2.2 Functional Neuroimaging

Functional neuroimaging includes several techniques that assess brain function and indirectly measure neuronal activity. These techniques have been used to learn about the functional anatomy of the living brain, to investigate the neural pathophysiology of psychiatric and neurological disorders, and to measure patterns of brain activation associated with cognition and specific human behaviors. In this section, we will focus primarily on *functional magnetic resonance imaging* (fMRI) and *positron emission tomography* (PET), which both provide indirect quantitative information about changes in local neuronal activity.

The fMRI blood oxygen level dependent (BOLD) method indirectly measures regional brain activity. An increase in neuronal activity in a specific brain region is associated with an increase in blood flow, providing glucose and oxygen resources in the form of oxygenated (oxy)hemoglobin. In general, the supply of oxyhemoglobin to an active region exceeds that necessary for neuronal metabolism. Thus, an increase in neuronal activity in a specific brain region is associated with a net increase in oxyhemoglobin and a decrease in deoxyhemoglobin in that area. Since deoxyhemoglobin has paramagnetic qualities (that reduce the fMRI BOLD signal), deoxyhemoglobin can be used as an intrinsic contrast agent, such that the reductions in deoxyhemoglobin associated with increased neuronal activity produce a larger fMRI signal. The fMRI BOLD technique provides excellent spatial resolution (a few mm on average) and requires no radiation exposure.

Positron emission tomography (PET) is another versatile imaging technique that depends on the use of a pharmacological compound that is labeled with a positron-emitting radioisotope. Similarly to the fMRI BOLD method, PET can be used to indirectly assay neuronal activity via changes in regional blood flow associated with neuronal activation. PET approaches that employ radioisotopes coupled to glucose can also be used to measure regional glucose metabolism, which is a measure of energy used in meeting neuronal metabolic demands. PET can also be used to determine the location and binding levels of many cellular constituents, most commonly neurotransmitters and neuroreceptors. This method has recently been extended to include measures of neurotransmitter release, which provide critical information about the specific neurotransmitter effects of food or food cue exposure. Limitations of PET include radiation exposure and lower spatial and temporal resolution compared to fMRI.

34.3 Perception of Food Characteristics

Food stimuli present a number of perceptual characteristics, such as visual appearance, smell, taste, and texture, all of which can have a different effect on a person's subjective experience. Investigating the unique roles of these attributes can improve our understanding of food-related behaviors, including preferences and aversions.

34.3.1 ERP/EEG Studies

The earlier studies began examination of food processing by observing changes in EEG characteristics during an exposure to food odors. Martin et al. (1998) reported that the odors of chocolate and spearmint resulted in a significant reduction in theta activity at the right frontal region compared with the odors of almond and cumin or no-odor control. Similar effects have been reported for other odors such as spiced apple (Lorig and Schwartz 1988) and the smell of cooking food when participants were hungry (Stacher et al. 1979). The reduction in EEG theta activity could be interpreted to reflect hedonic properties of the odor; however, similar reduced theta was also observed in the left temporal region for the odor of rotting meat, suggesting that this EEG response may reflect an odor's ability to attract or distract (Martin et al. 1998). Thus, the effects of food odors on EEG are most likely reflecting the general attention-getting rather than hedonic qualities.

More recently, Kettenman (Kettenman et al. 2005) used olfactory N1/P2 ERP responses (thought to be generated in the insular cortex) to investigate the role of taste on odor perception. While participants' attention was distracted by an unrelated visual tracking task, olfactory ERPs were recorded to odors presented concurrently with the taste strips placed at the center of the tongue. Behavioral data revealed that reported pleasantness rating of the odors varied with changes in the background taste: a fruity smell (*n*-butylacetate) was perceived as most pleasant during sweet taste stimulation; a citrus smell (octanal) was rated most pleasant when combined with sour taste; while a floral (linalool) smell was most pleasant in the no-taste condition. ERPs further revealed that when paired with the less optimal taste stimulus, brain processing of the odors was characterized by reduced initial attention (smaller N1 amplitude) to the stimulus and prolonged and enhanced early categorization processes (larger P2 amplitude with longer latency).

In addition to the basic taste and smell properties of food, humans may also perceive the food in terms of its potential energetic and reward value. Toepel et al. (2009) examined brain responses of normal-weight participants while they viewed photographs of high- and low-fat foods intermixed with nonfood images (kitchen utensils). Differences in visual ERPs to high- versus low-fat foods were observed beginning approximately 165 ms after stimulus onset. High-fat images elicited stronger brain responses with estimated sources within the lateral occipital cortex, the superior temporal cortex, and the postcentral gyrus of the left hemisphere. Low-fat images were associated with stronger activity in the left inferior frontal gyrus. Differences between high- and low-fat foods were also present at a later time period (309–371 ms), due to increased activity within the occipitotemporal cortex, the inferior parietal lobe, dorsal frontal areas of the left hemisphere, and in ventromedial as well as more dorsal and lateral prefrontal areas in the right hemisphere. These brain structures are typically engaged in decision-making processes and follow-up correlational analyses revealed greater strength of the responses in trials with shorter reaction times for both stimulus types. Such correlations were not observed in the earlier time period (166–230 ms).

34.3.2 fMRI/PET Studies

Neuroimaging studies have investigated various sensory food cues (e.g., taste, smell, visual, tactile), the effects of satiety and hunger, and the effects of food imagery (see Tataranni and Del Parigi 2003, for review). Multiple brain areas are involved in food perception, including frontal and occipital cortex and subcortical areas such as the brainstem dopaminergic regions, hypothalamus, and striatum (see Figs. 34.1–34.3). Visual food cues activate the fusiform gyrus (Killgore and Yurgelun-Todd 2005a, b). Food smells activate the olfactory bulb and signal the pyriform cortex (Rolls et al. 2005).

Fig. 34.1 Brain structures
implicated in processing of
food-related information.
The figure represents a
coronal (*upper*) and axial
(*lower*) T1-weighted
structural MRI image
depicting brain structures
implicated in processing of
food-related information.
Primarily limbic components
include amygdala, cingulate
gyrus, and hippocampal
gyrus. Hypothalamus has a
primary role in feeding and
satiety. Additional cortical
regions (insula, prefrontal,
and occipital) play a role in
detecting, assessing, and
integrating food-related
information. Dorsal striatum
integrates cortical and limbic
input. Thalamic regions are
involved in processing
stimuli (Based on Tatarranni
and Del Parigi 2003)
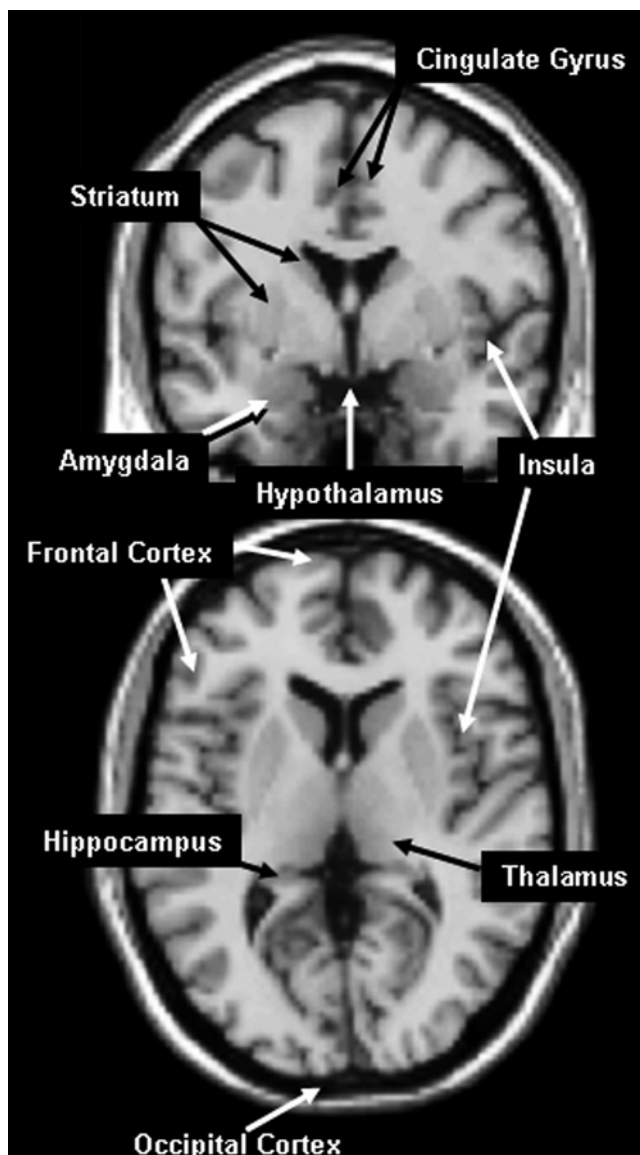
The taste of food activates cranial nerves V, VII, and IX, and this sensory information is integrated
in the nucleus tractus solitarius. Sensory information about taste is sent to the cortex via the ventral
preoptic nucleus of the thalamus and interpreted in the insula (Rolls et al. 2005). These sensory inte-
gration areas of the cortex then activate reward system structures including the orbitofrontal cortex
(OFC) and amygdala. The hippocampus is also activated in reward recognition (Rolls et al. 2005).
The ventral striatum/nucleus accumbens appears to be important in integrating information concern-
ing feeding and hunger, including information about reward and energy homeostasis (Kelley 2004).

To demonstrate the specificity of food cues across visual and tactile domains, St-Onge et al. (2005)
used fMRI at 1.5 T to examine regional brain activity in response to tactile or visual presentation of
foods compared with nonfoods in normal-weight participants who fasted for 12 h. Using a conjunc-
tion analysis to isolate regions activated in both tactile and visual presentations, these investigators
found that right the cingulate, left hippocampal, and parahippocampal gyri and bilateral regions of
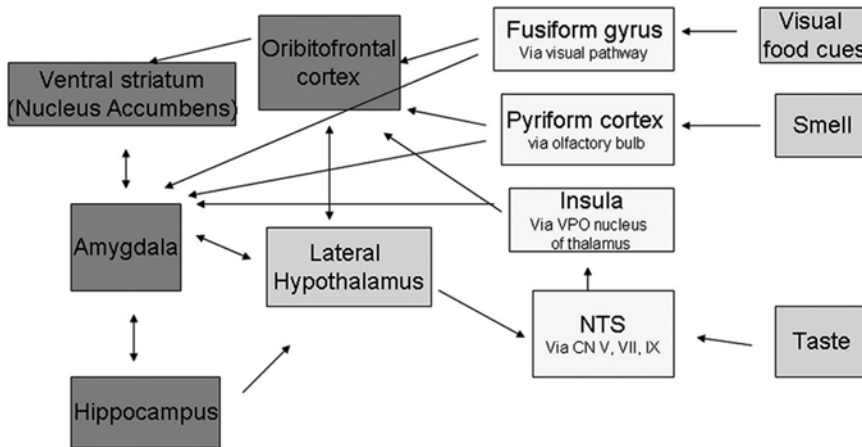
Fig. 34.2 Reward system activated by external stimuli. Feeding, as a survival behavior, is controlled not only by energy homeostasis but also by reward drive. While energy homeostasis is maintained by monitoring internal status, the natural reward system also responds to external signals, especially the recognition of certain foods as rewards
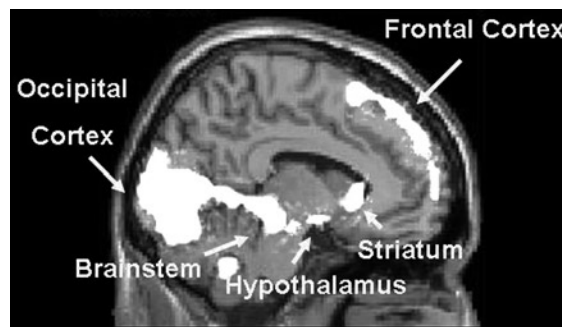
Fig. 34.3 A midline brain slice showing activation to viewing food cues using fMRI. Several brain regions activate in response to food cues, including the frontal cortex, occipital cortex (including vision centers), brainstem (areas including reward nuclei), hypothalamic region, and striatum. The right side of the figure is the front of the brain

superior temporal gyrus, insula, and caudate nuclei showed increased activations to food in both stimulus conditions. These structures are typically associated with memory, decision making, and interpretation processes.

Gordon et al. (2000) used PET to examine regional cerebral blood flow (rCBF) in healthy, fasted, normal-weight, female controls in response to high calorie, low calorie, and nonfood cues. Subjects viewed actual objects at a distance of 2 ft. Calorie content, palatability, and nutrient breakdown of the foods were not specified. Subjects were simultaneously given spoken descriptions of the stimuli (e.g., "this is a high calorie food with high fat content") and asked to evaluate their emotions while observing the object. The higher calorie foods elicited greater desire to eat than low calorie foods or nonfoods. Overall, reduced rCBF in the left temporo-insular region was noted during exposure to the high calorie foods versus the low calorie and nonfood conditions.

In a similar study, Killgore et al. (2003) used the fMRI BOLD method at 1.5 T to assess regional brain activation in response to viewing high and low calorie foods in normal-weight adult females. Vegetables, grains, and fruits were used as low calorie food images while prepared foods such as French fries, ice cream, cookies, etc., were used as high calorie food images. Participants rated the

food images for motivational salience on a scale ranging from highly aversive to highly appealing, with high calorie foods rated as significantly more appealing. Thus, the study assayed differences between images differing in calorie content and in motivational salience, with the two qualities inter-correlated. Food images were compared with neutral cues. Interestingly, a conjunction analysis of all food cues found increased activation in bilateral amygdala, bilateral anterior hippocampi, and in medial prefrontal cortex. However, a contrast of high calorie foods with baseline images showed robust activations in bilateral dorsolateral and medial prefrontal cortex, midline thalamus, and hypo-thalamus. A similar contrast of low calorie food images with baseline found relatively weak activa-tions in superior temporal, postcentral, parahippocampal, and orbitofrontal gyri. Additional analyses revealed a complex pattern of differential activations when high and low calorie stimuli were directly contrasted. In a follow-up analysis of this same cohort (Killgore and Yurgelun-Todd 2005a), these investigators examined the correlation between BMI and regional brain activity in the *a priori* selected regions of orbitofrontal cortex and anterior cingulate gyrus. In these healthy, normal-weight females, BMI was negatively correlated with orbitofrontal and cingulate activation in response to both high and low calorie foods. BMI during baseline image viewing was positively correlated with right middle orbitofrontal gyrus activation.

Interestingly, the observed pattern of response to high calorie foods appears to develop over time. In a rare study involving younger participants, Killgore and Yurgelun-Todd (2005b) examined cere-bral responses to food images in normal-weight girls, ages 9–15 years. Using methodology similar to the Killgore et al.'s (2003) study described earlier, adolescents and children underwent fMRI scans while viewing food images. Activation was found within the inferior orbitofrontal cortex, hippocam-pus, and fusiform gyri in response to food images. High calorie food images activated the left hip-pocampus and subgenual cingulate. Age correlated positively with activity within the oribitofrontal cortex and negatively with activity within the anterior cingulate gyrus. Low calorie foods activated the fusiform gyrus and demonstrated age-related increases in the left superior temporal gyrus and anterior cingulate. Nonfood images activated the fusiform gyrus and showed age-related increases in the pre-frontal cortex. On comparing these results with findings from their previous study on adults, Killgore and associates found that adolescents tended to show greater activation of the visual object-processing regions, which suggests that children process food images in a less complex manner than adults, for whom food images elicit a more emotional response. Killgore and Yurgelun-Todd suggest a develop-mental model of adolescent maturation whereby age-related changes in cerebral functioning develop from lower-order sensory processing toward higher-order processing of stimuli via prefrontal cortical systems involved in reward anticipation, self-monitoring, and behavioral inhibition.

Killgore and Yurgelun-Todd (2007) examined the role of the person's affective status (ratings on the Positive and Negative Affect Schedule) in the activity within the occipital cortex in response to high and low calorie foods. The results from a sample of 13 healthy women indicated that positive but not negative affective state affected early visual sensory processing of high calorie food stimuli, as reflected by activity within the lingual gyrus and calcarine cortex. No affect effects were observed for low calorie foods.

34.3.3 Conclusions

In sum, electrophysiological and neuroimaging studies reveal that food characteristics elicit similar brain responses as other attention-getting and motivationally salient stimuli. In addition, perception of food properties can be modulated by concurrently presented information in other modalities as reflected in smell–taste and sight–touch interactions. Furthermore, responses to food stimuli change

with age, progressing from basic sensory processing to more advanced analysis involving higher cognitive functions, such as motivation and inhibition. The following section will examine the role of the latter processes in greater detail.

34.4 Individual State/Belief Effects on Food Perception

The regulation of food intake is complex and results from integration of neural systems governing energy homeostasis, reward recognition and drive, and behavioral control (for reviews, see Sorensen et al. 2003; Sclafani 2004; Cone 2005; Marzo and Matias 2005; Munzberg and Myers 2005). Therefore, perception of food characteristics may be biased by other cognitive processes.

34.4.1 ERP/EEG Studies

Carretie, Mercado, and Tapia (2000) demonstrated that a person's appetite (motivation toward the food) could alter the amount of attention to food stimuli as reflected by negative parietooccipital ERPs. Participants completed a visual perception task where they were asked to identify whether each stimulus pair (cakes or faucets) made of an upright and inverted photo represented identical or different images. An index of appetite was obtained immediately after the ERP session by asking subjects to depict on a circle the portion of a cake they would like to eat at that moment. The largest appetite-related differences were observed at posterior (parietal and parietooccipital) scalp locations around 600 ms after food stimulus onset, but were not present for the nonfood stimuli.

Using hunger as a more extreme example of food motivation, Stockburger et al. (2008) examined whether 24-h food deprivation would result in increased attentional bias to food alone, to all appetitive stimuli (food and pleasant images), or to all emotional stimuli regardless of hedonic valence. ERPs were recorded while typical adults passively viewed food and appetitive or aversive nonfood images presented as a rapid serial stream to increase perceptual load. All participants were tested in a hungry and a satiated state. Hunger-related ERP effects were reflected in increased positive amplitudes to food pictures over posterior scalp areas within 170–210 ms and 270–310 ms after stimulus onset due to activity originating in occipito-temporo-parietal and frontal regions. The impact of the hunger on brain response to food stimuli was evidenced in the shift of topographic distribution from the pattern more typical of general selective attention to the engagement of food-selective visual-associative brain regions. There were no state-related differences in ERPs to nonfood pictures. Interestingly, hunger did not affect processing of the emotional aspects of the stimuli. Both pleasant and unpleasant pictures elicited a pronounced early posterior negative (EPN) component between 200 and 300 ms after stimulus onset.

Self-imposed food restraint may also alter food perception. Kemmotsu and Murphy (2006) utilized olfactory P3 response to assess attention to food (chocolate) versus nonfood (geraniol) odors in restrained and nonrestrained eaters. All participants completed two tasks that directed their attention to (attend) or away from (ignore) the stimuli. In the "attend" condition, participants performed odor magnitude estimation while in the "ignore" condition, they performed an unrelated visuomotor tracking task. Restrained eaters were expected to pay greater attention to the food odor regardless of the attentional condition, while ERPs to the food odor in nonrestrained eaters were predicted to have higher amplitudes in the "attend" than the "ignore" condition. The stimuli were presented in a single stimulus version of an oddball paradigm where an infrequent target stimulus is presented without the

intervening presentations of the frequent standard stimulus. As would be expected, all participants generated greater P3 amplitudes in the "attend" condition; however, restrained eaters had smaller P3 amplitudes to the food odor than nonrestrained eaters. Furthermore, while the nonrestrained eaters showed higher P3 amplitudes to the food odor in the "attend" than the "ignored" condition, this condition effect was not present in restrained eaters. Self-imposed restrictions in eating appeared to alter attention to food, which in turn may influence sensory processing of olfactory information. Restrained eaters could be trying to suppress thoughts about food and, thus, had a smaller attentional allocation to odor compared to nonrestrained eaters. Examination of an earlier P2 response thought to reflect early perceptual categorization revealed that in restrained eaters, latency of the fronto-central P2 to the chocolate odor correlated with the postsession hedonic rating, with shorter latencies in those who rated the odor to be more pleasant.

Food perception may also be subject to the influence of personal food choices not linked to concerns about body weight or shape. Stockburger et al. (2009) examined whether vegetarians' negative affect toward meat makes such stimuli stand out in passive and active viewing tasks. Viewing emotional (unpleasant and pleasant) versus neutral pictures typically results in the increased late positive potential (LPP) occurring between 300 and 700 ms after stimulus onset. Thus, meat stimuli in vegetarians were expected to generate a larger LPP response. The food images included meat, vegetable, and dessert dishes. Meat and vegetable images were matched with respect to amount, form, and colors of the displayed items. In the passive condition, participants were instructed to view the presented images, while in the active task, participants were asked to silently count the dessert pictures. Finally, they classified each food into liked, disliked, or neither groups. Vegetarians almost exclusively evaluated meat dishes as disliked. As anticipated, meat pictures elicited enlarged LPP response over posterior regions in vegetarians compared to omnivores, whereas there were no group differences in LPP to vegetable dishes. The enlarged LPP to meat dishes was present in vegetarians in both active and passive task conditions. These findings indicate that the attention capture by food stimuli can be altered by the emotional salience associated with symbolic meaning (Rozin 1996) due to the implicit stimulus relevance (Ito and Cacioppo 2000).

Recently, Nijs, Franken, and Muris (2008) examined whether processing of food-related information differs in normal-weight and obese individuals. If obesity were associated with enhanced motivation for food, larger P3 and LPP amplitudes for food stimuli would be expected. Furthermore, as LPP and P3 amplitudes reflect motivational tendencies, they should correlate positively with self-report measures of food craving and hunger. Participants passively viewed pictures of palatable foods as well as neutral (office items) pictures after eating a light meal 2 h before the start of the experiment. Centro-parietal P3 and LPP amplitudes were larger in response to food than the office supplies pictures, but there were no group differences. Positive correlations were observed between posterior P3 and LPP amplitudes and self-reported increase of hunger (but not food craving). However, such correlations were present for food cues and the office stimuli. The authors concluded that subjective feelings of hunger affected overall information processing rather than its food-relevant aspects. These findings were interpreted to suggest that obese individuals without explicit eating disorder symptoms might not respond differently to food cues as compared to normal-weight individuals.

34.4.2 fMRI/PET Studies

While energy homeostasis is maintained by monitoring internal status, the natural reward system also responds to external signals, especially the recognition of certain foods as rewards. The mesocorti-colimbic dopamine system – most notably the ventral tegmental area (VTA) and the nucleus accumbens

(NAc) – mediates the processing of reward and pleasure (Kelley and Berridge 2002). In mechanisms overlapping with those of addictive drugs, ingesting palatable foods (especially high sugar or fat), release brain opioids and dopamine in the VTA and NAc (Rada et al. 2005; Avena et al. 2007).

LaBar et al. (2001) investigated the effect of hunger on the regional brain activation using fMRI. Healthy adults were imaged in fasting and fed conditions. Stimuli consisted of food, tools, and Gaussian-blurred objects. Regions of food-specific activation seen more prominently in the fasting scans included amygdala, parahippocampal gyrus, and anterior fusiform gyrus. A conjunction analysis of regions activated across states revealed food-specific effects in insula and extrastriate cortex.

Amygdala inputs to the lateral hypothalamus can promote eating in response to reward recognition by overriding satiety signals (Petrovich and Gallagher 2003). The importance of the reward system in hyperphagia has been highlighted in recent studies that show subjects with high sensitivity to reward are more likely to be overweight (Davis et al. 2004). In a study to investigate the role of reward system in eating, Beaver et al. (2006) found that individuals high in reward drive have more frequent and intense food cravings and are more likely to be overweight or have other eating disorders. Reward drive as measured by the Behavioral Activation Scale has high correlation with activation of limbic system in response to looking at images of appetizing foods. Regions of increased activation included the ventral striatum, amygdala, midbrain, OFC, and ventral pallidum. This study also found that the left OFC is activated in response to appetizing foods and the right OFC is activated in response to disgusting foods.

There is a complex interaction between energy density, dietary composition, and palatability of food (for reviews, see Sorensen et al. 2003; Stubbs and Whybrow 2004). Palatability has multiple definitions and can be defined by a subjective perception or by directly tasting a particular food. Palatability generally rates the perceived or anticipated pleasurable or desirable aspects of a food. In general, as palatability increases, the amount of food consumed increases. Food content is also important, for example, higher fat and higher sugar foods increase feeding and weight gain in experimental models (Sclafani 2004). Adding variety to the diet also increases food intake (reviewed in Sorensen et al. 2003).

Holsen et al. (2005) examined food cues in fasted and fed healthy-weight children and adolescents ranging in age from 10 to 17 years old. Stimuli were the same as those used by LaBar et al. (2001) except that animal figures were substituted for tools. Subjects were asked to fast for 4 h and were given a standardized meal (similar nutrient content) of 500 kcal prior to the fed-state scan. About half the subjects were scanned initially in the fasting state. Participants were asked to remember the images they had seen and were told they would be tested at the end of the scans. Recall of food items was superior in the fasted state. An analysis of food versus nonfood cues across fasting and fed states produced increased regional brain activity in left insula, left inferior frontal cortex, left ventrolateral prefrontal cortex, right parahippocampal gyrus, and bilateral fusiform gyrus. In the fasting condition, a food versus nonfood contrast revealed increased activation in bilateral medial orbitofrontal cortex, left lateral orbitofrontal cortex, left medial frontal cortex, right superior parietal cortex, and bilateral cerebellum/fusiform gyrus regions. An *a priori* analysis was used to detect brain areas responding more greatly to food in the fasted than fed state. Areas with greater food-related activation in the fasting state included right amygdala, right medial orbitofrontal cortex, bilateral regions of the lateral orbitofrontal cortex, left medial frontal cortex, bilateral opercular and insular cortex, right parahippocampal gyrus, right cingulate gyrus, and left fusiform gyrus.

In addition to brain regions involved in energy homeostasis and reward recognition, the prefrontal cortex (PFC) is also active in response to food. There are several theories concerning PFC activation and feeding. The PFC is theorized to be part of a behavioral control circuit acting to restrain the intake of excessive food (Elman et al. 2006). It has also been suggested that the dorsolateral PFC is involved in recognition of long-term rewards, such as health, while the ventrolateral PFC is involved in recognition of immediate rewards (Tanaka et al. 2004). Tataranni and Del Parigi (2003) theorize that a satiation domain is located in the PFC, and an appetite-stimulating domain includes the OFC, insular cortex, anterior cingulate, and hypothalamic regions. They suggest that greater PFC activation is seen

in obese individuals because their hypothalamus and limbic areas are more resistant to satiety signals. Imaging studies have shown greater activation of the dorsal PFC activation in response to food cues in obese versus lean persons and in the fed state versus fasting state (Tataranni and Del Parigi 2003). Activation of the dorsal PFC is also higher in successful dieters versus obese nondieters (Del Parigi et al. 2007). Compared with adults, children were found to have less activation in the medial PFC and dorsolateral PFC when viewing high calorie foods (Killgore and Yurgelun-Todd 2005b).

Stoeckel et al. (2008) investigated whether the brain's reward system may be hyperactive in obese individuals during viewing of food images. Twelve obese and 12 normal-weight women viewed images of high and low calorie foods. The results revealed that in the obese compared with a control group, increased activation was observed in the regions associated with the reward system (amygdala, nucleus accumbens, and orbitofrontal cortex), as well as regions associated with motivational processes (anterior cingulate cortex, caudate nucleus, putamen, hippocampus, insula, and medial prefrontal cortex). In the control group, greater activation by high calorie foods was seen only in dorsal caudate, whereas low calorie foods were associated with greater activity in the lateral orbitofrontal cortex, medial prefrontal cortex, and anterior cingulate cortex.

In a recent review, Stice et al. (2009) reported that compared with normal-weight controls, obese individuals show greater activation of the gustatory cortex (insula/frontal operculum) and oral somatosensory regions (parietal operculum and Rolandic operculum) in response to anticipated consumption of palatable foods. The obese relative to lean individuals also showed less activation in the dorsal striatum in response to consumption of palatable foods and reduced striatal D2 dopamine receptor density. The latter finding suggests that at least in some cases, obesity may be genetically influenced. In an fMRI study by Stice et al. (2008), obese participants with at least one A1 allele of Taq1A (associated with decreased dopamine D2 receptors and compromised dopamine signaling in the striatum) were characterized by increased striatal activation (the caudate and putamen) in response to tasting a milkshake, with the degree of activation negatively associated with weight gain. For those without an A1 allele, increased striatal activation was related to greater weight gain.

34.4.3 Conclusions

Overall, results from ERP, fMRI, and PET studies consistently indicate that personal beliefs and motivational states have a direct effect on food perception. Evidence of such modulation is present even at early, preattentive stages of information processing (e.g., 100 ms after stimulus onset). Interestingly, studies in obese populations are less consistent in their findings – while fMRI data suggest increased activation of the reward system in response to high calorie foods in obese compared with healthy-weight persons, the ERP study failed to observe such group differences in attentional or motivational processes associated with viewing food images, possibly due to the obese group completing a nutritional training prior to the study. Given the evidence of potential genetic contributions to weight gain as well as the role of personal beliefs and opinions, future studies will need to examine food perception processes associated with obesity in greater detail.

34.5 Applications to Other Areas of Health and Disease

Investigations of food perception in typical healthy participants as well as the studies examining effects of food deprivation and hunger paved the way for an improved understanding of food-related behaviors in atypical populations. Prader-Willi syndrome (PWS) is a genetic condition resulting

from the failure to inherit a normal paternal copy of chromosome 15q11–q13, either through uniparental disomy (PWS-UPD), or when two maternal copies of chromosome 15 are inherited, or paternal deletion (PWS-Del) of 15q11–q13. PWS involves excessive eating and food-seeking, morbid obesity, and a distinctive behavioral phenotype including intellectual disabilities. Persons with this disorder are often identified at birth because of failure to thrive and poor muscle tone. Atypical eating behaviors develop in the early childhood. As they become adults, persons with PWS continue to require 24-h per day supervision due to food seeking, compulsivity, and other behavior problems. One major obstacle to studying food-related behaviors in persons with PWS is their tendency to provide socially desirable answers regarding their food choices and preferences during behavioral testing and interviews. Thus, neuroimaging studies offer an opportunity to improve our understanding of the reasons for observed eating behaviors.

Studies examining brain structures involved in processing food cues in persons with PWS reported abnormal patterns of neural activation when compared with normal-weight and obese controls. Holsen et al. (2006) examined nine participants with PWS and nine healthy-weight controls (HWC). fMRI scans were performed before and after eating a standardized meal. During the MRI scans, participants viewed pictures of food, animals, and blurred control images. The HWC group showed greater activation in the amygdala, orbitofrontal cortex, medial prefrontal cortex, and frontal operculum in the premeal scans when compared with their postmeal scans. The PWS group showed greater activation in the orbitofrontal cortex, medical prefrontal cortex, insula, hippocampus, and parahippocampal gyrus in the premeal scans when compared with their postmeal scans. Persons with PWS showed greater activation to food images after the meal than did the HWC (see also Dimitropoulos and Schultz 2008). Miller et al. (2007) used fMRI to investigate the response of individuals with PWS to food images after ingestion of an oral glucose load. Eight adults with PWS and eight normal-weight adults underwent fMRI while viewing food images after glucose loading. Relative to controls, participants with PWS produced greater activation in the ventromedial prefrontal cortex, suggesting that increased reward value for food may contribute to the excessive hunger commonly experienced by persons with PWS. Interestingly, in a study examining food preferences where participants viewed pictures of highly preferred foods and imagined eating them, Hinton, Holland, and Owen (2006) did not observe any increases in the activation of regions associated with food reward or incentive (amygdala, medial orbital frontal cortex) in adults with PWS (n = 13) compared to healthy-weight typical controls. Thus, although persons with PWS have reliable food preferences, their aberrant satiety may override input from pathways related to rewards from food. If so, aberrant satiety could lead to more indiscriminate food selections, and other properties of food than taste preference alone may be important in food perception and selection in PWS.

In a recent study, Key and Dykens (2008) used ERPs to examine the effect of the genetic subtype of PWS on food perception in 17 adults with PWS (8 UPD, 9 deletions). Given anecdotal evidence of persons with PWS consuming inappropriate food (e.g., raw meats, discarded food), the stimuli in the study (see Fig. 34.4) included color photographs not only of typical palatable foods, but also images of unusual combinations (e.g., an ice cream with bacon strips), and contaminated foods (e.g., a cake with bugs on it). Participants were asked to view the pictures and think whether they would consider eating the depicted foods. Group differences were observed for the N1 and P3 responses, reflecting perceptual categorization and motivational relevance, respectively. More specifically, the two genetic subtypes of PWS differed in their food perceptions processes. Analyses of the N1 amplitude indicated that participants in the deletion group categorized food stimuli in terms of composition (e.g., a hot dog vs hot dog with mustard) and seemed to ignore the quality dimension (odd combinations or contaminated foods). Those in the UPD group performed more similar to the typical controls and initially discriminated stimuli based on the suitability for consumption (i.e., separating
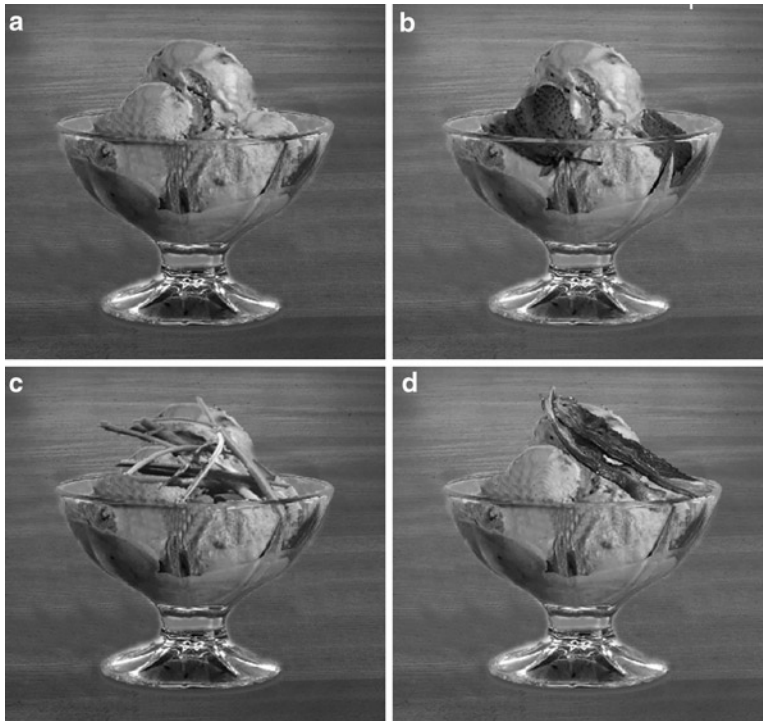
Fig. 34.4 Sample stimuli used in an ERP study of food perception in adults with Prader-Willi syndrome (Key and Dykens 2008). a, b, c, d. (**a**) Single palatable food (ice cream); (**b**) combined palatable foods (ice cream and strawberries); (**c**) single palatable food (ice cream) contaminated by a nonfood element (grass); (**d**) mismatched combination of two palatable foods (ice cream and bacon)

contaminated foods from the rest; see Fig. 34.5). The controls performed the most extensive discrimination, separating contaminated or combined stimuli from mismatched and single foods, respectively. Importantly, these early discrimination effects could not be attributed exclusively to the basic visual properties of the pictures or differences in individual food preferences, as the same food items appeared in each of the four conditions, and minor additions to the same original "single" food were used to create mismatched and contaminated stimuli. The condition effects observed in the P3 time window for all participants with PWS reflect the highly arousing, motivating, and salient nature of food images. The control participants did not show this later ERP effect most likely because they did not have hyperphagia, and given the passive nature of the task and the absence of an acute interest in food, their categorization of the stimuli could have been fully completed prior to the P3 time range. In contrast, persons with PWS show much greater interest in food and may be prone to carry out more extended analyses of food options.

Holsen et al. (2009) used fMRI to examine genetic subtype differences in persons with PWS in response to food images. Compared with the healthy-weight control group, both the deletion and UPD subgroups showed greater activity in response to food stimuli both before and after consuming a meal. Relative to the UPD subgroup, the deletion subtype showed increased activation of the food motivation network, especially in the medial prefrontal cortex and amygdala, regardless of the meal condition. In contrast, the UPD group showed greater activation postmeal in the dorsolateral prefrontal cortex and parahippocampal gyrus. The authors concluded that the deletion subgroup is characterized by reduced behavioral inhibition in response to food, whereas persons with UPD may be more able to maintain cognitive control over food-related impulses.

Fig. 34.5 Occipital ERP
waveforms in response to
food images in controls and
persons with PWS. Average
waveforms at 100 ms after
stimulus onset (marked as
N1) reflect group differences
in perceptual categorization
of the food stimuli. While the
control and PWS-UPD
groups processed images of
contaminated foods as a
separate category, the brain
activity of persons in the
PWS-deletion group failed to
reflect the same discrimina-
tion (Adapted from Key and
Dykens 2008. With
permission)
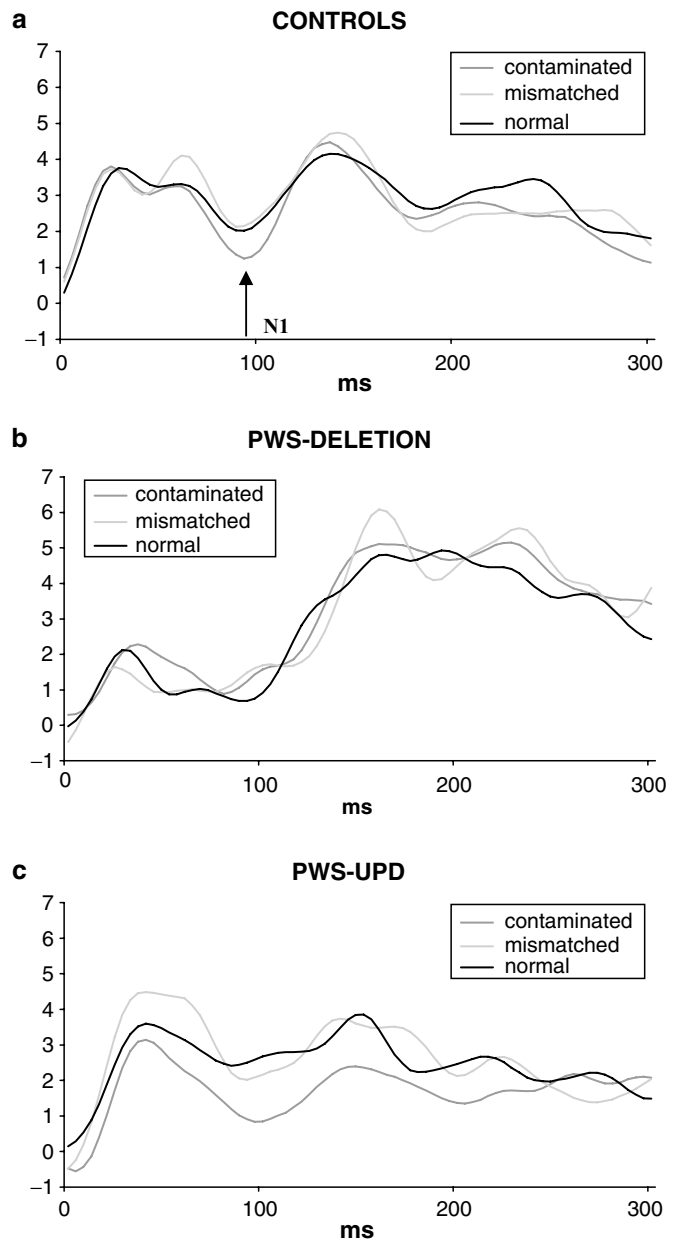
Summary Points

- Food-related stimuli are processed in the brain similar to other attention-grabbing and motivation-
  ally salient stimuli.
- Perception of food stimuli can be modulated by information from other modalities and/or by
  personal beliefs and motivational states.
- Brain responses to food stimuli change with age, progressing from basic sensory processing to
  more advanced analysis involving higher cognitive functions.
- Obesity may or may not be associated with altered food perception.
- Genetic characteristics may have an effect on brain processing of food-related information.

Definitions and Explanations

Electroencephalogram (EEG): A recording of electrical activity of the brain using electrodes placed on the scalp, typically described in terms of signal frequencies.

Event-related potential (ERP): A temporary brief change in EEG associated with an external or internal stimulus event, typically described as a sequence of negative and positive peaks.

Functional magnetic resonance imaging (fMRI): An imaging method that uses changes in brain blood flow to indirectly assess regional neuronal activity.

Positron emission tomography (PET): A nuclear imaging technique that uses radioactive tracers to measure local brain metabolism, blood flow, and cellular constituents such as neurotransmitter receptors and transporters.

Prader-Willi syndrome (PWS): A genetic disorder occurring in 1 of 10,000 live births and resulting from deletion of a set of genes on the paternal chromosome 15 (15q11–13) or an erroneous inheritance of two copies of the chromosome from the mother. In addition to mild-to-moderate intellectual disability, persons with PWS are characterized by an extreme, insatiable appetite, leading to chronic overeating (hyperphagia) and early onset obesity.

References

Avena NM, Rada P, Hoebel BG. Neurosci Biobehav Rev. 2007;32(1):20–39.

Beaver JD, Lawrence AD, van Kitzhuijzen J, Davis MH, Woods A, Calder AJ. J Neurosci. 2006;26(19):5160–6.

Carretie L, Mercado F, Tapia M. Motivation Emotion. 2000;24(1):1–12.

Cone RD. Nat. Neurosci. 2005;8(5):571–8.

Davis C, Strachan S, Berkson M. Appetite. 2004;42(2):131–8.

Del Parigi A, Chen K, Salbe AD, Hill JO, Wing RR, Reiman EM, Tataranni PA. Int J Obes. 2007;31:440–8.

Dimitropoulos A, Schultz R. J Autism Dev Disord. 2008;38(9):1642–53.

Elman I, Borsook D, Lukas SE. Neuropsychopharmacology. 2006;31(10):2091–120.

Gordon CM, Dougherty DD, Rauch SL, Emans SJ, Grace E, Lamm R, Alpert NM, Majzoub JA, Fischman AJ. Int J Eat Disord. 2000;27(2):163–71.

Hinton EC, Holland AJ, Owen AM. J Obesity. 2006;31:390–1.

Holsen LM, Zarcone JR, Thompson TI, Brooks WM, Anderson MF, Ahluwalia JS, Nollen NL, Savage CR. Neuroimage. 2005;27(3):669–76.

Holsen L, Zarcone J, Brooks W, Butler M, Thompson T, Ahwlualia J, Nollen N, Savage C. Neuropsychopharmacology. 2006;14:1028–37.

Holsen L, Zarcone J, Chambers R, Butler M, Bittel D, Brooks W, Thompson T, Savage C. Int J Obes. 2009;33:273–83.

Ito TA, Cacioppo JT. J Exp Soc Psychol. 2000;36:660–75.

Kelley, AE. Neurosci Biobehav Rev. 2004;27(8):765–76.

Kelley AE, Berridge KC. J Neurosci. 2006;22:3306–11.

Kemmotsu N, Murphy C. Physiol Behav. 2006;87:323–9.

Kettenmann B, Mueller C, Wille C, Kobal G. Chem Senses. 2005;30:i234–5.

Key AP, Dykens EM. J Intellect Disabil Res. 2008;52:536–46.

Killgore WD, Young AD, Femia LA, Bogorodzki P, Rogowska J, Yurgelun-Todd DA. Neuroimage. 2003;19(4):1381–94.

Killgore WD, Yurgelun-Todd DA. Neuroreport. 2005a;16(8):859–63.

Killgore WD, Yurgelum-Todd DA Dev Psychobiol. 2005b;47:377–97.

Killgore WD, Yurgelun-Todd DA. Int J Neurosci. 2007;117(5):643–53.

LaBar KS, Gitelman DR, Parrish TB, Kim YH, Nobre AC, Mesulam MM. Behav Neurosci. 2001;115(2):493–500.

Lorig TS, Schwartz GE. Psychobiology. 1988;16:281–4.

Martin G. Int J Psychophysiol. 1998;30:287–302.

Marzo V, Matias, I. Nat Neurosci. 2005;8(5):585–9.

Miller J, James GA, Goldstone A, Couch J, He G, Driscoll D, Liu Y J Neurol Neurosurg Psychiatry. 2007;78:615–9.

Munzberg H, Myers MG Jr. Nat Neurosci. 2005;8(5):566–70.

Nijs I, Franken I, Muris P. Eat Behav. 2008;9:462–70.

Petrovich GD, M Gallagher. Ann N Y Acad Sci. 2003;985:251–62.

Rada P, Avena NM, Hoebel BG. Neuroscience. 2005;134:737–44.

Rolls BJ, Drewnowski A, Ledikwe JH. J Am Diet Assoc. 2005;105(5):S98–103.

Rozin P, Vollmecke TA. Annu Rev Nutr. 1986;6:433–56.

Rozin P. Curr Dir Psyc Sci. 1996;5(1):18–24.

Sclafani A. Physiol Behav. 2004;81(5):773–9.

Sorensen LB, Moller P, Flint A, Martens M, Raben A. Int J Obes Relat Metab Disord. 2003;27(10):1152–66.

Stacher G, Bauer H, Steinringer H. Physiol Behav. 1979;23:325–31.

Stice E, Spoor S, Bohon C, Small DM. Science. 2008;322:449–52.

Stice E, Spoor S, Ng J, Zald D. Physiol Behav. 2009;97(5):551–60.

Stockburger J, Hamm A, Weike A, Schupp H. Behav Neurosci. 2008;122:936–42.

Stockburger J, Renner B, Weike A, Hamm A, Schupp H. Appetite. 2009;52:513–16.

Stoeckel L, Weller R, Cook III E, Twieg D, Knowlton R, Cox J. Neuroimage. 2008;41(2):636–47.

St-Onge MP, Sy M, Heymsfield SB, Hirsch J. J Nutr. 2005;135(5):1014–8.

Stubbs RJ, Whybrow S. Physiol Behav. 2004;81(5):755–64.

Tanaka S, Doya K, Okada G, Ueda K, Okamoto Y, Yamawaki S. Nat Neurosci. 2004;7:887–93.

Tataranni PA, Del Parigi A. Obes Rev. 2003;4(4):229–38.

Toepel U, Knebel J-F, Hudry J, le Coutre J, Murray M. Neuroimage. 2009;44:967–74.

Zani, A, Proverbio, AM. In: Zani A, Proverbio AM, editors. The cognitive electrophysiology of mind and brain. San Diego:Academic; 2003pp. 3–12.

Part V
General and Normative Aspects: Behavioral and Psychological

Chapter 35
The Breastfed Infant's Neurobehavioral Organization: Implications for Child Health and Cognitive Development

Sybil L. Hart, Shera C. Jackson, and L. Mallory Boylan

Abbreviations

AD/HD	Attention-deficit/ hyperactivity disorder
DHA	Docosahexaenoic acid
EEG	Electroencephalogram
EKG	Electrocardiogram
NBAS	Neonatal Behavioral Assessment Scale
REM	Rapid eye movement, or active, sleep state
SIgA	Secretory Immunoglobulin A

35.1 Introduction

With increasing regularity and conviction, breastfeeding is being advocated by American health organizations, including the American Academy of Pediatrics (AAP 2005), the American College of Obstetricians and Gynecologists (ACOG 2003), the American Academy of Family Physicians (AAFP 2007), the Surgeon General (Galson 2008), and the US Department of Health and Human Services Office on Women's Health (DHHS 2000), as well as major international organizations, such as the World Health Organization (WHO) and United Nations Children's Fund (WHO/ UNICEF, 2003; WHO/UNICEF/USAID/SIDA, 2009). The growing consensus has halted decreases in breastfeeding rates during the twentieth century that coincided with urbanization, technologic advances, and changing patterns of family life (Lawrence and Lawrence 2005). Although trends in breastfeeding began to change in the 1960s, and rates for 6-month-olds in the US rose from approximately 8% in 1971 (Lawrence and Lawrence, 2006) to approximately 43% in 2005 (CDC 2008), current levels still fall short of the Healthy People 2010 (2005) target of 50%. Similarly, exclusive breastfeeding (in which breast milk is not complemented by formula) occurs at rates of 12%, which is less than half the targeted rate of 25%.

S.L. Hart (✉)
Texas Tech University, Department of Human Development and Family Studies,
Lubbock, TX 79409-1230
e-mail: Sybil.hart@ttu.edu

Table 35.1 Key facts about breastfeeding

The breastfeeding mother
- is usually older, more educated, married, and has a higher income;
- in the United States, is more likely to be Asian, Pacific Islander, White, or Latino than non-Latino, American Indian, Alaskan, or Black/African American;
- has later return to fertility;
- has lower incidence of obesity, osteoporosis, premenopausal female-related cancers;[a] and
- may be protected from anxiety and depression;[b]
- in rare instances, breastfeeding is contraindicated. These circumstances pertain primarily to compromised maternal health and medication usage, e.g., HIV positive, HTLV-1.[a,c]

The breastfed infant
- has larger head circumference and is leaner;
- has lower incidence of GI disorders and infections, e.g., cholera, diarrhea, and otitis media, due to superior immune functioning;
- has sometimes been found having lower incidence of obesity, allergies, asthma, diabetes, cancers, cardiovascular disorders, and SIDS.[a,d]

[a]Centers for Disease Control and Prevention (2008), US Department of Health and Human Services (2000)
[b]Kendall-Tackett (2008)
[c]Field (2008), Hale (2008)
[d]Walker (2008)

Calls by health organizations, and the resurgence they brought about, have been driven primarily by mounting evidence of health benefits to breastfed infants and their mothers (see Table 35.1). To a lesser extent, breastfeeding is being promoted on the basis of advantages to cognitive development (Lucas et al. 1992; see Chap. 88). In this chapter we focus on the manner in which breastfeeding contributes to the young infant's neurobehavioral development. We consider differences between behaviors of breastfed versus bottle-fed infants, and how findings on various contrasts might explain or help account for some of the apparent benefits of breastfeeding to infant health and cognitive development.

35.2 NeuroBehavioral Development of the Breastfed Infant

Infant behavior has been of longstanding interest to parents. In recent years it has received increasing attention in the fields of developmental psychology and neuro-psychology. Contrastingly, infant behavior *as a function of breastfeeding* has a longer tradition of receiving attention by scholars in the fields of nutrition, nursing, medicine, and public health. Partly as a result of differences in the emphasis on feeding, and due to distinctions between the various disciplines in terms of their goals and methodological approaches, works touching on the breastfed infant's behavior have been scattered across a wide array of outlets, and infant behavior itself has been characterized in disparate ways. As we draw on these literatures, our focus will be on three broad constellations of infant behavior and their biophysiological correlates (Thoman et al. 1972). Following formulations in which the infant's neurobehavioral functioning is conceptualized as being organized on a continuum of "state," or level of consciousness spanning from deep sleep to crying (Als 1978; Brazelton and Nugent 1995), we will explore the two constellations of behavior that appear at either end of this continuum, and a third that appears toward its center, and includes social interaction skills and signs of alertness.

35.2.1 Crying

Early work in which 3- and 4-day-old infants were observed while exposed to sensory stimulation 30 min prior to feeding found that fussing and crying were more frequent among breastfed than bottle-fed infants (Bell 1966). Research on 2-day-olds' responses to different types of soothing techniques, such as rocking and being held upright (Korner and Thoman 1972), found that soothing methods were equally effective among breast- and bottle-fed infants. However, once the intervention had been terminated breastfed infants were more likely to cry. Based on mothers' diary accounts of crying, Bernal (1972) reported that durations of crying on days 5 through 9 among breastfed infants (84 min/day) were greater than those of bottled-fed infants (69 min/day). In a study of the neonate's response to auditory stimulation (Algeria and Noirot 1978), 3-day-olds were more likely to cry if they were being breastfed. In these early studies, findings that breastfed infants demonstrate greater crying were not explained, although several authors mentioned that hunger may have been a factor, especially in light of difficulty some mothers had reported in adhering to current recommendations to breastfeed on a 4-h schedule.

Despite trends in early studies that revealed greater crying among breastfed infants, there were exceptions, such as research by Simmons, Ottinger, and Haugk (1967). This work, comparing neonates before and after feeding, was conducted with the aim of determining the contribution of maternal characteristics. In addition to reporting greater crying among neonates of mothers with higher levels of prenatal anxiety, these investigators noted that crying prior to feeding was greater among bottle-fed infants.

A number of more recent studies have taken approaches that involve observations across lengthier blocks of time, as well as longitudinal designs which draw on parents' 24-h diary entries to discern diurnal variation and patterns of change across the first few months of life. Data based on researchers' observations during 4-h home visits when infants were 1 and 3 months of age (Crockenberg and Smith 1982) reported no differences in durations of crying between breast- versus bottle-fed infants. Using parents' diaries, a longitudinal study across the first 4 months of life (Lee 2000) found that crying peaked at 7 weeks, and differences between breastfed versus bottle-fed infants were nonsignificant. Barr, Kramer, Pless, Boisjoly, and Leduc (1989) found that by the age of 6 weeks overall durations of crying among breastfed infants (93 min/day) and bottle-fed infants (89 min/day) did not differ. They did observe, however, that breastfed infants' crying was more evident during the afternoon and evening, and disbursed across shorter, though more frequent, episodes.

A detailed longitudinal study by Lucas and St James-Roberts (1998) reported on durations of crying as well as colic, which was defined as intense, unsoothable crying, possibly due to pain. They found that whereas durations of crying among bottle-fed infants peaked at 2 weeks, durations among breastfed infants continued to increase until 6 weeks at which point durations among breastfed infants (52 min/day) exceeded those of formula-fed infants (36 min/day). Notably, findings on colic were reversed. Durations among 2-week-olds who were bottle-fed (23 min/day) exceeded those of infants who were breastfed (4 min/day). Similarly, a survey study (van der Wal et al. 1998) reported that "problematic crying," which was defined as crying which lasted for more than 3 h per day, was more likely to occur among formula-fed than breastfed infants.

Crying has also been assessed under conditions where it is elicited by painful procedures, like heel lances and venepuncture. In research on newborns' responses during a blood collection procedure, Gray, Miller, Philipp, and Blass (2002) found that infants who were permitted to breastfeed during the procedure spent less time crying (8.7 s) than controls (72.1 s) who lay swaddled in their bassinettes. This dramatic difference was mirrored by corresponding findings on heart rate. It has also been supported by studies on infants' responses to immunization injections (Abdel Razek and Az El-Dein 2009). To explore mechanisms that underlie the analgesic properties of breastfeeding, a number of

studies have incorporated control group conditions in which infants are provided with skin-to-skin contact, pacifiers, and sucrose solutions (Carbajal et al. 2003; Dilli et al. 2008; Efe and Ozer 2007; Reis et al. 2003). Generally, these find that breastfeeding is at least as effective as the combination of sucrose and a pacifier toward alleviating pain (Shah et al. 2007). Potentially, an argument for a unique effect of breastfeeding can be derived from work which compared four groups of breastfed infants on effects of glucose and/or breastfeeding within 45 min prior to inoculation (Gradin et al. 2004). This study found that the duration of crying among infants who had not received the 1 mL dose of glucose was greater (142 s) than that among infants who had received glucose (93 s). Crying was lower among infants who had been breastfed beforehand (63 s), and lowest among infants who had been breastfed beforehand and had also received glucose (18 s). The combined effects of prior breastfeeding and sucrose are striking. Whether they are limited to breastfed infants is unknown.

Taken together, these studies appear to suggest subtle differences. Peak durations of crying seem to occur later among breastfed infants whose episodes of crying appear also to be shorter in duration and more frequent. Bottle-fed infants may be more likely to cry with greater intensity. Whether breastfeeding reflects unique advantages to pain threshold is still unclear.

35.2.2 Alertness and Social Behavior

The quality of infants' neurobehavioral organization has been assessed using the Neonatal Behavioral Assessment Scale (NBAS; Brazelton and Nugent 1995). This instrument's 18 reflex items and 28 behavioral items are administered individually by a trained researcher during a 30–45-min procedure, generating data which are then reduced, usually to seven cluster scores (Lester et al. 1982), which reflect adequacy of different competencies (see Table 35.2). Since its introduction in the 1970s, the NBAS has become the dominant neonatal behavioral assessment, having been used in several hundred studies on intrauterine deprivation, maternal substance abuse, cesarean section, under-nutrition, prematurity, as well as cross-cultural studies. Although long-term predictive validity of the NBAS has not been established, the instrument is widely regarded as a valid descriptor of contemporary behavior (Lester and Tronick 2001).

The NBAS has been used in several studies which compared breastfed versus bottle-fed infants. Using neonates at the age of 37 h, DiPietro, Larson, and Porges (1987) explored effects of feeding method on NBAS performance as well as on several physiological measures of neurobehavioral functioning. Breastfed infants were found having longer heart rate, elevated heart period variability, and higher vagal tone, suggesting more optimal physiological organization. In contrast, breastfed infants' performance on the NBAS yielded scores on the *Range of State* cluster which suggested greater irritable reactivity. A small-scale study with 6-day olds (Maekawa et al. 1984) found that performance on the NBAS did not differ with the feeding method.

A third comparison (Hart et al. 2003) between breastfed vs. bottle-fed infants' performance on the NBAS used infants who were 9 days old. It was reasoned that because breastfeeding is more likely to have been established by this point (Lawrence and Lawrence 2006), it would be less likely that any differences between the two feeding groups would be confounded by differences in milk intake (Dollberg et al. 2001). In line with indications of the breastfed infant's more optimal physiological organization (DiPietro et al. 1987), findings revealed that breastfed infants had fewer *abnormal reflexes*, and surpassed formula-fed infants on items in the *orientation*, *motor*, and *range of state* clusters. These findings suggest exceptionally dramatic differences in favor of the breastfed newborn in terms of neurological organization, social interactive capacities, and especially in quality of alertness (see Figs. 35.1–35.4).

Table 35.2 Brazelton neonatal behavioral assessment scale (NBAS) clusters (From Brazelton and Nugent 1995; Lester and Tronick 2001; and http://www.brazelton-institute.com)

Cluster	Description of items
Habituation	The four items in this cluster assess the infant's ability to screen out aversive stimuli, including repeated auditory, visual, and tactile stimulation, while asleep. Scores are based on infant responses that are elicited by the examiner. For example, repeated presentation of bright light during the *response decrement to light* item is scored highest by the infant who transitions from sleep to drowsy states and back to sleep after only a few presentations of the light, suggesting superior skill in blocking out aversive stimulation thereby modulating level of consciousness with efficiency.
Orientation	This cluster includes seven items which assess the quality of overall alertness and the ability to attend to social and nonsocial stimuli during presentation by the examiner. A high score on the *animate visual* item, for example, is obtained by the infant capable of visually focusing on the examiner's face and tracking it smoothly as it moves in a range of directions.
Motor system	This cluster's five items evaluate qualities of muscle tone, and the control, integration, and symmetry of movement. Scores are based on an infant's elicited and spontaneously exhibited behaviors throughout the examination procedure. For example, the motor *maturity* item is scored more highly if movement of the arm involves smooth, wide-arc cycling rather than jittery or floppy motion.
Range of state	The four items in this cluster assess an infant's elicited and spontaneous *state*, i.e., level of consciousness, from deep sleep to full cry, and response to stressful stimulation. For example, the *rapidity of build-up* item addresses the onset of crying. Crying that is displayed only in response to a fair amount of stressful stimulation is scored higher than crying which is reached immediately and in response to minimal stress, or if crying fails to occur under even the most stressful conditions.
Regulation of state	These four items capture the infant's ability to modulate level of consciousness and cope with stressful stimulation. Scores are based on an infant's elicited and spontaneously exhibited behaviors throughout the examination procedure. For example, the *hand-to-mouth* item assesses the infant's capacity to self-sooth by voluntarily placing her hand or fist in her mouth and sucking on it for periods up to 15 s.
Autonomic stability	This cluster includes three items which record signs of stress related to homeostatic adjustments of the central nervous system. These include elicited and spontaneously occurring instances in which an infant exhibits markers of physiological stress, including tremors, startles, and changes in skin color.
Reflexes	The 18 items in this cluster aim to reflect the infant's neurological status. Scores are based on the infant's display of reflexive behaviors that are elicited by the examiner. For example, the *rooting* reflex is elicited by gently stimulating a corner of the mouth. The infant's head-turn toward the source of stimulated and movement of the mouth are scored more optimally than over-active mouthing or weak and misdirected movements.

35.2.3 Sleep

Several of the studies mentioned earlier also inquired into the quality and architecture of sleep. Differences in the duration of sleep were explored in a number of works in which contrasts between breast- and bottle-fed infants' sleep were addressed indirectly. Several of these studies reported that sleep duration did not differ with feeding method (Doan et al. 2007; Macknin et al. 1989; Parmelee et al. 1961; Quillin and Glenn 2004). Similarly, research that was more directly related to these contrasts,
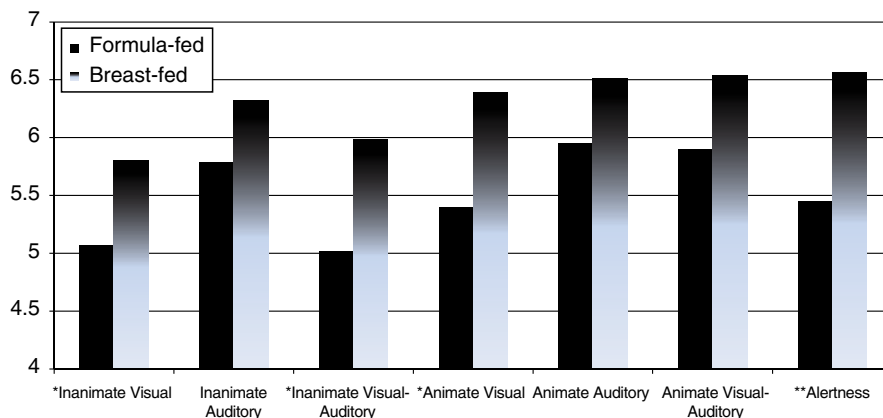
Fig. 35.1 Scores of breast- and bottle-fed 9-day-old infants on the *Orientation* cluster of the NBAS (From Hart et al. 2003). Higher scores denote superior performance; *denotes differences between pairs of means at $p < .05$; ** denotes differences between pairs of means at $p < .01$
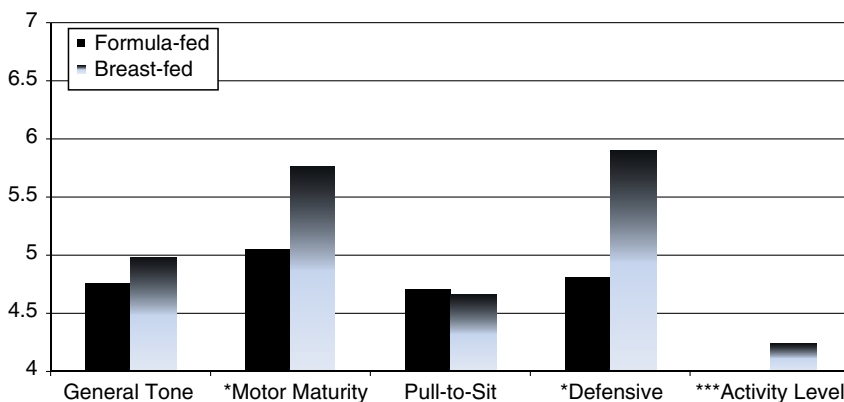
Fig. 35.2 Scores of breast- and bottle-fed 9-day-old infants on the *Motor* cluster of the NBAS (From Hart et al. 2003). Higher scores denote superior performance; *denotes differences between group means at $p < .05$; *** denotes differences between group means at $p < .001$
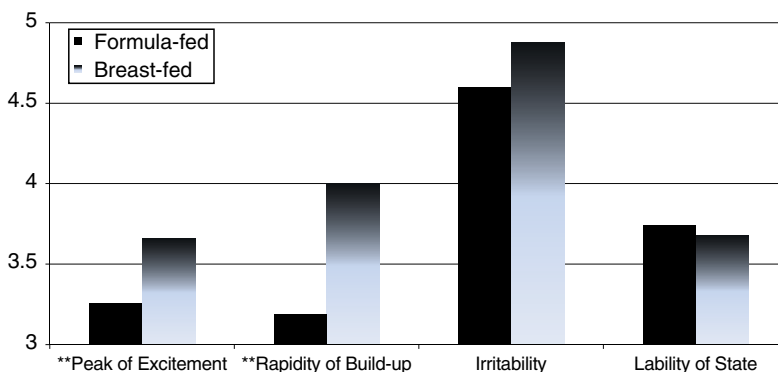
Fig. 35.3 Scores of breast- and bottle-fed 9-day-old infants on the *State Organization* cluster of the NBAS (From Hart et al. 2003). Higher scores denote superior performance; ** denotes differences between group means at $p < .01$
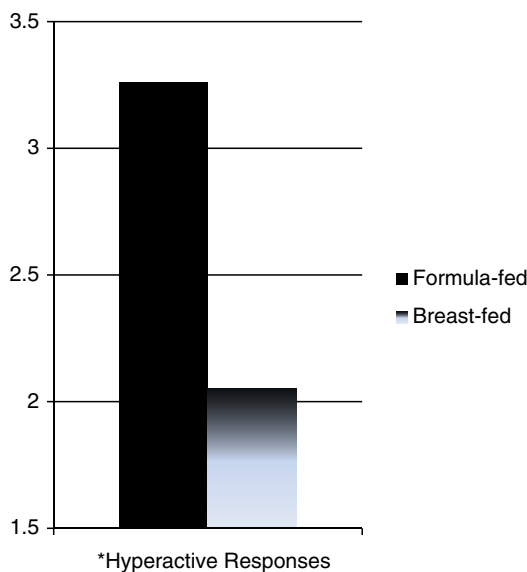
Fig. 35.4 Scores of breast- and bottle-fed 9-day-old infants on the *Reflexes* cluster of the NBAS (From Hart et al. 2003). Higher scores denote inferior performance; *denotes a difference at the level of $p < .05$ between this pair of means

such as the study of day-old neonates by DiPietro and associates (1987), reported that breastfed infants' sleep did not differ from that of bottle-fed infants. Diary data over a period of months (Lucas and St James-Roberts 1998) again found no differences in sleep duration between breastfed versus bottle-fed 2- and 6-week olds. In contrast, in their study of 6-day olds, Maekawa and associates (1984) found breastfeeding associated with infants spending more time asleep. Correspondingly, a longitudinal diary report (Lee 2000) noted that breastfed infants spent more time asleep.

Differences have also been sought in terms of frequency of awakening or length of sleep episode. Some studies reported no differences (Alley and Rogers 1986; Anders 1979). More recently, however, Lee's (2000) longitudinal study reported that frequency of awakening was greater among breastfed infants. Ball (2003) reported that feeding group differences were nonsignificant at 1 month but by 3 months, breastfed infants were found awakening more frequently. More frequent awakening was also reported in longitudinal research that was carried out over a period of 2 years (Elias et al. 1986). These investigators noted that the breastfed infant's pattern of adopting shorter sleep episodes appeared to be maintained into the second year among those who had not yet been weaned.

Latency to fall asleep was explored by Maekawa and associates (1984). Their study of 6-day olds found breastfeeding associated with infants falling asleep more quickly. This small-scale study is rather unique. Besides including detailed observations during large time blocks, it utilized a "within subjects" design in which each infant was exposed to both breast milk and formula, and so it stands out as a rare instance of experimental treatment in a field dominated by quasi-experimental approaches since group assignment is almost always based, due to ethical constraints, on self-selection. Higher levels of tryptophan in breast milk and formula have been associated with shorter sleep latency (Steinberg et al. 1992). As concentrations of tryptophan are typically higher in breast milk than formula (Lawrence and Lawrence 2006), corresponding differences in sleep behavior have been expected.

Finally, sleep behavior has been explored in terms of depth as well as arousability, that is, the ability to be awakened from sleep. In research with 1-day olds, DiPietro found no differences on

physiological measures, including electrocardiogram (EKG), and behavioral measures of rapid eye movement (REM) or active sleep and respiratory regularity function. However, work with 6-day olds by Maekawa and associates (1984) reported that breastfed infants spent greater amounts of time in deep sleep. A longitudinal study (Horne et al. 2004) on arousability of infants at three stages of age, 3 weeks, 2.5 months, and 5.5 months, revealed that 2.5-month olds are more easily awakened from active sleep if they are breastfed.

Overall, the few studies which explored the breastfed infant's sleep find evidence of subtle distinctions. Findings are still equivocal, but at present findings beyond the early neonatal stage appear to suggest that in the breastfed infant, sleep latency is shorter, awakening is more frequent which results in shorter sleep episodes, and arousability is greater.

35.3 Applications

Having discussed contrasts between breast- and bottle-fed infants, in the sections that follow we turn to examining features of the breastfed infant's behavior that may act as a moderating influence on child health and cognitive development. Rather than viewing infant behavior as an outcome measure, these works tend to regard infant behavior, or some aspect of behavior, as a driving influence on physical or psychological development.

35.3.1 Child Health

Breastfeeding has been associated with reduced risk for Sudden Infant Death Syndrome (SIDS) (Ford et al. 1993; Vennemann et al. 2009b). Defined as infant deaths that occur suddenly and unexpectedly, and whose manner and cause of death are not immediately obvious prior to investigation, SIDS is the leading cause of infant mortality in infants under 12 months in the United States, accounting for 2,250 deaths annually. Most cases occur in infants between the ages of 2 and 4 months (two websites on July 8, 2009: http://www.mayoclinic.com/health/sudden-infant-death-syndrome/DS00145 http://www.cdc.gov/SIDS/). By some estimates (Vennemann et al. 2009a), breastfeeding has been associated with a 50% reduction in rates of SIDS. The underlying mechanism is poorly understood but may relate to an infant's level of arousability under conditions marked by exceptional vulnerability. This was brought to light in longitudinal research which explored the nature of cortical arousal during sleep (Richardson et al. 2008). This study explored arousability in infants at the ages of 3-weeks, 2.5 months, and 5.5 months during deep/quiet and light/active sleep in both the prone and supine positions. Using physiological and electroencephalogram (EEG) markers, the investigators discovered increased proportions of cortical arousals among 2.5 month-olds while in the prone position, when vulnerability to SIDS is greatest. The investigators postulate that the enhanced propensity for cortical arousal may serve as a protective mechanism to promote arousal while an infant is especially vulnerable, either due to sleep position or period of maturation. Indeed, these results seem compatible with findings that breastfed infants were more easily aroused than formula fed infants at the age of 2.5 months (Horne et al. 2004).

These findings also beg the further question, how does breastfeeding relate to arousability? One possibility relates to sleeping arrangements, such as cosleeping, which tends to coincide with breastfeeding (McKenna et al. 2007). Another pertains to breast milk composition. Often explored in relation to sleep through attention to factors, such as tryptophan, responsible for inducing sleep (Sanchez et al. 2009) breast milk composition has also been explored with respect to factors associated with

arousability. These point to the role of docosahexaenoic acid (DHA) which has more often been investigated for its contribution to visual and neural development (Innis 2009). A small-scale study (Cheruku et al. 2002) explored associations between mothers' levels of plasma phospholipid DHA and several measures of sleep in their 1- and 2-day-old infants. In addition to finding differences in active and quiet sleep, the study reported greater wakefulness in 2-day olds of mothers with higher DHA.

In another area where health issues relate to sleep, the breastfed infant's sleep behavior has also been found associated with later risk for bed-wetting (Barone et al. 2006). Barone and associates reported a lower incidence of nocturnal enuresis among children who had been breastfed than matched controls who had been bottle-fed. They cited neurodevelopmental advantages associated with DHA as a possible underlying mechanism. Although risk for enuresis may be moderated by DHA, perhaps through its association with greater wakefulness (Cheruku et al. 2002), Barone's study has been questioned (Bennett 2006), largely for reliance on retrospective data, and so further work is needed before this possibility is substantiated.

It may be of interest to speculate on whether the breastfed infant's sleep behavior could relate to findings on obesity. Among several factors that have been found associated with risk for childhood overweight, recent research (Gillman et al. 2008; Taveras et al. 2008) identifies both breastfeeding and increased sleep as protective influences. The interrelationship between these two predictors is still unclear. Given that breastfeeding has at times been identified as being causally related to superior quality and duration of sleep (Lee 2000; Maekawa et al. 1984), it is possible to speculate that some aspect of breastfeeding plays the more fundamental role.

Finally, we might speculate on the possibility that the infant's capacity to perceive and regulate painful stimuli is moderated by breastfeeding. Evidence for this is still scant but its unveiling would account for some degree of robustness that generalizes across a range of health-related conditions that involve tolerance for discomfort.

35.3.2 Social and Cognitive Functioning

Research on infant cognition that has burgeoned during the past few decades has generated compelling evidence that the infant's perception of environmental stimuli and the ability to learn from such exposure is mediated by her current state (Cohen et al. 2006; Thoman 2001). It has also been well established that learning occurs during all the infant states. The crying infant learns to withdraw from painful stimuli, and as shown in research on infants' performance of the *Habituation* cluster of the NBAS, infants learn even while asleep. Indeed, the sleeping infant learns to filter sensory and perceptual stimuli, and if these are found to be sufficiently aversive, the high functioning infant will learn to screen them out completely. However, the most optimal state for learning to take place is one in which the infant is awake and alert. For example, research on memory in 3-month olds (Ohr et al. 1989) showed that the ability to re-learn a forgotten skill, in this case, the ability to activate a toy mobile using a kicking technique, depended on whether the infant happened to be alert or crying during the period in which the skill was being acquired. Findings revealed that upon returning to the lab a week following training, infants who had cried during the initial training visit were unable to reactivate the kicking technique, whereas those who had not cried had no difficulty.

The breastfed infant's more optimal performance of the NBAS, and especially behaviors which suggest superior alertness (Hart et al. 2003), may reflect the enhancing effects of some component of breast milk. For example, breastfed infants' more optimal performance on the NBAS has been found associated with naturally occurring higher concentrations of cortisol, SIgA, and DHA in breast milk (Hart et al. 2004, 2006). DHA may be especially important to neurological development

and intelligence, and more specifically, to key features of intellectual functioning, such as the ability to maintain attention. For example, a longitudinal study by Colombo and associates (2004) of infants and toddlers across the first 2 years of life explored maternal DHA levels at delivery in relation to infants' later skills on tasks relating to attention. Findings revealed that by the second year of life, infants of mothers with high DHA demonstrated superior ability to maintain attention. These infants were also found less easily distracted by the intermittent presentation of competing auditory/visual stimuli. Some have suggested that the breastfed infant's superior alertness may contribute to lower incidence of symptoms relating to attention-deficit/hyperactivity disorder (AD/HD) that have sometimes been reported in these children (Al Hamed et al. 2008; Julvez et al. 2007; Kadziela-Olech and Piotrowska-Jastrzebska 2005).

The breastfed infant's more optimal performance on the NBAS, and especially findings which suggest superior sociability (Hart et al. 2003) are also of importance to parenting behavior. Interactions among breastfeeding and bottle-feeding dyads (Jones et al. 2004; Kuzela et al. 1990; Lavelli and Poli 1998) are enhanced by the infant's prosocial behavior and responsivity to social stimulation, and these interaction contexts impact child outcomes. For example, an intervention study (Hart et al. 1998) found improved performance on the NBAS *sociability* cluster among 1-month olds who had been provided with daily exposure to stimulating parent–infant interactions. Not only do we find that infants are influenced by their parents, but, as suggested by the title of one of the more influential works in modern infancy research, *The Effect of the Infant on its Caregiver* (Lewis and Rosenblum 1974), the reverse is also true, that is, parents are influenced by their infants. Infants who are attentive and responsive are highly effective toward optimizing parents' behaviors and the nature of the dyadic context (Brazelton and Nugent 1995; Crockenberg and Smith 1982). Notably, this context of bidirectional influences serves as a platform for social development and the process through which attachment is gradually nurtured. In addition, it serves as the forum on which cognitive development takes place. Thus, we conclude by noting that while it is possible that breastfeeding may be beneficial to cognitive development through its enhancing effects on alertness, it is also possible that it does so through other avenues as well (Soliday 2007). One of these pertains to the more affectionate and stimulating parenting environment that is cultivated by the infant who is more sociable and responsive due to having been breastfed.

Summary Points

- Crying in the breastfed infant may be more frequent but of shorter duration and lesser intensity. Its relation to pain threshold is unclear.
- Breastfed newborns show more optimal social behavior, alertness, motor development, and neurological organization. Correspondingly, they are found having longer heart rate, elevated heart period variability, and higher vagal tone, suggesting more optimal physiological organization.
- Findings on the breastfed infant's sleep appear to suggest that sleep latency is of shorter duration, sleep episodes are shorter in duration, and arousability is greater.
- The breastfed infant's sleep architecture may relate to child health. Some potential benefits relate to SIDS, enuresis, and obesity.
- The breastfed infant's superior alertness may be implicated in more optimal cognitive performance and fewer symptoms of ADHD that have been found associated with breastfeeding.
- The breastfed infant's superior sociability and responsivity may have an enhancing effect on parenting behavior which, in turn, provides the infant with enhanced access to a stimulating environment that is advantageous to learning.

Key Terms

AD/HD: A neurobiological disorder, more typical in children and associated with developmentally inappropriate behavior, including poor attention skills, impulsivity, and hyperactivity.

Cortisol: A steroid hormone released by the cortex, outer layer, of the adrenal gland when a person is under stress. Classed as a glucocorticoid, it is synthesized in response to ACTH in the pituitary gland and acts by reducing the reserves of protein in all body cells except cells of the liver and gastrointestinal tract. It also makes fatty acids available for metabolic use.

DHA: A long-chain omega-3 polyunsaturated fatty acid important for optimal functioning of the brain and retina.

ECG: The recording of the brain's spontaneous electrical activity produced by the firing of neurons within the brain.

NBAS: Developed by T. Berry Brazelton and associates, this instrument is used to evaluate reflexes and behavior in neonates and infants up to the age of 60 days.

SIgA: Secretory IgA is a class of immunoglobulin found in some body secretions, e.g., saliva, respiratory secretions, milk, and colostrum, which is responsible for local immunity.

References

Abdel Razek A, Az El-Dein N. Int J Nurs Pract. 2009;15:99–104.

Algeria J, Noirot, E. Int J Behav Dev. 1978;1:291–312.

Al Hamed JH, Taha AZ, Sabra AA, Bella H. J Egypt Public Health Assoc. 2008;83:165–82.

Alley JM, Rogers CS. Pediatr Nurs. 1986;12:349–51.

Als H. Monogr Soc Res Child Dev. 1978;43:14–28.

American Academy of Family Physicians. Breastfeeding (Policy statement). 2007. Retrieved on June 24, 2009 from http://www.aafp.org/online/en/home/policy/policies/b/breastfeedingpolicy.html

American Academy of Pediatrics Section on Breastfeeding. Pediatrics 2005;115: 496–506.

American College of Obstetricians and Gynecologists. Executive board statement on breastfeeding. 2003. Retrieved on June 24, 2009 from http://www.acog.org/departments/underserved/breastfeedingStatement.pdf

Anders TF. Pediatrics. 1979;63:860–4.

Ball HL. Birth. 2003;30:181–8.

Barone JG, Ramasamy R, Farkas A, Lerner E, Creenan E, Salmon D, Tranchell J, Schneider D. Pediatrics. 2006;118:254–9.

Barr RG, Kramer MS, Pless IB, Boisjoly C, Leduc D. Pediatrics. 1989;84:514–21.

Bell RQ. Psychosom Med. 1966;28:177–80.

Bennett HJ. Pediatrics. 2006;118:1802–3.

Bernal J. Dev Med Child Neurol. 1972;14:362–72.

Brazelton TB, Nugent JK. Neonatal behavioral assessment scale. London: Mac Keith; 1995.

Carbajal R, Veerapen S, Couderc S, Jugie M, Ville Y (2003) BMJ. 326: 13

Centers for Disease Control and Prevention. Provisional data – National immunization survey. 2008. 2005 Births. Retrieved on June 24, 2009 from www.cdc.gov/breastfeeding/data/NIS_data; and http://www.cdc.gov/breastfeeding/data/NIS_data/2006/socio-demographic_any.htm;

Cheruku SR, Montgomery-Downs HE, Farkas SL, Thoman EB, Lammi-Keefe CJ. Am J Clin Nutr. 2002;76:608–13.

Cohen LB, Cashon CH, Kuhn D. In: Siegler RS, Damon W, Lerner RM, editors. Handbook of child psychology: Vol. 2, Cognition, perception, and language. 6th ed. NJ: Wiley, 2006. pp. 214–251.

Colombo J, Kannass KN, Shaddy DJ, Kundurthi S, Maikranz JM, Anderson CJ, Blage OM, Carlsen SE. Child Dev. 2004;75:1254–67.

Crockenberg SB, Smith P. Infant Behav Dev. 1982;5:105–19.

Dilli D, Kucuk IZ, Dallar Y. J Pediatr. 2008;154:385–90.

DiPietro JA, Larson SK, Porges SW. Dev Psych. 1987;23:467–74.

Doan T, Gardiner A, Gay CL, Lee KA. J Perinat Neonatal Nurs. 2007;21:200–06.

Dollberg S, Lahav S, Mimouni FB. J Am Coll Nutr. 2001;20:209–11.

Efe E, Ozer ZC. Appl Nurs Res. 2007;20:10–6.

Elias MF, Nicolson NA, Bora C, Johnston J. Pediatrics. 1986;77:322–9.

Feldman R (this volume) In: Preedy VR, Watson RR, Martin CR, editor. International handbook of behavior, diet and nutrition. New York: Springer, p.

Field T. Inf Behav Dev. 2008;31:481–7.

Ford RP, Taylor BJ, Mitchell EA, Enright SA, Stewart AW, Becroft DM, Scragg R, Hassal IB, Barry DM, Allen EM. Int J Epidemiol. 1993;22:885–90.

Galson SK. J Am Diet Assoc. 2008;108:1106.

Gillman MW, Rifas-Shiman SL, Kleinman K, Oken E, Rich-Edwards JW, Taveras EM. Obesity (Silver Spring). 2008;16:1651–6.

Gradin M, Finnstrom O, Schollin J. Early Hum Dev. 2004;77:57–65.

Gray L, Miller LW, Philipp BL, Blass EM. Pediatrics. 2002;109:590–3.

Hale TW. Medications and mother's milk. 13th ed. TX: Hale Publishing; 2008.

Hart S, Field T, Nearing G. J Pediatr Psychol. 1998;23:351–6.

Hart SL, Boylan LM, Border B, Carroll SR, McGunegle D, Lampe RM. Infant Behav Dev. 2004;27:101–6.

Hart SL, Boylan LM, Carroll S, Musick Y, Lampe RM. J Pediatr Psychol. 2003;28:529–34.

Hart SL, Boylan LM, Carroll SR, Musick YA, Kuratko C, Border BG, Lampe RM. J Pediatr Psychol. 2006;31:221–6.

Healthy People 2010. Midcourse review statement. 2005. Retrieved on May 13, 2008 from http://www.healthypeople.gov/Document/HTML/Volume2/16MICH.htm#_Toc494699668

Horne RS, Parslow PM, Ferens D, Watts AM, Adamson TM. Arch Dis Child. 2004;89:22–5.

Innis SM. J Pediatr Gastroenterol Nutr. 2009;48:S16–24.

Jones NA, McFall BA, Diego MA. Biol Psychol. 2004;67:103–24.

Julvez J, Ribas-Fito N, Forns M, Garcia-Esteban R, Torrent M, Sunyer J. Acta Paediatr. 2007;96:842–7.

Kadziela-Olech H, Piotrowska-Jastrzebska J. Rocz Akad Med Bialymst. 2005;50:302–6.

Kendall-Tackett KA. In: Mannel R, Marten PJ, Walker M, editor. Core curriculum for lactation consultant practice. Boston: Jones & Bartlett, 2008, p. 67–77.

Korner AF, Thoman EB. Child Dev. 1972;43:443–53.

Kuzela AL, Stifter CA, Worobey J. J Reprod Inf Psychol. 1990;8:185–94.

Lavelli M, Poli M. Infant Behav Dev. 1998;21:667–83.

Lawrence R, Lawrence R. Breastfeeding: A guide for the medical profession, 5th ed. St. Louis: Mosby; 2006.

Lawrence RA, Lawrence RM. Breastfeeding: A guide for the medical profession. Philadelphia: Mosby; 2005.

Lee K. Early Hum Dev. 2000;58:133–40.

Lester BM, Als H, Brazelton TB. Child Dev. 1982;53:687–92.

Lester BM, Tronick EZ. In: Singer LT, Zeskind PS, editor. Biobehavioral assessment of the infant. New York: Guilford; 2001, p. 363–380.

Lewis M, Rosenblum LA. The effect of the infant on its caregiver. New York: Wiley-Interscience; 1974.

Lucas A, Morley R, Cole TJ, Lister G, Leeson-Payne C. Lancet. 1992;339:261–4.

Lucas A, St James-Roberts I. Early Hum Dev. 1998;53:9–18.

Macknin ML, Medendorp SV, Maier MC. Am J Dis Child. 1989;143:1066–8.

Maekawa K, Nara T, Soeda A, Yokoi S, Kitani N. Jikeikai Med J. 1984;31:503–9.

McKenna JJ, Ball HL, Gettler LT. Am J Phys Anthropol Suppl. 2007;45:133–61.

Ohr PS, Fagen JW, Rovee-Collier C, Hayne H. Dev Psychobiol. 1989;22:69–80.

Parmelee AH Jr, Schulz HR, Disbrow MA. J Pediatr. 1961;58:241–50.

Quillin SI, Glenn LL. J Obstet Gynecol Neonatal Nurs. 2004;33:580–8.

Reis EC, Roth EK, Syphan JL, Tarbell SE, Holubkov R. Arch Pediatr Adolesc Med. 2003;157:1115–20.

Richardson HL, Walker AM, Horne RS. J Sleep Res. 2008;17:450–7.

Sanchez CL, Cubero J, Sanchez J, Chanclon B, Rivero M, Rodriguez AB, et al. Nutr Neurosci. 2009;12:2–8.

Shah PS, Aliwalas L, Shah V. Breastfeed Med. 2007;2:74–82.

Simmons JE, Ottinger D, Haugk E. J Am Acad Child Psychiatry. 1967;6:174–83.

Soliday E. Child Dev Perspect. 2007;1:19–25.

Steinberg LA, O'Connell NC, Hatch TF, Picciano MF, Birch LL. J Nutr. 1992;122:1781–91.

Taveras EM, Rifas-Shiman SL, Oken E, Gunderson EP, Gillman MW. Arch Pediatr Adolesc Med. 2008;162:305–11.

Thoman EB. In: Singer LT, Zeskind PS. editors. Biobehavioral assessment of the infant. New York: Guilford; 2001. p. 125–148.

Thoman EB, Leiderman H, Olson JP. Dev Psychol. 1972;6:110–8.

US Department of Health and Human Services. HHS Blueprint for Action on breastfeeding. 2000. Retrieved on June 24, 2009 from http://www.cdc.gov/breastfeeding/pdf/bluprntbk2.pdf

van der Wal MF, van den Boom DC, Pauw-Plomp H, de Jonge GA. Arch Dis Child. 1998;79:312–7.

Vennemann MM, Bajanowski T, Brinkmann B, Jorch G, Sauerland C, Mitchell EA. Pediatrics. 2009a;123:1162–70.

Vennemann MM, Bajanowski T, Brinkmann B, Jorch G, Yucesan K, Sauerland C, Mitchell EA, GeSID Study Group. Pediatrics. 2009b;123:e406–10.

Walker M. In: Mannel R, Martens PJ, Walker M, editors. Core curriculum for lactation consultant practice. Boston: Jones & Bartlett. 2008, p. 285–302.

WHO/UNICEF/USAID/SIDA. Innocenti declaration on the protection, promotion, and support of breast-feeding. Florence, Italy, 1990. Retrieved on June 24, 2009 from http://www.unicef.org/programme/breastfeeding/innocenti.htm

WHO/UNICEF. Global Strategy on Infant and Young Child Feeding and Care. WHO: Geneva, 2003. Retrieved on June 24, 2009 from http://whqlibdoc.who.int/publications/2003/9241562218.pdf

Chapter 36
Meal Composition and Cognitive Function

Louise Dye, Alexa Hoyland, Daniel Lamport, and Clare Lawton

Abbreviations

5-HT	5-hydroxytryptamine
Ach	Acetylcholine
BBB	Blood Brain Barrier
NA	Noradrenaline
CHO	Carbohydrate
IGT	Impaired glucose tolerance
NGT	Normal glucose tolerance
IFG	Impaired fasting glucose
OGTT	Oral glucose tolerance test
HbA1c	Glycated haemoglobin
MMSE	Mini Mental State Examination
GI	Glycaemic index
GL	Glycaemic load
LCPUFA	Long chain polyunsaturated fatty acids
DHA	Docosahexaenoic acid
EPA	Eicopentaenoic acid
ARA	Arachidonic acid

36.1 Introduction

36.1.1 What Are Cognitive Functions?

Cognitions (or cognitive functions) include those activities that allow animals (including humans) to perceive, understand, and act upon the environment in such a way as to optimize adaptation and performance. The development of cognitive abilities through evolution has clearly played a large role in allowing humans to gain mastery over the environment. Possessing brain processes that provide

L. Dye (✉)
Human Appetite Research Unit, Institute of Psychological Sciences,
University of Leeds, LS2 9JT, UK
e-mail: l.dye@leeds.ac.uk

accurate perception and memory of environmental events enables organisms to function successfully. Cognitive abilities clearly play a large part in daily activities and tasks, such as car driving, operating machinery, and school or work performance. These complex skills are composed of a number of individual cognitive processes such as attention to and perception of the environment, the acquisition, storage, organization, and retrieval of information, and the organization of effective response patterns. These processes form the basis for laboratory-based tests of individual cognitive functions. However, even memory, the cognitive function most widely studied in terms of macronutrient effects, is not comprehensively examined in these studies. Memory formation can be divided into encoding, storage, and retrieval; working memory is short-term memory used while performing a task; long-term memory can be declarative or explicit (knowing that) and nondeclarative or implicit (knowing how). Declarative memory includes episodic memory (personal experience) and semantic memory (known facts). Implicit memories consist of conditioning, priming, and skills, and are nonassociative. Hence memory when measured in the context of nutrition is unlikely to consider or discriminate between these various parameters of the cognitive function.

The validity and sensitivity of laboratory tests are an essential part of the methodology to assess the effects of foods and food components. In practice, a limited number of tests have been used to assess the effects of diet on mental performance. Because cognitions are so important to human functioning, they are usually operating at a high level and can be protected from degradation by applying extra effort. Consequently, it is not always easy to demonstrate the effect of any intervention (food or other) on performance on these tests. Despite this, there has been considerable interest and coverage of the possible effects of a multitude of meal components and nutraceuticals on mental performance. In addition to the relative effectiveness of the basic macronutrients, studies have also evaluated differences within each macronutrient, particularly carbohydrate (CHO). Other studies have considered the role of antioxidants, vitamins, and isoflavones (IF), as well as nutraceuticals such as ginseng (e.g., Kennedy and Scholey 2003) in the enhancement of cognition function and the prevention of cognitive decline. This review provides an overview of the effects of the major meal components on cognitive performance, considers how habitual dietary status may affect these relationships, and describes the how these effects impact on individuals suffering from relevant disease states.

36.1.2 Effects of Macronutrients on Mental Performance

In a comprehensive review of the effects of macronutrients on mental performance, Dye, Lluch, and Blundell (2000) concluded that macronutrients do appear to have effects on cognitive function. Studies of macronutrients given in combination suggest that fat slows reaction time but may produce greater performance accuracy (Smith et al. 1994). CHO improves memory but can impair peripheral processing, attention, and reaction time, depending on the time of day and type of CHO ingested as well as the CHO:protein ratio (Dye and Blundell 2002). It is also associated with feelings of fatigue (Reid and Hammersley 1999). The most heavily researched hypothesis regarding the effects of food on cognition involves brain utilization of glucose, because glucose provides the brain's only metabolic fuel. The normal level of blood glucose is 4–5.5 mmol/L, and this is tightly controlled by a series of hormonal mechanisms. When it falls below 2.2 mmol/L, hypoglycemia occurs. The decline in glucose associated with hypoglycemia in Type II diabetics has been shown to impair cognitive performance (Awad et al. 2004). Moreover, some nutritional interventions which facilitate a rise in blood glucose have been shown to enhance performance.

Glucose administration has been shown to benefit short-term and working memory in young adults and the elderly (Hall et al. 1989; Sünram-Lea et al. 2001). Performance on three memory tasks

was measured in participants who had, and had not, consumed breakfast (Benton and Parker 1998). Omission of breakfast was associated with poorer recall in two of the three memory tasks, but this effect was reversed by the administration of a glucose drink. Recovery from nadir and rising blood glucose have also been associated with better recall than falling blood glucose levels (Donohoe and Benton 1999). Blood glucose level has also been shown to be positively correlated with decision time (Benton and Owens 1993). However, the enhancement of cognitive function by glucose is not consistently reported (e.g., Craft et al. 1994; Scholey and Kennedy 2004), and induced hypoglycemia is not necessarily detrimental to cognitive function in normal samples (Gold et al. 1995). There are many participant and experimental factors which may modulate the relationship (Green and Gibson 2002).

Task difficulty influences the apparent effects of glucose on cognition. More difficult tasks produce higher cognitive demands, which may lead to an increase in glucose metabolism in the brain. In one study (Scholey et al. 2001), 25 g glucose was administered, and memory performance was tested after either serial sevens (a highly demanding task), or a control task. Both tasks were followed by word retrieval (verbal fluency). Glucose consumption improved performance on serial sevens and verbal fluency. Moreover, peripheral measures of blood glucose declined in the high cognitive demand condition. The potential mechanisms by which glucose availability might interact with task demand are considered next.

Some studies suggest that the absolute level of glucose may not be directly predictive of cognitive function (see Messier 2004 for a review). Messier et al. (1999) reported that the effects of 50 g glucose on word recall performance were dependent on glucoregulatory processes. Glucose ingestion reversed the performance decrement associated with poorer glucoregulation but did not impact on participants with better glucoregulation. It is also possible that a food may exert conflicting effects on different aspects of cognitive performance, by enhancing one function but simultaneously impairing another. In a recent study of the effects of breakfasts differing in macronutrient and calorie content on cognition in young adults, lower blood glucose levels tended to be associated with enhanced memory function (immediate and delayed word recall), particularly in participants with poorer glucose tolerance. In contrast, higher blood glucose levels were associated with better vigilance and RT performance (Nabb and Benton 2006). Further, the effect of 50 g glucose on memory for trigrams was dependent on initial blood glucose levels (Martin and Benton 1998). Those with higher levels of blood glucose showed better performance. However, after the glucose drink, falling levels of blood glucose were associated with better memory performance.

Not all effects of meals on performance are due to changes in glycemia, changes in performance can be mediated by serotonin (5-hydroxytryptamine, 5-HT) as well as glucose availability. Glucose is required for the synthesis of neurotransmitters such as serotonin (5-HT), noradrenaline (NA), and acetylcholine (ACh). The action of glucose on the cholinergic system may increase the synthesis of ACh (Messier 2004). Hence, the effects may not be solely related to the increased availability of neural fuel. Other studies suggest that stable performance is related to a balanced glucose metabolism and state of metabolic activation. The CHO:protein ratio of a meal can produce depletion or enhancement of tryptophan via an effect on the tryptophan : large neutral amino acid ratio (for a review of these mechanisms, see Gibson 2007). Where tryptophan availability is enhanced, faster memory scanning has been demonstrated in stress-prone subjects who may have receptor sensitization of the serotonergic system or 5-HT deficiency (Markus 1999). Tryptophan depletion selectively impairs memory consolidation in normal volunteers (Riedel et al. 1999).

Recently, a systematic review evaluated studies of the acute effects of macronutrients on cognitive performance, which met certain criteria in terms of experimental control, and which should therefore reflect most reliable research in the area (Hoyland et al. 2008). The review reported three major outcomes.

First, effects of macronutrients on cognitive performance were most often reported for memory in comparison with the other cognitive domains assessed, e.g., attention and psychomotor performance.

Second, tasks that required greater cognitive load tended to be more sensitive to macronutrient manipulations. In particular, tasks undertaken in a delayed context tended to report effects of macronutrients more consistently than those undertaken immediately following manipulation administration.

Third, tasks identified as consistently sensitive to glucose manipulations were working memory tasks (e.g., Serial Sevens Task) and verbal memory tasks (e.g., free word recall and cued word recall). The tasks appeared to be more sensitive when administered in a delayed context. There was also some evidence for improved word recognition, in addition to retrieval, when administered after a delay. Visuo-spatial memory also appeared to be sensitive to glucose, but other macronutrients also affected this cognitive domain.

Taken together, studies of the effects of glucose on cognition suggest that it enhances memory *provided* tests of sufficient difficulty are used to produce high cognitive demand in normal adults who are less vulnerable than undernourished or elderly samples (Dye et al. 2000).

36.1.3 Effects of Breakfast on Cognitive Function

Many studies have administered manipulations at breakfast time, partly because testing at this time of day means participants can present in a fasted state. Effects of breakfast manipulations have been reported on a range of cognitive functions. Breakfast studies suggest that the absence of breakfast consumption can lead to impaired cognitive performance on tests of reaction time and short-term memory (e.g., Smith et al. 1994). A "realistic" breakfast of cereal and milk improved visuo-spatial memory in a task requiring memory for sequences of lights relative to no breakfast (Smith et al. 1999).

However, beneficial effects of breakfast on cognition are not consistently reported and the null findings may relate to the cognitive domain examined. Despite quite confident claims that the absence of breakfast consumption is deleterious to mental performance, Pollitt and Mathews (1998) argue that no definitive conclusions about the cognitive benefits of breakfast can be drawn. There was no difference in word recall following a fast or one of three isoenergetic breakfasts of varying CHO and fat content nearly 3 h post breakfast (Lloyd et al. 1996). In addition, Uijtdehaage et al. (1994) reported no performance differences between CHO-rich and protein-rich breakfasts and a fast on a working memory task.

Other studies indicate that a mid-morning snack may be more important than breakfast. Benton et al. (2001) measured delayed free word recall in a breakfast and mid-morning snack manipulation. The provision of breakfast had no impact on performance but the provision of a 25 g CHO snack did; free word recall was enhanced 20 min after the snack. It is possible that individuals tend to perform at a high level on rising at the start of the day and performance may be harder to alter via nutritional manipulations at this time. This idea is supported by indications of time-of-day effects. Performance on the same task was better when measured at breakfast compared with lunch (Sünram-Lea et al. 2001). Consumption of breakfast may also influence motivation or introduce demand characteristics to the experiment as it is impossible to blind breakfast–no breakfast comparisons. In one study for example, breakfast consumption did not improve performance on a verbal recall task but participants spent longer attempting to recall the words in the breakfast condition (Benton et al. 2001) which could reflect greater motivation following breakfast.

Studies in samples other than healthy adults indicate that the effects of breakfast may be more profound in the elderly (e.g., Kaplan et al. 2001). In addition, there is a widely held belief that breakfast is important for the performance of children at school. This belief has promoted intense interest

in the capacity for breakfast to exert long-term effects on scholastic performance. Studies of school breakfast programs suggest that breakfast omission may detrimentally affect children's mental performance (e.g., Grantham-McGregor et al. 1998; Murphy et al. 1998). Studies most commonly report improved mathematics scores. However, these observed effects may not be the direct effect of breakfast. Often, the introduction of school breakfast programs leads to a concomitant rise in school attendance. Improvements in school performance may therefore be an artifact of increased attendance, rather than improvements to the ability to concentrate during the school or nutritional profile.

Intervention studies which examine the acute effects of breakfast on the cognitive performance of children have been reviewed by Hoyland et al. (2009) who concluded that while there is reasonable evidence to suggest beneficial effects of breakfast compared with breakfast omission, there is little evidence to recommend specific foods be consumed at breakfast to improve the performance of well-nourished children. Table 36.1 summarizes the impact of breakfast on cognitive function.

36.1.4 Effects of Lunch and the Postlunch Dip

The consensus view is that daytime sleepiness, or the afternoon decline in mental alertness (the so-called postlunch dip, PLD), is a circadian rhythm. This phenomenon has sparked considerable research interest in many European countries, given its association with a loss of work efficiency. It is difficult to disentangle the effects of lunch consumption from the rhythmic effects underlying the PLD. Cognitive declines could simply reflect the effect of a negative energy balance or a lack of available glucose.

In an early review of six studies examining circadian rhythms in mental performance, deficits (particularly those related to attention) were reported in the early afternoon (Monk and Folkard 1985). Increasing meal size at lunchtime produces more momentary lapses of attention, however, irrespective of food consumption performance on sustained attention tasks is impaired in the early afternoon, compared with the late morning (Smith and Miles 1986). This PLD effect is abolished by caffeine (Smith et al. 1990). See Table 36.2 for a summary of the PLD.

Circadian patterns in mood may interact with food intake. Diurnal variation in postprandial hormone and metabolic responses has been well documented (Hampton et al. 1996). Glucose and cortisol secretion (as responses to food intake) vary across the day and alertness peaks midmorning, then falls throughout the day (van Cauter 1990). The natural rhythm of cortisol exhibits diurnal attenuation. These rhythms may explain the different effects of meals on mood and performance across the day.

Table 36.1 Key features of breakfast and cognitive function

- Breakfast is more beneficial to cognition than no breakfast.
- It is not possible to define an "optimal" breakfast for cognitive function.
- School breakfast programs show benefits for cognition but this could be due to increased school attendance.
- Some groups are more likely to benefit from breakfast consumption, such as children and the elderly.
- Memory performance may be most influenced by breakfast consumption.

This table shows the key features of the impact that breakfast consumption has on cognitive performance

Table 36.2 Key features of the PLD

- The PLD is a natural circadian rhythm.
- Subjective alertness decreases postlunch consumption.
- The same food can have different effects at lunch compared with morning.
- The PLD can be abolished by caffeine.

Thus, the effects of alertness-enhancing foods are most likely to be detected if they are ingested at a time when alertness is naturally declining, and cognitive capacity is challenged by an appropriate cognitive test. For instance, the beneficial effects induced by afternoon snacks do not occur when these snacks are consumed in the late morning (Kanarek and Swinney 1990). Therefore, task selection in the design of a test battery and test meal design, should embrace these considerations. Furthermore, physiological measures, e.g., blood glucose, cortisol and heart rate, are important to confirm the metabolic state of the individual, at staggered times post ingestion.

Dietary interventions that potentially modulate the PLD are of research interest. Varying the glycemic index (GI; see next) offers a considerable opportunity for functional food development, with potentially positive effects on the extent and timing of postlunch inefficiency. Maintaining blood glucose appears to be beneficial. This can impact advice about breakfast consumption, snacking, and the development of functional foods, which modulate blood glucose. The effect of CHO at lunchtime is therefore an important consideration. See Table 36.2 for a summary of the PLD.

36.1.5 Effects of CHO at Lunchtime

No studies examining the effects of CHO at lunchtime have detailed the GI of the dietary manipulation. However, numerous studies have documented attenuated reactions following CHO at lunchtime. High CHO lunches produce a greater impairment on reaction time, than standard high fat meals, high protein meals, or conditions in which no lunch is given (for review, see Dye et al. 2000).

Reaction time has been shown to be slower after a low CHO/high fat lunch compared with a high CHO/low fat lunch. In contrast, reaction times were impaired following both high fat/low CHO and low fat/high CHO lunches when compared with a medium fat/medium CHO lunch, which produced optimal performance (Lloyd et al. 1994). Higher than usual proportions of fat or CHO may induce drowsiness or uncertainty, or potentially affect cognitive efficiency and motor performance.

36.1.6 Effects of GI and GL on Cognitive Function

Dietary interventions based on CHO are typically described using terms such as GI, glycemic load (GL), the ratio of slowly to rapidly available glucose, the proportion of simple to complex CHO, or the amount of rapidly versus slowly digested CHO. Both the quality (e.g., type/nature/source) and quantity of a CHO are important determinants of its glycemic response. As the GI by definition compares equal quantities of available CHO, it provides a measure of CHO quality not quantity.

Several studies have shown that low GI foods consumed at breakfast lead to better verbal memory over the morning (0–3 h post ingestion) compared to high GI foods in healthy adults, type 2 diabetics, and children (Benton et al. 2003; Ingwersen et al. 2007; Papanikolaou et al. 2006). The evidence examining acute effects of GI on attention is inconsistent. One study with children has shown improved attention following a high GI breakfast (Mahoney et al. 2005), whereas in contrast a low GI breakfast has been associated with improved attention in children (Ingwersen et al. 2007) and healthy middle-aged adults (Nilsson et al. 2009). In the healthy elderly and type 2 diabetics no associations between attention and GI have been observed (Kaplan et al. 2000; Papanikolaou et al. 2006).

The GL is the product of a food's GI and the amount of CHO per serving. GL imparts information about CHO quantity and reflects the glycemic response of actual food portions. In healthy individuals,

stepwise increases in GL have been shown to predict stepwise elevations in postprandial blood glucose and/or insulin response to specific foods (Brand-Miller et al. 2003). Low GI is not the same as low GL and meals which differ with respect to these characteristics could result in a different cascade of postprandial hormonal responses with the potential for different cognitive effects.

Gilsenan, De Bruin, and Dye (2009) provide a critical evaluation of eight studies that have explored the relationships between food CHO and cognitive performance and allow GL to be used as a basis for comparison. The key finding is that these provide insufficient evidence to support a consistent effect of GL on short-term cognitive performance. Both acute and long-term cognitive effects of GI and GL require further investigation, since the present evidence cannot support any definitive conclusions. However, the association between improved memory and low GI foods is consistent with the evidence linking a low GI diet to health benefits. A high GI diet has been associated with an increased risk of cardiovascular disease, type 2 diabetes, obesity, and cancer possibly due to postprandial hyperglycemia, and hyperinsulinemia (Gnagnarella et al. 2008). Given that there are prominent health recommendations to adopt low GI diets, the long-term cognitive impact of doing so requires evaluation. See Table 36.3 for a summary of GI and GL.

36.1.7 Effects of the Evening Meal

There is very little evidence examining the effect of evening meal manipulations on cognitive function. Smith et al. (1994) found that consumption of a 1,200–1,500 kcal meal resulted in better completion of sentences on a logical reasoning task compared to having no meal; however, there were no differences in sustained attention, word recall, or word recognition. To date there are no other studies that have examined cognitive performance in the evening and therefore the effects of GI, GL, or macronutrient manipulations of the evening meal on cognitive performance in the evening remain speculative.

Interestingly, a recent study found that the composition of the evening meal can affect cognition the following morning (Lamport et al. submitted). A high GI evening meal was associated with better word recall the following morning compared to a low GI evening meal. This suggests that nutritional manipulations may exert cognitive effects beyond the initial postprandial period. One explanation for a previous meal influencing cognitive function at the next meal relates to the "second meal effect" (Wolever et al. 1988). The second meal effect can influence glucose, insulin, fatty acids, and serotonin levels. For example, a low GI evening meal is associated with an improved glycemic response at breakfast compared with a high GI evening meal, even after an overnight fast (Wolever et al. 1988). The circadian rhythm of insulin sensitivity, when a relative insulin resistance occurs in the evening and night-times (Morgan et al. 2003) could explain why the same meal consumed in the evening can impair glucose and lipid tolerance much more than an equivalent daytime meal (Morgan et al. 1998).

Table 36.3 Key features of glycemic index and glycemic load

- High glycemic index foods typically cause blood glucose to rise rapidly to a high peak, whereas low GI foods are characterized by a slower rise and lower peak.
- High GI foods are often referred to as RAG (rapidly available glucose).
- Low GI foods are often referred to as SAG (slowly available glucose).
- HGI foods are associated with cardiovascular disease and diabetes.
- Glycemic load of a food is a calculated by GI × grams of carbohydrate/100.
- There is some evidence that the GI and GL of foods can affect cognitive function.

This table explains the nature of high and low glycemic index foods, and summarizes the impact these foods have on health and cognition. The definition of glycemic load (GL) is also shown

These findings suggest that the effect of evening meal manipulations on cognition should be examined during the postprandial period, the next day, and in relation to our habitual eating patterns which could contribute toward risk of cardiovascular disease (CVD) and type 2 diabetes and which in themselves may be associated with cognitive impairment (see next). A late eating pattern is part of our Western, industrial lifestyle, and could over time impair gluco-regulation, which could promote obesity and associated conditions. An extreme example of this relates to nightshift workers, whose postprandial metabolic profiles are impaired (Al-Naimi et al. 2004) and whose risk of CVD is approximately 1.4 times that of dayworkers.

36.2 Mechanisms of Action

Glucose level in the brain and the periphery is kept under tight control. The regulation of glucose transport across the blood–brain barrier (BBB) which occurs via GLUT1 transporters is not well understood (Convit 2005). Glucose levels in the brain are about 30% of those in peripheral blood and long-term elevations in peripheral glucose result in decreased glucose transport across the BBB (Pardridge et al. 1990) providing a hypothesis to explain impaired cognitive function in conditions associated with dysfunctions of glucoregulation such as diabetes. This would not however, explain the facilitatory effects of glucose in healthy adults.

There have been several processes proposed, operating alone or in combination, by which glucose might exert effects on cognition (Messier 2004). There is convincing evidence that astrocytes play an important role in energy regulation. These star-shaped glial cells, which surround neurons and lie in close proximity to the cerebral vasculature, are believed to constitute a likely site of glucose uptake as it crosses the BBB (Pellerin and Magistretti 1994). It is hypothesized that during neuronal activation, glucose is taken up by astrocytes, converted into lactate (by glycolysis), which is then released into the extracellular space to be taken up as an energy substrate by neurons (Tsacopoulos and Magistretti 1996).

During brain activation, e.g., under high cognitive task demand, utilization and local concentrations of glucose have been shown to alter. An increase in glucose uptake by the brain in young males undertaking a complex visuo-spatial motor task was observed in a study using Positron Emission Tomography (PET) suggesting that increased neural activity (e.g., learning a complex visuo-spatial motor task or verbal working memory) is associated with an increased use of glucose by the brain (Haier et al. 1992). In rats, a decrease in hippocampal interstitial glucose levels proportional to the difficulty of the maze was observed (McNay et al. 2000). However, in both studies peripheral glucose concentrations remained unchanged. This suggests that cognitive demand is accompanied by increased local glucose metabolism in those brain areas engaged in specific tasks.

The mechanisms by which GI and GL may affect cognitive function are currently unclear. GL is influenced by several factors which relate to the food itself (i.e., the other food components such as nature of starch, content of fat, protein, and fiber), eating behavior (i.e., rate of ingestion, frequency of food intake, composition of a meal), and physiological factors (i.e., gastric emptying rate, intra- and interindividual variation in glycemic response and hormonal responses; Arvidsson-Lenner et al. 2004). The mechanisms by which GI could affect cognition in relation to acute postprandial effects are likely to differ from those involved in the second meal cognitive effects seen later in the day or overnight. Acute effects may be driven by changes in glucose as described earlier. Overnight effects may involve insulin and free fatty acid fluctuations. Hormonal responses can affect brain function and behavior either through peripheral or central mechanisms. The memory-enhancing effects of peripherally injected peptide hormones were attenuated after vagotomy in rats, suggesting that gastrointestinal

hormones relay neural signals to the central nervous system which could influence cognitive processes (Flood and Morley 1998). Recent evidence suggests that circulating ghrelin crosses the BBB from the periphery where it binds to neurons, alters neuronal morphology, and affects generation of long-term potentiation, an important neural-level cognitive process (Diano et al. 2005).

Insulin also crosses the BBB. Improvements in cognitive function have been observed following infusion of insulin in healthy adults (Kern et al. 2001; see Park 2001 for a review). Glucocorticoids (e.g., cortisol) influence circulating glucose. Cortisol receptors are abundant in the hippocampus, a region strongly implicated in memory. There is evidence from both animal and human studies that glucocorticoids influence memory (see Gibson 2007 for a review). However, several gastrointestinal hormones are typically released in response to food consumption and it is therefore difficult to assess their specific effects on subsequent cognitive function.

36.3   Habitual Diet and Cognitive Function

The composition of the habitual diet could have important consequences for the physiological and behavioral patterns of the consumer. For example, phenotypes of habitual diet composition (low fat vs high fat) can be identified. It has been suggested that individuals habitually consuming different diets vary in certain physiological and behavioral characteristics (Blundell and Cooling 2000). Therefore, habitual diet may have an important influence on the effect of food on cognitive performance. For example, epidemiological studies such as the Rotterdam Study (Kalmijn et al. 1997) suggest that regular intake of oily fish is associated with lower incidence of dementia. Such evidence has led to scrutiny of the diets of those countries whose inhabitants show increased longevity and low incidence of conditions such as Alzheimer's disease and cognitive decline.

It is easy to assume that food and food components exert homogeneous effects in all individuals. However, the effects of foods may depend on usual dietary intake, i.e., habitual diet. Since humans have a strong volitional control over food intake, habitual food intake may mediate the potential of foods to exert effects on appetite and satiety, mood, and cognitive function.

Evidence from animal studies suggests that there may be differences between the chronic and acute impact of diets varying in fat content. Fat appears to affect cognitive performance in rodents, particularly where high fat diets and tasks of learning and memory are employed (Greenwood and Winocur 1990). Habitual consumption of a high fat diet may lead to physiological adaptations which could influence cognitive performance.

Naturalistic studies suggest that a habitual diet which influences parameters such as cholesterol levels may influence levels of performance. Low plasma cholesterol was associated with slower movement and decision time on a choice reaction time task (Muldoon et al. 1997).

Chronic or longer-term intervention studies are rare. However, the effect of regularity of meals has been studied and this may be important. For example, breakfast consumption is associated with greater wellbeing and a healthier lifestyle and regular breakfast consumers tend to have a healthier body weight and meet daily nutrient intake guidelines (Sjoberg et al. 2003). Cognitive effects of the habitual diet may influence the ease with which individuals are able to change their habitual dietary intake to reduce the likelihood of weight gain and obesity. This is particularly important in those individuals most likely to benefit from changing consumption patterns to prevent weight gain and future obesity (i.e., individuals with a high fat intake). In summary, the impact of the habitual diet and acute food intake on cognitive function is complex, with several other factors having both direct and indirect effects on cognition (see Fig. 36.1).
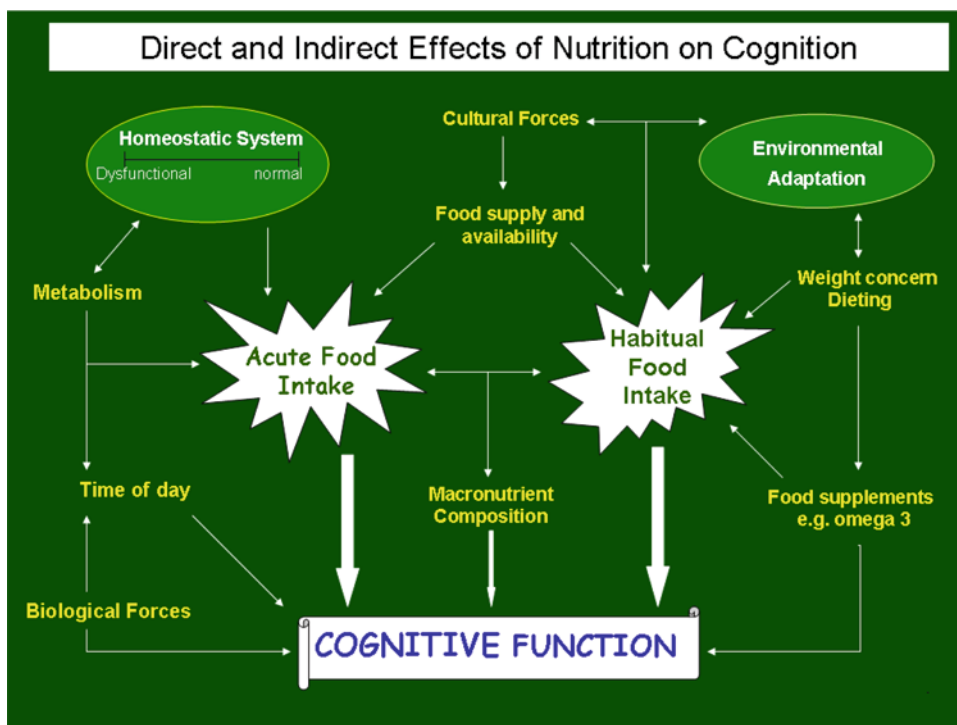
Fig. 36.1 Direct and indirect effects of nutrition on cognition. This diagram represents the different ways that diet and nutrition can impact upon cognitive function. Some factors such as acute food intake can have direct effects on cognition, whereas other factors such as an individual's metabolism can affect cognition indirectly by, for example, influencing acute food intake

36.4 Phytoestrogens and Cognitive Performance

Soy IF are a common source of phytoestrogens and are commonly consumed as part of the habitual South East Asian diet. Phytoestrogens are able to enter the brain and act both centrally and peripherally. Evidence from human and animal studies suggests that phytoestrogens could affect cognition via direct central action as well as by modulating the hormonal milieu (for a review, see Hill and Dye 2003).

Epidemiological evidence shows there to be a lower incidence of dementia in Asian populations compared to Western populations, particularly in the Japanese (Graves et al. 1996). However, cross-sectional and longitudinal studies have not shown positive associations of soy consumption and cognitive function in older adults (White et al. 2000). This may be because IF intake in Western populations is typically too low for cross-sectional or longitudinal analysis of the relationship between IF consumption and cognitive performance to be viable.

In recent years, there have been a number of attempts to investigate whether phytoestrogens affect cognitive performance using randomized intervention studies. This small body of literature gives a preliminary insight into how and when phytoestrogens might influence cognitive function. These studies suggest that soy IF can impact on cognitive function in healthy samples. For instance, Hill et al. (submitted) demonstrated 8 weeks intervention with 100 mg/day soy IF to be cognitively active in postmenopausal women and an effective treatment for hot flushes and sleep disturbance. Although effects on cognitive tasks sensitive to estrogen levels became apparent in line with an increase in estrogen after 4 weeks of soy IF, improvements in frontal lobe functioning were evident only after 8 weeks which may imply that changes in neuronal functioning may be necessary for these effects.
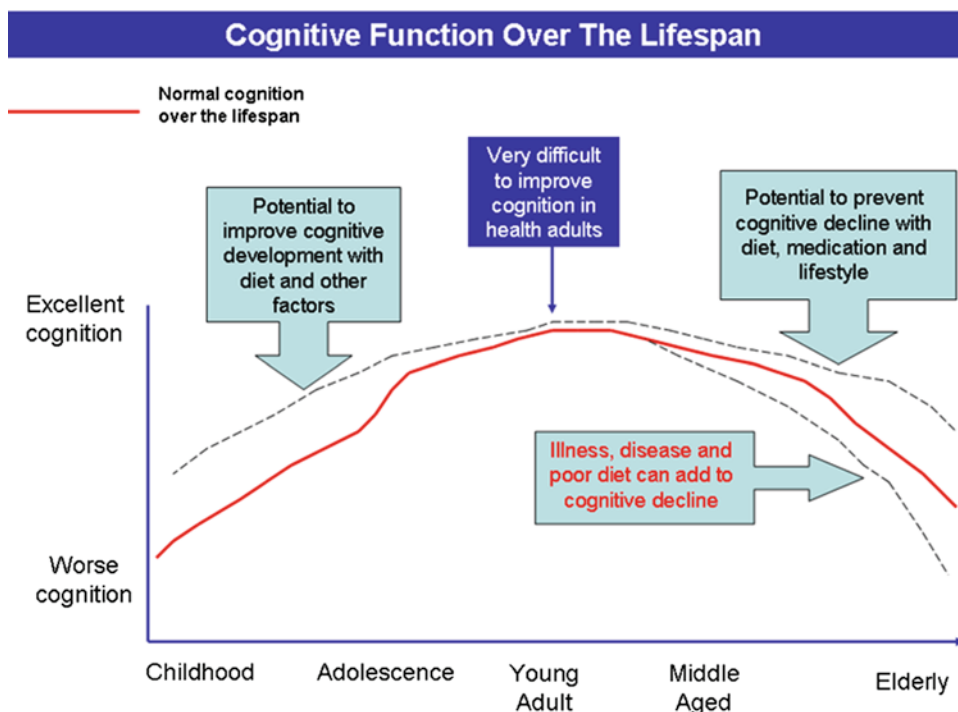
Fig. 36.2 Cognitive function over the lifespan. This diagram represents how cognitive function develops from childhood to a peak during adulthood, which is then followed by a decline associated with old age. Diet may enhance the development of cognitive function during childhood; however, there is little scope for nutritionally driven cognitive improvement during adulthood. Certain diets may help to prevent cognitive decline associated with old age

In contrast, benefits to symptomatology were evident in the first week of treatment, with no further improvement with increasing duration of the intervention.

36.5 Fish, Omega-3, and Cognitive Function

Derived from fish, the health benefits of cod liver oil (CLO) have widespread public acceptance and CLO was used in the treatment of rheumatism and rickets for almost two centuries. Epidemiological and intervention studies have indicated that modest fish intake was associated with decreased mortality in men with myocardial infarction (Burr et al. 1989) and lower incidence of dementia (Kalmijn et al. 1997). Fish (and CLO) contains long-chain polyunsaturated fatty acids (LCPUFA), particularly the omega-3 PUFAs: docosahexaenoic acid (DHA: 22:6n-3 or 22:6ω3) and Eicosapentaenoic acid (EPA: 20:5ω3 or 20:5ω3) while vegetable oils are the main sources of omega-6 PUFA arachidonic acid (ARA: 20:4n-6 or 20:4ω6). Early observations of a marked increase in LCPUFA in brain in the last trimester of pregnancy and first two years of life suggested their role in brain growth and animal studies confirmed that omega-3 PUFA were essential for the development of vision. Studies which consider the effects of supplementation with LCPUFAs prenatally and in infants are outside the scope of this review and have been the subject of recent Cochrane reviews (Simmer et al. 2008).

A recent Swedish study reported an association between reported fish consumption (more or less than once per week) at age 15 and cognitive performance assessed at military conscription 3 years

later, even after adjustment for socioeconomic factors (Åberg et al. 2009). In contrast, three recent randomized controlled trials which used omega-3 supplementation found no effects on cognitive function of DHA in 10–12-year-old children (Kennedy et al. 2009), EPA and DHA in mild to moderately depressed adults (Rogers et al. 2008) or elderly adults (van de Rest et al. 2008) treated for 8, 12, and 26 weeks, respectively. There have however, been no published studies which have examined the effects of interventions based on increased fish consumption so it is difficult to draw inferences about effects of consuming LCPUFAs delivered via the food chain versus supplementation with extracted LCPUFAs. Indeed, it is also possible that the health and possible cognitive benefits of fish consumption are related to other nutrients present in fish which remain to be investigated.

36.6 Applications to Other Areas of Health and Disease

Some physical illnesses are associated with impairment of cognitive function and dietary intake is a risk factor for the development of these conditions, e.g., atherosclerosis, type 2 diabetes, and hypertension. Obesity is a significant risk factor in the development of all these conditions, and has been associated with cognitive impairments independently of medical comorbidities (Boeka and Lokken 2008). Hence, our habitual diet can influence the development of diseases for example by promoting obesity.

The development of obesity and nutritional overconsumption are strongly associated with the development of diabetes and impaired glucose tolerance (IGT; see Table 36.4 and Fig. 36.3). Both IGT and diabetes, which are characterized by abnormalities in glucoregulation, are associated with cognitive impairments (Lamport et al. 2009). Consumption of certain foods and diets such as a low GI diet have been recommended as a method to control and potentially improve the abnormalities in glucose handling seen in individuals with IGT and type 2 diabetes. Although the cognitive effects of a habitual low GI diet are unknown, research has shown that long-term improvements in glucose handling produced by increased physical activity are associated with cognitive benefits (Watson et al. 2003). If improved glucoregulation is the mechanism by which cognitive benefits occur, then

Table 36.4 Diagnostic criteria for type 2 diabetes, impaired glucose tolerance (IGT), impaired fasting glucose (IFG), normal glucose tolerance (NGT)

	World Health Organization (WHO) 1999	American Diabetes Association (ADA) 2003
Diabetes		
Fasting glucose level	≥7.0 mmol/L	≥7.0 mmol/L
	or	or
2-h glucose level[a]	≥11.1 mmol/L	≥11.1 mmol/lL
IGT		
Fasting glucose level	<7.0 mmol/L (if measured)	Not required
	and	
2-h glucose level[a]	≥7.8 and <11.1 mmol/L	≥7.8 and <11.1 mmol/L
NGT		
Fasting glucose level	<6.1 mmol/L	<5.6 mmol/L
	and	and
2-h glucose level[a]	<7.8 mmol/L	<7.8 mmol/L

The ways in which the World Health Organization and the American Diabetes Association define normal glucose tolerance (NGT), impaired glucose tolerance (IGT), and type 2 diabetes. Diagnosis is determined by examining venous plasma glucose 2 hours after ingestion of a 75g oral glucose load

[a] Venous plasma glucose 2 h after ingestion of a 75 g oral glucose load
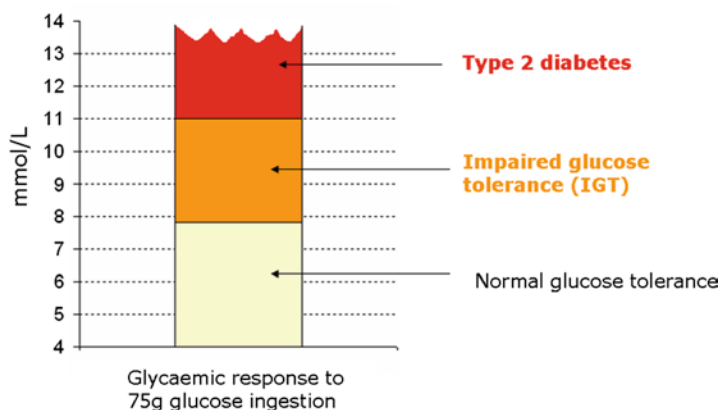
Fig. 36.3 Type 2 diabetes, impaired glucose tolerance, and normal glucose tolerance. Glucose regulation status is measured by examining blood glucose levels 2 h following consumption of 75 g glucose. Normal glucose tolerance is defined as <7.8mmol/L, impaired glucose tolerance is defined as ≥7.8 and <11.1 mmol/L, and type 2 diabetes is defined as >11.1 mmol/L

there is clear potential for cognitive benefits to accrue from a habitual diet which improves gluco-regulation, such as a low GI diet.

It is evident that cognitive decline could also be increased or prevented by our habitual diet. Rogers (2001) has reviewed the long-term impact of diet on mood and cognitive function in relation to these conditions. Intake of various nutrients (including LCPUFA, antioxidant vitamins, folate, and vitamin B12), chronic diseases (such as atherosclerosis, type 2 diabetes, and hypertension), and cognitive function appear to be associated. However, the majority of evidence comes from correlational and epidemiological studies rendering determination of cause and effect problematic. A sensible approach to this problem would be to assess the cognitive impact of prescribed dietary interventions for which the primary endpoint is to improve health and prevent disease.

36.7 *Key Points:* Design Issues

Overall, relationships between macronutrients and cognitive performance are not pervasive or clear-cut (Hoyland et al. 2008). For many measures of cognitive performance in young adults, findings are equivocal and beneficial effects are not universally reported. The choice of cognitive task may be important in the elucidation of an effect. Some tasks are more appropriate for use when a short-term effect of food is expected and others when a chronic long-term adaptation to a diet is being examined. The former, and arguably simpler, approach has been the focus of most recent research. Reaction time, attention, and memory measures are commonly used, with less evaluation of problem solving, verbal fluency, and psychomotor skill. Selection of task may be based on accessibility rather than likely effect of a nutrient on a particular cognitive process. Null findings may be observed because the chosen task requires cognitive processing that is largely unaffected by the nutrient under examination. A manipulation is unlikely to affect cognitive processing globally, and may be specific to certain faculties.

Future research would benefit from a greater range of more sensitive tasks, in order to identify effects of food on mental performance and to uncover causal relationships. Although Hoyland et al. (2008) identify memory as the most pertinent cognitive domain, tasks sensitive to performance changes in other modalities are lacking from the literature nor are all aspects of memory considered

simultaneously. There is a need for further rigorous investigation of the effects of macronutrients on performance, particularly the effects of protein, fat, and complex CHO on a wider range of cognitive functions. There is also a need to evaluate nutrients ingested via the usual diet versus those components ingested in a pure, derived, or supplement form.

Inconsistencies in findings may be explained by the multiple factors that may impact on mental performance in a study situation. Performance will be altered by individual ability, motivation, general arousal, previous learning, time of day, fatigue, the general ability of the sample, and individual differences in glycogen stores during study participation. Mood and arousal level may also exert effects on performance (Finnigan et al. 1998). Few studies have ensured that glycogen stores are not depleted on arrival for testing by providing a suitable meal on the evening prior or at breakfast before test sessions. The type of stimuli presented to participants may impact on outcome; emotional and neutral stimuli have been shown to alter the direction of the effect of glucose on a spatial memory task (Mohanty and Flint 2001).

Determining the optimal time to test postconsumption performance is also difficult. Two hours postconsumption appears to correspond to the peak response of diet-induced mood change but mental performance may not follow the same time course. The macronutrients consumed, glucose tolerance, and time of day will all affect timing of peak effects. Macronutrients in mixed composition meals may have interaction and/or temporal effects on performance. Moreover, meals designed to deliver different macronutrient compositions may differ in energy content, volume, and sensory properties (taste, pleasantness, and consistency), all features which may influence behavior and mental performance.

The chosen study design, baseline measures, outcome variables, and analysis performed may also lead to differences in observed findings. A macronutrient may alter only a small element of performance on a cognitive task, and a limited analysis of overall performance will not necessarily be sufficiently discerning to identify changes in performance. Study sample sizes are also frequently too small to detect effects of the magnitude likely to result from nutritional manipulations.

Summary Points

- Cognitive processes are well protected and glucose level in the brain is maintained under tight control.
- Many studies report that memory function may be improved by intake of glucose or more complex CHO, but this is not consistently reported.
- It is important to consider the role of habitual dietary status in studies of the acute effects of meals on cognitive function. A lack of experimental control over dietary status may obscure relationships between a particular food and cognitive function, and instead should be considered as a potentially important modulator of the relationship.
- There is gathering evidence that low GI breakfasts benefit memory in the short-term (0–3 h post ingestion); however, the long-term cognitive effects of GI and GL require further investigation. The association between improved memory and low GI foods is consistent with the evidence linking a low GI diet to health benefits.
- Future research should investigate the effect of nutritional manipulations in evening meals on cognitive function both in the evening and the following morning, which remains largely unexplored.
- The mechanisms by which GI and GL may affect cognitive function are currently unclear. However, it seems likely a combination of postprandial hormonal responses and changes in insulin, glucose, and free fatty acids contribute.
- Habitual diets which prevent the development of obesity and associated diseases such as diabetes may also serve to protect against cognitive decline. Future research should assess the cognitive impact of habitual dietary interventions the primary focus of which is to improve health and prevent disease (see Fig. 36.1).

Definitions and Explanations of Key Terms

GL: Glycemic load: This represents the quantity of CHO in a food portion and indicates the glycemic response to that portion. It is calculated as the food GI multiplied by the amount of CHO in grams, divided by 100.

GI: Glycemic index: This is an index of the blood glucose raising potential of the available CHO in foods. Glycemic responses to high GI foods are typically characterized by a rapid rise to a relatively high peak followed by a sharp decline, whereas low GI foods are characterized by a low peak and slow decline.

IGT: Impaired glucose tolerance. This is an abnormality in glucose regulation which is not as severe as diabetes. It is defined by plasma glucose levels between 7.8 and 11.1 mmol/L following consumption of 75 g of glucose (see Fig. 36.3).

Type 2 diabetes: This is the most severe abnormality in glucose regulation. It is defined by plasma glucose levels greater than 11.1 mmol/L at 2 h following consumption of 75 g of glucose.

CHO: Carbohydrate

LCPUFA: Long-chain polyunsaturated fatty acid.

References

Åberg MA, Åberg N, Brisman J, Sundberg R, Winkvist A, Toren K. Acta Pediatr. 2009;98:555–60.

Al-Naimi S, Hampton SM, Richard P, Tzung C, Morgan LM. Chronobiology Int. 200421:937–47.

Arvidsson-Lenner R, Asp NG, Axelsen M, Bryngelsson S, Haapa E, Jarvi A, Karlstrom B, Raben A, Sohlstrom A, Thorsdottir I, Vessby B. Scand J Nutr. 2004;48:84–9.

Awad N, Gagnon M, Messier C. J Clin Exp Neuropsyc. 2004;26:1044–80.

Benton D, Owens D. Psychopharmacology. 1993;113:83–8.

Benton D, Parker PY. Am J Clin Nutr. 1998;67:772–8.

Benton D, Ruffin MP, Lassel T, Nabb S, Messaoudi M, Vinoy S, Desor D, Lang V. Psychopharmacology. 2003;166:86–90.

Benton D, Slater O, Donohoe R. Physiol Behav. 2001;74:559–71.

Boeka AG, Lokken AL. Arch Clin Neuropsych. 2008;23:467–74.

Blundell JE, Cooling J. Bri J Nutr. 2000;83:S33–38.

Brand-Miller JC, Thomas M, Swan V, Ahmad ZI, Petocz P, Colagiuri S. J Nutr. 2003;133:2728–32.

Burr Ml, Fehilly AM, Gilbert JF, Rogers S, Holliday RM, Sweetnam PM, Elwood PC, Deadman, NM. Lancet. 1989;8666:757–61.

Convit A. Neurobiol Aging. 2005;26:31–5.

Craft S, Murphy C, Wemstrom J. Psychobiology. 1994;22:95–105.

Diano S, Farr SA, Benoit SC, McNay EC, da Silva I, Horvath B, Spencer Gaskin F, Nonaka N, Jaeger LB, Banks WA, Morley JE, Pinto S, Sherwin RS, Xu L, Yamada KA, Sleeman MW, Tschöp MH, Horvath TL. Nat Neurosci. 2005;9:381–8.

Donohoe RT, Benton D. Psychopharmacology. 1999;145:378–85.

Dye L, Blundell J. Brit J Nutr. 2002;88:187–211.

Dye L, Lluch A, Blundell, JE. Nutrition. 2000;16:1021–34.

Finnigan F, Hammersley R, Millar K. Appetite. 1998;31:361–75.

Flood JF, Morley JE. Brain Res. 1998;460:314–22.

Gibson EL. Nutr Bull. 2007;32:71–83.

Gilsenan MB, de Bruin EA, Dye L. Br J Nutr. 2009;101:941–9.

Gnagnarella P, Gandini S, La Vechia C, Maisonneuve P. Am J Clin Nutr. 2008;87:1793–1801.

Gold AE, Deary IJ, MacLeod KM, Friar BM. Physiol Behav. 1995;58: 501–11.

Grantham-McGregor SM, Chang S, Walker SP. Am J Clin Nutr. 1998;67: 785–9.

Graves AB, Larson EB, Edland SD, Bowen JD, McCormick WC, McCurry SM, Rice MM, Wenzlow A, Uomoto JM. Am J Epidemiol. 1996;144:760–71.

Greenwood CE, Winocur G. Behav Neural Biol. 1990;53:74–87.

Haier RJ, Siegel BV, MacLachlan A, Soderling E, Lottenberg S, Buchsbaum MS. Brain Res. 1992;570:134–43.

Hall JL, Gonder-Frederick LA, Chewning WW, Silveira J, Gold PE. Neuropsychologia. 1989;27:1129–38.

Hampton SM, Morgan LM, Lawrence N, Anastasiadou T, Norris F, Deacon S, Ribeiro D, Arendt J. J Endocrin. 1996;151:259–67.

Hill CE, Dye L. Curr Top Nutraceut Res. 2003;1:203–12.

Hill CE, Cassidy A, Murray P, Talbot D, Lawton CL, Dye L. Mol Nutr and Food Res. (under review)

Hoyland A, Dye L, Lawton C Nutr Res Rev. 2009;22:220–43.

Hoyland A, Lawton CL, Dye L. Neurosci Biobehav Rev. 2008;32:72–85.

Ingwersen J, Defeyter MA, Kennedy DO, Wesnes KA, Scholey AB. Appetite. 2007;49:240–4.

Kaplan RJ, Greenwood CE, Winocur G, Wolever TM. Am J Clin Nutr. 2000;72:825–36.

Kaplan RK, Greenwood CE, Winocur G, Wolever TMS. Am J Clin Nutr. 2001;74:687–93.

Kalmijn S, Launer LJ, Ott A, Witteman JCM, Hofman A, Breteler MMB. Ann Neurology. 1997;42:776–82.

Kanarek RB, Swinney D. Appetite. 1990;14:15–27.

Kennedy D, Jackson P, Elliott J, Scholey A, Robertson B, Greer J, Tiplady B, Buchanan T, Haskell C. Nutr Neurosci. 2009;12:48–56.

Kennedy DO, Scholey AB. Pharmacol Biochem Behav. 2003;75:687–700.

Kern W, Peters A, Freuhwald-Schultes B, Deininger E, Born J, Fehm HL. Clin Neuroendocrinol. 2001;74:270–80.

Lamport DJ, Hoyle E, Lawton C, Mansfield MW, Dye L. Submitted.

Lamport D, Lawton CL, Mansfield M, Dye L. Neurosci Biobehav Rev. 2009;33:394–413.

Lloyd HM, Green MW, Rogers PJ. Phys & Behav. 1994;56:51–57.

Lloyd HM, Rogers PJ, Hedderley DI, Walker AF. Appetite. 1996;27:151–64.

Mahoney CR, Taylor HA, Kanarek RB, Samuel P. Physiol Behav. 2005;85:635–45.

Markus CR. 1999 PhD thesis. Utrecht, University of Utrecht.

Martin PY, Benton D. Physiol Behav. 1998;67:69–74.

McNay EC, Fries TM, Gold PE. Proc Natl Acad Sci. 2000;97:2881–5.

Messier C. Eur J Pharmacol. 2004;490:33–57.

Messier C, Desrochers A, Gagnon M. Behav Neurosci. 1999;3:431–8.

Mohanty A, Flint RW Jr. Cogn Affect Behav Neurosci. 2001;1:90–5.

Monk TH, Folkard S. In: Folkard S, Monk TH, editors. Hours of work: temporal factors in work-scheduling. Chichester: Wiley, 1985.

Morgan L, Arendt J, Owens D, Folkard S, Hampton S, Deacon S, English J, Ribeiro D, Taylor K. J Endocrinol. 1998;157:443–51.

Morgan L, Hampton S, Gibbs M, Arendt J. Chronobiology Int. 2003;20:795–808.

Muldoon MF, Ryan CM, Matthews KA, Manuck SB. Psychosom Med. 1997;59:382–7.

Murphy JM, Pagano M, Nachmani J, Sperling P, Kane S, Kleinman R. Arch Pediat Adol Med. 1998;152:899–907.

Nabb S, Benton D. Physiol Behav. 2006;87:16–23.

Nilsson A, Radeborg K, Björk I. Eur J Clin Nutr. 2009;63:113–20.

Blundell JE, Cooling J. Bri J Nutr. 2000;83:S33–38.

Papanikolaou Y, Palmer H, Binns MA, Jenkins DJA, Greenwood CE. Diabetologia. 2006;49:855–62.

Pardridge WM, Triguero D, Farrell CR. Diabetes. 1990;39:1040–4.

Park CR. Neurosci Biobehav R. 2001;25:311–23.

Pellerin L, Magistretti PJ. Proc Natl Acad Sci. 1994;91:10625–9.

Pollitt E, Mathews R. Am J Clin Nutr. 1998;67:804–13.

Reid M, Hammersley R. Nut Res Rev. 1999;12:3–23.

Riedel WJ, Klassen T, Deutz NEP, van Someren A, van Praag HM. Psychopharmacology. 1999;141:362–9.

Rogers PJ. Proc Nutr Soc. 2001;60:135–43.

Rogers PJ, Appleton KM, Kessler D, Peters TJ, Gunnell D, Hayward RC, Heatherley SV, Christian LM, McNaughton SA, Ness AR. Brit J Nut. 2008;99:421–31.

Scholey A, Harper S, Kennedy D. Physiol Behav. 2001;73:585–92.

Scholey AB, Kennedy DO. Psychopharmacology. 2004;176:320–30.

Simmer K, Patole SK, Rao SC. Cochrane Database Syst Rev. 2008;CD000376.

Sjöberg A, Hallberg L, Höglund D, Hulthén L. Eur J Clin Nutr. 2003;57:1569–78.

Smith AP, Clark R, Gallagher J. Phys & Behav. 1999;67:9–17.

Smith AP, Kendrick A., Maben A, Salmon J. Appetite. 1994;22:39–55.

Smith AP, Miles C. Neuropsychobiology. 1986;16:117–20.

Smith AP, Rusted JM, Eaton-Williams P, Savory M, Leathwood P. Neuro. 1990;23:160.

Sünram-Lea S, Foster J, Durlach P, Perez C. Psychopharmacology. 2001;157:46–54.

Tsacopoulos M, Magistretti PJ. J Neurosci. 1996;16:877–85.

Uijtdehaage S, Shapiro D, Jaquet F. Biol Psychol. 1994;38:53–72.

van Cauter E. Horm Res. 1990;34:45–53.

van de Rest O, Geleijnse JM, Kok FJ, van Staveren WA, Dullemeijer C, Olderikkert MG, Beekman AT, de Groot LC. Neurology. 2008;71:430–8.

Watson GS, Reger MA, Cholerton BA, Asthana S, Baker LD, Rhoads K, Plymate S, Fishel M, Kahn S, Craft S. Neurology. 2003;60:1899–903.

White LR, Petrovitch H, Ross GW, Masaki K, Hardman J, Nelson J, Davis D, Markesbury W. J Am Coll Nutr. 2000;19:242–55.

Wolever TM, Jenkins DJ, Ocana AM, Rao VA, Collier GR. Am J Clin Nutr. 1988;48:1041–7

Chapter 37
Dietary Amino Acids and Mood

Reeta Rintamäki and Timo Partonen

Abbreviations

ArAA   Aromatic amino acids
BCAA   Branched-chain amino acids
GABA   Gamma-aminobutyric acid
LNAA   Large neutral amino acids
MDD   Major depressive disorder
NMDA   N-methyl-D-aspartate

37.1 Introduction

It is known that the dietary amino acids have an effect on brain functions. Some of the amino acids have influence on mood in particular through their actions as precursors for neurotransmitters. Tryptophan is a precursor for serotonin, tyrosine is a precursor for dopamine and noradrenaline, and glutamate is a precursor for gamma-aminobutyric acid (GABA; Table 37.1). These neurotransmitters are involved in the regulation of mood and behaviors. Mood disorders such as major depressive disorder (MDD) and bipolar disorder are often associated with dysfunction of these neurotransmitters, and the current medication for mood and anxiety disorders is based on drugs whose mechanisms of action influence serotonin, dopamine, and noradrenaline. Currently used sleeping pills have their effect through GABA receptor complexes.

Mood disorders are a significant public health problem worldwide. Patients with MDD have depressed mood, increased sadness and anxiety, and a loss of interest in usual activities. Patients with bipolar disorder have both depressed and manic episodes, during the latter mood being abnormally elevated. A single meal, depending on its protein and carbohydrate contents, can modify the uptake of the large neutral amino acids (LNAA) into the brain and their subsequent conversion to neurotransmitters. A hypothesis has been that some amino acids can thereby be helpful in treating mood disorders. However, there are limited data about the dietary amino acids in relation to mood or mood disorders.

R. Rintamäki (✉)
National Institute for Health and Welfare, Department of Mental Health and Substance Abuse Services, Mood, Depression and Suicidal Behaviour Unit, 30 (Mannerheimintie 166), FI-00271 Helsinki, Finland
e-mail: reeta.rintamaki@thl.fi

Table 37.1 Neurotransmitters synthesized from amino acids

Amino acid	Neurotransmitter
Tryptophan	Serotonin
Tyrosine	Dopamine, noradrenaline
Glutamate	GABA

GABA gamma-aminobutyric acid

This table lists dietary amino acids which work as precursors for neurotransmitters.

37.2 Amino Acids and Neurotransmitters

The 20 amino acids on which the proteins of the human body are built each has a metabolic fate of its own. Humans can produce 10 of these 20 amino acids. The remaining must be supplied in and taken from the food. There are eight (ten in infants) essential amino acids for us: isoleucine, leucine, lysine, methionine, phenylalanine, threonine, tryptophan, and valine. Histidine and arginine are essential amino acids for the children but not for the adults.

Amino acids are divided into subgroups by their chemical character. LNAAs include the aromatic amino acids (ArAAs, i.e., tyrosine, phenylalanine, and tryptophan) and the branched-chain amino acids (BCAA, i.e., leucine, isoleucine, and valine). The major source of amino acids is protein-rich food, like meat, fish, poultry, eggs, milk, and dairy products.

Many amino acids participate in a range of functions of the brain such as regulation of mood. Certain neurotransmitters (serotonin, dopamine, noradrenaline, and GABA) have a role in the pathogenesis of mood disorders, both MDD and bipolar disorder. These neurotransmitters are synthesized from the dietary amino acids in the brain.

Serotonin is an inhibitory neurotransmitter, which appears to play an important role in the central nervous system circuits that regulate mood, emotional behaviors, and sleep. Serotonin also influences appetite regulation, and it provides one of the links between mood and food. In the brain, serotonin is synthesized from tryptophan (Fig. 37.1). Reduced serotonergic transmission is associated with the pathogenesis of depressive illness. There is an increase in the activity of serotonin transporters in the brain of the depressed compared with healthy individuals. Most of the antidepressant medications act through the increase in serotonin neurotransmission. Abnormalities in the brain serotonin regulation are associated with eating disorders as well.

Dopamine is an inhibitory neurotransmitter, which is involved in regulation of motivation, concentration, psychomotor speed, and the ability to experience pleasure. In the brain, dopamine and noradrenaline are synthesized from tyrosine (Fig. 37.2). Reduced concentrations of dopamine metabolites
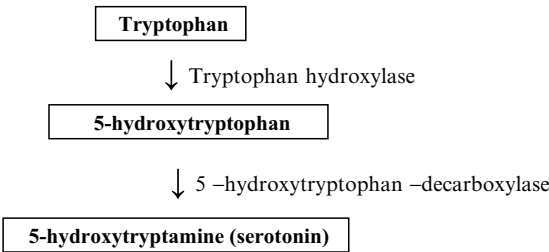
Fig. 37.1 Serotonin synthesis from tryptophan. This figure presents synthesis of serotonin from tryptophan. Tryptophan is first converted to 5-hydroxytryptophan by the enzyme tryptophan hydroxylase, 5-hydroxytryptophan is thereafter decarboxylated to 5-hydroxytryptamine (also called serotonin) by the enzyme aromatic acid decarboxylase
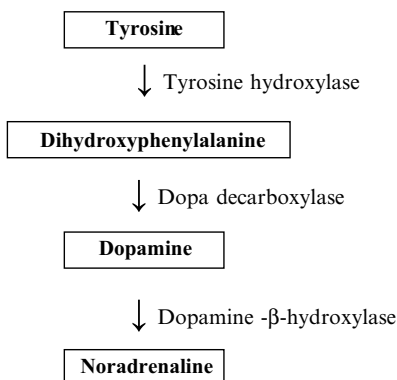
Fig. 37.2 Dopamine and noradrenaline synthesis from tyrosine. This figure presents synthesis of dopamine and noradrenaline from tyrosine. Tyrosine is converted to dihydroxyphenylalanine by the enzyme tyrosine hydroxylase, and thereafter dihydroxyphenylalanine is converted to dopamine by the enzyme dopa decarboxylase. Dopamine is converted to noradrenaline by the enzyme dopamine-β-hydroxylase
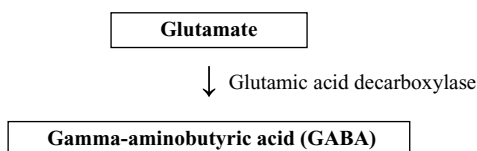
Fig. 37.3 The synthesis of gamma-aminobutyric acid (GABA) from glutamate. This figure is presents the synthesis of GABA from glutamate. GABA is synthesized in a single step from its precursor glutamate by the action of glutamic acid decarboxylase

in the brain of the depressed have been demonstrated. Neuroimaging studies support the hypothesis that MDD is associated with reduced dopamine transmission (Dunlop and Nemeroff 2007).

Noradrenaline is the primary neurotransmitter of the sympathetic nervous system in the periphery, but it is also prevalent in the brain. It is involved in mood regulation, sleep, expression of behaviors, and the general degree of alertness and arousal. Traditional antidepressants increase the concentrations of noradrenaline.

GABA is a major inhibitory neurotransmitter in the central nervous system. It modulates the activity of several neurotransmitters, including dopamine, serotonin, and noradrenaline. GABA is synthesized in a single step from its precursor glutamate by the action of glutamic acid decarboxylase (Fig. 37.3). GABA is involved in regulation of normal and pathological brain functions such as sleep and memory processes. GABA contributes to not only anxiety but also depressive disorders. Lowered levels of GABA have been found in plasma and platelets of the depressed (Brambilla et al. 2003). Anxiolytic drugs typically increase GABA neurotransmission.

37.2.1 How Dietary Amino Acids Alter Brain Serotonin and Catecholamine Synthesis?

Amino acids are taken into the brain across the blood–brain barrier, which is physically constructed of endothelial cells that line brain capillaries. The blood–brain barrier contains specific transport mechanisms for the LNAAs. All five LNAAs compete with each other for transport across the blood–brain

barrier. A change in the uptake rate of any given LNAA after a meal depends not only on how the level of an LNAA in the circulation is altered by the meal contents, but also on how the blood levels of the remaining LNAAs are modified (Fernström 1990).

Carbohydrates in the food stimulate the secretion of insulin, which increases the plasma concentration of tryptophan and decreases the levels of other LNAAs. This leads to increase in tryptophan and the subsequent serotonin concentrations in the brain (Fernström 1983). In contrast, proteins in the food raise the levels of all the LNAAs about equally, and therefore there is no change in the competition of the LNAA transporter across the blood–brain barrier and no change in the levels of tryptophan and serotonin in the brain.

Concerning tyrosine, nonprotein food reduces the levels of serum tyrosine and the other LNAAs, but does not affect tyrosine levels in the brain. After a protein-rich meal, tyrosine levels increase more than those of the remaining LNAA competitors, and therefore tyrosine and the subsequent dopamine levels rise in the brain (Fernström 1983; Fernström and Fernström 1987).

After ingestion of a meal which contains plenty of BCAAs, the plasma and brain concentrations of BCAAs increase and those of ArAAs decrease. Such effects are likely to reduce the synthesis of neurotransmitters serotonin, dopamine, and noradrenaline.

37.2.2 Tryptophan

Tryptophan is an essential amino acid. It is a precursor for serotonin synthesis. Free tryptophan is transported into the brain across the blood–brain barrier by an active protein shuttle for which five other LNAAs (valine, leucine, isoleucine, phenyalanine, and tyrosine) also compete. In the brain, serotonin is synthesized from tryptophan. Tryptophan is first converted to 5-hydroxytryptophan by the enzyme tryptophan hydroxylase; 5-hydroxytryptophan is thereafter decarboxylated to 5-hydroxytryptamine (also called serotonin) by the enzyme aromatic acid decarboxylase (Fig. 37.1). Serotonin is stored in synaptic vesicles where it stays until it is released by a neuronal impulse. Serotonin is destroyed by the enzyme monoamine oxidase and converted to an inactivate metabolite, 5-hydroxyindoleacetic acid. In addition, serotonin is converted to melatonin in the pineal gland at night. Melatonin is involved in synchronization of the circadian rhythms and in regulation of seasonal behaviors.

Entry of tryptophan to the brain depends on two key factors: first, the free plasma levels of tryptophan and, second, the concentrations of the remaining LNAAs that compete with tryptophan for transport across the blood–brain barrier. Dietary protein and carbohydrate content can influence the brain tryptophan and serotonin levels by having an effect on plasma amino acid profiles.

37.2.2.1 Tryptophan and Mood

Tryptophan is a precursor for serotonin, which is known to play a key role in many brain functions, such as mood regulation. Tryptophan depletion is used to investigate the actions of serotonin. The aim of tryptophan depletion is to lower down the brain serotonin levels by eliminating the amino acid precursor tryptophan and thereby causing the depletion.

Two techniques are commonly used in depletion studies. Removal of tryptophan from the diet reduces plasma tryptophan levels by 15–20%. Alternatively, a marked effect on tryptophan levels can be achieved by giving participants an amino acid load that does not contain tryptophan. Such amino acid load stimulates protein synthesis in the liver, which then uses up tryptophan free in the circulating plasma together with the other LNAAs that are administered.

Tryptophan depletions induce a rapid and substantial lowering of the total and free plasma levels of tryptophan. A number of studies have shown that acute tryptophan depletion causes depressive symptoms and results in worsening of mood in the depressed and those having vulnerability to depression. However, persons with no personal or family history of MDD tend not to have any change in mood following tryptophan depletion, despite the fact that tryptophan depletion did lower serotonin levels and metabolic activities in regions of the brain having relevance to regulation of mood (Ruhé et al. 2007).

A few studies of tryptophan depletion exist in patients with bipolar disorder. Patients on mood stabilizer have no response to tryptophan depletion, but those patients who have recovered recently have reported of manic symptoms after the depletion (Cappiello et al. 1997; Hughes et al. 2000). Recently, it has been demonstrated that acute tryptophan depletion may have an antimanic effect in patients with acute mania (Applebaum et al. 2007).

Tryptophan depletion has a selective effect on sweet consumption in overweight individuals and patients with binge eating. Acute lowering of the serotonin synthesis by tryptophan depletion increases the intake of sweet-tasting foods (Pagoto et al. 2009).

There are several reports which find that the plasma tryptophan concentration is clearly lower in patients with MDD than in psychologically healthy controls (Cowen et al. 1989). However, the dietary intake of tryptophan did not associate with MDD in a population-based study (Hakkarainen et al. 2003). Patients with bipolar disorder also have decreased tryptophan levels compared with controls (Hoekstra et al. 2006). For this reason, the tryptophan supplementation has been applied for the treatment of depressed patients, but the efficacy of tryptophan supplementation is limited.

Patients with MDD tend to consume more carbohydrates in their diet than nondepressed persons, and they have an increase in preference for sweet carbohydrate foods during depressive episodes (Christensen 2001). These patients are typically having atypical depressive symptoms, such as prolonged sleep duration, increased appetite, and weigh gain. It has been hypothesized that these individuals try to alleviate depression by craving carbohydrates that increase serotonin levels in the brain. The subsequent drowsiness is a common effect of a carbohydrate-rich meal, but in patients with atypical depressive symptoms or those with seasonal affective disorder a carbohydrate meal paradoxically leads to an increase in alertness (Rosenthal et al. 1989). Measurements from the hypothalamus have demonstrated that serotonin levels are low during the time before meals, rise in anticipation of food, and spike during the meal. In line with these findings, such drugs that enhance serotonin usage in the brain are appetite suppressants.

37.2.3 Tyrosine

Tyrosine is not an essential amino acid, because it can be made from the essential amino acid phenylalanine. In the brain, dopamine and noradrenaline are synthesized from tyrosine. Tyrosine is converted to dihydroxyphenylalanine by the enzyme tyrosine hydroxylase, and thereafter dihydroxyphenylalanine is converted to dopamine by the enzyme dopa decarboxylase. Dopamine is converted to noradrenaline by the enzyme dopamine-β-hydroxylase (Fig. 37.2). Tyrosine has the same transporter than the other LNAAs in the blood–brain barrier.

37.2.3.1 Tyrosine and Mood

In order to study the effects of tyrosine on mood, depletion studies similar to tryptophan depletions have been used. In these tyrosine depletion studies, participants are given an amino acid mixture free

of both tyrosine and the tyrosine precursor phenylalanine. Such depletion lowers the plasma tyrosine concentration and inhibits tyrosine brain entry by competition. In most of the studies, acute tyrosine and phenylalanine depletion does not induce depressive symptoms in healthy controls, whereas it affects patients who have been treated with noradrenergic medications and recovered recently. In the depressed, tyrosine depletion induces depressive symptoms and causes metabolic changes in brain areas that are relevant to regulation of mood (Hasler et al. 2008).

Acute dietary tyrosine depletion increases dopamine neurotransmission and reduces the intensity of manic symptoms in patients with bipolar disorder (McTavish et al. 2001; Scarnà et al. 2003). Patients with anorexia nervosa tend to have low plasma tyrosine levels (Ehrlich et al. 2009).

Dietary supplements that contain tyrosine and/or phenylalanine enhance alertness and arousal. However, there was no association between the dietary intakes of tyrosine or phenylalanine and MDD in a population-based study (Hakkarainen et al. 2003).

37.2.4 Glutamate

Glutamate is an essential amino acid. It is a precursor for GABA synthesis (Fig. 37.3). In addition, glutamate itself is a neurotransmitter. Glutamate is the major excitatory neurotransmitter in the cerebral cortex and has been indicated in the pathogenesis of mood disorders. Abnormalities in glutamatergic transmission, particularly concerning *N*-methyl-d-aspartate (NMDA) glutamate receptors, are postulated to play a role in both MDD and bipolar disorder.

37.2.4.1 Glutamate and Mood

The role of the NMDA glutamate receptor has been linked to mood disorders. Mood stabilizers such as lithium and valproic acid have an effect on the uptake and release of glutamate. Further, antiglutamatergic drugs like lamotrigine are demonstrated to have beneficial effects on depressive symptoms in patients with bipolar disorder. Increased levels of glutamate were observed in the frontal cortex and plasma from patients with bipolar disorder and those with MDD (Mitani et al. 2006; Hashimoto et al. 2007). Recently, low cerebrospinal fluid glutamate and glycine concentrations have been reported in mood disorders resistant to medication (Frye et al. 2007). The blood–brain barrier normally prevents any elevation in plasma glutamate levels from having an effect on the brain levels of the amino acid. Even great increments in the circulating glutamate concentration do not raise glutamate levels in the brain. For this reason, the dietary intake of glutamate will not affect the concentrations of glutamate and GABA. In agreement, the dietary intake of glutamate did not associate with MDD in a population-based study (Hakkarainen et al. 2003).

37.2.5 Other Amino Acids

Many amino acids can have a role in the functions of the brain. The following amino acids have also been connected to regulation of mood, but their relevance to mood remains elusive.

37.2.5.1 Serine

Serine is not an essential amino acid in the human diet. It is produced from hydroxypyruvate derived either from glucose or glycerol. Serine is thereafter used as a precursor for glycine through a process that transfers a methylene group to tetrahydrofolate. Serine acts as a partial agonist at the glycine modulation site of the glutamate receptor in the brain and therefore tends to have an effect on brain functions. Previously, high serine plasma concentrations were suggested to be a potential marker for psychotic disorder in general and for depressive disorder in particular (Mauri et al. 1998; Sumiyoshi et al. 2004). However, there are also reports of low serine plasma levels in depressive disorder with psychotic symptoms (Maes et al. 1998). The increased dietary intake of serine has been associated with the increased risk of hospital treatment due to MDD, but this association disappeared after excluding from analysis those who had reported depressed mood at study entry (Hakkarainen et al. 2003).

37.2.5.2 Glycine

Glycine is not an essential amino acid in the human diet. It is produced from serine. Glycine acts as an obligatory coagonist at the strychnine insensitive glycine modulatory site of the NMDA-type glutamate receptor. Increased plasma levels of glycine have been found in the depressed compared with psychologically healthy individuals. Normally, dietary glycine has no influence on the brain glycine levels. However, when glycine is administered in a sufficient quantity, it may pass through the blood–brain barrier and elevate glycine levels in the brain. However, in a population-based study, the dietary intake of glycine did not associate with MDD (Hakkarainen et al. 2003).

37.2.5.3 Lysine

Lysine, an essential amino acid, acts as a precursor for carnitine. Acetylincarnitine has a role in lipid metabolism and is synthesized from carnitine. Currently, there are no consistent data regarding the effect of lysine on brain functions or on mental disorder. The dietary intake of lysine was associated with the increased risk of hospital treatment due to MDD in a population-based study, but this association disappeared after excluding from analysis those who had reported depressed mood at study entry (Hakkarainen et al. 2003). As lysine fortification of wheat was demonstrated to reduce anxiety and distress among an economically disadvantaged population (Smriga et al. 2004), the role of lysine remains an enigma and needs elucidation.

37.2.5.4 Methionine

Methionine is an essential amino acid. It combines with adenosine triphosphate to produce *S*-adenosylmethionine (SAM) that facilitates the production of neurotransmitters in the brain (Papakostas et al. 2003). Depressed patients appear to have lower serum and cerebrospinal fluid SAM levels. However, the dietary intake of methionine did not associate with MDD in a population-based study (Hakkarainen et al. 2003).

37.2.5.5 Histidine

Histidine is an essential amino acid for children. It acts as a precursor for histamine that is a neurotransmitter in the brain. Histamine is derived as a result of the decarboxylation of histidine in a reaction that is catalyzed by the enzyme l-histidine decarboxylase. Histamine has been indicated in the control of arousal and sexual behaviors. There is a shortage of data on the dietary histidine in relation to mood. In a population-based study, the dietary intake of histidine did not associate with MDD (Hakkarainen et al. 2003).

37.2.6 The Recommendations of Amino Acids

In the Western industrialized countries, the intake of essential amino acids usually exceeds the daily recommendations. The recommendations for the daily intake of essential amino acids are presented in Table 37.2. Unlike with fat and starch, the human body does not store excess amino acids for later usage. This is the reason why we have to have amino acids every day.

Animal sources such as meat, fish, seafood, poultry, eggs, milk, and dairy products provide all the essential amino acids. In addition, some plant sources such as buckwheat contain a balanced set of the essential amino acids. It is not necessary to have all the essential amino acids from a single food product. All the essential amino acids will be supplied by consuming a range of plants such as a combination of cereal grains (wheat, corn, rice) and legumes (beans, peanuts).

37.2.6.1 Special Groups

The intake of particular amino acids can be disturbed in certain bowel diseases. For instance, Crohn's disease and celiac disease can compromise the absorption of amino acids. Celiac disease has been associated with the increased prevalence of depression prior to the diet treatment. Recently, it has been demonstrated that those celiac disease patients with depression have lower prediet serum tryptophan concentrations and improvement in depressive symptoms after start of the gluten-free diet. The improvement coincided with a decrease in celiac disease activity and an increase in serum concentrations of tyrosine and other BCAAs (Pynnönen et al. 2005).

Table 37.2 Daily requirements of essential dietary amino acids in adults (FAO/WHO/UNU 2007)

Amino Acids	mg/kg/day	mg/70 kg/day
Isoleucine	20	1400
Leucine	39	2730
Lysine	30	2100
Methionine + cysteine	15	1050
Phenylalanine + tyrosine	25	1750
Threonine	15	1050
Tryptophan	4	280
Valine	26	1820

This table presents daily requirements of essential amino acids in adults. In the first column, requirements are presented as mg/kg/day and in the second column as mg/70 kg/day

Intake of nutrients is abnormal in patients with anorexia nervosa or bulimia nervosa. These two eating disorders can affect the intake of the essential amino acids, on which there are however no published data.

There is a range of special diets with which the intake of proteins may not meet the daily recommendations in full. Strict vegetarian diets can reduce the intake of the essential amino acids as well. With a vegetarian diet, the individual should use a variety of plant food in order to have essential amino acids enough. Good sources of proteins for vegetarians are nuts and seeds, pulses, soy products and cereals. With weight-reducing diets, the individual should have enough proteins of a good quality. Athletes may use nutrients which may include BCAAs in order to improve physical performance. However, such nutrients tend to reduce tryptophan, tyrosine, and phenylalanine concentrations in the brain. This may have an impact in those with depression or having vulnerability to depression, if their habitual diet is limited.

37.2.7 The Timing of Eating

Both the timing and macronutrient contents of a meal influence sleep. A meal consumed close to the bedtime is associated with sleep disturbances. A number of macronutrients influences sleep through the actions of tryptophan. High carbohydrate diet tends to increase the ratio of the circulating tryptophan to the remaining LNAAs via a direct action of insulin. A high carbohydrate meal is likely to promote sleep via an increase in the brain tryptophan and serotonin levels. High carbohydrate meals induce more tiredness afterwards than low carbohydrate meals (Afaghi et al. 2007). Levels of tryptophan tend to peak at 2–4 h after the high carbohydrate meal. In contrast, tryptophan and LNAAs tend to peak at about 4 h after the ingestion of a high protein meal (Rogers 2001). A high intake of proteins appears to increase alertness.

37.2.8 Applications to Other Areas of Health and Disease

There are no data on the use of the dietary amino acids to improve mood beyond mood disorders (Table 37.3). However, the dietary intake of amino acids needs to take into account for chronic diseases in which the diet or the absorption of macronutrients does not meet the daily recommendations. For example, patients with bowel diseases have low tryptophan levels that may affect mood subsequently. Cancer patients may benefit from a good balance in the dietary amino acids intake.

Table 37.3 Key features of dietary amino acids and mood

1. Some amino acids influence the brain function directly or indirectly, but there is a lack of consistent data concerning dietary amino acids and mood.
2. Dietary amino acid tryptophan works as a precursor for neurotransmitter serotonin.
3. Serotonin is a neurotransmitter which is known to play an important role in the regulation of mood and sleep.
4. Dietary amino acid tyrosine works as a precursor for neurotransmitters dopamine and noradrenaline.
5. Also neurotransmitters, dopamine and noradrenaline, are involved in the regulation of mood.
6. Dietary amino acid glutamate is a precursor for GABA and it also works as a neurotransmitter itself.
7. In the future, more studies are needed to elucidate the effects of dietary amino acids on mood.

This table lists the key facts of dietary amino acids and mood including the three most important dietary amino acids to mood. GABA: gamma-aminobutyric acid

Poor therapeutic equilibrium in diabetes patients increases the plasma concentrations of BCAAs and reduces the transport of tryptophan, tyrosine, and phenylalanine into the brain. As a result, ArAA levels are low. Nutritionist and other professionals need to pay attention to and guide these patients.

Summary Points

- There are 20 amino acids and humans can produce 10 of them. Eight amino acids are essential for humans and these must be supplied for food. The major sources of amino acids are protein-rich food, such as meat, fish, poultry, eggs, milk, and dairy products.
- Some amino acids influence the brain function directly or indirectly, but there is a lack of consistent data concerning dietary amino acids and mood.
- Amino acid tryptophan is a precursor for neurotransmitter serotonin. Serotonin has a key role in mood and sleep regulation and dysregulation of serotonergic system is associated with low mood and mood disorders.
- Amino acid tyrosine is a precursor for neurotransmitters dopamine and noradrenaline. Dopamine and noradrenaline are involved in the regulation of motivation, psychomotor speed, concentrations, and the ability to experience pleasure. Low levels of dopamine and noradrenaline are associated with mood disorders.
- Neurotransmitter GABA is synthesized from amino acid glutamate, which also works as a neurotransmitter itself. GABA and glutamate also participate in mood and sleep regulation.
- Single meals, depending on their protein and carbohydrate content, can rapidly influence uptake of the LNAAs into the brain, as a result, directly modify their conversion to neurotransmitters.
- Carbohydrate meal increase tryptophan and serotonin levels in the brain and, usually induces drowsiness in healthy subjects but alertness in patients with seasonal affective disorder. Subjects with depression could try to alleviate the low mood by craving carbohydrates.
- Both timing and macronutrient content of meal can affect mood and sleep.
- Generally the daily recommendations of essential amino acids exceed. Individuals with special diet for example, vegetarians, should pay attention to their diets.

Definitions of Key Terms

Major depressive disorder (MDD) is a mood disorder in which patients have low mood or a loss of interest in usual activities. They have feelings of worthlessness, inappropriate guilt, or loss of self-esteem. Common symptoms are altered appetite and sleep. Patients could also have thoughts of death and suicide.

Bipolar disorder is a mood disorder where patients have mood swings that alternate between periods of mania and periods of depression. In mania patients have abnormally elevated or irritable mood accompanied symptoms such as increased energy, decreased need for sleep, rapid thinking and speech, and in some cases psychotic symptoms.

Mood is a relative long-lasting emotional state. Long-term disturbances of mood such as depression and bipolar disorders are considered mood disorders.

Amino acids have a carboxyl carbon group and an amino nitrogen group attached to a central alpha-carbon. They have variety roles in metabolism. Amino acids are joined together in long strings by peptide bonds to form proteins of differing shapes and sizes.

Essential amino acids have no synthetic pathways in humans; hence, these amino acids are essential to the diet.

Large neutral amino acids (LNAA) are tryptophan, valine, leucine, isoleleucine, phenyalanine, and tyrosine. They have one specific transporter in blood–brain barrier which they compete with each other.

Blood–brain barrier is the regulated interface between the peripheral circulation and the central nervous system. This restricts the passage of various chemical substances between the bloodstream and the neural tissue itself, while still allowing the passage of substances essential to metabolic function.

Neurotransmitters are chemicals which account for the transmission of signals from one neuron to next across synapses.

Serotonin is an inhibitory neurotransmitter in brain activating serotonin receptors. It plays an important role in brain systems that regulate mood, emotional behavior, and sleep. In the brain serotonin is synthesized from amino acid tryptophan.

Gamma-aminobutyric acid (GABA) is a major inhibitory neurotransmitter in the central nervous system. It has been shown to be involved in the regulation of sleep and memory. It is synthesized from glutamate in the brain.

Dopamine is a neurotransmitter in the brain activating the dopamine receptors. It has several functions in the brain, including important roles in behavior and cognition, motor activity, and mood. It is synthesized from amino acid tyrosine in the brain.

Noradrenaline is the primary neurotransmitter of the sympathetic nervous system in the periphery but it is also prevalent in the brain. It is involved in mood regulation, sleep regulation, expression of behavior, and the general degree of alertness and arousal. It is synthesized from amino acid tyrosine in the brain. Noradrenaline is also called norepinephrine.

References

Afaghi A, O'Connor H, Chow CM. Am J Clin Nutr. 2007;85:426–30.

Applebaum J, Bersudsky Y, Klein E. Bipolar Disord. 2007;9:884–7.

Brambilla P, Perez J, Barale F, Schettini G, Soares JC. Mol Psychiatry. 2003;8:721–37.

Cappiello A, Sernyak MJ, Malison RT, McDougle CJ, Heninger GR, Price LH. Biol Psychiatry. 1997;42:1076–8.

Christensen L. Clin Nutr. 2001;20:161–6.

Cowen PJ, Parry-Billings M, Newsholme EA. J Affect Disord. 1989;16:27–31.

Dunlop BW, Nemeroff CB. Arch Gen Psychiatry. 2007;64:327–37.

Ehrlich S, Franke L, Schneider N, Salbach-Andrae H, Schott R, Craciun EM, Pfeiffer E, Uebelhack R, Lehmkuhl U. Int J Eat Disord. 2009;42:166–72.

FAO/WHO/UNU Protein and amino acid requirements in human nutrition. WHO Technical Report Series 935, 2007.

Fernström JD. Physiol Rev. 1983;63:484–546.

Fernström JD. J Nutr Biochem. 1990;1:508–17.

Fernström MH, Fernström JD. Brain Res. 1987;401:392–6.

Frye MA, Tsai GE, Huggins T, Coyle JT, Post RM. Biol Psychiatry. 2007;61:162–6.

Hakkarainen R, Partonen T, Haukka J, Virtamo J, Albanes D, Lönnqvist J. Depress Anxiety. 2003;18:89–94.

Hasler G, Fromm S, Carlson PJ, Luckenbaugh DA, Waldeck T, Geraci M, Roiser JP, Neumeister A, Meyers N, Charney DS, Drevets WC. Arch Gen Psychiatry. 2008;65:521–31.

Hashimoto K, Sawa A, Iyo M. Biol Psychiatry. 2007;62:1310–6.

Hoekstra R, Fekkes D, Loonen AJ, Pepplinkhuizen L, Tuinier S, Verhoeven WM. Eur Neuropsychopharmacol. 2006;16:71–7.

Hughes JH, Dunne F, Young AH. Br J Psychiatry. 2000;177:447–51.

Maes M, Verkerk R, Vandoolaeghe E, Lin A, Scharpè S. Acta Psychiatr Scand. 1998;97:302–8.

Mauri MC, Ferrara A, Boscati L, Bravin S, Zamberlan F, Alecci M, Invernizzi G. Neuropsychobiology. 1998;37:124–9.

McTavish SF, McPherson MH, Harmer CJ, Clark L, Sharp T, Goodwin GM, Cowen PJ. Br J Psychiatry. 2001;179:356–60.

Mitani H, Shirayama Y, Yamada T, Maeda K, Ashby CR Jr, Kawahara R. Prog Neuropsychopharmacol Biol Psychiatry. 2006;30:1155–8.

Pagoto SL, Spring B, McChargue D, Hitsman B, Smith M, Appelhans B, Hedeker D. Eat Behav. 2009;10:36–41.

Papakostas GI, Alpert JE, Fava M. Curr Psychiatry Rep. 2003;5:460–6.

Pynnönen PA, Isometsä ET, Verkasalo MA, Kähkönen SA, Sipilä I, Savilahti E, Aalberg VA. BMC Psychiatry. 2005;5:14.

Rogers PJ. Proc Nutr Soc. 2001;60:135–43.

Ruhé HG, Mason NS, Schene AH. Mol Psychiatry. 2007;12:331–59.

Rosenthal NE, Genhart MJ, Caballero B, Jacobsen FM, Skwerer RG, Coursey RD, Rogers S, Spring BJ. Biol Psychiatry. 1989;25:1029–40.

Scarnà A, Gijsman HJ, McTavish SFB, Harmer CJ, Cowen PJ, Goodwin GM. Br J Psychiatry. 2003;182:210–3.

Smriga M, Ghosh S, Mouneimne Y, Pellett PL, Scrimshaw NS. Proc Natl Acad Sci USA. 2004;101:8285–8.

Sumiyoshi T, Anil AE, Jin D, Jayathilake K, Lee M, Meltzer HY. Int J Neuropsychopharmacol. 2004;7:1–8.

Chapter 38
Food Coloring, Sodium Benzoate Preservative, and D-serine: Implications for Behavior

Kenji Hashimoto

Keywords Sodium benzoate • NMDA receptor • D-Serine • D-Amino acid oxidase

Abbreviations

CBIO	5-chloro-benzo[*d*]isoxazol-3-ol
CSF	Cerebrospinal fluid
DAAO	D-amino acid oxidase
NMDA	*N*-methyl-D-aspartate
SRR	Serine racemase

38.1 Introduction

It has long been suggested that artificial food colorings and other food additives (AFCA) could affect behavior in children. Feingold (1975) made the initial claims regarding the detrimental effects of AFCA on childhood behavior. The main putative effects of AFCA are to produce overactive, impulsive, and inattentive behaviors including hyperactivity. Children who show these behavioral patterns are often diagnosed with attention-deficit hyperactivity disorder (ADHD). Subsequent studies showed only a small effect of AFCA on behavior in children (Weiss et al. 1980; Conners et al. 1976; Swanson and Kinsbourne 1980; Pollock and Warner 1990), but some studies failed to substantiate these latter findings (Mattes and Gittelman 1981; Gross et al. 1987). A meta-analysis of double-blind, placebo-controlled trials showed a significant effect of AFCA on the behavior of children with ADHD (Schab and Trinh 2004). However, there have been no population-based studies examining the prevalence of hyperactivity related to AFCA in children.

Bateman et al. (2004) reported a double-blind, placebo-controlled, artificial food coloring (20 mg daily) and sodium benzoate (45 mg daily) preservative challenge on hyperactivity in a general population sample of preschool children. There were significantly greater increases in hyperactive behaviors during the active period than during the placebo period based on parental reports, although there were no significant differences detected based on objective testing in the clinic (Bateman et al. 2004). This chapter suggests that a benefit would accrue to all children if artificial food coloring and sodium benzoate preservatives were removed from their diet (Bateman et al. 2004).

K. Hashimoto (✉)
Division of Clinical Neuroscience, Chiba University Center for
Forensic Mental Health, 1-8-1 Inohana, Chiba 260-8670, Japan
e-mail: hashimoto@faculty.chiba-u.jp
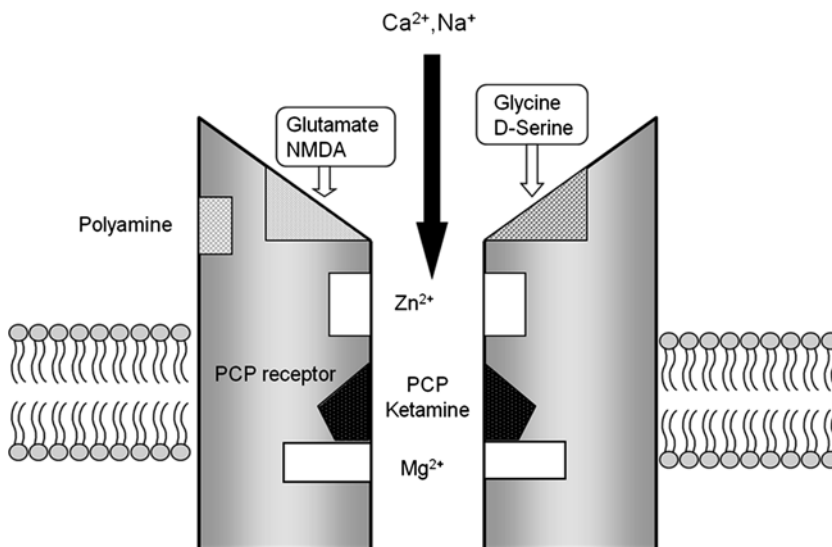
Fig. 38.1 The NMDA receptor complex. Glutamate and *N*-methyl-D-aspartate (NMDA) bind to the agonist site on the NMDA receptors. Phencyclidine (PCP), and ketamine bind to PCP receptor site on the inside of the NMDA receptors. Glycine and D-serine bind to a coagonist site (glycine modulatory site) on the NMDA receptors

A subsequent randomized, double-blind, placebo-controlled, crossover trial by the same group demonstrated that artificial coloring or sodium benzoate preservative (or both) in the diet results in increased hyperactivity in 3- and 8/9-year-old children in the general population (McCann et al. 2007). Children with hyperactivity were identified and tested with a mixture of food coloring and sodium benzoate that corresponded to an average daily intake during 1-week crossover challenge periods. Overall, they showed that 3- and 8/9-year-old children might have signs of hyperactivity when on a diet containing average amounts of coloring and addictives. However, the mechanisms underlying the relationship between the mixtures (artificial foods and/or sodium benzoate) and hyperactive behavior are currently unknown, although artificial coloring and sodium benzoate preservative represent only one aspect of hyperactivity in children (McCann et al. 2007; Eigenmann and Haenggeli 2007; Hashimoto 2008b).

In this chapter, the author would like to discuss the role of D-serine, the endogenous coagonist at the *N*-methyl-D-aspartate (NMDA) receptors (Fig. 38.1), on AFCA-associated hyperactivity in children.

38.2   D-Serine and D-amino Acid Oxidase (DAAO)

It was long believed that only L-isomers of amino acids existed in mammals, and D-amino acids were regarded as laboratory artifacts and categorized as "unnatural isomers." This term was widely used in biochemistry textbooks. D-Amino acids were prominent in bacteria, although there were occasional reports of D-amino acids being present in invertebrates (Corrigan 1969). Yet it should be noted that Dr. Hans Krebs accidentally discovered an enzyme (D-amino acid oxidase; oxygen oxidoreductase, EC 1.4.3.3, DAAO) in the kidney that recognized "unnatural" D-amino acids (but not their L-counterparts; Krebs 1935a, b). It was recognized that the job of DAAO was to degrade D-amino acids produced by bacteria from foods in the gut. Currently, DAAO is a well-characterized flavin adenine dinucleotide
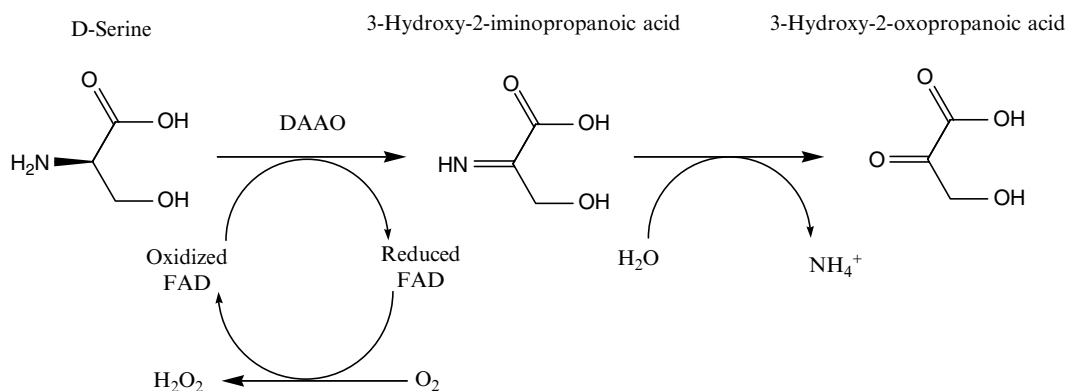
Fig. 38.2 Scheme of the reaction catalyzed by D-amino acid oxidase (DAAO). FAD-dependent enzyme DAAO catalyzes the oxidative deamination of D-amino acids with a strict stereospecificity to give α-keto acids and ammonia; FAD then reoxidizes on dioxygen (A slight modification from Pollegioni et al. 2007)

Fig. 38.3 Structure of human D-amino acid oxidase (DAAO). The human DAAO homodimer (A slight modification from Kawazoe et al. 2007)

(FAD)-dependent enzyme that catalyzes the oxidative deamination of D-α-amino acids to yield the corresponding α-keto acid and ammonia (Pollegioni et al. 2007; Fig. 38.2). The crystal structure of human DAAO was determined by molecular replacement of the porcine enzyme. The asymmetric unit contained four molecules of human DAAO in the form of two homodimers (Fig. 38.3). Basically, each of the four molecules showed the same conformation, and the overall dimeric structure of human DAAO was identical to the "head-to-head" structure of porcine DAAO (Kawazoe et al. 2007).

With the advance of chromatographic analysis techniques, it is now possible to measure small amounts of D-amino acids in lower and higher animals, plants, and foods. By the use of two-dimensional thin-layer chromatography and high-performance liquid chromatography, Nagata et al. (1992) reported the presence of free D-amino acids, including D-serine, in the kidneys and blood of mutant mice lacking DAAO. The contrasting maps of D-serine immunoreactivity and DAAO activity in the adult rat brain show the influence of DAAO on D-serine levels (Schell 2004). DAAO in the brainstem, medulla, and spinal cord keeps D-serine levels low. In addition, forebrain DAAO activity is undetected, and D-serine levels are very high, which strongly implies that DAAO is the major enzyme capable of destroying endogenous D-serine in the brain (Schell 2004). In the brain, gene expression of DAAO is detected in astrocytes (Horiike et al. 1994).

38.3 D-Serine and NMDA Receptor

Research in the past decade has consistently revealed significant levels of D-serine in mammalian brains including human (Hashimoto et al. 2007). In the rat brain, the distribution of D-serine was found to be similar to that of NMDA receptors (Fig. 38.1), suggesting that D-serine might be an endogenous agonist on NMDA receptors (Hashimoto and Oka 1997; Schell 2004). The origin of D-serine in mammals was unclear until serine racemase (SRR), which catalyzes the direct conversion of L-serine to D-serine, was isolated from the brain (Wolosker et al. 1999). Very recently, it was demonstrated that knockout mice for the SRR gene show decreased (>80%) levels of D-serine in the brain (Inoue et al. 2008; Basu et al. 2009), suggesting a major role of SRR in the production of D-serine in the mouse brain. A report using SRR knockout mice demonstrated that SRR exists in neurons, not glia (Miya et al. 2008). Therefore, knockout mice for the SRR gene will contribute to the analysis of the physiological and pathophysiological roles of D-serine in vivo.

Multiple lines of evidence suggest that a dysfunction in glutamatergic neurotransmission via the NMDA receptors (Fig. 38.1) might be involved in the pathophysiology of psychiatric diseases such as schizophrenia and ADHD (Goff and Coyle 2001; Hashimoto 2006, 2008a; Hashimoto et al. 2003, 2004, 2005b; Lehohla et al. 2004; Jensen et al. 2009). Treatment with D-serine revealed significant improvements in positive, negative, and cognitive symptoms in schizophrenia patients treated with antipsychotic drugs (Tsai et al. 1998), suggesting that the levels of D-serine may be decreased in the brains of schizophrenia patients. We reported that the serum levels of L-serine were significantly higher in patients with schizophrenia than in normal controls, and that the serum levels of D-serine and the ratio of D-serine to total serine were markedly lower in patients with schizophrenia than in normal controls (Hashimoto et al. 2003; Yamada et al. 2005). Subsequently, we found that the ratio of D-serine to total serine in the cerebrospinal fluid (CSF) was significantly lower in first episode and drug-naive patients with schizophrenia than in controls (Hashimoto et al. 2005a), suggesting that the synthetic and/or metabolic pathway of D-serine may be impaired in the brains of schizophrenia patients. Furthermore, Bendikov et al. (2007) reported a 25% decrease in D-serine levels in the CSF of patients with schizophrenia, although D-serine levels in the cortices of postmortem brains with schizophrenia were not altered (Hashimoto et al. 2007). Taken together, it is likely that alterations in the D-serine levels may play a role in the behavioral abnormalities in humans.

38.4 Sodium Benzoate and D-serine

Sodium benzoate (Fig. 38.4) is the sodium salt of benzoic acid and is used in a wide variety of cosmetic products (Nair 2001). In food chemistry applications, sodium benzoate is often used as a food preservative because it can inhibit microbial growth (Zhao and Doyle 2006). Sodium benzoate is also known as a competitive inhibitor of DAAO that binds to the enzyme's active site (Kd = 3 mM; Yagi et al. 1959, 1960; Massey and Ganther 1965). Mattevi et al. (1996) reported the crystal structure of the DAAO complex with benzoate by single isomorphous replacement and eightfold averaging. The benzoate molecule lays parallel to the flavin ring and is held in position by a salt bridge with Arg-283 (Mattevi et al. 1996; Fig. 38.4). The novel DAAO inhibitor, 5-chloro-benzo[*d*]isoxazol-3-ol (CBIO; IC_{50} = 180 nM for DAAO activity), has a mode similar to that of benzoic acid (Ferraris et al. 2008). The isoxazole group of CBIO plays a role similar to that of the carboxylate group of benzoic acid, forming a critical hydrogen bond network with Arg-283 and Tyr-228 (Ferraris et al. 2008; Fig. 38.4).

Furthermore, we reported that coadministration of CBIO could potentiate the efficacy of D-serine or D-alanine on prepulse inhibition deficits after administration of the NMDA receptor antagonist

Fig. 38.4 Complex of D-amino acid oxidase (DAAO) inhibitors with DAAO. Schematic illustration of the active site of DAAO in complex with sodium benzoate or 5-chloro-benzo[*d*]isoxazol-3--ol. (A slight modification from Ferraris et al 2008.)
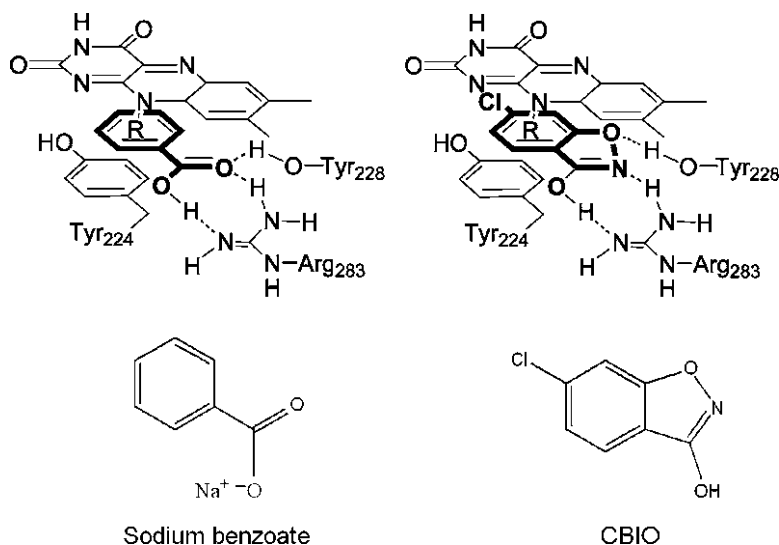
Fig. 38.5 Localizations of endogenous D-serine and D-amino acid oxidase (DAAO) in adult rat brain. (**a**) D-Serine was visualized with an antibody that recognizes glutaraldehyde-fixed D-serine. (**b**) DAAO was visualized in fixed brain slices by enzyme histochemistry (A slight modification from Schell 2004)
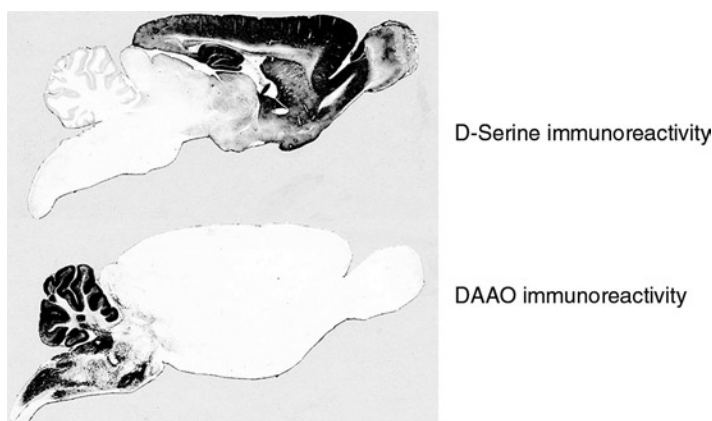
dizocilpine (Hashimoto et al. 2009; Horio et al. 2009). Therefore, these findings suggest that coadministration of D-serine (or D-alanine) and a DAAO inhibitor has therapeutic potential in the treatment of schizophrenia, as D-serine and D-alanine have been shown to be effective in patients with schizophrenia (Hashimoto et al. 2009; Horio et al. 2009).

It was shown that the distribution of D-serine levels is not correlated with DAAO activity in the adult brain (Fig. 38.5), although a high correlation between D-serine levels and NMDA receptors in the brain was detected (Schell 2004). Furthermore, no changes of D-serine in the forebrain of mice lacking DAAO were demonstrated (Morikawa et al. 2001), suggesting that DAAO is not likely to regulate D-serine levels in the forebrain, where the NMDA receptors are abundant (Hashimoto et al. 2005b). Thus, it seems that the DAAO inhibitors do not affect D-serine levels in the forebrain of adult rodents. Recently, we reported that, using in vivo microdialysis study of conscious and free-moving animals, treatment of the novel DAAO inhibitor CBIO did not alter the extracellular D-serine levels in the frontal cortex of adult rats and mice (Ferraris et al. 2008; Hashimoto et al. 2009). Considering the moderate affinity (Kd = 3 mM) of sodium benzoate with DAAO activity and the absence of changes in the forebrain D-serine levels induced by a DAAO inhibitor, it is unlikely that sodium benzoate can increase D-serine levels in the forebrain of adults, although detailed in vivo studies on the effects of sodium benzoate on brain D-serine levels are necessary (Hashimoto 2010).

Fig. 38.6 Possible mechanism of sodium benzoate preservative on hyperactivity in children. Alteration in brain D-serine levels due to the consumption of sodium benzoate preservative may play a role in hyperactivity in children.
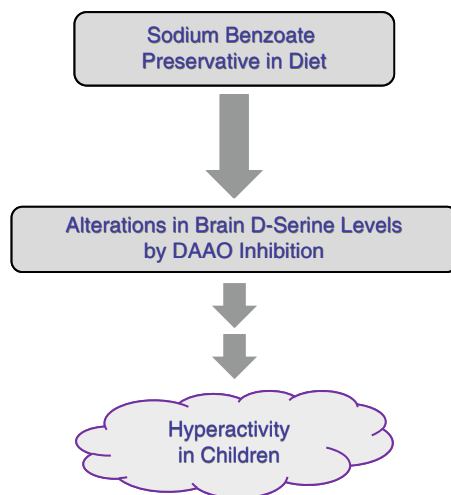
It has been suggested that D-serine may play different roles in the adult brain than in the developing brain, with these roles possible mirrored in distinctive localizations at different ages (Wang and Zhu 2003). A recent study demonstrated that D-serine plays an important role in neuronal migration (Kim et al. 2005), suggesting that D-serine serves as a coagonist for NMDA receptor-dependent cell migration at the developmental stage. Therefore, it is likely that alterations in the D-serine levels in the brains of children due to the consumption of sodium benzoate preservative might contribute to hyperactivity in association with this compound (Fig. 38.6).

In contrast, for many years emerging evidence has suggested the existence of cerebellar abnormalities in the pathophysiology of psychiatric diseases such as schizophrenia (Andreasen and Pierson 2008). Mice lacking DAAO activity show a higher D-serine level in the cerebellum that expresses the NMDA receptors (Morikawa et al. 2001). Therefore, it is possible that the increase in the cerebellar D-serine levels induced by the consumption of sodium benzoate preservative may, at least in part, play a role in the hyperactivity associated with this compound (Hashimoto 2010).

38.5 Conclusion

Considering the important role of D-serine in the neurotransmission via the NMDA receptor, the author proposes that alteration in D-serine levels due to the consumption of sodium benzoate preservative might play a role in hyperactivity in children (Hashimoto 2008b; Fig. 38.6), since D-serine plays a role in the developmental stage. Further investigation using animals is needed to establish whether sodium benzoate could affect hyperactive behavior associated with alteration in the brain levels of D-serine. Additionally, it may also be of interest to examine the effects of sodium benzoate on blood levels of D-serine after the consumption of this agent in children.

38.6 Applications to Other Areas of Health and Disease

The consumption of the preservative sodium benzoate may affect D-serine levels in the brains of children, as this compound is a potent inhibitor of DAAO, which can metabolize D-serine. The alteration in D-serine levels induced by sodium benzoate could alter the NMDA receptor function, which may

affect behavioral patterns in childhood. Therefore, the alteration in D-serine levels due to the consumption of the preservative sodium benzoate may be involved in health and disease in children.

Summary Points

- A double-blind, placebo-controlled study demonstrated that food coloring and/or the preservative sodium benzoate in the diet affects hyperactivity in children.
- Sodium benzoate is a potent inhibitor of DAAO, which can metabolize D-serine.
- Alterations in D-serine levels due to the consumption of sodium benzoate may alter the NMDA receptor function in the brain. Therefore, alterations in the D-serine levels may be involved in hyperactivity in children.

Definitions and Explanations

Sodium benzoate: Sodium benzoate is the sodium salt of benzoic acid and is used in a wide variety of cosmetic products and as a food preservative. Sodium benzoate is also known as a competitive inhibitor of DAAO, which can metabolize D-serine, the endogenous coagonist at the NMDA receptors.

NMDA receptor: The NMDA receptor is a specific type of ionotropic glutamate receptor. NMDA (*N*-methyl-D-aspartate) is the name of a selective agonist that binds to the NMDA receptors but not to other glutamate receptors. NMDA receptors play a role in learning and memory as well as in the pathophysiology of a number of neuropsychiatric diseases.

D-Serine: D-Serine is the endogenous coagonist at the NMDA receptors. D-serine is synthesized by SRR from L-serine, and D-serine is metabolized by DAAO.

Key Points

The preservative sodium benzoate is a potent inhibitor of DAAO, which can metabolize D-serine, the endogenous coagonist at the NMDA receptors in the brain. This compound can affect the levels of D-serine in the brain, resulting in alteration of the NMDA receptor function, which may affect behavioral patterns in children. Therefore, the alteration in D-serine levels by the consumption of sodium benzoate in children may be involved in the hyperactivity associated with this compound.

References

Andreasen NC, Pierson R. Biol Psychiatry. 2008;64:81–8.

Basu AC, Tsai GE, Ma CL, Ehmsen JT, Mustafa AK, Han L, Jiang ZI, Benneyworth MA, Froimowitz MP, Lange N, Snyder SH, Bergeron R, Coyle JT. Mol Psychiatry. 2009;14:719–27.

Bateman B, Warner JO, Hutchinson E, Dean T, Rowlandson P, Gant C, Grundy J, Fitzgerald C, Stevenson J. Arch Dis Child. 2004;89:506–11.

Bendikov I, Nadri C, Amar S, Panizzutti R, De Miranda J, Wolosker H, Agam G. Schizophrenia Res. 2007;90:41–51.

Conners CK, Goyette CH, Southwick DA, Lees JM, Andrulonis PA. Pediatrics. 1976;58:154–66.

Corrigan JJ. Science. 1969;164:141–9.

Eigenmann PA, Haenggeli CA. Lancet. 2007;370:1524–5.

Feingold BF. Am J Nurs. 1975;75:797–803.

Ferraris D, Duvall B, Ko YS, Thomas AG, Rojas C, Majer P, Hashimoto K, Tsukamoto T. J Med Chem. 2008;51:3357–9.

Goff DC, Coyle JT. Am J Psychiatry. 2001;158:1367–77.

Gross MD, Tofanelli RA, Butzirus SM, Snodgrass EW. J Am Acad Child Adolesc Psychiatry. 1987;26:53–5.

Hashimoto K. Clin Psychopharmacol Neurosci. 2006;4:3–10.

Hashimoto K. Clin Chem. 2008a;54:1413–4.

Hashimoto K. Clin Psychopharmacol Neurosci. 2008b;6:79.

Hashimoto K. J Psychopharmacol. 2010;24:1133–4.

Hashimoto K, Engberg G, Shimizu E, Nordin C, Lindstrom LH, Iyo M. Prog Neuropharmacol Biol Psychiatry. 2005a;29:767–9.

Hashimoto K, Fujita Y, Horio M, Kunitachi S, Iyo M, Ferraris D, Tsukamoto T. Biol Psychiatry 2009;65:1103–6.

Hashimoto K, Fukushima T, Shimizu E, Komatsu N, Watanabe H, Shinoda N, Nakazato M, Kumakiri C, Okada S, Hasegawa H, Imai K, Iyo M. Arch Gen Psychiatry. 2003;60:572–6.

Hashimoto A, Oka T. Prog Neurobiol. 1997;52:325–53.

Hashimoto K, Okamura N, Shimizu E, Iyo M. Curr Med Chem CNS Agents. 2004;4:147–54.

Hashimoto K, Sawa A, Iyo M. Biol Psychiatry. 2007;25:1310–6.

Hashimoto K, Shimizu E, Iyo M. Curr Psychiatry Rev. 2005b;1:151–63.

Horio M, Fujita Y, Ishima T, Iyo M, Ferraris D, Tsukamoto T, Hashimoto K. Open Clin Chem J. 2009;2:16–21.

Horiike K, Tojo H, Arai R, Nozaki M, Maeda T. Brain Res. 1994;652:297–303.

Inoue R, Hashimoto K, Harai T, Mori H. J Neurosci. 2008;28:14486–91.

Jensen V, Rinholm JE, Johansen TJ, Medin T, Storm-Mathisen J, Sagvolden T, Hvalby O, Bergersen LH. Neuroscience. 2009;158:353–64.

Kawazoe T, Park HK, Iwana S, Tsuge H, Fukui K. Chem Rec. 2007;7:305–15.

Kim PM, Aizawa H, Kim PS, Huang AS, Wickramasinghe SR, Kashani AH, Barrow RK, Huganir RL, Ghosh A, Snyder SH. Proc Natl Acad Sci USA 2005;102:2105–10.

Krebs HA. Biochem J. 1935a;29:1620–44.

Krebs HA. Biochem J. 1935b;29:1951–69.

Lehohla M, Kellaway L, Russell VA. Metab Brain Dis. 2004;19:35–42.

Massey V, Ganther H. Biochemistry. 1965;4:1161–73.

Mattes JA, Gittelman R. Arch Gen Psychiatry. 1981;38:714–8.

Mattevi A, Vanoni MA, Todone F, Rizzi M, Teplyakov A, Coda A, Bolognesi M, Curti B. Proc Natl Acad Sci USA. 1996;93:7496–501.

McCann D, Barrett A, Cooper A, Crumpler D, Dalen L, Grimshaw K, Kitchin E, Lok K, Porteous L, Prince E, Sonuga-Barke E, Warner JO, Stevenson J. Lancet. 2007;370:1560–7.

Miya K, Inoue R, Takata Y, Abe M, Natsume R, Sakimura K, Hongou K, Miyawaki T, Mori H. J Comp Neurol. 2008;510:641–54.

Morikawa A, Hamase K, Inoue T, Konno R, Niwa A, Zaitsu K. J Chromatogr B Biomed Sci Appl. 2001;757:119–25.

Nagata Y, Yamamoto K, Shimojo T, Konno R, Yasumura Y, Akino T. Biochim Biophys Acta. 1992;1115:208–11.

Nair B. Int J Toxicol. 2001;20(Suppl. 3):23–50.

Pollegioni L, Piubelli L, Sacchi S, Pilone MS, Molla G. Cell Mol Life Sci. 2007;64:1373–94.

Pollock I, Warner JO. Arch Dis Child. 1990;65:74–7.

Schab DW, Trinh NH. J Dev Behav Pediatr. 2004;25:423–34.

Schell MJ. Philos Trans R Soc Lond B. 2004;359:943–64.

Swanson JM, Kinsbourne M. Science. 1980;207:1485–7.

Tsai G, Yang P, Chung LC, Lange N, Coyle JT. Biol Psychiatry. 1998;44:1081–9.

Wang LZ, Zhu XZ. Acta Pharmacol Sin. 2003;24:965–74.

Weiss B, Williams JH, Margen S, Abrams B, Caan B, Citron LJ, Cox C, McKibben J, Ogar D, Schultz S. Science. 1980;207:1487–9.

Wolosker H, Blackshaw S, Snyder SH. Proc Natl Acad Sci USA. 1999;96:13409–14.

Yagi K, Ozawa T, Harada T. Nature. 1959;184(Suppl. 25):1938–9.

Yagi K, Ozawa T, Harada T. Nature. 1960;188:745–6.

Yamada K, Ohnishi T, Hashimoto K, Ohba H, Iwayama-Shigeno Y, Takao H, Toyota T, Minabe Y, Nakamura K, Shimizu E, Itokawa M, Mori N, Iyo M, Yoshikawa T. Biol Psychiatry. 2005;57:1493–503.

Zhao T, Doyle MP. J Food Prot. 2006;69:762–7.

Chapter 39
Malonyl-CoA Signaling in the CNS: Hypothalamic Control of Feeding Behavior and Energy Expenditure

M. Daniel Lane and Seung Hun Cha

Abbreviations

CNS	Central nervous system
SNS	Sympathetic nervous system
ACC	Acetyl-CoA carboxylase
MCD	Malonyl-CoA decarboxylase
FAS	Fatty acid synthase
icv	Intracerebroventricular
ip	Intraperitoneal
AICAR	5-aminoimidazole-4-carboxamide-1-β-D-ribofuranoside
NPY	Neuropeptide Y
AgRP	Agouti-related peptide
POMC	Propiomelanocortin
CART	Cocaine and amphetamine-regulated transcript

39.1 Introduction

The concept that an intermediate in fatty acid synthesis might function in the regulation of food intake and energy expenditure arose through the serendipitous discovery that fatty acid synthase (FAS) inhibitors, i.e., fungal-derived cerulenin or the structurally related synthetic derivative, C75, produce a dramatic reduction of food intake and massive weight loss (Loftus et al. 2000; Shimokawa et al. 2002; Kumar et al. 2002; Cha et al. 2004). These inhibitors have also been found to reverse adiposity caused by diet-induced obesity or mutations in leptin (*ob*/*ob*) or its receptor (*db*/*db*). Thus, these actions of the FAS inhibitors are independent of leptin, thus implicating a different signaling pathway. As intracerebroventricular (icv) administration of FAS inhibitors at very low levels (too low for systemic effects) was equally effective as intraperitoneal (ip) injection (Hu et al. 2003), it was concluded that the inhibitors acted centrally.

Strong precedents exist for a linkage between fatty acid synthesis and the inhibition of food intake (Lane 2008). Fatty acid synthesis occurs in lipogenic tissues during periods of energy surplus when

M.D. Lane (✉)

Department of Biological Chemistry, School of Medicine, The Johns Hopkins University, Baltimore, Maryland 21205

e-mail: dlane@jhmi.edu

Table 39.1 Key features of malonyl-CoA as an intermediate in the hypothalamic signaling pathway that monitors/regulates feeding behavior and energy expenditure

1. Malonyl-CoA levels in the hypothalamus fluctuate as the global energy status of the animal changes. Food restriction gives rise to a low malonyl-CoA level, while refeeding leads to a high level of malonyl-CoA in the feeding centers within the hypothalamus. Malonyl-CoA is an intermediate in a complex signaling pathway in these centers, which communicates through neuronal connections to higher brain centers that integrate this information to formulate a feeding response.
2. Circulating glucose entering/metabolized by the brain/hypothalamus serves as an indicator of global (whole body) energy status. Orexigenic and anorexigenic neuropeptide-producing neurons within the hypothalamus respond to changes in glucose level through the 5′-AMP kinase/malonyl-CoA signaling system by secreting the appropriate amounts of these reciprocally related neuropeptides that control the feeding behavior.
3. In addition to suppressing food intake, increasing hypothalamic malonyl-CoA level with FAS inhibitors or leptin provokes increased energy expenditure. This information, i.e., the "malonyl-CoA signal" is rapidly transmitted via the sympathetic nervous system (SNS) to skeletal muscle, which responds by increasing the expression of enzymes and regulatory proteins that control fatty acid oxidation. After several days of such SNS stimulation mitochondrial biogenesis is activated leading to an increase in the number of mitochondria.

excess physiological fuel is diverted into energy storage pathways – conditions known to cause downregulation of the orexigenic (NPY and AgRP) neuropeptides and upregulation of anorexigenic (POMC/αMSH and CART) neuropeptides in the hypothalamus (Shimokawa et al. 2002; Hu et al. 2003; Lane et al. 2005).

The key regulatory enzyme of fatty acid synthesis is acetyl-CoA carboxylase (ACC; Lane et al. 1979; Wakil et al. 1983; Hardie 1989), which catalyzes the synthesis of malonyl-CoA – a substrate for FAS (see Table 39.1). Thus, FAS inhibitors would be expected to cause a "build-up" of its substrate (malonyl-CoA) in the central nervous system (CNS). As discussed next, this response is now well documented (Hu et al. 2003; Wolfgang and Lane 2006). The "malonyl-CoA hypothesis" predicts that a FAS inhibitor-induced blockade of FAS, which increases hypothalamic malonyl-CoA, should be reversed by inhibiting malonyl-CoA formation with an ACC inhibitor, e.g., TOFA. This, in fact, is the case, as TOFA, administered icv before the FAS inhibitor prevents/reverses both the increase in hypothalamic malonyl-CoA and the closely correlated decrease in food intake (Hu et al. 2003). Together, these findings validated the concept that the level of hypothalamic malonyl-CoA is an indicator of energy status that mediates feeding behavior dependent upon the relative activities of ACC and FAS.

39.2 Inhibition of Brain FAS Alters Expression of Hypothalamic Orexigenic and Anorexigenic Neuropeptides and Suppresses Food Intake

The hypothalamus receives and interprets hormonal and other afferent signals that reflect the energy status of the animal (Schwartz et al. 2000; Schwartz and Porte 2005; see Fig. 39.1). Such signals trigger the expression/secretion of the orexigenic and anorexigenic neuropeptides that regulate food intake and energy expenditure, most notably the orexigens, NPY and AgRP; and the anorexigens, POMC/αMSH and CART. These neuropeptides are expressed by NPY/AgRP or POMC/CART neurons in the arcuate nucleus (Arc) of the hypothalamus, which send projections to other regions of the hypothalamus, e.g., the paraventricular nucleus, lateral hypothalamic area, ventral medial nucleus, and dorsal medial hypothalamus (Schwartz et al. 2000). Second-order neurons from these sites project to higher brain centers, where this information is integrated and behavioral responses are formulated.

FAS inhibitors have reciprocal effects on the expression of key orexigenic (NPY, AgRP) and anorexigenic (POMC and CART) hypothalamic neuropeptides of both lean and obese (*ob/ob*) mice

Fig. 39.1 Energy balance (*energy balance = caloric intake − caloric expenditure*) is monitored by the brain, notably the hypothalamus, which sends signals to higher brain centers where these signals are integrated and adjustments in food intake and energy expenditure are made
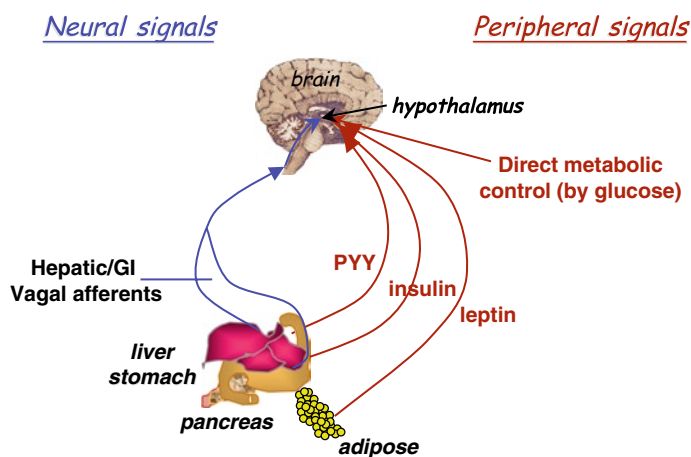
Fig. 39.2 Effects of long-term administration of a FAS inhibitor (i.e., C75) on adiposity of obese (*Ob/Ob*) mice. Similar results were obtained with leptin receptor-deficient *Db/Db* mice and dietary-induced obese mice

(Shimokawa et al. 2002; Kumar et al. 2002; Cha et al. 2004). In lean mice, the FAS inhibitor, C75, rapidly and almost completely blocks food intake and prevents fasting-induced upregulation of hypothalamic AgRP and NPY mRNAs, as well as downregulation of CART and POMC mRNAs. Thus, in lean mice FAS inhibitors interrupt the fasting-induced signals that activate expression of NPY and AgRP and suppression of POMC and CART. Likewise, in obese mice, C75 rapidly suppresses food intake, reduces body weight, and normalizes obesity-associated hyperglycemia and hyperinsulinemia (Fig. 39.2). As in lean mice, C75 prevents the fasting-induced increase of hypothalamic NPY and AgRP mRNAs in obese mice. Thus, the suppressive effect of C75 on food intake in lean mice appears to be mediated both by NPY/AgRP and POMC/CART neurons, whereas in obese mice the effect appears to be mediated primarily by NPY/AgRP neurons.

39.3 Identification of Malonyl-CoA as a Key Intermediate in the Hypothalamic Signaling Pathway That Regulates Feeding Behavior

To validate the "malonyl-CoA hypothesis," it was important to directly quantify hypothalamic malonyl-CoA concentration and test its relationship with feeding behavior. Since the amount of hypothalamic tissue in a mouse is small (10–20 mg) and malonyl-CoA concentration is low, the usual enzymatic methods to quantify this metabolic intermediate could not be used. Thus, a more sensitive enzymatic recycling method was adapted to hypothalamic tissue to specifically quantify malonyl-CoA (Hu et al. 2003). The assay utilizes bacterial (*Pseudomonas putida*) malonate decarboxylase, a multienzyme complex that contains both a malonyl-CoA decarboxylase and CoA transferase, to transfer CoA from the acetyl CoA generated by the decarboxylation of malonyl-CoA, to exogenous malonate. Initially, it is necessary to remove any free acetyl-CoA or propionyl-CoA in tissue extracts with citrate synthase and oxaloacetate.

39.3.1 Effect of Systemically Administered FAS Inhibitors

Comparisons were made of mice fed *ad libitum* with mice given a systemic intraperitoneal (ip) injection of the FAS inhibitor, C75, or vehicle (control). An additional pair- (isocaloric-)fed control group whose food intake was limited to that of the C75-treated mice received ip with vehicle. This control ruled out the effect of food intake on changes in food intake caused by the inhibitor. C75 reduced food intake by 90% compared with that of *ad lib*-fed controls during the 24-h period after injection (Kumar et al. 2002; Hu et al. 2003). The fact that pair-fed controls lost less body weight in 24 h than those receiving the FAS inhibitor indicated that the inhibitor, not only lowered food intake, but also increased energy expenditure (discussed next).

As a result of the "pair-fed restriction" of food intake the level of malonyl-CoA in the hypothalami was markedly reduced (by ~60%) compared with that of *ad lib*-fed controls. Despite the same reduction of food intake, the malonyl-CoA level of C75-treated mice was the same as that of *ad lib*-fed mice. Thus, ip administration of the inhibitor prevented the decrease in malonyl-CoA caused by "fasting."

As expected, blood glucose levels were reduced significantly by food intake restriction in the pair-fed mice when compared with that in mice fed *ad libitum* (Kumar et al. 2002). Nevertheless, blood glucose levels in C75-treated mice were still significantly higher than those of pair-fed partially fasted mice. Because blood glucose levels are affected by ip C75 treatment and fasting, it is possible that the observed differences in hypothalamic malonyl-CoA could have been due, at least in part, to peripheral hormonal effects.

These results are consistent with previous experiments (Kumar et al. 2002) in which the FAS inhibitor blocked the fasting-induced increase in orexigenic (NPY and AgRP) and decrease in anorexigenic (POMC and CART) neuropeptide mRNA expression. These findings were later verified by direct calorimetry, which showed caloric expenditure is significantly higher in FAS inhibitor-treated mice (Thupari et al. 2002).

39.3.2 Effect of Centrally Administered FAS Inhibitors

Short-term experiments were carried out with C75 administered by central icv injection to restrict its effects to the CNS (Hu et al. 2003). The central action of the FAS inhibitor was ensured with

a low dose (~1/100 that administered ip) injected directly into the ventricular system of fasted mice. The mice were then either given free access to food (refed and inhibitor-treated) or fasting was continued. Food intake by refed control mice over the next 2 h was substantial, whereas food intake by mice given inhibitor icv was almost totally (≥98%) suppressed. As expected, blood glucose levels of the fasted mice were reduced and within 2 h of being given access to food (refed controls) the levels increased by over twofold. Food intake was almost completely blocked by C75 treatment and the mice maintained the same low blood glucose level as fasted mice. This is in contrast to the longer-term (24 h) effect of the inhibitor where blood glucose levels were higher and blood fatty acid levels were lower than those of "fasted" pair-fed mice. Thus, in the short (~2 h) period following icv injection, FAS inhibitors do not provoke significant peripheral metabolic effects. The importance of glucose metabolism by the hypothalamic signaling system is discussed next.

The level of malonyl-CoA in the hypothalami of fasted mice is much lower than that of fasted mice that have been refed. Further, this difference occurs rapidly thus, within <2 h after refeeding, hypothalamic malonyl-CoA levels increase >5-fold (Hu et al. 2003). The response to icv administration of the FAS inhibitor, C75, to fasted mice is equally rapid increasing by ~4-fold in <2 h. Importantly, the increase is independent of food intake as it occurs despite the FAS inhibitor-induced blockade of food intake. Hence, the effect on malonyl-CoA level appears to be due to the central action of the inhibitor, as the effect is rapid, occurs following icv administration at a low dose, and is not accompanied by changes indicative of altered insulin and/or glucagon status.

The administration of icv FAS inhibitor or vehicle rapidly alters the expression of hypothalamic NPY, AgRP, and POMC. The levels of the orexigenic neuropeptides (NPY and AgRP) messages in hypothalami of fasted mice were >2-fold higher than those of refed mice, while the levels of the anorexigenic neuropeptide (POMC) message was ~2-fold lower than in refed mice. The changes in expression of these neuropeptides were rapid, occurring in ≤2 h (Hu et al. 2003). Likewise, the changes in neuropeptide levels provoked by icv injection of the FAS inhibitor to fasted mice were rapid and occur without a change in food intake, i.e., in effect the mice remained in a "fasted" state. Thus, icv FAS inhibitor blocks the fasting-induced changes in expression of the orexigenic and anorexigenic neuropeptides. The fact that this response is rapid (<2), i.e., similar to that of hypothalamic malonyl-CoA, supports the view that an increase of malonyl-CoA level is responsible for the changes in expression of the hypothalamic orexigenic and anorexigenic neuropeptides.

39.4 Reversal of the Central Effects of FAS Inhibitors Caused by a Blockade of Malonyl-CoA Formation

In the experiments described earlier, it was shown that icv administration of the ACC inhibitor, TOFA, prevented/reversed the suppression of food intake caused by the FAS inhibitor administered ip. Experiments were conducted to determine whether centrally administered TOFA could rapidly prevent/reverse the effect of icv FAS inhibitor on hypothalamic malonyl-CoA and food intake. As anticipated, the FAS inhibitor rapidly suppressed food intake (Hu et al. 2003). The suppressive effect of icv FAS inhibitor on food intake is immediately (<2 h) prevented by coinjected icv TOFA – the increase over that of mice injected icv with C75 alone being ~10-fold. TOFA also rapidly prevents the effect of icv FAS inhibitor administration on hypothalamic malonyl-CoA to the same extent as TOFA prevents the effect of C75 on food intake. The extent of the TOFA-induced changes are inversely proportional, which is consistent with malonyl-CoA acting as a negative mediator of food intake.

39.5 Genetic "Knockdown" of Hypothalamic FAS Gene Expression Increases Hypothalamic Malonyl-CoA Level and Decreases Food Intake and Adiposity

Semenkovich et al. (Chakravarthy et al. 2007) have crossed floxed FAS mice with RIP-Cre mice – Cre expression being driven by the rat insulin promoter. In addition to driving expression in pancreatic β-cells, this promoter also activates expression in select neuronal nuclei within the hypothalamus. While the floxed mice do not exhibit detectable change in the regulation of insulin expression/secretion by pancreatic β-cells, they exhibit a phenotype (FAS "knockdown") virtually identical to that of inhibition of hypothalamic FAS, i.e., a decrease of food intake, body weight, and adiposity (Chakravarthy et al. 2007). In collaboration with Clay Semenkovich and his colleagues, we found that hypothalamic disruption of the FAS gene caused a steady-state ~2-fold increase of hypothalamic malonyl-CoA. Consistent with the proposed regulatory role for hypothalamic malonyl-CoA in the regulation of body weight, mice with hypothalamic disruption/"knockdown" of the FAS gene exhibit decreased adiposity (Chakravarthy et al. 2007).

Thus, two independent lines of evidence, the central administration of FAS inhibitors and the disruption of the FAS gene in the hypothalamus, led to the same phenotype: elevated malonyl-CoA, lowered expression of the orexigenic, and increased expression of the anorexigenic neuropeptides and, as a consequence, a suppression of food intake.

39.6 Overexpression of Malonyl-CoA Decarboxylase (MCD) in the Ventral Hypothalamus Lowers Malonyl-CoA and Increases Food Intake and Adiposity

As shown earlier, increasing hypothalamic malonyl-CoA by icv injection of FAS inhibitors or by genetic knockdown of hypothalamic FAS suppresses food intake and adiposity. The question was raised whether lowering hypothalamic malonyl-CoA would have the inverse effect. To this end, an Ad-cMCD vector harboring a mouse cDNA encoding a cytosolic MCD (cMCD) was constructed with which to lower malonyl-CoA both in vivo in mice and ex vivo in GT1-7 hypothalamic neurons (Hu et al. 2005). The Ad-cMCD expression vector, along with a control vector (encoding adenoviral β-galactosidase) was introduced by bilateral stereotactic injection into the ventral region of the hypothalamus just below the third ventricle. This region encompasses the arcuate nucleus, which contains neurons that function in the regulation of feeding behavior. Expression of β-galactosidase verified the proper placement of the adenoviral expression vectors.

When delivered into the ventral hypothalamus, the expression of Ad-cMCD increases food intake and body weight (Hu et al. 2005). Moreover, Ad-cMCD expression in the ventral hypothalamus prevented/reversed the suppression of food intake provoked by icv-administered FAS inhibitor that increases hypothalamic malonyl-CoA. These findings were later verified by Rossetti's group, who found that expression of an adeno-associated viral vector expressing MCD into the hypothalamus caused a large increase of food intake and obesity (He et al. 2006).

The central (icv) administration of AICAR (5-aminoimidazole-4-carboxamide ribonucleoside) – a potent 5′-AMP kinase agonist – provokes phosphorylation/inactivation of ACC, lowers hypothalamic malonyl-CoA and increases food intake (Hu et al. 2005). These observations are consistent with the fact that treatment of hypothalamic GT1-7 neurons with AICAR, an activator to 5′AMP-kinase that
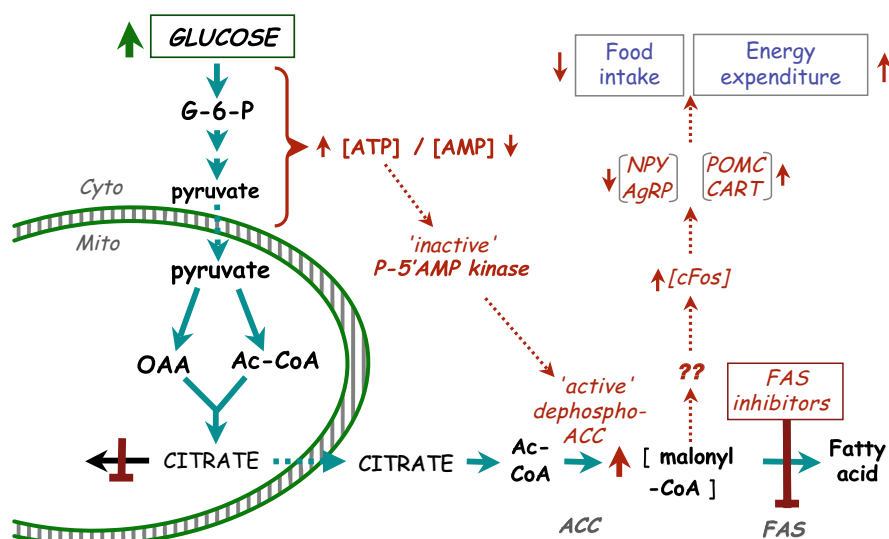
Fig. 39.3 Schematic model illustrating characterized events of the hypothalamic "AMP-kinase/malonyl-CoA signaling pathway" that regulates global energy balance (see text for details)

suppresses ACC, lowers malonyl-CoA (Hu et al. 2005). These effects correlate closely with the phosphorylation of ACC, an established target of AMP kinase (Hardie 1989).

Together these results confirm the role of malonyl-CoA in the hypothalamic regulation of feeding behavior. Further, they suggest that 5′-AMP kinase and ACC are intermediaries on the signaling pathway (see Fig. 39.3).

39.7 The Hypothalamic 5′-AMP Kinase/Malonyl-CoA Signaling Pathway

It was first discovered that either systemic or central administration of FAS inhibitors provokes a rise in hypothalamic malonyl-CoA level that is correlated with the suppression of food intake (Loftus et al. 2000). Further, the icv administration of an ACC inhibitor, which blocks hypothalamic malonyl-CoA formation, was found to prevent the blockade of food intake by FAS inhibitors (Loftus et al. 2000; Hu et al. 2003). Thus, it appeared that one or both of the enzymes, i.e., ACC and FAS, which bracket malonyl-CoA in the pathway of fatty acid synthesis must be involved in transmitting "malonyl-CoA signal" to neuronal centers that control feeding behavior. These and other findings suggested that fluctuations in hypothalamic malonyl-CoA are linked to changes in feeding behavior. A large body of evidence has since been gathered that places malonyl-CoA as an intermediary in the signaling pathway that senses changes in energy status and prompts changes in feeding behavior.

Changes in malonyl-CoA level during feeding and fasting cycles correlate closely with changes in the phosphorylation state/activity of 5′-AMP kinase and the phosphorylation state/catalytic activity of ACC (Winder et al. 1997). Both the liver and muscle isoforms of ACC, i.e., ACC1 and ACC2, respectively, are known to be phosphorylated and inhibited by 5′-AMP kinase (Hardie 1989; Winder et al. 1997; Winder and Hardie 1999). Both ACC isoforms are found in hypothalamic neurons. ACC2 and CPT1b are outer mitochondrial membrane proteins expressed in tissues in which malonyl-CoA regulates the CPT1-mediated translocation of fatty acids into the mitochondria (McGarry et al. 1978;

McGarry and Foster 1979; McGarry 2001). This provides a metabolic rationale for the participation of 5′-AMP kinase in regulating malonyl-CoA in the hypothalamus by phosphorylating ACC.

At the cellular level 5′-AMP kinase serves as a sensor of cellular "energy charge," i.e., the ATP level of the cell (Hardie 1989; Winder et al. 1997; Winder and Hardie 1999). 5′-AMP kinase responds to fluctuations in the cellular levels of ATP through changes in the level of 5′-AMP, an activator of 5′-AMP kinase whose concentration is inversely related to that of ATP. The relationship of the levels of the adenine nucleotides is determined by the reaction catalyzed by adenylate kinase – a ubiquitous enzyme found in most cells (see Reaction 1).

$$\text{ATP} + \text{AMP} \leftrightarrows \text{ADP} + \text{ADP}$$

adenylate kinase

$$(K_{eq} = 1.0) \qquad \text{Reaction 1}$$
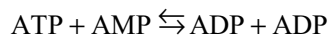
Since total adenine nucleotide concentration is constant and the K_{eq} for the reaction is ~1.0, it is evident that as the ATP level falls, the level of 5′-AMP rises.

A large body of evidence substantiates the key role played by 5′-AMP-kinase and ACC in the hypothalamic malonyl-CoA signaling pathway (see Fig. 39.3): (1) Refeeding or icv glucose administration after overnight food restriction activates 5′-AMP kinase in the hypothalamus or cells in culture – conditions that lead to the phosphorylation/inactivation of ACC (Wolfgang et al. 2007); (2) The level of ATP in the hypothalamus falls immediately (thus, the 5′-AMP level rises) with the onset of glucose metabolism in the CNS and is closely correlated with changes in the activities of other members of the 5′-AMP-kinase signaling pathway (Cha et al. 2008; Wolfgang et al. 2007); (3) Leptin, an anorexigenic hormone, reduces 5′-AMP kinase activity in the Arc and PVN of the hypothalamus, which would be expected to cause activation of ACC (Minokoshi et al. 2004; Kahn et al. 2005; Wolfgang et al. 2007). Subsequently it was found that leptin does, if fact, increase malonyl-CoA concentration in the hypothalamus (23,24); (4) Central administration of 5-aminoimidazole-4-carboxamide ribonucleoside (AICAR), an activator of 5′-AMP kinase, lowers hypothalamic malonyl-CoA and stimulates food intake (Hu et al. 2005). AICAR also activates the phosphorylation/inhibition of ACC and lowers malonyl-CoA concentration in a hypothalamic cell line in culture; (5) Genetic "knockdown" of hypothalamic FAS gene expression increases hypothalamic malonyl-CoA level and decreases food intake and adiposity (Chakravarthy et al. 2007); and (6) Overexpression of malonyl-CoA decarboxylase (MCD) in the ventral hypothalamus lowers malonyl-CoA and increases food intake and adiposity (Hu et al. 2005; He et al. 2006) and finally, (7) The icv administration of a FAS inhibitor rapidly induces c-Fos expression, an indicator of neuronal activation, in the Arc, PVN, and NTS.

These findings led to speculation that during fasting, an indicator of reduced "energy charge," the 5′-AMP/ATP ratio rises in hypothalamic neurons that control feeding behavior. Since ACC is a substrate of 5′-AMP kinase its phosphorylation inactivation produces a decrease in malonyl-CoA (Wolfgang et al. 2007).

To identify a neuronal event/s that occurs concomitant with the expression of the orexigenic and anorexigenic neuropeptides, cFos was selected, since its expression is an established indicator of neuronal activation (Mistry et al. 1994). Intracerebroventricular administration of a FAS inhibitor rapidly activates c-Fos expression in the hypothalamus, notably in the Arc, PVN, and also in the NTS (Gao and Lane 2003). Taken together with the rapid effects on ACC activity, this indicates that malonyl-CoA induces expression of cFos, which serves as the initiating event in the expression of the orexigenic and anorexigenic neuropeptides in the hypothalamic neurons that regulate feeding behavior. Based on these and other findings, the signaling pathway illustrated in Reaction 2 (see also Fig. 39.2) was formulated.

39.8 Glucose Sensing via the AMPK/Malonyl-CoA Signaling Pathway Produces Satiety

Food deprivation gives rise to a decreased blood glucose level – a state in which hypothalamic malonyl-CoA is at a minimum (Hu et al. 2003; Wolfgang et al. 2007). Upon refeeding or the icv administration of glucose, hypothalamic malonyl-CoA increases dramatically. Since glucose is the primary physiological fuel for the brain (Cahill 1970, 1971) and is a precursor of cytoplasmic malonyl-CoA (see Fig. 39.3), which suppresses food intake, the question is raised of whether there is a causal relationship between glucose supplied to the brain and hypothalamic malonyl-CoA. Immediately following glucose infusion into the CNS of fasted mice, malonyl-CoA level increases, orexigenic neuropeptide (NPY and AgRP) expression decreases, and anorexigenic neuropeptide (αMSH and CART) expression increases in the hypothalamus (Fig. 39.3; Wolfgang et al. 2007). Within 30 min after infusion, when the glucose-treated mice are given access to food, food intake is drastically reduced.

Glucose metabolism in the hypothalamus is known to rapidly reduce 5′-AMP kinase activity (Fig. 39.3; Wolfgang et al. 2007). Decreased 5′-AMP kinase activity allows the dephoshorylation/activation of ACC thereby increasing the level of malonyl-CoA – its reaction product. It was established that 5′-AMP kinase and ACC (Wolfgang et al. 2007) both respond to changes in blood glucose and function in transmitting the malonyl-CoA signal. Thus, increased glucose flux to the hypothalamus/CNS causes dephosphorylation and thereby, inactivation of 5′-AMP kinase which leads to activation of ACC and an increase in the level of malonyl-CoA. As discussed, an increase in hypothalamic malonyl-CoA suppresses food intake and increases energy expenditure. The events in this signaling system are outlined in Fig. 39.3 and Reaction 2.

Glucose alters hypothalamic [ATP]/[AMP] ratio and as a consequence, feeding behavior. ATP is the primary energy currency utilized by most cells to drive energy-requiring processes. At the cellular level 5′-AMP kinase serves as a sensor of "energy charge," i.e., the current ATP level of the cell (Hardie 1989; Winder and Hardie 1999; Winder et al. 1997). 5′-AMP kinase responds to fluctuations in the cellular levels of ATP through changes in the level of AMP, an activator of 5′-AMP kinase whose concentration is inversely related to that of ATP. Since total adenine nucleotide concentration is constant and for reasons already discussed, as the ATP level falls, the level of 5′-AMP rises. Thus, as the "energy charge" of a cell decreases due to ATP depletion, 5′-AMP kinase, is activated. From a global perspective, whole body energy status is assessed by the rate of glucose metabolism in the CNS. This in turn is linked to the intraneuronal 5′-AMP kinase system, which senses the "energy charge" of key neurons within the arcuate nucleus and neighboring neuronal nuclei in the ventral hypothalamus. As illustrated in Fig. 39.3, glucose entering the hypothalamic neurons is metabolized via the glycolytic pathway causing a rise in ATP level (Cha et al. 2008) and a fall in AMP level, which lowers phospho-5′-AMP kinase, raising 5′-AMP kinase activity, and thereby lowering the phosphorylation state of ACC and raising ACC activity (Wolfgang et al. 2007; Cha et al. 2008).

As discussed, changes in hypothalamic malonyl-CoA during the feeding and fasting cycles result in changes in the phosphorylation state and activity of ACC mediated by 5′-AMP kinase. ACC is found in hypothalamic neurons and is targeted for phosphorylation (thus, inhibition) by 5′-AMP kinase. Several lines of evidence indicate that hypothalamic ACC and thereby malonyl-CoA concentration, are regulated by 5′-AMP: (1) Conditions that lead to the activation of 5′-AMP kinase in neuronal cell culture and in the hypothalamus provoke phosphorylation/inactivation of ACC (Hu et al. 2005). (2) Leptin, an anorexigenic hormone produced by adipocytes, suppresses 5′-AMP kinase activity in the hypothalamus, including the Arc (Minokoshi and Kahn 2003; Kahn et al. 2005; Wolfgang et al.

2007; Gao et al. 2007). This action depresses ACC and thereby increases malonyl-CoA. (3) The central administration of AICAR, a 5′-AMP kinase activator, lowers hypothalamic malonyl-CoA and promotes food intake (Hu et al. 2005). AICAR also activates the phosphorylation/inhibition of ACC and lowers malonyl-CoA concentration in a hypothalamic cell line in culture. These findings indicate that during fasting the [AMP]/[ATP] ratio increases in neurons in critical hypothalamic nuclei, notably the Arc, causing phosphorylation/activation of 5′-AMP kinase, phosphorylation/inactivation of ACC, and a decreased malonyl-CoA level.

Hypothalamic malonyl-CoA has been shown to function globally in energy homeostasis by modulating food intake and energy expenditure. Only recently, however, was the speculated relationship to malonyl-CoA in the CNS demonstrated (Wolfgang and Lane 2008). It was shown that malonyl-CoA level rises in concert with the carbohydrate content of the diet consumed following food deprivation. Malonyl-CoA concentration peaks ≤1 h after refeeding or after peripheral glucose administration – the response being dependent on the dose of glucose administered and is blocked by the central/icv administration of an inhibitor of glucose metabolism, 2-deoxyglucose (2-DG) (Wolfgang et al. 2007; Cha et al. 2008). It should be noted that in blocking glucose metabolism in the CNS, 2-deoxyglucose blocks all glucose-dependent effects, including the 5′-AMP kinase/malonyl-CoA signaling system. The kinetics of change in hypothalamic malonyl-CoA after glucose administration parallels the suppression of phosphorylation of AMP kinase and ACC. Moreover, the blockade of glucose utilization in the CNS by central/icv 2-DG also prevented the effects of glucose on 5′-AMP-activated protein kinase, malonyl-CoA, all downstream events including hypothalamic orexigenic and an orexigenic neuropeptide expression and ultimately, food intake.

The levels of intermediates "5′-AMP kinase/malonyl-CoA signaling pathway" were quantified and found to change rapidly (≤1 h) following central glucose administration in a pattern consistent with that shown in Reaction 2:

$$\text{glucose} \rightarrow \uparrow [\text{ATP}] \rightarrow \downarrow [\text{5′-AMP}] \rightarrow \uparrow \text{5′-AMP kinase activity} \rightarrow \uparrow \text{ACC activity} \rightarrow \uparrow [\text{malonyl-CoA}] \rightarrow \uparrow]\text{cFos} \rightarrow \downarrow [\text{NPY}][\text{AgRP}] \text{ and } \uparrow [\alpha \text{ MSH}][\text{CART}] \rightarrow \downarrow \text{food intake Reaction 2}$$

Finally, it was shown (Wolfgang et al. 2007) that central/icv leptin increases hypothalamic malonyl-CoA and that the increase is additive with glucose administration. As leptin-deficient *ob/ob* mice showed no defect in the glucose- or refeeding-induced rise in hypothalamic malonyl-CoA after food deprivation, it can be concluded that leptin is not required for the "glucose effect." However, active glucose metabolism by the CNS is required for the "leptin effect" (Wolfgang et al. 2007). These studies show that hypothalamic malonyl-CoA responds to the level of circulating glucose and leptin, both of which affect energy homeostasis.

39.9 Fructose Sensing via the AMP-Kinase/Malonyl-CoA Signaling Pathway Produces Satiety

The metabolism of fructose by the CNS has the inverse effect of glucose on the 5′-AMP kinase/malonyl-CoA signaling pathway and feeding behavior (Cha et al. 2008). Although glucose and fructose enter the metabolism via the glycolytic pathway (see Fig. 39.4), the initial steps of hepatic fructose metabolism differ from those of glucose. Likewise, recent evidence (Cha et al. 2008) indicates that fructose metabolism occurs in regions of the CNS, notably the hypothalamus. It is known
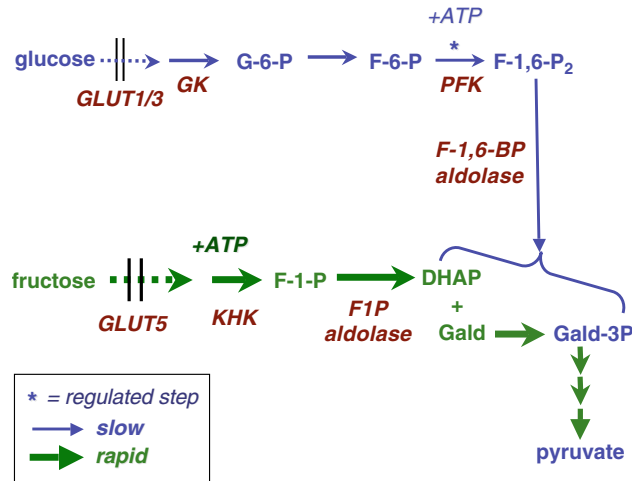
Fig. 39.4 Metabolic differences in the rates of metabolism of glucose and fructose in the hypothalamus. Fructose depletes $ATP \rightarrow \Uparrow [5' AMP] \rightarrow \Uparrow AMPK \rightarrow \Downarrow ACC \rightarrow \Downarrow$ M-CoA $\rightarrow \Uparrow$ food intake

that the initial steps of hepatic fructose metabolism utilize a different set of enzymes that allow this sugar to by-pass the rate-limiting step (catalyzed by phosphofructokinase) in the glycolytic pathway. Similar enzymes of fructose metabolism are found in regions of the CNS that play an important role in monitoring energy balance and satiety control (see (Cha et al. 2008)). These findings are consistent with a recent report (Miller et al. 2002) and a recent report from this laboratory (Cha et al. 2008) that centrally administered fructose provokes feeding. In contrast, the central administration of glucose causes satiety (Wolfgang et al. 2007; Cha et al. 2008). While some uncertainty remains regarding the extent to which fructose in systemic circulation can cross the blood–brain barrier to enter these regions of the brain (Lane and Cha 2009), recent studies show that fructose rapidly enters the hypothalamus (Lane and Cha 2009). It should be noted that these findings raise serious questions regarding the widespread use of "high fructose corn syrup" as a sweetener in numerous foods and soft drinks. This may constitute a heath problem for youth, who are the major consumers of soft drinks.

Investigations in the authors' laboratory (Lane and Cha 2009) show that the levels of intermediates in the hypothalamic pathway change rapidly following central fructose administration in a pattern consistent with Reaction 3:

$$\text{Fructose} \rightarrow\downarrow [\text{ATP}] \rightarrow\uparrow [5'\text{-AMP}] \rightarrow\uparrow 5'\text{-AMP kinase activity} \rightarrow\downarrow \text{ACC}$$
$$\text{activity} \rightarrow\downarrow \text{malonyl-CoA} \rightarrow\uparrow \text{food intake Reaction 3}$$
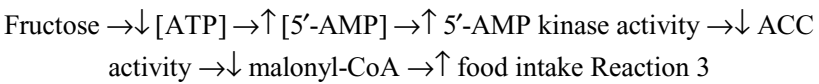
The metabolism of fructose in the hypothalamus is rapid because of its entry into glycolysis downstream of the major control point (the PFK, phosphokinase-catalyzed reaction; see Fig. 39.4). As a result, fructose has the inverse effect of glucose on intermediates in the AMP-kinase/malonyl-CoA signaling pathway and consequently on feeding behavior. The effects of fructose (in blue) *versus* glucose (in red) metabolism on the signaling pathway are illustrated in Fig. 39.5.
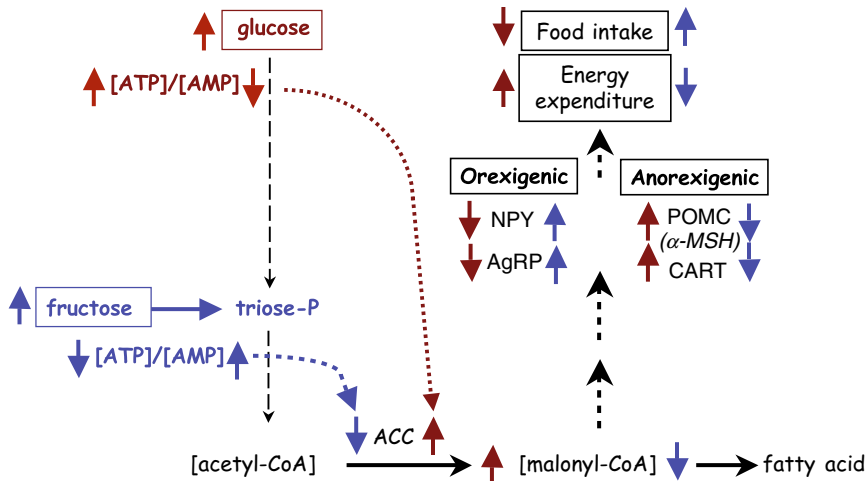
Fig. 39.5 Hypothalamic metabolism of and signaling by (**a**) *glucose* versus (**b**) fructose and its consequences on feeding behavior. *Red arrows* refer to hypothalamic glucose metabolism and *blue arrows* refer to hypothalamic fructose metabolism. ⬆ = increased and ⬇ = decreased level or activity of an intermediate, enzyme, or its activity. Entry of fructose into the glycolytic pathway by-passes the slow regulatory PFK-catalyzed step and thus, is metabolized more rapidly than glucose. As a result fructose depletes ATP -> elevated AMP, which lowers malonyl-CoA, increases the expression of the orexigenic, and decreases the expression of the anorexigenic neuropeptides, which leads to an increase in food intake and a decrease in energy expenditure

39.10 Hypothalamic Malonyl-CoA Activates Energy Expenditure in Skeletal Muscle via the Sympathetic Nervous System (SNS)

In addition to suppressing food intake, increasing hypothalamic malonyl-CoA level with FAS inhibitors (Kumar et al. 2002; Thupari et al. 2002; Cha et al. 2005, 2006) or leptin (Minokoshi et al. 2002) provokes increased energy expenditure. This effect was first noted in paired (i.e., isocaloric) feeding experiments in which pair-fed controls lost significantly less body weight than mice treated with a FAS inhibitor (Kumar et al. 2002). Both lean and obese pair-fed mice lost less body weight than their inhibitor-treated counterparts. These findings strongly indicated that, in addition to suppressing food intake, FAS inhibitors increase energy expenditure. Definitive proof that energy expenditure is increased was later obtained by indirect calorimetry (Thupari et al. 2002).

Consistent with signal transmission from the hypothalamus via SNS, centrally administered FAS inhibitor, C75, rapidly (<2 h) upregulated the expression (in skeletal muscle) of: β-adrenergic signaling molecules including norepinephrine; the β3-adrenergic receptor and cAMP; transcriptional regulators PGC-1α and ERRα; and the expression of key oxidative mitochondrial enzymes including pyruvate dehydrogenase kinase, medium-chain length fatty acyl-CoA dehydrogenase, ubiquinone:cytochrome-C reductase, cytochrome oxidase, as well as ATP synthase and UCP3 (Cha et al. 2006). Closely correlated with the increase of fatty acid oxidation in muscle is the rapid (<2 h) phosphorylation/inactivation of ACC2 and thereby, reduction of malonyl-CoA level in skeletal muscle. Lowering muscle malonyl-CoA, a potent allosteric inhibitor of muscle CPT1b, releases CPT1b from inhibitory constraint to facilitate the entry of fatty acids into mitochondria for β-oxidation (Cha et al. 2006). Closely correlated with these events are rapid increases in the expression of skeletal muscle PPARα, a transcriptional activator of fatty acid-oxidizing enzymes, and UCP3, a putative thermogenic mitochondrial uncoupling protein (Cha et al. 2006). Outlined in Fig. 39.5 is the
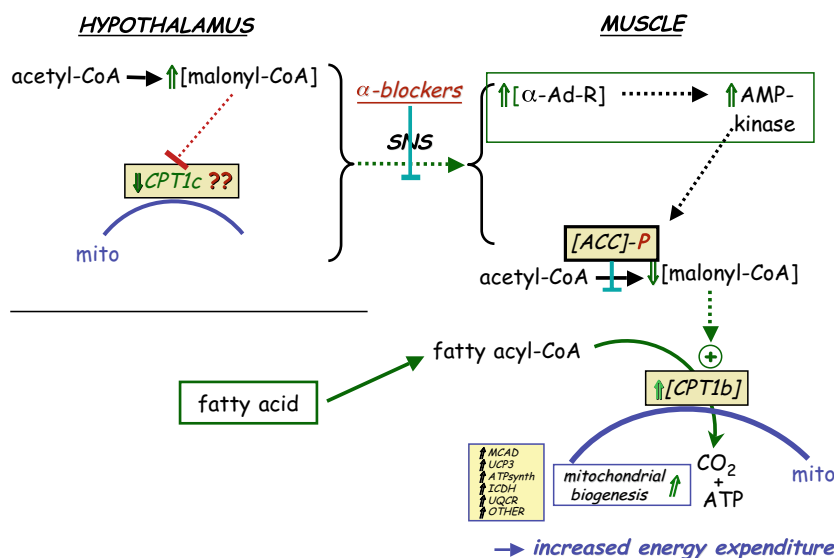
Fig. 39.6 Hypothalamic malonyl-CoA activates energy expenditure in the skeletal muscle via the sympathetic nervous system

sequence of events by which the hypothalamic "malonyl-CoA signal" is communicated to the skeletal muscle that gives rise to increased energy expenditure.

Also consistent with these rapid changes in mitochondrial enzyme levels is a somewhat slower increase in mitochondrial biogenesis. Thus, daily central administration of the FAS inhibitor, C75, over a 3-day period led to an increase in the number of mitochondria in white and red (soleus) skeletal muscles (Cha et al. 2006). Importantly, both α- and β-adrenergic blockers prevent these effects. Thus, both the SNS and the β-adrenergic nervous system are implicated in the rapid communication of the "malonyl-CoA signal" from the brain to the skeletal muscle.

39.11 Application to Other Areas of Health and Disease

Obesity is a pervasive problem in the USA where approximately 70% of the population is overweight and about 30% are classified as obese. It is evident that energy balance has gone awry in these two groups of individuals who consume more calories than they can burn. These excess calories are diverted into energy storage pathways, primarily fat synthesis and stored as fat in adipose tissue.

Obesity is a major risk factor for several prevalent disease states that are on the rise in the USA, namely type 2 diabetes and heart disease. This review deals with the mechanisms by which inputs to the brain including glucose, hormones, and neural signals are monitored in the hypothalamus and participate in the regulation of feeding behavior and energy expenditure.

39.12 Closing Remarks

Malonyl-CoA plays a key role in the regulation of energy balance by the CNS (Table 39.1). Levels of malonyl-CoA are determined by the complex interplay of enzymes (5′-AMP kinase, ACC, MCD, and FAS) that are responsive to nutrient availability. In the hypothalamus, malonyl-CoA alters the

expression of neuropeptides that regulate food intake and energy expenditure. Glucose metabolism by the hypothalamus triggers the AMP-kinase/malonyl-CoA signaling pathway and leads to a decrease in food intake. In contrast, fructose, which enters metabolism downstream of glucose by-passing the key regulatory control point, has the inverse effects on the activities of intermediates in the hypothalamic signaling pathway and increases food intake. Importantly, through these investigations we now have a better understanding of the mechanism by which food intake is monitored and regulated by the hypothalamus.

Summary Points

- Malonyl-CoA, an intermediate in the pathway of fatty acid synthesis, also serves as an intermediate in the hypothalamic signaling system that controls food intake.
- Malonyl-CoA is synthesized by ACC, which is regulated by phosphoryation/dephosphorylation – phosphorylation being carried out by 5′-AMP kinase.
- At the cellular level 5′-AMP kinase serves as a sensor of "energy charge," i.e., the current ATP level of the cell. 5′-AMP kinase responds to fluctuations in the cellular levels of ATP through changes in the level of AMP, an activator of 5′-AMP kinase.
- From a global perspective, whole body energy status is assessed by the rate of glucose metabolism in the CNS. This in turn is linked to the intraneuronal 5′-AMP kinase system, which senses the "energy charge" of key neurons within the arcuate nucleus and neighboring neuronal nuclei in the ventral hypothalamus.
- The metabolism of fructose by the hypothalamus has the inverse effect of glucose on the 5′-AMP kinase/malonyl-CoA signaling pathway and feeding behavior. Thus, glucose increases hypothalamic malonyl-CoA level and suppresses food intake, whereas fructose lowers hypothalamic malonyl-CoA level and stimulates food intake.

Key Definitions/Terms

Malonyl-CoA: An intermediate in the pathway of fatty acid synthesis, also serves as an intermediate in the hypothalamic signaling system that controls food intake

Energy charge: The current ATP level (or "energy level") of the cell.

Hypothalamus: A region of the midbrain located at the base of the 3rd ventricle. The hypothalamus contains groups of neurons that regulate numerous body functions, including food intake and hunger,

5′-AMP kinase: A regulatory enzyme that catalyzes the phosphorylation of key metabolic enzymes of energy metabolism. 5′-AMP kinase serves as a sensor of energy charge

Orexigenic: Refers to the state of hunger or the desire to eat.

Anorexigenic: Refers to the state of satiation or fullness.

References

Cahill GF Jr. N Engl J Med. 1970;282:668–75.
Cahill GF Jr. Diabetes. 1971;20:785–99.
Cha SH, Hu Z, Chohnan S, Lane MD. Proc Natl Acad Sci USA. 2005;102(14):557–62.
Cha SH, Hu Z, Lane MD. Biochem Biophys Res Commun. 2004;317:301–8.
Cha SH, Rodgers JT, Puigserver P, Chohnan S, Lane MD. Proc Natl Acad Sci USA. 2006;103:15410–5.

Cha SH, Wolfgang M, Tokutake Y, Chohnan S, Lane MD. Proc Natl Acad Sci USA. 2008;105:16871–5.

Chakravarthy MV, Zhu Y, Lopez M, Yin L, Wozniak DF, Coleman T, Hu Z, Wolfgang M, Vidal-Puig A, Lane MD Semenkovich CF. J Clin Invest. 2007;117:2539–52.

Gao S, Kinzig KP, Aja S, Scott KA, Keung W, Kelly S, Strynadka K, Chohnan S, Smith WW, Tamashiro K, Ladenheim EE, Ronnett GV, Tu Y, Birnbaum MJ, Lopaschuk GD, Moran TH. Proc Natl Acad Sci USA. 2007;104: 17358–63.

Gao S, Lane MD. Proc Natl Acad Sci USA. 2003;100:5628–33.

Hardie DG. Prog Lipid Res. 1989;28:117–46.

He W, Lam TK, Obici S, Rosetti L. Nat Neurosci. 2006;9:227–33.

Hu Z, Cha SH, Chohnan S, Lane MD. Proc Natl Acad Sci USA. 2003;100:12624–9.

Hu Z, Dai Y, Prentki M, Chohnan S, Lane MD. J Biol Chem. 2005;280:39681–3.

Kahn BB, Alquier T, Carling D, Hardie DG. Cell Metab. 2005;1:15–25.

Kumar MV, Shimokawa T, Nagy TR, Lane MD. Proc Natl Acad Sci USA. 2002;99:1921–5.

Lane MD. Encyclopedia of life aciences. John Wiley & Sons, Ltd. 2008. www.els.net doi: 10.1002/9780470015902. a0021317.

Lane MD, Cha SH. Biochem Biophys Res Commun. 2009;382:1–5.

Lane MD, HU Z., Cha SH, Dai Wofgang M, Sidhaya A. Biochem Soc Trans 2005;33:1063–7.

Lane MD., Watkins PA, Meredith MJ. Critical Rev Biochem. 1979;7:19–40.

Loftus TM., Jaworsky DE, Freyhywot GL, Townsend CA, Ronnett GV, Lane MD, Kuhajda FP. Science. 2000;288:2379–80.

McGarry JD. Biochem Soc Trans. 2001;29:241–5.

McGarry JD, Foster DW. J Biol Chem. 1979;254:8163–8.

McGarry JD, Leatherman GF, Foster DW. J Biol Chem. 1978;253:4128–36.

Miller CC, Martin RJ, Whitney ML, Edwards GL. Nutr Neurosci. 2002;5:359–62.

Minokoshi Y, Alquier T, Furakawa N, Kim YB, Lee A, Xue B, Mu J, Foufelle F, Ferre P, Birnbaum MJ, Stuck BJ, Kahn BB. Nature. 2004;428:569–74.

Minokoshi Y, Kahn BB. Biochem Soc Trans. 2003;31:196–201.

Minokoshi Y, Kim YB, Peroni OD, Fryer L, Muller C, Carling D, Kahn BB. Nature. 2002;415:339–43.

Mistry AM, Helferich W, Romsos DR. Brain Res. 1994;666:53–60.

Schwartz MW, Porte D Jr. Science. 2005;307:375–9.

Schwartz MW, Woods SC, Porte D Jr, Seeley RJ, Baskin DG. Nature. 2000;404:661–71.

Shimokawa T, Kumar MV, Lane MD. Proc Natl Acad Sci USA. 2002;99:66–71.

Thupari JN, Landree L.E, Ronnett GV, Kuhajda FP. Proc Natl Acad Sci USA. 2002;99: 498–502.

Wakil SJ, Stoops JK, Joshi VC. Annu Rev Biochem. 1983;52:537–79.

Winder WW, Hardie DG. Am J Physiol. 1999;277:E1–10.

Winder WW, Wilson HA, Hardie DG, Rasmussen BB, Hutber CA, Call GB, Clayton RD, Conley LM, Yoon S, Zhou B. J Appl Physiol. 1997;82:219–25.

Wolfgang MJ, Lane MD. J Biol Chem. 2006;281:37265–9.

Wolfgang MJ, Cha SH, Sidhaya A, Chohnan S, Cline G, Shulman GI, Lane MD. Proc Natl Acad Sci USA. 2007;104:19285–90.

Wolfgang MJ, Lane MD. Mol Endocrinol 2008;22:2012–20.

Chapter 40
Emotional and Behavioral Aspects of Chocolate Eating

E.L. Gibson

Abbreviations

fMRI   Functional Magnetic Resonance Imaging
LHPA   Limbic Hypothalamic Pituitary Adrenal Axis
PET   Positron Emission Tomography
TRP   Tryptophan
LNAA   Large Neutral Amino Acids

40.1 Introduction

Chocolate is unique: cocoa butter, the fat in chocolate, has an unrivalled melt-in-the-mouth property, which helps to deliver cocoa's special and complex aromas to the nose in such a delicious way. When sufficiently sweetened to counteract cocoa's inherent bitterness, this palatable sensory combination has a salience that is all too easy to recall later, and may even lift our mood. Chocolate's palatability is so widely appreciated that it has assumed a position of treat, gift, or hedonistic pleasure in many different cultures. The flip side of this hedonistic salience is that chocolate is also easily the most commonly and frequently craved of all foods, and is sought after as a comforting experience in times of emotional distress.

This chapter will address these unique facets of chocolate, by examining the nature of food hedonics, or sensory pleasure, and the relationship with food craving, and our understanding of why chocolate should so often be the target of craving, i.e. the irresistible urge to consume. It will also describe the concept of emotional or "comfort" eating, and evaluate the evidence that chocolate is an archetypal "comfort" food, i.e. is chosen during distress because it is able to relieve negative mood, and even enhance positive mood. This conceptualization also allows for individual variation in susceptibility to emotion-related eating, for which differing explanations will be considered here, from psychosocial to neuroendocrinological. In addition, evidence for other possible benefits from chocolate, and the mechanisms by which these might occur, will be examined. Recent evidence from behavioral neuroscience techniques, especially brain imaging such as functional magnetic resonance

E.L. Gibson (✉)
Clinical and Health Psychology Research Centre, Department of Psychology, Whitelands College,
Roehampton University, Holybourne Avenue, London SW15 4JD, UK
e-mail: l.gibson@roehampton.ac.uk

imaging (fMRI), relating to the experience of eating chocolate will be considered. The implications of such findings for understanding emotional and behavioral aspects of chocolate eating will be discussed.

40.2 Emotions and Eating

Whenever one is considering a fundamental drive on which survival depends, such as appetite and eating, emotion will always be an important factor. Furthermore, motivational states such as appetite are closely related to emotional states, both being considered "affective states" (Rolls 2007). Essentially, motivational states drive us to achieve goals, whereas emotions arise from achieving, or failing to achieve, those goals. This theoretical view is most clearly described by Rolls (2007, p. 11), who defines emotions as "states elicited by rewards and punishers": his disarmingly simple model is illustrated in Fig. 40.1. Thus, Rolls classifies different emotions on two dimensions (with intensity increasing toward the ends of the axes), one associated with delivery of reward (pleasure, elation) or punishment (fear, anxiety), and the other with the *absence* of (expected) reward (anger, frustration) or of punishment (relief). Naturally, food, and especially chocolate, is normally considered pleasurable, or rewarding; however, we will see that for some individuals, chocolate can induce an approach-avoidance conflict, so that emotional responses are not always positive. This hints at another layer of complexity, in that emotions themselves may be motivating, as those of us who sometimes seek "comfort," solace, or escape from aversive, negative emotions, through eating, can understand (see Table 40.1).
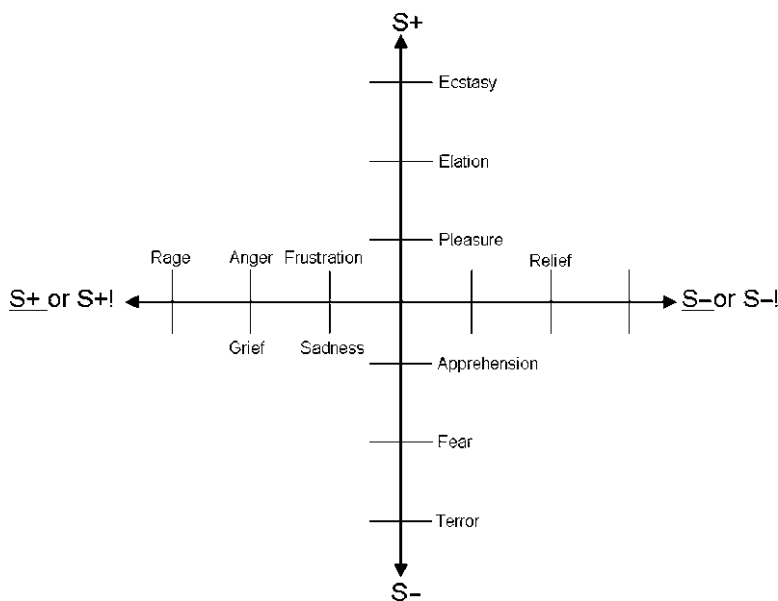
Fig. 40.1 Two-dimensional explanatory model of emotions as states elicited by rewards and punishers. Emotions represented on two dimensions, based on the definition of emotions as states elicited by rewards and punishers (Rolls 2007): intensity increases away from the center of the diagram. The vertical axis describes emotions associated with the delivery of a reward (*up*: S+) or punisher (*down*: S−). The horizontal axis describes emotions associated with the nondelivery of an expected reward (*left*: S+ = omission; S+! = termination) or the nondelivery of an expected punisher (*right*: S− = omission; S-! = termination) (Redrawn from Rolls 2007, Fig. 2.1, p. 14)

Table 40.1 Key features of negative mood

Key points	Explanation
Mood, emotions, and affect	These terms are often used interchangeably; however, emotions are usually considered to be caused by some event, such as obtaining a reward, or failing to do so, whereas moods may occur apparently spontaneously, and be longer lasting. Both could be considered forms of "affect."
Negative versus positive	Moods and emotions are usually classified as either positive (e.g. happy, relaxed) or negative (sad, anxious). Either mood could influence chocolate eating, for example by distracting the eater from conscious resistance.
Acute versus chronic negative mood	Negative mood, like positive mood, can be brief – an acute response to a short-lasting event. However, if the event is serious enough, and longer lasting, negative mood may become chronic, and even result in depression (a disabling level of negative mood). Individuals vary in their susceptibility to this.
Manipulation of mood	Mood can be altered experimentally, by exposing participants to music, films, short stories, or stressful tasks like public speaking. These effects are short-lasting, but can alter eating immediately afterwards, especially in people who eat for emotional reasons.
Chocolate and negative mood	Although eating chocolate is usually thought to be pleasurable, and so should enhance mood, people with ambivalent attitudes to chocolate may feel negative moods such as guilt for several hours later. Moreover, when negative mood occurs, e.g. due to stress, some people choose foods like chocolate as a means to recover from that aversive mood state.

Key features of negative mood are considered, with explanations, in relation to other emotions and to chocolate eating

The interplay between emotions and eating can be bidirectional, and is complicated by the influence of personality differences. In a recent review of the links between eating and emotions, Macht (2008) has proposed a "five-way model": the five components are as follows:

1. Emotions aroused by food stimuli affect food choice.
2. Emotions of high intensity suppress eating due to incompatible emotional responses.
3. Emotions of moderate intensity affect eating differentially depending on motivations to eat:

   (a) In restrained eating (consciously eating less than one would like to), negative and positive emotions enhance food intake due to impairment of cognitive control.
   (b) In emotional (comfort) eating, negative emotions elicit the tendency to be regulated by eating and, as a consequence, enhance intake of sweet and high fat foods (these being powerfully rewarding and so able to alter emotional states).
   (c) In normal eating, emotions affect eating in congruence with their cognitive and motivational features (e.g., food appears more pleasing during positive moods compared to negative moods).

Macht's flow diagram is reproduced here (Fig. 40.2), to help understand the structure and predictions from the model. Some of these concepts will be considered in more detail next, but there are clearly several ways in which eating and emotions can interact. For example, mood or emotions could influence food choice via a change of appetite, or by changing other behavior that constrains or alters food availability. In contrast, alteration of emotion may be an outcome, perhaps even consciously sought, of food choice – an example is "comfort eating," for which chocolate seems to be particularly relevant, as discussed next. Thus, emotions could provide internal stimuli or states that elicit beneficial, e.g. corrective, food choice. Furthermore, eating a particular food, or combination, can alter emotions via sensory (including hedonic) effects, associated social context, cognitive expectations, changes in appetite, or nutritional modulation of brain function (Gibson 2006).
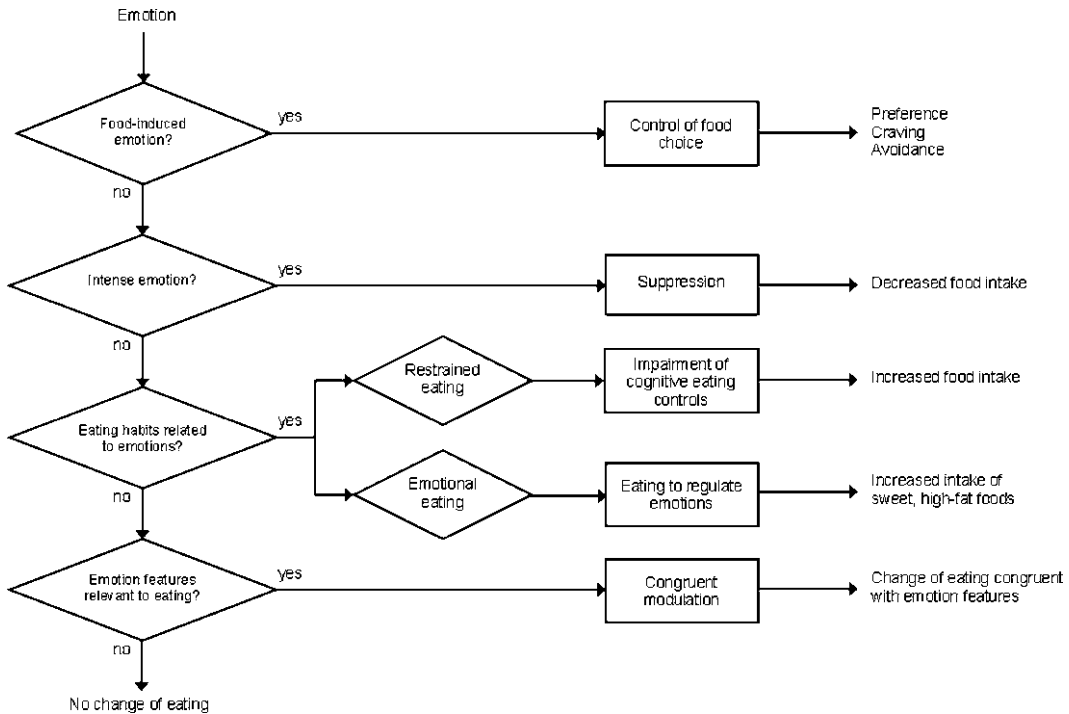
Fig. 40.2 Changes in eating predicted by characteristics of emotions. A flow diagram showing predicted changes in eating from Macht's "five-way model" of interactions between emotions and eating (Macht 2008: redrawn from Fig. 1, p. 5. With permission from the author)

40.3 Chocolate and Pleasure

40.3.1 Innate and Learned Sensory Pleasure

The pleasure that people experience from eating chocolate is an example of the first component of Macht's model; even so, it will be seen next that chocolate's influence on our emotions is not always positive. One of the factors contributing to the palatability of chocolate no doubt includes the way cocoa butter melts in the mouth, at just below body temperature. However, the primary reason is the combination of the creaminess of the cocoa butter and sweetness of sugar – it is well established that human beings love sweet fatty mixtures (Drewnowski and Greenwood 1983), as indeed do many other mammals. There are both innate and learned reasons for this: thus, the newborn infant (of most mammals other than cats) innately likes sweet taste (i.e., prior to any learning, or feeding), as judged by facial and oral responses (but dislikes sour and bitter tastes). Although this is often "explained" as an evolved liking for a sensory predictor of energy, it is at odds with the relatively small and arguably nonessential contribution that sweet foods would have made to our ancestral diets: nevertheless, sweetness is at least one cue to ripeness of nontoxic fruit and roots (Gibson and Brunstrom 2007). Another proposal has been that mammalian sweet liking may promote breastfeeding of nitrogen-rich mother's milk, since sweet" receptors on the tongue respond to chemical groups on both sugars and amino acids (Booth and Thibault 2000). Certainly, human breast milk itself is not a good reason to link sweetness with carbohydrate-derived energy, as it is hardly sweet, and most of the carbohydrate is in

oligosaccharide form (chains of sugar molecules), indigestible to infants: rather, it is thought that this form of carbohydrate in breast milk may have selective prebiotic (i.e., encouraging bacterial growth) and immune defence functions (Kunz et al. 2000).

Over and above any such innate preference, there is abundant evidence that animals including human beings learn rapidly to prefer foods that prove to be a good source of energy (Gibson and Brunstrom 2007). This is underpinned by recent ideas in behavioral neuroscience that show the brain to be a selfish and energy-hungry organ, quite prepared (and equipped) to divert glucose away from the periphery, and seek out energy-rich sources, to feed its constant need, especially during energy-demanding times (Peters et al. 2007). This "selfish brain" evolved to meet energy and nutrient requirements sufficient to ensure genetic continuity, rather than to live a long and healthy life (Palaeolithic hunter-gatherers could be both producing children and be grandparents when reaching the end of their lifespan typically in their early thirties): thus, it could be said that, from middle age onwards, our modern lives involve a struggle to teach our brains to be less selfish, and to care more about the health of our bodies.

Young children have no such concerns, and are particularly sensitive to energy variation in foods, and reliably show just this sort of learned preference for energy-rich foods (Kern et al. 1993): indeed, even among fruits and vegetables, energy density is probably the strongest determinant of their likes and dislikes (Gibson and Wardle 2003). Yet, one of the most energy-dense (and liked) fruits, the banana, is one-fifth as energy-dense as chocolate, so most children offered a free choice between fruit, vegetables, or chocolate have little difficulty making up their minds, to the disappointment of their elders. Thus, the sensory qualities of energy-rich foods like chocolate become predictors of energy delivery, and through experience become targets for our appetites whenever energy is needed: we not only learn to *like* them, but to *want* them when they will be most rewarding, i.e. when hungry. Nevertheless, it should be noted that the taste, or even sight and smell, of such foods, including chocolate, may be so rewarding as to "prime" our desire (wanting, craving) for the food even when not hungry (Lambert et al. 1991).

What is meant by the "reward" value of foods like chocolate? Given Rolls' definition of emotions as "states elicited by rewards and punishers" (before), any discussion of the interaction between chocolate and emotions should consider the rewarding aspects of chocolate. A reward is, in psychological terms, essentially a positive reinforcer: strictly speaking, such a reinforcer is an event which results in preceding, or contingent, behavior being increased, or repeated. However, to most people the term reward also carries connotations of pleasure, and indeed pleasure is one of the key *emotions* which are elicited by rewards. Here is the overlap between emotions and motivation mentioned earlier: feelings of pleasure reinforce our memory of the events that lead up to the pleasure, and motivate us to seek out those rewarding events or stimuli again. The psychological jargon for this acquired motivation, desire or "wanting" is "incentive salience" (Berridge 2009).

In common English, we talk of "liking" a particular food, and largely assume that somehow that also represents quite accurately the tendency to eat that particular food. At a crude level it does: for instance, a list of liked foods will on average be eaten more often by that person than a list of disliked foods (assuming they have the choice; Drewnowski and Hann 1999). Even then, food preferences cannot easily be categorized in simple sensory terms, but rather tend to group into more complex categories of food, such as dairy/dessert, meat, fruit, or vegetables (Wardle et al. 2001). A bit more reflection makes it clear that we often eat foods to which we are at best indifferent, whereas there may be foods that top our list of liking which regrettably we only rarely get to enjoy – life can be complicated. Chocolate may well be such a food for many people. Moreover, liking is really such an overarching way of categorizing our tendency to obtain pleasure from certain foods that we often find the term confusing in everyday use: "Oh, don't you like your dinner, dear?"; "Yes, thank you, it is delicious, but I just can't eat any more." Food liking, then, can be quite independent of any motivation to eat.

This illustrates why we also need a concept of "wanting" that is not synonymous with "liking," even if often they do occur together – indeed, according to Berridge (2009), maximum reward arises

from their co-occurrence. This is reminiscent of the French expression "l'appétit vient en mangeant," i.e. appetite comes with eating; this phenomenon, the "appetizer effect" of eating a liked food when hungry (wanting to eat) has been recorded in controlled conditions (Yeomans 1996) – the desire to eat rises above the level reported immediately before eating. This is echoed by evidence from repeated scans of brain activity using positron emission tomography (PET) while participants ate chocolate beyond satiety: differential activation of brain systems was found, with those areas thought to underlie reward or motivation activated during initial eating, whereas when chocolate eventually was no longer pleasant to eat, let alone wanted, aversive brain systems were active (Small et al. 2001).

"Wanting" reflects the momentary, or current, desire to obtain a goal, i.e. for this chapter, to eat chocolate. It might be thought of as a behavioral subset of "liking" if one assumes that one should not ever want something that one does not like. However, findings in drug addiction research suggest a more complex picture: chronic drug abusers appear often to *want* a drug (or at least objectively they seek and consume it) even when they report gaining little if any pleasure from taking it (Gibson and Desmond 1999). This may reflect the evidence that "wanting" (as mediated by incentive salience) need not be the sort of conscious desire we usually imagine, but instead can be elicited by brain mechanisms responding unconsciously to food (or food-related) stimuli. A major brain pathway for such unconscious wanting is the dopamine neurotransmitter circuitry of the subcortical mesolimbic system of the mid-brain, whereas conscious desire involves higher brain centers known to be critical in assessing reward value relative to need state, such as the orbitofrontal and insular cortices (Berridge 2009). Moreover, studies involving blocking of brain dopamine function show clearly that the ability to respond to palatable tastes with signs of sensory pleasure (liking) is not impaired by such procedures. By comparison, brain circuitry underlying "liking" for foods, or at least enhancement of sensory pleasure from them, involves endogenous opioid (morphine-like) and cannabinoid (cannabis-like) transmitter systems. Although these systems are also linked to food wanting in wider areas of the brain, the ability to stimulate liking seems particularly associated with small "hotspots" in a region of the brain known as the nucleus accumbens shell, and another called the posterior ventral pallidum (Berridge 2009). Both these areas have a history of association with rewarding actions of food and drugs – the latter activating the same systems but to a greater degree. This brings us to the topic of "craving" – a term that seems to be linked to chocolate almost as often as "milk." In the next section, the relevance of these concepts, and of the consequences of one's eating habits, to chocolate craving is discussed.

40.3.2 Chocolate and Craving

40.3.2.1 Craving as Energy Hunger

Craving is a term used to describe a strong urge to consume a substance, such that this impulse is hard to resist and also distracting (Smit and Rogers 2001). In adults, there is experimental support for the importance of the energy supplied by chocolate when hungry in reinforcing the development and maintenance of such a strong appetite, or craving, for chocolate. Thus, participants who were asked to eat chocolate for 2 weeks only when they were hungry, between meals, showed increased craving for chocolate (whether or not they were initially chocolate "cravers"); in contrast, those eating chocolate exclusively when full, just after meals, showed substantial reductions in their chocolate craving (Fig. 40.3; Gibson and Desmond 1999). Those fullness-trained participants also showed a significant reduction in the palatability of chocolate (pleasantness of taste), whereas there was no change in pleasantness of the taste in those eating chocolate hungry (both groups ate about the same amount). This is another example of the ways in which changes in liking (rated pleasantness) and wanting (craving) can be dissociated.

Fig. 40.3 Impact of concurrent appetitive state on chocolate craving. Change in craving for chocolate after eating chocolate exclusively when hungry or full (training state) and effect of test state (hungry, *open symbols*; full, *closed symbols*) before (pre) and after (post) a 2-week training period. Letters indicate significant differences of "post" means from "pre" means (Redrawn from Gibson and Desmond 1999. with permission)
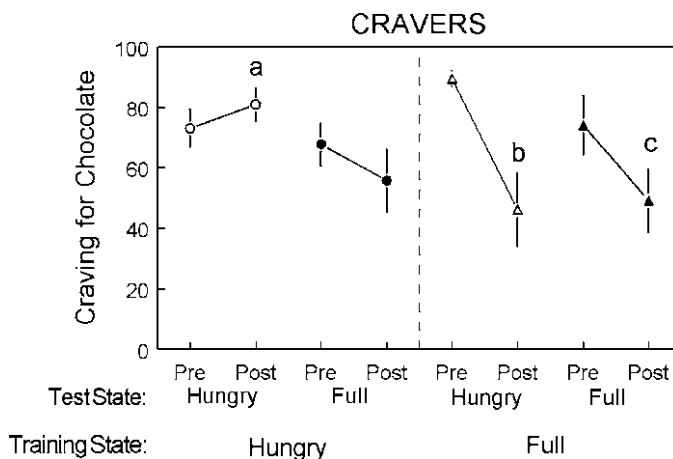
A link between hunger, energy from foods, and the tendency to crave them has recently been established by questionnaire survey (Gilhooly et al. 2007): in particular, participants reporting a susceptibility to overeat when hungry also reported more frequently craving energy-rich foods. This is not to say that we should expect cravings to continue to rise inexorably with hunger, for example during periods of fasting or food restriction: rather, if eating of craved foods is prevented, then the learned reinforcement of the craving will be extinguished, which explains why food cravings decline substantially in patients on very low calorie diets of limited foods (Martin et al. 2006).

A limitation of this "energy repletion" interpretation of chocolate craving is that it does not explain why chocolate so consistently tops the charts of most craved foods (Rozin et al. 1991) – unless one argues that the uniqueness and salience of chocolate's sensory properties provide the added ingredient of irresistibility. Otherwise, other energy-dense foods should be competing more equally for the top craved slot; nevertheless, most popularly craved foods are typically energy-rich and/or able to deliver rapid energy absorption (Gilhooly et al. 2007). In fact, although the experience of chocolate's sensory qualities in their entirety is of course what is craved most, the reliable cues to energy are the sweetness and creaminess, which are also found in white chocolate. Therefore, one might expect white chocolate to satisfy chocolate craving to some extent. This is indeed what has been found (Michener and Rozin 1994): habitual cravers of chocolate were asked to eat whatever the investigators had supplied them at the point at which they were craving chocolate. They then had to rate to what extent that food alleviated the craving. Participants reported that their craving was at least partly satisfied even 90 min later by white chocolate, which has similar sensory properties to milk chocolate but without the flavor of cocoa. This is consistent with an important role in chocolate craving for the experience of consuming the energy in it, though it may also reflect generalization of a learned response from some of chocolate's key sensory properties involved in satisfying craving.

40.3.2.2 Chocolate Craving as Drug Addiction

Interestingly, in that same study, eating capsules of untasted cocoa ingredients alone had no impact on craving, and no additional impact when combined with white chocolate (Fig. 40.4). This was interpreted as evidence against any pharmacological or nutrient-specific basis to the craving. Indeed, a decade ago, Gibson and Desmond (1999) reviewed the evidence for a pharmacological basis to chocolate craving: they concluded that there was little evidence for such a basis at that time. For example, it
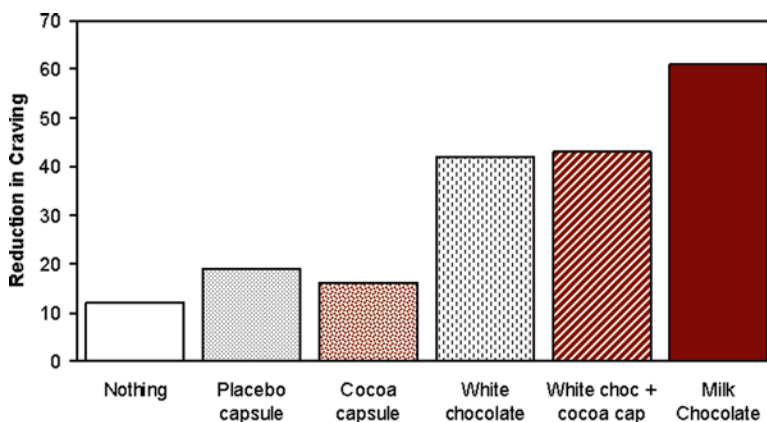
Fig. 40.4 Effects of eating cocoa ingredients, white, or milk chocolate on chocolate craving. Reduction in craving for chocolate after eating various chocolate-related treatments, as labeled. Values shown are the mean differences between craving rated on a 100-mm visual analog scale before and 90 min after treatment. Significantly different treatments are indicated by differing letters (Redrawn from Michener and Rozin 1994, Fig. 1. with permission from the authors)

was doubtful whether potentially psychoactive substances in chocolate such as the biogenic amines, tyramine and phenylethylamine, or the cannabinoid agonist, anandamide, actually entered the brain in sufficient quantities to be active, after degradation by enzymes. Moreover, these substances are widely available in other foods that do not appear to be commonly craved (Smit and Rogers 2001).

Nevertheless, chocolate in some form has a long history of being appreciated for its apparent psychoactive properties, whether by Aztec nobles, Spanish *conquistadores*, or seventeenth-century European dilettantes (Hetherington 2001), despite a dearth of scientific proof. Importantly then, it has been shown that the chocolate-specific combination of the methylxanthines, caffeine and theobromine (chemically, norcaffeine) – two stimulant compounds present in chocolate – produced improvements in both positive mood and performance (when administered at levels found in a 50-g bar of dark chocolate; Fig. 40.5; Smit et al. 2004). As shown in Fig. 40.5, these benefits were also matched by the bar-equivalent dose (11.6 g) of cocoa powder taken in a capsule, suggesting that there is no additional benefit from cocoa above that of the methylxanthines. These chemicals may well contribute to our liking, and potentially our craving for chocolate – and presumably its ancient popularity despite originally being consumed as rather bitter concoctions.

Furthermore, recent evidence suggests that the biogenic amine, beta-phenylethylamine, which exists in trace amounts in the brain and may be present in some chocolate (Smit and Rogers 2001), can in fact increase activity of brain neurotransmitter monoamines such as dopamine, noradrenaline, and serotonin, by inducing their release, and inhibition of their reuptake, by presynaptic nerve terminals, at least in rodent models. This has led to renewed interest in a role for phenylethylamine in liking and craving for chocolate (Riederer and Burger 2009), although it is still questionable whether dietary intake of phenylethylamine would influence brain levels, unless enzyme degradation was impaired.

40.3.2.3 Craving as Psychosocial Attribution

However, even though these chemicals may reinforce liking and consumption of chocolate, there is not yet any direct evidence that they contribute to, or even satisfy, chocolate craving. In fact, explanations for chocolate craving, and other food cravings, have moved away from pharmacological models
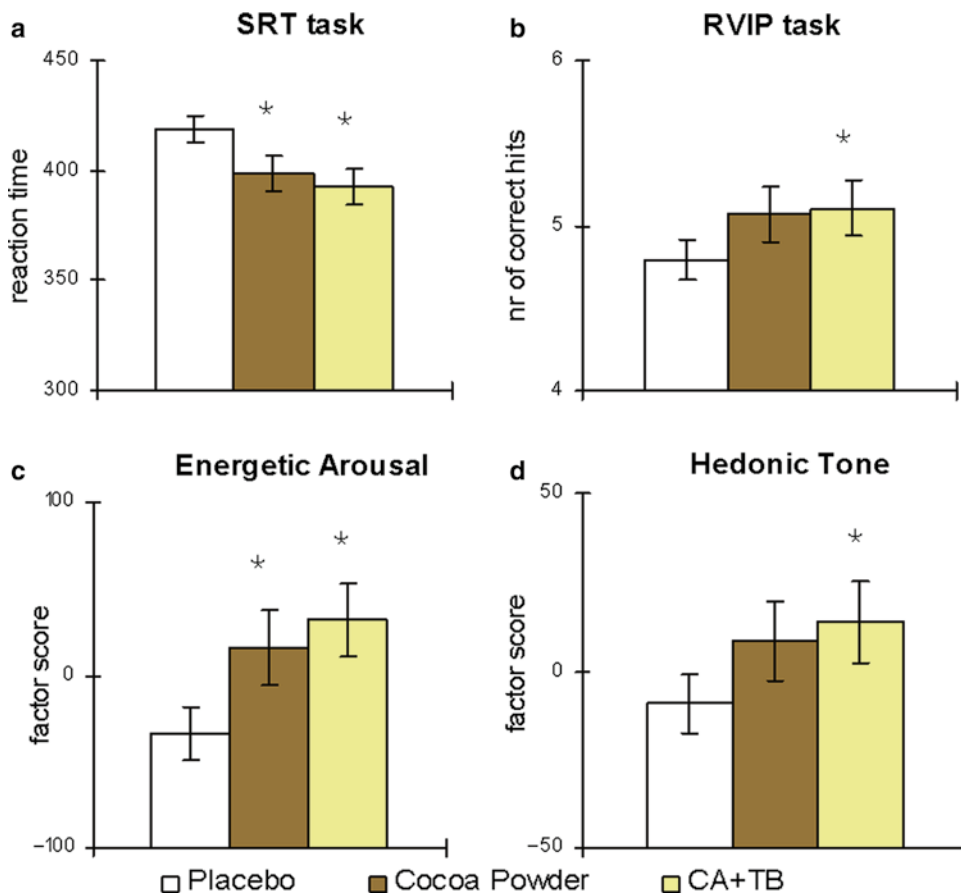
Fig. 40.5 Beneficial effects of caffeine and theobromine, or cocoa powder on mental performance and mood. Effects of prior consumption of capsules of placebo, cocoa powder, or combined caffeine and theobromine (CA+TB) on mental performance and mood: (**a**) Simple reaction time, (**b**) rapid visual information processing, (**c**) energetic arousal and (**d**) hedonic tone. Data shown are post-test treatment means ± 0.5 × LSD. Nonoverlapping error bars between placebo and nonplacebo treatments indicate significant difference after Bonferroni correction for multiple comparisons. *$p < 0.05$ (Reproduced from Smit et al. 2004. With permission of the authors and publisher, Springer-Verlag)

toward more sociocultural or psychosocial theories. A common theme that emerges is to consider craving for chocolate to arise from a sort of "approach-avoidance conflict," or ambivalence, as is so neatly captured by the phrase "naughty but nice" (Smit and Rogers 2001; Cartwright and Stritzke 2008). Thus, craving, or its flip side, addiction, may arise from both having a strong desire to eat chocolate but believing that its consumption should be carefully controlled or restricted (a "forbidden" food), presumably because of concern over its high energy, or sugar and fat, content. The difficulty in satisfying both masters leads to the attribution of the conflict as "addiction," which allows loss of control to be blamed on the food, and any desire for chocolate as "craving." This is supported by evidence that eating chocolate increases feelings of guilt in chocolate "addicts" (Macdiarmid and Hetherington 1995).

This "naughty but nice" attributional model also helps to explain another striking aspect of chocolate craving, i.e. the substantial gender difference, with surveys typically finding that the majority of women admit to craving chocolate at some point, whereas often the proportion of men admitting this

is closer to 20% (Rozin et al. 1991; Zellner et al. 2004). This gender difference in craving is clearer for chocolate than for foods in general. Attitudinal differences between men and women may be key: men often interpret food cravings as initiated by hunger, whereas women are more likely to blame negative mood, stress, or boredom (see next), although the data may reflect resistance to change from a lifelong habit.

40.3.2.4 Chocolate Craving and the Menstrual Cycle

However, a biological mechanism has also been proposed, i.e. perimenstrual chocolate craving driven by appetitive effects of sex hormones (Rozin et al. 1991). Certainly, changes in cravings and appetite seem frequently to be reported in association with the menstrual cycle, and sex hormones may well contribute to this (Buffenstein et al. 1995). Even so, there are problems with this interpretation: first, prospective studies of food craving do not show a clear relationship between chocolate craving and menstrual phase (Hormes and Rozin 2009). Second, there are large cultural differences; for example, Zellner et al. (2004) found that, whereas 40% of American women spontaneously reported craving chocolate perimenstrually, only 4% of Spanish women did so. Furthermore, in a cross-sectional survey comparing premenopausal and postmenopausal American women, Hormes and Rozin (2009) recently reported that overall chocolate craving does not decrease much between premenopausal (craved by 90% of women) and postmenopausal (craved by 77%). In particular, this decrease is not nearly as great as would be expected if it were largely driven by hormones of the menstrual cycle. Rather, Hormes and Rozin (2009) suggest that chocolate craving in women may be driven by an interaction between perimenstrual hormones and stress or emotional state (see next).

This raises the issue of chocolate craving or addiction being seen as obtaining relief from negative mood or emotions – a motivation that chocolate "addicts" often refer to, even though any benefit may be transient (Macdiarmid and Hetherington 1995). In this respect, craving for chocolate is often seen as part of a wider tendency to crave "carbohydrates," as a strategy to relieve negative mood or deal with stress. However, the term "carbohydrate craver" is a misnomer, given that the craved foods, like chocolate, are most consistently high in fat, and often sweet, though sometimes savory. This relationship between chocolate craving and relief from negative emotions and stress, and some possible mechanistic explanations, are considered in the next section.

40.4 Chocolate, Emotions, Stress, and Comfort Eating

40.4.1 Chocolate and the "Sugar Rush" Myth

Ask a member of the public, or for that matter a health professional, as to how chocolate might affect mood, and the chances are they will say that chocolate produces a "sugar rush," causing a brief elevation of mood followed by feelings of low or negative mood, even fatigue, apparently due to a rapid increase in blood sugar followed by its precipitous fall below normal levels. Yet, there is no scientific support for this notion: indeed, quite the opposite, since milk chocolate has been shown to be at worst a food of moderate glycemic index (Foster-Powell et al. 2002; i.e. the rise in blood glucose after eating chocolate is considerably below that following white bread of equal carbohydrate content). Possibly related is the finding that cocoa in dairy foods enhances the resulting rise in insulin

(Brand Miller et al. 2003), which might help to dispose of sugar ingested with chocolate. The cocoa butter and dairy fat probably also help to slow the rise in blood sugar after eating chocolate.

Although chocolate can be sugar-rich (over 60% by weight for some brands), contrary to popular opinion, controlled studies have found that dietary sugar does not have a dramatic, especially adverse, effect on behavior: where effects have been found, they tend to be positive, in the sense of improvements in mental function or short-lived increases in positive mood. Moreover, one of the more reliable findings is that people tend to feel calmer or more sleepy after sugar-rich dietary manipulations (Reid and Hammersley 1999; Benton 2008).

40.4.2   Mood Changes after Chocolate

As discussed before, there are sensory, nutritional, and psychopharmacological reasons why eating chocolate should improve mood. However, the impact of chocolate eating on mood and emotions depends, like other foods, on both the motivational, emotional, and attitudinal states of the eater (Reid and Hammersley 1999). Thus, many people who habitually eat, and crave, chocolate have ambivalent attitudes to it, enjoying the acute sensory pleasure of eating it, but subsequently feeling guilty about the health and weight consequences of doing so (Macdiarmid and Hetherington 1995; Cartwright and Stritzke 2008): this seems to be true even for 11–13-year-old children, at least those with aberrant concerns about eating and weight (Cartwright et al. 2007). Indeed, even *prior* to eating chocolate, chocolate "addicts" reported lower positive and higher negative mood than a control group (Macdiarmid and Hetherington 1995). Not surprisingly, such ambivalence is more common in women, and is associated with disordered eating tendencies: for example, when negative mood was induced in women, eating chocolate chip biscuits improved mood, but only in the women with bulimic eating tendencies (Kisler and Corcoran 1997). In contrast, in normal weight men in whom a positive mood was experimentally engendered, chocolate tasted more pleasant and stimulating, and appetite for it was increased, relative to when negative mood was induced (Macht et al. 2002). This evidence supports Macht's (2008) suggestion of emotion-congruent modulation of eating (item 3(c) of his five-way model; Fig. 40.2), i.e. subjective responses to eating depend on prior emotional state, which contrasts with eating to regulate emotions (see next). It may well be relevant that sex differences are also seen in the activity of brain pathways when chocolate is eaten to satiety during fMRI scanning: differential activation between men and women seems to indicate more involvement of brain emotional circuitry in women than in men (Smeets et al. 2006).

Not all women will succumb to negative feelings, such as guilt, after eating chocolate; in fact, Macht and Dettmer (2006) were able to divide women into those who showed a rise in guilt after eating a 50-g chocolate bar and those who did not, and showed that absence of guilt predicted a greater postchocolate rise in happiness. By comparison, after eating an apple, there was no increase in guilt but also a weaker rise in mood, relative to not eating. That study also shed light on the time course of these effects: guilt peaked 5 min after eating chocolate, whereas although mood was also high by 5 min, this increase was sustained at 30 min after eating. This suggests both immediate sensory and delayed postingestive (e.g., psycho-pharmacological or nutritional) components to the effect on mood. Both guilt and mood had more or less returned to baseline after 1 h, although at the last measurement (90 min), mood was still higher after chocolate than when nothing had been eaten.

It is clear then that eating chocolate can result in improved mood: however, it is also apparent that some people are more able to benefit from this than others. This opens up the possibility that chocolate could be used to regulate emotion, and in particular to alleviate negative mood states in vulnerable people. The evidence for this notion is considered in the next section.

40.4.3 Chocolate, Stress and Comfort Eating

Anecdotally, chocolate is often considered to be the archetypal "comfort food," i.e. a food that is able to relieve stress and negative mood or emotion. It is clear from the previous discussion that chocolate is likely to be a candidate for alleviating negative emotions, at least briefly, and in fact there is mounting evidence that chocolate is indeed particularly sought after in times of stress or discomfort.

Not everyone is a "comfort eater": surveys of people's eating habits under stress suggest that somewhere between a quarter and a half of the surveyed samples report eating more when stressed (Gibson 2006). The remainder report either eating about the same or less. Even so, there is evidence for a pattern of change in food choice under stress that supports chocolate as a key choice for eating when stressed, along with other fatty, energy-dense, and often sweet foods. Oliver and Wardle (1999) asked about perceived changes in intake of a number of specific foods or food categories during stress. This revealed an interesting pattern of effects of stress, which was partly independent of whether participants were grouped as reporting eating more, the same, or less overall when stressed. That is, sweets and chocolate were reported to be eaten more under stress by all groups, even those eating less overall; conversely, intakes of fruit and vegetables, and meat and fish, were reported as less or unchanged under stress in all groups (Fig. 40.6a; data analyzed by Gibson 2006). The changes for the staple food, bread, matched the overall group self-perceptions of changes in eating due to stress. These data imply that mechanisms governing effects of stress on food choice may be somewhat separate from those influencing overall appetite under stress, and that foods such as sweets and chocolate may be particularly useful in ameliorating stress. More recent surveys have leant support to these findings (Wallis and Hetherington 2009). Indeed, E. L. Gibson and K. Harris (unpublished data) have recently replicated the survey findings of Oliver and Wardle (1999) that stress selectively increases consumption of sweets and chocolate, especially in "stress eaters" but even in people who do not report typically eating more under stress (Fig. 40.6b). In that survey, measurement of eating attitudes helped characterize the type of person who may be particularly susceptible to comfort eating: stress eating tendency was strongly predicted by both emotional eating (i.e., stress or comfort eating) and uncontrolled (disinhibited) eating, as well as by the perception of being overweight; in contrast, cognitive restraint (the tendency to try to eat less than one wants to, for fear of gaining weight) did not predict stress eating.

These survey findings are also supported by experimental evidence: in a laboratory study, Oliver et al. (2000) induced stress using a public speaking condition prior to participants choosing lunch from a buffet meal of assorted categories of food. Stress produced a selective increase in the intake of sweet fatty food, chocolate cake, but specifically only in emotional eaters. This is further evidence for a particular relationship between stress, comfort eating, and sweet fatty foods like chocolate. It is intriguing therefore that comfort eating is associated with increased reactivity to stress, as measured by greater release of the stress hormone cortisol (Adam and Epel 2007). Furthermore, a recent fMRI study of brain activity in women found increased responsiveness in reward pathways for emotional versus nonemotional eating women when chocolate milk shake was anticipated or tasted, but only during induced negative mood (Bohon et al. 2009). Given that chocolate cravers also tend to be emotional eaters (Gibson and Desmond 1999), it is notable that another fMRI study of cravers versus noncravers found that chocolate cravers showed increased activation in brain reward pathways in response to the sight and taste of chocolate (Rolls and McCabe 2007). These findings fit well with the earlier evidence of exaggerated appetitive responses to chocolate seen in women who eat chocolate to excess compared with those who eat it in moderation (Hetherington and Macdiarmid 1995).

The link between comfort eating and increased responsiveness of the limbic hypothalamic pituitary adrenal (LHPA) axis, leading to greater release of cortisol from the adrenal cortex, may be key to understanding why sweet fatty foods are sought by comfort eaters. There is substantial evidence

Fig. 40.6 Reported changes in intake of various food categories from two samples of students who tend to eat either less, the same, or more overall when stressed. Reported changes in intake of various food categories during stress (*y*-axis; five-point scale), for three groups (*x*-axis): people who perceive eating less overall; those eating the same; those eating more overall under stress. The nonoverlapping lines illustrate a consistent relative pattern in the change in intake under stress for different foods. Note that intake of sweets and chocolate is raised by stress even in the group who perceived their overall intake to be less under stress. (**a**) Data are from a survey of 212 students (Adapted from Gibson 2006. With permission). (**b**) Unpublished data from a survey of 135 students at Roehampton University, London (Gibson and Harris unpublished data)
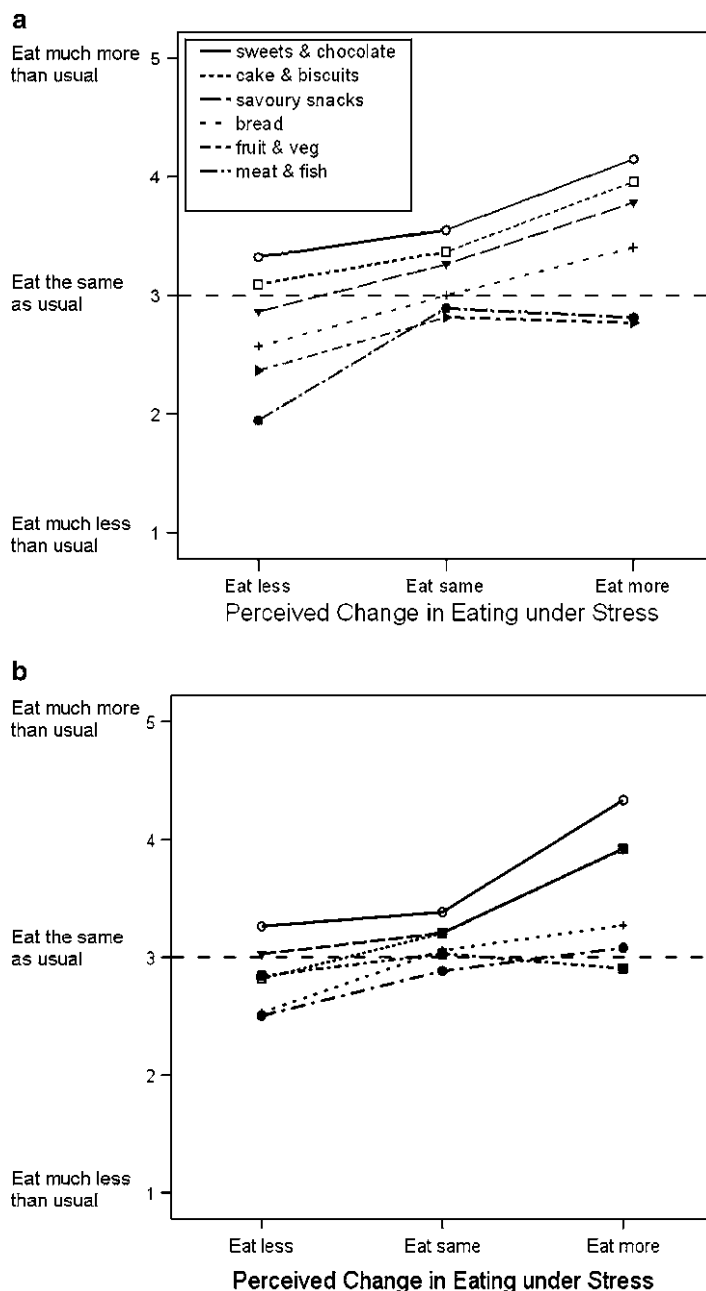
from animal studies that rats prefer such foods when stressed, and also that those foods have a beneficial effect, by restraining the activity of the LHPA axis, i.e. comfort foods (e.g., chocolate cookies) improve rats' abilities to cope with stress (Dallman et al. 2005). The importance of peripheral (e.g. insulin and endocrine action of adipose tissue) versus central routes for this sort of effect is not clear, though it seems likely that both have a role. Indeed, activation of such brain stress pathways can enhance the incentive salience (thus, wanting) of rewarding food cues, suggesting a critical interaction between stress and reward that could underlie comfort eating (Adam and Epel 2007).

40.4.4 Neurochemical Mediation of Chocolate Comfort Eating

40.4.4.1 Serotonin

This link between stress reactivity, reward sensitivity, and comfort eating raises another possibility – that chocolate is chosen as a comfort food because it may help to correct a deficiency in functioning of the neurotransmitter, serotonin, which is heavily involved in emotional states. Synthesis of the neurotransmitter serotonin (or 5-hydroxytryptamine or 5-HT) depends on dietary availability of the precursor essential amino acid, tryptophan (TRP): uptake into the brain of TRP in turn depends on its ratio to the large neutral, primarily branched-chain, amino acids (LNAA), with which it competes for transport from blood to brain. In brief, insulinogenic high carbohydrate meals, with little protein, raise this ratio and can result in increased serotonin synthesis in the brain (Fernstrom and Fernstrom 1995). There is in fact evidence to support this theory: when participants were divided into high or low stress-prone groups, as defined by a questionnaire measure of neuroticism, carbohydrate-rich/protein-poor meals (which raised plasma TRP/LNAA ratios) prior to a stressful task were found to block task-induced depressive feelings and release of cortisol, but only in the high stress-prone group (Markus et al. 1998). It was argued that, because stress increases serotonin activity, the poor stress-coping of this sensitive group might indicate a deficit in serotonin synthesis that is improved by this dietary intervention. If eaten in sufficient amounts on an empty stomach, chocolate might increase TRP availability to the brain via such a process, and so allow improved mood via enhanced serotonin release.

Macht (2008) has argued that this TRP-dependent mechanism would be too slow acting (probably taking 1–2 h after eating). However, it is still possible that a delayed mood enhancement via increased serotonin could reinforce a learned liking for chocolate (or sweet, fatty foods), and a tendency to choose it during negative emotions: then, merely anticipating the serotonin-dependent improvement in mood could be enough to raise the spirits immediately on eating chocolate. Macht and Mueller (2007) showed experimentally that eating chocolate lessened film-induced negative mood – an effect which occurred immediately after eating the chocolate, provided that the chocolate was palatable to the participant. Even though the mood change was only measured for a few minutes, the effect was greater in emotional eaters. However, there was no relationship to habitual chocolate consumption, so the authors concluded that the cause is more likely due to sensory effects than learned anticipatory ones.

40.4.4.2 Opioids

Another important neurochemical route for emotional effects of sweet, fatty, palatable foods such as chocolate is via stimulation of the endogenous opioid system. Endogenous opioid neuropeptides are released during stress, and are known to be important for adaptive effects such as resistance to pain and induction of positive mood, possibly by relief from aversive memories. They are also involved in motivational and hedonic processes in eating behavior, such as stimulation of appetite by palatable foods (Berridge 2009). Moreover, in animals and human infants, the ingestion of sweet and fatty foods, including milk, alleviates crying and other behavioral signs of distress, and this effect can be blocked by opioid antagonists (Blass et al. 1989). Such a mechanism probably explains why eating highly liked chocolate chip biscuits prior to a finger pressure test resulted in increased pain tolerance in female students, whereas an unliked food was ineffective (Mercer and Holder 1997) (Fig. 40.7). Opioids are also able to suppress the activity of the LHPA axis (Adam and Epel 2007), which suggests another route by which eating chocolate might help to alleviate stress.
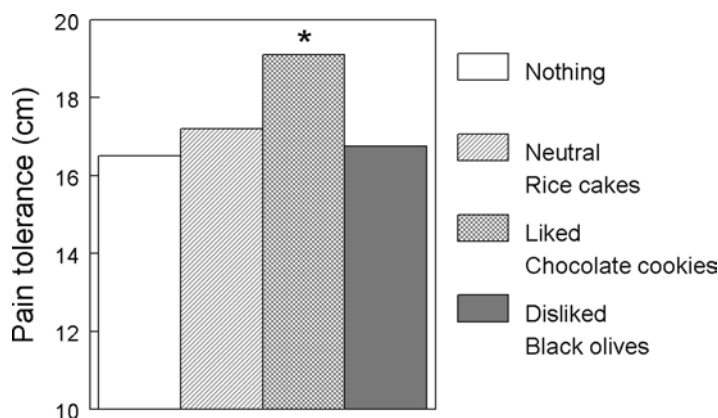
Fig. 40.7 Comparison of the impact of chocolate-flavored or nonchocolate foods on tolerance to pain in female students. Tolerance to pain from pressure on the finger after eating either nothing, rice cakes (a hedonically neutral food), chocolate cookies (highly liked food), or black olives (disliked food). The *y*-axis scale represents distance (cm) that a weight on a lever can be moved to exert pressure on the finger before the participant (US female students) can no longer tolerate the pain. Eating chocolate cookies produced higher tolerance than any other condition (*$p < 0.05$ that conditions were equal) (Redrawn from Mercer and Holder 1997. With permission from the authors)

40.5 Chronic Effects of Chocolate on Emotion and Behavior

40.5.1 Can a Chocolate Habit be Good for You?

There seems to be very little systematic research so far on effects of chronic chocolate consumption on emotions and behavior, aside from comparison of chocolate "addicts" or cravers versus non-cravers, as discussed before. One cross-sectional study of interest recruited pregnant mothers who were either regular or infrequent consumers of chocolate, and compared prenatal stress levels as well as their subsequent ratings of their child's temperament at 6 months of age (Raikkonen et al. 2004). Regular chocolate eaters rated their child's responsivity as more positive, and whereas prenatal stress was associated with increased ratings of fearfulness in the infants of low chocolate eaters, this was not seen for mothers who regularly ate chocolate. Such cross-sectional data need to be interpreted cautiously, but could suggest a stress-reducing and/or mood-enhancing action in mothers that transfers at least to the mothers' perception of their infants temperament.

One might expect other behavioral benefits from chronic chocolate consumption, such as improved mental function, given that cocoa (beverage) improves cerebral blood flow in the brain, as well as lowering blood pressure and benefiting cardiovascular health, presumably via action of its antioxidant polyphenol components, especially the flavanols (reviewed by McShea et al. 2008) – such compounds have been suggested to contribute to health and behavioral benefits from other foods (see Chap. 41, Section 41.5). However, the benefit to brain blood flow was not associated with any benefit to mental performance, at least in young adults. Furthermore, a randomized placebo-controlled study of effects of 6-weeks' consumption of chocolate (bar and beverage) by elderly participants failed to find any improvement in cognition, blood pressure, or blood lipids (Crews et al. 2008). Therefore, despite promising preclinical and epidemiological data on the health benefits of cocoa products, it is at present unclear whether long-term consumption of chocolate has measurable psychological benefits.

40.5.2 The Power of the Dark Side?

Central to the issue of beneficial effects of eating chocolate is the question as to whether it matters if the chocolate is milk chocolate or dark (plain) chocolate. At first the answer seems straightforward – both psychoactive and antioxidant or other pharmacotherapeutic effects of chocolate should be greater the more cocoa is present in the chocolate. Therefore, one would expect greater benefit from dark chocolate containing at least 70% cocoa than from milk chocolate. Even so, it is hard to predict whether a particular chocolate will be rich in antioxidant compounds, for example, because their formation depends on complex variables in the processing of the cocoa bean, which are not under close control (McShea et al. 2008). Nevertheless, there is of course increasing commercial interest in developing chocolate products that can claim to be reliably rich in beneficial compounds (Table 40.2). However, this is not the end of the problem, because animal studies suggest that highly palatable sweet or fatty energy-rich foods can help to alleviate stress. In that case, milk chocolate should be capable of producing beneficial effects such as mood enhancement and stress reduction, at least in some people, despite

Table 40.2 Key facts about chocolate

Key points	Facts
The origins of chocolate	Chocolate is derived from the beans of the tropical tree, *Theobroma cacao*, a native of Central and South America. The ancient Mayan and Aztec peoples of Central America fermented, roasted, and ground the cacao beans, and mixed this with spices into a highly valued drink that the Aztecs called *xocolatl*. This rather bitter tasting drink was prized for its energizing, medicinal, and aphrodisiac properties.
Arrival of chocolate in Europe	The Spanish conquistador Hernan Cortés brought cacao beans back to Spain in 1528, where, as a very rare commodity, monks secretly made a sweetened chocolate drink, adding milk and honey to suit the European taste, for the use of a privileged few cognoscenti. From the early seventeenth century, the chocolate drink gradually spread through the royal courts of Europe, and plantation production was established in Central America and the West Indies. The British doctor, Sir Henry Sloane, invented a medicinal milky chocolate drink in Jamaica in 1687, which eventually formed the origins of Cadbury's drinking chocolate. By the eighteenth century, taking a chocolate drink in Chocolate Houses was a regular way to start the day, and to do business, among fashionable urbanites.
First chocolate bars	Following the invention in 1828, by Dutchman Conrad van Houten, of a press to separate cocoa butter from cocoa liquor, creating cocoa powder, Joseph Fry made the first bars of eating chocolate in 1847. In Switzerland in 1875, Daniel Peter and Henri Nestlé added powdered milk to create a milk chocolate bar. The final key development was that of "conching," discovered by Rodolphe Lindt, a process of heating and grinding the cocoa to produce a much smoother texture. In 1905, Cadbury launched their "Dairy Milk" chocolate bar, which remains a favorite of UK consumers to this day. In 1907 in the United States of America, Milton Hershey launched his individual "KISSES" milk chocolates – chocolate for the masses had arrived.
Chocolate consumption	Large-scale chocolate consumption is mainly confined to developed nations with temperate climates. Perhaps appropriately, Switzerland and the UK compete for top spot, consuming about 10–11 kg/year per capita, which is twice the amount consumed in the USA.
Functional future of chocolate	As evidence mounts that cocoa and dark chocolate can have health benefits, such as antioxidant activity that may benefit the cardiovascular system, there is growing industrial interest in developing and promoting such benefits. Some chocolate is already being marketed as a functional food, and this trend looks set to continue at pace.

This table explores the history of the development of chocolate, from medicinal drink to confectionery bar, and its arrival in Europe. Current global consumption and future functional possibilities are also described

lower levels of apparently healthy ingredients. Still, dark chocolate varies hugely in the levels of fat or sugar used, and some brands may have more sugar and fat than milk chocolate; clearly, very bitter chocolate is unlikely to be popular as a comfort food and presumably less effective in producing sensory pleasure for most people, although it would be richer in potentially "active" ingredients.

40.6 Conclusion

Chocolate is a potent nutritional and sensory package. As a result, most people can enjoy a lifting of mood, or positive emotions, by eating chocolate. Furthermore, the combination of energy richness and some psychoactive ingredients tends to promote a liking for chocolate, and reinforce a habit for it. This habit, like others involving sensory pleasure, can lead to intense "wanting" or craving, which is often subconsciously elicited. Some people who seem to be prone to becoming "emotional eaters" (i.e., comfort eaters) show particularly enhanced emotional responses to chocolate, and are more likely to become habitual eaters, using chocolate to regulate their emotions. This habit may clash with their beliefs about possible negative consequences of eating chocolate, such as weight gain, and so lead to feelings of guilt afterwards. This emotional seesaw is attributional in origin and not some unsubstantiated physiological consequence of, for example, changes in blood sugar. This minority of consumers, who sometimes see themselves as chocolate "addicts" who constantly crave chocolate, is more likely to be female; this sex difference may be partly sociocultural, but could also indicate roles for neurochemical and hormonal mechanisms that interact with emotional regulation to promote a chocolate-eating habit. The good news is that cocoa-rich chocolate may be good for us, though long-term psychological benefits remain to be demonstrated.

40.7 Applications to Other Areas of Health and Disease

There is increasing evidence that cocoa-rich chocolate can have beneficial physiological effects, such as reducing blood pressure and markers of cardiovascular inflammation, and improving vascular function including blood flow in the brain (McShea et al. 2008). Fortunately, the fat in chocolate consists primarily of stearic and oleic fatty acids that do not raise harmful cholesterol, although a minority of the fat is palmitic acid which can raise cholesterol. Animal studies also suggest that the antioxidant compounds in chocolate might help to slow the progress of chronic neurological conditions such as dementia and Parkinson's disease; intriguingly, a recent report suggests that chocolate consumption is increased in patients suffering from Parkinson's disease, perhaps implying underlying self-medication (Wolz et al. 2009). Moreover, it is clear that caffeine and theobromine, which occur naturally in chocolate, can improve both mood and mental function. Nevertheless, there is not yet convincing evidence that long-term use of chocolate confers such benefits.

Chocolate is a well-known comfort food, bringing emotional relief to some people during times of stress, and any alleviation of stress is usually of benefit to health. Nevertheless, this has to be balanced against the potential additional energy intake that a chocolate habit may contribute to. Indeed, there are links between stress and obesity, which may partly be the result of increased comfort eating, as comfort foods are invariably energy dense. Therefore, some people may benefit from retraining their chocolate-eating habits, for example avoiding chocolate when hungry, and perhaps using cocoa-rich chocolate, so that they can curb consumption to levels where the balance shifts in favor of health benefits rather than weight gain.

Summary Points

- Emotions result when we interact with events that might reward or punish us: thus, emotions and eating are often closely linked. We usually experience pleasure from eating, and pleasure is one emotional response that encourages us to eat: this is often especially true for chocolate.
- Chocolate has unique sensory properties that may be innately pleasurable. Yet, it is also energy-rich, often in the form of a sweet fatty food, and a memorable experience. Such foods rapidly become liked and can lead to learning of strong habits, especially if regularly eaten when hungry.
- A feature of such habits is that the brain can motivate us to want to eat chocolate subconsciously, despite our best intentions, i.e. our attempts at cognitive control of our habit. This can lead to a sense of "craving" for chocolate.
- Although psychoactive ingredients in chocolate may not be responsible for forming a chocolate habit or for alleviating its craving, caffeine and theobromine, found naturally in chocolate, do have positive effects on mood and mental function, in doses found in a 50-g bar: this may help form a chocolate habit.
- Chocolate craving is also partly due to having particular beliefs about chocolate being "naughty" (too many calories), which conflicts with the brain's fundamental recognition that chocolate is very "nice." This helps explain why women are far more likely to be cravers than men.
- Two strategies may help reduce craving for chocolate: first, avoid eating chocolate when hungry. If eaten full, the sensory pleasure and energy delivery will have far less impact. Second, if chocolate can be avoided altogether for several weeks, craving will "extinguish" itself because the habit is no longer reinforced.
- Chocolate is a recognized comfort food, i.e. eating chocolate can alleviate stress, reduce negative emotional states, and even increase tolerance to pain. These effects may be the result of activation of brain pathways known to combat stress, process pain, and to regulate emotions.
- Although there is evidence that cocoa-rich chocolate may benefit health in the short-term, it remains to be demonstrated that a long-term habit of eating chocolate improves psychological well-being.

Definitions and Explanations

Functional magnetic resonance imaging (fMRI): A form of magnetic resonance imaging that allows detection of activity in the brain, overlaid on detailed brain structural images, without the use of radioactive isotopes. fMRI uses blood-oxygen-level-dependent (BOLD) changes in magnetic characteristics of blood that reflect the delivery of oxygen from blood to local activated neuronal sites.

Serotonin: A neurotransmitter (chemical signal between nerve cells), also known as 5-hydroxytryptamine (5-HT), present throughout the body, and involved in numerous functions in the brain, including control of blood pressure, pain, sleep, appetite, emotions, and cognition.

Brain opioids: A class of neurotransmitters or neuromodulators whose receptors include those binding opiate drugs. Opioids are found in the periphery as well as the central nervous system, and are particularly involved in mediating pleasure and euphoria, as well as relief of pain and stress.

Amino acid: Molecules containing an amine group (e.g. $-NH_2$), a carboxylic acid group ($-COOH$) and 1 of 20 organic structures. They form proteins and peptides, which are chains of amino acids. In human adults, eight "essential" amino acids, including tryptophan, cannot be synthesized internally and so have to be obtained from food.

Methylxanthines: Methylated (having a chemical group of additional carbon and three hydrogen atoms attached, in place of a single hydrogen) derivative of xanthine, an aromatic organic chemical structure common in nature. Examples include caffeine and theobromine (one less methyl group than caffeine), and typically have mild stimulant properties.

Limbic hypothalamic pituitary adrenal axis: A network in which neurones in the limbic system (emotional circuitry) of the brain, especially the hippocampus, activate neurones in the hypothalamus that in turn control the release of trophic hormones from the anterior pituitary gland. These then stimulate release of e.g. glucocorticoid hormones from the adrenal glands, including cortisol.

References

Adam TC, Epel ES. Physiol Behav. 2007;91:449–58.

Benton D. Crit Rev Food Sci Nutr. 2008;48:385–401.

Berridge KC. Physiol Behav. 2009;97:537–50.

Blass EM, Shide DJ, Weller A. Ann NY Acad Sci. 1989;575:292–305.

Bohon C, Stice E, Spoor S. Int J Eat Disord. 2009;42:210–21.

Booth DA, Thibault L, In: Berthoud HR, Seeley RJ, editors. Neural and metabolic control of macronutrient intake. Boca Raton: CRC Press; 2000. p. 61–91.

Brand Miller JC, Holt SH, de Jong V, Petocz P. J Nutr. 2003;133:3149.

Buffenstein R, Poppitt SD, McDevitt RM, Prentice AM. Physiol Behav. 1995;58:1067–77.

Cartwright F, Stritzke WG. Eat Behav. 20089:1–12.

Cartwright F, Stritzke WG, Durkin K, Houghton S, Burke V, Beilin LJ. Appetite. 2007;48:87–95.

Crews WD Jr, Harrison DW, Wright JW. Am J Clin Nutr. 2008;87:872–80.

Dallman MF, Pecoraro NC, la Fleur SE. Brain Behav Immun. 2005;19:275–80.

Drewnowski A, Greenwood MR. Physiol Behav. 1983;30:629–33.

Drewnowski A, Hann C. Am J Clin Nutr. 1999;70:28–36.

Fernstrom MH, Fernstrom JD. Am J Clin Nutr. 1995;61:312–9.

Foster-Powell K, Holt SHA, Brand Miller JC. Am J Clin Nutr. 2002;76:5–56.

Gibson EL. In: Shepherd R, Raats M, editors. Psychology of food choice. Wallingford: CAB International; 2006. p. 113–140.

Gibson EL, Brunstrom JM. In: Cooper SJ, Kirkham TC, editors. Progress in brain research: Appetite and body weight – integrative systems and the development of anti-obesity drugs. London: Elsevier; 2007. p. 271–300.

Gibson EL, Desmond E. Appetite. 1999;32:219–40.

Gibson EL, Harris K. The three factor eating questionnaire and its link with perceived stress, eating behaviour and food choice. Undergraduate Dissertation. Roehampton University. Unpublished.

Gibson EL, Wardle J. Appetite. 2003;41:97–8.

Gilhooly CH, Das SK, Golden JK, McCrory MA, Dallal GE, Saltzman E, Kramer FM, Roberts SB. Int J Obes. 2007;31:1849–58.

Hetherington MM. In: Hetherington MM, editors. Food cravings and addiction. Leatherhead: Leatherhead Publishing; 2001. p. 295–323.

Hetherington MM, Macdiarmid JI. Physiol Behav. 1995;57:27–35.

Hormes JM, Rozin P. Appetite. 2009;53:256–9.

Kern DL, McPhee L, Fisher J, Johnson S, Birch LL. Physiol Behav. 1993;54:71.

Kisler VA, Corcoran KJ. Addict Behav. 1997;22:461–7.

Kunz C, Rudloff S, Baier W, Klein N, Strobel S. Annu Rev Nutr 2000;20:699–722.

Lambert KG, Neal T, Noyes J, Parker C, Worrel P. Curr Psych Res Rev. 1991;10:297–303.

Macdiarmid JI, Hetherington MM. Br J Clin Psych. 1995;34:129–38.

Macht M. Appetite. 2008;50:1–11.

Macht M, Dettmer D. Appetite. 2006;46:332–6.

Macht M, Mueller J. Appetite. 2007;49:667–74.

Macht M, Roth S, Ellgring H. Appetite. 2002;39:147–58.

Markus CR, Panhuysen G, Tuiten A, Koppeschaar H, Fekkes D, Peters ML. Appetite 1998;31:49–65.

Martin CK, O'Neil PM, Pawlow L. Obesity. 2006;14:115–21.

McShea A, Ramiro-Puig E, Munro SB, Casadesus G, Castell M, Smith MA. Nutr Rev. 2008;66:630–41.

Mercer ME, Holder MD. Physiol Behav. 1997;61:311–8.

Michener W, Rozin P. Physiol Behav. 1994;56:419–22.

Oliver G, Wardle J. Physiol Behav. 1999;66:511–5.

Oliver G, Wardle J, Gibson EL. Psychosom Med. 2000;62:853–65.

Peters A, Pellerin L, Dallman MF, Oltmanns KM, Schweiger U, Born J, Fehm HL. Prog Neurobiol. 2007;81:61–88.

Raikkonen K, Pesonen AK, Jarvenpaa AL, Strandberg TE. Early Hum Dev. 2004;76:139–45.

Reid M, Hammersley R. Nutr Res Rev. 1999;12:3–23.

Riederer PF, Burger R. Psychopharmakother. 2009;16:26–31.

Rolls ET. Emotion explained. Oxford: Oxford University Press; 2007.

Rolls ET, McCabe C. Eur J Neurosci. 2007;26:1067–76.

Rozin P, Levine E, Stoess C. Appetite. 1991;17:199–212.

Small DM, Zatorre RJ, Dagher A, Evans AC, Jones-Gotman M. Brain. 2001;124:1720–33.

Smeets PA, de Graaf C, Stafleu A, van Osch MJ, Nievelstein RA, van der Grond J. Am J Clin Nutr. 2006;83:1297–305.

Smit HJ, Gaffan EA, Rogers PJ. Psychopharmacology 2004;176:412–9.

Smit HJ, Rogers PJ. In: Hetherington MM, editors. Food cravings and addiction. Leatherhead: Leatherhead Publishing; 2001. p. 325–349.

Wallis DJ, Hetherington MM. Appetite. 2009;52:355–62.

Wardle J, Sanderson S, Gibson EL, Rapoport L. Appetite. 2001;37:217–23.

Wolz M, Kaminsky A., Löhle M, Koch R, Storch A, Reichmann H. J Neurol. 2009;256:488–92.

Yeomans MR. Appetite. 1996;27:119–33.

Zellner DA, Garriga-Trillo A, Centeno S, Wadsworth E. Appetite. 2004;42:119–21.

Chapter 41
Psychological and Physiological Consequences of Drinking Tea

E.L. Gibson and J.A. Rycroft

Abbreviations

CVD   Cardiovascular disease
EGCG   Epigallocatechin gallate
LDL   Low-density lipoprotein (cholesterol)
DNA   Deoxyribonucleic acid
EEG   Electroencephalography
GABA   Gamma-aminobutyric acid
CFF   Critical flicker fusion test

41.1 Introduction

The beverage tea is second only to water in terms of global consumption of a drink, outstripping all other drinks put together: in the UK, 77% of adults drink tea, averaging nearly three mugs (540 mL) per day, with volume increasing with age (Gardner et al. 2007). Moreover, tea is known to most of the world's ethnic and cultural groups: therefore, putative effects of tea on health or behavior may assume considerable importance for public health. This chapter considers the evidence that tea may affect both these outcomes, through psychological and physiological consequences. There is now a very substantial literature relating tea to health, but there is only space here to summarize the evidence, concentrating in particular on studies in human beings, and the recent consensus. The impact of tea on psychological and behavioral outcomes is less thoroughly researched, but nevertheless several intriguing findings that have emerged in recent years are considered here.

It is important from the outset to define the term "tea" as used in this chapter, since tea can take many forms across the world. Here, tea refers to the most universally recognized form of beverage, a hot drink formed from infusing leaves and leaf buds from the shrub *Camellia sinensis* (familiarly

E.L. Gibson (✉)
Clinical and Health Psychology Research Centre, Department of Psychology,
Whitelands College, Roehampton University, Holybourne Avenue, London SW15 4JD, UK
e-mail: l.gibson@roehampton.ac.uk
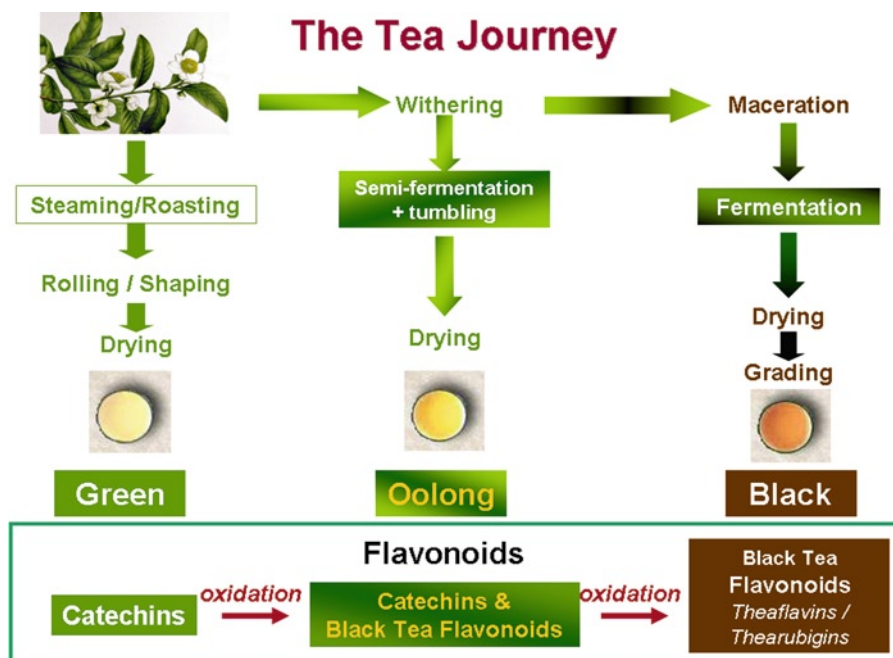
Fig. 41.1 The production journey for green, oolong, and black tea. The tea journey: a diagram summarizing the various stages of processing tea leaves, the type of tea produced, and the impact on its key components, the flavonoids (unpublished figure)

known as the tea plant) in hot or boiling water (though once cooled, this beverage can be drunk cold, as "iced tea"; extracts of tea also form the basis of bottled or canned forms). These tea leaves can be cultivated, picked, cured, and processed in a variety of ways, resulting in differing fermentation and oxidation, giving several classes of tea beverage, principally (in order of oxidation): white, green, oolong, black, and pu-erh teas (Fig. 41.1). In oriental countries, "red tea" is another (arguably more accurate) term for black tea, although, red tea is also a name used for an infusion of leaves from the South African "rooibos" (red bush) plant, which thus contains no *C. sinensis*, or caffeine. Indeed, infusions of a wide variety of other plants, fruits, and flowers are often referred to as "tea" (or its equivalent in the local language) in many cultures across the globe, and many of these may have both psychological and physiological effects relevant to health and well-being (Pardo de Santayana et al. 2005). However, such effects have not been scientifically or extensively researched for most of these other beverages: indeed, the vast majority of research on tea deals with forms of green or black tea, which are also the most commonly consumed varieties globally (Table 41.1); therefore, this is the nature of the evidence summarized in this chapter.

Nevertheless, restricting the scope of the chapter to infusions of the leaf of one plant does not result in a simple categorization or interpretation of evidence, since the forms of tea from *C. sinensis* vary in biochemical content as a result of cultivation of different varieties of the plant, as well as both preparation of the leaves (Fig. 41.1) and preparation of the infusion (e.g., temperature of the water and length of brewing time; Astill et al. 2001). Moreover, studies of the potential impact of tea on health and behavior have often used processed extracts of tea; this has the advantage of controlling dosage and preparation, but somewhat limits the possibility of generalizing results to any effects of drinking tea as a beverage.

Table 41.1 Key facts about tea

Key points	Facts
Origins of tea drinking	Tea originated in southeast Asia, where it has been drunk for at least 3000 years. However, tea did not arrive in Europe until the early seventeenth century, finally becoming fashionable in Britain in the late seventeenth century, whence it spread to the colonies – the British East India Company established tea plantations in India in the early nineteenth century.
Types of tea	True tea is a drink made by infusing in hot water the leaves from the tea plant, *Camellia sinensis*. These tea leaves can be cultivated, picked, cured, and processed in a variety of ways. However, the main process that differentiates tea is fermentation (oxidation) of the leaves. Thus, white tea (the youngest leaves), a Chinese yellow tea, and green tea are not fermented, but undergo steaming, roasting, and drying, resulting in delicate, light tea. Oolong tea is semi-fermented, giving a tea part way between green and black. Black tea and pu-erh ("shu" type) tea are fully fermented, although there is a variety of pu-erh tea, "sheng," which is unfermented like green tea. Within these broad tea types, there are numerous varieties.
Global tea production and consumption	Most tea is produced in East and South Asian countries, including China, Japan, India, Sri Lanka, Korea, Vietnam, and Indonesia. Other continents produce substantial amounts of tea including East Africa (especially Kenya), Central and South America. Turkey is also a major producer. About 70% of production is black tea, and 22% green tea. These top producers also tend to be big consumers, accounting for at least half of all production: however, the major importers of tea are (from the highest) Russia, UK, Pakistan, USA, Egypt, Japan, and Iran. These countries consume very different forms of tea, in terms of processing, variety, and preparation. Global tea consumption continues to grow, and has more than doubled since 1970.
Tea preparation	Water temperature is important for correct tea preparation, with the more delicate tea needing lower temperatures than the fermented one. Thus, for white, yellow, and green tea, water temperature should range from 66°C to 82°C (coolest for white tea). Oolong tea is best brewed using water at 82–88°C, whereas black and pu-erh tea require water near boiling point (99°C). Tea should always be steeped (brewed) for at least 30 s (which allows all the theanine to be released). If steeping is limited to 2 min or so, then several separate infusions can be obtained from the same leaves; each will have different flavor characteristics, as well as chemical components. Longer brewing, for 3–4 min, maximizes the release of antioxidant polyphenol compounds, although brewing beyond 5 min will tend to produce a bitter tea.
With or without milk?	Adding milk to tea was established early on in its arrival in Europe, although it is practiced elsewhere, such as Manchuria. It is the most common way to take tea in Britain, where the popular tea varieties are quite strongly flavored and astringent. There are mixed findings concerning the impact of milk on tea's health benefits, but it is likely that, when added as less than 10% of the volume, milk will have little impact on tea's effects.

This table gives key facts about the origins and global distribution of tea drinking, its varieties, production, and preparation of the tea drink

The approaches to studying effects of tea, or its components, on health, behavior, and well-being (a sense of positive health that is more than the absence of illness), vary from in vitro studies of chemical activity in "test tube" models, through experimental studies of tea dosing in animals and man, to epidemiological studies of relationships between habitual tea consumption in large populations and psychological and physiological outcomes. These outcomes are varied, but are grouped here as: cardiovascular (heart and circulatory) health; cancer risk; body weight and obesity; mental well-being and mood; and cognitive function or mental performance.

41.2 Cardiovascular Health

> Drinking a daily cup of tea will surely starve the apothecary
>
> (Ancient Chinese proverb)

Earlier epidemiological studies, including prospective studies looking at development of cardiovascular disease (CVD) over several years in large population samples, did not find conclusive evidence of either a beneficial or harmful effect of drinking tea, but instead, inconsistent results, despite experimental evidence that tea contained potentially beneficial chemicals; however, it was acknowledged that this may be due to close associations in some populations between tea drinking and other lifestyle factors that themselves may be detrimental to cardiovascular health (Hollman et al. 1999). In other words, in some populations, for example in the UK, frequent black tea drinking is popular in lower socioeconomic groups in which unhealthy behaviors are also common, and their confounded influence on heart health may not easily be separated, so that in such populations greater tea intake may even be associated with poorer cardiovascular health, at least in unadjusted analyses. However, a recent overall review of many such epidemiological studies, including populations where this behavioral confounding is not apparent, has concluded that (black) tea clearly has a positive association with coronary heart disease, with three mugs per day reducing risk by up to 71%, depending on the study and population (Gardner et al. 2007). Another meta-analysis of the epidemiological studies linking tea consumption to incidence of stroke, using data from nine studies involving 4,378 strokes among 194,965 individuals, also showed that consuming three or more cups of either green or black tea per day may reduce the risk of ischemic stroke by as much as 21% (Arab et al. 2009).

What properties of tea might benefit the cardiovascular system? The most likely candidates are the various plant chemicals found in tea, collectively known as polyphenol flavonoid compounds, as these are known to have antioxidant activity in vitro, which could suppress inflammatory processes that otherwise contribute to CVD. These components of tea include the catechin flavanols, particularly epigallocatechin gallate (EGCG), their oxidation (fermentation) products, the theaflavins, thearubigins, as well as the flavonols, quercetin, keampherol, and rutin (Fig. 41.2). Tea also contains a unique amino acid, theanine, which may have important effects on the brain (see next; refer Fig. 41.3 for structures of catechins and theanine).

Fig. 41.2 A comparison of the flavonoid contents of typical green and black tea. Pie charts showing the proportions of different classes of flavonoid compounds in average cups of green and black tea (% = % dry weight) (Based on data from Lakenbrink et al. 2000 and Astill et al. 2001. With permission)

Tea Flavonoid Content

Green tea

catechins (12%)

Average cup of Green Tea = 90 mg per 200 ml

Polymeric flavonoids (10%)

flavonols (10%)

Black Tea

theaflavins (12%)

flavonols (10%)

catechins (8%)

Average cup of black tea = 135 mg per 200 ml

thearubigins (70%)
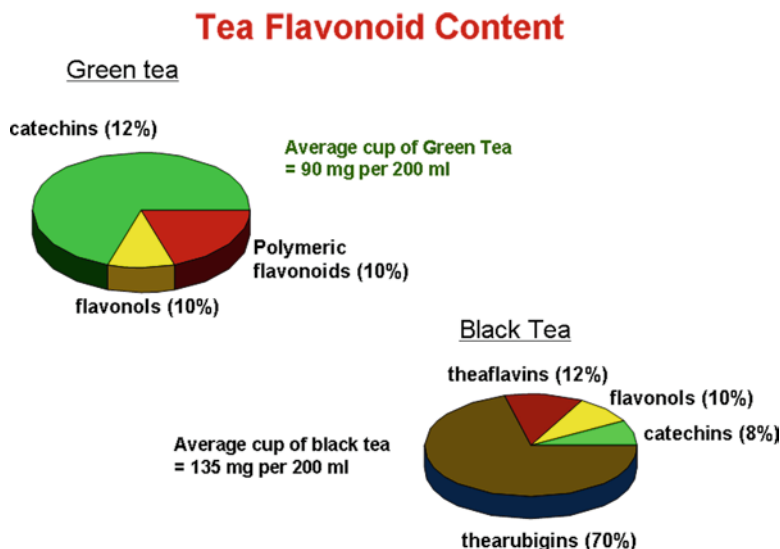
Fig. 41.3 The chemical structures of catechin and theanine. The chemical structures for two key components of tea: (**a**) the basic catechin structure and (**b**) the structure of the amino acid, theanine (an analog of glutamate and glutamine). Both structures were downloaded from Wikimedia Commons (http://commons. wikimedia.org/ – public domain images)
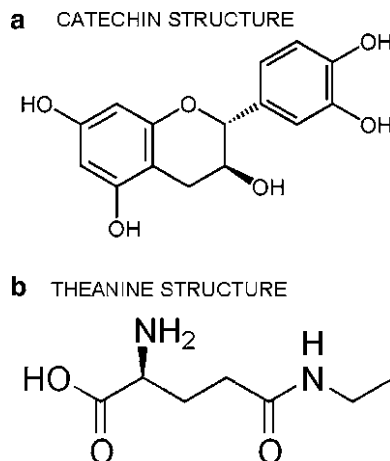
In many European populations, tea is the dominant source of flavonoids such as catechins – in the UK, accounting for as much as 80%, though rather less in the USA – although these are also found in red wine, chocolate, and apples, for example. It has been estimated that average intake of flavonoids in Western countries is about 65–250 mg/day (Erdman et al. 2007). Tea's importance in contributing catechins to the diet was illustrated by findings from a prospective study of elderly Dutch men, in whom high habitual dietary catechin intake reduced risk of dying from coronary heart disease by about 50% compared with low catechin intake; in contrast, once the contribution of tea had been statistically removed, the risk reduction was down to 20% and was not statistically significant (Arts et al. 2001).

In determining likely mechanisms for the impact of tea on cardiovascular health, experimental studies of tea, or its components, have revealed beneficial effects on vascular physiology that support probable health benefits of drinking tea on the cardiovascular system, in in vitro laboratory and animal models, and in clinical trials in human participants (Vita 2005). Several clinical studies have investigated two aspects in particular: (1) activation of blood platelets (assessed as aggregation of platelets with white blood cells or activated by factors such as adenosine diphosphate), which indicates risk of clot formation and inflammation of arterial walls, and is a key event leading to coronary heart disease; (2) responsiveness of the vascular endothelium (cellular lining of blood vessel walls) to changes in blood flow (i.e., dilatation vs constriction), which is thought to be an important indicator of the health of the cardiovascular system. In patients with established CVD, 4 weeks of drinking 900 mL of black tea per day did not reduce platelet aggregation compared to water, despite increased plasma flavonoid content, although the design cannot rule out an interaction with change in caffeine intake. In contrast, this same group did find that this tea "treatment" improved endothelial function in these patients (reviewed by Gardner et al. 2007). By comparison, in a recent double-blind, placebo-controlled study in a larger sample of healthy men, where caffeine intake was equated between treatment groups, 6 weeks of drinking four mugs of black tea per day was shown to inhibit platelet activation (aggregation with white blood cells), as well as lowering plasma levels of C-reactive protein, usually regarded as a general indicator of chronic inflammation (Fig. 41.4; Steptoe et al. 2007a).

Similar evidence is available from studies of effects of green tea, which is higher in levels of catechins, especially EGCG, than black tea (although the amount consumed will depend on how the tea is brewed). In epidemiological studies, where potentially confounding lifestyle and other factors are controlled for, an inverse association has been described between green tea consumption and CVD, including stroke and hypertension, in oriental populations (Tanabe et al. 2008). Clinical studies have been short term, but beneficial effects on vascular inflammation and blood lipids, including
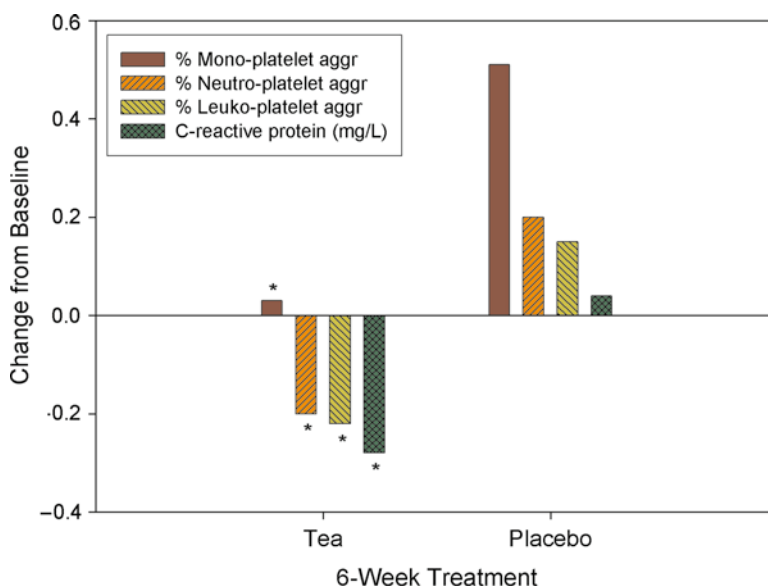
Fig. 41.4 Change from pretreatment baseline in measures of platelet activation and C-reactive peptide after drinking four mugs of black tea per day for 6 weeks, or a tea placebo (means adjusted for baseline values). Measures: "Mono-platelet aggr" = monocyte-platelet aggregation; "Neutro-platelet aggr" = neutrocyte-platelet aggregation; "Leuko-platelet aggr" = leukocyte-platelet aggregation. *$p < 0.05$ for significant differences between tea and placebo treatments (Based on data from Steptoe et al. 2007a. With the authors' permission)

reduced oxidation of low density lipoprotein (LDL) cholesterol, have been reported. Indeed, particularly impressive results were found in a recent randomized, double-blind placebo-controlled study administering decaffeinated green tea extract capsules for 3 weeks to healthy volunteers aged from 21 to 70: the green tea treatment reduced blood pressure, inflammation and oxidative stress (a cellular process that can damage DNA), and total and LDL cholesterol (Nantz et al. 2009).

However, there is still a need for longer-term placebo-controlled clinical studies. Moreover, it should be noted that recent ex vivo experimental assessment of tea flavonoid effects on vascular endothelium vasodilatation found that highly fermented black tea was equally as potent as green tea, suggesting that the theaflavins and thearubigins in black tea, to which green tea catechins are converted by fermentation, also have beneficial effects on endothelial function (Lorenz et al. 2009). Similarly, a very recent study showed that black tea dose-dependently improved flow-mediated dilation (a noninvasive measure of endothelial function) in healthy male volunteers (Grassi et al. 2009). These beneficial cardiovascular effects of tea are reminiscent of similar effects, including lowering of blood pressure, seen for diets high in fruit and vegetables: similar mechanisms may be involved and continue to be intensively researched.

41.3 Prevention of Cancer

The ability of components of tea to have physiological activity that benefits cardiovascular health, either by reducing inflammation or improving arterial vasodilatation, makes it possible that drinking tea will have other health advantages; key among these could be a reduction in the risk of cancer. Several mechanisms might account for tea's anticancer properties, but the principal ones are likely

to be reduction of DNA damage by oxidative stress, e.g. by scavenging (deactivation) of reactive oxygen species (free radicals) and binding of metals, metabolism and detoxification of carcinogens, modulation of carcinogenic gene expression, and lowering the rate of cell replication (Lambert et al. 2005). In addition, recent evidence suggests that flavonoids in tea may be able to induce apoptosis, i.e. a process of cell death important in regulating cell proliferation and thus cancer, as well as altering biochemical intracellular signaling pathways (de Mejia et al. 2009). Furthermore, even theanine may have anticancer activity (Liu et al. 2009).

Nevertheless, most laboratory studies use higher flavonoid concentrations than those likely to occur from normal tea drinking. Thus, it is important that this mechanistic evidence should be supported by evidence of inverse associations between tea consumption and cancer risk at a population level, i.e. epidemiological studies, where other potentially confounding influences are statistically adjusted for (Lambert et al. 2005). Although there are promising results from some studies showing such inverse associations, others have not supported those findings. For example, in prospective studies in older populations used to assess relations between dietary flavonoid intake and death from cancer, an inverse association was found in a Finnish cohort but not in two Dutch cohorts (Hollman et al. 1999). Gardner et al. (2007) recently reviewed epidemiological studies of associations between specifically black tea and cancer, and concluded that there was little evidence of a consistent protective effect. For example, in a large sample of Canadian men, no association was found between (mainly black) tea drinking and prostate cancer (Gardner et al. 2007). Moreover, a recent report from a very large sample of North American women aged over 45 found no association between total or site-specific cancer incidence and dietary intake of flavonols and flavones (Wang et al. 2009b). However, it should be noted that, in this population, tea is likely to be only a minor contributor to the intake of these flavonoids. In another sample from the USA, no association was found between tea intake and colorectal cancers (Gardner et al. 2007). In a Japanese sample, frequency of green tea intake was also not associated with gastric cancer (one of the most common cancers in Japan; Tsubono et al. 2001).

Conversely, green tea was associated with almost a 50% reduction in risk of gastric cancer in a Chinese population (Setiawan et al. 2001), and black tea was strongly protective against gastric cancer in an Indian population (Rao et al. 2002). Moreover, in a Japanese population, drinking more than ten cups per day of green tea reduced the risk of developing any cancer in both men and women by at least 40%, and onset of cancer was delayed, compared with low intake of green tea (Nakachi et al. 2000). These studies are dependent on accuracy of information concerning both tea intake and confounding factors: importantly, in a prospective study of Chinese men, urinary tea polyphenols were measured to estimate tea intake; high tea intake protected against gastric and esophageal cancers, but only in men who had a low intake of carotene, suggesting low consumption of vegetables (Sun et al. 2002). This could suggest that any protective effect of tea against cancer may be obscured if the diet is generally healthy. Such complex interactions are also indicated by a study of Dutch men and women, where protective effects of dietary flavonoids against colorectal cancers depended on the body size of participants, i.e. protection was only evident in overweight men and normal weight women (Simons et al. 2009), which suggests subtle interactions with other lifestyle, and perhaps genetic, factors.

In summary, despite very promising evidence from mechanistic laboratory studies suggesting that tea flavonoids could reduce the risk of cancer, epidemiological studies of relations between tea (or dietary flavonoid) intake and cancer incidence have produced inconsistent findings. The US Food and Drug Administration previously assessed all the epidemiological data available on green tea and cancer prevention and concluded that it is highly unlikely that green tea reduces the risk of prostate cancer and that there is no credible evidence to support a relationship between green tea consumption and a reduced risk of gastric, lung, colon/rectal, esophageal, pancreatic, ovarian, and combined cancers (FDA 2005). One reason could be that, to protect against cancer, tea intake may need to be both high and in populations that eat relatively low amounts of fruit and vegetables.

41.4 Body Weight, Appetite, and Obesity

> Tea's proper use is to amuse the idle, and relax the studious, and dilute the full meals of those who cannot use exercise, and will not use abstinence.
>
> > Samuel Johnson (1757) "Essay on tea."

Anecdotally, tea has long been believed to alter appetite; however, scientific evidence has been scarce until recently. Laboratory studies investigating potential cardiovascular benefits of black and green tea flavonoids revealed physiological effects that could be of benefit to obese humans at risk of insulin resistance and unhealthy blood lipid profiles (Ramadan et al. 2009). Consistent with this, the green tea flavanol EGCG, was found to promote postprandial insulin secretion in human beings (Weber 2004): this latter result is particularly interesting, as insulin is known to promote satiety and so constrain food intake (see Sect. 1.3 and 1.7 of this publication). In addition, short-term administration of green tea extract plus caffeine to ten healthy men increased fat oxidation and energy expenditure, through stimulation of the sympathetic nervous system (probably by inhibiting enzymatic degradation of the neurotransmitter noradrenaline), whereas caffeine alone was ineffective (Dulloo et al. 1999). Likewise, in 12 healthy men performing a 30-min cycling exercise, green tea extract (without caffeine) increased fat oxidation rate compared with placebo (Venables et al. 2008).

Eleven long-term clinical studies have recently been reviewed and meta-analyzed by Hursel et al. (2009): some of those are summarized here (but not cited, if included in that review). In a study of 104 obese Dutch men and women undergoing severe energy restriction for weight loss, the effect of green tea on weight regain after the restricted period was compared to placebo: there was no difference between groups; however, there was evidence that caffeine may reduce weight regain in habitually low consumers of caffeine. This shows that it is important to design studies that distinguish between effects of caffeine and the flavonoid components of tea. In another study by these same investigators, caffeine was standardized to 300 mg/day for both a green tea extract treated group and a placebo group, during a weight loss diet in women. There was no benefit from green tea on weight or fat loss; in fact, the women given green tea actually became hungrier than those on placebo.

However, in normal and overweight Japanese men and women, taking a drink containing green tea catechins twice or thrice a day for 12 weeks resulted in greater weight and fat loss than placebo (Kajimoto et al. 2005). During this period, participants were asked to maintain their usual diet; even so, the catechin drink also reduced total and LDL cholesterol. Similar results were found in a study of Japanese men comparing 12 weeks of drinking either oolong tea once per day or the same tea supplemented with green tea extract; body weight and fat loss, and reduction in LDL cholesterol, were greatest for the green tea extract group. Furthermore, in obese Thai men and women on a calorie-controlled diet (8.4 MJ/day) for 12 weeks, green tea treatment reduced body weight and increased resting energy expenditure compared to placebo. By comparison, in Taiwanese obese women taking green tea extract or placebo capsules for 12 weeks, there was no difference in weight loss, but blood cholesterol profiles were markedly improved by the tea extract. Despite these somewhat mixed findings, a meta-analysis of such studies concluded that evidence supports a small effect of green tea or catechins (or combined with caffeine) in enhancing weight loss or weight maintenance (Hursel et al. 2009).

Since then, another study monitored the effects of green tea consumption on body weight, body fat mass, as well as the distribution of fat (Wang et al. 2009a). A total of 182 moderately overweight Chinese subjects, aged between 18 and 55 years, were divided into four groups, with each group allocated a regular dose of green tea containing a different quantity of catechins. Amounts consumed ranged from 30 mg to almost 900 mg; an average cup of green tea contains between 50 and 100 mg of catechins. Participants in the study drank their designated tea divided in two daily doses. On days 0, 30, 60, and 90, measurements of body composition were taken to assess the effects that the prescribed tea had on body mass and fat.

The results showed that, relative to the control group consuming no green tea catechins, body weight, waist circumference, intra-abdominal fat, and the total lean mass all decreased after 90 days in the group that drank the tea with the highest concentration of catechins. The authors concluded that regular consumption of green tea with very high catechin content can, over a 90-day period, reduce body weight, body fat mass, and waist size in moderately overweight Chinese individuals.

41.5 Mental Well-being and Mood

If you are cold, tea will warm you; if you are too heated it will cool you. If you are depressed, it will cheer you; if you are excited, it will calm you.

W. E. Gladstone (British Prime Minister 1865)

In many cultures, it is an accepted folklore that drinking tea can acutely improve one's state of well-being, especially the ability to calm oneself, to relax, and escape for a moment from life's many pressures. However, there has been very little scientific investigation to support this notion. Of course tea normally contains caffeine, and, as described in the next section, this explains some, but not all, of the arousing potential of a regular cup of tea (Hindmarch et al. 2000). Yet, other aspects of tea may have important effects on mood: for example, drinking tea, but not coffee, was associated with feeling more relaxed, for women with high social support at work (see Steptoe et al. 2007b). Furthermore, the amino acid, l-theanine, unique to tea, has been shown to increase a psychophysiological measure of relaxation in human beings, i.e. increased electrical alpha-wave activity on the brain surface, as detected by electro-encephalographic (EEG) recording of brain electrical potential changes, or "brain waves" (Nobre et al. 2008), and to improve relaxation during restful conditions (Lu et al. 2004). However, another study measuring EEG after theanine-enriched green tea intake found evidence of increased attention but not relaxation (Dimpfel et al. 2007). Furthermore, several studies have found that theanine and caffeine can interact in affecting mental function (see below), and one study reported that theanine can ameliorate the increase in blood pressure seen after acute caffeine intake (Rogers et al. 2008).

If theanine aids relaxation, one might expect theanine to be of benefit during stress, as seems anecdotally to be the case for tea. There is evidence that this is indeed the case: thus, in participants who were acutely stressed by having to complete a difficult mental arithmetic task, theanine reduced the heart rate response to stress, and also reduced a well-known stress-sensitive response, a rise in salivary immunoglobulin A antibody levels, compared to placebo (Kimura et al. 2007).

One study has looked at the impact of drinking black tea (without milk) four times a day for 6 weeks on responses to stress in healthy men (Steptoe et al. 2007b). This was a randomized double-blind placebo-controlled study, where effects of caffeine were controlled by equating caffeine levels between tea and placebo drink groups. Participants underwent stressful laboratory tasks (role-play speech and mirror tracing tasks) at baseline, after a 4-week wash-out phase on placebo tea, and finally after 6 weeks on either active or placebo tea: 75 men completed the study. Blood samples were taken before and after the stress; heart rate and blood pressure were measured continuously during each session, and the hormone cortisol, known to increase under stress, was measured at several time points in saliva samples. The main findings were that, compared to placebo (a) tea treatment did not alter the stress-induced increases in heart rate and blood pressure; (b) tea drinking resulted in a faster poststress recovery of the cortisol response (Fig. 41.5); (c) participants given the active tea were more relaxed after stress than those given placebo (Fig. 41.6). Thus, drinking tea for 6 weeks did not alter the acute physiological responses during stress, but improved the hormonal and psychological recovery from stress.

If tea benefits mood and coping with stress, it might be expected to show some ability to protect against depression. There is indeed some support for this: a cross-sectional study of over 2000
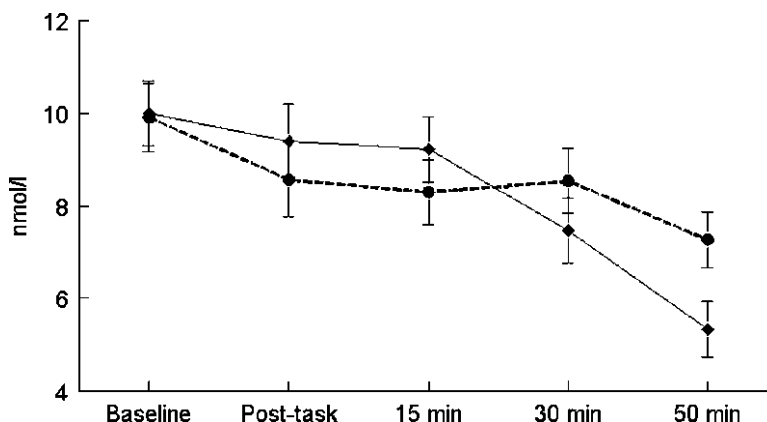
Fig. 41.5 Changes in salivary cortisol before, after, and during recovery from, stressful tasks, after either 6 weeks of drinking black tea or a placebo drink. Levels of the stress hormone, cortisol, in saliva samples taken before and after performing psychologically stressful tasks, and during subsequent poststress recovery. Cortisol levels fell more rapidly during recovery from stress (50 min later) for the group drinking black tea for 6 weeks (*solid line*), compared to the group drinking placebo tea (*dashed line*) (The figure is reproduced from Steptoe et al. 2007b. With the permission of the authors.)

Fig. 41.6 Effect of 6-week tea drinking vs. placebo on change in relaxation from before performing stressful tasks to after post-task recovery. Change in rated relaxation from before performing stressful tasks to after posttask recovery, 50 min later. Participants were less relaxed after stress following placebo treatment (*dashed line*), but more relaxed after drinking active tea for 6 weeks (*solid line*) (The figure is reproduced from Steptoe et al. 2007b. With the permission of the authors)
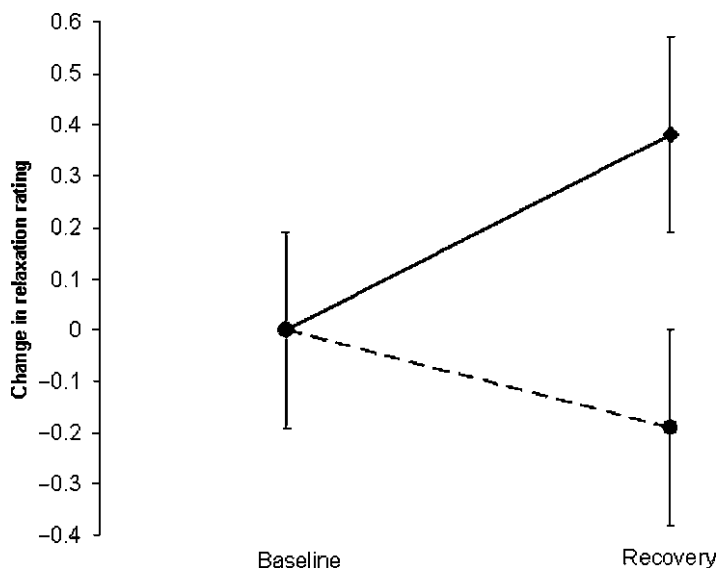
Finnish people found that respondents reporting daily tea drinking were significantly less depressed than those drinking tea less frequently, and there was no depression among those drinking five or more cups per day (Hintikka et al. 2005). This finding may also be relevant to the evidence that tea has neuroprotective effects (see next). A similar finding has been reported for a Japanese population, in relation to green tea and psychological well being (Hozawa et al. 2009): in over 42,000 Japanese over 40 years old, those drinking green tea at least five times per day were 20% less likely to report being psychologically distressed than those drinking tea less than once a day, after controlling for other lifestyle and demographic factors.

What could be the mechanisms by which tea benefits mood and psychological well-being? Animal studies have shown that the catechins in tea can act in the brain via type-A receptors for

gamma-aminobutyric acid (GABA-A), a major inhibitory neurotransmitter known to be involved in the calming, sedative, and anti-anxiety actions of benzodiazepine drugs like Valium (Vignes et al. 2006). Moreover, these catechins have recently been found to inhibit activity of neurones in the brain stem nucleus, the locus coeruleus (Chang et al. 2009). As the locus coeruleus is involved in brain arousal systems, this might indicate a mechanism for the calming effects of tea, although it is not clear that catechins absorbed from drinking tea could affect the brain in this way. Theanine also appears to act in the brain via another inhibitory amino acid transmitter, glycine, and via modulation of dopamine release (involved in attention and motivation, as well as motor control). Theanine is a structural analog of glutamate and glutamine, two neurotransmitters involved in excitatory brain transmission. As such, theanine is able to compete with glutamate and glutamine for their transporters, receptors, and metabolizing enzymes. By attenuating the action of glutamate and glutamine, theanine might affect cognitive function, or mood (Bryan 2008). There remains much to be learnt about the potentially complex mechanisms by which tea may modulate brain activity and so mental well-being.

41.6 Cognitive Function

My dear, if you could give me a cup of tea to clear my muddle of a head, I should better understand your affairs.

Charles Dickens (1894)

This section will consider two sorts of evidence in relation to tea and brain function: (a) that tea can acutely modulate cognitive function, i.e. as assessed by mental performance after short-term dosing with tea or its components; (b) that drinking tea, or ingesting its components, is associated with neuroprotective effects, i.e. effects on neuronal structure and function that prevent or ameliorate neurodegeneration and associated cognitive decline or dementia.

41.6.1 Acute Effects on Cognitive Function

More than a decade ago, it was shown that drinking black tea improved alertness acutely (within 10 min; Critical Flicker Fusion test, CFF) – an effect that was not matched by 100 mg caffeine and was more reliable than the effect of coffee on repeated testing over the day (Hindmarch et al. 1998). Nevertheless, that study also found no acute benefit of tea, coffee, or caffeine on tests of short-term memory. Subsequently, in a comparison of tea and coffee over a day, tea improved alertness (CFF) more than coffee (which had twice as much caffeine), whereas coffee showed some additional benefit for reaction times in a choice reaction time task (Hindmarch et al. 2000). Additionally, both these caffeinated drinks delayed and disrupted sleep, although tea less so than coffee. Finally, there are preliminary reports that black tea may improve focused attention, i.e. the ability to select and process only relevant sensory information from among multiple stimuli, although it is not clear to what extent that effect is independent of caffeine (Lipton Institute of Tea Factsheet, "Black tea and mental performance," 2009, Unilever; de Bruin et al. unpublished data).

Thus, there is some evidence that beneficial effects of tea on alertness may differ from those of caffeine per se. It is also worth noting here that there is increasing evidence that apparently beneficial effects of caffeine may largely be due to removal of cognitive impairment following overnight withdrawal from caffeine. Thus, unlike the positive effects seen in overnight withdrawn participants, no beneficial effects of caffeine on performance were found in participants who had abstained from

caffeine for 3 weeks prior to testing, and among those receiving placebo, these long-term withdrawn participants performed better than overnight withdrawn participants (Rogers et al. 2005). However, it is not known whether beneficial effects of tea, as distinct from caffeine, depend on acute withdrawal.

How might tea improve alertness and attention, other than via caffeine? One possibility is via the activity of theanine: as already mentioned, EEG recordings of brain activity after theanine administration suggest that it is able to produce a relaxed state without drowsiness that might improve sustained attention (Nobre et al. 2008; Gomez-Ramirez et al. 2009). One group examined the impact on performance of caffeine (150 mg) or theanine (250 mg) alone or in combination (Haskell et al. 2008). As expected, caffeine improved performance on several measures; however, theanine alone did not, and even impaired performance on a demanding mental arithmetic task, as well as increasing headaches 90 min later. Yet, the combination of caffeine and theanine improved performance above caffeine alone on more complex verbal tasks, and also caused the greatest increase in alertness. However, these effects on mood were not replicated by another group who used 250 mg of caffeine and 200 mg of theanine, alone or in combination (Rogers et al. 2008). In that study, theanine seemed to prevent the increase in alertness caused by caffeine, as well as the increase in blood pressure. The authors noted that this might help to explain why tea is often perceived to be more relaxing than coffee, and it is in line with changes in EEG activity described above. However, it is important to note that these doses of theanine and caffeine are considerably greater than would normally be found in a cup of tea. Nevertheless, when lower doses of caffeine (50 mg) and theanine (100 mg) were tested in another study, the combined treatment showed some improvement in attention and memory over caffeine alone and placebo (theanine was not tested alone), whereas the caffeine-related increase in alertness was again weaker in the presence of theanine (Owen et al. 2008). The effects of these same doses of caffeine and theanine have subsequently been shown to improve attention on a switch task but not to improve intersensory attention or subjective alertness (Einöther et al. 2010).

Could the flavonoid components of tea, especially the catechins, also contribute to any acute effects of tea on cognitive function? It may be plausible, given the animal evidence discussed in the previous section that catechins do alter brain neurotransmitter systems – indeed, the inhibition of locus ceoruleus neuronal activity by catechins (Chang et al. 2009) would be compatible with a more relaxed frame of mind after tea, though not obviously with improved attention – though they may not reach the brain in sufficient amounts. Furthermore, catechins and other flavonoids could improve blood flow in active areas of the brain via their vascular epithelial effects (see above). There are also several studies in rodents demonstrating that chronic consumption of catechins improves memory and other aspects of neuronal function (de Mejia et al. 2009), as well as promising results from human interventions administering some types of dietary flavonoids (mainly isoflavones) for weeks or months (Macready et al. 2009). Nevertheless, there do not appear to be any studies demonstrating short-term effects of tea flavonoids on cognitive performance, so the question of their contribution to any such effects from tea remains open.

41.6.2 Chronic Effects on Cognition and Brain Function

There is growing evidence from animal studies that various flavonoids, including tea catechins, can benefit neuronal growth and function, and furthermore act as neuroprotective agents, counteracting neurodegenerative processes, such as oxidative stress, that otherwise lead to dementia, Parkinson's disease, etc. (de Mejia et al. 2009; Macready et al. 2009). Moreover, theanine also appears to have neuroprotective effects in animals (Il Kim et al. 2009). To date, there do not appear to be any controlled interventions examining the impact of chronic tea intake (or tea components) on cognitive function in human beings.

Nevertheless, there are several epidemiological studies that have examined relationships between long-term tea consumption and brain or cognitive function. In a cross-sectional study of elderly

Japanese, higher green tea consumption, but not coffee, was associated with lower cognitive impairment (Kuriyama et al. 2006). In an elderly French population, risk of dementia after 5 years was reduced by 51% in those having the highest intake of dietary flavonoids at baseline (Commenges et al. 2000). In an American population, drinking two or more cups of tea per day was associated with a reduced risk of Parkinson's disease, independently of smoking or coffee drinking (Macready et al. 2009). In Chinese adults aged 55 or over, tea (mainly black or oolong) consumption at baseline was clearly associated with lower cognitive impairment or decline 1–2 years later (Ng et al. 2008). Finally, in 70–74-year-old Norwegians, habitual intake of tea, wine, and chocolate (all of which are rich in flavonoids including catechins) was dose-dependently and additively associated with better cognitive performance (Nurk et al. 2009). Taken together, these findings support beneficial effects on brain function from habitual consumption of tea.

41.7 Conclusions

It is becoming increasingly clear that tea, the beverage made from infusions of leaves from *C. sinensis*, can have both physiological and psychological effects that may benefit health. Tea contains plant chemicals known as flavonoids that have antioxidant properties and have been shown to benefit indicators of cardiovascular health in laboratory studies measuring effects on inflammation and vascular function, and in clinical trials administering fixed doses of tea or tea extracts. Population-based studies also, on balance, support a positive relationship between tea drinking and cardiovascular health.

Laboratory studies suggest that tea and its components, especially catechins, can have effects on cellular processes that might reduce the risk of developing cancer. However, results from population-based studies have been inconsistent, and currently it is not possible to conclude that tea reliably reduces cancer risk.

There is some evidence that high doses of catechins from green tea may promote weight loss, potentially by stimulation of fat oxidation. In terms of psychological effects, tea can improve cognitive function acutely, and to some extent independently of its caffeine content. One reason may be due to effects on the brain of the amino acid, theanine, which has been shown to alter brain electrical activity. Theanine seems to improve relaxation and aspects of attention, without overstimulation. Possibly related, tea can also ameliorate physiological responses to stress and help poststress relaxation. This might explain population evidence that links tea drinking with resistance to depression.

Finally, laboratory and animal studies suggest that tea and its components, both flavonoids and theanine, can have neuroprotective effects, suggesting resistance to neurodegeneration. This possibility is further supported by prospective epidemiological evidence indicating that populations drinking tea regularly show slower declines in cognitive function, or less risk of dementia with aging, while cross-sectional studies have found a positive association between tea consumption and cognitive function in the elderly.

In conclusion, there have been a large number of scientific studies investigating physiological and psychological effects of drinking tea. Overall, a number of health benefits may arise from tea, but the strongest evidence is for cardiovascular and neurological health.

41.8 Applications to Other Areas of Health and Disease

Gardner et al. (2007) have recently reviewed areas of health that may be affected by drinking tea, in addition to those discussed before.

41.8.1 Dental Health

The tea plant naturally accumulates fluoride from the soil, and so drinking tea can contribute to the beneficial effect that fluoride can have on preventing or treating damage to teeth enamel caused by dental caries, for example. The high levels of catechins in green tea may also protect against caries by inhibiting growth of oral bacteria.

41.8.2 Bone Health

It has been suggested that compounds in tea including fluoride, phytoestrogens, and caffeine may influence bone mineral density, especially in older people. There is limited evidence that drinking four or more cups per day may increase bone mineral density, and reduce the risk of hip fractures, independently of whether milk is added – although adding milk clearly contributes a significant amount of calcium in regular drinkers.

41.8.3 Hydration

Although high doses of caffeine can be diuretic, i.e. stimulating the kidneys to increase secretion of water, eventually leading to dehydration, there is no evidence that such an effect occurs at the levels of caffeine normally drunk in tea. On the contrary, it has been demonstrated that tea has a beneficial effect on hydration.

41.8.4 Iron Status

Polyphenols in tea can inhibit the absorption of iron from non-heme sources (i.e., plants). This appears only to be of concern to those who may already be at risk from low iron status: in such cases, drinking tea should be avoided within 1 h of meals.

Summary Points

- From a health point of view, the key components of tea are likely the flavonoid group of chemicals, including catechins, such as EGCG (high in green tea), their metabolites the theaflavins and thearubins (high in black tea), and the flavonols, as well as the amino acid, theanine.
- The flavonoids have antioxidant, as well as other biochemical effects, and these reduce inflammation and improve blood vessel dilatation, which may lead to better cardiovascular health.
- Despite laboratory evidence suggestive of cancer preventive properties of tea components, findings from population-based studies have been inconsistent, so it is not clear whether chronic tea drinking reliably reduces cancer risk.
- Green tea catechins, at least at high doses, appear to aid weight loss in overweight people, probably by increasing oxidation of fat.
- Tea can relieve effects of stress, and help with poststress recovery, both physiologically and psychologically.

- Tea can benefit acute cognitive performance, possibly by the action of theanine in the brain, where it appears to aid relaxation but also improves some forms of attention.
- Tea may protect the brain against degeneration: tea components are neuroprotective in the laboratory, and tea drinking is associated with less dementia in the elderly.

Key Terms

Polyphenol antioxidants: A group of chemicals based on a polyphenolic substructure, widely available in fruits and vegetables. These compounds show strong antioxidant activity in laboratory tests, although the extent to which dietary sources reach target sites in sufficient concentrations is debated. They may benefit health by deactivating reactive oxygen species (free radicals), so reducing inflammation and cell damage.

Flavonoids: A subclass of polyphenol antioxidants, some of which are common in tea, especially the catechins (strictly, flavonols) such as EGCG.

Reactive oxygen species: Often called free radicals, these are small molecules that are highly reactive due to the presence of oxygen ions with unpaired (free) electrons. They are a normal byproduct of oxygen metabolism in cells, but if levels rise (a state known as oxidative stress), reactive oxygen species can damage cell structures including DNA.

Electroencephalography: Recording of brain surface electrical activity through electrodes placed around the scalp. The electrical potentials reflect the sum of activity of millions of neurones, and result in rhythmic activity (brain waves) with frequencies between 1 and 20 Hz; these are classified (in increasing frequencies) as delta, theta, alpha, beta, and gamma waves, reflecting different brain states.

Cortisol: A steroid hormone produced in the cortex (outer shell) of the adrenal glands, in response to activation of the hypothalamic–pituitary–adrenal–neuroendocrine axis. Cortisol levels in blood or saliva rise rapidly in response to psychological stress, although they also display an underlying circadian rhythm (high in the early morning and low in the evening).

References

Arab L, Liu W, Elashoff D. Stroke. 2009;40:1786–92.

Arts IC, Hollman PC, Feskens EJ, Bueno de Mesquita HB, Kromhout D. Am J Clin Nutr. 2001;74:227–32.

Astill C, Birch MR, Dacombe C, Humphrey PG, Martin PT. J Agric Food Chem. 2001;49:5340–7.

Bryan J. Nutr Rev. 2008;66:82–90.

Chang KC, Yang JJ, Wang-Hsu ECH, Chiu TH, Hsu FC. Neurosci Lett. 2009;452:141–5.

Commenges D, Scotet V, Renaud S, Jacqmin-Gadda H, Barberger-Gateau P, Dartigues JF. Eur J Epidemiol. 2000;16:357–63.

de Mejia EG, Ramirez-Mares MV, Puangpraphant S. Brain Behav Immun. 2009;23:721–31.

Dimpfel W, Kler A, Kriesl E, Lehnfeld R, Keplinger-Dimpfel IK. Nutr Neurosci. 2007;10:169–80.

Dulloo AG, Duret C, Rohrer D, Girardier L, Mensi N, Fathi M, Chantre P, Vandermander J. Am J Clin Nutr. 1999;70:1040–5.

Einöther SJL, Martens VEG, Rycroft JA, De Bruin EA. Appetite. 2010;54, 406–09.

Erdman JW Jr, Balentine D, Arab L, Beecher G, Dwyer JT, Folts J, Harnly J, Hollman P, Keen CL, Mazza G, Messina M, Scalbert A, Vita J, Williamson G, Burrowes J. J Nutr. 2007;137:718S–37S.

FDA Green Tea and Reduced Risk of Cancer Health Claim (Docket no. 2004Q-0083) Centre for Food Safety and Applied Nutrition. Silver Spring: US FDA, 2005.

Gardner EJ, Ruxton CH, Leeds AR. Eur J Clin Nutr. 2007;61:3–18.

Gomez-Ramirez M, Kelly SP, Montesi JL, Foxe JJ. Brain Topog. 2009;22:44–51.

Grassi D, Mulder TP, Draijer R, Desideri G, Molhuizen HO, Ferri C. J Hypertension 2009;27:774–81.

Haskell CF, Kennedy DO, Milne AL, Wesnes KA, Scholey AB. Biol Psychol. 2008;77:113–22.

Hindmarch I, Quinlan PT, Moore KL, Parkin C. Psychopharmacol. 1998;139:230–8.

Hindmarch I, Rigney U, Stanley N, Quinlan P, Rycroft J, Lane J. Psychopharmacol. 2000;149:203–16.

Hintikka J, Tolmunen T, Honkalampi K, Haatainen K, Koivumaa-Honkanen H, Tanskanen A, Viinamaki H. Eur J Epidemiol. 2005;20:359–63.

Hollman PCH, Feskens EJM, Katan MB. Proc Soc Exp Biol Med. 1999;220:198–202.

Hozawa A, Kuriyama S, Nakaya N, Ohmori-Matsuda K, Kakizaki M, Sone T, Nagai M, Sugawara Y, Nitta A, Tomata Y, Niu K, Tsuji I. Am J Clin Nutr. 2009;90:1390–6.

Hursel R, Viechtbauer W, Westerterp-Plantenga MS. Int J Obes. 2009;33:956–61.

Il Kim T, Lee YK, Park SG, Choi IS, Ban JO, Park HK, Nam SY, Yun YW, Han SB, Oh KW, Hong JT. Free Radic Biol Med. 2009;47:1601–10.

Kajimoto O, Kajimoto Y, Yabune M, Nakamura T, Kotani K, Suzuki Y, Nozawa A, Nagata K, Unno T, Sagesaka YM, Kakuda T, Yoshikawa T. J Health Sci. 2005;51:161–71.

Kimura K, Ozeki M, Juneja LR, Ohira H. Biol Psychol. 2007;74:39–45.

Kuriyama S, Hozawa A, Ohmori K, Shimazu T, Matsui T, Ebihara S, Awata S, Nagatomi R, Arai H, Tsuji I. Am J Clin Nutr. 2006;83:355–61.

Lakenbrink C, Lapczynski S, Maiwald B, Engelhardt UH. J Agric Food Chem. 2000;48:2848–52.

Lambert JD, Hong J, Yang GY, Liao J, Yang CS. Am J Clin Nutr. 2005;81:284s–91s.

Liu Q, Duan HY, Luan JL, Yagasaki K, Zhang GY. Cytotechnol. 2009;59:211–7.

Lorenz M, Urban J, Engelhardt U, Baumann G, Stangl K, Stangl V. Basic Res Cardiol. 2009;104:100–10.

Lu K, Gray MA, Oliver C, Liley DT, Harrison BJ, Bartholomeusz CF, Phan KL, Nathan PJ. Human Psychopharmacol Clin Exp. 2004;19:457–65.

Macready AL, Kennedy OB, Ellis JA, Williams CM, Spencer JP, Butler LT. Genes Nutr. 2009;4:227–42.

Nakachi K, Matsuyama S, Miyake S, Suganuma M, Imai K. Biofactors. 2000;13:49–54.

Nantz MP, Rowe CA, Bukowski JF, Percival SS. Nutrition. 2009;25:147–54.

Ng TP, Feng L, Niti M, Kua EH, Yap KB. Am J Clin Nutr. 2008;88:224–31.

Nobre AC, Rao A, Owen GN. Asia Pac J Clin Nutr. 2008;17(Suppl. 1):167–8.

Nurk E, Refsum H, Drevon CA, Tell GS, Nygaard HA, Engedal K, Smith AD. J Nutr. 2009;139:120–7.

Owen GN, Parnell H, De Bruin EA, Rycroft JA. Nutr Neurosci. 2008;11:193–8.

Pardo de Santayana M, Blanco E, Morales R. J Ethnopharmacol. 200598:1–19.

Ramadan G, El-Beih NM, El-Ghffar EAA. Br J Nutr. 2009;102:1611–9.

Rao DN, Ganesh B, Dinshaw KA, Mohandas KM. Int J Cancer. 2002;99:727–31.

Rogers PJ, Heatherley SV, Hayward RC, Seers HE, Hill J, Kane M. Psychopharmacol. 2005;179:742–52.

Rogers PJ, Smith JE, Heatherley SV, Pleydell-Pearce CW. Psychopharmacol. 2008;195:569–77.

Setiawan VW, Zhang ZF, Yu GP, Lu QY, Li YL, Lu ML, Wang MR, Guo CH, Yu SZ, Kurtz RC, Hsieh CC. Int J Cancer. 2001;92:600–4.

Simons CCJM, Hughes LAE, Arts ICW, Goldbohm RA, van den Brandt PA, Weijenberg MP. Int J Cancer 2009;125:2945–52.

Steptoe A, Gibson EL, Vuononvirta R, Hamer M, Wardle J, Rycroft JA, Martin JF, Erusalimsky JD. Atheroscler. 2007a;193:277–82.

Steptoe A, Gibson EL, Vuononvirta R, Williams ED, Hamer M, Rycroft JA, Erusalimsky JD, Wardle J. Psychopharmacol. 2007b;190:81–9.

Sun CL, Yuan JM, Lee MJ, Yang CS, Gao YT, Ross RK, Yu MC. Carcinogen. 2002;23:1497–503.

Tanabe N, Suzuki H, Aizawa Y, Seki N. Int J Epidemiol. 2008;37:1030–40.

Tsubono Y, Nishino Y, Komatsu S, Hsieh CC, Kanemura S, Tsuji I, Nakatsuka H, Fukao A, Satoh H, Hisamichi S. N Engl J Med. 2001;344:632–6.

Venables MC, Hulston CJ, Cox HR, Jeukendrup AE. Am J Clin Nutr. 2008;87:778–84.

Vignes M, Maurice T, Lante F, Nedjar M, Thethi K, Guiramand J, Recasens M. Brain Res. 2006;1110:102–15.

Vita JA. Am J Clin Nutr. 2005;81:292s–7s.

Wang H, Wen Y, Du Y, Yan X, Guo H, Rycroft JA, Boon N, Kovacs EM, Mela DJ. Obesity (Silver Spring). 2009a.

Wang L, Lee IM, Zhang SM, Blumberg JB, Buring JE, Sesso HD. Am J Clin Nutr. 2009b;89:905–12.

Weber P. Agro Food Ind Hi-Tech. 2004;15:20–2.

Chapter 42
Coffee and Its Effects on the Brain

Marcellino Monda, Giovanni Messina, Claudia Vicidomini, Andrea Viggiano,
Domenico Tafuri, Teresa Iannaccone, Sergio Chieffi, and Bruno De Luca

Abbreviations

fMRI   Functional magnetic resonance imaging
HRV   Heart rate variability
LF   Low frequency
HF   High frequency

42.1 Introduction

Caffeine is the most widely consumed drug in the world; it is found in foods such as coffee, tea, cocoa, and cola. In many countries, coffee is the beverage that the largest proportion of adults reports consuming over the day other than water. The first population that used coffee as a beverage in the history was in the highlands of Ethiopia and possibly also some populations in nearby highland areas of Sudan and Kenya. Anyway, coffee was effectively cultivated by Arabs since the fourteenth century and was introduced in the New World and in much of the rest of the tropics since the seventeenth century (Smith 1985). Today it is cultivated in many of the moist tropics and subtropic areas including Puerto Rico, the Virgin Islands, Guam, and Samoa (Burkill 1997).

The annual amount of coffee consumed per person is 8–12 kg in the Scandinavian Countries, 4.2 kg in USA, and 2.8 in UK, as reported in Fig. 42.1. A recent epidemiological study regarding beverage consumption of Canadian adults reports the consumption of coffee at different ages (Garriguet 2008): 50 years old or older men were more likely to report having had coffee rather than water; the exception to this trend toward coffee consumption was in 19- to 30-year-old people, who were more likely to report having had milk the previous day and also preferred soft drinks rather than coffee. Among those who drank coffee, consumption peaked at ages from 31 to 50, with an average annual intake of caffeine of 639 g for men and 586 g for women; by age 71 or older, this intake was considerably lower (489 and 398 g respectively). Coffee accounts for about 80.6% of the caffeine intake in adults, while tea and soft drinks account for 12.3% and 5.9%, respectively. Key fact of coffee influences on nervous system are reported in Table 42.1.

M. Monda (✉)
Department of Experimental Medicine, Section of Human Physiology, and Clinical Dietetic Service,
Second University of Naples, Via Costantinopoli 16, 80138 Naples, Italy
e-mail: marcellino.monda@unina2.it

CONSUMPTION OF COFFEE
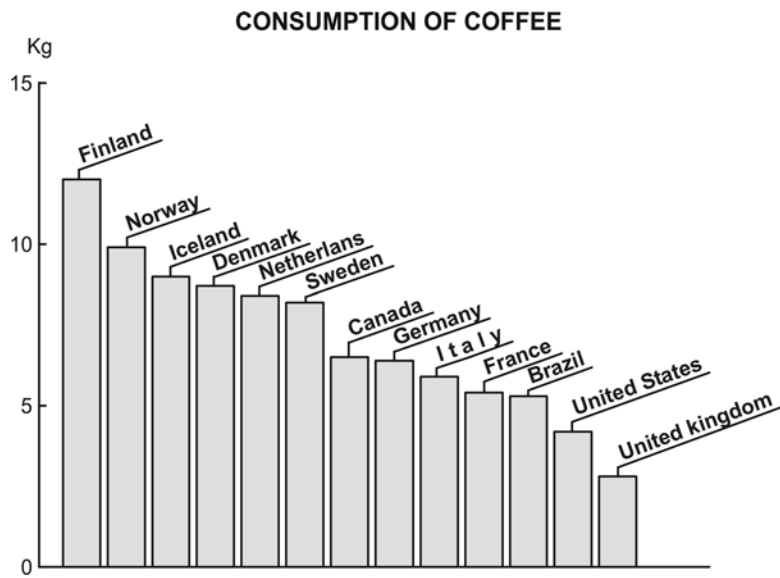
Fig. 42.1 Consumption of coffee. Annual consumption of coffee per capita. These data are referred to 2007, as reported by Euromonitor International

Table 42.1 Key facts of coffee influences on nervous system

1. The caffeine content of a cup of coffee ranges from 65 to 360 mg depending on the type of coffee and the type of preparation.
2. Coffee influences general sleep quality.
3. Coffee improves short-term memory and speeds up reaction times.
4. Coffee modifies the activity of the autonomic nervous system.
5. Coffee reduces the prevalence of some neurodegenerative diseases, including the Alzheimer's and the Parkinson's diseases.
6. Coffee can be considered a functional food.

This table lists the principal properties of coffee

This table indicates the neuro-vegetative modifications induced by subjects, which utilize coffee beverage

The caffeine content of a cup of coffee ranges from 65 to 360 mg, whereas the caffeine content of a cup of decaffeinated coffee is less than 10 mg, as reported in Table 42. 2. The main effects of caffeine include a variety of stimulatory effects on the central nervous system; caffeine increases respiratory rate, produces bronchodilatation, lipolysis, and diuresis. It can cause gastrointestinal disturbances, palpitations and, sometimes, even cardiac arrhythmias (Chou and Benowitz 1994; Mehta et al. 1997). It has been suggested that caffeine may be potentially hypertensive (Nurminen et al. 1999). Caffeine is a natural alkaloid, methylxanthine. About 99% is absorbed after oral ingestion, the blood concentration peaks 1–1.5 h after the ingestion, and its half-life in adults is 3–6 h. Caffeine is metabolized by the cytochrome P450 hepatic enzyme system (Monda et al. 2009).

Caffeine is the most widely consumed central nervous system stimulant. Three main mechanisms of action of caffeine on the central nervous system have been described. Mobilization of intracellular calcium and inhibition of specific phosphodiesterases only occur at high, unusual, concentrations of caffeine. The most likely mechanism of action of methylxanthine is the antagonism of adenosine receptors. Caffeine increases energy metabolism throughout the brain but at the same time decreases cerebral blood flow, inducing a relative brain hypoperfusion. Caffeine activates noradrenaline neurons and seems to affect the local release of dopamine. Many of the alerting effects of caffeine may be related to the action of methylxanthine on serotonin neurons. Methylxanthine induces dose–response

Table 42.2 Caffeine content of coffee drinks

Type	Volume (mL)	mg of caffeine
Starbucks Grande Coffee	500	330–360
Drip	250	115–175
Brewed	250	80–135
Instant	250	65–100
Brewed decaffeinated	250	4–5
Espresso	50	70–100

The caffeine content of a cup of coffee ranges from 65 to 360 mg, while the caffeine content of a cup of decaffeinated coffee is less than 10 mg, as reported by US Food and Drug Administration

increases in locomotor activity in animals. Its psychostimulant action on man is, however, often subtle and not very easy to detect. The effects of caffeine on learning, memory, performance, and coordination are mainly related to methylxanthine actions on arousal, vigilance, and fatigue. Caffeine exerts evident effects on anxiety and sleep which vary according to individual sensitivity, and children, in general, do not appear to be more sensitive than adults. The central nervous system does not seem to develop a great tolerance to the effects of caffeine although dependence and withdrawal symptoms have been reported (Nehlig et al. 1992).

42.2 Effects on Sleep

Caffeine is a widely used stimulant with marked variability in the behavioral response between individuals. Positive behavioral responses may include increased alertness and physical activity, although these may represent a withdrawal reversal mechanism operating in habitual caffeine users (James and Gregg 2004; Roger et al. 2003; Yeomans et al. 2002), whereas responses such as heightened nervousness and sleep disturbance would be considered negative (Hughes et al. 1991; Heath et al. 1998). Some people experience no effects whatsoever of caffeine ingestion. Significant individual differences in the extent of wakefulness (i.e., delay of sleep onset) and soundness of sleep due to caffeine have been observed in subjects who were blind to placebo or caffeine administration 1 h prior to bedtime (Goldstein et al. 1965).

Luciano et al. (2007) have reported that individual differences in coffee-attributed sleep disturbances depend on additive genetic and environmental factors, and that these factors were distinct from those influencing general sleep quality and dimensions such as anxiety and depression. Interestingly, the chromosomal region 2q is significantly correlated to coffee-attributed insomnia in both sexes; other regions of interest, but falling short of the significant criterion, are on regions 17q, 5q, 10q, 13q, and 6p.

Sin et al. (2009) have recently reported a systematic review about the effectiveness of caffeine abstinence on the quality of sleep. The authors browsed several electronic databases and reference lists of articles regarding the correlation between caffeine consumption and sleep deprivation. They selected the articles according to predefined inclusion and exclusion criteria. Two reviewers assessed the quality of trials, which were selected according to the Jadad quality assessment scale, and they included those trials scoring 3 or above; three randomized control trials fulfilled the selection criteria among which two trials scored at least 3 on the Jadad scale, so they included these two trials in the systematic review. The design and outcome measurements of these two trials were not homogeneous, so they did not combine the results but they conducted a critical appraisal. In one trial, caffeine abstinence was associated with significant lengthening of sleep duration and better sleep quality; in the other trial, subjects had less difficulty falling asleep when they drank decaffeinated coffee. This result showed

that caffeine abstinence for a whole day could improve sleep quality, so health practitioners are recommended to include caffeine abstinence in the instructions for sleep hygiene.

42.3 Effects on Memory

Coffee improves short-term memory and speeds up reaction times by acting on the brain prefrontal cortex, according to a recent study by Koppelstaetter et al. (2008), in which functional magnetic resonance imaging (fMRI) was used to determine what areas of the brain were activated by coffee. Prior to testing, the group under examination fasted for 4–6 h and abstained from caffeine and nicotine for at least 24 h. They were then given either a cup of coffee (containing 100 mg of caffeine) or a caffeine-free placebo drink. After 20 min all participants underwent fMRI scans while carrying out a memory and concentration test. Few days later, the experiment was repeated under the same conditions but each subject received the other drink. During the memory tests, a fast sequence of capital letters was shown to the participants; a single letter was then flashed on screen and subjects had to quickly decide whether this letter was the same one which appeared second-to-last in the earlier sequence. They had to respond by pressing a "Y" for yes or "N" for no. All subjects showed an activation of the working memory part of the brain, but those who received caffeine had a significantly greater activation in parts of the prefrontal lobe, particularly the anterior cingulate gyrus. These areas are involved in "executive memory," attention, concentration, planning, and monitoring. This type of memory is used when, for example, you look up a phone number in a book and then mentally store it before dialing. These results suggest that caffeine modulates neuronal activity in those brain areas associated with executive and attentive functions during a working memory task.

42.4 Effects on Anticipatory Processes

Tieges et al. (2006) studied the effects of moderate amounts of caffeine on task maintenance or task switching, using single-task blocks (AAAA, BBBB) or mixed-task blocks (AABB), in which participants were switched predictably between two tasks; in these experiments, switch cost was the longer reaction times on task-switch trials (e.g., AB) compared to task-repeat trials (e.g., BB), while mixing cost was the longer reaction times in task-repeat trials compared to single-task trials. In a double-blind, within-subjects experiment, two caffeine doses (3 and 5 mg/kg body weight) or a placebo were administered to 18 coffee drinkers; both caffeine doses reduced switch costs compared to placebo. Event-related brain potentials revealed a negative deflection developing within the preparatory interval, which was larger for switch than for repeat trials; caffeine also increased this switch-related difference. These results suggest that coffee consumption enhances task-switching performance by enhancing anticipatory processing such as task set updating, presumably through the neurochemical effects of caffeine on the dopaminergic system.

42.5 Effects on Degenerative Brain Diseases

Alzheimer's disease is a common problem in occidental elderly population. Although research is leading to improvements in our understanding of the underlying biology, we still have little understanding of

the environmental risk factors associated with this disorder. Caffeine, an easily modifiable environmental factor, may have a protective effect on the likelihood of developing Alzheimer's disease. Although epidemiological studies reported that a regular consumption of coffee seemed to be protective for Alzheimer's disease in Canadian people (Lindsay et al. 2002), further investigations are needed to determine whether caffeine consumption could have a major affect on the development of Alzheimer's disease or on age-related cognitive decline (Rosso et al. 2008).

The results of case-control studies and of prospective investigations in men suggest that the consumption of coffee could also protect against the risk of Parkinson's disease, although the effective constituent of coffee for this effect is not clear. To address the hypothesis that caffeine is protective against Parkinson's disease, Ascherio et al. (2001) examined the correlation between the risk of this disease and coffee or caffeine consumption among participants in two ongoing cohorts: the Health Professionals' Follow-Up Study and the Nurses' Health Study. This study population comprised 47,351 men and 88,565 women who were free of Parkinson's disease, stroke, or cancer at baseline. A comprehensive life style and dietary questionnaire was completed by the participants at baseline and updated every 2–4 years. During the follow-up (10 years for men, 16 years for women), a total of 288 new cases of Parkinson's disease was documented. After adjustment for age and smoking, the relative risk of Parkinson's disease for men in the top one-fifth of caffeine intake compared with those in the bottom one-fifth was 0.42 (95% CI: 0.23–0.78; p for trend < 0.001). An inverse correlation was also observed with coffee consumption (p for trend = 0.004), with caffeine intake from noncoffee sources (p for trend < 0.001), and with tea consumption (p for trend = 0.02) but not with decaffeinated coffee consumption. Among women, the relationship between caffeine or coffee intake and the risk of Parkinson's disease was U-shaped, with the lowest risk observed at moderate intakes (1–3 cups of coffee/day). The correlation between caffeine intake and the risk of Parkinson's disease was similarly observed in both fast and slow caffeine metabolizers, in agreement with evidences from animal models showing that both caffeine and its major metabolite, paraxanthine, are neuroprotective (Tan et al. 2007). These data support a possible protective effect of moderate doses of caffeine on the risk of Parkinson's disease.

42.6 Effects on the Autonomic Nervous System

Espresso is the main type of coffee drink in most of southern Europe. It is also popular throughout much of the rest of Europe and in Argentina, Brazil, Cuba, and in the urban centers of North America, Australia, and New Zealand. Espresso is a coffee beverage brewed by forcing steam or very hot water under high pressure through finely ground, darkly roasted coffee beans. Monda et al. (2009) have studied the effects of coffee on the autonomic nervous system in young, healthy people. This study analyzed the effect of a cup of espresso coffee on the power spectral analysis of the heart rate variability (HRV), which is a method to evaluate the activity of the sympathetic and parasympathetic nervous system. In young, healthy, sedentary subjects, the HRV-power spectrum was evaluated over a period of 5 min before and 150 min after the administration of espresso coffee (75 mg of caffeine) or decaffeinated coffee (<10 mg of caffeine) in the supine or in the seated position. The absolute values of the spectrum were summed in the low (LF) and high frequencies (HF). The LF and HF values were used to estimate the sympathetic and parasympathetic activity, respectively. In the supine position, coffee increased HF, while decaffeinated coffee caused little modifications of HF (Fig. 42.2). In the seated position, HF was not modified by coffee or decaffeinated coffee. Coffee and decaffeinated coffee did not induce any modification of LF in both positions (Fig. 42.3). This experiment demonstrated that espresso coffee influences the parasympathetic activity in the supine position, underlining the effects of coffee on the activity of the autonomic nervous system.

Fig. 42.2 High frequency
power. High frequency power
in supine or seated subjects
after administration of a cup
of espresso coffee or
decaffeinated coffee at time 0.
The high frequency is an
index of the parasympathetic
activity. The asterisk
indicates statistical difference
($P < 0.05$) between coffee
group and decaffeinated
group in supine position
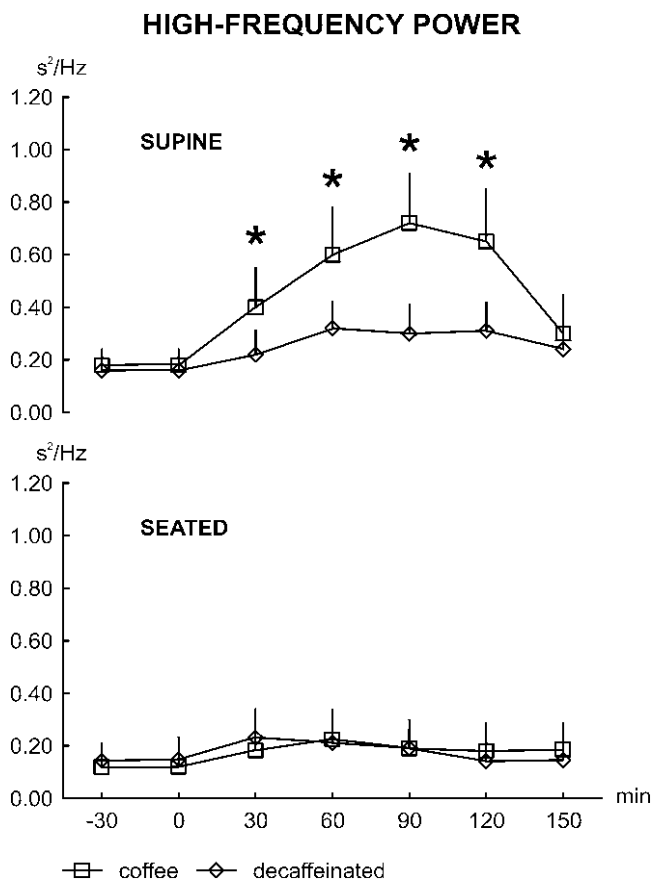
Corti et al. (2002) demonstrated that coffee induces comparable increases in sympathetic activity and blood pressure in nonhabitual coffee drinkers, whereas habitual coffee drinkers exhibited lack of blood pressure increase despite sympathetic activation due to coffee. Because in that experiment decaffeinated coffee also increased blood pressure and sympathetic activity in nonhabitual drinkers, ingredients other than caffeine could be responsible for the cardiovascular activation.

Anyway, the restriction of coffee or caffeinated beverages is no longer indicated in the seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) guidelines for the treatment of hypertension. In fact, no clear association between coffee and the risk of hypertension, myocardial infarction, or other cardiovascular diseases has been demonstrated. In contrast to early studies, recent research indicates that habitual, moderate coffee intake does not represent a health hazard (Sudano et al. 2005).

42.7 General Considerations

Dórea and da Costa (2005) reported the association between coffee-drinking and health benefits that support the concept of coffee as a functional food; definitions of functional foods vary but are essentially based on foods' ability to give some positive effects of the quality of life, or physical and mental performance, of regular consumers. The worldwide use of coffee for social engagement, leisure, enhancement of work performance, and well-being is widely recognized. Depending on the

Fig. 42.3 Low frequency power. Low frequency power in supine or seated subjects after administration of a cup of espresso coffee or decaffeinated coffee at time 0. The low frequency is an index of the sympathetic activity. No statistical difference was noted between coffee groups and decaffeinated groups
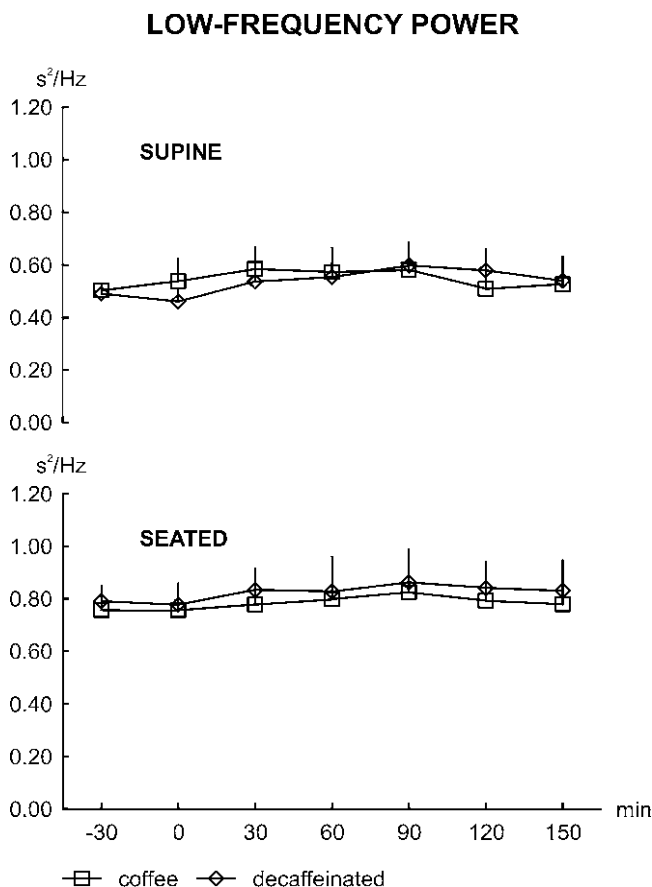
quantities consumed, it can affect the intake of some minerals (K, Mg, Mn, Cr), niacin, and antioxidant substances. Epidemiological and experimental studies have shown positive effects of regular coffee-drinking on various aspects of health, such as psychoactive responses (alertness, mood change), neurological (infant hyperactivity, Alzheimer's and Parkinson's diseases) and metabolic disorders (diabetes, gallstones, liver cirrhosis), and gonad and liver function. Anyway, most reviews do not mention coffee as fulfilling the criteria for a functional food. Unlike other functional foods that act on a defined population with a special effect, the wide use of coffee-drinking impacts a broad demographic (from children to the elderly), with a wide spectrum of effects.

42.8 Applications to Other Areas of Health and Disease

The influences of coffee consumption on the functions of the peripheral and the central nervous system can also influence the mechanisms of the diseases affecting other systems, including the cardiovascular system, the renal system or the gastro-intestinal system. Thus, further investigations are needed to better clarify when and to what extent a greater or a reduced coffee intake can have preventive effects or can ameliorate the symptoms or the evolution of specific pathologies. The modifications due to coffee consumption on biological functions should obviously be extended also to the many other caffeine-containing foods and soft drinks.

Key Terms

Coffee: Brewed beverage prepared from roasted seeds of the coffee plant, commonly called coffee beans. Today, coffee is one of the most popular beverages worldwide.

Caffeine: Bitter, white crystalline xanthine alkaloid that is a psychoactive stimulant drug. Caffeine was discovered by a German chemist, Friedrich Ferdinand Runge, in 1819.

Sleep disturbance: Modification of normal pattern of sleep due to different possible causes, including the use of psychoactive substances, such as caffeine.

Memory systems: These include working memory, explicit long-term memory, and implicit long-term memory; they are stimulated by coffee consumption.

Neurodegenerative diseases: Progressive dysfunction and death of neuronal cells in selected areas in the nervous system, leading to alterations of some of the brain functions; the Alzheimer's and the Parkinson's diseases are two of the most important neurodegenerative diseases.

Autonomic nervous system: This comprises the sympathetic nervous system and the parasympathetic nervous system. It is part of the nervous system responsible for the control of involuntary muscles, e.g. heart and other viscera such as bladder, bowels, and so on, meaning that it regulates body functions that are not consciously directed.

References

Ascherio A, Zhang SM, Hernán MA, Kawachi I, Colditz GA, Speizer FE, Willett WC. Ann Neurol. 2001;50:56–63.

Burkill HM. (1997). The useful plants of West Tropical Africa. Kew, UK: Royal Botanic Gardens.

Chou TM, Benowitz NL. Comp Biochem Physiol. 1994;109:173–89.

Corti R, Binggeli C, Sudano I, Spieker L, Hänseler E, Ruschitzka F, Chaplin WF, Lüscher TF, Noll G. Circulation. 2002;106:2935–40.

Dórea JG, da Costa TH. Br J Nutr. 2005;93:773–82.

Garriguet D. (2008) Beverage consumption of Canadian adults. Health Reports, Canada.

Goldstein A, Warren R, Kaizer S. J Pharmacol Exp Ther. 1965;149:156–9.

Heath AC, Eaves LJ, Kirk KM, Martin NG. Twin Res. 1998;1:176–88.

Hughes JR, Higgins ST, Bickel WK. Arch Gen Psychiatry. 1991;48:611–7.

James JE, Gregg ME. Hum Psychopharmacol. 2004;19:333–41.

Koppelstaetter F, Poeppel TD, Siedentopf CM, Ischebeck A, Verius M, Haala I, Mottaghy FM, Rhomberg P, Golaszewski S, Gotwald T, Lorenz IH, Kolbitsch C, Felber S, Krause BJ. Neuroimage. 2008;39:492–9.

Lindsay J, Laurin D, Verreault R, Hébert R, Helliwell B, Hill GB, McDowell I. Am J Epidemiol. 2002;156:445–53.

Luciano M, Zhu G, Kirk KM, Gordon SD, Heath AC, Montgomery GW, Martin NG. Sleep. 2007;30:1378–86.

Mehta A, Jain AC, Mehta MC, Billie M. Acta Cardiol. 1997;52:273–83.

Monda M, Viggiano A, Vicidomini C, Viggiano A, Iannaccone T, Tafuri D, De Luca B. Nutr Neurosci. 2009;12:43–8.

Nehlig A, Daval JL, Debry G. Brain Res Brain Res Rev. 1992;17:139–70.

Nurminen ML, Niittynen L, Korpela R, Vapaatalo H. Eur J Clin Nutr. 1999;55:831–9.

Rogers PJ, Martin J, Smith C, Heatherley SV, Smit HJ. Psychopharmacology. 2003;167:54–62.

Rosso A, Mossey J, Lippa CF. Am J Alzheimers Dis Other Demen. 2008;23:417–22.

Sin CW, Ho JS, Chung JW. J Clin Nurs. 2009;18:13–21.

Smith, RF. In: Clifford MN, Willson KC, editors. Coffee: botany, biochemistry, and production of beans and beverage. Westport, CN: AVI Publishing Company; 1985. p. 83–103.

Sudano I, Binggeli C, Spieker L, Lüscher TF, Ruschitzka F, Noll G, Corti R. Prog Cardiovasc Nurs. 2005;20:65–9.

Tan EK, Chua E, Fook-Chong SM, Teo YY, Yuen Y, Tan L, Zhao Y. Pharmacogenet Genomics. 2007;17:1001–5.

Tieges Z, Snel J, Kok A, Wijnen JG, Lorist MM, Richard Ridderinkhof K. Biol Psychol. 2006;73:101–13.

Yeomans MR, Ripley R, Davies LH, Rusted JM, Rogers PJ. Psychopharmacology. 2002;164:241–9.

Chapter 43
Selective Attention as a Mediator Between Food Motivation and Disposition to Act

Jaime A. Pineda and David S. Leland

Abbreviations

ERP	Event-related potential
fMRI	Functional magnetic resonance imaging
IFG	Inferior frontal gyrus
IPL	Inferior parietal lobule
LC	Locus coeruleus
MNS	Mirror neuron system
NA	Nucleus accumbens
OFC	Orbitofrontal cortex
PF	Parietal frontal
PFC	Prefrontal cortex
PMv	Premotor ventral
PPC	Posterior parietal cortex
PWS	Prader-Willi syndrome
RT	Reaction time
SMA	Supplementary motor area
STS	Superior temporal sulcus
VTA	Ventral tegmental area

43.1 Introduction

Food is a primary motivator of behavior. It is a fundamental physiological requirement for all animals and, in humans and other social species, central to a host of social interactions, such as hunting, foraging, shared meals, and trade, which can yield other tangible and social rewards. In order to successfully acquire food, one must make effective use of relevant cues, for example colors indicating ripe fruit. This is complicated, however, by the fact that the physical and social environments offer a near-limitless supply of information, only some of which is useful to the pursuit of food. This over-abundance of information, coupled with limitations on time and neural resources, provided evolutionary pressure for brain mechanisms enabling selective attention toward motivationally salient

D.S. Leland (✉)
Department of Psychology, University of Wisconsin - Eau Claire, 105 Garfield Ave, Eau Claire, WI 54702, USA
e-mail: lelandds@uwec.edu
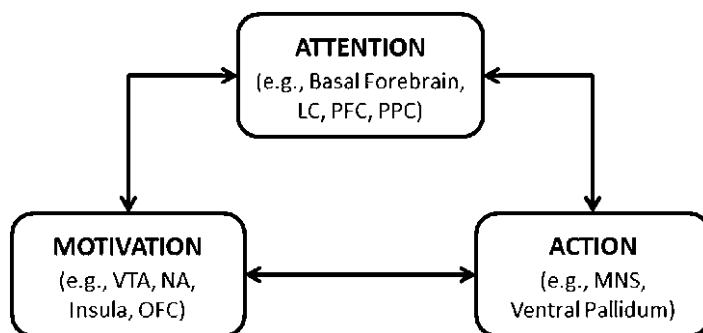
Fig. 43.1 Attention as mediator between motivation and action. Brain regions that attribute motivational salience to incentive stimuli can trigger action through relatively direct connections but also via their influence on attentional networks, allowing more flexibility and control over behavior. Movement and attention toward these appetitive stimuli also can have reciprocal effects, increasing motivational salience by facilitating the sensory and evaluative processes that identify and empower them as incentives. *LC* locus coeruleus, *MNS* mirror neuron system, *NA* nucleus accumbens, *OFC* orbitofrontal cortex, *PFC* prefrontal cortex, *PPC* posterior parietal cortex, *VTA* ventral tegmental area

information. That is, there is a bias toward enhanced processing of goal-related information at the expense of other information. Attentional biases toward food-related stimuli afford them preferential access to perceptual and cognitive resources, prioritizing learning and decision-making related to food and facilitating action to acquire and consume food. This chapter explores the psychological and neural underpinnings of selective attention toward food-related stimuli in the context of its mediation between motivation and action (Fig. 43.1), providing a framework for understanding the multidimensional factors that contribute to normal and disordered eating.

43.2 Motivation

43.2.1 Subcortical Mechanisms

Motivation is the goal-oriented force in behavior, contributing to its initiation, direction, intensity, and persistence in the face of obstacles. Motivation to seek and consume food arises in part from internal cues generated by homeostatic processes that monitor and regulate nutritional status and immediate energy needs. A significant amount of motivation-related neural circuitry lies below the cerebral cortex. The hypothalamus, in particular, is an important region for regulating neural and endocrine systems. Discrete nuclei of the hypothalamus play significant roles in the control of homeostatic signals relating to eating, drinking, and temperature regulation (Garcia-Segura et al. 2008). Electrical stimulation of these areas leads to an enhancement or inhibition of the corresponding behavior, while lesions produce the opposite results. The hypothalamus and related structures regulate homeostatic processes using chemical signals in the form of neurotransmitters, neuromodulators, and neurohormones.

External cues are another major influence on food motivation, and they, too, exert their influence through chemical signaling (see Table 43.1). The mesolimbic dopamine pathway is a key neurotransmitter circuit for motivation that responds to food and food-related cues. It originates in the ventral tegmental area (VTA) of the midbrain and projects to the nucleus accumbens (NA) of the striatum and other forebrain limbic targets. This neural system is important not only for food motivation but

Table 43.1 Major neurotransmitters and their roles in food-related behavior

Neurotransmitter	Roles in food-related behavior
Glutamate	Food-cue association learning
GABA	Disinhibition of circuits for food-directed attention and action
Acetylcholine	Attention to food stimuli; control of muscles for eating
Dopamine	Food-related reinforcement, cognition, and movement
Norepinephrine	Food-related arousal and attention
Serotonin	Appetite and food-related mood effects

Listed in this table are six of the central nervous system's major neurotransmitters. Each has a wide variety of functions, some of which pertain to appetite, food acquisition, and eating as indicated

for other conditioned and unconditioned reinforcers, including sex, addictive drugs, and money. As a natural (unconditioned) reinforcer, food generally increases the probability of behaviors that lead to its acquisition and consumption. Through associative learning, stimuli associated with food can become conditioned reinforcers in their own right.

Positive reinforcers are commonly referred to as "rewards," and because rewards of various kinds cause a release of dopamine in the NA, many researchers once concluded that dopamine serves as a common denominator for pleasure in the brain. This hedonic theory of mesolimbic dopamine has been challenged over the past several years and is being replaced by a set of theories focusing on cognition and disposition to act rather than subjective feelings, as a way to more specifically account for how dopamine activity contributes to goal-directed behavior (Schultz 2006; Salamone et al. 2007; Berridge 2009). The evidence for this new perspective comes in large part from studies of food motivation. For instance, when mesolimbic dopamine function is compromised by lesions or dopamine blockers, animals still prefer and will seek larger food rewards if they do not require substantially more effort to obtain than smaller ones (Salamone et al. 2007), and will still produce hedonic facial expressions when force-fed sweet solutions, even when they will not work to obtain them (Berridge 2009). Berridge has argued that there are distinct but functionally integrated circuits mediating food "liking" (hedonia) and "wanting" (incentive salience), with mesolimbic dopamine more closely (but not exclusively) tied to the latter. Furthermore, VTA dopamine neurons have been observed to shift their response from presentation of actual food rewards to presentation of the cues that predict them over the course of instrumental learning (Schultz 2006). Computational modeling and empirical findings suggest that VTA neurons signal a violation of reward expectancy and are important in learning to predict rewards on the basis of associated cues.

43.2.2 Cortical Mechanisms

Food-related cues, both environmental and social, along with affective states, also contribute to appetitive behavior. While subcortical circuits account for basic aspects of food motivation and are relatively well-conserved across species, mammals in general and primates especially have cortical mechanisms that allow for more complex motivations. Examples of this include flexible and relative preferences between food alternatives, inhibition of appetitive urges, and social facilitation of eating. These more recently evolved mechanisms have not replaced the subcortical ones, but are anatomically and functionally integrated with them, such that subcortical circuits serve as a foundation while cortical elements allow for an expanded repertoire of motivations, behaviors, and subjective experiences.

Wang et al. (2004) showed that at least two cortical regions in particular, the insula and orbitofrontal cortex (OFC), appear to play such a role and are critically involved in processing food-related stimuli and influencing the appetitive behavior of humans.

The insula represents certain sensory qualities of food such as taste and texture (exteroceptive cues; Rolls 2006). It is especially important, however, for the sensation of internal physiological states such as hunger (interoceptive cues) and appears to play a role in conscious awareness of these states (Craig 2003). The insula receives inputs from areas that include the amygdala, somatosensory cortex, and various thalamic nuclei. The OFC receives projections from the insula as well as the amygdala, eating-related subcortical nuclei (e.g., lateral hypothalamus), and multimodal sensory regions (Rolls 2006). Functional neuroimaging in humans shows that visual stimuli associated with the taste of glucose and pictures of foods, as compared to pictures of locations, activate the OFC and some interconnected areas (Simmons et al. 2005). OFC activity is not related directly to the primary stimulus properties of food; it instead shows highly flexible responses reflecting context-specific motivational and affective value. For instance, monkey OFC neurons that initially respond to multiple foods will reduce their response to those that have been consumed to satiation but not to others, suggesting a neural basis for food-specific satiety (Rolls 2006). The OFC also contains a number of neurons that respond to reward-predicting stimuli in a manner similar to that of dopamine neurons in the VTA (Schultz 2006).

The insula and OFC can be thought of as limbic-related cortices, given their functional roles and dense interconnections with limbic structures such as the amygdala, which influences behavior by linking sensory properties of a stimulus with its incentive value. All of these regions carry out their reward functions in conjunction with the dopamine system, including its sources (VTA and substantia nigra) and target structures (e.g., striatum, anterior cingulate cortex). Together, this circuitry allows for the evaluation of context-specific relative reward value and for the learning and prediction of reward contingencies.

The effect of motivation on disposition to act is mediated in part by subcortical efferent connections from the NA to the ventral pallidum and hypothalamus, which in turn can trigger overt eating behavior. Likewise, the OFC is important for preparation of more complex motor action via its connections to regions such as premotor cortex, which is involved in the simulation of action (Cavada et al. 2000). Motivated behaviors are, however, distinct from reflexive ones in that they do not involve fixed, obligatory motor patterns. Rather, goal-directed behavior is adaptive to changing internal and external conditions, and as such requires cognitive processes to provide flexibility of approach. Selective attention is one of the key components of the cognitive apparatus that provides such flexibility and that is recruited in the pursuit of food and other goals.

43.3 Selective Attention

43.3.1 Theories of Selective Attention

Selective attention (see Table 43.2) is one of the most studied topics in cognitive neuroscience. One traditional view of attention is as a unitary, supramodal mechanism subserved by anatomical circuits distinct from those involved in information processing (Posner and Petersen 1990). Posner and colleagues (Posner and Dehaene 1994; Posner and Rothbart 2007) have proposed a modern version of this idea by suggesting a triarchic model consisting of orienting, alerting, and executive attention subsystems. The orienting or posterior system appears to subserve spatial attention with or without

Table 43.2 Key features of selective attention

1. Selective attention is a process by which certain information receives increased cognitive processing at the expense of other information
2. Attention helps guide the sensory organs (orienting), increase the perceived intensity of stimuli (alerting), organize and control the flow of information (executive attention), and prepare the body for action (premotor attention)
3. The triarchic model of attention focuses on brain structures thought to produce attention-specific effects that are separate from other information processing
4. The premotor theory suggests that attention is the result of brain activity for sensory and motor processing that is under inhibition to prevent action until that inhibition is released
5. Attention can be directed to regions of space (spatial attention) even without movement of the sensory organs, making it possible to isolate and study attention effects (e.g., by having subjects keep their eyes fixated at one location while they pay attention for events at others)
6. Tools such as functional magnetic resonance imaging (fMRI) and event-related potentials (ERPs) can be used to detect the neural processes underlying attention
7. Behavioral studies, brain imaging, and neuroanatomy indicate that selective attention is controlled in part by motivational processes, consistent with its role in facilitating goal-directed behavior

This table lists key facts about selective attention, including some of its theories, purposes, and means of investigation

movement of the eyes toward attended stimuli, and is associated primarily with areas in the superior parietal cortex, temporal–parietal junction, frontal eye fields, and superior colliculi. The alerting system involves the noradrenergic-locus coeruleus (LC) system and the right frontal as well as parietal cortices. Finally, the executive or anterior attentional system appears to be involved in attentional recruitment and control of brain areas in order to perform complex cognitive tasks. This anterior system primarily involves the anterior cingulate, lateral ventral prefrontal cortex (PFC), and basal ganglia. Although consistent with a great deal of observations, the existence of such unique and anatomically circumscribed neural systems devoted specifically to attention has been criticized (Corbetta and Shulman 2002). One alternative that is potentially more consistent with the disposition to act as presented in this chapter is the premotor theory of attention. In this perspective, attention derives from activation of the same circuits that process sensory and motor information. For example, selective attention for spatial locations would result from the activity of circuits involved in the computations necessary for eye movement, arm reaching movements, walking, and other motor activities (Eimer et al. 2005), while selective attention for object recognition would derive from activity in cortical areas responsible for object property processing (Duncan and Nimmo-Smith 1996). According to this view of attention, the difference between selective spatial attention and overt actions directed toward a target in space is that in both cases a motor plan is prepared but only in the latter case is that plan executed.

Evidence in favor of the premotor theory of attention derives primarily from findings that some parietal and frontal cortical areas appear to incorporate and share systems for spatial representation, action control, and attention (Graziano and Gross 1998). Damage to these areas can produce inattention (neglect) to particular regions of space and deficits in movement directed toward those regions of space, as well as motor deficits for effectors (e.g., the hand) represented in the damaged areas. The cortical areas that program spatially specific movements are influenced by other cortical areas (e.g., presupplementary motor area or pre-SMA) and by subcortical centers (e.g., basal ganglia). These centers are thought to exert inhibitory control that, when released, allows movement to occur. Without such a release, the portion of the spatial map activated by the intended movement nonetheless gains a selective attention advantage over other locations for information-processing resources (Rizzolatti et al. 1987).

43.3.2 Attention to Motivational Targets

Selective attention toward motivationally salient stimuli may result as a natural consequence of the mesolimbic dopamine activity associated with them. "Wanted" stimuli are those that acquire incentive salience, becoming "attractive" and "attention-grabbing" (Berridge 2009, p. 538), which helps them compete with other stimuli for cognitive processing and the triggering of action. VTA neurons increase their baseline firing in response to the earliest unexpected reward or cue predictive of reward (Schultz 2006), suggesting that these cues may garner selective attention as the animal learns reward associations and prepares for action. One way this may occur is through disinhibition of basal forebrain cholinergic neurons, which potentiate sensory cortex activity and may underlie attention shifts and motor preparation in the PFC (Parikh et al. 2007) and posterior parietal cortex (PPC; Reep and Corwin 2009). These cholinergic neurons are under inhibitory control by GABAergic neurons in the NA, which in turn are inhibited by dopaminergic VTA neurons. Thus, disinhibition of basal forebrain cholinergic activity by mesolimbic dopamine may constitute a neural substrate for the preferential allocation of attentional resources toward motivationally salient stimuli such as food cues.

43.3.3 Attention to Food Stimuli

Selective attention toward food-related stimuli has been demonstrated behaviorally in humans, primarily using modified Stroop and spatial attention paradigms (see "Features of Selective Attention Tasks" at the end of this chapter). A Stroop bias toward food-related words has been demonstrated in subjects with normal eating patterns following food deprivation (Channon and Hayward 1990; Formea and Burns 1996; Francis et al. 1997; Braet and Crombez 2003) and in some cases even without (Lavy and Vandenhout 1993; Overduin et al. 1995). A spatial attentional bias toward the location of food stimuli has been shown as well in normal subjects who are especially hungry (Mogg et al. 1998) or have fasted (Placanica et al. 2002), and again in some cases whether or not subjects fasted (Leland and Pineda 2006). Most food attentional bias studies have focused on groups with eating disorders and dietary restraint. Dobson and Dozois (2004) conducted a meta-analysis of modified Stroop studies and concluded that bulimics but not anorexics or dieters exhibit a greater food word Stroop effect than controls (although both bulimics and anorexics did demonstrate a larger Stroop effect for words related to weight and body image). One spatial attention task has demonstrated bias toward food images that is greater in those with eating disorders (Shafran et al. 2007), while another found, in a nonclinical sample, greater bias among those who report that external cues (e.g., food stimuli) have a particularly large influence on their motivation to eat (Brignell et al. 2009).

Mohanty et al. (2008) used functional magnetic resonance imaging (fMRI) in their study of food-related attentional bias. In hungry but not satiated subjects, cues predicting the location of food image targets activated the amygdala, posterior cingulate, LC, and substantia nigra more than did cues predicting the location of nonfood (tool image) targets. PPC and OFC activations, meanwhile, were correlated with speed of attentional shifts. This study grouped food image trials and tool image trials into separate blocks, which can produce carry-over effects from trial to trial within each block. Thus, the food block effects could be due to general arousal as opposed to selective spatial attention, but the results are consistent with expected spatial attention effects, particularly in the PPC, given its association with visuospatial processing.

   The finding of increased activation in the LC is of particular interest as that area, the primary source of norepinephrine signals in the central nervous system, projects to limbic and cortical structures and appears to mediate attention effects indexed by the P3 component of the electrophysiological event-related potential (ERP; Foote et al. 1991). Various factors influence the amplitude and latency of the P3, including attentional focus. Kok (2001) has suggested that the P3 reflects allocation of attentional resources in the categorization of important events. In our study of food words as cues in a spatial attention task (Leland and Pineda 2006), we found a P3-type component with greater amplitude evoked by food words than neutral words (Fig. 43.2). This appeared to be an effect of selective attention and not general arousal since food- and neutral-word trials were randomly mixed within each block. Attention-related ERP effects also have been found in response to food odor stimuli in normal eaters although not restrained eaters, which may reflect a motivation to suppress attention to food-related stimuli (Kemmotsu and Murphy 2006). Furthermore, attention-related ERPs to images of food varying in degree of suitability for human consumption (e.g., sanitary versus contaminated) appear to differentiate controls from individuals with Prader-Willi syndrome (PWS; Key and Dykens 2008). The ERPs of PWS patients, who are characterized by intellectual deficits and hyperphagia (abnormally increased appetite for and consumption of food), may reflect the impact of maladaptive food cue salience on selective attention. Attending excessively to food quantity and/or not enough to food quality/safety may be an important contributor to this and other eating disorders.
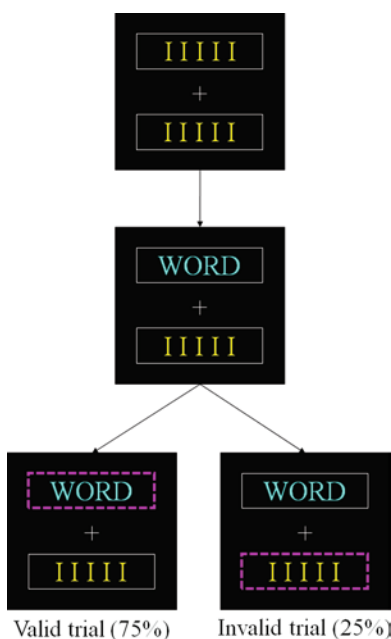
Fig. 43.2 Spatial attention task using words as cues. Each trial of this task begins with visual fixation at a central cross and masks (*filler letters*) at top and bottom locations. The mask is replaced by a word at one of the two locations (50% chance each; word/mask color also counterbalanced). After a variable delay, the box outline surrounding either the word or the mask briefly flashes magenta (shown with a *dashed line* above), signaling the subject to respond by pressing a button. The target surrounds the cue 75% of the time (valid trials) and surrounds the mask 25% of the time (invalid trials), creating an attentional set whereby subjects tend to focus attention on the frequently predictive cue location. Responses to validly cued targets are faster than those to invalidly cued targets (the "validity effect"), reflecting the costs/benefits of attention. Effects of emotion and motivation on attention can be studied by comparing salient and neutral cue word conditions (e.g., food words versus school/art supply words) and testing for a difference in the validity effect (Adapted with permission from Leland and Pineda 2006, p. 70)

43.4 Action

43.4.1 A Feedback Loop for Eating

The mesolimbic dopamine pathway associated with motivation projects to areas such as the ventral pallidum and hypothalamus, which in turn can activate brainstem circuits for eating. One manner in which selective attention can mediate the guidance, initiation, and intensity of eating behavior is by successively narrowing the range of decisions and behaviors toward food-related stimuli (including food itself). The orienting effects of selective attention can lead to shifts of sensory organs toward attended stimuli, for instance movement of the eyes so as to place cues in the center of the visual field. Attended stimuli have greater sensory salience and detectability, which may in turn facilitate their identification and evaluation as incentives. Siep et al. (2009), for instance, found that focusing attention on food images during fMRI modulated food reward processing activity in the OFC and amygdala. Thus, motivation, attention, and action may work together in a positive feedback loop until physical proximity and motivational salience are sufficient to trigger food consumption. A feedback loop of this sort would be consistent with the reciprocal connectivity of the VTA, which receives excitatory inputs from nearly all of its direct and indirect cortical targets, and it is consistent with contemporary views of mesolimbic dopamine as playing a role in incentive salience (Berridge 2009), reward learning (Schultz 2006), and behavioral activation (Salamone et al. 2007).

43.4.2 Social Eating and the Mirror Neuron System

Higher level cognitive mechanisms may help explain the power of food cues in the social context, in particular the impact of seeing others eat. People tend to eat more at meals shared with others (de Castro and de Castro 1989), which may be due in part to mimicry of others' behavior. Mirror neurons in the frontal and parietal cortices show increased firing rates during not only execution of action but also during observation of the corresponding action performed by others and may be a substrate for this influence (Rizzolatti and Craighero 2004). The mirror neuron system (MNS; Fig. 43.3) has been widely defined as consisting of three interrelated regions: ventral premotor area (PMv) of the inferior frontal gyrus (IFG; area F5 in monkeys), parietal frontal (PF) in the rostral cortical convexity of the inferior parietal lobule (IPL) of the PPC, and the superior temporal sulcus (STS). Since the MNS is involved in both motor representation/execution and visuomotor representation, it is hypothesized to be important for observational learning, empathy, and mimicry. The MNS has often been thought of as reacting automatically in a bottom-up fashion to observed action, but neuroimaging and behavioral studies show that top–down influences, including selective attention, increase MNS activity and facilitate subjects' responses that are congruent with observed actions (Chong and Mattingley 2009). Furthermore, selective attention may be drawn to stimuli not only endogenously through top-down control but exogenously by the motivational salience of stimuli, as suggested in the previous section.

In fact, Gallese et al. (1996) noted that when macaques observed actions oriented toward food-related stimuli, mirror neurons in the premotor cortex were reliably activated whereas the response to similar actions toward non-food items had a tendency to habituate. Similarly, Fogassi et al. (2005) found mirror neurons in the inferior parietal cortex that would respond differently to grasping (executed or observed) for the purpose of eating as compared to the purpose of placing an object in a container. In fact, a majority of those parietal neurons studied were influenced by the ultimate goal
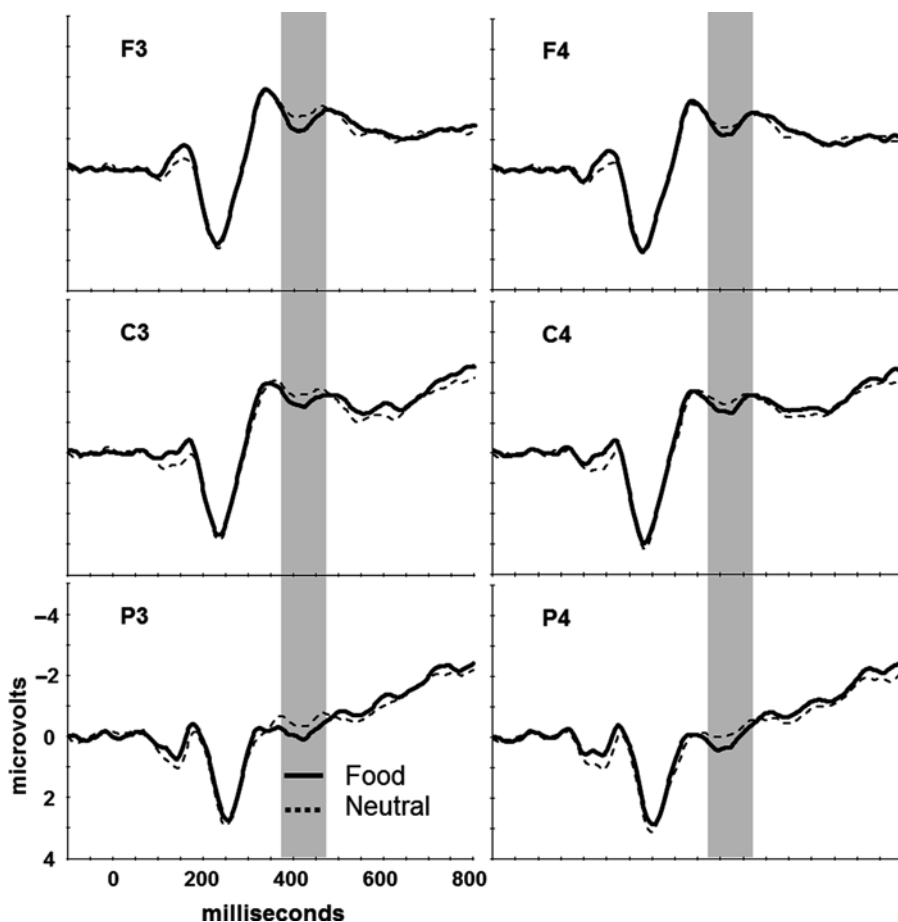
Fig. 43.3 Event-related potentials (ERPs) to food and neutral cue words. Words serving as spatial cues in a selective attention paradigm (see "Features of Selective Attention Tasks" at the end of this chapter) evoked brain electrical activity that differed based on semantic category. A positivity peaking approximately 420 ms after stimulus onset (shown with gray background) had greater amplitude in response to food words (e.g., "PIZZA") than a control set of school/art supply words (e.g., "PAINT"). This P3-like positivity may reflect enhanced attention as a consequence of motivational salience. Waveforms represent grand averages (*n* = 20). *F3* left frontal, *F4* right frontal, *C3* left central, *C4* right central, *P3* left parietal, *P4* right parietal (Adapted with permission from Leland and Pineda 2006, p. 77)

of the action even during the time period in which the grasping motions were identical. Studying humans with fMRI, Cheng et al. (2007), reported that hunger enhanced activation in response to food-related stimuli in the parahippocampal formation, OFC, and amygdala, consistent with their motivational salience, but also that hunger increased activation in areas of the MNS, including IFG and PPC. Indeed, IFG and amygdala activations were positively correlated with self-reported hunger. These studies demonstrate a special influence of food-related cues and intentions on MNS activity that could be mediated by selective attention mechanisms. As described previously, forebrain acetylcholine plays a role in selective attention and is disinhibited by mesolimbic dopamine. These cholinergic projections target various parts of the cortex, including specifically PPC, one of the MNS areas activated in the Cheng et al. study. Thus, consistent with more general findings that selective attention influences the MNS and motor-matching behavior, eating more with others could reflect in

part a chain of events in which food stimuli activate motivational systems that focus attention on visuomotor stimuli serving as a model for one's own potential eating behavior.

Human behavior in uncertain environments, particularly with respect to food, appears to be grounded in flexible actions. Evidence shows not only that action is biased toward food but that such actions may be prepared but not executed in a type of virtual simulation, in accordance with the premotor theory of attention. The ability to interrupt and cancel these types of preparatory responses to external events would confer flexibility and adaptability on individual behavior. The human MNS is one mechanism that allows for such preparation of actions toward food. More broadly, mechanisms both subcortical and cortical, evolutionarily old and new, enable the formation of dynamic goal states that can shape equally dynamic behaviors via the influence of selective attention.

43.5 Applications to Other Areas of Health and Disease

Much of the attentional bias work reviewed in this chapter has been conducted using participants with eating disorders. The framework presented suggests that it might be prudent to consider differences in motivation, attention, and action, as well as the connections between them psychologically and neurologically, in exploring the etiology of eating disorders (see Table 43.3). For example, it has been suggested that dopaminergic differences constitute a risk factor for obesity in the form of increased sensitivity to reward (e.g., Davis et al. 2007). Peciña et al. (2003) have shown increased motivation and effort to obtain food (wanting) but no increase in orofacial expressions suggesting increased hedonia (liking) in mice genetically engineered to have abnormally high dopamine levels. Motivation to eat is not synonymous with nor necessarily caused by increased pleasure from eating, in much the same way that drug craving is by no means equivalent to or consistently related to drug-induced pleasure. On that point, it is noteworthy that all of the research approaches covered in this chapter with respect to food also have been applied to the study of drug use and drug dependence, and the implications are essentially the same for how motivation, attention, and action appear to interact to produce drug-seeking and consumption behavior.

Table 43.3 Questions for theory, research, and treatment

1. How separable are pathways for food motivation versus other rewards? What impact might pharmacological treatment targeting food motivation in eating disorders have on other goal-directed behaviors? How about effects of treatment for drug dependence on food motivation?
2. What roles do controlled (conscious) and automatic (unconscious) processes play in the links between food motivation, attention, and action? Can raising individuals' awareness of these links help treat disorders involving compulsive eating?
3. How do neural pathways for food motivation interact with circuitry underlying cognitive processes other than attention (e.g., perception, memory, and decision-making) to ultimately influence normal and disordered eating behavior?
4. If the mirror neuron system plays a role in facilitating eating and other consumptive behaviors, can it also play a role in behavioral treatments aimed at inhibiting or otherwise changing such behavior through modeling and imitation?

The role of attention in food motivation and behavior is one small piece of a larger puzzle involving other cognitive mediators and other motivations. Addressing the questions in this table will be important for furthering our understanding of both normal and disordered behaviors, food-related and otherwise

43.6 Features of Selective Attention Tasks

In a *modified Stroop task*, one assesses whether subjects take longer to name the color of words with emotional or motivational salience (e.g., food-related words) than nonsalient control words. Such a difference in reaction time (RT) is presumed to result in part from added difficulty in shifting attention from the semantic properties of salient words to the color in which those words are displayed, although other sources of response conflict can produce RT differences. Attentional biases also have been investigated using modified tests of visual spatial attention. For instance, in the classic "Posner paradigm" subjects respond to visual targets (e.g., dots) that are preceded by nontarget cues (e.g., boxes). Cues that correctly indicate the location of subsequent targets (e.g., a box surrounding the area where the dot will soon appear) are considered "valid" while cues associated with another location (usually the opposite hemifield) are considered "invalid." The "validity effect" refers to the RT benefit for target responses on validly as opposed to invalidly cued trials. By directing attention to the correct location, valid cues are thought to facilitate detection and response, while invalid cues impair detection and response by diverting attention from the correct location. Ordinarily, cues in this paradigm convey spatial information but have no other meaning. The task is easily modified, however, by using emotionally or motivationally salient stimuli, such as food-related words (Fig. 43.4), as cues. Since the subject's task is simply to respond to targets, the semantic content of the cues is irrelevant, yet those stimuli with special salience may nonetheless increase the focus of attention to their location, magnifying the validity effect by increasing the benefit of valid cueing and/or increasing the cost of invalid cueing. A similar spatial cueing task that is used more commonly to assess attentional bias is the *visual probe* (or dot probe) task. In this paradigm, two cues appear simultaneously (one in each hemifield), followed by a target at one or the other location. One of the two cues is an emotionally or motivationally salient stimulus while the other cue has no such salience. If RT is faster to targets appearing at salient cue locations than neutral cue locations, the effect is interpreted as reflecting increased attention as a result of the emotional or motivational content of the cue stimulus, just as it is in the Posner paradigm.
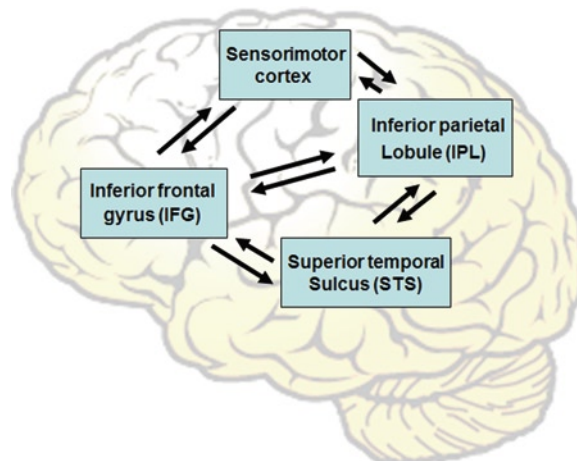
Fig. 43.4 The mirror neuron system (MNS). Schematic of areas in the human brain, such as inferior frontal gyrus (IFG) and inferior parietal lobule (IPL), that contain mirror neurons. Along with the superior temporal sulcus (STS), these make up the "core" of the mirror neuron system (MNS). Additional areas, such as sensorimotor cortex, comprise an "extended" mirror system

Summary Points

- Food is a primary motivator of behavior because it is both a physiological necessity and a central element of much social activity.
- Motivation is based not simply on a pleasure principle but on neural systems involved in predicting rewards and directing attention and behavior toward them even in the absence of pleasure.
- Selective attention is important for motivation because it prioritizes the processing of goal-relevant information and allows for adaptive responses to a changing environment rather than mere reflexive eating.
- Selective attention to food-related information has been demonstrated with both behavioral tasks and brain activity measures.
- Evolutionarily old brain systems allow for relatively simple motivational states and attentional influences on action, while their integration with more recently evolved structures enables more flexible, dynamic behavior.
- The MNS appears to play a role in translating seeing into doing and thus may help explain why people tend to eat more in the presence of others.
- Differences in how food motivation, attention, and action processes interact in the brain may help explain particular eating behavioral patterns, including those associated with eating disorders.

Key Terms

Feedback loop: A system that feeds some of its outputs back to itself as inputs. Positive feedback occurs when such input is excitatory, causing a continual increase in system activity, while negative feedback tends to stabilize system activity since the more active it is the more it opposes itself.

Hedonic theory of dopamine: A theory that argues that mesolimbic dopamine mediates the subjective pleasure associated with delivery of a reward.

Homeostasis: The tendency to maintain stability of an internal state by monitoring for changes and making adjustments to compensate for them.

Limbic system: A network of brain structures that is important for aspects of emotion, motivation, memory, and other behavioral functions.

Mirror neuron system: A network of frontal, parietal, and temporal lobe regions with neurons that increase firing rates during execution of an action or observation of a corresponding action performed by others. The MNS may be a neural basis for translating seeing into doing or performing a "simulation" of action without executing it.

Motivation: The goal-oriented force in behavior, contributing to its initiation, direction, intensity, and persistence in the face of obstacles.

Premotor theory of attention: A theory that argues that attention derives from an activation of the same circuits that process sensory and motor information.

Reward: A positive reinforcer; a stimulus whose presentation increases the future probability of behaviors leading to its delivery. The term "reward" can be controversial due to its connotation of subjective pleasure and the notion that such pleasure gives rewards their reinforcing quality.

Salience: The state or quality of standing out, for instance due to attentional selection, greater sensory intensity (sensory salience), or goal-relevance (motivational salience). According to

> Berridge (2009), rewards and the cues that predict them acquire "incentive salience," which leads to "wanting" them.
>
> **Selective attention:** The selection of some information for increased processing at the expense of other (unattended) information.
>
> **Spatial attention:** Attention selectively directed toward a location in space, conferring its information-processing benefits to stimuli at that location.
>
> **Triarchic model of attention:** A theory that argues that attention is a mechanism separate from information processing and that it consists of orienting, alerting, and executive subsystems.

References

Berridge KC. Physiol Behav. 2009;97:537–50.

Braet C, Crombez G. J Clin Child Adolesc. 2003;32:32–9.

Brignell C, Griffiths T, Bradley BP, Mogg K. Appetite 2009;52:299–306.

Cavada C, Company T, Tejedor J, Cruz-Rizzolo RJ, Reinoso-Suarez F. Cereb Cortex. 2000;10:220–42.

Channon S, Hayward A. Int J Eat Disorder. 1990;9:447–52.

Cheng Y, Meltzoff AN, Decety J. Cereb Cortex. 2007;17:1979–86.

Chong TTJ, Mattingley JB. In: Pineda JA, editor. Mirror neuron systems: the role of mirroring processes in social cognition. New York: Humana; 2009. p. 213–33.

Corbetta M, Shulman GL. Nat Rev Neurosci. 2002;3:201–15.

Craig AD. Curr Opin Neurobiol. 2003;13:500–5.

Davis C, Patte K, Levitan R, Reid C, Tweed S, Curtis C. Appetite 2007;48:12–9.

de Castro JM, de Castro ES. Am J Clin Nutr. 1989;50:237–47.

Dobson KS, Dozois DJA. Clin Psychol Rev. 2004;23:1001–22.

Duncan J, Nimmo-Smith I. Percept Psychophys. 1996;58:1076–84.

Eimer M, Forster B, Van VJ, Prabhu G. Neuropsychologia.2005; 43:957–66.

Fogassi L, Ferrari PF, Gesierich B, Rozzi S, Chersi F, Rizzolatti G. Science 2005;308:662–7.

Foote SL, Berridge CW, Adams LM, Pineda JA. Prog Brain Res. 1991;88:521–32.

Formea GM, Burns GL. J Psychopathol Behav. 1996;18:105–18.

Francis JA, Stewart SH, Hounsell S. Cognitive Ther Res. 1997;21:633–46.

Gallese V, Fadiga L, Fogassi L, Rizzolatti G. Brain 1996;119:593–609.

Garcia-Segura LM, Lorenz B, Don Carlos LL. Reproduction 2008;135:419–29.

Graziano MS, Gross CG. Exp Brain Res. 1998;118:373–80.

Kemmotsu N, Murphy C. Physiol Behav. 2006;87:323–9.

Key APF, Dykens EM. J Intell Disabil Res. 2008;52:536–46.

Kok A. Psychophysiology. 2001;38:557–77.

Lavy EH, Vandenhout MA. Behav Cogn Psychoth. 1993;21:297–310.

Leland DS, Pineda JA. Clin Neurophysiol. 2006;117:67–84.

Mogg K, Bradley BP, Hyare H, Lee S. Behav Res Ther. 1998;36:227–37.

Mohanty A, Gitelman DR, Small DM, Mesulam MM. Cereb Cortex. 2008;18:2604–13.

Overduin J, Jansen A, Louwerse E. Int J Eat Disorder. 1995;18:277–85.

Parikh V, Kozak R, Martinez V, Sarter M. Neuron 2007;56:141–54.

Pecina S, Cagniard B, Berridge KC, Aldridge JW, Zhuang XX. J Neurosci. 2003;23:9395–402.

Placanica JL, Faunce GJ, Job RFS. Int J Eat Disorder. 2002;32:79–90.

Posner MI, Dehaene S. Trends Neurosci. 1994;17:75–9.

Posner MI, Petersen SE. Annu Rev Neurosci. 1990;13:25–42.

Posner MI, Rothbart MK. Annu Rev Psychol. 2007;58:1–23.

Reep RL, Corwin JV. Neurobiol Learn Mem. 2009;91:104–13.

Rizzolatti G, Craighero L. Annu Rev Neurosci. 2004;27:169–92.

Rizzolatti G, Riggio L, Dascola I, Umilta C. Neuropsychologia 1987;25:31–40.

Rolls ET. Philos T Roy Soc B. 2006;361:1123–36.

Salamone JD, Correa M, Farrar A, Mingote SM. Psychopharmacology 2007;191:461–82.

Schultz W. Annu Rev Psychol. 2006;57:87–115.

Shafran R, Lee M, Cooper Z, Palmer RL, Fairburn CG. Int J Eat Disorder. 2007;40:369–80.

Siep N, Roefs A, Roebroeck A, Havermans R, Bonte ML, Jansen A. Behav Brain Res. 2009;198:149–58.

Simmons WK, Martin A, Barsalou LW. Cereb Cortex. 2005;15:1602–8.

Wang GJ, Volkow ND, Telang F, Jayne M, Ma J, Rao M, Zhu W, Wong CT, Pappas NR, Geliebter A, Fowler JS. Neuroimage 2004;21:1790–7.

Chapter 44
The Pleasures and Memory of Food and Meals

Paul Rozin and Dina Gohar

44.1 Food and Pleasure

The two fundamental needs that animals must continuously meet are the need for food and for air. While breathing occurs almost automatically, eating involves organized activity, including search and selection. For generalist animals that eat a wide variety of foods, learning plays a major role in the discovery of what is edible and what is not (Rozin 1976). The learned behavior that results in finding food is reinforced by the pleasure produced by the food itself. Thus, pleasure plays an important role in the experience of and learning about food. In contrast, breathing – or the "capture" of air – is associated with little pleasure; it is only the absence of air that rapidly produces a state of distress and displeasure. The special link between food and pleasure is well illustrated by the innate positivity of sweet tastes for many generalist mammals. Food generalists, like humans, have few innate signals that indicate nutrition; however, they do have an innate positive response to sweetness and an innate avoidance of things that taste bitter (Steiner 1979). Both of these in-born biases make nutritional sense, as sweetness signals calories while bitterness typically predicts toxicity. In addition, humans may have an innate preference for fatty textures, which, like sweetness, predict sources of calories.

44.2 Preadaptation

First, an understanding of preadaptation is necessary for a better grasp of the relationship between food and pleasure in humans. Preadaptation is a fundamental process in biological and cultural evolution by which something that evolves for one purpose is co-opted for another (Mayr 1960). A particularly appropriate example is the mouth and its various structures, such as the tongue and teeth, which clearly evolved for the predigestive processing of food. When language evolved in humans, however, the location of the mouth as the entry and exit point for air (in addition to food) led speech via the mouth to become the major means of communication. In this context, the teeth, tongue, and other food-adaptations in the mouth were used for the articulation of sound; that is, they were preadapted for language.

The major role preadaptation plays in biological evolution is dwarfed by its role in cultural evolution. After all, in the latter, there is purpose; that is, an individual can realize the potential of using

————————————————

P. Rozin (✉)

Department of Psychology, University of Pennsylvania, 3720 Walnut St, Philadelphia, PA 19104-6241, USA
e-mail: rozin@psych.upenn.edu

an existing practice for a new purpose and use that foresight to create the link. In biological evolution, on the other hand, the link to the new purpose has to initially arise by chance. Whether biological or cultural, preadaptation has played a key and dual role in the interplay of food and pleasure in humans. First, food and the food system – originally designed purely for nutrition – have become so elaborated in human cultures that food serves many purposes besides nutrition. Second, the pleasure system was originally designed as a response to certain sensory experiences (e.g., sweetness) so that continued interaction with such sensory events would be sought after and fostered (Pfaffman 1960). Pleasure was linked to energy homeostasis: likely sources of calories were pleasant experiences, especially in the face of hunger (Cabanac 1971).

Pleasure can be defined as a positive experienced state that we seek and try to maintain or enhance. However, the pleasure system became involved in many more cognitive and elaborate experiences as the human brain (and world) grew increasingly complex (Rozin 1999). That is, this basic pleasure system may have been co-opted, along with the development of human cognitive capacities, to become attached to entities other than sensory experiences that would potentiate greater success in negotiating the world. Thus, although humans may have a basic pleasure system similar to that of animals, its range of elicitors is much greater.

44.3 The Expansion of Pleasure

There are at least three types of pleasure that humans experience, and all three are expressed in the food domain. Take, for instance, the act of drinking wine. Karl Duncker (1941) asks whether the object of pleasure is the wine (the object), the drinking of the wine (the communication with the object), or the sensory experience of drinking the wine (the experience of communication with the object). In the case of wine, the answer is clearly the last: the experience of the flavor. Indeed, Jeremy Bentham (1789/1948) assigns a fundamental role to sensory pleasure, which forms the basis for other types of pleasure. Sensory pleasures, considered part of the primitive pleasure system, derive primarily from the contact senses that cover the body surface and apertures, such as the flavor for foods. In contrast, esthetic pleasures are not physically localizable and are more abstract, though they are also linked to sensory input. Mastery pleasures derive from achieving something of value through acquisition of some sort of skill or sophistication. Although much of eating involves sensory and fundamental pleasures, such as the feeling of chocolate melting in one's mouth, fully enjoying more complex dishes or becoming a wine connoisseur (to use an extreme example) clearly involves esthetic and mastery pleasures.

It is worth noting that sensory pleasure is more resilient than other types of pleasure, though. That is, one can frequently enjoy the same sensory pleasure without too much adaptation. Indeed, the taste of a piece of chocolate or the experience of sexual orgasm can provide pleasure over and over, and the level of pleasure typically remains high in the long-term. In the short-term, however, there is a tendency for the pleasure produced by a sensory experience to wane, a phenomenon termed sensory-specific satiety (Rolls et al. 1986). Nonetheless, components of the sensory pleasure system, particularly those involving pain as well as many positive skin and mouth sensations, generally show remarkably little hedonic habituation.

Combinations of sensory pleasures do not obey any simple, hedonic algebra. For instance, both meat and whipped cream are positive sensory pleasures for most Europeans and Americans, but their combination (when one is aware of how it was produced) typically results in an unpleasant sensory experience. Indeed, sensory pleasures may be relatively simple, but they are extremely context-dependent. For example, the good smell of a piece of cheese can rapidly turn negative if one discovers that the

smell is actually spoiled milk or coming from a body product, so a good sensory pleasure depends on its origin. Humans may also develop a liking for a variety of innately negative experiences, such as bitter tastes (e.g., coffee or bittersweet chocolate) and sensory irritants (e.g., chili pepper or scotch whiskey) (Rozin 1982). In such cases, through interactions with the food in question in a social context, one's initial negative response to a taste (e.g., the burn of chili pepper) undergoes a hedonic reversal and becomes positive (Rozin 1990). Billions of humans have experienced this particular hedonic reversal. We have called this reversal "benign masochism" because we believe that the enjoyment of such innately negative experiences depends upon our realization that the negative sensory experience is not actually threatening. This may be a case of "mind over body," we enjoy the experience because our body is signaling danger but we know, cognitively, that there is no danger. There is an element of mastery here.

44.4 Preadaptation and Food

In human cultural evolution, food has become involved in many aspects of human life (see Kass (1994) for a history of this evolution within Western culture). First, food plays a major role in social life: the capture of food often involves cooperation, and the consumption of food is typically a social occasion. Indeed, the meal is often the main period of family social interaction. Second, food becomes a signal of ethnic or national identity, as well as a social signal when it serves as a gift. Third, sharing food is a sign of intimacy, a literal sharing of substance. And, just as sharing substance with admirable or beloved folk is elevating, sharing with those seen as inferior can be considered degrading. Fourth, food becomes a moral substance to some degree. Food is quite explicitly moral in Hindu India (Appadurai 1981), but even in modern American culture, a particular food can stand for corporate greed, human cruelty (as with meat for moral vegetarians), or worker oppression among some individuals. Thus, it is clear that a comprehensive understanding of the role of food in the modern world involves far more than nutrition. The preadaptation of food as nutrition for other human activities is demonstrated in Fig. 44.2. One of the most striking aspects of food preadaptation is the use of food words as metaphors (which are, essentially, preadaptations), as when we say that, "Joan is a sweet person" or "Let's get to the meat of the argument." Kass (1994) captures the elaborate nature of food, in that food and eating, in addition to table manners, become signs of civilization: "We eat as if we don't have to. We exploit an animal necessity, as a ballerina exploits gravity" (p. 158).

Preadaptation and Functions of Food

Nutrition

Social marker | Aesthetic experience | Moral vehicle | Metaphor
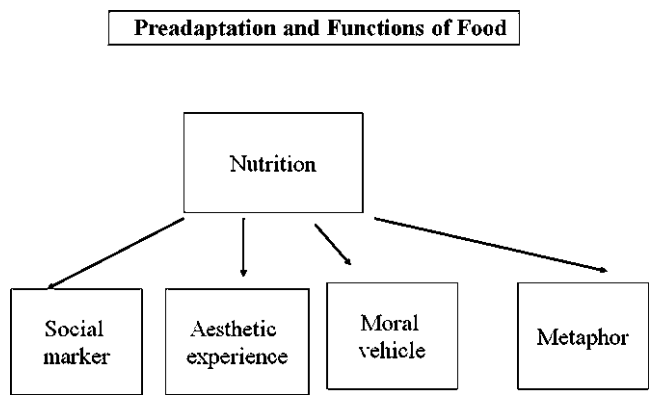
Fig. 44.1 Food and preadaptation. As a result of preadaptation, food has developed far greater meaning than nutrition; for instance, food is often used as a social marker, an esthetic experience, a moral vehicle, and as a metaphor

Fig. 44.2 A schematic model of food choice. A schematic model of food choice, based principally on a model developed by Sobal et al. (2006), but also includes an enlargement of the area designated "Person" as well as the sequence from "Person" to "Action/Choice"

44.5 Food in the Late Twentieth Century Developed World

The role of food and its associated pleasure has become even more complex in the late twentieth century developed world. That is, for the approximately 15% of living humans who do not fear a shortage of food and for whom food constitutes a minority of total expenses. This situation is surely the case for North Americans and Western Europeans, and has inverted the traditional human relation to food in many ways (summarized in Table 44.1).

Humans evolved in an environment similar to that of many other mammals; the search for food, its identification and selection, capture, and consumption were major activities. Food was scattered widely in the environment, and considerable energy was spent in finding adequate food. Generally, food-related problems involved finding enough food, as opposed to the risk of over-consumption. If our ancestors, like most other mammals, happened upon a rich source of energy and nutrients, the bias was certainly to consume it. However, in the late twentieth century developed world, food is plentiful and surrounds us. Moreover, food is cheap; in developed countries, less than a quarter of the

Table 44.1 Key points of the contrast between the human ancestral and the modern developed world food environments

Ancestral environment	Modern developed world environment
1. Food scattered and not abundant	Food plentiful
2. Obtaining food requires energy expenditure (optimal foraging)	Minimal energy needed to obtain food
3. Relatively few energy-dense natural foods other than animal products; fat and sweet rarely combined	Development of "super foods" such as chocolate
4. Modest variety of foods	Enormous variety of foods
5. Most deaths due to acute causes	Epidemiological revolution: Most deaths due to degenerative diseases
6. Relation between eating and its negative consequences is usually clear (e.g., food poisoning)	Relation between eating and its negative consequences is usually subtle, and occurs over decades

This table lists the key differences between the human ancestral food environment and that of the modern developed world

total amount of income is typically spent on food (Table 44.1, line 1). Therefore, humans, shaped by evolution to function in a world with scattered food, are now faced with abundant piles of it.

In this modern environment, the link between energy expenditure and energy consumed has also been broken. Food foraging typically required energy, making survival depend on spending less energy in foraging than is gained as a result. In fact, food foraging in most species (and data on this come from many species) is exquisitely calibrated so that the animal spends as little energy as possible to get the maximum energy yield, a phenomenon called optimal foraging. It is now possible, however, for the human optimal forager in North America to achieve the forager's dream: energy input without almost any expenditure. A weekly drive to the supermarket, or in the extreme, a few clicks of a computer mouse, can bring dinner or even a week's worth of food. Therefore, the second major change in the modern food world is that an organism built to minimize energy expenditure while obtaining sufficient food has created a world in which there is almost no energy cost of eating (Table 44.1, line 2).

The human generalist has certain innate biases that are useful in locating food. Two major biases are the preference for sweet and fatty foods, which are both characteristic of milk, the first food of mammals. In nature, sweet and fatty sensations usually occur at high levels in different foods. Yet, human ingenuity has led to the creation of an aromatic food that is both sweet and fatty: chocolate. Chocolate is representative of a whole set of "super foods" developed by humans to cater to their tastes. Nothing resembling milk chocolate grows on real trees or bushes, but the development of such super foods has resulted in a modern food world that tempts the palate more than nature ever could (Table 44.1, line 3).

A generalist animal, insofar as it consumes nonanimal foods, needs to consume a range of plants to obtain adequate nutrients. Thus, generalist animals tend to seek variety in their diet. Although there is a risk in trying new foods, since they may be toxic or imbalanced, the advantages of having a range of sources of energy and nutrient are great. In the modern food market, an unprecedented variety of foods is now available from all over the world. In general, variety promotes intake, so this is yet another force at work in the modern world that promotes food consumption (Table 44.1, line 4).

Finally, recent medical advances, particularly in the twentieth century, greatly increased longevity in the developed world. In particular, in what is called the epidemiological revolution, infectious diseases declined rapidly as a cause of mortality by the late twentieth century. This decline was due to a number of advances, including the development of antibiotics and the enactment of a variety of public health measures, such as the regulation of tap water processing (Table 44.1, line 5). As a result of these changes, what was often a palpable link between what one ate and its consequences

(e.g., the onset of illness within hours of consumption, typically gastrointestinal in nature) became a much more subtle link between patterns of food choice and the development of degenerative diseases taking place over decades (Table 44.1, line 6). No animal is designed to modify its current behavior based on the perception of modest risk changes that will manifest themselves in decades. Thus, in the modern developed world, humans rely on the medical community to provide information about the long-term risks of certain food consumptions and eating habits (e.g., overeating increasing the risk of obesity), but there are few salient consequences of engaging in the activities associated with long-term risks.

44.6 Food Choice in the Modern world

Food choice used to be easy: if a familiar and tasty food was available, it was eaten. In the modern world, though, there are so many eating opportunities that obesity is a common threat; thus, the modern-day individual is faced with far more complicated choices concerning food. Much of what we eat is due to habit or routine, or is simply determined by what is in front of us (as represented in Fig. 44.2, described below, by the line from environmental food options directly to action, bypassing the personal food system). The options, though, can be staggeringly large, whether we are facing our own opened refrigerator or a restaurant buffet. A number of investigators offer a framework for understanding food choice in terms of three components: the person, the food, and the situation/environment (Meiselman 1996; Sobal et al. 2006). This is a useful framework, so long as we keep in mind that, ultimately, both the food and the environment are filtered through the person. Consequently, it is the perceived product(s) and environment that influence choice. The sociologist Jeffrey Sobal and his colleagues (e.g., Sobal et al. 2006) have made the most complete attempt to describe the full context of the process of food choice. Their model is based primarily on interviews with adult Americans and is appropriately complex. A modified version of this model is presented in Fig. 44.2. Upon examination of this figure, the importance of social factors becomes clear. As Sobal et al. (2006) note: "This model assumes that a key process in selecting foods is the construction of food choices based on cognitions and social negotiations. Overall, people are assumed to construct food choices in a variety of ways by actively selecting what, when, where, with whom, and how to eat." The biggest determinants of what we eat and how much we eat are two environmental/economic variables: what is available and how much it costs.

In terms of the interaction between existing (affordable) food choices and the person, there are three major determinants of choice for developed world humans. First, the single most potent determinant of food choice for most people is the presumed palatability of the food; that is, the amount of pleasure (e.g., sensory effects, primarily flavor) anticipated to result from its consumption. Individuals across cultures share the universal, genetically determined preferences for sweet and aversion to bitter. As a child grows up, however, his or her tendency to consume anything that goes in the mouth and does not have an innately aversive taste is shaped and refined by experience and instruction, so that culture-wide practices are communicated and internalized (e.g., what to eat and when). Many of these cultural influences fall under the heading of either cuisine (Rozin 1982) or appropriateness (Schutz 1989). From these genetically based predispositions, culture-based rules, attitudes and practices, and personal experience, individuals develop particular sets of food-related beliefs, preferences, and practices, which have been termed `personal food systems' by Sobal and his colleagues (Sobal et al. 2006). The other two major determinants of food choice are convenience, including the ease of procurement, preparation, and actual ingestion (e.g., shelled peanuts are much more convenient than peanuts in shells), and anticipated health consequences. For many North Americans, food

choice is often a battle between pleasure and health concerns. The enormous number of health claims made on food labels in supermarkets testifies to the importance of such considerations for the consumer. Indeed, in part because of our predilection for sweet and fatty foods, there is generally a conflict between what we like and what we perceive to be healthy. Nevertheless, eating remains driven primarily by pleasure.

44.7 Applications to Areas of Health: The Interactions of Pleasure, Health, Convenience and Norms

A number of forces, as we have indicated, conspire to make the eating situation problematic in the developed world. Individuals are frequently faced with multiple options for highly palatable (often high calorie) inexpensive foods, easily delivered (high on convenience). Such an obesogenic environment confronts serious worries about long-term health. In fact, just the presence of a variety of foods often increases consumption. Research has documented that presenting humans with a variety of foods within a meal can increase meal size and the magnitude of this effect varies with the distinctiveness of the foods (Rolls et al. 1986) Moreover, the variety effect occurs whether the foods are presented sequentially or simultaneously Indeed, many have concluded that the problem of obesity lies primarily in the environment we have created (e.g., Brownell and Horgen 2004; Hill and Peters 1998; Levitsky 2005; Nestle 2002; Rolls 2003; Rozin 2005; Wansink 2004). The problematic nature of food is exacerbated for women, whose Western cultural norms include a distinct preference for thin bodies. Consequently, for example, 57% of a large sample of American college women report that they are often or almost always concerned about their weight (Rozin et al. 2003). However, such thin female ideals are themselves unrealistic, and often promote a level of thinness that is thinner than what most men desire.

Nevertheless, conflicting norms for thinness on esthetic grounds and restricted dietary choices to promote longevity are at odds with one another. Long-term health prospects, which are made prominent through the media and other cultural routes, now face off against the foods we like most. This conflict between tasty and healthy food is perhaps most exaggerated in North Americans. Although it is easy to divide foods into good and bad, such a division makes minimal nutritional sense. For instance, chocolate is not an unhealthy food, but is simply high in calories, and should thus be consumed (and savored) in modest amounts. Thus, a major problem, especially clear in North American women of European origin, is that eating, despite being an enjoyable necessity, is viewed as potentially more harmful than helpful. Of course, while eating can indeed be harmful to health, not eating is much more harmful, and has much more pressing serious health effects.

44.8 Cultural Solutions

Indeed, we are faced with a plethora of information about risks of certain dietary patterns, often with associated risk factors that are hard for laymen to understand, but we are not educated about how to assimilate such information. Thus, culture has to catch up in educating the human mind to negotiate the world of thousands of tempting choices. At present, there is minimal education about nutrition and the balancing of risks and benefits necessary for making intelligence choices (e.g., trying to eliminate fat or salt from the diet is not a realistic or even desirable option). Moreover, as with modern computer technologies, our ability to produce extraordinarily appealing foods, priming the pleasure side of eating, has not kept up with cultural inventions to properly control and direct food intake.

Nevertheless, cultures vary in their success at facilitating the basic activities of humans, For example, it is probably fair to say that the American higher education system is particularly good, but public transportation systems are more effective in Western Europe. There are corresponding differences is success of handling the plethora of delicious foods in the modern developed world. It is our belief, supported by research conducted by Paul Rozin and the French food sociologist Claude Fischler (Fischler and Masson 2008; Rozin 2005; Rozin et al. 2003) that French culture has handled the conflicts resulting from the modern developed food world much better than American culture. For instance, the French are notably less obese than Americans, and have a lower incidence of cardiovascular disease. Yet, this increased health does not result from a more restrictive or worry-ridden eating environment. On the contrary, the French spend more on food, and almost certainly have more food experience than Americans (because their meals typically last much longer). They seem to get more pleasure from food, and yet remain thinner. Our research, using surveys of French and Americans as well as observations of their food environments, has been directed at understanding this "French Paradox." Several factors, summarized in Table 44.2 below, contribute to the proclivity toward experiencing less stress and more pleasure from eating among the French as well as their lower rates of obesity.

Many of these cultural differences are also present in other continental Western European countries to some extent (Fischler and Masson 2008). While it may be difficult to get North Americans to change some of their attitudes to food, the effort is certainly worthwhile. In addition, changing the food environment is very likely to have a positive effect. For instance, salience can affect food choice within a meal (Stunkard and Levitz 1975), as dessert choices in a hospital cafeteria were affected by placement. Thus, changing the modern North American food environment by making less healthy food choices less accessible and reducing portion sizes, for example, may eventually curb the obesity epidemic. The unfortunate fact is, however, that virtually all humans like sweet and fatty foods, and prefer to procure such delicious foods without expending too much energy. Americans have been particularly good at delivering this type of food in inexpensive, attractive, and convenient ways to people, and this success seems to be spreading throughout the world. Strong cultural traditions about food and eating, as in France, may curb this tendency to eat almost continuously.

Table 44.2 Food-Related differences between the French and Americans

1. The French see food as more central to life and as more related to pleasure.
2. The French tend to think of food as something to be eaten and enjoyed, as opposed to something that will have effects on the body, like medicine.
3. The French have stronger collective food values (partly because the USA is a very multi-ethnic country); thus, there are stronger cultural guidelines about what is a proper meal. Partly as a result of this fact, the French have fewer food options.
4. The French feel more comfortable about eating and see it as a positive experience.
5. The French think of eating as a more social event, with longer meals and social interactions being an essential part of the meal.
6. The French tend not to snack between meals.
7. The French eat more slowly, but eat less, as their portion sizes are smaller.
8. The French standards for good eating focus more on quality while American standards focus more on quantity.
9. It is probably true, but not yet documented, that the French get more physical activity than Americans. This may be the case partly because of their traditional patterns of local shopping in several markets and partly because of their lower reliance on automobiles.

A summary of factors that contribute to the French tendency to gain more pleasure from eating, experience less stress related to eating, and have lower body weight on average, than do Americans (based on our research including surveys and observations of the food environment)

44.9 The Temporal Domains of Pleasure

As the human mind expands its capacities, there arises a distinct sense of the present, the past, and the future. That is, perhaps uniquely, humans can conceive of themselves as existing at an experienced moment in the present and simultaneously as individuals with a history and future of experiences. According to Aristotle, "What is pleasant is the activity of the present, the hope of the future, and the memory of the past" (Nichomachean Ethics, Book 9, Chap. 7); that is, at any point in time there are three temporal frames for pleasure. In fact, humans are sufficiently complicated that they can not only anticipate an event but also anticipate the pleasure of later remembering that event. In the food domain, the event in question is typically a meal.

44.10 The Meal as the Focus of Eating: Experienced, Anticipated and Remembered Food Experiences

The meal is a natural unit – a recognized semantic category across languages and cultures – by which we typically organize and remember our days (Pliner and Rozin 2000; Meiselman 2000). In fact, memory is an important determinant of meal initiation or continuation; unlike normal controls, amnesiacs who do not distinctly remember that they have just eaten will eat a second and even third full lunch if these are served in sequence with intervals of 10–30 min (Rozin et al. 1998). Memories are also important because when we make choice in the present – such as one about food – it is typically based on our memories of relevant past experiences with the same or similar foods, rather than on our actual experience with the foods. Thus, the relationship between the memorial representation of the meal and the actual experience of the meal is of particular importance. While we probably would not accurately remember an ordinary meal weeks later, we tend to remember special meals, either because of their remarkably high (or low) culinary quality or unusualness, or because of important events that occurred during them (e.g., first dates or proposals of marriage).

Yet, the study of pleasure, in the food and other domains, has focused almost entirely on the direct, actual experience of pleasure until recently. Following in Aristotle's footsteps, however, Daniel Kahneman and his colleagues (Kahneman et al. 1997) have pointed out that there are three temporal domains of pleasure: anticipated, experienced, and remembered. Experienced pleasure is on-line and momentary, whereas the pleasure accessed or reconstructed in remembered and anticipated pleasure is a mentally constructed entity termed integrated pleasure. Experienced pleasure and pain, in this view, function to influence or guide the behavior of the moment, while anticipated and remembered pleasure may guide ongoing behavior and play a role in decisions of future courses of action. Of course, a remembered pleasure may be sufficiently vivid to function in many ways as an experienced pleasure. Furthermore, in real life, we spend a fair amount of the present in thinking about the future and the past. The amount of pain we experience at the dentist, which lasts seconds, is surely experienced for much longer in our memory and anticipation. The same would be true for a superb and distinctive meal, which may take an hour or two, but may be "consumed" in memory for many more subsequent hours.

This tripartite distinction was also stressed by Jon Elster and George Loewenstein (1992) in their discussion of backward and forward consumption, and more recently by Bryant (2003) in his work adopting a temporal perspective on the process of savoring; that is, the pleasures of reminiscing about the past, savoring the present, and anticipating the future. This tripartite distinction is not only important

in and of itself, but also raises the question of the relations among experienced, remembered, and anticipated pleasure. In fact, the same experience can differ when considered from these three perspectives. For instance, a vegetarian can enjoy an eating experience, and then discover that there was meat in one of the dishes, thus ruining the memory of this formerly pleasant experience. In addition, there can be a mismatch between anticipated and experienced pleasure, such as when one looks forward to a meal that does not turn out to be very good. Indeed, Gilbert and colleagues (see Wilson and Gilbert 2003 for a review) have demonstrated that people overestimate the intensity and duration of their emotional reactions to future events in a variety of domains (including food), a phenomenon known as the impact bias. That is, an individual may anticipate experiencing much greater pleasure from a meal than actually ends up being the case. Moreover, people are very poor, almost random, at predicting how their liking for a new food or other product will change even over a week in which they will consume it (Kahneman and Snell 1992; Rozin et al. 2006), and they don't seem to get better at predicting their "hedonic trajectories" with time or age.

Thus, it is perhaps not surprising that Kahneman and colleagues maintain that the mapping functions between experienced and remembered or anticipated pleasure are complex and may be nonmonotonic. Their research, centered on experienced and remembered pain has demonstrated that two aspects of a painful experience powerfully determine the memories for it: the peak level (which disproportionately affects the remembered pain) and the rapidity of the offset (sharp offsets are remembered as more painful). In contrast, one important aspect of a painful episode is *not* well-represented in memory: duration. For example, five minutes of pain are represented in memory as about as unpleasant as ten minutes of the same pain. This phenomenon has been termed duration neglect (Fig. 44.3).

Most of the work generated by the experienced–remembered–anticipated framework has dealt with negative experiences. With respect to memories for meals, and particularly the remembered pleasure of meals, we know relatively little. This is particularly important because typically when we choose a meal, or when we recommend a meal or restaurant to others, we are consulting our memory of the experience. People seem to generally prefer experiences in which pleasure increases with time. Are certain parts of the meal disproportionately determinative of our evaluation of the meal? One study (Anderson and Norman 1964) showed a primacy effect for forecasted pleasure of a meal; that is, participants generally rated meals beginning with three high-rated foods followed by three low-rated foods as better than those presented in the reverse order. A few other studies (e.g., Rogozenski and Moskowitz 1982) have demonstrated that the main course has a disproportionate effect on meal liking. The disproportionate effect of the main dish in these studies, although it is in the middle of the meal, may be because the entrée is the largest amount of food served and thus consumes the most time, and is usually the most expensive part of the meal, too. The main dish is also often the most palatable and may, in many cases, represent the peak of liking. In addition, these aforementioned studies determined that dessert is the second most predictive meal component, which is compatible with the idea that end of a sequence also contributes disproportionately to memory, a phenomenon known as the recency effect. Thus, overall these studies support the notion that meal liking is not a simple unweighted linear function of components.

The question of whether duration neglect exists in meals (or more generally, the experience of sequences of foods) has also recently been studied. For instance, do we tend to rate meals with 4 versus 8 ounces of our favorite food as equally pleasurable afterward? A set of studies involving brief or full-meal eating experiences suggest that duration neglect holds for the memory of meals. That is, doubling the amount of a particular food in a meal (often the favored food) has no effect at all on the perceived pleasure of the entire meal (Rode et al. 2007). The existence of duration neglect with respect to food implies that, with respect to memories of a meal, small portions of a highly favored dish will have roughly the same memorial effect as large portions.
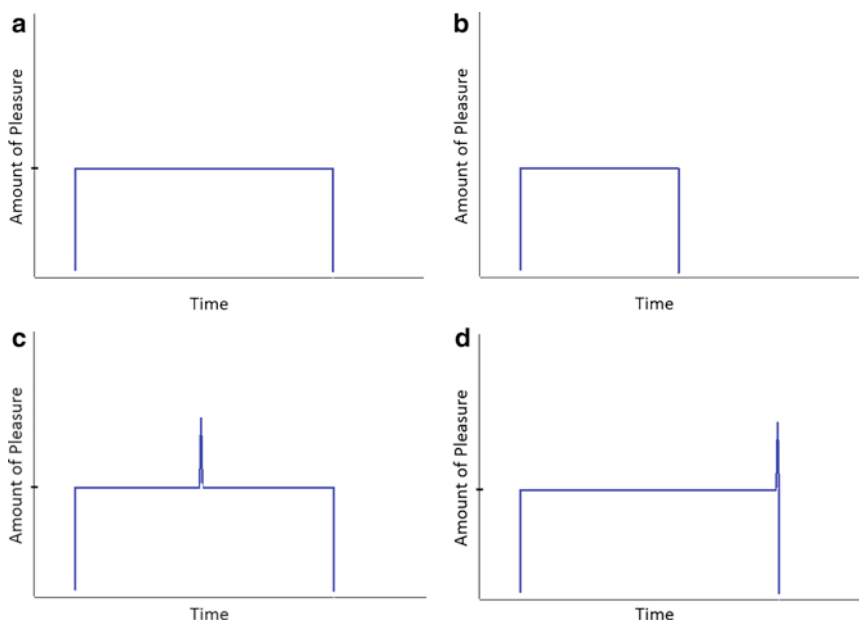
Fig. 44.3 Diagrammed examples of cognitive biases in memory for pleasure. (**a**) Is a representation of a standard pleasurable experience. (**b**) Duration neglect: The figure represents an experience that brings the same amount of pleasure as (**a**) (same height) but for half the period of time (half the length of (**a**)). Experience (**b**) is remembered as equally pleasurable as Experience (**a**), despite being shorter in duration. (**c**) Peak: Experience (**c**) is the same as experience (**a**) (same total area) except for a mid-peak of pleasure. However, this short peak of pleasure has a disproportionate effect on overall remembered pleasure of the experience: Experience (**c**) is remembered as significantly more pleasurable than experience (**a**) (or (**b**)). (**d**) Peak and End: Experience (**d**) is similar to Experience (**c**) except for a brief rising peak in pleasure at the end. As in experience (**c**), this peak has a disproportionate effect; even more so, since it occurs at the end (and is thus subject to the recency effect). Thus, Experience (**d**) is probably remembered as more pleasurable than Experience (**c**), and definitely deemed more pleasurable than Experience (**a**). For comparison, a standard experience (**a**) is depicted that brings a certain amount of pleasure (represented as the total area in the rectangle) for a certain amount of time. Experience (**b**) is remembered as equally pleasurable as experience (**a**) even though it occurs for half the time, a demonstration of duration neglect. Experience (**c**) demonstrates the disproportionate effect of peaks in pleasure, such that the total experienced pleasure is the same in (**a**) and (**c**), but (**c**) is retrospectively judged more pleasant. Experience (**d**) demonstrates that a peak in pleasure occurring at the end (recency or end effect) typically has the most remembered pleasure (with the same amount of experienced pleasure as (**a**), (**c**) and (**d**)). These schematic representations come primarily from work on negative pleasure (pain) as summarized in Kahneman et al. (1997) and Rozin (1999), but also include some parallel work on the pleasures of food (e.g., Rode et al. 2007)

44.11 Conclusion

Food intake and food choice represent major public health issues in the twenty-first century. We still do not have a satisfactory model for either what controls the amount of food humans eat, or how they make food choices. Nevertheless, it is clear that in both cases, pleasure plays a major role, but biological factors, individual experience, environmental effects, and cultural influences are also at work. A number of books also review the state of knowledge in this broad area. For the benefit of the reader, we cite some of them here (Barker 1982; Beardsworth and Keil 1995; Booth 1994; Meiselman 1996; Sobal 2006).

Summary Points

- The pleasure system, originally designed as a response to certain sensory experiences (e.g., sweetness), became involved in many more elaborate cognitive experiences as the human brain (and world) grew increasingly complex.
- Pleasure – a positive experienced state that we seek and try to maintain or enhance – plays an important role in the experience of and learning about food for humans
- As a result of preadapation, a comprehensive understanding of the role of food in the modern world involves far more than nutrition.
- The modern developed world food environment differs significantly from the human ancestral food environment in many ways that foster over-consumption and obesity. As a result, for many North Americans, food choice is often a battle between pleasure and health concerns.
- However, other cultures, such as the French, have done a better job of handling the conflicts resulting from the modern developed food world; as a result, the French experience more pleasure and less stress from eating as well as lower rates of obesity than Americans.
- Pleasure can also be studied using a temporal perspective; that is, in addition to on-line experienced pleasure, one can experience pleasure from anticipating a future event (e.g., a meal) or remembering a past one.
- Kahneman and colleagues have found that the mapping functions between experienced and remembered or anticipated pleasure are complex and may be nonmonotonic. The peak level and rapidity of offset disproportionately affect remembered pain, while duration has little effect.
- Similar studies in the food domain have documented the existence of duration neglect, suggesting that small portions of a highly favored dish will have roughly the same memorial effect as large portions.

List and Definition of Key Terms

Esthetic pleasures: Pleasures that are also linked to sensory input but are more abstract and are not physically localizable. For example, the enjoyment of a complex meal or music involves esthetic pleasures.

Mastery pleasures: Pleasures that derive from achieving something of value through acquisition of some sort of skill or sophistication. For example, becoming a wine connoisseur clearly involves mastery (as well as esthetic) pleasures.

Optimal foraging: A term used to describe the calibration of food foraging in most species such that the animal spends as little energy as possible to get the maximum energy yield. Humans in the modern developed world can now obtain food without any energy expenditure at all, which is partly why obesity is on the rise.

Pleasure: A positive experienced state that we seek and try to maintain or enhance.

Preadaptation: A fundamental process in biological and cultural evolution by which something that evolves for one purpose is co-opted for another. For example, the mouth, which originally evolved for eating, became preadapted for language as well.

Primacy effect: A cognitive bias that results from the disproportionate salience of initial stimuli or observations.

Recency effect: A cognitive bias that results from the disproportionate salience of final stimuli or observations.

Schematic model of food choice: A model first developed by Sobal et al. to understand food choice in terms of three components: the person, the food, and the situation/environment.

Sensory pleasures: Pleasures derived primarily from the contact senses that cover the body surface and apertures (e.g., the feeling of food in one's mouth and its flavor), which constitute the primitive pleasure system.

Super foods: High-calorie foods developed by humans to cater to their tastes; for instance, chocolate, which is both sweet and fatty.

Temporal framework of pleasure: Classification consisting of remembered, experienced, and anticipated pleasures, and the distinctive relations among them.

Duration neglect: A term used to describe the finding that the duration of an experience is neglected – that is, not well-represented – in the memory of that experience.

References

Anderson NH, Norman N. J Abnorm Social Psychol. 1964;69:467–71.

Appadurai A. Am Ethnologist 1981;8:494–511.

Beardsworth A, Keil T. Sociology on the menu. London: Routledge; 1995.

Barker LM. The psychobiology of human food selection. Westport: AVI; 1982.

Bentham J. Principles of morals and legislation. New York: Hafner; 1948.

Booth DA. Psychology of nutrition. London: Taylor & Frances; 1994.

Brownell KD, Horgen KB. Food fight. Chicago: Contemporary Books; 2004.

Bryant FB. J Mental Health. 2003;12:175–96.

Cabanac M. Science. 1971;173:1103–7.

Duncker K. Philos Phenomenol Res. 1941;1:391–430.

Elster J, Loewenstein G. In: Loewenstein G, Elster J, editors. Choice over time. New York: Russell Sage Foundation; 1992. p. 213–234.

Fischler C, Masson E. Manger. Français, Européens et Amérricains face à l'alimentation. Paris: Odile-Jacob; 2008.

Hill JO, Peters JC. Science. 1998;280:1371–4.

Kahneman D, Snell J. J Behav Decis Mak. 1992;5:87–200.

Kahneman D, Wakker PP, Sarin R. Quart J Econ. 1997;112:375–405.

Kass L. The hungry soul. New York: Free Press; 1994.

Levitsky DA. Physiol Behav. 2005;86:623–32.

Mayr E. In: Tax S, editors. Evolution after Darwin: Vol. 1, The evolution of life. Chicago: University of Chicago Press; 1960. p. 349–380.

Meiselman HL. In: Meiselman HL, MacFie HJH, editors. Food choice, acceptance and consumption. London: Blackie Academic & Professional; 1996. p. 239–263.

Meiselman HL. (ed.) Dimensions of the meal: the science, culture, business, and art of eating. Gaithersburg: Aspen; 2000.

Nestle M. Food politics. How the food industry influences nutrition and health. Berkeley: University of California; 2002.

Pfaffman C. Psychol Rev. 1960;67:253–68.

Pliner P, Rozin P. In: Meiselman H, editor. Dimensions of the meal: the science, culture, business, and art of eating. Gaithersburg: Aspen; 2000. p. 19–46

Rode E, Rozin R, Durlach P. Appetite. 2007;49:18–29.

Rogozenski JG Jr, Moskowitz HR. J Food Service Syst. 1982;2:139–61.

Rolls BJ, Hetherington M., Burley VJ, van Duijvenvoorde PM. In: Kare MA, Brand JG, editors. Interaction of the chemical senses with nutrition. New York: Academic; 1986. p. 247–268.

Rolls BJ. Nutr Today. 2003;38:42–53.

Rozin E. In: Barker LM, editor. The psychobiology of human food selection: Westport: AVI; 1982. p. 189–203, 225–254.

Rozin P. In Green BG, Mason JR, Kare MR, editors. Chemical senses, Volume 2: Irritation. New York: Marcel Dekker; 1990. p. 231–269.

Rozin P. In: Kahneman D, Diener E, Schwarz N, editors. Well being: The foundations of hedonic psychology. New York: Russell Sage; 1999. p. 109–133.

Rozin P. J Nutr Educ Behav. 2005;37:107–12.

Rozin P. The selection of food by rats, humans and other animals. In: Rosenblatt J, Hinde RA, Beer C, Shaw E, editors. Advances in the Study of Behavior, New York: Academic Press; 1976;6:21–76.

Rozin P, Bauer R, Catanese D. J Personal Social Psychol. 2003;85:132–41.

Rozin P, Dow S, Moscovitch M, Rajaram S. The role of memory for recent eating experiences in onset and cessation of meals. Evidence from the amnesic syndrome. Psychological Science. 1998;9:392–96.

Rozin P, Hanko K, Durlach P. Appetite. 2006;46:297–303.

Rozin P, Kabnick K, Pete E, Fischler C, Shields C. Psychol Sci. 2003;14:450–45.

Schutz HG. In: Thomson DMH, editor. Food acceptability. Essex: Elsevier Applied Science Publishers; 1989. p. 115–134.

Sobal J, Bisogni CA, Devine CM, Jastran M. In: Shepherd R, Raats M, editors. The psychology of food choice. Oxfordshire: CABI; 2006. p. 1–18.

Steiner JE. In: Reese HW, Lipsitt LP, editors. Advances in child development and behavior (vol. 13). New York: Academic; 1979. p. 257–295.

Stunkard AJ, Levitz LS. Cited in Levitz LS In: Bray GA, editor. Obesity in perspective (vol. 2, part 2). Washington, DC: US Government Printing Office; 1975; p. 53–60.

Wansink B. Ann RevNutr. 2004;24:455–79.

Wilson TD, Gilbert DT. In: Zanna M, editor. Advances in experimental social psychology. New York: Elsevier; 2003. p. 345–411.

Chapter 45
Explicit and Implicit Attitudes to Food

Maria Czyzewska, Reiko Graham, and Natalie A. Ceballos

Abbreviations

BMI	Body mass index
IAT	Implicit Association Test
EAST	Extrinsic Affective Simon Task
TFEQ-R	Three Factor Eating Questionnaire-Revised
g	Grams
kg	Kilograms
EEG	Electroencephalogram
ERP	Event-related potentials
fMRI	Functional magnetic resonance imaging

This article reviews recent developments in our understanding of attitudes as predictors of eating behavior, with special emphasis placed on a newly introduced construct of implicit attitudes. Implicit attitudes are defined as automatic affective associations elicited by objects (e.g., environmental cues, words, images, etc.) that are often inaccessible to conscious monitoring and intentional regulation. They influence immediate, spontaneous responses to attitude-relevant stimuli encountered in the environment. In contrast, explicit attitudes reflect deliberate, self-reported evaluations of the afore-mentioned stimuli that are accessible to introspective scrutiny, and under intentional control (e.g., Greenwald et al. 1998; Fazio and Olson 2003).

45.1 Implicit Versus Explicit Attitudes: Theory

Several theoretical models have been proposed to explain relationships between both types of attitudes (e.g., Fazio and Towles-Schwen 1999; Wilson et al. 2000; Strack and Deutsch 2004; Gawronski and Bodenhausen 2006). The MODE model (e.g., Fazio and Towles-Schwen 1999; Fazio and Olson 2003) posits that attitudes can influence behavior via two types of processes: deliberate and spontaneous.

M. Czyzewska (✉)
Department of Psychology, Texas State University, 601 University Drive,
San Marcos, TX, USA
e-mail: mc07@txstate.edu

The deliberate mode involves systematic processing of relevant information (e.g., a cost-benefit analysis of potential behavioral responses), the outcome of which determines the impact of an attitude on behavior. The processes involved are effortful, and therefore require motivation and opportunity (e.g., sufficient time and cognitive resources). In contrast, spontaneous processes produce immediate responses through automatic activation of relevant attitudes.

These early dual-process ideas were partially adopted by the Reflective-Impulsive Model of behavior regulation (Strack and Deutsch 2004), which is of particular interest to researchers interested in implicit cognition in addiction and disordered eating. According to this model, implicit attitudes represent the evaluative component of the impulsive system, responsible for reactions to environmental stimuli. These automatic evaluations result from spreading of activation through a network of associations in a memory system, triggered by encountered stimuli and linked to spontaneous behavioral tendencies of approach or avoidance. In contrast, the reflective system requires attentional control and regulates deliberate behavior according to long-term goals and personal standards. In some circumstances, the systems can generate conflicting behavioral tendencies (e.g., a restrained eater who experiences the desire to consume an appetizing high-calorie dessert). The ability to overcome the impulsive reaction (i.e., to restrain from eating the dessert) depends on the strength of the impulsive tendency and the availability of control resources in the reflective system. Consequently, conditions that impair control resources such as stress, fatigue, information overload, or the influence of alcohol are expected to reduce the regulatory capacity of the reflective system and to increase the likelihood of impulsive behavior. The reactivity of the impulsive system to environmental stimuli is moderated by motivational states. For example, a state of deprivation (e.g., hunger) is predicted to increase accessibility of environmental and behavioral schemata associated with need satisfaction (i.e., establish a perceptual readiness and a behavioral preparedness) and temporarily enhance perceived attractiveness of need-relevant objects (e.g., food).

Both models suggest that situational circumstances differentially impact the predictive validity of explicit and implicit attitudes. Explicit attitudes are expected to be predictive of behavior if a person has available cognitive resources and motivation to exert self-control, whereas implicit attitudes are linked to behavior occurring in states of low motivation and/or conditions in which resources are reduced.

45.2 Implicit Attitudes: Assessment

Unlike explicit, consciously represented attitudes that are traditionally assessed by different forms of self-report methods (e.g., questionnaires, rating scales), the measurement of implicit attitudes requires an indirect approach to quantify the strength of evaluative associations with attitude-eliciting stimuli. Some researchers proposed the term *indirect measures* as a more adequate description of these assessment methods because it emphasizes the nature of the testing procedure without implying assumptions about the nature of the implicit test outcomes (e.g., De Houwer 2006; Fazio and Olson 2003).

Several experimental tasks have been developed over the last decade to assess implicit attitudes, such as the Implicit Association Test, IAT (Greenwald et al. 1998), the single category IAT (Karpinski and Steinman 2006), the affective priming task (Fazio et al. 1995), the Extrinsic Affective Simon Task (EAST; De Houwer 2003), and the Go/No-go Association Task (Nosek and Banaji 2001). Despite their diversity, all available implicit measures share several common features and theoretical assumptions, some of which remain controversial (for review see Gawronski et al. 2007; Wittenbrink and Schwarz 2007). All are computerized tasks that require fast responses to long sequences of stimuli (e.g., words or images), and indices of implicit attitudes are derived from reaction times. The underlying assumption for most of these tasks is that responses are facilitated if consecutive stimuli

are closely associated. Conversely, responses are expected to be slower when consecutive stimuli have conflicting features (i.e., they trigger antagonistic attitudes). Therefore, the response latencies to a configuration of stimuli, arranged according to a design unique to each implicit task procedure, are used to infer the strength and quality of implicit associations among the stimuli.

The tasks most commonly used to assess implicit attitudes include the Implicit Association Task, IAT (e.g., Greenwald et al. 1998), the affective priming task (e.g., Fazio 2001; Fazio et al. 1995; Hermans et al. 1994), and the Extrinsic Affective Simon task, EAST (De Houwer 2003).

45.2.1 Implicit Association Test, IAT

The Implicit Association Test (IAT) measures the strength of associations between targeted concepts (e.g., high- vs. low-calorie food) and evaluative valence concepts (e.g., pleasant vs. unpleasant) by comparing response latencies in a double categorization task (e.g., Greenwald et al. 1998, 2003). In a computerized version of IAT, a participant is shown a long sequence of stimuli (words or images) in the center of the computer screen and is required to classify each stimulus, as quickly as possible, into one of four classes: attribute category (e.g., pleasant) versus attribute contrast (e.g., unpleasant) or target category (e.g., high-calorie food) versus target contrast (e.g., low-calorie food). In the crucial segment of the test (i.e., double categorization) the labels of one target category (i.e., related to attitude object) paired with one attribute category (i.e., valence) are presented on both sides of the top of the screen, one pair on each side (e.g., left side: high-calorie food or pleasant, right side: low-calorie food or unpleasant; see Fig. 45.1). Participants complete the categorization task by pressing
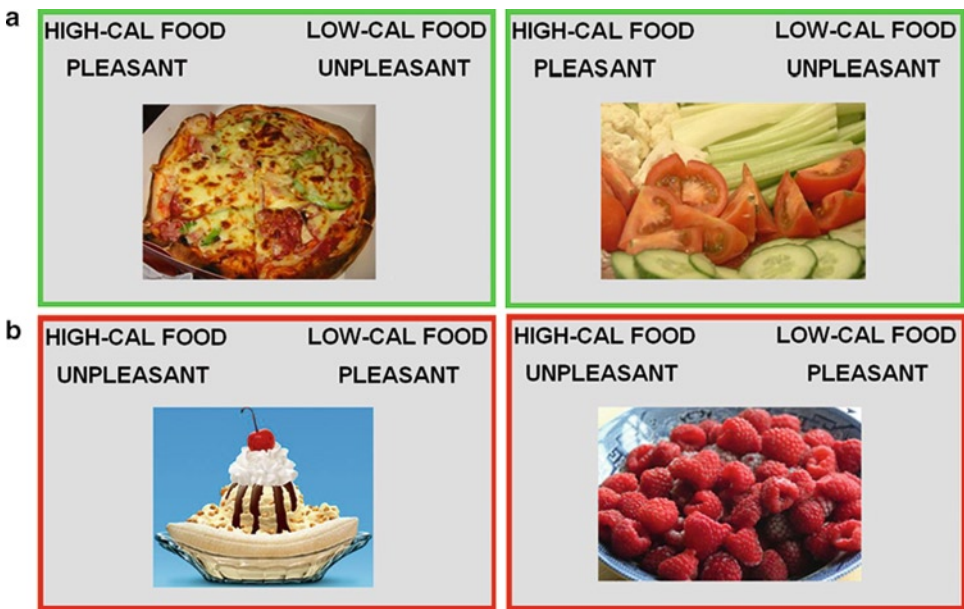
Fig. 45.1 Schematic examples of congruent (**a**) and incongruent (**b**) IAT trials for typical food preferences (i.e., implicit attitudes to high-calorie foods are more positive relative to low-calorie). It is assumed that the categorization task of food stimuli is performed faster on congruent trials compared to incongruent. The difference in reaction times to congruent and incongruent pairings provides indirect evidence of implicit attitudes to high-calorie food relative to low-calorie

Table 45.1 Key facts of the implicit association test

1. The technique was developed by social psychologists in mid-1990s (Greenwald et al. 1995, 1998) to investigate implicit stereotypes

2. Since introduction, the method has received significant attention and been used in numerous studies in various research areas (e.g., social, clinical, health, and consumer psychology)

3. It is intended to measure the strength of association between targeted concepts (e.g., high- vs. low-calorie food) and evaluative attributes (e.g., pleasant vs. unpleasant)

4. It is a computerized task that requires classification of stimuli into one of four categories with two response keys; the differences in reaction time of specific segments of the task are used as indices of implicit attitudes

5. Examples of the IAT, procedural details and extensive links to relevant literature can be accessed at https//implicit.harvard.edu

6. The IAT typically outperforms alternative implicit attitude tests (e.g., affective priming task or EAST) in psychometric properties but the technique is not free of limitations

7. The controversial issues include:

    (a) IAT measures the *relative* implicit evaluation (e.g., evaluation of high- vs. low-calorie food) and therefore, the results have to be interpreted not as an absolute evaluation of one target (e.g., high calorie food) but in the context of a specific contrast category

    (b) IAT might primarily assess evaluative associations with *categories* used in the task (e.g., high- vs. low-calorie foods) instead of evaluation of individual exemplars (i.e., specific food stimuli)

    (c) IAT results are influence by choice of contrast categories and category labels (e.g., healthy vs. unhealthy food)

    (d) IAT assessment can be confounded by processes unrelated to implicit evaluation (e.g., familiarity of the stimuli or category labels)

8. Various modifications of the basic IAT procedure attempt to address some of the limitations (e.g., Single Target IAT, Go/No Go Association Test)

The table summarizes key facts of the Implicit Association Test (for more comprehensive discussion see Lane et al. 2007)

keys corresponding to the side of the screen that includes a category label relevant to presented stimuli. It is assumed that on trials in which pairing of the target category and evaluative attribute is congruent with person's attitude to a displayed stimulus (e.g., response to a picture of pizza when high-calorie food is paired with pleasant) the categorization task is easier and therefore performed faster than if the pairing is incongruent (e.g., high calorie and unpleasant). The difference in reaction times to congruent and incongruent pairings provides indirect evidence of how the attitude-related knowledge is organized (for more details about the IAT procedure and psychometric properties of the test, see Lane et al. 2007).

The key facts of the Implicit Association Tests are summarized in Table 45.1. As discussed in the literature, the limitations of the IAT include the fact that the results of the test are strongly influenced by the attributes made salient by the labels used in the stimuli categorization task (e.g., De Houwer 2001; Karpinski and Hilton 2001) and by contrast category in the double categorization task (e.g., Robinson et al. 2005). Also, some argue that the IAT primarily measures associations at the category level rather than at the level of individual exemplars (e.g., high-calorie food overall vs. ice cream; De Houwer 2002). Some of these limitations are addressed by experimenting with modifications to the basic IAT procedure, for instance, by using a single category IAT (Karpinski and Steinman 2006) or the Go/No-go Association Task (Nosek and Banaji 2001).

45.2.2 Affective Priming Task

The Affective Priming Task, unlike the IAT, allows for the measurement of affective associations to stimuli in a way that is unbiased by the bipolar categories used in a categorization task (e.g., Fazio and Olson 2003). The task involves presentation of a prime that is evaluatively consistent or inconsistent
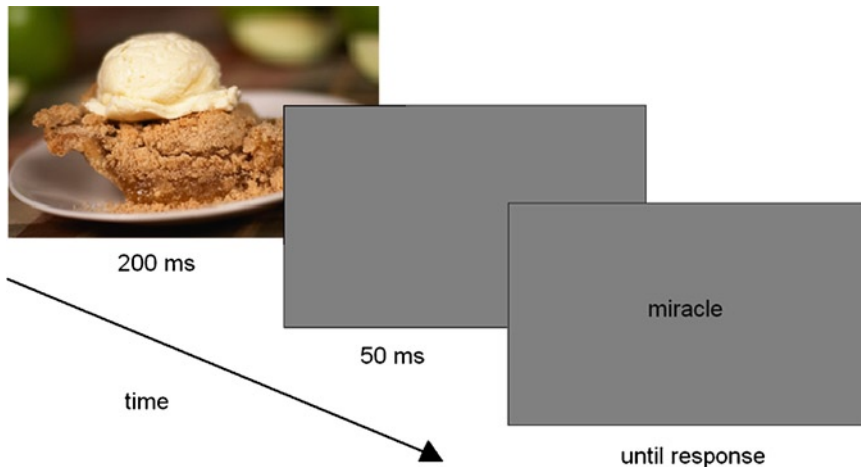
Fig. 45.2 Schematic example of a single trial of the affective priming task. It is assumed that the responses to target words (e.g., miracle) are faster if their valence is consistent with the implicit attitude to primes (e.g., positive to apple pie) compared to trails in which an automatic evaluation of the prime is inconsistent with the target word valence

with a subsequently presented target. The presentation of a stimulus (e.g., words or images related to food) as a prime is expected to activate associated evaluations and, therefore, to facilitate responses to evaluatively consistent targets (e.g., Fazio 2001). In this computerized task, participants are asked to evaluate a long sequence of rapidly presented stimuli (words or images) using bipolar valence categories (e.g., good vs. bad, positive vs. negative, pleasant vs. unpleasant). Participants respond by pressing designated response keys, and reaction time data are recorded. The presentation of each evaluated stimulus is primed (i.e., preceded) by an attitude-related stimulus (e.g., word or image related to different types of food) or a control item (i.e., word or image not related to food). The reaction times to evaluated stimuli that are primed by affectively consistent attitude-related stimuli (e.g., food pictures) are expected to be shorter than they would be if the prime/evaluated target combination were incongruent in valence. Figure 45.2 shows an example of a single trial of an Affective Priming task designed to assess attitudes to different types of food.

In this task, the difference in average reaction time to positive versus negative words preceded by the same food primes indicated the direction of implicit attitudes toward these foods (e.g., if a person has a positive implicit attitude to a high-calorie food, then his/her reaction time to a positive word primed by that high-calorie food image was expected to be shorter than his/her reaction time to a negative word primed by the same high-calorie food image).

The affective priming task has been successfully applied to examine existing and newly acquired food preferences (e.g., Lamote et al. 2004; Verhulst et al. 2006; De Houwer et al. 2009 for discussion of the psychometric properties of this test).

45.2.3 The Extrinsic Affective Simon Task, EAST

The Extrinsic Affective Simon Task (i.e., EAST) was developed as a modification of the original IAT paradigm in order to avoid problems with the potential biasing effects of category labels (De Houwer 2003). Unlike the IAT, the EAST procedure requires participants to choose between a positive or negative response to an attitude-related stimulus (word or image) on the basis of a nonevaluative
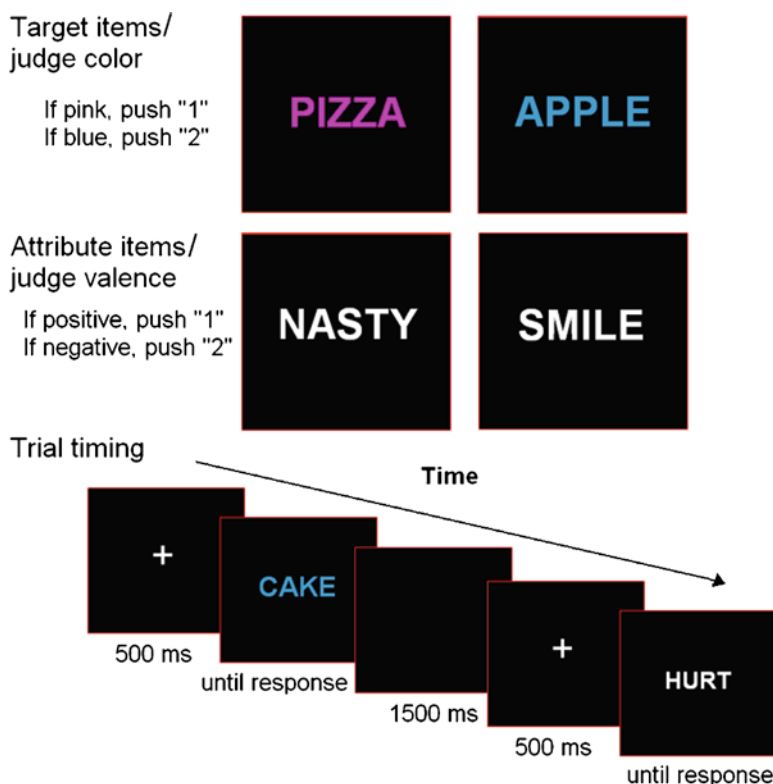
Fig. 45.3 Schematic example of the trial types and timeline used in the EAST. The four trial types are randomly presented and response type (color vs. valence judgments) is signaled by font color (white = valence judgment, blue or pink = color judgment). Response keys and target item font color are counterbalanced across subjects

feature. A part of the task is designed to develop extrinsic associations between a specific response key (e.g., right vs. left) and an evaluative meaning (e.g., positive vs. negative), resulting in the establishment of an extrinsically positive key (e.g., right) and an extrinsically negative key (e.g., left). In the subsequent segment of the task, participants are asked to categorize attitude-relevant stimuli (e.g., food-related) with respect to an irrelevant-to-stimulus valence property (e.g., color or shape) using the same two response keys (see Fig. 45.3).

The four trial types are randomly presented and response type (e.g., color vs. valence judgments) is signaled by font color (white = valence judgment, blue or pink = color judgment). Response keys and target item font color are counterbalanced across subjects.

For example, in the first part of the task (i.e., the extrinsic association component) participants could be asked to perform a typical stimulus evaluation task by pressing the right key if the presented word corresponds to positive attribute (e.g., friendly) or negative attribute (e.g., hostile). The following segment would instruct participants to categorize words based on their color using the positive response key if the word is printed in red and using the negative response key if the word is printed in green (the matching of colors/valence of the response key is counterbalanced across participants). The color words consist of attitude-related stimuli (e.g., names of food items) and controls (i.e., attribute words printed in white) to which participants are instructed to respond by indicating their valence (i.e., press a key designated as positive or negative in the previous, evaluative categorization part of the task). Subsequently, the implicit association effect is defined as the reaction time difference

in responding to food related items with a positive valence key (i.e., printed in red) versus a negative valence key (i.e., printed in green).

The EAST paradigm has been used to investigate implicit cognition in addiction (e.g., De Houwer et al. 2004; Ames et al. 2007; Birch et al. 2006) and attitudes to food (e.g., Craeynest et al. 2005; Roefs et al. 2005a; Seibt et al. 2007); however, psychometric characteristics of this method remain largely unexamined. There is evidence that the IAT outperforms the EAST in terms of reliability and predictive validity (De Houwer and De Bruycker 2007).

45.3 Individual Differences in Implicit Food Attitudes (Quasi-Experimental Designs)

Several studies have examined differences in explicit and implicit attitudes to food among participants who were expected to vary in food preferences or in their ability to control eating behavior (e.g., eating disordered vs. nonclinical or obese vs. normal weight individuals). The results of these studies, which attempted to reveal interindividual differences in automatic food preferences by comparing groups in quasi-experimental designs, have not produced conclusive results.

Roefs and Jansen (2002) examined implicit and explicit attitudes toward high-fat foods among obese versus normal weight individuals using an IAT with two target categories: high-fat versus low-fat food words and an evaluative attribute (positive vs. negative). Contrary to expectations, the results revealed a significantly stronger *negative* implicit attitude toward high-fat foods among obese participants compared to normal-weight controls. No differences were found between the groups in explicit attitudes to food: all participants reported a higher preference for low-fat versus high-fat foods. However, a subsequent study conducted in the same laboratory, but with different implicit measures (i.e., an affective priming task instead of an IAT), failed to replicate the original results, finding no significant differences between obese and normal weight adults in implicit evaluations of foods varying in fat content or palatability (Roefs et al. 2005b (Experiment 2), 2006).

Czyzewska and Graham (2008) extended previous research on high versus low fat foods by comparing implicit and explicit attitudes to three types of foods: high-calorie nonsweet, high-calorie sweet, and low-calorie foods. Female participants, varying in body mass index (BMI) status (healthy weight, overweight, and obese), completed an affective priming task (implicit) with pictures of food as primes and positive and negative words as targets of evaluative categorization. This procedure was followed by explicit rating of the same food images. The results showed a significant interaction between BMI status and type of food in terms of implicit food preferences. Implicit attitudes to high-calorie sweet foods (e.g., ice cream, cake) were significantly more *negative* in the obese group compared to healthy weight and overweight groups. However, relative to other weight groups, the obese participants exhibited significantly more *positive* implicit attitudes to high calorie nonsweet foods (e.g., pizza, steak meal). Regardless of BMI group, all participants exhibited negative implicit attitudes to low calories foods. In contrast to implicit measures of food preference, analysis of explicit ratings revealed no interaction between food type and BMI status: all participants rated high calorie nonsweet foods significantly lower than high calorie sweet and low calorie foods. A similar pattern of implicit food preferences across groups with different body weight status has also been demonstrated in a Mexican population (Czyzewska et al. 2009). Overall, the results of both studies suggest that implicit attitudes to high-calorie food, assessed by affective priming, are better predictors of unhealthy body weight, as compared to measurement of corresponding explicit attitudes. However, these findings are limited, as the behavioral consequences of differences in implicit attitudes to food across BMI groups (e.g., eating disinhibition) were not addressed.

Similar to research conducted with adults, studies examining implicit and explicit food preferences among children of different body weight statuses has produced inconsistent outcomes. A study investigating children's attitudes to healthy and unhealthy food (Craeynest et al. 2005) showed that obese children have more positive implicit attitudes to food in general (i.e., healthy and unhealthy food alike) as compared to their normal weight peers. However, across groups, no evidence of differential implicit preferences to specific types of food was found. Furthermore, no significant differences were noted between groups in their explicit attitudes to food. The implicit food preferences were measured with the EAST using food names of three healthy foods (e.g., tomato) and three unhealthy foods (e.g., crisps) as target stimuli. All target stimuli were also explicitly rated by participants. The same food attitude assessment methods were used in a longitudinal study designed to evaluate the outcomes of youth obesity treatment (Craeynest et al. 2008a). However, results indicated that participants' body weight loss in the course of the treatment was not accompanied by any significant changes in either explicit or implicit attitudes to food. In another study involving children of different BMI statuses, Craeynest et al. (2008b) investigated implicit associations between arousal and food varying in fat content using a modified version of the IAT. The modified IAT was used to assess associations between high- versus low-fat food (target category) and calm versus active (arousal attribute category). There were two versions of the IAT, one with positive words that varied in arousal (e.g., quick – high; relaxed – low) and another with negative words (e.g., impatient – high; drowsy – low). The exemplars of target category were images of lean and high-fat foods. The results revealed significant implicit associations between high-fat foods and arousal in both positive and negative versions of the IAT, which did not differ between the overweight and control groups.

Similarly, researchers examining implicit attitudes to high-fat versus low-fat food in clinical groups have found no support for the hypothesis that restrained eaters displayed greater implicit liking for high-fat palatable foods, as compared to unrestrained eaters (Roefs et al. 2005a). Another study revealed implicit preferences for palatable foods over unpalatable, independently of the food fat content, among unrestrained eaters but not among anorexia nervosa patients. According to the authors, these findings might indicate an overall decrease of the rewarding properties of food in this clinical group (Roefs et al. 2005b Experiment 1).

45.4 Situational Moderators of Attitudes as Predictors of Impulsive Eating (Experimental Designs)

Recently, several studies have attempted to verify the theoretical prediction that situational factors moderate the predictive validity of implicit versus explicit food attitudes.

Hofmann et al. (2007) demonstrated that reducing self-regulation capacity by performing an ego-depleting task (e.g., Baumeister et al. 2007) increases the relationship between implicit attitudes to candies and subsequent eating behavior. In contrast, among participants whose self-regulation capacity was not impaired by experimental manipulation, the amount of consumed candies was predicted by explicitly expressed dietary restraint standards but not by implicit attitudes.

Hofmann and Friese (2008) demonstrated that alcohol moderates the relative influence of implicit versus explicit attitudes on eating behavior. Using a single category variant of the IAT, the researchers showed that implicit attitudes to M&M's predicted amount of candies eaten, but only among participants who had previously consumed alcohol (experimental condition: acute administration of 0.4 g alcohol/kg in a vodka and orange juice mix). The eating behavior of participants without acute alcohol consumption (control condition) was primarily determined by explicit attitudes (i.e., self-reported restrained eating assessed by the Cognitive Restraint subscale of the Three Factor Eating

Questionnaire-Revised [TFEQ-R], Stunkard and Messick 1985). These results appear consistent with the model of impulsive-reflective behavior regulation (Strack and Deutsch 2004). Candy consumption was primarily regulated by explicit attitudes (i.e., reflective system) when the capacity to control behavior was uncompromised by alcohol. However, when control resources were diminished by alcohol, the automatic evaluation of M&M's (i.e., implicit attitudes) had a stronger impact on eating behavior (i.e., candy consumption became regulated by the impulsive system). However, as noted by Hofmann and Friese (2008), the mechanisms underlying the observed effects of alcohol on the relationships between implicit versus explicit attitudes and eating behavior cannot be determined conclusively. One explanation for these results is that alcohol could impair reflective regulation; however, it is equally likely that alcohol amplified impulsiveness (i.e., the strength of impulsive regulation), or both (for details see Hofmann and Friese 2008). Further investigation is needed to clarify the role of alcohol in the regulation of eating behavior. Nevertheless, the study lends credence to the idea that certain states (e.g., with alcohol-consumption vs. without) can elicit dissociations between implicit versus explicit attitudes as behavioral predictors and validates the distinction between these two constructs (i.e., two types of attitudes).

Friese et al. (2008) obtained further evidence supporting the notion that the relative predictive validity of explicit versus implicit food attitudes depends on the availability of executive/control resources. The availability of control resources was experimentally manipulated by introducing a concurrent cognitive load at the time of food selection (i.e., impairment of cognitive capacity – Experiment 1), or suppression of emotion while viewing a disturbing movie (i.e., impairment of self-regulatory resources – Experiments 2 and 3). The implicit attitudes to targeted foods/drinks (i.e., chocolate vs. fruits – Experiment 1; potato chips and beer – Experiment 2 and 3, respectively) were measured with standard or one-category IATs. Explicit attitude measures consisted of rating scales. At the end of the testing sessions, all participants were given the opportunity to sample items corresponding to foods targeted by attitude assessment (e.g., chocolates). The findings across all three studies confirmed researchers' expectations: implicit attitudes were predictive of participants' food choice behavior but only in conditions of reduced control resources. Conversely, explicit attitudes were predictive of behavior under conditions of full resources.

Several studies have examined the effect of hunger on automatic attitudes to food (Seibt et al. (2007); Safford and Scheffler 2008). In a series of three experiments, Seibt and colleagues demonstrated that participants who reported having a last meal more than 2 h earlier (i.e., deprived group) exhibited more positive implicit attitudes to food compared to a satiated group (last meal less than 2 h earlier). The effect of food deprivation on implicit food evaluation was assessed with the IAT using names of food and sport-related words as categorized stimuli (Experiment 1) and replicated with the EAST (Experiment 2). This approach allowed researchers to establish the robustness of the effect across different assessment methods and food-related stimuli (see also Stafford and Scheffer 2008 for similar findings).

The nature of the relationship between implicit attitudes toward food and attentional capture by food images remains an intriguing research question. Mogg et al. (1998) examined the effects of hunger on attentional biases toward food-related stimuli (words) using a dot-probe task and found that hungry participants were more likely to shift their attention toward food-related words relative to control words. Furthermore, the magnitude of this attentional effect was predicted by subjective hunger ratings. Further delineation of the relationships between implicit attitudes, attentional capture by food-related stimuli, hunger, and subsequent eating behavior will help to elucidate the exact means through which implicit attitudes may affect behavior.

Researchers have shown that these changes in automatic evaluative response to food-related stimuli under deprivation are accompanied by increased disposition to approach responses among participants with and without eating disorders (Seibt et al. 2007). For instance, when the EAST procedure

was modified so that the evaluative response was indicated by either pulling (approach) or pushing away (avoidance) the lever of a joystick in response to pictorial food stimuli, approach responses (toward the participant) were significantly faster among hungry participants compared to satiated participants (Seibt et al. 2007). In addition, a recent study (Harmon-Jones and Gable 2009) examined the neural correlates of approach-motivated processing elicited by pictures of desserts by examining electrical brain activity (EEG) during a selective attention task. In this study, female participants were required to identify either global or local features of Navon letters (large letters made up of closely spaced smaller letters) preceded either by dessert pictures or by neutral pictures. The purpose of this study was to examine how approach-related stimuli (desserts) affect attention and how this might be manifested in the brain. Processing of dessert pictures was associated with a narrowing of attention (an advantage for local features or the smaller letters), accompanied with increased activity over left frontal brain areas, which has been hypothesized to reflect approach-related motivation (Davidson 1995). Furthermore, these effects were positively correlated with individual differences in the number of minutes since last eating, corroborating the notion that, in addition to implicit attitudes, approach responses to food are moderated by hunger.

Taken together, the findings that hunger temporarily enhances automatic valence and approach responses to food-related words and images suggest that need states such as hunger exert their effects through the impulsive system, consistent with the Reflective-Impulsive Model (Deutsch and Strack 2006). According to this model, deprivation states modulate reactivity of the impulsive system by increasing behavioral preparedness (e.g., increased accessibility of behavioral schemata, appropriate for need satisfaction) and perceptual readiness for need-relevant stimuli (e.g., lower perceptual thresholds). Furthermore, deprivation temporarily increases the automatic valence of need-related objects (e.g., food items) and behaviors leading to need satisfaction (e.g., eating). For instance, a recent study (Stockburger et al. 2008) examining event-related electrical potentials as recorded at the scalp (ERPs) found that food deprivation specifically modulated ERPs elicited by food pictures early in the processing stream (approximately 170–300 ms after picture onset). This effect was most likely due to enhanced activity in the occipito-temporal brain regions associated with visual processing. Similar early effects in posterior brain regions have also been observed with food-related words (Leland and Pineda 2006).

Neuroimaging studies also support the notion that hunger is related to increased reactivity in the impulsive system. For example, LaBar et al. (2001) observed that food deprivation resulted in increased activity to food pictures in the amygdala, a subcortical limbic structure known to be involved in processing emotional/highly arousing stimuli, and in visual-associative regions in inferotemporal cortex. Hungry states in both adults (Morris and Dolan 2001) and children and adolescents (Holsen et al. 2005) elicit similar activations, not only in the amygdala and visual areas, but also in orbitofrontal cortex and the insula (areas associated with reward and interoception), suggesting that the patterns of neural activity that underlie food motivation are set relatively early in development (i.e., during childhood).

Hoefling and Strack (2008) have expanded upon the aforementioned work by examining the interaction between food deprivation, implicit/explicit attitudes, and disinhibition/restrained eating. The restrained and unrestrained eaters' explicit ratings and implicit evaluations of high- and low-calorie foods were examined both in food-deprived and satiated states with the EAST (De Houwer 2003). Among all participants, food deprivation increased the implicit valence of foods independent of caloric content. This effect was not significant for explicit evaluations of food items. Consistent with the authors' hypotheses, restrained eaters revealed a dissociative pattern of negative explicit but positive implicit attitudes towards high calorie foods, but not towards low calorie foods. Furthermore, the restrained eaters' explicit ratings of high calorie foods were more negative than those obtained from the unrestrained eaters, but the opposite pattern was exhibited for implicit evaluations (i.e., more positive among restrained vs. unrestrained). These conflicting evaluations arising from the reflective

and impulsive systems and the factors affecting the resolution of this conflict (the predominance of one system over another) are of critical importance to healthy food choices, particularly in individuals with weight management issues (restrained eaters).

In a related study, Stewart and Samoluk (1995) compared the acute effects of food deprivation and the chronic effects of restrained eating on the processing of appetitive cues (food and alcohol words) relative to control words (leisure words) using a modified version of the Stroop task. In this task, participants were required to name the font color of various words as quickly as possible, while ignoring their semantic content. Slowed color-naming reaction times for appetitive cues relative to control cues are indicative of interference (the automatic capture of attention by the to-be-ignored dimension). Longer latencies for appetitive cues as a function of hunger state were not observed (but see Channon and Hayward 1990; Lavy and van den Hout 1993). Rather, dietary restraint was associated with attentional capture by appetitive cues such that highly restrained eaters had significantly longer color-naming latencies compared to moderate or low restraint eaters. Thus, chronic dietary restraint seems to exert effects that are independent of hunger, possibly reflecting an underlying preoccupation with food (Stewart and Samoluk 1995) that has been observed with self-report measures (e.g., Herman and Polivy 1980). This finding may also account for similar effects (i.e., increased color-naming latencies for food-related words) observed in individuals with anorexia and bulimia relative to controls (e.g., Channon et al. 1988; Cooper et al. 1992).

45.5 Application to Other Areas of Health and Disease

The interplay between explicit and implicit attitudes and their effects on eating behaviors have important implications for health, ranging from the control of obesity (and diseases for which obesity is a significant risk factor) to eating disorders and disorders of body image. Results from the 2003–2004 National Health and Nutrition Examination Survey estimate that 66% of US adults are either overweight or obese, while approximately 17% of children and adolescents aged 2–19 years are overweight (Ogden et al. 2006). Recent data from the World Health Organization (2002) suggest that obesity is a major global health issue. With its accompanying risks for serious health problems, such as coronary heart disease, diabetes, skeletomuscular and respiratory problems, it is not surprising that obesity has been targeted as a major health issue (World Health Organization 2002). Emphasis has been placed on weight management and physical activity as the primary means of ameliorating this problem. As a consequence, dietary restraint (i.e., restricted eating) will be at the forefront of many weight management strategies. Understanding how food attitudes interact with other factors like motivational states to influence eating behaviors will give us a better understanding of the situations that elicit unhealthy food choices, leading to more effective strategies to minimize impulsive, and often unhealthy, behaviors.

Our understanding of disordered eating, whether that which accompanies anorexia or bulimia nervosa, or that which arises as a result of psychiatric illness (e.g., major depression) or emotions such as stress, will also benefit from clarification of how implicit and explicit attitudes interact to affect eating behaviors. As mentioned previously, attentional biases towards food-related stimuli (i.e., increased color-naming latencies for food-related words) have been observed in individuals with anorexia and bulimia relative to controls (e.g., Cooper et al. 1992; Channon et al. 1988). Both behavioral and neuroimaging studies suggest that disordered eating may arise in part from heightened reactivity of the impulsive system.

A recent neuroimaging study examining neural responses to food pictures in females (grouped as those with binge-eating disorder, bulimia, overweight and normal weight) after a 12-h fasting period

(Schienle et al. 2009) found that food images were rated as more pleasant and arousing than control pictures and evoked a general pattern of activity in orbitofrontal, anterior cingulate, and insular cortices consistent with hunger responses reported in other neuroimaging studies (LaBar et al. 2001; Morris and Dolan 2001; Holsen et al. 2005). However, orbitofrontal activations were most pronounced in the binge-eating group, which was interpreted as reflecting the heightened incentive value of food images in this group (Schienle et al. 2009). In contrast, bulimics showed enhanced insula and anterior cingulate activation to food pictures relative to other groups. This finding is intriguing, given the involvement of the insula in food-related responses in general, and in the interoceptive aspects of emotional experience (Craig 2008), while enhanced cingulate activity could reflect the recruitment of selective attention (Schienle et al. 2009).

Emotions can also differentially moderate appetitive responses associated with the impulsive system. Killgore and Yurgelun-Todd (2006) examined the neural responses of normal weight women who viewed photographs of high- and low-calorie foods while undergoing functional magnetic resonance imaging (fMRI). Self-reported levels of positive and negative affect had differential effects on several important appetite-related regions, most notably the orbitofrontal cortex, depending on the calorie content of the food images. When viewing high-calorie foods, women in good moods exhibited increased activity in satiety-related regions (lateral orbitofrontal cortex), but when viewing low-calorie foods, positive affect was associated with increased activity in hunger-related regions (in particular, the medial orbitofrontal, anterior cingulate, and insular cortices). The opposite pattern of activity was observed for negative affect: negative affect was associated with decreased activity in satiety-related areas in response to high-calorie foods and decreased activity in hunger areas in response to low-calorie foods. Although these results await replication, they suggest a possible neural mechanism underlying emotional eating and may explain why cravings for high calorie foods are often reported after experiencing heightened negative emotions.

45.5.1 Interaction of Food-Related Behaviors and Addiction

Further, viewing food-related pathology in terms of an "addiction" to food could provide an innovative approach to the understanding and treatment of conditions such as binge eating and obesity. Although several neurotransmitters are thought to play a role in regulating food intake, dopamine is of particular interest due to its importance in modulating food reward via the mesolimbic pathway of the brain (from the ventral tegmental area in the brainstem, via the nucleus accumbens, into the orbitofrontal cortex). From a neurobiological perspective, addiction is thought to progress through a process of "incentive sensitization" in which appetitive motivations are important (e.g., Robinson and Berridge 1993). In this framework, the term sensitization refers to the hypersensitization of the reward circuitry of the brain (namely, the amygdala, nucleus accumbens, anterior cingulate, and orbitofrontal cortices) to the effects of addictive substances and stimuli associated with addictive substances. This sensitization effect occurs through the release of the neurotransmitter dopamine, which is elicited not only by "rewards" such as addictive substance (e.g., alcohol, tobacco, and illicit drugs), but also by "natural" rewards such as food and sex. Such hypersensitization or hyperarousal to implicit associations may influence behavior without conscious awareness (e.g., Robinson and Berridge 1993). That is, once an individual uses and becomes sensitized to a substance, neurotransmitter systems within the reward/addiction centers of the brain will be more likely to be activated by the presence of that substance, or even to related cues such as the sight or smell of a substance.

Applying the incentive-sensitization theory to the case of food-related addictions, the exposure to specific foods (such as high-calorie desserts) may sensitize the brain's addiction circuits, leading

to hyperarousal in the presence of these foods or in response to dessert-related cues such as words (e.g., cheesecake, pie, or candy), images (e.g., pictures of cheesecake pie or candy) or other sensory stimuli (e.g., the smell of cheesecake, pie, or candy). Eventually, with increased consumption of high calorie desserts, addictive behaviors may develop, in part through mechanisms that are below the level of conscious control (e.g., implicit, impulsive, and automatic; Houben and Wiers 2008; Evans and Coventry 2006). In keeping with this hypothesis, Wang and colleagues (2001) found that striatal D2 dopamine receptor availability (including D2 availability in the nucleus accumbens) was significantly lower in severely obese individuals relative to controls – a pattern that is also observed in drug-addicted individuals. Furthermore, individual differences in D2 receptor availability were negatively correlated with BMI across all subjects. These findings raise the possibility that "food addicts", especially those who are obese, may persist in engaging in pathological (but rewarding) behaviors such as overeating as a way of compensating for decreased activation in these reward circuits.

In summary, recognizing the potentially common pathways between overindulgence in dopamine-eliciting substances and activities could lead to new and innovative means of measuring, preventing, and treating a wide range of health risk behaviors.

Summary Points

- Theory predicts that explicit (i.e., self-reported) attitudes are predictive of deliberate behaviors (e.g., intentional food choices) and implicit (i.e., automatic) attitudes are linked to impulsive actions (e.g., disinhibition in eating).
- Explicit attitudes are expected to be predictive of behavior if a person has available cognitive resources and motivation to exert self-control, whereas implicit attitudes are linked to behavior occurring in states of low motivation and/or conditions in which resources are reduced.
- Several computerized tasks have been developed over the last decade to indirectly assess implicit attitudes based on a response time to attitude-related stimuli; IAT, Affective priming task and EAST are among those most commonly used by researchers interested in studying eating behavior.
- Results of studies that attempted to reveal interindividual differences in implicit food attitudes by comparing groups in quasi-experimental designs (i.e., obese vs. normal weight individuals or eating disordered vs. nonclinical) have not produced conclusive results.
- More consistent and promising are results emerging from experimental studies, which tested theoretical prediction by manipulating the availability of self-regulatory resources or motivational states (i.e., food deprivation).
- Depletion of cognitive resources, whether via ego-depletion or alcohol administration, appears to facilitate the implicit valence of food and increase the influence of implicit (automatic) versus explicit (reflective) attitudes on eating behavior (see Tables 45.2–45.4 for summary).
- Food deprivation appears to temporarily enhance automatic valence and approach responses to food-related stimuli, suggesting that need states such as hunger exert their effects through the impulsive system, consistent with the Reflective-Impulsive Model predictions.
- Neuroimaging studies also support the notion that hunger is related to increased reactivity in the impulsive system (see Table 45.5 for summary).
- Viewing food pictures while hungry leads to increased neural activity in the amygdala, a subcortical limbic structure of the brain known to be involved in processing emotional/highly arousing stimuli, and in visual-associative regions in the brain's inferotemporal cortex.
- Viewing images of food appears to evoke neural activity within several brain regions including the orbitofrontal cortex, the anterior cingulate, and the insular cortices. Positive and negative

Table 45.2 Summary of food-related studies using implicit association tests

Authors	Task description	Population(s)	Study design	Outcome
Roefs and Jansen (2002)	Target: high-fat vs. low-fat food words Evaluative attribute: positive vs. negative words	Obese vs. normal-weight adults	Quasi-experimental, cross-sectional	More *negative* implicit attitudes to high-fat foods among obese participants vs. normal-weight controls
Craeynest et al. (2008b)	Targets: high- vs. low-fat foods Arousal attributes: calm vs. active words	Overweight vs. normal-weight adults	Quasi-experimental, cross-sectional	Implicit associations between high-fat foods and arousal but no group differences
Hofmann et al. (2007)	Targets: pictures of M&Ms. Evaluative attribute: positive/negative pictures and words	Healthy adults	Experimental, Cross-sectional *Manipulation: Ego depletion*	Ego-depletion increased the relationship between implicit attitudes to candies and subsequent eating behavior
Hofmann and Friese (2008)	Targets: pictures of M&Ms. Attribute stimuli: positive pictures and words, negative pictures and words	Healthy adults	Experimental, cross-sectional *Manipulation: alcohol administration*	With alcohol administration, implicit attitudes to M&M's predicted amount of candies eaten
Friese, Hofmann, and Wanke (2008)	Targets: foods/drinks (i.e., chocolate vs. fruits – Experiment 1, potato chips and beer – Experiment 2 and 3) standard or one-category IATs	Healthy adults	Experimental, cross-sectional *Manipulation: cognitive load or emotion suppression*	Implicit attitudes were predictive of participants' food choice behavior but only in conditions of reduced control resources
Seibt, Hafner, and Deutsch (2007, Experiment 1)	Targets: foods vs. sport-related words Evaluative attribute: positive vs. negative words	Healthy adults	Experimental, cross-sectional *Manipulation: hunger*	The satiated group exhibited more positive implicit attitudes to food compared to a deprived group

This table provides the reader with a comprehensive overview of studies that have used IATs for implicit attitudes assessment to investigate reactions to food-related stimuli, along with descriptions of study populations, designs, and main outcomes

Table 45.3 Summary of food-related studies using Extrinsic Affective Simon Tasks

Authors	Task description	Population(s)	Study design	Outcomes
Roefs et al. (2005a, Experiment 2)	Target stimuli: palatable vs. unpalatable food names	Restrained and unrestrained eaters	Quasi-experimental, cross-sectional	Null: The hypothesis that restrained eaters would show a stronger liking for (high-fat) palatable foods was not supported
Craeynest et al. (2005)	Target stimuli: food names of healthy foods and unhealthy foods	Obese and normal weight children	Quasi-experimental, cross-sectional	Null: Across groups, no evidence of differential implicit preferences to specific types of food was found
Craeynest et al. (2008a)	Target stimuli: food names of healthy foods and unhealthy foods	Children undergoing a youth obesity treatment program.	Quasi-experimental, longitudinal	Null: Participants' body weights were not accompanied by significant changes in attitudes to food
Seibt, Hafner and Deutsch (2007, Experiment 2)	Target stimuli: flower names, food names, and non-words	Healthy adults	Experimental, cross-sectional *Manipulation = hunger*	The satiated group exhibited more positive implicit attitudes to food compared to a deprived group
Hoefling and Strack (2008)	Target stimuli: high-calorie and low-calorie food-related words and control words	Restrained and unrestrained eaters	Experimental, cross-sectional *Manipulation = hunger*	Across groups, hunger increased the implicit valence of foods, independent of caloric content. Restrained eaters: dissociative patterns of explicit and implicit attitudes toward high-calorie foods

This table provides the reader with a comprehensive overview of studies that have used EASTs for implicit attitudes assessment to investigate reactions to food-related stimuli, along with descriptions of study populations, designs, and main outcomes

Table 45.4 Summary of food-related studies using affective priming tasks

Authors	Task description	Population (s)	Study design	Outcome
Roefs et al. (2005a, Experiment 1)	Primes: High- and low-fat food words; Targets: Positive and negative words	Restrained and unrestrained eaters	Quasi-experimental, cross-sectional	Null: No differences in implicit attitudes to high/low fat food between groups
Roefs et al. (2005b, Experiment 1)	Primes: high/low fat and palatable/unpalatable food words; Targets = negative and positive words	Female Anorexia nervosa patients and unrestrained eaters	Quasi-experimental, Cross-sectional	Unrestrained controls only: implicit preference for palatable foods vs. unpalatable foods
Roefs et al. (2005b, Experiment 2)	Primes: High/low fat and palatable/unpalatable foods; Targets: Negative and positive words	Obese adult females and unrestrained eaters	Quasi-experimental, cross-sectional	Null: no group differences in implicit attitudes to food
Roefs et al. (2006)	Primes: high/low-fat and palatable/unpalatable food words; Targets: Positive and negative words	Obese and normal weight adults	Quasi-experimental, cross-sectional	Null: no significant differences between obese and normal weight adults in implicit evaluations of foods varying in fat content or palatability
Czyzewska and Graham (2008)	Primes: Pictures of high/low calorie and sweet/savory foods; Targets: Positive and negative words	Female participants, varying in BMI status	Quasi-experimental, cross-sectional	Differential pattern of implicit attitudes to food categories between BMI groups but no differences in explicit attitudes

This table provides the reader with a comprehensive overview of studies that have used affective priming tasks for implicit attitudes assessment to investigate reactions to food-related stimuli, along with descriptions of study populations, designs, and main outcomes

Table 45.5 Summary of food-related studies using electroencephalographic (EEG), event-related potential (ERP) and neuroimaging methodologies

Authors	Task description	Population	Study design	Outcome
LaBar et al. (2001)	Participants viewed images of food, tools and Gaussian-blurred objects and detected blinking stimuli	Healthy adults	Experimental, Cross-sectional Methodology: fMRI, *Manipulation: hunger*	Food deprivation was associated with increased activity to food pictures in the amygdala and in visual-associative regions of the inferotemporal cortex
Stockburger et al. (2008)	Participants passively viewed food and nonfood pictures	Healthy adults, males only	Experimental, Cross-sectional Methodology: ERP, *Manipulation: hunger*	Food deprivation modulated ERPs elicited by food pictures 170–300 ms after picture onset, likely due to enhanced activity in the occipito-temporal brain regions
Harmon-Jones and Gable (2009)	Selective attention task. Global or local features of Navon letters were identified, preceded either by dessert or neutral pictures	Healthy adults, females only	Experimental, Cross-sectional Methodology: EEG	Processing of dessert pictures was associated with a narrowing of attention and increased activity over left frontal brain areas
Schienle et al. (2009)	Participants passively viewed pictures of high-calorie food, disgust-inducing items, and neutral items	Females with binge-eating disorder, bulimia, overweight and normal weight	Quasi-experimental, cross-sectional Methodology: fMRI	Food images evoked activity in orbitofrontal, anterior cingulate, and insular cortices. Orbitofrontal activations were most pronounced in the binge-eating group. Bulimics showed enhanced insula and anterior cingulate activation
Killgore and Yurgelun-Todd (2006)	Participants viewed images of high- and low-calorie foods, as well as nonedible food-related utensils	Healthy adults, females only	Experimental, Cross-sectional Methodology: fMRI	Self-reported levels of positive and negative affect had differential effects on appetite-related brain regions depending on the calorie content of the food images; the opposite for negative affect

This table provides the reader with a comprehensive overview of studies that have used EEG, ERP, and/or neuroimaging methodologies to investigate reactions to food-related stimuli, along with descriptions of study populations, designs, and main outcomes

mood states may have an important effect on the activity of these brain regions, depending on the calorie content of food images.
- In some cases, unhealthy eating behaviors may be viewed as a "food addiction" in which the exposure to specific foods may sensitize the brain's addiction circuits leading to hyperarousal in the presence of these foods or related cues.
- A better understanding of the roles of implicit and explicit attitudes in eating behavior regulation (i.e., impulsive vs. deliberate actions) will help us to better understand why diets so often fail and may inform about the factors affecting the development and treatment of disordered eating in general.

Definitions of Key Terms

Explicit attitudes: Deliberate, self-reported evaluations of the attitude-related objects (e.g., food) that are accessible to introspective scrutiny; traditionally assessed by different forms of self-report methods (e.g., questionnaires, rating scales).

Implicit attitudes: Automatic affective associations elicited by objects (e.g., environmental cues, words, images, etc.) that are often inaccessible to conscious monitoring and intentional regulation and influence immediate, spontaneous responses to attitude-relevant stimuli encountered in the environment.

Control resources: A construct used in psychology to describe a capacity to exert volitional control on behaviors and mental states (e.g., emotions).

Reward value: The hedonic value or amount of pleasure derived/anticipated from a particular behavior (e.g., eating, doing drugs). Objects with high reward value are assumed to capture attention and elicit approach-related behaviors. It is speculated that objects with high reward value (e.g., high calorie foods) exert their effects on attention and behavior via the impulsive system.

Orbitofrontal cortex: An area of the frontal lobes, behind the eyes, that receives inputs from sensory and emotional processing regions of the brain. Although the functions of the orbitofrontal cortex is not well understood, it is thought to be involved in sensory integration, representing the reward value of stimuli, in decision-making and the formation of expectations, and in the regulation of behavior, in particular with regard to reward and punishment (Bechara et al. 1994).

Amygdala: A subcortical structure of the limbic system located in the medial temporal lobes with rich interconnections with other areas of the limbic system that control emotional responses and the insular, anterior cingulated sensory and frontal areas. The amygdala plays a central role in coordinating behavioral, autonomic, and hormonal responses to stimuli with motivational significance.

Insular cortex: An area of the cerebral cortex that is hidden from view, lying underneath the frontal and anterior temporal lobes. This region receives inputs from the autonomic and somatosensory nervous systems, as well as areas involved in processing emotion, and is thought to be involved in processing information about an individual's current interoceptive state (see Craig 2008 for a review), including hunger, cravings, and satiety. This region is thought to play key role in emotional processing and a role in decision-making on a "gut level" in general.

Anterior cingulate cortex: The frontal region of cingulate cortex, which is situated above the corpus callosum in the medial areas of the brain which is interconnected with emotional regions (limbic system) and appears to play a role in a wide variety of functions, such as regulating autonomic activity, selective attention, reward anticipation, decision-making, and the resolution of conflict.

References

Ames SL, Grenard JL, Tush C, Sussman S, Wiers RW. Exp Clin Psychopharmacol. 2007;15:204–18.

Baumeister R, Vohs KD, Tice DM. Curr Dir Psychol Sci. 2007;16:351–5.

Bechara A, Damasio AR, Damasio H, Anderson SW. Cognition. 1994;50:7–15.

Birch CD, Stewart SH, Zack M. In: Wiers RW, Stacy AW, editors. Handbook of implicit cognition and addiction. Thousands Oaks: Sage; 2006. p. 267–80.

Channon S, Hayward A. Int J Eating Disord. 1990; 9:447–52.

Channon S, Hemsley D, de Silva P. Br J Clin Psychol. 1988;27:259–60.

Cooper MJ, Anastasiades P, Fairburn CG. J Abnorm Psychol. 1992;101:352–5.

Craeynest M, Crombez G, De Houwer J, Deforche B, Tanghe A, De Bourdeaudhuii I. Behav Res Ther. 2005;43:1111–20.

Craeynest M, Crombez G, De Houwer J, Deforche B, De Bourdeaudhuii I. J Behav Ther Exp Psychiatry. 2006;37:347–57.

Craeynest M, Crombez G, Deforche B, Tanghe A, De Bourdeaudhuii I. Eat Behav. 2008a;9:41–51.

Craeynest M, Crombez G, Koster EH, Haerens L, De Bourdeaudhuii I. J Behav Ther Exp Psychiatry. 2008b;38:354–68.

Craig AD. In: Lewis M, Haviland-Jones JM, Barrett LF, editors. Handbook of emotions. New York: Guilford; 2008. p. 272–88.

Czyzewska M, Graham R. Eat Behav. 2008;9:303–12.

Czyzewska M, Padilla B, Graham R, Ceballos N. American Psychological Society Annual Meeting, San Francisco, CA, 2009.

Davidson RJ. In: Davidson RJ, Hugdahl K, editors. Brain asymmetry. Cambridge: MIT; 1995. p. 361–87. Houben K, Wiers RW. Behav Res Methods. 2008;40:1134–1143.

De Houwer J. J Behav Ther Exp Psychiatry. 2002;33:115–133.

De Houwer J. J Exp Soc Psychol. 2001;37:77–85.

De Houwer J. In: Wiers RW, Stacy AW, editors. Handbook of implicit cognition and addiction. Thousand Oaks: Sage; 2006. p.11–28.

De Houwer J. J Exp Psychol. 2003;50:77–85.

De Houwer J, Crombez, G, Koster EH, DeBeul N. J Behav Ther Exp Psychiatry. 2004;35:275–286.

De Houwer J, De Bruycker E.. Br J Soc Psychol. 2007;46:401–21.

De Houwer J, Teige-Mocigemba S, Spruyt A, Moors A. Psychol Bull. 2009;135:347–8.

Deutsch R, Strack F. In: Wiers RW, Stacy AW, editors. Handbook of implicit cognition and addiction. Thousand Oaks: Sage; 2006. p. 45–59.

Dovidio JE, Kawakami K, Johnson C, Johnson B, Howard A. J Exp Soc Psychol. 1997;33:510–40.

Evans JSBT, Coventry K. In: Wiers RW, Stacy AW, editors. Handbook of implicit cognition and addiction. Thousand Oaks: Sage; 2006. p. 29–43.

Fazio RH. Cogn Emotion. 2001;15:115–41.

Fazio RH, Olson MA. Annu Rev Psychol. 2003;54:297–327.

Fazio RH,Towles-Schwen T. In: Chaiken S, Trope Y, editors. Dual process theories in social psychology. New York: Guilford; 1999. p. 97–116.

Fazio RH, Jackson JR, Dunton BC, Williams CJ. J Pers Soc Psychol. 1995;69:1013–27.

Friese M, Hofmann W, Wanke M. Br J Soc Psychol. 2008;47:397–419.

Gawronski B, Bodenhausen GV. Psychol Bull. 2006;132:692–731.

Gawronski B, LeBel EP, Peters KR. Perspect Psychol Sci. 2007;2:181–93.

Greenwald AG, McGhee DE, Schwartz JLK. J Pers Soc Psychol. 1998;74:1464–80.

Greenwald AG, Nosek BA, Banaji MR. J Pers Soc Psychol. 2003;85:107–216.

Harmon-Jones E, Gable PA. Psychol Sci. 2009;20:406–9.

Herman CP, Polivy J. In: Stunkard A, editor. Obesity. Philadelphia: Saunders; 1980. p. 208–25.

Hermans D, De Houver J, Eelen P. Cogn Emotion. 1994;8:515–33.

Hoefling A, Strack F. Appetite. 2008;51:681–9.

Hofmann W, Friese M. J Abnorm Psychol. 2008;117:420–7.

Hofmann W, Rauch W, Gawronski B. J Exp Soc Psychol. 2007;43:497–504.

Holsen LM, Zarcone JR, Thompson TI, Brooks WM, Anderson MF, Ahluwalia JS, Nollen NL, Savage CR. Neuroimage. 2005;27:669–76.

Houben K, Wiers RW. Behav Res Methods. 2008;40:1134–1143.

Karpinski A, Hilton JL. J Pers Soc Psychol. 2001;81:774–88.

Karpinski A, Steinman RB. J Pers Soc Psychol. 2006;91:16–32.

Killgore WDS,Yurgelun-Todd DA. Int J Eat Disord. 2006;39:357–63.

LaBar KS, Gitelman DR, Parrish TB, Kim Y-H, Nobre AC, Mesulam MM. Behav Neurosci. 2001;115:493–500.

Lamote S, Hermans D, Baeyens F, Eelen P. Appetite. 2004;42:279–86.

Lane KA, Banaji MR, Nosek BA,Greenwald AG. In: Wittenbrink B, Schwarz N, editors. Implicit measures of attitudes. New York: Guilford; 2007. p. 59–102.

Lavy EH, van den Hout MA. Behav Cogn Psychother. 1993;21:297–310.

Leland D, Pineda J. Clin Neurophysiol. 2006;117:67–84.

Mogg K, Bradley BP, Hyare H, Lee S. Behav Res Ther. 1998;36:227–37.

Morris JS, Dolan RJ. J Neurosci. 2001;21:5304–10.

Nosek BA, Banaji MR. Soc Cogn. 2001;19:625–64.

Ogden CL, Carroll MD, Curtin LR, McDowell MA, Tabak CJ, Flegal KM. JAMA. 2006;295:1549–55.

Payne B, Cheng CM, Govorun O, Stewart BD. J Exp Soc Psychol. 2005;89:277–93.

Robinson MD, Meier BP, Zetocha KJ, McCaul KD. Basic Appl Soc Psychol. 2005;27:201–12.

Robinson TE, Berridge KC. Brain Res Rev. 1993;18:247–91.

Roefs A, Jansen A. J Abnorm Psychol. 2002;111:517–21.

Roefs A, Heramn CP, MacLeod CM, Smulders FTY, Jansen A. Appetite. 2005a;44:103–14.

Roefs A, Stapert D, Isabella LAS, Wolters G, Wojciechowski F, Jansen A. Eat Behav. 2005b;6:151–63.

Roefs A, Quaedackers L, Werrij MQ, Wolters G, Havermans R, Nederkoorn C, van Breukelen G, Jansen A. Behav Res Ther. 2006;44:715–36.

Schienle A, Schäfer A, Hermann A, Vaitl D. Biol Psychiatry. 2009;65:654–61.

Seibt B, Hafner M, Deutsch R. Eur J Soc Psychol. 2007;37:359–79.

Stafford LD, Scheffler G. Appetite. 2008;51:731–4.

Stewart SH, Samoluk SB. Int J Eat Disord. 1997;21:129–35.

Stockburger J, Weike AI, Hamm AO, Schupp HT. Behav Neurosci. 2008;122:936–42.

Strack F, Deutsch R. Pers Soc Psychol Rev. 2004;8:220–47.

Stunkard AJ, Messick S. J Psychosom Res. 1985;29:71–83.

Verhulst F, Hermans D, Baeyens F, Spruyt A, Eelen P. Appetite. 2006;46:137–43.

Wang G-J, Volkow ND, Logan J, Pappas NR, Wong CT, Zhu W, Netusil N, Fowler JS. Lancet. 2001;357:354–7.

Wentura D, Rothermund K. In: Wittenbrink B, Schwarz N, editors. Implicit measures of attitudes. New York: Guilford; 2007. p. 195–215.

Wilson TD, Lindsey S, Schooler TY. Psychol Rev. 2000;107:101–26.

Wittenbrink B, Schwarz N. Implicit measures of attitudes. New York: Guilford; 2007.

WHO/FAO Expert Consultation on Diet Nutrition and the Prevention of Chronic Diseases. WHO Technical Report Series 916. Geneva: World Health Organization; 2002.

Chapter 46
Impact of Eating and Lifestyle Behaviors on Body Weight: Beyond Energy Value

Vicky Drapeau, Marion Hetherington, and Angelo Tremblay

Abbreviations

BMI   Body mass index
RMR   Resting metabolic rate
SQ   Satiety quotient
STR   Sensitivity to reward
TFEQ   Three-factor eating questionnaire
VAS   Visual analogue scale

46.1 Introduction

The excess body fat characterizing obesity is well recognized for its conformity with the first law of thermodynamics. Specifically, this notion stipulates that a large body fat deposition is necessarily the outcome of an excess energy intake over expenditure over time. For many scientists and health professionals, this observation is sufficient to deduce that an unhealthy diet with a high fat content and lack of physical activity should be the main causes of obesity. However, recent research reveals that factors with "no energetic value" might have a better predictability of variations in body fat.

Eating behaviors are part of these factors which have been identified to play an important role in the regulation of energy balance and thus body weight. In this chapter, we describe eating behaviors by referring to experimental research and related clinical experience which are generally overlooked in obesity treatment. The intention is not to provide a full review of the literature regarding behaviors implicated in body weight variations, which has been done elsewhere (Elfhag and Rossner 2005), but rather to highlight some eating behaviors that could be assessed in a clinical context. Another aim of this chapter is to provide potential solutions which could help health professionals in obesity treatment and prevention.

V. Drapeau (✉)

Department of physical education, Laval University, Quebec City, Canada
e-mail: vicky.drapeau@fse.ulaval.ca

46.2 Eating and Lifestyle Behaviors Influencing Body Weight

46.2.1 *Restriction and Attempts to Lose Weight*

Restrained eating and attempts to lose weight are experienced by a large proportion of obese individuals referred within clinical settings. This is not surprising since energy or specific macronutrient restriction is the main strategy recommended in most popular diets (Freedman et al. 2001; Volpe 2006) and that moderate energy restriction (–500 kcal/day) remains one of the main weight loss strategies recommended in the last Canadian obesity guidelines (Lau et al. 2007). Although this seems to be the most convenient solution to create an energy deficit, it is maybe counterproductive in the long term since most of the weight loss interventions which include restriction showed a low rate of success for weight loss maintenance in the long term (Wadden 1993; Freedman et al. 2001; Wing and Hill 2001; Gilden Tsai and Wadden 2006; Sherer and Sherer 2008). These observations are consistent with the controversy surrounding restrained eating and body weight. Indeed, restrained eating has not always been associated with lower energy intake or lower body weight (Lawson et al. 1995; Lindroos et al. 1997; Hays et al. 2002; Provencher et al. 2003). Instead, some studies have shown higher body weight gain over time in individuals with high restraint scores compared to those individuals with a lower restraint score (Klesges et al. 1992; Stice et al. 1999; Drapeau et al. 2003).

It is also relevant to question whether dietary restriction and weight loss behaviors could be responsible for the increase in hunger and negative affect associated with weight loss (Stein et al. 2007). Accordingly, it has been observed that hunger increases in obese individuals submitted to a moderate energy restriction (Doucet et al. 2000b) and represents a predictor of weight regain in weight-reduced obese individuals (Pasman et al. 1999). The relationship between energy restriction and changes in appetite sensations has been observed in many studies. Recently, Gilbert et al. quantified this relationship in a group of obese women subjected to a moderate energy restriction (–2,900 kJ/day). They estimated that for each kilogram of body fat loss, a 5.8 mm increase in desire to eat and a 3.6 mm decrease in fullness on a 150 mm line scale were predicted (Gilbert et al. 2009). In another study, Chaput et al. (2007c) investigated the impact of weight loss until weight loss plateau (no further weight loss during a 1-month period) on changes in hunger, restrained eating, and depression. After 7–14 months of intervention and a body weight loss of 11.2% baseline level, appetite sensations such as the desire to eat, hunger, and prospective food consumption increased along with restrained eating. Interestingly, depression, as measured with the Beck Depression Inventory (Beck 1961), also increased between baseline and the plateau.

Energy restriction could also lead to more severe eating behavior problems such as binge eating. Accordingly, Wadden et al. (2004) reported in a randomized control trial comparing two levels of energy restriction (1,000 kcal/day meal replacement or 1,200–1,500 kcal balanced deficit diet) that more individual cases of binge eating episodes were observed in the 1,000 kcal/day meal replacement condition. Even though binge eating episodes can be observed after severe energy restriction (Wadden et al. 2004), and moderate energy restriction can enhance, in some individuals, the negative affect and subjective sensations of hunger (Chaput et al. 2007c) (which could lead to binge eating), it is important to note that energy restriction per se is not sufficient to produce binge eating. Indeed, almost half of binge eaters report that their first binge eating episode occurred at a time when they were not dieting (National Task Force on the Prevention and Treatment of Obesity 2000). In support of this observation, a recent study observed that negative mood and hunger were both significantly higher during prebinge than during nonbinge periods, and that negative mood was even higher after binge eating (Stein et al. 2007). However, binge episodes were more frequently attributed by participants to mood

than to hunger or abstinence violation (Stein et al. 2007). Consequently, binge eating could emerge as a function of attempts to restrict intake, difficulty to resist temptation to eat, and to comply with even a moderately energy-restricted diet, particularly when this influences negative affect and hunger.

It is interesting to note that restrained eating is often coupled with disinhibition which means that efforts to restrict coexist with the tendency to abandon such efforts resulting in overeating. This can be particularly true for rigid restraint, i.e., an all-or-nothing approach to eating, dieting, and weight management. Rigid application of restraint has been associated with higher disinhibition, higher body mass index (BMI), as well as to more frequent and more severe binge eating episodes (Westenhoefer et al. 1999). However, it is not clear whether restrained eating occurs in response to the obese/overweight state, to unwanted weight gain in lean individuals, or the desire to prevent future weight gain. Thus, restrained eating and attempts to lose weight may reflect a general susceptibility to weight gain. Part of this susceptibility is evidenced in the tendency to break (cognitive) restraint (or dieting) and to overeat (disinhibition).

Beside their impact on energy intake and binge eating episodes, restrained eating and multiple attempts to lose weight can also modulate the biological environment in a manner that they render individual efforts to lose weight useless. Accordingly, intervention studies have shown that the decrease in energy expenditure during energy restriction and weight loss can be much higher than that predicted from body weight or body fat loss under conditions of standardized physical activity (Leibel et al. 1995; Doucet et al. 2001). This phenomenon is also called "adaptive thermogenesis" (Major et al. 2007). In one study, measured resting metabolic rate (RMR) had fallen by 469 and 635 kJ/day more than predicted after only 2 weeks of energy restriction in men and women, respectively, and this difference reached 953 and 614 kJ/day after 8 weeks of treatment (Doucet et al. 2001). This adaptation does not necessarily return to normal after body weight stabilization and can be observed without initial body weight loss. Thus, it has also been observed that changes in RMR remain below predicted levels in men (–622 kJ/day) once body-weight stability recovered (Doucet et al. 2001). In some cases, this phenomenon could explain why little or no weight loss is observed in response to energy restriction. Indeed, a decrease in RMR has also been observed in response to energy restriction without significant body weight loss (Prentice et al. 1991; Wadden et al. 1996). An example of this phenomenon is the case of an obese woman who was resistant to weight loss when submitted to a traditional energy deficit of 2,100 kJ/day (Tremblay et al. 2007) in our clinical settings. Even though this woman reported good compliance, she did not lose weight at the end of the weight loss program intervention. Measured RMR before and after the intervention showed a decrease equivalent to the energy deficit (2,100 kJ), which could explain the resistance to weight loss. This case may well represent an exception but it emphasizes the importance of considering adaptive thermogenesis as a phenomenon that has the capacity to compensate for the prescribed energy restriction and thus limit the efficiency of weight reduction programs. It is also important to note that this adaptive thermogenesis in response to energy restriction can be observed in any component of total energy expenditure (Major et al. 2007).

In a clinical context, a greater than predicted decrease in energy expenditure can complicate weight loss, its maintenance, and the clinical care of the patient because it is generally not considered by health professionals treating obesity. Often, it is identified as "underreporting" or even "lying" when weight loss does not occur. Because restriction represents an important component of weight loss interventions, health professionals should be aware that adaptive thermogenesis may explain weight loss difficulty in some individuals as well as a related restraint behavior. Thus, for some individuals, restrained eating and actual efforts to lose weight, which represent no energy value per se, can have significant influence on energy balance (intake or expenditure) and influence body weight.

Table 46.1 Key features on resting metabolic rate and adaptive thermogenesis

1. Basal metabolic rate which represents the energy used by the vital organs of the whole body while at rest is the most important component of total energy expenditure contributing up to 70% of total energy expenditure. The thermic effect of food contributes for about 10% of total energy expenditure and activities for about 20% of total energy expenditure. Each component of energy expenditure can adapt according to variations in energy balance
2. Basal metabolic rate is not commonly measured in research settings because it necessitates very restrictive circumstances when a person is awake. A more common measurement, used under less strict but standardized conditions, is resting metabolic rate (RMR). Consequently, RMR is slightly greater than basal metabolic rate
3. Many factors can influence resting metabolic rate: lean body mass, age, heredity, physical activity, and gender. Lean body mass is the most important predictor of RMR
4. A general estimate of RMR for an adult is about 1 kcal/day which represents about 1,440 kcal/day
5. Normally, RMR decreases during weight loss as a function of the decrease in lean tissue. This decrease is sometimes more important than what could be predicted by the loss of lean tissue. This phenomenon has been described as adaptive thermogenesis
6. In some individuals, this phenomenon can exceed what is recommended by a nutritionist and may explain why some individuals are resistant to body weight loss. From a clinical standpoint, such adaptive response represents a major obstacle for weight loss intervention aimed to modify feeding behaviors and energy intake

This table lists the key features of resting metabolic rate including the components of energy expenditure, the difference between basal and resting metabolic rate, the definition of resting metabolic rate, and the impact of weight loss on this variable

46.2.2 Disinhibition, Impaired Satiety Signals and Vulnerability to Food Cues

It is common to find obese individuals who report difficulties in recognizing hunger and/or satiation during the course of a day (Drapeau et al. 2000). Those individuals often claim that their eating is out of control even though they do not present with an eating disorder such as *binge eating*. This is consistent with what can be observed in a more standardized context. Accordingly, obese individuals have been characterized with impaired satiety signals when submitted to a test meal compared to normal weight controls (Blundell and Gillett 2001; Barkeling et al. 2007). Moreover, higher disinhibition and hunger scores have also been observed in a group of obese individuals claiming problems with appetite sensations compared to lean or obese controls (Barkeling et al. 2007). This probably explains why disinhibition has been associated with body weight gain or regain over time (Karlsson et al. 1994; Fogelholm et al. 1999; McGuire et al. 1999; Hays and Roberts 2008). Recently, Bryant et al. (2008) proposed that disinhibition is representative of a thrifty phenotype suggesting an important role of this behavior in body weight regulation.

In our clinical setting, we observed that about 10% of obese individuals consulting for weight loss difficulties express either very little or no change in appetite sensations when submitted to a standardized breakfast. A stimulation of appetite sensations following the test meal has also been observed in some individuals who reported that food can sometimes "stimulate" their appetite (Fig. 46.1). This test meal includes the consumption of a standardized breakfast (i.e. 2,504 kJ for women and 3,066 kJ for men) after 12 h of fasting and the completion of visual analog scales (VAS) on appetite sensations before and after the meal (see Drapeau et al. 2005 for more details). With this evaluation, individual satiety signals have been assessed by calculating the satiety quotient (SQ), which is the difference between appetite sensations measured before and after a test meal divided by the energy content of the meal (a high SQ would indicate a normal/high satiety signal, whereas a low SQ indicates impaired satiety signals). Using this marker, we were able to identify obese individuals who were more susceptible to overeating (Drapeau et al. 2005). Accordingly, SQ for fullness was negatively associated with total energy intake as well as relative energy intake (total energy intake – metabolic rate). These results were confirmed in a second study conducted in a larger cohort of men
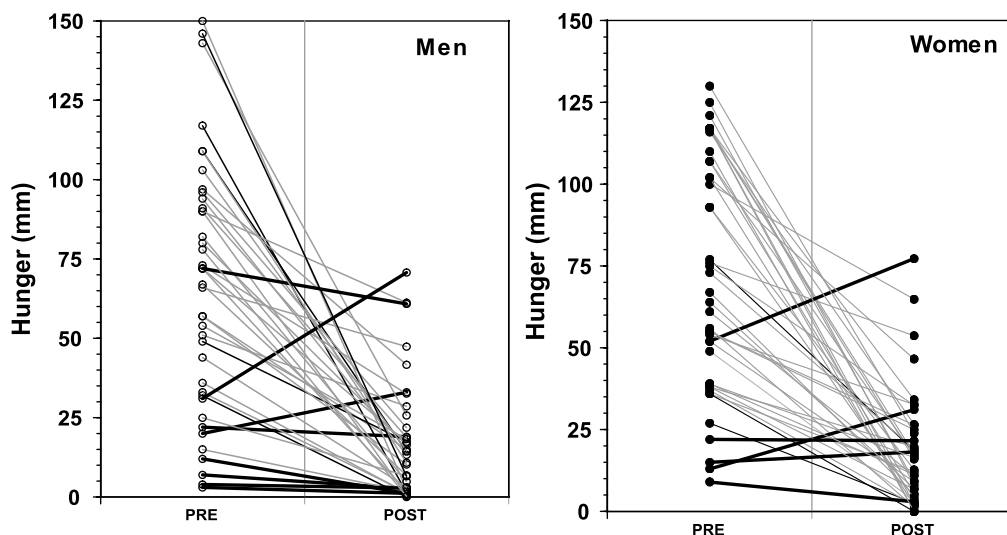
Fig. 46.1 Hunger levels before (PRE) and after (POST) a standardized test meal in men and women
Visual analog scale (*VAS*) scores for hunger in men (*n* = 98) and women (*n* = 68) before (PRE) and after (POST) the meal test. PRE values represent appetite sensations in a fasting state and POST values represent the mean of the 60 min postmeal appetite sensation recordings. Bold lines represent participants with impaired satiety signal capacity or with low satiety quotient

and women who were tested twice (before and after a weight loss program) (Drapeau et al. 2007). In this case, the negative relationship between SQ for fullness and total energy intake was stronger for women. It is important to note here that there was no significant relationship between the meal-induced change in appetite sensations and BMI in both men and women.

Based on these observations, it can be hypothesized that impaired satiety signals could favor overconsumption and thus increase the risk to gain weight over time in some obese individuals. This hypothesis is supported by studies that show an impaired hypothalamic response after a glucose load (Matsuda et al. 1999) and a different neuronal activity in response to satiety (Gautier et al. 2001) or to visual and auditory stimuli of binge type foods (Geliebter et al. 2006) in obese individuals compared to nonobese. Impaired satiety signals could also explain body weight loss variability in some individuals engaged in a weight loss program or weight regain. This is consistent with the observation of an increase in hunger after weight loss (Doucet et al. 2000b) and its association with weight regain (Pasman et al. 1999).

It has also been argued that some individuals are disproportionally vulnerable to food cues in the environment. These individuals may express a general tendency to be impulsive (Nasser et al. 2004) but specifically have difficulty resisting foods which are energy dense and highly palatable (Davis et al. 2007). Clearly, this will have important consequences for the treatment of the obese patients since some individuals are highly primed toward food cues. Indeed, energy restriction may exacerbate an underlying tendency to seek out these foods and to overconsume them. An investigation of sensitivity to reward (STR) and weight status revealed a strong relationship between STR, overeating, and BMI (Davis et al. 2007). STR was also associated with preference for high energy density foods including those high in fat and sugar (Davis et al. 2007). Thus, personality traits such as vulnerability to food cues or sensitivity to reward may be indirectly linked with BMI through their effects on eating behavior including the tendency to overeat and expressed preference for high energy density foods. This is an important argument in support of personalized treatment strategies since dispositional traits cannot be changed but their impact on eating and weight loss can be managed

(Hetherington 2007). It is also plausible that individuals expressing impaired satiety signal or presenting high disinhibition scores could be more vulnerable to food cues or sensitivity to reward. Therefore, the detailed characterization of these phenotypes could lead to more specific behavioral interventions that aim to decrease the power of food cues or include a specific medication known to influence sensitivity to reward centres.

46.2.3 Attention Toward Food and Distraction

Attention during eating represents another eating behavior that has the potential to influence appetite control and energy intake. During the meal, there is the opportunity to monitor the moment by moment changes in appetite sensations. For example, the subjective appeal of a food (pleasantness and/or desire to eat) tends to decline from the beginning to the end of a meal or snack (Hetherington et al. 2006). This phenomenon has been termed "sensory specific satiation" since the changes in pleasantness tend to affect the eaten food and foods which share sensory properties whilst leaving the pleasantness and desire for other foods largely unchanged. Introducing a different food during intake of a snack or meal appears to delay the development of satiation and can increase meal size. To examine the impact of introducing variety within a snack, we conducted an experiment involving four laboratory sessions to eat popcorn. In one session participants ate the snack with no interruptions (control), in another they ate the snack but rated the pleasantness of that snack during eating (same condition), and in the remaining sessions they ate the snack but at 1 min intervals were interrupted to taste and rate an alternative food either in the same taste domain (congruent) or a different domain (incongruent). Focussing on the eaten food to taste and rate at intervals appeared to inhibit intake compared to introducing other foods to taste and rate (Hetherington et al. 2006). Similarly ratings of pleasantness decreased as predicted in this condition but remained higher in the congruent and incongruent conditions. This suggests that having attention drawn to the pleasantness of the food as it is eaten will reduce both its appeal and the amount consumed.

Attention to the food whilst eating seems to be important in the development of satiation, since providing distractions during a meal appears to extend the duration and size of the episode. Wansink has termed this phenomenon "Mindless Eating" (Wansink et al. 2006). Thus, eating a meal or snack with the radio or TV on seems to increase the amount eaten compared to eating alone with no distractions. For example, Bellisle and her colleagues have conducted two experiments examining the effects of listening to the radio (Bellisle and Dalix 2001) or watching television (Bellisle et al. 2004) during a meal and found that both "distracters" increase energy intake compared to eating the meal alone without distraction. In the first of these experiments, it was reported that restrained eaters were especially susceptible to the impact of distraction and there was a significant correlation between restraint score and the difference in energy intake between the control and radio conditions (Bellisle and Dalix 2001). This indicates that there may be individual differences in the extent to which distracters influence food intake. Ironically, behaviors associated with limiting food intake such as dietary restraint appear to increase individual vulnerability to the effects of distraction.

Similarly, restraint is associated with overeating under conditions of stress (Lattimore and Maxwell 2004; Wallis and Hetherington 2004). This phenomenon seems to be stronger when restraint is combined with high disinhibition levels (Haynes et al. 2003). Stress imposes a relatively high level of cognitive demand on the restrained eater and this interferes with intake monitoring (Ward and Mann 2000). Given that limiting food intake in order to lose or maintain body weight is effortful, if restrained eaters are engaged in an activity which has a high cognitive load, then this may disinhibit

intake by preventing monitoring required to maintain strict dietary restraint. On the other hand, if restrained eaters are reminded of their plans to restrict intake and cues for maintaining behavioral control are made salient, this tends to enhance restraint (Ward and Mann 2000). Clearly, attention plays an important role both in the normal development of satiation and in the ability of those restricting food intakes to maintain behavioral control around food. In normalizing eating control, clinical management of obese individuals might include recommendations to focus on eating (without distraction) and to pay attention to the sensations of hunger and fullness as these change during the eating episode.

46.2.4 Modern Lifestyle and Eating Behaviors

Even if epidemiological evidence revealed a relationship between sleep duration and the risk of weight gain many years ago (Locard et al. 1992), the scientific community has awaited laboratory experiments before paying significant attention to short sleep duration as a risk factor of obesity. This demonstration involved the study of feeding behaviors and related hormones. Specifically, the experimental reduction of sleep time was found to increase plasma ghrelin concentration and to decrease plasma leptin level (Spiegel et al. 1999, 2004). As expected, an increase in some appetite sensations, e.g. hunger and desire to eat, also resulted from sleep deprivation. This agrees with data collected in the Quebec Family Study which showed that short sleepers displayed plasma leptin concentrations which were lower than those predicted by their body fat (Chaput et al. 2007b). More recently, results of this study indicated a greater propensity to hypoglycemia in short sleepers (Chaput et al. 2009a), which has been interpreted as concordant with the glucostatic theory of appetite control(Chaput and Tremblay 2009b). It is also noteworthy to emphasize that the same proneness to hypoglycemia and weight gain was observed in long sleepers tested in the Quebec Family Study (Chaput et al. 2007a, 2009a) and who may represent a subgroup of individuals with suboptimal sleep quality. Taken together, these observations suggest that suboptimal sleep duration, particularly short sleeping, may represent an important risk factor of weight gain, as shown in Table 46.2. Since mean sleep duration has decreased by more than an hour over the last decades, short sleeping appears as a modern lifestyle behavior which also significantly affects feeding behaviors.

Modernity has also accentuated the importance of cognitive effort in daily labor activities. Although mental work does not increase energy expenditure to a quantitatively significant extent (Chaput and Tremblay 2007), it exerts a profound effect on spontaneous energy intake and related metabolic variables. In a first study that we initiated to document this issue, Laval University female students increased by 229 kcal their mean energy intake during a buffet-type meal compared to control session (Chaput and Tremblay 2007). In a subsequent study (Chaput et al. 2008), this effect was confirmed and was accompanied by an increase in cortisolemia and plasma glucose instability. When subjects of this study were subdivided on the basis of the intensity of their cognitive effort, the increase in energy intake and glycemic instability (Chaput and Tremblay 2009b) as well as in cortisolemia (Chaput and Tremblay 2009a) was found to be greater in those for whom mental work was more demanding. Surprisingly, the hyperphagic effect of mental work was at least partly dissociated from changes in appetite sensations (Chaput et al. 2008), suggesting that demanding mental work can negatively influence the perception of satiety signals.

In summary, modern lifestyles and globalization have promoted a new way of living that produces obesogenic effects. These may include an increase in the concentration of orexigenic hormones such

Table 46.2 Impact of different eating and lifestyle behaviors on weight gain (kg)[a] over a 6-year follow-up period relative to the reference category [b,c]

Risk factors	Mean weight gain relative to the reference category (kg)	(95% confidence interval)
• High alcohol intake (≥10 g/day)	0.39	(0.07–0.74)
• High dietary lipid intake (≥40% fat/day)	0.61	(0.06–1.18)
• Nonconsumption of multivitamin and dietary supplement	0.87	(0.37–1.41)
• High dietary restraint behavior (≥8 TFEQ scores)	1.09	(0.59–1.63)
• Nonparticipation in high-intensity physical exercise	1.23	(0.63–1.88)
• High susceptibility to hunger behavior (≥5 TFEQ score)	1.28	(0.68–1.94)
• Low dietary calcium intake (<600 mg calcium/day)	1.3	(0.70–1.98)
• High disinhibition eating behavior (≥6 TFEQ score)	1.46	(0.96–2.05)
• Short Sleep duration (<6 h/day)	1.65	(1.05–2.31)

[a]Model adjusted for age, sex, baseline body mass index, length of follow up, socioeconomic status, and all other risk factors. TFEQ: Three-Factor Eating Questionnaire, $N = 283$ (Adapted from Chaput et al. 2009b)
[b]Reference categories: Alcohol: ≥10 vs 0 g/day; Lipid intake: ≥40% vs <30% kcal/day; Multivitamin and dietary supplements: nonconsumers vs consumers; Dietary restraint: ≥8 TFEQ score vs ≤4 TFEQ score; Intense physical activity participation: 0 vs 30 min/day; Susceptibility to hunger: ≥5 TFEQ score vs ≤2 TFEQ score; Calcium intake: <600 vs ≥1,000 mg/day; Disinhibition eating: ≥6 TFEQ score vs. ≤3 TFEQ score; Sleep duration <6 vs ≥7 h/day
[c]The data present the mean weight gain (kg) above baseline weight over time for individuals with the risk factors relative to the reference category. For instance, after adjustment, short-duration sleepers gained 1.65 kg more than those reporting sleeping >7 h a day. High disinhibition behavior and short sleep duration were the best predictors of body weight fluctuations over time

as ghrelin, the decrease in the concentration of anorexigenic hormones such as leptin, an increase in energy intake with or without concordant changes in appetite sensations, and a decrease in the precision of some regulated processes such as glycemic stability.

46.2.5 Eating and Lifestyle Behaviors in Body Weight Regulation

The literature summarized above suggests many factors can themselves promote a positive energy balance and body weight gain. In some cases, the impact on energy balance can be more important than traditionally recognized factors such as high lipid intake. To pursue this idea further we recently analyzed data of the Quebec Family Study to examine the importance of lifestyle factors in body weight changes compared to dietary factors either within a cross-sectional context or over a 6-year follow-up (Chaput et al. 2009b). In the cross-sectional context, short sleep patterns and high disinhibition behavior represented the two factors associated with the higher risk of overweight and obesity (odd ratio of 3.80 and 3.81, $p < 0.01$, respectively). Moreover, as shown in Table 46.2, high disinhibition behavior and short sleep duration were the best predictors of body weight fluctuations over time. The trend to adopt restrained eating behavior was also a good predictor of body weight fluctuations compared to more traditional risk indicators of weight gain such as high fat diet and low participation in vigorous physical activities. In other words, this reanalysis of data of the Quebec Family Study demonstrated that the best predictors of weight gain are factors with no intrinsic energy value such as suboptimal feeding behaviors. They are also factors that are generally overlooked in weight control interventions.

46.3 Potential Solutions

46.3.1 Satiating Meals

The failure to promote long term weight loss with energy restriction together with the impact of disinhibition, distraction, and impaired satiety signals on body weight emphasize the need for less restrictive strategies which could help to control eating behaviors and body weight. Functional foods which combine the key nutrients and food ingredients to promote a short term increase in satiety and/or a spontaneous decrease in energy intake (Table 46.3) could represent a good alternative to minimize the increase in hunger while inducing an energy deficit. We thus tested functional meals specifically designed to increase satiety and decrease spontaneous energy intake in healthy men (Poortvliet et al. 2007). Results showed that a functional food served as the main course of a meal acutely decreased energy intake during the rest of the meal (–744 kJ) as well as hunger, desire to eat, and prospective food consumption after the meal, compared to a control meal. This was observed without compromising the palatability of the functional food. Also of interest is the fact that spontaneous energy intake was also decreased in the subsequent meal. These results suggest that vulnerable individuals, i.e. those with impaired satiety signals or high disinhibition, could benefit from less restriction and more satiating nutritional strategies such as the consumption of foods with enriched nutrient content favoring satiety, resulting in a reduced total energy intake.

Since the complete elimination of restriction is difficult to achieve in a weight loss context, individuals characterized by vulnerable phenotype could be encouraged to practice more flexible restriction (i.e. eating smaller portions) which has been associated with lower BMI (Westenhoefer et al. 1999), higher weight loss (Provencher et al. 2007), and a better weight control over time (Hays and Roberts 2008).

46.3.2 Clinical Evaluation

Considering the impact of these eating behaviors and influences on energy intake and body weight, the characterization of these patterns could be important in the development of more individualized weight control interventions. In this context, there is a need to develop and validate clinical tools

Table 46.3 Key nutrients of satiating meals

Nutrients	Reference
• Low lipid content	(Lissner et al. 1987; Tremblay et al. 1989, 1991)
• Low energy density and large food volume	(Stubbs et al. 1995; Bell et al. 1998; Rolls et al. 1998, 1999a, b,, 2005)
• Low glycemic index carbohydrates	(Ludwig 2000; Roberts 2003; Warren et al. 2003)
• Minimal alcohol content	(Tremblay et al. 1995; Tremblay and St-Pierre 1996)
• High protein content	(Skov et al. 1999; Eisenstein et al. 2002)
• High dietary fiber content	(Howarth et al. 2001; Pereira and Ludwig 2001; Koh-Banerjee and Rimm 2003)
• Optimal level of vitamins and minerals	(Doucet et al. 2000a; Johnston 2005)
• High calcium	(Zemel et al. 2000; Jacqmain et al. 2003)
• Capsaicin	(Yoshioka et al. 2001)
• Oolong tea	(Rumpler et al. 2001)
• Green tea catechins	(Dulloo et al. 1999; Berube-Parent et al. 2005; Diepvens et al. 2005; Westerterp-Plantenga et al. 2005)

This table presents the key nutrients which can produce a short-term increase in satiety and/or a spontaneous decrease in energy intake

which could help to characterize individuals who may be more at risk of overeating under these influences.

The evaluation of appetite sensations before and after a standardized meal could represent a first step in the characterization of obese individuals with impaired satiety signals and possibly more vulnerable to "eating distracters". As shown before, VAS appetite sensations measured before and after a meal can be useful to identify individuals more susceptible to excess energy intake (Drapeau et al. 2005, 2007). If more generally applied in the clinical context, a standard test meal could improve the identification of those individuals with specific impaired appetite perception leading to more individualized treatment strategies to improve weight loss efficacy. For example, these individuals could benefit from a pharmaceutical agent such as Sibutramine since it has been shown to decrease both hunger and anticipated food consumption, and to increase satiety scores (Hansen et al. 1999).

Since eating when distracted can increase energy intake, dietary records including "activities during meals" could also help to identify problematic eating episodes and individuals more susceptible to overeat during distraction. This tool, often used in behavioral therapy, can also help individuals to be more vigilant about eating and aware of their appetite sensations. Greater vigilance during eating and focus on changes in appetite may facilitate satiation. Therapists treating patients presenting with overeating are often advised to pay more attention both to the general experience of hunger and fullness as well as how these alter during a meal. In particular, therapists encourage patients to eat only when hungry, to eat slowly to savor each mouthful of food, and to stop eating before they feel full. This requires a great deal of attention and involves forming new habits to control appetite and meal size (Verplanken 2006). The identification of eating distracters will also necessitate recommendations to focus on eating and the sensation of hunger and fullness as these alter during the eating episode.

Finally, other lifestyle factors such as short sleep duration and a knowledge-based work environment should also be considered in a clinical context since they can, through their effect on eating behaviors and physiological systems, favor a positive energy balance.

46.3.3 Physical Activity

Physical activity provides stimulation that can modify feeding behaviors. To our knowledge, King et al. (1994) were the first investigators who performed a clear demonstration of the acute decrease in hunger feeling following exercise. More recently, we have studied the effect of exercise intensity on spontaneous food intake and related feeding behaviors under conditions of exercise sessions of similar energy cost but strongly differing in the intensity of the exercise stimulus (Imbeault et al. 1997). The assessment of *ad libitum* food intake after exercise revealed that the short-term energy compensation was lower after the high compared to the low intensity exercise, even if ratings of appetite sensations were comparable. This suggests that vigorous physical activity may promote a beneficial effect on satiety quotient, i.e. by promoting satiety with a reduced postexercise energy intake. Our clinical experience also demonstrates that this effect is not without limits, particularly in response to weight loss (Doucet et al. 1999).

46.4 Conclusion

The increasing obesity prevalence worldwide emphasizes the need to develop new strategies to control body weight. The multifactorial aetiology of obesity indicates that the individualized predisposition to gain weight is driven by factors which can be different from those promoting excess body weight in another individual. This multifactorial aspect of obesity development also implies

that the excess energy intake over expenditure is not only the consequence of environmental factors having an "energy value" per se, e.g., high fat-high energy dense diet and low participation in vigorous physical activities. This energy imbalance can also result from nonenergetic factors that are a source of stimuli promoting overeating. In this article, we have presented often overlooked eating behaviors which have the potential to influence energy balance based on recent experimental research and related clinical experience. Accordingly, some individuals can overeat when attention is distracted away from food while others are more prone to overeating either through disinhibition, impaired satiety signals, restrained eating, and attempts to lose weight or through an enhanced sensitivity to food cues. We also presented some related factors such as short sleep patterns and mental work that can significantly influence eating behaviors and thus body weight. These vulnerable phenotypes require personalized treatment to tackle specific difficulties which could influence food intake. This is justified by the observation that for some, vulnerability to weight gain is higher than what can be explained by an unhealthy diet composition and sedentariness.

In this context, it becomes obvious that a "one size fits all" approach to weight loss is not appropriate. Personalized approaches to weight loss may represent a long-term solution to overcome obesity. The clinical corollary of this reality is that a successful obesity treatment should be based on a data set that helps health professionals to identify the vulnerable phenotype(s) of a patient and to prescribe a weight reducing strategy that takes into account individual differences. In reality, most health professionals do not have limitless resources or optimal working facilities to adequately identify specific vulnerability phenotypes. Therefore, a more comprehensive but focussed clinical evaluation program which could identify behaviors that have the potential to influence body weight is needed to personalize and improve obesity treatment.

46.5 Authorship and Conflicts of Interest

Each author contributed to drafting the manuscript and reviewed it. None of the authors had any conflict of interest.

Summary Points

- Best predictors of weight gain are not always traditional factors having an energetic value
- Restriction and attempts to lose weight are counterproductive for body weight control as they can increase the risk of disinhibition, negative affect, binge eating episode, as well as decrease resting metabolic rate
- Attention toward food seems to help control eating behaviours
- Eating in the presence of distractors can increase the amount of food eaten. This can be exacerbated in some individuals such as restrained individuals
- Disinhibition represents an eating behavior predicting weight gain and could reflect obese individuals with impaired satiety signals
- Individuals expressing impaired satiety signal may represent vulnerable phenotype to food cues and to reward
- It seems that modern lifestyle behaviors such as short sleeping pattern and mental work can increase energy intake by altering the concentration of orexigenic/anorexigenic hormones such as ghrelin and leptin and other regulated processes such as glycemic stability

- Satiating meals could represent a less restrictive strategy which could help control eating behaviors and body weight particularly in individuals displaying impaired satiety signals
- A clinical evaluation which aims to characterize traditional and less traditional factors influencing body weight could be important in the development of more individualized weight control interventions
- Vigorous physical activity can help control or modify eating behaviors

---

Key Terms

Restriction: Restriction refers to cognitive dietary restraint and reflects the intent to restrict food intake in order to control body weight. It can be measured with the Three-Factor Eating Questionnaire

Disinhibition: Disinhibition represents overconsumption of food in response to a variety of stimuli, such as emotional stress, associated with a loss of control on food intake. It can also be measured with the Three-Factor Eating Questionnaire

Hunger: Or susceptibility to hunger refers to food intake in response to feelings and perceptions of hunger. It can also be measured with the Three-Factor Eating Questionnaire

Eating distracters: Situation (e.g. stress) or environmental cues (e.g. TV) which decreased the attention toward food while eating. Action also referred as "Mindless eating"

Satiating meal: Functional food characterized by healthy and satiating attributes. See Table 46.2 (also referred as healthy meal course)

Mental work: Knowledge-based demanding tasks such as writing with computer imposes a significant cognitive effort

Food cues: Environmental stimuli associated with food intake

Body mass index: Index for relating a person's body weight to their height. It is calculated by dividing a person's weight in kilograms (kg) by their height in meters (m) squared

RMR: Minimal energy required to perform vital body functions such as respiration and heart rate while the body is at rest (see table 46.1)

Satiety quotient: Index of individual's satiety signal capacity

STR: Individuals who are inherently highly sensitive or more vulnerable to food cues

TFEQ: Questionnaire used to access three main eating behaviors in adults: cognitive restraint, disinhibition and susceptibility to hunger

VAS: Testing technique for measuring subjective or behavioral phenomena. i.e. appetite sensations. For example, an individual would indicate, on a 150 mm scale, how he felt at the moment of completing the following question: How strong is your desire to eat? (very weak (0 mm) to very strong (150 mm))

References

Barkeling, B., N. A. King, et al. Characterization of obese individuals who claim to detect no relationship between their eating pattern and sensations of hunger or fullness. Int J Obes (Lond) 2007;31(3):435–9.

Beck AT. Arch Gen Psychiatry. 1961;4:571.

Bell EA, Castellanos VH, Pelkman CL, Thorwart ML, Rolls BJ. Am J Clin Nutr. 1998;67:412–20.

Bellisle F, Dalix AM. Am J Clin Nutr. 2001;74:197–200.

Bellisle F, Dalix AM, Slama G. Appetite. 2004;43:175–80.

Berube-Parent S, Pelletier C, Dore J, Tremblay A. Br J Nutr. 2005;94:432–6.

Blundell JE, Gillett A. Obes Res. 2001;9(Suppl 4):263S–70S.

Bryant EJ, King NA, Blundell JE. Obes Rev. 2008;9:409–19.

Chaput JP, Tremblay A. Physiol Behav. 2007;90:66–72.

Chaput JP, Tremblay A. Obes Facts. 2009a;2:249–54.

Chaput JP, Tremblay A. Int J Obes (Lond). 2009b;33:46–53.

Chaput JP, Despres JP, Bouchard C, Tremblay A. Diabetologia. 2007a;50:2298–304.

Chaput JP, Despres JP, Bouchard C, Tremblay A. Obesity (Silver Spring). 2007b;15:253–61.

Chaput JP, Drapeau V, Hetherington M, Lemieux S, Provencher V, Tremblay A. Depress Anxiety. 2007c;24:518–21.

Chaput JP, Drapeau V, Poirier P, Teasdale N, Tremblay A. Psychosom Med. 2008;70:797–804.

Chaput JP, Despres JP, Bouchard C, Astrup A, Tremblay A. Sleep Med. 2009a: S1389–9457(08)00371–7 [pii]10.1016/j. sleep.2008.09.016.

Chaput JP, Leblanc C, Perusse L, Despres JP, Bouchard C, Tremblay A. Obesity (Silver Spring). 2009b.

Davis C, Patte K, Levitan R, Reid C, Tweed S, Curtis C. Appetite. 2007;48:12–9.

Diepvens K, Kovacs EM, Nijs IM, Vogels N, Westerterp-Plantenga MS. Br J Nutr. 2005;94:1026–34.

Doucet E, Imbeault P, Almeras N, Tremblay A. Obes Res. 1999;7:323–33.

Doucet E, Després J-P, Bouchard C, Tremblay A. Int J Obes Relat Metab Disord. 2000a;24:S157.

Doucet E, Imbeault P, St-Pierre S, Almeras N, Mauriege P, Richard D, Tremblay A. Int J Obes Relat Metab Disord. 2000b;24:906–14.

Doucet E, St-Pierre S, Almeras N, Despres JP, Bouchard C, Tremblay A. Br J Nutr. 2001;85:715–23.

Drapeau V, Bérubé S, Tremblay A. Obes Res. 2000;8:70S.

Drapeau V, Provencher V, Lemieux S, Despres JP, Bouchard C, Tremblay A. Int J Obes Relat Metab Disord. 2003;27:808–14.

Drapeau V, Blundell J, Therrien F, Lawton C, Richard D, Tremblay A. Br J Nutr. 2005;93:273–80.

Drapeau V, King N, Hetherington M, Doucet E, Blundell J, Tremblay A. Appetite. 2007;48:159–66.

Dulloo AG, Duret C, Rohrer D, Girardier L, Mensi N, Fathi M, Chantre P, Vandermander J. Am J Clin Nutr. 1999;70:1040–5.

Eisenstein J, Roberts SB, Dallal G, Saltzman E. Nutr Rev. 2002;60:189–200.

Elfhag K, Rossner S. Obes Rev. 2005;6:67–85.

Fogelholm M, Kukkonen-Harjula K, Oja P. Int J Obes Relat Metab Disord. 1999;23:203–10.

Freedman MR, King J, Kennedy E. Obes Res. 2001;9(Suppl 1):1S–40S.

Gautier JF, Del Parigi A, Chen K, Salbe AD, Bandy D, Pratley RE, Ravussin E, Reiman EM, Tataranni PA. Obes Res. 2001;9:676–84.

Geliebter A, Ladell T, Logan M, Schneider T, Sharafi M, Hirsch J. Appetite. 2006;46:31–5.

Gilbert JA, Drapeau V, Astrup A, Tremblay A. Appetite. 2009.

Gilden Tsai A, Wadden TA. Obesity (Silver Spring). 2006;14:1283–93.

Hansen DL, Toubro S, Stock MJ, Macdonald IA, Astrup A. Int J Obes Relat Metab Disord. 1999;23:1016–24.

Haynes C, Lee MD, Yeomans MR. Eat Behav. 2003;4:369–83.

Hays NP, Roberts SB. Obesity (Silver Spring). 2008;16:52–8.

Hays NP, Bathalon GP, McCrory MA, Roubenoff R, Lipman R, Roberts SB. Am J Clin Nutr. 2002;75:476–83.

Hetherington MM. Proc Nutr Soc. 2007;66:113–23.

Hetherington MM, Foster R, Newman T, Anderson AS, Norton G. Physiol Behav. 2006;87:263–71.

Howarth NC, Saltzman E, Roberts SB. Nutr Rev. 2001:59:129–39.

Imbeault P, Saint-Pierre S, Almeras N, Tremblay A. Br J Nutr. 1997;77:511–21.

Jacqmain M, Doucet E, Despres JP, Bouchard C, Tremblay A. Am J Clin Nutr. 2003;77:1448–52.

Johnston CS. J Am Coll Nutr. 2005;24:158–65.

Karlsson J, Hallgren P, Kral J, Lindroos AK, Sjostrom L, Sullivan M. Appetite. 1994;23:15–26.

King NA, Burley VJ, Blundell JE. Eur J Clin Nutr. 1994;48:715–24.

Klesges RC, Isbell TR, Klesges LM. J Abnorm Psychol. 1992;101:668–74.

Koh-Banerjee P, Rimm EB. Proc Nutr Soc. 2003;62:25–9.

Lattimore P, Maxwell L. Eat Behav. 2004;5:315–24.

Lau DC, Douketis JD, Morrison KM, Hramiak IM, Sharma AM, Ur E. Cmaj. 2007;176:S1–13.

Lawson OJ, Williamson DA, Champagne CM, DeLany JP, Brooks ER, Howat PM, Wozniak PJ, Bray GA, Ryan DH. Obes Res. 1995;3:153–61.

Leibel RL, Rosenbaum M, Hirsch J. N Engl J Med. 1995;332:621–8.

Lindroos AK, Lissner L, Mathiassen ME, Karlsson J, Sullivan M, Bengtsson C, Sjostrom L. Obes Res. 1997;5:175–82.

Lissner L, Levitsky DA, Strupp BJ, Kalkwarf HJ, Roe DA. Am J Clin Nutr. 1987;46:886–92.

Locard E, Mamelle N, Billette A, Miginiac M, Munoz F, Rey S. Int J Obes Relat Metab Disord. 1992;16:721–9.

Ludwig DS. J Nutr. 2000;130:280S–3S.

Major GC, Doucet E, Trayhurn P, Astrup A, Tremblay A. Int J Obes (Lond). 2007;31:204–12.

Matsuda M, Liu Y, Mahankali S, Pu Y, Mahankali A, Wang J, DeFronzo RA, Fox PT, Gao JH. Diabetes. 1999;48:1801–6.

McGuire MT, Wing RR, Klem ML, Lang W, Hill JO. J Consult Clin Psychol. 1999;67:177–85.

Nasser JA, Gluck ME, Geliebter A. Appetite. 2004;43:303–7.

National Task Force on the Prevention and Treatment of Obesity. Arch Intern Med. 2000;160:2581–9.

Pasman WJ, Saris WH, Westerterp-Plantenga MS. Predictors of weight maintenance. Obes Res. 1999;7:43–50.

Pereira MA, Ludwig DS. Pediatr Cl North Am. 2001;48:969–80.

Poortvliet PC, Bérubé-Parent S, Drapeau V, Lamarche B, Richard D, Després J-P, Blundell JE, Angelo Tremblay. Effects of functional food on spontaneous energy intake, satiety and palatability. Br J Nutr. 2007;97:584–90.

Prentice AM, Goldberg GR, Jebb SA, Black AE, Murgatroyd PR, Diaz EO. Proc Nutr Soc. 1991;50:441–58.

Provencher V, Drapeau V, Tremblay A, Despres JP, Lemieux S. Obes Res. 2003;11:783–92.

Provencher V, Begin C, Tremblay A, Mongeau L, Boivin S, Lemieux S. Obesity (Silver Spring). 2007;15:957–66.

Roberts SB. Nutr Clin Care. 2003;6:20–6.

Rolls BJ, Castellanos VH, Halford JC, Kilara A, Panyam D, Pelkman CL, Smith GP, Thorwart ML. Am J Clin Nutr. 1998;67:1170–7.

Rolls BJ, Bell EA, Castellanos VH, Chow M, Pelkman CL, Thorwart ML. Am J Clin Nutr. 1999a;69:863–71.

Rolls BJ, Bell EA, Thorwart ML. Am J Clin Nutr. 1999b;70:448–55.

Rolls BJ, Roe LS, Beach AM, Kris-Etherton PM. Obes Res. 2005;13:1052–60.

Rumpler W, Seale J, Clevidence B, Judd J, Wiley E, Yamamoto S, Komatsu T, Sawaki T, Ishikura Y, Hosoda K. J Nutr. 2001;131:2848–52.

Sherer EL, Sherer JA. JAAPA. 2008;21:31–4, 39.

Skov AR, Toubro S, Ronn B, Holm L, Astrup A. Int J Obes Relat Metab Disord. 1999;23:528–36.

Spiegel K, Leproult R, Van Cauter E. Lancet. 1999;354:1435–9.

Spiegel K, Tasali E, Penev P, Van Cauter E. Ann Intern Med. 2004;141:846–50.

Stein RI, Kenardy J, Wiseman CV, Dounchis JZ, Arnow BA, Wilfley DE. Int J Eat Disord. 2007; 40:195–203.

Stice E, Cameron RP, Killen JD, Hayward C, Taylor CB. J Consult Clin Psychol. 1999;67:967–74.

Stubbs JR, Harbon GH, Murgatroyd PR, Prentice AM. Am J Clin Nutr. 1995;62:316–29.

Tremblay A, St-Pierre S. Am J Clin Nutr. 1996;63:479–82.

Tremblay A, Plourde G, Després JP, Bouchard C. Am J Clin Nutr. 1989;49:799–805.

Tremblay A, Lavallée N, Alméras N, Allard L, Després JP, Bouchard C. Am J Clin Nutr. 1991;53:1134–7.

Tremblay A, Wouters E, Wenker M, St-Pierre S, Bouchard C, Després J-P. Am J Clin Nutr. 1995;62:639–44.

Tremblay A, Major G, Doucet E, Trayurn T, Astrup A. Future Lipidol. 2007;2:651–8.

Verplanken B. Br J Soc Psychol. 2006;45:639–56.

Volpe SL. J Cardiovasc Nurs. 2006;21:34–9.

Wadden TA. An Int Med. 1993;119:688–93.

Wadden TA, Foster GD, Stunkard AJ, Conill AM. Int J Eat Dis. 1996;19:5–12.

Wadden TA, Foster GD, Sarwer DB, Anderson DA, Gladis M, Sanderson RS, Letchak RV, Berkowitz RI, Phelan S. Am J Clin Nutr. 2004;80:560–8.

Wallis DJ, Hetherington MM. Appetite. 2004;43:39–46.

Wansink B, Painter JE, Lee YK. Int J Obes (Lond). 2006;30:871–5.

Ward A, Mann T. J Pers Soc Psychol. 2000;78:753–63.

Warren JM, Henry CJ, Simonite V. Pediatrics. 2003;112:e414.

Westenhoefer J, Stunkard AJ, Pudel V. Int J Eat Disord. 1999;26:53–64.

Westerterp-Plantenga MS, Lejeune MP, Kovacs EM. Obes Res. 2005;13:1195–1204.

Wing RR, Hill JO. Annu Rev Nutr. 2001;21:323–41.

Yoshioka M, Doucet E, Drapeau V, Dionne I, Tremblay A. Br J Nutr. 2001;85:203–11.

Zemel MB, Shi H, Greer B, Dirienzo D, Zemel PC. FASEB J. 2000;14:1132–8.

Chapter 47
Food Neophobia and Sensation Seeking

Thomas R. Alley and Kathleen A. Potter

Abbreviations

AISS	Arnett Inventory of Sensation Seeking
CDC	Centers for Disease Control and Prevention
FAS	Food Attitude Survey
FNS	Food Neophobia Scale
FNSC	Food Neophobia Scale for Children
FSQ	Food Situations Questionnaire
SS	Sensation Seeking
SSS	Sensation Seeking Scale
UFST	Unknown Flavor Sampling Test
VARSEEK	Variety Seeking Tendency Scale
WTNF	Willingness to Taste Novel Food test

Food neophobia, a reluctance to eat unfamiliar foods, is a common trait that has been widely studied in birds and mammals. Humans are among the many species that display food neophobia, and despite the relative safety and availability of most food items in modern society, uncertainty about unfamiliar foods continues to have an important impact on dietary intake. Research on humans has revealed sizable and, to some extent, predictable individual differences in the prevalence and severity of food neophobia. One particularly notable predictor is the personality trait of *sensation seeking (SS)*, simply defined as a person's willingness to take risks in order seek out novel or intense stimuli. This chapter presents a review of food neophobia as it influences food choice and diet, and examines the role of sensation seeking as well as several other factors that have an effect on *food neophobia*, such as age and sex.

47.1 The Omnivore's Dilemma and Food Choice

The koala bear doesn't worry about what's for dinner: If it looks and smells and tastes like a eucalyptus leaf, it must be dinner. The koala's culinary preferences are hardwired in its genes. But for omnivores like us… a vast amount of brain space and time must be devoted to figuring out which of all the many potential dishes nature lays on are safe to eat. We

T.R. Alley (✉)
Department of Psychology, 418 Brackett Hall, Clemson University, Clemson, SC 29634-1355, USA
e-mail: willet@musc.edu

rely on our prodigious powers of recognition and memory to guide us away from poisons (Isn't that the mushroom that made me sick last week?) and toward nutritious plants (The red berries are the juicier, sweeter ones).

(Pollan 2006, p 3–4)

Being omnivores, humans eat a wide variety of foods. Such diversity has a number of benefits, most notably including (1) a greater likelihood of consuming our required nutrients and (2) less chance of going without something to eat despite changes in seasons, climate (e.g., droughts), prey density, etc. However, a willingness to eat a wide variety of foods also has potential costs. Each time we are presented a food item with which we have little or no familiarity, we must weigh the risk of not consuming the item (and possibly missing out on a good food source) with the risk of ingesting something potentially dangerous (e.g., allergens or poisons), or that will produce an unpleasant sensory experience. This approach/avoidance conflict when facing unfamiliar potential foods was discussed in a landmark 1976 paper by Paul Rozin and is termed the "omnivore's dilemma". The above quote from Michael Pollan's book, *The Omnivore's Dilemma* (2006), highlights this risk.

It has been demonstrated that humans show interest in unfamiliar foods; however, deciding to eat novel foods is often coupled with fear and anxiety (Rozin 1976), and laboratory research shows that people do tend to see novel foods as a bit more dangerous than familiar ones (Pliner et al. 1993). In modern society, where foods are generally safe, the continued presence of food neophobia (a psychological trait characterized by a general reluctance to eat new/unusual foods) actually has an adverse effect on diet/food choice. The evolutionary adaptation to avoid potential dangers associated with novel foods results in a human tendency to reject unfamiliar foods (Rozin 1976; Domjan 1977), thus limiting our diet to the familiar even though our diet could, and often should, be far more varied. In addition, food neophobia must not stop infants from acquiring preferences for new foods during weaning.

47.2 Neophobia: Measurement Tools and Psychometrics

A number of methods have been used to measure neophobia, most using questionnaires. The most commonly used scale to measure food neophobia in adults is the *Food Neophobia Scale* (FNS) developed by Pliner and Hobden (1992; Table 47.1). This 10-item scale has acceptable test-retest reliability and internal consistency (Pliner and Hobden 1992; Knaapila et al. 2007), and has been translated into several languages including French (Ton Nu 1996 – Unpublished, as reported in Reverdy et al. 2008), Swedish (Koivisto and Sjoden 1996), and Finnish (Pliner et al. 1998). FNS scores are not significantly

Table 47.1 The ten-item Food Neophobia Scale (FNS)

1. I am constantly sampling new and different foods[a]
2. I don't trust new foods
3. If I don't know what a food is, I won't try it
4. I like foods from different cultures[a]
5. Ethnic food looks too weird to eat
6. At dinner parties, I will try new foods[a]
7. I am afraid to eat things I have never had before
8. I am very particular about the foods I eat
9. I will eat almost anything[a]
10. I like to try new ethnic restaurants[a]

Each item requires a rating on a 7-point Likert scale: disagree strongly, disagree moderately, disagree slightly, neither disagree nor agree, agree slightly, agree moderately, and agree strongly

[a]Five items on this scale are reverse scored (Pliner and Hobden 1992)

related to pickiness (Pliner and Hobden 1992), which will be briefly discussed later. The scores are related to responses to novel, but not familiar foods (Pliner et al. 1998). Confirmatory factor analysis and other techniques have shown an acceptable or better fit of cross-cultural data from the USA, Finland, and Sweden for the FNS, although suggesting that a smaller number of items may work better (Ritchey et al. 2003). There is ample evidence of validity for the FNS in the form of correlations with food selection and diet, as discussed in the following section.

For young children, Pliner (1994) has developed the Food Neophobia Scale for Children (FNSC). This 10-item scale is completed by mothers and includes items such as "My child will eat almost anything". A self-report scale for children has been developed and tested in France (Rubio et al. 2008). Both scales have been validated with behavioral tests of food neophobia. Older children, between the ages of 7 and 12, may complete the Food Situation Questionnaire (FSQ) developed by Loewen and Pliner (2000; see Table 47.2). In so far as they have been examined, all of these scales have good psychometric properties.

Other survey instruments have been used to measure food neophobia or similar traits such as "food adventurousness". Ullrich et al. (2004), measured "food adventurousness" with a single question: "How often do you try unfamiliar foods?" Even this simple measure produced significant predictions of liking for spicy foods and bitter fruits and vegetables. Van Trijp and Steenkamp (1992) developed the more sophisticated Variety Seeking Tendency Scale (VARSEEK) scale to measure the tendency of consumers to seek variety in food choices. The 8-item VARSEEK-scale has high internal consistency and has been used successfully to predict some of the variation in reported cheese consumption and in the exploration of varieties of cheeses, among Finnish adults (Van Trijp et al. 1992). VARSEEK scores are significantly correlated with those on the FNS (Meiselman et al. 1999). Finally, Frank and van der Klaauw (1994) developed the Food Attitude Survey (FAS) to assess food preference patterns. Subjects were asked to evaluate an extensive list of food items and indicate their opinion of each food item

Table 47.2   The Food Situations Questionnaire (FSQ)

LO-STIM subscale

1. "If your Mom or Dad made something for dinner that you had never tasted before, how would you feel about eating that?"
2. "If your Mom made a new and different kind of sandwich for your lunch box, how would you feel about eating the sandwich?"
3. "If you went on a picnic with your friend's family, and they brought a food that you had never seen before, how would you feel about having some of their food?"
4. "If your family went on a trip to a new place and all the food there was stuff you'd never had before, how would you feel about eating the food ?"
5. "If your Mom served a new kind of vegetable for dinner, how would you feel about eating that?"

HI-STIM subscale

6. "If dessert at your friend's house was cannoli with chocolate sauce, how would you feel about eating that kind of dessert?"
7. "If you went to a friend's birthday party and they had cassava chips there for you to try, how you feel about trying some of those?"
8. "If your favorite aunt or uncle took you out for lunch and bought you kirschenkeks, how would you feel about eating that?"
9. "If you went on a school trip with your class and for dessert you got chocolate cake with frangelico icing, how would you feel about eating that kind of cake?"
10. "If there was a Halloween party at school and the teacher brought some chayote for the children, how would you feel about trying some of that?"

Each item describes hypothetical situations in which novel foods might be encountered. Subjects (children) must report how they would feel about tasting or eating each item. The two subscales represent willingness to try novel foods in nonstimulating (LO-STIM) and highly stimulating (HI-STIM) circumstances (Loewen and Pliner 2000)

based upon its familiarity and their willingness to consume it using a 5-point scale. The scale ranged from "I really like this food. I think it tastes good" to "I've never tried this food, and never intend to try it." Using the original 1994 scale as well as a shortened version (Raudenbush et al. 1995), Frank et al. were able to identify individual differences in responses or attitudes toward foods, similarly to the FNS, and grouped people into categories similar to neophobic ("won't tryers") and neophilic ("likers"), with an additional intermediate group of "dislikers". The FAS has good reliability (Frank and van der Klaauw 1994). Meiselman et al. (1999) found high stability over a period of 1–2 years in a longitudinal study of college students using both the FNS and VARSEEK scales.

One potential shortcoming of survey instruments such as the FNS is that they present food selection in a hypothetical manner. While survey methods have, on the whole, been well supported by examination of the actual food choices of respondents (see below), the method is indirect in that the questions ask what a person *would do* in a given scenario rather than presenting the situation itself and then assessing how the person actually responds. Moreover, some exceptions have been reported, such as the finding that variety-seeking tendency (VARSEEK) does not always predict food choice behavior (Lähteenmäki and Van Trijp 1995). For such reasons, a number of studies have used tests of actual (i.e., "behavioral") neophobia. That is, various methods have been developed to determine actual behavioral responses (selection or avoidance) of unfamiliar foods. For example, Reverdy et al. (2008) used both the FNS (French adaptation) and an assessment of the actual willingness to taste novel food (WTNF), testing 180 French children (8–10 years old). WTNF was evaluated by presenting eight unknown/uncommon food items to the participants. Each child would then have to separate the food items into two groups based on whether or not they would be willing to sample the item. Further, all subjects were told that after they had sorted all of the items, they would have to actually taste one of the items they selected as "willing to eat". Scores from the adapted FNS were positively correlated with the WTNF test ($r = 0.421$, $p = 0.000$).

Another behavioral test of food neophobia is the Unknown Flavor Sampling Test (UFST) (Potter and Alley 2009). For this test, participants (college students) were presented with eight small containers with distinctly and unusually colored jellybeans (small candies) in each. They were then given the instructions to "evaluate each container, but not yet eat the items" and indicate (1) if they thought they knew what the flavor was ("yes" or "no") and (2) if they would be willing to try it. It is important to note that while the participants did not actually eat the jellybeans, they were given the impression that they might have to eat them. Because many participants believed that they knew the flavor of the jellybeans, which were supposed to be unknown, the UFST score was calculated as the ratio of the number of unknown, rejected beans to the total number of unknown beans (M = 0.31, SD = 0.32). FNS scores of these students were highly correlated with scores from the UFST ($r = 0.634$, $p = 0.000$; see Fig. 47.1).

In the next section, we review some of the group and individual differences in food neophobia. Before proceeding, it is important to make a distinction between *food neophobia* and *pickiness*: people with food neophobia are reluctant to eat novel foods, whereas picky (or "finicky") eaters resist eating many familiar foods (Galloway et al. 2003). Food neophobia is specifically a reluctance to consume a food item that is unfamiliar, while pickiness may be influenced by a number of other variables (e.g., texture). In essence, one can exhibit pickiness and food neophobia, but pickiness is not necessarily a part of neophobia (for a review see Dovey et al. 2008). Psychometric analysis has repeatedly found that pickiness and neophobia are distinct traits (cf. Pliner and Salvy 2006). Parents commonly complain about the "pickiness" of their children, with one study finding that 50% of mothers of 19–24-month-old infants judged them to be "picky" (Carruth et al. 2004), but the problem may often be neophobia. Education may prove useful, leading parents to see the importance of early eating experiences and learning about foods. Better parenting should follow if parents realize that children like familiar foods but can learn to accept new foods if they are provided repeatedly and without threat of punishment or enticement of rewards.
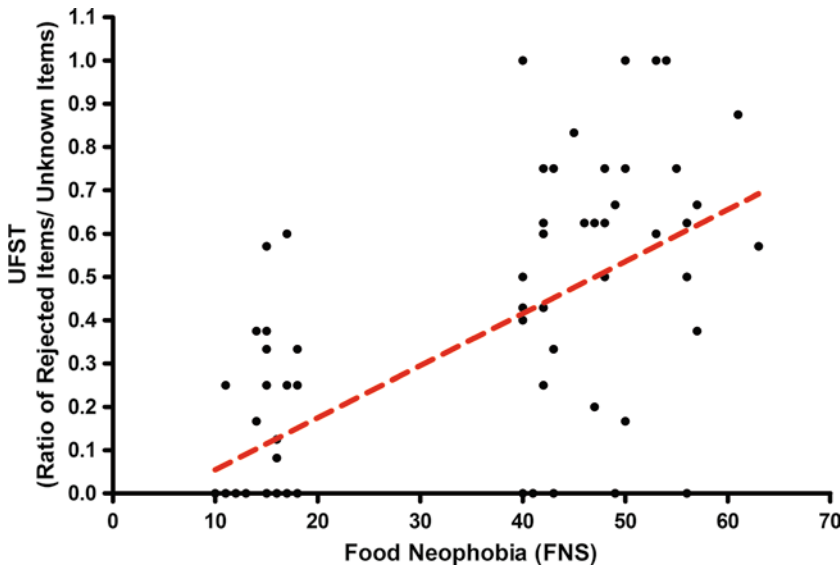
Fig. 47.1 Students' showed similar responses when asked about their neophobic tendencies using the more hypothetical FNS as well as during an actual behavioral assessment (UFST). FNS and UFST scores were highly correlated ($r = 0.634$, $p = 0.000$) (Potter and Alley 2009)

47.3 Food Neophobia and Diet: A Dual Relationship

47.3.1 Food Neophobia Influences Diet

Certainly a reluctance to eat unfamiliar foods can have an impact on diet. Validity studies of the FNS bear this out: Overall, scores on the FNS and other measures of neophobia appear to have good predictive validity. For instance, a French study of 603 children (Rubio et al. 2008) found that the children's choices and their willingness to try new types of food were significantly correlated with scores on the authors' neophobia questionnaire, and Pliner, Lähteenmäki, and Tuorila (1998) found FNS scores to be related to willingness to eat and anticipated liking for novel foods. Likewise, FSQ scores have predicted actual willingness to taste novel foods in a laboratory setting and, in fact, predict such willingness better than parents' reports of their own children's neophobia (Loewen and Pliner 2000). Also, as mentioned previously, FNS scores are significantly correlated with behavioral expression of food neophobia (WTNF: Reverdy et al. 2008 and UFST: Potter and Alley 2009). Perhaps most impressive are results from a longitudinal study showing that food neophobia scores predict later food preferences and variety. Specifically, Skinner et al. (2002) found the best predictor of the number of foods liked at age 8 to be the food neophobia scores at age 4 (as well as the number liked at that age).

By restricting intake of unfamiliar foods, food neophobia can increase the safety of one's diet. However, by reducing the number and variety of attractive foods, neophobia also can be expected to have an adverse impact on diet. Research supports this expectation. For instance, children who exhibit higher food neophobia consume lesser amounts of vegetables (Galloway et al. 2003) and, compared to neophilic individuals, have significantly less variety in their diets (Carruth et al. 1998; Falciglia et al. 2000). Another study demonstrated that Finns with high food neophobia were less likely to have tasted or eaten a sample of 20 foods than were those with low food neophobia, and their FNS scores significantly predicted the willingness to try unfamiliar foods and even some familiar

foods (Tuorila et al. 2001). Similarly, greater food neophobia was correlated with a higher frequency of untried foods (Russell and Worsley 2008) and with less frequent visitation to ethnic restaurants (Olabi et al. 2009). Lähteenmäki and Van Trijp (1995) found similar results with the VARSEEK scale: variety-seeking tendency was positively correlated with the self-reported number of well-liked alternatives on a list of 38 sandwich fillings ($r = 0.35$) and with the number of fillings that were reported to be eaten at least once or twice per month ($r = 0.37$).

Food neophobia appears to have differential effects on diet, affecting some food groups more than others. Russell and Worsley (2008) found the strongest effects of food neophobia for vegetables, followed by meats and fruit. The same three food groups were associated with neophobia in a study by Cooke et al. (2003), who suggest that these three food groups are particularly dangerous (i.e., prone to cause illness or initiate allergic reaction). They surmise that this pattern for stronger neophobia for such items is evolutionarily adaptive, and thus has been retained. Given the toxins in many plants, and the bacteria in meats, the argument seems sound for vegetables and meat. Fruits, however, are not particularly dangerous, but Cooke et al. argue that many children consider fruits and vegetables to be similar, and, consequently, extend their rejection to these as well. Moreover, both fruits and vegetables can have a strong bitter taste component, and our innate negative response to bitter taste is believed to be an adaptive trait useful for avoiding toxins. Rejection of bitter taste can be overcome with experience, but it appears this may be less likely in people with food neophobia, resulting in more rejection of bitter fruits and vegetables (see Ullrich et al. 2004).

47.3.2 Diet Influences Food Neophobia

Just as neophobia can affect diet, diet can affect neophobia. If the cause of food neophobia is avoidance of dangerous or unpleasant foods, then sampling new foods, as long as they are safe and palatable, should allow for learning that will reduce neophobia. Research clearly demonstrates that repeated exposure to a food can increase one's willingness to consume it. For example, Sullivan and Birch (1994) demonstrated that repeated exposure to a novel food increased acceptance of that food item by infants. This reflects, at least in part, the mere-exposure effect (Zajonc 1968, 2001) whereby repeated exposure to a particular pattern of sensory input increases liking for that pattern.

Even a single sampling of a novel food can be sufficient to reveal pleasant sensory effects and to suggest its safety. Hence, it would not be surprising if a single exposure could overcome the neophobia, as some research indicates (Pliner and Hobden 1992), but other research finds multiple exposures to be necessary. Based on two studies (Birch and Marlin 1982; Pliner 1982) that used multiple exposures to previously novel foods (up to 20), it appears that as many as ten exposures may be required to overcome avoidance of an unfamiliar food. This estimate is based on the average result, so one may expect fewer exposures to be needed for individuals who are less neophobic than average. Furthermore, when persuaded to try an unfamiliar food, people who are more neophobic (higher FNS scores) tend to rate the foods as less pleasant (Arvola et al. 1999; Raudenbush and Frank 1999). Thus, even after sensory information about an unfamiliar food is obtained by direct experience, the neophobic's negative response toward the food may be reduced but not eliminated. A more positive perspective on overcoming food neophobia is provided by a recent study that expanded the range of novel foods available to participants (Williams et al. 2008). This study demonstrated that the number of exposures required for voluntary consumption of novel foods decreases as more foods are added to the diet. That is, fewer exposures are needed to render unfamiliar foods acceptable as the number of acceptable foods increases. This result is based on a small clinical sample and should be replicated, but it may reveal a pathway to reduced food neophobia that could make interventions by parents and dietitians easier and more effective.

A similar finding is that food neophobia is negatively associated with "expected pleasantness" of a novel food item (Tuorila et al. 1994; Raudenbush and Frank 1999), and that once a novel food is actually tasted, the phobia can be overcome (Pliner and Hobden 1992). The fact that neophobia tends to decrease with age from early childhood well into adulthood (see next section) provides additional, albeit indirect, evidence for this claim in that more food experiences come with increasing age. Additional indirect evidence is the finding that food professionals have low food neophobia scores compared to non-specialists or to students enrolled in food service training courses (Frank and Kalisewicz 2000), and that neophobia is lower in adults with more international travel experience (Olabi et al. 2009).

The specificity of the effects of experience on neophobia remains unclear. That is, does repeated exposure to novel foods promote a general reduction in food neophobia, or does it only affect those specific foods to which one is exposed? The mere-exposure effect is typically capable of producing more positive responses not only to the specific exposed stimuli, but also to similar stimuli (Zajonc 2001). A generalized mere-exposure effect can explain the data of Pliner, Pelchat, and Grabski (1993) that indicate a general reduction in neophobia following "forced" exposure to tasty novel foods.

The results of at least one study, however, indicate that generalization does not always occur. Sullivan and Birch (1994) investigated the effects of repeated exposure to one of three variants (sweetened, salted, or plain) of a novel food (tofu) on children's preferences. After 15 tasting sessions, the children showed increased preference only for the particular flavor/food combination they had repeatedly tasted, with a decreased preference for the other versions. These results indicate that it is not just particular foods themselves that become more acceptable with experience, but the specific flavors associated with them. This much more specific effect of exposure than typically expected for a mere-exposure effect (see above) may be age related. Pliner et al. (1993) tested adults, whereas Sullivan and Birch (1994) tested infants. Moreover, a more recent study (Loewen and Pliner 1999) tested both older (10–12-year-old) and younger (7–9-year old) children, finding that exposure to unfamiliar foods increased willingness to try a different group of novel foods only for older children.

More research is needed. Whether food-specific, flavor-specific or general, it also remains unclear whether the reduction in food neophobia is temporary, and whether occasional exposure to unpleasant or harmful novel foods might counter this effect. We do know that consuming novel foods or flavors that are followed by an adverse physiological reaction typically produces an immediate (single exposure), strong, and long-lasting aversion in humans and many other species. Learning to avoid an item following even a single negative encounter is beneficial from an evolutionary perspective, since an immediate and long-lasting aversion to toxic foods is highly adaptive. FNS scores have been found to be higher in adults with a history of getting sick after eating a new food (Olabi et al. 2009), although they are not correlated with the tendency to suffer from motion sickness (Alley et al. 2006). An adverse sensory experience may produce a relatively strong and long-lasting effect as well, particularly if a bitter taste component is involved since, in our evolutionary past, bitter tastes often signaled toxins.

In brief, it appears that the trait of food neophobia presents a tendency to both avoid and to dislike novel foods, and to see more unfamiliar foods as disgusting. In combination, these tendencies should substantially increase the resistance of dietary change in neophobic individuals as compared to neophilics.

47.4 Factors that Influence Food Neophobia

Factors affecting reactions to novel foods are of constant interest to nutritionists, health educators, and food marketers, all of whom try to influence people to incorporate novel foods into their diets. The preceding section showed that gaining familiarity with a food can remove the neophobic

rejection, but neophobia may block consumption in the first place, and exposure (consumption), particularly if not repeated, may not change preferences enough to alter diet or preferences. Other factors are known to influence food neophobia. Unfortunately, many such factors are not amenable to manipulation: that is, one cannot change the age, sex or genetics of a neophobic individual.

47.4.1 Age Differences and Developmental Trends

In general, food neophobia tends to decline as a person ages (cf. Pliner and Salvy 2006). For example, a study of Swedish families found that younger children had higher food (and general) neophobia than older children, and also that those children were more neophobic than their parents (Koivisto-Hursti and Sjoden 1997). Likewise, McFarlane and Pliner (1997) tested people 10–79 years old, finding that older subjects were generally more willing to try novel foods than younger ones (but with no change in willingness between the age group of 23–39 years old and that of 40 years and older).

There appears to be two significant exceptions to this developmental trend. First, there is a period of relatively low food neophobia in infancy up to around the age of 2 years whereupon it rises rapidly peaking sometime around age 4. Second, there is an increase in neophobia seen in many elderly individuals. From the perspective of influence on lifelong behavior, the most important exception includes the period in infancy when children normally are making the transition to solid foods. While humans begin life consuming a single food that provides all nutrients, they must eventually shift to a much more complex diet in which a variety of foods must be consumed in order to fulfill our nutritional requirements. Food neophobia could pose a serious hurdle for this important developmental transition but, fortunately, there is little neophobia during this period (Birch 1998). Cashdan has argued that there may be a sensitive period for learning about food that coincides with lower food neophobia (Cashdan 1994, 1998). The rapid rise in food neophobia beginning around age 2 should have a protective function since the older child becomes increasingly independent and able to exert more control over what does, and does not, get consumed. Additional research is needed to determine if age at weaning has an effect (e.g., potentially delaying) on the onset of this rapid rise in food neophobia.

Another factor mitigating the potential impact of food neophobia in infancy is the prior exposure to flavors in utero and in breast milk. Some flavors from a pregnant woman's diet can be carried in the amniotic fluid and swallowed by her fetus (Mennella 1995; Mennella et al. 1995). Human milk also transmits flavors from the maternal diet to the breast fed infant; in contrast, the formula fed infant has a less varied exposure to flavors from food. This exposure via breast milk is believed to lead to better acceptance of novel foods offered during weaning (see Maier et al. 2008; and below). However, the effects may be temporary: a study of food neophobia in 2–5-year old children (Russell and Worsley 2008) found no difference between breast-fed and formula-fed children.

Neophobia may increase again with old age, as reported in a Finnish study (Tuorila et al. 2001). Likewise, Knaapila et al. (2007) found a slight but significant positive correlation between age and FNS scores in both Finnish ($r = 0.23$) and British ($r = 0.21$) samples of adults aged 18–78 and 17–82 years, respectively. The dietary constriction that can result from such increases in neophobia may contribute to the increased incidence of nutritional deficits in the elderly. In addition, there appears to be an interaction of age with type of food, such that people become more willing to try ethnic foods as they age, but less willing to try other kinds of novel foods (cf. Pliner and Salvy 2006).

47.4.2 Sex Differences

Studies of sex differences in food neophobia have reported inconsistent results. Some have described finding greater food neophobia in males and others in females, and others have failed to find a significant difference. Among the studies that have found higher food neophobia in males, Koivisto-Hursti and Sjoden (1997) found that 9-year-old boys were more neophobic than 9-year-old girls, and that fathers had more food neophobia than mothers. Finnish men were also found to be more neophobic than women (Tuorila et al. 2001).

In contrast, Frank and van der Klaauw (1994) found more "won't try" responses by women than by men on the FAS. Additional reports that men have a greater tendency than women to seek unusual and new foods (Logue and Smith 1986; Alley and Burroughs 1991; see section on Gender and Age Correlates below) support the prediction that men are less neophobic.

Reviewing survey and behavioral studies of neophobia separately, Pliner and Salvy (2006) conclude that both types of research usually fail to find gender differences. Some additional research not covered in their review finds no differences, supporting their conclusion. Specifically, Russell and Worsley (2008) found no sex difference in a sample of 2–5-year old Australian children, and Cooke et al. (2003) found no sex difference in a large sample of 2–6-year-old British children. Likewise, Alley et al. (2006) found no sex difference in FNS scores in a sample of 308 university students.

47.4.3 Genetics

Koivisto-Hursti and Sjoden (1997) reported finding some evidence of familial resemblance with respect to both food and general neophobia. While such similarities can result from experience rather than genetic inheritance, there is good evidence for a large genetic component. Recent research (largely based on adult women) examining both family and twin samples indicates that about two thirds of the variation in food neophobia is genetically determined (Knaapila et al. 2007). [Interestingly, this value is very close to the estimates of about 0.54–0.64 for the heritability of sensation seeking (see Zuckerman 2007, pp. 32ff.), which is related to food neophobia, as reviewed below]. A large-scale study (Cooke et al. 2007) of 5,390 twin pairs, aged 8–11 years, gave an even higher estimate of heritability: 0.78 (95% CI = 0.76–0.79).

47.4.4 Information and Social Influences

Pliner, Pelchat, and Grabski (1993) found that both fear of dangerous foods and expectations of unpleasant sensory experiences are significant determinants of the resistance to novel foods. Conversely, healthiness and sensory pleasantness are the motives most often cited when people are asked why they eat the foods they do (e.g., Rappaport et al. 1992). If we are averse to trying new foods in large part because of fear of dangerous or unpleasant substances, then it seems that information that promotes opposite expectations – good taste and safety – should reduce neophobia. In short, the results of pertinent studies (briefly reviewed below) show that such information is sometimes effective. Martins and Pliner (2005) found that resistance to trying new foods is also associated with beliefs about the disgusting properties of these foods. Similarly, Pliner (reported in Pliner et al. 2006) reports finding a strong positive correlation between the FNS and a measure of disgust. Disgust is a powerful block to consumption (Rozin and Fallon 1987) and may prove difficult to overcome so that "disgusting" novel foods will be consumed and, eventually, preferred. In general, foods of animal origin are most likely to provoke disgust.

The effectiveness of experience in increasing preferences for specific foods (see above) is a good, but indirect, indication of the effect of sensory information on responses to foods. Repeated exposure to the sensory properties of a once novel food provides direct specification of these key properties of foods. Likewise, a lack of adverse physiological consequences can provide direct specification of food safety. Nonetheless, the results of a study on 121 adults, Tuorila et al. (1994) showed that sensory information could *decrease* liking for novel foods, even though it increased liking for familiar ones, and a recent study of "sensory education" found only limited and temporary effects on neophobia (Reverdy et al. 2008). Can indirect evidence about foods in the form of verbal information or social influence be more effective?

The results for verbal information are inconsistent and reveal a need for further research. McFarlane and Pliner (1997) tested the willingness to taste six familiar and six unfamiliar foods in 401 volunteers ranging from 10 to 79 years old. Each received no information, taste likeability information, or nutrition information. Their results indicated that nutrition information could be effective for young adults, at least for those for whom nutrition is important. Pelchat and Pliner (1995) found that taste information increased willingness to try novel foods at young ages (10–14 years); a result McFarlane and Pliner (1997) failed to confirm.

Social influence can have powerful effects on diet. It is even capable of countering the strong learned aversions of poisoned rats to food previously containing the poison (Galef 1986). Studies on humans also show significant, if less impressive, effects of social influence on acceptance of, and preferences for, foods (cf. Birch 1990). For instance, Birch (1980) showed that children tend to like and select the same foods as peers. Research on social influence via modeling has found positive, but limited and qualified results: under some circumstances, mothers, teachers, and peers have all been shown to be effective models for consumption of a novel food (cf. Pliner and Salvy 2006). Addessi et al. (2005) demonstrated a reduction in food neophobia in young children for the same type of food as was seen being consumed by others.

Flight, Leppard, and Cox (2003) reasoned that both higher socioeconomic status and dwelling in urban (versus rural) environments may increase exposure to diverse cultures and expand knowledge of foods. Consequently, they expected these to be negatively associated with food neophobia, but found only weak support for this in their sample of over 900 Australian high school students. Nonetheless, other research has supported this perspective: Food neophobia scores collected from 1083 Finns decreased with increasing education and with the degree of urbanization (Tuorila et al. 2001).

47.5 Sensation Seeking and Food Neophobia

Given that food neophobia reflects, in good part, risk avoidance, it should be expected that FN would be correlated with a personality trait associated with risk-taking. *Sensation seeking (SS)* is a personality trait defined by a person's willingness to seek out novel, complex, and intense stimuli while being willing to take risks (physical or social) in order to have such experiences (Zuckerman, 1979, 1994). SS has also been described as "not only a potential for taking risks, but… more generally a quality of seeking intensity and novelty in sensory experience" (Arnett 1994). SS has been fairly well studied for several decades, and it has been repeatedly demonstrated that SS can be influential in determining an individual's behavioral choices. Scholarly considerations of the biological and psychological correlates of this trait are summarized in three books by the pioneer and leading scholar of SS research and theory, Marvin Zuckerman (Zuckerman, 1979, 1994, 2007). Some of the key attributes are highlighted in Table 47.3.

Table 47.3 Sensation seeking summary points

Definition	A personality trait reflecting a person's willingness to seek out novel, complex, and intense stimuli while being willing to take risks (e.g., physical and social) in order to have such experiences
Common measurement instruments	1. Sensation seeking scales (Zuckerman)
	2. Arnett Inventory of Sensation Seeking (AISS)
Selected correlates (cf. Zuckerman 1994, 2007)	Risky behaviors
	• Risky sex (e.g., multiple partners; sex with strangers)
	• High risk sports (e.g., skydiving, hang gliding, mountain climbing)
	• Risky driving (e.g., speeding; driving under the influence)
	Illegal drug use
	Tobacco and alcohol use
	Gambling
	Risky vocations
	Eating habits and food preferences (attraction to unusual, novel and/or stimulating foods)
	Social attitudes (liberal and permissive)

Summarized information about key personality trait Sensation Seeking

47.5.1 Neophobia and Sensation Seeking

The primary tool for measuring SS is Zuckerman's sensation seeking scale (SSS). Zuckerman has created at least six different scales over the years in an attempt to accurately measure one's sensation seeking tendencies (Zuckerman et al. 1964; Zuckerman and Link 1968). Many of these scales are widely accepted and have even been translated and/or adapted by other researchers. SS is associated with risk taking in a wide variety of arenas including driving, sports, drug use, and sexual behavior. As noted above, trying unfamiliar foods is inherently risky, so it would be surprising if there were no discernable effects on food choice.

Zuckerman has recognized that food selection should be related to sensation seeking tendencies. He hypothesized that sensation seekers prefer those foods that are "less bland and more stimulating" (Zuckerman 1994). Therefore, he includes a food choice item on his SSS (Zuckerman et al. 1964; Zuckerman, 1979, 1994) that asks participants to choose between "I order the dishes with which I am familiar, so as to avoid disappointment and unpleasantness" or "I like to try new foods that I have never tasted before."

As predicted, scores on the FNS are correlated with the Experience Seeking subscale of the SSS (Pliner and Hobden 1992). This and other research (e.g., Frank and van der Klaauw 1994; Pliner and Melo 1997; Potts and Wardle 1998; Loewen and Pliner 2000) seem to indicate a definite relationship between neophobia and sensation seeking. Likewise, a Japanese study (Terasaki and Imada 1988) reported a modest correlation between experience eating very unusual foods and the Thrill and Adventure Seeking subscales of the SSS.

While the Zuckerman scales are commonly used, some researchers have attempted to shorten and adapt them or, in several cases, create their own scales (e.g., Hoyle et al. 2002; Madsen et al. 1987; Michel et al. 1999). Arnett (1994) created what is probably the best known alternative scale, the Arnett Inventory of Sensation Seeking (AISS). Arnett felt that when measuring sensation seeking, one should use *novelty* and *intensity* of stimulation as the subscales rather than Zuckerman's *novelty* and *complexity* of stimulation. His reasoning was that the subscale of complexity was difficult to define clearly and, in most cases, was actually a better measure of intensity than complexity. Finally,

Table 47.4 Arnett Inventory of Sensation Seeking (AISS)

  1. I can see how it would be interesting to marry someone from a foreign country
  2. When the water is very cold, I prefer not to swim even if it is a hot day[a]
  3. If I have to wait a long time, I'm usually patient about it[a]
  4. When I listen to music, I like it to be loud
  5. When making a trip, I think it is best to make as few plans as possible and just take it as it comes
  6. I stay away from movies that are said to be frightening or highly suspenseful[a]
  7. I think its fun and exciting to perform or speak before a group
  8. If I were to go to an amusement park, I would prefer to ride the roller coaster or other fast rides
  9. I would like to travel to places that are strange and far away
 10. I would never like to gamble with money, even if I could afford it[a]
 11. I would have enjoyed being one of the first explorers of an unknown land
 12. I like a movie where there are a lot of explosions and car chases
 13. I don't like extremely hot and spicy foods[a]
 14. In general, I work better when I'm under pressure
 15. I often like to have the TV on while I'm doing something else, such as reading or cleaning up
 16. It would be interesting to see a car accident happen
 17. I think it's best to order something familiar when eating in a restaurant[a]
 18. I like the feeling of standing next to the edge on a high place and looking down
 19. If it were possible to visit another planet or the moon for free, I would be among the first to sign up
 20. I can see how it must be exciting to be in a battle during a war

Each item requires a rating on a 4-point Likert scale: 1 = Does not describe me at all, 2 = Does not describe me very well, 3 = Describes me somewhat, and 4 = Describes me very well
[a]Six items on this scale are reverse scored (Arnett 1994)

and perhaps most importantly, the AISS gave more emphasis to the idea of socialization effects on SS behavior rather than purely biological motivation. Hence, Arnett's scale takes into account such external influences as peer pressure and societal practices. The AISS includes 20 statements that are ranked on a 4-point Likert scale (Table 47.4). Like Zuckerman's SSS, the AISS includes an item (ordering "something familiar when eating in a restaurant") that can be seen as assessing food neophobia, and another (about "hot and spicy foods") that may be related to food neophobia. Arnett (1994) has found high internal reliability (0.83–0.86).

As mentioned previously, scores on Zuckerman's SSS were found to be negatively correlated with one's neophobic tendencies (Pliner and Hobden 1992), so it is not surprising that AISS scores also have been shown to be correlated with FNS scores. Alley et al. (2006) found a significant correlation between participants' scores on the FNS and the AISS ($r = -0.42$, $p = 0.0001$) (Fig. 47.2). While such negative correlations indicate that higher sensation seeking is correlated with lower neophobia, one might well take issue with the significance of these correlations because both measures of SS (SSS or AISS) include one or two items that explicitly assess food neophobia. Alley et al. (2006), however, removed these items from the computation of their participants' AISS scores, finding that even without the two food-related items, FNS scores remained correlated with sensation seeking ($r = -0.35$, $p < 0.001$).

47.5.2 Sensation Seeking and Other Food Constructs

In addition to familiarity, SS logically should be associated with some other sensory aspects of food, with high SS associated with more attraction to, and consumption of, foods that are hot (spicy), highly flavored, or unusually textured. However, such tendencies may be masked by other factors that can have a pronounced effect on food choice, particularly genetic differences in taste sensitivity
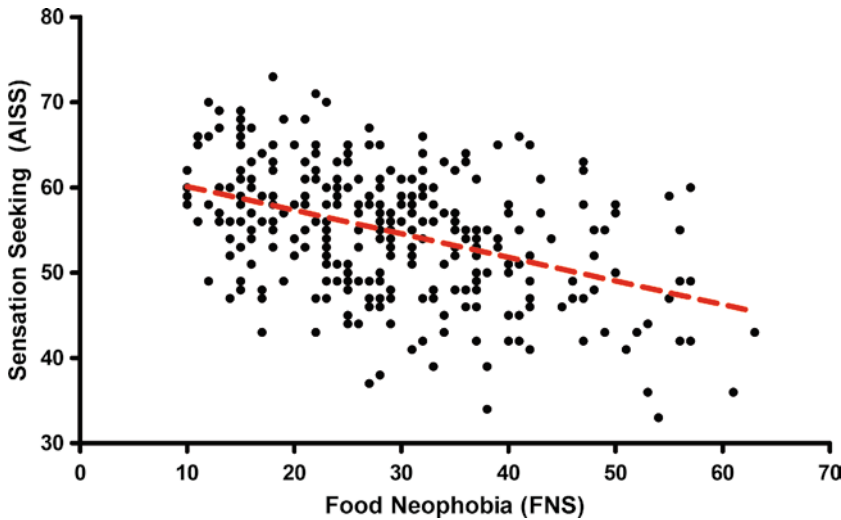
Fig. 47.2 FNS and AISS correlation College students ($N = 305$) were administered the FNS (M = 29.12, SD = 11.24) and AISS (M = 54.81, SD = 7.41). A significant negative correlation was found between FNS and AISS scores ($r = -0.611$, $p = 0.000$), suggesting that higher SS scores (greater AISS scores) were associated with lower levels of neophobia (i.e., lower FNS score) (Potter and Alley 2009)

and cultural differences in the use of spices and condiments. So, for instance, a person who is a "supertaster" and thereby more sensitive to bitter (among other) tasting substances, may be more adverse to bitter tastes than normal (unless they also are high in the "food adventurousness" aspect of sensation seeking; cf. Ullrich et al. 2004). Nonetheless, research supports these conjectured ties of food preferences and sensation seeking. Studies show that a preference for spicy hot foods is related to sensation seeking or thrill seeking (Rozin and Schiller 1980). This preference may even be driven by sensation seeking, but there is insufficient research to establish this causal connection. Likewise, high sensation seekers, both male and female, apparently have stronger preferences for foods with unusual spices (Logue and Smith 1986) or for foods that are spicy, sour or crunchy (Kish and Donnenwerth 1972; Zuckerman 1979; Terasaki and Imada 1988).

Researchers have also found that a person's arousal level is important when considering the tendency to seek out a new or stimulating situation, as Zuckerman has argued. Pliner and Melo (1997) found a significant interaction between sensation seeking and arousal level that influenced the number of new foods participants ate. This leads to the inference that one's arousal level before being presented with new foods could impact his/her willingness to try them. Several studies show that arousal level can affect the foods that one chooses to eat (Pliner and Melo 1997; Loewen and Pliner 2000; Pliner and Stallberg-White 2000). Similarly, Stallberg-White and Pliner (1999) found that when a food choice is only hypothetical (a nonarousing situation), high sensation seekers make more neophilic choices.

47.5.3 Sensation Seeking: Gender and Age Correlates

Previous research has shown that men tend to have stronger sensation seeking tendencies than women. This sex difference has been seen in American, Canadian, and Australian subjects (Zuckerman 1978; Ridgeway and Russell 1980; Ball et al. 1984). Given that higher sensation seeking is associated with lower food neophobia, the sex difference in sensation seeking suggests that men are more attracted by and willing to try new and unusual foods, whereas women are more likely to seek familiar foods. Researchers, however, have sometimes found no sex differences or even a

reversal of the pattern expected based on greater SS in men (see previous discussion). Such inconsistency demands further research and analysis.

The results from two studies indicate that men tend to have stronger preferences for spicy foods than women (Logue and Smith 1986; Alley and Burroughs 1991). The more recent study had 148 people between 17 and 32 years old complete questionnaires concerning past and current food use and preferences, as well as food and condiment use in one actual meal. Their responses clearly support the prediction that men tend to have a stronger preference for hot foods (e.g., hot peppers) than women. Moreover, men reported a greater previous consumption of unusual foods, and a higher current preference for them. Logue and Smith (1986) reported that their female subjects expressed lower preferences for spicy foods than their male counterparts.

In addition to gender differences, it has also been shown that age can impact one's sensation seeking tendencies. Typically, SS is higher in younger individuals and declines as a person ages. This has been seen in a number of populations, including Australian, German, and English individuals (Zuckerman 1978; Ball et al. 1984; Roth et al. 2005). This trend is largely opposite from that for FN, at least for the period from adolescence to mid-life, showing that SS and FN, while correlated, are separate traits.

47.5.4 Applications to Other Areas of Health and Disease

Understanding the impact of sensation seeking and neophobia on food choice, as well as their potential interactions, is critical to many aspects of human health. Reducing food neophobia may be an effective means of improving dietary quality by increasing the variety of foods consumed. A good example of this has been seen in breast fed versus formula fed infants. Formula fed infants are bound to have less varied exposure early in life to flavors from foods compared to similar breast fed infants. Research suggests that an infant's early experience with flavors in human milk has a positive effect on the transition to, and acceptance of, solid foods. Sullivan and Birch (1994) found that breast-fed infants consumed greater amounts of a novel food (their first vegetable) than formula-fed infants. Human milk-fed infants have been noted to have a faster acceptance of the first transition foods offered. Thus, educating parents about this additional benefit of breast feeding could ultimately increase the quality and variety of diets seen in their children, and might serve to help lessen the prevalence of other medical disorders such as obesity.

According to the US Centers for Disease Control and Prevention (CDC), in the years 2003–2006, 12.4% of children ages 2–5, 17% of children ages 6–11, and 17.6% ages 12–19 were considered obese (CDC.gov 2009). The CDC suggests that parents should work hard to reduce a child's risk of becoming obese, as childhood obesity increases the likelihood of that child staying obese into adulthood, which in turn increases the risk for many other health issues such as high blood pressure and diabetes. Parents who are knowledgeable about food neophobia in children and the advantages of providing a wide variety of healthy foods during childhood should be more likely to promote healthy diets (cf. Skinner et al. 2002; Nicklaus 2009). As discussed above, food neophobia in children is associated with lower variety in diets in general and with particularly low intake of three important food groups: fruits, vegetables, and protein foods. Indeed, Falciglia et al. (2000) found evidence of less healthy eating in neophobic children than for average and neophilic children. A similar finding was reported by Russell and Worsley (2008). Significant contributors to this pattern were less dietary variety and higher consumption of saturated fat in the neophobic children (Falciglia et al. 2000). If, due to exposure or any other reason, high calorie foods have more predictable sensory qualities than lower caloric foods, then high calorie foods may be especially preferred by neophobic eaters.

Given the prevalence of food neophobia in children, particularly for the aforementioned food groups, having a better understanding of the role of food neophobia in the development of eating habits and food preferences is imperative. The design of effective interventions to improve children's diets should incorporate our understanding of neophobia. Furthermore, the impact of food neophobia on long-term food consumption should be considered when attempting to prevent obesity as well as poor nutrition. As Cooke et al. (2003) suggest, "guiding parents in the technique of regular and repeated taste exposure (particularly to vegetables, fruit, meat, and eggs) has the potential to improve the diets of young children at what may be a sensitive period for developing lifelong healthy eating patterns" (p. 206).

Summary Points

- Humans have a wide range of food items available for consumption. Humans and other omnivores must evaluate new foods and decide between rejecting the novel food (and potentially missing out on a good food source) or trying the item (and possibly ingesting something harmful or disagreeable). This choice is referred to as the "omnivore's dilemma".
- Food neophobia is a reluctance/fear of eating food items with which one is unfamiliar. Evolutionarily speaking, this trait is advantageous since being cautious when deciding to eat an unknown item could prevent ingesting dangerous toxins or allergens. However, in modern society (when most foods are safe), this trait can have adverse effects on one's diet when people restrict their diet to familiar items only.
- The most commonly used measure for assessing neophobia is the FNS, developed in 1992 by Pliner and Hobden. Other tools used to measure neophobia include the FNSC and, for older children, the Food Situation Questionnaire (FSQ) developed by Loewen and Pliner (2000). To determine actual neophobic behavioral responses, the willingness to taste novel food (WTNF) and UFST can be used.
- Food neophobia can have a significant impact on an individual's diet, and vice versa. Individuals with higher levels of food neophobia tend to consume less varied diets and consume lesser amounts of vegetables, fruits, and meats. Repeated exposure to novel food items can increase one's propensity to accept (i.e., consume) the item.
- Both the age and sex of an individual can influence food neophobia. In general, food neophobia tends to decline with age, with younger children being more neophobic than older children and children in general being more neophobic than their parents. There are two exceptions to this general trend: (1) there is a period of low neophobia in infants when they are transitioning to solid food, and (2) there is an increase in food neophobia in the elderly. Research on sex differences in food neophobia is inconsistent and may be insignificant, but more research is needed to elucidate the effect of gender on food neophobia.
- Sensation seeking (SS) is a personality trait defined by a person's willingness to seek out novel, complex, and intense stimuli while being willing to take risks (e.g., physical and social) in order to have such experiences. Food selection is related to SS tendencies and scales commonly used to measure SS include at least one food choice question. Higher SS is correlated with lower food neophobia.
- As with food neophobia, the age and sex of an individual can influence SS. Typically, SS is higher in younger individuals and declines as a person ages. Men typically have stronger SS tendencies than women, and given that higher SS is associated with lower food neophobia, it is possible that men are more attracted by and willing to eat new and unusual foods.

Key Terms

Arnett Inventory of Sensation Seeking: Developed by Arnett in 1994 as an alternative to the sensation seeking scale. This scale includes 20 statements that are ranked on a 4-point Likert scale (see Table 47.3).

Food Neophobia: A psychological trait defined by a person's fear (phobia) or unwillingness to consume new (neo) or unknown food items.

Food Neophobia Scale: Developed by Pliner and Hobden in 1992, this is the most commonly used scale to measure food neophobia in adults (see Table 47.1).

Omnivore's Dilemma: Each time a potential but unfamiliar food item is encountered, one must decide to avoid it, and, possibly, miss out on a good food source, or eat it, and, perhaps, ingest something dangerous. This choice is known as the "omnivore's dilemma".

Pickiness: Picky (or "finicky") eaters resist eating many familiar foods (Galloway et al. 2003). Food neophobia is specifically a reluctance to consume a food item that is unfamiliar, while pickiness may be influenced by other variables (e.g., texture).

Sensation Seeking: A personality trait defined by a person's willingness to seek out "novel, complex, and intense" stimuli while being willing to take risks in order to have such experiences (Zuckerman 1994).

Sensation Seeking Scale: Developed and refined by Zuckerman, this is a commonly used scale to measure sensation seeking in adults.

References

Addessi E, Galloway AT, Visalberghi E, Birch LL., 2005; Appetite. 45:264–71.

Alley TR, Burroughs WJ., 1991; J Gen Psychol. 118:201–14.

Alley TR, Willet KA, Muth ER., 2006; Percept Motor Skill. 102:683–90.

Arnett J., 1994; Pers Indiv Differ. 16:289–96.

Arvola A, Lahteenmaki L, Tuorila H., 1999; Appetite. 32:113–26.

Ball IL, Farnill D, Wangeman JF., 1984; Brit J Psychol. 75:257–65.

Birch LL., 1980; Child Dev. 51:489–96.

Birch LL. In: Capaldi ED, Powley TL, editors. Taste, experience, and feeding. Washington, DC: American Psychological Asssociation; 1990. p. 116–35.

Birch LL., 1998; P Nutr Soc. 57:617–24.

Birch LL, Marlin DW., 1982; Appetite. 3:353–60.

Carruth BR, Skinner J, Houck K, Moran J 3rd, Coletta F, Ott D., 1998; J Am Coll Nutr 17:180–6.

Carruth BR, Ziegler PJ, Gordon A, Barr SI., 2004; J Am Diet Assoc. 104:s57–64.

Cashdan E., 1994; Hum Nature. 5:279–91.

Cashdan E., 1998; Soc Sc Inform. 37:613–32.

CDC.gov. (2009); Online. http://www.cdc.gov/obesity/childhood/index.html

Cooke L, Wardle J, Gibson EL., 2003; Appetite. 41:205–6.

Cooke LJ, Haworth CM, Wardle J., 2007; Am J Clin Nutr. 86:428–33.

Domjan M. In: Baker LM, Best MR, Domjan M, editors. Learning mechanisms in food selection. Texas: Baylor University Press; 1977. p. 151–79.

Dovey TM, Staples PA, Gibson EL, Halford JC., 2008; Appetite. 50:181–93.

Falciglia GA, Couch SC, Gribble LS, Pabst SM, Frank R., 2000; J Am Diet Assoc. 100:1474–81.

Flight I, Leppard P, Cox DN., 2003; Appetite. 41:51–9.

Frank RA, Kalisewicz S., 2000; Appetite. 34:335.

Frank RA, van der Klaauw NJ., 1994; Appetite. 22:101–23.

Galef BG Jr. J Comp Psychol. 1986;100:432–9.

Galloway AT, Lee Y, Birch LL., 2003; J Am Diet Assoc. 103:692–8.

Hoyle RH, Stephenson MT, Palmgreen P, Pugzles Lorch E, Donohew RL., 2002; Pers Indiv Differ. 32:401–14.

Kish GB, Donnenwerth GV., 1972; J Consult Clin Psych. 38:42–9.

Knaapila A, Tuorila H, Silventoinen K, Keskitalo K, Kallela M, Wessman M, Peltonen L, Cherkas LF, Spector TD, Perola M., 2007; Physiol Behav. 91:573–8.

Koivisto UK, Sjoden PO., 1996; Appetite. 26:89–103.

Koivisto-Hursti UK, Sjoden P, 1997; Appetite. 29:89–103.

Lähteenmäki L, Van Trijp H., 1995; Appetite. 24:139–51.

Loewen R, Pliner P., 1999; Appetite. 32:351–66.

Loewen R, Pliner P., 2000; Appetite. 35:239–50.

Logue AW, Smith ME., 1986; Appetite. 7:109–25.

Madsen DB, Das AK, Bogen I, Grossman EE., 1987; Psychol Rep. 60:1179–84.

Maier AS, Chabanet C, Schaal B, Leathwood PD, Issanchou SN., 2008; Clin Nutr. 27:849–57.

Martin Y, Pliner P. Appetite. 2005;45:214–224.

McFarlane T, Pliner P., 1997; Appetite. 28:227–38.

Meiselman HL, Mastroianni G, Buller M, Edwards J., 1999; Food Qual Prefer. 10:1–8.

Mennella JA., 1995; J Hum Lact. 11:39–45.

Mennella JA, Johnson A, Beauchamp GK., 1995; Chem Senses. 20:207–9.

Michel G, Mouren-Siméoni MC, Perez-Diaz F, Falissard B, Carton S, Jouvent R., 1999; Pers Indiv Differ. 26: 159–74.

Nicklaus S., 2009; Appetite. 52:253–5.

Olabi A, Najm NEO, Baghdadi OK, Morton JM., 2009; Food Qual Prefer. 20:353–62.

Pelchat ML, Pliner P., 1995; Appetite. 24:153–65.

Pliner P., 1982; Appetite. 3:283–90.

Pliner P., 1994; Appetite. 23:147–63.

Pliner P, Hobden K., 1992; Appetite. 19:105–20.

Pliner P, Melo N., 1997; Physiol Behav. 61:331–5.

Pliner P, Salvy SJ. In: Shepard R, Raats M, editors. The psychology of food choice. Cambridge, MA: CABI; 2006. p. 75–92.

Pliner P, Stallberg-White C., 2000; Appetite. 34:95–103.

Pliner P, Pelchat M, Grabski M., 1993; Appetite. 20:111–23.

Pliner P, Lahteenmaki L, Tuorila H., 1998; Appetite. 30:93.

Pollan M., The omnivore's dilemma: a natural history of four meals. New York: Penguin.

Potter KA, Alley TR. In Preparation.

Potts HW, Wardle J., 1998; Appetite. 30:79–92.

Rappaport L, Peters G, Huff-Corzine L, Downey R., 1992; Ecol Food Nutr. 28:171–89.

Raudenbush B, Frank RA., 1999; Appetite. 32:261–71.

Raudenbush B, van der Klaauw NJ, Frank RA., 1995; Appetite. 25:1–15.

Reverdy C, Chesnel F, Schlich P, Koster EP, Lange C., 2008; Appetite. 51:156–65.

Ridgeway D, Russell JA., 1980; J Consult Clin Psych. 48:662–4.

Ritchey PN, Frank RA, Hursti UK, Tuorila H., 2003; Appetite. 40:163–73.

Roth M, Schumacher J, Brähler E., 2005; Pers Indiv Differ. 39:1261–71.

Rozin P. In:Rosenblatt J, Hinde RA, Shaw E, 1976; editors. Advances in the study of behavior. New York:Academic; p. 21–76.

Rozin P, Fallon AE., 1987; Psychol Rev. 94:23–41.

Rozin P, Schiller D., 1980; Motiv Emotion. 4:77–101.

Rubio B, Rigal N, Boireau-Ducept N, Mallet P, Meyer T., 2008; Appetite. 50:408–14.

Russell CG, Worsley A., 2008; J Nutr Educ Behav.40:11–9.

Skinner JD, Carruth, BR, Bounds, W, Ziegler PJ., 2002; J Am Diet Assoc. 102:1638–47.

Stallberg-White C, Pliner P., 1999; Appetite. 33:209–21.

Sullivan SA, Birch LL., 1994; Pediatrics. 93:271–7.

Terasaki M, Imada S., 1988; Pers Indiv Differ. 9:87–93.

Ton Nu C., 1996; Préférences et néophobie alimentaires à l'adolescence Doctoral Thesis (Thèse de Doctorat). Paris: ENGREF; – Unpublished.

Tuorila H, Meiselman HL, Bell R, Cardello AV, Johnson W., 1994; Appetite. 23:231–46.

Tuorila H, Lahteenmaki L, Pohjalainen L, Lotti L., 2001; Food Qual Prefer. 12:29–37.

Ullrich NV, Touger-Decker R, O'sullivan-Maillet J, Tepper BJ., 2004; J Am Diet Assoc. 104:543–9.

Van Trijp HCM, Steenkamp J-BEM., 1992; Eur Rev Agric Econ.19:181–95.

Van Trijp HCM, Lahteenmaki L, Tuorila H., 1992; Appetite. 18:155–64.

Williams KE, Paul C, Pizzo B, Riegel K., 2008; Appetite. 51:739–742.

Zajonc RB., 1968; J Pers Soc Psychol. 9:1–27.

Zajonc RB., 2001; Curr Dir Psychol Sci. 10:224–8.

Zuckerman M. In: London H, Exner J, 1978. editors. Dimensions of personality. New York: Wiley Interscience

Zuckerman M., 1979; Sensation seeking: beyond the optimal level of arousal. Hillsdale, NJ: Erlbaum; 1979.

Zuckerman M., 1994; Behavioral expressions and biosocial bases of sensation seeking. Cambridge, NY: Cambridge University Press; 1994.

Zuckerman M., 2007; Sensation seeking and risky behavior. Washington, DC: American Psychological Association; 2007.

Zuckerman M, Link K., 1968; J Consult Clin Psychol. 32:420–6.

Zuckerman M, Kolin EA, Price L, Zoob I., 1964; J Consult Psychol. 28:477–82.

Chapter 48
The Effects of Prior Beliefs and Learning on Consumers' Acceptance of Genetically Modified Foods: Implications for Diet and Behavior*

Wallace E. Huffman, Matthew Rousu, Jason F. Shogren, and Abebayehu Tegene

Abbreviations

GM	Genetic modification
GMO	Genetically modified organism
WTP	Willingness to pay is the maximum amount that an individual is willing to pay for one unit of a good
$U(Y)$	Maximum household indirect utility as a function of household income (Y)
$V(Y - L)$	Maximum household indirect utility as a function of household income (Y) but subject to a lost (L)
$E(U)$	The expected value of household utility (U)
p^i	The probability of a bad outcome under state of the world $i = inf$ (decision maker has informed prior beliefs), *no-I* (decision maker has uninformed prior beliefs), US, USA, United States
\$	US dollar

Classification codes: C91, D12, D82

New food products made from genetically modified crops appeared in US supermarkets starting in 1996 (see Table 48.1). The genetic modification consisted of herbicide tolerance and insect resistance that have been introduced into field crops through the use of techniques in modern biotechnology. Herbicide tolerance and insect resistance are so-called input traits that reduce the expected cost of production to farmers (Fernandez-Cornejo and McBride 2002; FAO 2004), but have no direct benefit to consumers and pose some risks (Chern and Rickertsen 2004; FAO 2004). Consequently, GM products have been subject to much controversy (claims by environmental groups of reducing biodiversity, new food safety concerns due to allergens, and ethical concerns regarding the movement of genes across species), and they have raised important new issues in trade talks especially between the USA and the European Union.

*The authors are C.F. Curtiss Distinguished Professor of Agriculture and Professor of Economics, Iowa State University; Assistant Professor, Susquehanna University; Stroock Distinguished Professor of Natural Resource Conservation and Management, Department of Economics and Finance, University of Wyoming; and Senior Economist, Food and Rural Economics Division, ERS, US Department of Agriculture

W.E. Huffman (✉)
Department of Economics, Iowa State University, Ames, IA 50011, USA
e-mail: whuffman@iastate.edu

Table 48.1 Some key features of genetically modified foods

Genetic modification: The application of bioengineering using recombinant DNA or gene splicing methods to create new organism, sometimes called biotechnology

First successful GM crops: Starting in 1996, GM cotton, corn, canola, and soybean became available that contain genes from soil bacterial that encoded the ability of plants to be herbicide tolerant or toxic to insects. For example, in cotton, corn, canola, and soybean, the GM crop varieties encoded resistance to a particular herbicide, which generally kills all plants that comes in contract with it. In cotton, GM crop varieties were also encoded to produce a toxic substance that kills key pests in the cotton bud-bollwormcomplex, and in corn, GM crop varieties were encoded with resistance to the Europeancorn borer. One might ask what is the alternative to these, the so-called farmer traits, which area type of biological control of pests? Most likely it would be one or more applications of agricultural chemicals, but might also include the use of a crop rotation containing two or more crops

New potential: New bioengineering methods have been developed to produce fresh vegetables that contain consumer traits of high antioxidants and vitamin C

Current situation: In the US more than 90% of the soybean acreage is planted to herbicide tolerant varieties; 80% of the corn acreage is planted to varieties either herbicide tolerant, insect resistant or both. In cotton, more that 75% of the acreage is either herbicide tolerant, insect resistant or both. In canola, 50% of the acreage is planted to herbicide tolerant varieties. GMOs for consumer traits are about to enter the market

Health concerns: There is no evidence that any individual has been harmed by a GMO organism inserted to commercial crop varieties

This table lists some key facts about genetic modification and biotechnology, including some historical underpinnings of the technology

Huffman et al. (2003) examined the effects of GM-food labels on bidding behavior of participants in an experimental auction, and Rousu et al. (2007) developed a methodology to value the contribution of third-party objective information in a setting with conflicted information. An important question is how decision makers use information when they make decisions about GMOs. For example, individuals generally possess some information about a topic, say GMOs, and they may acquire or be exposed to new information. The issue then becomes what weight is placed on these two types of information. For example, if a decision maker has very strong beliefs he or she may be unaffected by new information. Alternatively, he or she may know nothing about a topic and, hence, place all the weight on new information. More generally we can expect decision makers to use both types of information with weights that sum to one. This type of decision making process can be summarized in Bayes theorem (Grether 1980).

Earlier papers, while interesting, have not focused on the contributions of decision makers beliefs, called subjective prior beliefs, about genetic modification in an experimental auction-market setting. However, other literature applying Bayesian decision making include a discussion of prior beliefs about attributes of goods (Akerlof 1970; Hirshleifer and Riley 1992; Molho 1997; Stigler 1961), new information, and Bayesian learning (DeGroot 1970; Molho 1997, pp. 248–49; Tirole 2003, pp. 373).[1] This paper summarizes new evidence of the role of consumer's prior beliefs about genetic modification and diverse, new information about genetic modification on their WTP for foods that might be genetically modified. The information is of two broad types: subjective prior beliefs that arise from prior investments in information and new information from interested and disinterested parties. In the GM-food debate, the interested parties are classified as the agricultural biotech industry and environmental groups. The agricultural biotech industry consists of the private companies that market GM crop input traits to farmers and distribute probiotech information publically – Monsanto, Syngenta, Pioneer Hi-bred – and the Council for Biotechnology Information, a private trade association. The anti-GM environmental groups include Greenpeace, Friends of the Earth, and Action Aid. Furthermore, Huffman and Tegene (2002) have speculated about the potential value of

---

[1] These beliefs could, however, be uninformative or diffuse (DeGroot 1970)

independent, third-party information in such a conflicted market, and Rousu et al. (2007) have injected independent, third-party information into a set of economic experiments to assess its value.[2] In these food experiments, label types and information treatments were randomly assigned to sessions or trials. In this setting, participants who perceived themselves to be at least somewhat informed about genetic modification bid significantly less for GM-labeled foods than those who considered themselves to be uninformed. An important issue is how prior information affects the interpretation of new information, which this study emphasizes.

If consumers place heavy weight on information from interested parties, including cheap talk or hearsay, their welfare will be lower than if they use objective information (Akerlof 1970; Molho 1997; Morris and Shin 2002). Hence, consumers who have uninformed prior beliefs will have their bidding behavior affected by information from interested parties, but consumers who have informed prior beliefs may be relatively unaffected or place little weight on this type of information (Schultz 1975; Huffman 2001; Tversky and Kahneman 1981; Kahneman 2003). Another possibility is that the presence of third-party information affects the way that consumers use information from interested parties in formulating their bids.

The centerpiece of this research has been a set of experiments conducted in 2001 and which is summarized in Huffman et al. (2003) and Rousu et al. (2007). In these experiments, a hybrid methodology was developed using laboratory auctions that combined the methods of economic experiments, statistical experimental design, and survey design. These auctions are broadly called WTP experiments constructed such that it was in each participant's best interest to bid their true preferences, and furthermore, the winners were expected to "pay" what they "say" or "bid" – they executed winning bids by paying cash for experimental commodities. To add diversity to the set of experimental participants, experiments were conducted at two locations.[3] The model, results, and conclusions follow.

48.1 Methodological Considerations

A simple conceptual framework provides a useful device for helping to understand the observed behavior of consumers. Economists have shown that individuals frequently place less weight on prior beliefs than on new information when bidding on lotteries (e.g., see Grether 1980; Tversky and Kahneman 1974). This work, however, has been extended in two important ways. First, adopt the Bayesian concept of subjective beliefs instead of assuming that prior beliefs are always "fact" or objective beliefs (DeGroot 1970). Second, recognize that prior beliefs and new information from interested and disinterested parties may affect consumer's WTP for a new product that might have some risks, e.g., environmental or human harm.

Consumer utility or satisfaction from consuming genetically modified food products is best represented as depending on prior beliefs about genetic modification. Following Kivi and Shogren (2005), we define state-dependent indirect utility functions for a "good outcome" $U(Y)$ and a "bad outcome" $V(Y – L)$ that are independent of an individuals' prior beliefs or the amount of new information that they have acquired/received. The indirect utility functions give maximum utility for a

---

[2] Independent, third-party information is sometime referred to as verifiable information (Milgrom and Roberts 1986)

[3] An alternative methodology is to use state preference or contingent value surveys. In these surveys a random sample of households are contacted and asked to respond to hypothetical product preference or willingness to pay options. This approach has the advantage of being able to be administered relatively inexpensively to a large sample, which can give precision (for examples see Johnston et al. 2001). However, because responses are hypothetical, they are not bound by a budget constraint. This can lead to hypothetical biases or credibility problems that do not vanish as the sample size increases. For examples, see Diamond and Hausman (1994) and Fox et al. (1998)

given level of income, Y and $Y - L$, and they are weighted by the individuals' subjective probabilities conditioned on their prior beliefs: p^I, probability of a bad outcome, given the participant has informed prior beliefs, and p^{no-I}, probability of bad outcome given the participant has uninformed prior beliefs, to obtain a consumer's expected utility:

$$U\left(Y - WTP^I\right) = EU^I = p^I\left(I, \inf\right)V\left(Y - L\right) + \left(1 - p^I\left(I, \inf\right)\right)U\left(Y\right), \tag{48.1}$$

$$U\left(Y - WTP^{no-I}\right) = EU^{no-I} = p^{no-I}\left(\inf\right)V\left(Y - L\right) + \left(1 - p^{no-I}\left(\inf\right)\right)U\left(Y\right) \tag{48.2}$$

Hence, a consumer's indirect utility is a function of his or her household income, Y, minus his or her WTP for the food products. A consumer is assumed to perceive that the "bad state of nature" will occur with probability p, which differs between those who have informed and uninformed prior beliefs. The posterior probability of a bad (good) outcome or state of nature is determined by a combining together prior beliefs and new information on GM technologies and food, denoted by "*inf.*"

To simplify, it is useful to normalize utility such that U = 1 and V = 0 and, hence, a consumer's expected utility is:

$$EU^I = \left(1 - p^I\left(I, \inf\right)\right), \tag{48.3}$$

$$EU^{no-I} = \left(1 - p^{no-I}\left(\inf\right)\right). \tag{48.4}$$

Next, consider a consumer's determination of the subjective probability of a bad outcome on GM foods, given the following parameterization:

$$p^I = \alpha_0 + \alpha_{\inf}, \tag{48.5}$$

$$p^{no-I} = \alpha_{\inf}. \tag{48.6}$$

Now α_0 is the effect of the informed consumers' prior beliefs about GM on their posterior beliefs about GM, and $\alpha_{\inf}$ is the effect of new information on their posterior beliefs. If prior beliefs are informative, that is, they are not diffuse priors (DeGroot 1970), it is useful to assume $0 < \alpha_0 < p$. Now consumers who have uninformed prior beliefs are expected to place more weight on information from interested parties than participants who have informed prior beliefs. Also it seems plausible (Rousu et al. 2007) that the injection of third-party information affects the way that consumers use information from interested parties in forming their bids. Rearranging (48.5) and (48.6), we obtain the following relationship between posterior probabilities:

$$p^I = p^{no-pI} + \alpha_0 \tag{48.7}$$

Substitute for p^I in (48.3) to obtain

$$EU^I = \left(1 - p^{no-I} - \alpha_0\right) \tag{48.8}$$

and take the difference in expected utility between (48.4) and (48.8) to obtain

$$U\left(Y - WTP^I\right) - U\left(Y - WTP^{no-I}\right) = -\alpha_0 \tag{48.9}$$

Hence, this simple decision framework shows formally that consumers who have the same indirect utility values and receive the same information treatment may have differences in expected utility due only to different *prior beliefs*. More generally, differences in an individual's expected utility are due to differences in prior beliefs and information.

WTP for GM-labeled foods could be higher or lower, depending on the prior beliefs and the content of the new information they obtain/receive. Some evidence has shown that prior beliefs and information that they receive affect WTP. This evidence is summarized below.

48.2 Empirical Considerations

A summary of evidence from food experiments shows how prior beliefs of consumers and new information about genetic modification affect their WTP for standard food products. A few details about this data are presented and more details can be found in the studies by Rousu et al. (2007) and Huffman et al. (2003). Three dissimilar food products were auctioned in a laboratory setting: vegetable oil, tortilla chips, and potatoes. An important feature of the GM food products is that the refining process for vegetable oils, say from soybean oil, all of the amino acids are removed leaving pure lipid or fat, and the resulting oil is chemically indistinguishable irrespective of the use of GM or non-GM soybeans to make the oil. The tortilla chips are a processed product made from yellow corn that might be contaminated by GM-traits for herbicide tolerance or insects resistance, and consumers might have different concerns for GM content here than in russet potatoes that were genetically modified for virus resistance.

Because we are interested in the performance of grocery store and supermarket shoppers, individuals over 18 years of age were chosen for the food experiments.[4] Moreover, they were chosen randomly from two major Midwestern metropolitan areas by a random digital dialing method and contacted by an independent agency to obtain their agreement to participate, given instructions of how to get to the project site, and told that they would be paid $40 for their participation.

To help balance the number of participants in lab sessions and maintain randomness in assignment, arriving participants were alternately assigned to one of two concurrent sessions. Each group/session consisted of 13–16 individuals. After taking a seat in the lab or classroom, participants were asked to complete a questionnaire containing questions about their socioeconomic characteristics and prior beliefs about new technologies, and paid $40. A critical part of the methodology of these experiments is that each session or trial followed exactly the same protocol. Participants were first asked to learn about the auction mechanism. To do this, they engaged in a round of bidding on a candy bar to learn the mechanism of the random nth price auction. In this auction bids are placed and collected by the session monitor, who then arrays them from highest to lowest. Then a random n is drawn from the uniform distribution of 1 to say 13 (when there are 14 participations), suppose it is five, then the four highest bidders pay the fifth highest price. This random nth-price auction mechanism has been shown to be superior to a second-price Vickery auction (where the highest bidder pays the second highest price) for eliciting consumers' entire demand curve for new goods (Shogren et al. 2001). After winners were chosen, they were asked to engage in a second practice round containing a candy bar, box of pens, and a deck of cards to get them familiar with placing three bids on dissimilar goods simultaneously. Winning bids were announced, and participants were given a short quiz on the auction mechanism that was followed by discussion and clarification. This was done to check up on participants' understanding of the auction mechanism.

---

[4]Although several studies have used only college undergraduates in laboratory auctions of food items (including Lusk et al. 2001;Hayes et al. 1995), they are not the best choice for participants when the items being auctioned are ones sold in grocery stores or supermarkets. For example, Katsaras et al. 2001, using a national random sample of grocery store shoppers, showed that the share of college-age (18–24 years) shoppers falls far below their share in the population, 8.5% of shoppers versus 12.8% in the US Census of Population. College students obtain a large share of their food from school cafeterias and a small share from grocery stores and supermarkets compared to older shoppers (Carlson et al. 1998)

Next, one of the six information treatments was randomly assigned and released in each session or trial. These treatments were constructed from the three basic information types defined for these experiments. They were the (1) *industry perspective* – provided by a group of leading biotechnology companies, including Monsanto and Syngenta (Council for Biotechnology Information 2001); (2) *environmental group perspective* – from Greenpeace, a leading environmental group or biotech antagonist (Greenpeace 2001a, b; Friends of the Earth 2001, 2003); and (3) *third-party perspective* – from an independent group of scientists, professionals, religious leaders, and academics, none with a financial stake in GM foods. This third type of information is to be viewed as an informed objective assessment, given the state of science, and without significant direct financial interest in genetic modification. The three information types were packaged into *six information treatments*: (1) the biotech industry perspective; (2) the environmental group perspective; (3) agricultural biotech industry and environmental perspectives; (4) agricultural biotech industry and third-part perspectives; (5) environmental group and third-party perspectives; or (6) all three perspectives. When a trial/session received pro- and antibiotech information, the order was randomized among the participants. Third-party information, however, was always distributed last.

Next, they were asked to go one-by-one in an orderly fashion to the front of the lab/room to view the three experimental products (32 oz. of vegetable oil made from soybeans, 16 oz. tortilla chips made from yellow corn, and 5 lb of russet potatoes) and to place their bids. They were then asked to view another set of these three goods, having different GM-food-label information, and place a new set of bids.[5] In one round participants were bidding on food products that were labeled as genetically modified (GM) and in the other round the food products had a plain-label.[6] Among the two rounds of bidding on experimental goods, one was chosen randomly by the auction monitor to be a binding round in which winners were expected to complete their exchange of money for experimental goods. The actual exchange took place in an adjacent room.[7]

To get a better grasp of the demographic attributes of participants, Table 48.2 provides summary statistics for the sample of participants used in a series of Huffman's GM food papers. Although participants are slightly skewed toward women, Katsaras et al. (2001) showed that women make up a disproportional share of grocery shoppers: 83% of shoppers versus 52% in the US Census of

Table 48.2 Characteristics of auction participants (*N* = 172) variable definition mean St. Dev (Huffman et al. 2007)

Gender	1 if female	0.62	0.49
Age	The participant's age	49.5	17.5
Married	1 if the individual is married	0.67	0.47
Education	Years of schooling	14.54	2.25
Household	Number of people in participant's household	2.78	1.65
Income	The household's income level (in thousands)	57.0	32.6
White	1 if participant is white	0.90	0.30

This table reports on the average value of socio-economic attributes of a sample of individuals used in a number of Huffman's experiments

---

[5] Participants were never told how many total rounds of bidding they would engage in. All participants engaged in a total of four rounds of bidding including the two practice rounds. At the start of the auction of the food products that might be GM, the participants were told that they would be expected to purchase a maximum of one unit of each auctioned commodity. After the second round of bidding on food products that might be GM, the auction part of the experiment ended

[6] The sequence was determined randomly

[7] A strength of this methodology is that each participant engaged in very few rounds of bidding (two rounds on experimental products), which reduces behavior modification associated with the experience of participating in an experiment

Population. Although the demographics of the sample do not perfectly match the population reported by the USA census demographic characteristics for these regions, they are similar and provide a sufficient representation for probing into labeling and information effects on WTP for GM food products.

A key factor for being able to investigate the role of a consumers' prior beliefs is having available preauction information of the type: "Regarding genetically modified foods: How informed do you consider yourself?" The participants were offered the following six options: extremely well informed, well informed, somewhat informed, not very informed, not informed at all, and I don't know. In particular, this information was collected before the start of the lab auction of GM-foods and release of new information.[8] Table 48.3 summarizes these responses and shows that 41.9% of the 172 participants were at least somewhat informed about genetic modification before our auction experiments. The other 58.1% were classified as "uninformed." Hence, a majority of the participants in these experiments were "uninformed about genetic modification." However, a substantial share of them claimed to be informed.

To gain a better understanding of the data from the WTP experiments, sample mean information for average bid prices for GM- and plain-labeled foods for all participants and for participants who had informed and uninformed priors is reported in Table 48.4.[9] Among all participants and commodities, average bids were 14% lower for GM than for plain-labeled commodities (part A). Among participants who had informed prior beliefs about GM foods, the average difference for the bid price of a plain-labeled product less the bid price for GM-labeled counterpart was 18% (part B). Among participants who had uninformed prior beliefs, the average difference for the bid price of a plain-labeled product less the bid price for the GM-labeled counterpart was 11% (part C). Across the two groups, informed and uninformed, the difference is 49%. The difference between these two percentages is not significantly different from zero at the 5% level.

Of central interest is the impact of participants' subjective prior beliefs about genetic modification in a market where information from two types of interested parties is injected. Table 48.4 summarizes the mean differences in bid prices from participants for GM- and plain-labeled food products due to the release of information from interested parties, the agricultural biotech industry or environmental NGOs, given prior beliefs. Part A summarizes the bid prices in a market without third-party information. When participants, both those who had informed and uninformed

Table 48.3 Response of participants to the pre-experiment question of "How informed are you about genetic modification?" (*N* = 172) (Huffman et al. 2007)

Category category	Relative frequency (%)
Extremely well informed	3.5
Well informed	5.8
Somewhat informed	32.6
Not very informed	40.1
Not informed at all	15.7
I don't know total	2.3
	100.0

This table presents the relative frequency of sample participant's response to the survey question of how well they were informed about genetic modification

[8] No effort was made to test participant's beliefs for objectiveness; they are subjective beliefs

[9] Participants who were informed and uninformed did not differ significantly by age, gender, etc

Table 48.4 Mean bids for participants by commodity and type (Huffman et al. 2007)

Part A: Mean bids – all participants and treatments (*N* = 172)

	Mean bid	Standard deviation	Median	Minimum	Maximum
GM OIL	0.91	0.84	0.75	0	3.99
OIL	1.05	0.85	1.00	0	3.79
GM CHIPS	0.93	0.86	0.70	0	3.99
CHIPS	1.08	0.85	0.99	0	4.99
GM POTATOES	0.78	0.67	0.69	0	3
POTATOES	0.91	0.67	0.80	0	3.89

Part B: Mean bids for participants who had informed prior beliefs about genetic modification (*N* = 72)

	Mean bid	Standard deviation	Median	Minimum	Maximum
GM OIL	0.93	0.88	0.77	0	3.99
OIL	1.10	0.89	1.00	0	3.79
GM CHIPS	0.86	0.81	0.75	0	3.50
CHIPS	1.05	0.74	1.00	0	2.99
GM POTATOES	0.73	0.61	0.75	0	2.30
POTATOES	0.92	0.59	0.88	0	2.00

Part C: Mean bids for participants who had uninformed prior beliefs about genetic modification (*N* = 100)

	Mean bid	Standard deviation	Median	Minimum	Maximum
GM OIL	0.90	0.82	0.68	0	3.25
OIL	1.01	0.82	0.99	0	3.29
GM CHIPS	0.97	0.90	0.69	0	3.99
CHIPS	1.10	0.92	0.99	0	4.99
GM POTATOES	0.81	0.72	0.60	0	3.00
POTATOES	0.90	0.73	0.75	0	3.89

This table provides sample mean (average) and median (mid-point observation) value of participant's willingness to pay or bids on six types of food products. Measures of variability include the standard deviation of bid prices and minimum and maximum values

prior beliefs, received only the industry perspective, the mean bid price differences between GM- and plain-labeled products were very small, less than plus or minus 11 cents per product. For participants who had informed prior beliefs about genetic modification and received only the environmental group perspective, the mean bid price differences were 50–60 cents per product, but only the 52 cent difference for potatoes was significantly different from zero at the 5% level. For participants who had uninformed prior beliefs, mean bid price differences were less, 32–37 cents per product, and all are significantly different from zero at the 5% level. For participants who had informed priors and received both the agricultural biotech and environmental group perspectives, the discount for GM products is an average of 29–51 cents per product, but the 40 cent differential for potatoes is the only one of these three differences that is significantly different from zero at the 5% level. In contrast, participants who had uninformed prior beliefs did not discount GM-products.

Part B of Table 48.5 summarizes bids from consumers who received third-party information. When participants, both with informed and uninformed prior beliefs, received only probiotech information followed by third-party information, the mean bid-price difference between GM- and plain-labeled food items was small and similar to those reported in part A. When participants had informed priors and received antibiotech information followed by third-party information, mean bid price differences were 7–20 cents per food item, which is much smaller than the outcome without third-party information

Table 48.5   Mean difference in bid prices of participants for plain-labeled less bid price for GM-labeled food products due to information from interested parties, conditional on prior beliefs (Huffman et al. 2007)

Part A: Participants who did not receive third-party GM-information			
Information treatments	Vegetable oil	Tortilla chips	Potatoes
Received only probiotechnology information, given informed priors ($N = 13$)	−$0.10 $p = 0.63$	$0.11 $p = 0.32$	$0.02 $p = 0.93$
Received only probiotechnology GM-information, given uninformed priors ($N = 17$)	$0.03 $p = 0.68$	$0.00 $p = 0.94$	−$0.08 $p = 0.13$
Received only antibiotechnology GM-information, given informed priors ($N = 8$)	$0.50 $p = 0.12$	$0.61[*] $p = 0.09$	$0.52[**] $p = 0.05$
Received only antibiotechnology GM-information, given uninformed priors ($N = 21$)	$0.34[***] $p < 0.01$	$0.37[***] $p < 0.01$	$0.32[***] $p < 0.01$
Received probiotechnology and antibiotechnology GM-information, given informed priors ($N = 10$)	$0.51 $p = 0.12$	$0.29[*] $p = 0.08$	$0.40[**] $p = 0.05$
Received probiotechnology and antibiotechnology GM-information, given uninformed priors ($N = 18$)	$0.00 $p = 0.97$	$0.01 $p = 0.90$	$0.07 $p = 0.24$
Part B: Participants who received third-party GM-information			
Information treatment	Vegetable oil	Tortilla chips	Potatoes
Received probiotechnology and third-party GM-information, given informed priors ($N =14$)	$0.13 $p = 0.17$	$0.09 $p = 0.52$	$0.07 $p = 0.28$
Received probiotechnology and third-party GM-information, given uninformed priors ($N =14$)	−$0.09 $p = 0.26$	$0.07 $p = 0.43$	−$0.05 $p = 0.38$
Received antibiotechnology and third-party GM-information, given informed priors ($N = 13$)	$0.07 $p = 0.17$	$0.10 $p = 0.55$	$0.20[*] $p = 0.08$
Received antibiotechnology and third-party GM-information, given uninformed priors ($N=16$)	$0.29 $p = 0.21$	$0.33[*] $p = 0.10$	$0.26[*] $p = 0.08$
Received probiotechnology, anti-biotechnology and third-party GM-information, given informed priors ($N = 14$)	$0.16[*] $p = 0.08$	$0.10[*] $p = 0.07$	$0.10 $p = 0.15$
Received probiotechnology, antibiotechnology and third-party GM-information, given uninformed priors ($N = 14$)	$0.03 $p = 0.77$	−$0.08 $p = 0.28$	−$0.06 $p = 0.42$

*Statistically significant at the 10% level using a two-sided t-test

**Statistically significant at the 5% level using a two-sided t-test

***Statistically significant at the 1% level using a two-sided t-test

This table reports on various statistical tests of equality of bid price differences across the three commodities. We are generally looking for differences that are statistically significant. Those are the ones that we have greatest confidence in

(as reported in part A). The most significant of these three outcomes is for potato, but now the bid price difference is only significant at the 10% level. When those who had uninformed priors receive this same set of information treatments, the bid price differences are similar to those in part A in which third-party information was excluded. With third-party information, the differences are at best significant at the 10% level. When participants who had informed priors received all three types of new information, their mean bid price differences were only 10–16 cents per product, which is much lower than the outcome when third-party information was not injected (as reported in part A). Two of these differences are different from zero at only the 10% level. When participants who had uninformed priors received all three types of information, however, their mean price differences were similar to those reported when third-party information was not injected. Hence, the evidence is that bidding behavior was affected by participants' prior beliefs and new information injected into the experiments from interested parties and from a third-party.

Table 48.6 Do the informed and uninformed bid differently? Test of null hypothesis that difference in mean bid price differences for plain-labeled less bid price for GM-labeled food items is zero for participants who had informed and uninformed prior beliefs (Huffman et al. 2007)

Part A: Participants who did not receive third-party information			
Information treatments	Vegetable oil	Tortilla chips	Potatoes
Received probiotechnology GM-information only (N = 30)	t = 0.67 p = 0.51	t = −0.92 p = 0.37	t = −0.55 p = 0.59
Received antibiotechnology GM-information only (N = 29)	t = −0.61 p = 0.54	t = −0.92 p = 0.36	t = −0.99 p = 0.33
Received both probiotechnology and antibiotechnology GM-information (N = 28)	t = −1.83 p = 0.08	t = −1.94 p = 0.06	t = −2.22 p = 0.04
Part B: Participants who received third-party information			
Information treatments	Vegetable oil	Tortilla chips	Potatoes
Received probiotechnology and third-party GM-information (N = 28)	t = −1.85 p = 0.08	t = −0.15 p = 0.89	t = −1.45 p = 0.16
Received antibiotechnology and third-party GM-information (N = 29)	t = 0.87 p = 0.39	t = 0.92 p = 0.36	t = 0.36 p = 0.71
Received probiotechnology, antibiotechnology, and third-party GM-information (N = 28)	t = −0.93 p = 0.36	t = −2.00 p = 0.06	t = −1.66 p = 0.11

This table is testing to see if bid price differences exist by whether the participants have informed prior beliefs about genetic modification or whether they are uninformed conditional on information treatment and commodity. The results are mixed

Table 48.6 summarizes the results for statistical tests of bid price differences for plain and GM-labeled products, conditional on participant's prior beliefs about genetic modification. Part A reports the results for statistical tests for participants who did not receive third-party information. This is a "difference-in-differences" test (see Wooldridge 2002, pp. 283–291, 128–131). It is of interest to test the null hypothesis that the difference-in-mean bid-price difference for plain-labeled and GM-labeled food items is zero across participants who had informed and uninformed prior beliefs. When the participants received only the agricultural biotech industry perspective or the environmental group perspective, no significant difference-in-differences existed at the 5% significance level. If they received the probiotech and antibiotech perspectives, the estimate of the difference-in-differences estimator was significantly different from zero for potatoes (5% level) and tortilla chips (6% level). For vegetable oil, the estimate of difference-in-differences is not significantly different from zero.

Because third-party information is of potentially great social benefit, Part B of Table 48.5 summarizes difference-in-differences results for a situation in which third-party information was injected. The information treatments are (i) probiotech and third-party, (ii) antibiotech and third-party, and (iii) all three types of information. None of the estimates of the difference-in-difference estimator for these tests is significantly different from zero at the 5% level. The third-party information lowers the relative weight placed on information received from interested parties when bids are placed on food items that might be genetically modified. Furthermore, when third-party information is injected into the experiment, prior beliefs about genetic modification have relatively little impact on bidding behavior of participants. Of considerable interest is that both participants who had informed and uninformed prior beliefs behaved in our experiments as if they took the third-party information seriously.

Another dimension of the data is differences in bid prices due to information treatment effects for people who received third-party information, conditional on prior beliefs. Table 48.7 summarizes these results. The null hypothesis is that the difference in mean bid prices for plain- and GM-labeled

Table 48.7 Results for difference-in-differences estimator: Null hypothesis that difference in bid prices for plain-labeled less bid price for GM-labeled food items under different information treatments is zero, given participants' prior beliefs (no third-party information) (Huffman et al. 2007)

Part A: Participants whose prior beliefs were uninformed about genetic modification			
Information treatments	Vegetable oil	Tortilla chips	Potatoes
Received only probiotechnology GM-information versus received only antibiotechnology GM information.	t = 2.11 p = 0.04	t = 2.71 p = 0.01	t = 3.53 p = 0.00
Received only probiotechnology GM-information versus received probiotechnology and antibiotechnology GM-information.	t = 0.20 p = 0.84	t = −0.04 p = 0.97	t = −1.96 p = 0.06
Received only antibiotechnology GM-information versus received probiotechnology and antibiotechnology GM-information	t = 2.03 p = 0.05	t = 2.68 p = 0.01	t = 2.26 p = 0.03
Part B: Participants who had informed prior beliefs about genetic modification			
Information treatments	Vegetable oil	Tortilla chips	Potatoes
Received only probiotechnology GM-information versus received only antibiotechnology GM-information.	t = 1.78 p = 0.09	t = 1.76 p = 0.09	t = 1.72 p = 0.10
Received only probiotechnology GM-information versus received probiotechnology and antibiotechnology GM-information.	t = −1.76 p = 0.09	t = −0.96 p = 0.35	t = −1.45 p = 0.16
Received only antibiotechnology GM-information versus received probiotechnology and antibiotechnology GM-information	t = −0.02 p = 0.98	t = 0.98 p = 0.34	t = 0.43 p = 0.68

This table reports on test of no difference in bid prices of participants due to the type of information treatment that they received, by commodity. The results are mixed

food items under two different information treatments is zero, holding prior beliefs of participants constant. For participants who held uninformed prior beliefs, the estimate of difference-in-differences estimator is significantly different from zero (5% level) for all three food items when participants receive pro- versus antibiotech information. They are also significantly different from zero when participants receive antibiotech information versus pro- and antibiotech information. In fact these two sets of hypotheses produced t-values that look very similar (part A). When participants received pro- versus pro- and antibiotech information the estimate of the difference-in-difference estimator was not significantly different from zero. When participants had informed priors, none of the estimates of the differences-in-differences estimator was significantly different from zero at the 5% level (part B). Hence, a very important result is that participants' prior beliefs affect the relative weight placed on new information from interested parties when third-party information is unavailable.

Another dimension of the data is seen by considering the effects of different combinations of information from interested parties when third-party information is injected, conditional on prior beliefs. For participants who had uninformed priors, three of nine tests shown in Table 48.8, part A, for the estimate of the difference-in-differences estimator are rejected at the 6% level: for potatoes when participants received only probiotech information versus received only antibiotech, and for tortilla chips and potatoes when participants received only antibiotech information versus pro- and antibiotech information. For participants having informed prior beliefs (part B), none of the coefficients of the difference-in-differences estimator is significantly different from zero at the 6% level. With the injection of third-party information, participants who have uninformed prior beliefs about GM bid differently on plain- versus GM-labeled food products than for those who had informed prior beliefs. Those participants who are uninformed behave as if they place greater weight on new information than the informed participants even when it comes from interested parties.

Table 48.8 Results for differences-in-differences estimator when participants received third-party GM-information: Null hypothesis that difference in bid price for plain-labeled less bid price for GM-labeled food items under different information treatments is zero, conditional on participants' prior beliefs (Huffman et al. 2007)

Part A: Participants who had uninformed prior beliefs about genetic modification			
Information treatments	Vegetable oil	Tortilla chips	Potatoes
Bid prices when received probiotechnology and verifiable GM-information versus bids when received antibiotechnology and third-party GM-information.	$t = 1.53$ $p = 0.14$	$t = 1.22$ $p = 0.23$	$t = 1.99$ $p = 0.06$
Bids when received probiotechnology and verifiable GM-information versus bids when received probiotechnology, antibiotechnology, and third-party GM-information.	$t = -0.93$ $p = 0.36$	$t = 1.37$ $p = 0.18$	$t = 0.16$ $p = 0.87$
Bids when received antibiotechnology and verifiable GM-information versus bids when received probiotechnology, anti-biotechnology, and third-party GM-information	$t = 0.99$ $p = 0.33$	$t = 1.95$ $p = 0.06$	$t = 1.98$ $p = 0.06$
Part B: Participants who had informed prior beliefs about genetic modification			
Information treatments	Vegetable oil	Tortilla chips	Potatoes
Bids when received probiotechnology and verifiable GM-information versus bids when received antibiotechnology and third-party GM-information.	$t = -0.55$ $p = 0.58$	$t = 0.03$ $p = 0.97$	$t = 1.13$ $p = 0.27$
Bids when received probiotechnology and verifiable GM-information versus bids when received probiotechnology, antibiotechnology, and third-party GM-information.	$t = -0.25$ $p = 0.80$	$t = -0.03$ $p = 0.98$	$t = -0.42$ $p = 0.68$
Bids when received antibiotechnology and verifiable GM-information versus bids when received probiotechnology, antibiotechnology, and third-party GM-information	$t = -0.89$ $p = 0.38$	$t = 0.02$ $p = 0.98$	$t = 0.78$ $p = 0.44$

This table shows how third-party information affects bid prices. The results are mixed

It is interesting that individuals who had informed prior beliefs about genetic modification coming into our experiments discounted GM-labeled food products more highly than those participants having uninformed prior beliefs. This behavior suggested that their prior information was somewhat negative. Participants who had uninformed prior beliefs about genetic modification before our experiments exhibited the greatest change in bidding behavior due to the injection of new information. Information from interested parties caused a significant change in participants' bidding behavior, and when third-party information was injected their bidding behavior was further modified. Hence, those participants who had informed prior beliefs were relatively unaffected by all types of new information. They may already have made a significant investment in information about genetic modification, and the marginal impact of new information including third-party information was small and not statistically significant.

48.3 Reflections

Our research has shown out that consumers' prior beliefs and new information that they receive while deciding their WTP (both from interested parties and third-party sources) for food products that might be genetically modified. This contradicts findings of Viscusi (1997) and Tversky and Kahneman (1974, 1992) who argued that people frequently ignore base rates. One potential explanation for this

difference of outcome is that instead of measuring prior beliefs as objective knowledge (e.g., monetary lotteries), we asked lab participants to give us information about their prior knowledge about genetic modification. They were asked the following question: "How informed are you about genetic modification?" and they were given five options: extremely well informed, well informed, somewhat informed, not very informed, and not informed at all. This information is subjective, and we use this as their subjective prior belief. Furthermore, we examined their use of prior beliefs and new information to inform decision on willingness to pay for common food items available in grocery stores and supermarkets and not in a lottery.

In additional research, Colson et al. (2009) have assessed consumers' WTP for new food products – fresh potato, tomato, and broccoli – that contain product enhanced consumer attributes of antioxidant and vitamin C levels introduced using genetic modification. The potato is unique in that it has been grown by farmers for 8,000 years under diverse conditions. It has large genetic diversity, but it is very difficult to manipulate the genes by using conventional breeding methods but easy using new bioengineering methods.

These experiments used a new set of data collected from individuals chosen from a random set of telephone numbers in two major metropolitan cities who were contacted by an independent survey group in 2007 to obtain their agreement to participate and willing participants came to a central location or lab. Their WTP was obtained in a series of multiple-round random nth price experimental auctions with randomized food labels and information treatments. Three information types: agro-biotech industry perspective, environmental group perspective, and a third-party perspective are packaged into five information treatments. The three information statement are similar to those of the 2001 experiments reported on above, but the information statements of the agro-biotech industry and third-party in this latter research clearly make a distinction between GM due to moving genes across species, i.e., transgenic, versus moving genes within species, i.e., intragenic. They find that consumers are willing to pay significantly more for bioengineered products from intragenic than transgenic transfers or for conventional products. Supporting earlier research (Rousu et al. 2007), consumers' WTP for these GM food products are affected significantly by the food label and type of information injected into the decision making process.[10] Moreover, these results provide evidence for the first time that consumers are willing to pay a premium for new GM fresh vegetables with enhanced antioxidant and vitamin C levels relative to a similar plain-labeled food product. This information is valuable to consumers, growers, and potential developer of new GM foods. Moreover, a type of GM food product has now been identified where the food industry has an incentive to voluntarily label as GM or more likely to trademark.

48.4 Application to Other Areas of Diet and Behavior

The building evidence from food experiments, including the effects of food labels, information statements, and Bayesian learning, is applicable to adults' decisions on a wide range of choices that affect diet, nutrition, and overall health. In particular, methods in this paper are applicable to lifestyle choices on diet and obesity. The evidence suggests that careful use of food labels and information can affect consumers' choices so that they are more likely to choose new food products that improve their diet and healthy and may reduce their probability of being obese.

---

[10] In these experiments, individuals who claimed to be informed about genetic modification coming into the experiments bid more for intragenic product enhanced fresh vegetables than did the other individuals

Summary Points

- This line of research has shown that experimental economics is a useful tool for analyzing the behavior of consumers as reflected in willingness to pay for foods that may be genetically modified.
- Consumers exhibit Bayesian learning in making decision on how much they are willing to pay for fresh vegetables that might be enhanced with antioxidants and vitamin C, i.e., they in general use information from their prior beliefs and new information injected into the experiment.
- Food labels and information statements affect consumers' willingness to pay for food that may be genetically modified, and these tools may be used to change consumers' diets and health.
- Both skeptics and proponents of new technologies (i.e., interested parties) might try to manage information to achieve private objectives. This is most likely to occur when much is unknown scientifically about the impacts of new technologies or when third-party information is limited or unavailable (Milgrom and Roberts 1986; Huffman and Tegene 2002). Opponents to a new product or technology may try to target people who are relatively uninformed about the technology because the evidence is that they are receptive to new information. Proponents of a new technology can identify consumers who have positive informed prior beliefs about new products or technology because they are easy converts to buying the new product or technology.
- Genetic modification may become an important tool for producing food products with consumer traits of enhanced nutrient value. Genetic modification can also be used to dramatically lowering arcylamide levels in fried potatoes, which have been shown to cause cancer and have been largely banned in French fries sold in California.
- Processor traits can also be enhanced using genetic modification. The latter traits include reduced bruising during the processing of potatoes in food plants, which would reduce waste.
- The key issue, however, is to identify product attributes that consumers value and cannot be introduced by conventional plant breeding. If bioengineering can introduce these traits to food crops, it would improve food quality.

Definition

Genetic modification: The application of bioengineering using recombinant DNA to create new living organism, sometimes called biotechnology

---

References

Akerlof GA. Quart J Econ 1970;84:488–500.

Carlson A, Kinsey J, Nadav C. University of Minnesota, St. Paul, Retail Food Industry Center, Work Pap 1998;98–105.

Chern WD, Rickertsen K. In: Evenson R, Santaniello V, editors. Consumer acceptance of genetically modified foods. Cambridge, MA: CABI; 2004. p. 95–110.

Colson G, Huffman WE, Rousu M. Iowa State University, Department of Economics, Work. Pap; 2009.

Council for Biotechnology Information (2001) Frequently Asked Questions. http://my.webmd.com/en/faq/default. asp?MID = 10

DeGroot MH. Optimal statistical decision. New York: McGraw Hill; 1970.

Diamond PA, Hausman JA. J Econ Persp 1994;8:45–64.

FAO. The state of food and agriculture: agricultural biotechnology, 2003–2004. Rome, Italy:FAO; 2004.

Fernandez-Cornejo J., McBride WD. USDA, ERS Agr. Econ. Report No. 810; 2002.

Fox JA, Shogren JF, Hayes DJ, Kliebenstein JB. Amer J Agr Econ. 1998;80:455–65.

Friends of the Earth (2001) The need for labeling genetically engineered foods. http://www.foe.org/safefood/fact-shtgelabel.htm

Friends of the Earth (2003) Environmental hazards of genetically engineered plants. http://www.foe.org/camps/comm/safefood/gefood/factsheets/envirohazfacts.html

Greenpeace International (2001a) Public concern. <http://www.greenpeace.org/%7 Egeneng/reports/food/intrfo07.htm>

Greenpeace International (2001b) The potential for allergic reactions. <http://www.greenpeace.org/%7Egeneng/reports/food/intrfo11.htm>

Grether DM. Quart J Econ 1980;95:537–57.

Hayes DJ, Shogren JF, Shin SY, Kliebenstein JB. Amer J Agr Econ 1995;77:40–53.

Hirshleifer J, Riley JR. The analytics of uncertainty and information. New York: Cambridge University Press; 1992.

Huffman WE. In: Gardner BL, Rausser GC, editors. Handbook of agricultural economics, vol A. Amsterdam, The Netherlands: Elsevier Science/North-Holland; 2001. p. 334–81.

Huffman WE, Tegene A. In: Santaniello V, Evenson RE, Zilberman D, editors. Market development for genetically modified food. New York: CAB International; 2002. p. 179–90.

Huffman WE, Shogren JF, Rousu M, Tegene A. J Agr Res Econ 2003;28:481–502.

Huffman WE, Rousu M, Shogren JF, Tegene A. J Econ Beh Org 2007;63:193–206.

Johnston RJ, Wessells CR., Donath, H, Asche F. J Agr Res Econ. 2001;26:20–39.

Kahneman D. Amer Econ Rev. 2003;93:1449–75.

Katsaras N, Wolfson P, Kinsey J, Senauer B. University of Minnesota, St. Paul, The Retail Food Industry Center, Work. Pap. 01–01; 2001.

Kivi PA, Shogren JF. Ambiguity in food safety valuation. University of Wyoming, Work. Pap. Presented at 2002 World Congress of Environmental and Resource Economists; 2005.

Lusk JL, Daniel MS, Mark D, Lusk CL. J Agr Res Econ. 2001;26:40–57.

Milgrom P, Roberts J. RAND J Econ.1986;17:18–32.

Molho I. The economics of information. Malden, MA: Blackwell; 1997.

Morris S, Shin HS. Amer Econ Rev. 2002;92:1521–34.

Rousu M, Huffman WE, Shogren JF, Tegene A. Econ Inq. 2007;45:409–32.

Schultz TW. J Econ Lit. 1975;13:827–46.

Shogren JF, Margolis M, Koo C, List JA. J Econ Beh Org. 2001;46:409–21.

Stigler GJ. J Polit Econ. 1961;69:213–25.

Tirole J. The theory of industrial organization. Cambridge, MA: MIT Press; 2003.

Tversky A, Kahneman D. Science. 1974;185:1124–31.

Tversky A, Kahneman D. Science. 1981; 211:453–8.

Tversky A, Kahneman D. J Risk Uncert. 1992;5:297–323.

Viscusi WK. Econ J. 1997;107:1657–70.

Wooldridge JM. Econometric analysis of cross section and panel data. Cambridge, MA: MIT Press; 2002.

Chapter 49
Food Cravings: A Central Construct in Food Intake Behavior, Weight Loss, and the Neurobiology of Appetitive Behavior

Corby K. Martin, F. Joseph McClernon, Anastasia Chellino, and John B. Correa

Abbreviations

EMA	Ecological momentary assessment
FCCQ-T	Food Chocolate Craving Questionnaire – Trait
FCI	Food Craving Inventory
FCI-J	Food Craving Inventory for Japanese
FCQ-S	Food Craving Questionnaire – State
FCQ-T	Food Craving Questionnaire – Trait
OCQ	Orientation to Chocolate Questionnaire
QCSRF	Questionnaire on Craving for Sweet or Rich Foods

49.1 Introduction

Food craving studies appeared infrequently in the scientific literature until the mid-1980s and important studies on the phenomenology and prevalence of food cravings were conducted in the 1990s. Over the last decade, there has been an increase in food craving research that was likely influenced by the development of new methods to measure food cravings and associated phenomena, such as brain activation. Further, the rise in obesity prevalence led scientists to investigate factors that affect food intake behavior and the association between food cravings and food intake was a logical area of research. The purpose of this chapter is to review the food craving literature and explore the associations between food cravings and food intake, body weight, dieting, and brain activation.

49.2 Food Craving Definition and Etiology

The construct of food craving, as well as its definition, has been influenced by research on drug abuse and addiction. Kozlowski and Wilkinson (1987) reviewed the substance abuse literature and concluded that a proper definition of craving requires that the substance be intensely desired. White

C.K. Martin (✉)

Ingestive Behavior Laboratory, Pennington Biomedical Research Center,
6400 Perkins Rd., Baton Rouge, LA, USA
e-mail: Corby.Martin@pbrc.edu

et al. (2002) considered this recommendation and defined a food craving as "an intense desire to consume a particular food that is difficult to resist." Other authors also noted that food cravings represent a strong desire to consume a food (Cepeda-Benito et al. 2000b), and people who report food cravings indicate that it can be difficult to resist eating food in response to cravings. Food cravings differ from hunger by at least one important feature: consumption of a specific food is believed to alleviate food cravings, while consumption of many different types of foods alleviates hunger (Pelchat and Schaefer 2000).

The etiology of food cravings has been the subject of considerable debate. It has been hypothesized that food cravings are elicited by a nutrient deficiency or food restriction (Weingarten and Elston 1990). This hypothesis appears logical, but it is not supported by scientific evidence. If this hypothesis were true, food cravings should increase during weight loss diets, yet they decrease (Harvey et al. 1993; Lappalainen et al. 1990; Martin et al. 2006, 2008a) or are unaffected (Gilhooly et al. 2007) by weight loss diets. Further, restriction of certain types of foods results in a decrease, not an increase, in craving for the restricted foods (Martin et al. 2008a), and food deprivation is not a necessary condition for the occurrence of food cravings (Hill et al. 1991). Lastly, nutritional deficiencies are not associated with food cravings, and people crave foods high in certain nutrients, while failing to crave other foods with higher levels of the same nutrient (Weingarten and Elston 1990). This evidence indicates that the etiology of food cravings is not heavily influenced by nutritional deficiencies or food restriction.

The role of conditioning in the etiology of food cravings, however, has gained empirical support. Food cravings can develop from pairing consumption of certain foods with hunger, suggesting that food cravings are a conditioned expression of hunger (Gibson and Desmond 1999). In the Gibson and Desmond study, individuals assigned to eat chocolate only when hungry developed greater craving for chocolate over a 2-week period, but chocolate cravings decreased among individuals assigned to only eat chocolate when full. Similarly, the biopsychosocial theory of food cravings suggests that food cravings can also develop by pairing food intake with other conditions, such as physical locations (watching a movie) or internal states (emotional arousal or dysphonic mood) (Rogers and Smit 2000). Conversely, conditioning also appears to influence the development of food aversion. Food aversion during pregnancy appears to be the result of pairing consumption of certain foods with nausea (Bayley et al. 2002; Fairburn et al. 1992).

The conditioning model of food cravings is consistent with the above noted finding that food restriction does not increase, and frequently decreases, food cravings (Harvey et al. 1993; Lappalainen et al. 1990, Martin et al. 2006, 2008a). This may occur for a number of reasons. First, when certain foods are restricted during diets, there are limited opportunities to pair consumption of those foods with stimuli that precipitate eating behavior, which limits the development of food cravings. Second, stimuli that once elicited food cravings would no longer be followed by consumption of the craved food, and existing cravings would diminish in frequency or intensity due to extinction. Although the conditioning model of food craving etiology has been supported by experimental evidence (Gibson and Desmond 1999) and the results of trials that involved food restriction (Harvey et al. 1993; Lappalainen et al. 1990; Martin et al. 2006, 2008a), additional research is warranted to further explicate the role of conditioning in food craving etiology.

49.3 Assessment of Food Cravings

Food cravings can be quickly and affordably measured by self-report inventories. Studies prior to 2000 primarily relied on instruments created to measure cravings for specific studies, and the psychometric properties of many of these instruments were not thoroughly examined. In recent years,

Table 49.1 List of self-report inventories designed to quantify food cravings, including the type of cravings measured (general craving vs. cravings for specific types of foods), if the questionnaire measures state or trait cravings, and the reference article

Questionnaire	Type of craving		Trait or state cravings		Reference
	General	Specific	Trait	State	
FCQ-T	x		x		Cepeda-Benito et al. (2000b)
FCQ-S	x			x	Cepeda-Benito et al. (2000b)
FCCQ-T		x	x		Rodriguez et al. (2007)
FCI		x	x		White et al. (2002)
FCI-J		x	x		Komatsu (2008)
QCSRF		x	x		Toll et al. (2008)
OCQ		x	x		Cartwright and Stritzke (2008)

Note. Abbreviations: *FCQ-T* Food Craving Questionnaire – Trait, *FCQ-S* Food Craving Questionnaire – State, *FCCQ-T* Food Chocolate Craving Questionnaire – Trait, *FCI* Food Craving Inventory, *FCI-J* Food Craving Inventory for Japanese, *QCSRF* Questionnaire on Craving for Sweet or Rich Foods, *OCQ* Orientation to Chocolate Questionnaire

however, inventories have been developed and validated to measure many aspects of cravings, including cravings for specific types of foods (White et al. 2002) and state and trait food cravings (Cepeda-Benito et al. 2000b). Furthermore, at least two of these instruments have been modified to measure food cravings in non-English speaking samples (Cepeda-Benito et al. 2000a; Komatsu 2008). The properties of existing self-report instruments to measure food cravings are reviewed here in the order in which the first version of the instrument was published. Additionally, Table 49.1 provides a summary of the characteristics of the inventories.

49.3.1 Food Craving Questionnaire – Trait (FCQ-T) and State (FCQ-S) Versions

The Food Craving Questionnaire has two forms to measure trait (FCQ-T) and state (FCQ-S) food cravings (Cepeda-Benito et al. 2000b). Ratings for the FCQ-T are made on a six-point scale, with "Never" scored as 1 and "Always" scored as 6. Ratings for the FCQ-S are made on a five-point scale, with "Strongly disagree" scored as 1 and "Strongly agree" scored as 5. The FCQ measures the phenomenological aspects of food cravings, and does not measure cravings for specific foods. The FCQ-T includes nine subscales used to measure trait cravings: intention and planning to consume food, positive reinforcement resulting from eating, negative reinforcement resulting from eating, lack of control of eating, preoccupation with foods, craving as a physiological state, emotions caused by cravings, environmentally induced cravings, and guilt-triggered cravings.

The FCQ-S measures state cravings or cravings that are occurring "at this moment." The FCQ-S has five subscales: desire to eat, positive reinforcement from eating, negative reinforcement from eating, lack of control of eating, and craving as a physiological state.

The subscales of the FCQ-T exhibit acceptable test-retest reliability coefficients (0.72–0.88). The FCQ-S has lower test-retest reliability coefficients (0.40–0.63), reflecting the expected instability of state cravings (Cepeda-Benito et al. 2000b). Both the FCQ-T and FCQ-S have adequate internal consistency (coefficient-alpha 0.81–0.94) and discriminant validity (Cepeda-Benito et al. 2000b). The validity of a Spanish language version of the FCQ has also been supported (Cepeda-Benito et al. 2000a).

49.3.2 Food Chocolate Craving Questionnaire-Trait (FCCQ-T)

The Food Chocolate Craving Questionnaire-Trait (FCCQ-T) (Rodriguez et al. 2007) is a modified version of the Food Craving Questionnaire-Trait (FCQ-T) (Cepeda-Benito et al. 2000b). The FCCQ-T utilizes nine subscales similar to the FCQ-T, but the questions within these subscales are specific to chocolate cravings. Both English (coefficient-alpha 0.76–0.92) and Spanish (coefficient-alpha 0.69–0.90) versions of the FCCQ-T have adequate internal consistency, a stable factor structure, and support for their construct validity (Rodriguez et al. 2007).

49.3.3 Food Craving Inventory (FCI)

The FCI measures cravings for specific types of foods by asking respondents to rate the frequency of cravings over the previous month for 28 food items (White et al. 2002). Ratings are made on a five-point scale ranging from "Never," scored as 1, to "Always/almost every day," scored as 5. Higher scores indicate more frequent food cravings. The FCI has four scales that constitute the higher-order construct of food craving, which is represented by the total score. The four scales are: sweets (e.g., brownies, ice cream), high fats (e.g., bacon, fried fish), carbohydrates/starches (e.g., baked potatoes, pasta), and fast-food fats (e.g., pizza, French fries). The FCI has acceptable internal consistency (coefficient-alpha 0.76–0.93) and test–retest reliability coefficients (0.79–0.91), and a stable factor structure (White et al. 2002). Lastly, a state version of the FCI is undergoing validation. This version of the FCI measures cravings for specific types of foods that are occurring "at this moment."

49.3.4 Food Craving Inventory for Japanese (FCI-J)

The FCI was modified to measure food cravings in Japanese females by removing food items unfamiliar to Japanese culture and adding items eaten in Japan. The resulting FCI-J (Komatsu 2008) was validated in samples of Japanese female undergraduate students, and the following five-factor model was supported: sweets, snacks, western foods, sushi, and rice (Komatsu 2008). Support was found for the reliability and validity of the FCI-J and it serves as a valuable tool to quantify culture-specific aspects of food cravings.

49.3.5 Questionnaire on Craving for Sweet or Rich Foods (QCSRF)

The QCSRF measures cravings for sweet or rich foods in smokers. The QCSRF has nine items and a two-factor structure (Toll et al. 2008). The first factor (Relief/Control) assesses the expectation that sweet or rich foods will alleviate negative affect and perceptions of self-control over eating. The second factor (Intensity) measures the intensity of cravings. Higher scores on the Relief/Control factor indicate greater endorsement that the food may relieve negative affect and lower self-control over eating. Higher scores on the Intensity factor indicate more intense cravings. Both factors of the QCSRF show adequate internal consistency (coefficient alpha = 0.87–0.90). The Intensity scale was positively correlated with weight gain from previous attempts to quit smoking (Toll et al. 2008).

49.3.6 *Orientation to Chocolate Questionnaire (OCQ)*

The OCQ is a 14-item self-report inventory that measures three dimensions of chocolate cravings: avoidance of chocolate, approach to chocolate, and guilt related to chocolate consumption. Agreement with each item is rated using a Likert scale (1 = "not at all" to 9 = "very strongly") (Cartwright and Stritzke 2008). When administered to young adults, the three dimensions of the OCQ were found to differentially correlate with frequency and quantity of chocolate consumption, supporting its concurrent validity (Cartwright and Stritzke 2008).

49.4 Food Craving Prevalence

The estimated prevalence of food cravings varies among studies and the discrepant estimates are likely due to the use of different definitions and methods to measure food cravings, as well as demographic differences among the study samples. Nevertheless, there is a consensus that food cravings are common, and occur in 58–97% of adults sampled from industrialized countries (Gendall et al. 1997; Weingarten and Elston 1991). More women report food cravings than men (Weingarten and Elston 1991), and food cravings and food intake increase during the luteal phase of the menstrual cycle (Dye and Blundell 1997; Johnson et al. 1994). The majority of pregnant women report food cravings, primarily for sweet foods (chocolate, fruit, fruit juice, etc.) (Bayley et al. 2002; Fairburn et al. 1992). People report approximately 3–4 food cravings per week (Hill and Heaton-Brown 1994; Hill et al. 1991), with the majority of food cravings occurring in the evening (Hill et al. 1991). Craved foods are frequently high in energy density and fat (Gilhooly et al. 2007), and the most frequently craved food in industrialized countries, particularly among women, is chocolate (Weingarten and Elston 1991). Indeed, the majority (90%) of people who report cravings crave chocolate; further, chocolate cravings comprise 49–60% of food cravings (Hill and Heaton-Brown 1994; Hill et al. 1991).

49.5 The Association Between Food Cravings, Hunger, and Food Intake

Conceptual differences exist between food cravings and hunger (Pelchat and Schaefer 2000), though the two constructs are associated with each other (Cepeda-Benito et al. 2000b; Steel et al. 2006; White et al. 2002). Food cravings are believed to precipitate eating behavior (Weingarten and Elston 1990) and frequently result in consumption of the craved food (Hill and Heaton-Brown 1994; Weingarten and Elston 1991). Among females diagnosed with bulimia nervosa, food cravings can also precipitate binge eating (Waters et al. 2001), which implies that a large amount of food can be ingested in response to food cravings. In other samples and in laboratory settings, however, it appears that food cravings do not always lead to the consumption of a large amount of food (Martin et al. 2008b), though additional research is needed to more thoroughly explore the amount of food eaten in response to food cravings in naturalistic settings.

   In the laboratory, cravings for specific types of foods were associated with consumption of similar foods (Martin et al. 2008b). In this study, the association was examined between the four scales of the FCI and consumption of M&M's® chocolate candies, jelly beans, regular (high-fat) potato chips, and low-fat potato chips. The sweets scale correlated significantly with intake of jelly beans and M&M's®, and the high fats scale correlated with intake of regular potato chips, but not low fat chips (Table 49.2).

Table 49.2 Pearson correlation coefficients between food craving (FCI scales) and consumption (g) of specific foods (Reprinted from Martin et al. (2008b, p. 325). Copyright 2008, with permission from Elsevier)

FCI scales	Grams consumed				
	Baked Lay's®	Jelly beans	Regular Lay's®	M&M's®	Total intake
High fats	−0.04	−0.03	0.27**	0.16	0.13
Sweets	0.01	0.20*	0.13	0.19*	0.20*
Carbohydrates	0.02	0.10	0.14	0.13	0.14
Fast food fats	0.06	0.05	0.13	0.18*	0.15
Total score	0.01	0.13	0.23*	0.23*	0.22*

Note. $*p < 0.05$, $**p < 0.01$ (1-tailed)

49.6 The Association Between Food Cravings and Body Mass

The association between food cravings and food intake suggests that food cravings might also be associated with body mass, and evidence suggests that this is the case. Food cravings are associated with body mass index among people diagnosed with type 2 diabetes (Delahanty et al. 2002). Further, obesity is associated with cravings for high fat foods (White et al. 2002), and obesity is associated with sweet cravings among people diagnosed with binge eating disorder (White and Grilo 2005).

Weight loss diets reduce food cravings, but no robust relations have been found between baseline levels of cravings or change in cravings and weight loss (Martin et al. 2006). People who lose more weight during a diet, however, do not indulge in cravings as frequently as those who lose less weight (Gilhooly et al. 2007). Despite the lack of scientific evidence suggesting that food cravings are associated with weight loss treatment outcome, participants most frequently reported food cravings as the reason for failing to adhere to a diet during controlled feeding studies (Hall and Most 2005). Therefore, clinicians are encouraged to explore peoples' beliefs and fears about food cravings before and during weight loss treatment. Research is also warranted to determine the temporal relation between food cravings and food intake or poor adherence to dietary recommendations. This research is possible with the use of ecological momentary assessment (EMA) methodology (Stone and Shiffman 1994), which utilizes communication technology (e.g., cell phones, Smartphones) to collect data from participants in real-time while they reside in their natural environment. EMA data can be used to identify the antecedents and consequences of behavior without relying on retrospective recall, which can introduce bias.

49.7 The Effect of Dietary Restraint, Food Restriction, and Dieting on Food Cravings

The effect of food restriction and dieting on food cravings is an important consideration in the etiology of cravings. Furthermore, anecdotal reports from clinical settings suggest that people frequently believe that food restriction during dieting will increase food cravings, and fear of increased food cravings can affect the likelihood of enrolling in a weight loss program. Research in this area has been complicated by a number of factors, such as the use of different methods to measure food cravings and induce food restriction, and studies appear to produce discrepant findings. The seemingly discrepant findings are not necessarily incompatible, however, as described in this section.

49.7.1 Dietary Restraint and Food Cravings

Dietary restraint is measured with self-report questionnaires and refers to the intent to restrict caloric intake, though people that report high levels of dietary restraint are not necessarily in energy deficit or losing weight (Stice et al. 2007). Dietary restraint has been found to be associated with the development of binge eating pathology (Field et al. 1999) and obesity onset (Stice et al. 2005), particularly among adolescent or college-aged female samples; therefore, dietary restraint is an important construct worthy of investigation.

Cross-sectional studies provide mixed support for an association between self-reported dietary restraint and food cravings. Some (Hill et al. 1991) but not all (Rodin et al. 1991) studies report a significant association between dietary restraint and food cravings.

49.7.2 Short-Term Food Restriction

The effect of short-term food restriction was examined in at least two studies that enrolled samples of college-aged females (Coelho et al. 2006; Polivy et al. 2005). In one study, restrained and unrestrained female participants were assigned to a chocolate deprivation, vanilla deprivation, or no deprivation condition for 1 week (Polivy et al. 2005). Deprivation had no effect on reported food cravings, but restrained participants in the chocolate deprivation condition ate more chocolate than restrained and unrestrained participants in the other groups (Polivy et al. 2005). In another study, female undergraduates were randomly assigned to a carbohydrate restriction, protein restriction, or no restriction control group for 3 days (Coelho et al. 2006). Carbohydrate restriction was associated with more carbohydrate cravings during the study and increased carbohydrate intake during a food intake test. Protein restriction was associated with more cravings for protein-rich foods, but was not associated with increased protein intake during the food intake test (Coelho et al. 2006).

These studies provide important data on short-term restriction of certain types of food and the study designs merit discussion. First, as previously noted, the studies measured changes in cravings that occurred over the short-term (days) in response to food restriction. Second, although neither energy balance nor weight change were measured, it is unlikely that participants would have experienced a significant energy deficit or weight loss if they followed the study instructions. These details and study strengths are important when considering the effects of dieting/weight loss on food cravings, as outlined in the following section.

49.7.3 Food Restriction During Diets Marked by Energy Deficit and Weight Loss

Food restriction and dieting, which is marked by energy deficit and weight loss, decreases food cravings (Harvey et al. 1993; Lappalainen et al. 1990; Martin et al. 2006, 2008a). However, some studies find that dieting increases (Pelchat and Schaefer 2000) or has no effect on food cravings (Gilhooly et al. 2007). More restrictive diets result in larger reductions in food cravings (Harvey et al. 1993; Lappalainen et al. 1990; Martin et al. 2006), as illustrated in Fig. 49.1, and food cravings remain suppressed even after a varied diet is restored following a restrictive monotonous diet (Fig. 49.2). Recent evidence also suggests that the macronutrient content of the diet affects changes in cravings
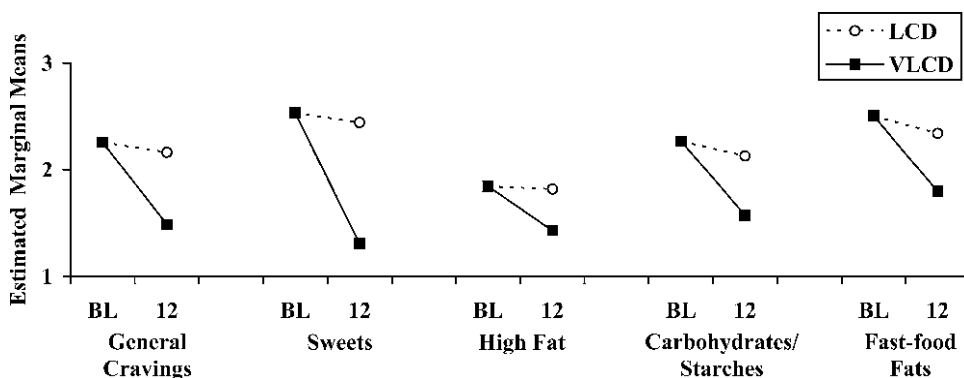
Fig. 49.1 Change in food cravings (estimated marginal means), measured with the Food Craving Inventory (FCI), from baseline (BL) to week 12 of a food-based low calorie diet (LCD) and very low calorie diet (VLCD) that relied on liquid shakes for the first 12 weeks. The VLCD group demonstrated significantly larger decreases on all craving scores compared to the LCD group ($p < 0.01$) (Reprinted from Martin et al. (2006, p. 119). Copyright 2006, with permission from Nature Publishing Group)

Fig. 49.2 Mean Food Craving Inventory (FCI) scores of VLCD participants who completed an FCI at baseline, VLCD Weeks 6 and 12, and Refeeding Week 6. By Refeeding Week 6, participants had transitioned off of liquid shakes and were consuming a solid food-based diet. All FCI scores decreased significantly between baseline and VLCD Week 6 and did not change significantly thereafter. Additionally, all FCI scores were significantly lower at all three dieting points than at baseline (Reprinted from Martin et al. (2006, p. 119). Copyright 2006, with permission from Nature Publishing Group)
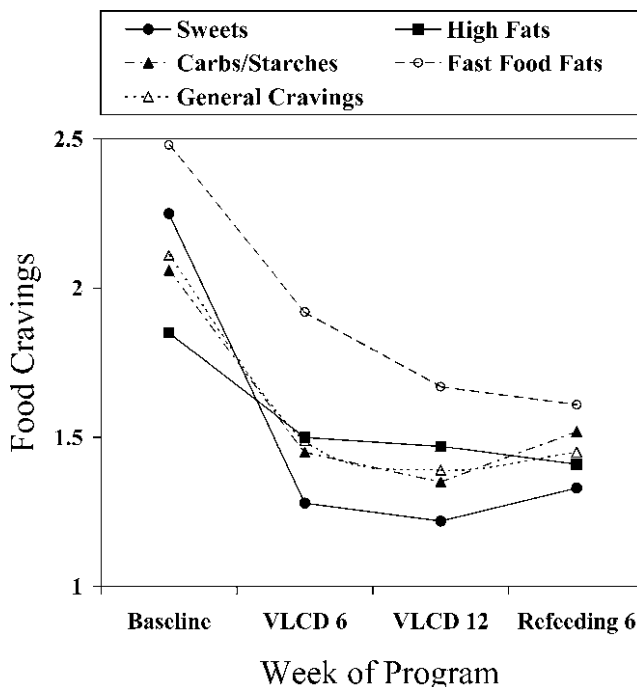
for specific types of foods. Over 2 years, a low-fat diet reduced cravings for high-fat foods, while a low-carbohydrate diet reduced cravings and preferences for foods high in carbohydrate (Martin et al. 2008a). These results indicate that restricting consumption of certain types of foods results in decreased cravings and preferences for the restricted foods.

Although the effect of weight loss on food cravings might appear counterintuitive, it provides some support for the conditioning model of food craving etiology, as previously discussed. The effect of dieting on hunger levels should also be considered in interpreting these findings. Hunger is

unchanged or reduced during dieting (Rosen et al. 1982) and more restrictive diets result in larger decreases in hunger (Wadden et al. 1987). These results suggest that dieting has similar effects on food cravings and hunger, which is not necessarily surprising since hunger and food cravings are associated with each other (Cepeda-Benito et al. 2000b; Steel et al. 2006; White et al. 2002). Moreover, these findings can guide research to identify the mechanism by which food cravings decrease during dieting. For example, it has been hypothesized that change in hunger mediates the relation between dieting and change in food cravings (Martin et al. 2006), but this hypothesis has not been fully tested.

The studies reviewed in this section provide data on the course of food cravings (and hunger) during long-term (weeks to years) food restriction in the context of weight loss diets. It is unclear, however, if similar food craving reductions would be observed when certain types of foods are restricted and weight is maintained. Moreover, change in food cravings over the short-term (days) was not thoroughly assessed in the studies reviewed in this section. The studies reported by Polivy et al. (2005) and Coelho et al. (2006) suggest that short-term food restriction during energy balance might have very different effects on food cravings, and this is an area worthy of future investigation. Moreover, the possibility that change in hunger might mediate the relation between dieting and food craving change requires examination.

49.7.4 Reconciling the Empirical Findings

To summarize, there is mixed support for an association between self-reported dietary restraint and food cravings, and the effect on food cravings of short-term food restriction, which is not likely associated with an energy deficit or weight loss, is inconsistent. Longer-term food restriction that is accompanied by a significant energy deficit and weight loss is associated with a decrease in food cravings. Although these findings appear discrepant, they are not necessarily incompatible when the following issues are considered.

First, the dietary restraint studies, which inconsistently found an association between restraint and food cravings, were primarily cross-sectional and when an association was found the magnitude of the association was modest (Hill et al. 1991). Additionally people who report high levels of dietary restraint are not necessarily in energy deficit or losing weight (Stice et al. 2007). In some samples, dietary restraint is predictive of pathological eating behavior. Therefore, the investigation of food cravings and dietary restraint is warranted, but equating dietary restraint with dieting marked by weight loss is not supported by the research and, similarly, the results from studies on food cravings and dietary restraint will not necessarily be reflective of findings from studies where food cravings were assessed during weight loss.

Second, important differences exist between the studies on short-term food restriction and longer-term food restriction that is also accompanied by weight loss. Participants in the short-term food restriction studies were young college-age females who were presumably not actively losing weight during the study. These samples also appeared to be relatively lean or healthy weight, with a smaller proportion of the samples being overweight or obese. Importantly, these studies measured food cravings in the days following food restriction. The longer-term food restriction studies involved an energy deficit sufficient of promoting significant weight loss and relied on samples of predominantly middle-aged overweight/obese males and females. These studies are limited, however, because they rarely included assessment of craving change after only a few days of food restriction or energy deficit. Consequently, it is possible that food cravings remain stable or increase in the days following the onset of food restriction and energy deficit, and subsequently decrease.

Key Features of Food Cravings

- Food cravings are a common phenomenon whose etiology appears related to conditioning or pairing the consumption of certain foods with hunger, emotional states, physical locations, or activities.
- Dieting and weight loss reduce the frequency of food cravings and more restrictive diets result in larger reductions in food cravings. There is no compelling evidence for potential dieters to fear an increase in food cravings during a diet.
- Randomized controlled trials are warranted to test the efficacy of techniques to manage food cravings and quantify the independent effects of food and calorie restriction on food craving change.

Fig. 49.3 Key features of food cravings

Third, very few studies used the same instrument to measure food cravings, making comparisons among studies problematic. As outlined in this chapter, inventories are available that have good support for their factor structure and psychometric properties. Investigators are encouraged to rely on these or other instruments whose reliability and validity has been supported in future research. Moreover, the cited studies relied on mostly retrospective reports of craving (e.g., questionnaires filled out at weekly sessions). Ecological momentary assessment (EMA) studies should be conducted to more precisely evaluate the temporal course of food craving in the context of ad libitum and restricted food intake.

Although it is difficult to compare the results among some studies due to their differences, these differences demonstrate the importance of each type of study and the how the results can guide future research. For instance, it appears food restriction in the absence of an energy deficit or weight loss has a limited or inconsistent effect on food cravings, while the degree of calorie restriction during weight loss diets appears to be associated with the degree to which food cravings decrease. The findings indicate that future research is needed to quantify the extent to which cravings are affected by: (1) longer-term restriction of specific types of foods during weight maintenance and (2) restriction of specific types of foods during diets that vary in the size of the energy deficit or magnitude of weight loss. Our results suggest that both the degree of energy restriction (Martin et al. 2006) and the macronutrient content of the restricted foods (Martin et al. 2008a) have a direct impact on craving reductions, yet the relative contribution of each manipulation is unknown. Key features of food cravings are summarized in Fig. 49.3.

49.8 Neurobiology of Food Cravings

Exposure to visual and/or olfactory cues associated with preferred foods can elicit craving for those foods. Cues have been shown to drive appetitive behavior (Jansen 1998) and are used to great advantage by advertisers (Halford et al. 2008). Even non-food visual cues (e.g., fast food restaurant logos) can become associated with food reward and promote consumption (Robinson et al. 2007), demonstrating the role of conditioning in appetitive behavior. Recently, neuroimaging studies have demonstrated that exposure to food cues results in activation of a network of brain regions subserving attention, appetitive motivation, and reward (Killgore et al. 2003; LaBar et al. 2001; Simmons et al. 2005; Stoeckel et al. 2008; St-Onge et al. 2005; Wang et al. 2004). At a functional level, this network evaluates information about the potential reward value of environmental cues and initiates behavioral responses aimed at obtaining and consuming food. Specific nodes of this network include the

ventral striatum, which is involved in reward signaling, prefrontal cortex areas involved in the initiation and control of behavior, memory areas including the hippocampus, and regions involved in both stimulus driven and willful attention including the anterior cingulate cortex and fusiform gyrus. Interestingly, exposure to visual cues activates brain regions that are also activated by taste stimuli including the orbitorfrontal cortex and operculum-insula (Rolls 2006). Activation in these regions in response to visual cues (in the absence of taste cues) suggests that visual food information potentially modulates taste and other gustatory information processing.

The specific neural underpinnings of food craving are beginning to be elucidated. In a recent study, brain responses to chocolate taste and visual cues were examined in women who endorsed being cravers or noncravers of chocolate (Rolls and McCabe 2007). Compared to noncravers, cravers exhibited greater activation in response to the sight of chocolate in the orbitorfrontal cortex and ventral striatum, and greater activation to the combined taste and sight of chocolate in the anterior cingulate cortex. In addition to identifying neural correlates of specific food preferences, neuroimaging techniques have been used to examine brain activation during imagining craved foods versus imagining a monotonous diet among subjects who just completed a 2-day bout of a monotonous diet. Compared to individuals who maintained their normal diet, individuals on the monotonous diet exhibited greater activation while imagining liked foods in the hippocampus, insula, and the caudate nucleus (part of the dorsal striatum) (Pelchat et al. 2004).

The studies above provide a first look at the neurobiological basis of food craving. Neuroimaging studies suggest that food cravings appear idiosyncratic and distinct from the subjective experience of hunger. Thus, the findings of the above studies should be considered distinct from those that have examined brain responses to cues depicting foods generally agreed to be appetitive (e.g., donuts, hamburgers) since such foods may not be craved universally (Killgore et al. 2003; Stoeckel et al. 2008). For similar reasons they are distinct from studies which have evaluated the effects of food deprivation and/or overfeeding on brain responses to food cues (Cornier et al. 2007; LaBar et al. 2001; Siep et al. 2009) since these studies manipulate hunger, not necessarily craving.

The extant data thus suggest that exposure to imagined or actual craved foods increases activation in brain regions subserving reward, motivation, and memory. Additional work is necessary to evaluate whether dietary interventions change brain responses to craved foods and whether this modulation can be delineated from those caused by changes in hunger. Asked another way, does the neural circuitry that underlies food craving differ from that underlying hunger and do the two overlap? To the degree that food craving might represent a "liking" of food rather than "wanting," it could be hypothesized that food craving would elicit activation of reward regions (e.g., ventral striatum), whereas hunger would elicit activation of areas subserving compulsive responding (e.g., dorsal striatum). Regions involved in the selection, planning, initiation, and control of behaviors may serve as a final common pathway of both circuits. Additional studies that specifically manipulate both craving and hunger will be necessary to address this question.

49.9 Treatment of Food Cravings

Food cravings are frequently addressed or treated in the context of weight management programs, where techniques are used to reduce the frequency and severity of food cravings and to minimize subsequent food intake. This approach relies on cognitive-behavioral techniques, including distraction and confrontation (Brownell 2000). Patients are also trained to distinguish the difference between food cravings and hunger, and to identify situations or stimuli that elicit food cravings. Once these stimuli are identified, the antecedents and consequences of food cravings and subsequent

food intake can be evaluated and cognitive-behavioral techniques can be used to modify these contingencies. For example, if watching a movie in the evening is associated with a craving for popcorn, patients can prepare and be trained to use relaxation or distraction techniques during the movie to avoid eating popcorn until the food craving diminishes. Assuming the patient successfully avoids eating popcorn during movies, the association between movie watching and cravings will decrease over time. Stimulus control techniques can also be utilized, and stimuli that elicit food cravings can be avoided.

The relation between food cravings and hunger, and the theory that food cravings develop from pairing food intake with external or internal stimuli (e.g., hunger, physical locations, emotions) (Gibson and Desmond 1999; Rogers and Smit 2000) suggest that following a healthy meal plan (three meals per day with planned snacks) and managing hunger will reduce the frequency of food cravings. Other aspects of following a healthy meal plan are also hypothesized to reduce food cravings, such as eating in the same location in the absence of other stimuli, e.g., television or music. The finding that food cravings decrease during weight loss diets, during which participants follow a healthy meal plan (Martin et al. 2006, 2008a), supports this hypothesis, but the effect of meal regulation and hunger management in the absence of weight loss is unclear. Indeed, understanding the independent effects of energy deficit/weight loss and meal regulation/hunger management on food cravings would significantly improve our understanding of the etiology of food cravings and how to most effectively address them.

Acceptance-based approaches (Hayes et al. 1999) can also be used to cope with food cravings. This approach involves cognitive-behavioral principles, but it does not attempt to directly reduce the frequency of food cravings. Rather, the patient is trained to be mindful, and to experience and accept the phenomenon of food cravings with the recognition that the ability to control internal experience is limited.

To our knowledge, there are only two studies that empirically examined the efficacy of specific treatments to manage food cravings. First, an acceptance-based approach was found to help participants who were sensitive to food-rich environments manage food cravings and food intake (Forman et al. 2007). This study also found that cognitive strategies helped participants manage food cravings. Second, acute vagus nerve stimulation in depressed participants was found to change cravings for sweet foods, with approximately half the participants experiencing an increase, and half a decrease, in sweet cravings (Bodenlos et al. 2007).

In reviewing the literature on food cravings, directions for future research are apparent. These directions for future research are outlined in Fig. 49.4.

Directions for future research.

- Further research into the role of conditioning in the etiology and maintenance of food cravings
- Examination of the duration of food cravings that do and do not lead to food intake
- Determination of the amount of food typically consumed in response to food cravings
- Examination of the temporal relation between food cravings and food intake, as well as the antecedents and consequences of food cravings and intake using ecologically valid methodology, such as Ecological Momentary Assessment
- Clarification of the course of food cravings during short- and long-term food restriction while people are in energy balance
- Examination of short-term changes in food cravings during food restriction accompanied by an energy deficit and weight loss
- Examination of differential brain activation associated with hunger and food cravings
- Evaluation of the efficacy of treatments for food cravings in the context of weight loss

Fig. 49.4 Directions for future research

49.10 Applications to Other Areas of Health and Disease

Food cravings are an important construct for patients and clinicians involved in weight management and the treatment of conditions associated with weight gain or obesity (e.g., cardiovascular disease, type 2 diabetes, and hypertension). The food craving literature is also relevant to other conditions, such as renal insufficiency, that require modification and management of the amounts and types of foods eaten. Finally, the role of food cravings in the etiology of overeating or binge eating in certain subsamples is worthy of further investigation.

Summary Points

- In industrialized countries, 58–97% of the population report food cravings (Gendall et al. 1997; Weingarten and Elston 1991).
- Chocolate is the most frequently craved food, particularly among women (Weingarten and Elston 1991).
- Several self-report instruments with acceptable psychometric properties are available to quantify food cravings.
- Overweight and obesity are associated with cravings for high fat foods in individuals with type 2 diabetes (Delahanty et al. 2002) and cravings for sweets in individuals diagnosed with binge eating disorder (White and Grilo 2005).
- In laboratory settings, food cravings are associated with the consumption of similar foods (Martin et al. 2008b).
- Food restriction accompanied by an energy deficit and weight loss reduces food cravings, and more restrictive diets result in larger decreases in food cravings (Harvey et al. 1993; Lappalainen et al. 1990; Martin et al. 2006, 2008a).
- Neuroimaging studies indicate that exposure to imagined or actual craved foods increases activation in brain regions subserving reward, motivation, and memory (Killgore et al. 2003; Simmons et al. 2005; Wang et al. 2004; St-Onge et al. 2005; LaBar et al. 2001; Stoeckel et al. 2008).

Key Terms

Food craving: a desire to consume a specific food or beverage that is difficult to ignore or satisfy with consumption of an alternative food or beverage.

Energy deficit: a state of negative energy balance, where energy expenditure exceeds energy intake.

Dietary restraint: the intent to limit food intake; dietary restraint is not necessarily synonymous with calorie restriction or an energy deficit.

Food restriction: limiting the intake of specific types of foods; food restriction can occur in the presence or the absence of an energy deficit.

Neuroimaging: indirectly or directly measuring the structure and activation of the brain.

References

Bayley TM, Dye L, Jones S, Debono M, Hill AJ. Appetite. 2002; 38:45–51.

Bodenlos JS, Kose S, Borckardt JJ, Nahas Z, Shaw D, O'Neill PM, George MS. Appetite. 2007; 48:145–53.

Brownell KD. The LEARN program for weight management 2000. Dallas: American Health Publishing; 2000.

Cartwright F, Stritzke WG. Eat Behav. 2008; 9:1–12.

Cepeda-Benito A, Gleaves DH, Fernandez MC, Vila J, Williams TL, Reynoso J. Behav Res Ther. 2000a; 38:1125–38.

Cepeda-Benito A, Gleaves DH, Williams TL, Erath SA. Behav. Ther. 2000b; 31:151–73.

Coelho JS, Polivy J, Herman CP. Appetite. 2006; 47:352–60.

Cornier MA, Von Kaenel SS, Bessesen DH, Tregellas JR. Am J Clin Nutr. 2007; 86:965–71.

Delahanty LM, Meigs JB, Hayden D, Williamson DA, Nathan DM. Diabetes Care. 2002; 25:1992–8.

Dye L, Blundell JE. Hum Reprod. 1997; 12:1142–51.

Fairburn CG, Stein A, Jones R. Psychosom Med. 1992; 54:665–72.

Field AE, Camargo CA Jr, Taylor CB, Berkey CS, Frazier AL, Gillman MW, Colditz GA. J Am Acad Child Psy. 1999; 38:754–60.

Forman EM, Hoffman KL, McGrath KB, Herbert JD, Brandsma LL, Lowe MR. Behav Res Ther. 2007; 45:2372–86.

Gendall KA, Joyce PR, Sullivan PF. Appetite. 1997; 28:63–72.

Gibson EL, Desmond E. Appetite. 1999; 32:219–40.

Gilhooly CH, Das SK, Golden JK, McCrory MA, Dallal, GE, Saltzman E, Kramer FM, Roberts SB. Int J Obes. 2007; 31:1849–58.

Halford JC, Boyland EJ, Hughes GM, Stacy L, McKean S, Dovey TM. Public Health Nutr. 2008; 11:897–904.

Hall, DM, Most MM. J Am Diet Assoc. 2005; 105:1285–88.

Harvey J, Wing RR, Mullen M. Appetite. 1993; 21:105–15.

Hayes SC, Strosahl KD, Wilson KG. Acceptance and commitment therapy: An experiential approach to behavior change. New York: Guilford; 1999.

Hill AJ, Heaton-Brown L. J Psychosom Res. 1994; 38:801–14.

Hill AJ, Weaver CF, Blundell JE. Appetite. 1991; 17:187–97.

Jansen A. Behav Res Ther. 1998; 36:257–72.

Johnson WG, Corrigan SA, Lemmon CR, Bergeron KB, Crusco AH. Physiol Behav. 1994; 56:523–27.

Killgore WD, Young AD, Femia LA, Bogorodzki P, Rogowska J, Yurgelun-Todd DA. Neuroimage. 2003; 19:1381–94.

Komatsu S Appetite. 2008; 50:353–8.

Kozlowski LT, Wilkinson MA. Brit J Addict. 1987; 82:31–6.

Labar KS, Gitelman DR, Parrish TB, Kim YH, Nobre AC, Mesulam MM. Behav Neurosci. 2001; 115:493–500.

Lappalainen R, Sjoden PO, Hursti T, Vesa V. Int J Obes. 1990; 14:679–88.

Martin C, Rosenbaum D, Geiselman P, Wyatt H, Klein S, Hill J, Foster G. Obesity. 2008a; 16:S88–9.

Martin CK, O'Neil, PM, Pawlow, L. Obesity 2006; 14:115–21.

Martin CK, O'Neil PM, Tollefson G, Greenway FL, White MA. Appetite. 2008b; 51:324–26.

Pelchat ML, Johnson A, Chan R, Valdez J, Ragland JD. Neuroimage. 2004; 23:1486–93.

Pelchat ML, Schaefer S. Physiol Behav. 2000; 68:353–9.

Polivy J, Coleman J, Herman CP. Int J Eat Disord. 2005; 38:301–9.

Robinson TN, Borzekowski DLG, Matheson DM, Kraemer HC. Arch Pediat Adol Med. 2007; 161:792–7.

Rodin J, Mancuso J, Granger J, Nelbach E. Appetite. 1991; 17:177–85.

Rodriguez S, Warren CS, Moreno S, Cepeda-Benito A, Gleaves DH, Fernandez MC, Vila J. Appetite. 2007; 49:245–50.

Rogers PJ, Smit HJ. Pharmacol Biochem Behav. 2000; 66:3–14.

Rolls ET. Philos T Roy Soc B. 2006; 361:1123–36.

Rolls ET, McCabe C. Eur J Neurosci. 2007; 26:1067–76.

Rosen JC, Hunt DA, Sims EA, Bogardus C. Am J Clin Nutr. 1982; 36:463–9.

Siep N, Roefs A, Roebroeck A, Havermans R, Bonte ML, Jansen A. Behav Brain Res. 2009; 198:149–58.

Simmons WK, Martin A, Barsalou LW. Cereb Cortex. 2005; 15:1602–8.

St-Onge MP, Sy M, Heymsfield SB, Hirsch J. J Nutr. 2005; 135:1014–8.

Steel D, Kemps E, Tiggemann M. Appetite. 2006; 46:36–40.

Stice E, Cooper JA, Schoeller DA, Tappe K, Lowe MR. Psychol Assess. 2007; 19:449–58.

Stice E, Presnell K, Shaw H, Rohde P. J Consult Clin Psych. 2005; 73:195–202.

Stoeckel LE, Weller RE, Cook EW 3rd, Twieg DB, Knowlton RC, Cox JE. Neuroimage. 2008; 41:636–47.

Stone AA, Shiffman S. Ann Behav Med. 1994; 16:199–202.

Toll BA, Katulak NA, Williams-Piehota P, O'Malley S. Appetite. 2008; 50:25–32.

Wadden TA, Stunkard AJ, Day SC, Gould RA, Rubin CJ. Int J Obes. 1987; 11:239–49.

Wang GJ, Volkow ND, Telang F, Jayne M, Ma J, Rao M, Zhu W, Wong CT, Pappas NR, Geliebter A, Fowler JS. Neuroimage. 2004; 21:1790–7.

Waters A, Hill A, Waller G. Behav Res Ther. 2001; 39:877–86.

Weingarten HP, Elston D. Appetite. 1990; 15:231–46.

Weingarten HP, Elston D. Appetite. 1991; 17:167–75.

White MA, Grilo CM. Eat Behav. 2005; 6:239–45.

White MA, Whisenhunt BL, Williamson DA, Greenway FL, Netemeyer RG. Obes Res. 2002; 10:107–14.

Chapter 50
Non-sensory Factors Which Influence Choice Behavior of Foods That Have a Positive Effect on Health

Gastón Ares

50.1 Introduction

Major changes in dietary patterns have occurred during the last decade, mainly due to the acceleration of industrialization, urbanization, economic development, and market globalization (World Health Organization 2003). These changes have led to a replacement of plant-based diets by high fat energy dense diets with an important contribution from animal-based foods, which have caused an increase in the energy density of the diet, with a greater consumption of fat and added sugars in foods, an increase in saturated fat intake, a reduction of the intake of complex carbohydrates and dietary fiber, and a decrease in the consumption of fruits and vegetables (World Health Organization 2002). Such dietary changes, together with a shift in lifestyle toward more sedentary patterns, have had a significant impact on the health and nutritional status of populations and have led to an increase of the occurrence of chronic diseases, causes of disability, and premature death in both developed and developing countries (World Health Organization 2003). These chronic diseases include obesity, diabetes mellitus, cardiovascular disease, hypertension, stroke, and some types of cancer. According to the World Health Organization, in 2001 chronic diseases contributed to approximately 60% of the 56.5 million total reported deaths in the world, and it has been projected that chronic diseases will account for three-quarters of all deaths in 2020 (World Health Organization 2002).

Diet has been identified as one of the main factors that can contribute to the prevention of chronic diseases (World Health Organization 2003). Research has shown that there are certain food components, regarded as nonnutrients, which have biological activities on our body. The consumption of these compounds might be responsible for the beneficial effects connected to some foods and diets, and could help preventing the occurrence of some chronic diseases. These nonnutritive components, which are mainly secondary plant metabolites and dietary fiber, are mostly present in some foods in small quantities and have only limited caloric value. Therefore, the development of foods enriched with these nonnutrients can constitute a way to cope with the chronic disease epidemic.

In this context, the concept of functional foods was developed in Japan in the 1980s and launched in the USA and Europe since the mid-1990s (Menrad 2003). Several definitions have been used but there is consensus on the fact that functional foods can be regarded as foods that beneficially affect

G. Ares (✉)

Sección Evaluación Sensorial, Departamento de Ciencia y Tecnología de Alimentos, Facultad de Química.
Universidad de la República (UdelaR), Gral. Flores 2124. C.P. 11800, Montevideo, Uruguay
e-mail: gares@fq.edu.uy

one or more target functions in the body beyond adequate nutritional effects, in a way that is relevant to either an improved state of health and wellbeing or a reduction of risk of disease (Margaret 2002).

Persuading people to make healthier food choices and to consume functional foods could provide important public health effects, such as decreased mortality and increased quality of life (Siró et al. 2008). The success of functional foods depends on consumers' acceptance of these products as part of their daily diet. Therefore, one key aspect to support the development of functional foods is to better understand consumers' perception of this type of food product and to identify the determinants of consumers' acceptance of functional foods (van Kleef et al. 2002).

Consumers do not perceive functional foods as specific products, different from their conventional counterparts (Urala and Lähteenmäki 2003). On the other hand, consumers perceive them as member of the particular food category to which they belong (Urala and Lähteenmäki 2003; Siró et al. 2008). Thus, when shopping for a functional food product within a certain food category, consumers have to choose between functional and conventional foods. For this reason, a large number of factors affect consumers' choice behavior of functional foods. In the present chapter these factors are reviewed, stressing the importance of non-sensory factors.

50.2 Factors Affecting Consumers' Choice Behavior of Functional Foods

Food choice is a very complex process which involves many different interrelating factors. The key facts about food choice behavior are summarized in Table 50.1.

Different food choice models have been developed to understand food choice behavior and to illustrate the factors that influence this process (Sheperd and Sparks 1994). In general, variables influencing food choice could be divided into three main categories: those related to the food, to the person making the choice and to the external economic and social environment within which the choice is made. Figure 50.1 shows an overview of some of the factors that have been extensively reported to be determinants of consumers' food choice behavior.

As has been mentioned before, consumers perceive functional foods as regular food products, similar to their conventional counterparts. Therefore, consumers' choice of this type of product is influenced by the same characteristics, including sensory quality, price, and convenience, as any conventional product. Thus, factors affecting consumers' choice behavior of functional foods could also be divided into the abovementioned categories. Non-sensory factors are the main determinants of consumers' interest in purchasing functional foods. Key features about non-sensory factors affecting consumers' food choice behavior are summarized in Table 50.2. Although the sensory characteristics also play a key role in consumers' interest in functional foods, they are the main determinants

Table 50.1 Key facts of consumers' food choice behaviour. This table lists the key facts of food choice behavior, including its characteristics and the main factors that affect it

Key facts of food choice behavior
• Food choice behavior could be regarded as consumers' choices regarding the foods they eat everyday.
• Understanding consumers' food choice behavior is important for functional foods development and marketing, and may contribute to the improvement of health by positively influencing food habits.
• Food choice behavior is a complex process, which is affected by many interrelating factors including sensory and non-sensory characteristics.
• Factors affecting consumers' food choice behavior could be grouped in the characteristics of the food, the characteristics of the consumer and finally factors related to the environment in which the consumers make their choices.
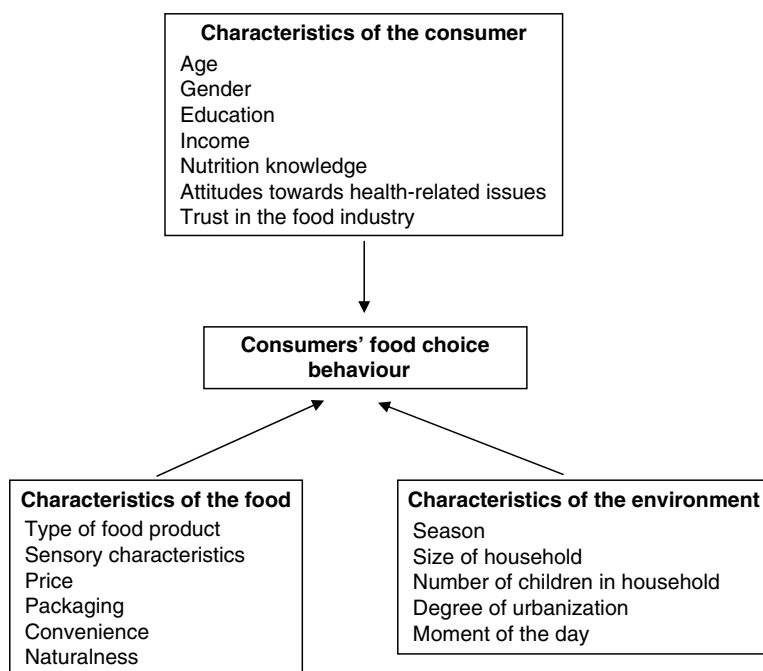
Fig. 50.1 Factors affecting consumers' food choice behavior. This figure shows the main factors that have been reported to affect consumers' food choice behavior. These factors could be grouped in those related to the food, those related to the consumer making the choice, and those related to the environment in which the choice is made

Table 50.2   Key facts of non-sensory factors affecting consumers' food choice behaviour. This table lists the key facts of non-sensory factors affecting consumers' food choice behavior

Key facts of non-sensory factors affecting food choice behavior
• Although sensory characteristics of food products have been claimed the most important variables affecting consumers' food choices, non-sensory variables also play a key role.
• Non-sensory factors affecting consumers' food choices could basically be regarded as all the variables that are not related to the sensory characteristics of the product.
• Non-sensory variables include product characteristics such as brand, price, and convenience; characteristics of the consumer, and characteristics of the environment in which consumers decide their choices.
• Non-sensory factors have been reported to be the most important determinants of consumers' interest in functional foods.

of consumers' decision to repeat the purchase of a certain functional food after they have tried it. On the other hand, consumers might be driven by their interest in improving their health status when purchasing a functional food for the first time.

According to several authors, the characteristics of the consumer are the most important in determining attitudes toward functional foods, followed by those related to the food (Lähteenmäki 2003; Verbeke 2005; Urala and Lähteenmäki 2007; Verbeke 2006; Herath et al. 2008; Siró et al. 2008). The key factors affecting consumers' choice behavior of functional foods are listed in Table 50.3. In particular, socio-demographic background, personal motivations, and attitudes toward health-related issues are the key determinants of consumers' acceptance of functional foods (Siró et al. 2008).

Table 50.3 Key features affecting consumers' choice behavior of functional foods. This table lists the key variables that have been reported to affect consumers' choice behavior of functional foods, i.e., consumers' choice of foods that have a positive influence on health

Type of characteristics	Features
Characteristics of the person	– Socio-demographic characteristics (gender, age, educational level, socio-economic class, number of children in household) – Interest in health-related issues – Nutritional knowledge
Characteristics of the product	– Type of product (base product and functional ingredient) – Sensory characteristics – Health claim – Brand – Price

50.3 Characteristics of the Consumer

50.3.1 Socio-demographic Variables

Although the explanatory power of socio-demographic variables in explaining consumers' food behavior has been decreasing (Dagevos 2005), their role in functional foods acceptance cannot be ignored. Socio-demographic variables have been reported to have a great influence on consumer acceptance of functional foods; being gender, age, education, and socioeconomic class the characteristics with the highest influence. Despite the fact that clear gender and age differences have been identified, there is no consensus on how other socio-demographic variables affect functional foods acceptance.

Table 50.4 summarizes the influence of socio-demographic variables in functional food acceptance. As shown, according to most studies, consumers of typical functional foods have been identified as females, well educated, higher socio-economic class, and older than 55 years.

Females have been reported to be more familiar with functional foods, and to more frequently consume these food products than men (Childs and Poryzees 1998; Bogue and Ryan 2000; Herath et al. 2008; Verbeke 2005, 2006; Labrecque et al. 2006; Siró et al. 2008). This has been related to the fact that women are usually more interested in health-related issues (Roininen et al. 1999; Beardsworth et al. 2002). The higher interest of females toward functional foods has important implications considering that they are frequently the person responsible for food selection and shopping in the household and therefore they could affect other peoples' eating patterns (Siró et al. 2008). Thus, women's interest in functional foods could lead to the adoption of this food category by other people in their household, particularly children.

Regarding age, as shown in Table 50.4, middle-aged and elderly people are usually more aware of health-related issues because they are more likely to be diagnosed with a lifestyle-related disease than younger consumers (Verbeke 2006), which may explain the reported higher intention to purchase functional foods (Poulsen 1999; Herath et al. 2008). Moreover, older consumers seem to show different attitudes toward type of functionality than younger ones, preferring functional foods that have short-term effects on health rather than the prevention of diseases. According to Bogue and Ryan (2000) older Irish people were more interested in functional foods that reduce the risk of cancer, while younger consumers were more interested in foods that increase their energy level. Furthermore, Ares et al. (2008a) reported that Uruguayan consumers' interest in preventing cardiovascular diseases seemed to lower with age, whereas interest in lowering cholesterol and blood pressure increased with age. Therefore, age not only influences interest in functional foods but also what types of functional foods consumers are interested in.

Table 50.4 Influence of socio-demographic characteristics on consumers' interest in functional foods. This table summarizes how socio-demographic characteristics such as gender, age, education, and socio-economic class have been reported to affect consumers' interest in functional foods. The table lists the most positive group toward functional foods for each socio-demographic characteristic, together with the source from which the information was extracted.

Socio-demographic characteristic	Group more interested in functional foods	Source
Gender	Females	Childs and Poryzees (1998)
		Poulsen (1999)
		Bogue and Ryan (2000)
		Beardsworth et al. (2002)
Age	Older than 35	Childs and Poryzees (1998)
	Between 34 and 54 years old	Herath et al. (2008)
	Older than 55	Poulsen (1999)
		Anttolainen et al. (2001)
Education	Well educated	Childs (1997)
	Higher-educated	Anttolainen et al. (2001)
	Less formal educated	Herath et al. (2008)
Socio-economic class	Higher income	de Jong et al. (2003)
	Higher socio-economic class	Hilliam (1996)
	Lower income	Herath et al. (2008)

As shown in Table 50.4, several authors have reported that higher income and higher education contribute to consumers' willingness to consume functional foods; which has been attributed to higher awareness about this type of foods and to a higher ability to pay a premium price for them. On the other hand, Herath et al. (2008) reported that Canadian consumers more receptive toward functional foods tend to have received less formal education and be in lower income households, which have been attributed to the fact that they might face more health problems and they could not have a healthy diet through the foods they usually afford to consume.

It is important to remark that the influence of socio-demographic variables could not be analyzed without taking into account the type of functional food and its health claim, since there are clear differences in the influence of socio-demographic variables between different functional food products (Poulsen 1999; de Jong et al. 2003).

50.3.2 Attitudes Toward Health

Consumers can only be expected to choose functional foods over conventional ones if the former are perceived as healthier. Consumers must be interested in achieving or preserving a good health status, and they must think of functional foods as important in helping them staying healthy (Krystallis et al. 2008). Besides, consumers have to be informed about their beneficial health effect, they must trust in the health claim, perceive it as safe, and they must have a perceived need for using the product (Lähteenmäki 2003). Therefore, attitudes toward health are central in determining consumers' acceptance of functional foods.

In general, consumers think they are responsible for their own health status (Ares et al. 2008a,b,c) and are aware of the relationship between diet and health. This suggests that, generally speaking, consumers are aware of the fact that certain foods could have a positive influence on their health. However, according to Verbeke (2005) consumers' perception of the role of diet on health did not affect functional foods acceptance.

Apart from being aware of the influence of their food choices on health, consumers need to be interested in improving their wellbeing, staying healthy, and preventing disease. Several studies have

reported that consumers more interested in preserving their health condition or preventing disease have a more positive attitude toward functional foods (Ares et al. 2008c, 2010).

Thus, in order to consume functional foods, consumers should think that these food products will have a relevant positive effect on their health status. Perceived reward was reported to be the strongest single predictor for willingness to use functional foods by Urala and Lähteenmäki (2007), whereas Cox et al. (2004) found that self-efficacy was the best predictor of the intention to consume a functional food with a stated memory improvement claim. Furthermore, Herath et al. (2008) stated that a key driver of functional foods acceptance is perceived disease threat. According to several authors, the interest in functional foods is affected by the health condition of the consumers and their family (van Kleef et al. 2005; Verbeke 2005). Personal experiences with illness and the existence of a family member with a specific health problem increase the probability of accepting functional foods. Verbeke (2005) reported that the existence of a family member with a health problem increased the acceptance of functional foods by Belgian consumers.

However, although consumers' interest in health-related issues is central in determining their choice behavior of functional foods, it is not enough to support the consumption of functional foods (Krystallis et al. 2008). For example, de Jong et al. (2004) reported that only 11% of the consumers with high cholesterol levels reported being users of cholesterol-lowering spreads.

50.3.3 Influence of Nutritional Knowledge

According to Labrecque et al. (2006) high knowledge on the health benefits of functional foods is also relevant for the acceptance of these products, together with health and product-related benefits, beliefs, and credibility of information.

Nutritional knowledge has been claimed to have a great influence on dietary behavior (Patterson et al. 1995; Wardle et al. 2000). Several studies have reported that increasing nutritional knowledge is associated with higher intake of fruits and vegetables (Wardle et al. 2000; Patterson et al. 1995). However, according to several authors the influence of nutritional knowledge on food preferences and selection is rather small (Räsänen et al. 2003). Crites and Aikman (2005) suggested that increasing nutrition knowledge makes health a more important determinant of attitudes but that overall attitudes and behavior change less due to the fact that other evaluative bases are not affected by nutritional knowledge.

However, nutritional knowledge has been reported to affect consumers' choice behavior of functional foods. Ares et al. (2008b) reported that nutritional knowledge significantly affected consumers' perceived healthiness and willingness to try functional foods concepts which consisted of combinations of base products and nutritional modifications. According to these authors, consumers with low nutritional knowledge were not interested in the addition of fiber or antioxidants to healthy products such as bread, yogurt, or milk desserts, decreasing their willingness to buy scores. On the other hand, consumers with high nutritional knowledge increased their willingness to purchase scores, and were interested in functional foods which consisted of healthy products enriched with fiber and antioxidants.

Moreover, Wansink et al. (2005) reported that consumers who had both attribute-related knowledge and consequence-related knowledge of functional foods were more willing to consume these products than those who had only one type of information. As shown in Table 50.5, whereas only 11% of the consumers who had no knowledge about soy consumed this product, 68% of consumers who had both knowledge about the healthy characteristics of soy and their consequences on health, consumed it. Thus, in order to accept functional foods, consumers should know that the food contains

Table 50.5 Influence of nutritional knowledge on soy consumption (Wansink et al. 2005). This table summarizes results reported by Wansink et al. (2005) about the relationship of nutritional knowledge and soy consumption. Consumers were segmented according to their type of knowledge about soy in four groups: those who had no knowledge about soy (comprising 143 consumers), those who had knowledge about the attributes of soy (composed of 277 consumers); those who had knowledge about the consequences on health of soy consumption (composed of 122 consumers), and those who had knowledge about both soy attributes and the consequences on health of soy consumption (comprising 63 consumers). For each of these segments percentage of consumers who consume soy is reported. As shown, soy consumption was higher for the group who had both attribute and consequence knowledge

Type of knowledge	Percentage of consumers who consume soy (%)
No knowledge of soy ($n = 143$)	11
Attribute knowledge only ($n = 277$)	15
Consequence knowledge only ($n = 122$)	24
Attribute and consequence knowledge ($n = 63$)	68
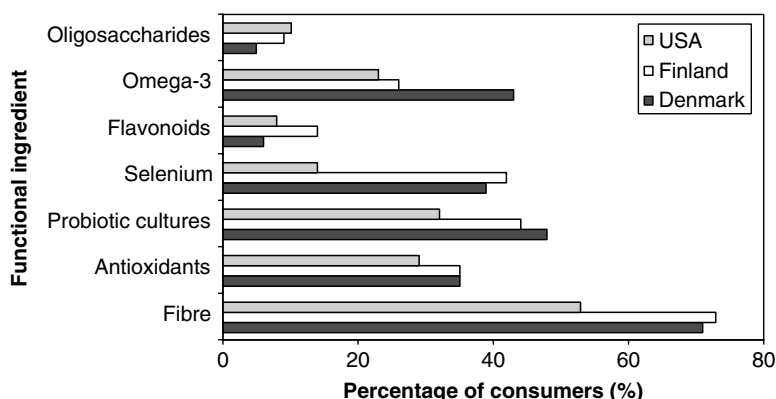
Fig. 50.2 Percentage of consumers aware of the health effect of different functional ingredients (Bech-Larsen et al. 2001). This figure shows the percentage of consumers who are aware of the health effect derived from the consumption of different ingredients commonly used in functional foods formulation, in three different countries: USA, Finland, and Denmark, as reported by Bech-Larsen et al. (2001)

a certain functional ingredient and which are the consequences related to the consumption of that particular functional ingredient.

Furthermore, consumers have a limited knowledge of the health effects of functional ingredients. As shown in Fig. 50.2, a low percentage of consumers is aware of the health effect of several functional ingredients. For example, only 6–14% of the consumers in Denmark, Finland, and USA is aware of the health effect of flavonoids and oligosaccharides, whereas between 20% and 40% of the consumers is aware of the health effects of other widely spread functional ingredients such as omega-3 and antioxidants. Therefore, there is a strong need for information and communication activities to consumers in order to encourage functional foods consumption (Menrad 2003). Therefore, the use of health claims might be necessary for assuring that consumers are aware of the health benefits of the product and therefore consider substituting conventional foods by their functional alternatives.

50.3.4   Trust in Functional Foods

Trust in functional foods also plays an important role since consumers do not directly and immediately experience the health benefits of these products (Siegrist et al. 2008; Verbeke 2005). Consumers

have to trust in the claimed health benefits of functional foods in order to consume them. For example, Niva et al. (2003) reported that trust was determinant of the frequency of use of cholesterol-lowering spread. According to these authors 32% of Finish consumers were doubtful about functional foods. Moreover, Labrecque et al. (2006) reported that credibility of information about functional foods was an important determinant of the acceptance of functional foods.

Trust in the food industry also affects consumers' acceptance of functional foods. As reported by Siegrist et al. (2008), consumers who trust in the food industry are more likely to buy functional foods compared to those who do not trust in it.

Moreover, the production of functional foods requires the use of novel technologies in order to incorporate functional ingredients. Therefore, consumers might perceive this type of products as less natural than their conventional counterparts and therefore might not be chosen by consumers who perceive naturalness as an important attribute underlying their food choices. According to Jonas and Beckman (1998) Danes consumers perceived functional foods as unnatural and impure, which decreased their interest and willingness to buy these food products.

According to Urala and Lähteenmäki (2007) consumers' confidence in functional foods is related to both trust in the health claims and to perceived safety. A segment of consumers might be suspicious about the possible harmful effects of functional foods. Besides, O' Connor and White (2010) reported that risk associated with functional foods was also a determinant of consumers' willingness to use this type of product.

Therefore, functional food consumers might be those who are interested in taking care of their health status, who receive, understand, and trust the 'message' of functional foods and who feel in control of their health condition.

50.4 Characteristics of the Product

50.4.1 Type of Functional Food

Functional foods can basically be regarded as a carrier product enriched with a functional ingredient with a positive effect on health. Consumers' acceptance of functional foods depends on the carrier product, the consumer, and the health claim attached to it (Lähteenmäki 2003).

The perceived healthiness of the base product has a great influence on consumers' perception of functional foods. Carrier products with a healthy image have been reported to be more attractive than carriers with an unhealthy image (van Kleef et al. 2005; Ares et al. 2008a; Siegrist et al. 2008). Consumers' attitudes toward functional foods are more positive when intrinsically healthy products, such as yogurt, cereals, bread, and juice are considered (Siró et al. 2008). However, the opposite trend has been reported by Bech-Larsen et al. (2001). These authors stated that consumers considered the enrichment of "non healthy" foods more justified than enrichment of foods which are perceived as healthy per se.

Consumers' perception of the functional ingredient is also important in determining functional foods acceptance. Familiar functional ingredients (e.g., vitamins, fiber, minerals) are usually preferred to novel functional ingredients (e.g., polyphenols, selenium, flavonoids) due to the fact that consumers are not aware of the health benefits of the latter group of ingredients (Bech-Larsen et al. 2001; Siró et al. 2008). Regarding the health effect of the functional ingredient, van Kleef et al. (2005) and Siegrist et al. (2008) reported that consumers rated physiological health claims as more

attractive than psychological health claims; whereas van Trijp and van der Lans (2007) reported that yogurts with the added benefits of reducing the negative impact of stress or improving concentration had lower consumer appeal than products strengthening the body's natural defense system. However, consumers do not perceive functional ingredients independently from the carrier product (van Trijp and van der Lans 2007; Siegrist et al. 2008). Poulsen (1999) stated that consumers prefer functional ingredients that are already contained in the base product.

Moreover, van Kleef et al. (2005) explored carrier product and health claim compatibility for 100 hypothetical products. In their study they did not find a significant interaction between health claim and carrier. This result implies considerable flexibility in the design of functional foods, since the attractiveness of the health claim is not affected by the carrier.

Therefore, consumers' prior thoughts about the healthiness of the base product and the functional ingredient are key determinants of their attitudes toward functional foods and sometimes might override the influence of health claims (Siró et al. 2008).

50.4.2   Influence of Information

Functional foods are usually characterized using different types of claims. There are basically three types of health claims, as shown in Table 50.6 (ILSI Europe 1999). Considering the low level of awareness of the health effect of functional ingredients, food companies usually use "enhanced function" or "reduced disease risk" health claims to efficiently communicate the health effect of functional foods to consumers. The extent to which consumers find health claims appealing and trusty depends on the content and format of the message (Mazis and Raymond 1997).

Basically, message of health effects could be formulated to provide a potential benefit (e.g., "enhanced function") or to prevent a negative situation (e.g., "reduced disease risk"). The use of one type of claim depends on which has the greater persuasive impact on consumers (van Kleef et al. 2005). According to Krishnamurthy et al. (2001), in the context of attribute framing, people react more positively to positive than negative messages. Therefore, it has been stated that health claims that emphasize the positive influence of functional foods are preferred over health claims that emphasize the prevention of diseases (Krishnamurthy et al. 2001). In this context, enhanced function claims might be more appealing to consumers than reduced disease risk claims, because the former evoke positive associations from memory (van Kleef et al. 2005). 'Reduced disease risk' might confront consumers with illness and problems they might suffer in the future. However, little research has been carried out on this topic and results in literature regarding the effect of claims are rather contradictory. While van Kleef et al. (2005) reported that Dutch consumers reacted more favorably to

Table 50.6 Type and description of claims used in functional foods. This table lists and describes the different types of claims that are used on the labels of functional foods to assure that consumers are aware of the presence of the functional ingredient and of the relationship between the consumption of that ingredient and its positive effect on health

Type of claim	Description
Nutrient content	Characterize the level of a nutrient in a food (e.g., high in fiber)
Enhanced function	Relationship between the consumption of a food or food ingredient that contributes beneficially to one or more target functions in the body (e.g., reduce cholesterol level)
Reduced disease risk	Relationship between the consumption of a food or food ingredient and reduction of the risk of a specific disease or an undesirable health condition (e.g., reduce the risk of cancer)

"disease reduced risk" claims than to "enhanced function" framed health claims; Bech-Larsen et al. (2001) reported the opposite trend. van Kleef et al. (2005) have reported that consumers preferred health claims that stress the prevention of physiologically based illnesses. This could be explained considering that in many cases negative information is more informative, attracts more attention, and stimulates deeper processing than positive information.

50.4.3 Influence of Brand and Price on Consumers' Acceptance of Functional Foods

Today's consumers have to trade several factors against each other in order to select which food they buy or eat. In the case of functional foods, consumers might have to trade health, sensory, and other non-sensory factors, such as brand, price, and convenience, when deciding to buy a certain functional food. Research about consumer perception of functional foods has been focused on their health and sensory characteristics. However, the influence of non-sensory factors such as brand and price, on consumer perception of functional foods has not received much attention.

The importance of brand in consumers' perception of food products has been extensively reported (Jaeger 2006). According to Keller (1998) brand consists of a promise, a guarantee or contract with the manufacturer and a symbolic means and sign of quality.

On the other hand, price could influence consumer purchase intention in two different ways: it could lower purchase intention due to a greater monetary sacrifice, or it could have a positive impact on purchase impact because of an increase in perceived product quality (Jaeger 2006). Functional foods might be more expensive than their conventional counterparts and might affect consumers' acceptance. According to several authors there is a group of consumers who are not affected by a price increase, and are willing to pay premium price for functional foods (Poulsen 1999; Bogue and Ryan 2000). However, consumers seem to be only willing to accept limited price increase for functional foods (Menrad 2003), such as 30–50% when compared to their conventional counterparts (Siró et al. 2008). Thus, price increase should be taken into account for encouraging functional foods consumption.

According to a study carried out by Ares et al. (2010), brand is a key attribute influencing consumers' choice behavior of functional yogurts. In this study, consumers were asked to choose among different yogurt concepts differing in functionality (regular yogurt, enriched with fiber and antioxidants), brand (national familiar, national unfamiliar, and foreign familiar), price (low, regular, and high), and health claims (with and without "reduced disease risk" health claim). Results showed that non-sensory product factors, such as brand and price, have an important impact on consumer decision to buy functional foods. As shown in Table 50.7, the importance attributed to brand was similar to that of the type of yogurt when deciding which type of yogurt they would buy, regardless of consumers' interest in health-related issues. Price showed a relative importance close to 20%, suggesting that it could also affect consumer decisions regarding the purchase and consumption of functional foods. There was a small tendency that consumers more interested in health issues were less sensitive to an increase in price (Table 50.7). Results suggested that consumer choice of functional yogurts might be highly affected by their brand since, the influence of type of yogurt was similar to the influence of brand for both clusters. Therefore, the development of functional foods could be regarded as an alternative for small companies to differentiate their products and make them more attractive for consumers. However, considering the influence of brand, large food companies have more chances to develop functional foods that are appealing for consumers.

Table 50.7 Relative importance of different non-sensory factors in consumers' choice behavior of functional yogurts, for consumers with high and low interest in health-related issues (Ares et al. 2009). This table summarizes results reported by Ares et al. (2009) about the influence of different non-sensory factors on consumers' choice of functional and regular yogurts. Consumers were segmented into two groups according to their interest in health-related issues: 55 consumers with high interest in health-related issues and 48 consumers with low interest. Consumers had to choose between regular and functional yogurt concepts differing in brand, price, and the presence of health claims. From consumers' choices, the relative importance of each of the evaluated non-sensory variables was calculated for each consumer segment. As shown, brand and type of yogurt had the highest relative importance, regardless of consumers' interest in health-related issues

Consumer segment	Relative importance (%)			
	Type of yogurt	Brand	Price	Health claim
High interest in health-related issues ($n = 55$)	38.3	37.3	17.8	6.6
Low interest in health-related issues ($n = 48$)	37.3	28.9	24.1	8.0

50.5 Other Non-sensory Characteristics

Apart from brand and price, there are other non-sensory factors related to the product which could influence consumers' choice behavior of functional foods. However, these factors, which include convenience and packaging, have not been much studied.

Convenience can be regarded as measure of a food product's ease of preparation. Considering consumers' time constraint in today's world, convenience has become an important non-sensory factor influencing consumers' food choice (Jaeger 2006). According to Urala and Lähteenmäki (2003), convenience is also an important factor in determining consumers' choice of functional foods. Consumers would probably not be willing to compromise convenience for health-related issues and therefore functional foods should be developed maintaining the convenience of their conventional counterparts.

Packaging plays a major role in attracting consumer attention and influencing consumer purchase decisions. In the current self-service economy, packaging provides food companies the last chance to persuade consumers to buy the product before brand selection. Therefore, packaging might consist on a relevant factor for affecting consumers' purchase decisions of functional foods. However, no studies have been found reporting the influence of this non-sensory attribute in functional foods acceptance.

50.6 Influence of Sensory Characteristics

Despite the aim of the present chapter was to review the influence of non-sensory variables on consumer perception of functional foods, the importance of sensory characteristics could not be left unmentioned. In order to gain the health benefits derive from functional foods consumption, consumers need to include them as part of their usual diet for a relatively long period of time, and consequently the sensory properties of functional foods should not discourage sustained consumption. Negative changes in the sensory characteristics of foods due to the addition of functional ingredients might cause potential aversive consumer reactions (Siró et al. 2008). The addition of many functional ingredients results in the appearance of off flavors that decreases the sensory quality of the product. Several authors have reported consumers are hardly willing to consume functional foods they do not like (Tuorila and Cardello 2002; Cox et al.; 2004; Verbeke 2006). These findings suggest that consumers expect functional foods to have good sensory properties that provide them hedonic pleasure, apart from having a positive influence on their health, being not willing to compromise on the taste of functional foods for eventual health benefits. Thus, the development of functional foods

with bad sensory characteristics is a risky option since consumers might not be willing to repeatedly consume them (Verbeke 2006).

50.7 Applications to Other Areas of Health and Disease

Understanding consumers' choice behavior of functional foods could provide valuable information for improving their acceptance of this type of food product. Knowing what consumers take into account when deciding to buy or to reject a certain functional food product could lead to the design of products that successfully address consumers unfulfilled needs and could avoid the development of products that are destined to fail in the market. Moreover, information about what consumers take into account when selecting functional food products could be useful in the design of marketing strategies to encourage their consumption. This could increase consumers' awareness and interest in functional foods, improving the health status of the population and helping chronic disease prevention.

Summary Points

- Consumers do not perceive foods with a positive effect on health (i.e., functional foods) as a separate food category, different from their conventional counterparts.
- Consumer willingness to purchase functional foods is not unconditional, being influenced by several sensory and non-sensory factors.
- Health-related issues are central in determining consumers' acceptance of functional foods.
- Consumers' awareness of the health effect of different functional ingredients is limited, which indicates the necessity of using health claims to appropriately communicate these benefits to consumers and encourage functional foods consumption.
- Product characteristics such as brand, price, packaging, and convenience should be taken into account when developing functional foods since they play an important role in consumers' perception.
- Despite the influence of non-sensory characteristics, sensory characteristics of functional foods should be considered since consumers are hardly willing to compromise on the taste of functional foods for eventual health benefits.

Definitions and Explanations of Key Terms or Words Used in the Chapter

Choice behavior: is the act of making a selection among two or more alternatives, usually after a period of deliberation or consideration of the characteristics of each alternative.
Functional foods: are foods that have a positive effect on health beyond adequate nutritional effects, resulting in an improved state of health and wellbeing or a reduction of disease risk.
Non-sensory factors: are variables that are not related to the product's sensory characteristics and affect consumers' choice behavior.
Attitude: is a construct that represents an individual's disposition to respond favorably or unfavorably to an item.
Chronic diseases: are diseases of long duration and generally slow progression, such as cancer or cardiovascular diseases.

References

Anttolainen M, Luoto R, Uutela A, Boice JD, Blot WJ, McLaughlin JK, et al. J Am Diet Assoc. 2001; 101:1365–8.

Ares G, Giménez A, Gámbaro A. J Sens Stud. 2008a; 23:614–30.

Ares G, Giménez A, Gámbaro A. Appetite. 2008b; 50:663–8.

Ares G, Giménez A, Gámbaro A. J Sci Food Agric. 2008c; 88:2061–8.

Ares G, Deliza R, Giménez A. Food Qual Pref. 2010; 21:361–7.

Beardsworth A, Bryman A, Keil T, Goode J, Haslam C, Lancashire E. Br Food J. 2002; 107:470–91.

Bech-Larsen T, Grunert KG, Poulsen JB. The acceptance of functional foods in Denmark, Finland and the United States. A study of consumers' conjoint evaluations of the qualities of functional food and perceptions of general health factors and cultural values. Working paper no 73. MAAP, Århus; 2001.

Bogue J, Ryan M. Market-oriented new product development: Functional foods and the Irish consumer. Agribusiness Discussion Paper No. 27. National University of Ireland, Cork; 2000.

Childs NM. J Consum Market. 1997; 14:433–47.

Childs NM, Poryzees GH. Brit Food J. 1998; 9:419–426.

Cox DN, Koster A, Russell CG. Appetite. 2004; 33:55–64.

Crites SL, Jr., Aikman SN. Eur J Clin Nutr. 2005; 59:1191–200.

Dagevos H. Appetite. 2005; 45:32–9.

de Jong N, Ocké MC, Branderhorst HAC, Friele R. Brit J Nutr. 2003; 89:273–81.

de Jong N, Simojoki M, Laatikainen T, Tapanainen H, Valsta L, Lahtikoski M, et al. Preventive Med. 2004; 39:849–855.

Dodds WB, Monroe KB, Grewal D. Effects of price, brand, and store information on buyers product evaluations. J Market Res. 1991; 28:307–19.

Herath D, Cranfield J, Henson S. Appetite. 2008; 51:256–65.

Hilliam M. Nutr Rev. 1996; 54:S189–94.

Hilliam M. Aust J Dairy Tech. 2003; 58:98–103.

ILSI Europe Brit J Nutr. 1999; 81:S1–S27.

Jaeger SR. Food Qual Pref. 2006; 17:132–44.

Jonas MS, Beckman SC. Functional foods: consumer perceptions in Denmark and England. MAAP Working Paper No. 55. MAPP, Århus; 1998.

Keller KL. Strategic brand management: Building, measuring and managing brand equity. Englewood Cliffs: Prentice-Hall; 1998.

Krishnamurthy P, Carter P, Blair E. Org Behav Human Dec Proc. 2001; 85:382–99.

Krystallis A, Maglaras G, Mamalis S. Food Qual Pref. 2008; 19:525–38.

Labrecque JA, Doyon M, Bellavance F, Kolodinsky J. Can J Agric Econ. 2006; 54:647–61.

Lähteenmäki L. In: Mattila-Sandholm T, Saarela M, editors. Functional dairy products. Cambridge: Woodhead Publication; 2003. p. 346–57.

Lähteenmäki L, Lyly M, Urala N. In: Frewer L, van Trijp H, editors. Understanding consumers of food products. Cambridge: Woodhead Publication; 2007. p. 412–27.

Margaret A. Concepts of functional foods. ILSI Europe Concise Monograph Series. ILSI Europe, Belgium; 2002.

Mazis MB, Raymond MA. J Consum Affairs. 1997; 31:10–26.

Menrad K. J Food Eng. 2003; 56:181–8.

Niva M, Mäkelä J, Piiroinen S. Domestic berries and plant stanols. Acceptability of functional foods in Finland. Helsinki: National Consumer Research Centre; 2003.

O'Connor EL, White KM. Food Qual Pref. 2010; 21:75–81.

Patterson R, Kristal A, Lynch J, White E. J Nutr Educ. 1995; 27:86–92.

Poulsen JB. Danish consumers' attitudes towards functional foods. Working paper no 62. MAPP, Århus; 1999.

Räsänen M, Niinikoski H, Keskinen S, Helenius H, Talvia S, Rönnemaa T. Appetite. 2003; 41:69–77.

Roininen K, Lähteenmäki L, Tuorila H. Appetite. 1999; 33:71–88.

Shepherd R, Sparks P. In: MacFie HJH, Thomson DMH, editors. Measurement of food preferences. London: Blackie Academic & Professional; 1994. p. 202–26.

Siegrist M, Stampfli N, Kastenholz H. Appetite. 2008; 51:526–9.

Siró I, Kápolna E, Kápolna B, Lugasi S. Appetite. 2008; 51:456–67.

Tuorila H, Cardello AV. Food Qual Pref. 2002; 13:561–9.

Urala N, Lähteenmäki L. Nutr Food Sci. 2003; 33:148–58.

Urala N, Lähteenmäki L. Food Qual Pref. 2007; 18:1–12.

van Kleef E, van Trijp HCM, Luning P. Appetite. 2005; 44:299–308.

van Kleef E, van Trijp HCM, Luning P, Jongen WMF. Trends Food Sci Tech. 2002; 13:93–101.

van Trijp HCM, van der Lans IA. Appetite. 2007; 48:305–24.

Verbeke W. Food Qual Pref. 2005; 16:45–57.

Verbeke W. Food Qual Pref. 2006; 17:126–31.

Wansink B, Westgren RE, Cheney MM. Nutr. 2005; 21:264–68.

Wardle J, Parmenter K, Waller J. Appetite. 2000; 34:269–75.

World Health Organization. Diet, physical activity and health.Geneva: World Health Organization; 2002.

World Health Organization. Diet, nutrition and the prevention of chronic disease.Geneva: World Health Organization; 2003.

Chapter 51
The Concept of Chronotype in Eating Behaviors

Christoph Randler

Abbreviations

CSM   Composite scale of morningness
EDI-2   Eating disorder inventory-2
MCTQ   Munich chronotype questionnaire
MEQ   Morningness–eveningness questionnaire
SCN   Suprachiasmatic nucleus
TFEQ   Three-factor eating questionnaire

51.1 Introduction: The Concept of Chronotype

Human individuals organize their lives in an approximately 24-h rhythm. This rhythm is innate and it is based on an endogenous pacemaker (Dunlap 2004; Koukkari and Sothern 2006). This innate biological rhythm exists, even when environmental inputs, such as sunlight or clocks, are absent (Burgess and Eastman 2008; Czeisler et al. 1999). The endogenous pacemaker is directed by the suprachiasmatic nucleus (SCN) in the brain (Dunlap 2004).

The underlying mechanism of this circadian preference is the variability of a set of psychological, behavioral, and biological variables which have roughly a 24-h oscillation (i.e., a circadian rhythm; Burgess and Eastman 2008). Diurnal changes have been found in both biological (e.g., body temperature and levels of hormone secretion) and psychological variables (e.g., mood and performance; Tankova et al. 1994).

However, there are large interindividual differences in humans. Some are morning "Larks" or early risers, mostly active early in the morning, achieving their maximum of mental and physical activity in the morning and becoming tired early in the evening. In contrast, "Owls" usually have difficulties getting out of bed, and need a longer time to have their senses recovered in the morning, but "Owls" are able to work till late evening and they often achieve their physical and mental daily height during late afternoon and evening hours.

These individual differences in chronotype, timing of sleeping or biological rhythms are viewed as an interesting facet of personality (Matthews 1988). Although these differences were often viewed

C. Randler (✉)

Biology, Department of Natural Sciences, University of Education Heidelberg,
Im Neuenheimer Feld 561–2, D-69120 Heidelberg, Germany
e-mail: randler@ph-heidelberg.de

Table 51.1 Key features of chronotype. Table gives a short overview over the concept of chronotype or morningness–eveningness which is different from sleep length because it is related to the timing of sleeping

People differ in their individual sleep–wake cycle

Chronotype reflects these individual differences in sleep–wake cycles

Early chronotypes get up and go to bed early

Late chronotypes get up and go to bed late

Chronotype is not linked with sleep length

Chronotype reflects the timing of sleeping (wake time, sleep onset)

Chronotype focuses on the question "When do you sleep?" rather than "How long do you sleep?"

Chronotype is heritable, but environmental and social factors contribute

Women are earlier chronotypes than men

The sleep–wake cycle changes during the lifespan

Table 51.2 Questionnaires used in chronobiological/chronopsychological research. The table depicts the most relevant questionnaires used in chronobiological research as means of paper–pencil tests. Other instruments might include hormone secretion or body temperature but questionnaires are useful to screen large samples

Measurement	Acronym	No. of questions	Type	Measure	Original
Morningness–eveningness questionnaire	MEQ	19	Mixed format questions	Preference, clock times	Horne and Östberg (1976)
Composite scale of morningness	CSM	13	Likert type	Preference, clock times	Smith et al. (1989)
Basic language morningness scale (based on CSM, but easier wording)	BALM	13	Likert type	Preference, clock times	Brown (1993)
Preference scale (based on the CSM)	PS	12	Likert type	Preference compared to others	Smith et al. (2002)
Circadian type inventory (some refinements; especially for shift workers)	CTI	30 (18; 11)	Likert type	Flexibility/ amplitude of rhythms	Folkard (1987), Di Milia et al. (2005)
MEQ short form	rMEQ	5	Mixed format questions	Preference, clock times	Adan and Almirall (1991)
CSM short form	rCSM	7	Likert type	Preference, clock times	Randler (2009), Di Milia (2009)
BALM short form	–	7	Likert type	Preference, clock times	Pornpitakpan (2000)
Munich chronotype questionnaire	MCTQ		Mixed-format questions	Clock-based	Roenneberg et al. (2004)

in some kind of dichotomous manner ("Larks" and "Owls"), they also reflect a continuum between both extremes (Natale and Cicogna 2002). There are different terms to define the concept, such as chronotype, morningness–eveningness, circadian preference/typology, or diurnal preference (see Tables 51.1 and 51.2).

51.2 What Determines Chronotype?

Chronotype is seen and understood as an individuals' innate or intrinsic component of the body (biological rhythm). This indicates that the biological rhythm of every individual is based on some intrinsic (endogenous) component of the body that can be influenced – at least partially – by social and environmental factors (Randler 2008c,2008d). At first, some genes have been identified that were associated with the variability in the circadian clock (e.g., Archer et al. 2003; Carpen et al. 2005).

Further, chronotype is heritable, and there were correlations between twins (Hur et al. 1998), and parents and children (Leonhard and Randler 2009). Heritability estimates suggest that between 12% and 29% (Klei et al. 1998), and up to 54% of the variance in circadian preference is determined by genes (Hur et al. 1998). One may assume that chronotype genes are the genetic and heritable basis, but the real expression of chronotype reflects some kind of social, cultural, and environmental factors, leading individuals with identical genotype to different "real" or lived chronotypes. As in other animals, it has been suggested that sunrise may act as an important zeitgeber to entrain the circadian clock (Natale et al. 2009; Randler 2008c; Roenneberg et al. 2007). These studies found that people living in more easterly regions within the same time zone are more morning oriented than the people living in the westerly regions (Randler 2008d). However, other environmental or sociocultural aspects have rarely been studied (Caci et al. 2005; Randler and Díaz-Morales 2007), but it seems that the interplay between these factors is needed to determine an individual's chronotype. Also, it seems that chronotype is unrelated to the social economic status (Paine et al. 2006).

51.3 Changes in Chronotype During the Lifespan

There are significant changes in morningness–eveningness during the lifespan from childhood to retirement. We have only very limited evidence of the age groups of very young children, but at the primary school level (6–10 years), young children often are morning orientated. During the age of puberty, adolescents shift from morningness to eveningness. This shift typically occurs at the age of 12–14 years in many countries and cultures (Díaz-Morales et al. 2007; Randler 2008a, 2008c). At the age of 19–21 years, humans again experience a shift back toward morningness (Roenneberg et al. 2004; Tonetti et al. 2008). This shift is currently supposed to be a marker for the end of adolescence (Roenneberg et al. 2004). From then on, people become more and more morning orientated until retirement, and, again, after retirement there is a paucity of data. People therefore experience a shift toward eveningness during puberty, then back to morningness at the end of adolescence and become progressively more morning oriented parallel with an increasing age. During puberty and adolescence, young people show a delay of rise/wake and bed/sleep times during the weekend (Fig. 51.1).
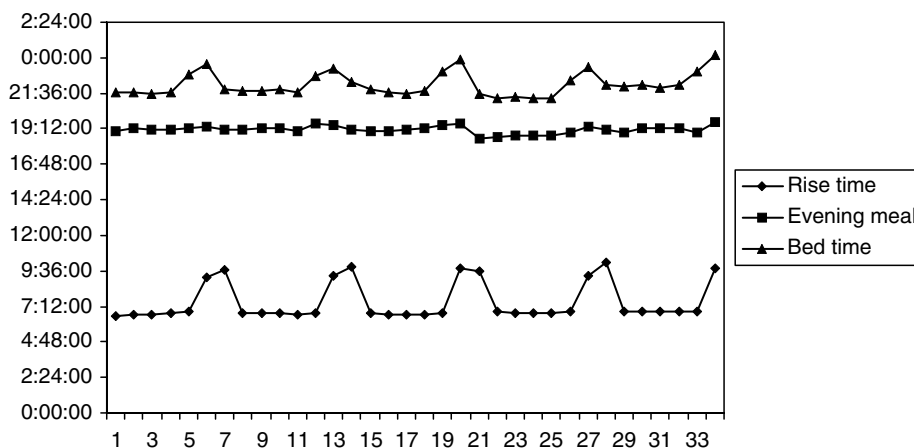
Fig. 51.1 Rise times, bed times, and evening meal times of adolescents during 35 days (based on sleep log data). The figure shows the weekend delay in bed times and rise times. Adolescents go to bed later on Friday and Saturday, and get up later on Saturdays and Sundays. However, evening meal times remain more or less stable. Based on Becht & Randler (unpublished data)

At the weekend, rise times were about 2 h later, and bed times were shifted accordingly. However, meal times (with the exception of breakfast) remain more or less stable (see below).

The changes might be caused by sex hormones as well as by psychosocial aspects (Carskadon et al. 1993). It has been suggested that these changes are in accordance with pubertal development (Carskadon et al. 1993), and hence, linked with the increase of sex hormones. Correlational analyses provide evidence that adolescents scoring higher on eveningness are also in a higher pubertal developmental stage (Carskadon and Acebo 1993; Randler et al. 2009). Supporting evidence for the hypothesis that sex hormones are linked with changes in morningness–eveningness comes also from a study on menopause in women. During menopause, sex hormones rapidly decrease, which is linked with a change toward a higher morning orientation (Randler and Bausback 2010).

51.4 Sex/Gender Differences in Chronotype

Sex differences in chronotype have been found in some studies that compared biological (physiological) measurements between men and women (see Tankova et al. 1994). However, most survey studies using questionnaires did not reveal differences between the sexes in chronotype, e.g., because of a missing age-adjustment or because of small sample sizes. Boys and men are more evening oriented than girls and women given a similar age range (Tonetti et al. 2008). These results have been confirmed by a meta-analysis (Randler 2007). Interestingly, women had a more significantly advanced sleep phase than males, that is, they were earlier chronotypes or more morning orientated only during the years when sex hormones were present (Tonetti et al. 2008). This gives supporting evidence for the function of sex hormones. The differences between the sexes may result from receptors for sex hormones in the SCN which is the location of the circadian pacemaker (Kruijver and Swaab 2002).

51.5 Psychological Correlates of Chronotype

Chronotype has been found to correlate with psychological constructs which makes it interesting for psychological aspects of eating behaviors. For example, eveningness was associated with Eysenck's personality dimension of extraversion (Tankova et al. 1994; Cavallera and Giudici 2008), and morningness was associated with the conscientiousness scale of the Big Five Inventory (Randler 2008b; Tonetti et al. 2009). Also, higher or better academic performance was related to morningness (Wolfson and Carskadon 2003; Randler and Frech 2006).

Eveningness was associated with a number of psychological and psychosomatic disturbances, such as depression (Chelminski et al. 1999; Drennan et al. 1991), or seasonal affective disorder (Natale et al. 2005), while morningness was related to satisfaction with life (Randler 2008f).

51.6 How to Measure Chronotype

Chronotype can be measured by a variety of methods. From a biological viewpoint, physiological measurements can be used to assess the chronotype of humans, e.g., by measuring the daily rhythm of body temperature. Morning types or larks have their lowest body temperature during the early parts of the night, while evening types have their lowest temperature in the early morning. Similarly,

the hormone melatonin, peaks some hours earlier in "Larks" than in "Owls". Also, the cortisol awakening response is higher and more pronounced in morning types (Kudielka et al. 2006).

However, these immediate or direct assessments of chronotype are costly and often time consuming, preventing us from large-scale studies or rendering them impossible. To this end, a set of questionnaires have been developed to assess an individuals' chronotype. The most widely used measurements are depicted in Tables 51.2 and 51.3. Some of these questionnaires are also available as a short or reduced version. The correlations between the scales are usually high because nearly all these questionnaires measure a more or less similar construct (e.g., Randler 2009). Therefore, one should use the questionnaire adequate to the study situation, e.g., when time is a constraint it may be possible to use only the short form of the CSM or the Morningness–Eveningness Questionnaire (MEQ). However, in studies where more resources are available, it might be helpful to combine measurements.

In recent times, the scales were improved from a psychometric point of view. The factor structure of the questionnaires is still not fully resolved (Caci et al. 2009). However, this is to be expected in measurements that are more or less newly developed, but many characteristics, such as wake/rise time, bed time, and physical or mental peak performance correlate with the scores on the respective scales. Also, the MEQ has been validated by hormonal measures, such as cortisol (Kudielka et al. 2006) or by melatonin. There is some evidence for the validity of these scales both from a psychometric point of view (reliability, factor structure), and from external validation (by assessment of alertness or hormonal profiles).

The lark–owl continuum has metric scale level. In addition, it is possible to group individuals by using cut-off scores (e.g., extreme lark, moderate lark, intermediate, moderate owl, extreme owl).

51.7 Chronotype and Eating Behaviors

Only very few studies have assessed the relationship between chronotype and eating behaviors. Schubert and Randler (2008) used the CSM in combination with the German version of the Three-Factor Eating Questionnaire (TFEQ) (Pudel and Westenhöfer 1990). The questionnaire is based on three basic constructs of eating behavior: cognitive restraint, disinhibition, and perceived hunger. Schubert and Randler (2008) found a positive correlation between "Larks" (high CSM scores) and cognitive restraint, and negative relationships between CSM scores and disinhibition, and between CSM scores and perceived hunger (Fig. 51.2). Their results indicate that chronotype is linked with eating behavior and that individuals skewed toward eveningness experience more disinhibited eating and perceive more hunger.

The cognitive restraint scale can be divided into two subscales, flexible and rigid control of eating behavior (Westenhöfer et al. 1999). In their study there was an association between morningness and flexible control, with morning oriented individuals scoring higher on the flexible control scale, but there was no association between CSM scores and rigid control (Schubert and Randler 2008).

51.8 Chronotype and Food Intake

As morningness–eveningness was associated with the psychological constructs of eating behaviors, further studies explored the relationship between food intake and chronotype; two studies focused on this specific aspect. In one, a proxy of midpoint of sleep was used (Fleig and Randler 2009), in

Fig. 51.2 Relationship between the perceived hunger scale from the Three-Factor Eating Questionnaire and scores on the composite scale of morningness (*CSM*). High CSM scores reflect morningness, and low CSM scores reflect eveningness. The data were obtained from the perceived hunger scale from the Three-Factor Eating Questionnaire. High scores represent higher expression of perceived hunger. The negative relationship indicates that evening oriented persons perceive more hunger (data based on Schubert and Randler 2008)
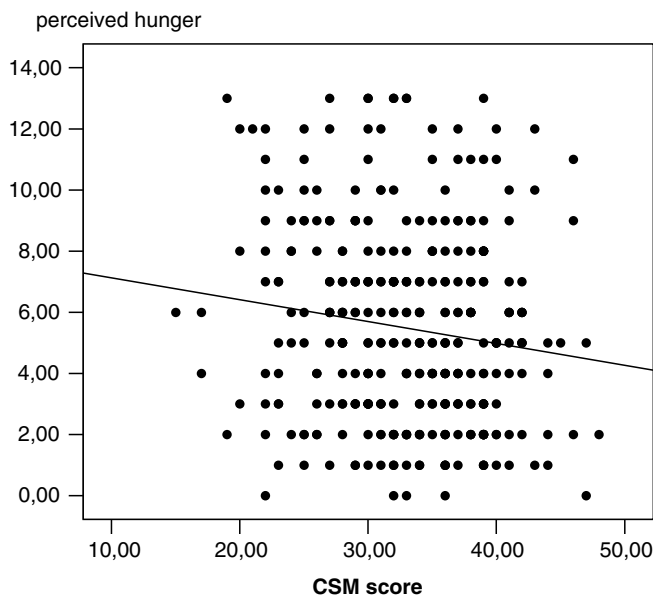
another one the CSM. The first study was based on food logs reporting food intake in adolescents, while the second used a food–frequency list to assess food intake. Fleig and Randler (2009) analyzed different groups of food. Food logs were distributed among adolescent school pupils to asses their food intake. The caloric value was calculated for each pupil, and the calories were assigned to different food types. In a regression analysis, the authors revealed a positive correlation between chronotype and fast food consumption (standardized $\beta = 0.260$), between chronotype and cola and caffeinated drinks (standardized $\beta = 0.163$), and a negative correlation between chronotype and dairy products (standardized $\beta = -0.177$). No relationship was found between chronotype and either sweets, or vegetables and salad, or meat. These results indicate that earlier chronotypes (or individuals skewed toward morningness) consumed less fast food, less caffeinated drinks but more dairy products. In general, this suggests a healthier lifestyle in morning oriented adolescents. Using a food–frequency list based on a Likert-type format in adolescents, there were negative correlations between CSM scores and fast food, meat, coffee, and caffeinated drinks, suggesting that adolescents oriented toward eveningness consumed more of these food items (unpublished data). In some aspects, both studies are in agreement (fast food and coffee are consumed more in evening types), but in some they disagree which may be a result of the sample size (the food log study had less participants), or in the format of the questions: While the Likert-type scale measures food intake frequency in retrospect (e.g., over the past four weeks), the food logs measure the real intake rate, but usually over a shorter period. Further research is therefore needed to investigate the relationship between food intake and chronotype.

51.9 Chronotype and Eating Disorders

Few studies examined the relationship between eating disorders and chronotype. For example, nocturnal eating was associated with eating disorders such as binge eating (Greeno et al. 1995) and bulimia nervosa patients had a sleep onset about 1 h later than healthy individuals (Latzer et al. 1999).

Fig. 51.3 Relationship between eating disorders and chronotype in adolescent girls. High CSM scores reflect morningness, and low CSM scores reflect evening-ness. The mean of the three scales of the eating disorder inventory-2 (*EDI-2*) is based on three scales: bulimia, drive for thinness, and body dissatisfaction. High scores represent higher expression of eating disorders. Thus the negative relationship indicates that evening orientated persons suffer more from eating disorders (Data based on Schmidt and Randler 2010)
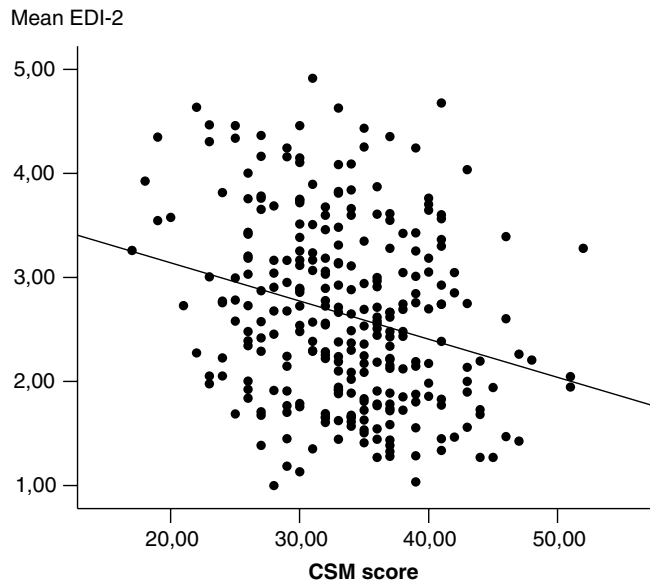
Kasof (2001) found correlational evidence between eveningness and bulimic behavior in University students of both sexes, suggesting that evening types are higher at risk. In adolescent girls, Schmidt and Randler (2010) reported correlations between three scales of the Eating Disorder Inventory-2 (EDI-2) and the CSM (Fig. 51.3). Individuals scoring higher on eveningness reported higher scores on the drive for thinness, the bulimic, and the body dissatisfaction scale. Natale et al. (2008) compared women around the age of 30 in a clinic for eating disorders with a control group of healthy women of similar age. These authors also found that women suffering from eating disorders were later chronotypes, and they suggest that the disorder leads to a later chronotype. However, the data on adolescents suggest that eveningness is an unspecific risk factor for eating disorders. It seems clear that eating disorders and chronotype are linked with each other, but the correct direction seems not yet fully resolved.

51.10 Chronotype and Meal Times

Meal times differed between weekdays and weekends in many persons, and the largest differences are found in breakfast time. In adolescents, breakfast times differed significantly between weekdays (mean 6:36) and weekends (9:15), while meal times of lunch and dinner were similar (lunch: 13:15 versus 13:10; dinner: 18:51 versus 18:56). A look at the variance (SD) shows that at all three meal times, the variance was higher on weekends (Fleig and Randler 2009). Caloric intake at breakfast was higher on the weekend compared to week days, while intake at lunch and dinner did not differ (Fig. 51.4). In adults, results were similar and lunch and dinner times remained rather stable when comparing weekends with weekdays, but adults also showed a delay in breakfast times (7:27 on weekdays versus 8:32 on weekend days, Costa et al. 1987).

   Also, chronotype influences the timing of meals in adolescents. Mean breakfast time at the weekend was later in late chronotypes which was a result of later rise times of late chronotypes. As rise times in late chronotypes differ more between weekdays and weekends, this suggests a more regular
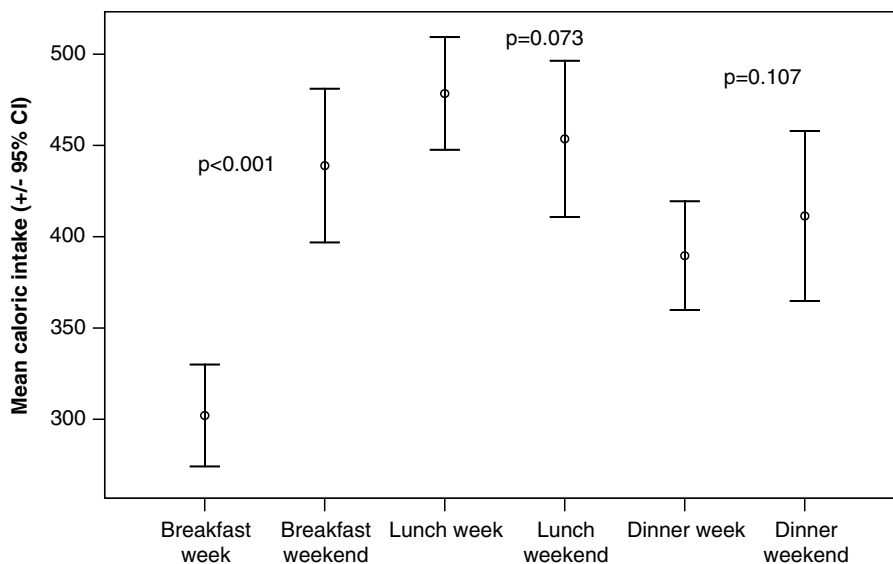
Fig. 51.4 Caloric intake in adolescents according to meal time. Caloric intake was measured using food logs in adolescent school pupils. Statistical comparisons show significant differences in intake at breakfast. Pupils ate more at weekend breakfast (from unpublished data, Fleig and Randler). Data are means and 95% confidence intervals

lifestyle in earlier chronotypes. Dinich (2003) asked people about their most preferred meal during the day. Evening oriented persons showed a preference for evening dinner, and morning types preferred the breakfast.

51.11 Chronotype and Drug Abuse

Chronotype was found to be linked with addiction, e.g., with alcohol and cigarette consumption, i.e., evening oriented people smoked more cigarettes (Wittmann et al. 2006) or were more often habituated smokers (Randler 2008e). Cigarette smoking has been associated with delayed sleep onset and with a shorter sleep duration, i.e., smokers tend to go to bed later than nonsmokers and they sleep shorter. Adan et al. (2004) found differences in mood and activation between high- and low-dependent smokers and nonsmokers. Wittmann et al. (2006) found that people living against their own biological clock are more often smokers which might be a consequence of "social jetlag." People of later chronotypes who would like to go to bed and get up later than their normal daily schedule might tend more to cigarette smoking to compensate for their distortion of their daily rhythm.

51.12 Chronotype and Obesity

Recent studies showed a significant relationship between sleep duration and obesity, suggesting that short sleepers acquire a higher Body Mass Index (review: Cappuccio et al. 2008) However,

Table 51.3   Key features of the morningness–eveningness questionnaire. The table gives an overview over the key concepts that have the different questionnaires in common

The questionnaires are based on Likert-type questions and on clock times
The questionnaire often asks for preferences ("When would you like to get up if you are entirely free to plan your day?")
A total score is obtained by adding the scores for each items
The total score can be used for correlational analyses
Groups (Owls or Larks) can be defined by cut-off scores
The questionnaires differ in length

Table 51.4   Correlation between body mass index (BMI; z-transformed) and sleep–wake variables in adolescents, based on unpublished data from Randler and Hammer

	BMI z-scores
Average sleep duration	−0.185**
Sleep length on weekdays	−0.176**
Sleep length on free days	−0.108 ns
Rise time week day	0.155**
Rise time weekend	0.145*
Bed time week day	0.278***
Bed time free days	0.269***

***Denotes $p < 0.001$, ** $p < 0.01$, *$p < 0.05$; *ns* not significant. Please note that the sleep length was calculated from rise times and bed times (which means time in bed). The data indicate that bed times seem to have the most relevant influence on BMI

the influence of chronotype has not been assessed in any previous study, but it might indeed be the timing of sleeping rather than the sleep duration itself (see Table 51.4). In a study based on adolescents, there were significant relationships between sleep–wake variables and BMI (Hammer and Randler, unpublished data, see Table 51.4, Fig. 51.5). The data further suggest that it is the timing of sleeping (or chronotype), rather than the sleep length itself with later chronotypes having a higher BMI. Here, further studies are needed to find the optimal predictor for this relationship.

51.13 Applications to Other Areas of Health and Disease

A very interesting facet of the study of health and disease might be the application of chronotype questionnaires and to look at these relationships in more detail in further studies. One question, e.g., emerging in the study of eating disorders is whether an eveningness orientation is a risk factor or a premorbid trait for eating disorders (Schmidt and Randler 2010), or whether eating disorders themselves influence and modulate the circadian preference and shift individuals to an evening orientation (Natale et al. 2008). Another interesting aspect is whether problematic eating behavior is a result of disruption of the circadian timing or whether it is a prerequisite.

Further, we do not know much about the relations of different hormones that influence the sleep–wake cycle and hormones that affect eating behavior in humans.
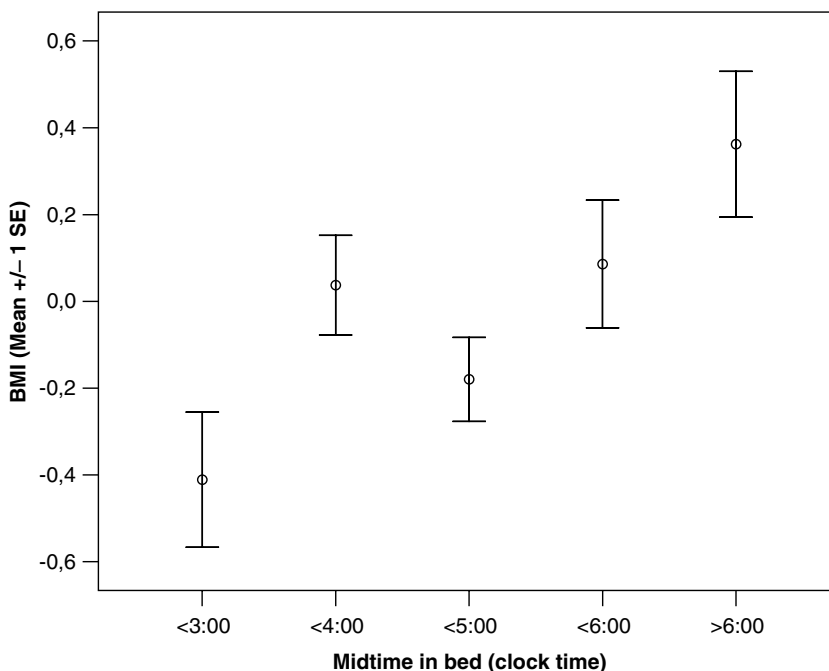
Fig. 51.5 BMI (z-scores) according to midpoint of time in bed, which is the midpoint between bed time and rise time on free days. Z-scores were obtained for each gender and age class separately. Midtime in bed measure as the clock time between going to bed and rising based on 284 adolescents. Early chronotypes have an early midtime in bed, late chronotypes have a late midtime. Body mass index was obtained by self-report. Late chronotypes had a higher body mass index when controlling for age and gender. Data are means and one standard error

Summary Points

- Individuals skewed to eveningness (or late chronotypes) have a more problematic eating behavior, scoring higher on disinhibition and perceived hunger of the TFEQ.
- Individuals skewed to morningness (or early chronotypes) score higher on the cognitive restraint scale and the flexible control subscale.
- Individuals skewed to eveningness (or late chronotypes) showed higher incidence of eating disorders, and scored higher on the scales drive for thinness, bulimic behavior, and body dissatisfaction.
- Evening oriented adolescents ate more fast food, and consumed more cola and caffeinated drinks.
- Meal times between weekend and weekdays differ at breakfast but not at lunch and dinner with later meal times at the weekend.
- Evening oriented persons exhibit a less regular lifestyle (e.g., in meal times).
- Eveningness (or late chronotype) was related to higher consumption of alcohol and cigarettes.

Key Terms

Circadian preference/typology: is a description of the preference of an individual for a specific time of day, e.g., whether an individual prefers morning or evening hours for physical and mental activity.
Chronotype: some kind of classification of people into different classes, e.g., into larks and owls. However, chronotype is usually measured on a metric or continuous scale, and can also be

grouped into three, five, or seven groups. Late chronotypes have a late midpoint of sleep and a low score in the psychological questionnaires (MEQ, CSM), and early chronotypes have an early midpoint of sleep and high scores on the psychological questionnaires.

Eveningness: the orientation toward evening hours. This is measured by a questionnaire (Table 51.2). Individuals scoring high on eveningness were often called Owls.

Lark: In a European context, this considers an early awakening bird, the skylark (*Alauda arvensis*), and it is used as a synonym for early rising people.

Midpoint of Sleep: the midpoint between two clock times, the timing of sleep onset when an individual starts sleeping, and the timing of awakening. Somebody with a sleep onset at 0:00 and a wake time of 6:00 has his/her midpoint of sleep at 3:00. This midpoint can be calculated for workdays and for free days. In most persons, the midpoint of sleep on free days is later than on work days.

Morningness: the orientation toward morning hours. This is measured by a questionnaire (Table 51.2). Individuals scoring high on eveningness were often called Larks.

Owl: this is a synonym for persons staying out late and going to bed late.

References

Adan A, Prat G, Sanchez-Turet M. Addiction. 2004; 98:1599-607.
Archer SN, Robilliard DL, Skene DJ, Smits M, Williams A, Arendt J, et al. Sleep. 2003; 26:413-5.
Bailey SL, Heitkemper MM. Chronobiol Int. 2001; 18:249-61.
Burgess HJ, Eastman CI. J Biol Rhythms. 2008; 23:374-6.
Caci H, Adan A, Bohle P, Natale V, Pornpitakpan C, Tilley A. Chronobiol Int. 2005; 22:523-40.
Caci H, Deschaux O, Adan A, Natale V. Sleep Med. 2009; 10:240-5.
Cappuccio FP, Taggart FM, Kandala N-B, Currie A, Peile E, Stranges S, et al. Sleep. 2008; 31:619-26.
Carpen JD, Archer SN, Skene DJ, Smits M, von Schantz M. J Sleep Res. 2005; 14:293-7.
Carskadon MA, Vieira C, Acebo C. Sleep. 1993; 16:258-62.
Cavallera GM, Giudici S. Pers Ind Diff. 2008; 44:3-21.
Chelminski I, Ferraro FR, Petros TV, Plaud JJ. J Affective Dis. 1999; 52:19-29.
Costa G, Lievore F, Ferrari P, Gaffuri E. Chronobiologia. 1987; 14:383-91.
Czeisler CA, Duffy JF, Shanahan TL, Brown EN, Mitchell JF, et al. Science. 1999; 284:2177-81.
Di Milia L, Smith PA, Folkard S. Pers Ind Diff. 2005; 39:1293-1305.
Díaz-Morales JF, Davila de Leon MC, Sorroche MG. Chronobiol Int. 2007; 24:435-47.
Drennan MD, Klauber MR, Kripke DF, Goyette, LM. J Affect Dis. 1991; 23:93-8.
Dunlap JC. Chronobiology biological timekeeping. Sunderland, MA: Sinauer; 2004.
Fleig D, Randler C. Eating Behav. 2009; 10:115-8.
Folkard S. Circadian type inventory. Dept. Psychol.: Sheffield; 1987.
Greeno CG, Wing RR, Marcus MD. Int J Eating Dis. 1995; 18:343-9.
Hur YM, Bouchard TJ, Lykken DT. Pers Ind Diff. 1998; 25:917-25.
Kasof J. Pers Ind Diff. 2001; 31:361-9.
Klei L, Reitz P, Miller M, Wood J, Maendel S, Gross D, et al. Chronobiol Int. 1998; 22:1041-54.
Koukkari WL, Sothern RB. Introducing biological rhythms: a primer on the temporal organization life, with implications for health, society, reproduction, and the natural environment. Amsterdam: Springer; 2006.
Kruijver FPM, Swaab DF. Neuroendocrinology. 2002; 75:296-305.
Kudielka BM, Federenko IS, Hellhammer DH, Wüst S. Biol Psychol. 2006; 72:141-6.
Latzer Y, Tzschinsky O, Epstein R, Klein E, Peretz L. Int J Eating Disorders. 1999; 26:315-21.
Leonhard C, Randler C. Chronobiol Int. 2009; 26:510-25.
Matthews G. Eur J Pers. 1988; 2:277-93.

Natale V, Cicogna PC. Pers Ind Diff. 2002; 32:809-16.

Natale V, Adan A, Fabbri M. Sleep. 2009; 32: 423-426.

Natale V, Adan A, Scapellato P. Psychiatry Res. 2005; 136:51-60.

Natale V, Ballardini D, Schumann R, Mencarelli C, Magelli V. Pers Ind Diff. 2008; 45:549-53.

Paine SJ, Gander PH, Travier N. J Bio Rythms 2006; 21:68-76.

Pudel V, Westenhöfer J. Fragebogen zum Eßverhalten (FEV). Hogrefe, Göttingen; 1990.

Randler C. Pers Ind Diff. 2007; 43:1667-75.

Randler C. Biol Rhythm Res. 2008a; 39:151-61.

Randler C. Pers Ind Diff. 2008b; 45:191-6.

Randler C. Chronobiol Int 2008c; 25:565-75.

Randler C. Chronobiol Int. 2008d; 25:1017-28.

Randler C. Soc Ind Res. 2008e; 86:297-302.

Randler C. Soc Behav Pers. 2008f; 36:673-80.

Randler C. Biol Rhythm Res. 2009; 40:413-23.

Randler C, Bausback V. Biol Rhythm Res. 2010; 41: in press

Randler C, Díaz-Morales JF. Eur J Pers. 2007; 21:419-27.

Randler C, Frech D. Biol Rhythm Res. 2006; 37:233-9.

Randler C, Bilger S, Díaz-Morales JF. J Psychol. 2009; 143:509-20.

Roenneberg T, Kuehnle T, Pramstaller PP, Ricken J, Havel M, Guth A, et al. Curr Biol. 2004; 14:1038-9.

Roenneberg T, Kumar CJ, Merrow M. Curr Biol. 2007; 17:44-5.

Schmidt S, Randler C. J Ind Diff. 2010; 31:38-45.

Schubert E, Randler C. Appetite. 2008; 51:501-5.

Tankova I, Adan A, Buela-Casal G. Pers Ind Diff. 1994; 16:671-84.

Tonetti L, Fabbri M, Natale V. Chronobiol Int. 2008; 25:745-59.

Tonetti L, Fabbri M, Natale V. Chronobiol Int. 2009; 26:337-47.

Torsvall L, Akerstedt T. Scand J Work Env Health 1980; 6:283-90.

Westenhoefer J, Stunkard A, Pudel V. Int J Eating Dis. 1999; 26:53-64.

Wittmann M, Dinich J, Merrow M, Roenneberg T. Chronobiol Int. 2006; 23:497-509.

Wolfson AR, Carskadon MA. Sleep Med Rev. 2003; 7:491-506.

Chapter 52
Feeding and Sleep Behavior

Chin Moi Chow and Christopher Paul Herrera

Abbreviations

SWS	Slow wave sleep
BMI	Body mass index
CHO	Carbohydrates
GI	Glycemic index
HFLC	High fat–low carbohydrate
LFHC	Low fat–high carbohydrate
MSLT	Multiple sleep latency test
EEG	Electroencephalography
REMS	Rapid eye movement sleep
NREM	Nonrapid eye movement
TRP	Tryptophan
5HT	5-Hydroxy-tryptamine (serotonin)
LNAA	Large neutral amino acids
CCK	Cholecystokinin
PS	Paradoxical sleep

52.1 Introduction

Feeding is associated with a rise in body temperature resulting from an increased metabolic rate. Its influence on sleep is mediated not through the ingestion process but by the by-products of macronutrients. Because feeding occurs during the wake period, feeding and sleeping are mutually exclusive. On the other hand, wakefulness and feeding are mutually inclusive. Hypocretin, a neuropeptide which stimulates both food ingestion and wakefulness in humans and in rats, shows stable levels in the wake period (Fujiki et al. 2001; Nishino et al. 2000). Melatonin, which is released at dark onset, depresses food intake and increases sleep propensity (Bermudez et al. 1983).

C.M. Chow (✉)
Delta Sleep Research Unit, Discipline of Exercise and Sport Science,
The University of Sydney, Lidcombe NSW 1825, Australia
e-mail: chin-moi.chow@sydney.edu.au

Normal feeding behavior usually consists of three regular meals, with the majority of the meals taken in the light phase of the light–dark cycle. However, regular feeding behavior is evolving in view of food abundance, availability of fast foods, and a busy lifestyle resulting in irregular meals and feeding on-the-go being more prevalent. Dieting with food restriction is commonly practiced in those who are concerned with weight gain, while fasting is observed as part of religious beliefs (Ramadan), and in the animal kingdom during hibernation (bears, ground-squirrels, reptiles), egg incubation (ducks, geese), breeding and molting (penguins), and when food becomes sparse. Whilst feeding is often associated with lethargy and subjective sleepiness, not sleeping enough has been shown to impact directly on feeding behavior. Objectively measured electroencephalographic (EEG) changes offer a dimension not attainable in subjective sleep measures. EEG measures reveal that sleep is usually entered through Stage 1 drowsy sleep, followed by "true" sleep characterized by the sleep EEG spindle structure (Stage 2) and deep sleep (Stage 3 or slow wave sleep, SWS), then rapid eye movement sleep (REMS). Stages 1–3 do not exhibit rapid eye movements and are collectively known as nonrapid eye movement (NREM) sleep. This chapter covers three areas of interest: macronutrient effects on sleep, feeding behavior and sleep patterns, and sleep duration and appetitive behavior.

52.2 Diet and Sleep

There is considerable scientific evidence detailing the effects of dietary intake on sleep. The main dietary constituents that can readily influence sleepiness are the macronutrients of carbohydrates (CHO) and fat, with opposing effects from protein. Whilst sleepiness is increased after CHO– or fat-based meals, macronutrient ingestion per se does not promote sleepiness. Postprandial sleepiness is primarily influenced by the circadian timing (time of day) of the meals and the macronutrient content via neurochemical changes. Secondary factors include patterns of habitual feeding and gender. Because feeding can alter sleep patterns, it will become vital for dietitians, nutritionists, and other allied health practitioners to understand the relationship between diet and sleep, since poor sleep (seen in shift workers and in those with insomnia and depression) has implications for poor health outcomes. Figure 52.1 depicts the factors influencing postprandial sleepiness; the most significant factors are those at the base levels of the pyramid.

Fig. 52.1 Factors impacting postprandial sleepiness. The factors influencing postprandial sleepiness are presented on the pyramid. The most significant factors are those at the base levels of the pyramid. Note it is possible that these factors may interact with each other at any level
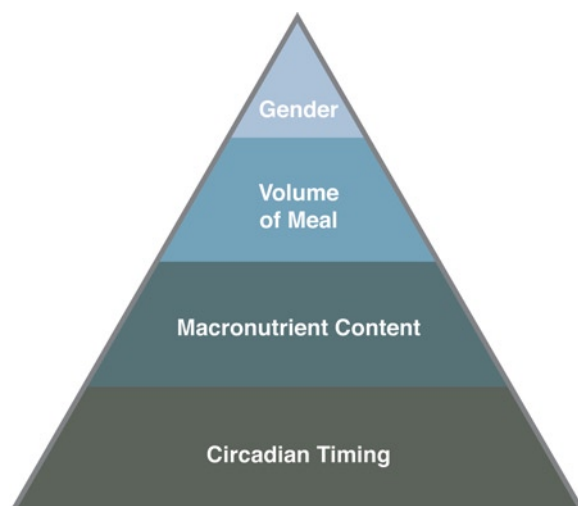
52.2.1 Circadian Timing of Meals

Sleep and metabolism are tightly regulated by the circadian clock that is located in the suprachiasmatic nucleus of the hypothalamus (Kovac et al. 2009). The body clock keeps time of all biological rhythms. Circadian rhythms are those with an oscillation of approximately 24 h. These rhythms not only display peaks and troughs of activity at different times of the day, but show phase relationships. For an example, the peak core temperature that occurs at around 1600–1800 h is linked to alertness, whereas the temperature nadir occurring at around 0400–0600 h is linked to sleepiness. Not surprisingly, the time of day that meals are eaten exerts an influence on postprandial sleepiness. A biphasic response was observed after a high-fat–low-carbohydrate (HFLC) or a low-fat–high-carbohydrate (LFHC) meal provided at breakfast or lunch. The response showed an increase in alertness that lasted for up to 30 min followed by a shift toward sleepiness that was greatest between 1100–1400 h independent of the meal type (Wells and Read 1996; Wells et al. 1998). The initial increase in alertness may be explained by the thermic effect of the meal, while the postprandial sleepiness coincides with the postlunch dip, a circadian phenomenon (Monk 2005). This phenomenon has been examined in a study where a 3 h sleep opportunity was allowed after either a CHO liquid lunch meal or a no food condition. Sleep occurred in both conditions suggestive of a strong postlunch circadian dip, however, sleep duration was markedly increased following food intake (Zammit et al. 1995), suggesting that in addition to the circadian effect, the meal itself impacted sleep.

Harnish and colleagues queried if postprandial sleepiness was due to the ingestion process related to gustatory, olfactory, and/or visual cues associated with a meal (Harnish et al. 1998). They explored this question using the Multiple Sleep Latency Test (MSLT) with four nap opportunities tested at 1700 h and terminating at 2100 h. They offered participants a mixed macronutrient meal (energy from fat 46% and from carbohydrates 42%) or a sham meal (chewed and expectorated) in a crossover study, where the meal allocation was randomized and counter-balanced. There was only a small difference in the postprandial sleep between the feeding and sham feeding conditions at 2 h postprandially. However, sleepiness was delayed with progression of the remaining nap studies, which likely reflects an increased state of alertness linked to the circadian temperature peak as well as the thermic effects of the meal.

52.2.2 Macronutrients and Sleep

Meals high in CHO and fats are more effective in promoting sleep compared to protein meals. An increase in sleepiness has been reported at breakfast after high CHO meals compared to high protein meals (Leathwood and Pollet 1983). Postprandial sleepiness after HFLC and HCLF meals may be present for up to 4 h depending on the measurement tool used. In several studies, subjective measures of sleepiness were present at 60 min following meal consumption (Lloyd et al. 1994, 1996; Spring et al. 1982/1983; Wells et al. 1998; Wells and Read 1996; Leathwood and Pollet 1983), whereas objective measures of sleepiness (MSLT and Akerstedt EEG analysis) were present between 1.5 and 4 h, respectively (Wells et al. 1998).

It is apparent that macronutrients impact on nocturnal sleep. Early evidence showed that SWS is immediately increased after intravenous administration at bedtime of either pure glucose or of an amino acid mixture, whereas increases in REMS occurred after glucose administration only (Lacey et al. 1977). Dietary intake of CHO similarly shows this trend in REMS. A dose–response effect for

increased REMS was present after iso-caloric diets with low, medium, and high CHO content (100, 300, and 600 g, respectively) (Phillips et al. 1975). Further, an increase in REMS was evident after a low calorie CHO snack given 45 min before the usual bedtime (Porter and Horne 1981). In accordance with these results, a reduction in CHO intake (e.g. 50 g/day or completely eliminated as in a very low carbohydrate diet), resulted in a reduction in REMS (Afaghi et al. 2008; Kwan et al. 1986), total sleep time (Kwan et al. 1986), and increased SWS (Afaghi et al. 2008).

Afaghi et al. 2007 tested the efficacy of a high versus a low glycemic index (GI) CHO meal and the timing of the high GI meal (4 h versus 1 h before the usual bedtime) on the sleep patterns of healthy adults. The subjects took significantly less time to fall asleep after the high GI compared to the low GI isocaloric meal eaten 4 h before their usual bedtime (Afaghi et al. 2007). They also took less time to fall asleep after the high GI meal ingested 4 h before bedtime than after that ingested 1 h before bedtime. Remarkably, there were no differences to other stages of sleep. In a separate study, when a cereal-type bedtime snack was given just prior to bedtime, there was a reduction in sleep latency and a more restful sleep reported in healthy subjects (Brezinova and Oswald 1972).

52.2.3 Macronutrients and Neurochemicals

Carbohydrates may positively influence sleep, given that the glycemic level of a meal importantly dictates the availability of tryptophan (TRP) to the brain. TRP is a crucial amino acid that links diet and sleep, as it is the biological precursor to serotonin (5HT), which is an intermediary to the synthesis of melatonin, a sleep-inducing agent. The availability of TRP depends on its concentration in relation to the other large neutral amino acids (LNAA), since each competes for a single transport protein across the blood–brain barrier (Wurtman 1988). Postprandial sleepiness may therefore be linked to the nutrient-specific macronutrient ingestion and changes to the ratio of TRP/LNAA. Figure 52.2 illustrates the postprandial changes in the ratio of TRP/LNAA after two carbohydrate-based meals (sucrose, high GI; raw starch, medium GI) and one fat and protein meal. There is a clear GI dose-dependent increase in the TRP/LNAA ratio after CHO-based meals, and a decreased ratio after a protein and fat meal (Lyons and Truswell 1988). The time required for digestion and absorption
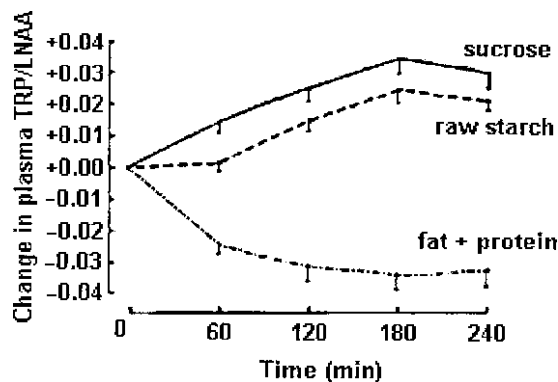
Fig. 52.2 Postprandial change in TRP/LNAA after carbohydrate and fat + protein meals. The mean change in plasma TRP/LNAA ratio in 13 subjects after sucrose (high GI), raw starch (medium GI), or fat+protein evening meals is shown. Vertical bars represent SEM. Values after sucrose were significantly different from corresponding raw-starch ($p < 0.05$, Neuman–Keul's test). Values after fat+protein were significantly different from both corresponding carbohydrate meals ($p < 0.001$) *TRP* tryptophan, *LNAA* large neutral amino acids, *GI* glycemic index (Data are from Lyons and Truswell 1988. With permission from the Publishers)

Fig. 52.3 Meal composition leads to changes in serotonin (*5HT*). Percent change observed in platelet-poor plasma 5HT levels after the administration of test meals: meal 1, carbohydrate; meal 2, protein-rich; meal 3, fat-rich. *5HT* 5-hydroxytryptamine or serotonin (Data are from Blum et al. 1992. With permission of the Publishers)
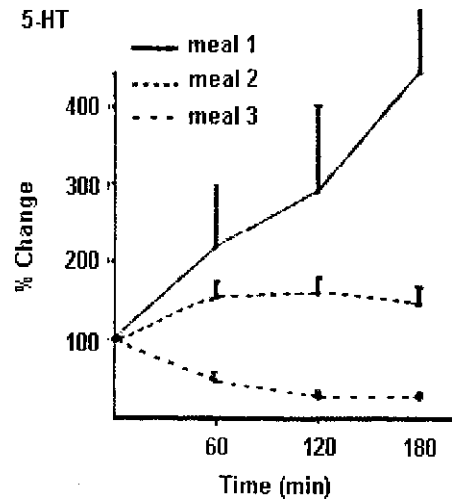
of the macronutrients relates to the plasma appearance of TRP, since the TRP/LNAA ratio peaks between 2 and 4 h after ingestion of a high-CHO meal. This peak rise in the TRP/LNAA ratio has been replicated for evening meals (Lyons and Truswell 1988) providing evidence for a mechanistic role of high GI meals for sleep improvement.

High GI meals, through hastened entry of glucose into the blood, facilitate a greater insulin response that mediates the selective uptake of LNAA into skeletal muscle, leaving TRP that is largely bound to plasma albumin free to cross into the brain for conversion into serotonin (5HT) (Wurtman 1988). This cascade of events has been shown to lead to an increase in 5HT production. Figure 52.3 shows the postprandial levels of platelet-poor plasma (PPP)-5HT after a CHO-, fat-, or protein-rich meal (Blum et al. 1992). As can be seen the level of PPP-5HT was significantly increased from baseline after the CHO-rich meal (4.47-fold) compared to after the fat-rich meal (1.66-fold) (Fig. 52.3), reflecting a reduction in the glycemic response when fat is added to a meal. Increased PPP-5HT is likely responsible for the increase in REMS after CHO intake, since increased levels of plasma tryptophan correlate positively with REMS in normal individuals (Chen et al. 1974).

The increase in postprandial sleepiness after fat-based meals may be explained by the release of the neuropeptide cholecystokinin (CCK) in response to the delivery of fatty acids and protein-rich chyme to the duodenum. It has been shown that increased levels of CCK are present at approximately 3 h after digestion of HFLC meals or after intraduodenal infusion of lipids (Wells et al. 1995). Postprandial sleepiness was present after both conditions compared to saline infusion. The authors suggested that postprandial sleepiness after ingestion of fat may be explained by an increased CCK level that is mediated by vagal afferent signals to the brain (Schwartz et al. 1993). Evidence in the animal model corroborates these findings (Fara et al. 1969; Murray et al. 1993). Despite the soporific effects of high fat meals, increased fat intake may lead to positive energy balance and may contribute to weight gain.

52.2.4 Impact of Habitual Feeding Behaviors and Gender

It is apparent that habitual food choices (Lloyd et al. 1996) and gender both greatly influence subjective sleepiness (Wells et al. 1998). Meals that deviate from habitual intake with respect to the time of day, volume, or macronutrient content may cause a decline in subjective mood state and increased

sleepiness (Lloyd et al. 1994, 1996). It is unclear if the carbohydrate feeding behavior and choice of foods at breakfast have a physiological basis, however, it is possible that this behavior is signaled by a low blood glucose level following an overnight fast (Robertson et al. 2002) and may be synchronized with the sleep–wake cycle (Krauchi et al. 2002). In fact, mood has been shown to improve after an LFHC breakfast meal, showing a decrease in fatigue when compared to an HFLC meal, a mixed macronutrient meal, and when no breakfast meal was provided (Lloyd et al. 1996). However, subjective alertness declined after big lunches compared to small lunches irrespective of habitual lunch size (Craig and Richardson 1989). Additionally, solid meals but not liquid meals increase sleepiness compared to an equal volume of water (Orr et al. 1997). Gender may also modify the dietary effects on sleepiness. In females, a decline in alertness is more prominent for those eating larger-sized meals compared with their usual sized lunch-time meals (Smith et al. 1991). In another study, females tended to report greater postprandial sleepiness than males (Wells and Read 1996); however, other subjective mood states such as feelings of lethargy, boredom, and mental slowness have been reported across genders independent of meal type (Smith et al. 1988).

52.3 Fasting and Sleep Patterns

It could be said that nutritional sufficiency is marked by a normal sleep pattern. However, fasting or overfeeding, on either end of a continuum from insufficiency to over-sufficiency, induces an altered pattern of sleep. Sleep is severely disturbed in patients with anorexia nervosa (Lacey et al. 1975) and in obesity (Dixon et al. 2005). The sleep of both groups is characterized by an increased wake time, decreased SWS, and REMS. Re-feeding in anorexia (Lacey et al. 1975) brings about normalization of sleep patterns. The changes in sleep pattern with food restriction (acute or chronic fasting) present a paradoxical picture in that acute fasting of several days increases SWS, whereas chronic fasting decreases SWS. Attention is drawn to SWS, a sleep stage marked by low frequency, high amplitude activity on the EEG. SWS, the deepest stage of sleep, is usually intense and present in large amounts in the first of 4–6 sleep cycles that occur during nocturnal sleep. SWS is determined by prior sleep and waking and represents a marker of the sleep homeostatic process (Borbely 2001). Importantly, SWS has the lowest metabolic rate of all sleep stages and lowest brain glucose metabolism (Heiss et al. 1985), which is 10–15% lower than when lying quietly awake (Dewasmes et al. 1989). Thus, changes to SWS with acute or chronic fasting take on metabolic significance. Additionally, the onset of SWS coincides with the release of growth hormone (Sassin et al. 1969), which plays a key role in glucose homeostasis, particularly in brain glucose levels during the nocturnal fast. Growth hormone spares glucose for the brain by increasing blood glucose through antagonism of insulin release, and increasing hepatic glycogen storage through gluconeogenesis, as well as stimulation of fat oxidation and suppression of protein oxidation. Thus, increases in SWS appear metabolically apt where lipid store is adequate and fat oxidation sustains energy supply (acute stages of fasting), whereas diminished SWS is favored where lipid reserve is low or depleted (chronic fasting). The relationship between SWS and acute and chronic fasting and re-feeding is depicted in Fig. 52.4 and preempts the supporting literature (cross-sectional and longitudinal) that follows.
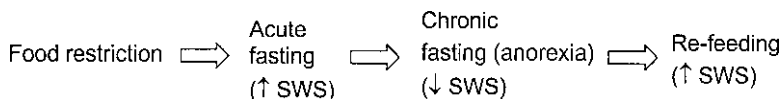
Fig. 52.4 Paradoxical relationship between SWS, food restriction, and re-feeding. Acute fasting of several days increases SWS, whereas chronic fasting decreases SWS. When re-feeding occurs, SWS is restored. *SWS* slow wave sleep

Acute fasting of 3–4 days promotes an increase in SWS in man (MacFadyen et al. 1973; Karacan et al. 1973), geese (Dewasmes et al. 1984), emperor penguins (Dewasmes et al. 1989), and pigeons (Rashotte et al. 1998), although not in the rat (Dewasmes et al. 1989). Changes in REMS or paradoxical sleep (PS, equivalent to human REMS) were variable, showing decreases (Dewasmes et al. 1989; MacFadyen et al. 1973), increases (Dewasmes et al. 1984), and no change (Rashotte et al. 1998; Karacan et al. 1973). In these species, starvation mediates falls in metabolic rate and energy expenditure. SWS appearance is apt given a low metabolic state and low brain glucose metabolism during this sleep state (Heiss et al. 1985). Further, the paralleled growth hormone release mobilizes lipids to yield energy substrates while sparing glucose for the brain. Thus, increases in SWS present a survival strategy that sustains energy supply through a lowered metabolic state and increased fat mobilization. Karacan et al. (1973) noted considerable variability in the individual growth hormone response to fasting during the sleep period. They noted that those who typically did not exhibit a peak response (5 ng/mL) during the baseline, non-fasting night showed the strongest sleep growth hormone response to fasting, although the peak level was reached by all subjects on the fasting night.

As fasting continues into a chronic nature, adipose store progressively becomes depleted. The timing of depletion depends on body size and types (ecto-, meso-, and endomorphs). Depletion signals the beginning of increased protein utilization and a critical period during which death may occur should fasting continue. Chronic fasting, contrasting acute fasting, is associated with a reduction in SWS duration, REMS, and increased wakefulness. These findings have been observed in anorexia nervosa (Lacey et al. 1975) and in geese (Dewasmes et al. 1984). Dewasmes and colleagues proposed that sleep changes may be linked to changes in body fuels (Fig. 52.5). They demonstrated three periods of fasting in animals that hibernate and also in those that do not (e.g. the rat). Period I corresponds to acute fasting of 3–5 days, with reduction in metabolic rate, but high rate of fat mobilization; Period II corresponds to chronic fasting, where lipids contribute to 94% and protein to 6% of energy expenditure; and Period III, the critical period that marks the beginning of increased protein utilization and potential death. In the case of the geese, the authors showed a progressive increase in SWS and PS through Periods I and II, and a downward direction for these sleep parameters in Period III (Fig. 52.5). The reduction in both SWS and PS was observed in parallel with an increased wake period.

In premenopausal women, restricted energy intake over 4 weeks led to a delay in sleep onset but notably a reduction in SWS (Karklin et al. 1994). Their sleep findings resemble those seen in chronic starvation. Although their dietary strategy did not involve total food restriction, the women exhibited a

Fig. 52.5 SWS and fasting in geese. Percentages of slow wave sleep per 24 h in fed geese and their change over course of long-term fasting. Fasting begins at 0 time. The solid line represents least-square regression equations for relations of proportions of SWS to time of fasting, within limits of the three periods *SWS* slow wave sleep (Data are from Dewasmes et al. 1984. With permission from the Publishers)
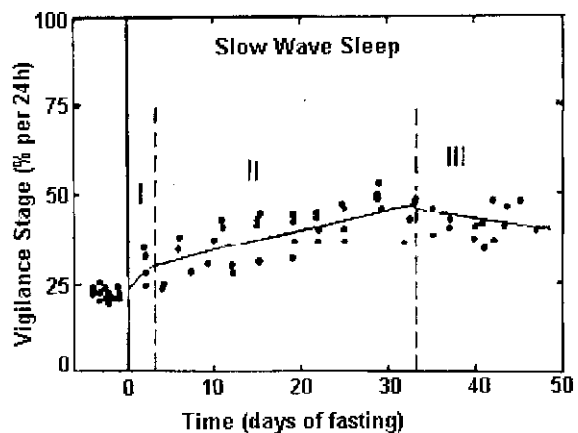
hypometabolic state, as indicated by a significant decrease in plasma triiodothyronine (T_3) (Karklin et al. 1994). Furthermore, they lost around 8% of their initial body mass (baseline mean body mass being 71.2 ± 8.0 kg) (Karklin et al. 1994), and it may be inferred that they lost substantial amount of fat mass.

In two studies of young, growing rats, total food restriction over 4 days saw a reduction in SWS coincident with an increased wake time and decreased PS (Guesdon et al. 2005; Minet-Ringuet et al. 2004). Both studies noted that food restriction induced a reduction of fat mass and only half of the adipose tissue store remained at the end of the 4-day food restriction, given the low reserve in these young animals. These studies are more in line with the chronic starvation state, where substantial fat mass reduction is linked to a decrease in SWS. Similar sleep data have been reported in very lean rats (Danguir and Nicolaidis 1979).

52.4 Sleep Deprivation and Appetitive Behavior

Humans are sleeping less, averaging 7 h compared to 9 h a century ago. Emerging evidence demonstrates an important relationship between short sleep, appetite regulation and body mass, and energy metabolism. Short sleep refers to duration of less than 6 h, whereas long sleep refers to more than 9 h on a typical night. Short or long sleep is linked to an increase in body mass index (BMI), demonstrating a U-shaped relationship in children and adolescents (Taheri 2006), and in adults (Fig. 52.6) (Taheri et al. 2004; Chaput et al. 2007). A meta-analysis of cross-sectional data of 30 studies showed a consistent picture of short sleep duration, predicting an increased body mass in adults (Cappuccio et al. 2008), but these findings may not directly translate to longitudinal outcomes. In the Whitehall II study, an association at baseline was found but there was no evidence that sleep duration influenced body mass change over 5 years (Stranges et al. 2008).

Although causality for the U-shaped association has not been proven, there are physiological data implicating a mechanistic link between sleep duration and BMI. For example, in short sleepers (Taheri et al. 2004) and in those who were sleep deprived with only 4 h of sleep per night for two nights (Spiegel et al. 2004), increases in appetite with potential weight gain have been implicated with demonstrable decreases in the appetite suppression hormone, leptin (secreted by adipocytes), and
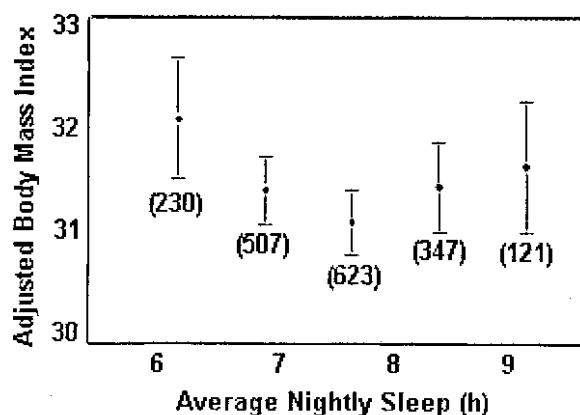
Fig. 52.6 The relationship between BMI and average nightly sleep. Mean BMI and standard errors for 45-min intervals of average nightly sleep after adjustment for age and sex. Average nightly sleep values predicting lowest mean BMI are presented by the central group. Average nightly sleep values outside the lowest and highest intervals are included in those categories. The number of visits is indicated below the standard error bars. Standard errors are adjusted for within subject correlation (Data are from Taheri et al. 2004. With permission from the Publishers)

increases in the appetite-stimulating hormone, ghrelin (secreted by the stomach). Short sleep duration is associated with increased fat intake (Shi et al. 2008). Under conditions of ad libitum food intake, healthy individuals who were sleep restricted (5.5 h for 14 d) favored food of higher CHO content from snacks (65% versus 61%) compared with nonrestricted conditions (8.5 h for 14 days) (Nedeltcheva et al. 2009b). However, there were insignificant differences in serum leptin and ghrelin between the two sleep conditions (Nedeltcheva et al. 2009a). Sleep fragmentation showed a significant, albeit small increase in overnight energy expenditure (Bonnet et al. 1991), arguing against the connection between short sleep and increases in body mass. Nonetheless, a body of evidence showed that sleep restriction alters glucose metabolism by significantly decreasing glucose tolerance (Nedeltcheva et al. 2009a; Spiegel et al. 2004). Further, both short and long sleep times are associated with an increased risk of impaired glucose intolerance and type 2 diabetes (Chaput et al. 2007). Thus, it appears that sleeping less than the optimal amount needed for an individual holds a link to increased body mass and impaired glucose metabolism. However, its causal relationship to increased weight gain and risk of obesity or diabetes remains to be further explored. Certain predisposing conditions such as an increased opportunity to eat, food availability and selection, and physical inactivity may be additive effects that potentiate weight gain and obesity (Fig. 52.7), as suggested by Taheri (2006).

In contrast to human findings, the laboratory rat exhibits characteristic behavior of hyperphagia and demonstrable weight loss following sleep deprivation, in particular PS deprivation. Many studies performed PS deprivation by taking advantage of muscle atonia that characteristically occurs during this sleep stage in a classic flower pot or platform technique (Martins et al. 2006). The experimental rat is placed on a platform (6.5–7 cm in diameter) surrounded by water in a container. When muscle atonia occurs, the rat touches or makes facial contact with or falls into the water, and wakes up. Food ingestion in sleep-deprived animals shows variable patterns. In the acute 24 h of PS deprivation, both reduction (Martins et al. 2008; Hanlon et al. 2005) and increases (Suchecki et al. 2003) have been reported, whereas an early study described no change in overall food intake, although there was a reduction in meal size that was compensated by an increase in meal frequency during the period of sleep deprivation (Elomaa 1981). After 4–5 days of PS deprivation, increased free-feeding behavior
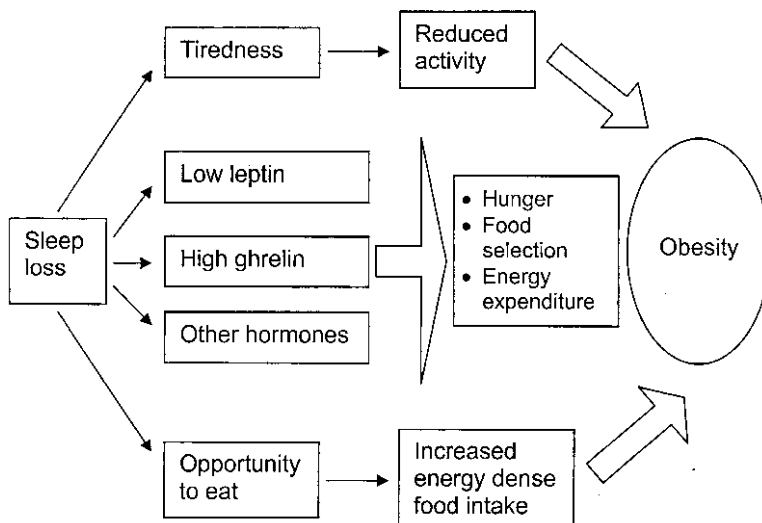
Fig. 52.7 The potential mechanisms through which short sleep duration could result in obesity. Short sleep duration can affect both energy intake and energy expenditure. It results in tiredness that may hamper physical activity, and alters metabolic hormones to increase appetite and affect food selection. Additionally, extra time awake provides increased opportunity for food intake. Other potential mechanisms include effects of sleep on basal metabolic rate, thermic effect of food, and nonexercise activity thermogenesis (Data are from Taheri 2006. With permission from the Publishers)

was consistently observed (Bergmann et al. 1989; Hanlon et al. 2005). In addition, a universal finding in the rat, following sleep deprivation, was the negative energy balance that was explained by increased energy expenditure (Elomaa 1981; Suchecki et al. 2003; Hanlon et al. 2005; Martins et al. 2008; Galvao Mde et al. 2009) and activation of brown fat thermogenesis (Koban and Swinson 2005). In sleep-deprived rats, increased energy metabolism was evidenced by an increased nonspecific motor activity such as eating, drinking, climbing (Suchecki et al. 2002), and gnawing (Martins et al. 2008).

Uniquely, sleep restriction induces a preference for CHO-rich foods in humans (Nedeltcheva et al. 2009b; Spiegel et al. 2004) and in rats (Bhanot et al. 1989; Suchecki et al. 2003). Shift workers who remain awake for periods up to 24 h demonstrate an increased CHO craving (Wurtman and Wurtman 1995). Sleep deprivation is a form of stress, which may mediate changes in appetitive behavior. Healthy females under experimentally induced stress responded with greater food consumption and preference for more sweet food, and these subjects showed high levels of cortisol (Epel et al. 2001). The appetitive behavior may represent a coping strategy for stress, since a high CHO diet decreases cortisol level and alleviates feelings of depression in humans (Markus et al. 2000). Indeed, following sleep deprivation, increased stress corresponds with an increased sympathetic and hypothalamic–pituitary–adrenal (HPA) axis activity (Fadda and Fratta 1997; Suchecki et al. 1998), increased level of cortisol (Galvao Mde et al. 2009; Spiegel et al. 1999) and adrenocorticotropic hormone (Galvao Mde et al. 2009; Suchecki et al. 2003).

52.5 Food Deprivation, Sleep Deprivation, and Brain Glycogen

SWS is increased with food deprivation (acute fasting of 3–4 days). Its appearance may be metabolically beneficial in that brain glycogen accumulation occurs during sleep, whereas it is mobilized on waking (reviewed comprehensively in (Brown 2004)). Brown cited that depletion of glycogen of 40% occurred after sleep deprivation for 12–24 h and complete repletion took place after recovery sleep. Upon SWS initiation, brain glycogen content increased by 70% above waking levels. Although brain glycogen store is low (0.5–1.5 g, 0.1% of total brain weight) relative to the well-fed liver (100 g, 6–8% of the weight of the liver) and skeletal muscle (400 g, 1–2% of the weight of skeletal muscle), its accumulation following sleep deprivation was a slow process and reached its baseline level only after 9 h of recovery sleep. More rapid repletion has been observed. Whilst these data were based on rat studies, nuclear magnetic resonance detection of ^{13}C glucose labeling of glycogen in human brain has been obtained. Sleep deprivation in humans and rats stimulates an increase in food intake with particular preference for CHO and energy dense foods (see earlier section). Thus, elevated blood glucose increases insulin release and facilitates brain glucose uptake via insulin-insensitive GLUT1 and insulin-sensitive GLUT4 glucose transporters and glycogen storage (Brown 2004). A synthesis of these findings proposes that (1) food and sleep deprivation leads to a state of brain glycogen deficit and (2) recovery SWS and the appetitive behavior (preference for carbohydrate intake) function to replete glycogen in both conditions as depicted in Fig. 52.8.

52.5.1 Application to Health and Disease

Altered feeding and sleeping behaviors are common amongst dieters, shift workers, and those leading a busy life style. Both the meal timing and its macronutrients have direct impact on sleep, while sleeping less than an individual's requirement stimulates appetite and influences food choices. Short sleep is
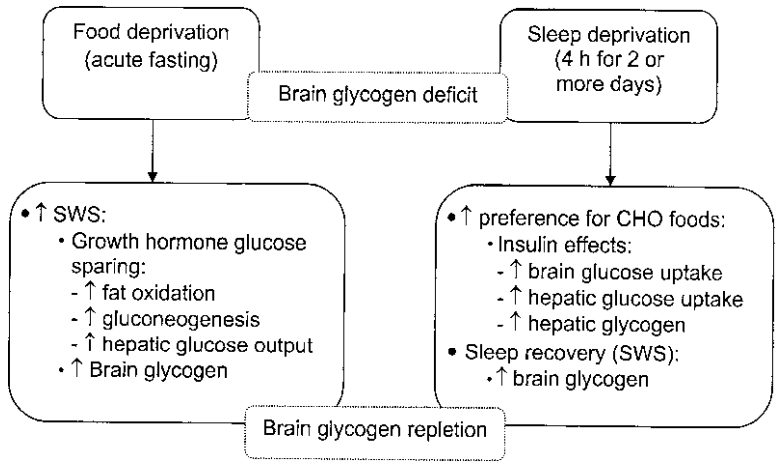
Fig. 52.8 Proposed relationship between food deprivation, sleep deprivation, and brain glycogen stores. Brain glycogen deficit occurs following either food or sleep deprivation. Acute fasting of several days promotes an increase in SWS. Sleep deprivation (sleeping a maximum 4 h per night) for 2 or more days increases preference for CHO foods and is followed by sleep recovery with increases in SWS. This appetitive behavior and increased SWS in both conditions function to replete glycogen stores. *SWS* slow wave sleep, *CHO* carbohydrates

Table 52.1 Key factors for managing sleep. This table reflects the key factors used in the management of sleep difficulties. CHO: carbohydrate difficulties

1. Practice sleep hygiene
   - Follow a regular sleep and wake time 7 days a week
   - Sleep in a quiet, dark, and cool environment
   - Avoid excessive caffeine, nicotine, and alcohol prior to bedtime
   - Avoid daytime napping, except in circumstances such a shift work or certain sleep disorders when napping can be beneficial
2. Macronutrients
   - Use natural foods rich in tryptophan (milk, yoghurt, cheese, soybean, sesame seeds, spinach, or turkey) in combination with CHO-based meals
   - Use moderately high GI CHO for evening meals. Use low GI foods for daytime meals to sustain energy
   - Keep evening meal 3–4 h before usual bedtime
   - Use a light CHO snack at bedtime if needed
3. Exercise
   - Exercise 20–40 min 3–4 times per week at least 5–6 h before usual bedtime
   - Avoid strenuous exercise closer to bedtime
4. Seek professional guidance
   - Consult general practitioner or sleep specialist if sleep difficulties continue

associated with poor health outcomes and is becoming the norm, as healthy people self-select to sleep less adding to those who have sleeping difficulties due to shift work, insomnia, depression, the normal aging process, sleep disorders, underlying pathology, the effects of medications, or being menopausal. Thus, the use of macronutrients as an adjunct to exercise may have health and sleep benefits when practiced several hours before the usual bedtime and in coordination with the appropriate sleep hygiene practices (described in Table 52.1). For example, an evening meal that consists of moderately high GI foods may promote sleep onset for those with difficulty sleeping. Meanwhile, low GI foods are recommended for daytime meals and especially for those who are overweight, obese, or with diabetes.

Macronutrients may also be used to an advantage for managing sleep difficulties in shift workers and those with insomnia and depression. Sleep initiation and duration may improve by using

moderately high GI foods after their night shift (or when sleep is planned). Given that the efficacy of high GI foods on sleep is founded on tryptophan, natural foods rich in tryptophan (milk, yoghurt, spinach) are particularly suitable in combination with a CHO-based meal. Choosing a light meal low in GI with a portion of protein during the shift (or when alertness is desired) may circumvent post-prandial sleepiness and lethargy as sleep propensity increases. Similarly, avoiding high fat and large meals prior to or during a night shift may reduce postprandial sleepiness.

Summary Points

- Food ingestion has a direct influence on sleep through its macronutrients, largely carbohydrate and fat.
- Carbohydrates, in particular those with a high glycemic index, shorten sleep onset by increasing tryptophan availability to the brain.
- High-fat meals promote sleep through cholescystokinin released by the small intestine.
- Postprandial sleepiness, following a lunch meal, depends on the thermic effects of food and coincides with the circadian phenomenon of postlunch dip.
- Increased prior wakefulness or sleep deprivation intensifies postprandial sleepiness.
- Under-feeding alters sleep patterns: in many species, acute fasting of 3–4 days increases SWS with variable REMS, whereas chronic fasting decreases SWS and REMS with paralleled increased wakefulness.
- The sleep changes associated with fasting may be linked to changes in the fuel stores of protein and fat. The two extreme conditions of a feeding continuum, anorexia nervosa, and obesity show marked sleep disturbances.
- SWS, occupying 20% of total sleep time, is time-locked to growth hormone release and brain glycogen accumulation.
- Greater SWS appearance during fasting may reflect brain glucose sparing effects via fat mobilization mediated through the action of growth hormone.
- SWS diminishes as lipid stores become depleted in chronic fasting.
- Sleep duration affects appetitive behavior: in humans short sleep stimulates an increased appetite and risk of weight gain, although causality has not been established for the association between short sleep and BMI.
- In rats, short sleep stimulates hyperphagia and weight loss that may be explained by brown adipose tissue thermogenesis.

Definitions

Light–dark cycle: Alternating period of light and dark over 24 h
Circadian rhythm: Endogenous 24 h rhythms of behavior and physiological function (e.g. core body temperature, sleep–wake) linked to the light–dark cycle
Glycemic Index: A number scale (0–100) used to rank carbohydrates on their ability to increase blood glucose levels compared to an equal amount of pure glucose (GI = 100). High GI foods (GI ≥ 70) promote a greater surge in blood glucose compared to moderate or low GI foods (GI ≤ 55)
Cholecystokinin: A neuropeptide released by the duodenum of the small intestine, in response to fatty acids and protein chyme from the stomach
Postprandial: Following a meal

Thermogenesis: The production of heat

Postlunch dip: A naturally occurring, daily period of increased fatigue or lethargy usually present between 1400 and 1600 h

MSLT: An EEG test of daytime sleepiness consisting of four nap opportunities at 2-h intervals

Akerstedt EEG Test: An EEG test consisting of a static 5 min period with eyes open in which the EEG is analyzed by spectral power analysis

Stage 1 (sleep): A state of drowsiness marked by a decrease in the EEG alpha rhythm, and low voltage mixed frequency waves

Stage 2 (sleep): Commonly used to identify the onset of sleep, this sleep stage is characterized by specific morphology in the EEG; namely the sleep spindle (12–14 Hz EEG burst) and the k-complex (sharp negative–positive deflection)

Stage 3 (sleep): A state of deep sleep characterized by high-voltage, low-frequency (0.5–3.9 Hz) EEG waves accompanied with a low threshold in skeletal muscle tone

Slow wave sleep: A term used to identify deep sleep (Stage 3 sleep)

Rapid eye movement sleep: A period of sleep characterized by low voltage mixed frequency waves, bursts of rapid eye movements or quiescence, and associated with skeletal muscle atonia

Nonrapid eye movement sleep: A term used to group sleep stages 1, 2, and 3

Gluconeogenesis: Formation of glucose from noncarbohydrate sources

Paradoxical sleep: Equivalent to rapid eye movement sleep; used to describe the period of sleep in animals characterized by muscle atonia and low-voltage, mixed-frequency EEG

References

Afaghi A, O'Connor H, Chow CM. Am J Clin Nutr. 2007; 85:426–30.

Afaghi A, O'Connor H, Chow CM. Nutr Neurosci. 2008; 11:146–54.

Bergmann BM, Everson CA, Kushida CA, Fang VS, Leitch CA, Schoeller DA, et al. Sleep. 1989; 12:31–41.

Bermudez FF, Forbes JM, Injidi MH. J Physiol. 1983; 337:19–27.

Bhanot JL, Chhina GS, Singh B, Sachdeva U, Kumar VM. Indian J Physiol Pharmacol. 1989; 33:139–45.

Blum I, Vered Y, Graff E, Grosskopf R, Don R, Harsat A, et al. Metabolis. 1992; 41:137–40.

Bonnet MH, Berry RB, Arand DL. J Appl Physiol. 1991; 71:1112–8.

Borbely AA. Arch Ital Biol. 139:53–61.

Brezinova V, Oswald I. Brit Med J. 1972; 2:431–3.

Brown AM. J Neurochem. 2004; 89:537–52.

Cappuccio FP, Taggart FM, Kandala NB, Currie A, Peile E, Stranges S, et al. Sleep. 2008; 31:619–26.

Chaput JP, Despres JP, Bouchard C, Tremblay A. Diabetologia. 2007; 50:2298–304.

Chen CN, Kalucy RS, Hartmann MK, Lacey JH, Crisp AH, Bailey JE, et al. Brit Med J. 1974; 4:564–6.

Craig A, Richardson E. Int Arch Occ Env Hea. 1989; 61:313–9.

Danguir J, Nicolaidis S. Physiol Behav. 1979; 22:735–40.

Dewasmes G, Buchet C, Geloen A, Le Maho Y. Am J Physiol. 1989; 256:R476–80.

Dewasmes G, Cohen-Adad F, Koubi H, Le Maho Y. Am J Physiol. 1984; 247:R663–71.

Dixon JB, Schachter LM, O'Brien PE. Int J Obesity. 2005; 29:1048–54.

Elomaa E. Physiol Behav. 1981; 26:487–93.

Epel E, Lapidus R, McEwen B, Brownell K. Psychoneuroendocrino. 2001; 26:37–49.

Fadda P, Fratta W. Pharmacol Res. 1997; 35:443–6.

Fara JW, Rubinstein EH, Sonnenschein RR. Science. 1969; 166:110–1.

Fujiki N, Yoshida Y, Ripley B, Honda K, Mignot E, Nishino S. Neuroreport. 12:993–97.

Galvao Mde O, Sinigaglia-Coimbra R, Kawakami SE, Tufik S, Suchecki D. Psychoneuroendocrinol. 2009; 34:1176–83.

Guesdon B, Minet-Ringet J, Tome DG, Even PC. Behav Brain Res. 2005; 164:156–64.

Hanlon EC, Andrzejewski ME, Harder BK, Kelley AE, Benca RM. Behav Brain Res. 2005; 163:58–69.

Harnish M, Greenleaf S, Orr W. Physiol Behav. 1998; 64:93–6.

Heiss WD, Pawlik G, Herholz K, Wagner R, Wienhard K. Brain Res. 1985; 327:362–6.

Karacan I, Rosenbloom AL, Londono JH, Salis PJ, Thornby JI, Williams RL. Psychosomatics. 1973; 14:33–7.

Karklin A, Driver HS, Buffenstein R. Am J Clin Nutr. 1994; 59:346–50.

Koban M, Swinson KL. Am J Phsyiol-Endoc M. 2005; 289:E68–74.

Kovac J, Husse J, Oster H. Mol Cells. 2009; 28:75–80.

Krauchi K, Cajochen C, Werth E, Wirz-Justice A. J Biol Rhythm. 2002; 17:364–76.

Kwan RM, Thomas S, Mir MA. J Nutr. 1986; 116:2393–402.

Lacey J, Stanley P, Hartman M, Koval J, Crisp A. Electroen Clin Neuro. 1977; 44:275–80.

Lacey JH, Crisp AH, Kalucy RS, Hartmann MK, Chien CN. Brit Med J. 1975; 4:556–8.

Leathwood P, Pollet P. J Psychiatr Res. 1983; 17:147–54.

Lloyd HM, Green MW, Rogers PJ. Physiol Behav. 1994; 56:51–7.

Lloyd HM, Rogers PJ, Hedderley DH. Appetite. 1996; 27:151–64.

Lyons PM, Truswell AS. Am J Clin Nutr. 1988; 47:433–9.

MacFadyen U, Oswald I, lewis SA. J Appl Physiol. 1973; 35:391–4.

Markus R, Panhuysen G, Tuiten A, Koppeschaar H. Physiol Behav. 2000; 70:333–42.

Martins PJ, D'Almeida V, Nobrega JN, Tufik S. Sleep. 2006; 29:1233–8.

Martins PJ, Nobrega JN, Tufik S, D'Almeida V. Physiol Behav. 2008; 93:229–34.

Minet-Ringuet J, Le Ruyet PM, Tome D, Even PC. Behav Brain Res. 2004; 152:335–40.

Monk TH. Clin Sport Med. 2005; 24:e15–23.

Murray BE, Clarke KA, Rumsey RDE. Pro Nutr Soc. 1993; 52:359A.

Nedeltcheva AV, Kessler L, Imperial J, Penev PD. J Clin Endocr Metab. 2009a; 94:3242–50.

Nedeltcheva AV, Kilkus JM, Imperial J, Kasza K, Schoeller DA, Penev PD. Am J Clin Nutr. 2009b; 89:126–33.

Nishino S, Ripley B, Overeem S, Lammers GJ, Mignot E. Lancet. 2000; 355:39–40.

Orr WC, Shadid G, Harnish MJ, Elsenbruch S. Physiol Behav. 1997; 62:709–12.

Phillips F, Chen CN, Crisp AH, Koval J, McGuinness B, Kalucy RS, et al. Lancet. 1975; 2:723–5.

Porter J, Horne J. Electroen Clin Neuro. 1981; 51:426–33.

Rashotte ME, Pastukhov IF, Poliakov EL, Henderson RP. Am J Physiol. 1998; 275:R1690–702.

Robertson MD, Henderson RA, Vist GE, Rumsey RDE. Am J Clin Nutr. 2002; 75:505–10.

Sassin JF, Parker DC, Mace JW, Gotlin RW, Johnson LC, Rossman LG. Science. 1969; 165:513.

Schwartz GJ, McHugh PR, Moran TH. Am J Physiol; 1993; 265:R872–6.

Shi Z, McEvoy M, Luu J, Attia J. Int J Obes (Lond). 2008; 32:1835–40.

Smith A, Leekam S, Ralph A, McNeill G. Appetite. 1988; 10:195–203.

Smith A, Ralph A, McNeill G. Appetite. 1991; 16:85–91.

Spiegel K, Leproult R, Van Cauter E. Lancet. 1999; 345:1435–9.

Spiegel K, Tasali E, Penev P, Van Cauter E. Ann Intern Med. 2004; 141:846–50.

Spring B, Maller O, Wurtman J, Digman L, Cozolino L. J Psychiatr Res. 1982/1983; 17:155–67.

Stranges S, Cappuccio FP, Kandala NB, Miller MA, Taggart FM, Kumari M, et al. Am J Epidemiol. 2008; 167:321–9.

Suchecki D, Antunes J, Tufik S. J Neuroendocrinol. 2003; 15:815–21.

Suchecki D, Lobo LL, Hipolide DC, Tufik S. J Sleep Res. 1998; 7:276–81.

Suchecki D, Tiba PA, Tufik S. J Neuroendocrinol. 2002; 14:549–54.

Taheri S. Arch Dis Child. 2006; 91:881–4.

Taheri S, Lin L, Austin D, Young T, Mignot E. PLoS Medicine. 2004; 1:e62.

Wells AS, Read NW. Physiol Behav. 1996; 59:1069–79.

Wells AS, Read NW, Craig A. Brit J Nutr. 1995; 74:115–23.

Wells AS, Read NW, Idzikowski C, Jones J. J Appl Physiol. 1998; 84:507–15.

Wurtman RJ. Clin Neuropharmacol. 1988; 11(Suppl 1):S187–93.

Wurtman RJ, Wurtman JJ. Obes Res. 1995; 3(suppl):477s–80s.

Zammit GK, Kolevzon A, Fauci M, Shindledecker R, Ackerman S. Sleep. 1995; 18:229–31.

Chapter 53
Healthy Choices? The Implications of Direct and Indirect Stimuli for Product Perception and Food Consumption

Vivianne H.M. Visschers and Thomas A. Brunner

Abbreviation

FOP   Front-of-package label

53.1 Introduction

Consumers are exposed to many environmental stimuli as they make their daily food choices. External stimuli can influence their food choice and, ultimately, their diet and health. For example, many people take the price of food products into account when deciding what to eat. Others may be affected by what people around them eat, even though they are not aware of this influence.

External stimuli are defined in this chapter as all cues in the environment or context that may affect people's food consumption. We divide them in direct and indirect stimuli. *Direct stimuli* are those that are meant to help people to make an informed food choice, e.g., a nutrition table helps consumers to determine the healthfulness of a food product. People will consciously notice this type of stimulus as being relevant to their product perception and food choice.

On the other hand, people are unaware that they use *indirect stimuli* in their food choices. Although they may observe these types of stimuli and their outcomes, the influence of the stimulus itself on their food perception, choice, or consumption goes unnoticed. For example, people appear to eat more when they eat in a group, simply because more people around the table make the meal last longer than when eating alone (Pliner et al. 2006). People then have a longer opportunity to eat, although they do not notice this happening.

We rely on Bargh's (1990) description of *unconscious processing* in our explanation of how direct and indirect stimuli influence food perception, choice, and consumption. In his auto-motive model of unconscious motivations, Bargh proposed that stimuli from the environment can automatically trigger decisions through experience. He suggested that people do not need a conscious intent to start a behavior; indeed, they may not even be able to access this intent or motive. Some scholars assume that unconscious or automatic processes primarily determine behavior, and that in the case of food choice, people scarcely notice how environmental stimuli affect their food consumption (e.g., Dijksterhuis et al. 2005). Based on this assumption, we can also argue that people do not always process direct

———————————————
V.H.M. Visschers (✉)
ETH Zurich, Institute for Environmental Decisions, Consumer Behavior,
Universitaetstrasse 22 CHN J75.2, 8092 Zurich, Switzerland
e-mail: vvisschers@ethz.ch

information consciously. In other words, consumers may not be aware of the decision process; i.e., how they process the direct information in their minds, or how they come to a decision or behavior. An example would be someone who reads a magazine article about vitamins in fruit. Reading is, of course, a relatively *conscious process*. This person then makes his weekly grocery list, but now lists more fruits than he would usually do, although he did not consciously make a decision to eat more fruit.

In this chapter, we will discuss how direct and indirect stimuli can affect people's food consumption and other related factors, such as their perception of food. First, we discuss how direct stimuli related to food products can influence consumers. These stimuli are presented on and around food products and are intended to inform consumers; examples would be nutrition tables or nutrition claims. Second, we examine how indirect stimuli can affect people's food consumption. More specifically, we examine how stimuli that are present in the food environment can determine how much people eat. The relationship between these two types of stimuli is then discussed. Last, we suggest possible applications of our findings to other areas of health and disease.

53.2 Direct Stimuli

In the following section, *nutrition information* on food products is taken as an important example of direct information, because nutrition information is intended to act as a decision aid to help consumers make healthy food choices. Because of the complexity of nutrition information, such as nutrition tables, its full understanding often requires extensive cognitive elaboration. Other examples of direct stimuli related to food are advertisements around foods, and information in the media or from the social environment.

Many food products present nutrition information in the form of a table or a claim on their package. Nutrition tables include the amounts of energy and of at least three nutrients (i.e., protein, carbohydrate, and fat) per 100 g or milliliters in a product. Several studies have indicated that people pay little attention overall to this type of information, although they often say they do (see Higginson et al. 2002; Cowburn and Stockley 2005 for an overview). A recent study showed a more refined finding; namely, that visual attention to nutrition information depends on people's motivation and the product's design (Visschers et al. 2010, see Fig. 53.1). This implies that nutrition information should be conspicuously and attractively designed, as well as being easily understandable.

53.2.1 Direct Information as Reference

Although a number of previous studies examined the effect of different presentation formats of nutrition information on food products on their use and understanding, these studies did not provide clear results about effectiveness of this information itself on understanding (e.g., Feunekes et al. 2008; Geiger et al. 1991; Lewis and Yetley 1992; Van Kleef et al. 2007). Other studies in consumer psychology showed that when people evaluate a product, the presence of *reference information* and the type of reference information seem to affect their evaluation of this product (i.e., the evaluability principle, Hsee 1996).

For example, people were asked to compare two products on two attributes. One was easy to evaluate (e.g., the degree of under- or overfilling of an ice cream cup), while the other was more difficult to evaluate on its own, but was more important for product perception (e.g., the size of the ice cream cup). When people received information about the two attributes, based on only one product,

Product x Type of Motivation
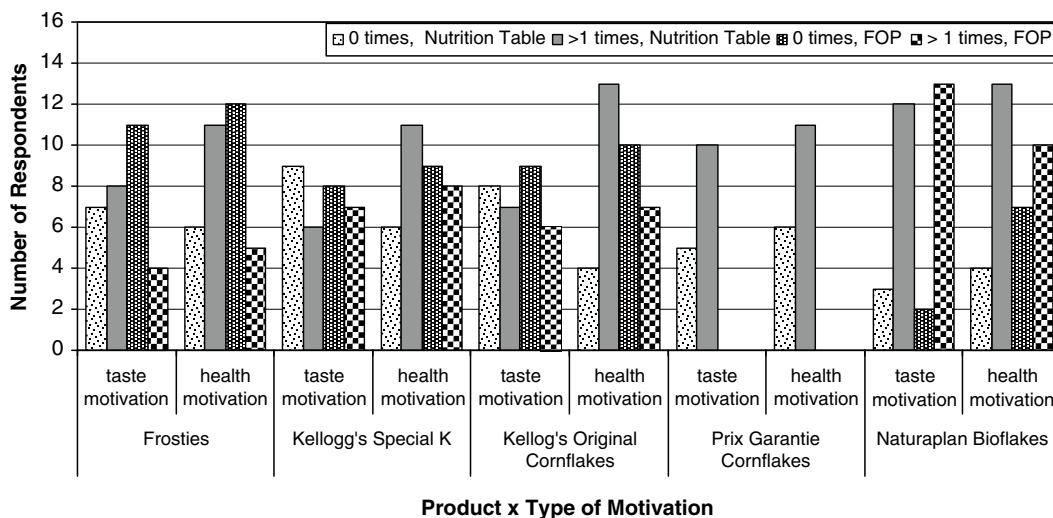
Fig. 53.1 Effect of type of motivation on respondents' attention to nutrition tables, and front-of-package labels on different products. This bar graph presents the number of respondents that looked at least once at the nutrition table or front-of-package label (*FOP*) (Visschers et al. 2010, with permission from the authors). The frequency numbers are presented per product and per type of motivation. Half of the 32 respondents were motivated to choose a healthy product and the other half were motivated to look for a tasteful product. While they were doing this, their visual attention was recorded by an eye tracker, an instrument to measure people's eye movements. The results presented in this bar graph show that the majority of the respondents paid attention to the nutrition table on each product. This did not differ between the two types of motivation or the products (χ^2s < 6.23, ps > 0.18). The type of product did influence whether people noticed the FOP on the five products ($\chi^2(3) = 13.05$, $p = 0.005$); most respondents noticed the FOP on the Naturaplan Bioflakes but most respondents did not notice the FOP on the other products. Note that the package of Prix Garantie Cornflakes did not present an FOP

they evaluated the product on the easy-to-evaluate attribute and neglected the hard-to-evaluate attribute (Hsee 1996, 1998). As a result, they valued a small cup of ice cream that was overfilled more highly than a larger, underfilled cup containing more ice cream. When they could evaluate the two ice creams on both attributes, they compared the products on the hard-to-evaluate attribute so that this attribute determined their evaluation. Now they preferred the larger, underfilled ice cup containing more ice cream.

Thus, to use the hard-to-evaluate attribute, a comparison with another product was needed: the content of the underfilled cup was related to the content of overfilled cup. People make better choices when they can refer the values of an attribute that lacks clear boundaries to those of another product. In line with this finding, reference information related to nutritional value may help people choosing healthy food products.

Examples of reference information in nutrition tables could be the average level of fat in similar products or the average number of kilocalories in a healthy alternative of this type of food. Four studies by Viswanathan and Hastak (2002) tested reference stimuli presented either as the *average amount* of a nutrient in the product category (i.e., in all chocolates) or as the *range* of the nutrient in the product category. Adding one of these two reference formats to the standard nutrition table improved respondents' understanding of the product's nutritional value, compared to the percentage daily value information.

Feunekes et al. (2008, Study 1) also indicated the importance of reference information about a product's nutritional value. They examined people's understanding of six different nutrition labels

on food products, e.g., a multiple traffic light, a healthier choice tick, or a health protection factor. The labels indicated the overall nutritional value of the product. Participants least understood, liked, and trusted the Health Protection Factor (i.e., a pictogram in which the healthiness was presented by a number, such as is seen on sunscreen lotions). A possible explanation for this finding may be that the Health Protection Factor did not include any reference information; consumers were not informed about the meaning of the presented number or about its maximum score.

In another experiment, various nutrition tables, which differed on reference information, were examined using a hedonic product and a product with a healthy image: chocolate and yogurt (Study 1, Visschers and Siegrist 2009). Respondents received one of six nutrition tables and rated the presented product on its attractiveness and perceived healthiness. Except for the standard nutrition table, all other five tables included reference information, such as a nutrition table with a bar that presented the summarized nutrition quality of the product together with the average nutrition quality of the product category (see Fig. 53.2). The findings indicated that reference information in the nutrition tables affected participants' product perception. The respondents evaluated the chocolate presented in the nutrition table with reference information as less attractive than when it was presented with the standard nutrition table (see Fig. 53.3). Thus, people's perception of the chocolate seemed to be more in line with its actual nutritional value after seeing the reference information than it was after reading the standard information.

Nutrition tables with or without reference information did not affect the product perception of the healthy-image product (i.e., the yogurt) in this study. The authors suggested that this was due to the high nutritional value of the presented yogurt so that reference information could not increase respondents' healthiness perception. Visschers and Siegrist (2009) therefore conducted a second study with a similar design, but which presented a low-nutritional value yogurt and a high-nutritional value yogurt. This time, reference information in nutrition tables appeared to affect people's healthiness perception of a product with a healthy image, if it had a low nutritional value (see Fig. 53.4). Moreover, this effect was influenced by people's nutrition–health awareness. The reference information did not change either the product's attractiveness or the product perception of the high-nutritional yogurt.

In sum, the effect of nutrition tables with reference information on product perception appears to depend on two conditions (Visschers and Siegrist 2009). First, the nutritional value of the product-at-hand determines whether reference information can change people's perception of the product. Nutrition tables with reference information can change consumers' perception of food products with

Fig. 53.2 The NDI plus product category nutrition table. In this nutrition table, the NDI score of a chocolate is compared to the average NDI score of all chocolates. The table is an example of one of the six tables presented to participants in Visschers and Siegrist (2009, Study 1) (Reprinted from Appetite. 52: 505–512. Copyright (2009), with permission from Elsevier)

Nutrition Information BonChoc		
	100 g contain ca.	**1 Bar (= 29 g) contains ca.**
Energy	2284 kJ / 546 kcal	662 kJ / 158 kcal
Fat	32g	9.3g
Saturated fat	19g	5.5g
Carbohydrate	60g	17.4g
Sugar	55g	15.9g
Fiber	2g	0.6g
Sodium	0.63g	0.18g
Protein	6g	1.7g

Unhealthy / Healthy

BonChoc
Nutritional Value: 0.80

All Sorts of Chocolate
Nutritional Value: 1.36
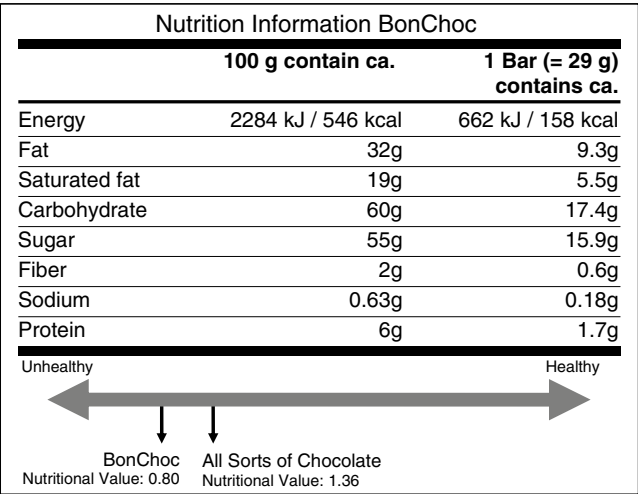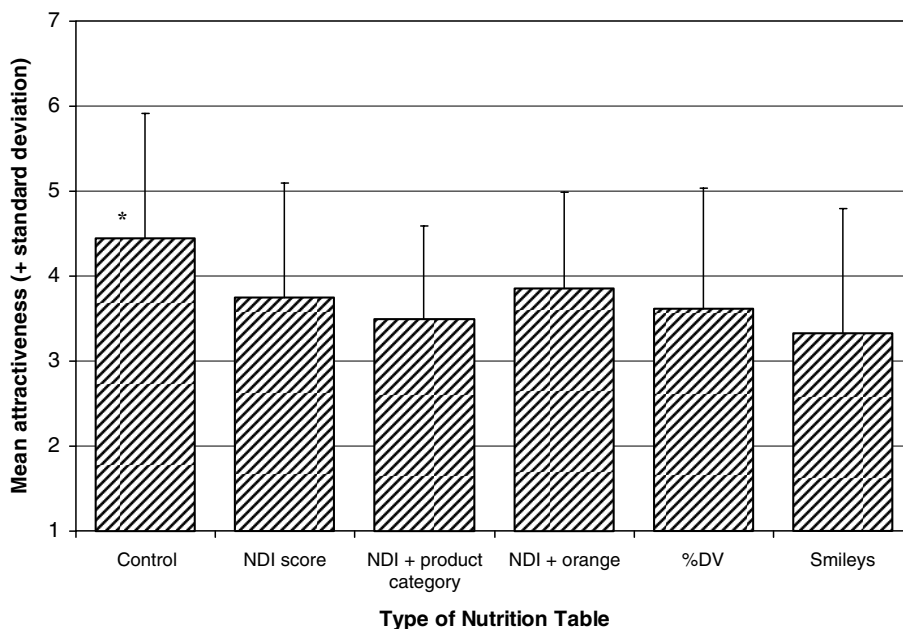
Fig. 53.3 Respondents' mean attractiveness rating for chocolate for each nutrition table.
This bar graph shows respondents' mean attractiveness rating of chocolate after seeing one of six nutrition tables (Study 1, Visschers and Siegrist 2009, with permission from the authors). The respondents who had seen the Control nutrition table (see *) rated the chocolate as more attractive than the respondents who had seen one of the other nutrition tables, $F(5, 143) = 3.97$, $p = .002$. The Control nutrition table was the standard nutrition table, which only included the values of eight nutrients. The NDI Score nutrition table consisted of the nutrition density score (*NDI*) of the product, together with five stars in which the corresponding NDI score was colored black. The NDI plus Product Category nutrition table included alongside the NDI score of the product at hand, the average NDI score of the product category on a bar (Fig. 53.2). The NDI plus Orange nutrition table was a bar with the NDI score of the product and the NDI score of a very healthy product, namely an orange. The percentage daily value (%DV) nutrition table presented the standard table plus the %DV for each nutrient. Last, the Smiley's nutrition table included the standard information plus a positive, negative, or neutral smiley for each nutrient. Except for the Control nutrition table, all other tables included reference information

low nutritional value, compared to the standard nutrition table; whereas these tables do not seem to affect the perception of products with high nutritional value. Second, the type of product that is presented in the nutrition table determines what kind of perception is changed within the individual. Reference information in nutrition tables can only influence the primary association with a product (e.g., chocolate = tasty and yogurt = healthy) and only when this is not in line with the actual nutritional value of the product.

Moreover, direct information should be mentioned very explicitly, such as in graphical comparisons of a food's healthiness to that of other products. For example, in four studies, Raghunathan et al. (2006) showed that if consumers receive only nutritional information about the product-at-hand (similar to the standard nutrition table), information that a product is healthy results in less perceived tastiness than does information that a product is unhealthy. People therefore seem to apply the rule: unhealthy = tasty if they can only evaluate one product. In contrast, when they can compare the same product based on reference information, their tastiness perception is more in agreement with the product's actual nutritional value.

Direct nutrition information was also presented explicitly for comparison in a study about the effect of fat reduction in foods (Visschers and Siegrist in press). Respondents could compare the fat contents of two products presented in nutrition tables and were asked to choose one of two products
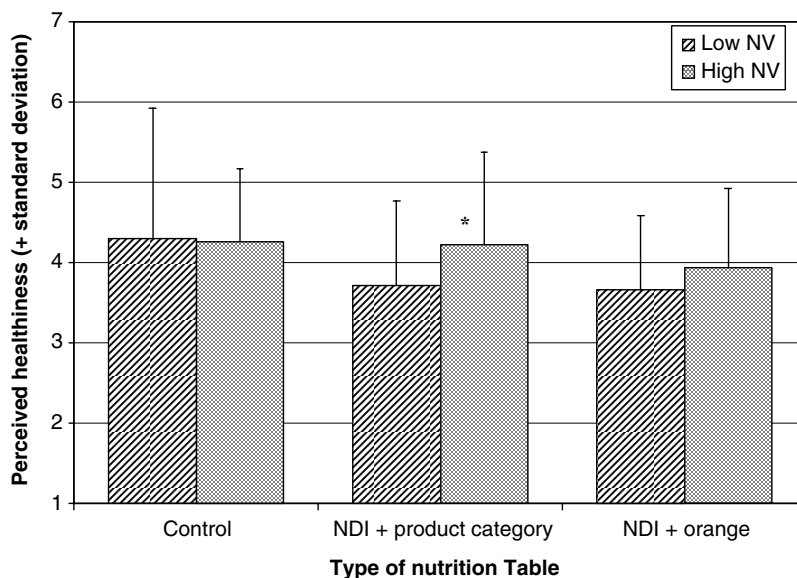
Fig. 53.4 Mean perceived healthiness ratings of low-nutritional value and high-nutritional value yogurts per nutrition table. In this graphic, the mean perceived healthiness of yogurts is presented per nutrition table (Study 2, Visschers and Siegrist 2009, with permission from the authors). Respondents rated the healthiness of either a low-nutritional value (low NV) yogurt or a high-nutritional value (high NV) yogurt, presented with one of three nutrition tables. The three nutrition tables were selected from Study 1 (see Legend to Fig. 53.3 for a description). Results showed that the type of nutrition table affected the perceived healthiness of the yogurts, $F(2, 172) = 3.04$, $p = .05$. Respondents who evaluated the NDI plus Product Category nutrition table rated the low NV yogurt as less healthy than the high NV yogurt, $t(58) = -1.76$, $p = .04$ (see *). The perceived healthiness did not differ between the low-NV yogurt and high-NV yogurts in the Control nutrition table or in the NDI plus Orange table, $-1.09 < ts < .14$, $ps > .28$

or none. The fat content of these two products was reduced in two following steps. Crisps A always contained less fat (reduced-fat product) than Crisps B (full-fat product). At the last step, respondents compared a zero-fat product (Crisps A) with a reduced-fat product (Crisps B). Although most respondents at first favored the reduced-fat product over the full-fat product, after a considerable fat reduction, most preferred the product with some fat over the zero-fat product (see Table 53.1).

Therefore, two standard nutrition tables can also function as references, if they are explicitly presented side-by-side. These direct stimuli can steer people in their food choice. The type of reference offered seems to determine which criterion people use for their choice. If two products appear similarly tasteful, they choose the healthiest product (i.e., reduced fat). If both products are already low in fat, they look for the tastier alternative (i.e., some fat rather than no fat).

53.2.2 Direct Information as Qualitative Translator

Another way in which direct information can influence product perception and food choice is as a translator of quantitative information. For example, health labels on products translate the quantitative information of the nutrition table into a qualitative interpretation. A chocolate bar that contains 546 kcal and 32 g of fat per 100 g, of which 19 g are saturated fat, may be presented with a red traffic light label for fat on its package so that the consumer can easily see that this is not a very healthy product.

Table 53.1 Percentage of respondents choosing Crisps A, Crisps B, or none of the products, at each fat reduction step. In this table, the percentage of respondents that chose Crisps A, Crisps B, or none of the two products is presented per fat reduction step. Crisps A always contained less fat than Crisps B. Crisps A contained almost zero fat at Step 2, and zero fat at Step 3. The random sample of this study contained 80 adults. More respondents chose Crisps A, the reduced fat product, at Step 1. This percentage significantly decreased after a substantial fat reduction: more respondents then chose Crisps B ($\chi^2_F(2) = 15.03$, $p = .001$) (Data are from Visschers and Siegrist in press. With permission from the authors)

Fat reduction step	Choice		
	Crisps A	Crisps B	None
Step 1: 15 vs. 27 g	63.75	10	26.25
Step 2: 1 vs. 23 g	50	25	25
Step 3: 0 vs. 22 g	42.5	31.25	26.25

Table 53.2 Key facts for direct and indirect stimuli related to food consumption. This table presents the key facts of direct and indirect stimuli related to food consumption. The key facts include the presentation, mental processing, functioning, and the kind of effects of direct and indirect stimuli

1. Direct stimuli are information about food products that are intended to influence consumers; for example, through their liking, health perception, or consumption.
2. Consumers can consciously notice direct stimuli and can process them elaboratively, but this need not be the case.
3. Indirect stimuli are not consciously processed by consumers.
4. Indirect stimuli affect consumers' food consumption through priming: indirect stimuli initiate an association that is related to food consumption, e.g., body weight.
5. Direct stimuli first affect people's product perception and food choice before they influence food consumption. Direct stimuli can evoke automatic responses related to food consumption, if they are more familiar.
6. Indirect stimuli can only determine food consumption; that is, they can increase or decrease the consumption volume if one is already eating.
7. Consumers' motivation plays a role in the effects of both direct and indirect stimuli. People should be motivated to pay attention to, and to mentally process, direct stimuli in order for these to affect food perception. People should only be somewhat motivated so that the indirect stimuli can influence their food consumption. The motivation should be related to the indirect stimuli.

A nutrition *claim* that communicates a product's low-fat content seems to affect consumer preference for it. Several studies found that consumers rated products with low-fat claims as less tasty than the same products without this claim or than similar products with more fat (Solheim and Lawless 1996; Kähkönen and Tuorila 1998; Stubenitsky et al. 1999). Solheim and Lawless (1996) asked consumers first to taste a reduced-fat product and to report their taste evaluation. The consumers then saw a low-fat claim, together with this product, while they again tasted the product. Consumers found the taste of the product to be better before seeing the low-fat claim than after. When presented the other way around, when people first estimated the expected pleasantness of a food, only based on a low-fat claim, and then rated the product's pleasantness on its actual taste, they expected a bad taste at first but corrected this rating after tasting the product (Kähkönen and Tuorila 1998). Nutrition claims about fat content thus affect people's taste perception.

Nutrition *labels* can also function as translators of nutrition information, such as the healthy choice label or a front-of-package label. Products with a nutrition label appear to be perceived as healthier than the same products without a label. Feunekes et al. (2008) used various labeling formats to investigate their effects on the perceived healthiness of healthier and less healthy food

products. Respondents had to evaluate the products before and after the labels were presented to them. The presence of the labels primarily increased the perceived healthiness of the healthier products (see Fig. 53.5). A nutrition label on unhealthier products slightly decreased the perceived healthiness, compared to the same products without a label.

Nutrition information formats that include *verbal descriptors* of the nutrition values (e.g., "fat: high, carbohydrates: medium" etc.) seem to increase consumers' understanding of the individual nutrient levels (Levy et al. 1996; see Cowburn and Stockley 2005 for a review; British Market Research Bureau 2009). However, the studies showed varying effects of verbal descriptors on people's health estimates of the products. Verbal descriptors per nutrient in front-of-package labels (FOPs) caused better health estimations of the presented products than did FOPs lacking this information (British Market Research Bureau 2009). In contrast, Levy et al. (1996) examined verbal descriptors for each nutrient in nutrition tables. Participants were asked to make health ratings of products, based on one of various nutrition table formats. The verbal descriptors in the nutrition table resulted in health ratings that differed much more from the products' actual healthiness than other formats, such as the standard nutrition table.
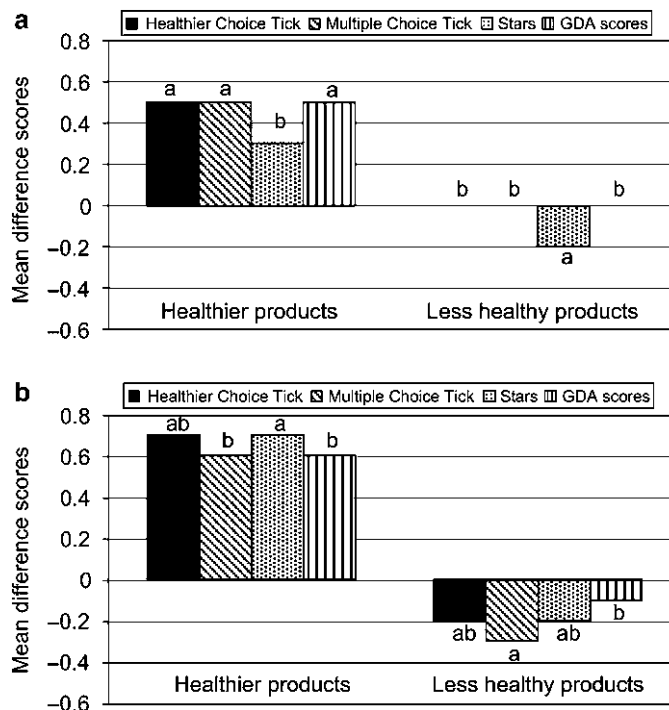
Fig. 53.5 Mean differences in perceived healthiness ratings for healthier and less healthy products per nutrition label, when respondents compared a product pair (**a**), or chose a product from a shopping basket (**b**). These bar graphs present respondents' mean difference in perceived healthiness ratings of healthier and less healthy products before and after doing one of two tasks. Figure 53.5a shows the mean differences in perceived healthiness ratings when respondents had compared two products. Figure 53.5b presents these when respondents had to choose one product from a shopping basket. The products were labeled with one of four nutrition labels: the Healthier Choice Tick, the Multiple Choice Tick, Stars, or the GDA scores (Guideline Daily Amounts). The presence of one of the four labels appeared to increase respondents' perceived healthiness of the healthier products and slightly decreased the perceived healthiness of the less healthy products. Note: Means that do not share letters in the same category differ at $p < .01$. Data are from Feunekes et al. (2008) (Reprinted from Appetite. 50: 57–70. Copyright (2009), with permission from Elsevier)

Overall, various qualitative translators have been investigated. It appears that a general qualitative translator, such as a nutrition label, can influence people's health perception of the product. A fat-reduction claim can change people's taste perception. Similarly, as specific products are primarily associated with specific perceptions, a specific qualifier only appears to affect people's primary association (i.e., with fat). The effects of verbal descriptors per nutrient on healthiness perception do not appear to be very consistent.

53.3 Indirect Stimuli

Much information exists in the food and eating environment that consumers do not directly relate with the food they perceive or consume. These stimuli are processed without awareness and indirectly affect how much people eat. Simply seeing a food product can stimulate consumption (Boon et al. 1998; Painter et al. 2002), making stockpiling a trigger for higher food intake (Chandon and Wansink 2002). Perceived variety is another factor that increases consumption (Rolls et al. 1981), even if the taste of the food items is identical; for example, when food items are colored differently (Khan et al. 2005). The effect of package size (Wansink 1996) and size of portion servings on food intake is well supported (Edelman et al. 1986; Rolls et al. 2007). People will eat more of even a less-favored food if it is offered from a large container compared to a smaller one (Wansink and Kim 2005). Besides package size, the form of packaging and the form of the utensil used for eating also affects consumption volume (Wansink and van Ittersum 2003). For example, people drink more from short and wide glasses than from tall and narrow ones that hold the same volume, as shown in Fig. 53.6.

53.3.1 Seemingly Unrelated Indirect Stimuli

However, there are other factors that are not that closely related with food that also have an influence on how much people consume. Pleasant lighting, decor, or music make the eating experience more comfortable and enjoyable, and therefore lead people to spend more time eating (Lyman 1989; Stevenson et al. 1999; Caldwell and Hibbert 2002). Effort related to food, i.e., the ease of reaching food, access to food, or convenience with which food can be consumed, is one of the strongest influences on consumption (Schachter et al. 1974; Engell et al. 1996; Levitsky 2002; Painter et al. 2002).

Fig. 53.6 An example of short and wide glasses and tall and narrow glasses. People drink more from short and wide glasses (*left*) than from tall and narrow ones

Distracters, such as reading or watching television, can also increase food intake by initiating, obscuring, or extending consumption (Bellisle and Dalix 2001; Wansink and Park 2001). Finally, the number of other people present while eating increases food intake in a linear manner (De Castro and Brewer 1992; Pliner et al. 2006).

Another explanation, besides the longer duration of the meal mentioned in the introduction, for higher food intake when in the company of others comes from the literature on modeling eating behavior. These experiments usually include a naïve participant who eats in the presence of a confederate of the experimenter. The confederate is instructed to eat a lot in half of the sessions and only little in the other half of the sessions. The main conclusion from the research on modeling is that people eat more when their eating companions eat more and people eat less when their eating companions eat less (Nisbett and Storms 1974; Polivy et al. 1979; Rosenthal and Marx 1979; Conger et al. 1980). Individual differences, such as hunger, obesity, dieting, or social desirability, do not affect this companion effect (Rosenthal and Marx 1979; Goldman et al. 1991; Herman and Polivy 2005). To explain why people eat more when accompanied, Herman et al. (2003) suggest that in most eating situations, people unconsciously look at other people for guidance as to how much is appropriate to eat. Thereby, the person who eats the most sets an upper limit for food intake. Of course, the larger the group, the more likely it will include a person who eats a lot.

Another factor influencing how much people eat, without being aware of it, was found by running an extended version of the standard modeling experiment. Johnston (2002) used an ice cream tasting task and instructed a confederate to eat a lot of ice cream in half of the sessions and only little ice cream in the other half of the sessions. Besides varying food intake, the physical appearance of the confederate was varied as well: in half of the sessions, the confederate was of normal weight and in the other half the confederate was obese. With the normal-weight confederate, the well-known modeling effect was found. Participants ate a lot of ice cream when the confederate ate a lot and participants ate only little ice cream when the confederate ate little. However, with the obese confederate, participants ate little ice cream, no matter how much the confederate ate; i.e., the modeling effect was inhibited. It seems that the obese confederate somehow caused participants to reduce their food intake to a minimum.

Recently, Brunner and Siegrist (2009) replicated and extended the study by Johnston (2002). Instead of an obese confederate, they used bathroom scales that they placed in the experimental room in half of the sessions. The confederate in their study was always of normal weight. Participants were instructed to taste and rate chocolate. The authors found that in the sessions with the scales present, participants did not model the confederate's eating behavior; i.e., they ate little, even if the confederate ate a lot of chocolate. Without the scales, the modeling effect could be replicated (see Fig. 53.7). Put another way, relatively unobtrusive scales that were placed a few meters away from the person had a dramatic influence on that person's consumption volume, even if an eating companion was present who set the upper limit of food intake much higher.

In a second study, Brunner and Siegrist (2009) used a verbal statement rather than scales. The experimenter remarked at the beginning of every other session that chocolate makes people fat but also happy. She said this in a rather humorous way, making participants think that it was a joke that was not related to the experiment. The verbal statement exerted the same influence as the scales. Without the statement, participants modeled the behavior of the confederate; whereas, when the statement was given, participants ate little chocolate even if the confederate ate a lot of it (see Fig. 53.8).

Finally in a third study, Brunner and Siegrist (2009) ran an experiment without a confederate. Participants were again invited to take part in a chocolate tasting. Half of them filled in questions about gender, age, size, and particularly weight before the tasting, the other half of participants started directly with the tasting and filled out their demographics and weight at the end of the study. Results showed that merely reminding participants of their weight by letting them declare how much
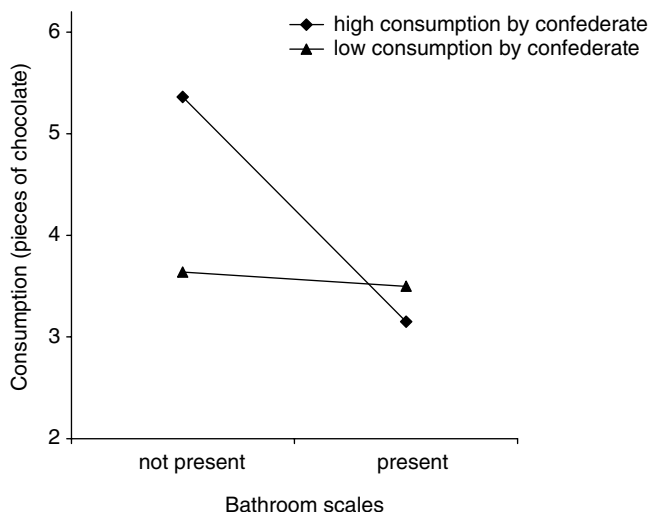
Fig. 53.7 Consumption frequencies of chocolate in the presence or absence of bathroom scales, when the confederate had a high versus a low consumption. This line graph shows the effects of a bathroom scales prime in combination with the consumption behavior of a confederate on people's consumption volume (Study 1, Brunner and Siegrist 2009, with permission from the authors). When the bathroom scales were not present, respondents who were accompanied by a confederate who consumed a lot of chocolate also consumed a lot of chocolate, and they consumed more than respondents who were accompanied by a confederate who consumed a small amount of chocolate. When the bathroom scales were present, the consumption volume of the confederate did not influence the consumption of the respondents; respondents ate a small amount of chocolate, whether the confederate consumed a large amount or a small amount (interaction effect: $F(1, 50) = 4.26$, $p < .05$)
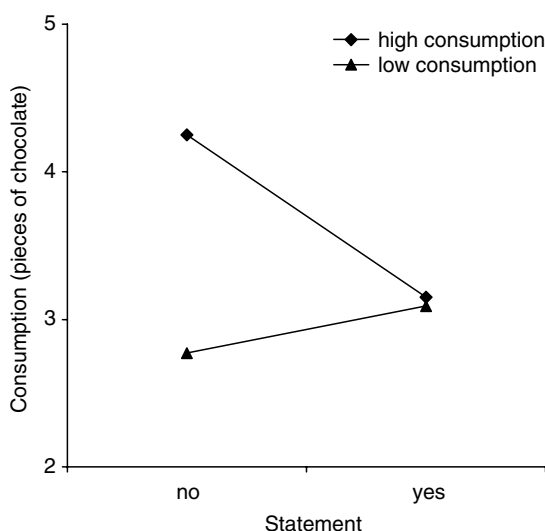
Fig. 53.8 Consumption frequencies of chocolate in the presence or absence of a statement that chocolate makes people fat, when the confederate had a high versus a low consumption. This line graph shows the effects of a remark by the experimenter that chocolate makes people fat, in combination with the consumption behavior of a confederate on people's consumption volume (Study 2, Brunner and Siegrist 2009, with permission from the authors). When the experimenter did not make this remark, respondents who were accompanied by a confederate who consumed a lot of chocolate also consumed a lot of chocolate and more than respondents who were accompanied by a confederate who consumed a small amount of chocolate. When the experimenter made this remark, the consumption volume of the confederate did not influence the consumption of the respondents; respondents ate a small amount of chocolate, whether the confederate consumed a large amount or a small amount (interaction effect: $F(1, 42) = 3.15$, $p < .10$)

they weigh reduced food intake in the following chocolate tasting. In addition, there was an interesting interaction between the *priming* condition and the degree to which participants monitored their body weight. Only for the primed participants, i.e., for participants who declared their weight before tasting the chocolate, was monitoring body weight negatively related with consumption volume. No correlation was found for participants who directly started with the tasting; i.e., it did not matter how strongly they monitored their weight.

It is important to mention that none of the participants was aware of the influence that resulted from the scales, the experimenter's remark, or the declaration of body weight in any of the three studies. Therefore, the three studies show very clearly that eating behavior, and particularly consumption volume, is affected by unobtrusive external information that is processed unconsciously. The factor that was found to influence food intake was a priming of body weight related cognitions. Whenever participants were primed with weight cognitions, they reduced their food intake.

53.3.2 Subliminal Priming

The findings of Brunner and Siegrist (2009) can be related to *subliminal* priming. In experiments using subliminal priming, information is presented just below the normal limits of human perception. These cues are unrecognized by the conscious mind but might affect thoughts and behavior on an unconscious level. In 1957, James Vicary received much media attention by claiming to have significantly increased sales of Coca Cola and popcorn in a movie theatre by subliminally flashing the message "drink Coca Cola" and "eat popcorn" onto the movie screen (Henderson 1957). Vicary himself admitted later on in an interview that his data were not very meaningful – the whole story was a hoax (Danzig 1962). Fifty years later, Vicary's dream partly came true. Subliminally priming thirst resulted in participants drinking more than unprimed participants, but only when participants were thirsty (Strahan et al. 2002). It appeared possible to even prime a specific brand of drink. Subliminally priming "Lipton Ice" increased participants' preference for that brand, but again only for thirsty participants (Karremans et al. 2006; see also Veltkamp et al. 2008).

The question is raised as to why subliminal priming only works for thirsty participants in these studies. Strahan et al. (2002) refer to Higgins' (1996) notion that priming mainly affects behavior in situations in which the intended behavior is applicable. Therefore, priming thirst only results in drinking behavior if participants have the opportunity to drink and if they want to drink because they are thirsty. Hence, priming can only exert its power when people are already motivated to pursue the related goal.

53.3.3 Comparing Subliminal and Supraliminal Priming

The same reasoning that holds for subliminal priming may also hold for *supraliminal* priming (i.e., stimuli above the threshold of human perception), as long as the information is processed without awareness. Most people are motivated, at least to some degree, to monitor their body weight. Therefore, Johnston's (2002) as well as Brunner and Siegrist's (2009) studies show that the behavior of eating less was applicable. Participants had the opportunity to eat, but priming the concept "body weight" increased the motivation to eat little. Brunner and Siegrist's (2009) third study shows very

clearly that two conditions are needed to reduce food intake effectively: both a priming of body weight cognitions and the motivation to monitor body weight. Recall that the degree of monitoring body weight did not influence consumption volume in the unprimed participants. However, primed individuals decreased their consumption volume quite strongly if they were motivated to monitor their body weight.

Brunner and Siegrist (2009) suggested that most people were motivated to some extent to monitor their body weight. Consequently, they found significant results in the other two studies in which they did not directly control for body weight monitoring. Without the motive to monitor body weight, priming alone would hardly be adequate to decrease food intake. From an ethical point of view, this is somewhat of a relief, as it indicates that priming alone will not be sufficient to impose just any behavior upon someone. People need to have at least some degree of motivation before they can be directed toward a specific behavior.

To conclude, there is a good deal of evidence to support the idea that eating behavior – and consumption volume in particular – is heavily affected by external stimuli that are processed without awareness. These indirect cues can be closely related to food, such as portion size, but they can also be more distant, such as lighting or any cue that subconsciously activates cognitions about body weight.

53.4 Discussion

This chapter focused on the influence of direct and indirect stimuli on food perception and consumption. The take-home message might be that indirect and direct stimuli affect consumers under different conditions. Dual process theories of information processing essentially posit that people can process information both elaborately and consciously (also called central, systematic, or analytical processing), as well as intuitively and more automatically (i.e. peripheral, heuristic, or experiential processing, see Petty and Cacioppo 1986; Chaiken et al. 1989; Fazio and Towles-Schwen 1999). Which of these two processing modes is more prominent in a certain situation appears to depend on people's motivation for deliberate processing and their opportunity to do so, such as their available time and cognitive abilities (Fazio and Towles-Schwen 1999). Figure 53.9 shows how indirect and direct stimuli affect food choices, following dual process theories.

As people mostly do not consider indirect stimuli as important for their food choice or consumption, they are not motivated to process these elaborately, but do so rather automatically. If participants in a priming study recognize a cue as a prime, its effect on behavior is lost as they switch to conscious processing (see Bargh and Chartrand 2000). The indirect stimulus should instead be familiar to the observer so that it is automatically associated with the appropriate behavior. Furthermore, unconsciously processed information can only affect behavior that a person has already planned to carry out and that fits the situation. Related to food, a prime can therefore only increase or decrease food consumption or direct a food choice if the person is already in a choice situation. In other words, a prime cannot initiate food consumption without the underlying motivation to do so. Thus, the presence of the scales in the studies by Brunner and Siegrist (2009) could only influence how much of the offered chocolate participants ate. If they had not offered food to the participants, but instead had examined participants' behavior in general after seeing the prime, they probably would not have found any effect of the prime, as people would have had to initiate a new behavior on their own.

Direct stimuli are more likely to be processed deliberately, as consumers generally consider these to represent important information for a food choice and are therefore motivated to understand them.
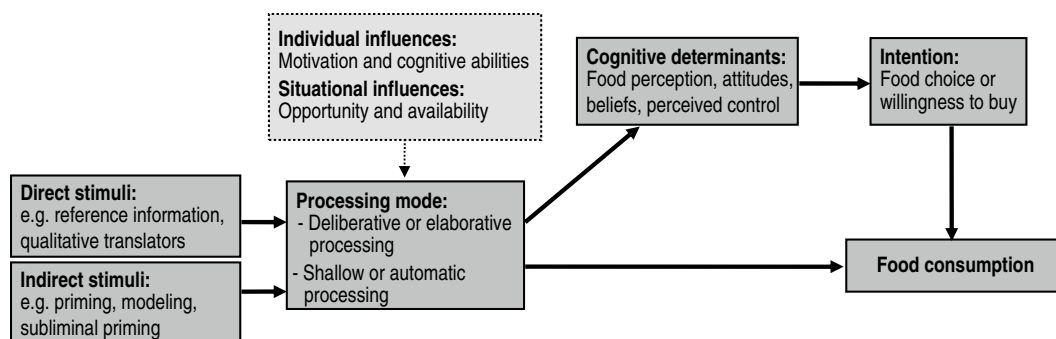
Fig. 53.9 Schematic presentation of the influence of direct and indirect stimuli on food consumption and its prede-termining factors, based on dual process theories. The model presented in this figure explains how direct and indirect stimuli affect people's food perception, choice, and consumption. The processing mode of these two types of informa-tion (i.e., how they are processed) mainly determines the effect of the information on consumers. Processing modes are derived from dual process theories of information processing (see Petty and Cacioppo 1986; Chaiken et al. 1989; Fazio and Towles-Schwen 1999), which posit that people will process information deliberatively if they are motivated, if they have the cognitive abilities, and if given an opportunity to do so, as well as when the necessary information is available; otherwise, they will use shallow or automatic processing. Deliberative processing affects food consumption indirectly; it first influences the cognitive determinants related to the food and then people's intention before they change food consumption. Shallow or automatic processing determines food consumption directly

As a result, direct stimuli can affect not only people's behavior, but also several factors that underlie this behavior, such as the perception of the product or the intention to buy it.

Besides the different ways of processing direct and indirect information, these two types of information may seem dissimilar in two other respects. First, they have different presentation modes; direct stimuli are mostly intended to influence consumers and thus are explicitly presented on the food-at-hand, whereas indirect stimuli are not explicitly indicated to people, as they are mostly not related to the food itself. Second, direct and indirect stimuli differ in the kind of effects they can have on consumers. The studies reviewed in this chapter mainly examined consumers' product perception and product choice, after receiving direct information. The effect of indirect stimuli, on the other hand, was investigated with respect to consumption volume. This latter depen-dent variable could also be measured in studies that examine the influence of direct information on people. However, based on cognitive behavior change theories (e.g., Ajzen 1991), many researchers assume that direct information first has to change people's product perception (i.e., attitude), and the intention to buy this product, before the actual consumption behavior can be altered. It is there-fore commonly accepted to study direct stimuli related to these two predetermining factors of behavior.

Nevertheless, direct information does not always have to be processed consciously. As mentioned in the introduction of this chapter, consumers seem to respond to most external cues (including direct information) automatically (Dijksterhuis et al. 2005). For example, a parent may be inclined to grab the mini chocolate bars that are put up at the checkout because they are presented with a picture of happy children, which reminds him of his children, without considering whether the children even like these chocolate bars. Moreover, previous research has shown that cognitive behavior change theories are not the only predictors of food consumption behavior. Factors that are not included in these models, such as habit strength, sometimes play a greater role in behavior (e.g., De Bruijn et al. 2007). Inclusion of a behavior measure is therefore recommended when investigating the influence of direct stimuli on consumers.

Furthermore, this overview implies that direct and indirect stimuli are not as unrelated as the reviewed studies in this chapter may have suggested. For example, consumers may automatically associate an established health label on food products with a high level of healthiness, so that they will choose to consume a product that is presented with this type of label, without paying attention to the type of product or to the nutrition table. However, some health labels are assigned per product category, e.g., fat-free ice cream and regular ice cream are both snacks – the former can be assigned with a health label, whereas the latter cannot. However, both contain more fat and sugar than a regular yogurt, which cannot be presented with a health label in its category. The health label on a food product may automatically trigger the idea that it is healthy and people might therefore choose this product, without consciously considering the product's actual content. In this situation, direct information is used as a simple decision rule or heuristic, namely "health label implies healthy food."

Our review also showed that for both direct and indirect stimuli, people need to have some kind of motivation so that the stimuli can influence their perception or behavior. Brunner and Siegrist (2009) showed that people who are motivated to monitor their body weight are, to a greater extent, affected by a body weight prime than are those who do not have this motivation. However, too much motivation may hurt the priming effect. The priming of cognitions about body weight probably does not make a difference for people who are consciously and constantly monitoring their body weight. It then results in a ceiling effect and additional priming of this behavior no longer matters. On the other hand, priming alone also does not work. Motivation is necessary, but sometimes is not sufficient to activate behavior. In these cases, priming can prod people into action (see Herman and Polivy 1984).

Motivation also plays a role in the effect of direct stimuli on food perception and choice. In the second study by Visschers and Siegrist (2009), the effect of the various nutrition tables, with and without reference information, was affected by people's nutrition–health awareness. Additionally, in another study, these same authors revealed that people's visual attention to food packages could be directed more at nutrition information if they had a health goal than if they had a hedonic goal in their product choice (Visschers et al. 2010).

To conclude, the influence of direct and indirect stimuli depends on the individual's motivation and the situation. People who are highly health-motivated are interested in health and nutrition information and, consequently, will pay attention to nutrition information that is directly displayed. New or unfamiliar situations and important decisions will also stimulate people to consider the information offered deliberately. Indirect stimuli will mostly affect people when they have a moderate motivation level and the situation does not allow or does not stimulate a deep level of processing of the information and cues that are present. Over time, direct stimuli can function as indirect stimuli, once people are very familiar with them and no longer see the need to contemplate their meaning. The food environment thus includes direct and indirect stimuli, which sometimes initiate healthy choices. Consumers are exposed to a large amount of information when dealing with food; luckily, some of the cues are indirect so that the consumers are not constantly overwhelmed.

53.5 Applications to Other Areas of Health and Disease

The knowledge of how direct and indirect stimuli can influence food perception, choice, and consumption can be very well applied into the field of health communication. Doctors and counselors provide patients with information for making informed decisions; for example, about, a

treatment plan. Much research has investigated how the format and the content of this information can influence patients (i.e., direct stimuli). However, little attention has been paid to investigating, for example, how the communication situation (e.g., the doctor's conversational technique), which may convey indirect information, affects patients' decisions. Patient information leaflets or other developments of medication instructions could be regarded as another application field. Lastly, the findings reported in this review may be interesting in terms of the development of health interventions, especially those that promote healthy eating. Health interventions today are mostly theory- and evidence-based. The information that is communicated to the relevant population and the methods applied in a health campaign could profit from more knowledge of direct and indirect stimuli.

Summary Points

- When people only receive information about two attributes of one product, they base their evaluation on the easier-to-evaluate attribute and neglect the harder-to-evaluate attribute, although the latter may be more important for the evaluation (i.e., evaluability principle).
- People make better product choices or product evaluations when they can directly compare products on relevant characteristics.
- Direct nutrition information mainly changes people's primary association with a food product (e.g., chocolate = tasty).
- Direct nutrition information can only change people's product perception if this perception was not in line with the product's actual nutritional value.
- People can process information in two ways: one is a more deliberate and elaborate process; the other is based on intuition and automaticity.
- External stimuli that are processed without awareness affect human behavior. For eating behavior, these cues can be closely related with food (e.g., salience, package size) or more distant (e.g., music, distracters such as reading).
- In modeling experiments, participants' consumption volume is influenced by a confederate who either eats a lot or only little. The modeling effect has been demonstrated various times and has been regarded as a very robust phenomenon.
- Priming cognitions about "body weight" is strong enough to inhibit the modeling effect. These cognitions reduced food intake of participants, even in the absence of an eating companion. The motivation to monitor body weight is a significant covariate for primed participants.
- Subliminal priming has also been shown to influence eating behavior. Participants drink more when primed with thirst, but only when they are thirsty.
- Priming only works when the resulting behavior is applicable, i.e., there must be an opportunity to show the behavior, and the behavior must be motivated to some extent. The underlying motive is essential (e.g., thirsty participants, participants who are eager to monitor their body weight).
- Supraliminal priming works in the same way as does subliminal priming, as long as the stimuli are processed without awareness. If participants recognize the cue as a prime, its effect on behavior is lost.

> **Definitions of Key Terms**
>
> **Conscious information processing**: Any mental elaboration of information that is under some deliberate control.
>
> **Direct stimuli**: Cues or information that are presented to people with the intention of affecting their perception, choice, or behavior. People can process direct stimuli elaborately, which does not ascertain that they process them fully consciously.
>
> **External information**: All stimuli that are present in the decision context and that may affect people's thoughts and behavior.
>
> **Indirect stimuli**: Cues or information that unconsciously affect people's behavior, although people do not notice them as relevant for their current behavior or do not even consciously perceive them.
>
> **Nutrition information**: Information on and around a food product that informs consumers about the nutritional value of the product.
>
> **Priming**: The influence of an earlier presented stimulus on the response to a current stimulus.
>
> **Reference information**: Information about an attribute of a product or a range of products that functions as a comparison in the evaluation of another product.
>
> **Subliminal**: Presentation of a stimulus below the normal limits of human perception.
>
> **Supraliminal**: Presentation of a stimulus above the normal limits of human perception.
>
> **Unconscious information processing**: The mental elaboration of information or cues from the environment without being aware of doing so, although one may be aware of the information/cue and of its outcome (a thought or behavior).

References

Ajzen I. Organ Behav Hum Dec. 1991; 50:179–211.

Bargh JA. In: Higgins ET, Sorrentino RM, editors. Handbook of motivation and cognition: Foundations of social behavior. New York: Guilford; 1990. p. 93–130.

Bargh JA, Chartrand TL. In: Reis HT, Judd CM, editors. Handbook of research methods in social and personality psychology. Cambridge: Cambridge University Press; 2000. p. 253–85.

Bellisle F, Dalix A-M. Am J Clin Nutr. 2001; 74:197–200.

Boon B, Stroebe W, Schut H, Jansen A. Brit J Health Psych. 1998; 3:27–40.

British Market Research Bureau. Comprehension and use of UK nutrition signpost labelling schemes. London: Food Standards Agency; 2009.

Brunner T, Siegrist M. Primed to eat less: How unobtrusive external cues influence how much we eat. Unpublished manuscript. Zurich: Swiss Federal Institute of Technology Zurich; 2009.

Caldwell C, Hibbert S. Psychol Market. 2002; 19:895–917.

Chaiken S, Liberman A, Eagly AH. In: Uleman JS, Bargh JA, editors. Unintended thought. New York: Guilford; 1989. p. 212–52.

Chandon P, Wansink B. J Marketing Res. 2002; 39:321–35.

Conger J, Conger A, Costanzo P, Wright L, Matter J. J Pers. 1980; 48:258–71.

Cowburn G, Stockley L. Public Health Nutr. 2005; 8:21–8.

Danzig F. Advertising Age. 1962; 33.

De Bruijn G-J, Kremers SPJ, de Vet E, de Nooijer J, van Mechelen W, Brug J. Psychol Health. 2007; 22:899–916.

De Castro J, Brewer E. Physiol Behav. 1992; 51:121–5.

Dijksterhuis A, Smith PK, van Baaren RB, Wigboldus DHJ. J Consum Psychol. 2005; 15:193–202.

Edelman B, Engell D, Bronstein P, Hirsch E. Appetite. 1986; 7:71–83.

Engell D, Kramer M, Malafi T, Salomon M, Lesher L. Appetite. 1996; 26:129–38.

Fazio RH, Towles-Schwen. In: Chaiken S, Trope Y, editors. Dual process theories in social psychology. New York: Guilford; 1999. p. 97–116.

Feunekes GI, Gortemaker IA, Willems AA, Lion R, van den Kommer M. Appetite. 2008; 50:57–70.

Geiger CJ, Wyse BW, Parent CR, Hansen RG. J Am Diet Assoc. 1991; 91:800–7.

Goldman S, Herman C, Polivy J. Appetite. 1991; 17:129–40.

Henderson C. Wall Street J. 1957; 1:14.

Herman C, Polivy J. Physiol Behav. 2005; 86:762–72.

Herman C, Roth D, Polivy J. Psychol Bull. 2003; 129:873–86.

Herman P, Polivy J. In: Stunkard A, Stellar E, editors. Eating and its disorders. New York: Raven Press; 1984. p. 141–56.

Higgins E. In: Higgins E, Kruglanski A, editors. Social psychology: Handbook of basic principles. New York: Guilford Press; 1996. p. 133–68.

Higginson CS, Kirk TR, Rayner MJ, Draper S. Nutr Food Sci. 2002; 32:145–52.

Hsee CK. Organ Behav Hum Dec. 1996; 67:247–57.

Hsee CK. J Behav Decis Making. 1998; 11:107–21.

Johnston L. Soc Cognition. 2002; 20:18–35.

Kähkönen P, Tuorila H. Appetite. 1998; 30:13–23.

Karremans J, Stroebe W, Claus J. J Exp Soc Psychol. 2006; 42:792–8.

Khan U, Dhar R, Wertenbroch K. In: Ratneshwar S, Mick DG, editors.Inside consumption: Frontiers of research on consumer motives, goals, and desires. London: Routledge; 2005. p. 144–65.

Levitsky D. Appetite. 2002; 38:143–8.

Levy AS, Fein SB, Schucker RE. J Public Policy Mark. 1996; 15:1–15.

Lewis CJ, Yetley EA. J Am Diet Assoc. 1992; 92:62–6.

Lyman B. A psychology of food. More than a matter of taste. New York: Van Nostrand-Reinhold; 1989.

Nisbett R, Storms M. In: London H, Nisbett R, editors. Thought and feeling: Cognitive alternation of feeling states. Chicago, IL: Aldine; 1974. p. 190–208.

Painter J, Wansink B, Hieggelke J. Appetite. 2002; 38:237–8.

Petty RE, Cacioppo JT. Communication and persuasion: Central and peripheral routes to attitude change. New York: Springer; 1986.

Pliner P, Bell R, Hirsch ES, Kinchla M. Appetite. 2006; 46:189–98.

Polivy J, Herman C, Younger J, Erskine B. J Pers. 1979; 47:100–17.

Raghunathan R, Naylor RW, Hoyer WD. J Mark. 2006; 70:170–84.

Rolls B, Roe L, Meengs J. Obesity. 2007; 15:1535–43.

Rolls B, Rowe E, Rolls E, Kingston B, Megson A, Gunary R. Physiol Behav. 1981; 26:215–21.

Rosenthal B, Marx R. Addict Behav. 1979; 4:215–21.

Schachter S, Friedman L, Handler J. In: Schachter S, Rodin J, editors. Obese humans and rats. Potomac, MD: Erlbaum; 1974. p. 61–4.

Solheim R, Lawless HT. Food Qual Prefer. 1996; 7:137–43.

Stevenson R, Prescatt J, Boakes R. Chem Senses. 1999; 24:627–35.

Strahan E, Spencer S, Zanna M. J Exp Soc Psychol. 2002; 38:556–68.

Stubenitsky K, Aaron JI, Catt SL, Mela DJ. Food Qual Prefer. 1999; 10:367–76.

Van Kleef E, van Trijp H, Paeps F, Fernández-Celemín L. Public Health Nutr. 2007; 1–11.

Veltkamp M, Aarts H, Custers R. J Exp Soc Psychol. 2008; 44:866–73.

Visschers VHM, Hess R, Siegrist M. Public Health Nutr. 2010; 13:1099–106.

Visschers VHM, Siegrist M. Appetite. 2009; 52:505–12.

Visschers, VHM, Siegrist M. When reduced fat causes increased preference: How fat reduction in nutrition tables and numeracy skills affect food choices. Appetite. In press, corrected proof, DOI: 10.1016/j.appet.2010.09.001.

Viswanathan M, Hastak M. J Public Policy Mark. 2002; 21:305–18.

Wansink B. J Mark. 1996; 60:1–14.

Wansink B, Kim J. J Nutr Educ Behav. 2005; 37:242–5.

Wansink B, Park S. Food Qual Prefer. 2001; 12:69–74.

Wansink B, van Ittersum K. J Cons Res. 2003; 30:455–63.

Part VI
General and Normative Aspects: Physiological

Chapter 54
The Physiological Relationships Between the Brainstem, Vagal Stimulation, and Feeding

Andreas Stengel and Yvette Taché

Abbreviations

BMI	Body mass index
CART	Cocaine- and amphetamine-regulated transcript
CCK	Cholecystokinin
DMV	Dorsal motor nucleus of the vagus nerve
ERK	1/2 extracellular signal-regulated kinase 1/2
GES	Gastric electrical stimulation
$GHS\text{-}R_{1a}$	Growth hormone secretagogue receptor type 1a
GLP-1	Glucagon-like peptide-1
5-HT	Serotonin
IP	Intraperitoneal
IV	Intravenous
MCH	Melanin-concentrating hormone
MCH_1	Melanin-concentrating hormone receptor 1
N	Number
NO	Nitric oxide
NTS	Nucleus of the solitary tract
PYY	Peptide YY
RYGB	Roux-en-Y gastric bypass
SP	Substance P
TRH	Thyrotropin-releasing hormone
Ucn 2	Urocortin 2

54.1 Introduction

Brain sites regulating food intake receive an impressive range of peripheral signals from the gastrointestinal tract, endocrine pancreas, liver, and adipocytes that are integrated from the brainstem to the forebrain to maintain appropriate meal size and energy homeostasis. These peripheral signals

---

A. Stengel (✉)
CURE: Digestive Diseases Research Center, David Geffen School of Medicine,
University of California, Los Angeles, Building 115, Room 117, Los Angeles, CA, USA
e-mail: astengel@mednet.ucla.edu

reach the brain either directly via the bloodstream and by crossing or bypassing the blood–brain barrier or via receptors located on afferent neurons of which the vagus nerve has been the most important and extensively studied (Cummings and Overduin 2007). This chapter will describe the role of the vagus nerve and affiliated brainstem nuclei in the control of food intake with a major focus on circulating gut peptides. In addition, in the light of the rising incidence of obesity in developed countries (James 2008), modulation of vagal activity as possible strategy in the treatment of adiposity and associated diseases will also be discussed.

54.2 Vagally Mediated Sensing in Stomach, Small Intestine, and Pancreas

Endogenous factors that influence vagal afferent activity encompass mechanoreceptors stimulated by gut distention along with gut peptides released from enteroendocrine cells (Dockray 2004; Chaudhri et al. 2008). In the stomach, the afferent fibers of the vagus nerve located in the external muscle layers are sensitive to stretch and tension, and encode changes in volume and luminal pressure resulting from ingested food (Phillips and Powley 2000). However, vagal afferent fibers are also located in the gastric mucosa (Berthoud 2008). Since the gastric oxyntic mucosa contains a variety of endocrine cells (Bordi et al. 2000), vagal fibers are strategically positioned to detect released gastric hormones. Ghrelin is the only peripherally produced food intake stimulating hormone and its major site of synthesis are X/A-like cells of the gastric corpus (Date et al. 2000). Ghrelin levels rise before a meal and are suppressed upon meal ingestion and convergent evidence supports an initial mediation through vagal pathways (Cummings et al. 2001). The ghrelin receptor, the growth hormone secretagogue receptor type 1a (GHS-R$_{1a}$), is expressed on vagal afferent fibers and in neurons of the nodose ganglion that contains cell bodies of vagal afferents in rats and humans (Table 54.1) (Date et al. 2002a; Burdyga et al. 2006). The stimulation of food intake following intravenous (IV) injection of ghrelin in rats was abolished by subdiaphragmatic vagotomy or after capsaicin pretreatment which selectively ablates small diameter afferents (Date et al. 2002a). Ghrelin also failed to stimulate food intake in human subjects that underwent surgical procedures resulting in complete truncal vagotomy (Le Roux et al. 2005). However, a vagal-independent action on food intake has also been reported when ghrelin was administered intraperitoneally (IP) in rats (Arnold et al. 2006). As ghrelin is released from X/A-like cells into the circulation, it is likely that vagal mechanisms reported to play a role upon systemic injection of the peptide are the main physiological relevant gut–brain pathway. Leptin is a 16-kDa protein expressed in the gastric mucosa (Bado et al. 1998) besides being one of the important adipose tissue-derived food-intake decreasing hormones

Table 54.1 Gastrointestinal peptide and protein hormones regulating food intake that involve vagal pathways

Hormones	Production sites	Receptors
Ghrelin	Gastric X/A-like cells	GHS-R$_{1a}$
Leptin[a]	Gastric chief and P cells	Leptin
CCK	Intestinal I cells	CCK$_1$
GLP-1	Intestinal L cells	GLP-1
PYY$_{3-36}$	Intestinal L cells	Y$_2$
Glucagon	Pancreatic α cells	Glucagon[b]

This table lists peptide and protein hormones derived from the gastrointestinal tract and their receptors, most of which have been identified on vagal afferent fibers

[a]Also largely produced by adipocytes

[b]Not been identified on vagal afferents

(Friedman and Halaas 1998). The presence of the leptin receptor in nodose ganglia (Buyse et al. 2001) (Table 54.1) and activation of gastric vagal afferent fibers by leptin (Wang et al. 1997) indicate that leptin action may involve, in addition to a direct central action, a vagal component that was established particularly in the context of its synergistic interaction with cholecystokinin (CCK) (Barrachina et al. 1997). Therefore, gastric vagal afferents encode inputs from mechanical changes in luminal pressure and volume as well as chemoreceptors activated by specific gastric peptide and protein hormones which are transmitted to the hindbrain through ascending vagal projections.

In the small intestine, vagal afferents are present in the lamina propria but not the epithelium (Berthoud et al. 1995). CCK is produced in intestinal I cells (Cummings and Overduin 2007) which are in close proximity to vagal afferent fibers (Berthoud 2008). The afferent vagus nerve expresses both CCK_1 and CCK_2 receptors (Wren and Bloom 2007), and CCK-induced early satiation is mediated via the CCK_1 receptor (Table 54.1) (Wren and Bloom 2007). Vagal afferents are activated by CCK which is released in response to ingestion of fatty acids and proteins (Berthoud 2008). Glucagon-like peptide-1 (GLP-1) is produced in intestinal L cells (Cummings and Overduin 2007) and displays food intake-reducing properties (Chelikani et al. 2005). Converging evidence established that peripherally released GLP-1 mediates its effects via the vagus nerve. This is supported by the gene expression of the GLP-1 receptor on vagal afferent fibers (Cummings and Overduin 2007) (Table 54.1), the increase in vagal afferent fiber activity upon IV injection of GLP-1 reaching physiological concentrations (Bucinskaite et al. 2009), the activation of nodose ganglia neurons in vitro by GLP-1 (Kakei et al. 2002), and the suppression of IP injection of GLP-1-induced reduction of meal size by subdiaphragmatic vagal deafferentation (Rüttimann et al. 2009). Peptide YY (PYY) is also produced in intestinal L cells (Cummings and Overduin 2007) and circulates in two molecular forms, PYY_{1-36} which binds to Y_1, Y_2, and Y_5 receptors, and PYY_{3-36} which selectively binds to Y_2 and Y_5 receptors (Keire et al. 2002). Consistent reports indicate that the anorexigenic effect of PYY_{3-36} (Batterham et al. 2002; Chelikani et al. 2006) is mediated via the Y_2 receptor (Cummings and Overduin 2007). The Y_2 receptor is expressed on vagal afferents (Cummings and Overduin 2007) and vagotomy abolishes the anorexigenic effect of PYY_{3-36} (Table 54.1) (Koda et al. 2005). Therefore, although there is a direct effect of circulating PYY_{3-36} at hypothalamic and medullary sites receptive for humoral factors regulating feeding (Batterham et al. 2002), the vagus nerve also seems to play an important role in mediating PYY's food intake inhibition.

Glucagon produced in pancreatic α cells (Date et al. 2002b) decreases food intake (Moran 2006), an effect which is also mediated by vagal afferents (Berthoud 2008), although glucagon receptors have not been identified on vagal afferents (Table 54.1) (Woods et al. 2006). In contrast, the pancreatic hormones amylin and insulin seem to signal humorally to other peripheral organs such as the liver and brain areas outside of the blood–brain barrier namely the area postrema which has been identified as neurophysiological substrate of amylin's satiety effect (Berthoud 2008). Taken together vagal afferent fibers sense mechanical information. In addition, peptides released from several enteroendocrine cells lining the lumen of the gastrointestinal tract, act on cognate receptors expressed on vagal afferents (Dockray 2009) and activate vagal ascending pathways projecting to the brainstem influencing neuronal activity of specific nuclei and those of interconnected brain structures.

54.3 Interactions Between Gut Peptides Signaling to the Brain

As described above gut peptides play an important role in modulating the activity of vagal afferents and thereby mediating information to the brain. As during feeding and fasting, the release of gut peptides is not singly but simultaneously affected, a number of studies have evaluated their possible

interactions. A synergistic effect between the short-term modulator of food intake CCK-8 and the long-term signal of energy balance leptin has been well characterized (Wang et al. 2000). Leptin-injected IP at subthreshold doses did not influence food intake alone but decreased food intake when coinjected with a subthreshold dose of CCK-8 (Barrachina et al. 1997). This was linked with an increased gastric vagal afferent discharge and Fos expression, a marker for neuronal activation, in brain nuclei regulating food intake (Barrachina et al. 1997). Also, coinfusion of CCK and GLP-1 reduces caloric intake with a greater magnitude than an additive effect suggesting a synergistic interaction between these two peptides (Gutzwiller et al. 2004). Furthermore, urocortin 2 (Ucn 2) coinjected with CCK-8 suppressed food intake and delayed gastric emptying, under conditions when the two peptides alone had no effect (Gourcerol et al. 2007). This synergistic interaction takes place directly on gastric vagal afferent fibers as demonstrated at the electrophysiological level in an isolated gastric vagus preparation using infusion of subthreshold doses of Ucn 2 and CCK-8 and molecular level with the expression of receptors for both peptides in the nodose ganglia (Gourcerol et al. 2007). Another study showed that IP injection of ghrelin-induced increase in food intake and Fos expression in specific hypothalamic nuclei regulating food intake was completely abolished by coinjection with CCK-8 (Kobelt et al. 2005). Likewise, peripheral injection of bombesin abolishes ghrelin's orexigenic effect (Kobelt et al. 2006). These examples highlight the importance of the interaction between gut peptides influencing vagal activity and their impact to regulate food intake and digestive functions.

Feeding status also differentially influences the expression of receptors in the nodose ganglia providing additional control mechanisms of vagal sensory information to the brain (Dockray 2009). For instance, the expression of the cannabinoid receptor CB_1 and the melanin-concentrating hormone receptor 1 (MCH_1), both mediating food intake-stimulating effects, is increased after fasting, whereas the expression of the Y_2 receptor mediating PYY's anorexigenic effect is decreased (Dockray 2009). Conversely, re-feeding decreases the expression of CB_1 and MCH_1, through CCK_1-dependent mechanisms (Dockray 2009). In contrast, CCK stimulates the expression of the Y_2 receptor (Burdyga et al. 2008). Besides regulating the expression levels of receptors, CCK increased the expression of the anorexigenic cocaine- and amphetamine-regulated transcript (CART) and decreased the expression of the orexigenic melanin-concentrating hormone (MCH) (Dockray 2009). The stimulatory effect of CCK on CART expression can be blocked by exogenous ghrelin (Dockray 2009). Taken together, these data indicate a complex interplay between gut peptides and the regulation of receptor and ligand expression depending upon the metabolic status and thereby vagal-dependent signaling regulating food intake.

54.4 Brainstem Integration of Vagal Input

The gut signals sent to the brain via ascending vagal afferent fibers are first transmitted to the nucleus of the solitary tract (NTS) located in the dorsal medulla. The coding from vagal afferent terminals in the NTS involves the release of glutamate and the activation of catecholaminergic neurons (Rinaman et al. 1995). Glutamate receptors are present on NTS neurons, and treatment with glutamatergic N-methyl-d-aspartate (NMDA) receptor antagonists blocks peripheral CCK-induced reduction of food intake (Schwartz 2006). CCK also activates the extracellular signal-regulated kinase (ERK) 1/2 and cAMP responsive element-binding protein (Sutton et al. 2004). The ERK pathway seems to be necessary for CCK's action as shown by an attenuated food intake-suppressive effect after treatment with U0126 to block ERK signaling (Sutton et al. 2004). The molecular mechanisms involved in the integration of various satiety signals within the NTS represent a novel field of investigations that require further studies particularly the relationship between glutamatergic transmission of gut negative-feedback signals and the control of food intake.

From the NTS, information is further transmitted to interconnected forebrain structures such as the hypothalamus, amygdala, and cortex. In turn, the NTS also receives information from hypothalamic nuclei such as the paraventricular nucleus of the hypothalamus and limbic structures like the central nucleus of the amygdala through descending projections (Schwartz 2006). Therefore, the NTS integrates central as well as peripheral signals in order to regulate food intake (Schwartz 2006). Moreover, hindbrain nuclei such as NTS and ventrolateral medulla (VLM) directly influence energy expenditure. These brainstem nuclei affect fat mobilization from white adipose tissue (Shi and Bartness 2001) and signal to brown adipose tissue through descending projections from the nucleus raphe pallidus (Morrison 2001) which plays an important role in body weight regulation (van Marken Lichtenbelt et al. 2009). However, the brainstem is also able to control food intake independently without input to or from forebrain structures. Brainstem transected rats (chronically decerebrated rats) are able to control meal size similarly as intact controls (Grill and Kaplan 2002) suggesting that the caudal brainstem is able to integrate peripheral signals in order to induce meal termination.

54.5 Vagal Efferent Function

The efferent vagus nerve innervates the gastrointestinal tract up to the last third of the transverse colon (Cannon–Boehm point) and is involved in the regulation of digestion, absorption, and propulsion of nutrients. Acute vagotomy increases fundic tone and decreases antral motility resulting in impaired reservoir function of the stomach (Travagli et al. 2006). Most of the neurons of the dorsal motor nucleus of the vagus nerve (DMV) are cholinergic (Travagli et al. 2006), whereas only few neurons express nitric oxide (NO) synthase (Krowicki et al. 1997) or catecholamines (Kalia et al. 1984) which could be involved in gastric relaxation (Travagli et al. 2006). Most vagal preganglionic fibers activate cholinergic nicotinic receptors (Schemann and Grundy 1992) resulting in the activation of gastric myenteric cholinergic neurons (Miampamba et al. 2001) which coordinates the stimulation of gastric acid and pepsin secretion and propulsive motor function (Taché et al. 2006).

Neurons of the DMV are activated by thyrotropin-releasing hormone (TRH) positive nerve fibers which originate from TRH neurons in the raphe pallidus, raphe obscurus, and the parapyramidal regions resulting in a stimulation of gastric secretion, motor function, and blood flow (Taché 2009). Serotonin (5-HT) and substance P (SP) that are colocalized in TRH-synthesizing neurons and also released in response to activation of these neurons potentiate the action of exogenous and endogenous TRH on gastric acid secretion and motility (Taché 2009). In contrast, SP coreleased with TRH reduces the excitatory action of TRH (Taché 2009), thereby modulating the TRH effect. Injection of TRH analog into the medulla increases food intake via a vagus-dependent increase of circulating ghrelin levels (Ao et al. 2006). Moreover, sham feeding (exteroceptive olfactory and visual sensory inputs without ingestion of food and associated oropharyngeal stimulation) activates the brainstem TRH signaling pathway and contributes to the vagal-dependent cephalic phase of gastric acid secretion (Taché 2009). Collectively these data strongly support a physiological role for brainstem TRH in the vagal regulation of gastric function associated with digestive processes and food intake.

Like preganglionic neurons, excitatory postganglionic neurons mediate their actions mostly via acetylcholine release resulting in an increase of gastrointestinal peristalsis and tone (Miampamba et al. 2001; Travagli et al. 2006). In contrast, inhibitory postganglionic neurons mediate their effects possibly through NO and vasoactive intestinal polypeptide (Goyal et al. 1980; Desai et al. 1991) resulting in relaxation for instance at the pyloric level allowing emptying of the stomach. Taken together, medullary TRH controls food intake through activation of gastric vagal efferent activity thereby modulating the release of the orexigenic ghrelin and gastric functions to coordinate the various

components linked with food ingestion such as accommodation, mixing with gastric acid and pepsin secretion, and propulsion into the intestine (Taché 2009).

The efferent vagus nerve also plays an important role in the homeostasis of blood glucose levels through its effect on the liver and pancreas. Medullary TRH induces vagal-dependent insulin release from pancreatic ß cells in rats (Taché 2009) resulting in an enhanced glucose tolerance. Moreover, vagal activation inhibits enzymes involved in glucose production and stimulates enzymes for glycogen synthesis in the liver (Shimazu 1971).

54.6 Applications to Other Areas of Health and Disease – Clinical Implications

Overweight, obesity (body mass index, BMI > 30, Table 54.2), and associated diseases are a major health issue both in the USA (Ogden et al. 2006) and worldwide (James 2008) mainly contributing to morbidity and mortality in industrialized countries (Flegal et al. 2007). Two-thirds of the adult US American population are either overweight or obese (Flegal et al. 1998; Marx 2003) and the prevalence is still rising (Table 54.3) (Flegal et al. 1998). Therefore, the World Health Organization has declared obesity as the greatest threat to human health (Wynne et al. 2004). Public health initiatives have failed to reverse the rising incidence of obesity (Wren and Bloom 2007) and the drug treatment options are very limited so far (Gura 2003). Other treatment options involve targeted alterations of vagal nerve functions such as gastric electrical stimulation (GES) and bariatric surgery.

GES devices have been advocated early on, besides pharmacologic, surgical, and cognitive approaches to reduce food intake and treat obesity (Abell et al. 2006). GES involves electrodes placement on the outer lining of the stomach along the lesser curvature which are connected to a subcutaneously implanted pacemaker-like device allowing the delivery of low-level electrical stimulation on the stomach wall (Abell et al. 2006; Zhang and Chen 2006). Animal studies have shown that electrical stimulation near the lesser gastric curvature decreases food intake (Cigaina et al. 1996; Zhang et al. 2009). Also, 1 year long GES studies performed so far in morbidly obese subjects

Table 54.2 Classification of the BMI (kg/m²)

Category	BMI range (kg/m²)
Underweight	16.5–18.4
Normal	18.5–24.9
Overweight	25.0–29.9
Obese	30.0–39.9
Morbidly obese	40.0–49.9
Super obese	>50

This table shows the BMI (calculated from a person's weight and height) ranges used as a diagnostic tool to identify weight problems within a population such as underweight, overweight, and different grades of obesity

Table 54.3 Key facts highlighting the rising prevalence of worldwide overweight and obese population (Adapted from James 2008)

	2002	2007	2015 (estimation)
At least overweight (BMI >25)	1.4 billion	1.5 billion	2.3 billion
Obese (BMI >30)	356 million	523 million	704 million

This table shows the worldwide rising prevalence of overweight and obesity since 2002 and projection to 2015

Table 54.4 Non placebo-controlled clinical trials with a duration >1 year investigating the effects of gastric electrical stimulation on body weight in patients with morbid obesity

N	Body weight loss (%)	References
24	24	Cigaina (2002)
69	21	De Luca et al. (2004)
101	20	Shikora (2004)
30	23	Shikora (2004)
9	26	Bohdjalian et al. (2006)
8	0	Hoeller et al. (2006)

This table summarizes the clinical reports showing the 20–26% reduction in body weight in a number (N) of morbidly obese patients undergoing gastric electrical stimulation

Table 54.5 Human studies with a duration of >1 year investigating the effects of RYGB in obese patients

N	Body weight loss	References
251	31% after 5 years	Yale (1989)
157	30% after 3 years	Waters et al. (1991)
39	35% after 4 years	Balsiger et al. (2000)
1,025	28% after 10 years	Sugerman et al. (2003)
34	25% after 10 years	Sjostrom et al. (2004)

This table shows the weight reducing effect of RYGB bypass in longitudinal 3–10 years studies in obese patients

N indicates the number of patients enrolled in each clinical study

(BMI > 40) showed a decrease in body weight (Cigaina 2002; De Luca et al. 2004; Shikora 2004; Zhang and Chen 2006; Bohdjalian et al. 2006), whereas one study failed to show an improvement in patients that had previously failed to lose weight after adjustable gastric banding (Table 54.4) (Hoeller et al. 2006). Several reports on mechanisms involved in GES action indicate that reduced appetite and increased satiety linked with alterations of gut hormones regulating food intake may be part of decrease in body weight (Hasler 2009). Experimental studies also showed alterations in responsiveness of brain circuitries involved in food intake (Zhang and Chen 2006). There is evidence that GES enhances vagal afferent signaling (Peles et al. 2003) and reduces vagal parasympathetic efferent activity (Hasler 2009) which may contribute to these changes.

Bariatric surgery is the most effective treatment for long-term weight loss in morbidly obese patients so far with Roux-en-Y gastric bypass (RYGB) being the most commonly performed (Table 54.5) (Tanner and Allen 2009). This procedure consists of opening the stomach 2–3 cm distal from the angle of His, forming a small gastric pouch, dividing the small bowel 20 cm distal of the ligament of Treitz, performing a gastro-jejunostomy and re-anastomosis of the small intestine by entero-enterostomy (Fig. 54.1) (Tanner and Allen 2009). The underlying mechanisms causing the sustained weight loss are still poorly understood. Reduction of ghrelin levels has been discussed as a possible contributing mechanism. One study showed very low circulating ghrelin levels and loss of meal-related ghrelin changes after RYGB (Cummings et al. 2002). This procedure may damage ventral as well as dorsal gastric branches of the vagus nerve (Fig. 54.1) which seems to be involved in ghrelin regulation as shown in human studies where atropine reduced ghrelin levels (Maier et al. 2004). Also, vagotomized rats do not show the fasting-induced increase of ghrelin (Simonian et al. 2005) and central vagal stimulation by medullary TRH increases circulating ghrelin in rats (Ao et al. 2006). Furthermore, exogenous ghrelin failed to stimulate food intake in patients that had undergone surgical procedures involving vagotomy (Le Roux et al. 2005). Therefore, altered vagal-dependent ghrelin

Fig. 54.1 Graphic representation of procedure and vagal innervation before and after Roux-en-Y gastric bypass (RYGB). The physiological situation is shown in (**a**), gastric bypass using Roux-en-Y anastomosis consists of cutting stomach and jejunum, forming a small gastric pouch and re-anastomose stomach and jejunum and duodenum and jejunum respectively (**b**). Ventral and dorsal gastric branches of the vagus nerve can be damaged during this procedure (**b**)
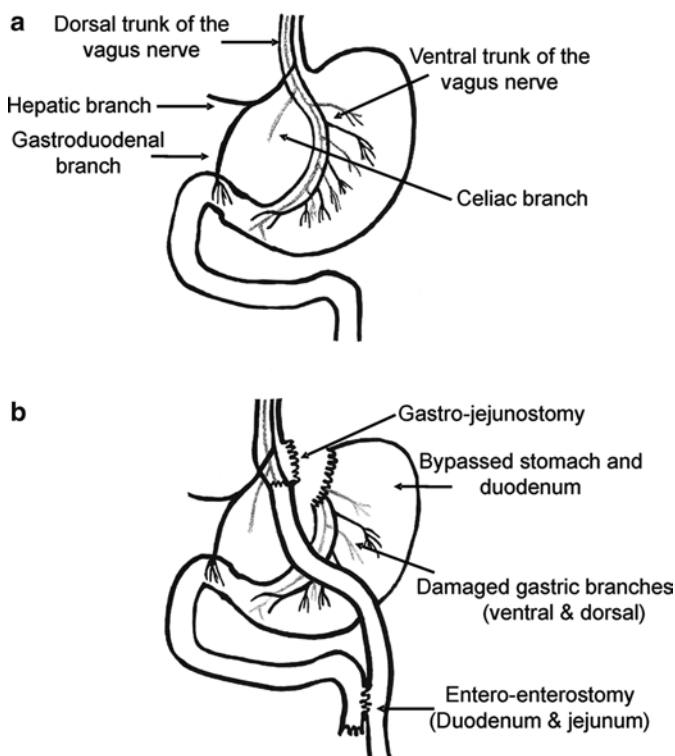
release and related orexigenic signaling might contribute to the surgery-induced weight loss. Moreover, even when the vagus nerve is left intact the threshold for stimulation of vagal afferents by nutrients could be lowered leading to increased afferent signaling which can give rise to increased perception of fullness and nausea (Powley et al. 2005). As the stomach size is reduced by 90%, patients ingest just a small amount of food and the stretching of the wall of the stomach pouch conveys the sensation of fullness through vagal afferents, similar to that eaten by a large meal. However, more studies, especially in animal models using targeted selective vagotomy, are needed to increase the understanding of mechanisms underlying the weight loss after RYGB.

54.7 Conclusion

The vagus efferent nerve innervates the gastrointestinal tract including adjacent organs such as the pancreas and liver and is involved in the regulation of food intake, gastrointestinal digestive function, and glucose control. Afferent vagal fibers encode mechano- and chemo-sensory stimuli originating from the gut and adipose tissues and relay this information to brainstem nuclei connected with circuitries regulating food intake and associated digestive processes. In light of the rapidly rising prevalence of obesity and associated fatal diseases, efficient treatments are urgently needed. The most effective treatment of morbid obesity, the bariatric surgery technique RYGB, may involve alterations of vagal afferents and efferents in regulating food intake contributing to the observed weight loss. Further experimental studies will enhance our understanding of vagal signaling under those conditions and the possible targeted surgical modification. This may lead to a more effective and highly targeted antiobesity treatment.

Summary Points

- Vagal afferents respond to mechanical and chemical signals, such as gut peptides, protein hormones, and neurotransmitters by increased activity which is transmitted first to the brainstem and interconnected forebrain circuits regulating food intake.
- The afferent vagus nerve sends signals first to the nucleus of the solitary tract (NTS) through ascending projections from the nodose ganglion.
- The caudal brainstem circuitry is able to integrate peripheral signals in order to induce meal termination autonomously.
- The efferent vagus nerve controls gastric motility and integrates gastric accommodation to ingested food and propulsive motor activity to empty the stomach content and is involved in glucose homeostasis.
- The incidence of obesity is rapidly rising in industrialized countries and treatment options are very limited so far.
- Gastric electrical stimulation (GES) is a procedure used in patients with morbid obesity which showed 20–25% efficiency to decrease excess body weight in a number of non-placebo-controlled clinical studies. The underlying mechanism may involve alterations of vagal activity.
- Roux-en-Y gastric (RYGB) bypass is the most effective (25–35% body weight loss) treatment for patients with morbid obesity (BMI >40). Vagal denervation-induced decrease of circulating ghrelin levels, along with increased vagal sensory signaling through activation of mechanoreceptors, may be contributing mechanisms causing sustained weight loss.

Definition and Explanation of Key Terms Used in This Article

The parasympathetic **vagus nerve** is the cranial nerve X originating from the brainstem providing innervation of the viscera in the thoracic and abdominal cavity up to the last third of the transverse colon.

Ghrelin is the only peptide hormone peripherally produced and centrally acting known to stimulate food intake. The main source of ghrelin is X/A-like cells of the stomach.

The **nodose ganglion** contains cell bodies with peripheral processes forming the afferent fibers of the vagus nerve with ascending projections to the brain medulla and descending projections innervating the gut.

Capsaicin is a neurotoxin isolated from red pepper that is an important tool to selectively ablate afferent fibers.

The **nucleus of the solitary tract (NTS)** is located in the brainstem and receives input from the facial (VII), glossopharyngeal (IX), and vagus afferent nerve and regulates visceral functions including gastrointestinal functions.

The **dorsal motor nucleus of the vagus nerve (DMV)** located in the brainstem ventral to the NTS is part of the dorsal vagal complex and contains cell bodies of which axons constitute the efferent vagus innervating the gut.

Gastric electrical stimulation is a treatment approach for morbid obesity involving stimulation of electrodes placed next to the lesser curvature of the stomach. Short pulse stimulation is used to reduce food intake and decrease body weight.

Roux-en-Y gastric bypass (RYGB) is the most effective treatment option for long-term weight loss in patients with morbid obesity and therefore the most common technique among bariatric surgery approaches.

Key Facts of Vagal Stimulation

1. Vagal afferent fibers send signals from the stomach, small intestine, and the first two-thirds of the transverse colon to the hindbrain in response to mechano- and chemo-stimulation resulting from changes in luminal pressure and volume and specific peptide and protein hormone release from enteroendocrine cells and adipose tissue.
2. The efferent vagus nerve controls gastric and intestinal motility to coordinate the various components of food ingestion linked first with the accommodation of food and second its propulsion after mixing with gastric acid and pepsin secretion.

Key Features of the Brainstem

1. The signals sent to the brainstem via the afferent ascending vagal fibers are first transmitted to neurons in the nucleus of the solitary tract (NTS) located in the dorsal medulla.
2. The caudal brainstem is able to integrate peripheral signals and induce a reflex signal leading to meal termination.
3. The molecular mechanisms involved in the integration of satiety signals in the NTS and the consecutive regulation of food intake represent a novel field of investigations.

References

Abell TL, Minocha A, Abidi N Am J Med Sci. 2006;331:226–32.

Ao Y, Go VL, Toy N, Li T, Wang Y, Song MK, Reeve JR Jr, Liu Y, Yang H Endocrinology. 2006;147:6004–10.

Arnold M, Mura A, Langhans W, Geary N J Neurosci. 2006;26:11052–60.

Bado A, Levasseur S, Attoub S, Kermorgant S, Laigneau JP, Bortoluzzi MN, Moizo L, Lehy T, Guerre-Millo M, Le Marchand-Brustel Y, Lewin MJ Nature. 1998;394:790–93.

Balsiger BM, Kennedy FP, Abu-Lebdeh HS, Collazo-Clavell M, Jensen MD, O'Brien T, Hensrud DD, Dinneen SF, Thompson GB, Que FG, Williams DE, Clark MM, Grant JE, Frick MS, Mueller RA, Mai JL, Sarr MG Mayo Clin Proc. 2000;75:673–80.

Barrachina MD, Martinez V, Wang L, Wei JY, Taché Y Proc Natl Acad Sci USA. 1997;94:10455–60.

Batterham RL, Cowley MA, Small CJ, Herzog H, Cohen MA, Dakin CL, Wren AM, Brynes AE, Low MJ, Ghatei MA, Cone RD, Bloom SR Nature. 2002;418:650–54.

Berthoud HR, Kressel M, Raybould HE, Neuhuber WL Anat Embryol (Berl). 1995;191:203–212.

Berthoud HR. Regul Pept. 2008;149:15–25.

Bohdjalian A, Prager G, Aviv R, Policker S, Schindler K, Kretschmer S, Riener R, Zacherl J, Ludvik B Obes Surg. 2006;16:627–34.

Bordi C, D'Adda T, Azzoni C, Ferraro G Microsc Res Tech. 2000;48:258–71.

Bucinskaite V, Tolessa T, Pedersen J, Rydqvist B, Zerihun L, Holst JJ, Hellstrom, PM. Neurogastroenterol Motil. 2009;21:978–e78.

Burdyga G, Varro A, Dimaline R, Thompson DG, Dockray GJ Am J Physiol Gastrointest Liver Physiol. 2006; 290:G1289–G1297.

Burdyga G, de Lartigue G, Raybould HE, Morris R, Dimaline R, Varro A, Thompson DG, Dockray GJ J Neurosci. 2008;28:11583–592.

Buyse M, Ovesjo ML, Goiot H, Guilmeau S, Peranzi G, Moizo L, Walker F, Lewin, MJ, Meister B, Bado A Eur J Neurosci. 2001;14:64–72.

Chaudhri OB, Salem V, Murphy KG, Bloom SR Annu Rev Physiol. 2008;70:239–55.

Chelikani PK, Haver AC, Reidelberger RD Am J Physiol Regul Integr Comp Physiol. 2005;288:R1695–706.

Chelikani PK, Haver AC, Reeve JR Jr, Keire DA, Reidelberger RD Am J Physiol Regul Integr Comp Physiol. 2006;290:R298–305.

Cigaina V. Obes Surg. 2002;12(Suppl 1):12S–16S.

Cigaina VV, Saggioro A, Rigo VV, Pinato G, Ischai S Obes Surg. 1996;6:250–53.

Cummings DE, Purnell JQ, Frayo RS, Schmidova K, Wisse BE, Weigle DS Diabetes 2001;50:1714–19.

Cummings DE, Weigle DS, Frayo RS, Breenc PA, Ma MK, Dellinger EP, Purnell JQ N Engl J Med. 2002;346:1623–30.

Cummings DE, Overduin J J Clin Invest. 2007;117:13–23.

Date Y, Kojima M, Hosoda H, Sawaguchi A, Mondal MS, Suganuma T, Matsukura S, Kangawa K, Nakazato M Endocrinology. 2000;141:4255–61.

Date Y, Murakami N, Toshinai K, Matsukura S, Niijima A, Matsuo H, Kangawa K, Nakazato M Gastroenterology 2002a;123:1120–28.

Date Y, Nakazato M, Hashiguchi S, Dezaki K, Mondal MS, Hosoda H, Kojima M, Kangawa K, Arima T, Matsuo H, Yada T, Matsukura S Diabetes 2002b;51:124–9.

De Luca M, Segato G, Busetto L, Favretti F, Aigner F, Weiss H, de Gheldere C, Gaggiotti G, Himpens J, Limao J, Scheyer M, Toppino M, Zurmeyer EL, Bottani G, Penthaler H Obes Surg. 2004;14(Suppl 1):S33–9.

Desai KM, Zembowicz A, Sessa WC, Vane JR Proc Natl Acad Sci USA. 1991;88:11490–94.

Dockray G. Curr Opin Pharmacol. 2004;4:557–60.

Dockray GJ. Physiol Behav. 2009;97:531–6.

Flegal KM, Carroll MD, Kuczmarski RJ, Johnson CL Int J Obes Relat Metab Disord. 1998;22:39–47.

Flegal KM, Graubard BI, Williamson DF, Gail MH JAMA. 2007;298:2028–37.

Friedman JM, Halaas JL Nature. 1998;395:763–70.

Gourcerol G, Wang L, Wang YH, Million M, Taché Y Endocrinology. 2007;148:6115–623.

Goyal RK, Rattan S, Said SI Nature. 1980;288:378–80.

Grill HJ, Kaplan JM Front Neuroendocrinol. 2002;23:2–40.

Gura T. Science. 2003;299:849–52.

Gutzwiller JP, Degen L, Matzinger D, Prestin S, Beglinger C Am J Physiol Regul Integr Comp Physiol. 2004;287:R562–7.

Hasler WL. Neurogastroenterol Motil. 2009;21:229–43.

Hoeller E, Aigner F, Margreiter R, Weiss H Obes Surg. 2006;16:1160–65.

James WP. J Intern Med. 2008;263:336–52.

Kakei M, Yada T, Nakagawa A, Nakabayashi H Auton Neurosci. 2002;102:39–44.

Kalia M, Fuxe K, Goldstein M, Harfstrand A, Agnati LF, Coyle JT Neurosci Lett. 1984;50:57–62.

Keire DA, Bowers CW, Solomon TE, Reeve JR Jr Peptides. 2002;23:305–21.

Kobelt P, Tebbe JJ, Tjandra I, Stengel A, Bae HG, Andresen V, van der Voort IR, Veh RW, Werner CR, Klapp BF, Wiedenmann B, Wang L, Taché Y, Mönnikes H Am J Physiol Regul Integr Comp Physiol. 2005;288:R751–8.

Kobelt P, Goebel M, Stengel A, Schmidtmann M, van der Voort IR, Tebbe JJ, Veh RW, Klapp BF, Wiedenmann B, Wang L, Taché Y, Mönnikes H Am J Physiol Regul Integr Comp Physiol. 2006;291:R903–913.

Koda S, Date Y, Murakami N, Shimbara T, Hanada T, Toshinai K, Niijima A, Furuya M, Inomata N, Osuye K, Nakazato M Endocrinology. 2005;146:2369–75.

Krowicki ZK, Sharkey KA, Serron SC, Nathan NA, Hornby PJ J Comp Neurol. 1997;377:49–69.

Le Roux CW, Neary NM, Halsey TJ, Small CJ, Martinez-Isla AM, Ghatei MA, Theodorou NA, Bloom SR J Clin Endocrinol Metab. 2005;90:4521–4.

Maier C, Schaller G, Buranyi B, Nowotny P, Geyer G, Wolzt M, Luger A J Clin Endocrinol Metab. 2004;89:4729–33.

Marx J. Science. 2003;299:846–9.

Miampamba M, Yang H, Sharkey KA, Taché Y Am J Physiol Gastrointest Liver Physiol. 2001;280:G979–91.

Moran TH. Obesity (Silver Spring). 2006;14(Suppl 5):250S–53S.

Morrison SF. Clin Exp Pharmacol Physiol. 2001;28:138–43.

Ogden CL, Carroll MD, Curtin LR, McDowell MA, Tabak CJ, Flegal KM JAMA. 2006;295:1549–55.

Peles S, Petersen J, Aviv R, Policker S, Abu-Hatoum O, Ben-Haim SA, Gutterman DD, Sengupta JN Am J Physiol Gastrointest Liver Physiol. 2003;285:G577–85.

Phillips RJ, Powley TL Brain Res Brain Res Rev. 2000;34:1–26.

Powley TL, Chi MM, Schier LA, Phillips RJ Physiol Behav. 2005;86:698–708.

Rinaman L, Hoffman GE, Dohanics J, Le WW, Stricker EM, Verbalis JG J Comp Neurol. 1995;360:246–56.

Rüttimann EB, Arnold M, Hillebrand JJ, Geary N, Langhans W Endocrinology. 2009;150:1174–81.

Schemann M, Grundy D Am J Physiol. 1992;263:G709–718.

Schwartz GJ. Phil Trans R Soc Lond B Biol Sci. 2006;361:1275–80.

Shi H, Bartness TJ Brain Res Bull. 2001;54:375–85.

Shikora SA. Obes Surg. 2004;14(Suppl 1):S40–48.

Shimazu T. Biochim Biophys Acta. 1971;252:28–38.

Simonian HP, Kresge KM, Boden GH, Parkman HP Neurogastroenterol Motil. 2005;17:348–54.

Sjostrom L, Lindroos AK, Peltonen M, Torgerson J, Bouchard C, Carlsson B, Dahlgren S, Larsson B, Narbro K, Sjostrom CD, Sullivan M, Wedel H N Engl J Med. 2004;351:2683–93.

Sugerman HJ, Wolfe LG, Sica DA, Clore JN Ann Surg. 2003;237:751–58.

Sutton GM, Patterson LM, Berthoud HR J Neurosci. 2004;24:10240–47.

Taché Y, Yang H, Miampamba M, Martinez V, Yuan PQ Auton Neurosci. 2006;125:42–52.

Taché Y. In: Zafra MA, Molina F, Puerto A, edidors. The cephalic/neural phase in nutrition. Research Signpost. 2009; pp. 47–58.

Tanner BD, Allen JW Am Surg. 2009;75:103–112.

Travagli RA, Hermann GE, Browning KN, Rogers RC Annu Rev Physiol. 2006;68:279–305.

Van Marken Lichtenbelt WD, Vanhommerig JW, Smulders NM, Drossaerts JM, Kemerink GJ, Bouvy ND, Schrauwen P, Teule GJ N Engl J Med. 2009;360:1500–508.

Wang L, Barachina MD, Martinez V, Wei JY, Taché Y Regul Pept. 2000;92:79–85.

Wang YH, Taché Y, Sheibel AB, Go VL, Wei JY Am J Physiol. 1997;273:R833–7.

Waters GS, Pories WJ, Swanson MS, Meelheim HD, Flickinger EG, May HJ Am J Surg. 1991;161:154–7.

Woods SC, Lutz TA, Geary N, Langhans W Phil Trans R Soc Lond B Biol Sci. 2006;361:1219–35.

Wren AM, Bloom SR Gastroenterology. 2007;132:2116–30.

Wynne K, Stanley S, Bloom S J Clin Endocrinol Metab. 2004;89:2576–82.

Yale CE. Arch Surg. 1989;124:941–6.

Zhang J, Chen JD Aliment Pharmacol Ther. 2006;24:991–1002.

Zhang J, Tang M, Chen JD Obesity (Silver Spring). 2009;17:474–80.

Chapter 55
Anticipatory Physiological Regulation in Feeding Biology

Michael L. Power and Jay Schulkin

Abbreviations

AgRP	Agouti-related protein
CCK	Cholecystokinin
CNS	Central nervous system
GHS receptor	Growth hormone secretory receptor
mRNA	Messenger ribonucleic acid
NPY	Neuropeptide Y
Ob-Rb	Short, soluble form of the leptin receptor
POMC	Proopiomelanocortin

55.1 Introduction

Behavior, physiology, and metabolism are not merely reactive. Animals anticipate. Sometimes the anticipation is driven by acute events. The senses convey information about the external environment to the central nervous system, which interprets the information within the constraints of experience, and intrinsic, evolved tendencies. The central nervous system sends messages to the appropriate peripheral organs to begin the physiological cascades that prepare the organism to respond to the anticipated challenge. In other instances these anticipatory changes reflect internal, clock-like rhythms. For example, the secretion of many hormones (e.g., cortisol, leptin, ghrelin) becomes entrained in light of longer term, repeated conditions. These circadian rhythms allow an animal to be in the most appropriate physiological state at different time points. Animals change state driven by their own internal clocks. In all of these cases, the changes in physiological state can be in advance of the potential need.

Anticipatory responses are associated with central nervous system coordination of physiology. Some authors (e.g., Schulkin 2003) have emphasized how the central coordination of physiology, anticipatory

―――――――――――――

M.L. Power (✉)

Research Department, American College of Obstetricians and Gynecologists,
Washington, DC 20090–6920
and
Nutrition Laboratory, Conservation Ecology Center, Smithsonian
National Zoological Park, MRC 5503 Washington, DC 20013-7012
e-mail: powerm@si.edu; mpower@acog.org

Table 55.1 Key features of anticipatory physiological responses in feeding biology

1. Cephalic phase responses increase the efficiency of absorption and metabolism of nutrients from ingested food by stimulating multiple organ systems in anticipation of feeding

2. For example, the hormone insulin is secreted from the pancreas and acts to regulate circulating glucose concentration; insulin has a cephalic phase response in which the pancreas secretes insulin in anticipation of eating, before any actual change in circulating glucose. Loss of this anticipatory response compromises glucose control

3. Gastric secretion of leptin appears to have a cephalic phase; leptin pairs synergistically with CCK to decrease feelings of hunger and to reduce food intake

4. Ghrelin secretion is hypothesized to be part of the cephalic phase response and either stimulates feelings of hunger or is stimulated by these feelings

5. Learned associations can affect cephalic phase responses, either increasing or decreasing the magnitude of the response. Also, making food available at consistent times can modify the circadian rhythms of some cephalic phase responses (e.g., ghrelin)

6. Cephalic phase responses serve to keep peripheral physiology in synchrony with behavior and motivation

This table lists key features of anticipatory physiological responses in feeding biology, otherwise known as cephalic phase responses

physiological responses, and the interplay of physiology and behavior appear not to be fully incorporated into the classic homeostatic paradigm of physiological regulation. The concept of allostasis, defined as the "…process by which an organism achieves internal viability through bodily changes of state," has been proposed as an alternative (Schulkin 2003). Many of the examples of allostatic regulation provided by Schulkin (2003) involve the concept that the hormones that regulate peripheral physiology in response to a challenge are also involved in changing central motive states of the brain, and thus induce behaviors that aid the animal to meet the challenge.

The regulation of food intake is a paradigmatic example of the linkage of peripheral physiology with central motive states, and the concept that behavior and physiology act together to preserve viability (Table 55.1). The hormones insulin and ghrelin are excellent examples of this concept. Both act to influence and regulate peripheral physiology and metabolism in response to immediate cues and also to long-term learning. Both also act in the brain, and are signaling molecules in neural circuits important to the regulation of food ingestion (Clegg et al. 2003; Cowley et al. 2003). Both also have cephalic phase responses that are important in feeding biology.

55.2 Importance of Anticipatory Responses in Feeding Biology

Because we feed in discrete meals, food enters our bodies in pulses. Meals result in perturbations of the internal milieu that must be accommodated (Woods 1991). Our internal milieu cannot be strictly constant. The digestive system and numerous other organ systems (e.g., liver, kidney, adipose tissue) constantly change to accommodate conditions of nutrient excess (feeding) followed by potential nutrient deficits (between meals). The secretory responses that regulate absorption, storage, and mobilization of nutrients change over the day, sometimes favoring a net deposit into storage pools and sometimes favoring a net mobilization into extracellular fluid.

These changes take time. Cephalic phase responses, anticipatory digestive and metabolic responses to cues that feeding is imminent, allow organisms to get "ahead of the curve." They improve the efficiency with which animals digest food, and absorb and metabolize the liberated nutrients. They also prime the organism to meet the resulting homeostatic challenges presented by the influx of nutrients (Woods 1991).

55.2.1 *Cephalic Phase Responses*

The term cephalic phase response generally refers to digestive and metabolic responses to food cues generated by the central nervous system that act to prepare the organism to ingest, digest, absorb, and metabolize food (Pavlov 1902; Powley 1977). These anticipatory physiological responses increase the efficiency with which an organism incorporates food into its tissue (Woods 2006).

The concept of cephalic phase response was first introduced by Pavlov in his work on the alimentary tract and its secretions. The original term proposed by Pavlov was "psychic secretions" (see Powley 1977). The change in terminology to cephalic phase responses was both to distance the concept from the mystical notions associated with the word psychic, and to reflect the fact that there are relevant anticipatory responses that are not secretions (e.g., gastric motility, thermogenesis).

For Pavlov, salivary secretions were digestive secretions, serving the same intrinsic function as gastric and intestinal secretions – enabling the animal to utilize food for bodily needs (Pavlov 1902). He demonstrated in dogs that salivation varied with the food ingested. For example ingesting dry food stimulated greater salivation than ingesting wet food. He also, famously, demonstrated that salivation can occur in anticipation of feeding (Pavlov 1902). He extended the work to gastric secretions, and showed that they too could be stimulated by the sight, smell, and taste of food. Anticipatory secretion of other digestive fluids has been demonstrated as well. Digestive secretions are anticipatory as well as reactive.

The concept of cephalic phase responses has changed little since the original demonstrations. It was revitalized by Powley (1977), with special emphasis on the cephalic phase insulin response, extending the concept from digestion to metabolism. In functional terms cephalic phase responses are anticipatory changes in physiology and metabolism that serve to prepare the digestive tract to digest food and absorb nutrients, and to prepare other organ systems (e.g., liver, adipose tissue) to metabolize and store the absorbed nutrients. The gut and brain work together to acquire and utilize the nutrients necessary for life. Recent evidence suggests that cephalic phase responses not only prepare an animal to eat, but they may also play a role in appetite and satiety, and thus in the beginning and ending of a meal. For example, both ghrelin and leptin secreted by the stomach appear to exhibit a cephalic phase. Thus, by the first bite of food, or even before, physiological processes have been set in motion that will influence the duration of the meal and the amount of food eaten.

55.2.1.1 Evidence for Cephalic Phase Responses

There is a considerable literature on cephalic phase responses. Cephalic phase responses have been demonstrated in a wide range of mammals, including humans, nonhuman primates, dogs, cats, sheep, rabbits, and rats (Powley 1977); but cephalic phase responses have been demonstrated in other vertebrate taxa as well. Their evolutionary origin would appear to be quite ancient; for example striped bass display cephalic phase insulin and glucagon responses (Papatryphon et al. 2001). Some of these cephalic phase responses are general, and some appear to be specific to the taste of the food, i.e., responses to sweet substances differ from those to bitter substances. Even the sight of food within sealed plastic containers stimulated gastric secretions in humans (Feldman and Richardson 1986). Adding smell and taste to the sensory experience increased the response (Feldman and Richardson 1986). In humans, dogs, and rats, palatability of the offered food is positively correlated with the extent and magnitude of the cephalic salivary and gastric secretions (reviewed in Powley 1977). Thus appetite, or the psychological state of wanting food, directly affects the physiological processes of digestion and metabolism (Pavlov 1902; Powley 1977).

Fig. 55.1 Plasma insulin
concentration following a
sham feeding. The sham-fed
subjects (*filled circles*) show
a cephalic phase insulin
response occurring minutes
after tasting food. The
subjects who fasted (*open
circles*) show a continuously
stable concentration of
insulin in the plasma (Data
from Teff 2000)
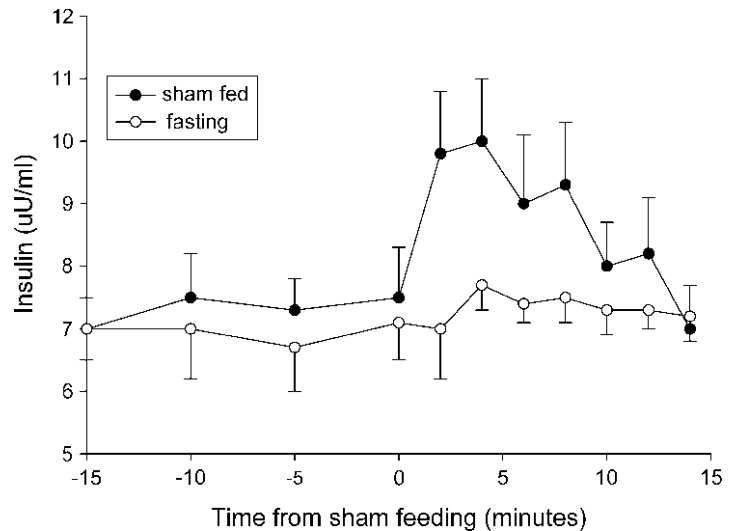
Cephalic phase responses can be demonstrated using the technique of sham feeding. In humans, this consists of masticating the test diet or tastant, but not swallowing it. In animal models, the use of fistulas at different parts of the GI tract allows an animal to masticate and swallow, but keeps the food from the GI tract below the fistula. Thus food sensory cues can be restricted to sections of the alimentary canal. Sham feeding stimulates a number of changes in the gastrointestinal tract, the circulatory system, and in behavior. Sham feeding induces the secretion of peptides from the pancreas, resulting in an anticipatory rise in circulating insulin concentration (Fig. 55.1).

Pavlov (1902) demonstrated that food placed directly into the stomach of dogs was poorly digested; however, if sham feeding preceded the intragastric intubation, then digestion was enhanced. Several clinicians in the 1800s and early 1900s independently discovered that patients with fistulas who needed to be fed by gastric intubation fared much better if they were allowed to chew and taste food prior to the delivery of the meal to their stomach. Appetite increased, and patients were better able to maintain body weight. One patient insisted on swallowing the masticated food, even though it was shortly regurgitated from his esophogeal pouch (reviewed in Powley 1977).

But cephalic phase responses do more than just enhance digestion; they enhance metabolism as well. Glucose is a prime example of a nutrient whose blood concentration is actively regulated by both reactive and anticipatory physiology. If blood glucose falls below a critical concentration it can lead to rapid brain damage and then death. High concentrations of blood glucose are potentially toxic, and are associated with macular degeneration, brain cell death, and higher mortality after stroke (Williams et al. 2002; Gentile et al. 2006). A number of mechanisms have evolved to resist changes in blood glucose concentration, and keep it within safe levels. Glucose is constantly being shuttled among different pools, or perhaps more precisely, the energy contained in glucose is shuttled among these pools.

Insulin is the primary peptide regulating glucose metabolism. Insulin increases glucose storage (in the form of glycogen) in liver and muscle, decreases lipolysis and gluconeogenesis, and increases fatty acid synthesis by adipose tissue (Porte et al. 2005). The net result is to lower blood glucose concentration by increasing the conversion of glucose to other energy storage molecules (glycogen and fat) and decreasing the production of glucose from the liver. An increase in blood glucose is met with an increase in insulin secretion from the pancreas. However, circulating insulin can increase even in the absence of a blood glucose change in anticipation of feeding.

In humans and rats there is a robust cephalic phase insulin response (reviewed in Powley 1977; Powley and Berthoud 1985; Teff 2000). If food is masticated and tasted, the pancreas rapidly begins

Fig. 55.2 Plasma insulin concentration following ingestion of a mixed nutrient sandwich. The data shows an initial pulse of insulin secretion between 0 and 10 min after ingestion followed by a larger, more sustained secretion in response to the absorption of digested nutrients (Data from Teff 2000)
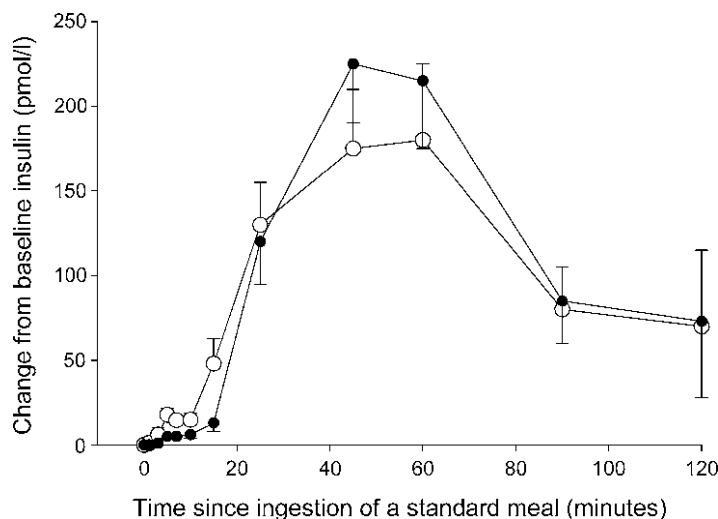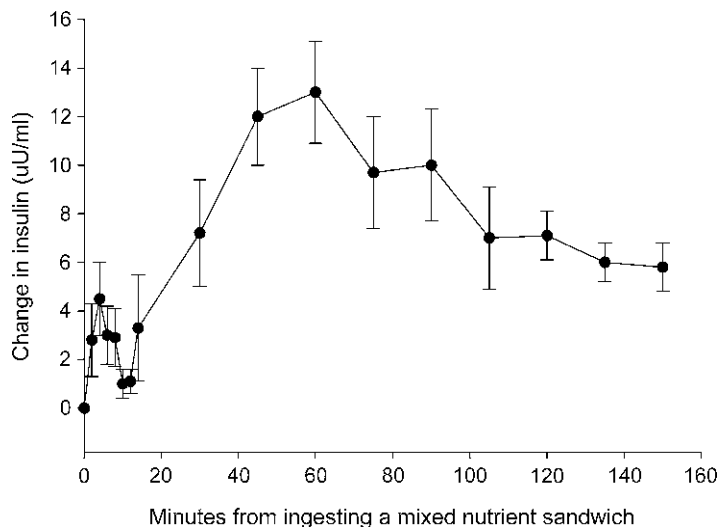
Fig. 55.3 Plasma insulin concentration following ingestion of a standard meal. The cephalic phase insulin response to a meal was partially blocked by the infusion of trimethaphan (*filled circles*) relative to saline infusion (*open circles*). In the saline infused women a small increase in insulin was observed at 5, 7, and 10 min after beginning a meal, although blood glucose did not show a significant increase until 15 min. Insulin levels were higher in the saline infused women compared to the trimethaphan infused women at 3, 7, and 15 min after beginning the meal (Data from Ahren and Holst 2001)

to secrete insulin, as well as other peptides. This initial pulse of insulin secretion is followed by a larger, more sustained insulin secretion in response to the absorption of digested nutrients (Fig. 55.2). The cephalic phase insulin response thus anticipates and mimics, at an attenuated level, the postabsorptive insulin response to changes in blood glucose concentration (Teff 2000).

Although the magnitude of the cephalic phase insulin response is small compared to the postprandial response, it has significant physiological effects (e.g., Ahren and Holst 2001). Preventing the cephalic phase response, for example, through infusion of trimethaphan, results in both significantly higher peak blood glucose concentration and impaired reduction of glucose within the first hour postprandial (Figs. 55.3 and 55.4). Thus the absence of a cephalic phase insulin response compromises glucose control

Fig. 55.4 Blood glucose concentrations following ingestion of a standard meal. There were no significant differences in blood glucose between saline (*open circles*) and trimethaphan (*filled circles*) infused women for the first 25 min after beginning the meal. In both groups blood glucose was not significantly different from baseline until 15 min. At 45 and 60 min saline infused women had significantly lower blood glucose concentrations (Data from Ahren and Holst 2001)
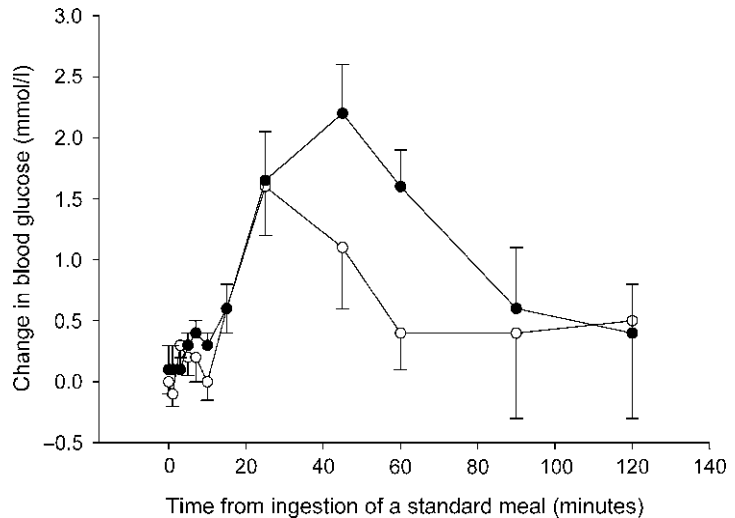
and can lead to hyperinsulinemia (Berthoud et al. 1980). Administration of insulin immediately prior to or at the beginning of a meal, i.e., during the preabsorptive period, improves glucose control in obese humans (Teff and Townsend 1999) and in type 2 diabetics (Bruttomesso et al. 1999).

55.2.1.2 Evidence for Central Nervous System Contribution

Conditioned taste preferences and conditioned taste aversions provide strong proof that responses to food cues can be learned and modified (Booth 1972; Rozin 1976). Most animals readily learn to avoid food sources that render them ill; a special visceral learning linked to food ingestion (Garcia et al. 1974; Rozin 1976). Bait shyness linked to poison is an important adaptation (Richter 1953).

Rats, and many other animals, generally like sweet tasting substances. However, rats can be conditioned to react aversively to sweet solutions by rendering them ill after ingestion. They will decrease their intake of the sweet solutions when they are exposed to them again; they also emit species specific oral/facial rejection responses as opposed to the normal positive oral/facial responses associated with desired foods (Berridge et al. 1981). Importantly, the cephalic insulin response is now decreased to orally infused sweet solution (Fig. 55.5; Berridge et al. 1981).

Cephalic phase responses can also be stimulated by operant conditioning; i.e., animals can learn to associate arbitrary sensory stimuli with the availability of food, and then will react as if the food itself has been perceived. Animals have been conditioned to time of day (Woods et al. 1970), sounds, tastes in water, and visual cues (e.g., Pavlov 1902; Woods et al. 1977) among others. For example, rats fed at a certain time everyday begin to secrete insulin (Woods et al. 1970) and ghrelin (Drazen et al. 2006) in a circadian pattern in anticipation of feeding.

55.2.2 The Paradox of Feeding

Cephalic phase responses are not just about digestion. They serve postabsorptive metabolism and physiology as well as digestion. They prepare the organism to assimilate the ingested nutrients. This is a key adaptation, as although feeding is necessary for survival, it also presents a significant challenge to homeostasis, in what has been termed the paradox of feeding (Woods 1991).

Fig. 55.5 Plasma insulin concentration following an oral infusion of various solutions. The cephalic phase insulin response to an orally infused sugar solution was significantly attenuated in rats that had been conditioned by pairing the sugar solution with a poison that caused gastrointestinal upset. There was no consistent insulin response to a sodium chloride solution (Data from Berridge et al. 1981)
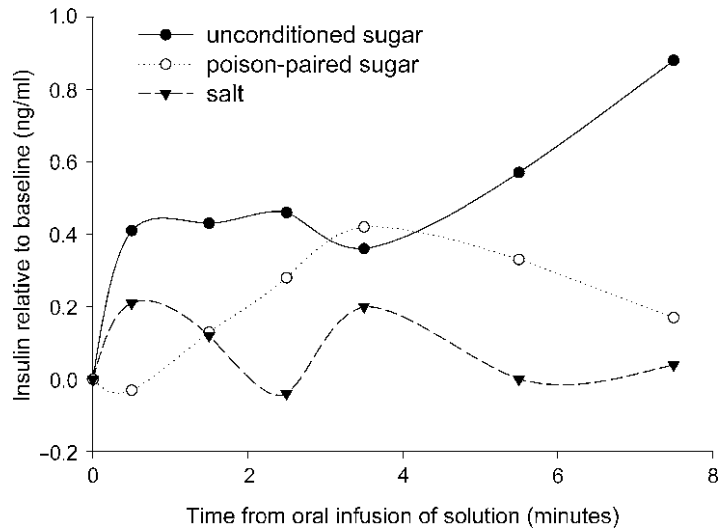
The homeostatic paradigm has guided thought and research on physiology for over 100 years. Starting from the work of Claude Bernard (1865) to Walter Cannon (1935), the concept that stability of the internal milieu is required for health and survival has been a central tenet. Woods (1991) eloquently presented the fundamental paradox of feeding from this physiological perspective. Organisms must consume food in order to survive; however, the act of consumption results in an influx of bioactive substances into the body, and presents a challenge to the stability of the internal milieu. Nutrients are required, but many nutrients are also toxic; they have maximal as well as minimal levels for concentration in the blood. Feeding can have negative as well as positive effects and requires metabolic adaptations to return the intercellular fluid to its homeostatic set points.

Although both of us have questioned the primacy of the homeostatic paradigm (Schulkin 2003; Power 2004), neither of us denies the importance of homeostasis in understanding functional and adaptive aspects of physiology. We have merely argued that homeostasis does not represent all of physiological regulation, and that often animals are required to abandon homeostasis to serve the goal of being a viable organism (defined in the evolutionary sense as capable of passing on its genetics to future generations). Viability, not stability, is the parameter of evolutionary importance (see Power 2004). In the case of the challenges presented by digesting, absorbing, and metabolizing nutrients, however, the homeostatic paradigm provides insight into the selective pressures driving the evolution of complementary digestive and metabolic adaptations. In particular, it highlights the inherent contradictions between adaptive changes that enhance the efficiency of digestion and absorption of nutrients with the necessity of maintaining the blood stream within critical parameters for many of the absorbed nutrients.

Anticipatory digestive responses to food cues increase the rapidity and efficiency with which food is transformed into nutrients, and thus can be absorbed through the intestinal walls. This increased efficiency in absorption presents both advantages and challenges to the organism. The main advantage is obvious; the digestive tract can process a greater amount of food per unit time, and thus the rate of nutrient transfer from the environment to the animal is greater. This allows, among other possible effects, greater total food intake, shorter latency time between meals, shorter total feeding/foraging time to meet requirements, an increased ability to meet requirements on foods of lower quality or that are scarce in the environment, or combinations of these effects. However, the more quickly and efficiently an organism can digest and absorb ingested food, the greater the potential

disruption to the homeostatic conditions of the internal milieu. This requires correspondingly rapid and efficient metabolic responses in order to accommodate the pulse of nutrients entering the blood stream, keep the concentrations within tolerable limits, and eventually return the intercellular fluid to the "normal" range. This is the third phase of feeding; regulation of the absorption and metabolism of digested nutrients. Anticipatory metabolic responses to sensory contact with food or food cues that aid this phase of feeding have been demonstrated, most notably the cephalic phase insulin response (e.g., Powley and Berthoud 1985), previously discussed.

Digestive and metabolic cephalic phase responses likely would have evolved in concert. The advantages of rapid and efficient digestion and assimilation of nutrients are tempered by the subsequent greater perturbation of homeostasis due to the rapid influx of these efficiently acquired nutrients. Anticipatory, cephalic phase metabolic responses serve to ameliorate the challenge to homeostasis, and thus allow increases in digestive and absorptive efficiency. The net effect of the coordination of these processes establishes many of the constraints on feeding, such as maximal meal size and frequency, types of foods that can be eaten, the efficiency with which nutrients can be incorporated into the body, and so forth. Thus one adaptive function of satiety is to restrain feeding in defense of homeostasis (Woods 1991).

55.2.3 Cephalic Phase Responses in Appetite and Satiety

Cephalic phase responses have been suggested to play a role in appetite and satiety (Powley 1977; Woods 1991, 2006). Palatable foods generally result in more robust cephalic phase responses than do less preferred foods. Preventing cephalic phase responses results in animals and humans eating smaller meals (reviewed in Woods 1991). Cephalic phase responses would appear to allow larger meals, presumably due to their ability both to stimulate digestive processes and to address the challenge to homeostasis of the subsequent absorbed nutrients. It has also been suggested that cephalic phase responses are linked to motivation to feed, and thus may actually play a more direct role in determining meal size and total daily food intake beyond the permissive one of ameliorating negative consequences of feeding.

Insulin and leptin are important signaling molecules relevant to feeding biology. Basal circulating concentrations of insulin and leptin are in proportion to fat mass. Both insulin and leptin are transported across the blood–brain barrier, and act centrally to regulate appetite, reduce food intake, and possibly increase energy metabolism (Woods et al. 2003). Leptin is primarily produced by adipose tissue. Insulin is produced by the pancreas, but insulin signaling is affected by adipose tissue and has potent effects on adipose tissue.

Circulating levels of both insulin and leptin are regulated. Insulin secretion responds to changes in blood glucose or amino acid concentration. At basal levels, leptin generally reflects total adipose tissue; however, leptin synthesis and secretion are regulated by a number of factors. Insulin, glucocorticoids, and estrogens, among others, increase leptin secretion; androgens, free fatty acids, and growth hormone, among others, decrease leptin secretion (Kershaw and Flier 2004). Leptin secretion also varies by the type or location of the fat; i.e., subcutaneous fat generally has higher leptin secretion compared to visceral fat (Fain et al. 2004; Kershaw and Flier 2004). Fasting reduces circulating leptin far out of proportion of any fat loss, and refeeding will rapidly return circulating leptin to previous levels. In very lean populations of humans (Kuzawa et al. 2007) and nonhuman primates (Banks et al. 2001) circulating leptin generally is very low and is a poor indicator of total fat mass.

Leptin and insulin differ in important ways; circulating levels of leptin and insulin appear to reflect different fat depots. Leptin concentration is more reflective of subcutaneous fat, and insulin is

more reflective of visceral fat. Visceral fat also is more sensitive to insulin than is subcutaneous fat. Because of the differences between men and women in the proportion of visceral to subcutaneous fat, in general leptin is better correlated with total adipose mass in women, and insulin is more highly correlated to total adipose mass in men (Woods et al. 2003).

Men and women differ in the responses to central insulin and leptin. Men are more sensitive to central insulin, and women are more sensitive to central leptin. For example, intranasal insulin reduced feelings of hunger in men but not in women (Hallschmid et al. 2004). In men, intranasal administration of insulin led to weight loss, and specifically fat loss; it resulted in weight gain, primarily extracellular water, in women. Similar results have been obtained in rats. Central insulin was more effective in reducing food intake in male rats, while female rats were more sensitive to central leptin (Clegg et al. 2003).

Leptin also is a gut peptide. It is synthesized and secreted by the gastric mucosa, and appears to be secreted during meals (Bado et al. 1998). Vagal stimulation results in gastric mucosal leptin secretion, but no increase in plasma leptin concentration (Sobhani et al. 2002), suggesting that gastric leptin is secreted during the cephalic phase of gastric secretions, and acts in a paracrine fashion. Leptin receptor mRNA is present in vagal afferent neurons that innervate the gastric fundus, suggesting that leptin may have direct stimulatory effects on vagal afferents (Peters et al. 2005). Infusions of leptin into the celiac artery, but not the jugular vein, significantly reduced intake of a sucrose solution by rats (Peters et al. 2005).

Some of the leptin secreted by the gastric mucosa appears to survive the gastric acid and travels intact to the intestine where it is thought to perform multiple functions regulating the absorption of lipid, carbohydrate, and protein (reviewed in Picó et al. 2003). The functional form of the leptin receptor (Ob-Rb) is expressed in human jejunum and ileum (Morton et al. 1998). Leptin has been shown to inhibit d-galactose absorption (Lostao et al. 1998) and increase the intestinal absorption of small peptides (Morton et al. 1998). Leptin also stimulates cholecystokinin (CCK) secretion (Guilmeau et al. 2003). Leptin and CCK form a positive feedback loop; plasma CCK stimulates gastric leptin secretion (Bado et al. 1998) and duodenal infusion of leptin in rats increased plasma CCK comparable to the effects of feeding (Guilmeau et al. 2003). Leptin and CCK appear to act synergistically to activate vagal afferent neurons (Peters et al. 2004).

CCK has direct effects on meal size. Giving exogenous CCK to rats resulted in meals that were shorter on average than the meal duration of control rats. However, the treated rats ate a greater number of meals per day, and total daily food intake did not differ between treated and control rats (West et al. 1984). In rats without expression of CCK receptor type A, meals were of greater duration and consisted of greater amounts ingested. The number of meals per day decreased; however, the net effect was an overall greater daily food intake, and eventual obesity (Moran and Kinzig 2004).

Thus, in addition to its role in long-term energy balance, leptin has been suggested to play a role in short-term satiety signals, either directly via vagal afferents or indirectly through stimulation of CCK secretion. Indeed, leptin and CCK appear to act synergistically to reduce both long- and short-term food intake (Barrachina et al. 1997; Matson and Ritter 1999). The short-term regulation of food intake may function more as a defense of homeostasis than as a means of achieving neutral energy balance.

55.2.4 Ghrelin

Ghrelin is the only gut peptide known so far to stimulate food intake. Ghrelin is secreted into the bloodstream by the stomach and intestines. Exogenous ghrelin rapidly increases food intake in rats (Wren et al. 2001b) and humans (Wren et al. 2001a). Indeed, ghrelin is as potent at stimulating feeding

as neuropeptide Y (NPY). Starvation increases ghrelin plasma concentration and refeeding rapidly decreases circulating ghrelin (Ariyasu et al. 2001).

Ghrelin has been suggested to act to initiate feeding (Cummings et al. 2001, 2004). However, it is uncertain whether under natural conditions ghrelin truly serves to initiate feeding or whether its main function is to prepare the body for an expected meal (Frecka and Mattes 2008). Ghrelin has effects on peripheral organs that would serve to prepare the digestive tract for food. For example, ghrelin stimulates gastric acid secretion (Date et al. 2001), gastric emptying (Levin et al. 2006), gastrointestinal motility (Trudel et al. 2002), and pancreatic secretions (Sato et al. 2003). Of course these are not mutually exclusive functions. Indeed they are complementary; an example of a hormone serving to coordinate peripheral physiology with central motive states.

Ghrelin is an ancient regulatory molecule; it has been detected in chickens, fish, and bullfrogs (Tritos and Kokkotou 2006). In addition to its functions regulating appetite, ghrelin is a potent secretagogue of growth hormone from the pituitary through binding to the growth hormone secretory (GHS) receptor (Takaya et al. 2000). Circulating ghrelin exists in both an acylated and nonacylated form. The nonacylated form does not activate the GHS receptor, but does appear to have effects on glucose homeostasis, lipolysis, adipogenesis, cell apoptosis, and cardiovascular function, suggesting that another receptor might exist (Tritos and Kokkotou 2006). Ghrelin is produced by the post-translational cleavage of a prepropeptide of 117 residues; an alternative cleavage of this prepropeptide produces obestatin (Zhang et al. 2005). Intriguingly, obestatin has been shown to suppress food intake (Zhang et al. 2005), though the effect has not been reliably replicated. Thus the ghrelin gene appears to produce two distinct peptide hormones with opposing actions. These facts highlight the importance of post-translational mechanisms in understanding gene effects.

The processes that affect evolutionary change are limited in that they can only work on existing variation. There are many examples of ancient regulatory molecules, like ghrelin, which, over time, became adapted and co-opted to serve multiple, diverse functions. These regulatory molecules serve as "information molecules," transmitting information among organ systems and coordinating the responses of peripheral organs and the central nervous system to external and internal challenges to an organism's viability. An evolutionary perspective predicts that these molecules will have multiple and diverse functions. Ghrelin is an important gut peptide that is also a neuropeptide. Based on its known functions, ghrelin serves to coordinate peripheral physiology with appetite.

55.2.4.1 Ghrelin and Cephalic Phase Responses

When human volunteers were provided meals on a fixed schedule, plasma ghrelin concentration displayed a consistent pattern of being low immediately after a meal, slowly increasing, and then displaying a pronounced increase in concentration immediately prior to the next meal followed by an equally dramatic decline immediately after the meal (Cummings et al. 2001; Fig. 55.6). The pattern of ghrelin concentration was roughly opposite to the pattern of insulin concentration, but in phase with the circadian cycle of leptin concentration, though much more variable than leptin concentration. Because the meals were provided at fixed times, this evidence supports the hypothesis that the surge in ghrelin secretion prior to meals is a cephalic phase response that serves to initiate feeding and/or to prepare the person to digest and metabolize food.

Frecka and Mattes (2008) investigated the pattern of circulating ghrelin in 21 human subjects with either a habitual long or short interval between breakfast and lunch. The patterns of circulating ghrelin differed between these two groups exactly as their feeding habits would predict. Ghrelin increased prior to the anticipated meal time, and then declined after the meal was eaten. There was no difference between groups in the nadir of circulating ghrelin after breakfast or in the amount of time postbreakfast the nadir occurred. The time interval between the postbreakfast nadir and the prelunch

Fig. 55.6 Mean plasma ghrelin concentration over a 24-h period with three set meals. Mean plasma ghrelin in 10 human subjects (9 women and 1 man) over a 24-h period consuming breakfast (B), lunch (L), and dinner (D) at set times (8:00, 12:00, and 17:30). Subjects were aware of when meals were to be provided and the time (Data from Cummings et al. 2001)
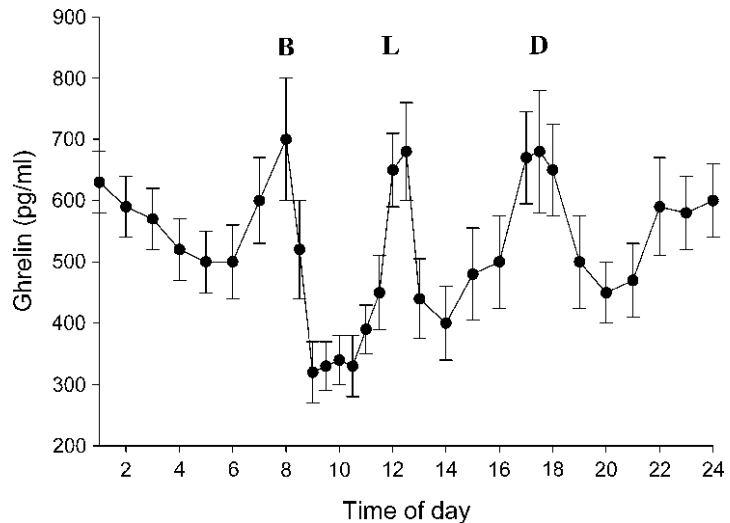
ghrelin peak was significantly longer for the habitual long interval group; but the peak ghrelin levels did not differ. In both groups the ghrelin peak occurred about 20–30 min prior to lunch. Circulating ghrelin concentration was associated with the subjects' reports of feeling hungry; however, changes in hunger appeared to precede changes in ghrelin concentration, leading Frecka and Mattes (2008) to suggest that the primary role of ghrelin was to prepare the gut in anticipation of feeding as opposed to directly increasing motivation to feed. The pattern of circulating insulin was opposite to that of ghrelin, and was consistent with a role for insulin in regulating ghrelin secretion, a finding in concordance with previous research (e.g., Cummings et al. 2004).

Further evidence for a cephalic phase component to ghrelin secretion patterns comes from a study involving rats fed either ad lib or at a fixed time. Freely feeding rats had a peak of ghrelin secretion just before the dark phase of their light cycle. The meal-trained rats had a significantly higher peak of ghrelin secretion just before the time they had become accustomed to have access to food (Drazen et al. 2006), even though that was during the light phase of their day, during which rats usually are less likely to feed.

Ghrelin secretion appears to have a cephalic phase for both the anticipatory rise before a meal and the decline with the initiation of feeding. In a study of real and sham feeding in human volunteers, serum ghrelin concentration always increased just prior to the meal. Whether the volunteers actually ate or performed a sham feeding, serum ghrelin concentration initially declined (Arosio et al. 2004). These results are consistent with the pattern of plasma ghrelin in six humans (three men and three women) accustomed to eating three meals per day who fasted over a 33-h period. Plasma ghrelin increased on both mornings (around 8:00), the middle of the day (12:00–13:00) and in the early evening (17:00–19:00). These increases were followed by a spontaneous decline in plasma ghrelin despite the fact that the subjects were fasting (Fig. 55.7; Natalucci et al. 2005). Thus the pattern of circulating ghrelin appeared entrained, and eating food was not required for the decline in circulating ghrelin postmeal time.

These results in rats and humans suggest that appetite can be entrained to a circadian clock. It suggests that hunger can occur in anticipation of food being available, but if the food is not delivered, then the system reverts to a "nonfeeding" state. Perhaps the readers are familiar with the phenomenon of being hungry, but not able to eat; after several hours the feelings of hunger recede. Of course the scent and sight of food can bring them back intensified, but otherwise, a person will no longer be "hungry" despite having not fed.
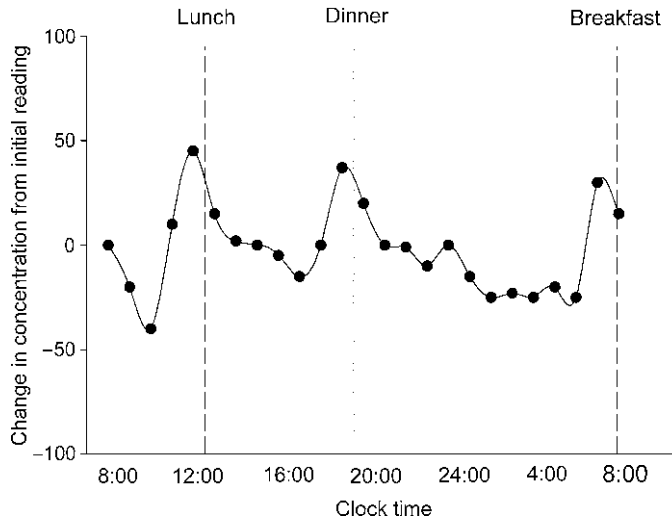
Fig. 55.7 Blood ghrelin concentration during a 32-h period of fasting. Men and women (three and three) were accustomed to eating breakfast, lunch, and dinner at approximately 8:00, 12:30, and 18:30; they then fasted for approximately 32 h, starting at midnight. Blood was collected via catheter every 20 min starting at 8:00 for 25 h when they were fed breakfast. The pattern of circulating ghrelin concentration showed a consistent pattern of rising before the expected meal time, and declining afterward, even when no food was ingested (Data from Natalucci et al. 2005)

Ghrelin is associated with hunger (Cummings et al. 2001, 2004; Levin et al. 2006; Frecka and Mattes 2008), though whether ghrelin expression stimulates hunger or is stimulated by hunger is debated. Ghrelin is expressed in the brain, especially in many areas of the hypothalamus, but also in the amygdala, bed nucleus of the stria terminalis, and cortex (Cowley et al. 2003). In the hypothalamus ghrelin frequently colocalized with NPY and stimulated activity of NPY and agouti-related protein (AgRP) neurons (Cowley et al. 2003). The effects of ghrelin in the arcuate nucleus are especially intriguing; ghrelin increased the activity of NPY neurons and inhibited POMC neurons (Cowley et al. 2003). The GHS receptor is expressed in most NPY neurons (Willesen et al. 1999). Ghrelin increases gene expression of both NPY and AgRP (Goto et al. 2006). The orexigenic effects of ghrelin are abolished in NPY and AgRP null mice (Chen et al. 2004).

Although the hypothalamus and especially the arcuate nucleus has garnered much recent attention, brain circuits relevant to feeding behavior are widely distributed in the brain. Ghrelin expression and effects in other brain regions, both forebrain and brainstem, deserve attention. For example, ghrelin administration in caudal brainstem has potent orexigenic effects (Faulconbridge et al. 2003, 2005). These effects are mediated by GHS receptors and NPY, as in the hypothalamus, but appear to represent a distinct neural circuit from the hypothalamic circuit and to rely on different NPY receptors (Faulconbridge et al. 2005).

55.3 Conclusions

Physiological and metabolic systems serve the survival and reproductive capabilities of the organism (fitness). In real-world situations animals are constantly balancing competing imperatives. It can be argued that the resolution and prioritization of those competing imperatives is a principal function of

the central nervous system. Another principal function of the CNS is the coordination of responses to and in anticipation of challenges. The central nervous system is intimately involved in physiological regulation.

Anticipatory, feedforward systems are vital to regulatory physiology. Physiology is not merely reactive. Cephalic phase responses are a fundamental concept in regulatory physiology; a paradigmatic example of anticipatory physiological responses. They need to be integrated across the diverse regulatory information molecules that are being discovered. They need to be viewed in an adaptive, evolutionary perspective. They represent, in our opinion, the results of feedforward evolutionary pressures; an "arms race," if you will, between the imperatives of increasing the rate of nutrient acquisition and of defending the internal milieu.

Some cephalic phase responses (e.g., ghrelin and insulin) appear to affect appetite (central motive states) as well as peripheral physiology, and thus are involved in coordinating physiology and behavior. Cephalic phase responses serve to increase meal size/duration (efficiency of digestive and metabolic responses) and thus increase food intake per meal. They also begin endocrine cascades to terminate a meal. There are multiple reasons, in addition to energy balance and adipose tissue homeostasis, to terminate a meal. Defense of homeostasis (sensu Woods 1991) is an important consideration.

Another simple, and perhaps little considered factor, is that animals have many necessary functions to perform to be viable. There are strong incentives and redundant neural circuits reinforcing feeding behavior. There have to be equally strong mechanisms to stop feeding in the presence of available food or animals would be constantly feeding, regardless of other imperatives. There are many constraints on animals, but time is a universal one. Animals, to be viable, must apportion their time among the various activities necessary for survival and reproduction. Motivation should vary over the circadian cycle, and peripheral physiology should be in synchrony with behavior. Cephalic phase responses are adaptive mechanisms to achieve these purposes for feeding biology.

Summary Points

- Anticipatory feeding responses prepare organisms for physiological imbalances due to the ingestion of nutrients.
- These anticipatory feeding responses, termed cephalic phase responses, improve the efficiency of food digestion, absorption, and metabolism.
- The central nervous system is intimately involved in cephalic phase responses; organisms can learn when to expect food. Some cephalic phase responses can become entrained to a circadian rhythm.
- Insulin has a cephalic phase response and circulating insulin increases in anticipation of feeding; loss or attenuation of this response compromises the ability to regulate circulating glucose levels.
- Ghrelin is a gut peptide that acts in the brain to stimulate food intake. It also acts on peripheral organs to prepare for a meal.
- In humans and rats fed at consistent times over many days, ghrelin has been shown to have a circadian rhythm that matches the expected meal times. This circadian rhythm is evident even if the human subjects are fasting.
- One function of the circadian rhythm of ghrelin may be to align motivation and peripheral physiology, such that feeding behavior and the preparatory physiological changes to enhance digestion and metabolism occur at the times of expected food availability.

Key Terms

Homeostasis: A term popularized by the American physiologist W.B. Cannon in the 1920s to describe the physiological processes that serve to maintain the stability of the internal milieu, a concept originally proposed by Claude Bernard in the late 1800s. A modern definition is the physiological processes that serve to protect the viability of the organism by resisting changes to its internal states. An example relevant to this essay is the secretion of insulin from the pancreas to maintain circulating blood glucose within certain boundaries.

Allostasis: The physiological processes that serve to protect the viability of an organism by changing its internal states. This concept has been proposed in recognition of the fact that not all adaptive physiological regulation is homeostatic (resisting change). Many regulatory processes serve to change an animal's state in response to external or internal conditions. The distinction between homeostatic and allostatic processes can often be difficult, and can depend on the time frame perspective. Both concepts can be incorporated into the concept of regulatory physiology as the total of processes that act to adjust an organism's internal state in response to challenges in order to enhance the organism's evolutionary fitness.

Cephalic phase response: An anticipatory physiology response to either the sensing of food or to the expectation that food will become available that serves to prepare the body to digest, absorb, and metabolize nutrients.

Insulin: A peptide hormone secreted by the pancreas. Insulin serves to regulate circulating glucose concentration by regulating aspects of glucose and lipid metabolism primarily in muscle, liver, and adipose tissue.

Ghrelin: A peptide hormone secreted by the stomach. Ghrelin acts in the brain to stimulate appetite and food ingestion, and acts in the periphery to prepare the gut to digest food.

Leptin: A peptide hormone primarily secreted by adipose tissue; but also by the stomach. Leptin acts in the brain to suppress appetite.

Circadian rhythm: Cyclical changes to an organism's physiology and metabolism that usually occur over a roughly 24-h cycle. In this essay the circadian rhythm of circulating ghrelin is discussed in the context of expected meal times.

References

Ahren B, Holst JJ. Diabetes. 2001;50:1030–38.

Ariyasu H, Takaya K, Tagami T, Ogawa Y, Hosuda K, Akamizu T, Suda M, Koh T, Natusi K, Toyooka S, Shirakami G, Usui T, Shimatsu A, Doi K, Hosoda H, Kojima M, Kanagawa K, Nakao K. *J Clin Endocrinol Metab*. 2001;86:4753–58.

Arosio M, Ronchi CL, Beck-Peccoz P, Gebbia C, Giavoli C, Cappiello V, Conte D, Peracchi M. *J Clin Endocrinol Metab*. 2004;89:5101–4.

Bado A, Levasseur S, Attoub S, Kermorgant S, Laigneau JP, Bortoluzzi MN, Moizo L, Lehy T, Guerre-Millo M, Le Marchand-Brustel Y, Lewin MJ. *Nature*. 1998;394:790–93

Banks WA, Phillips-Conroy JE, Jolly CJ, Morley JE. *J Clin Endocrinol Metab*. 2001;86:4315–20.

Barrachina MD, Martinez V, Wang L, Wei JY, Tache Y. *Proc Natl Acad Sci USA*. 1997;94:10455–460.

Bernard C. *An introduction to the study of experimental medicine*, Greene, HC, trans. Dover New York: Publications; 1865.

Berridge KC, Grill HJ, Norgren R. *J Comp Physiol Psychol*. 1981;95:363–82.

Berthoud HR, Trimble ER, Siegal EG, Bereiter DA, Jeanrenaud B. *Am J Physiol*. 1980;238:E336–40.

Booth DA. *J Comp Physiol Psychol*. 1972;81:457–71.

Bruttomesso D, Pianta A, Mari A, Valerio A, Marescotti MC, Avogaro A, Tiengo A, Del Prato S. *Diabetes*. 1999;48:99–105.

Cannon WB. *Am J Med Sci*. 1935;189:1–14.

Chen HY, Trumbauer ME, Chen AS, Weingarth DT, Adams JR, Frazier EG, Shen Z, Marsh DJ, Feighner SD, Guan X-M, Ye Z, Nargund RP, Smith RG, Van der Ploeg LHT, Howard AD, MacNeil DJ, Qian S. *Endocrinology*. 2004;145:2607–12.

Clegg DJ, Riedy CA, Smith KA, Benoit SC, Woods SC. *Diabetes*. 2003;52:682–7.

Cowley MA, Smith RG, Diano S, Tschöp M, Pronchuk N, Grove KL, Strasburger CJ, Bidlingmaier M, Esterman M, Heiman ML, Garcis-Segura LM, Nillni EA, Mendez P, Low MJ, Sotonyi P, Friedman JM, Liu H, Pinto S, Colmers WF, Come RD, Horvath TL. *Neuron*. 2003;37:649–61.

Cummings DE, Purnell JQ, Frayo RS, Schmidova K, Wisse BE. *Diabetes*. 2001;50:1714–9.

Cummings DE, Frayo RS, Marrmonier C, Aubert R, Chapelot D. *Am J Physiol Endocrinol Metab*. 2004;287:E297–304.

Date Y, Nakazato M, Murakami N, Kojima M, Kangawa K, Matsukura S. *Biochem Biophys Res Commun*. 2001; 280:904–7.

Drazen DL, Vahl TP, D'Alessio DA, Seeley RJ, Woods SC. *Endocrinology*. 2006;147:23–30.

Fain JN, Bahouth SW, Madan AK. *Int J Obesity*. 2004;28:616–22.

Faulconbridge LF, Cummings DE, Kaplan JM, Grill HJ. *Diabetes*. 2003;52:2260–65.

Faulconbridge LF, Grill HJ, Kaplan JM. *Diabetes*. 2005;54:1985–93.

Feldman M, Richardson CT. *Gastroenterology*. 1986;90:428–33.

Frecka JM, Mattes RD. *Am J Physiol Gastrointest Liver Physiol*. 2008;294:G699–707.

Garcia J, Hankins WG, Rusiniak KW. *Science*. 1974;185:824–31.

Gentile NT, Seftchick MW, Huynh T, Kruus LK, Gaughan J. *Acad Emerg Med*. 2006;13:174–80.

Goto M, Arima H, Watanabe M, Hayashi M, Banno R, Sato I, Nagasaki H, Oiso Y. *Endocrinology*. 2006;147: 5102–9.

Guilmeau S, Buyse M, Tsocas A, Laigneau JP, Bado A. Diabetes. 2003;52:1664–72.

Hallschmid M, Benedict C, Schultes B, Fem H-L, Born J, Kern W. *Diabetes*. 2004;53:3024–29.

Kershaw EE, Flier JS. *J Clin Endocrinol Metab*. 2004;89:2548–56.

Kuzawa CW, Quinn EA, Adair LS. *Am J Phys Anthropol*. 2007;132:642–9.

Levin F, Edholm T, Schmidt PT, Grybäck P, Jacobsson H, Degerblad M, Höybye C, Holst JJ, Rehfeld JF, Hellström PM, Näslund E. *J Clin Endocrinol Metab*. 2006;91:3296–302.

Lostao MP, Urdaneta E, Martinez-Anso E, Barber A, Martinez JA. *FEBS Lett*. 1998;423:302–6.

Matson CA, Ritter RC. *Am J Physiol Regul Integr Comp Physiol*. 1999;276:R1038–45.

Moran TH, Kinzig KP. *Am J Physiol Gastrointest Liver Physiol*. 2004;286:G183–88.

Morton NM, Emilsson V, Liu YL, Cawthorne MA. *J Biol Chem*. 1998;273:26194–201.

Natalucci G, Reidl S, Gleiss A, Zidek T, Frisch H. *Eur J Endocrinol*. 2005;152:845–50.

Papatryphon E, Capilla E, Navarro I, Soares JH Jr. *Fish Physiol Biochem*. 2001;24:31–39.

Pavlov IP. The work of the digestive glands. London: Charles Griffin; 1902.

Peters JH, Karpiel AB, Ritter RC, Simasko SM. *Endocrinology*. 2004;145:3652–7.

Peters JH, McKay BM, Simasko SM, Ritter RC. *Am J Physiol Regul Integr Comp Physiol*. 2005;288:R879–84.

Picó C, Oliver P, Sánchez J, Palou A. *Br J Nutr*. 2003;90:735–41.

Porte D Jr, Baskin DG, Schwartz MW. *Diabetes*. 2005;54:1264–76.

Power ML. In: Schulkin J, editor. Allostasis, homeostasis and the costs of adaptation. Cambridge: Cambridge University Press; 2004. pp. 343–64.

Powley TL. *Psychol. Rev*. 1977;84:89–126.

Powley TL, Berthoud H-R. *Am J Clin Nutr*. 1985;42:991–1002.

Richter CP. *Ann NY Acad Sci*. 1953;56:225–39.

Rozin P. In: Rosenlatt JS, Hinde RA, Shaw E, Beer C, editors. Advances in the study of behavior. New York: Academic; 1976.

Sato N, Kanai S, Takano S, Kurosawa M, Funakoshi A, Miyasaka K. *Jpn J Physiol*. 2003;53:443–9.

Schulkin J. Rethinking homeostasis: Allostatic regulation in physiology and pathophysiology. Cambridge: MIT Press; 2003.

Sobhani I, Buyse M, Goiot H, Weber N, Laigneau JP, Henin D, Soul JC, Bado A. Gastroenterology. 2002;122:259–63.

Takaya K, Ariyasu H, Kanamoto N, Iwakura H, Yoshimoto A, Harada M, Mori K, Komatsu Y, Usui T, Shimatsu A, Ogawa Y, Hosoda K, Akamizu T, Kojima M, Kangawa K, Nakao K. *J Clin Endocrinol Metab*. 2000;85:1169–74.

Teff KL. *Appetite*. 2000;34:206–13.

Teff KL, Townsend RR. *Am J Physiol Regul Integr Comp Physiol*. 1999;277:R198–208.

Tritos NA, Kokkotou EG. *Mayo Clin Proc*. 2006;81:653–60.

Trudel L, Tomasetto C, Rio MC, Bouin M, Plourde V, Eberling P, Poitras P. *Am J Physiol Gastrointest Liver Physiol*. 2002;282:G948–52.

West DB, Fey D, Woods SC. *Am J Physiol Regul Integr Comp Physiol*. 1984;246:R776–87.

Willesen MG, Kristensen P, Rømer J. *Neuroendocrinology*. 1999;70:306–16.

Williams LS, Rotich J, Qi R, Fineberg N, Espay A, Bruno A, Fineberg SE, Tierney WR. Neurology. 2002;59:67–71.

Woods SC *Psychol Rev*. 1991;98:488–505.

Woods SC. *Obesity*. 2006;14:171S–8S.

Woods SC, Hutton RA, Makous W. *Proc Soc Exp Biol Med*. 1970;133:965–8.

Woods SC, Vasselli JR, Kaestner E, Szakmary GA, Milburn GA, Vitiello MV. *J Comp Physiol Psychol*. 1977;91:128–33.

Woods SC, Gotoh K, Clegg DJ. *Exp Biol Med*. 2003;228:1175–80.

Wren AM, Seal LJ, Cohen MA, Byrnes AE, Frost GS, Murphy KG, Dhillo WS, Ghatei MA, Bloom SR. *J Clin Endocrinol Metab*. 2001a;86:5992.

Wren AM, Small CJ, Abbott CR, Dhillo WS, Seal LJ, Cohen MA, Batterham RL, Taheri S, Stanley SA, Ghatei MA, Bloom SR. *Diabetes*. 2001b;50:2540–47.

Zhang JV, Ren P-G, Avsian-Kretchmer O, Luo C-W, Rauch R, Klein C, Hseuh A. *Science*. 2005;310:996–9.

Chapter 56
Food Intake and Heart Rate Variability: Toward a Momentary Biopsychosocial Understanding of Eating Behavior

Hiroe Kikuchi, Kazuhiro Yoshiuchi, Ken Ohashi, Fumiyo Sato, Yoshiyuki Takimoto, Akira Akabayashi, and Yoshiharu Yamamoto

Keywords Heart rate variability • Ecological momentary assessment

Abbreviations

AN	Anorexia nervosa
BED	Binge eating disorder
BMI	Body mass index
BN	Bulimia nervosa
BPV	Blood pressure variability
BRS	Baroreflex sensitivity
cEMA	Computerized ecological momentary assessment
ECG	Electrocardiography
EMA	Ecological momentary assessment
HF	High frequency
HRV	Heart rate variability
LF	Low frequency
PDA	Personal digital assistant
RSA	Respiratory sinus arrhythmia
SBP	Systolic blood pressure

56.1 Introduction

Heart rate variability (HRV) is a term which refers to variations of heartbeat intervals of sinus rhythm (Task Force of the European Society of Cardiology the North American Society of Pacing Electrophysiology 1996). Heart rate is under the control of the cardiac autonomic nervous system. HRV is analyzed by various methods such as time domain analysis, frequency domain analysis, and nonlinear analysis (Table 56.1). Frequency domain analysis provides a power spectrum, which shows the power distribution along the frequency of the variation. Based on physiological studies on the

Y. Yamamoto (✉)
Educational Physiology Laboratory, Graduate School of Education,
The University of Tokyo
e-mail: yamamoto@p.u-tokyo.ac.jp

Table 56.1 Key facts of autonomic nervous system and heart rate variability

1. The autonomic nervous system (ANS) is the part of the peripheral nervous system that acts as a control system.
2. The ANS controls visceral functions such as heart rate, digestion, respiration rate, salivation, perspiration, diameter of the pupils, urination, and sexual function.
3. The ANS is divided into two parts: the sympathetic nervous system (SNS) and parasympathetic nervous system (PNS).
4. Functionally, the SNS and PNS are complementary in maintaining a balance in the tonic activities of many visceral structures and organs.
5. The SNS is concerned primarily with organ responses during rage and fright, such as increase of heart rate and blood pressure.
6. The PNS is concerned primarily with conservation of energy and maintenance of organ function during periods of minimal activity such as decrease of heart rate and blood pressure.
7. Heart rate variability (HRV) usually indicates variations of instantaneous RR intervals.
8. HRV is used for noninvasive investigation of the cardiovascular ANS function.

This table lists the key facts of the autonomic nervous system (ANS) including the function of the ANS, the complementary functions of the sympathetic nervous system and parasympathetic nervous system, and the association between the ANS and heart rate variability

transmission frequency properties of sympathetic and parasympathetic controls and those involving autonomic blockades, the power of the high frequency (HF) component (0.15–0.40 Hz) is considered to reflect cardiac parasympathetic activity and the power of the low frequency (LF) component is considered to reflect both cardiac sympathetic and parasympathetic activities. Therefore, HRV is used for the noninvasive investigation of cardiovascular autonomic functions. HRV is also known to have a prognostic value in life-threatening cardiac diseases.

In this chapter, HRV in two extreme states of food intake will be discussed first. One is obesity as a consequence of excess food intake, and the other is anorexia nervosa as an example of extremely low body weight resulting from insufficient food intake. Then, the need for a momentary biopsychosocial understanding of the interplay between eating behavior and the underlying physiology, and how this can be achieved, will be addressed.

56.2 Obesity and Heart Rate Variability

The autonomic nervous system is involved in the regulation of energy expenditure and is assumed to contribute to the pathophysiology of obesity. In addition, obese subjects suffer from an increased risk of cardiovascular diseases, and it has been speculated that the cardiac autonomic function may in part explain this risk. Reduced heart rate variability itself is also known to predispose patients with life-threatening cardiac diseases to sudden cardiac death (Goldberger et al. 2008). Therefore, the autonomic nervous system is thought to play a role in obesity and related complications, and HRV in obesity has been investigated (Table 56.2).

Previous studies on HRV in obese subjects have almost consistently showed that parasympathetic nervous activity indexed by HF power of HRV is more significantly decreased in obese subjects than in nonobese controls (Piccirillo et al. 1998; Karason et al. 1999; Skrapari et al. 2007). Although sympathetic activity has been suggested to increase in obesity in studies using other indexes like plasma norepinephrine levels, conclusions concerning sympathetic nervous activity from previous studies are rather inconsistent. One reason is that no frequency component of HRV is affected solely by sympathetic activity, which makes the interpretation of the results difficult. The ratio of LF power to HF power (LF/HF) of HRV is sometimes used as an index of cardiac sympathetic function. However, the results of LF/HF are still inconsistent (Piccirillo et al. 1998; Skrapari et al. 2007).

Table 56.2 Studies on obesity and heart rate variability

First author, Country, year	Sample size, description, baseline age (mean or range)	Measurement and analysis	Variables of HRV	Major results
Cross sectional study				
Chen, Taiwan, 2008	77 Obese (BMI > 28)/CON (BMI < 23) Without HT 29.6/ 28.1	512 beats Power spectral analysis (FFT)	VLF(0.01–0.04 Hz), LF(0.04–0.15 Hz), HF(0.15–0.40 Hz), TP(0.01–0.40 Hz), nLF, nHF	nLF, nHF: obese < CON. In obese subjects, waist and waist–hip ratio were positively correlated with nLF, LF/HF, and negatively correlated with nHF.
Skrapari, Greece, 2007	60 Obese (BMI > 30)/CON (BMI < 25) Without HT 42.7/42.8	5 min, supine Power spectral analysis (CGSA)	HF (0.15–0.5 Hz), LF (0.05–0.15 Hz), TP (0.003–0.50 Hz), LF/HF	LF: obese < CON, HF: obese < CON, LF/HF: obese > CON
Piccirillo, Italy, 1998	43 Moderately obese(BMI < 40)/massively obese (BMI > 40)/CON (BMI <26) Without HT 47.0/ 52.0/ 48.1	10 min, supine & HUT Power spectral analysis (autoregressive)	TP, HF (0.15–0.40 Hz), LF (0.04–0.15 Hz), VLF (–0.04 Hz), nHF, nLF, LF/HF	nLF at rest and HUT: massively obese < moderately obese, CON (decreased LF may reflect the inability to respond to the neurotransmitter of SNS)
Longitudinal study				
Poirier, USA, 2003	8 Obese (BMI >= 40) Without uncontrollable HT 18–50 (inclusion criteria)	24 h Time domain analysis, power spectral analysis (details NA)	SDNN, SDANN, rMSSD, pNN50, VLF (0.0033–0.04 Hz), LF (0.04–0.15 Hz), HF (0.15–0.40 Hz), LF/HF	After weight loss, LF, HF, SDNN, and SDANN increased during both diets. rMSSD and pNN50 increased only during high carb diet.
	Weight loss by diet (3 mm) followed by weight maintenance by high fat diet and high carb diet (3 mm)			
Laaksonen, Finland, 2003	41 Obese with metabolic s yndrome (BMI 30–45, waist >=102 in M and >= 90 in W) 49.2	5 min, paced breathing (0.2 Hz) Power spectral analysis (modified covariance autoregressive model)	TP (0–0.40 Hz), LF (0.04–0.15 Hz), HF (0.15–0.40 Hz)	After weight loss, TP, LF increased. These changes gradually attenuated during weight maintenance.
	Weight loss by VLCD (9 weeks) followed by weight mainte- nance by either orlistat or placebo with a mildly hypocaloric diet			

(continued)

Table 56.2 (continued)

First author, Country, year	Sample size, description, baseline age (mean or range)	Measurement and analysis	Variables of HRV	Major results
Emdin, Italy, 2001	Weight loss by hypocaloric diet (8 mm) Obese(BMI > 30.5 in men, 27.3 in women)/lean Without HT 39/34	24 h Power spectral analysis (autoregressive) for every 256 beats	VLF (0.003–0.03 Hz), LF (0.03–0.15 Hz), HF (0.15–0.40 Hz)	LF: obese < lean. LF/HF was positively associated with fasting plasma insulin (after adjustment for sex, age, HR and BMI). After weight loss, LF was increased.
Karason, Sweden, 1999	Weight loss by either gastric surgery or diet (1 year follow up) Obese (BMI 31–52)/ CON (BMI 17–27) 7 obese took antihypertensive medication 49/49	24 h Time domain analysis, power spectral analysis (FFT) for every 5 min	SDNN, SDANN, SDNN index, LF (0.05–0.15 Hz), HF (0.15–0.40 Hz)	SDNN, SDANN, SDNN index, HF: obese < CON Both LF and HF were negatively associated with BW after adjustment for age, sex, smoking, and antihypertensive treatment. Weight decreased only in those treated with surgery and not in those treated with diet. After weight loss, SDNN index and HF increased. Changes in both daytime HF and daytime LF were negatively associated with BW after adjustment for age, sex, smoking, and antihypertensive treatment.
Hirsch, USA, 1991	Weight gain & loss by fluid formula Normal-obese (BMI 23.4–49.9) Without HT 20–48	256 s, supine & standing Power spectral analysis (FFT)	LF (0.04–0.10 Hz), resp.F (respiratory freq. +/- 0.06 Hz), LF/resp.F	With 10% increase in BW, resp.F declined and HR rose.

This table lists studies on obesity and heart rate variability. *VLCD* very low calorie diets, *BMI* body mass index, *CON* control, *HT* hypertension, *HUT* head-up tilt, *CGSA* coarse-graining spectral analysis, *FFT* fast Fourier transform, *NA* not available, *TP* total power, *VLF* power of very low frequency component, *LF* power of low frequency component, *HF* power of high frequency component, *nLF* normalized power of low frequency component (LF/(TP-VLF)), *nHF* normalized power of high frequency component (HF/(TP-VLF)), *resp.F* power of respiratory frequency component, *SNS* sympathetic nervous system, *BW* body weight, *HR* heart rate. Refer to definition and explanation of key terms for SDNN, SDANN, SDNN index, rMSSD, and pNN50

Some researchers have speculated that no apparent activation of sympathetic nervous activity indexed by HRV has been due to a postreceptor downregulation process or heterogeneous sympathetic nervous activation among organs.

Decreased parasympathetic nervous activity has not only been observed in a cross-sectional study but also in a longitudinal study. Hirsch et al. (1991) reported that a 10% increase in body weight due to increased caloric intake is associated with a decline in parasympathetic activity indexed by the power of the respiratory frequency component. Furthermore, several studies have shown that cardiac parasympathetic activity mainly indexed by the HF power of HRV is increased with body weight reduction regardless of the method used for reduction (e.g., gastric surgery, diet therapy) (Karason et al. 1999; Laaksonen et al. 2003; Poirier et al. 2003), and a change in HF power is negatively correlated with a change in body weight (Karason et al. 1999). It is sometimes discussed whether altered cardiac autonomic function is a cause of obesity or a result of obesity. These longitudinal studies suggest that obesity causes changes in cardiac autonomic function.

The mechanism of autonomic nervous system change in obesity is still unknown. Recently, Chen et al. (2008) reported that in obese subjects, HF power was negatively correlated with waist circumference and waist to hip ratio, but not with the body mass index (BMI), and suggested that central rather than general obesity is related to the change in the cardiac autonomic function. In relation to central obesity, leptin, insulin, and the resistance of leptin and insulin seen in obese subjects may also play a role in linking obesity with the sympathetic nervous function, as increased leptin and insulin levels are thought to increase sympathetic nervous activity (Paolisso et al. 2000; Emdin et al. 2001). However, their relationships to parasympathetic nervous activity as reflected by the decreased HF power of HRV are less clear.

Some researchers claim that caloric restriction itself may affect HRV because their study with a 1-year follow-up after gastric surgery showed that an improvement of HRV was apparent in the acute body weight reduction phase but was attenuated in the later follow-up period, and the improvement of HRV was correlated with caloric intake but not with BMI or insulin resistance (Bobbioni-Harsch et al. 2008).

56.3 Anorexia Nervosa and Heart Rate Variability

Anorexia nervosa (AN) is a major subtype of eating disorder characterized by a refusal to maintain minimally normal body weight, intense fear of obesity, and body image disturbances. From the nutritional viewpoint, AN is a state of severely low body weight due to decreased and limited food intake.

Since AN has a high mortality rate and its major cause of death is cardiac complications such as cardiac sudden death, HRV in AN patients has been investigated (Table 56.3). However, the results of the studies have been inconsistent. Some have reported that sympathetic nervous activity was decreased while parasympathetic nervous activity did not change (Kreipe et al. 1994; Rechlin et al. 1998), while others have reported that parasympathetic activity was increased with or without a decrease in sympathetic activity (Petretta et al. 1997; Galetta et al. 2003). One report showed that both sympathetic and parasympathetic activities were decreased (Melanson et al. 2004).

Recently, Ishizawa et al. investigated HRV in AN by using frequency domain analysis and fractal analysis, together with blood pressure variability (BPV) and baroreflex sensitivity (BRS) in order to evaluate cardiac autonomic function more reliably and to evaluate cardiovascular risk (Ishizawa et al. 2008). A total of 32 AN patients and 37 healthy normal weight controls underwent 10-min beat-to-beat recording of heartbeat interval and systolic blood pressure (SBP). Spectral analysis was performed for heartbeat interval and SBP time series. Detrended fluctuation analysis (Peng et al. 1995),

Table 56.3 Studies on anorexia nervosa and heart rate variability

First author, country, year	Sample size, description, baseline age (mean or range)	Measurement and analysis	Variables of HRV	Major results
Ishizawa, Japan, 2008	69 AN/CON 22.9/24.3	10 min, supine Power spectral analysis (FFT), DFA	LF (0.04–0.15 Hz), HF (0.15–0.40 Hz), TP, α1	HF, TP: AN > CON, LF/HF, α1: AN < CON
Vigo, Argentina, 2008	52 AN/ BN/ CON 26.6/ 23.2/ 26.2	10 min, supine, paced breathing (0.2–0.33 Hz) Time domain analysis, power spectral analysis (FFT), DFA, Poincare plots, Approximate Entropy (ApEn)	SDNN, LF (0.03–0.14 Hz), HF (0.14–0.40 Hz), RRr, α1, ApEn	lnLF: AN < CON, α1: AN < CON, ApEn: BN < AN, CON
Melanson, USA, 2004	16 AN/ CON 29/ 24	24 h, 5 min, supine (paced breathing) Time domain analysis, power spectral analysis (FFT)	SDNN, SDANN, rMSSD, pNN50, VLF (0.003–0.04 Hz), LF (0.04–0.15 Hz),HF (0.16–0.40 Hz), LF/HF	24 h-rMSSD, 24 h-pNN50, SDNN, SDANN: AN < CON VLF, 24 h-LF, 24 h-HF: AN <CON
Galetta, Italy, 2003	75 AN/ thin/ CON 17.5/ 17.7/ 18.1	24 h Time domain analysis, power spectral analysis (FFT)	SDNN, SDANN, SDNN index, rMSSD, pNN50%, LF (0.04–0.15 Hz), HF (0.16–0.40 Hz), LF/HF	SDNN, SDANN, SDNNindex: AN > thin, CON rMSSD, pNN50: AN > thin, CON HF: AN > thin, CON LF/HF: AN < thin, CON
Rechlin, Germany, 1998	64 AN inpatient/ CON 23/23.4 4 men in AN and 2 men in CON	5 min, supine & standing Power spectral analysis (FFT)	LF (0.01–0.05 Hz), MF (0.05–0.15 Hz), HF (0.15–0.50 Hz)	In acutely ill AN, LF both when supine and standing, MF both when supine and standing, HF when standing were decreased. In recovered AN, LF when supine was decreased but others were not. Caution needed: frequency range of LF in this study is different from that of other studies

Petretta, Italy, 1997	33	AN/ thin/ CON 20/ 22/ 21	24 h, Time domain analysis, power spectral analysis (FFT)	SDNN, SDANN, SDNN index, rMSSD, pNN50%, ULF (0.00066–0.0033 Hz), VLF (0.0033–0.04 Hz), LF (0.04–0.15 Hz), HF (0.16–0.40 Hz), TP, LF/HF	SDNN, SDANN, SDNNindex: AN > CON, thin; rMSSD, pNN50%: AN > CON, thin; lnHF: AN > CON, thin
Kreipe, USA, 1994	16	AN/CON 18.6/ 20.9	256 s, supine & standing, Power spectral analysis (FFT)	LF (0.01–0.15 Hz), HF (0.15–0.60 Hz), LF/HF	LF when supine: AN < CON, HF change after standing: not seen in AN, but seen in CON

This table lists studies on anorexia nervosa and heart rate variability. *AN* anorexia nervosa, *BN* bulimia nervosa, *CON* control, *FFT* fast Fourier transform, *DFA* detrended fluctuation analysis, *NA* not available, *TP* total power, *ULF* power of ultra low frequency component, *VLF* power of very low frequency component, *LF* power of low frequency component, *MF* power of mid frequency component, *HF* power of high frequency component, *nLF* normalized power of low frequency component (LF/(TP-VLF)), *nHF* normalized power of high frequency component (HF/(TP-VLF)), *RRr* autocorrelation coefficient of RR intervals, *ApEn* approximate entropy, *BMI* body mass index. Refer to definition and explanation of key terms for SDNN, SDANN, SDNN index, rMSSD, and pNN50

Fig. 56.1 Heartbeat intervals of an anorexia nervosa patient and a healthy control. Representative data of heartbeat intervals for both groups are shown. (**a**) An anorexia nervosa patient. (**b**) A healthy control. Insets show HF power of HRV, power ratio of LF to HF of HRV, and scaling exponent α1 for the respective data. *y.o.* years old, *BMI* body mass index, *HF* power in the low frequency range, *LF/HF* ratio of power in the low frequency range to that in the high frequency range
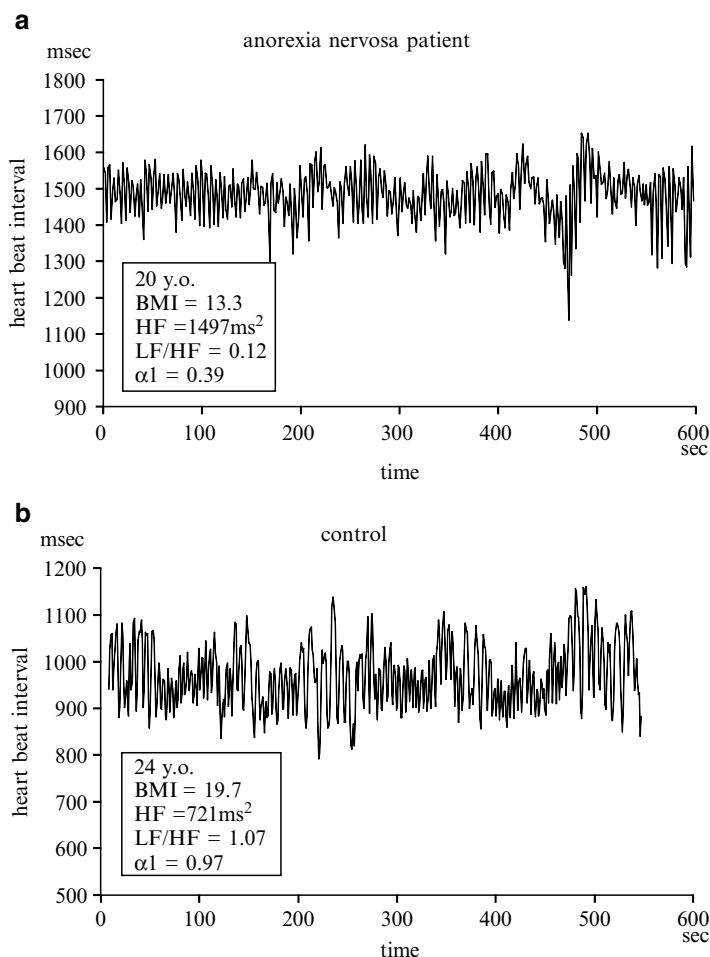
which has been used for risk stratification in cardiac patients (Huikuri et al. 2000; Mäkikallio et al. 2001b), was also conducted for quantifying the fractal correlation of HRV and the short-term scaling exponent α1 was calculated. Representative data of heartbeat interval variability for AN patients and controls are shown in Fig. 56.1.

In AN compared with healthy controls, HF power of HRV, total power of HRV, and BRS were significantly higher, and LF power of BPV, LF/HF of HRV, and the scaling exponent α1 of HRV were significantly lower. These results suggested increased parasympathetic nervous responsiveness in AN, which could be considered as an adaptive response to caloric deprivation, although it may be contrary to the increased risk of cardiac complication because decreased, rather than increased, parasympathetic nervous activity is usually related to death in cardiac patients. The results also suggested that, despite decreased sympathetic nervous responsiveness which may lead to a decreased risk of cardiac sudden death, there was a decrease in the scaling exponent α1, known to be associated with higher mortality (Huikuri et al. 2000; Mäkikallio et al. 2001b).

Although it is rational that responses of HRV in AN are in the opposite direction compared to obese subjects, the mechanism which causes such responses and the relationship with restricted food intake is still unclear and needs to be further investigated.

56.4 Bulimia Nervosa and Heart Rate Variability

Obesity and AN are thought to be conditions where excess or restricted food intake and resultant increased or decreased body weight or fat may affect the cardiac autonomic nervous function probed by HRV. However, there is another condition where the change of HRV mimics that in AN, while food intake and body weight are not severely reduced. That is bulimia nervosa (BN).

BN is another type of eating disorder, characterized by regularly repeated binge eating episodes with compensational behavior, which may be purging, such as vomiting and overuse of laxative, or something other than purging, such as overactivity and fasting. BN patients usually show normal body weight or slightly increased body weight.

BN is also known to cause cardiac complications, as does AN. In addition, some studies (Faris et al. 2008) have suggested that the ability to feel satiety in BN patients is compromised, and vagal function, although it is a visceral afferent function, might be involved in this. The natural course of BN is more benign than that of AN, and HRV in BN has attracted less attention than that in AN. Still, there have been a few studies on BN and HRV.

Kennedy et al. (1989) reported that vagal tone measured by respiratory sinus arrhythmia (RSA), which usually corresponds to HF power of HRV, increased in BN as well as in AN. Rissanen et al. (1998) reported that vagal tone measured by RSA was higher in BN than in healthy controls and, after 8 weeks of treatment by fluoxetine combined with cognitive behavior therapy, vagal tone was decreased to the level of healthy controls. Although the pharmacological effect of SSRI is not negligible when interpreting the changes after treatment, BN patients have been consistently reported to have elevated cardiac parasympathetic nervous activity without a significant change in body weight or fat, which is reversible with treatment.

These changes of HRV in BN cannot be explained by changes in body weight and fat or caloric restriction. Possible factors that may affect HRV are psychological symptoms and behaviors (e.g., eating patterns which cannot be measured by caloric intake, repeated binging, and purging), and further investigation is necessary.

56.5 Binge Eating Disorder and Heart Rate Variability

Another example which suggests that HRV change can be explained not only by body weight and fat or food intake but also by eating behavior or psychological factors is the study of cardiac parasympathetic regulation in obese women with or without binge eating disorder (BED).

BED is categorized as an eating disorder, though it is not treated as discriminated disease entity yet. BED is characterized by repeated binge eating which is similar to BN, but not accompanied by compensatory behaviors, which usually leads to overweight or severe obesity.

Friederich et al. (2006) compared cardiac parasympathetic activity of obese subjects with BED and those without BED. HF power of HRV during rest was not different between obese subjects with and without BED. The decrease in HF power of HRV during mental stress (a standard Stroop Color-Word Interference Test and a delayed auditory feedback task) was more pronounced in obese subjects with BED than those without BED. Hunger score and binge eating frequency were negatively correlated with the change of HF power of HRV during mental stress (i.e., more hunger and more frequent binge eating were related to a greater reduction in HF power of HRV). They pointed out that the hyper-responsiveness of HF power of HRV may be related to the psychopathology of BED.

In BN, it is argued that an increased baseline parasympathetic activity is related to binge eating, while this is not true in obese BED because there are no significant differences in HF power of HRV

at rest between obese subjects with and without BED. However there still is a difference in HF power change during mental stress between obese patients with and without binge eating. Again, further investigation is necessary to clarify the relationships between body weight, food intake, binge eating, psychopathology, and HRV at rest and its response to stress.

56.6 Need for a Biopsychosocial Understanding

As previous studies of obese subjects and AN patients have shown, HRV is thought to be related to food intake or body weight. However, as shown in cases of BN and obese BED, HRV cannot be explained only by the amount of digested and absorbed food, nor by body weight and fat. Behavior (e.g., binge eating and purging) itself is considered to affect HRV. Thus, the frequency and timing of such behavior (e.g., How often does a patient binge? When was the last binge eating before the electrocardiography (ECG) was recorded?) may have to be accurately assessed. Coexistent psychological pathology is also thought to affect HRV because it is well known that the heart rate is under the strong influence of emotional as well as affective factors. Therefore, in order to understand the relationship between HRV and food intake in more detail, it should be investigated and interpreted together with behavioral and psychological factors.

Furthermore, food intake itself is also known to be associated with psychological and even social factors. It should be investigated not only from the physiological viewpoint (energy balance as physiological homeostasis) but in the context of interactions with biological (autonomic nervous system activity, energy expenditure, etc.), psychological (psychological stress, mood states, etc.), behavioral (binging, purging, etc.), and social (companion, situation, etc.) factors. This is called the "biopsychosocial" point of view.

Eating disorders are extreme but good examples of disorders which involve biological, behavioral, and psychological/psychiatric pathology, and especially require a biopsychosocial approach. The importance of such an approach, however, is not limited to eating disorders but it may also be applicable to other conditions such as obesity, and even to healthy subjects when promoting healthy eating.

56.7 What Is Ecological Momentary Assessment and Why Is It Important?

What kind of methods would enable us to conduct a biopsychosocial investigation of eating behavior? First, an appropriate method for evaluating psychosocial factors in real daily life is required. Laboratory tests have the advantage that they can provide detailed data. However, the ecological validity of them is compromised. To date recalled self-reports, such as questionnaires filled in based on the subjects' recalled self-report, have often been used for evaluating subjective symptoms or experience in daily life settings, such as psychological stress, mood states, pain, and so on. It is pointed out that there is the disadvantage of recall bias in such evaluations based on recalled self-reports.

Therefore, in 1994, ecological momentary assessment (EMA) was proposed as a more appropriate method to record and evaluate mainly subjective symptoms (Stone and Shiffman 1994). EMA is a method in which subjects record their symptoms and phenomena precisely when and where they occur. Formerly, it was carried out by using paper-and-pencil diaries, but faked compliance due to hoarding and so on was inevitable when using paper-and-pencil diaries. Computerized EMA (cEMA), in which subjects use portable computers or personal digital assistants (PDA) as electronic diaries, is able to overcome the faked compliance by recording time of data inputs and is being used more

often. The accuracy in time is advantageous, especially when investigating temporal relationships between factors.

Actually, EMA has already been applied to BN and BED, after Smyth et al. (2001) pointed out the usefulness of EMA in eating disorder studies. Stein et al. (2007) conducted a study using EMA in 33 BED patients and reported that negative mood was significantly higher at prebinge than at nonbinge times and was also higher at postbinge times than at prebinge times in BED patients. Hilbert et al. (2007) conducted a study using EMA in 20 BED and 20 BN patients and 20 controls, and also reported that negative mood was significantly higher at prebinge times than prior to regular eating in BN and BED. They also found that negative mood increased after binge eating compared with those at prebinge times and during binge eating. Engel et al. (2007) conducted a study using EMA in 133 BN patients and reported that anger, which was one aspect of negative mood, was related to binge eating in BN patients. They found that the preceding anger level and the variability of the preceding anger predicted binge eating.

Most previous studies utilizing EMA in BED and BN have focused on binge eating as an event and on its correlates such as mood states. Food intake as an amount of energy or nutrition has rarely been measured, though self-reported binge eating episodes had to be confirmed to be large enough to qualify as binge eating. The measurement of energy intake could also be important when investigating other conditions without binge eating, such as obesity. In order to achieve a biopsychosocial investigation of eating behavior, data concerning energy intake, as well as physiological data such as physical activity and heart rate, should also be collected in the context of EMA, as mentioned above.

56.8 Concept of "Mobile Nurse"

Recently, Struzik et al. (2007) proposed the concept of the so-called "Mobile Nurse." Mobile Nurse is a system consisting of PDA which can communicate, through a bidirectional wireless network, with various wireless sensors for monitoring physiological variables such as ECG and physical locomotor activity, and software which works on PDA. As it is able not only to collect various kinds of symptoms and signs concurrently but also to combine, analyze, and integrate them on site, Mobile Nurse is primarily intended to enable on-site diagnoses and treatment prescriptions. It is also a powerful tool to give us a comprehensive understanding of human behavior, including eating behavior, from biopsychosocial aspects.

In order to integrate recording and evaluation of food intake into the above system, a PDA-based food recording system making an accurate food intake evaluation for a prolonged time in a daily setting is necessary.

56.9 Development of PDA-based Food Recording System

Self-monitoring of food intake is clinically important in body weight reduction and hitherto it has been applied to patients with obesity. However, previously used food recording systems are mostly based on paper-and-pencil diaries. It has been pointed out that food recording systems using paper-and-pencil diaries have shortcomings similar to those mentioned above in the case of EMA, i.e., faked compliance. It is also said that the inconvenience or burden for subjects is substantial if they have to calculate the energy and nutrients consumed by looking up the meals they have had in a calorie chart themselves. This is not practical, especially if recording goes on for a long time.

To overcome these problems, PDA-based systems have been developed for food recording systems, too. Actually this can be considered as the application of cEMA to food recording. As mentioned in connection with cEMA, PDA-based food recording systems can prevent faked compliance because PDA can record the time when data are input and therefore this may possibly even improve the reliability. Furthermore, it may reduce the inconvenience to the subjects, having a food database within it and making the recording and calculating process easier.

There have been several studies using PDA-based food recording systems. However, the reliability of the systems has rarely been confirmed. In one previous study investigating the accuracy of the PDA-based food recording system, although data recorded by the PDA-based system were significantly correlated with the data acquired by 24-h dietary recall, it was also reported that a major cause of errors in consumed energy estimated by the PDA-based system was errors in estimated portion sizes (Beasley et al. 2005).

Recently, it has been suggested that photos of menus may be helpful to reduce errors in estimated portion sizes. Fukuo et al. (2009) developed a PDA-based food recording system with a calorie database including photos of menus (Fig. 56.2), and studied its reliability and practicability in 44 healthy adults and 16 adult patients with type 2 diabetes mellitus. Subjects recorded their food intake and the times of starting meals as soon as possible after finishing meals for seven consecutive days. On the eighth day, they were interviewed by dietitians and food intake on the seventh day was evaluated by a 24-h dietary recall method, which at the time was regarded as a standard.

Daily intake of energy, proteins, carbohydrates, and fats was not different between PDA-based systems and a 24-h dietary recall method in either healthy adults or diabetes patients. In an analysis of the Pearson correlation and intraclass correlation coefficient of absolute agreement, there were significant correlations between daily intake of energy and respective nutrients estimated by the PDA-based system and those estimated by a 24-h recall method in both subject groups (Figs. 56.3 and 56.4).

The compliance rate was 0.98 ± 0.06 (mean ± SD) in healthy adults and 0.98 ± 0.03 (mean ± SD) in diabetic patients. The adherence rate, which was a proportion of inputs made within a predefined time

Fig. 56.2 Captured screen of PDA-based food recording system. After selecting menus, photos of menus are displayed on the screen. Subjects can estimate the portion sizes by reference to these photos. *PDA* personal digital assistant

Fig. 56.3 Consistency of daily total energy intake estimated by PDA-based food recording system and 24-h dietary recall method in healthy adults. Abscissa is for 24-h dietary recall method and ordinate is for PDA-based food recording system. Each dot stands for one subject. If estimations by the two methods agree, the dot is on the diagonal line shown in the plot. Pearson correlation coefficient is 0.854 ($P <$ 0.001) for these data, supporting the accuracy of this food recording system. *PDA* personal digital assistant

healthy controls
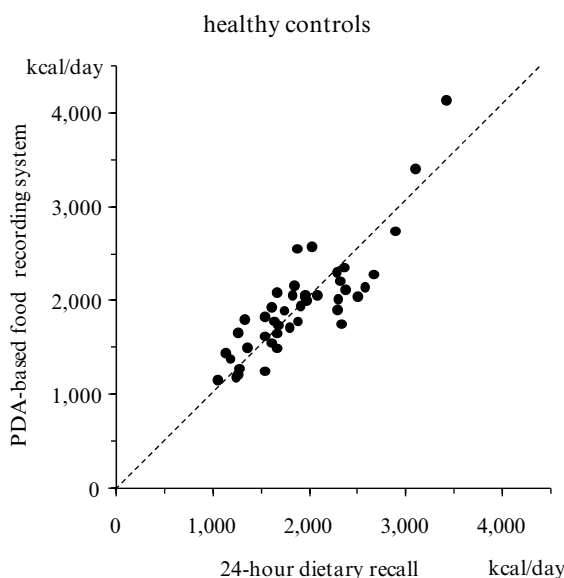
Fig. 56.4 Consistency of daily total energy intake estimated by PDA-based food recording system and 24-h dietary recall method in patients with type 2 diabetes mellitus. Abscissa is for 24-h dietary recall method and ordinate is for PDA-based food recording system. Each dot stands for one subject. If estimations by the two methods agree, the dot is on diagonal line shown in plot. Pearson correlation coefficient is 0.808 ($P <$ 0.001) for these data, supporting the accuracy of this food recording system. *PDA* personal digital assistant

diabetes mellitus
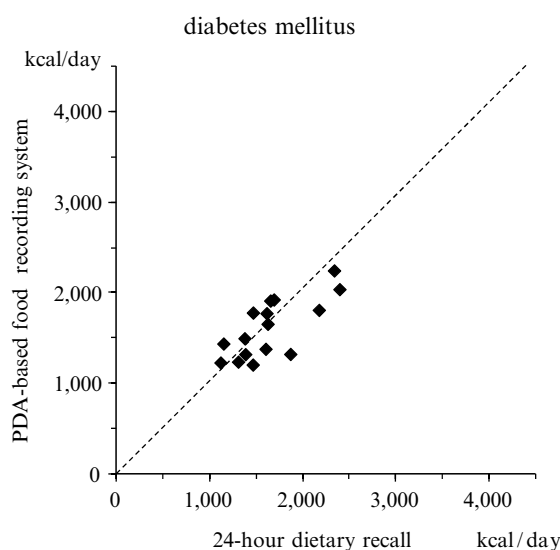
after the meal, was 0.41 ± 0.17 within 1 h, 0.53 ± 0.16 within 2 h, 0.73 ± 0.17 within 6 h in healthy adults and 0.59 ± 0.31, 0.66 ± 0.27, and 0.79 ± 0.21, respectively, in diabetic patients. This newly developed PDA-based food recording system was shown to have a good accuracy and a high compliance rate.

56.10 Application in Healthy Subjects

The "Mobile Nurse" system combined with the PDA-based food recording system described above could be a promising tool for a comprehensive understanding of human eating behavior. Preliminary results of a pilot study utilizing these systems in healthy adults are shown below.
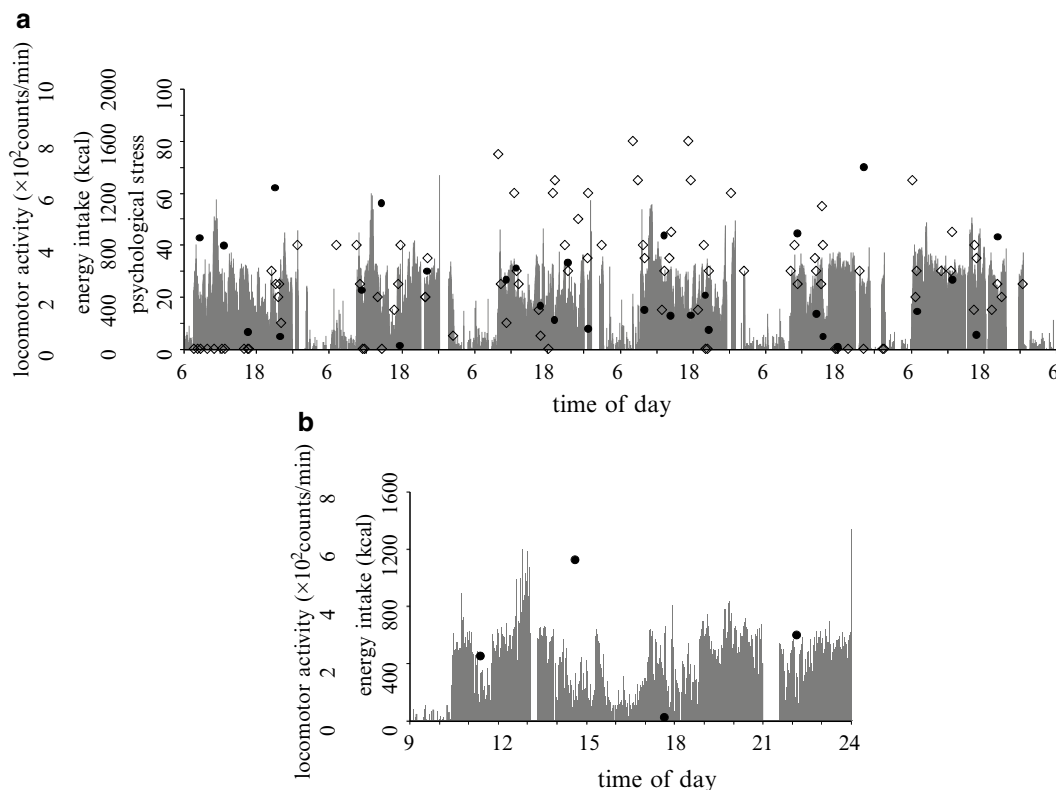
Fig. 56.5 Data example of locomotor activity, momentary psychological stress, and energy intake from one healthy graduate student. (**a**) Bar chart shows locomotor activity. *Filled circles* show energy intake. *Open diamonds* show momentary psychological stress. (**b**) A part of (**a**) is magnified. It seems that increased locomotor activity was followed by increased energy intake and decreased locomotor activity was followed by decreased energy intake

Healthy undergraduate and graduate students wore watch-type computers for seven consecutive days. They recorded psychological stress, mood states, appetite, and circumstances (whom they were with and where they were) using the computers as electronic diaries just before and after meals and snacks, as well as at random prompts, when waking up and when going to bed. They also recorded food intake by the PDA-based food recording system just after meals and snacks. Locomotor activity was also recorded continuously by an actigraph installed inside the watch-type computer (Kikuchi et al. 2007).

A total of 20 subjects made 509 recordings of food intake and 1,628 recordings of other factors such as psychological stress and mood states. Representative data are shown in Fig. 56.5. Locomotor activity was continuously recorded and shows diurnal cycles (high in the daytime and low at night). When data were considered in more detail (Fig. 56.5b), it seemed that increased locomotor activity (12:00–14:30) was followed by increased energy intake (14:30) and decreased locomotor activity (19:00–22:00) was followed by decreased energy intake (22:00). The relationship between the psychological factor and energy intake can also be considered. Figure 56.6 is a scatter plot of energy intake and the momentary depression score of one student just before eating. In this student, the momentary depression score before eating is significantly and negatively correlated with energy intake, suggesting that energy intake was smaller in more depressive mood states.

In order to investigate the relationship between locomotor activity and food intake, the total amount of locomotor activity since the last eating was calculated for each meal and snack, and multilevel

Fig. 56.6 Data example of momentary depression score before eating and energy intake from one subject. In this student, the momentary depression score before eating was negatively correlated with energy intake ($r = -0.417$, $p = 0.030$). The linear regression line is shown in the plot
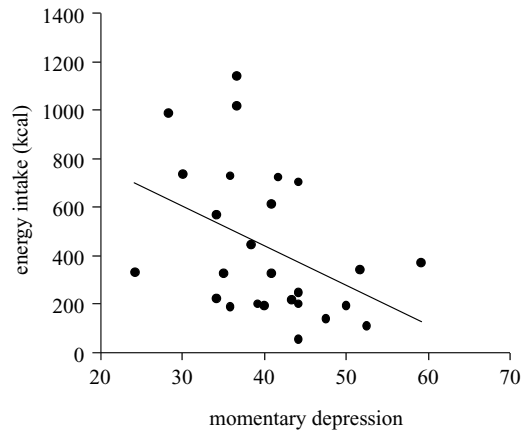
Table 56.4 Energy intake and accumulated locomotor activity. This table shows the results of the pilot study utilizing the newly developed PDA-based food recording system and actigraph (509 recordings made by 20 subjects). Multilevel modeling was used to test the effect of accumulated locomotor activity since last eating on energy intake with control for meal types. The effect of accumulated locomotor activity was significantly positive, suggesting that greater locomotor activity was followed by increased energy intake. Accumulated locomotor activity was dealt with in units of 10^3 counts per minute. Estimated parameters shown in this table are based of the following model:

Level 1:

$Energy_{ij} = \pi_{0i} + \pi_{1i} Activity_{ij} + \pi_{2i} Mealtype(B)_{ij} + \pi_{3i} Mealtype(L)_{ij} + \pi_{4i} Mealtype(D)_{ij} + \varepsilon_{ij}$

Level 2:

$\pi_{0i} = \gamma_{00} + \zeta_{0i}$
$\pi_{1i} = \gamma_{10}$
$\pi_{2i} = \gamma_{20}$
$\pi_{3i} = \gamma_{30}$
$\pi_{4i} = \gamma_{40}$

$Energy_{ij} = (\gamma_{00} + \zeta_{0i}) + \gamma_{10}Activity_{ij} + \gamma_{20}Mealtype(B)_{ij} + \gamma_{30}Mealtype(L)_{ij} + \gamma_{40}Mealtype(D)_{ij} + \varepsilon_{ij}$

	Coefficient (S.E.)	*F* value	*p* value
Intercept (kcal)	264.5 (70.6)		
Effect of accumulated locomotor activity	2.17 (0.86)	$F(1, 232) = 6.34$	$p = 0.013$
Effect of meal types		$F(3, 45) = 48.9$	$p < 0.0001$

$Energy_{ij}$ is energy intake of ith subject's jth eating and $activity_{ij}$ is corresponding accumulated locomotor activity. Meal types are controlled by incorporating them into the model using dummy variables: $Mealtype(B)_{ij}$, $Mealtype(L)_{ij}$, and $Mealtype(D)_{ij}$. Mealtype(B) takes one when the meal type is breakfast and otherwise equals zero. Mealtype(L) is for lunch, Mealtype(D) is for dinner, and a snack is the reference. Intercept (energy intake when the accumulated locomotor activity is zero and the meal type is a snack) is modeled as a random effect by including a residual ζ_{0i}, and estimated value of the average of individual true intercept (γ_{00}) is shown in the table. γ_{10} is the slope representing the effect of accumulated locomotor activity and γ_{20}, γ_{30}, and γ_{40} are the difference in energy intake between respective meal types and snacks. S.E.: standard estimation

modeling (Schwartz and Stone 1998) was used to test the effect of the accumulated amount of locomotor activity on energy intake. There was a significantly positive association between energy intake and the accumulated amount of locomotor activity since the last eating (Table 56.4). An example of data from one subject is plotted in Fig. 56.7 to show the relationship between accumulated locomotor activity and energy intake. The result is intuitive because it means that a greater amount of accumulated locomotor activity was followed by more food intake. What is remarkable with the results,
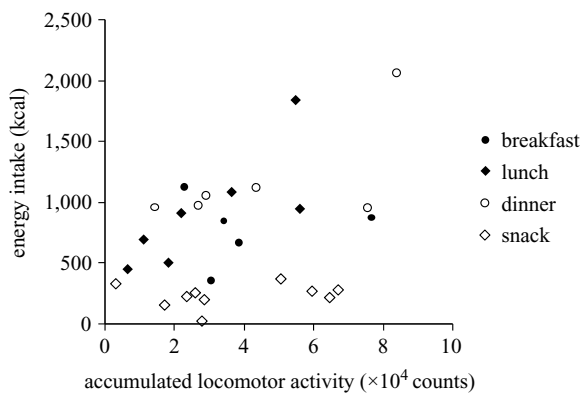
Fig. 56.7 Data example of accumulated amount of locomotor activity and energy intake from one subject. Abscissa is for accumulated amount of locomotor activity since the last eating and ordinate is for energy intake. Accumulated locomotor activity was positively associated with energy intake after controlling for meal types. *Filled circle* breakfast, *filled diamond* lunch, *open circle* dinner, *open diamond* snack

however, is that the fact is confirmed in usual daily settings, not in a laboratory, by using an objective measurement of locomotor activity as a biological factor and a newly developed, accurate, and onsite PDA-based food recording system. It is important in further research to evaluate how such relationships between biological and (eating) behavioral factors could be altered in pathological cases with abnormal food intakes.

Although an example using locomotor activity as the biological factor is introduced here, the same kind of investigation can also be applied to heart rate and heart rate variability with an appropriate sensor. If food intake and heart rate variability are analyzed together with other biological, psychological, and social factors captured in daily settings, a more comprehensive understanding of food intake from a biopsychosocial viewpoint will be achieved.

56.11 Applications to Other Areas of Health and Disease

HRV is used as a predictor for prognosis of cardiac diseases. Decreased SDNN from 24-h Holter ECG has been shown as a predictor for all-cause mortality after acute myocardial infarction (Kleiger et al. 1987; La Rover et al. 1998) and in chronic heart failure patients (Nolan et al. 1998; Bilchick et al. 2002; Cygankiewicz et al. 2009). Scaling exponent α1 from DFA has also been reported to be a predictor for all-cause and cardiac mortality in patients with acute myocardial infarction (Huikuri et al. 2000) and chronic heart failure (Mäkikallio et al. 2001a). More powerful predictors have recently been proposed (Schmidt et al. 1999; Bauer et al. 2006; Kiyono et al. 2008) for risk stratification of cardiac patients, and the analyses of HRV constitute modern data analyzers for Holter ECG.

EMA has been applied to conditions other than BN and BED which were introduced here (Yoshiuchi et al. 2008). With the advantage of greater reliability when assessing subjective symptoms than conventional methods, EMA has hitherto often been used to investigate pain-related diseases such as arthritis and headache, and fatigue in conditions such as cancer and chronic fatigue syndrome so far.

In this chapter, locomotor activity has been analyzed in relation to energy intake. Recently, it has been suggested that an analysis of locomotor activity to know how active and resting periods are

interwoven throughout daily lives can reveal an alteration in behavior in major depressive disorder (Nakamura et al. 2007) and the putative animal model (Nakamura et al. 2008). With the development of appropriate analysis methods, locomotor activity could thus be a psychological as well as a physiological indicator.

Summary Points

- Heart rate variability is used for the noninvasive investigation of cardiovascular autonomic function.
- In obese subjects, HF power of HRV, which reflects parasympathetic nervous activity, is reported to be decreased. Some longitudinal studies have also reported that decreased HF power in obese subjects is ameliorated by body weight reduction.
- In anorexia nervosa patients, though reports on HRV are rather inconsistent, some studies suggest that cardiac parasympathetic nervous activity indexed by HF power is increased, which is a change in the opposite direction to that in obese subjects.
- Because HRV as well as food intake can be affected not only by biological factors but also by psychosocial factors such as emotional and/or mood states and behavior, a biopsychosocial perspective is needed to achieve a comprehensive understanding of HRV and food intake.
- The recently developed PDA-based food recording system combined with electronic diaries and sensors collecting physiological information is a promising tool for a biopsychosocial understanding of food intake.

Definition or Explanations of Key Terms

Heart rate variability (HRV): The variation in the interval between consecutive heartbeats. HRV is regarded as an indicator of cardiac autonomic nervous activity and is also known to have a predictive value of mortality in certain cardiac diseases. HRV is analyzed by various methods such as time domain analysis, frequency domain analysis, and nonlinear and fractal analysis.

SDNN: Standard deviation of normal-to-normal (NN) intervals (intervals between adjacent QRS complexes of sinus rhythm). Either 5-min recordings or 24-h recordings are recommended.

SDANN: Standard deviation of the average NN intervals calculated over 5 min. This estimates the variation due to cycles longer than 5 min.

SDNN index: Mean of the 5-min standard deviations of NN intervals calculated over 24 h. This estimates the variation due to cycles shorter than 5 min.

pNN50: Percentage of differences of successive NN intervals which are longer than 50 ms.

RMSSD: Square root of the mean squared differences of successive NN intervals.

ULF: Power in the ultra low frequency range (≤ 0.003 Hz).

VLF: Power in the very low frequency range (0.003–0.04 Hz).

LF: Power in the low frequency range (0.04–0.15 Hz).

HF: Power in the high frequency range (0.15–0.40 Hz).

LF/HF: Ratio of LF power to HF power.

Ecological momentary assessment (EMA): An assessment method mainly used for recording subjective experiences such as symptoms and behavior. In EMA, subjects record phenomena at the moment when it occurs and at the place where it occurs, usually by using portable computers or personal digital assistants as electronic diaries. This can maximize ecological validity by avoiding recall bias.

References

Bauer A, Kantelhardt JW, Barthel P, Schneider R, Mäkikallio T, Ulm K, Hnatkova K, Schömig A, Huikuri H, Bunde A, Malik M, Schmidt G. Lancet. 2006;367:1674–81.

Beasley J, Riley WT, Jean-Mary J. Nutrition. 2005;21:672–7.

Bilchick KC, Fetics B, Djoukeng R, Fisher SG, Fletcher RD, Singh SN, Nevo E, Berger RD. Am J Cardiol. 2002;90:24–8.

Bobbioni-Harsch E, Sztajzel J, Barthassat V, Makoundou V, Gastaldi G, Sievert K, Chassot G, Huber O, Morel P, Assimacopoulos-Jeannet F, Golay A. Obesity. 2008;17:247–53.

Chen GY, Hsiao TJ, Lo HM, Kuo CD. Clin Nutr. 2008;27:212–7.

Cygankiewicz I, Zareba W, Vazquez R, Bayes-Genis A, Pascual D, Macaya C, Almendral J, Fiol M, Bardaji A, Gonzalez-Juanatey JR, Nieto V, Valdes M, Cinca J, de Luna AB, MUSIC Investigators. Am J Cardiol. 2009;103:1003–10.

Emdin M, Gastaldelli A, Muscelli E, Macerata A, Natali A, Camastra S, Ferrannini E. Circulation. 2001;103:513–9.

Engel SG, Boseck JJ, Crosby RD, Wonderlich SA, Mitchell JE, Smyth J, Miltenberger R, Steiger H. Behav Res Ther. 2007;45:437–47.

Faris PL, Hofbauer RD, Daughters R, Vandenlangenberg E, Iversen L, Goodale RL, Maxwell R, Eckert ED, Hartman BK. Physiol Behav. 2008;94:136–53.

Friederich HC, Schild S, Schellberg D, Quenter A, Bode C, Herzog W, Zipfel S. Int J Obesity. 2006;30:534–42.

Fukuo W, Yoshiuchi K, Ohashi K, Togashi H, Sekine R, Kikuchi H, Sakamoto N, Inada S, Sato F, Kadowaki T, Akabayashi A. J Am Diet Assoc. 2009;109:1232–6.

Galetta F, Franzoni F, Prattichizzo F, Rolla M, Santoro G, Pentimone F. J Adolescent Health. 2003;32:416–21.

Goldberger JJ, Cain ME, Hohnloser SH, Kadish AH, Knight BP, Lauer MS, Maron BJ, Page RL, Passman RS, Siscovick D, Siscovick D, Stevenson WG, Zipes DP, American Heart Association, American College of Cardiology Foundation, Heart Rhythm Society. Circulation. 2008;118:1497–518.

Hilbert A, Tuschen-Caffier B. Int J Eat Disorder. 2007;40:521–30.

Hirsch J, Leibel RL, Mackintosh R, Aguirre A. Am J Physiol. 1991;261:R1418–23.

Huikuri HV, Mäkikallio TH, Peng CK, Goldberger AL, Hintze U, Møller M. Circulation. 2000;101:47–53.

Ishizawa T, Yoshiuchi K, Takimoto Y, Yamamoto Y, Akabayashi A. Psychosom Med. 2008;70:695–700.

Karason K, Mølgaard H, Wikstrand J, Sjöström L. Am J Cardiol. 1999;83:1242–7.

Kennedy SH, Heslegrave RJ. J Psychiatr Res. 1989;23:267–73.

Kikuchi H, Yoshiuchi K, Ohashi K, Yamamoto Y, Akabayashi A. Cephalalgia. 2007;27:1236–43.

Kiyono K, Hayano J, Watanabe E, Struzik ZR, Yamamoto Y. Heart Rhythm. 2008;5:261–8.

Kleiger RE, Miller JP, Bigger JT Jr, Moss AJ. Am J Cardiol. 1987;59:256–62.

Kreipe RE, Goldstein B, DeKing DE, Tipton R, Kempski MH. Int J Eat Disorder. 1994;16:159–65.

Laaksonen DE, Laitinen T, Schönberg J, Rissanen A, Niskanen LK. J Hypertens. 2003;21:371–8.

La Rovere MT, Bigger JT Jr, Marcus FI, Mortara A, Schwartz PJ. Lancet. 1998;351:478–84.

Mäkikallio TH, Huikuri HV, Hintze U, Videbaek J, Mitrani RD, Castellanos A, Myerburg RJ, Møller M, DIAMOND Study Group (Danish Investigations of Arrhythmia and Mortality ON Dofetilide). Am J Cardiol. 2001a;87:178–82.

Mäkikallio TH, Huikuri HV, Mäkikallio A, Sourander LB, Mitrani RD, Castellanos A, Myerburg RJ. J Am Coll Cardiol. 2001b;37:1395–402.

Melanson EL, Donahoo WT, Krantz MJ, Poirier P, Mehler PS. Am J Cardiol. 2004;94:1217–20.

Nakamura T, Kiyono K, Yoshiuchi K, Nakahara R, Struzik ZR, Yamamoto Y. Phys Rev Lett. 2007;99:138103-1–4.

Nakamura T, Takumi T, Takano A, Aoyagi N, Yoshiuchi K, Struzik ZR, Yamamoto Y. PLoS ONE. 2008;3:e2050.

Nolan J, Batin PD, Andrews R, Lindsay SJ, Brooksby P, Mullen M, Baig W, Flapan AD, Cowley A, Prescott RJ, Neilson JM, Fox KA. Circulation. 1998;98:1510–6.

Paolisso G, Manzella D, Montano N, Gambardella A, Varricchio M. J Clin Endocr Metab. 2000;85:1810–4.

Peng CK, Havlin S, Stanley HE, Goldberger AL. Chaos. 1995;5:82–7.

Petretta M, Bonaduce D, Scalfi L, de Filippo E, Marciano F, Migaux ML, Themistoclakis S, Ianniciello A, Contaldo F. Clin Cardiol. 1997;20:219–24.

Piccirillo G, Vetta F, Viola E, Santagada E, Ronzoni S, Cacciafesta M, Marigliano V. Int J Obes Relat Metab Disord. 1998;22:741–50.

Poirier P, Hernandez TL, Weil KM, Shepard TJ, Eckel RH. Obes Res. 2003;11:1040–7.

Rechlin T, Weis M, Ott C, Bleichner F, Joraschky P. Biol Psychiat. 1998;43:358–63.

Rissanen A, Naukkarinen H, Virkkunen M, Rawlings RR, Linnoila M. J Clin Psychopharm. 1998;18:26–32.

Schmidt G, Malik M, Barthel P, Schneider R, Ulm K, Rolnitzky L, Camm AJ, Bigger JT Jr, Schömig A. Lancet. 1999;353:1390–6.

Schwartz JE, Stone AA. Health Psychol. 1998;17:6–16.

Skrapari I, Tentolouris N, Perrea D, Bakoyiannis C, Papazafiropoulou A, Katsilambros N. Obesity. 2007;15:1685–93.

Smyth J, Wonderlich S, Crosby R, Miltenberger R, Mitchell J, Rorty M. Int J Eat Disorder. 2001;30:83–95.

Stein RI, Kenardy J, Wiseman CV, Dounchis JZ, Arnow BA, Wilfley DE. Int J Eat Disorder. 2007;40:195–203.

Stone AA, Shiffman S. Ann Behav Med. 1994;16:199–202.

Struzik ZR, Yoshiuchi K, Sone M, Ishikawa T, Kikuchi H, Kumano H, Watsuji T, Natelson BH, Yamamoto Y. Method Inform Med. 2007;46:130–4.

Task Force of the European Society of Cardiology the North American Society of Pacing Electrophysiology. Circulation. 1996;93:1043–65.

Vigo DE, Castro MN, Dörpinghaus A, Weidema H, Cardinali DP, Siri LN, Rovira B, Fahrer RD, Nogués M, Leiguarda RC, Guinjoan SM. World J Biol Psychia. 2008;9:183–9.

Yoshiuchi K, Yamamoto Y, Akabayashi A. Biopsychosoc Med. 2008;2:13.

Chapter 57
Branched-Chain Amino Acids and Central Fatigue: Implications for Diet and Behavior

Eva Blomstrand

Abbreviations

BCAA	Branched-chain amino acids
CR10	The Borg CR10 scale®
DA	Dopamine
FFA	Free fatty acids
LNAA	Large neutral amino acids
NE	Norepinephrine
5-HT	5-Hydroxytryptamine
5-HIAA	5-Hydroxyindole acetic acid
VO_{2max}	Maximal pulmonary oxygen uptake

57.1 Introduction

The branched-chain amino acids (BCAA: leucine, isoleucine, and valine), which are essential components of our diet, share a similar chemical structure (Table 57.1; Fig. 57.1 depicts the structure of leucine). In contrast to most other amino acids, which are metabolized primarily in the liver, the BCAA are metabolized mainly in skeletal muscle. However, their less extensive metabolism in other tissues has several important functions, e.g., in the case of the brain, supplying energy, providing nitrogen for synthesis of the neurotransmitter glutamate, and modulating the synthesis of the mono-amines dopamine (DA), norepinephrine (NE), and 5-hydroxytryptamine (5-HT). It is this latter process, and in particular, the role of BCAA in regulating the synthesis of 5-HT, which will be discussed here.

The rate-limiting step in the synthesis of the monoamines is the transport of their precursors tyrosine (DA and NE) or tryptophan (5-HT), across the blood–brain barrier (Newsholme and Leech 1983; Young 1986). The transport protein involved is common for the large neutral amino acids (LNAA; tyrosine, phenylalanine, tryptophan, and BCAA) and since this transporter is almost saturated at normal plasma levels of LNAA, competition for entry occurs (Fernstrom 2005;

E. Blomstrand (✉)
The Åstrand Labaratory, The Swedish School of Sport and Health Sciences,
Box 5626 114 86 Stockholm, Sweden
e-mail: eva.blomstrand@gih.se

Table 57.1 Key features of branched-chain amino acids

1. Leucine, isoleucine, and valine are known as the branched-chain amino acids (BCAA) because of their similar structure; Fig. 57.1 depicts the structure of leucine
2. The BCAA are essential amino acids, i.e., they must be provided in the diet
3. Dietary proteins such as meat, poultry, fish, egg, milk, and cheese contain 15–20 g BCAA/100 g protein
4. The BCAA are primarily metabolized in skeletal muscle, i.e., they escape the liver and ingestion of BCAA therefore leads to a rapid rise in their concentration in peripheral blood
5. BCAA, in particular leucine, stimulate protein synthesis

Notes: This table lists the key facts of the branched-chain amino acids including dietary sources, metabolism, and regulatory functions

$$CH_3 \diagdown \atop CH_3 \diagup CH - CH_2 - \overset{\overset{\displaystyle NH_2}{|}}{CH} - COOH$$
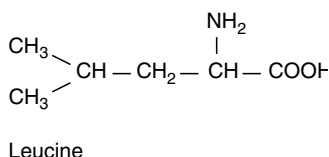
Leucine

Fig. 57.1 Chemical structure of leucine. The branched-chain structure is common for leucine, isoleucine, and valine; only minor differences exist in their chemical structure

Pardridge 1998). Accordingly, elevating or lowering plasma concentrations of BCAA can reduce or enhance, respectively, the transport of tyrosine and tryptophan into the brain and thereby the synthesis of DA and NE and of 5-HT, respectively (Fernstrom 2005; Choi et al. 2009). Dietary intake of protein and carbohydrates, as well as ingestion of BCAA, results in pronounced alterations in plasma ratios of tyrosine and tryptophan in relation to the other LNAA, alterations associated with changes in central fatigue and cognitive function (Blomstrand et al. 1997; Gijsman et al. 2002; Portier et al. 2008).

57.2 Central Fatigue During Physical Exercise

57.2.1 Causes of Fatigue

Fatigue during physical exercise can be described as the inability to maintain a certain force or rate of work, depending on the nature of the exercise. Such fatigue may be related to central and peripheral factors, both of which are influenced by the intensity and duration of the exercise, environmental conditions, nutritional intake, and the physical condition of the individual involved. Peripheral fatigue reflects, by definition, changes in the exercising muscles, whereas central fatigue is an outcome of dysfunction or limitations within the central nervous system.

Extensive investigation of peripheral fatigue has revealed several causative metabolic changes, e.g., depletion of substrates for the production of energy or accumulation of products which impair muscle contraction (see Sahlin 2006). Central fatigue is more difficult to quantitate, particularly in connection with dynamic exercise such as cycling or running. Consequently, less is presently known about what causes this latter form of fatigue, although several mechanisms have been proposed, including (1) elevation of the plasma level of ammonia, due primarily to its enhanced rate of production by the exercising muscle; (2) a reduction in the blood level of glucose due to the depletion of hepatic glycogen stores; (3) elevated circulating levels of cytokines released from muscle; and (4) increased release of neurotransmitters, especially 5-hydroxytryptamine (5-HT) in the brain.

57.2.2 Synthesis of 5-HT and Its Role in Fatigue

In 1963, Barchas and Freedman (1963) reported for the first time that the level of 5-HT in the brain was elevated after rats had swum until becoming exhausted. Later, Romanowski and Grabiec (1974) proposed that this increase could be related to central fatigue, although the underlying mechanism was not known. Subsequently, a number of confirmatory investigations have also demonstrated that sustained exercise results in an increase in the release and turnover of 5-HT in certain parts of the brain of experimental animals (see Chaouloff 1997; Meeusen et al. 2006). Figure 57.2 illustrates the various responses to sustained exercise in different brain regions. Tryptophan is similarly elevated in all areas measured, whereas 5-HT levels are increased only in brain stem and hypothalamus (Blomstrand et al. 1989).
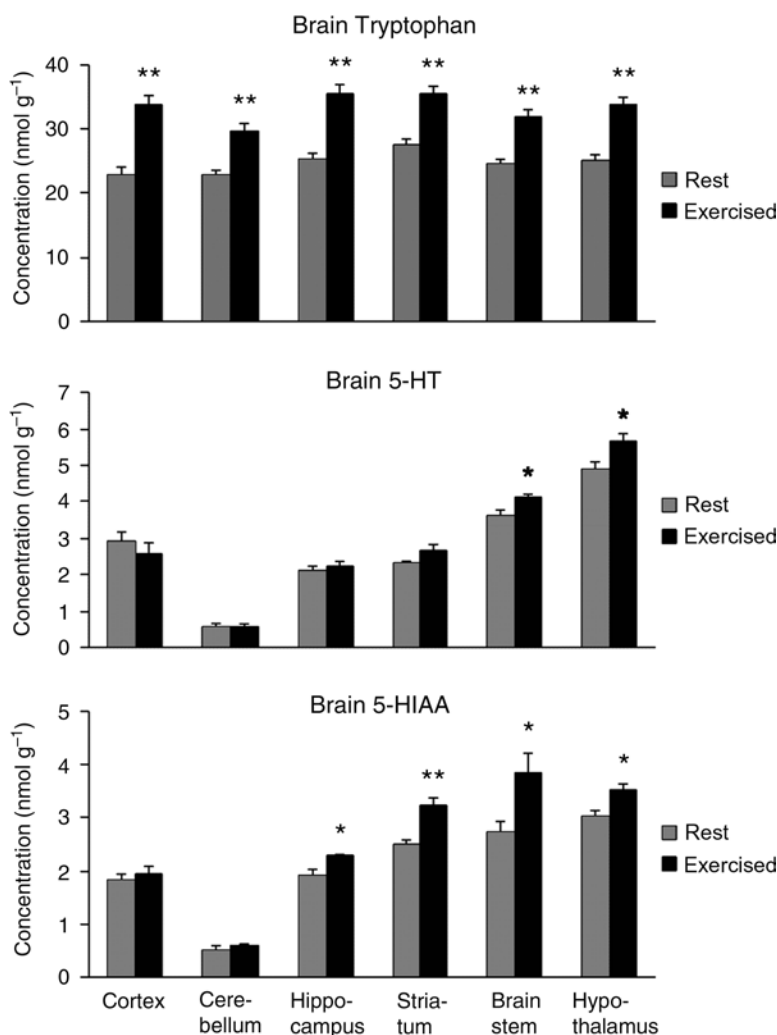
Fig. 57.2 The effects of sustained running on concentrations of tryptophan, 5-hydroxytryptamine (5-HT), and 5-hydroxyindole acetic acid (5-HIAA) in different regions of the rat brain. Tryptophan is similarly elevated in all areas measured after sustained running, but the effect on 5-HT and 5-HIAA levels vary between different regions. The values are presented as means $\pm$ SE for 8–10 animals. $^{*}P < 0.05$ and $^{**}P < 0.01$ for rest in comparison to postexercise (Reprinted from Blomstrand et al. 1989. With permission)

The potential involvement of 5-HT in central fatigue was first examined in more detail employing pharmacological manipulation of rodents. For instance, administration of an agonist of 5-HT to rats impairs running performance in a dose-related manner (Bailey et al. 1992, 1993) and administration of a 5-HT antagonist improves running performance (Bailey et al. 1993). In another approach to evaluating the role of 5-HT in connection with fatigue, Caperuto et al. (2009) subjected rats to a 5-week exhaustive exercise training program and found that the hypothalamic level of 5-HT remained elevated 24 h after the last exercise session. At this same time-point the endurance performance of these animals was 35% lower than that of rats trained moderately and with no elevation in their hypothalamic concentration of 5-HT.

While the results on rodents clearly indicate a role of 5-HT in fatigue, studies on human subjects are less conclusive. Studies employing drugs selectively inhibiting the 5-HT reuptake have provided various results in connection with endurance exercise; some support (Wilson and Maughan 1992; Struder at al. 1998), while others argue against the involvement of 5-HT in fatigue (Meeusen et al. 2001; Strachan et al. 2004). Furthermore, oral administration of a $5-HT_{1A}$ agonist was found to reduce time to fatigue (Marvin et al. 1997), whereas 5-HT antagonists did not influence performance (Pannier et al. 1995; Meeusen et al. 1997). The complexity of the 5-HT system as well as the use of different drugs, in some cases acting on both 5-HT and DA receptors complicates interpretation of these findings especially since exercise itself influences the metabolism of DA, which may also be involved in the development of fatigue, either directly or through inhibition of 5-HT synthesis in certain regions of the brain. The effect of pharmacological alteration of neurotransmission during exercise has been comprehensively reviewed by Meeusen et al. (2006).

When an elevated level of 5-HT was first proposed to cause central fatigue, the underlying mechanism was unknown. In the mid-1980s the following hypothesis was put forward (Newsholme et al. 1987): The first reaction in the synthesis of 5-HT is catalyzed by the enzyme tryptophan hydroxylase. Because this enzyme is not saturated with its substrate under physiological conditions, the rate of 5-HT synthesis is sensitive to alterations in brain levels of tryptophan, which are regulated not only by the plasma concentration of tryptophan, but also by the plasma levels of the other large neutral amino acids (LNAA), including the BCAA, which compete for the same carrier system (see above). "Therefore, increases in the plasma concentration ratio of tryptophan/BCAA could lead to an increase in the rate of entry of tryptophan into the brain and hence in the concentration of 5-HT. Such changes can occur in sustained exercise" (Newsholme et al. 1987), see Fig. 57.3.

57.2.3 Changes in the Ratio of Tryptophan/BCAA Concentrations in Plasma

The contribution of protein to energy metabolism in the form of amino acids during physical exercise has been estimated to be only 3–6%, much less than the contributions made by carbohydrates and fats, which are the major fuels for skeletal muscle. Regardless of this relatively minor contribution to energy production, the metabolism and plasma levels of amino acids are affected in pronounced ways that depend primarily on the intensity and duration of the physical exercise. During prolonged exercise of low- to moderate intensity, BCAA are taken up by muscle, which is consistent with an increased rate of oxidation, which eventually reduces their plasma concentrations (Ahlborg et al. 1974; Blomstrand et al. 2005). The aromatic amino acids are primarily taken up by the liver and their plasma concentrations, including tryptophan, either increase or remain unchanged during prolonged exercise of moderate intensity (Ahlborg et al. 1974; Blomstrand et al. 2005).

Of importance in this connection is the fact that tryptophan is the only amino acid that binds to albumin in the plasma, to an extent of as much as 90% and thus only 10% of the total plasma tryptophan is in the free form (Curzon et al. 1973). Since, free fatty acids (FFA) and tryptophan compete for
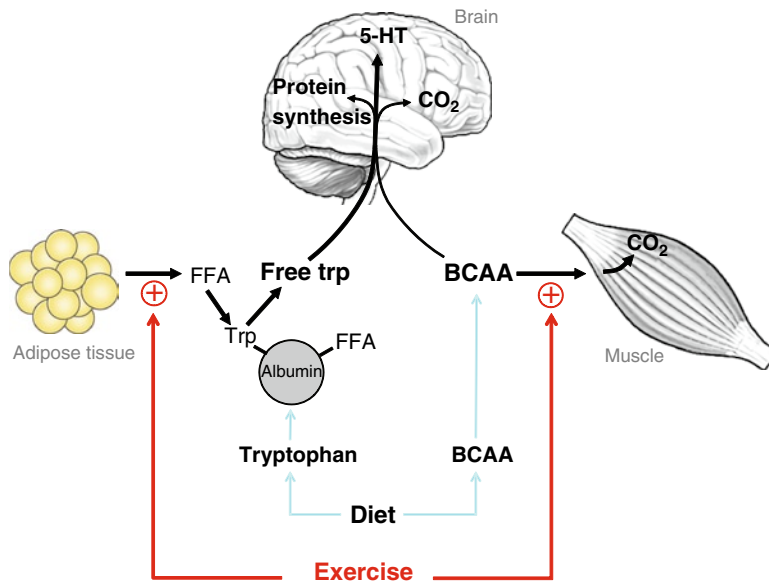
Fig. 57.3 Metabolic changes which may cause central fatigue. During prolonged exercise, BCAA are taken up by the muscle and the plasma concentration decreases. Exercise also elevates the plasma level of FFA due to their enhanced release from adipose tissue as a consequence of sympathetic nervous activity, which should displace tryptophan (Trp) from albumin and thereby increase the concentration of free tryptophan. An increase in the plasma ratio of free tryptophan/BCAA favors the transport of tryptophan into the brain and increases the synthesis and release of 5-HT from some neurons, which could lead to central fatigue

the same binding sites on albumin (Curzon et al. 1973), the elevated plasma levels of FFA associated with exercise (due to their enhanced release from adipose tissue, as a consequence of sympathetic nervous activity) should displace tryptophan from albumin and thereby elevate the concentration of unbound tryptophan (Curzon et al. 1973). As expected, there is a positive correlation between the plasma levels of free tryptophan and FFA in human subjects (Blomstrand et al. 1997). Several investigations have documented an increase in plasma levels of free tryptophan and, consequently, a marked elevation in the plasma ratio of free tryptophan/BCAA both during and, especially, after prolonged exercise, as well as during intermittent types of exercise such as soccer and tennis (Blomstrand et al. 1991a; Davis et al. 1992; Lehmann et al. 1995; Strüder and Weicker 2001). Only minor changes in the plasma ratio of total tryptophan/BCAA were observed during exercise, which leads into the discussion around whether it is the level of free or total tryptophan that governs uptake by the brain.

57.2.4 Regulation of Tryptophan Uptake by the Brain

57.2.4.1 Studies on Rodents

A number of studies have been conducted on experimental animals regarding the regulation of tryptophan transport into the brain and varying results have been reported in different situations. Certain studies on food deprived or immobilized animals have indicated that it is the free level that regulates this uptake, whereas dietary investigations on experimental animals have provided evidence that this is not the case (see Fernstrom and Fernstrom 2006). This conclusion receives additional support from the recent demonstration that dietary intake of carbohydrates and/or proteins with varying amino acid

contents results in an approximately eightfold variation in the cortical content of tryptophan that is clearly related to the ratio of total tryptophan/other LNAA in plasma (Choi et al. 2009).

In contrast, in exercising animals a pronounced elevation of the plasma concentration of free tryptophan is associated with a nearly proportional rise in the brain level of tryptophan, with no such relationship to the total concentration of tryptophan (Chaouloff et al. 1985, 1986). In an attempt to distinguish the effect of exercise from that of the elevated levels of free tryptophan, Chaouloff et al. (1985) injected nicotinic acid into rats prior to their running on a treadmill for 1 h, which totally blocked the release of fatty acids from adipose tissue, but, surprisingly, the concentration of free tryptophan increased as did the brain level of tryptophan. A comprehensive review and discussion of the importance of free *versus* total tryptophan in plasma for the uptake into the brain in relation to the complex activation of the 5-HT system in brain neurons has been provided by Fernstrom and Fernstrom (2006).

57.2.4.2 Studies on Human Subjects

Measurements of tryptophan and 5-HT levels are not possible to perform on the human brain; nonetheless, brain exchange of tryptophan may give some indication of changes in brain 5-HT synthesis following exercise or nutritional supply. During a 3-h session of ergometer cycling at 60% of maximal oxygen uptake (VO_{2max}), the arterial concentration of free tryptophan rises continuously, whereas the total concentration remains unchanged. Since brain blood flow was not altered during exercise, the arterial-jugular venous concentration difference may be employed as an indicator of the net uptake of amino acids into the brain. At the same time as the arterial concentration of free tryptophan rises, net uptake of tryptophan by the brain (measured as the difference in concentrations in the artery and the jugular vein) occurs (Table 57.2). In addition, ingestion of carbohydrates during this exercise attenuated the elevation of plasma levels of free tryptophan and prevented the uptake of this amino acid into the brain (Blomstrand et al. 2005). Altogether, the results indicate that the free tryptophan level plays a major role for the uptake of tryptophan by the brain during prolonged exercise.

In the same experiment, there was an uptake of BCAA by the brain during exercise despite a reduction in their plasma concentrations as well as the plasma ratio of BCAA/other LNAA (Blomstrand et al. 2005). This observation was unexpected, but may suggest that the activity of the transport system is enhanced during physical exercise. There is some evidence from studies on rodents that stimulation of β-adrenergic receptors located at the blood–brain barrier increases the amino acids transport into brain (Eriksson and Carlsson 1988; Takao et al. 1992). The exercise-induced increase in plasma

Table 57.2 Arterial concentration (μmol L^{-1}) and the arterial-jugular venous (a-jv) concentration difference (μmol L^{-1}) of aromatic and branched-chain amino acids (BCAA) at rest and after 180 min ergometer cycling at 60% of VO_{2max}

Amino acid	Rest		Exercise 180 min	
	Arterial concentration	(a-jv) difference	Arterial concentration	(a-jv) difference
Tyrosine	55 ± 3	–1.4 ± 1.0	78 ± 4[*]	0.8 ± 0.5
Phenylalanine	65 ± 2	–0.7 ± 0.9	81 ± 1[*]	1.8 ± 0.6[**]
Tryptophan				
Free	12 ± 1	–0.4 ± 0.2	20 ± 2[*]	–0.4 ± 0.3
Total	61 ± 2	–0.3 ± 1.1	55 ± 5	1.7 ± 0.5[**]
ΣBCAA	505 ± 12	8 ± 9	470 ± 25[*]	18 ± 2[**]

Notes: The arterial concentration of free tryptophan rises during sustained exercise, whereas the total concentration remains unchanged. At the same time, net uptake of tryptophan by the brain (measured as the difference in concentration in the artery and the jugular vein) occurs. The values presented are the means ± SE for five subjects. ΣBCAA is the sum of valine, leucine, and isoleucine. [*]$P < 0.05$ vs. rest and [**]$P < 0.05$ different from zero (Reprinted from Blomstrand et al. 2005. With permission)

levels of E and NE, which stimulate the β-adrenergic receptors, may therefore facilitate transport of LNAA over the blood–brain barrier. The significance of the enhanced uptake of BCAA during exercise remains unclear, although leucine may act as a regulator of the excitatory neurotransmitter glutamate (Hutson et al. 2001), thereby playing another role in neurotransmission in addition to affecting the synthesis and release of 5-HT.

Whether ingestion of BCAA during exercise, which raises their plasma concentrations, would influence the uptake of tryptophan by the brain has not yet been examined, but two observations suggest that this may be the case. First, intravenous infusion of ~5 g BCAA during 150 min (arterial concentration rose from 353 to 770 μmol L^{-1}) under resting conditions does enhance uptake of these amino acids by the human brain and, in addition, the brain uptake of the aromatic amino acid tyrosine was diminished (tryptophan was not analyzed) (Sato et al. 1981). Secondly, administration of valine to rats prevents the exercise-induced increase in tryptophan uptake as well as the release of 5-HT (Chaouloff et al. 1985; Gomez-Merino et al. 2001; Smriga et al. 2006).

57.2.5 Supplementation of BCAA During Exercise

57.2.5.1 Studies on Human Subjects

In line with the considerations discussed above, raising the plasma level of BCAA and thereby counterbalancing the increase in free tryptophan that occurs both during and after sustained or intermittent exercise should reduce transport of tryptophan into the brain, decrease the rate of 5-HT synthesis, and delay mental fatigue. Ingestion of BCAA has exerted positive effects on both mental performance and perceived exertion in both field studies and controlled laboratory experiments, as illustrated by the following experiments. When subjects were supplied with 6–9 g of a mixture of BCAA (plasma level increased from 450 to 1,150 μmol L^{-1}) during ergometer cycling

0	Nothing at all	
0.3		
0.5	Extremely weak	Just noticeable
0.7		
1	Very weak	
1.5		
2	Weak	Light
2.5		
3	Moderate	
4		
5	Strong	Heavy
6		
7	Very strong	
8		
9		
10	Extremely strong	"Maximal"
11		
•	Absolute maximum	Highest possible

The Borg CR 10 scale®
© Gunnar Borg, 1982, 1998, 2004

Fig. 57.4 The category-ratio scale CR10. The Borg CR10 scale can be used for measuring most kinds of perceptions and experiences, including pain and perceived exertion as well as changes in mood and emotions (Reprinted from Borg 2004, 2008. With permission)

Fig. 57.5 Ratings of mental fatigue (CR10) during exercise. The subjects were supplied a mixture of the three BCAA in aqueous solution or a placebo consisting of flavored water during 60 min ergometer cycling at 70% of VO_{2max} followed by 20 min of maximal exercise. When subjects ingested BCAA their ratings of mental fatigue was lower than during ingestion of placebo. The values presented are means ± SE for 7 subjects. *$P < 0.05$ between the trials during the 0–60-min period of exercise when the rate of work was the same (Reprinted from Blomstrand et al. 1997. With permission)
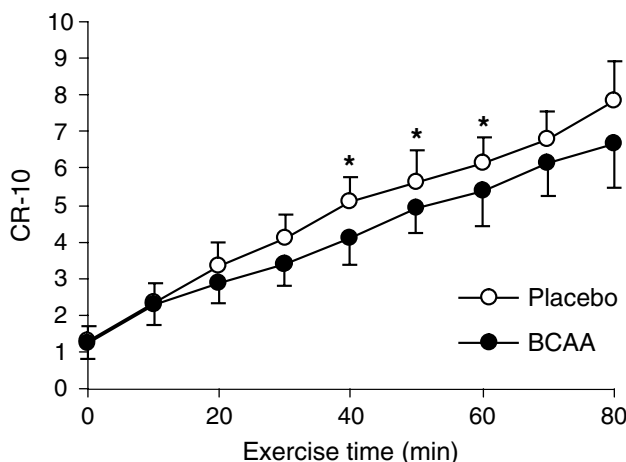
at 70% of VO_{2max}, their ratings of perceived exertion and mental fatigue Figure 57.4 were reduced (Fig. 57.5) and their cognitive performance after the exercise improved (Blomstrand et al. 1997). Similarly, during an off-shore race lasting 32 h, ratings of fatigue were lowered and a decline in short-term memory prevented by ingestion of a high-protein supplement and large amounts of BCAA (Portier et al. 2008).

In addition, physical performance improved in a warm environment (evaluated as time to exhaustion at 40% of VO_{2max}) from 137 to 153 min when BCAA (9–16 g) were ingested (Mittelman et al. 1998). However, the performance was not significantly affected in temperate conditions (Blomstrand et al. 1997), raising the possibility that central fatigue is more pronounced during exercise in the heat than at cooler temperatures. Support for this proposal has been presented by Pitsiladis et al. (2002), who observed higher serum levels of prolactin (an indicator of central 5-HT activation) during exercise at 30°C than at 10°C. In contrast, administration of paroxetine, an inhibitor of 5-HT reuptake, to human subjects during exercise in the heat had no influence on either performance or the endocrine response (Strachan et al. 2004). Two additional studies were thereafter conducted in the heat and both failed to detect an effect of BCAA supplementation on physical performance (Cheuvront et al. 2004; Watson et al. 2004). However, in the former study, subjects were supplied with BCAA together with *carbohydrates*, a supplementation protocol which has been employed in several other studies and which likely reduces the development of fatigue (see below).

Ingestion of carbohydrates is known to improve physical performance during sustained exercise; therefore many studies have investigated the effect of drinks containing both BCAA and carbohydrates as described in the following experiments. An improvement in the subjects´ mental agility (evaluated as performance on various psychological tests) was observed following sustained competitive exercise (i.e., a soccer match or a 30-km cross-country race) (Blomstrand et al. 1991a; Hassmén et al. 1994), but not after exercise in the heat under controlled laboratory conditions in comparison to intake of carbohydrates alone (Cheuvront et al. 2004). Similarly, during exercise under controlled laboratory conditions no additional benefit to physical performance was provided

by addition of BCAA to a solution of carbohydrates (Blomstrand et al. 1995; Van Hall et al. 1995; Davis et al. 1999; Cheuvront et al. 2004). However, the fact that inclusion of carbohydrates attenuates the increase in plasma level of free tryptophan (Davis et al. 1992), as well as in the uptake of tryptophan by the brain (Blomstrand et al. 2005), may explain the absence of any effect by BCAA in these experiments. In contrast, ingestion of 16 g BCAA together with carbohydrates during a marathon race improved running performance in a subgroup of "slower" runners (Blomstrand et al. 1991b). This experimental protocol has both advantages and disadvantages: the advantage is the competitive situation as such and that a large number of subjects can be studied; however, the weakness is the difficulty in controlling the experimental conditions.

The divergent reports regarding the influence of supplementation with BCAA on physical performance may relate not only to differences in the type, intensity, and duration of the exercise employed, but also to the *fitness level* of the subjects. Regularly training, which is associated with enhanced synthesis of 5-HT, may lead to adaptive changes in neurotransmission involving 5-HT that may delay fatigue. Such changes are likely to attenuate the possible beneficial effects of BCAA with respect to central fatigue. Some evidence suggests that well-trained athletes exhibit a reduced neurosensitivity to 5-HT (i.e., downregulation of the sensitivity of the 5-HT receptor as measured by a smaller increase in serum levels of prolactin following a challenge with buspiron, a 5-HT_{1A} agonist or a 5-HT_{2c} agonist) in comparison to sedentary individuals (Jakeman et al. 1994; Broocks et al. 1999). Although nine weeks of endurance training was insufficient to produce any change in neuroendocrine response to buspirone (Dwyer and Flynn 2002), this training period may have been too short to cause alterations which may result from years of training. In contrast, Strachan and Maughan (1999) could not detect any difference in prolactin release by trained and untrained individuals treated with d-fenfluramine, an inhibitor of the release and reuptake of 5-HT; however, the dose of d-fenfluramine may have been insufficient to induce a response (Strachan and Maughan 1999).

57.2.5.2 Studies on Rodents

Supplementation of BCAA to experimental animals seems to give a clear response with regard to physical performance. Intraperitoneal injection of BCAA to rodents before running on a treadmill improved their exercise capacity (run time to exhaustion was 30–35% longer than after saline infusion; the BCAA level rose from 522 to 1,497 µmol L^{-1} and from 426 to 751 µmol L^{-1}, respectively) in two studies (Calders et al. 1997, 1999). Moreover, voluntary intake of BCAA positively correlated with the volume of exercise in freely moving rats (Smriga et al. 2006). Only in one study, when rats were fed BCAA or water before prolonged treadmill running no difference in time to fatigue was detected (Verger et al. 1994). Similar to the situation in human subjects, supplementation of carbohydrates (glucose) to rats improved running performance but addition of BCAA gave no further improvement in exercise capacity (Calders et al. 1999).

Also in experimental animals, exercise training affects the central 5-HT sensitivity; a significant reduction in the sensitivity of the 5-HT_{1A} receptor occurs as rapidly as after 5 or 6 weeks of exercise training (Dwyer and Browning 2000). Furthermore, another exercise-induced adaptation which may influence the central 5-HT activity involves the rate of 5-HT synthesis in neurons. The protein level of the rate-limiting enzyme in this process, tryptophan hydroxylase, was reported to be reduced in rats following 6 weeks of endurance training and, furthermore, decreased levels of tryptophan and 5-HT were observed in certain regions of the brains of trained animals following nonexhaustive exercise in comparison to sedentary controls (Langfort et al. 2006).

57.2.6 Possible Adverse Effects of BCAA

In light of the effects which acute intake of BCAA might have on neurotransmission, it is necessary to discuss possible adverse effects of such intake as well. Ingestion of 5–10 g BCAA in connection with (before, during, and after) physical exercise elevates the plasma levels of these amino acids for 3–4 h, a relatively short period of time. The accompanying temporary reduction in the uptake of other LNAA into the brain is thus unlikely to have negative effects on sleep or cause changes in mood. Furthermore, it is unlikely that the rate of protein synthesis in the brain is reduced as a result of decreased uptake of other LNAA. Long-term use of BCAA, i.e., ingestion of 30–50 g/day (in addition to the dietary consumption) for 2 years is tolerated well, with no adverse effects being reported (Fernstrom 2005).

On the other hand, ingestion of large amounts of BCAA in connection with exercise may be detrimental to performance by enhancing the production of ammonia, which can be toxic to the brain. When 20–30 g is ingested as a bolus prior to or during exercise, a rise in plasma levels of ammonia has been observed in certain studies, but not others (see Blomstrand 2006); whereas smaller amounts (7–10 g or 100 mg/kg body weight) taken repeatedly during exercise and recovery do not result in any increase in the release of ammonia from muscles (Blomstrand and Saltin 2001). With such relatively small amounts of BCAA, which are sufficient to counterbalance the elevated concentration of free tryptophan during and after exercise (Blomstrand et al. 1997), there is no indication that this fatigue will occur earlier due to elevated levels of ammonia in the blood.

57.3 Applications to Other Areas of Health and Disease

BCAA have been employed to treat or improve the condition of several groups of patients, including those with hepatic encephalopathy, amyotrophic lateral sclerosis (ALS), phenylkenonuria (PKU), bipolar illness (periods of mania), schizophrenia (tardive dyskinesi), spinocerebellar degeneration, and cancer (see Fernstrom 2005). The specific effects of BCAA on central fatigue and cognitive performance may be beneficial in connection with some conditions.

Postoperative fatigue experienced by patients following major surgery can persist for many days. Pronounced increases in serum levels of free tryptophan have been observed in such patients, and, moreover, their rating of fatigue is correlated to both the concentration of free tryptophan and the ratio of free tryptophan/BCAA in plasma (McGuire et al. 2003). According to the hypothesis concerning central fatigue presented above, the rate of 5-HT synthesis should be elevated in these patients, which may contribute to their feeling of fatigue. The authors suggest that provision of BCAA may help to overcome fatigue under these conditions by elevating plasma levels of BCAA, thereby counterbalancing the rise in free tryptophan and consequently slowing down the synthesis of 5-HT.

Other groups of patients who may benefit from ingestion of BCAA are those with psychiatric disorders, including mania and schizophrenia, which are associated with overactivity of dopaminergic pathways. Some evidence indicates that ingestion of BCAA can reduce dopamine function in healthy individuals, as well as the clinical ratings of mania in patients (Gijsman et al. 2002; Scarna et al. 2003).

Summary Points

- Physical exercise results in elevated synthesis and release of 5-HT in the brain of experimental animals.
- In human subjects, endurance exercise is associated with changes in the ratio of free tryptophan/other LNAA in the plasma which promote transport of tryptophan into the brain and possibly also the synthesis of 5-HT.
- There is a net uptake of both tryptophan and BCAA by the brain during sustained endurance exercise, suggesting that the activity of the transport system is enhanced.
- Ingestion of BCAA, which raises their concentrations in plasma, counterbalances the increase in free tryptophan during sustained exercise, reduces fatigue, and improves cognitive performance.
- Under certain conditions, BCAA can also improve physical performance, but this is dependent on the type of exercise, the amount and composition of the supplement administered and the fitness level of the subjects.
- The mechanisms underlying the influence of BCAA on central fatigue may not only involve a reduction in tryptophan uptake, but also a direct effect on metabolism and/or neurotransmission in the brain.

Definitions of Key Terms

Blood–brain barrier: The capillary network surrounding brain cells which is impermeable to, e.g., amino acids, so that specific transporters are required for uptake.
Branched-chain amino acids: Essential amino acids metabolized primarily in skeletal muscle.
Central fatigue: Fatigue caused by failure or limitations within the central nervous system.
Cognitive performance: Performance in standardized psychological tests.
Endurance exercise: For example, running or cycling.
Fatigue: The inability to maintain a given power output or rate of work.
Large neutral amino acids: Tyrosine, phenylalanine, tryptophan, and branched-chain amino acids.
Low-intensity exercise: 30–50% of VO_{2max}.
Moderate-intensity exercise: 60–75% of VO_{2max}.
Physical performance: Often measured as time to exhaustion at a given rate of work or time to complete a given distance (time trial).
5-hydroxytryptamine: A neurotransmitter involved in the regulation of mood, sleep, and arousal.

References

Ahlborg G, Felig P, Hagenfeldt L, Hendler R, Wahren J *J Clin Invest.* 1974;53:1080–90.
Bailey SP, Davis JM, Ahlborn EN *Acta Physiol Scand.* 1992;145:75–6.
Bailey SP, Davis JM, Ahlborn EN *Int J Sports Med.* 1993;14:330–33.
Barchas JD, Freedman DX *Biochem Pharmacol.* 1963;12:1232–5.
Blomstrand E. *J Nutr.* 2006;136:544S–7S.
Blomstrand E, Saltin B *Am J Physiol Endocrinol Metab.* 2001;281:E365–74.
Blomstrand E, Perrett D, Parry-Billings M, Newsholme EA *Acta Physiol Scand.* 1989;136:473–81.
Blomstrand E, Hassmén P, Newsholme EA *Acta Physiol Scand.* 1991a;143:225–6.

Blomstrand E, Hassmén P, Ekblom B, Newsholme EA *Eur J Appl Physiol Occup Physiol.* 1991b;63:83–8.

Blomstrand E, Andersson S, Hassmén P, Ekblom B, Newsholme EA *Acta Physiol Scand.* 1995;153:87–96.

Blomstrand E, Hassmén P, Ek S, Ekblom B, Newsholme EA *Acta Physiol Scand.* 1997;159:41–9.

Blomstrand E, Møller K, Secher NH, Nybo L *Acta Physiol Scand.* 2005;185:203–9.

Borg G. The Borg CR Scales® Folder. Methods for measuring intensity of experience. Hasselby, Sweden: Borg Perception; 2004, 2008.

Broocks A, Meyer T, George A, Hillmer-Vogel U, Meyer D, Bandelow B, Hajak G, Bartmann U, Gleiter C, Rüther E *Neuropsychopharmacology.* 1999;20:150–61.

Calders P, Pannier J-L, Matthys DM, Lacroix EM *Med Sci Sports Exerc.* 1997;29:1182–6.

Calders P, Matthys D, Derave W, Pannier J-L *Med Sci Sports Exerc.* 1999;31:583–7.

Caperuto EC, dos Santos RVT, Mello MT, Costa Rosa LFBP *Clin Exp Pharmacol Physiol.* 2009;36:189–91.

Chaouloff F. *Med Sci Sports Exerc.* 1997;29:58–62.

Chaouloff F, Elghozi JL, Guezennec Y, Laude D *Br J Pharmacol.* 1985;86:33–41.

Chaouloff F, Kennett GA, Serrurier B, Merino D, Curzon G *J Neurochem.* 1986a;46:1647–50.

Cheuvront SN, Carter R 3rd, Kolka MA, Lieberman HR, Kellogg MD, Sawka MN *J Appl Physiol.* 2004;97:1275–82.

Choi S, DiSilvio B, Fernstrom MH, Fernstrom JD *Physiol Behav.* 2009;98:156–62.

Curzon G, Friedel J, Knott PJ *Nature.* 1973;242:198–200.

Davis JM, Bailey SP, Woods JA, Galiano FJ, Hamilton MT, Bartoli WP *Eur J Appl Physiol Occup Physiol.* 1992;65:513–19.

Davis JM, Welsh RS, De Volve KL, Alderson NA *Int J Sports Med.* 1999;20:309–14.

Dwyer D, Browning J *Acta Physiol Scand.* 2000;170:211–16.

Dwyer D, Flynn J *Exp Physiol.* 2002;87:83–9.

Eriksson T, Carlsson A *Life Sci.* 1988;42:1583–9.

Fernstrom JD. *J Nutr.* 2005;135:1539S–46S.

Fernstrom JD, Fernstrom MH *J Nutr.* 2006;136:553S–9S.

Gijsman HJ, Scarna A, Harmer CJ, McTavish SFB, Odontiadis J, Cowen PJ, Goodwin GM *Psychopharmacology.* 2002;160:192–7.

Gomez-Merino D, Béquet F, Berthelot M, Riverain S, Chennaoui M, Guezennec CY *Int J Sports Med.* 2001;22:317–22.

Hassmén P, Blomstrand E, Ekblom B, Newsholme EA *Nutrition.* 1994;10:405–10.

Hutson SM, Lieth E, LaNoue KF *J Nutr.* 2001;131:846S–50S.

Jakeman PM, Hawthorne JE, Maxwell SRJ, Kendall MJ, Holder G *Exp Physiol.* 1994;79:461–64.

Langfort J, Baranczuk E, Pawlak D, Chalimoniuk M, Lukacova N, Marsala J, Gorski J *Cell Mol Neurobiol.* 2006;26:1327–42.

Lehmann M, Huonker M, Dimeo F, Heinz N, Gastmann U, Treis N, Steinacker JM, Keul J, Kajewski R, Haussinger D *Int J Sports Med.* 1995;16:155–9.

McGuire J, Ross GL, Price H, Mortensen N, Evans J, Castell LM *Brain Res.* 2003;60:126–30.

Marvin G, Sharma A, Aston W, Field C, Kendall MJ, Jones DA *Exp Physiol.* 1997;82:1057–60.

Meeusen R, Roeykens J, Magnus L, Keizer H, De Meirleir K *Int J Sports Med.* 1997;18:571–7.

Meeusen R, Piacentini MF, Van Den Eynde S, Magnus L, De Meirleir K *Int J Sports Med.* 2001;22:329–36.

Meeusen R, Watson P, Hasegawa H, Roelands B, Piacentini MF *Sports Med.* 2006;36:881–909.

Mittleman KD, Ricci MR, Bailey SP *Med Sci Sports Exerc.* 1998;30:83–91.

Newsholme EA, Leech AR Biochemistry for the medical sciences. Chichester: Wiley; 1983. pp. 784–6.

Newsholme EA, Acworth IN, Blomstrand E In: Benzi G, editor. Advances in myochemistry. London: John Libbey; 1987. pp. 127–33.

Pardridge WM. *Neurochem Res.* 1998;23:635–44.

Portier H, Chatard JC, Filaire E, Jaunet-Devienne MF, Robert A, Guezennec CY *Eur J Appl Physiol.* 2008;104:787–94.

Pannier JL, Bouckaert JJ, Lefebvre RA *Eur J Appl Physiol.* 1995;72:175–8.

Pitsiladis YP, Strachan AT, Davidson I, Maughan RJ *Exp Physiol.* 2002;87:215–26.

Romanowski W, Grabiec S *Acta Physiol Pol.* 1974;25:127–34.

Sahlin K. In: Hargreaves M, Spriet L., editors. Exercise metabolism, Champaign: Human Kinetics. 2006. pp. 163–86.

Sato Y, Eriksson S, Hagenfeldt L, Wahren J *Clin Physiol.* 1981;1:151–65.

Scarna A, Gijsman HJ, McTavish SFB, Harmer CJ, Cowen PJ, Goodwin GM *Br J Psychiatry.* 2003;182:210–13.

Smriga M, Kameishi M, Torii K *J Nutr.* 2006;136:548S–52S.

Strachan AT, Maughan RJ *Med Sci Sports Exerc.* 1999;31:547–53.

Strachan AT, Leiper JB, Maughan RJ *Exp Physiol.* 2004;89:657–64.

Strüder HK, Weicker H *Int J Sports Med.* 2001;22:482–97.

Strüder HK, Hollmann W, Platen P, Donike M, Gotzmann A, Weber K *Horm Metab Res*. 1998;30:188–94.

Takao Y, Kamisaki Y, Itoh T *Eur J Pharmacol.* 1992;215:245–51.

Van Hall G, Raaymakers JSH, Saris WHM *J Physiol.* 1995;486:789–94.

Verger PH, Aymard P, Cynobert L, Anton G, Luigi R *Physiol Behav*. 1994;55:523–6.

Watson P, Shirreffs SM, Maughan RJ *Eur J Appl Physiol*. 2004;93:306–14.

Wilson WM, Maughan RJ *Exp Physiol*. 1992;77:921–4.

Young SN. In: Wurtman RJ, Wurtman JJ., editors. Nutrition and the brain (vol 7). New York: Raven Press; 1986. pp. 49–88.

Chapter 58
The Menstrual Cycle: Psychological, Behavioral, Physiological, and Nutritional Factors

Olga van den Akker

Abbreviations

ACOG	American College Obstetricians and Gynecology
DSM III	Diagnostic and Statistical Manual III
GnRH	Gonadotropin-releasing hormone
FSH	Follicle-stimulating hormone
LH	Luteinizing hormone
NIMH	National Institute of Mental Health
PMDD	Premenstrual dysphoric disorder
PMS	Premenstrual syndrome

58.1 Introduction

The occurrence of menses (menstruation) during the female cycle indicates the functionality of the menstrual cycle, which starts at menarche (onset of first menses at puberty) and dissipates at menopause (time period of cessation of last menses). Although numerous factors can affect the functioning of this cycle, the timing of menarche appears to be genetically determined (van den Akker et al. 1987) and related to height and nutritional (or energy) factors (Nichols et al. 2006). Menopause occurs when women run out of oocytes, which may be related to smoking and parity, although genetic factors, social, hormonal, and environmental exposures/interactions could also be relevant (Nichols et al. 2006). Body mass index does not appear to be associated with menopause (Kalichman et al. 2007). The menstrual cycle is also complex because it incorporates hormonal, neuroendocrine, physical, and psychological changes which recur regularly (cyclically) throughout a woman's reproductive life span. Some changes experienced during the menstrual and premenstrual phases of the cycle can cause problems. For example, it has been suggested that menstrual cycle irregularities or cycle length (linked to metabolic and hormonal abnormalities, insulin resistance, and imbalances in hyperestrogens and hyperandrogens) could potentially increase the incidence/occurrence of cardiovascular disease (Rubba et al. 2008). In infertile women with polycystic ovarian syndrome, the clinical

Olga van den Akker (✉)
Department of Psychology, Middlesex University, The Town Hall, The Burroughs,
Hendon, London, NW4 4BT, UK
e-mail: o.vandenakker@mdx.ac.uk

Table 58.1 Key facts of the menstrual cycle

The menstrual cycle provides an environment fit for reproductive functioning
The cyclic rhythm depends on the synchronized functioning of a number of coordinated systems — particularly the endocrine system
The premenstrual dysphoric syndromes are characteristic of menstrual cycle dysfunctions
Premenstrual dysphoria includes physiological, psychological, and behavioral symptoms
Specific food cravings during premenstrual dysphoric states have led to the hypothesis that nutritional factors may explain some of the etiology of premenstrual distress
To date, no effective treatment for premenstrual dysphoria exists

Note: This table lists the key facts of the human female menstrual cycle, endocrine control, premenstrual dysphoria, problems of defining and treating premenstrual dysphoria

characteristics are irregular menses and high insulin levels (Hyperinsulinemia) (Myer et al. 2005). Similarly, links between nutrition (such as carbohydrate cravings) and enhanced mood (through a tryptophan-mediated increase in brain serotonin) have been reported (Corsica and Spring 2008). Physiological and psychological (including mood or dysphoric) disturbances of the menstrual cycle have been studied by researchers from many disciplines and orientations, but interrelationships between the various processes identified have not been unambiguously demonstrated. However, there is no doubt that internal (e.g., hormonal) and external (e.g., nutritional) factors influence the experience of the menstrual cycle. The focus of this chapter is on nutrition and its possible link to mood disturbances during the premenstrual phase of the menstrual cycle. The summary points are detailed in Table 58.1.

58.2 Hormonal Control of the Menstrual Cycle

The cerebral control of the menstrual cycle, through the involvement of the hypothalamus, which is seated deep within the brain, is to produce hormones that control numerous essential functions such as hunger, thirst, sleep, sex drive, body temperature, and mood (see Table 58.2). Many of these are also closely linked to nutritional and behavioral factors. In fact, all cells in the body (including the brain) have hormone receptors, and any deficiencies in the tight control of hormonal functioning can cause a whole series of other problems, one having a knock-on effect on yet another (e.g., diabetes and stunted growth in children). Specifically, cyclic changes in appetite, overeating, or food cravings have been identified as one of several criteria for premenstrual dysphoric mood disorders (Braverman 2007). Similarly, deficiencies in nutritional input (when people have lost too much body weight) as in anorexia nervosa or famine can lead to amenorrhea (the cessation of menses), whereas too much food intake over long periods of time, as in obesity, can lead to infertility.

The hypothalamus also influences the release of hormones from glands such as the pituitary gland through neural and hormonal loops. The pituitary is located relatively near the hypothalamus and this gland produces hormones that control the activity of endocrine glands and is therefore also called the "master gland" (Coll et al. 2007). For example, the pituitary gland secretes growth hormone, thyroid-stimulating hormone, antidiuretic hormones, and prolactin, which stimulates breast development and later milk production in women.

The menstrual cycle is controlled by the endocrine system as shown in Fig. 58.1, which shows how the hypothalamus controls much of the positive and negative feedback mechanisms, initiating the release and inhibition of hormones and other endocrine substances. The onset of puberty is triggered by an increase in initial gonadotropin-releasing hormone (GnRH) from the hypothalamus.

Table 58.2   Hormonal control of functions

The menstrual cycle	Hunger	Kidney function
Ovulation	Digestion	Blood pressure
Pregnancy	Energy	Blood cell production
Fertility	Sugar and fat metabolism	Immune system functioning/ wound healing
Sleep	Salt and water balance	Libido
Growth	Hair/bones	Moods

Note: This table lists the hormonal control of a number of physiological and behavioral functions
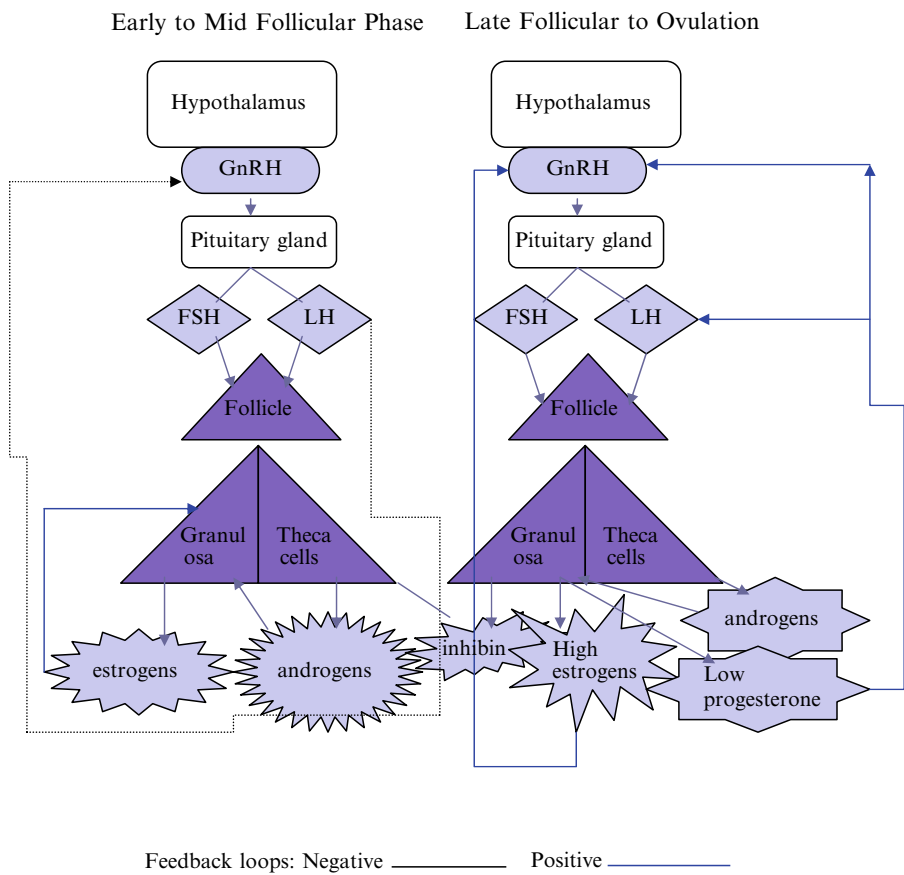
Fig. 58.1 Endocrine control of the menstrual cycle. The hypothalamus controls much of the positive and negative feedback mechanisms initiating the release and inhibition of hormones and other endocrine substances. Positive and negative feedback loops inform hormone-releasing glands (pituitary and other endocrine glands such as the ovaries), during the mid-to-early follicular phase of the cycle on the left, and the late follicular to ovulatory phase on the right

This leads to an increase in pituitary luteinizing hormone (LH), which triggers the pubertal events of the female menstrual cycle. Following puberty, during the cyclic menstrual phase, the hypothalamus responds to low levels of estrogen by producing a hormone to stimulate GnRH secretion from the anterior pituitary. The pituitary gland acts in unison with the hypothalamus, as do the hormones estrogen and androgen secreted as a result of follicular development. This is called the follicular phase. With continued growth of the follicles, estrogen production within the follicle maintains

sensitivity to LH and follicle-stimulating hormone (FSH). These activities in turn increase the number of LH receptors, allowing luteinization and ovulation to occur (the ovulatory phase). Circulating estradiol levels trigger ovulation, which then triggers a rise in progesterone along with a second rise in estrogen – the luteal phase. The latter part of the luteal phase is what is often referred to as the premenstrual phase, which is associated with a fall in hormone levels, allowing gonadotropins to increase again, initiating a new cycle.

The organs producing the hormones are the pituitary, adrenals, thyroid, ovaries, and testes. Hormones (specific proteins produced by human endocrine organs) contribute to the maintenance of cellular functions and homeostasis, or maintaining an effective balance, pending diurnal, environmental variation (place as well as toxins medications and pollutants), psychological functioning, including changes in stress levels, dietary function, and food intake. Aging processes cause hormone levels to decrease and health maintenance problems tend to increase. Although a naturally occurring and well-tuned cyclic event incorporating the timely integration and interactions of many different systems, menstrual cycle functioning can be accompanied by a number of uncomfortable or distressing disorders, one of which occurs just before the onset of menses, or in the premenstrual phase of the menstrual cycle.

58.3 Premenstrual Dysphoric Syndrome

The premenstrual syndrome is a combined psychological, behavioral, and physiological problem characterized by mood swings, depression, anxiety, irritability, crying, impaired concentration/memory, anger, aggression, insomnia, bloating, cramping, breast tenderness, acne, food cravings, weight gain, hot flushes, and palpitations. Premenstrual symptoms are reported by huge numbers of women across the globe, recently estimated to occur in between 70–90% of women who have menstrual cycles, with an estimated 20–40% describing these as problematic, affecting their daily functioning (termed as the Premenstrual Syndrome or PMS) and 3–8% reporting impairment in quality of life as a result of severe PMS symptoms – termed as Premenstrual Dysphoric Disorder (PMDD; Mishell 2005). Despite reports of the significant social, psychological, and economic effects of PMS/PMDD, the syndromes have been relatively under-recognized in large-scale epidemiological studies (Ussher and Perz 2006) or in research determining the relative health burden of PMS (Halbreigh et al. 2003). Theoretical research exploring etiological factors of PMS/PMDD has failed to reach consensus (Bancroft 1993; van den Akker et al. 1995a–c; Ussher 1996), and treatment effectiveness and appropriateness remain uncertain (Gold 1994; Halbreigh et al. 2003). In addition to medical treatment, consisting largely of antidepressant medication (Bose et al. 2008), behavioral treatments have also been shown to have some effect on improving the occurrence of symptoms during the premenstruum, and this is likely to be the result of learning to cope with the symptoms (Estes 1993; Hunter et al. 2002). Educational and informational packages for the treatment of PMS symptoms have also been offered with some successes reported (Bancroft 1993; Huston and Fujitsubo 2002). Changes in dietary behavior have been reported to occur in a self-help study, which qualitatively reported changes in the perception of the impact of PMS/PMDD (Ussher and Perz 2006).

However, the variation in symptoms from slight to moderate and severe necessitates accurate diagnosis and *targeted* treatment. The lack of etiology and resultant lack of effective treatments are likely to be the result of the lack of unity of the expression of PMS/PMDD, with the possibility that separate conditions with separate etiologies exist. In addition to the etiological elusiveness of the problem, the numerous interactive systems of the menstrual cycle, and the unreliability of diagnosis, the cycle is likely to be influenced by nutritional needs. For example, absorption and expulsion or

repulsion of certain foods or nutrients are likely to be influenced by variations in behaviors and variations in fluctuating hormone levels. This chapter reviews the evidence presented by research on the link between PMS and nutrition. Media reports of cures and potions reported to help the population in its cyclic suffering are prolific, although there is little evidence of their efficacy (Yonkers et al. 2008). It should be noted that because of the wide ranging effects of PMS, the willingness of sufferer's partners and employers of sufferers as well as those afflicted themselves to try and believe in these self-help remedies is huge. Businesses have latched onto the magnitude of the need for a miracle cure for this prolific curse and have also extolled the virtues of substances and lifestyles of unproven utility.

First, a definition of PMS is warranted because an accurate diagnosis is essential in research attempting to delineate the causes and treatment effects of PMS. Following years of debates and research which has failed to accurately define the study populations, undeniably hampered progress in the area. The National Institutes of Health consensus conference on PMS in 1980 put forward a rigorous set of criteria for defining this previously loosely defined syndrome. The Diagnostic and Statistical Manual III (DSM III) adopted the criteria to define the severe form of PMS. They termed it the Late Luteal Phase Dysphoric Disorder, but was subsequently termed Premenstrual Dysphoric Disorder (PMDD). The criteria for fulfillment of a diagnosis of PMDD are shown in Table 58.3.

DSM IV, the revised classification system, describes the research criteria for PMDD, which includes a prospective evaluation and confirmation of at least two consecutive menstrual cycles, focusing on the timing of the symptoms as shown in Table 58.4. A 30% increase in symptoms from the follicular to late luteal phase is a necessary criterion (NIMH 1983). The diagnostic PMDD criteria are for severe and disruptive PMS, and therefore do not include many women across populations suffering from milder though also debilitating or impairing symptoms. It is also important to note that the specificity of the diagnosis includes all symptoms, which may limit the opportunity to unravel subsyndromes, for example, those primarily psychological in nature versus those driven by water retention. It is possible that seeking a unified etiology is not realistic, but we will move on with those reservations in mind. The cumbersome daily monitoring of symptoms to ensure an accurate

Table 58.3 Diagnostic criteria for PMDD

Symptom	Timing
Presence of at least 5 luteal phase symptoms	Timing of symptoms must be confirmed using daily charting/diaries over a minimum of 2 cycles
At least one symptom must be a mood symptom	
Evidence of functional impairment is necessary	

Note: The table shows the diagnostic criteria which must be met by a woman presenting with premenstrual dysphoric disorder

Table 58.4 Revised diagnostic criteria for PMDD – American Psychiatric Association (2000)

Symptom	Timing
Presence of at least 5 luteal phase (primary) symptoms in most cycles	Timing of symptoms must be confirmed using daily charting/diaries over a minimum of 2 cycles
At least one symptom must be a mood symptom (primary symptom)	Symptoms must be present most of the time 1 week before menses remitting within a few days of menstrual onset
Evidence of functional impairment is necessary in work, school, other usual activities and/or relationships	
Symptoms must not be an exacerbation of another condition	

Note: The table shows the revised diagnostic criteria which must be met by a woman presenting with premenstrual dysphoric disorder

diagnosis is essential as reports of prospective and retrospective ratings of symptoms do not always correlate (van den Akker and Steptoe 1985; ACOG 2000; Wyatt et al. 2002; Steiner et al. 2006).

There are popular reports (Hope-Riedesel 2008) detailing specific types of PMS (e.g., Guy Abraham, -UCLA), ranging from Type A (Anxiety), C (Carbohydrate Cravings), D (Depression), H (Hyperhydration and water imbalance), and P (Pain). These predominant types of PMS are purportedly caused by high estrogen levels coupled with vitamin, calcium, magnesium, and zinc deficiencies (for Type A); sensitivity to insulin (Type C); higher levels of progesterone (Type D); sodium sensitivity (Type H); and eating the right fats and avoidance of wrong fats (Type P).

However, although altered mood is a significant symptom of severe PMS, it is important to differentiate clinical affective disorders (clinical depression) from cyclic mood swings such as PMS. People with clinical affective depression may also have PMS, in which case their symptoms may worsen during the premenstrual phase of the cycle. However, women with PMS are not usually also diagnosed with clinical affective disorders, so treatments for them should be differentiated.

58.4 Nutritional Factors and the Menstrual Cycle

Because of its cyclic nature, endocrine hormones have been held responsible, as have changes in serotonin and tryptophan neurotransmitter levels. It has also been suggested that nutritional/dietary factors can influence the chemical changes and severity of PMS experienced. For example, Table 58.5 shows the relationships observed between nutritional factors and biochemical changes affecting psychological functions.

It stands to reason therefore that nutritional replacement of these dietary deficiencies is necessary to restore the balances of organ and reproductive functioning and hence do away with aggravating factors, excesses, and toxicities. However, research demonstrating the exact mechanisms of dietary deficiencies is not conclusive, as will be shown below.

Nutrition is in part guided by neuroendocrine and hormonal control systems, and is also under the control of psychological and behavioral factors. Some conditions associated with the menstrual cycle have been targeted with nutritional therapies where biochemistry and nutrition are combined into a therapeutic substance or dosage for the alleviation of unpleasant symptoms or dysfunctioning. Nutritional therapy is usually associated with naturopathy, or drug-free medicine to treat people with malaise. It is therefore considered a holistic approach, because it attempts to treat the body as a whole curing causes of symptoms, not just masking the symptoms. A nutritional approach to menstrual cycle-related conditions such as PMS is to consider PMS the result of extra nutritional demands not being met, or for example, sugar levels behaving erratically. Nutritional therapy is actually a really old form of therapy, practiced widely before modern drugs became household therapies. It is

Table 58.5 Relationships between nutrition, biochemical, and psychological factors

Vitamin B6 is related to an imbalance of estrogen, which can lead to impaired mood
Deficiencies in fatty acids (e.g., evening primrose oil) needed to produce prostaglandins
An excess in calcium from too much dairy produce forces depletion of magnesium because they compete for absorption, leading to a deficiency of one and toxicity of other
Deficiencies of vitamins A, C, E, and other B vitamins and iron and zinc are also contributory factors
Excesses of dietary salt, alcohol, caffeine, smoking, and animal fats can aggravate symptoms

Note: This table shows a number of the relationships which have been identified between nutritional, biochemical, and psychological variables

based on whole body health and well-being, detecting deficiencies and supplementing through nutritional advice or supplements. Previous research has explored the effect of carbohydrates on depression in general and PMS in particular. If PMS low mood is treated with medications such as SSRIs (selective serotonin reuptake inhibitors), they may mask any nutritional deficiency underlying the root cause of PMS.

There are links between biochemical states and nutrition, for example, the neurotransmitter serotonin is involved with appetite regulation and mood. Low serotonin levels in the brain can cause depression directly, and can lead to carbohydrate cravings (such as sweets and salty snacks), commonly reported in the luteal phase in women reporting PMS. Studies of the effects of carbohydrate intake have suggested mood-related benefits, possibly through an enhanced transport of tryptophan to the brain, which in turn might lead to an increase in the synthesis of tryptophan (Freeman et al. 2002). Murphy and Wagner's (2008) review of mood disorders and vitamin D indicates that there may be a biochemical mechanism between vitamin D and PMS, seasonal affective disorders, non-specific mood disorder, and major depression affecting women. The media has produced several reports of the advantages of taking vitamin D and calcium to alleviate PMS (e.g., BBC News 2005), but no underlying theoretical model demonstrating the pathways for these relationships have been documented. Other correlational but not causal research has demonstrated a decreased premenstrual regional cerebral blood flow in the temporal lobes in women with PMS – compared using scans taken post menstruation – and no such changes were observed in non-PMS sufferers (Buchpiguel et al. 2000).

Increased cravings for particular food types in conjunction with impaired mood have been reported decades ago (e.g., Morton et al. 1953; Smith and Saunder 1969; Wurtman et al. 1989; Brzezinski et al. 1990). More recent research also reported a significant increase in caloric (mainly fat) intake and a modest increase in alcohol craving in women with PMDD in the luteal phase compared to the follicular phase (Reed et al. 2008). These cyclic changes were not present for their control group, suggesting that the dysphoria may be related to the altered food consumption and desire. However, other research failed to find these effects for PMS or cycle phase (Bryant et al. 2006). Nevertheless, interactions between (mood-enhancing) drugs and nutrition intake have also been reported (e.g., Haney et al. 1997; 2008) suggesting that pharmacological treatment targeting depressive symptoms may exacerbate nutritional changes in women suffering from premenstrual mood disorders. Studies reporting nutritional effects for cycle-related dysphoria are likely to have contributed to the increased interest in herbal and homeopathic remedies instead of the less agreeable pharmaceutical treatments (Bramwell and Dye 2006).

In a recent systematic review of the literature, Canning et al. (2006) evaluated the efficacy of alternative nutritional and herbal treatments in studies using randomized research designs. Although the gold standard suggests that diagnosis using daily monitoring is clearly desirable, their review included retrospective determination of PMS/PMDD status (both definitions were used) to ensure that a comprehensive number was included in their evaluation. The review also incorporated studies of oral contraceptive pill users. Canning et al. included vitamin B6, magnesium, calcium, vitex agnus castus, evening primrose oil, St John's Wort and Ginkgo Biloba. Of the 113 articles identified, 26 studies were included in the review. Table 58.6 shows the positive and negative outcomes of the nutritional supplements/treatments reported in the review.

The study clearly shows a positive effect of calcium, and a relatively positive outcome for half the studies assessing the effectiveness of vitamin B6. The authors note that the efficacy of magnesium and evening primrose oil were not confirmed and that insufficient quality research has been carried out on Vitex agnus castus, St John's Wort and Ginko Biloba. They also point out that unfortunately, accurate comparisons cannot be made in the absence of some uniformity of diagnosis and assessment of improvement.

Table 58.6 Efficacy of treatments reported in a systematic review of nutritional supplements/treatments for PMS/PMDD by Canning et al. (2006)

Treatment	Studies reporting an Improvement in PMS/PMDD	Studies reporting no Improvement in PMS/PMDD
Calcium	Thys-Jacobs et al. (1989, 1998)	–
Magnesium	Facchinetti et al. (1991) Walker et al. (1998)	De Souza et al. (2000) Walker et al. (2002)
Vitamin B6	Abraham and Hargrove (1980) Barr (1984) Doll et al. (1989) Kendall and Schnurr (1987) Williams et al. (1985)	Diegoli et al. (1998) Hagen et al. (1985) Malmgren (1987) Smallwood et al. (1986) Stokes and Mendels (1972)
Evening Primrose Oil	Ockerman et al. (1986) Puolakka et al. (1985)	Collins et al. (1993) Khoo et al. (1990)
Vitex agnus castus	Atmaca et al. (2003) Halaska et al. (1998) Schellenberg (2001)	Turner and Mills (1993)
St John's Wort	–	Hicks et al. (2004)
Ginko Biloba	Tamborini and Taurelle (1993)	–

Note: This table shows the studies supporting improvements in premenstrual dysphoric symptoms and nutritional supplement

58.5 Conclusion/Summary

Nutritional effects on the menstrual cycle have been studied increasingly over the last couple of decades, rapidly matching the interest previously generated by the pharmacological effects of menstrual cycle functions and disorders. To date, it is impossible to extrapolate clear pathways within the research of menstrual cycle dysphoric mood such as premenstrual distress, although there is less doubt about the effects of nutritional variables on menarche and fertility. It is possible that effective theoretical pathways of nutrition on cyclic dysphoric mood have been so elusive because of the difficulty in accurate diagnosis of mild, moderate, and severe premenstrual dysphoria. Nevertheless, more research is warranted on the specific effects of nutrition on menstrual cycle disorders such as premenstrual dysphoria.

58.6 Applications to Other Areas of Health and Disease

Women reporting discomfort of distress for menstrual cycle-related symptoms are in a majority. Considering the complex nature of the human female reproductive system it is unsurprising that many other conditions in relation to women's reproductive health also defy ready explanations of etiology and consequently elude effective targeted treatment. It is advisable that regular monitoring of impairments in behaviors, such as concentration and alterations in mood states, such as irritability, anxiety, and depression are given due consideration by health care professionals and researchers. Behavioral and nutritional interventions may have positive effects on well-being in a number of ways, even if such interventions do not target proven etiological factors.

Summary Points

- The main function of the menstrual cycle is to secure an environment fit for reproductive functioning.
- The menstrual cycle depends on the adequate functioning of a number of coordinated systems, particularly the endocrine system.

- Menstrual cycle dysfunctions include premenstrual dysphoric syndromes.
- Premenstrual dysphoria is difficult to define and nutritional effects on premenstrual dysphoria have been variously studied.
- Etiological factors and treatment efficacy of premenstrual dysphoria are uncertain.

Definitions of Key Terms

The menstrual cycle: A regularly recurring 28-day cycle occurring in females.

Premenstrual syndrome/premenstrual dysphoric disorder: A psychological and physiological disorder of unknown etiology.

Dietary supplements: Some dietary supplements such as homeopathic medicines, vitamin B6, calcium, or magnesium may be useful in reducing some symptoms of PMS.

Menses: The overt blood flow from the uterus to the vagina during the monthly menstrual cycle.

Menarche: One of the later stages of puberty marked by the first occurrence of menses starting around the age of 12 in girls.

Menopause: One of the early stages of menopause marked by the cessation of the last occurrence of menses averaging around the age of 52 in women.

Nutrition: The materials necessary to support life.

Endocrine system: The endocrine system controls some of the hormone-releasing mechanisms in the body.

Hormones: Small amounts of chemicals released by cells affecting other parts of the body or organs.

References

ACOG. American College of Obstetrics and Gynecology: ACOG Practice Bull: Premenstrual syndrome. Washington: ACOG; 2000. April, 15.

Abraham G, Hargrove J *Infertility*. 1980;3:155–65.

van den Akker O, Steptoe A *Br J Psychiatry*. 1985;147:164–69.

van den Akker O, Steptoe A *J Psychophysiol*. 1987;1:149–58.

van den Akker O, Steptoe A. *Psychosom Med*. 1989;51:319–28.

van den Akker O, Steptoe A. *Br J Midwifery*. 1994;2 Suppl. 5:223–115.

van den Akker O, Neale M, Stein G, Murray R *Acta Genet Med Gemellol*. 1987;36:541–48.

van den Akker O, Eves F, Service S, Lennon B *Soc Sci Med*. 1995a;40 Suppl. 10:1417–23.

van den Akker O, Eves F, Stein G, Murray RM *J Psychosom Res*. 1995b;39 Suppl. 4:477–87.

van den Akker O, Packer A, Eves F *Health Care Women Int*. 1995c;16 Suppl. 3:263–72.

Atmaca M, Kumru S, Tezcan E *Hum Psychopharmacol*. 2003;18:191–5.

Bancroft J. *Psychol Med*. 1993;241:1–47.

Barr W. *Practitioner*. 1984;228:425–7.

BBC News. (2005). http://news.bbc.co.uk/go.pr/fr/-/hi/health/4087312.stm

Bose Usman S, Indusekhar R, O'Brien S.) *Best Pract Res Clin Obstet Gynaecol*. 2008;2:251–60.

Bramwell R, Dye L Guest editorial. *J Reprod Infant Psychol*. 2006;24:287–8.

Braverman P. *J Pediatr Adolesc Gynecol*. 2007;20:3–12.

Bryant M, Truesdale K, Dye L *Br J Nutr*. 2006;96:888–94.

Brzezinski A, Wurtman J, Wurtman R, Gleason R, Greenfield J, Nader T *Obstet Gynecol*. 1990;76:296–301.

Buchpiguel C, Alavi A, Crawford D, Freeman E, Newberg A *J Psychosom Obstet Gynaecol*. 2000;21 Suppl. 3:157–65.

Canning S, Waterman M, Dye L *J Reprod Infant Psychol*. 2006;24 Suppl. 4:363–78.

Coll A, Farooqi I, O'Rahilly S *Cell*. 2007;129 Suppl. 2:251–62.

Collins A, Cerin A, Coleman G, Landgren B *Obstet Gynecol*. 1993;81:93–7.

Corsica J, Spring B *Eat Behav*. 2008;9:447–54.

De Souza M, Walker A, Robinson P, Bolland K *J Womens Health Gend Based Med*. 2000;9:131–9.

DSM III-R. *Diagnostic and statistical manual*. 3rd ed. revised. Arlington: American Psychiatric Association; 1987.

DSM IV. *Diagnostic and statistical manual*. 4th ed. Arlington: American Psychiatric Association; 2000.

Diegoli M, Da Fonseca A, Diegoli C, Pinotti J *Int J Gynaecol Obstet*. 1998;62:63–7.

Doll H, Brown S Thurston A, Vessey M *J R Coll Gen Pract*. 1989;39:364–8.

Estes J. *Diss Abstr*. 1993;54 Suppl. 2A: 424.

Facchinetti F, Borella P, Sances G, Fioroni LP, Nappi RE, Genazzani AR *Obstet Gynecol*. 1991;78:177–81.

Freeman E, Stout A, Endicott J, Spiers P *Int J Gynaecol Obstet*. 2002;77, 253–4.

Gold J., editor. *Premenstrual dysphoria: Myths and realities*. London: American Psychiatric Press; 1994.

Hagen I, Nesheim B, Tuntland T *Acta Obstet Gynecol Scand*. 1985;64:667–70.

Halaska M, Raus K, Beles P, Martan A Paithner KG *Ceska Gynekol*. 1998;63:88–92.

Halbreigh U, Borenstein-Perlstein T, Kahn L *Psychoneuroendocrinology*. 2003;28:1–23.

Haney M, Comer S, Fischman M, Foltin R *Psychopharmacology*. 1997;132:311–4.

Haney M, Hart C, Vosburg S, et al. *Psychopharmacology*. 2008;197:157–68.

Hicks S, Walker A, Gallagher J, Middleton RW, Wright J *J Altern Complement Med*. 2004;10:925–32.

Hope-Riedesel D. The cycle diet. Com. http://cyclediet.com.types_of_pms.php. Accessed 06/01/09; 2008.

Hunter M, Ussher J, Cariss M, Browne S, Jelley R, Katz M *J Psychosom Res*. 2002;53:811–7.

Huston J, Fujitsubo L *PMDD: A guide to coping with premenstrual dysphoric disorder*. Oakland: New Harbinger; 2002.

Kendall K, Schnurr P *Obstet Gynecol*. 1987;70:145–9.

Khoo S, Munro C, Battistutta D *Med J Aust*. 1990;153:189–92.

Kalichman L, Malkin I, Kobyliansky E *Menopause*. 2007;14 Suppl. 1:135–40.

Malmgren R. *Neuropsychobiology*. 1987;18:83–8.

Mishell D. *Am J Manag Care*. 2005; Suppl 11:S473.

Morton J, Addition H, Addition R, Hunr L, Sullivan JJ *Am J Obstet Gynecol*. 1953;65:1182–91.

Murphy P, Wagner C *J Midwifery Womens Health*. 2008;53 Suppl 5:440–6.

Myer C, McGrath B, Tweede H *J Clin Endocrinol Metab*. 2005;90:5711–6.

Nichols H, Trentham-Dietz A, Hampton JM, Titus-Renstoff L, Egan KM, Willett WC, Newcomb PA *Am J Epidemiol*. 2006;164 Suppl 10:1003–11.

NIMH. *National Institute of Mental Health premenstrual syndrome workshop guidelines*. Rockville: National Institute of Mental Health; 1983.

Ockerman P, Backrack I, Glans S, Rassner S *Recent Adv Clin Nutr*. 1986;39:411–4.

Puolakka J, Makarainen L, Vinikka L, Ylikorkala O *J Reprod. Med*. 1985;30:149–53.

Reed S, Levin F, Evans S *Horm Behav*. 2008;54:185–93.

Rubba F, Mattielo A, Chiodini P, Celentano E, Galasso R, Ciardullo A, Gentile M, Triassi M, Rubba P, Panico S *Nutr Metab Cardiovasc Dis*. 2008;18:659–63.

Schellenberg R. *BMJ*. 2001;322:134–7.

Smallwood J, Ah-Kye D, Taylor I *Br J Clin Prac*. 1986;40:532–4.

Smith S, Sauder C *Psychol Med*. 1969;31:281–7.

Steiner M, Pearlstein T, Cohen L Endicott J, Kornstein SG, Broberts C, Roberts DL, Yonkers K *J Womens Health*. 2006;15:57.

Stokes J, Mendels J *Lancet*. 1972;1:1177–8.

Tamborini A, Taurelle R *Rev Fr Gynecol Obstet*. 1993;88:447–57.

Thys-Jacobs S, Ceccarelli S, Bierman A, Weisman H, Cohen M-A, Alvir J *J. Gen. Intern. Med*. 1989;4:183–9.

Thys-Jacobs S, Starkey P, Bernstein D, Tan J Calcium carbonate and the premenstrual syndrome: Effects on premenstrual and menstrual symptoms. *Am J Obstet Gynecol*. 1998;179:444–52.

Turner S, Mills S *Complement Ther Med*. 1993;1:73–2.

Ussher J. *Ann. Rev. Sex Res*. 1996;7:218–51.

Ussher J, Perz J *J Reprod Infant Psychol*. 2006;24 Suppl 4:347–62.

Walker A, De Souza M, Vickers M, Abeyasekera A, Collins ML, Trinca LA *J Womens Health*. 1998;7:1157–65.

Walker A, De Souza M, Marakis G, Robinson PA, Morris AP, Bolland KM *Med Hypotheses*. 2002;58:213–20.

Williams M, Harris R, Bernard C, Dean C *J Int Med Res*. 1985;13:174–9.

Wurtman J, Brzezinski A, Wurtman R, Laferrere B *Am J Obstet Gynecol*. 1989;161:1228–34.

Wyatt K, Dimmock P, Hayes-Gill B, Crowe J, O'Brien S *Fertil Steril*. 2002;78 Suppl 1:96–101.

Yonkers K, O'Brien S, Eriksson E *Lancet* 2008; 371:1200–10.

Chapter 59
Feeding Behavior and Body Mass Index

Gian Franco Adami

Abbreviations

BE	Binge eating
BED	Binge eating disorder
BMI	Body mass index
BW	Body weight
CR	Cognitive restraint
DIS	Disinhibition
EE	Energy expenditure
NE	Night eating

59.1 Introduction

The human body is a machine that obtains energy from the environment through food and uses energy for functioning, for moving, for modifying the environment, and for obtaining other food. According to the first principle of thermodynamics, energy cannot be dissipated, and therefore when energy intake exceeds energy expenditure (EE), the surplus is stored in the adipose tissue and then body weight (BW) increases. When energy intake however is inadequate to meet requirements, energy derived from adipose tissue breakdown is used as fuel, and then BW reduces. Consequently, any factor causing weight change, whether psychological, behavioral, pharmacological, endocrinal, or anything else, must ultimately act on energy intake, or output, or some combination of these (Garrow 1988).

Because under physiological conditions BW remains substantially stable over time, a very complex regulatory mechanism must be postulated which exactly matches the effects of unpredictable factors, such as physical activity and food intake, which are affected by individual behavior and by the individual–environmental relationship, and with biological processes that remain completely independent of the environment and the subject's willpower.

Human body EE is accounted for both by the energy required for the body's biological functioning as well as by the energy employed during physical activity. Usually, the former represents more than two-thirds of the total. In developed industrialized countries, strenuous exercises for long amounts

G.F. Adami (✉)
Department of Surgery, University of Genova, Largo Rosanna Benzi 8, 16132 Genova, Italy
e-mail: adami@unige.it

of time are not required, and only a very few individuals (usually only the top agonistic athletes) are engaged in strenuous physical activity for many hours a day over long periods. Therefore, nearly all subjects living in the western world must be regarded as practically sedentary. EE due to physical activity, which accounts for no more than 20% of total EE, is substantially similar in all individuals. Consequently, BW regulation is closely and directly dependent on food intake.

59.2 Food Intake and Body Weight

59.2.1 *Weight Gain and Weight Loss*

When food intake permanently increases, EE remaining constant, a corresponding increase in BW develops. The increase in BW consists in energy-consuming lean body mass as well as the metabolically nearly inert adipose tissue (Fig. 59.1). In a normal subject, the former represents two-thirds of the accumulated weight. Therefore, considering for lean and fat tissue an overall EE of 40 kcal/kg/day and 5 kcal/kg/day, respectively, a one kilogram increase in BW corresponds to an increase in total EE of about 17–20 kcal/day (Forbes 1987; Nelson et al. 1992). Weight gain stops when the increase in EE alone, because of the weight gain, counterbalances the increase in energy intake that gave rise to the weight-gaining process (Forbes 1990). Assuming a permanent increase in energy intake (or a permanent decrease in EE) of 100 kcal/day, the body must accumulate (or lose) 6 kg before reaching a new energy equilibrium. At this point, the BW stabilizes once again, although at a higher level (Forbes 1990). The weight gain process obviously takes a long period of time due to the substantial energetic cost of weight accumulation. A kilogram of tissue consisting of fat and lean tissue in the proportion 3:1 contains about 7,000 kcal and, as such, 6,000 kcal beyond the actual EE must be introduced cumulatively (Fig. 59.2). In addition, while BW accumulates, the body's EE progressively increases and the difference between energy intake and expenditure gradually decreases, further slowing down the weight gain process (Forbes 1990; Tremblay et al. 1992).

The same applies when energy intake is permanently decreased (or EE permanently increases) and BW reduces. In subjects of normal weight, the weight loss implies a loss of both fat and lean tissue in proportion of 3:1, thus obviously leading to a reduction of EE of 17/20 kcal/kg/day for each kilogram of
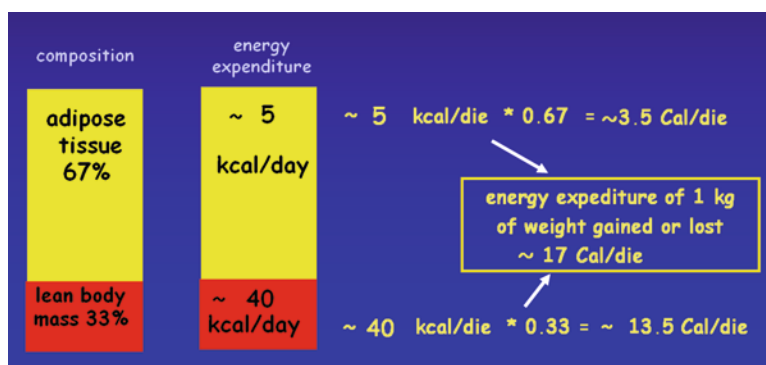
Fig. 59.1 Composition and energy expenditure of the weight gained (or lost). The weight gained or lost by a person of normal weight includes 70% of adipose tissue and 30% of lean body mass. Taking into account the energy expenditure of adipose tissue and lean body mass, one kilogram of weight gain (or lost) leads to an increase (or a decrease) of the total energy expenditure of 17 kcal/day
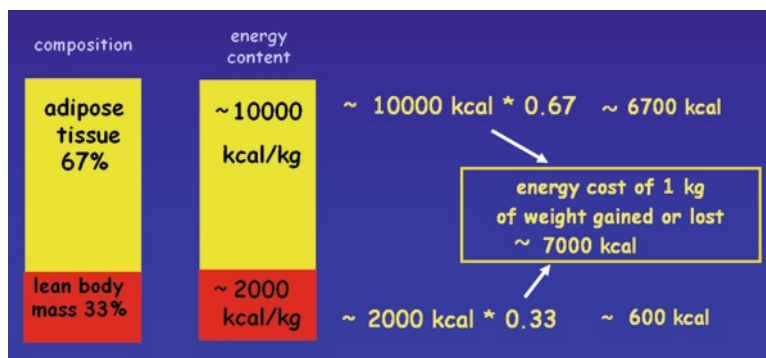
Fig. 59.2 Composition and energy cost of weight gained (or lost). The weight gained by a person of normal weight includes 70% of adipose tissue and 30% of lean body mass. Taking into account the energy content of adipose tissue and lean body mass, for accumulating one kilogram, an amount of 6,000 kcal beyond the energy expenditure has to be cumulatively introduced
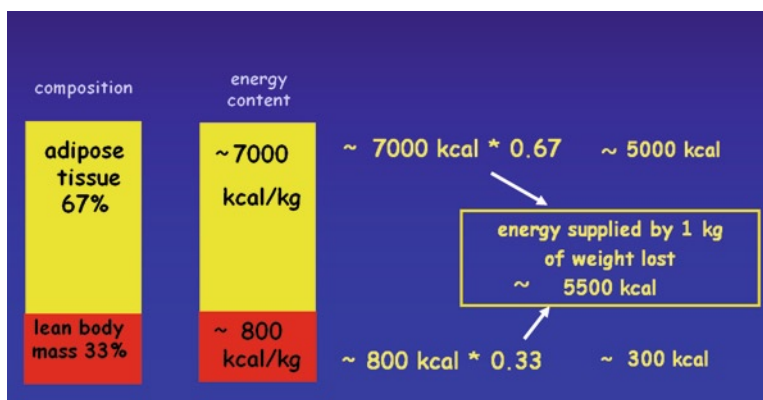
Fig. 59.3 The composition and energy content of the tissue broken down in the weight loss process. The weight lost by a person of normal weight includes 70% of adipose tissue and 30% of lean body mass. Taking into account the energy content of adipose tissue and lean body mass, for losing one kilogram of body weight it is necessary to cumulatively reduce the energy intake under the current energy expenditure of 5,500 kcal

weight lost (Forbes 1987). When the reduced EE due to the weight loss process quantitatively matches the reduced energy intake when the weight loss process itself has initiated, weight loss comes to a standstill, and BW stabilizes at a lower level. As with weight gain, weight loss requires a lengthy interval of time because of the sizeable energy content of the tissue broken down to meet energy requirements (Fig. 59.3) and because of the progressive reduction of the energetic imbalance (van der Kooy et al. 1992).

The composition of weight gain is substantially dependent on initial BW, with heavier subjects accumulating a greater percent of adipose tissue in comparison with their leaner counterparts (Fig. 59.4). Consequently, overweight and obese individuals have an EE of accumulated mass that is lower than that of leaner persons, and values tend to decrease progressively with the increase of BW. Therefore, in comparison with lean people, overweight or obese individuals must build up more weight to compensate for the same permanent increase in food intake, and need smaller energy imbalances to put on the same weight. From a bioenergetic perspective, the control of BW would be poorer in the overweight and in obese subjects than in leaner individuals (Forbes 1987).
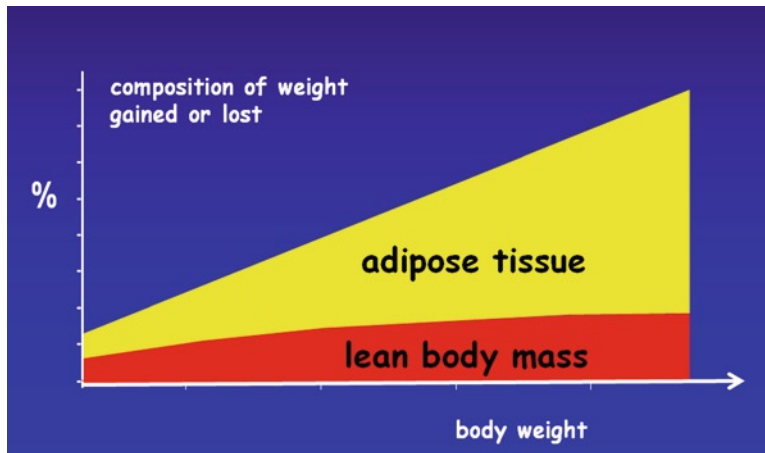
Fig. 59.4 Relationship between body weight and composition or weight gained (or lost). The composition of weight gained (or lost) is dependent on the initial body weight, with the heavier subjects accumulating (or losing) a greater percent of adipose tissue than the leaner ones. Therefore, 1 kg of weight gained (or lost) by an obese patient necessitates that a greater amount of energy be built up and implies a smaller increase in energy expenditure that that gained (or lost) by a lean individual

In contrast, the composition of weight loss is not only accounted for by the initial BW. It is also quite dependent on the degree of the food intake imbalance that has promoted the weight loss itself. A quantitatively reasonable decrease in food intake leads to the loss of lean and fat mass in the physiological proportion predicted by the initial BW. In the same way as for weight gain, when faced with a negative energy imbalance the body loses fat mass and lean tissue in a 3:1 ratio. Conversely, when food consumption is drastically reduced, the percentage of lean tissue lost sharply increases, reaching 50–60% of the total. In fact, when the supply of carbohydrates is notably reduced, the body is forced to breakdown muscle proteins to synthesize glucose for the requirements of encephalic structures that are unable to use different energy sources. Therefore, when energy intake of food is considerably reduced, overphysiological erosion of lean body mass occurs, with a resulting overdecrease of EE. In conclusion, drastic reduction of food intake causes rapid weight loss that is due to loss of lean tissue with higher water content, which then results in the prompt decrease of EE. Excessive loss of lean mass causes a sharp decrease of EE both in absolute and in percentage values, thus making a subject more prone to weight regain which can even exceed initial values (Flatt and Tremblay 2006; Chaston et al. 2007).

59.2.2 Conclusions

From such close relationships between food intake and EE, three important conclusions may be drawn. First of all, under steady conditions, a particular individual food intake matches a particular individual BW. A subject's BW is dependent on actual eating habits through the years, and is not affected by occasional episodes of "over" or "under" eating. Furthermore, it is worthwhile to note that slight and nearly imperceptible differences in customary food intake correspond to very clear and significant differences in BW. It can therefore be argued that obese and overweight people may indeed eat more than their lean counterparts, although not as much as is commonly believed and, in particular, not in proportion to their greater body mass. Furthermore, when interindividual differences in genetics, body composition, and in EE are taken into account, it is possible for an overweight person to eat less than a leaner one, or for individuals with the same BW to have quite

different food intakes. Thirdly, due to the particular lengthiness of the process, weight gain (or loss) is not result clearly and directly associated with the increase (or decrease) in energy intake. In fact, actual weight is a consequence of behavioral changes that occurred much earlier, and often a subject feels that he or she is getting fatter without any appreciable change in food intake. This might certainly cause doubts and cognitive dissonances.

59.3 The Regulation of Body Weight and Food Intake

As said above, insignificant and nearly imperceptible changes in food intake correspond to substantial and very clear changes in BW. Also to be considered is that food intake represents the effects of substantially unpredictable individual behavior. However, in the long run, although a very large quantity of calories is processed, the subject's BW remains essentially constant. Clearly, to obtain such a result a very subtle, accurate, and precise regulatory system is required.

59.3.1 The Set-Point Theory

Over the last few decades, a great deal of attention has been paid to the mechanisms that regulate food intake and, indirectly, body weight (Berthoud 2002). According to a biomedical model of homeostasis, the body and the brain act in a self-regulatory manner to produce an optimal and stable status for the organism. According to such a model, if we eat more and put on weight, then several signals will act in the brain to inhibit food intake and, conversely, if we eat too little, the system will increase food seeking and intake. The net result of these actions would be the relative stability of BW over time (Berthoud 2002; Harris 1990). The regulating center is located in the hypothalamus, in strict relationship with the forebrain (via direct and indirect neural and neurochemical connections) and also with the body (via hormone receptors and substrate sensors assigned to the neuron membrane). The regulation center receives a mix of information pertaining to the size of energy stores and the body metabolic status, as well as the presence of acute or chronic conditions that can potentially impact the energy balance. Furthermore, it collects signals on the characteristics of food via the olfactory and gustatory systems, on the status of the gastrointestinal tract, and on the body's capacity to take and absorb food. From the forebrain, moreover, the hypothalamus receives information about the general status of arousal and about the availability of food in the environment via visual and auditory cues. Finally, regulating center activity is strongly influenced by higher cortical function such as memory, representations, learned experiences, and cognition. From the regulation center, two types of output signals begin. At first, the hypothalamus leads the forebrain to stimulate the individual to proper specific actions with the aim of procuring and ingesting food, in parallel with the cognitive, emotional, and motivational processes that influence the behavioral action. Furthermore, it is thought that the pituitary–endocrine axis hypothalamus modulates the gastrointestinal handling and processing of food. Obviously, the brain should be regarded as more than a processor of information. It is in fact a self-activation organ that issues commands to the somatic, autonomic, and endocrine systems. The input systems transmit a varied and rich pattern of stimuli potentially available for the organization and for the execution of ingestive behavior. It appears plausible, however, that the conscious 'executive brain' cannot possibly listen to all of these inputs all the time, and the concepts and mechanisms of arousal and selective attention are thought to sharpen the sensitivity of the conscious brain to behavior-specific information. Such monitoring of

most of the myriad of inputs is constantly going on at a subconscious level, and although not resulting in overt behavior, can lead to autonomic and endocrine adjustments as well as the modulation of other ongoing behaviors (Berthoud 2002).

59.3.2 Population Data and the Bioenergetic Hypothesis

The problem is the nonconformity of weight stability predictions that should be the comprehensive results of this model and the actual situation in the western world, where the rise in mean BW among the general population and the increase in the prevalence of overweight and obesity are evident problems (Ogden et al. 2006). In addition, even individuals of normal and stable BW often employ deliberate or cognitive strategies to remain stable, including dietary restraint and exercise regimens. Consequently, in an environment that is hostile toward weight stability, these physiological signals relating to internal energy status are weak and not as potent in controlling eating behavior (Rowland et al. 2008).

In accordance with the aforementioned bioenergetic mechanisms, a slight and imperceptible increase in customary food intake leads to a very evident and sizeable increase in body weight. Furthermore, in overweight and obese subjects the weight gain is facilitated. A similar increase in customary food intake would therefore produce a greater increase of body mass than in their lean counterparts (Weinsier et al. 1993). Due therefore to the weakness and insufficient functions of the biological self-regulatory system, in the favorable environment (food readily available) existing in western developed countries, an unavoidable increase in food intake with foregone weight gain does occur, and an increasing number of individuals are biologically or behaviorally vulnerable to becoming overweight or obese. From the bioenergetic hypothesis follows that most people get fatter when they are unaware they are eating more and without having changed their feeding patterns. In other words, in our affluent society, a person eating of his or her own free will and according to his or her culture is doomed to put on weight in the end. Therefore, it is quite understandable that a subject can become obese even without profound changes in eating habits and behavior. Often a small and unconscious increase in customary food intake is sufficient. Therefore, in the majority of cases, eating patterns of the overweight and obese individuals do not include feeding patterns that are characteristic of weight status. Current BW simply results from the fact that in the past these individuals have eaten more than their EE. At present, regardless of the body mass index level, a stable BW means that food intake is equal to EE. If food consumption is, however, greater than EE, body weight augments, and vice versa (Garrow 1988). In conclusion, actual BW is determined by the amount of energy overall introduced via food in comparison with energy expenditure, and this is not primarily dependent on eating habits or behavior.

While in humans weight gain is made easier, some physiological mechanisms offer strong resistance to weight loss. These biological functions have undoubtedly been essential to the survival of mankind during an evolutionary period of millions of years. When food intake is sharply reduced, the loss of an overphysiological amount of lean tissue causes a reduction in EE in absolute terms, and therefore tends to limit weight loss (van der Kooy et al. 1992; Rumpler et al. 1991). Furthermore, when the energy balance becomes negative, lean body mass energy requirements decreases, thus determining a reduction of body energy expenditure as percentage values (Rumpler et al. 1991). In addition, laboratory studies and clinical experience have demonstrated that food deprivation, in and of itself, is a strong impulse toward the loss of control over food intake, and therefore leads to overeating for the purpose of compensating energy imbalance (Herman and Mack 1975). In western developed countries, an environment rich in food compels individuals to eat more and to store energy surpluses. Furthermore, food is easily available for nearly all of the population and famine is only a vague memory (Rowland et al. 2008). It is therefore unsurprising that not only weight loss but also weight maintenance throughout the years becomes the consequence of a cognitive and voluntary effort to restrict energy intake.

59.3.3 Social Stigmatization Against Obesity

In contrast to an environment noted for the great abundance and availability of food, in today's western industrialized world all individuals are pressured to be thin, and a strong and widespread stigmatization against obesity does exist. However, certain people have a genetic predisposition toward obesity, and others are more inclined biologically or psychologically to be overweight. Basic human biological, psychological, and genetic makeup has not changed in the last century, and the radical shift in weight, at the population level, has been triggered in large part by the current environment. It stands to reason that patients therefore have absolutely no personal responsibility for their overweight or obese status. Nevertheless, overweight and obese subjects experience a pattern of denigration and condemnation that is pervasive in western developed countries, and which is common for both genders, of all ages, and in all socioeconomic levels. Individuals who have a body mass that is higher than the standard accepted body mass are considered unattractive and repulsive, and quite frequently have difficulties at work and with their personal lives. A common belief is that being overweight is a direct consequence of overeating and of lack of physical activity. The obese person is therefore considered a greedy and lazy person, who refuses the principles of activity, thrift, and moderation that are the bases of the affluence of industrialized western countries starting from the Protestant Reform of the seventeenth century. Therefore, a large number of obese and overweight people make continuous but unsuccessful attempts to lose weight, and feel guilty about their weight status. As mentioned above, in an environment with an abundance of food, the vast majority of normal subjects keep food intake cognitively under control in order to avoid undesirable weight gain. The pervasive social weight bias may indirectly induce some lean individuals with psychological distress and body image disparagement to further reduce energy intake simply to improve somatic morphology and then relieve psychological discomfort. Social hatred directed against the overweight and obesity may therefore be harmful for obese and lean subjects alike (Puhl and Brownell 2003).

59.3.4 Laboratory Data

In past years, a great deal of investigation has been carried out with the aim of detecting one or more characteristic eating patterns in obese patients. If aberrant eating behavior of deviant eating style had been demonstrated, the modification of such aspects would have resulted in permanent weight loss and then in the steady recovery from obesity.

Several studies have been performed in experimental settings that compared lean subjects and obese patients. Evaluated were: meal size, frequency of food consumption, correlation between the size of a meal and interval before the next meal, timing of eating, the individual's susceptibility to hunger, satiation duration, eating topography, food consumption rate, attitudes, and beliefs about food. However, only highly contrasting and inconclusive results were achieved. When data on customary food intake are analyzed, the fact that weight gaining process takes place over time must be considered, and that the individual's current BW is substantially dependent on ingestive behavior that had taken place over many months or years. In a laboratory setting, only the current feeding pattern can be described, which obviously might well be independent of the daily eating style and does not take the subject's motivations, expectations, and emotional aspects regarding food consumption into account (Blundell and Gillett 2001; Blundell and King 2000). On the other hand, human food intake is strictly dependent upon eating habits and behaviors, which are highly variable among different populations and cultures, and which are completely unpredictable on an individual basis; as it is essentially subject to individual will and environmental pressure. Furthermore, as aforementioned,

the amount of food eaten (i.e. energy introduced which is the main determinant of BW) may be increased (or decreased) without perceptible modifications of eating habits and behavior, and the subject may be completely unaware of these quantitative changes. It is clear that few and nearly imperceptible changes in habits or behaviors in the end are nearly impossible to detect and to quantify even with careful interviews or instruments structured for behavioral assessment.

Since the main determinant of BW is the amount of energy cumulatively introduced with food, only alterations in eating habits and behaviors actually involving permanent changes in energy intake can produce body weight modification. By contrast, changes in energy intake *do* produce changes in BW even without having an effect on eating habits and behavior.

59.3.5 Conclusions

Summing things up, in human beings feeding behavior is essentially influenced by external and cultural cues resulting from an evolutionary period with food shortages lasting ten of millions of years and with biological control that is not potent enough to control BW stability in a current environment rich in food. Furthermore, according to the bioenergetic model, minor and nearly imperceptible changes in current food consumption can cause quite significant and sizeable increases in body mass, without any change in eating patterns and behavior. These facts account for the dramatic increase in the prevalence of overweight and obesity occurring in the western developed world. These considerations, moreover, along with the inconclusiveness of behavioral research on this topic, support the assumption that specific eating patterns or eating behaviors do not exist that on their own characterize the obese and the overweight status.

59.4 Eating Patterns in Overweight Individuals and Obese Patients

Clinical experience, psychometric investigations, and epidemiological studies indicate that there are different behavioral traits that are more common in obese patients and in overweight subjects in comparison with lean individuals. These are: cognitive restraint (CR), the tendency to disinhibition (DIS), and night eating (NE). However, no evident correlation between the presence of these behaviors and BMI level or the degree of obesity was observed. In addition, these eating patterns can be present in lean individuals who have never been obese as well as in eating disordered patients with very low levels of BMI. Conversely, a significant number of obese or overweight patients have completely normal eating patterns, and do not demonstrate any of these behavioral aspects. Therefore, the hypothesis that these behaviors represent a characteristic eating pattern for the obese or the overweight can be excluded. On the contrary, it can be hypothesized that only in susceptible patients do these behavioral traits lead to weight gain and to the maintenance of a BW greater than is standard, while other subjects can put on weight and become obese without demonstrating any of these behaviors.

59.4.1 Assessment of Cognitive Restraint and Disinhibition over Food Intake

There are some methodological difficulties in the population as well as in the clinical assessment of restrained eating and disinhibition over food intake.

Restrained eating describes the tendency of people to cognitively and voluntarily restrict food intake and eat less than desired to achieve weight loss or to prevent weight gain. CR is assessed by self-reported questionnaires that explore the subject's capacity to limit alimentary consumption and the cognitive and behavioral strategies used for this purpose. The most widely used questionnaires are: the "Restraint Scale", a ten-item instrument evaluating dieting behavior and weight loss (Herman and Polivy 1975), the "Three Factor Eating Questionnaires", that measures both the CR and the tendency to disinhibition over food intake (Stunkard and Messick 1985), and the "Dutch Eating Behavior Questionnaire", that taps restraint, external, and emotional eating. The Restraint Scale includes some questions about the extent of weight loss achieved in past years and the weight reduction actually obtained during a dieting period, while the Three Factor Eating Questionnaire and the Dutch Eating Behavior Questionnaire do not require specific answers on weight variations and therefore may highlight much more easygoing and flexible individual attitudes toward food limitation. Disinhibition over food intake reflects a tendency toward overeating, and includes eating in response to negative emotion, overeating when others are eating, not being able to resist the stimulation to eat, and overeating in response to the palatability of food.

The loss of control over food intake can be highlighted as only isolated binge eating (BE) episodes, whereas eating behavior in the nonbinge period may be completely normal. In these cases, the assessment of DIS requires clinical evaluation and/or a structured or a semi-structured interview. CR and DIS can also be evaluated by the Eating Disorder Examination in these cases, which assesses a broad range of eating behaviors and attitudes toward BW and shape (Faiburn and Cooper 1993). This survey also provides a semi-quantitative evaluation of the degree of eating disturbances as well as a profile of individuals according to scores on four subscales that assess key aspects of eating disorder psychopathology: Restraint, Eating Concern, Shape Concern, and Weight Concern.

59.4.2 Cognitive Restraint and BMI

The notion of CR was introduced to describe individuals' tendency to restrict food intake and consume less food than desired for the purpose of achieving weight loss or preventing weight gain. Anorexia nervosa and some cases of bulimia nervosa patients exert very firm control over food intake and actually markedly reduce their energy intake thus maintaining BMI values for years at very low levels. The hypothesis that eating disorders are caused by an antecedent mental disorder, currently believed to be an obsessive compulsive disorder, has been clinically implemented over the course of many years (Kaye et al. 2004). However, a long period of semi-starvation by healthy human volunteers demonstrated not only the emergence of psychiatric symptoms including obsessive–compulsive symptoms but also the same pattern of eating behavior characterized by a low level of intake, slow eating rate, and a high level of satiety typical of anorexia nervosa patients. It has therefore been suggested that the pattern of eating behavior might mediate between the starved condition and the psychopathology of anorexia nervosa, and that effective nutritional support plays a key role in the therapy of the patients with eating disorders (Zandian et al. 2007).

59.4.3 Cognitive Restraint and Food Intake

Though eating disordered patients very often refer that they exert strong control over food intake, cross-sectional population studies have shown positive association between CR and BMI values;

heavier subjects more frequently reporting self-limitation of customary food consumption and/or a CR at higher degree in comparison with their lean counterparts (Lluch et al., 2000; Beisiegel and Nickols-Richardson 2004). This apparently contradictory fact may be accounted for by biological, behavioral, and psychological factors. As said above, in developed western countries the obese and the overweight status is subject to strong social discrimination, which in some cases leads to psychological distress. It is therefore not surprising that overweight or obese individuals make constant, though fruitless, efforts to reduce food consumption in order to lose weight. So far in our culture, physical appearance is rated more important for women than for men and it is not surprising that in some studies the positive association between CR and BMI was found to be stronger in the female gender. However, most population and clinical studies failed to evidence a clear relationship between the degree of CR and the current food intake. Presumably, the high degree of CR in obese and overweight patients is completely useless and represents only vain attempts that cannot be put in practice. Furthermore, in the end, restrained eating may alter metabolic functioning toward anabolism, which may increase the degree of difficulty in losing weight and may even cause weight gain. The chronic limitation of food intake triggers energy sparing mechanisms that have been evolutionarily conditioned throughout the course of million of years of food scarcity and which have allowed mankind to survive and thrive across the planet.

Finally, it has been observed that subjects with high degrees of CR tend to overeat when self-control is undermined due to psychological or environmental reasons. In the end, they therefore eat more than their low restraint counterparts, consequently put on weight. This is assumed to be support for the hypothesis of counter-regulatory eating among restrained eaters, at least in laboratory settings. Specifically, studies have noted that if restrained eaters are forced to "violate" their diet by eating high-caloric foods (or foods they think are high caloric) or by drinking alcohol, their subsequent laboratory consumption of food is increased. Unrestrained (or nondieting) subjects, on the other hand, appropriately regulate the effects of the high-caloric food or drink by reducing their laboratory consumption of food.

59.4.4 Cognitive Restraint and Body Weight Changes

To verify the association between CR and weight changes, longitudinal investigations were conducted during weight reduction programs, only a few of which evaluated the general population. The majority of these studies carried out on clinical samples of overweight or obese patients show that baseline dieting or dietary restraint is actually associated with an increased risk of weight gain, sometimes exclusively in women. The magnitude of the risk is modest, but this finding represents the clears empirical evidence that dieting facilitates weight gain. In contrast, when the general population is considered, restrained eating, though cross-sectionally associated with BMI levels and other adiposity variables, would not promote weight gain over time either in normal people or in overweight subjects (de Lauzon-Guillan et al. 2006). This supports the hypothesis that this behavioral strategy is more developed in subjects who are prone to put on weight and/or ask for professional help with slimming. In general, it can be employed safely for the control of BW or to avoid weight gain without detrimental effects on metabolic activity or eating overall.

59.4.5 Two Different Forms of Restraint

The apparent incongruity of these statements can be explained by the existence of two different types of CR, which affect daily eating behaviors in different ways, and which represent distinct characteristics of restraint because they relate differently to disturbed eating patterns and to successful weight

control. Flexible control is associated with lower self-reported energy intake, moderate and realistic weight loss expectations, and avoidance of drastic and extreme attitudes about limitation of food consumption. This flexible CR is well evidenced by the Three Factor Eating Questionnaire, and yields the high probability of successful weight reduction during the 1-year weight loss program. By contrast, the rigid and drastic CR registered by the classical Restraint Scale most likely leads to the loss of control over food intake, to overeating and then weight gain, and can be based on psychological distress (Westenhoefer et al. 1999). The existence of two different types of CR is indirectly supported by the changes in eating behavior observed following biliopancreatic diversion, a very effective procedure for the surgical treatment of severe obesity that can be used as an effective experimental model for understanding human eating behavior (Scopinaro et al. 1998). Due to the permanent limitation of intestinal absorption of energy-rich foods because of gastrointestinal tract rearrangement, patients operated on achieve and maintain satisfactory weight loss with a completely free diet. It must therefore be assumed that they have completely abandoned any concerns about weight, food, and diet. In these patients, a sharp reduction of the Restraint Score was obviously observed, while the CR score of the Three Factor Eating Questionnaire remains substantially unchanged with respect to the preoperative data (Adami et al. 1993, 2001). As a result, it may be suggested that in comparison with the behavior evidenced by the classical Restraint Scale, the CR score of the Three Factor Eating Questionnaire taps into an eating pattern that is quite different, i.e. a much more flexible and reasonable CR promoting weight loss and maintenance and counteracting overeating (Adami et al. 1993, 2001). Therefore, for the successful result of weight loss strategies, behavioral and attitudinal changes must be governed by the principles of flexible and reasonable control over food intake. Drastic and rigid restraint however should be discouraged. The literature, moreover, provides a greater consensus that in individuals unaffected by eating disorders deleterious effects of restrained eating are mediated by disinhibition. Most population and clinical investigations in fact have demonstrated that subjects were more susceptible to weight gain when restraint eating is accompanied by other behaviors showing a tendency toward a loss of control, such as emotional eating, binge eating, or eating with a highly uncontrolled eating score (Polivy and Herman 1999; Westenhoefer et al. 1994).

59.4.6   Conclusions

As mentioned above, in population and in laboratory studies, CR is not related to current food intake, while in dieters and in "free" eaters the tendency toward disinhibition is positively associated with overeating. These findings lead to important clinical conclusions. CR may be associated with a higher tendency to overeat and to disinhibition over food intake, and it is very likely that the high BMI levels observed in restrained eaters is substantially due to the concomitant behavioral trait that leads to the loss of control. Further evidence of this theory comes from the cross-sectional studies that have revealed that those individuals who were heaviest had a high disinhibition and low restraint score, while those individuals who expressed a high disinhibition and high restraint score had a somewhat lower BMI level. It therefore appears that at lower disinhibition levels CR may represent a highly efficient strategy for weight loss and maintenance (de Lauzon-Guillan et al. 2006).

In conclusion, the positive association between BMI levels and CR is mediated by the tendency to disinhibition over food intake. Therefore, extreme and drastic CR would easily bring about the disruption of control over eating and then subsequently to overeating, in that such behavior was assumed to counteract an excessively high degree of DIS (Bryant et al. 2007).

59.5 Disinhibition and BMI

Control over food intake can be disrupted intermittently during the so-called BE episodes. Daily eating behavior, however, may show a general tendency toward the loss of control over food intake which is *not* characterized by acute events. Moreover *both* aspects may be present in the same person (Dykes et al. 2004; de Zwaan 2001; Wadden et al. 1993). All of these behavioral traits can be associated positively with BMI values and other adiposity variables. However, these eating attitudes may also be observed in eating disordered patients with low or very low BMI levels.

59.5.1 Binge Eating

An episode of binge eating is characterized by the consumption of a large quantity of food in a moderate amount of time, accompanied by a subjective sense of loss of control over eating. In patients with anorexia and bulimia nervosa, the BE episode is followed by purging type behavior which the patient, in order to avoid weight gain, specifically engages in to eliminate an excess of calories consumed. The most common purging behaviors are vomiting, taking diuretics or laxative drugs, or engaging in strenuous exercise. In these cases, BE is associated with low or very low BMI values in anorexic patients and with normal or low BMI values in the bulimic ones. Moreover, overweight and obese individuals may complain of episodes of BE without assumption of compensatory behaviors. When BE episodes which are not followed by purging behavior occur more than three times a week and are accompanied by marked psychological distress about the BE episode itself, patients must be considered as having a Binge Eating Disorder (BED), which can be considered as a distinct and significant eating disorder associated with obesity (Spitzer et al. 1993) (Table 59.1). Patients with BED usually also have behavioral indicators of the tendency to lose control over food intake such as eating more rapidly than is normal, eating until uncomfortably full, eating large amounts of food when not hungry, eating alone because they are embarrassed and feeling depressed, disgusted and guilty about overeating (Spitzer et al. 1993). The lifetime prevalence of BED among the general population is 0.5–4%, while among obese patients seeking treatment, BED is observed in 15–50% of patients. Prevalence of BED reaches 50–60% in bariatric surgery patients with higher BMI values (Adami et al. 1996; Stunkard and Allison 2003). The frequent association of BED with psychiatric comorbidity, the very good response to many forms of treatment, and the difficulties of establishing definite diagnostic criteria have given rise to the hypothesis that BED should not be considered a specific clinical eating disorder; it could, how-

Table 59.1 Diagnostic criteria for binge eating disorder

1. Recurrent episodes of binge eating
2. During the binge eating episodes at least three behavioral indicators of loss of control
3. Marked distress regarding binge eating
4. The binge eating occurs on average at least twice a week for a 6-month period
5. Does not currently meet the criteria for bulima nervosa

A binge eating episode is characterized by eating in a discrete period of time (e.g., 2 h) an amount of food that is definitely larger that most people would eat during a similar period of time. Eating much more rapidly than usually, eating until feeling uncomfortably full, eating a large amount of food when not hungry, eating with no planned mealtimes, eating alone because of being embarrassed and feeling disgusted with oneself, and very guilty after overeating are behavioral indicators of loss of control

ever, could simply represent a marker for psychopathology or psychological distress in obese patients (Dingemans et al. 2002). BED patients generally report a far greater number of reducing diets in their past compared with their nonbinge counterparts at similar BMI levels. Both clinical as well as population studies have demonstrated the positive association between dietary restraint and the tendency toward disinhibition with respect to food intake (de Zwaan 2001; Adami et al. 1996). A question arises over whether patients complaining of BE or showing a high tendency to disinhibition should increase their CR in order to limit the effects of BE and overeating on BW. Or does excessive CR leads itself to the loss of control and to bingeing? Longitudinal investigations carried out in nonclinical populations have clearly demonstrated that in patients with BED, CR is used as long-term compensatory behavior with the goal of preventing weight gain provoked by disinhibition or BE episodes. In other words, dietary restraint is probably only a secondary effect of disinhibition (Dingemans et al. 2002). In contrast, in formerly obese subjects, long after biliopancreatic diversion, when BW has steadily returned to within nearly normal limits and any concern of the subjects for food, dieting, and body shape should have been completely abandoned, binge eating tends to disappear and the tendency to DIS reduces. This suggests a causal effect for CR over disinhibition (Adami et al. 1993, 1996). Stable weight loss attributed to bariatric surgery is followed in the majority of postoperative obese subjects by marked improvement not only in eating behavior, but also of the quality of life and psychological status (Adami et al. 1996; Herpetz et al. 2003). Considering that BE is a marker of psychopathology, it may be suggested that the complete abandonment of rigid dieting behavior, as well as the relief of psychological distress which was due to the obese status, plays a fundamental role in the postoperative disappearance of BE and in the reassuming of satisfactory control over eating.

59.5.2 Disinhibition in the Everyday Eating Pattern

In the everyday eating pattern, disinhibition is a behavioral trait that reflects a tendency toward the loss of control over food intake and to overeating when faced with an environment dense in alimentary stimuli. Examples include eating in response to negative influences, overeating when others are eating, not being able to resist the stimulation to eat, and overeating in response to the palatability or to the variety of food (Bryant et al. 2007).

59.5.3 Disinhibition and Body Weight

Clinical and population studies have demonstrated that DIS is positively associated with BMI and obesity variables. Studies using a cross-sectional design show positive association in groups of individuals of differing dieting status and in individuals with varying weight histories between DIS and BMI across different socioeconomic gradients and degrees of obesity. Furthermore, it is widely reported that obese and overweight individuals have higher DIS scores compared with normal weight individuals (Dykes et al. 2004). In addition, prospective studies show that DIS predicts current BMI and can predict weight gain over several years, and that in weight loss regimens, disinhibition is predictive of poorer success with weight loss as well as long-term weight regain (McGuire et al. 1999).

Disinhibition may not act in isolation; however, it frequently exerts its effect by interaction with the level of CR. When a high level of disinhibition is combined with a high level of restraint, the relationship between DIS and weight is weakened. In fact, cross-sectional studies have shown that

those individuals with the highest BW had a high DIS and low restraint, while those who expressed a high DIS and high restraint had a somewhat lower BMI. Likewise, among the high restraint patients, higher BMI levels were observed in those subjects showing a greater tendency to disinhibition in comparison with the BMI level of individuals who demonstrated better control over food intake (Polivy and Herman 1999; Westenhoefer et al. 1994).

59.5.4 Disinhibition and Food Intake

While CR is generally unrelated to the actual food intake, a sizable number of population, clinical, and laboratory investigations employing a wide variety of techniques together have demonstrated that DIS leads in fact to greater food consumption both in normal subjects and in overweight and obese patients (Westenhoefer et al. 1994; Ouwens et al. 2003). In other words, disinhibition is almost inevitably linked to the increased tendency to eat when people are subjected to various challenges or interventions which threaten to disturb their energy balance, while CR may only reflect an individual objective that is not actually achieved. Individuals with greater tendencies of DIS tend to be sedentary, and when engaged in physical activity they usually increase food consumption (Bryant et al. 2007). Studies investigating the relationship between DIS scores and the peptides (ghrelin and leptin) known to play significant roles in energy homeostasis have only produced inconclusive results (Adami et al. 2002a; St Pierre et al. 2004). In fact, though in severely obese patients a high DIS score is associated with high and low ghrelin and leptin levels, respectively, there is no evidence that low ghrelin or high leptin levels can trigger disinhibition. Furthermore, the hypothesis that abnormal serum ghrelin or leptin serum levels simply reflect hormonal resistance caused by the obesity – without any association to eating behavior patterns – cannot be ruled out.

Other studies highlighted that high DIS scores are positively related to a greater taste for and consumption of high-fat foods, sweet foods, and alcohol, and negatively related to the consumption of vegetables, fruits, and high-fibre breads. These unhealthy food choices may not only contribute to overweight and obesity, but also to poorer general health (Higgs and Eskenazi 2007).

In conclusion, longitudinal prospective studies found an association between disinhibition over food intake and BE on the one hand and being overweight and putting on weight over a 20-year period on the other. Clinical investigations, moreover, have demonstrated that reducing disinhibition binge cessation tends to be associated with weight stabilization, while continued BE is associated with ongoing weight gain, thus undoubtedly indicating a link between DIS and the risk of obesity. Based on this data, it is difficult to avoid the conclusion that DIS and BE are associated with weight gain and, in many cases, ultimately contribute to the development of obesity.

59.5.5 Disinhibition and Psychological Status

Moreover, disinhibition emerges as an important and dynamic trait, with influences that go beyond eating patterns, and incorporate other behaviors that contribute to weight regulation and obesity and may play a role in the development of eating disorders (Brown et al. 2006). In fact, some researchers have shown that DIS is associated with personality factors that are counterproductive to the maintenance of a good level of control over food intake, encourage overeating, and promote adverse psychological health (de Zwaan et al. 2003; Ghiz and Chrisler 1995; Lawson et al. 1995). In bulimia nervosa patients, DIS is related to BE severity and to more severe eating disorder pathology. Moreover, in eating

disordered patients, DIS was also found to be associated with a lower level of psychological health, with higher neuroticism, lower extroversion, lower self-esteem, and with the presence of severe depression, anxiety, and body disparagement. It must be suggested that the conflict created by high CR, which is the rule among most eating disordered patients, and the presence of a high degree of DIS cause derangement in the control of eating and exacerbate psychological symptoms. In summary, individuals with a high of DIS are characterized by a strong propensity to overeat, put on weight easily, have a greater taste for food, a preference for high-fat foods, and have a lower EE due to sedentary behavior. These data can be considered in relation to the thrifty genotype that favored genetic adaptation allowing humans to survive for millions of years in the face of food scarcity and famine, by selective pressure on physiology (Bryant et al. 2007). The adaptive potential of physiology protective against periodic food scarcity can be extended to a behavioral dimension leading to overeating when food is available, favors high-fat foods, promotes fat deposition, and encourages energy conservation by being sedentary. In the course of the million of years of the evolutionary period, this highly advantageous eating behavior led to the individual's survival and has made the diffusion of mankind possible. Proposals have been made that the behavioral trait "disinhibition" be more appropriately renamed as "opportunistic eating". In an obesogenic environment, such as the western developed world, opportunistic eating has become counterproductive behavior promoting weight gain and may be the main cause of the greatly increased prevalence of overweight, obesity, and other metabolic diseases observed in the last few decades. Opportunistic eating is furthermore at odds with the prevailing health message in the western world, and appears to be highly dysfunctional. The unavoidable conflict between biological disposition and environmental forces could lead to the degradation of emotional well-being, to loss of self-esteem, and other indications of poor psychological health, thus contributing to the onset and maintenance of eating disorders. In this context, disinhibition seems to play a significant mediating role between the 'person' and the 'environment', and has multiple physiological and psychological components (Bryant et al. 2007).

59.5.6 Night Eating and BMI

Night eating was first described as a specific behavior pattern more than 40 years ago (Table 59.2). Since then, NE has not aroused great interest and has only recently attracted a great deal of attention. The original criteria for defining NE is: no appetite for breakfast, 50% or more of total food intake after 7:00 p.m., and trouble getting to sleep and/or staying asleep. In addition, positive association between the presence of NE and BMI levels was observed in the population as well as in clinical studies (Stunkard 1959; Stunkard and Allison 2003).

Recent epidemiological investigation studies have highlighted a link between night eating and obesity. The NE syndrome is fairly uncommon in the general population. It is present in nonobese people, but is more common among the obese (Striegel-More and Franko 2008). The prevalence of NE increases with increasing weight from 10% to 20% in obesity clinics and from 30% to 50% among

Table 59.2 Diagnostic criteria for night eating

1. No appetite for breakfast
2. About 50% or more of total food intake after 7:00 p.m.
3. Trouble getting to sleep and/or staying asleep

The diagnostic criteria for night eating may change according to the eating habits of the reference population. In the population with a Mediterranean eating style, consuming food after the evening meal or in the night is considered an inclusion criterion for night eating

obese patients evaluated for surgical treatment (Stunkard and Allison 2003; Adami et al. 1999; Colles et al. 2007). Moreover, the association between NE and stress and a depressed mood has been described consistently (Pawlow et al. 2003; Marshall et al. 2004). The original inclusion criterion is not suitable in populations in which current eating styles are different from those in the USA or Northern European countries. Different criteria were adopted: eating hyperphagia, eating after dinner, fully alert night time awakenings accompanied by snack consumption (Powers et al. 1999; Adami et al. 2002b). The core clinical feature of NE appears to be a delay in the circadian timing of food intake (O'Reardon et al. 2005). Energy intake is reduced in the first half of the day and greatly increased in the second half so sleep is disrupted in the service of food intake. NE is distinguished from bulimia nervosa and BED by the lack of associated compensatory behaviors, the timing of food intake, and the fact that food ingestion amounts are small, amounting to repeated snacks rather than true binges. Different inclusion criteria are necessary in populations with different daily eating styles. A link between abnormal neuroendocrine patterns and NE has been suggested, with elevated serum cortisol levels consistent with the hypothesis that NE may be a stress-related disorder (Birketvedt et al. 1999). In addition, the usual rise of both melatonin and leptin levels at night was blunted among NE patients, suggesting that these hormones were not performing their usual functions of maintaining sleep and suppressing hunger, respectively (Birketvedt et al. 1999). Obese patients with NE continued to exhibit this behavior even long term, following biliopancreatic diversion after BW had nearly normalized, BE episodes had disappeared, and disinhibition over food intake had markedly reduced (Adami et al. 1999). This finding indicates that BE and NE are distinct though sometimes overlapping eating behaviors, and it strongly supports the neurohormonal hypothesis for NE.

While NE is traditionally considered as an obesity-related eating pattern, and retrospective recall in clinical samples suggests that NE may often precede the onset of obesity, there are indications that half of the overweight people presenting with NE reported being of normal weight before the onset of NE. This suggests that NE may be a pathway to excess weight. However cross-sectional community studies have not borne out this association (Striegel-More and Franko 2008; O'Reardon et al. 2005; Devlin 2007).

The clinical significance of NE is still unclear due to the very different diagnostic criteria preventing comparison between different cohorts and the lack of accurate and large longitudinal populations of interventional investigations. Data in the literature indicate that NE is a behavior that is closely related to obesity, with an increase in frequency corresponding with an increase of BMI. NE appears to be clearly distinct from BE; therefore, overeating of NE seems to be independent from the physiological mechanism that leads to the loss of control over food intake.

59.6 Conclusions

BW accurately depicts the energetic relationship between the individual and the environment. When food intake, and then energy intake, permanently increases, BW increases and consequently EE increases. When the increase of EE matches the increase of energy intake that initiated the weight gain process, the BW will stabilize again, though at a higher level. The same applies to the reduction of energy intake and to weight loss. For each individual, therefore (assuming any other condition is constant), a particular amount of current food intake corresponds to a particular BW. Longitudinal and cross-sectional investigations have showed that very little and nearly imperceptible differences in current food intake correspond to quite important changes in BW. Therefore, it is easily conceivable for an individual to put on weight without being aware of increasing food intake. Furthermore, the differences in food intake between lean individuals and overweight and obese patients could be very little and,

considering the interindividual variations in EE, it is quite possible for a heavier person to eat less than a leaner one. Obesity is due to the concomitant action of genetic predisposition and the environment, and patients have no responsibility for their overweight or obese status. Ten million years of natural evolution in a hostile environment favored the genetic adaptation that has allowed humans to survive in the face of food scarcity and famine. The structural, metabolic, and behavioral characteristics acquired by selective pressure on physiology on the one hand compel individuals to eat and to consume energy-rich food and on the other hand facilitate energy sparing. In an obesogenic environment such as developed western countries, these characteristics have become counterproductive and in predisposed subjects promote obesity, along with different comorbidities that accompany excess adiposity.

Most cross-sectional and longitudinal investigations produce clear evidence that the amount of food consumed plays a major role in the development or maintenance of obesity for the vast majority of overweight people or obese patients, while specific eating patterns may lead to over consumption or may simply be associated with the obese status.

CR is an eating pattern that describes the tendency to cognitively and voluntarily restrict food intake and eat less than desired in order to achieve weight loss or to prevent weight gain. CR is positively associated with overweight and obesity, and reflects the patient's need to improve his or her health, social acceptability, and quality of life. However, CR does not necessary correspond to an actual limitation of food intake and in some cases even leads to the loss of control and to overeating and therefore to an exacerbation of the overweight and obese status. In contrast, individuals demonstrating a high tendency of disinhibition and loss of control over food intake have food consumption that is actually greater than their counterparts with low disinhibition levels; disinhibition is believed to be an eating pattern that may lead to overweight and obesity. In an evolutionary perspective, disinhibition is considered to be an adaptive behavior which contrasts food shortage and famine, and in an environment which is dense in food, can ingenerate cognitive distortion and emotional distress. In fact, in eating disordered patients, high disinhibition levels or the presence of binge eating is generally associated with poor psychological functioning. NE is a feeding pattern that has not yet been defined precisely and which is associated positively with obesity and is characterized by sleep disturbances and by delay in circadian assumption of food. NE may play an important role in the weight gain process via biochemical and/or behavioral pathways different from that of disinhibition over food intake.

59.7 Applications to Other Areas of Health and Disease

Obesity results from the interaction between a biological structure programmed to spare energy and an environment with plenty of food. A specific feeding pattern differentiating overweight and obese patients from lean persons does not exist. Weight gain and the maintenance of a BW in the overweight or in the obese range is a quantitative phenomenon, requiring for the weight gain process an energy intake that is higher than EE, or sufficiently high-energy intake for weight maintenance. The feeding patterns that are commonly associated with obesity simply favor the increase in food intake and/or are simply a consequence of the obese status. In perspective, the fight against obesity as social disease must be more focused on the environment than on the individual.

Summary Points

- Slight and nearly unapparent permanent increases in energy intake lead in the end to a consistent and well appreciable increase in body weight. Therefore, the amount of food consumption by overweight or obese patients might be very similar to that of normal persons.

- Longitudinal clinical and population studies failed to highlight clear and specific differences in eating habits and behaviors between obese patients and normal weight individuals.
- A million year evolution period has conditioned the human body to continue to exist in spite of famine and food shortages. In an environment dense in food that characterizes western developed countries, the mechanisms that guaranteed survival for most in bygone centuries now account for the dramatic rise in the prevalence of overweight and obesity.
- In this sense, obesity should be considered as a true social disease.
- Most of the eating habits and behaviors observed in overweight and obese individuals simply favor weight gain and must be considered as consequences more than causes of the obese status.
- In perspective, the fight against obesity as a social disease should be focused more on the environment that on individual behavior.

Definitions of Key Terms

Body mass index (BMI): Body mass index is the ratio of body weight in kilograms and stature in meters squared. It is the most reliable parameter of the degree of obesity, normal values being 20–25 kg/m², and higher values indicating the obese status.

Energy expenditure: The amount of energy required by the body for living, eating, and for moving in the environment.

Lean body mass: Lean body mass is represented by all body sectors containing water and which do not comprise fat such as muscle, viscera, bone. Interstitial fluid and fat is the body sector that consumes energy.

Eating habits and behavior: Behaviors that the individual engages with respect to eating. Eating habits comprise food selection, the daily timing of eating, and habitual eating patterns.

Social stigmatization toward overweight and obesity: In western developed countries, overweight subjects and obese patients are considered ugly, avid, and lazy, and unable to fit the current physical standard of leanness and effectiveness. Stigmatization leads to blame and discrimination in the workplace and social life, determining impairment of psychological functioning and a very poor quality of life.

Cognitive restraint: The subject's efforts to limit food intake for the purpose of losing weight or avoiding weight gain. Due to the great social stigmatization existing in the western developed world toward overweight and obesity, cognitive restraint is a common eating attitude both in obese patients and in persons of normal weight. However, cognitive restraint does not correspond in every case to an actual decrease in food intake.

Disinhibition: The tendency to lose control over food intake in the daily eating pattern. This behavior compels the subject to overeat when food is available, and may therefore represent a factor promoting individual survival in conditions of food shortage.

Binge Eating: An episode represented by the consumption of large amounts of food in a limited period with the clear feeling of loss of control. In anorexia and bulimia nervosa patients this eating behavior is accompanied by purging behaviors such as vomiting or assuming diuretics or laxatives taken to eliminate the excess of calories and to avoid weight gain.

Night eating: The habit of consuming food late in the evening after dinner or when waking at night.

References

Adami GF, Campostano A, Ravera G, Leggieri M, Scopinaro N. Behav Med. 2001;27:121–6.

Adami GF, Campostano A, Cella F, Scopinaro N. Int J Obes Relat Metab Disord. 2002a;26:1125–8.

Adami GF, Campostano A, Marinari GM, Ravera G, Scopinaro N. Nutrition. 2002b;18:587–9.

Adami GF, Gandolfo P, Dapueto R, Jurich D, Scopinaro N. Int J Eat Disord. 1993;14:81–6.

Adami GF, Gandolfo P, Meneghelli A, Scopinaro N. Int J Eat Disord. 1996;20:405–13.

Adami GF, Meneghelli A, Scopinaro N. Int J Eat Disord. 1999;25:335–8.

Beiseigel JM, Nickols-Richardson SM. Appetite. 2004;43:47–53.

Berthoud HR. Neurosci Biobehav Rev. 2002;26:393–428.

Birketvedt GS, Florholmen J, Sundsfjord J, Osterud B, Dinges D, Bilker W, Stunkard A. JAMA. 1999;282:657–63.

Blundell JE, King NA. Exercise, appetite control, and energy balance. Nutrition 2000;16:519–22.

Blundell JE, Gillett A. Obes Res. 2001;9 Suppl 4:263S–270S.

Brown K, Bryant E, Naslund E, King N, Blundell J. Obes Rev. 2006;7:330.

Bryant EJ, King NA, Blundell JE. Obes Rev. 2007;9:409–19.

Chaston TB, Dixon JB, O'Brien PE. Int J Obes (Lond). 2007;31:743–50.

Colles SL, Dixon JB, O'Brien PE. Int J Obes (Lond). 2007;31:1722–30.

de Lauzon-Guillain B, Basdevant A, Romon M, Karlsson J, Borys JM, Charles MA, FLVS Study Group. Am J Clin Nutr. 2006;83:132–8.

Devlin MJ. Is there a place for obesity in DSM-V? Int J Eat Disord. 2007; 40 Suppl:S83-8.

de Zwaan M. Int J Obes Relat Metab Disord. 2001;25:S51–5.

de Zwaan M, Mitchell JE, Howell L, Monson N, Swan-Kremeier L, Crosby RD, Seim HC. Compr Psychiatry. 2003;44:434.

Dingemans AE, Bruna MJ, van Furth EF. Int J Obes Relat Metab Disord. 2002;26:299–307.

Dykes J, Brunner EJ, Martikainen PT, Wardle J. Int J Obes Relat Metab Disord. 2004;28:262–8.

Faiburn CG, Cooper Z. In: Faiburn CG, Cooper Z, eds. Binge eating. Nature, assessment and treatment. New York: Guilford Press; 1993. p. 317–60.

Flatt JP, Tremblay A. In: Bray GA, Bouchard C, eds. Handbook of obesity. New York: Marcel Dekker; 2006. p. 705–32.

Forbes GB. In: Forbes GB, ed. Human body composition. Growth, aging, nutrition, and activity. New York: Spinger. 1987. p. 209–47.

Forbes GB. Am J Clin Nutr. 1990;52:224–7.

Garrow JS. In: Garrow JS, ed. Obesity and related diseases. Edinburg, UK: Churchill Livingstone; 1988. p. 101–33.

Ghiz L, Chrisler JC. J Clin Psychol. 1995;51:499–518.

Harris RBS. Role of set-point theory in regulation of BW. FASEB J. 1990;4:3310–8.

Herman CP, Mack D. J Pers. 1975;43:647–60.

Herman CP, Polivy J. J Abnorm Psychol. 1975;84:666–72.

Herman CP, Polivy L, Leone T. In: Mela D, ed. Food, diet and obesity. Cambridge, UK: Woodhead; 2005. p. 115–36.

Herpertz S, Kielmann R, Wolf AM, Langkafel M, Senf W, Hebebrand J. Int J Obes Relat Metab Disord. 2003;27:1300–14.

Higgs S, Eskenazi T. Eat Behav. 2007;8:236–43.

Hill AJ. Br J Nutr. 2004;92:S15–8.

Kaye WH, Bulik CM, Thornton L, Barbarich N, Masters K. Am J Psychiatry. 2004;161:2215–21.

Lawson OJ, Williamson DA, Champagne CM, DeLany JP, Brooks ER, Howat PM, Wozniak PJ, Bray GA, Ryan DH. Obes Res. 1995;3:153–61.

Lluch A, Herbeth B, Mejean L, Siest G. Dietary intakes, eating style and overweight in the Stanislas Family Study. Int J Obes Relat Metab Disord, 2000;24:1493–9.

Marshall HM, Allison KC, O'Reardon JP, Birketvedt G, Stunkard AJ. Int J Eat Disord. 2004;35:217–22.

McGuire MT, Wing RR, Klem ML, Lang W, Hill JO. J Consult Clin Psychol. 1999;67:185.

Nelson KM, Weinsier RL, Long CL, Schutz Y. Am J Clin Nutr. 1992;56:848–56.

Ogden CL, Carroll MD, Curtin LR, McDowell MA, Tabak CJ, Flegal KM. JAMA. 2006;295:1549–55.

O'Reardon JP, Peshek A, Allison KC. Night eating syndrome : diagnosis, epidemiology and management. CNS Drugs 2005;19:997–1008.

Ouwens MA, van Strien T, van der Staak CP. Appetite. 2003;40:291–8.

Pawlow LA, O'Neil PM, Malcolm RJ. Int J Obes Relat Metab Disord. 2003;27:970–8.

Polivy J, Herman CP. Int J Eat Disord. 1999;26:153–64.

Powers PS, Perez A, Boyd F, Rosemurgy A. Int J Eat Disord. 1999;25:293–300.

Puhl RM, Brownell KD. Obes Rev. 2003;4:213–27.

Rowland NE, Vaughan CH, Mathes CM, Mitra A. Physiol Behav. 2008;93:97–109.

Rumpler WV, Seale JL, Miles CW, Bodwell CE. Energy-intake restriction and diet-composition effects on EE in men. Am J Clin Nutr. 1991;53:430–6

Scopinaro N, Adami GF, Marinari GM, Gianetta E, Traverso E, Friedman D, Camerini G, Baschieri G, Simonelli A. World J Surg. 1998;22:936–46.

Spitzer RL, Yanovski SZ, Wadden TA, Wing RR, Marcus MD, Stunkard AJ, Devlin M, Mitchell JE, Hasin D, Horne, RL. Int J Eat Disord. 1993;13:137–53.

St Pierre DH, Karelis AD, Cianflone K, Conus F, Mignault D, Rabasa-Lhoret R, St Onge M, Tremblay-Lebeau A, Poehlman ET. J Clin Endocrinol Metab. 2004;89:5993–7.

Striegel-Moore RH, Franko DL. Annu Rev Clin Psychol. 2008;4:305–24.

Stunkard AJ. Psychiatr Q. 1959;33:284–94.

Stunkard AJ, Allison KC. Int J Obes Relat Metab Disord. 2003;27:1–12.

Stunkard AJ, Messick S. J Psychosom Res. 1985;29:71–83.

Tremblay A, Després JP, Thériault G, Fournier G, Bouchard C. Am J Clin Nutr. 1992;56:857–62.

van der Kooy K, Leenen R, Deurenberg P, Seidell JC, Westerterp KR, Hautvast JG. Int J Obes Relat Metab Disord. 1992;16:675–83.

Wadden TA, Foster GD, Letizia KA, Wilk JE. Int J Eat Disord. 1993;14:17–25.

Weinsier RL, Bracco D, Schutz Y. Predicted effects of small decreases in EE on weight gain in adult women. Int J Obes Relat Metab Disord. 1993;7:693–700.

Westenhoefer J, Broeckmann P, Munch AK, Pudel V. Appetite. 1994;23:27–41.

Westenhoefer J, Stunkard AJ, Pudel V. Int J Eat Disord. 1999;26:53–64.

Zandian M, Ioakimidis I, Bergh C, Södersten P. Physiol Behav. 2007;92:283–90.

Chapter 60
Blood Glucose Patterns and the Control of Feeding Behavior: A New Framework for the Control of Meal Initiation

L. Arthur Campfield, Alexandra C. Smith, and Françoise J. Smith

Abbreviations

CCK   Cholecystokinin
CNS   Central nervous system
GDR   Glucose disposal rate
GPR   Glucose production rate
TDBG   Transient declines in blood glucose

60.1 Introduction

Curiosity, interest, and questions about the acquisition, preparation, and presentation of food, the cultural importance of food, appropriate diet and menu selection to promote optimal nutrition, states of hunger and satiety, regulation of body fat, body weight, and energy balance naturally arise in most of us from our daily experiences and contact with food. Among scientists with interests and training in nutrition, physiology, behavior, neuroscience, metabolism, physiological psychology, and/or behavioral neuroscience, many have given at least passing thought and perhaps even a little professional attention and effort to the regulation of feeding behavior. However, a few become so captivated by this complex, multifactorial regulatory system at the interface between "internal" physiology and the "external" world that they then devote their working scientific lives to grappling with these issues. These scientists from many different disciplines continually try to tease out and identify the fundamental facts, the organs, tissue, cells and molecules, the physiological mechanisms, the levels and patterns of organization, and the decision algorithms and rules involved. Their ultimate goal is to provide a deep and complete mechanistic understanding of the regulation of feeding behavior. The subject of this review is our perspective on the current status and, what we believe are, promising future directions of this search for a more complete understanding of the regulation of feeding behavior in laboratory rats and humans. We attempt to provide a new framework for understanding the control of feeding behavior, with special emphasis on the evolution of hunger and the initiation of feeding, including theoretical and experimental components.

L.A. Campfield (✉)
Department of Food Science and Human Nutrition, College of Applied Human Sciences,
Colorado State University, Fort Collins, CO 80523-1571, USA
e-mail: campfield@cahs.colostate.edu

60.2 Technological Innovation and a Rebirth for the Role of Blood Glucose in the Control of Meal Initiation

A signal for the initiation of freely taken meals in rats with continuous access to familiar food has been identified: a brief fall and rise in blood glucose concentration before ingestion of food (Fig. 60.1). The identification of this signal was a direct result of a series of technological innovations leading to computer-based continuous monitoring of blood glucose in freely moving rats (Steffens, 1969; Nicolaidis, 1974; Louis-Sylvestre and Le Magnen, 1980; Campfield et al., 1985).

The ability to monitor blood glucose continuously in freely behaving animals, in contrast to discrete blood sampling at fixed 10-, 15-, or 30-min intervals, led to renewed consideration of the role of blood glucose in meal initiation. Transient declines in blood glucose were first described by Louis-Sylvestre and Le Magnen (1980), who showed that a fall in blood glucose was correlated with meal initiation in the rat. They observed that blood glucose concentration declined 6–8% at 5.0 ± 0.3 min before meal onset in both the dark and light phases of the light–dark cycle. Other experimental studies have defined the composite time course of the functional coupling between transient decline in blood glucose and meal initiation that is shown in Fig. 60.1.

We have confirmed and extended these initial findings. We have provided experimental evidence supporting the hypothesis that spontaneous, self-resolving transient declines in blood glucose precede and signal meal initiation in free-feeding rats. This evidence was obtained using online, computer-based technology for continuous monitoring of blood glucose concentration in freely behaving rats. The experimental set-up used in the experimental studies is shown in Fig. 60.2. In nondeprived free-feeding rats, this signal precedes food-seeking behavior and the initiation of a meal but does not predict the size of the meal or the timing of meal termination (Table 60.1).

To evaluate the role of insulin in meal initiation, another series of experiments characterized the time course of plasma insulin concentrations before, during, and after meal initiation. In these and related studies, blood was continuously withdrawn from freely moving male and female Wistar rats at the rate of 25 µL/min and pooled over 4-min intervals. Sampling began at least 40 min. before an
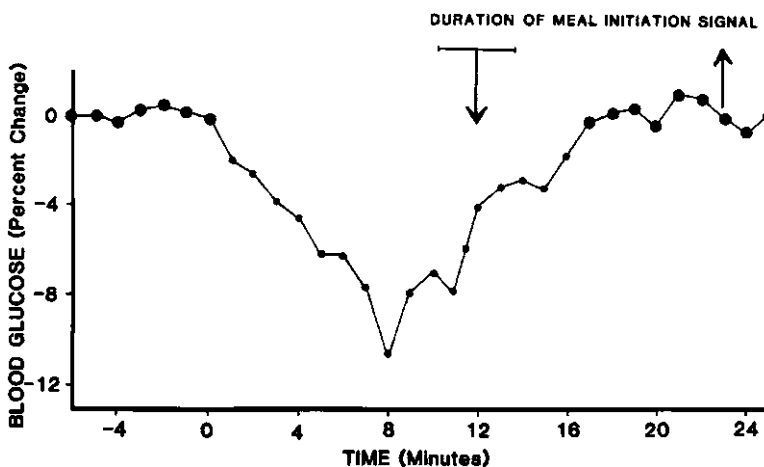
Fig. 60.1 Composite time course of the functional coupling between transient decline in blood glucose and meal initiation. Average time course of blood glucose concentration is expressed as percent change from baseline concentrations. Data are mean values. Estimates of the onset and offset times for the meal initiation signal to be above threshold are indicated by downward and upward arrows, respectively. For details, see text (From Campfield and Smith, 1986. With permission from Elsevier Science)
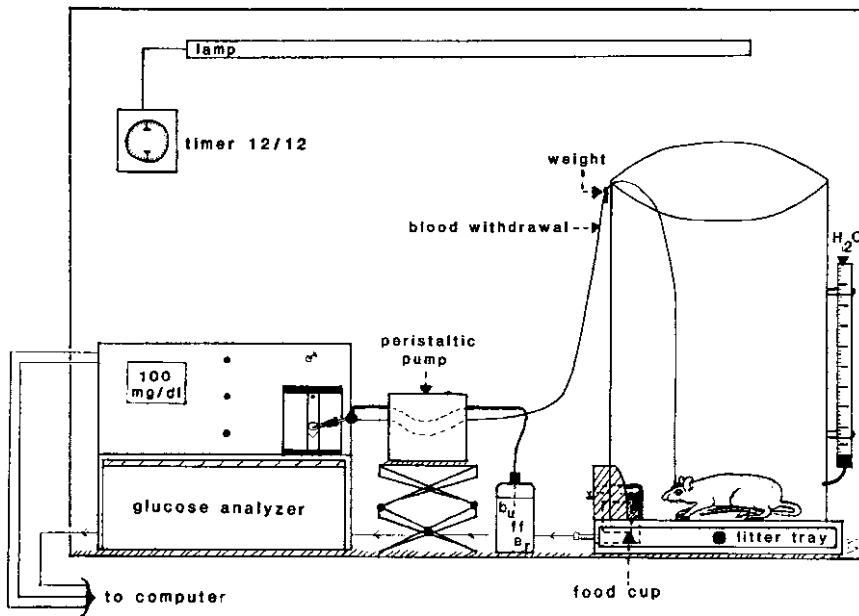
Fig. 60.2 Experimental set-up for studies of continuous recording of blood glucose concentration and meal initiation in rats. Note that the animal remains in its home cage during blood glucose recording. Food cup is sitting on a beam fitted with strain gauges to provide a continuous electrical signal proportional to the weight of the food cup. 12/12, 12 h of lamp turned on followed by 12 h of lamp turned off to establish the light–dark cycle (From Campfield et al. 1985. With permission from Elsevier Science)

Table 60.1 Key features of transient declines in blood glucose

1. A signal for the initiation of freely taken meals in rats with continuous access to familiar food has been identified: a brief fall and rise in blood glucose concentration before ingestion of food. The identification of this signal was a direct result of a series of technological innovations leading to computer-based continuous monitoring of blood glucose in freely moving rats.

2. Transient declines in blood glucose were first described by Louis-Sylvestre and Le Magnen in 1980, who showed that a fall in blood glucose was correlated with meal initiation in the rat.

3. A spike of insulin in the plasma, probably vagally mediated, may play a role in the origin of the transient declines in blood glucose that precede meal initiation.

4. Any changes in blood glucose concentration from baseline values are detected by peripheral and central glucose responsive neural elements and recognized by the central neural network that controls feeding behavior.

5. Unless other events interfere with the meal initiation program or the act of feeding, the meal initiation program, when activated, generates all of the motor acts required for expressing meal initiation behavior.

6. If the peripheral metabolic state cannot maintain glucose homeostasis over the next time interval, without additional energy intake from a meal, a transient decline in blood glucose in response to a probe signal will occur. On the other hand, if glucose homeostasis can be maintained over the next time interval without additional energy intake (e.g., liver glycogen breakdown and utilization), a transient decline in blood glucose will not occur.

7. The necessary conditions for a fall and rise in blood glucose concentration in rats to be recognized as a transient decline in blood glucose have been calculated from our experimental data set.

8. The following necessary conditions must be met sequentially by all transient declines in blood glucose that signal meal initiation in rats: (1) the slope of the falling phase must be within -0.4 and -1.5 mg/dL.min; (2) the nadir of the decline must be at least 6% below baseline and must occur between 40% and 60% of the total duration of the decline, and the total duration of the transient decline must be longer than 6 min; and (3) the slope of the rising phase must be within 0.5 and 1.5 mg/dL.min.

9. The goal of this research is not the *pattern* but rather the *patterns* that together form the central representations of meal initiation, maintenance, and termination.

This table lists the key facts of the transient declines in blood glucose that precede and signal meal initiation. Transient decline in blood glucose are a spontaneous, self-resolving pattern of blood glucose concentration that falls and then rises back toward the stable baseline level that precede and signal meal initiation in nondeprived, free-feeding rats. This signal precedes food-seeking behavior and the initiation of a meal but does not predict the size of the meal or the timing of meal termination

anticipated meal and was continued for up to 100 min. Plasma insulin was stable during intermeal intervals, briefly increased by 50%, and then returned to basal levels. The peak of the insulin spike occurred at 26 or 13 min (males and females, respectively) before meal initiation and preceded the transient decline in blood glucose. The plasma insulin concentration in female rats before meal initiation is shown in Fig. 60.3. However, in experiments in which feeding did not occur, plasma insulin remained constant (coefficient of variation 11%) throughout the sampling period. Hepatic vagotomy abolished the insulin spike. Plasma insulin reached its lowest point just before the meal in most experiments, as reported originally by Strubbe et al. (1977). These data suggest that a spike of insulin in the plasma, probably vagally mediated, may play a role in the origin of the transient declines in blood glucose that precede meal initiation (Campfield and Smith, 1990a, b, 1999, 2003; Inoue and Bray 1979; Ritter and Taylor, 1990). However, the presence of the insulin spike is not required for meal initiation.

60.3 The Pattern as Signal Model: Pattern Detection and Recognition Theory of Meal Initiation

Increasing attention has been focused on behavioral sequences or patterns. Well-established orosensory motor patterns have been described by Grill and Norgren (Grill and Norgren, 1978; Norgren, 1983). Also, stereotypic satiety behavioral sequences have been described by GP Smith and co-workers
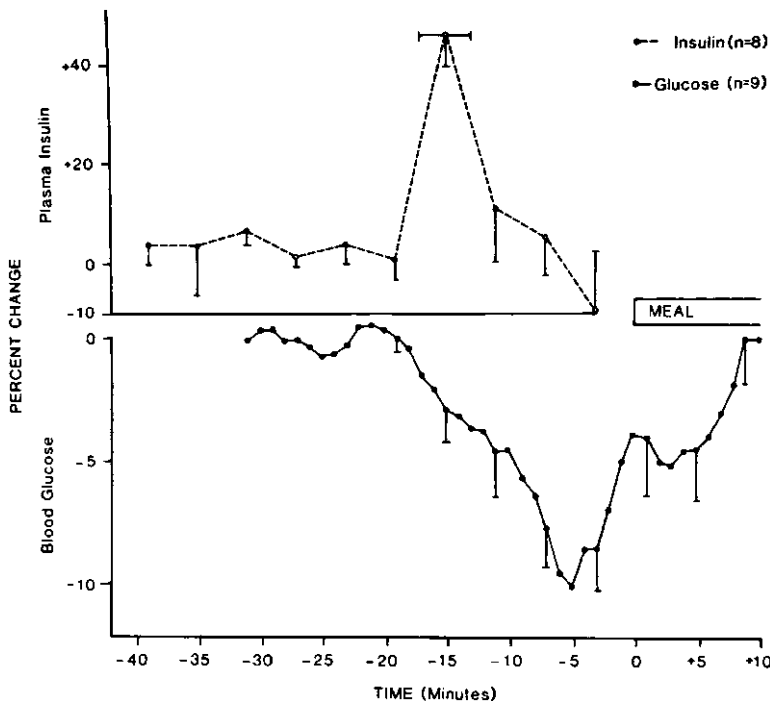
Fig. 60.3 Plasma insulin and blood glucose concentration profiles before meal initiation in lean female rats. The figure is a composite; the continuous blood sampling for insulin (*top*) and continuous recording of blood glucose (*bottom*) were performed in different experiments. Note the spike in plasma insulin before meal initiation, indicated by the left-hand edge of the rectangle labeled "meal" (From Campfield and Smith, 1986. With permission from Elsevier Science)

(Antin et al., 1975; Gibbs et al., 1973; Smith and Gibbs, 1994). Thus complex motor programs underlying feeding are thought to reside in the central nervous system (CNS), and signals related to body stores or specific molecules may "initiate" or "trigger" them under appropriate circumstances (Stricker, 1990).

The consideration of sequences in which a complex temporal and/or spatial pattern fulfills the role of initiator of these motor programs has emerged as an alternative theoretical construct (Campfield and Smith, 1990a, b, 2003). Thus the temporal pattern of a specific molecule (e.g., transient decline in blood glucose), the pattern of several molecules (e.g., nutrient flux across the intestine), the temporal pattern of a specific molecule in a specific context of other patterns (e.g., insulin before, during, or after a meal; oral signals; or gastric distension) or the spatial pattern caused by the passage of a specific molecule through body compartments (e.g., glucose interacting with multiple glucose receptive neural elements; insulin in the brain and cerebrospinal fluid; leptin from adipocytes to the brain) may act as control signals that the CNS uses to organize feeding behavior. Within this conceptual framework, it is not the store or molecule (neither its concentration nor the absolute amount) but rather the "dynamic pattern" of the molecule that conveys critical "information" to the CNS.

Another key element of the pattern as signal concept is the notion of *representation* of peripheral events and states within the CNS. The CNS may contain "*representations*" or "*maps*" of metabolic and behavioral states: absorptive and postabsorptive states, hunger, and satiety. Although often thought of in terms of spatial maps, transformations, or homunculi, *representation* in this context is considered to be a dynamic pattern of activity in a set of neurons that function as a central analog of sensory somatic or visceral events. Thus, we seek these *representations* of peripheral body stores, the metabolic state, and the external world, and how these *representations* interact to control feeding behavior (Damasio, 2003).

What form would these *representations* take? These *representations* would probably be patterns of electrical and/or neurochemical activity of one or more neural networks controlling feeding. Thus, in this theoretical construct, patterns in the periphery carry information that is detected and recognized by central neural networks, which results in modified patterns of activity of these neural networks. Specific patterns of activity of these networks are postulated to correspond to the behavioral states associated with meal initiation and meal termination. If we could capture a visual image of the patterns of activity of the feeding network before, during, and after a meal, we would see a transition from the pattern characteristic of the intermeal interval to that of meal initiation and food ingestion, followed by a transition back to the pattern corresponding to satiety. Perturbation or shaping of feeding behavior would be then translated into modulation of these complex activity patterns and their integration by the brain.

Since formulating this conceptual framework for feeding behavior in a review published in 1990 (Campfield and Smith, 1990a, b) and expanded in 2003 (Campfield and Smith, 2003), experimental results have confirmed its utility both in terms of explanatory power and an ability to tightly link feeding behavior and physiology. We remain optimistic about its potential to refocus our field on the *message* rather than the *messenger*. This point of view also has the potential to synthesize much of our field because, rather than debating the merits of transient declines in blood glucose, or hypothalamic norepinephrine, or hindbrain CCK, or circulating leptin, or brain insulin, we can ask how all of these components or elements of the pattern are integrated to elicit specific behaviors underlying feeding. This hypothesis is also focused on the detection and recognition of these multiple patterns by the widely distributed neuronal networks controlling feeding. Thus the goal of the search is not the *pattern* but rather the *patterns* that together form the central representations of meal initiation, maintenance, and termination. The integrative focus of this conceptualization has much in common with and is a descendent of earlier integrative approaches of the balance of lipogenesis and lipolysis rates (Le Magnen, 1980, 1985, 1992; Kennedy, 1953), combining energy flux in the plasma

(Booth, 1968, 1978) and neurons that integrate specific molecular signals (Nicolaidis, 1974; Nicolaidis and Even, 1984; Stricker, 1990). However, this concept has an even broader focus on the totality of central representations of peripheral events related to feeding (e.g., glucose concentrations (Niijima, 1983)). Finally, the ability of the "pattern as signal" construct to integrate the dynamics of blood glucose before, during, and after meals into one or more important messages related to feeding behavior suggests that a similar focus on the patterns of insulin, leptin, and CCK rather than a focus on the location or concentration of these hormones may also yield important insights.

The experimental studies presented and reviewed in our previous publications (Campfield et al., 1985, 1996; Campfield and Smith, 1986, 1990a, b, 2003; Smith and Campfield, 1993) have led to the formulation of a signal detection and recognition theory of meal initiation. The major assertions of this theory are that: (1) transient declines in blood glucose represent "endogenous metabolic patterns," (2) transient declines in blood glucose are signals in the form of "patterns" that are detected and recognized by the central neural network that controls feeding behavior, and (3) these patterns are "mapped into" meal initiation under free-feeding conditions. The phrase *mapped into meal initiation* is meant to describe the process of transformation, in the mathematical sense, or establishing a unique correspondence between the recognition of the transient decline in blood glucose and the activation of the motor program for feeding within the CNS.

The distinguishing feature of this assertion is that it is the temporal pattern, shape, or waveform of blood glucose dynamics rather than the glucose molecule, or the absolute decrease in blood glucose, or blood glucose concentration, or glucose utilization that is detected and contains "critical information" that is extracted by the central nervous system to control meal initiation.

We propose that the processes of detection and recognition of a transient decline in blood glucose, and its mapping into meal initiation behavior are accomplished by the set of spatially and temporally distributed processes shown in Fig. 60.4. Meal initiation will occur only if a "timing or probe signal" was generated recently and a transient decline in blood glucose is detected in the brain and recognized. Figure 60.4 depicts the information and signal flow through the set of sequential processes without regard to the anatomical localization of the process. The "timing or probe signal" represents an "inquiry" or "interrogation" or "probing" of the periphery by the CNS regarding its ability and capacity to maintain glucose homeostasis in upcoming time interval. This signal is generated by a signal generator (in the CNS) that controls its frequency or timing. The signal acts on the biochemical subsystem that regulates blood glucose concentration and, depending on the peripheral metabolic state and its ability and capacity to "maintain glucose homeostasis" over the next time interval, a transient decline in blood glucose (TDBG) will be generated or not. An averaged transient decline in blood glucose is shown in Fig. 60.1.

Any changes in blood glucose concentration from baseline values are detected by peripheral and central glucose responsive neural elements, which form the "TDBG detector" process shown in Fig. 60.4. The recognition of the presence of a transient decline in blood glucose that meets all the necessary criteria from among the many changes in blood glucose concentration occurring in the peripheral blood is reported by the TDBG recognition process. This process is located in both the CNS and the periphery, and its output acts on the "decision algorithm" process. The decision algorithm unit computes the conditional probability of activating the stored meal initiation program given the state of the three inputs it receives: (1) output from the TDBG recognition process, the recognition of TDBG; (2) peripheral metabolic state; and (3) presence of a recent "probe or timing signal." If a transient decline in blood glucose is recognized in the presence of a favorable peripheral metabolic state along with the recognition of recent generation of the "probe of timing" signal, then the output of the decision algorithm will be "yes" and the meal initiation program will be activated. By a "favorable metabolic state" we mean the later part of the intermeal interval, which would allow a transient decline in blood glucose in response to the probe or timing signal. The transient decline in blood

Fig. 60.4 Proposed information and signal flow in the pattern detection and recognition model of meal initiation. The information flow chart is shown without regard for the anatomic location of each process. The process of meal initiation begins with the generation of a "probe or timing signal" within the brain, continues as this signal "passes through" the peripheral metabolic system acting on the blood glucose regulatory system, and ends with an affirmative decision to activate the "meal initiation program." The blood glucose regulatory system generates an insulin spike and a transient decline in blood glucose (represented by the sketch; *middle*). See text for details (From Campfield and Smith, 2003. With permission from American Physiological Society)
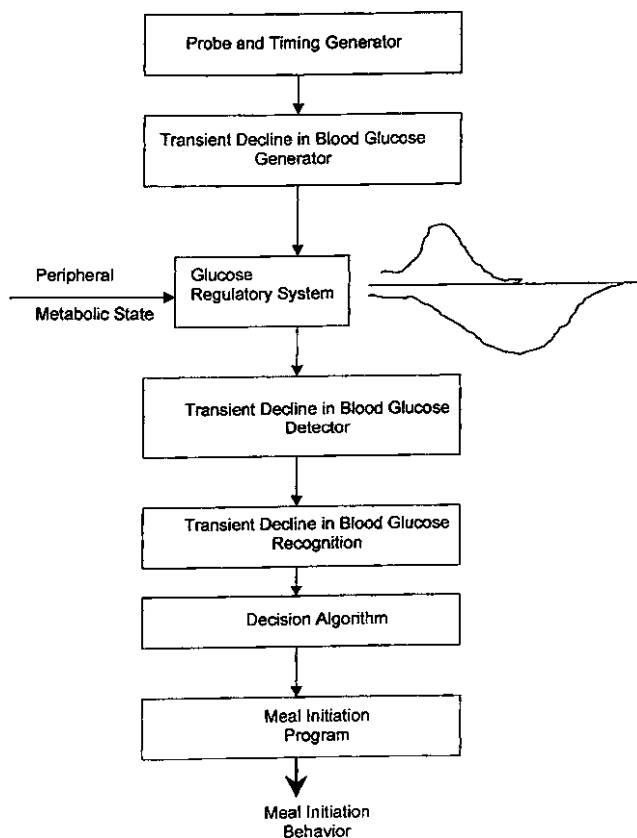
glucose will indicate that additional energy intake from a meal may be required to maintain blood glucose over the coming time interval (see below). An "unfavorable" metabolic state would be just after a meal. Unless other events interfere with the meal initiation program or the act of feeding, the meal initiation program, when activated, generates all of the motor acts required for expressing meal initiation behavior (Campfield and Smith, 2003).

Our current working hypothesis is as follows. In free-feeding rats, we have shown that there are brief, spontaneous plasma insulin peaks antecedent to each decline in blood glucose (Campfield and Smith, 1990a, b, 2003). We postulate that a "probe or timing signal" generated by the CNS results in a brief change in the firing rate of the parasympathetic (vagal) and/or sympathetic nervous system efferents that innervate pancreatic B-cells, liver, adipose tissue, and the gastrointestinal tract. The change in autonomic firing rate causes a brief insulin spike from pancreatic B-cells, along with other responses, which, in the presence of an appropriate peripheral metabolic state, induces a transient decline in blood glucose by decreasing hepatic glucose production and/or increasing peripheral glucose disposal. In the presence of sustained hyperglycemia, the brief insulin spike, along with other responses, may have to be larger in magnitude to induce a transient decline in blood glucose. The peripheral metabolic state is postulated to "condition," in a probabilistic sense, or "gate," in a signal flow sense, the likelihood of a feeding response to the activation of vagal and/or sympathetic efferents. Thus, a central/peripheral interaction is proposed in which a centrally generated meal initiation signal must "pass through" the peripheral metabolic system, and it will be mapped into feeding behavior only if a transient decline in blood glucose of the correct shape or pattern occurs in response to a recent probe signal.

If the output of the decision algorithm remains in the "no" state, either because of the absence of a transient decline in blood glucose or the failure of a decline to meet all the criteria for meal initiation or failure of recognition, or an unfavorable peripheral metabolic state (e.g., recent meal), the TDBG recognition unit will be reset to the "no decline" state. If the peripheral metabolic state cannot maintain glucose homeostasis over the next time interval, without additional energy intake from a meal, a transient decline in blood glucose in response to a probe signal will occur. On the other hand, if glucose homeostasis can be maintained over the next time interval without additional energy intake (e.g., liver glycogen breakdown and utilization), a transient decline in blood glucose will not occur. However, if a transient decline in blood glucose occurs but is ignored and no food is eaten, the only consequence may be the occurrence of the next transient decline in blood glucose sooner than expected. In this case, blood glucose may be maintained through novel involvement or activity of the liver or other organs.

The model assumes that some "probe or timing signals" will not result in transient declines in blood glucose and, therefore, meal initiation will not be observed. Therefore, a prediction of our model is that the number of probe or timing signals should be greater than the number of meals.

The processes of *detection* and *recognition* are considered distinct in our formulation because we interpret our experimental results to mean that the minute-by-minute blood glucose concentration is detected by glucose responsive peripheral afferents and central neurons. Thus blood glucose is continuously represented and always available to the CNS. The process of *detection* begins with a representation of the relatively steady intermeal concentration of blood glucose ("baseline") and "reports" the detection of all departures in blood glucose concentration from that baseline to the TDBG recognition unit. In contrast, the unique process of *recognition* that an ongoing pattern of blood glucose concentration "matches" or "fits" the criteria for a transient decline in blood glucose is the function of the TDBG recognition unit. Thus the *recognition* of a transient decline in blood glucose is the result of a two-step process: (1) detection that the blood glucose concentration is changing and (2) the recognition that the pattern of the blood glucose change meets the criteria for transient declines in blood glucose. Another way of looking at the function of these two processes is that the *TDBG recognition unit* must recognize the shape or pattern of transient declines, but only transient declines, out of the set of all other changes in blood glucose concentration detected throughout the day.

The necessary conditions for a fall and rise in blood glucose concentration in rats to be recognized as a transient decline in blood glucose have also been calculated from our experimental data set. The following necessary conditions must be met sequentially by all transient declines in blood glucose that signal meal initiation in rats: (1) the slope of the falling phase must be within -0.4 and -1.5 mg/dL.min; (2) the nadir of the decline must be at least 6% below baseline and must occur between 40% and 60% of the total duration of the decline, and the total duration of the transient decline must be longer than 6 min; and (3) the slope of the rising phase must be within 0.5 and 1.5 mg/dL.min.

These necessary conditions, which specify an approximately symmetrical fall and rise in glucose concentration, shown in Fig.60.1, provide a first-order approximation of the criteria for recognition of a transient decline in blood glucose by the TDBG recognition unit in our model. The conditions required for a "yes" output of the decision algorithm and activation of the meal initiation program are proposed to be as follows: the recognition of a transient decline in blood glucose that was generated by a receptive or favorable peripheral metabolic state in response to the "recent" generation of a probe or timing signal by the CNS. As discussed above, if the output of the decision algorithm remains in the "no" state, because these criteria were not met, the TDBG recognition unit will be reset to the "no" decline state.

The conceptual basis and a basic structure of our working hypothesis are represented in our working model shown in Fig.60.5. Many aspects of the model remain to be determined in quantitative
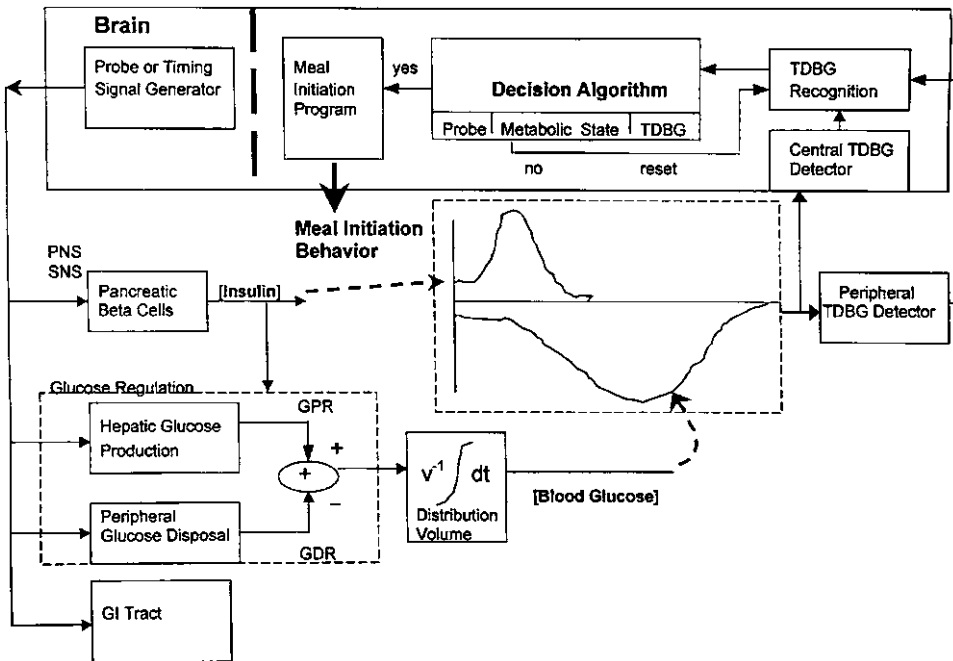
Fig. 60.5 Block diagram representation of the information and signal flow in our conceptual model of the pattern detection and recognition theory of meal initiation. A "probe or timing signal" is generated within the brain (*top left*) and causes a brief change in firing rate of the parasympathetic (PNS) and/or sympathetic (SNS) afferents which innervate pancreatic B-cells, glucose regulatory system, and gastrointestinal (GI) tract (*middle* and *bottom left*). If additional energy (a meal) is needed to maintain glucose homeostasis over the next time interval, the probe signal (e.g., insulin spike) will "pass through" the peripheral metabolic system acting on the blood glucose regulatory system and generate a transient decline in blood glucose (represented by the sketch; *middle*). Changes in blood glucose concentration will be detected by peripheral and central glucose responsive neural elements (*middle* and *top right*) and then the transient decline in blood glucose is "recognized" in the brain (*top right*). If the criteria of the decision algorithm (*top*) are satisfied (transient decline recognized, favorable peripheral metabolic state, recent probe signal), the "meal initiation program" will be activated and meal initiation behavior will be observed (*top left*). If the decision criteria are not satisfied, the "recognition" unit will be reset and meal initiation will not be observed until the next transient decline in blood glucose occurs. *TDBG* transient decline in blood glucose, *GPR* glucose production rate, *GDR* glucose disposal rate, *probe* Probe signal (see text), *Metabolic State* Peripheral metabolic state, v Effective blood volume through which glucose is distributed (From Campfield and Smith, 2003. With permission from American Physiological Society)

terms. This model, and the hypotheses on which it is based, provide a new framework for the understanding of feeding behavior, with special emphasis on the evolution of hunger, the initiation of feeding and its dependence on patterns of blood glucose.

60.4 Physiological and Behavioral Studies of Transient Declines in Blood Glucose as a Signal for Meal Requests and Increased Hunger Ratings: Studies in Humans

The purpose of our human studies was to examine the hypothesis that hunger and meal initiation in humans could be related directly to patterns of blood glucose. Our specific objective was to answer the following questions: (1) Do transient declines in blood glucose concentration occur in human

subjects? (2) If so, do they precede changes in hunger ratings and meal requests? A major limitation of the previous human experiments on the role of blood glucose in hunger has been the necessity of discrete blood sampling on experimenter-determined schedules (Stunkard et al., 1955; VanItallie et al., 1953; VanItallie and Hashim, 1960; Pollack et al., 1989; VanItallie, 1990; Campfield and Smith, 2003).

Each of 18 healthy adults (nine males and nine females) was housed individually in a room isolated from time cues the night before and during the study at the Clinical Research Center of The Rockefeller University Hospital. They were informed that blood glucose and other biorhythms including hunger and thirst would be monitored. Following an overnight fast, a double-lumen cannula for blood withdrawal was placed in the antecubital vein; blood and heparin mixture was withdrawn at a rate of 55 μL/min (blood withdrawal rate ~25 μL/min), and blood glucose concentration was monitored over a 2–6-h period. Breakfast was not served. Subjects controlled the room lighting and rested, slept, read, or wrote during the experiment. Visual analog ratings of internal state including hunger and satiety were completed approximately twice each hour using a quasi-random schedule when the subjects were not asleep. Subjects could request a meal at any time but were not required to do so. A verbal (spoken) request was required to obtain a meal. The experiment ended when the meal was presented to the subject. The methodology utilized in these studies is described in more detail elsewhere (Campfield et al., 1996).

The average time course of blood glucose concentration during the experiment is shown in Fig.60.6a. Overall, in 83% of the 18 subjects, both changes in hunger ratings and spoken meal requests were preceded by, and significantly correlated with, spontaneous, brief transient declines in blood glucose (nadir: ~ -10% below baseline at 27 min). The recordings of blood glucose concentration during the experiment for two subjects are shown in Fig.60.6b and c. The pattern, magnitude, and time course of these declines was similar to those observed in rats (Campfield et al., 1996).

The significant association between increased expression of hunger and transient declines in blood glucose observed was tested in a second study in which insulin infusions were used to induce transient declines in blood glucose that mimicked the spontaneous transient declines observed before meal requests. Subjects were admitted to a metabolic research room isolated from food and time cues in the Clinical Research Center of The Rockefeller University Hospital where they remained for 3 days. Each subject was studied twice. After an overnight fast, cannulas for blood withdrawal and intravenous infusion were placed in the subject's veins, blood glucose concentration was monitored, and visual-analog hunger ratings were obtained over a 2–4-h period. Breakfast was not served. After a stable blood glucose baseline was obtained, a sterile solution of either saline or insulin (5 mU/kg) was injected intravenously in <2 min. Hunger ratings were obtained up to four times an hour. This dose of insulin was selected based on pilot studies in other healthy subjects. Two days later, the experiment was repeated and the other solution (either insulin or saline) was infused.

Combining the results in five subjects indicates that hunger ratings increased (mean delta -22 ± 5 mm) after insulin-induced transient declines in blood glucose concentrations (nadir ~ -11% at 38 min). These results support and strengthen the conclusion that the transient decline in blood glucose represents a temporal pattern that reflects an antecedent physiological event or provides a signal related to the expression of hunger in humans. These results are consistent with many reports in the literature of hunger after insulin administration (Campfield and Smith, 2003).

Fig. 60.6 (continued) were 83.3 ± 3 mg/dL. (**b**) and (**c**) Examples of temporal evolution of blood glucose concentration before meal requests in two subjects. Blood glucose concentration is shown on the ordinate and is expressed as mg/dL. The abscissa is time in minutes. Spoken meal requests are indicated by the dotted *arrow* (From Campfield et al. 1996. With permission from Elsevier Science)

BLOOD GLUCOSE DYNAMICS PRIOR TO MEAL REQUEST IN HUMAN SUBJECTS
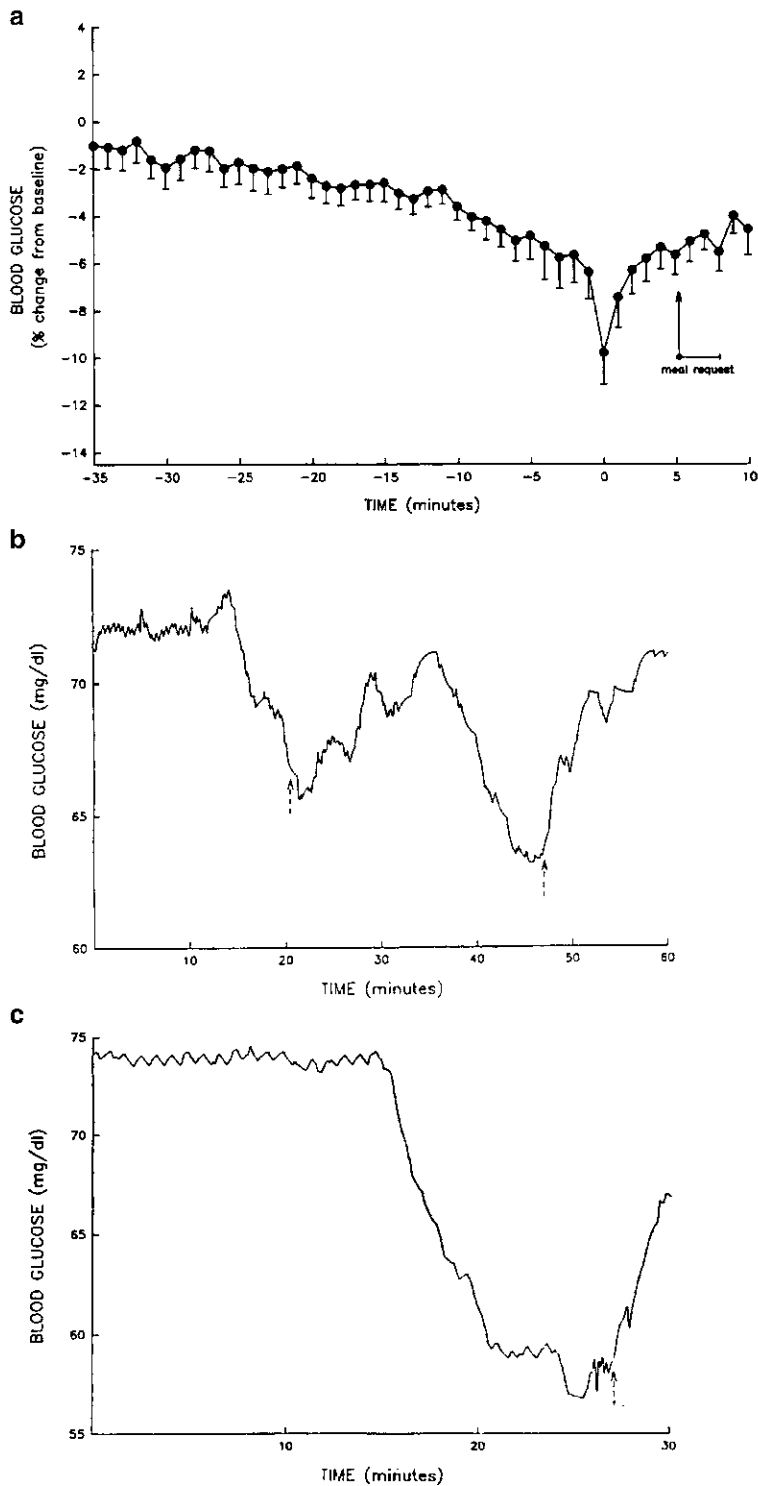
Fig. 60.6 (a) Average time course of the transient decline in blood glucose in time-isolated humans. Blood glucose concentrations are expressed as percent change from the baseline concentration in this figure. The minimum glucose concentration has been taken as the *time 0* reference. Data were selected each minute from the reference point and averaged in each of 18 experiments. Data are means ± SEM. The meal request is indicated by the vertical *arrow*. Mean baseline glucose concentrations

These combined behavioral and metabolic experiments answer both of the specific questions we posed in the affirmative under these experimental conditions. These experiments, using continuous, online monitoring and visual analog ratings of hunger, have demonstrated an association between transient declines in blood glucose concentration and meal requests and changes in hunger ratings in human subjects isolated from food and time cues. This association was observed following both spontaneous and insulin-induced transient declines in blood glucose. Most of the deviations in blood glucose observed closely resemble the patterns of blood glucose dynamics shown to precede and signal meal initiation in rats (Campfield et al., 1985; Campfield and Smith, 1986, 1990a, b, 2003; Smith and Campfield, 1993). This suggests that, at least under these experimental conditions, a signal for hunger in humans is associated with transient declines in blood glucose that is similar to that observed in rats.

These results are consistent with some, but not all, previous studies of the relationship of blood glucose and human hunger (Bernstein and Grossman, 1956; Hervey 1971, 1988; Stunkard et al., 1955; VanItallie, 1990, VanItallie et al., 1953; VanItallie and Hashim, 1960). A retrospective analysis of blood samples collected at random intervals averaging 20 min before and after lunch from seven subjects living in time isolation for several days was conducted (Pollack et al., 1989). This study failed to demonstrate a significant deviation in plasma glucose concentration before meal requests. This failure in the absence of continuous monitoring of blood glucose, based on discretely measured and mathematically interpolated plasma glucose levels, does not imply that no such correlation exists and does not invalidate the extension of the hypothesis, supported by these results summarized here, that blood glucose dynamics play a role in the onset of human hunger.

Although there is evidence, reviewed above, supporting the proposition that the transient decline in blood glucose is causally related to meal initiation in rats and meal request in humans, the "true" signal for meal initiation may be (1) an "originating event," neuronal and/or biochemical, that causes the transient decline in blood glucose concentration; (2) the "transient decline in blood glucose concentration"; (3) a covarying "metabolic and/or neural signal"; or (4) an "event," neuronal and/or biochemical, "in response" to the transient decline in blood glucose concentration. The determination of which of these alternatives is correct will require further research on meal initiation. Nevertheless, the studies reviewed here strongly suggest that transient declines in blood glucose (1) represent an "endogenous signal" for meal initiation; (2) their detection and mapping into meal initiation can be viewed as a "pattern detection and recognition problem"; (3) may be useful "probes," or experimental interventions, to elucidate the operation, nature, and decision algorithms of the widely distributed neural network that controls meal taking and, thus, feeding behavior; and (4) play an important role in the regulation of individual meals and by interacting with longer-term regulatory systems, such as the brain insulin system (Woods and Nolan, 1997; Woods et al., 1998), or the leptin pathway (Campfield and Smith, 1990a, b, 1999, 2003; Campfield et al., 1995; Woods et al., 1998; Zhang et al., 1994), also may play an important role in the regulation of body energy storage.

60.5 Implications

The identification of a potential signal for meal initiation imbedded in blood glucose dynamics is significant because it provides a biological basis, and, thus, additional justification, for the continued experimental study of feeding behavior in humans in both the laboratory and metabolic ward. This finding, therefore, gives added confidence to the investigation of metabolism and biochemistry as related to human feeding behavior. The existence of a biochemical and physiological signal for hunger and meal requests in humans argues strongly for renewed interest in the experimental study of

hunger and the development of biologically based strategies for the reshaping of disordered feeding behavior. This new research may provide important information about the interaction and relative importance among the several factors in the decision-making process that ultimately leads to the perception and behavioral expression of hunger in humans. These results may provide a biological foundation for a more complete and complex understanding of human feeding behavior that should emerge from future, biologically based behavioral research. It is also hoped that this increased understanding will allow more precise diagnosis of disordered feeding and improved and more efficacious treatment of these devastating conditions.

On a more speculative note, transient declines in blood glucose may also play a role in the behavioral and metabolic adaptation or "learning" that occurs following alterations in food availability and lighting schedules, food and diet options, cost of working for food, as well as the conditioned feeding situation. Studies of rats working for food and in conditioned feeding suggest such a role (Campfield and Smith, 2003; Weingarten and Martin, 1989), but additional studies will be required to fully explore this possibility.

Is the "pattern as signal" conceptualization advocated here simply a complementary theoretical construct to the other more established concepts in the control of feeding or is it a competing, alternative notion with more explanatory power? The ultimate ability of this construct to explain adequately meal initiation and/or the intermeal interval or other aspects of feeding behavior remains to be determined by further research. However, the successful extension of this paradigm in the last 2 decades to additional animal models of disordered feeding (e.g., experimentally diabetic and genetically obese rats) and the successful extension to the domain of human meal requests and changes in hunger ratings demonstrate the explanatory power, the applicability of a general theoretical construct from rats to humans, and provide increased confidence in this approach. These patterns of blood glucose and plasma insulin concentration in rats and humans must be subjected to further and more rigorous experimental tests and additional patterns have to be identified and tested. The impressive successes of this approach suggest to the authors that its application to the numerous disparate and competing findings in feeding research may provide insight and, possibly, facilitate the development of a more complete understanding.

60.6 Final Thoughts

Has the description and appreciation of the pattern of blood glucose concentration that precedes and signals meal initiation in rats and meal requests in humans led us to a new conceptual "world view" and established the "pattern as signal paradigm" for future consideration of the problem of the regulation of feeding behavior? Alternatively, has the path we followed to our current formulation just led us full circle back to a more complex, but not substantially different, formulation of Mayer's glucostatic hypothesis? (Mayer, 1953, 1955; Campfield and Smith, 2003) The answer to these questions is both yes and no. Mayer's original proposal was consistent with the state of knowledge regarding the regulation of metabolism with its emphasis on tissues utilization of metabolic substrates in the early 1950s. During this period of rapid growth of metabolic biochemistry, the mechanistic details of the utilization of these substrates or "fuels" in newly emerging metabolic pathways in the peripheral tissues were being described. Yet Mayer made the insightful and essential link between peripheral metabolism, brain metabolism, and the regulation of feeding behavior and body energy balance by defining as critical the *rate of glucose utilization in an undefined brain region*. Our current theoretical formulation still contains as a critical element the peripheral and central detection and recognition of not the utilization of glucose but rather the pattern of blood glucose concentration.

Yet it makes a much more explicit and dynamic statement about the shape of transient declines in peripheral blood glucose that are required to initiate spontaneous feeding behavior in rats or the perception of hunger in humans. We have now defined the precise antecedent conditions required, in terms of the shape of the transient declines in blood glucose, for meal initiation or meal requests. Although the precise pattern required to be detected and recognized by the central and peripheral nervous system has been specified, the neural mechanisms that underlie this detection and the algorithms used to perform this pattern recognition and map this pattern into the initiation of feeding or meal requests remain to be elucidated by future research. In our formulation we have specifically defined the "what," the transient decline in blood glucose, which signals a transition in the prevailing behavioral state to meal initiation, but leaves the "how," the origin of the transient decline in blood glucose and its detection, as a theoretical construct. This situation is in marked contrast to the glucostatic theory, in which both the signals responsible for organizing feeding behavior (what) and the origin and the detection of those signals (how) were only vaguely, at best, specified. Whether this theoretical construct will serve the same important role as an organizing principle and have same positive impact on the focus, direction, productivity, and increased understanding as Mayer's glucostatic hypothesis based on glucose utilization remains to be seen as the future of our field emerges.

We hope that the unraveling and identification of the mechanisms responsible for the origins and the detection of transient declines in blood glucose will be a focus of the feeding research in the coming years. However, this search will only be a special case of the more general and, in our opinion, the most critical and important problem in our field: the central and peripheral integration of both peripherally and centrally generated signals into the exquisite and elegant regulation of feeding behavior and body energy balance. If the theoretical concept presented here proves to be helpful in resolving this essential problem and continues to be useful in thinking about feeding behavior and its physiological bases, then a small change in blood glucose will have indeed had a large effect on behavior.

60.7 Applications to Other Areas of Health and Disease

A more complete understanding of the control of feeding behavior, with special emphasis on the evolution of hunger and the initiation of feeding, will have direct applications to the understanding and, hopefully, the treatment of eating disorders: anorexia, bulimia, binge eating, and night eating, as well as the epidemic metabolic diseases – obesity, type 2 diabetes, and metabolic syndrome. In addition, this conceptual framework may provide a deeper understanding of both normal and disordered metabolic regulation. Successful extension of this paradigm in the last 2 decades to additional animal models of disordered feeding (e.g., experimentally diabetic and genetically obese rats) and the successful extension to the domain of human meal requests and changes in hunger ratings demonstrate the explanatory power, the applicability of a general theoretical construct from rats to humans, and provide increased confidence in this approach.

Secondly, the experimental study of hunger may lead to the development of biologically based strategies for the reshaping of disordered feeding behavior. This research may provide important information about the interaction and relative importance among the several factors (learning, memory, past experiences, emotions, feelings) in the decision-making process that ultimately leads to the perception and behavioral expression of hunger in humans.

Finally, transient declines in blood glucose may also play a role in the behavioral and metabolic adaptation or "learning" that occurs following alterations in food availability and lighting schedules, food and diet options, cost of working for food, as well as the conditioned feeding situation. Studies

of rats working for food and in conditioned feeding suggest such a role, but additional studies will be required to fully explore this possibility. This research may have application to a better understanding of adaptation to crossing time zones and shift work.

Summary Points

- This chapter provides a new framework for understanding the control of feeding behavior, with special emphasis on the evolution of hunger and the initiation of feeding, including theoretical and experimental components.
- Experimental evidence supports the hypothesis that spontaneous, self-resolving transient declines in blood glucose precede and signal meal initiation in nondeprived, free-feeding rats. This signal precedes food-seeking behavior and the initiation of a meal but does not predict the size of the meal or the timing of meal termination.
- The precise antecedent conditions required, in terms of the shape of the transient declines in blood glucose, for meal initiation or meal requests have been defined.
- In the signal detection and recognition theory of meal initiation, patterns in the periphery carry information that is detected and recognized by central neural networks. These specific patterns of activity are postulated to correspond to the behavioral states associated with meal initiation and meal termination.
- The major assertions of the theory are that: (1) transient declines in blood glucose represent "endogenous metabolic patterns," (2) transient declines in blood glucose are signals in the form of "patterns" that are detected and recognized by the central neural network that controls feeding behavior, and (3) these patterns are "mapped into" meal initiation under free-feeding conditions.
- The distinguishing feature of the theory is that it is the temporal pattern, shape, or waveform of blood glucose dynamics rather than the glucose molecule, or the absolute decrease in blood glucose, or blood glucose concentration or glucose utilization that is detected and contains "critical information" that is extracted by the central nervous system to control meal initiation.
- If a transient decline in blood glucose is recognized in the presence of a favorable peripheral metabolic state and the recognition of recent generation of the "probe or timing" signal, then the output of the decision algorithm will be "yes" and the meal initiation program will be activated.
- If the peripheral metabolic state cannot maintain glucose homeostasis over the next time interval, without additional energy intake from a meal, a transient decline in blood glucose in response to a probe signal will occur. On the other hand, if glucose homeostasis can be maintained over the next time interval without additional energy intake (e.g., liver glycogen breakdown and utilization), a transient decline in blood glucose will not occur.
- Experimental results have confirmed its utility both in terms of explanatory power and an ability to tightly link feeding behavior and physiology.
- This model, and the hypotheses on which it is based, provide a new framework for the understanding of feeding behavior, with special emphasis on the evolution of hunger, the initiation of feeding and its dependence on patterns of blood glucose.
- An association between transient declines in blood glucose concentration and meal requests and changes in hunger ratings in human subjects isolated from food and time cues has been demonstrated. This association was observed following both spontaneous and insulin-induced transient declines in blood glucose. Most of the deviations in blood glucose observed closely resemble the patterns of blood glucose dynamics shown to precede and signal meal initiation in rats.

- These results support and strengthen the conclusion that the transient decline in blood glucose represents a temporal pattern that reflects an antecedent physiological event or provides a signal related to the expression of hunger in humans.
- This suggests that, at least under these experimental conditions, a signal for hunger in humans is associated with transient declines in blood glucose that is similar to that observed in rats.
- Studies reviewed here strongly suggest that transient declines in blood glucose: (1) represent an "endogenous signal" for meal initiation; (2) their detection and mapping into meal initiation can be viewed as a "pattern detection and recognition problem"; (3) may be useful "probes," or experimental interventions, to elucidate the operation, nature, and decision algorithms of the widely distributed neural network that controls meal taking and, thus, feeding behavior; and (4) play an important role in the regulation of individual meals and by interacting with longer-term regulatory systems, such as the brain insulin system or the leptin pathway, also may play an important role in the regulation of body energy storage.
- Successful extension of this paradigm in the last 2 decades to additional animal models of disordered feeding (e.g., experimentally diabetic and genetically obese rats) and the successful extension to the domain of human meal requests and changes in hunger ratings demonstrate the explanatory power, the applicability of a general theoretical construct from rats to humans, and provide increased confidence in this approach.

Definitions of Key Terms

Meal initiation: Meal onset – the transition from the intermeal interval (with no feeding behavior) to the beginning of feeding (meal) resulting from the activation of the motor program for feeding within the CNS.

Transient decline in blood glucose: A spontaneous, self-resolving pattern of blood glucose concentration that falls (approximately 10% below baseline) and then rises back toward the stable baseline level that precede and signal meal initiation in nondeprived, free-feeding rats. This signal precedes food-seeking behavior and the initiation of a meal but does not predict the size of the meal or the timing of meal termination.

Representation: Construction of "analogs", "surrogates" or "maps" of metabolic and behavioral states within the CNS: absorptive and postabsorptive states, hunger (meal initiation, maintenance and termination), and satiety. Both peripheral and central components are included in the maps.

Central representation of peripheral events: Representation of peripheral blood glucose, plasma insulin or plasma leptin concentrations or other metabolic events within the CNS.

Pattern as signal model/construct: A theory which is distinguished by the assertion that it is the temporal pattern, shape, or waveform of blood glucose dynamics rather than the glucose molecule, or the absolute decrease in blood glucose, or blood glucose concentration or glucose utilization that is detected and contains "critical information" that is extracted by the central nervous system to control meal initiation.

Signal detection and recognition theory of meal initiation: Specific patterns of blood glucose concentration in the periphery carry information that is detected and recognized by central neural networks. These specific patterns of activity are postulated to correspond to the behavioral states associated with meal initiation and meal termination.

Mapped into meal initiation: Description of the process of transformation, in the mathematical sense, or establishing a unique correspondence between the recognition of the transient decline in blood glucose and the activation of the motor program for feeding within the CNS (meal initiation).

Timing or probe signal: Representation of an "inquiry" or "interrogation" or "perturbation" of the periphery by the CNS to determine its ability and capacity to maintain glucose homeostasis in upcoming time interval. This signal is generated by a signal generator (in the CNS) that controls its frequency or timing.

Favorable metabolic state: The later part of the intermeal interval, which would allow a transient decline in blood glucose in response to the probe or timing signal.

Parasympathetic and sympathetic NS: Firing rate of the parasympathetic (vagal) and/or sympathetic nervous system efferents which innervate pancreatic B-cells, liver, adipose tissue, and the gastrointestinal tract. The change in autonomic firing rate causes a brief insulin spike from pancreatic B-cells, along with other responses, which, in the presence of an appropriate peripheral metabolic state, induces a transient decline in blood glucose by decreasing hepatic glucose production and/or increasing peripheral glucose disposal.

Pass through: A centrally generated meal initiation timing or probe signal is applied to the peripheral metabolic system. Depending on the response of the peripheral metabolic system, it may result in the onset of feeding; it will be mapped into feeding behavior only if a transient decline in blood glucose of the correct shape or pattern occurs in response to a recent probe signal.

Detection: The process of detection begins with a representation of the relatively steady intermeal concentration of blood glucose ("baseline") and "reports" the detection of all departures in blood glucose concentration from that baseline.

Recognition: A unique process of determining that an ongoing pattern of blood glucose concentration "matches" or "fits" the criteria for a transient decline in blood glucose.

TDBG detection process: Any changes in the patterns of blood glucose concentration from baseline values are detected by peripheral and central glucose responsive neural elements.

TDBG recognition process: A unique process of determining that an ongoing pattern of blood glucose concentration "matches" or "fits" the criteria for a transient decline in blood glucose.

Decision algorithm: The decision algorithm unit computes the conditional probability of activating the stored meal initiation program given the state of the three inputs it receives: (1) output from the TDBG recognition process, the recognition of TDBG; (2) peripheral metabolic state; and (3) presence of a recent "probe or timing signal."

Vagotomy, hepatic: Complete surgical cutting of the vagus nerve that innervates the liver.

Coefficient of variation: A measure of the variation of a mean; CV = SD/mean.

References

Antin J, Gibbs J, Holt J, Young RC, Smith GP. J Comp Physiol Psychol. 1975;89:784–90.

Bernstein LM, Grossman MI. J Clin Invest. 1956;35:627–33.

Booth DA. J Comp Physiol Psychol. 1968;65:13–6.

Booth DA. In: Booth DA, ed. Hunger models. London: Academic; 1978. p. 227–78.

Campfield LA, Smith FJ. Brain Res Bull. 1986;17:427–33.

Campfield LA, Smith FJ. Int J Obesity. 1990a;14:15–33.

Campfield LA, Smith FJ. In: Stricker EM, ed. Handbook of behavioral neurobiology. Neurobiology of food and fluid intake. Vol. 10. New York: Plenum; 1990b. p. 183–206.

Campfield LA, Smith FJ. In: Bray GA, ed. Bailliere's clinical endocrinology and metabolism. London: Bailliere Tindal; 1999. p. 13–30.

Campfield LA, Smith FJ. Physiol Rev. 2003;83:25–58.

Campfield LA, Brandon P, Smith FJ. Brain Res Bull. 1985;14:605–16.

Campfield LA, Smith FJ, Guisez Y, Devos R, Burn P. Science. 1995;269:546–9.

Campfield LA, Smith FJ, Rosenbaum M, Hirsch J. Neurosci Biobehav Rev. 1996;20:133–7.

Damasio A. Looking for spinoza: joy, sorrow and the feeling brain. New York: Harcourt; 2003.

Gibbs J, Young RC, Smith GP. J Comp Physiol Pyschol. 1973;84:488–95.

Grill HJ, Norgren R. Brain Res. 1978;143:281–97.

Hervey GR. Proc Nutr Soc. 1971;30:109–16.

Hervey GR. Int J Vitam Nutr Res. 1988;58:477–90.

Inoue S, Bray GA. Life Sci. 1979;25:561–6.

Kennedy GC. Proc R Soc Lond B Biol Sci. 1953;140:578–92.

Le Magnen J. Behav Brain Sci. 1980;4:561–607.

Le Magnen J. Hunger. London: Cambridge University Press; 1985.

Le Magnen J. Neurobiology of feeding and nutrition. San Diego: Academic; 1992.

Louis-Sylvestre J, Le Magnen J. Neurosci Biobehav Rev. 1980;4:13–5.

Mayer J. N Engl J Med. 1953;249:13–6.

Mayer J. Ann NY Acad Sci. 1955;63:15–43.

Nicolaidis S. Proc IUPS. 1974;26:122–3.

Nicolaidis S, Even P. Compte Rendu Sci Acad Sci. 1984;298:295–300.

Niijima A. J Auton Nerv Syst. 1983;9:207–20.

Norgren R. J Auton Nerv Syst. 1983;9:67–77.

Pollack CP, Green J, Smith GP. Physiol Behav. 1989;46:529–34.

Ritter S, Taylor JS. Am J Physiol Regul Integr Comp Physiol. 1990;258:R1395–401.

Smith FJ, Campfield LA. Am J Physiol Regul Integr Comp Physiol. 1993;265:R1423–9.

Smith GP, Gibbs J. Ann NY Acad Sci. 1994;713:236–41.

Steffens AB. Physiol Behav. 1969;4:823–6.

Stricker EM. Handbook of behavioral neurobiology. Neurobiology of food and fluid intake. Vol. 10. New York: Plenum; 1990.

Strubbe JH, Steffens AB, De Ruiter L. Physiol Behav. 1977;18:181–6.

Stunkard AJ, VanItallie TB, Reiss BB. Proc Soc Exp Biol Med. 1955;89:258–61.

VanItallie TB. Int J Obesity. 1990;14:1–10.

VanItallie TB, Hashim SA. Am J Clin Nutr. 1960;8:587–94.

VanItallie TB, Beaudoin R, Mayer J. J Clin Nutr. 1953;1:208–16.

Weingarten HP, Martin GM. Physiol Behav. 1989;19:735–40.

Woods SC, Nolan LJ. Appetite. 1997;28:281–2.

Woods SC, Seeley RJ, Porte D Jr, Schwartz MW. Science. 1998;280:1378–83.

Zhang Y, Proenca R, Maffei M, Barone M, Leopold L, Friedman JM. Nature. 1994;372:425–31.

Chapter 61
Dynamics of Feeding Behavior: Role of Hypothalamic and Satiety Signals

B.S. Zanutto and J.E.R. Staddon

Abbreviations

NTS	Nucleus tractus solitarius
SSs	Satiety signals
CCK	Cholecystokinin
PYY	Peptide YY
Set Point$_{ST}$	Set point for short-term regulation
Set Point$_{LT}$	Set point for long-term regulation
PVN	Paraventricular nucleus
LHA	Lateral hypothalamic
$x(t)$	The satiation value
Φ	Satiation value of a specific food
θ	Threshold value equal to Set Point$_{ST}$
SS	Output of a cascaded series of leaky integrators
i	Number of integrator
V_i	State of integrator i
a_i	Time parameter of integrator i ($0 < a_i < 1$)
b_i	Input weight
PIM	Post-interruption meal
IMI	Intermeal interval
CINT	Cascaded INTegrator

61.1 Introduction

Animals do not feed at random. Even grazers, like whales and cattle, who must ingest low-energy-density food for many hours each day, tend to prefer to eat at certain times. Omnivores such as rats, cats, dogs – and humans – whose food has more energy, eat in *meals*, relatively short bouts of concentrated eating that are approximately periodic and separated by intervals when the animal either rests or does other things. Meal patterns are affected by external factors such as taste (the evolutionary predictor of food quality) learning, social situation, stress and emotion, and many others, and the way that these variables interact is complex and not fully understood.

B.S. Zanutto (✉)
IIBM-Universidad de Buenos Aires, and IBYME-CONICET, Argentina
e-mail: silvano@fi.uba.ar

For many years, beginning perhaps with Le Magnen (1985), repletion–depletion has been implicitly assumed to be the process that underlies feeding behavior. This approach has led to numerous attempts to identify the physiological signal that triggers eating (Campfield and Smith 2003; Zorrilla et al. 2005), an essential ingredient of any homeostatic model. Unfortunately, as research progressed, the number of candidate trigger signals increased to the point that a homeostatic model seemed to be unworkable. But recent behavioral data from our laboratory and others (Staddon and Zanutto 1997; Staddon 2001; Zanutto and Staddon 2007) has shown that the effects of eating interruption on meal patterns in rats can be accounted for by a relatively straightforward feedback model that is consistent with neurophysiological data. Describing this model and its relationship to current physiological understanding is the topic of this chapter.

61.2 Signals for Satiety and Long-Term Weight Regulation

Endogenous factors that modify the size of an ongoing meal are called satiety signals (SSs). For example, cholecystokinin (CCK), generated during and after a meal, provides information to the brain that inhibits feeding and leads to meal termination. SSs are generated in the gastrointestinal tract and abdominal viscera, as well as in the mouth (taste factors: Travers and Norgren 1987; Ritter et al. 1994). They provide information about mechanical (e.g., stomach stretch, volume) and chemical properties of food (e.g., via peptides such as cholecystokinin (CCK), ghrelin, and peptide YY (PYY)), that have been linked to short-term (within-a-day) feeding behaviors. Amylin (Chance et al. 1991) and glucagon (Geary 1998), secreted from the pancreatic islets during meals, reduce meal size. SSs are relayed to the hindbrain, mainly to the nucleus tractus solitarius (NTS), either indirectly via nerves from the gastrointestinal tract, especially the vagus (e.g., CCK and glucagon), or else circulate via the blood and interact with local receptors in the hindbrain (e.g., amylin) (Woods 2004).

The hindbrain (mainly the NTS), via several hypothalamic nuclei, also receives signals that are influenced by the fat mass of the body. The best-known adiposity signals are the hormones leptin and insulin. The amount of leptin secreted from fat cells (adipocytes) is directly related to the amount of stored fat (Havel et al. 1996; Ahren et al. 1997). Insulin is secreted from pancreatic ß cells in response to increases in glucose. Moreover, basal insulin in the absence of elevated glucose is directly related to total body fat (Bagdade et al. 1967; Polonsky et al. 1988). Obese individuals have high basal insulin, whereas lean individuals have relatively low levels. Thus, circulating leptin and insulin levels are each a good indicator of body fat, and both hormones are able to enter the brain from the blood and stimulate specific neural receptors. These two adiposity signals (leptin especially) have been linked to longer-term weight regulation (over months and years) (Marx 2003).

Some gut-related peptides are also long-term regulators. Rodents and humans with reduced PYY levels in response to food intake tend to obesity. Chronic administration of PYY reduces adiposity in rodents. Also, PYY-null mice (unable to produce the hormone because the gene for PYY has been knocked out) are hyperphagic and develop marked obesity and are hypersensitive to exogenous PYY: chronic treatment with PYY reverses their obese phenotype (Batterham et al. 2006). The effect of this hormone has also been studied in obese children, where there is a reciprocal relationship between obesity and PYY (Roth et al. 2005; Ellacott et al. 2006).

These data suggest that there is substantial redundancy in the orexigenic (appetite-stimulating) system, with an evolutionary bias toward energy storage. Despite this redundancy, the neurophysiological pathways suggest that feeding is regulated by a negative feedback loop, where the hypothalamus provides the long-term regulatory input to the NTS, which acts as the set point for short-term regulation (Set Point$_{ST}$).

Many areas of the brain are sensitive to long-term regulators. Leptin receptors have been found on the paraventricular nucleus (PVN) and lateral hypothalamic (LHA) neurons, implicating them as direct targets for regulation by circulating adiposity signals. PVN stimulation inhibits food intake, whereas the opposite is true for stimulation of the LHA (Bray et al. 1990) and adjacent perifornical area (Stanley et al. 1993). Correspondingly, bilateral PVN lesions cause a hyperphagic obesity syndrome, whereas bilateral lesioning of the LHA causes anorexia and weight loss (Stellar 1954; Bray et al. 1990).

Several neuropeptides synthesized in PVN neurons reduce food intake and body weight when administered centrally. Hypothalamic areas including the PVN, zona incerta, perifornical area, and LHA are richly supplied by axons from the arcuate nucleus, which has greater concentrations of leptin and insulin receptors than other hypothalamic sites (Elmquist et al. 1998; Schwartz et al. 2000; Elmquist and Flier 2004; Cone 2005; Fan et al. 2004). The arcuate nucleus has at least two distinct populations of neurons with opposite effects on food intake, responding not only to leptin and insulin, but also to gut hormones (the best studied are ghrelin and, recently, PYY). The first population produces orexigenic neuropeptide Y and agouti-related protein (NPY/AgRP). The second population produces the anorexigenic (appetite-suppressing) proopiomelanocortin and cocaine- and amphetamine-regulated transcript (POMC/CART).

61.3 Computational Theory of Feeding Behavior

The NTS (and other hindbrain regions) integrates endogenous inputs transmitted through the parasympathetic and sympathetic fibers and blood as well as the hypothalamic input involved in energy homeostasis. The NTS is so important that appropriately lesioned rats may even starve to death. We showed that the NTS works like a comparator in a control system (Zanutto and Staddon 2007). These endogenous NTS-inputs are regulatory, acting to oppose external factors, such as a reinforcement schedule or interruption of feeding that tends to reduce the SSs below the Set Point$_{ST}$. They express the short-term motivation for eating. It is this system that regulates meal duration and intermeal interval.

Signals related to body fat (adiposity signals) regulate long-term feeding behavior and therefore body weight. Administration of insulin into the brain reduces food intake and body weight (Wood et al. 1979; Schwartz et al. 1992; Wood et al. 2000), and mice with a genetic deletion of neuronal insulin receptors are hyperphagic and obese (Bruning et al. 2000). Intraventricular administration of leptin reliably reduces food intake and body weight in rats (Seeley et al. 1996) and mice (Campfield et al. 1995). Also, chronic administration of PYY reduces adiposity in rodents and in PYY- null mice (Batterham et al. 2006). In obese children there is a reciprocal relationship between obesity and PYY (Roth et al. 2005; Ellacott et al. 2006).

Figure 61.1 shows how these data fit into our computational model. The hypothalamic efferents to the NTS are concerned with long-term regulation. The Set Point$_{LT}$ in the hypothalamus is modulated by signals for adiposity as well as some gut signals and external factors (learning, emotion, etc.) The output of this modulation then becomes the short-term set point. Set Point$_{ST}$ is then compared with a variety of satiety signals, both neuronal and hormonal associated with taste and bulk factors of ingested food (CCK, glucagon, etc.). The output of this comparison, after a delay, initiates or terminates eating.

The CINT[1]1 Model We consider feeding behavior with factors such as habit (learning), social situation, stress, and arousal held as constant as possible and in the absence of competition among motivational systems (hunger versus sex, versus thirst, etc.) (Staddon and Zanutto 1997; Staddon 2001); i.e., we look at feeding assuming that the only relevant factors are metabolism and food intake.

_____

[1]**C**ascaded **INT**egrator
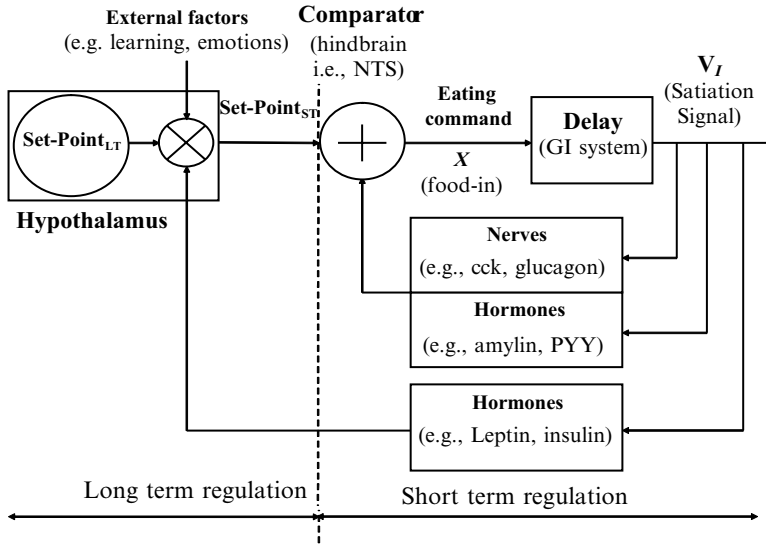
Fig. 61.1 The block diagram of a system modeling long- and short-term regulation of feeding. Eating leads to delayed SSs (grouped in V_I). When the feedback SSs falls below Set Point$_{ST}$, the command is "eat": otherwise, the command is "stop eating." Set Point$_{ST}$ is made up of the hypothalamic inputs resulting from the modulation of Set Point$_{LT}$ in the hypothalamus by adiposity, some gut signals, and external factors (learning, etc.)

If the feeding schedule is ad libitum (i.e., food is always available), then the equations for the I-unit cascaded (delay-block) system are:

$$x(t) = \Phi, \quad \text{if } V_I(t) < \theta, \quad \text{otherwise}, \quad x(t) = 0, \tag{61.1}$$

where $x(t)$ is the satiation value which is the input to the system at each discrete time step, and Φ is a constant which is some function of the physical properties of the food (e.g., weight, type, caloric, and protein values, etc.) provided by the experimenter (i.e., bang-bang control). The response rule is: if $x(t)$ is below Set Point$_{ST}$ (θ): eat (satiation value = Φ); otherwise, do not eat. Because rats show some spontaneous variation in eating patters from day to day, the details are never identical from one day to the next; in simulations we therefore include a small "noise" variation in the Set Point$_{ST}$, θ.

The SS is the output of a cascaded series of leaky integrators where the output of integrator i is the input to the next integrator $i + 1$. V_I, the SS, is the output of the last integrator in the series, which is determined as follows. In discrete time, for the first integrator:

$$V_1(t+1) = a_1 V_1(t) + b_1 x(t), \tag{61.2}$$

and for subsequent integrators:

$$V_i(t+1) = a_i V_i(t) + b_i V_{i-1}(t), \quad 1 < i \leq I, \tag{61.3}$$

where V_i is the state of integrator i, a_i is the time parameter of integrator i ($0 < a_i < 1$), and b_i is the input weight.

Two integrators are the minimum necessary to produce a delayed signal SS, but three ($I = 3$) give a better fit to our data. The behavior of the model depends much more on its sequential structure than

on particular parameter values, or even the number of integrators, so long as there are more than two. Moreover, to accommodate feedback from physiological satiety signals with different delays, the output of each integrator can be fed back separately without changing the model's essential properties.

61.4   The Model Accounts for Experimental Effects on Feeding Behavior

1. *Eating patterns in free-feeding rats*. Figure 61.2 compares raster plots of eating patterns in six rats and model predictions. The top panel shows meal pattern; model predictions are shown on the bottom. The patterns generated by the model (which include a small "noise" term added to the Set Point$_{ST}$, θ) are indistinguishable from the pattern of eating bouts shown by the rats.
2. *Meal-intermeal correlations*. We analyzed the correlation between the meal and the following intermeal interval (IMI). Correlations between meal size and the following intermeal are reported
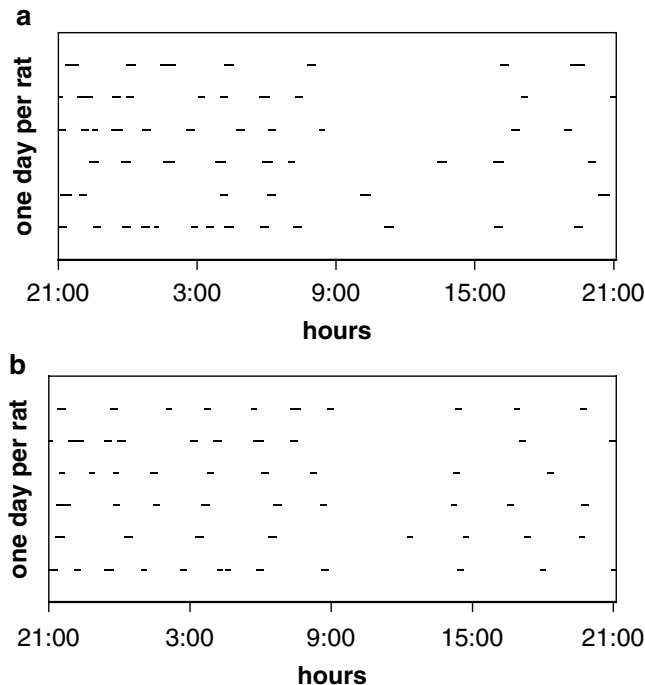
Fig. 61.2 Meal patterns in six rats under free feeding conditions. Compare rasters of meals in six rats (**a**) and simulated by the model (**b**). Parameters of the model: $a_1 = \lambda$, $a_i = a_i - 1 + \lambda(1 - a_i - 1)$, $b_i = 1.7(1 - a_i)$. $\lambda = 0.985$, $\Phi = 1.1$. One time step = 1 s. Set point$_{ST}$ (θ) varies smoothly between two saturation values, θ_{dark} and θ_{light}: θ $(t + 1)$ = θ (t) × $(1 - 0.00005)$ + 0.00005 × $(\theta_{day}$ + noise); θ_{day} could take two values depending on the simulated period (*light* or *dark*): $\theta_{dark} = 0.13$, $\theta_{light} = 0.12$. Noise = white noise (amplitude = 0.007) to simulate observed spontaneous variation in meal size and IMI. The set time to eat a pellet was 6 s, followed by a refractory period of 4 s. A meal began with the first pellet after $V_1 < \theta$ and was considered to end after 3 min of no eating ($V_I \geq \theta$; the 3 min were not included in meal duration). Initial conditions: At the beginning of each condition, V_1 and V_2 were set to 0; $V_3 = 0.12$, to allow for eating on the previous day. To simulate the limit on IMI, V_I was bounded between zero and $0.0017 + \theta$. The relation between eating tendency and operant lever pressing was: when eating tendency >0, lever-press rate was 2/s (estimated from observational data) (Modified from Zanutto and Staddon 2007: doi:10.1371/journal.pcbi.0030097.g001)

to be moderately positive, but intermeal interval and the following meal size correlations are rare (Levitsky 1974; Collier and Johnson 1990). Using a linear regression analysis, we found in rats (Zanutto and Staddon 2007) that at night and under free conditions, IMI increased as a function of the previous meal size and the meal size increased as a function of the previous IMI. The CINT model reproduces this same pattern.

3. *Meal patterns after enforced fasting.* The model can reproduce the pattern of ingestion of food following days-long fasting in naive rats. Figure 61.3 compares cumulative eating data showing the effects of enforced fasts of 1–4 days on food intake in a group of rats (Levitsky et al. 1976) with predictions from the CINT model. The model and data cumulative curves match closely.

We also studied the eating pattern in rats when feeding is unpredictably interrupted (for 1, 2, or 3 h), the interruption being initiated when the animal attempts to begin a new meal (Zanutto and Staddon 2007). Figure 61.4 compares raster plots of eating patterns in individual rats and the model prediction. On the top, there are ten consecutive days; the first day has no interruptions and the following days have them at onset times indicated by diamonds. The figure shows that the model (bottom two panels) duplicates the general eating pattern.

The model shows that a short (<3 h) interruption in feeding is limited to the first postinterruption meal (PIM), which is larger than preceding and subsequent meals; i.e., an interruption affects only the first PIM. This is in agreement with Le Magnen (1985), who found that when eating is interrupted for a few hours, the first (and only the first) meal is extra long. Eating rate and meal size thereafter both revert to normal values (the *first-meal effect*).

The difference between the number of pellets of the PIM and the number of pellets of the previous meal is proportional to the duration of the interruption. We also analyzed the IMI after the PIM. We found that it is longer than usual, although smaller than the saturation (maximum possible) value. There is no correlation between the size of the PIM and subsequent IMI. The size of the meals after
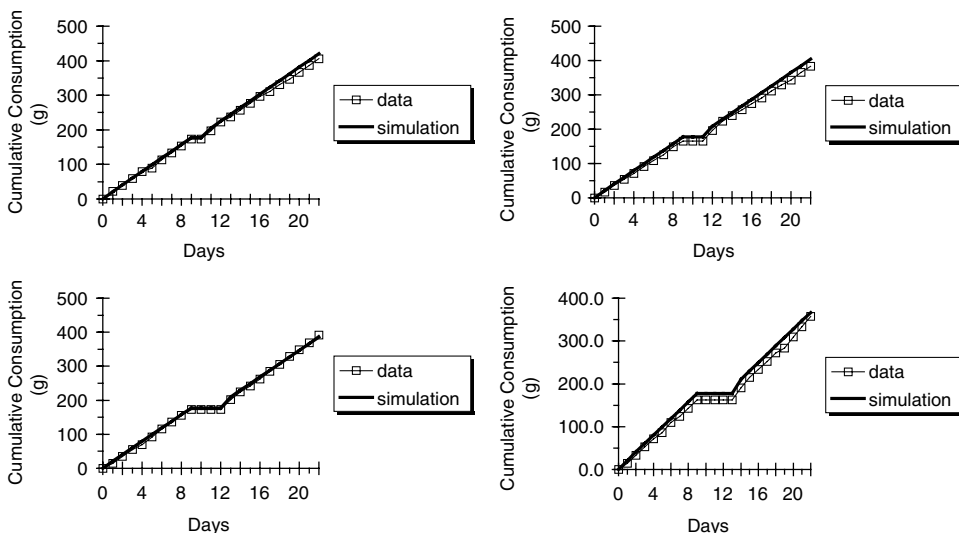
Fig. 61.3 *Top panel*: The effects on cumulative daily ingestion of 1–4 days of food deprivation starting on the ninth day. *Inset* shows a typical cumulative eating record across the whole 22-day experiment for the 4-day condition. *Fine lines and markers*: group–average data from Levitsky et al. (1976); *heavy line*: Simulation
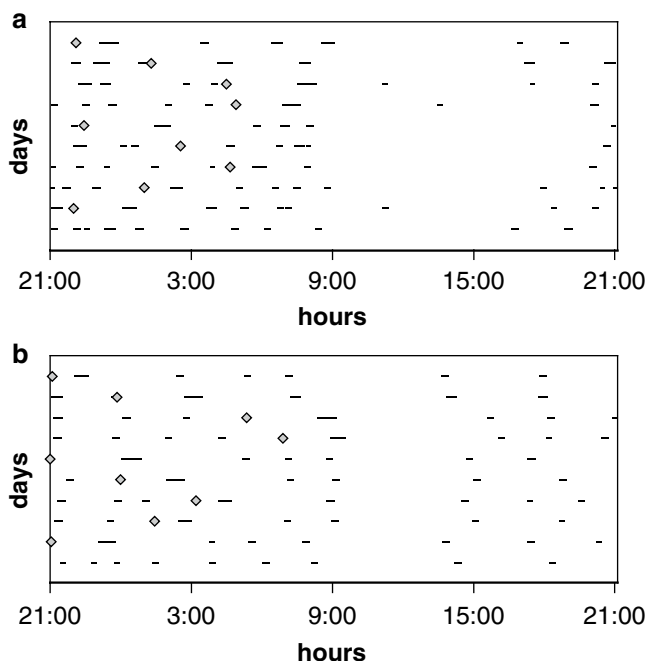
Fig. 61.4 Meal Patterns in Rats under free feeding and with unpredictable interruptions. Compares rasters of meals in a single rat (**a**) and as simulated by the model (**b**). (a) shows ten consecutive days, the first with no interruptions and the following with interruptions. The *diamonds* show times when the rat attempted to start a new meal, but was interrupted. (b) shows the model predictions (Modified from Zanutto and Staddon 2007: doi:10.1371/journal.pcbi.0030097.g001)

the PIM is not significantly different from other meals. Finally, the interruption (plus the previous IMI) evokes a larger subsequent meal size than a spontaneous IMI of similar length, indicating a change in the animal's motivation to eat. CINT duplicates all these effects.

4. *Adaptation to operant schedules.* In experimental procedures extensively explored by George Collier and his associates, rats in a "closed economy"[2] are required to make two types of operant response (usually, lever-pressing), termed "procurement" and "consumption" responses. Procurement responses earn the opportunity to engage in consumption responses. Consumption responses are made for the opportunity to eat. When the animal has ceased (for at least 10 min, usually) to make a consumption response the animal must make another round of responses on the procurement lever for further access to the consumption lever.

Figure 61.5 compares model predictions of mean meal size and meal frequency as procurement cost (ratio value) increases, with data from Collier et al. (1972). The simulation shows data from the fifth day of training. The simulation duplicates the increasing meal size and decreasing meal frequency as procurement cost is increased.

Figure 61.6 compares the effect of increasing consumption cost in data from Collier et al. (1972) with a CINT simulation. Simulation and data both show that meal size and meal frequency are relatively invariant as consumption cost increases.

---

[2]That is, where rats must get all their food via the operant schedule.

Fig. 61.5 The effect of increasing procurement cost in the Collier et al. (1972) experiment. Data: mean meal size (*light line*, *open squares*) and meal frequency (*light line*, *open squares*) of a single rat in a closed economy. Simulation: *heavy lines*
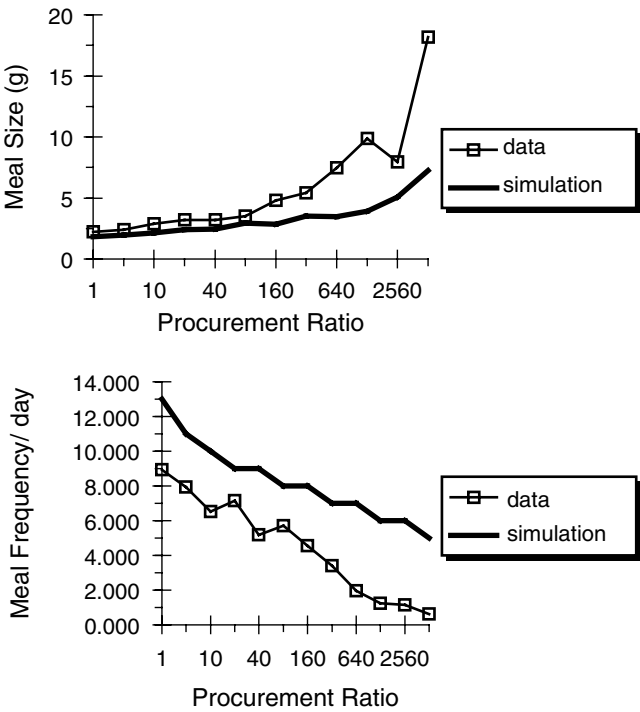
Fig. 61.6 The effect of increasing consumption cost in the Collier et al. (1972) experiment. Data: mean meal size (*light line*, *open squares*) and meal frequency (*light line*, *open squares*) of a single rat in a closed economy. Simulation: *heavy lines*
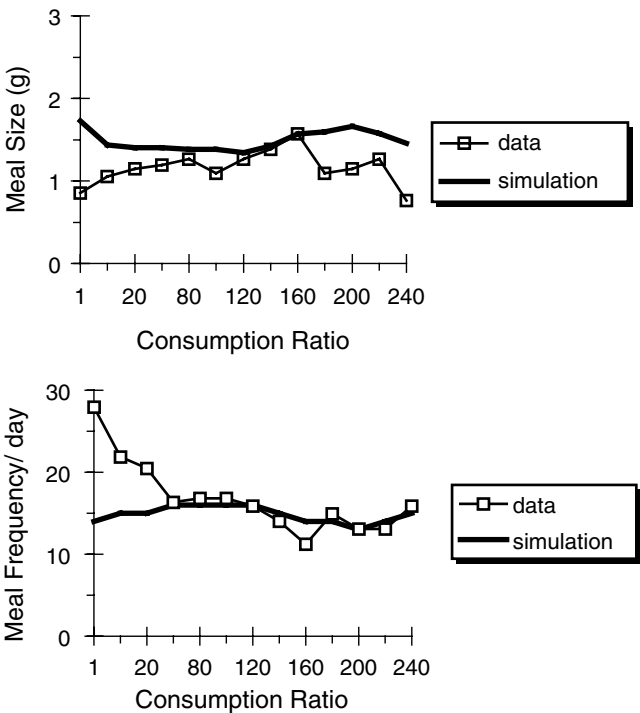
61.5 Implications for Obesity and Health

In the CINT model, total food intake is essentially independent of parameter values other than the set points. Different parameters will yield fewer, larger meals or more frequent smaller ones. But the total amount ingested remains roughly constant.

According to the CINT model, one way to change feeding behavior over the long term is to change Set Point$_{ST}$. Since Set Point$_{LT}$ is assumed to be fixed, the only routes to change are via the two variable pathways (hypothalamic inputs to the NTS): signals for body fat (e.g., leptin and insulin) as well as for some gut signals (e.g, PYY) and psychological factors (learning, arousal, etc.). In animal studies, a drop in leptin levels results in an increase in food intake until the leptin levels are restored. Similar effects have been seen with changes in insulin (Wood et al. 1979; Schwartz et al. 1992; Campfield et al. 1995; Seeley et al. 1996; Wood et al. 2000; Bruning et al. 2000).

In humans, psychological factors such as learning and arousal (as well as adiposity signals) affect overall food intake in ways that are not fully understood. Hence the effects of, for example, mechanical fat reduction are hard to interpret. On the one hand, clinical data from liposuction patients report that although leptin level goes down (e.g., after liposuction), food intake increases until levels are back up. On the other hand, in one study (Talisman et al. 2001) patients report loss of appetite 1–3 weeks after liposuction. These data do not contradict our computational theory, since psychological factors may well affect the outcome of elective surgery.

There are other ways to modify the hypothalamic inputs to the NTS. As was said, PYY is a hormone released into the bloodstream from the gut that regulates hunger and acts in the arcuate nucleus of the hypothalamus. From a regulatory point of view, PYY might be used directly as a slimming agent (Roth et al. 2005; Chelikani et al. 2006; Batterham et al. 2006). There is a connection between protein intake and PYY: when the amount of protein in a person's diet is increased, it speeds up and prolongs the feeling of satiation (Batterham et al. 2007).

According to the computational theory, the role of external factors such as taste, learning and habits, social situation, stress, and emotion modulates the Set-Point$_{LT}$, yielding an output that comprises Set-Point$_{ST}$, which in turn affects the initiation and termination of meals. In this way a very tasty food would increase the Set-Point$_{ST}$ (θ) so that meal size would be greater, and vice versa if the food is not tasty. If Set-Point$_{ST}$ increases, the meal size will increase and IMI will decrease (and vice versa if Set-Point$_{ST}$ decreases).

As was said earlier, SSs provide information about mechanical (e.g., stomach-stretch, volume) as well as chemical properties of food. High-fiber (low-caloric) foods, even with satiation value (Φ, the value of the satiation variable x) similar to that of other foods of comparable caloric value, have greater volume; consequently, the stomach-stretch and volume components of SSs will increase faster than with other foods. Thus, people will end a meal of high-fiber food sooner, after ingesting fewer calories, than a low-fiber meal.

Recall that after a period when feeding is interrupted (fasting) only the first meal is longer than others and occasional fasting causes no weight loss, compared with control animals who do not fast. Fasting does cause changes in metabolism, however, which becomes more efficient in converting food into energy (Levitsky et al. 1976). An obvious possibility, therefore, is that a short diet that involves some fasting or much-reduced eating will only produce a temporary weight loss. Lost weight may be restored when the dieting regimen comes to an end.

Because feeding is the prototypical motivational system, controlling feeding is equivalent to controlling the motivation for eating. In the model ingested food inhibits eating, but the inhibitory effect is delayed; so, if you want to lose (or not gain) weight eat slowly or in small bites, just like your mother told you! In this way, you will give the process of satiation ($V_I \geq \theta$,) time to catch up – rather than outrunning it by eating fast.

The simulations make three simple points: (1) feeding regulation in rats is bang–bang rather than proportional control. Eating is regulated in on–off fashion under most conditions rather than being proportional to the difference between set point$_{ST}$ and SSs. (2) The satiating effects of eating are delayed in a way that can be modeled by a simple first-order linear system. Finally (3) long-term regulation (i.e., control of body weight) is separable from short-term regulation (i.e., control of meal pattern). Long-term regulation is controlled by a set-point$_{ST}$ provided by the hypothalamic input, which comprise set-point$_{LT}$ modulated by adiposity and some gut signals, and external factors (e.g., learning and motivation). Short-term regulation is controlled by SSs that vary from minute to minute rather than over days.

References

Ahren B, Mansson S, Gingerich RL, Havel PJ. Am J Physiol Regul Integr Comp Physiol. 1997;273:R113–20.

Bagdade JD, Bierman EL, Porte D Jr. J Clin Invest. 1967;46:1549–57.

Batterham RL, Heffron H, Kapoor S, Chivers JE, Chandarana K, et al. Cell Metab. 2006;4:223–33.

Batterham RL, Ffytche DH, Miranda Rosenthal J, Zelaya FO, Gareth J, Barker GJ, Dominic J, Withers DF, Williams SCR. Nature. 2007;450:106–9.

Bray GA, Fisler J, York DA. Front Neuroendocrinol. 1990;11:128–81.

Bruning JC, et al. Science. 2000;289:2122–5.

Campfield LA, Smith FJ. Physiol Rev. 2003;83:25–58.

Campfield LA, Smith FJ, Guisez Y, Devos R, Burn P. Science. 1995;269:546–9.

Chance WT, Balasubramaniam A, Zhang FS, Wimalawansa SJ, Fischer JE. Brain Res. 1991;539:352–4.

Chelikani PK, Haver AC, Reeve JR Jr, Keire DA, Reidelberger RD. Am J Physiol. 2006;290:R298–305.

Collier G, Johnson DF. Physiol Behav. 1990;48:771–7.

Collier G, Hirsch E, Hamlin P. Physiol Behav. 1972;9:705–16.

Cone RD. Nature Neurosci. 2005;8:571–8.

Ellacott KLJ, Halatchev IG, Cone RD. Peptides. 2006;27:340–9.

Elmquist JK, Flier JS. Science. 2004;304:63–4.

Elmquist J, Maratos-Flier E, Saper C, Flier J. Nature Neurosci. 1998;1:445–50.

Fan W, Ellacott KLJ, Halatchev IG, Takahashi K, Yu P, et al. Nature Neurosci. 2004;7:335–6.

Geary N. New York: Oxford University Press; 1998. p. 291.

Havel PJ, Kasim Karakas S, Mueller W, Johnson PR, Gingerich RL, et al. J Clin Endocrinol Metab. 1996;81:4406–13.

Le Magnen J. Hunger. New York: Cambridge University Press; 1985. p. 157.

Levitsky DA. Physiol Behav. 1974;12:779–87.

Levitsky DA, Faust I, Glassman M. Physiol Behav. 1976;17:575–80.

Marx J. Science. 2003;299:846–9.

Polonsky KS, Given E, Carter V. J Clin Invest. 1988;81:442–8.

Ritter S, Dinh T, Friedman M. Brain Res. 1994;646:53–64.

Roth CL, Enriori PJ, Harz K, Woelfle J, Cowley MA, et al. J Clin Endocrinol Metab. 2005;90:6386–91.

Schwartz MW, Figlewicz DP, Baskin DG, Woods SC, Porte D Jr. Endocr Rev. 1992;13:387–414.

Schwartz MW, Woods SC, Porte DJ, Seeley RJ, Baskin DG. Nature. 2000;404:661–71.

Seeley RJ, van Dijk G, Campfield LA, Smith FJ, Nelligan JA, Bell SM, et al. Horm Metab Res. 1996;28:664–8.

Staddon JER. Motivation, III incentive and schedule effects. Adaptive dynamics: The theoretical analysis of behavior. Cambridge: MIT/Bradford; 2001. pp. 423.

Staddon, JER, Zanutto, BS. In: Bouton ME, Fanselow MS, editors. Feeding dynamics: Why rats eat in meals and what this means for foraging and feeding regulation. Washington: American Psychological Association; 1997. pp. 131–62.

Stanley BG, Willett VL III, Donias HW, Ha LH, Spears LC. Brain Res. 1993;630:41–9.

Stellar E. Psychol Rev. 1954;61:5.

Talisman R, Belinson N, Modan-Moses D, Canti H, Orenstein A, Barzilai Z, Parret G. Aesth Plast Surg. 2001;25:262–5.

Travers S, Norgren R. Annu Rev Neurosci. 1987;10:595–632.

Woods SC. Am J Physiol Gastrointest Liver Physiol. 2004;286:G7–13.

Woods SC, Lotter EC, McKay LDm, Porte D Jr. Nature. 1979;282:503–5.

Woods SC, Schwartz MW, Baskin DG, Seeley RJ. Ann Rev Psychol. 2000;51:255–77.

Zanutto BS, Staddon JER. PLoS Comput Biol. 2007;3:e97.doi:10.1371/journal.pcbi.0030097.

Zorrilla EP, Inoue K, Fekete EM, Tabarin A, Valdez GR, et al. Am J Physiol Regul Integr Comp Physiol. 2005;288:R1450–67.

Chapter 62
Food Unpredictability and Foraging

Sarah E. Overington and Louis Lefebvre

62.1 Introduction

The primary aim of this book is to examine the interactions between diet, nutrition, and behavior in humans. It is useful, however, to broaden that scope by examining variation in feeding behavior across a wide range of species, to see if general rules apply. When we consider all organisms as part of a global food web, we soon recognize the immense diversity of food types and food distributions. Some food types are abundant and found in high densities such as krill, insect swarms, or forests full of leaves. Other foods come in smaller packages, such as solitary animals that, once killed, provide a single meal for a predator. Some food types, like grasses and leaves, can be available year-round, whereas others, like nectar and fruit, may only be edible for a few weeks or days. Some foods are highly mobile, such as animal prey; others are sessile but distributed in small dense clusters, such as nectar and fruit, while still others are distributed over a large area, such as grasses and herbivores. Each of these food characteristics imposes specific demands on the behavior and cognition of foragers. On top of all this, the fact that food is not always predictably distributed across space and time adds an additional layer of complexity. In this chapter, we examine the ways in which the predictability of food can drive changes in four key aspects of behavior related to foraging: (1) Feeding specialization, (2) sampling and information use, (3) food defense, and (4) movement patterns. We then discuss strategies that individuals may use to make food more predictable, such as agriculture in humans or hoarding of food in rodents and birds. We begin by considering what food predictability means.

62.2 Defining Food Predictability

In foraging theory, food is considered predictable if an individual can make an accurate estimate of its location, quality, and/or quantity based on factors such as season, time of day, landmarks, or temperature (Stephens and Krebs 1986). Given this definition, it would be difficult to define a given food source in absolute terms as "predictable" or "unpredictable," because this depends on the forager's ability to perceive the cues that provide information about food. While humans may be able to communicate the degree to which they perceive food to be predictable ("on Saturday the farmer's market

S.E. Overington (✉)
Department of Biology, McGill University, 1205 Avenue Docteur Penfield, Montreal, Quebec, Canada H3A 1B1
e-mail: sarah.overington@mcgill.ca

will be open unless it rains"), it is much more difficult to determine whether or not other animals have the information necessary to predict the quantity, quality, or location of food. Nonetheless, we expect that if food is stable through time and in space (Fig. 62.1A), a forager should consider it to be more predictable than if it appears, like seeds in desert environments, in patches that depend on where and when it happens to rain (Fig. 62.1B). Anthropogenic food sources – such as a well-stocked birdfeeder – are examples of highly predictable food.

The availability of food may change over many different time scales, from minutes to decades. Although this means that food is not consistently available at a given time or at a given place, this variability may be generally predictable (Fig. 62.1A). Cherry trees bloom in the springtime; apples mature on their trees in autumn; millions of ungulates move across the Western Serengeti in Africa in late May, as the local habitat dries up. Foragers can plan their yearly activities based on the availability of these food sources, and it is reasonable to assume that foragers can predict that many flowers will bloom in the springtime. On the other hand, there are many unpredictable qualities of these foods (Fig. 62.1B). For example, individual hunters may not be able to predict when and where the best feeding opportunities will arise within the great ungulate migration. Although fruit trees may ripen in the fall, they may not be perfectly synchronized. If they are far apart from each other, foragers may not be able to predict the best location for finding food at a given time. In nature, nothing is perfectly predictable. In this chapter, we consider predictability as a continuum
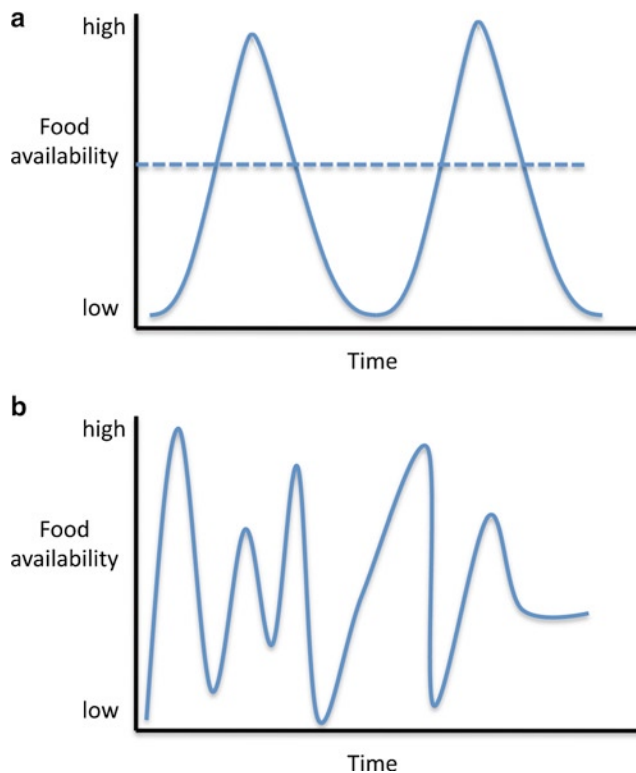
Fig. 62.1 A general overview of the way food availability may change through time. This figure illustrates several ways that food may vary through time. Food availability may be consistent throughout the year (**a**, *dashed line*), or it may vary in a predictable (**a**, *solid line*) or unpredictable manner (**b**). For examples, please see main text

and base our discussion on the relative predictability of one food type compared to another. Using historical, natural, experimental, and theoretical examples, we will examine how changes to the relative predictability of food influence foraging behavior. Given the great diversity of food types and the difficulty in classifying a food as "predictable," "unpredictable," "variable," or "stable," we strive to present examples as clearly as possible and to rely on the researchers' definitions of these terms. We explore these definitions in more detail in a box devoted to the topic ("Key facts on defining food unpredictability").

62.3 Jack-of-All-Trades, Master of None? Feeding Specialization and Food Predictability

In the neotropics, army ants (*Labidus praedator*) flush other insects from their hiding places as they move across the landscape. When a raid begins, birds that are nearby get an easy meal, plucking startled insects from the ants' wake. Although this is a very efficient way for the birds to feed, none of them rely entirely on this ant species, because the timing and size of raids are very unpredictable (Dobbs and Martin 1998).

When food is predictable, foragers may optimize their feeding efficiency by specializing on one type of food. Some animals have evolved feeding structures that are uniquely adapted to their preferred foods. Hummingbirds, for example, are highly efficient at extracting nectar from flowers due to their elongated bills. Anteaters have modified snouts to feed exclusively on ants and termites. Animals may also develop specialized behavioral patterns. A striking example is the use of tools by New Caledonian crows (*Corvus moneduloides*). These birds feed on insects, but cannot reach their bills deep enough into tree bark to extract prey. Instead, they make tools out of stiff Pandanus leaves and *Cunonia vieillardii* twigs to reach into crevices (Hunt and Gray 2004). It is generally assumed that with specialization comes increased efficiency (Bernays 1999). Social insects (e.g., ants, bees) provide examples of this; the efficiency of caste specialization is presumed to be a major factor in driving their success (Chittka and Muller 2009).

Specialists may be highly efficient at foraging on their preferred food type, but they are also dependent on this food type being consistently available. The trade-off between generalist and specialist foraging strategies is illustrated in Fig. 62.2. When the availability of a particular food is unpredictable, it may be better to compromise feeding efficiency and instead broaden the diet, thereby increasing the probability of finding suitable food. In a field study of hummingbirds, Pimm (1978) demonstrated that some individuals began to eat a wider variety of nectars when feeders were stocked in an unpredictable manner. Another example comes from Darwin's finches on the Galapagos Islands. In the early 1980s, there was a period of unusually heavy rains followed by many years of severe drought. This unpredictable climatic fluctuation served as a natural experiment on the islands. In a study of young birds born around the time of this transition, Grant and Grant (1989) found that the only individuals that survived the drought were those that used a wide variety of feeding techniques; birds that did not shift their behavior died. Thus, by expanding their feeding repertoire they were able to thrive despite the unpredictable food availability. The relationship between generalism and unpredictability appears to hold true in many systems. In plant-pollinator communities in California, areas with variable (and unpredictable) climatic conditions contain a greater proportion of generalist species (Moldenke 1975). For Platyhelminth monogeneans, a group of parasites that live on the gills and skin of fish, specialization on a single host species appears to be linked to the degree to which the host species is predictably available (Simkova et al. 2006). Even human societies may broaden their usual diets when unpredictable events lead to resource scarcity (e.g., Harris and Mohammed 2003).

Fig. 62.2 Potential trade-offs between feeding specialization and feeding generalizm. Although specialists may be more efficient at feeding on their preferred food type (**a**), they are dependent on the availability of that food for successful foraging. Part (**b**) illustrates the presumed costs and benefits of specialization vs. generalism: As the abundance of food type B increases, specialists on that food type will be highly successful. Generalists do not forage as efficiently, but their foraging success is independent of the fluctuations in food type B because they can find other food
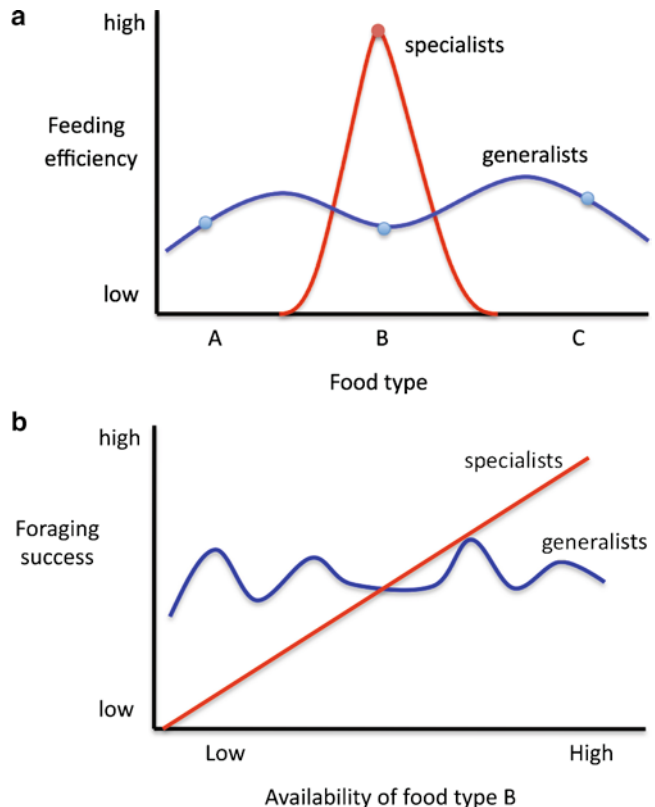
An individual's diet breadth may also change based on early experience, as demonstrated by an experiment carried out by Gray (1981). In this experiment, the predictability of food given to young white-footed mice (*Peromyscus leucopus*) was manipulated. One group received a constant diet of Brazil nuts, shredded coconut, oatmeal, and sesame seeds. The other group was given a different amount of one of these food types, chosen randomly, each day. When the mice were 3 months old, their food preferences were tested. Individuals who had been raised on the fluctuating food types chose a much greater diversity of foods than those raised in a stable environment, supporting the prediction that fluctuating (unpredictable) food conditions can lead individuals to widen their diet breadth. This strategy might also carry over into reproductive decisions. In some species, mothers "hedge their bets" when the environment is unpredictable by producing offspring that show a greater variety of sizes, increasing the chances that at least one of the offspring will be able to live under whatever environmental conditions arise (Crean and Marshall 2009).

62.4 Models of Feeding Specialization and Food Unpredictability

The idea that individuals should be generalists when food is variable and/or unpredictable is well supported in theoretical biology. Classic models by Levins and MacArthur established that environmental instability is one factor that limits the degree to which species can specialize (e.g., MacArthur and Levins 1967). Lynch and Gabriel (1987) focused on the effect of environmental variability on tolerance curves, graphical representations of the types of environmental conditions an organism can

withstand. In this model, the variance of a given environmental state could increase or decrease around a mean value. They noted that when temporal environmental variance is high, genotypes with a broad tolerance are favored. We would expect that an even broader tolerance would result from a variable, unpredictable resource.

Given that so many species feed in flocks, schools, or other social groups, game theory can also be a useful theoretical tool for determining the best strategy that an individual should use in a given situation. In this type of model, we assume that individuals behave in a way that maximizes their "payoffs," which may represent either the energetic gains for each individual or their fitness gains depending on the time scale we are interested in (i.e., within one generation, or over multiple generations). We can then describe alternate behavioral strategies that individuals in the population may use. We recently used this approach to examine the way in which unpredictability influences foraging behavior (Overington et al. 2008). We considered a situation in which there were two different types of food in the environment, and two different feeding strategies: Specialists that could eat only one food type, and generalists that could eat both. In this simple situation, we would expect that all individuals should be generalists, because this would allow them to eat whatever food they encountered. When we varied food predictability in our model, the results changed. Specialists were modeled to be much more efficient than generalists at feeding on their preferred food type. Thus, we found that when food was entirely predictable, the proportion of specialists in the population was 90%. As food became less predictable, however, this proportion decreased steadily until specialists made up just over 50% of the population, despite their much greater feeding efficiency (Fig. 62.3). It is important to note that in this model all types of food were always available, though their predictability and abundance varied. In reality, unpredictable food types may sometimes be entirely unavailable. In this case, only generalists would survive and all specialists would perish. Thus, the situation described in our model and in Fig. 62.3 is a conservative one.
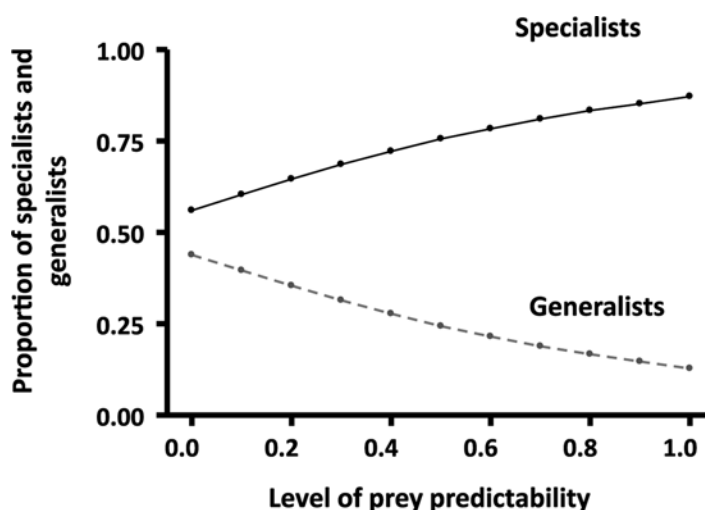
Fig. 62.3 Outcome of a game theory model testing the effects of food predictability on the proportion of specialist feeders in a population. The results of a game theory model testing the optimal feeding strategy as a function of food (prey) predictability. This figure shows that for each value of prey predictability, from 0 (completely unpredictable) to 1 (completely predictable) the population reaches an equilibrium proportion of specialists and generalists. Despite a significant advantage in terms of feeding efficiency for specialists, generalists make up almost 50% of the population when food is unpredictable. For details of the model, see main text (Reproduced from Overington et al. (2008). With permission)

62.5 Constraints on Feeding Specialization or Generalism

Although both theoretical and empirical evidence shows that individuals should generalize when food is unpredictable, the transition from specialization to generalism may not always be possible within one individual's lifetime. While a specialist may use innate behavior to locate prey, a generalist must be able to recognize a wider range of food types and adjust foraging behavior accordingly. This kind of behavioral flexibility presents both physical and cognitive challenges for individuals.

If we return to the example of the hummingbird, the physical challenges of generalizing are clear. If a competing species takes all of the birds' preferred flowers, it may be able to switch to a new flower type to find nectar. But if a sudden drought wipes out all flowers, its small size and specialized bill limit its ability to switch to a different food type. In some cases, physical limitations can be overcome through behavioral flexibility. The woodpecker finch of the Galapagos Islands provides an elegant example. This bird sometimes uses small twigs or cactus spines to extract insects from tree bark by holding the tool in its bill. Tebbich and colleagues (2002) observed birds in two locations on Santa Cruz, one of the islands of the Galapagos archipelago off the coast of Ecuador. One site had abundant and consistently available food, while the other had less food overall, and highly variable amounts of different food types. Through field observations at these sites, they found that birds living at the less predictable site used tools much more frequently than birds living in the predictable habitat. Although tool-use takes more time and energy than just using the bill to get food, this behavior allows individuals in less predictable habitats to eat a wider variety of food.

There may also be cognitive limits to feeding flexibility. Cognition includes many of the processes that allow individuals to interact with the environment, such as perception, learning, and memory (Shettleworth 1998). All else being equal, an individual that uses a wider variety of feeding techniques will need to assess a wider variety of foods and make a greater variety of decisions about when, where, and how to forage than a specialist. Bumblebees (*Bombus impatiens*), for instance, take longer to learn the most efficient foraging techniques when they are feeding on a greater variety of flowers (Dukas and Real 1993). For cabbage butterflies (*Pieris rapae*), learning about a new flower type decreases their ability to feed on a flower type they have eaten in the past (Lewis 1986). Empirical studies support the idea that species that are able to feed on a wider variety of foods have greater cognitive capacity than those that specialize. In birds and primates, the frequency of novel feeding behavior reported for a species is positively correlated with brain size, after taking into account body size (Lefebvre et al. 1997; Reader and Laland 2002). In bats, species that use a wider variety of hunting techniques have greater relative brain volumes than those using fewer techniques (Ratcliffe et al. 2006), and a study of 24 mammalian species found that behavioral repertoire was positively correlated with relative brain size (Changizi 2003). Indeed, feeding flexibility and the ability to innovate are central to one of the major hypotheses for increases in brain size across species, and unpredictable food sources may play a role in brain size evolution.

62.6 Finding Out About Food: Sampling and Social Information

In this chapter, we consider food to be predictable if an individual can estimate with a high probability the location, quality, and/or quantity of food based on environmental cues. Within this definition, there are different ways we might consider predictability. First, the environment may vary in a random manner, thus being unpredictable for everyone. Alternatively, an individual may enter a new, unfamiliar habitat that is highly variable, but where locals can predict food availability. These two forms of predictability can have important consequences for the way in which individuals use information – their own, or that of others.

In sea birds such as kittiwakes, the location of food is driven by highly predictable tidal cycles, and experienced individuals use their local knowledge to find food by focusing their search adjusted to the season and time of day (Irons 1998). When individuals cannot predict the location, quality, or quantity of food available based on environmental cues, they may invest more of their time in exploring and testing out local areas to gain more information (Dall et al. 2005). Returning to an area that did not previously contain food is known as "sampling" (Shettleworth et al. 1988), and the frequency with which an individual samples is therefore the "sampling rate." When the quality or location of food is uncertain, individuals are expected to increase their sampling rates. Alternatively, individuals may look for information from others instead of through their own sampling (Hall and Kramer 2008). Consider the following scenario. You arrive in a new neighborhood, and you are looking for a place to buy bread. There are several stores that appear to sell bread, but you cannot judge their relative quality based on physical characteristics (e.g., the brightness of the sign or the cleanness of the windows), or previous knowledge of the company. In this case, you might instead compare how busy each place is, or the type of people entering and leaving each store. By doing this, you are relying on social information to reach your decision. This scenario is illustrated in Fig. 62.4. Many animals appear to shift to using social information when they do not have sufficient information to predict the location or quality of a food source.

The value of social information was demonstrated in a recent simulation model by Hancock and Milner-Gulland (2006). In this model, individual foragers move around a lattice containing cells that represent patches of a resource. Foragers use rules to decide where to move in each round of the simulation. The environment is heterogeneous, with each patch containing food of different value. This variability can be made unpredictable by changing the accuracy with which individuals can predict the direction of the nearest high-value cell, and thus the likelihood that they will move in the best direction. The authors found that when foragers could not predict the best patches on their own (i.e., they had an equal probability of moving to a high-value or low-value patch), social information could greatly increase foraging efficiency. In the model, social information was of the simplest kind: when another forager was in a good patch, they exerted a "pull" on others, attracting them to the same patch. When the authors added this simple social pull, all foragers were much more successful.
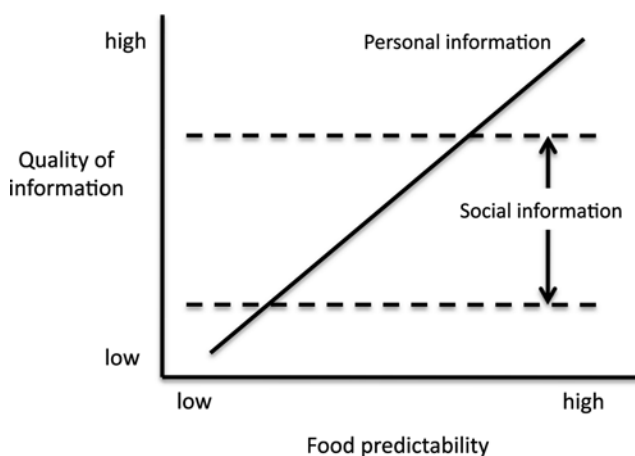
Fig. 62.4 The relative value of personal and social information when food is unpredictable. This figure illustrates the idea that as an individual is better able to predict the value or location of food, the value of his/her own information increases (we use a linear relationship here, but other relationships may also be valid). On the other hand, when they are unable to predict the location or quality of food, social information may be more valuable. The reliability of social information may be high (*upper line*) or low (*lower line*), thus changing the value of the information

Empirical evidence also shows that animals shift to using social information when they cannot predict the location of food. In an experimental study of blue jays (*Cyanocitta cristata*), McLinn and Stephens (2006) manipulated both food certainty and signal reliability. They gave individual birds two options for where to look for food: a green box, and a red box. In the "certain" condition, food was consistently found in the same colored box in each trial, whereas in the "uncertain" condition the food was randomly assigned to a given box, and the bird could not predict its location. The signal was a light that flashed when food could be found in, for example, the red box. The reliability of the signal was measured as the probability that it gave the correct information. Overall, they found that individuals relied on signals when the location of food was uncertain and signals provided accurate information. This result is not surprising and can likely be generalized. When the location or quality of food is unpredictable, individuals will rely on signals given by others, as long as those signals are reliable.

62.7 Defending Food

Once an animal finds food, it must decide whether it is better to expend energy searching for more food, or to have a guaranteed food source and expend some energy defending it against others. The relative value of these options may depend on both the spatial distribution of food (whether it is spread out or found in dense clusters) and its predictability. Resource Defense Theory (Brown 1964) provides a useful framework. This theory states that individuals should behave aggressively during feeding if this maximizes the energy they can obtain from the food source. Thus, an individual that is too aggressive when food cannot be defended would spend too much time fighting and not enough time eating. When food is predictable, an individual may benefit from guarding the area surrounding the food source, as the energetic costs of fighting will be paid back by consistent access to food. In contrast, if food is unpredictable, the individual may not be physically able to defend the food, as it will be impossible to be accurately positioned to defend food of which the location is unknown. The relative value of defending food increases with predictability, as illustrated in Fig. 62.5. It may also be impossible for the animal to assess whether the cost of fighting is worth the food reward. Thus, when food is unpredictable, foragers should be less aggressive toward one another.
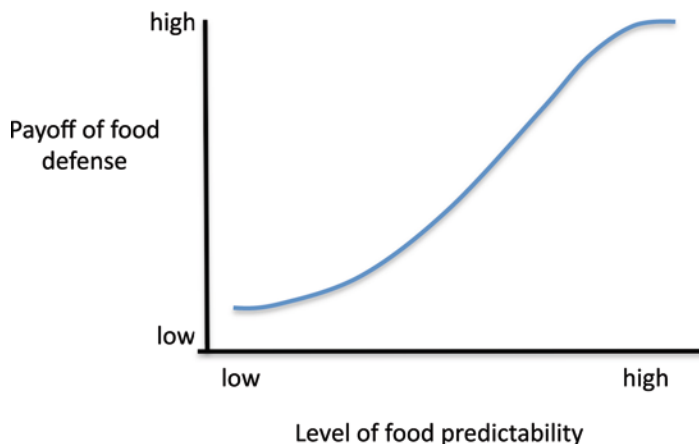
Fig. 62.5 The value of defending food as a function of food predictability. This figure illustrates the predictions of Resource Defense Theory (see main text and Definitions) as they relate to food predictability. As food becomes more predictable, the value of defending that food increases for an individual. As a result, we would expect that territorial defense would be more prevalent for animals feeding on a predictable, spatially clumped resource

An example of this principle in action is behavior of the Zenaida dove (*Zenaida aurita*) of Barbados. One population of these birds lives near a harbor, feeding on huge piles of spilled grain. The piles are abundant, but only available when there is overflow from a delivery – the timing of which is not predictable. Birds in this population do not defend territories, but instead feed close to one another in large aggregations. In almost all other areas of the island, mated pairs of Zenaida doves aggressively defend year-round territories. These birds forage on seeds that are uniformly distributed in the grass, and consistently available. Experimental manipulations of seed supplies at the harbor cause group-feeding doves to start defending their food. A small patch of seed provided every day at the same time and place leads to a large increase in aggression and a decrease in the number of doves that attempt to feed there. Conversely, the same amount of seed scattered over a wide area and provided at random times and in random places leads to the same nonaggressive aggregative feeding normally seen at the harbor (Goldberg et al. 2001).

Experiments in captivity also show that predictability leads to increased aggression. Dubois and Giraldeau (2004) recorded the aggressive behavior of nutmeg manikins (*Lonchura punctulata*) on a large feeding grid, where food was hidden in small holes at regular intervals. In some tests the holes containing food had clearly marked covers. In other tests, none of the holes were marked as containing food. Thus, in one case birds could predict the spatial distribution of food, and in the other they could not. Birds behaved much more aggressively toward one another when food was predictable than when it was unpredictable. However, this aggressiveness decreased when food was in very high density, whether it was predictable or not. When food is found in high densities, it is often uneconomic to defend because it attracts too many competitors arriving from all directions.

A classic model approach to understanding aggressive interactions between individuals is the "hawk–dove" game theory paradigm. In the foraging version of this game, two foragers arrive at a resource at the same time, and each contestant has the same two possible strategies (hawk or dove). Imagine two students arriving late to a dessert table to find that there is only one remaining piece of cake. The hawk strategy would involve fighting for the piece of cake, and either winning or losing the entire piece. The dove strategy would split the piece of cake in two so that each student gets half. Of course, the success of each strategy depends on what other individuals are doing. If most students are doves, a hawk could be very successful because he or she would be likely to win the fight for the cake. If everyone fights for the cake, the chance of actually winning the fight might be low and the costs of fighting (e.g., physical injury) could be high. This hawk–dove game can be seen as a way of predicting the conditions under which individuals should defend their food against others. In a recent modification of the basic hawk–dove model, we found that food predictability can influence the proportion of hawks and doves in a population. In this model, we maintained a relatively low cost of fighting. Even so, the proportion of individuals using the hawk strategy increased as food became more predictable, and decreased when it was unpredictable (Overington et al. 2008).

62.8 The Effects of Food Predictability on Movement Patterns

If an individual plans to spend her entire life in one location, she must be sure that there is sufficient food to sustain her. If food is abundant and predictable, a sedentary lifestyle allows individuals to invest their energy in maintaining their home, and they may also defend their resources against intruders. On the other hand, when food is unpredictable, individuals may not have the option of becoming sedentary. A possible example of this principle is the invention of agriculture (the Neolithic Revolution) around 10,000 years ago. Although the reasons for this transition are still under debate (Weisdorf 2005), it is clear that through the domestication of plants and animals – and

the creation of a predictable, abundant food supply – humans were able to adopt a sedentary lifestyle. Indeed, differences in the nomadic tendencies of many species can be closely tied to the availability of food.

Many animals migrate toward the equator as temperatures drop and their preferred food becomes less abundant. The decision to migrate may depend on both the variability and the predictability of food. For example, trout begin their migration when environmental cues suggest that conditions will soon shift toward unpredictability (Ovidio et al. 1998). Migratory behavior varies widely among species of birds, and even among populations of a single species. One pattern that has been observed is called "leap-frog" migration, in which birds such as Dunlins (*Calidris alpina*) that breed in the Northern part of the species range migrate further South in the winter that birds living closer to the mid-point range. Alerstam and Hogstedt (1980) suggested that this could be driven by the unpredictability of the start of spring in temperate regions. They argued that the timing of spring is more predictable in the more Northern zones, allowing birds to time their return based on cues such as light. On the other hand, the arrival of spring in temperate zones is less predictable. Because birds that breed in the temperate part of the range have greater competition for nest sites and cannot accurately predict when spring will arrive, they must stay relatively close by to time their migration. If this is indeed the case, then predictability could be an important ecological factor driving the variation in migratory behavior within some bird populations.

The predictability of food can drive yearly movement patterns, like migration, but it can also influence movement on shorter timescales. Along the coast of Australia, waves batter the shore. At midshore levels wetting is driven by tidal cycles and is therefore relatively predictable. In the highest parts of the intertidal zone, the temporal and spatial patterns of wetting are unpredictable, changing based on weather patterns. Some animals, such as the periwinkle (*Littorina unifasciata*), must wait to be submersed in water to feed, and in these high intertidal zones they cannot predict when they will be submersed. Accordingly, periwinkles in the highest areas have highly variable feeding behavior, changing the direction and distance they move while foraging much more than snails in more predictable sites (Chapman 2000). On a smaller spatial scale, coral reefs can be variable environments, with some parts of a reef containing more predictable food sources than do others. Ongoing research by Katrine Turgeon and colleagues suggests that longfin and dusky damselfish (*Stegastes diencaeus and S. adustus*) seek out these predictable habitats, and that males with high-quality territories (with predictable access to food) have greater reproductive success (K. Turgeon, personal communication).

In addition to these field observations, there is also experimental evidence that food predictability influences movement. European starlings (*Sturnus vulgaris*) that are unexpectedly shifted to a new, less desirable food source will reduce the amount of food they eat and spend more time exploring the environment for other options (Freidin et al. 2009).

62.9 Making Food Predictable (Hoarding, Caching, Agriculture)

Not all animals track changes in food supply by moving. Instead, some deal with unpredictable food by making them more predictable. The Neolithic Revolution can be viewed in this way; by growing plants and domesticating animals approximately 10,000 years ago, humans were able to create predictable sources of food. Similarly, the damselfish we described above increase the predictability of their food patches by cultivating algae on their territories within the coral reef (Hata and Kato 2006).

Some animals respond to variable and unpredictable food sources by hoarding or caching food when it is abundant. Squirrels, chipmunks, and many birds gather seeds and nuts to store for the winter when these foods will not be available. If the variability of food were perfectly predictable, individuals would be able to store just the optimal amount of food before winter. However, the timing and location of re-appearance of food after the winter varies each year, and individuals must store as much as they can to account for this unpredictability.

Individuals might also build up fat reserves to prepare for times of low food availability, and there is evidence that they may over-store when conditions seem less predictable. Although Great tits (*Parus major*) are very small (around 20 g), these birds thrive in Britain throughout the year and therefore deal with large climatic fluctuations. In an experimental study, Bednekoff and Krebs (1995) found that birds gain more mass when their access to food is unpredictable, even when the overall amount of food is controlled for. This seems to be true for many small passerines in Northern climates. In a study of Dark-eyed juncos (*Junco hyemalis*), Rogers and Reed (2003) found that birds increased their fat storage when temperature dropped faster than expected, and when there was more snowfall than usual. They interpreted these observations as evidence that birds-stored more fat – which is energetically costly for them to carry around – when there are unexpectedly sudden changes in temperature, suggesting that food availability will be less predictable than usual.

62.10 Costs of Food Unpredictability

Based on the topics discussed in this chapter, we would expect that food predictability could have far-reaching consequences for the health of humans and other animals, as, in theory, unpredictable food should drive individuals to: (a) eat a wider variety of foods, potentially giving up the advantages of specialization; (b) spend more time watching and learning from others; (c) share their food instead of defending it for themselves; (d) increase movement and exploration of the landscape; and/or (e) invest in storing or hoarding food to deal with periods of food shortage. All of these may have energetic costs for individuals, potentially influencing health and reproduction.

The direct costs of food unpredictability on health have been documented for a range of species. For example, brown capuchin monkeys (*Cebus apella*) that are fed on a predictable schedule are more active, more social, and less tense than those that are not (Ulyan et al. 2006). As illustrated above, physiological traits such as body mass may also be affected by food unpredictability. Small passerines are able to build up excess body mass to compensate for unpredictability of food during the winter months (Bednekoff and Krebs 1995). On the other hand, quail (*Coturnix c. japonica*), hooded crows (*Corvus cornix*) and magpies (*Pica pica*) all lose body mass when they are fed on an unpredictable food cycle, even when the total amount of food is controlled (Acquarone et al. 2002; Boon et al. 1999; Cucco et al. 2002). In magpies, unpredictable feeding also leads to decreased levels of haematocrit and lowered T-lymphocyte cell-mediated immune response (Cucco et al. 2002). Food predictability also appears to affect the timing of reproduction in birds, with birds in less predictable environments breeding later in the season (Bridge et al. 2009).

Natural variation in human food supplies across the globe suggests that food predictability affects the well being of human populations both psychologically and physiologically. In a study of folktales in human cultures, Cohen (1990) found that tales written during times of food unpredictability included more capricious aggression, and saw this as a reflection of increased social unrest. As evidenced by the chapters in this volume, food availability (or the lack thereof) has major impacts on human health, and the prospect of local food scarcity is therefore an important concern.

62.11 Applications to Other Areas of Health and Disease

Diet seems to be closely linked to the evolution of our own species. The metabolic demands of a large brain may have necessitated dietary shifts toward sufficiently nutrient-rich foods (Leonard, this volume). When food is unpredictable but nutritional demands are high, there is a great deal of pressure to increase the efficiency of techniques to find, capture, and process foods. In this chapter, we have seen that food unpredictability can favor group foraging, a generalist diet and flexible, innovative strategies of opportunistic feeding. These behavioral strategies may also be cognitively demanding; both innovativeness (Reader and Laland 2002) and group living (Dunbar and Shultz 2007) are associated with increasing size of the cortex in nonhuman primates. Many of these traits have been pushed to extremes in humans, and it has been proposed that resource predictability may thus be an important factor to consider in human evolution. For instance, Richerson and Boyd (2000) have proposed that climate unpredictability has been one of the major drivers of both neural and cultural evolution in humans. "Since the late Miocene," they write, "organisms have had to cope with increasing variability in many environmental parameters at time scales on which strategies for phenotypic flexibility would be highly adaptive (…) The largest increases in encephalization per unit time by far is the shift from Miocene and Pliocene species to modern ones, coinciding with the Pleistocene climate deterioration." Ideas like these are necessarily a bit speculative, but it is difficult to apply to humans the methods on which most of this chapter is based: experimental manipulations of food predictability cannot be conducted on human populations for obvious reasons, and comparative interspecific comparisons are impossible because there is only one extant hominin species.

Food unpredictability may also be relevant to the study of food-borne diseases. If animals faced with unpredictable food distributions should be opportunistic, innovative generalists, they also face the associated risks of food poisoning and exposure to a wider array of pathogens because of their broad, flexible diets. A carrion or leaf specialist can more easily evolve defenses against bacteria, parasites and plant toxins than can a species exposed to a wide diversity of pathogens that change frequently. This idea is supported by the results of a recent study by Garamszegi et al. (2007), in which the authors found that highly innovative bird species (based on the number of reports of innovative feeding behavior in the literature) also had higher blood parasite loads and larger immune organs than less innovative species. Path analysis suggests that innovative feeding behavior exerts increased demands on the immune system.

Flexible, generalist, feeding behavior may also increase the risk of contracting specific diseases, such as salmonellosis (Tizard 2004), or mycoplasmal conjunctivitis (Fischer et al. 1997) in birds. Although extension of these results to humans is difficult, in part because of the methodological limitations mentioned above, we can nevertheless predict that exposure to a wide and frequently changing array of pathogens and food toxins has had a strong influence on mortality patterns in our hominid past, as well as the evolution of our immune systems.

On a more contemporary note, the importance of predictable access to food for human populations is well documented by nutritionists (e.g., this volume). However, it is important to consider the fact that humans form part of a global food web, and that many of our food sources are themselves predators. Thus, as development and deforestation lead to massive changes in the environment, food sources become less predictable for many species. As food becomes less predictable, this can cause species to change their behavior patterns either through behavioral flexibility or on evolutionary timescales (as described throughout this chapter), or may ultimately lead to extinction. The ideas laid out in this chapter can provide a predictive framework for how species will deal with these changes. For example, we would expect that highly specialized species will have more difficulty than generalists in adjusting to less predictable conditions. Species that are able to feed in groups (e.g., pigeons)

may be better able to take advantage of clumped resources (e.g., garbage piles) than species that defend exclusive territories. Depending on where they are found, mobile species will be able to seek out better conditions, while sessile species are more limited. All of these patterns, in turn, have consequences for the human food supply.

Box 62.1 Key facts on human foraging behavior in an ecological context

1. Foraging behavior can be defined such that it includes all aspects of feeding behavior, from searching for food, handling food, to ingesting food.
2. Under this definition, all food decisions including, for example, food purchases can be considered components of foraging in the broadest sense.
3. Differences in human foraging behavior can be studied at different scales, from the individual to the whole species level.
4. Foraging behavior in humans can vary along several axes, including (1) degree of food specialization, (2) amount of movement and travel required to find food, (3) type of information used to find food or make feeding decisions, and (4) the degree to which food can be monopolized or defended.
5. Some aspects of foraging behavior are limited by biology; there are some foods that humans cannot digest.
6. Many aspects of human foraging behavior are flexible, and can be adjusted based on current conditions and food availability.
7. Many species arrive at similar ways of dealing with similar ecological conditions, either through behavioral flexibility or convergent evolution. It can therefore be useful to compare some aspects of human behavior to that of other animals. This need not imply that our behavior is determined by genetics or even by ecology, but it may provide some insight into food decisions of individuals.
8. In this chapter, we focus on food unpredictability. When food is unpredictable, the foraging behavior that is optimal may change (see Table 62.1), and humans can adjust themselves accordingly. Many of these changes can occur within an individual's lifetime. For example, when food is unpredictable or scarce, a greater variety of foods may be incorporated into the diet.

Table 62.1 Predicted effects of food unpredictability on foraging behavior

Aspect of foraging behavior	Effects of increasing unpredictability	Illustrative examples
Feeding specialization	Shift from specialist to generalist feeding	Parasites (Simkova et al. 2006), hummingbirds (Pimm 1978), mice (Gray 1981)
Sampling and information use	Increase sampling rate	Pigeons (Shettleworth et al. 1988)
	Increase reliance on social information	Blue jays (McLinn and Stephens 2006)
Food defense	Less food defense and aggression	Zenaida doves (Goldberg et al. 2001)
Movement patterns	Greater exploration and movement	Periwinkle (Chapman 2000)

This table summarizes four ways in which food unpredictability can shift foraging behavior in a range of species, and provides an example of each of these shifts

Box 62.2 Key facts on defining food unpredictability

Experimental studies of the effects of food predictability require an operational definition of predictability. In this box, we describe a series of studies, some of which are also covered in the main text, and highlight the way in which the authors have defined unpredictability.

A recent experimental study with humans showed that food rewards (juice and water) had a greater influence on brain activity when they were unpredictable (Berns et al. 2001). In this study, the rewards were considered predictable when a drink was given every 10 s, and juice and water were alternated. In the unpredictable treatment, the interval between rewards was randomized, as was the order of juice and water. This is similar to a study of hooded crows (*Corvus cornix*) in which unpredictable feeding schedules was linked to greater fluctuations in weight and lower overall weight (Acquarone et al. 2002). In one experiment, some individuals were fed 100 g of food per day, while others were given a different amount each day, though the average amount of food was 100 g/day. In a second experiment, both the amount of food and the timing of feeding each day were randomly assigned for the unpredictable group, while the predictable group was fed the same amount of food (in this case, 150 g) at the same time each day. This same approach was used in study of magpies in which food predictability was shown to have negative impacts on immune responses (Cucco et al. 2002).

Given that stereotypic behavior is known to be a problem in captive animals, some studies have sought to test whether unpredictability of feeding schedules or food types are preferred. This was tested in a recent study on pigs (De Jonge et al. 2008), in which individuals were first trained on a feeding device, and then given choices between predictable and unpredictable feeding, in terms of (a) the amount of time before they received the food after activating the task and (b) the type of food reward they received. In each case, the variable (time/type of food) was chosen randomly in the unpredictable treatment, while it was kept constant in the predictable treatment. Overall, subjects preferred the predictable choices.

Another way to define predictability is by manipulating the information available to an individual. Two studies discussed in this chapter have used this approach (nutmeg manikins, Dubois and Giraldeau 2004; blue jays, McLinn and Stephens 2006). In these studies, individuals may either learn that a particular color signals the location of food (predictable), or that the color of the signal is unrelated to the location of food (unpredictable).

Summary Points

- The spatial and temporal distribution of food plays an important role in shaping individual behavior.
- When the spatial and temporal distribution of food is unpredictable, there are a number of ways that individuals should shift their behavior to maximize feeding efficiency.
- Although specialists can be more efficient at finding/processing food, they suffer a cost when their preferred food source is unpredictable. Thus, food unpredictability favors feeding generalism.
- When individuals cannot predict the location or quality of food, they may increase their sampling of the environment to gain information. Alternatively, they may rely on information from others.
- Food predictability may influence movement patterns of individuals across many spatial scales.
- Unpredictable food is unlikely to be defendable against others. Thus, food predictability can play a role in the degree to which animals aggressively defend territories or search and feed instead in unaggressive groups.

- Agriculture, food hoarding, and excess fat storage are all strategies to make food more predictable.
- Food predictability may have direct effects on health, increasing stress levels and decreasing immune responses.

Definitions

Foraging: In the broadest sense, foraging involves the search, capture, handling, and ingestion of food.

Food abundance: The amount of a given food type which is available in a given section of the environment.

Food variability: The degree to which the location, quality or quantity of a given food type fluctuates through time or space.

Food predictability: The degree to which an individual can accurately estimate the location, quality, or quantity of food, before actually sampling the food, using information from the physical or social environment.

Food distribution: The manner in which food is spread throughout the environment.

Spatial food distribution: The location and density of food in different parts of the environment.

Temporal food distribution: The changes over time in presence and/or density of food in different parts of the environment.

Feeding specialist: An individual/species whose diet is composed of very few or even a single food type.

Feeding generalist: An individual/species whose diet encompasses many different types of food.

Feeding flexibility: The degree to which an individual/species is able to change the types of food it eats or the foraging techniques it uses.

Resource defense theory: Introduced by Brown (1964), this theory states that individuals will only fight aggressively for a resource (i.e., food, access to mates) if this allows the individual to retain the benefits from that resource that outweigh the costs of aggression. RDT provides a predictive framework for the evolution of territorial defense.

Opportunism: The speed with which an animal searching for or exploiting one food type can shift to another food type when physical or social cues about its immediate availability arise.

References

Acquarone C, Cucco M, Cauli SL, Malacarne G. Ibis. 2002;144:E155–63.
Alerstam T, Hogstedt G. Ornis Scand. 1980;11:196–200.
Bednekoff PA, Krebs JR. Funct Ecol. 1995;9:457–62.
Bernays EA. Ann Entomol Soc Am. 1999;92:944–51.
Berns GS, McClure SM, Pagnoni G, Montague PR. J Neurosci. 2001;21:2793–8.

Boon P, Visser GH, Daan S. Neth J Zool. 1999;49:233–49.

Bridge ES, Schoech SJ, Bowman R, Wingfield JC. J Exp Zool A. 2009;311A:35–44.

Brown JL. Wilson Bull. 1964;76:160–9.

Changizi MA. J Theor Biol. 2003;220:157–68.

Chapman MG. Hydrobiologia. 2000;426:75–87.

Chittka L, Muller H. Comm Integr Biol. 2009;2:1–4.

Cohen A. Am Anthropol. 1990;92:474–9.

Crean AJ, Marshall DJ. Phil Trans Roy Soc B. 2009;364:1087–96.

Cucco M, Ottonelli R, Raviola M, Malacarne G. Acta Oecol. 2002;23:271–6.

Dall SRX, Giraldeau LA, Olsson O, McNamara JM, Stephens DW. Trends Ecol Evol. 2005;20:187–93.

De Jonge FH, Ooms M, Kuurman WW, Maes JHR, Spruijt BM. Appl Anim Behav Sci. 2008;114:93–104.

Dobbs RC, Martin PR. Wilson Bull. 1998;110:293–5.

Dubois F, Giraldeau LA. Anim Behav. 2004;68:21–5.

Dukas R, Real LA. Anim Behav. 1993;46:637–44.

Dunbar RIM, Shultz S. Science. 2007;317:1344–7.

Fischer JR, Stallknecht DE, Luttrell MP, Dhondt AA, Converse KA. Emerg Infect Dis. 1997;3:69–72.

Freidin E, Cuello MI, Kacelnik A. Anim Behav. 2009;77:857–65.

Garamszegi LZ, Erritzoe J, Moller AP. Biol J Linn Soc. 2007;90:441–55.

Goldberg JL, Grant JWA, Lefebvre L. Behav Ecol. 2001;12:490–5.

Grant BR, Grant PR. Am Nat. 1989;133:377–93.

Gray L. Genetic and experiential differences affecting foraging behavior. In: Kamil AC, Sargent TD, editors. Foraging behavior: ecological, ethological and psychological approaches. New York: Garland; 1981. pp. 455–73.

Hall CL, Kramer DL. Anim Behav. 2008;76:1609–19.

Hancock PA, Milner-Gulland EJ. Ecology. 2006;87:2094–102.

Harris FMA, Mohammed S. Ambio. 2003;32:24–9.

Hata H, Kato M. Biol Lett. 2006;2:593–6.

Hunt GR, Gray RD. Anim Cogn. 2004;7:114–20.

Irons DB. Ecology. 1998;79:647–55.

Lefebvre L, Whittle P, Lascaris E, Finkelstein A. Anim Behav. 1997;53:549–60.

Lewis AC. Science. 1986;232:863–5.

Lynch M, Gabriel W. Am Nat. 1987;129:283–303.

MacArthur R, Levins R. Am Nat. 1967;101:377–85.

McLinn CM, Stephens DW. Anim Behav. 2006;71:1119–29.

Moldenke AR. Oecologia. 1975;21:219–42.

Overington SE, Dubois F, Lefebvre L. Behav Ecol. 2008;19:836–41.

Ovidio M, Baras E, Goffaux D, Birtles C, Philippart JC. Hydrobiologia. 1998;372:263–74.

Pimm SL. Am Zool. 1978;18:797–808.

Ratcliffe JM, Fenton MB, Shettleworth SJ. Brain Behav Evol. 2006;67:165–76.

Reader SM, Laland KN. Proc Nat Acad Sci USA. 2002;99:4436–41.

Richerson PJ, Boyd R. In: Heyes C, Huber L, editors. The evolution of cognition. Cambridge: MIT; 2000. pp. 329–46.

Rogers CM, Reed AK. J Avian Biol. 2003;34:112–18.

Shettleworth SJ. Cognition, evolution, and behavior. New York: Oxford University Press; 1998.

Shettleworth SJ, Krebs JR, Stephens DW, Gibbon J. Anim Behav. 1988;36:87–105.

Simkova A, Verneau O, Gelnar M, Morand S. Evolution. 2006;60:1023–37.

Stephens DW, Krebs JR. In: Stephens DW, Krebs JR, editors. Foraging theory. Princeton: Princeton University Press; 1986. pp. 75–102.

Tebbich S, Taborsky M, Fessl B, Dvorak M. Ecol Lett. 2002;5:656–64.

Tizard I. Semin Avian Exot Pet. 2004;13:50–66.

Ulyan MJ, Burrows AE, Buzzell CA, Raghanti MA, Marcinkiewicz JL, Phillips KA. Appl Anim Behav Sci. 2006;101:154–60.

Weisdorf JL. J Econ Surv. 2005;19:561–86.

Chapter 63
The Impact of Family Meals on Diet and Food Behaviors

Sarah J. Woodruff and Rhona M. Hanning

63.1 Family Meals

Potential influences on healthy eating have recently garnered much research attention, particularly those that affect children and adolescents, given the high prevalence of overweight and obesity (Shields 2005; Ogden et al. 2006). Using the construct of social cognitive theory, individuals can be influenced by myriad factors, including the individual, interpersonal, organizational, community, and public policy. Very little is known about the influence of the family (i.e., interpersonal factor) on youth food intake and behaviors even though the family is the main socializing agent until adolescence. The family directly determines the physical and social environment which can ultimately influence behaviors, habits, and attitudes through socialization and modeling (Ritchie et al. 2005). In particular, one possible explanation/influence may include food availability and access. Parents/siblings have the potential to influence diet quality and food behaviors through demographics (e.g., socioeconomic status, food expenditures, education, or employment of parent/adolescent), behavior modeling (e.g., food preferences/aversions, modeling), the shared environment (e.g., food availability/supply, food rules, communication), and parenting style (e.g., use of food reward/restrictions) (Woodruff and Hanning 2008). Food per se or mealtimes are often a common forum for communication in the home and can be used as a health promotion and intervention strategy.

Given the importance of family influence on diet quality, one easy-to-measure variable that may be a proxy for family food behaviors is the family meal. The family meal is usually an occasion for communication and interaction among family members, in which all family members consume similar types of food. With regard to diet quality and food intake, Fig. 63.1 illustrates how family meals can potentially influence food intake and behaviors. The family meal (e.g., scheduling, food preparation/purchasing patterns, television use), individual characteristics (e.g., age, weight status, culture/race, schedules), and food-related behaviors (e.g., food availability/accessibility, vegetarianism, dieting status, fast food use) all interact to potentially influence food intake (Woodruff and Hanning 2008). However, not only can family meals potentially influence diet quality and food behaviors, but other health behaviors (e.g., physical activity, behaviors

S.J. Woodruff (✉)
Department of Kinesiology, University of Windsor, 401 Sunset Avenue, Windsor, Ontario N9B 3P4, Canada
e-mail: woodruff@uwindsor.ca
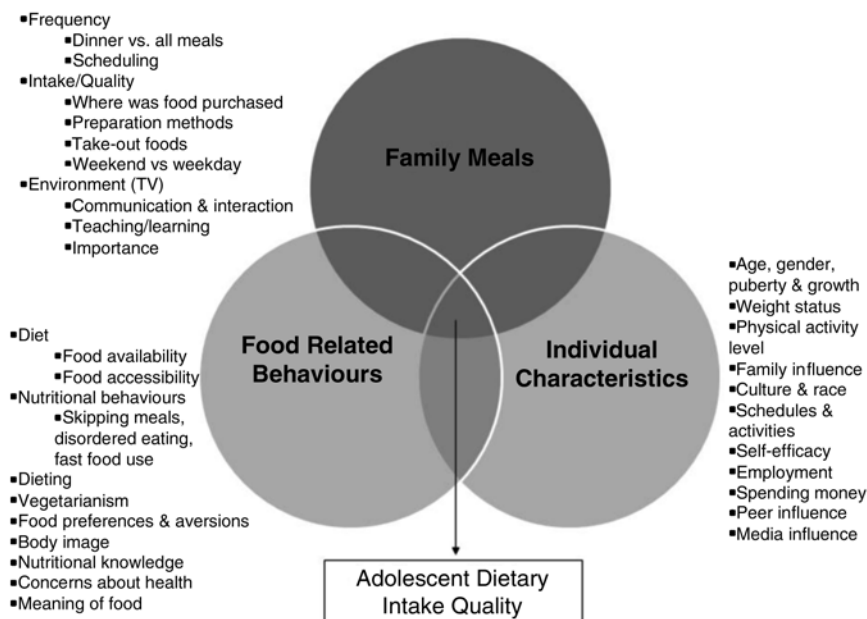
Fig. 63.1 Family meals, individual characteristics, and food related behaviours influence on diet quality. This figure depicts the influence of family meals, individual characteristics, and food related behaviours on adolescent dietary intake quality. Factors can work in isolation or can be inter related with others. Figure reprinted from: Woodruff SJ, Hanning RM. A Review of Family Meal Influence on Adolescents' Dietary Intake. Canadian Journal of Dietetic Practice and Research. 2008:69(1):14-22

leading to eating disorders/obesity, psychological adjustment, high-risk behaviors, and school performance) too.

63.2 Definition

Family meals can have many different meanings for each individual. Perhaps it invokes a blissful family image of everyone sitting happily around a large dining room table; for others it might be picking up something on the go and eating in the car on the way to soccer practice. Some families may have a special night of the week that is dedicated to a family ritual (e.g., pizza night or Sunday roast beef supper), while children and/or adolescents who live between two households, may have one ritual in one household and something completely different in the other. In an earlier focus group study among adolescents, Neumark-Sztainer et al. (2000) found that there were large variations in frequency of family meals, not only between participants but also within participants. Ever changing family demographics, busy schedules, and the development of convenience foods seem to have decreased the importance and/or frequency of family meals in today's society.

Defining family meals can be problematic as both individuals and researchers struggle with how to capture something that is so unique to each family. Table 63.1 lists the research definition of family meals by study, as some researchers have utilized the *dinner* meal (Gillman et al. 2000; Videon

Table 63.1   Key definitions of family meals

Dinner

- How often do you sit down with other members of your family to eat dinner or supper? (Gillman et al, 2000; Granner et al, 2004; Taveras et al, 2005)
- How many times was at least one parent was present when they ate their evening meal in the past seven days (Videon and Manning, 2003)
- How often do you sit down with other members of your family to eat dinner or supper?
- In the last 5 school days, how many times did all or most of your family living in your house eat an evening meal together? (Utter et al, 2008)
- The respondents reported the number of days in a typical week their family ate dinner together (Sen 2006 & 2009)
- How often they ate dinner together with their family (Custers and van den Bulck, 2009)s
- Typically, how many days per week do you eat dinner or supper with at least one parent? (Woodruff and Hanning, 2009a)

All meals

- During the last seven days, how many times did all, or most, of your house eat a meal together? (Neumark-Sztainer, 2003 & 2004; Burgess-Champoux et al, 2009; Eisenberg et al, 2009; Fulkerson et al, 2009)
- How often do you have breakfast/evening meal together with your mother or father? (Verzeletti et al, 2009)
- How often they ate breakfast/lunch together with their family (Custers and van den Bulck, 2009)

This table lists the research definition of family meals used by various studies.

and Manning 2003; Granner et al. 2004; Taveras et al. 2005; Veugelers et al. 2005; Utter et al. 2008; Sen 2009; Woodruff and Hanning 2009a) while others have included *eating breakfast* or *all meals* (Boutelle et al. 2001; Neumark-Sztainer et al. 2003; Eisenberg et al. 2004; Neumark-Sztainer et al. 2004; Marquis et al. 2005; Burgess-Champoux et al. 2009). This makes comparison across studies difficult; however, there is no reason to believe that the benefits of eating the evening meal together would differ from eating other meals and/or snacks together.

To avoid a nuclear family bias, researchers have also had to consider who must be in attendance in order to for a meal to be defined as a *family* meal. Various circumstances have been used within the literature (see Table 63.1), such as *when at least one parent is present* (Videon and Manning 2003; Woodruff and Hanning 2009a) or *when all or most of the family living in a house is there* (Neumark-Sztainer et al. 2003; Neumark-Sztainer et al. 2004; Utter et al. 2008; Burgess-Champoux et al. 2009; Sen 2009). The influence of including other members of a family (e.g., grandparents, aunts, and/or uncles) and/or friends has not been carefully examined. Some literature is emerging on the nutritional impact of *family-style* meals and/or social eating with friends, for example in lunch rooms at schools (Woodruff and Hanning 2009b) or in older adult facilities (Altus et al. 2002; Nijs et al. 2006).

63.3 Prevalence

Regular family meals (five or more meals per week) have been reported by 25–70% of children and adolescents and 11–44% report family meals on 2 or fewer days per week (see Table 63.2) (Gillman et al. 2000; Neumark-Sztainer et al. 2003; Videon and Manning 2003; Neumark-Sztainer et al. 2004; Veugelers et al. 2005; Sen 2006; Utter et al. 2008; Verzeletti et al. 2009; Burgess-Champoux et al. 2009; Custers and Van den Bulck 2009; Eisenberg et al. 2009; Fulkerson and Neumark-Sztainer et al. 2009; Sen 2009; Woodruff and Hanning 2009a). The large variation can be partly attributed to the age of participants from the different studies as family meal frequency seems to decline with

Table 63.2 Family meal frequency

Authors	N	Age	Study/Region	Family Meal Frequency
Gilman et al (2000)	16,202	9-14 yrs	Nurses' Health Study II (USA)	Everyday 35% Most days 40% Never/some 17%
Neumark-Sztainer et al (2003, 2004)	4,746	11-18 yrs	ProjectEat I (USA)	≥7 days 27% 3-6 days 40% ≤2 days 33%
Videon and Manning (2003)	18,777	11-21 yrs	National Longitudinal Study of Adolescent Health (USA)	6-7 days 48% 4-5 days 21% ≤ 3 days 31%
Veugelers et al (2005)	5,200	Grade 5	Nova Scotia (Canada)	≥5 days 57% 3-4 days 15% ≤2 days 28%
Utter et al (2008)	3,245	12-20 yrs	New Zealand	Everyday 42% 3-4 days 30% ≤2 days 28%
Verzeletti et al (2009)	14,407	11-16 yrs	Health Behavior in School-Aged Children Study (Belgium and Italy)	Not daily evening meal with parent: 37% (Belgium) and 22.5% (Italy)
Sen (2006, 2009)	5,014	12-15 yrs	National Longitudinal Survey of Youth (1997 data)	≥5 days 70% 3-4 days 14% ≤2 days 16%
Burgess-Champoux et al (2009)	677	T1 = 12 yrs T2 = 17 yrs	ProjectEat II (USA)	Regular at both times: 22% Regular at T1: 38% Regular at T2: 8% Not regular at both times: 32%
Custers and van den Bulck (2009)	710	Grade 7, 9, and 11	Belgium	Always 13% One meal/yr is not FM 20% >once/month 21% <once/month 28% Once/day without family 18%
Eisenberg et al (2009)	806	17 yrs	ProjectEat II (USA)	FM with TV 29% FM without TV 27% No regular FM 44%
Fulkerson et al (2009)	2,516	Middle and high school students	ProjectEat II (USA)	(T1) ≥3 days 66.5% (T1) 1-2 days 20% (T1) Never 13.5% (T2) ≥3 days 57% (T2) 1-2 days 26% (T2) Never 17%
Woodruff and Hanning (2009a)	3,223	Grade 6-8	Ontario and Nova Scotia (Canada)	6-7 days 70% 3-5 days 19% ≤2 days 11%

This table lists family meal frequency by individual study (including author, sample size and age, and geographical area). FM: family meal, T1: time 1/baseline, T2: time 2/follow-up.

increasing age (Gillman et al. 2000; Granner et al. 2004; Burgess-Champoux et al. 2009; Wurback et al. 2009). Further, it is interesting to note that the majority of studies have been conducted using one family member's account of meal time (usually the child or adolescent); yet when two family members are questioned, some discord exists between parent and child responses. Parents tend to report more regular family meals than adolescents (Boutelle et al. 2001; Fulkerson et al. 2006), while adolescents tend to report greater scheduling difficulties (Fulkerson et al. 2006). However, social

eating tends to be valued among children/adolescents and parents. Overwhelmingly, 89% of male and 93% of female young adults agree that eating together with family or friends is enjoyable and 76% of males and 82% of females believe it to be important to sit down and eat at least one meal a day with other people (friends or family) (Larson et al. 2009). Among adolescents (7th–12th grade), the majority (63%) and most of their parents (98%) reported the importance of eating a meal together as a family (Fulkerson et al. 2006).

The potential significance of family meals is that it passes on family traditions/values to the next generation. At the table, parents are able to act as role models, teach life lessons, and interact with their children in a meaningful way every day. Parents reported many benefits of family meals, including time for conversation, feelings of togetherness, shared nutrition, and ceremony (Fulkerson et al. 2008). Shared family meals can be a time for education. An earlier study investigating parents as role models reported that nutrition is often a topic of conversation at the dinner table (Gillespie and Achterburg 1989), which suggests that the dinner table can used as a teaching and learning environment (e.g., food and table manners, cooking/preparation techniques). Finally, parental modeling was specifically reported among low income adolescent girls, who consumed more calcium when they saw important others (mother, father, friends) drinking milk (Lee and Reicks 2003), which is similar to another study of daughters who eat fruits and vegetables modeled after their parents (Fisher et al. 2002).

Many health promotion/nutrition specialists are increasingly becoming aware of the importance of family meals. For example, in many countries (e.g., Malaysia, Thailand, Japan), family meals are promoted in their national food guide recommendations. Specifically, the *Dietary Guidelines for Japanese* suggests "happy eating makes for happy family life; sit down and eat together and talk; treasure family taste and home cooking," and the *Malaysian Nutrition Guide for Early Childhood Care* suggests "making mealtimes an enjoyable experience." Unfortunately, North American food guides seem to focus on specific food groups and serving sizes and tend to stay away from food behaviors.

63.4 Family Cohesion

As Story and Neumark-Sztainer (2006) wrote, "family meals have long been considered essential for the unity of the family and a symbol for family interactions" (p. 261). Regular family meals may be a proxy for family connectedness and cohesion as family members are spending time together at the table. Family meals often become ritualistic, and as earlier reported, "Family rituals and routines often reinforce the importance of family and its members" (Woodruff and Hanning 2008, p. 17). Families that have more frequent family meals also tend to have rules/rituals about other things, thereby creating greater family cohesion. In a large study (n = 81,247 of 9th–12th grade adolescents), family connectedness was a protective factor for disordered eating patterns (Croll et al. 2002), and according to data from the longitudinal (10 years) National Heart, Lung, and Blood Institute Growth and Health Study (NGHS), family meals during childhood were related to various health outcomes in adolescents through the mediating factors of family cohesion and coping skills (Franko et al. 2008). More frequent family meals during the first 3 years of the study predicted greater family cohesion and problem and emotion-focused coping in Years 7 and 8; family cohesion mediated family meals and risk of smoking in Year 10; and problem-focused coping mediated family meals and both stress and disordered eating-related attitudes and behaviors in Year 10 (Franko et al. 2008). Finally, measures of general family connectedness, priority of family meals, and positive mealtime environment were significantly positively associated with psychological wellbeing and inversely associated with depressive symptoms and unhealthy weight-control behaviors among an ethnically diverse sample of at-risk-for-overweight and overweight youths (n = 1,351 adolescents) (Fulkerson et al. 2007).

63.5 Obstacles

Anywhere from half to a third of children and adolescents do not have regular family meals. There are numerous potential reasons, but the most often cited reason for not eating together is lack of time due to work/sports/activity schedules (Neumark-Sztainer et al. 2000; Fulkerson et al. 2006; Larson et al. 2009). Other reasons for lack of family meals include: no time to cook/buy groceries, don't know how to cook (Fulkerson et al. 2006), family doesn't all like the same foods (Neumark-Sztainer et al. 2000; Fulkerson et al. 2008), healthy food takes longer to prepare (Fulkerson et al. 2006), can create hostile reactions (Fulkerson et al. 2006), shared meals are unpleasant due to dissatisfaction with family relationships (Neumark-Sztainer et al. 2000), teen desire for autonomy (Neumark-Sztainer et al. 2000) and/or that eating together is idealized, so therefore unattainable. Approximately 55% of adolescents and 79% of parents suggested that they somewhat or strongly agree that different schedules make it difficult for the family to eat meals together (Fulkerson et al. 2006). Among 50 employed parents, long hours and/or nonstandard hours and schedules were positively associated with take-out meals, missed family meals, choosing preprepared entrees, eating while working, restaurant meals, and missed breakfast (Devine et al. 2009). See Table 63.3 for suggestions for parents trying to increase the frequency of family meals.

63.6 Family Meals and Diet Quality

A recent systematic literature review identified that, in most studies, family meals were linked to higher overall diet quality (Woodruff and Hanning 2008). Specifically, research has shown that family meals are associated with higher intakes of fruit and vegetable (Gillman et al. 2000; Neumark-Sztainer et al. 2003; Videon and Manning 2003; Utter et al. 2008; Fulkerson et al. 2009), grains (Neumark-Sztainer et al. 2003), dairy (or calcium-rich) foods (Neumark-Sztainer et al. 2003; Videon and Manning 2003), proteins (Neumark-Sztainer et al. 2003), minerals (iron, folate, fiber; Gillman et al. 2003; Neumark-Sztainer et al. 2003), and vitamins (A, C, E, B_6, B_{12}; Gillman et al. 2003; Neumark-Sztainer et al. 2003). Furthermore, family meals have been negatively associated with having fried foods away from home (Gillman et al. 2000) and sugar sweetened beverages (Gillman et al. 2000; Neumark-Sztainer et al. 2003; Verzeletti et al. 2009; Woodruff and Hanning 2009a). Lastly, family meals were reported to be positively associated with overall diet quality, using various diet quality indices (Veugelers et al. 2005; Woodruff and Hanning, 2010).

Table 63.3 Suggestions for parents to increase family meal frequency

- Try to make family meals a priority
- Aim for at least 3-4 family meals/week
- Look for creative ways to increase family meals
- Avoid topics likely to lead to arguments at meals
- Plan ahead; know what you are having for dinner before dinner time
- Buy the groceries ahead of time, choose foods that will please everyone
- Start with one or two meals a week, gradually increase
- If dinner doesn't fit into schedules, try for breakfast
- Try to incorporate all family members into planning, preparing, and clean up
- Turn off the television
- Avoid contentious issues

This table lists key suggestions for parents trying to increase family meal frequency (some taken from Neumark-Sztainer, 2009a).

In the first longitudinal study of adolescent food behaviors, family meals during middle school were associated with healthier food behaviors (e.g., breakfast consumption, less fast food consumption) 5 years later (Burgess-Champoux et al. 2009). Further, family meal frequency during adolescence predicted higher intakes of fruit, vegetables, dark green and orange vegetables, more breakfast meals (females only), more frequent family meals, and lower intake of soft drinks during adulthood (Larson et al. 2007). Larson et al. (2007) advise that family meals during adolescence may have lasting positive influence on diet quality and meal patterns in young adulthood. Future research needs to investigate whether the positive influence persists into adulthood.

Finally, family meals may influence other food behaviors also (Woodruff and Hanning 2008). Family meals have been reported to be associated with consuming breakfast (Videon and Manning 2003; Utter et al. 2008; Fulkerson et al. 2009; Woodruff and Hanning 2009a), limiting soft drink and/or sugar sweetened beverage consumption (Gillman et al. 2000; Neumark-Sztainer et al. 2003; Verzeletti et al. 2009; Woodruff and Hanning 2009a), and having high self-efficacy for healthy eating (Woodruff and Hanning 2009a). We recently reported (Woodruff and Hanning 2009a) that participants who consumed breakfast (versus skipped breakfast) were likely to have higher dinner meal frequency (OR = 1.81) even after adjusting for dieting status and concerns of high body weight. Families who are more likely to eat dinner together may understand the importance of healthy food behaviors; thus they may be more likely to consume breakfast together (Woodruff and Hanning 2009a). Our work (2009a) also identified that participants who reported consuming soft drinks two to six times/week (OR = 1.54), once/week (OR = 1.93), once/month (OR = 1.94), or rarely/never (OR = 1.79) were likely to have a higher family meal frequency compared to those consuming soft drinks at least once/day. These results are similar to those from US studies, which also reported negative associations between family meal frequency and soft drink consumption (Gillman et al. 2000; Neumark-Sztainer et al. 2003; Verzeletti et al. 2009). It is possible that children and adolescents who consume more frequent family meals may also have family meal rules that prevent soft drink consumption (in favor of milk and/or water) during meals (Woodruff and Hanning 2009a).

63.7 Location and Environment

The location of family meals may be an important predictor of overall diet quality. When a meal is consumed at home with other family members present, most often some of the food consumed will be shared (although, not always) and therefore will be of similar quality. Alternatively, when food is consumed outside of the home (such as at a restaurant), each individual usually has their choice of what to eat and, therefore, overall quality of the meal can vary between family members. In a recent study, we (2009b) used a cluster analysis to group together meal environments in just over 3,000 grade six, seven, and eight students from Ontario and Nova Scotia, Canada and reported that 72% of the sample consumed dinner at home, with family and prepared by family members (versus (1) 7% who ate at home, with family, but was self-prepared, (2) 4% who ate at home, with family, from food that was purchased at a convenience store/vending machine/other place, (3) 8% who ate at home alone, (4) 6% who ate with family at a restaurant/fast food outlet, and (5) 3% who skipped dinner altogether). Interestingly, the likelihood of a lower diet quality increased when students consumed dinner in a restaurant/fast food outlet, even though it was consumed with family (OR = 0.51), or skipped dinner altogether (OR = 0.53) rather than consuming dinner at home with, and prepared by, family members (Woodruff and Hanning 2009b). In the United States, frequent fast food use for family meals (at least three times per week) was associated with less milk and vegetables being served with meals at home and higher total intake of fast foods and salty snack foods for both parents

and adolescents, in addition to higher weight status among parents (Boutelle et al. 2007). Furthermore, eating outside of the home for family meals may be becoming more popular. In a small study of parents (n = 107) of 8–10 year olds who reported frequent family meals, family dinners were reportedly eaten at full-service restaurants, purchased from fast-food establishments, or picked up as take-out foods at least weekly (47%, 28.3%, and 23.8%, respectively; Fulkerson et al. 2008). Consuming food outside of the home (as opposed to inside the home) has been associated with higher intakes of fat, sugar, and salt, and lower intakes of fiber and calcium (Lin et al. 1999a; Cluskey et al. 2008) in addition to contributing more energy as a percentage of total calories compared to eating in the home (Lin et al. 1999b). In terms of overall diet quality, family meals may provide better nutrition if consumed in the home, possibly due to more control over types of food served, cooking preparation, and portion size.

In a recent review paper, we (2008) suggested that distractions during family meals (such as the television) may reduce or eliminate communication and interaction for those eating together. Figure 63.2 illustrates the prevalence of watching television during family meals among a small sample (n = 395) of grade six students from Ontario, Canada. The finding is similar to that of grade 5 students from Nova Scotia, Canada for whom 44% reported watching supper in front of the television less than once/week (Liang et al. 2009). Results from the United States are similar, such that watching television during family meals was reported in 27–33.5% of adolescents (Feldman et al. 2007; Eisenberg et al. 2009). Adolescents (n = 4,746) who reported watching television during family meals consumed lower intakes of vegetables, dark green/yellow vegetables, calcium-rich food, and grains and higher intake of soft drinks compared to those not watching television during meals (Feldman et al. 2007). Coon et al. (2001) also reported that students in grade 6–8 consumed higher amounts of pizza, snack foods, and soda and fewer fruits and vegetables than those who did not watch television while eating with family meals. A potentially confounding variable between family meals and overweight/obesity status, however, might be watching television while eating, as dinner in front of the television was positively and independently associated with overweight status among grade 5 students from Nova Scotia (Liange et al. 2009). Nevertheless, eating together while watching
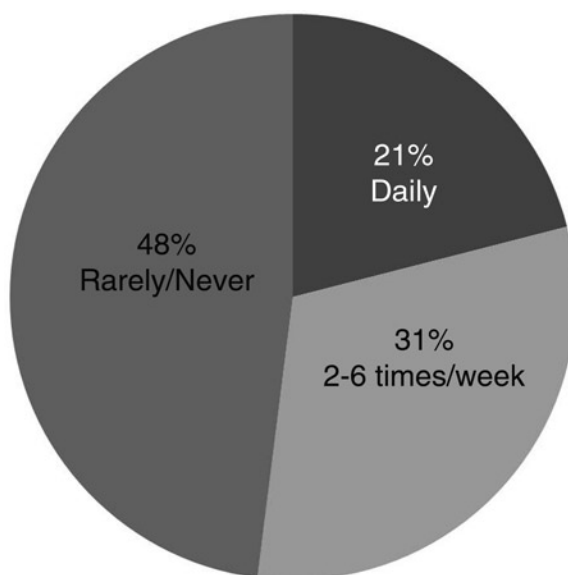
Fig. 63.2 Watching television during family meals (n=395 grade six students). This graph depicts the percentage of students (n=395 grade 6 students) watching television during family meals

television was associated with better diet quality than not eating together at all (Feldman et al. 2007). Other possible distracters from family meals include cell phone use, computer game play, and book reading, as identified among 12, 14, and 16 year olds from Belgium (Custers and van den Bulck 2009). However, these newer technologies are so far limited in the research literature.

63.8 Eating Disorders and Obesity

Body weight status is arguably a measure of diet quality, and family meals have the potential to decrease the risk of eating disorders and obesity among children and adolescents. The strength of the research is stronger for family meals and eating disorders (versus obesity), such that eating in a social setting seems to discourage unhealthy eating behaviors and secretive eating. Family meal frequency has been negatively associated with extreme and less extreme weight control (males and females; Neumark-Sztainer et al. 2004; Fulkerson et al. 2006), chronic dieting (females; Neumark-Sztainer et al. 2004), bulimia (Ackard and Neumark-Sztainer 2001; Fulkerson et al. 2006), and concern about high body weight (Woodruff and Hanning 2009a).

In a longitudinal study, regular family meals (≥5 meals/wk) at baseline were associated with lower prevalence of extreme weight control behaviors (e.g., self-induced vomiting, use of laxatives, diet pills, or diuretics) (OR = 0.71) after 5 years, even after adjusting for sociodemographic characteristics, body mass index, family connectedness, parental encouragement to diet, and extreme weight control behaviors at baseline among females (Neumark-Sztainer et al. 2008). Family meals may also have a protective effect against other disordered eating behaviors (e.g., eating very little, fasting, using food substitutes, skipping meals, smoking, binge eating, and chronic dieting), however findings with bivariate analyses were not confirmed in adjusted models (Neumark-Sztainer et al. 2008). It may be possible that individuals with weight issues and/or disordered eating patterns prefer to not eat in front of others. It may also be possible that poor body image and/or disordered eating behaviors are a result of a negative family meal atmosphere and/or poor family relations (Neumark-Stzainer et al. 2008; Woodruff and Hanning 2009a). Neumark-Sztainer et al. (2004) suggests that families may be able to protect their children from engaging in harmful disordered eating behaviors through enhanced communication, caring relationships, and for females, more enjoyable family meals.

Conflicting results exist for the correlation between family meals and overweight/obesity status. In many cases, associations between family meal frequency and obesity often exist cross-sectionally, yet disappear in longitudinal analyses (Taveras et al. 2005; Fulkerson et al. 2008; Utter et al. 2008). For example, among a large cohort of 9–14 year old children (n = 14,431) participating in the *Growing up Today* study (Taveras et al. 2005), the odds of being overweight was 0.85 among children who ate family dinner on *most days* or *every day* compared with those who ate family dinner *never or some days*. However, in a longitudinal model, the odds ratios between previous year frequency of eating family dinner and 1-year incidence of becoming overweight were 0.95 and 1.04 for children who ate family dinner on *most days* and *every day*, respectively, compared with those who ate family dinner *never or some days* (Taveras et al. 2005). Only in one longitudinal study (3 years) following normal weight students from the time they entered kindergarten, were there significant inverse associations between family meal frequency and overweight by the third grade. Children who were consistently overweight were also more likely (OR = 1.08) to consume fewer family meals (Gable et al. 2007). However, the age of participants may influence the longitudinal results (as Gable et al. (2007) participants are much younger than Taveras et al. (2005), Fulkerson et al. (2008), and Utter et al. (2008)).

Some studies have reported an inverse relationship between family meals and overweight/obesity status (Veugelers et al. 2005; BeLue et al. 2009; Wurbach et al. 2009), particularly among adoles-

cents at risk of academic failure (Fulkerson et al. 2009) and those attending alternative high schools (Kubik et al. 2009). For example, at-risk adolescents who reported never eating family dinner were significantly more likely to be overweight (OR = 2.8), and food insecure (OR = 6.0) than adolescents who reported five to seven family meals per week (Fulkerson et al. 2009). Interestingly, Sen (2006) suggested that family dinner frequency may be associated with overweight status in white participants, but not blacks or Hispanics. Possible reasons for the racial and ethnic differences may include differences in the types and portions of food consumed at family meals; however, limited research exists. Finally, a potential confounding variable between family meals and overweight/obesity status might be watching television while eating, as dinner in front of the television was positively and independently associated with overweight status among grade 5 students from Nova Scotia (Liang et al. 2009).

The protective nature of family meals on weight status may be confounded by sex, as reported in an interesting paper on shared risk and protective factors for overweight and disordered eating in adolescents (Neumark-Sztainer et al. 2007). Family meals (in addition to regular meal patterns and media exposure to messages about weight loss) were associated with eating disorder and overweight/obesity status, particularly among females but not males (Neumark-Sztainer et al. 2007). In a recent review paper discussing recommendations for health care providers to prevent obesity and eating disorders in children and adolescents, Neumark-Sztainer (2009b) encourages more frequent and more enjoyable family meals as one of the top five recommendations. Although the associations observed in epidemiological studies do necessarily *prove* that eating family meals more frequently will result in change, many agencies have adopted similar guidelines. For example, the American Medical Association Expert Committee recommendations for childhood obesity was to *encourage family meals on most, and preferably all, days of the week* (Rao 2008), and the Ontario Ministry of Health and Long Term Care report *Healthy Weights, Healthy Lives* recommend *enjoying family meals whenever possible* (MHLTC 2004).

63.9 Applications to Other Areas of Health and Disease

63.9.1 *Psychological Adjustment, High Risk Behavior, and School Performance*

Family meals are known to be associated with better psychological adjustment, decreasing high risk behavior, and better school performance in children and adolescents (see Table 63.4). In a large study of 6–12 grade students (n = 99,462) from 25 states in the United States, family meal frequency was consistently positively associated with both internal (e.g., commitment to learning, positive values, social competencies, and positive identity) and external assets (e.g., support, boundaries, and expectations) (Fulkerson et al. 2006). Most noticeably, family meals may provide a formal or informal check in time for family members, thereby allowing parents to be aware of their children's emotional well-being (Eisenberg et al. 2004). Family dinner frequency was also inversely related to depressive symptoms and suicide involvement in adolescents (Eisenberg et al. 2004) and adolescents at risk (Fulkerson et al. 2009). Fulkerson et al. (2007) argue that greater psychological well-being is associated with making family time at meals a priority and creating a positive mealtime atmosphere.

Furthermore, family meals were consistently negatively associated with all high-risk behaviors (e.g., substance use, sexual activity, depression/suicide, antisocial behaviors, violence, school problems,

Table 63.4 Family meal associations to other areas of health and disease

Health Issue	Specific Factor
Psychological adjustment	• Internal assets (+)
	• External assets (+)
	• Depression (−)
	• Suicide (−)
High risk behaviours	• Substance abuse* (−)
	• Cigarette smoking* (−)
	• Alcohol* (−)
	• Marijuana* (−)
	• Sexual activity (−)
	• Antisocial behaviour (−)
	• Violence (−)
	• School problems (−)
	• Binge eating/purging (−)
	• Excessive weight loss (−)
Academic performance	• Grade point average (+)
	• High motivation to do well in school (+)
	• School engagement (+)
	• Reporting 1 or more hours of homework (+)

This table lists the associations (positive or negative) of family meals to other areas of health and disease. Positive association (+), negative association (−), and association only evident among females *

binge eating/purging, and excessive weight loss) (Fulkerson et al. 2006). Regular family activities, including family meals and/or religious activities, prospectively predicted declines in a lower frequency of adolescent risky sexual behaviors (Coley et al. 2009). Significantly higher prevalence of cigarette smoking, alcohol, and marijuana use were found for adolescent reporting regular family meals versus no regular family meals (Eisenberg et al. 2004; Eisenberg et al. 2009). It is noteworthy that many of the significant associations were found in females and not in males (Fisher et al. 2007; Eisenberg et al. 2009), which may be a function of how females (versus males) interact with other family members (Davies and Lindsay 2004; Eisenberg et al. 2009). Long term protective effects of family meals were also evident among females in a longitudinal study, as family meal frequency at baseline was associated with significantly lower odds of cigarette smoking, alcohol use, and marijuana use at 5 years follow up, even after for controlling for baseline substance abuse and additional covariates (again, no differences were observed for males; Eisenberg et al. 2008). It may be that family meals reflect more supervised time and therefore less time to engage in risky behaviors (Eisenberg et al. 2004). It is also possible that family meals make children and adolescents spend more time at home and therefore are restricted from potentially negative peer pressure situations (Eisenberg et al. 2004).

The association between family meals and school performance also seems to be apparent in children and adolescents. Eisenberg et al. (2004) reported that greater family meal frequency decreased the odds (OR = 0.88 and OR = 0.99 for males and females, respectively) of a low grade point average. Furthermore, in a large sample of adolescents (nearly 100,000 grade 6–12 students) greater family meal frequency increased the likelihood of having a high motivation to do well in school (OR = 1.5), school engagement (OR = 1.6), and reporting one or more hours of homework daily (OR 1.5), even after adjusting for demographic and family variables (Fulkerson et al. 2006).

Summary Points

- The family may influence childhood and adolescent food behaviour and attitudes through demographics, behaviour modeling, shared environment, and parenting style.
- Family meals are difficult to define (e.g., dinner or all meals; at least one parent or do all family members have to be present; location; does everyone have to be eating the same thing).
- Family meals occur regularly (5 or more days/week) in approximately 25-70% of children and adolescents, and 11-44% on two or fewer days/week.
- Family meals seem to have a positive association with diet quality, food behaviours, body weight status, psychological adjustment, high risk behaviours, and school performance.
- Family meals may be a proxy for family connectedness and family cohesion.
- Obstacles for family meals include scheduling, lack of knowledge regarding food preparation, dissatisfaction with family relationships, and adolescent desire for autonomy.
- Tips to increase family meal frequency include planning ahead (e.g., know what you are having for dinner before dinner), get all family members involved (planning and preparation), be flexible about timing (e.g., if dinner doesn't work for your family, what about breakfast?), be a good role model, turn off the television, discuss non-contentious issues.

Definition

Family meal: usually an occasion for communication and interaction among family members, in which all family members consume similar types of food
Diet quality: a measure of how well one's dietary intake meets the current dietary recommendations
Food behaviour: any behaviour (action) that is related to food and/or food intake

---

References

Ackard DM, Neumark-Sztainer D (2001) Eat Disord. 9:239–249.
Altus DE, Engelman KK, Mathews RM (2002) J Gerontol Nurs. 28:47–53.
BeLue R, Francis LA, Rollins B, Colaco B (2009) J Adolesc Health. 45:517–524.
Boutelle KN, Fulkerson JA, Neumark-Sztainer D, Story, French SA (2007) Public Health Nutr. 10:16–23.
Boutelle KN, Lytle LA, Murray DM, Birnbaum AS, Story M (2001). J Nutr Educ. 33:128–133.
Burgess-Champoux TL, Larson N, Neumark-Sztainer D, Hannan PJ, Story M (2009). J Nutr Educ Behav. 41:79–86.
Cluskey M, Edlefsen M, Olson B, Reicks M, Auld G, Bock MA, boushey CJ, Bruhn C, Goldberg D, Misner S, Wang C, Zaghloul S (2008). J Nutr Educ Behav. 40:72–79.
Coley RL, Votruba-Drzal E, Schindler HS (2009). Child Dev. 80:808–827.
Coon KA, Goldberg J, Rogers BL, Tucker KL (2001). Pediatrics. 107:E7.
Croll J, Neumark-Sztainer D, Story M, Ireland M (2002). J Adolesc Health. 31:16s6–175.
Custers K, Van den Bulck J (2009). Public Health Nutr. 22:1–7.
Davies PT, Lindsay LL (2004). J Fam Psychol. 18:160–170.
Devine CM, Farrell TJ, Blake CE, Jastran M, Wethington E, Bisogni CA (2009). J Nutr Educ Behav. 41:365–370.
Eisenberg ME, Neumark-Sztainer D, Feldman S (2009). Prev Med. 48:585–587.
Eisenberg ME, Neumark-Sztainer D, Fulkerson JA, Story M (2008J Adolesc Health. 43:151–156.
Eisenberg ME, Olson RE, Neumark-Sztainer D, Story M, Bearinger LH (2004). Arch Pediatr Adolesc Med. 158:792–796.
Feldman S, Eisenberg ME, Neumark-Sztainer D, Story (2007). J Nutr Educ Behav. 39:257–263.
Fisher LB, Miles IW, Austin SB, Camargo CA Jr, Colditz GA (2007). Arch Pediatr Adoelsc Med. 161:959–966.
Fisher J, Mitchell D, Smickiklas-Wright H, Birch L (2002). J Am Diet Assoc. 102:58–64.
Franko DL, Thompson D, Affenito SG, Barton BA, and Stiegel-Moore RH (2008). Health Psychol. 27:S109–117.

Fulkerson JA, Kubik MY, Story M, Lytle L, Arcan C (2009). J Adolesc Health. 45:389–395.

Fulkerson JA, Story M, Neumark-Sztainer D, Rydell S (2008). J Am Diet Assoc. 108:706–709.

Fulkerson JA, Neumark-Sztainer D, Hannan PJ, Story M (2008). Obesity (Silver Spring). 16:2529–2534.

Fulkerson JA, Strauss J, Neumark-Sztainer D, Story M, and Boutelle K (2007). J Consult Clin Psychol. 75:181–186.

Fulkerson JA, Neumark-Sztainer D, Story M (2006). J Am Diet Assoc. 106:526–532.

Fulkerson JA, Story M, Mellin A, Leffert N, Neumark-Sztainer D, French (2006) J Adolesc Health. 39:337–345.

Gable S, Chang Y, Krull JL (2007) J Am Diet Assoc. 107:53–61.

Gillespie AH, Achterberg CL (1989) J Am Diet Assoc. 89:509–512.

Gillman MW, Rifas-Shiman SL, Frazier AL, Rockett HR, Camargo CA, Jr, Field AE. et al. (2000) Arch Family Med. 9:235–240.

Granner ML, Sargent RG, Calderon KS, Hussey JR, Evans AE, Watkins KW (2004). J Nutr Educ Behav. 36:173–180.

Kubik MY, Davey C, Fulkerson JA, Sinard J, Story M, Arcan C (2009) Am J Health Behav. 33:600–609.

Larson NI, Nelson MC, Neumark-Sztainer D, Story M, Hannan PJ (2009). J Am Diet Assoc. 109:72–79.

Larson NI, Neumark-Sztainer D, Hannan PJ, Story M (2007). J Am Diet Assoc. 107:1502–1510.

Lee S, Reicks M (2003). J Am Diet Assoc. 103:1526–1529.

Liang T, Kuhle, Veugelers PJ (2009). Public Health Nutr. 12:2457–2463.

Lin MH, Gurthrie J, Frazao E (1999a). Food Review. 22:2–10.

Lin MH, Gurthrie J, Frazao E (1999b) in E. Frazao (ED) Nutrient contribution of food away from home. America's eating habits. Washington DC: USDA, pp 213–242.

Marquis M, Filion YP, Dagenais F (2005). Can J Diet Pract Res, 66:12–18.

Ministry of Health and Long Term Care. (2004). *Chief Medical Officer of Health Report. Healthy Weights Healthy Lives*. Retrieved June 22, 2006. Available from http://www.health.gov.on.ca/english/public/pub/ministry_reports/cmoh04_report/cmoh_04.html.

Neumark-Sztainer D (2009a). Family meals and why they are worth the effort: What have we learned from Project Eat? Alberta Milk: Nutrition File Seminar Key Note Speaker, Edmonton & Calgary, Alberta.

Neumark-Sztainer D (2009b). J Adolesc Health. 44:206–213.

Neumark-Sztainer D, Eisenberg ME, Fulkerson JA, Story M, Larson NI (2008). Arch Pediatr Adolesc Med. 62:17–22.

Neumark-Sztainer D, Wall MM, Haines JI, Story MT, Sherwood NE, van den Berg PA (2007). Am J Prev Med. 33:359–369.

Neumark-Sztainer D, Wall M, Story M, Fulkerson JA (2004). J Adol Health. 35:350–359.

Neumark-Sztainer D, Hannan PJ, Story M, Croll J, Perry C. (2003). J Am Diet Assoc. 103:317–322.

Neumark-Sztainer D, Story M, Ackard DM, Moe J, Perry C. (2000). J Nutr Ed. 32:329–334.

Nijs KA, de Graff C, Siebelink E, Blauw YH, Vanneste V, Kok FJ, van Staveren WA (2006). J Gerontol A Biol Sci Med Sci. 61:935–942.

Ogden CL, Caroll MD, Curtin LR, McDowell MA, Tabak CJ, Flegal KM. (2006). J Am Med Assoc. 295:1549–1555.

Rao G (2008). Am Fam Physician. 78:56–63.

Ritchie LD, Welk G, Styne D, Gerstein DE, Crawford PB. (2005). J Am Diet Assoc. 105:70–79.

Sen B (2009). J Adolesc. [epub ahead of print].

Sen B (2006). Obesity (Silver.Spring). 14:2266–2276.

Shields M. (2005). *Overweight Canadian children and adolescents* (Statistics Canada). http://www.statcan.gc.ca/pub/82–620-m/2005001/pdf/4193660-eng.pdf

Story M, Neumark-Sztainer D (2006). NutrToday. 40:261–266.

Taveras EM, Rifas-Shiman SL, Berkey CS, Rockett HR, Field AE, Frazier AL, et al (2005). Obesity Research. 13:900–906.

Utter J, Scragg, R, Schaaf D, and Mhurchu CN (2008). Int J Behav Nutr Phys Act. 5:50.

Verzeletti C, Maes L, Santinello M, Vereecken CA (2009). Eur J Public Health. [Epub ahead of print]

Veugelers PJ, Fitzgerald AL, Johnston E (2005). Can J Public Health. 96:212–216.

Videon TM, Manning CK (2003) J Adol Health. 32:365–373.

Woodruff SJ, Hanning RM (2009a). J Adolesc Health. 44:431–436.

Woodruff SJ, Hanning RM (2009b). Can J Diet Pract Res. 70:118–124.

Woodruff SJ, Hanning RM (2008). Can J Diet Pract Res. 69:14–22.

Woodruff SJ, Hanning RM, McGoldrick K, Brown KS (2010). Eur J Clin Nutr. 64(5): 454–60.

Wurbach A, Zellner K, Kromeyer-Hauschild K (2009). Public Health Nutr. 12:1115–1121.

Chapter 64
Television and Food Choice

Emma J. Boyland and Jason C.G. Halford

Abbreviations

AAP   American Academy of Pediatrics
BMI   Body Mass Index
HFSS   High Fat, Sugar and/or Salt Foods
IOM   Institute of Medicine
Ofcom   Office of Communications
WHO   World Health Organisation

64.1 Introduction

This chapter considers the extent to which television can affect our food preferences, choices, and consumption. Television is an extremely popular leisure time pursuit worldwide and is the dominant sedentary pastime among children and adolescents (Swinburn and Shelly 2008). However, in the context of a global obesity epidemic and concerns over poor diet quality, particularly in young people, questions have been raised as to the impact television viewing has on our dietary choices and subsequently our overall health.

64.2 Childhood Diet, Ill Health, and Obesity into Adulthood

The prevalence of overweight and obesity has risen dramatically in both developed and developing countries over the last few decades. A 2004 survey estimated that 18% of European school children (approximately 14 million children in the 25 EU member states) are overweight, of whom three million are thought to be obese (Lobstein et al. 2004). Worldwide, 1.1 billion adults and 10% of children are now classified as overweight or obese (Haslam and James 2005). Obesity in childhood has numerous adverse consequences in the short-term, including psychological ill health, cardiovascular

E.J. Boyland (✉)
Kissileff Laboratory for the Study of Human Ingestive Behaviour, School of Psychology, Eleanor Rathbone Building, Bedford Street South, University of Liverpool, Liverpool, L69 7ZA, UK
e-mail: e.boyland@liverpool.ac.uk

risk factors, asthma, chronic inflammation, diabetes (types I and II), orthopedic abnormalities, and liver disease (Reilly and Wilson 2006). Additionally, there is considerable evidence to suggest that obesity persists from childhood (particularly adolescence) into adulthood. Around 60% of obese children and 80% of obese adolescents are likely to become obese adults; thus, in the longer term, pediatric obesity is associated with further problems as an adult, such as adverse socioeconomic outcomes, cancers, depression, arthritis, and premature mortality (Reilly and Wilson 2006).

Although obesity is a well publicized and highly recognized public health concern, a lack of clarity over the etiology of obesity has been a particular barrier to the development of effective strategies for obesity prevention (Prentice and Jebb 1995). Whilst genetic and familial associations with obesity suggest that individual susceptibility may play a role, the recent rapid rise in levels of overweight and obesity suggests that environmental and behavioral changes are largely responsible, as the epidemic has occurred against a relatively constant genetic (and therefore metabolic) background (Prentice and Jebb 1995). As obesity is ultimately a consequence of energy intake exceeding energy expenditure, it can be concluded that the current epidemic is due to an environment that promotes the behaviors that cause obesity – namely, a virtually unlimited supply of convenient, relatively inexpensive, highly palatable, energy dense foods – all factors promoting overconsumption (Hill and Peters 1998). Epidemiological studies have previously shown a positive relationship between dietary fat intake and obesity and, indeed, the proportion of fat in the British diet has increased from 0.6 kJ of fat for each kilojoule of carbohydrate in the diet in 1940, to 0.9 kJ fat per kilojoule of carbohydrate in 1990 (Prentice and Jebb 1995).

In the USA, trends in young peoples' nutrient intakes and eating patterns between the 1970s and 2004 have recently been highlighted (McGinnis et al. 2006). The report indicates that carbohydrate intake has increased over this time, total fat and saturated fats consumed remain at levels that exceed dietary recommendations, snacking has increased steadily during this period, and that currently a large proportion of total calories are consumed from foods and beverages with high calorie and low nutritional content (McGinnis et al. 2006). The survey also suggests that consumption of fruits, vegetables, and whole grains is well below the recommended daily intake. The report concludes that, overall, young people in the USA are in energy imbalance due to a significantly increased caloric intake over the past 25 years (McGinnis et al. 2006).

During the 1970s and earlier, the term "diet quality" referred to the consumption of a diet with sufficient calories, protein, and micronutrients as to prevent diseases of deficiency. In contrast, it is now based upon "the principles of adequacy, variety, proportionality, and moderation" (McGinnis et al. 2006, p. 45), as well as recommending high intake of fruits, vegetables, and whole grains (nutrient-dense foods) and limited intake of fats and added sugars (McGinnis et al. 2006). Nevertheless, despite increases in our understanding of nutrition, it is clear that there is still much discrepancy between habitual food consumption and the recommended diet. It has been suggested that television may play a role in this disparity, at least partially through the introduction of food cues in advertisements, potentially affecting food preferences and choice.

64.3 The Importance of Childhood Food Preferences and Diet

It is widely believed that children 'eat what they like' and that children's food preferences are highly indicative of their habitual consumption (Cooke and Wardle 2005). Each of us is born with a few genetic predispositions that govern early development of food preferences, notably a liking for sweet and salty foods and an aversion to sour and bitter flavors (Birch 1999). Indications of such early preferences can be rapidly ascertained by examining infants' facial expressions (Benton 2004). Children typically prefer sweeter tastes than adults, and the preference for a salty taste develops by approximately 4 months of age (Benton 2004).

Also, we are predisposed to initially rejecting novel foods (neophobia) and to learn preferences by creating associations between foods and the contexts in which they are consumed and the consequences of their consumption (Birch 1999). Therefore, as consuming an energy-dense food is a satisfying subjective experience, there is a tendency to learn to prefer energy-dense foods (those high in fat and/or sugar) (Benton 2004). This tendency may have been adaptive in the past in times of famine, or for particularly young children requiring energy for growth, but in the context of today's readily available supply of palatable food it can be a considerable risk factor predisposing an individual to obesity (Benton 2004). Indeed, a preference for fatty foods in children between the ages of 3 and 5 years has previously been found to predict skinfold thickness which is a reliable index of adiposity (Fischer and Birch 1995). Additionally, neophobia typically declines with age, potentially as a result of children having tried a greater number of foods without experiencing adverse postingestive consequences (Cooke and Wardle 2005).

Given the rising levels of obesity (discussed in the next section), it appears that food preferences are currently influencing food selection to be inconsistent with recommended dietary guidelines and thus are promoting eating behaviors causing weight gain and ultimately leading to overweight and obesity (Birch 1999). However, because, beyond initial predispositions, learning plays a central role in the development of food preferences, this suggests that preferences are modifiable and that learned preferences towards healthier foods could be encouraged (Birch 1999).

It is, therefore, critical to ascertain those factors that influence the development of food preferences and choice in children, in order to identify those aspects of the environment that are potentially obesigenic for those individuals with a genetic susceptibility to weight gain. One such factor that has been implicated in food preference and choice is television viewing.

64.4 Television Viewing Is Linked to a Poor Diet and Obesity

For over 20 years television has consistently been linked with negative health effects, particularly in children, including violent behavior, academic performance, and perhaps most notably nutrition, dieting, and obesity (AAP 2001). Given that television is a pervasive source of entertainment, particularly amongst children and adolescents, this is a concern. In the UK, children between the ages of 4–15 years watch an average of 17.2 h of television per week (Ofcom 2004). In addition, it has been reported that 71% of 8–11 year olds and 75% of 12–15 year olds have a TV set in their bedroom (Ofcom 2006), a factor that has been associated with an even greater risk of overweight (Dennison et al. 2002).

64.4.1 Obesity

A 1985 study by Dietz and Gortmaker was the first to link high television viewing with a greater risk of overweight and obesity. In a sample of over 10,000 children, this study demonstrated significant associations between time spent watching television and the prevalence of obesity, such that obesity prevalence was shown to increase by 2% for each additional hour of television viewed (Dietz and Gortmaker 1985). Since that study, much additional evidence has been gathered to support this relationship both in childhood and extending into adulthood. Importantly, it has even been shown that television viewing in childhood can independently predict increased adult body mass index, indicating that there could be a causal link (Viner and Cole 2005).

In a cross-sectional study, Andersen et al. (1998) found that boys and girls who watched 4 or more hours of television each day had greater body fat and a greater body mass index than those who watched less than 2 h per day. Furthermore, Dennison et al. (2002) found that not only was the amount of time spent viewing television related to the prevalence of overweight, but that the presence of a television in a child's bedroom increased their weekly viewing by 4.8 h and further strengthened the risk of overweight. The effects appear to persist into adulthood, and as Jeffery and French (1998) showed, television viewing hours were positively associated with both energy intake and body mass index in women aged 20–45 years.

Importantly, the association between television viewing and obesity remains significant even when other potential confounding variables such as socioeconomic status, familial tendency to overweight (Hancox and Poulton 2006) and, critically, levels of physical activity (Epstein et al. 2008) are taken into account. Therefore, it is not simply the case that television viewing is linked to obesity because it is a sedentary activity, displacing physical activity, and thus lowering overall energy expenditure; rather, the association appears to be due to the effects of television viewing on food intake.

64.4.2 Diet

Several studies have demonstrated that energy intake increases during television viewing. Crespo et al. (2001) found that girls who watched 5 or more hours of television a day consumed on average an extra 732 kJ (175 kcal) a day compared to those watching 1 h or less of television per day. Wiecha et al. (2006) found an even bigger increase in intake, with each additional hour of television viewing associated with an additional 167 kcal per day. The cumulative effect of a small daily increase in kcal intake could contribute to a positive energy balance (intake exceeding expenditure) and therefore at least partially explain the relationship between television viewing and obesity (discussed above).

Typically, increases in caloric intake associated with television viewing are mainly due to increases in the consumption of foods that are both energy dense and low in nutrients (Davison et al. 2006), so television viewing is associated with poor overall diet quality. The amount of time spent viewing television is predictive of unhealthy conceptions about food and poor eating habits generally (Signorielli and Lears 1992). One study found that television viewing was inversely associated with intake of fruit and vegetables among adolescents, whereby fruit and vegetable intake decreased by 0.16 servings per day with each additional hour increase in television viewing (Boynton-Jarrett et al. 2003). Another found that children from families with high television use derived more of their daily energy intake from meats, pizza, salty snacks, and soda and less from fruit, vegetables, and juices than children from families with low television use (Coon et al. 2001).

In addition, eating whilst watching television (whether it is eating snacks in front of the television or having television viewing as part of the meal time routine) has been shown to affect food choice and caloric intake. Marquis et al. (2005) showed that eating in front of the television was positively correlated with children's general consumption of French fries, salty snacks, ice cream, confectionery, pastries, sweetened cereals, fruit beverages, and soft drinks, and negatively correlated with overall consumption of raw vegetables. It has been suggested that children in particular consume a substantial proportion of their daily energy whilst watching television, 20% and 25% for weekdays and weekend days respectively (Matheson et al. 2004), therefore television viewing could have a significant impact on both the types of foods selected and the overall level of consumption.

This section of the chapter has demonstrated that there is a considerable amount of evidence to suggest that television viewing has a detrimental effect on food choice, overall diet quality, and levels

of adiposity in children, adolescents, and adults. It has been suggested that these effects may be due to the influence of television food advertising.

64.5   The Extent and Nature of Television Food Advertising

Internationally, television remains the primary medium used for advertising food and drink products, comprising approximately 75% of all advertising spend in the UK in recent years (Hastings et al. 2003). Although both the nature and extent of such advertising varies between countries, typically a majority of the advertisements broadcast are for unhealthy products. It has been estimated that for every US$1 the World Health Organisation (WHO) spends on promoting healthy nutrition, US$500 is spent by the food industry promoting processed foods (Escalante de Cruz et al. 2004). In the UK in 2003, Nestle alone spent £43 million promoting breakfast cereals and chocolate, Kellogg spent £30 million promoting their cereals and Coca-Cola funded their soft drink advertising with £26 million (Escalante de Cruz et al. 2004).

An international study in 1996 found that food advertising comprised the largest category of advertised products to children in the vast majority of countries, and that confectionery, breakfast cereals (often sweetened), and fast food restaurants overall accounted for over half of all food advertisements (Dibb 1996). Also noted was the lack of advertising of healthier food products, with adverts for fruits and vegetables virtually nonexistent (Dibb 1996). Food advertising ranged from 84% of all advertisements (Netherlands) to 12% (Sweden) (Dibb 1996).

Dibb (1996) also carried out a nutritional analysis of the foods advertised to children on UK television, and found that over 60% were products high in fat, 50% were high in sugar, and over 60% were high in salt. Overall, 95% of the advertisements were for high fat, sugar, and/or salt foods, and worryingly, this was a fairly consistent pattern found across the countries studied (Dibb 1996). In 1998, Lewis and Hill reported that during their 91 h recorded sample of UK television, 828 adverts were broadcast of which half were for food products. 60% of these were for breakfast cereals and confectionery/snacks (Lewis and Hill 1998). It is clear that the foods advertised reflect a dietary pattern that would be associated with increased risk of obesity and are not in line with recommended nutritional guidelines (WHO 2003).

Advertising to children on television has come under much criticism, relating to the types of products advertised (typically energy-dense foods not conducive to a healthy diet) and the way in which they are advertised (use of persuasive marketing techniques such as brand equity characters, celebrity endorsement, etc). There are also concerns over young children's cognitive ability to understand the persuasive nature of advertising and therefore their ability to judge it critically (Oates et al. 2003). Such concerns have led Sweden to ban advertising to children under-12 years old on their terrestrial television stations (Oates et al. 2003), and for the UK to bring in new legislation to limit the advertising of unhealthy food products to children on television (Ofcom 2007).

64.6   Television Food Advertising Effects on Food Preferences, Choices, and Consumption

Food advertising has often been proposed as a candidate for the association between television viewing and adiposity. In an interesting study, Lobstein and Dibb (2005) found that there was a significant and positive correlation between the prevalence of overweight amongst school children and the number of

adverts for sweet or fatty foods broadcast per 20 h of children's television broadcast. Crucially, it was also found that prevalence of overweight negatively correlated with the number of healthy foods advertised over the same period of time (Lobstein and Dibb 2005).

In addition to this, there is now a considerable body of evidence from experimental studies to suggest that food advertising on television does impact upon food preferences, choices, and consumption.

64.6.1 Food Preferences and Choice

As far back as 1976, it was reported that the hours of commercial television children watched each week correlated significantly with purchasing-influencing attempts made to their parent while food shopping (Galst and White 1976). Brody et al. (1981) also noted that, in their study, the children who watched a cartoon embedded with food commercials made more requests for the advertised foods in a subsequent artificial shopping environment than the children who had watched the cartoon with no commercials.

Borzekowsi and Robinson's (2001) much cited randomized, controlled trial showed preschool children a videotape of a cartoon either with or without embedded commercials, and then asked the children to identify their food preferences from pairs of similar products, one of which had been shown in the commercials. Children who had seen the videotape with the embedded commercials were significantly more likely to select the advertised product than children who had not seen the commercials (Borzekowsi and Robinson 2001). More recently, Robinson et al. (2007) reported that children preferred the taste of food and drink items displaying the McDonalds branded packaging to identical products in matched but unbranded packaging. Interestingly, it was also found that children with a greater number of television sets in their homes were more likely to prefer the taste of the products in McDonalds branded packaging (Robinson et al. 2007).

Halford et al. (2008) demonstrated that following exposure to nonfood advertisements, overweight and obese children showed a significantly greater preference for branded items than normal weight children; however, following food advertisements these weight status differences were not apparent. This suggests that television food advertisement exposure can produce an obesigenic food preference response in normal weight children that is typically found in overweight and obese children (Halford et al. 2008).

64.6.2 Consumption

In an early study, Gorn and Goldberg (1982) found that children who viewed daily candy commercials were more likely to select candy than fruit as an afternoon snack. Hitchings and Moynihan (1998) interviewed 9–11 year olds regarding their recall of food advertisements and obtained 3-day food diaries to ascertain consumption. Parents of the children were also interviewed to establish the food requests that had been received. A significant positive association was found between the food advertisements recalled and the foods consumed, particularly for soft drinks, crisps, and savory snacks (Hitchings and Moynihan 1998). Four out of the ten of the most requested food items were amongst the ten most frequently recalled television food advertisements (Hitchings and Moynihan 1998).

More recently, Halford et al. (2004) exposed 9–11 year old children to eight food or eight nonfood advertisements followed by the same cartoon in a within-participant, randomized study. Following

viewing, children's consumption of sweet and savory, high and low fat snack foods was measured. Exposure to food advertising increased food intake in all children (Halford et al. 2004) (Fig. 64.1). This finding was later replicated in 5–7 year old children (Halford et al. 2007a) (Fig. 64.2). Interestingly, a further study demonstrated that not only did food advertising exposure produce a substantial and significant increase in caloric intake (of high fat and/or sweet energy-dense snacks) in all children, but also that this increase in intake was largest in the obese children (Halford et al. 2007b). This suggests that overweight and obese children are more responsive to food promotion, and that such promotion specifically stimulated the intake of energy-dense snacks (Halford et al. 2007b) (Table 64.1). Indeed, in this study there was a significant, positive correlation between BMI (as standard deviation scores for age and gender) and food intake after exposure to food adverts (Halford et al. 2007b) (Fig. 64.3). Buijzen et al. (2008) found that children's exposure to food advertising was significantly related to their consumption of both advertised brands and generic energy dense product categories.

An Australian survey study showed that heavier TV use and more frequent viewing of commercial television were independently associated with more positive attitudes towards junk food; heavier TV use was also independently related to higher self-reported junk food consumption (Dixon et al. 2007). However, advertisements for healthier food products have also been shown to have an impact. Dixon et al. (2007) also found that advertisements for nutritious foods promoted positive attitudes and beliefs concerning these foods.

Hastings et al. (2003) carried out a systematic review of the existing literature and concluded that food promotion "is having an effect, particularly on children's preferences, purchase behavior, and consumption." The report states that "the advertised diet contrasts sharply with that recommended by public health advisors, and themes of fun and fantasy or taste, rather than health and nutrition, are used to promote it to children. Meanwhile, the recommended diet gets little promotional support." (Hastings et al. 2003). A report by the World Health Organization and the Food and Agriculture Organization of the United Nations also acknowledged that the promotion of energy-dense foods is a "probable" cause of increasing prevalence of overweight and obesity in children worldwide (WHO
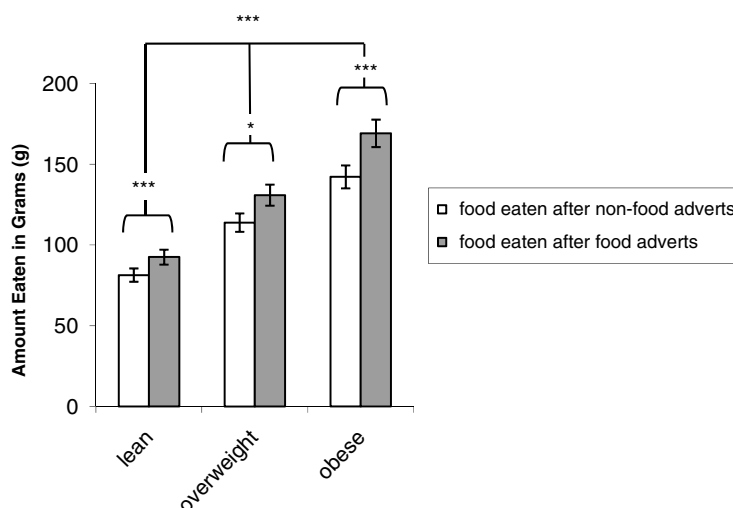
Fig. 64.1 Lean, overweight and obese children's food consumption after toy and food advert exposure. A graph to show the weight of food eaten after viewing the advertisements by lean, overweight, and obese groups in the session with nonfood advertisements (*open columns*) and in the session with food advertisements (*filled columns*); mean values with SE bars; ***$p < 0.001$; **$p < 0.01$; *$p < 0.05$
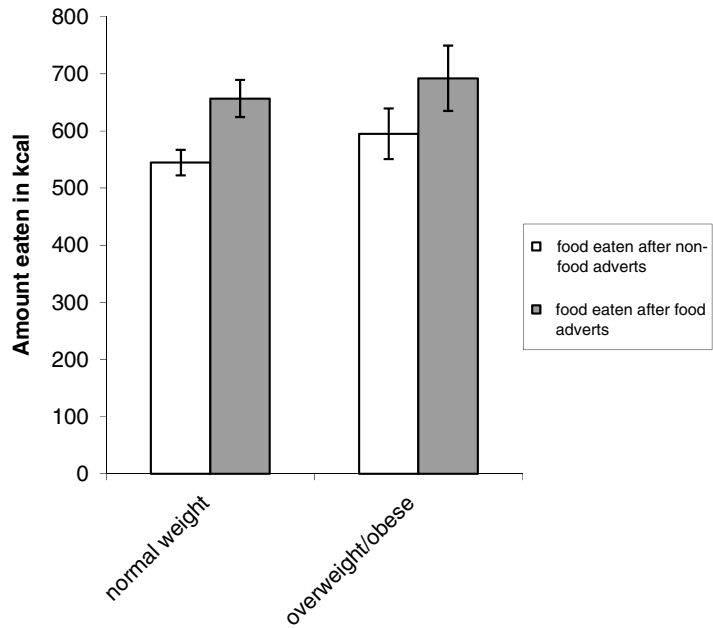
Fig. 64.2 Normal weight and overweight/obese children's food consumption after toy and food advertisement exposure. A graph to show the weight of food eaten after viewing the advertisements by normal weight and overweight/obese groups in the session with nonfood advertisements (*open columns*) and in the session with food advertisements (*filled columns*); mean values with SE bars; ***$p < 0.001$; **$p < 0.01$; *$p < 0.05$

2003). The Institute of Medicine (IOM) reviewed 155 studies of food advertising and its effects on children and concluded that exposure to television advertising is associated with adiposity in children aged 2–11 years (IOM 2005).

64.7 Intervention Strategies: Reduce Television Viewing and Limit Food Advertising

Previous sections have discussed the association between television viewing and obesity, and particularly the role of television food advertising in this relationship. It is therefore logical that intervention strategies must be designed to address these issues (Tables 64.2 and 64.3).

One randomized, controlled trial in the US has already demonstrated that interventions designed to reduce television viewing can be effective at reducing body mass index. In the Robinson (1999) study, 192 children were randomly assigned to either an intervention or a control group. The intervention group received 6 months of guidance sessions to encourage reduced television, videotape, and videogame use. Subsequently, those children in the intervention group had significantly decreased television viewing and number of meals eaten in front of the television and most importantly, decreased body mass index in comparison to the control group (Robinson 1999). Interestingly, another study found that in a group of obese children and their parents, reinforcing decreased sedentary behaviors such as television viewing resulted in greater weight loss than directly reinforcing increased physical activity (Epstein et al. 1995).

Table 64.1 Intake of each food item in toy and food advertisement conditions

Food item	Mean intake (g) after toy adverts (±SEM)				Mean intake (g) after food adverts (±SEM)				Significance (whole group)
	NW	OW	OB	Whole group	NW	OW	OB	Whole group	
Crisps	6.4 (±1.1)	8.8 (±2.0)	10.2 (±2.7)	7.7 (±1.0)	12.4 (±1.5)	15.2 (±2.8)	22.3 (±3.0)	14.9 (±1.3)	$p < 0.001$
Snack a Jacks	3.3 (±0.6)	1.7 (±0.4)	7.5 (±1.9)	3.7 (±0.5)	4.0 (±0.7)	2.9 (±0.8)	9.3 (±3.0)	4.7 (±0.7)	Non sig. $p = 0.052$
Chocolate Buttons	18.7 (±2.7)	20.9 (±4.5)	17.7 (±3.3)	19.1 (±2.0)	42.9 (±3.7)	42.5 (±7.6)	71.9 (±9.8)	48.2 (±3.6)	$p < 0.001$
Jelly Sweets	33.3 (±3.4)	30.4 (±5.9)	28.7 (±7.5)	31.7 (±2.8)	55.7 (±4.9)	72.2 (±8.2)	58.8 (±8.7)	60.5 (±3.8)	$p < 0.001$
Grapes	48.1 (±6.5)	61.7 (±9.8)	45.5 (±13.1)	51.0 (±5.0)	76.7 (±10.8)	77.7 (±12.4)	64.4 (±17.2)	74.7 (±7.5)	$p = 0.001$

This table shows the mean intake of each food item after both toy (control condition) and food advertisements (experimental condition). Figures are presented as mean (± SEM) for each weight status group. *NW* normal weight, *OW* overweight, and *OB* obese
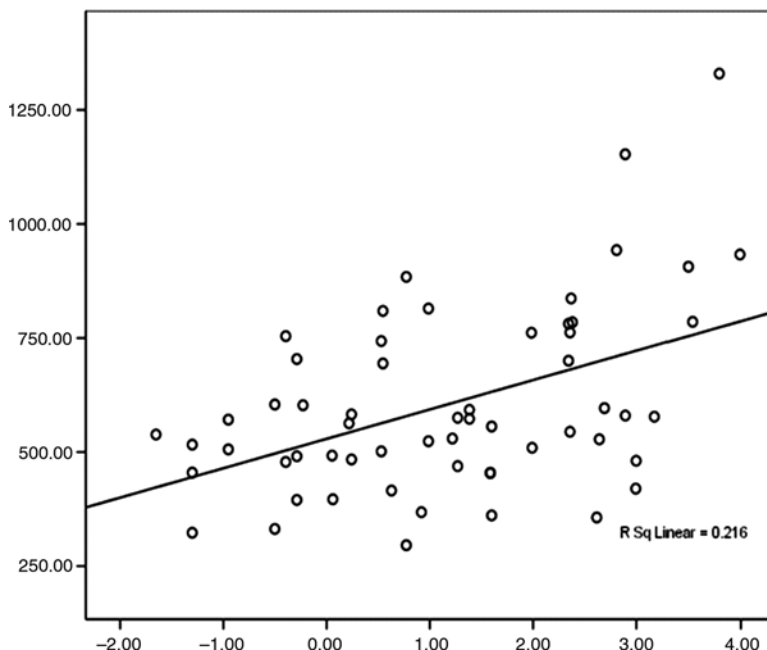
Fig. 64.3 A correlation between body mass index (BMI) standard deviation score and food intake after exposure to food advertisements. This figure shows a significant and positive correlation between BMI standard deviation score (*x* axis) and energy intake in kilocalories after exposure to food advertisements (*y* axis)

As previously mentioned, concerns over television food advertising have led campaigners to call for regulatory changes regarding such advertising, particularly to children. The UK has recently implemented new legislation designed to limit the advertising of high fat, sugar, and/or salt (HFSS) foods to children, as of January 2009 the advertising of HFSS foods is banned on dedicated children's channels (Ofcom 2007). Advertising of such foods is also prohibited in and around programming of particular appeal to children on all channels (Ofcom 2007). However, it remains to be seen if these new laws are effective at reducing children's exposure to HFSS advertising, particularly because of the way programs "of particular appeal to children" are calculated, using the proportion of children in the audience as opposed to the overall viewing figure; therefore, if a program is also watched by adults it is unlikely to be covered by the restrictions even if over a million children are watching (Which 2006). Indeed, one survey found that there is a clear discrepancy between the most popular programs watched by children and the programs covered by the restrictions. Out of the 30 most popular programs with 4–15 year olds, the first program to be included in the restrictions is the 27th most popular program in the list – HFSS advertising would be free to continue around the 26 more popular programs before this (Which 2006).

There has been much debate in the UK and around the world regarding the negative effects of "junk food" advertising, but unfortunately, very little attention has been devoted to potential strategies to increase healthy food advertising to encourage healthy eating amongst children. This is despite evidence that such "counter-advertising" can be an effective strategy for promoting healthy behavior, either through ensuring that television channels must broadcast "antijunk food" messages or requiring a greater proportion of healthy food than unhealthy food advertisements be shown (Dixon et al. 2007).

Future intervention strategies must focus on combined efforts to reduce television viewing, limit unhealthy food advertising, and promote healthy food advertising in order to influence children's

Table 64.2 Key points about obesity and food choice

1. Levels of overweight and obesity have risen at dramatic rates in recent decades.
2. Worldwide, 1.1 billion adults and 10% of children are now classified as overweight or obese.
3. Obesity in childhood has numerous adverse consequences in the short-term, including psychological ill health, cardiovascular risk factors, asthma, chronic inflammation, diabetes (types I and II), orthopedic abnormalities, and liver disease.
4. Obesity is caused by energy intake consistently exceeding expenditure over time.
5. Children's food preferences are key determinants of their habitual diet.
6. Each of us is born liking sweet and salty foods and disliking sour and bitter flavors.
7. A preference for fatty foods in children between the ages of 3 and 5 years has previously been found to predict adiposity (fatness).

This table lists the key points of food choice and how this relates to obesity, including current levels of obesity, the effects of obesity on health, the principle cause of obesity, why we like certain foods, and how this food choice may lead to weight gain

Table 64.3 Key facts of television viewing and food advertising

1. Television viewing is related to overweight and obesity.
2. This relationship may be related to the effects of television viewing on food intake.
3. There is considerable evidence that television food advertising affects food and brand preferences, caloric intake, purchase requests, and purchase behaviors in children and adolescents.
4. Strategies to reduce television viewing in order to tackle obesity in young people appear to be promising.
5. The effectiveness of recent food and drink advertising restrictions in the UK are yet to be assessed.
6. Parallels can be drawn between efforts to restrict television food advertising, the previous banning of cigarette advertising, and potential restrictions on alcohol advertising on television.

This table lists the key facts of television viewing and food advertising as they relate to eating behavior. This includes the link between television viewing and obesity, how television viewing (via exposure to food advertising) may affect our food choices, the importance of strategies to reduce television viewing in young people and lessons that can be learnt from other similar issues such as the banning of advertising of alcohol and tobacco products to children

food preferences and choices toward a more nutritious and balanced diet, perhaps helping to limit the rising rates of obesity in children and adolescents.

64.8 Applications to Other Areas of Health and Disease

Parallels have been drawn between efforts to change the balance food advertising exposure in order to improve children's food preferences in relation to nutritious foods as opposed to energy-dense food items, and efforts to reduce cigarette smoking and alcohol consumption in youth through restrictions in advertising.

Evidence from the literature on cigarette smoking suggests that this is a potentially worthwhile strategy. In the late 1960s the US Federal Communications Commission required that any television station that broadcast cigarette commercials must also provide free air time for public service announcements with an antismoking message (Dixon et al. 2007). During the three years that these announcements were being broadcast cigarette consumption fell at a much greater rate than in the years immediately before or after this initiative – suggesting that these negative messages about smoking were largely responsible for the reduced rates (Dixon et al. 2007).

In common with obesity, alcohol consumption amongst children and adolescents is a significant and growing health problem often causing negative health consequences and potentially premature mortality. Also, there is evidence to suggest that exposure to alcohol advertising influences alcohol

consumption, particularly relating to patterns of heavy drinking (Nicholson and Hoye 2009). Between 2001 and 2007, spending by the alcohol industry on television advertising rose by more than 50% to $923 million, providing over 300,000 advertisements in 2007 alone (Nicholson and Hoye 2009). Evaluation of the impact of restrictions in food advertising on food preferences and choice is essential in order to discern the most effective strategies for modifying eating behaviors, and such evaluation may also inform future strategies designed to tackle the problem of youth alcohol drinking.

64.9 Conclusion

In summary, amid the current obesity epidemic, questions have been raised about the influence of television viewing and particularly television food advertising on the development of food preferences and therefore food choice in children. Considerable research evidence has been assimilated to demonstrate effects of exposure to food advertising on children's brand preferences, food preferences, food intake, and the number of requests children make to parents for products they have seen advertised. The effectiveness of recent restrictions regarding television advertising of energy-dense foods has yet to be fully elucidated, but certainly empirical evidence suggests that interventions to reduce television viewing, to limit exposure to high fat, sugar, and/or salt foods and to increase the media promotion of healthy, nutritious food groups could be beneficial in encouraging children to make better dietary choices.

Summary Points

Childhood diet, ill health, and obesity into adulthood

- Levels of childhood and adult obesity have risen dramatically over the last 30 years.
- Overweight and obesity are associated with a number of adverse health and psychosocial consequences.
- Obesity is caused by an energy imbalance, whereby energy intake exceeds expenditure over time.
- Overconsumption of dietary fat is a contributing factor to the obesity epidemic.

The important of childhood food preferences and diet

- Food preferences are crucial determinants of children's habitual diets.
- Although some preferences are innate, others are learnt through experience.
- It is critical to understand the factors that affect the development of food preferences in order to promote healthy eating behaviors.

Television viewing is linked to a poor diet and obesity

- Television is one of the most popular leisure time pursuits across the globe.
- Television viewing is associated with obesity in children and adults.
- Television viewing is specifically associated with increased caloric intake, increased snacking, reduced intake of fruit and vegetables and poorer overall diet quality.

The extent and nature of television food advertising

- Television is the primary medium used for advertising food and drink items.
- A majority of the foods advertised are high in fat, sugar, and/or salt.

Television food advertising effects on food preferences, choices and consumption

– There is a correlation between the frequency of energy-dense food advertising on television and the prevalence of obesity in numerous countries.
– Television food advertising influences children's purchase requests, brand preferences, food preferences, and consumption.
– Advertisements for healthier food products increases positive attitudes toward these items and also have a small but beneficial effect on consumption.

Intervention strategies: reduce television viewing and limit food advertising

– Reduced television viewing can effectively reduce body mass index
– Both, limiting energy-dense food advertising and encouraging healthy food advertising could be effective strategies towards improving children's food preferences and choices.

Applications to other areas of health and disease

– Reducing exposure to advertising for potentially harmful products is a strategy that has been shown to be effective at decreasing cigarette consumption.
– Similar strategies are also likely to be useful for reducing alcohol consumption in young people.

Definitions of Key Terms

Obesity: An excess of body fat. Obesity is defined as a body mass index (BMI) of 30.0 kg/m^2 or greater.
Adiposity: The accumulation of adipose (fatty) tissue.
Food preference: The selection of one item over another, with liking as the basis for selection.
Energy-dense foods: Foods with a high number of kilojoules or calories per amount of food.
Energy intake: The caloric content of food ingested, related to hunger, satiety, and nutrient absorption.
Energy expenditure: The amount of calories expended through resting metabolic rate, thermogenesis, and physical activity.

References

Apologies, this citation should read 2006 and be referenced as follows: McGinnis, J.M., Gootman, J.A., Kraak, V.I., eds. (2006). Food marketing to children and youth: threat or opportunity? Washington, D.C.: National Academies Press.
American Academy of Pediatrics. Pediatrics. 2001;107:423–6.
Andersen RE, Crespo CJ, Bartlett SJ, Cheskin LJ, Pratt M. JAMA. 1998;279:938–42.
Benton D. Int J Obes. 2004;28:858–69.
Birch LL. Ann Rev Nutr. 1999;19:41–62.
Borzekowski DLG, Robinson TN. JADA. 2001;101:42–6.
Boynton-Jarrett R, Thomas TN, Peterson KE, Wiecha J, Sobol AM, Gortmaker SL. Pediatrics. 2003;112:1321–6.
Brody GH, Stoneman Z, Lane S, Sanders AK. Fam Relat. 1981;30:436–9.
Buijzen M, Schuurman J, Bomhof E. Appetite. 2008;50:231–9.
Cooke LJ, Wardle J. Br J Nutr. 2005;93:741–6.
Coon KA, Goldberg J, Rogers BL, Tucker KL. Pediatrics. 2001;107:7–15.
Crespo CJ, Smit E, Troiano RP, Bartlett SJ, Macera CA, Andersen RE. Arch Pediatr Adolesc Med. 2001;155:360–5.
Davison KK, Marshall SJ, Birch LL. J Pediatrics. 2006;149:32–7.
Dennison BA, Erb TA, Jenkins PL. Pediatrics. 2002;109:1028–35.

Dibb S. A spoonful of sugar – Television food advertising aimed at children: An international comparative survey. UK: Consumers International; 1996.

Dietz WH, Gortmaker SL. Pediatrics. 1985;75:807–12.

Dixon HG, Scully ML, Wakefield MA, White VM, Crawford DA. Soc Sci Med. 2007;65:1311–23.

Epstein LH, Valoski AM, Vara LS, McCurley J, Wisniewski L, Kalarchian MA, Klein KR, Shrager LR. Health Psych. 1995;14:109–15.

Epstein LH, Roemmich JN, Robinson JL, Paluch RA, Winiewicz DD, Fuerch JH, Robinson TN. Arch Pediatr Adolesc Med. 2008;162:239–45.

Escalante de Cruz A, Phillips S, Visch M, Saunders DB. Malaysia: Consumers International; 2004.

Fischer R, Birch JL. JADA. 1995;95:759–64.

Galst JP, White MA. Child Dev. 1976;47:1089–96.

Gorn GJ, Goldberg ME. J Con Res. 1982;9:200–5.

Halford JCG, Gillespie J, Brown V, Pontin EE, Dovey TM. Appetite. 2004;42:221–5.

Halford JCG, Boyland EJ, Hughes G, Oliveira LP, Dovey TM. Appetite. 2007a;49:263–7.

Halford JCG, Boyland EJ, Hughes GM, Stacey L, McKean S, Dovey TM. Public Health Nutr. 2007b;11:897–904.

Halford JCG, Boyland EJ, Cooper GD, Dovey TM, Smith CJ, Williams N, Lawton CL, Blundell JE. Int J Pedivatric Obes. 2008;3:31–8.

Haslam DW, James PT. Lancet. 2005;366:1197–209.

Hastings G, Stead M, McDermott L, Forsyth A, MacKintosh AM, Rayner M. Review of research on the effects of food promotion to children. The University of Strathclyde, Glasgow: Centre for Social. Marketing; 2003.

Hancox RJ, Poulton R. Int J Obes. 2006;30:171–5.

Hill JO, Peters JC. Science. 1998;280:1371–4.

Hitchings E, Moynihan PJ. J Hum Nutr Diet. 1998;11:511–7.

IOM. Preventing childhood obesity: health in the balance. Washington, DC: The National Academies Press; 2005.

Jeffery RW, French SA. Am J Public Health. 1998;88:277–81.

Lewis MK, Hill AJ. Int J Obes. 1998;22:206–14.

Lobstein T, Dibb S. Obes Rev. 2005;6:203–8.

Lobstein T, Baur L, Uauy R. Obes Rev. 2004;5:5–104.

Marquis M, Filion YP, Dagenais F. Can J Diet Pract Res. 2005;66:12–8.

Matheson DM, Killen JD, Wang Y, Varady A, Robinson TN. Am J Clin Nutr. 2004;79:1088–94.

McGinnis JM, Gootman JA, Kraak VI. Food marketing to children and youth: threat or opportunity? Washington, DC: National Academies Press; 2006.

Nicholson M, Hoye R. JAMA. 2009;301(14):1479–82.

Oates C, Blades M, Gunter B. J Marketing Man. 2003;19:401–9.

Office of Communications (Ofcom). Childhood obesity: Food advertising in context; 2004, 22nd July.

Office of Communications (Ofcom). Media literacy audit: Report on media literacy amongst children; 2006, 2nd May.

Office of Communications (Ofcom). Television advertising of food and drink products to children: Final statement; 2007, 22nd February.

Prentice AM, Jebb SA. BMJ. 1995;311:437–49.

Reilly JJ, Wilson D. Childhood obesity. Br Med J. 2006;333:1207–10.

Robinson TN. JAMA. 1999;282:1561–7.

Robinson TN, Borzekowski DLG, Matheson DM, Kraemer HC. Arch Pediatr Adolesc Med. 2007;161:792–7.

Signorielli N, Lears M. Health Commun. 1992;4:245–57.

Swinburn B, Shelly A. Int J Obes. 2008;32:S132–36.

Viner RM, Cole TJ. J Pediatrics. 2005;147:429–35.

Which?. Television advertising of food and drink products to children: Further consultation; 2006, Ofcom, 19 December.

Wiecha JL, Peterson KE, Ludwig DS, Kim J, Sobol A, Gortmaker SL. Arch Pediatr Adolesc Med. 2006;160:436–42.

World Health Organisation. Diet, nutrition and the prevention of chronic diseases: Report of a joint WHO/FAO expert consultation. WHO technical report series, No. 916, Geneva: World Health Organisation; 2003.

Chapter 65
The Construction of Eating Episodes, Food Scripts, and Food Routines

Carole A. Bisogni, Margaret Jastran, and Christine E. Blake

65.1 Introduction

Food choice involves how people think, feel, and act related to food and eating. Food choice not only affects the health and well-being of individuals and families, but it also impacts agriculture, the environment, business, culture, and the economy at local, regional, national, and global levels. Complex and dynamic, food choice involves a wide array of interacting factors and processes that are biological, psychological, social, cultural, geographic, political, and economic (Sobal et al. 2006; Sobal and Bisogni 2009).

Understanding food choice at the individual level is particularly challenging when the food system provides a myriad of options and culture accepts eating in many different ways, times, and places. In many groups, traditional ways of eating (e.g. meals prepared at home or a pattern of three meals per day) are being replaced by eating more foods prepared away from homes, consuming fewer family meals, and eating in individualized ways. Researchers and health practitioners need ways to conceptualize food choice to allow for the different styles by which people, think, feel, and act related to food and how they do this in specific situations. Studies of dietary change for health reasons indicate that people often have trouble maintaining new food behaviors because of situational factors, the surrounding details or the specific circumstances in which they eat (Janas et al. 1993; Falk et al. 2000).

This chapter discusses concepts and methods developed by the interdisciplinary Cornell Food Choice Research Group for understanding how people experience their eating situations. The chapter begins with a description of the conceptual model developed by this group, the Food Choice Process Model, a representation of the factors and processes involved in individual food choice from people's perspectives. The next sections describe a study of situational eating and the concepts of eating episodes, food scripts, and food routines that emerged from this study. The chapter concludes with a discussion of ways that the model and these concepts may be applied in research and health promotion (Table 65.1).

65.2 The Food Choice Process Model

The Food Choice Process Model (Fig. 65.1) is an inductive, conceptual model of food choice that is based on how adults construct their thoughts, feelings, and actions related to food and eating (Furst et al. 1996; Sobal et al. 2006; Sobal and Bisogni 2009). This model was developed using

C.A. Bisogni (✉)
Division of Nutritional Sciences, 183 MVR Hall, Cornell University, Ithaca, NY 14853, USA
e-mail: cab20@cornell.edu

Table 65.1 Key Features of eating episodes, food scripts and food routines

1. The concept of eating episodes seeks to capture the multidimensional experience of eating and drinking in specific situations by describing the details of the food/drink, time, location, social setting, mental processes, physical condition, and other activities
2. The concept of food scripts draws upon schema theory to understand how a person's cognitions are linked to food behavior in specific situations. Food scripts encompass the person's food choice values, expectations, and plans for behaving in the situation
3. Food routines are the repeating food behavior episodes and sequences of episodes that become best-fit solutions for a person's food choice values and schedules. Food routines provide stability but are modifiable as circumstances change

This table describes the key features of eating episodes, food scripts, and food routines derived from research reported in Bisogni et al. (2007), Blake et al. (2008), and Jastran et al. (2009)
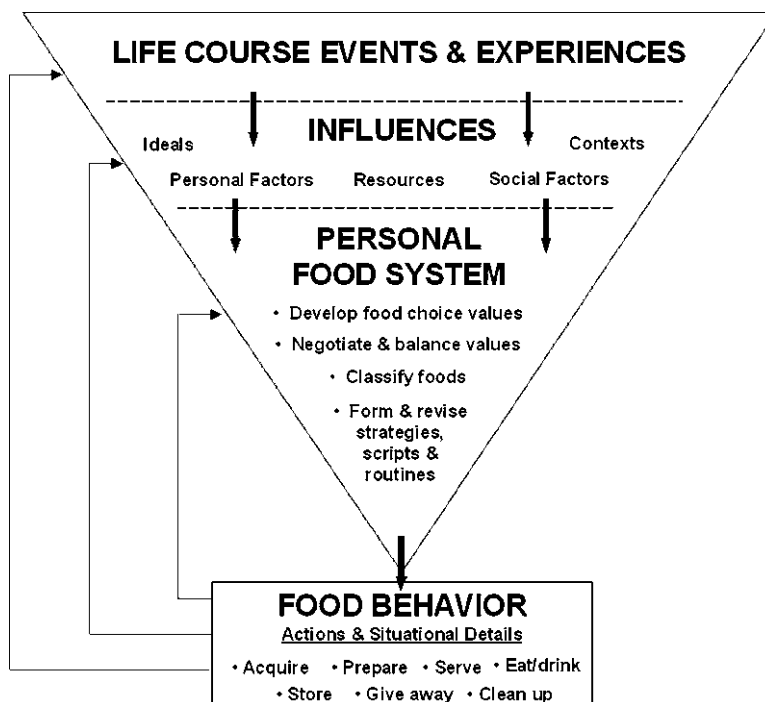
Fig. 65.1 A Food Choice Process Model. The Food Choice Process Model has four major components: Life Course Events and Experiences, Influences, Personal System, and Food Behavior. The first two parts of the model represent the many diverse and extensive factors shaping a person's food choice in general, while the third and fourth parts of the model portray a person's cognitive, affective, and behavioral processes of food choice (Adapted from Furst et al. 1996; Sobal et al. 2006; Sobal and Bisogni 2009)

qualitative methods that involved in-depth, open-ended interviews with adults and analysis of verbatim transcripts (Furst et al. 1996). The model has been refined and elaborated upon through several studies (Falk et al. 1996, 2001; Devine et al. 1998; Furst et al. 2000; Connors et al. 2001; Smart and Bisogni 2001; Blake and Bisogni 2003; Bisogni et al. 2007; Blake et al. 2007, 2008; Jastran et al. 2009). By focusing on the factors and processes in food choice that people themselves describe, the model takes a different perspective from other models of food choice that are developed primarily from experts' perspectives (Sobal et al. 2006; Sobal and Bisogni 2009).

The Food Choice Process Model portrays people as actively involved in constructing the ways that they think, feel, and act related to food in response to their past experiences and a host of factors

both personal and environmental. The model emphasizes people's own interpretations of the general and specific circumstances in which they eat and their perceptions of how they think, feel, and act. This view of food choice helps understand individual differences while also representing that people construct food choice in biological, physical, and social worlds that are changing and beyond their control. In this way, the model views a person as having agency in that they direct their own food choice to a large extent, but it also acknowledges the roles of biological factors and societal structures (Sobal et al. 2006; Sobal and Bisogni 2009).

This model has four major components: Life Course Events and Experiences, Influences, Personal System, and Food Behavior. The first two parts of the model represent the many diverse and extensive factors shaping a person's food choice in general while the third and fourth parts of the model portray a person's cognitive, affective, and behavioral processes for food choice. In this model, Life Course Events and Experiences are viewed as creating a wide array of Influences that affect the Personal Food System, which a person constructs to guide Food Behavior. However, a person's food behavior in different situations subsequently becomes a life course experience that may impact the Influences or cause a person to modify the Personal Food System.

Life Course Events and Experiences represent the historical, social, and geographic setting of birth and upbringing that affect how a person thinks, feels, and acts related to food and eating (Devine et al. 1998, 1999; Devine 2005). Also important are other events and experiences throughout a person's life such as changing roles and relationships, changing areas of residence, changing resources, the acquisition of knowledge and skills, or development of health conditions. These past events and experiences shape people's meanings and feelings related to food and eating, and provide models for behaving.

As a result of the Life Course, a person's food choice is shaped by a myriad of factors, which are grouped into five types of Influences: Ideals, Personal factors, Resources, Social factors, and Context (Sobal et al. 2006; Sobal and Bisogni 2009). Ideals represent the cultural meanings and standards for food and eating that people have developed through socialization and acculturation. Personal factors encompass the characteristics of the individual, including physiological factors (e.g. sensory perceptions, health conditions) and psychological characteristics of the person (e.g. preferences, personality, identity). Resources are the assets available for food choice, including tangible resources (e.g. money, facilities, equipment) and intangible human resources (e.g. time, knowledge, skills). Social factors are the relationships with other people that affect food choice, such as spouses, children, parents, relatives, coworkers, employers, employees, or friends. Contexts are the broader environmental factors that impact food choice, including physical surroundings (e.g. climate, geography, living space, workplace), the food system (e.g. agriculture, food manufacturing, grocery stores, restaurants), and the information setting (e.g. advertising, health information, nutrition information).

The Personal Food System represents the mental processes through which people manage these influences and develop options, tradeoffs, and approaches to food behaviors (Sobal et al. 2006; Sobal and Bisogni 2009). The Personal Food System considers how people make sense of food and eating given the opportunities and the boundaries set by the Influences. Research to date has proposed six processes within the Personal Food System, but these processes do not necessarily occur in sequence. The dynamic and interacting processes involve: (1) constructing food choice values (Furst et al. 1996; Falk et al. 2001; Smart and Bisogni 2001); (2) negotiating food choice values (Furst et al. 1996; Connors et al. 2001; Smart and Bisogni 2001); (3) classifying foods (Furst et al. 2000; Blake et al. 2007; Blake 2008); (4) forming and revising strategies to implement food choice values (Furst et al. 1996; Falk et al. 1996); (5) forming and revising food scripts (Blake et al. 2008); and (6) forming and revising food routines (Jastran et al. 2009).

Food choice values are the important considerations that a person constructs related to food and eating (Furst et al. 1996; Falk et al. 1996, 2001; Smart and Bisogni 2001). Common categories of food choice values are taste, health, cost, convenience, and managing relationships, but people may

have other important considerations, such as ethics, religion, family traditions, and the environment. People may hold culturally shared or individualized meanings for these values. For example, people's meanings for healthy eating may vary (e.g. low-fat, low-calorie diet, nutrient dense, natural, or organic foods; Falk et al. 2001).

Although people may seek to achieve all of their food choice values in food behaviors, their options often involve conflicts between food choice values (Furst et al. 1996; Connors et al. 2001; Sobal and Bisogni 2009). For example, a person may perceive the healthiest food as too expensive or as taking too long to prepare; a wife may sometimes compromise the food she enjoys to accommodate the preferences of her spouse. Therefore, people regularly have to make tradeoffs among their food choice values in different situations. People describe constructing unique systems for setting priorities and balancing their values over different food behaviors. They do this using personally defined time frames (e.g. meals, workdays/nonworkdays, school year/summer vacation, or before/after activities) and in ways that feel comfortable to them (Connors et al. 2001; Smart and Bisogni 2001).

People construct classification systems for foods that help them make decisions. (Furst et al. 2000; Blake et al. 2007; Blake 2008). Classification systems group foods in ways that people find meaningful from perspectives that are cultural (e.g. symbolic foods, high status foods), social (e.g. foods my friends eat, foods my children like), contextual (e.g. what is available in the setting), and personal (e.g. foods that relax me, vegetables I like) (Furst et al. 2000; Blake et al. 2007; Blake 2008). Whereas health professionals typically categorize foods into groups based on the properties of the food (i.e. commodity type or nutrient composition), people use a variety of classifying systems including personal experience (e.g. what I like, what makes me feel good) and context (e.g. what others like, what is available in this setting) (Blake et al. 2007).

Food strategies are the heuristics, guidelines, and rules that people develop to achieve their food choice values (Falk et al. 1996; Sobal et al. 2006; Sobal and Bisogni 2009). Developing and using strategies is another way that people simplify the many decisions they encounter in daily food and eating. Some examples of strategies are always having a vegetable at lunch and dinner to promote health, usually splitting desserts in restaurants to save money and calories, or turning off the telephone at family dinners so that the meal can be relaxing (Falk et al. 1996; Sobal et al. 2006; Bisogni et al. 2007; Blake et al. 2008).

The processes of the Personal Food System that are closest to behavior are the formation and revision of food scripts and food routines (Sobal and Bisogni 2009). Scripts address the detailed mental processes that guide food behavior in specific settings including appraisal of situations and procedural knowledge about what to do (Blake et al. 2008). Routines involve repetitive food behaviors and the details in which these behaviors occur (Jastran et al. 2009). Later sections of the chapter will elaborate on food scripts and food routines.

The final component of the Food Choice Process Model is Food Behavior. This component includes food-related actions as well as the situational details in which an action occurs as experienced by the person (Bisogni et al. 2007). Situational details involve not only what food is consumed but also who is present, where the action happens, when the action happens, what else is going on, and other factors involved as perceived by the person. Food-related actions encompass a wide spectrum that can be organized into the following types: food acquisition, preparation, serving, eating, storing, giving away, and cleaning up (Sobal and Bisogni 2009). These types of behaviors may be considered individually, but they must also be viewed as interconnected. For example, to cook a big dinner on Sunday that will provide leftovers for Monday dinner, a substantial amount and variety of food must be purchased and prepared. The dinner involves extensive serving, consumption, and cleaning up. Storage of the leftovers is thoughtful so that Monday's dinner can involve fewer and less complex steps of preparation, eating, and cleanup.

Overall, the Food Choice Process Model views the factors and processes involved in food choice as complex, interacting, dynamic, and interpreted from the person's perspective (Sobal et al. 2006; Sobal and Bisogni 2009). People develop personal food systems in an ever-changing environment as they proceed through their life course and experience a multitude of influences. Their food behaviors become part of their life course experiences and also impact the influences in an ongoing manner. People's food behaviors also shape their personal food systems as people interpret and evaluate food behavior experiences. As a result, they may revise food choice values or the ways that they negotiate values. They may also revise their food classifications, strategies, scripts, and routines.

In the Food Choice Process Model, the distinctions between the components of the model are blurry, and the model is not intended to be mechanistic. Instead the goal is to provide a conceptual framework that identifies and organizes the extensive array of disparate factors and processes that are involved in food choice from people's perspectives (Sobal et al. 2006; Sobal and Bisogni 2009). The model is unusual in attempting to represent a holistic perspective that integrates ideas from multiple disciplines, attends to factors and processes at both macro and micro levels, and accounts for structural factors, personal agency, and time. Researchers could draw upon the model to generate hypotheses about how people think, feel, and act related to food (e.g. Devine et al. 1999).

65.3 Situational Eating Study

Applying the perspective that people construct food choice (Sobal et al. 2006; Sobal and Bisogni 2009), researchers studied situational eating among working adults to learn about the individualized ways that these adults experienced eating in their daily lives (Bisogni et al. 2007). Forty-two adults (21 men, 21 women) working in nonmanagerial, nonprofessional positions provided seven, consecutive-day, 24-h qualitative recalls of their food and beverage consumption. In daily recalls participants reported foods and beverages consumed, the location, people present, their feelings at that time, and other activities in which they were involved while eating or drinking. Interviewers used open-ended questions and avoided using traditional meal labels such as breakfast, lunch and dinner to be open to participants' interpretations. Additional qualitative interviews provided supplementary information about the factors and processes that were important to these adults and their typical food behaviors in different locations, such as evening meals at home (Blake et al. 2007).

This study of situational eating provided rich data about how people eat in their natural settings that enabled researchers to elaborate on components of the Food Choice Process Model. The concepts of eating episodes, food scripts, and food routines emerged from this study and are described in the next sections.

65.4 Eating Episodes

Eating episodes are characterized by seven dimensions experienced at the time of consumption: food and drink, location, social setting, time, mental processes, activities, and physical condition (Bisogni et al. 2007). As shown in Table 65.2, each dimension is a cluster of features that can be used to further characterize the eating episode from the person's perspective. For example, food can be described as type of food, quantity of food, preparation, source, and how eaten. Time involves chronological time but also the timing of the episode in relation to other activities (before work, after school) and the perception of time (e.g. killing time, in a hurry).

Table 65.2 Dimensions and features of eating episodes that a person may experience using an example from the case of a working mother of a 2-year-old daughter (Adapted from Bisogni et al. 2007)

Dimension	Features	Examples
Food and drink	Types; Forms; Amounts; Sources; Packaging, Nutrient composition	Coffee, black, large mug, made at home
Location	General, Specific	Home, at kitchen table
Time	Chronological, Relative, Perceived	6:30 am, before work
Social setting	Persons present, Social processes	Caring for daughter
Mental processes	Dominant values	Feeling rushed, Being a good mom
Physical condition	Nourishment, Other	Waking up
Activities	Type, Salience	Feeding daughter

This table lists the seven dimensions of an eating episode and the features within each dimension that can be used to understand an eating episode from a person's perspective

This concept of eating episodes with multiple dimensions is consistent with and extends work by other food choice researchers (Meiselman 1996; Sparks and Shepherd 1992) that describe situational eating as involving the person, the food, and the setting. This view is also consistent with psychological models of person–environment interactions that emphasize the importance of a person's perception of the situation (Lewin et al. 1936) and the dynamic and reciprocal nature of person–environment interactions (Magnusson and Torestad 1992)

Participants in the situational eating study used various types of descriptors to label their eating episodes as they reported their 24-h recalls (Bisogni et al. 2007). As shown in Table 65.3, 73% of episodes had conventional meal labels (e.g. breakfast, lunch, dinner), other conventional labels (e.g. break, snack), or modified conventional labels ("early dinner," "little snack"). More than one-fourth of the episodes were assigned uniquely constructed labels ("my little pick me up," "morning coffee," "my relaxing time"). The common use of conventional labels shows the shared language that existed among these participants. The modified conventional labels and uniquely constructed labels gave clues to the dimensions of the episode that were salient to the person. For example, "my relaxing time" was used by a grounds keeper to describe his lunch time at home where he could rest and get away from work.

Figure 65.2 shows how the concept of eating episodes relates to the Food Choice Process Model. Eating is one type of food behavior that can be viewed as occurring in multidimensional episodes to represent the person's experience. People assign their own labels to these episodes. People develop scripts and routines as part of their personal food systems that shape these eating episodes. The scripts and routines are shaped by other parts of the personal food system and also by the influences and life course events and experiences. Eating episode experiences then become life course experiences and also may affect the influences and the personal food system. Based on a particular eating episode, a person may choose to alter the script or routine.

To further illustrate the concept of eating episodes, Table 65.4 summarizes the sequence of eating episodes on a workday reported by a mother of a young child. This mother begins the day with "my first coffee" at home before going to work and while feeding her toddler. After driving her daughter to childcare and while still en route to work, she fuels herself quickly and cheaply at a fast food restaurant with more coffee and a breakfast sandwich, which she calls her "morning food stop." By noon she is hungry again so she heats up a frozen entrée and has a "working lunch" at her desk where she is trying to catch up. In midafternoon she buys her "afternoon treat" from the vending machine, which she eats at her desk. After work, she picks up her daughter and heads home where by 6:00 she is feeding her daughter, having her own "bite before dinner," and planning what she will eat for dinner. Her husband is out of town so her "supper without Dan" is a ham sandwich, soup, and salad, but she feels tired of ham and thinks she should be eating more vegetables. During dinner she is watching and talking to her

Table 65.3 Types of labels adults used to describe eating episodes in study of situational eating that analyzed 1,448 eating and drinking episodes reported in 7-day situational recalls by 42 US working adults (Adapted from Bisogni et al. 2007)

Label types	Percent of episodes assigned label type (n = 1448)	Examples of labels
Conventional	40%	*Breakfast, lunch, dinner, supper, brunch*
Other conventional	23%	*Drink, snack, break*
Modified conventional	9%	*Big dinner, quick and easy dinner*
Uniquely constructed	28%	*Midnight eating, relaxing time, morning coffee*

Study participants used conventional labels to describe eating episodes 40% of the time, other conventional labels 23% of the time, modified conventional labels 9% of the time, and uniquely constructed labels 28% of the time across 1,448 eating episodes. Examples of each type of label are shown
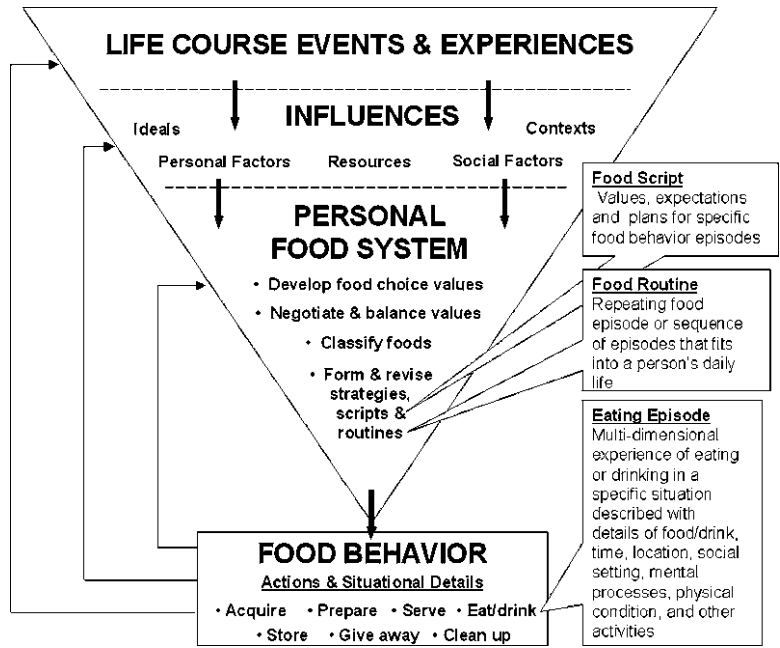
Fig. 65.2 Elaboration on eating episodes, food scripts, and food routines in the Food Choice Process Model. This figure of the Food Choice Process Model shows that food scripts and food routines are components of the personal food system. Eating episodes are a way to describe eating and drinking behaviors (Adapted from Furst et al. 1996; Sobal et al. 2006; Bisogni et al. 2007; Sobal and Bisogni 2009)

daughter who is playing. At 9:30 this mom relaxes while watching a favorite TV show when she has some crackers and soda before going to bed.

The representation of episodes as multidimensional emphasizes that to understand situational eating, researchers must be open to the person's perspective on the experience. For the person involved, the episode may be less about food and more about the other dimensions such as social setting or other activities. Whereas time, location, appetite, and people present are often considered characteristics of eating episodes, researchers have paid less attention to other dimensions, particularly social processes (i.e. how the people are interacting), mental processes (what people are thinking about related and unrelated to food), and the other nonfood activities occurring at the same time.

Table 65.4 Summary of eating episodes, dimensions, and labels in 1 day for a working mother of a 2 year-old daughter

Episode dimensions	Episodes in a 24-h period and labels used by person to describe them						
	My first coffee	My morning food stop	Working lunch	Afternoon treat	Bite before dinner	Supper without Dan	My TV snack
Food	Coffee	Coffee, Fast food breakfast sandwich	Juice, Frozen entrée from home	Chocolate bar from vending machine	Crackers, Juice	Ham sandwich, Canned soup, Salad, Water	Crackers, Diet soda
Time	6:30 a.m. before work	7:45 a.m. on way to work after child at daycare	Noon	3:00 p.m., a few hours before end of work	6:00 p.m. after work, before cooking	7:00 p.m. before putting daughter to bed	9:15 p.m. before going to bed
Location	Home at kitchen table	Car in driver's seat	Work at desk	Work at desk	Home in kitchen	Home in kitchen on floor	Home in living room
Mental processes	Feel rushed, Be a good mom	Feel rushed, Get fueled, Get good buy	Get fueled, Catch up with work	Deserve a treat, Chocolate keeps me going	Plan what's for my dinner, Feel happy to be home	Tired of ham sandwich, should buy more vegetables	Enjoying favorite show, Relaxing
Social setting	Caring for daughter	Alone	Alone	Alone	Talking with daughter	Talking with daughter	Alone
Physical condition	Waking up	Feeling hungry	Hungry	Sluggish	Tired	Awkward sitting on floor	Tired
Activities	Feeding daughter	Driving to work	Answering e-mail	Reading reports	Feeding daughter	Watching daughter	Watching TV

The columns of this table show the seven eating episodes reported by a working mother for 1 day. The rows show how the dimensions can capture the details of her experience

65.5 Food Scripts

To simplify decision making processes in recurring eating episodes, people develop food scripts that guide their behavior. Food scripts are a person's expectations and plans for acting in the situation. The term script is derived from schema theory which is used to explain how people store, retrieve, and use information (Spradley 1972; Markus 1977; Rumelhart 1984; Nishida 1999; Wagner 2005). Schemas are generalized collections of knowledge stored in long-term memory and constructed from past experience that contain organized and related categories and scripts that guide behavior in subsequent familiar situations (Olson 1981; Baldwin 1992; Axelson and Brinberg 1992; Blake and Bisogni 2003).

An individual's current food scripts are based on past food and eating experiences (Furst et al. 1996). Scripts are derived from past planning, prior actions that were successful, or habitual actions, and their invocation in new situations is thought to immediately precede the initiation of action (Schank and Abelson 1977; Baldwin 1992). How a person interprets an eating episode is important because perception of a present situation as similar to a past well-known situation can evoke an existing script (Baldwin 1992). Schema theory assumes that people actively construct their lives, including ways of eating that are tailored to different situations. The concept of food scripts elaborates on the cognitive processes within the Personal Food System of the Food Choice Process Model to provide a better understanding of how people translate Influences into episode-specific food behaviors (Furst et al. 1996; Connors et al. 2001; Sobal et al. 2006).

Scripts guide behavior in recurrent eating episodes because they contain sequential information about key events common in those episodes (Schank and Abelson 1977; Abelson 1981; Baldwin 1992; Holmberg and MacKenzie 2002; Wagner 2005). The elements of a script usually have an inherent temporal sequence that is logically determined and collectively describes an episode (Lakshmi-Ratan and Iyer 1988). In some instances the temporal sequence is less rigid and scripts contain if–then statements to accommodate different possibilities within a given situation (Baldwin 1992; Blake et al. 2008).

Researchers explored the concept of food scripts in the situational eating study that was previously described (Bisogni et al. 2007; Blake et al. 2008). Researchers focused on understanding food scripts for the evening meal, considered to be one of the most important eating episodes of the day by many nutrition professionals because it has significant social and nutritional implications (e.g. Gillman et al. 2000; Bove and Sobal 2006). In a series of open-ended questions participants were asked to talk about the things they do when they eat, how they do them, and why they do these things in each eating episode with further probing questions about the importance of the episode, foods, other people, roles, identities, emotions, and activities.

Researchers analyzed participants' reports about their evening meals through an iterative process of reviewing the literature and analyzing emergent themes. Researchers formulated and delineated seven key concepts for comparing and contrasting participants' evening meal scripts: dominant values, expectations, plans, strategies, procedures, scope, and flexibility. Dominant values were considerations that participants explained as important for the evening meal (Connors et al. 2001). Expectations were participants' descriptions of how the evening meal would proceed and what would be happening, such as time, place, people, activities, and emotions. Plans consisted of the behavior sequences involved in the evening meal episode, such as shopping, deciding what to have for a meal, and cooking. Each behavior in the sequence was associated with strategies and procedures (Schank and Abelson 1977; Baldwin 1992). Strategies were seen as typical approaches to the behaviors (Baldwin 1992) or "knowing what to do," such as sharing meal preparation responsibilities. Procedures were the "knowing how" to do these behaviors, or the details of who would be doing

what in preparing the meal. Scope referred to the starting and ending points of the script in terms of the number of different types of food behaviors that were involved. Flexibility considered how many if-then statements the script contained as the person explained alternative expectations, strategies, plans, and procedures for the meal.

Using these concepts, the researchers summarized the evening meal script for each participant. Script summaries depicted participants' interconnected dominant values, expectations, and plans that included strategies and procedures. The researchers then examined scripts for the evening meal across participants using the constant comparative method to identify commonalities and differences (Strauss and Corbin 1990). From this analysis, eight kinds of scripts for the evening meal emerged, with each of the participants represented in one kind of script. Researchers named each kind of script to reflect the group of participants it represented (e.g. "Provider Script," "Anything Goes Script," "Family Cook Script," "Just Eat Script").

Dominant values. Participants expressed many values for the evening meal with the most common being "family time." For example, participants said "the most important thing about dinner at home is for the family to be together eating together" and "that time is just family time." Others expressed valuing uninterrupted quiet so they could relax during the evening meal. These participants said, "having some down time, relaxing… not rushing around [is important]" and "[I try to] eat without interruption. It don't happen that often. I mean that's my relax time. After a hard day's work, all I want to do is come home, chill out, relax." Other values included getting the family fed, having foods that everyone likes, just eating, having a nutritious meal, recreating childhood experiences, and entertaining guests. Dominant values frame an individual's food script and are similar to goals described in the schema literature as a desired end to a sequence of actions (Schank and Abelson 1977; Trzebinski 1985; Baldwin 1992).

Expectations. General expectations for the evening meal were represented in participants' overall summaries of how things would "go" for this meal. Participants described what they expected to happen at the evening meal (e.g.,"Dinner is usually about 6:30 to 7:00"), who they expected to be there and how they would behave (e.g., "I expect anyone that sits at my kitchen table to be somebody who respects and cares about the people at that table"), their own anticipated emotional state (e.g., "So I usually feel relaxed and content and happy to be there."), expected satisfaction with the outcome ("[I'm satisfied] when things go smoothly and you don't burn anything and everything tastes good and everything goes together and it's a nice time together when there's not a lot of static"), and whether the episode would be a positive or negative experience (e.g., "[dinner is] the most relaxed situation, it's the best situation…because there's less pressure and we don't have to follow any food chain guidelines or whatever. (laughs) Just him and me. It's fun that way.") Participants' general expectations provided insight about their conceptualization of the evening meal as a whole.

Plans, strategies, and procedures. Information about what to do in various situations is contained in the plans, strategies, and procedures (Baldwin 1992; Nishida 1999). Evening meal scripts included planned sequences of different behaviors that included but were not limited to arranging, shopping, deciding what to have, getting input from others, preparing food, serving food, announcing the meal, arranging seating, eating, meal time conversation, other meal time activities, and cleaning up. Evening meal plans also included interconnected detailed strategies for the different behaviors and specific procedures used to carry out these strategies.

Strategies describe behaviors that are linked to dominant values. For example, a participant who valued "family time" described strategies that would encourage an extended and enjoyable time for the family members to eat together such as arranging seating for a sit-down dinner or putting food on the dining table instead of having people serve themselves from the kitchen.

Procedures differentiate the "knowing what" of strategies from "knowing how" by providing specific steps and rules for behavior. Procedures are specific to the different behaviors participants described for the evening meal such as planning, cooking, or interacting and for the strategies employed.

Script scope and flexibility. Participants' evening meal scripts varied in scope. Scripts began and concluded at different points depending on participants' involvement and the importance they placed on the evening meal. Some scripts began many hours before the actual consumption of food. The plans of these participants included multiple food-choice behaviors such as premeal arranging, shopping or buying food, preparing food, eating, meal interactions, and cleaning up. Although many of these activities occurred before or after consumption, participants still included them as part of their scripts for the evening meal. Other participants' plans were smaller in scope because they began and ended at or near the consumption of food.

Participants with more meal responsibilities tended to have more detailed scripts. They described thinking about the evening meal in advance and making various decisions like where to eat, what to have, or who to eat with. Although many of the food behaviors occurred before or after consumption, participants included them as part of their evening meal scripts. Participants with less detailed scripts often began their plans with waiting for the food to be ready and did not include much detail about meal preparation or cleanup.

Participants' evening meal scripts differed in flexibility depending upon the extent to which they had to accommodate day-to-day variations in timing, weather, people, foods, other activities, and moods. Participants used "if-then" statements as they explained the alternative behaviors, strategies, and procedures that occurred when different aspects of the evening meal changed. Participants with irregular schedules used more if-then statements in their evening meal scripts compared to participants with more consistent schedules.

Examples of evening meal scripts with different levels of scope and flexibility are shown in Fig. 65.3. The "Provider Script" shows extensive scope and some flexibility. In contrast, the "Anything Goes Script" has considerable flexibility but not much scope.

Kinds of evening meal scripts. Figures 65.4 and 65.5 present examples of script summaries for two participants with very different kinds of behaviors related to evening meals. The "Family Cook Script" example represents the evening meal of a working father who is the cook for these meals. The "Just Eat Script" example represents the evening meals of a man who lives with his girlfriend. These scripts show the household's behaviors leading up to the evening meal, how household members share or do not share in the responsibilities with their spouses/partners, and how spending time with children is related to the food choice scripts.

Case studies. Two evening meal case studies (Tables 65.5 and 65.6) elaborate on the scripts summarized in Figs. 65.4 and 65.5 by showing the relationships between dominant values, expectations, strategies, and procedures. The first case presents a father who described himself as "head of the table" (Table 65.5). Researchers considered his script to be representative of a "Family Cook Script" because it covered a wide range of food behaviors from planning to cleanup. He used many if-then statements to describe different possibilities and his script contained a lot of detail. His dominant value was "for the family to be together, eating together," and his script shows what this means and how he makes this happen.

The second case study (Table 65.6) presents the evening meal script of a man who lived with his girlfriend and had no involvement in meal planning, preparation, or cleanup. His script is representative of the participants having a "Just Eat Script" because it is very simple with limited detail. His dominant value was to "get full" and his script demonstrates how he achieves this value.

65.6 Food Routines

The idea of repetitive eating episodes and repetitive sequences of eating episodes is not surprising, but the concept of food routines has not been examined extensively in research. Much of daily life includes repetition. Work and family life provide structures that are similar day-to-day, promoting
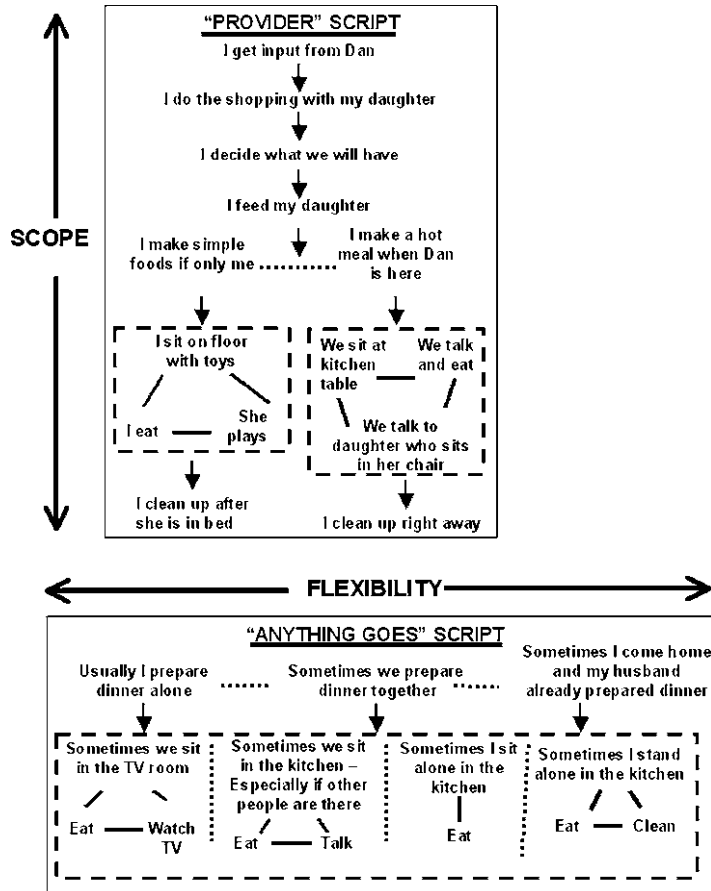
Fig. 65.3 Examples of evening meal script summaries depicting different combinations of script scope and flexibility. ↓ Sequential behaviors, — alternative behaviors, \ simultaneous behaviors, ⬚ behaviors while eating

Fig. 65.4 Food script summary for a person with a "Family Cook" evening meal script. ↓ Sequential behaviors, — alternative behaviors, \ simultaneous behaviors, ⬚ behaviors while eating
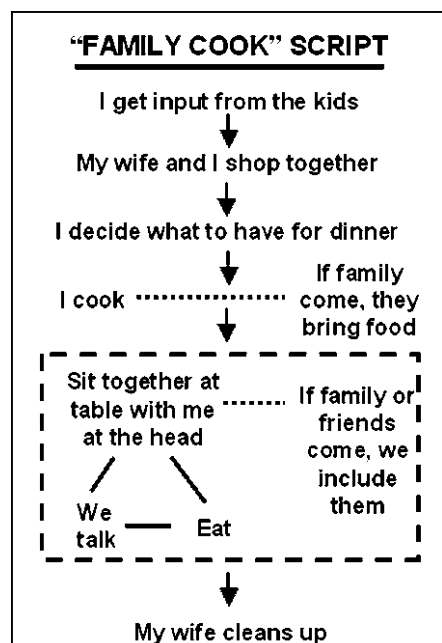
Fig. 65.5 Script summary
for one participant with a
"Just Eat" evening meal
script. ↓ Sequential behaviors,
— alternative behaviors,
\ simultaneous behaviors,
⸬ behaviors while eating
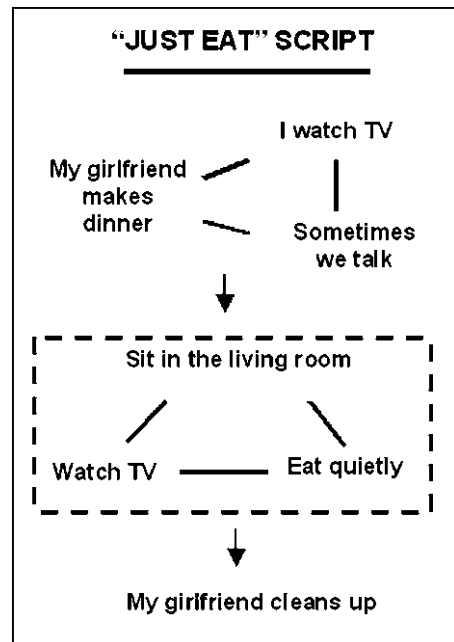
construction of food routines to create greater ease in daily life (e.g. Khare and Inman 2006). Routines are well recognized behavior patterns that people often employ to provide organization, simplicity, efficiency, and security in life, as well as a sense of comfort (Connors et al. 2001; Zisberg et al. 2007). Routines bring stability and familiarity to daily and weekly events and create a feeling of normalcy (Ilmonen 2001). Predictable routines are an adaptive resource for dealing with change (e.g. Zisberg et al. 2007). Consequently, most people have routines for many aspects of daily life, especially activities involving work and family. Time scarcity, common in modern life, also prompts many people to develop and maintain routines that streamline recurrent decisions and tasks (Jabs et al. 2007).

In the situational eating study described earlier, participants frequently reported repetition in food/drinks consumed, time and location for eating, social features, activities, thoughts/feelings, or physical conditions (Bisogni et al. 2007; Jastran et al. 2009). In addition, they often reported repetitive patterns of episodes over a day in that the number, timing, and order of eating episodes were similar over a number of days when the person's family or work schedule remained the same. They often referred to "my routine," and the seven consecutive days of recalls prompted them to acknowledge this repetition to themselves and the interviewers. Typical comments from participants included "Then after work I had some peanuts, which you'll be hearing from me every day…" and "just like yesterday. I follow the same exact routine on the days I work early".

When the working mother's daily eating episodes shown in Table 65.4 are viewed from the perspective of food routines, it shows the repetitive nature of eating episodes for this working mother and the sequences of episodes that create a typical food routine for her on a workday. The day begins with "my first coffee," which precedes a larger morning meal with more coffee, which is linked to lunch and so on. Her uniquely constructed labels for these episodes, such as "my first coffee," "my morning food stop," and "bite before dinner," indicate how familiar and predictable these eating episodes are to her. In each episode, dimensions such as a regular time of day for a certain food or a certain social setting create the routine. For example, the working mother has a workday routine of drinking coffee as she feeds her young child in the morning and then, after delivering the child to the

Table 65.5 Summary of general expectations, dominant values, and the strategies and procedures for different behaviors in an evening meal script from a father whose script was considered by researchers to be a "Family Cook Script"

Participant example of "Family Cook Script" for evening meals	
"Typically" me, my wife, and our two sons	
General expectation	"I think that's the one time of the day that all other differences are set aside and that's why it's so special. It doesn't matter if we've all had a bad day. Dinner is when we're together, and, nothing else matters as far as, who did what, or, who's mad at who"
Dominant values	"The most important thing about **dinner at home** is for the family to be together, eating together"
Get input	
Strategy	"…somewhere during the week, I try to get it…we try to get input…from the kids mainly, on what they want to eat"
Procedure	"They give suggestions of things they'd like. They'll have eaten something in a restaurant and say 'can you make this?'…. Or…I've made something and they'll say 'wow that's really good!'…for example, rice pilaf. Now that they know I know how to make rice pilaf…they don't buy the prepackaged mix….So we make it from scratch and it's actually a lower cost…. And they actually eat everything that's there. Like I said they make a lot of suggestions on different foods"
Shop together	
Strategy	"Me and [my wife] do [the shopping] together…we make the decisions together…On food"
Decide what to have for dinner	
Strategy	"[I think] 'what are we gonna eat and how can we do it without causing a battle?'…it doesn't makes sense to…make something and know the kids aren't gonna eat any of it…. Or something that [my wife] doesn't like."
Procedure	"There's enough foods out there that all four of us can be happy at the same time…as far as foods that we would eat for **dinner**, we never fix anything that the four of us won't eat…. If there's something I particularly want, I can have it for a different meal… because we're talking **dinner** when it's the four of us…. And if it's something I really want, I will make it to bring for **lunch**, or make it when the boys aren't there."
	"if it's just, my wife and the boys, we keep it pretty simple. We know they're not that vegetable eaters so, we don't, elaborate on vegetables…. Almost all of our **dinners** are a **protein based meal**. So these are just our, again, proteins, um, and there's some fast foods in here. Um, we do eat fast food sometimes…[protein food] is our **main meal**. … And then we build around it…Dessert…dessert, uh, for us is something that, we do have a couple hours later…beverages varies…. I mean it goes from water, the boys drink regular soda. Tammy and I drink diet sodas. We only have 2% milk. Sometimes the boys drink juice, occasionally [my wife] and I have a glass of wine"
Decide what to have if we have family or friends come	
Strategy	"[if we have family come] The quantity of food [is different]…. And the variety."
Procedure	"If it's other family, we will, do a lot more salads, a lot more, variety in the meal. I mean everybody will, it's almost like a **potluck dinner**. Where everybody'll bring a lot more things…. So, it ends up being a lot more food. …if the whole family's there, we do desserts occasionally, they bring it…cause they bring it"
Cook	
Strategy	"I usually do all…I usually do the majority of the cooking."
Procedure	"I was in food service for 25 years before coming to [my present work]. I like to really, well I guess I can say simplify. Last night's **dinner** was simple, it was just grilled chicken. But I also like at the same time to experiment with different sauces, like that. Or, there are times when I cook that I really super-garnish everything…. One thing is as far as the tasks, I am capable of having everything come off the stove at the exact same time. Or off of two different cooking surfaces. Like you know I can be out at the grill and have something on the stove or and in the oven and have everything get done at the exact same time. From years of experience for one thing. But also the task that has to go along with it that I'm not as good as I should be, or at least my wife tells me I'm not, is you know cleaning everything as I go. (laughs)…if I'm prepping vegetables, I don't prep them on the counter next to the stove, I prep them on the counter next to the sink. Because that's where the garbage disposal is"

(continued)

Table 65.5 (continued)

Participant example of "Family Cook Script" for evening meals

Sit together, eat, and talk cordially

Strategy	"**Typical dinner at home** now is that we all sit at the dining room table, and eat dinner. Occasionally, we will, congregate in the uh, living room or the TV room. **Typical dinner** now is around the dining room table, all of us talking, eating, taking our time."
Procedure	"At our dinner table I think I'm Robert Young [paternalistic father character in 1950's TV show].… I'm at the head of the table…. I don't steer the conversation, but [my wife] and I sit side by side. And the boys sit side by side…there's 4 of us at the table…[my wife] sits across from [my older son]. I sit across from [my younger son]. …they can talk to each other without talking across the table. …And, I really do at times feel like Robert Young, that I am at the head of the table. And that's my spot at the table…and we're cordial and, we don't argue at the dinner table"

Sit, eat, and talk if we have family or friends come

Strategy	"So we all sit together"
Procedure	"When you have family come in, whether it's my mom or mother in-law, father in-law, sister in-law like that, it's typically around the dining room table unless it's a **barbeque** or **picnic**…but even then we'll set a table up outside and sit around a table…it takes a lot longer to eat because we're doing a lot more conversation"
Strategy	"It's a hit or miss thing where somebody might pop in, and, if they're there at mealtime, we eat…. I would just include them in the meal"
Procedure	"We don't hold off meals because somebody is there…we just go ahead and start eating, and invite them to stay. It would more than likely be at the dinner table again, if it's dinner…we would pretty much make them part of the family for that meal"

This is a summary of an elaborate evening meal script. The top of the table shows the general expectations and dominant values for this meal. The remaining parts of the table show the strategies and procedures for each of the behaviors: Get input; Shop together; Decide what to have for dinner; Decide what to have if we have family or friends come; Cook; Sit together, eat, and talk cordially; Sit, eat, talk if we have family or friends come

Table 65.6 Summary of general expectations, dominant values, and the strategies and procedures for different behaviors in an evening meal script from a man whose script was considered by researchers to be a "Just Eat Script"

Participant example of "Just Eat Script" for evening meals

Dominant value	"To get full"
General expectation	"[I'm usually] Glad to be home, relaxed…. …I'm just happy the way it is, [just me and] my girlfriend"

Find out what is for dinner

Strategy	"I don't decide anything for dinner."
Procedure	"Dinner's there when I get there, so I don't know. I don't decide any dinners…. I say what's for dinner?…. I don't like that part of it, if I have to wait, that's why I'm glad dinner's done when I get there…. I like it when I want it"

Talk with girlfriend while she prepares dinner

Strategy	"[while she makes it I] Talk about what's going on, watch a little TV….That's about it really"

Eat and watch TV

Strategy	"I really don't like to sit there and talk, I'd rather eat…. We can talk after…. I don't want it to get cold…[my girlfriend is] the same. She'd rather just eat unless something's important"
Procedure	"[I'm usually] Watching TV. Talking about what else I had to do at my house…[we sit] In the living room. I don't eat at the kitchen table ever…. I've got one there, it's stacked full of papers and everything else on it"

This is a summary of a simple evening meal script. The top of the table shows the general expectations and dominant values for this meal. The remaining parts of the table show the strategies and procedures for each of the behaviors: Find out what is for dinner; Talk with girlfriend while she prepares dinner; Eat and watch TV

childcare facility, the mother stops at the same fast food restaurant each day that she passes on her way to work to get a breakfast sandwich and more coffee. There are occasional deviations from this workday food routine, but she reports that it is fairly typical for her.

Food routines are linked to work and family schedules. Sequences of eating episodes that recur on work days, days off, and weekends illustrate how closely food routines are tied to work and family schedules. People's food routines are shaped by many aspects of their own and others' lives including physical needs (i.e. hunger or fatigue at a certain time of day), food availability in particular places and time, norms for eating in different locations and social settings, mode and duration of transportation to and from activities, and patterns of sleep and relaxation. For parents, the presence, ages, and activities of their children impact food routines a great deal (Devine et al. 2009). Very often, day of the week, time of day, specific activities, and particular foods are linked in food routines. For example, a father explained, "During the fall, when the kids have late soccer practices, we'll pick up a pizza or subs on Tuesdays and Thursdays." A mother reported that she was sure of the time of a meal because it coincided with her young child's favorite TV show. "That's an everyday routine (time for lunch) just because Sponge Bob is on at 12:30."

For workers, the conditions and activities of employment may impose particular limitations or opportunities for eating that determine food routines (Bisogni et al. 2007; Jastran et al. 2009; Devine et al. 2009). Some people do not eat at work because of the hours, nature, or location of the job whereas others may have access to abundant foods and beverages. Standardized break times, lunch rooms, and coworkers' preferences may also determine food routines. People develop routines for eating that fit their personal preferences, job requirements, and family circumstances in different ways. For example, after the morning bus run, a school bus driver eats "breakfast" at the same restaurant Monday through Friday, with time, social setting, location and even food repeating 5 days a week. "I always sit at this table and get the same breakfast…5 days a week after my morning bus run." Another example is a man who worked from 11 p.m. to 7 a.m. who never ate during his work hours because he wanted to eat on his family's daytime meal schedule.

Figure 65.6 illustrates how the workday eating routine for the mother described earlier (Table 65.4) is linked to her family and work responsibilities on a typical workday. She adjusts her own eating around her parenting and job requirements, often multitasking when she is caring for her daughter or working at her desk. Her routine for lunch may predictably vary depending upon her workload and her coworker's availability. Her evening meal will also vary in a planned way depending on whether or not her husband is home.

The modified and conventional episode labels this mother uses (e.g. "working lunch," "social lunch," "supper with Dan") reflect how she sees her eating routines as linked to her work and family responsibilities. Other examples of how people's eating episode labels reveal the connection of eating routines to work and family schedules are "family night out," "unwind time," or "swim lesson night dinner" (Bisogni et al. 2007).

The concept of food routines and schematics for representing them (e.g. Fig. 65.6) are useful ways to capture regularity in eating from the perspective of the individual. People may construct ways of eating different from the traditional pattern of three meals per day that are labeled with the conventional terms of breakfast, lunch, and dinner. A weekday versus weekend distinction may not be appropriate for people who work on weekends but have some weekdays off. A parent who cares for a child on some days of the week but not others may report even different types of repetition over the week. Using traditional meal patterns as the sole reference point for examining food patterns is limiting. Food routines focus on the regularity in episodes and sequences of eating episodes

MOTHER'S WORKDAY SCHEDULE		ROUTINE EATING EPISODES

Early morning, feeding toddler, waking up → "My first coffee"

After bringing toddler to childcare, driving to work → "My morning food stop"

Noon at work → If too much work → "Working lunch"
Noon at work → If co-workers available → "Social lunch"

When especially hungry in afternoon at work → "Afternoon treat"

At home while fixing & feeding toddler's dinner → "Bite before dinner"

Evening meal → When Dan is working → "Supper without Dan"
Evening meal → When Dan is home → "Hot supper with Dan"

After toddler is asleep → When Dan is working → "My TV snack"
After toddler is asleep → When Dan is home → "Our late treat"

Fig. 65.6 Example of how one working mother's food routines are linked to her work and family schedule on a workday. The mother's workday schedule shows the sequence of daily activities for her work and family responsibilities. At certain times (e.g. noon at work and the evening meal), her eating routine changes in a predictable way, depending upon certain conditions

from the person's perspective and the ways that food behavior is linked to other important aspects of life. Asking people to explain their food routines in their own words, rather than asking them to describe what they eat for breakfast, lunch, or dinner, enables researchers to learn much about how they eat and why.

Food routines are developed as best-fit solutions for food choice values. Gallimore and Lopez (2002) described routines for everyday decisions as related to repeating situations and representing the compromises between goals and practical limitations. Personal goals and typical situations have previously been identified as contributing to routine development (e.g. Betsch et al. 1998). The participants in the situational eating study also explained that they constructed food routines in response to their food choice values, such as taste, cost, convenience, health, and managing social relationships (Bisogni et al. 2007; Jastran et al. 2009). For example, when social relationships are the most important value, people develop routines around the need to spend time with others. "Our regular Sunday night routine is to just watch TV while we eat and talk and cuddle together on the couch." Routines are often part of the solutions to complex circumstances. Conflicting food preferences among family members can encourage developing routines for eating certain foods when particular people are absent from meals. "When my husband has to work late and won't be home for dinner, I always fix a salad, which he would not like to eat for dinner if he were home. It's my chance to eat what I like."

To balance food choice values that conflict, people often construct sets of routines, with one routine for restricting certain foods and another for indulging in them (Connors et al. 2001; Jastran et al. 2009). People who are usually very frugal might eat only foods purchased from discount stores, but routinely eat an expensive food when visiting a relative because it is the relative's routine way of treating them. "Friday nights we get take out" is a common food choice routine for

those who save money by cooking meals at home on most other days of the week. People also balance their values through routines for eating out once a week and giving the family cook a break on a weekly basis.

Routines that emphasize convenience ("quick and easy meal") and no decision making ("pizza night routine") are especially important to people such as working parents who often feel that time is very scarce and life is exhausting (Jabs et al. 2007). For example, a working mother explained, "I know in the morning at [specific fast food restaurant] what I'm going to get to eat on the way to work…. So I'm not taking time to think about it." Routines may be developed to involve multitasking with other activities such as child care, work, home care, or personal care. Persons for whom saving time is a priority in food routines might explain "I supervise homework and do laundry while I eat my dinner." A "relaxing dinner" may be rare in this stage of their lives and never considered as routine.

Food routines provide stability but are adaptable to change. Routines enhance people's lives by setting boundaries and allowing a person to plan and predict (Gallimore and Lopez 2000). Families benefit from organized routines (Fiese et al. 2006) that can promote adaptability to unforeseen stressful events (Zisberg et al. 2007) and improve health outcomes (Denham 2003). Food routines add predictability to life and contribute to simplification of daily tasks related to food and eating. As best-fit solutions, food routines become predictable and even comfortable. People who like their routines want to keep things the same "I don't like it when things at work disrupt my usual routine… it's more comfortable to keep doing it the same way." Food routines are described as feeling "normal" and something "I can count on." The security of having a personally designed system that works well and feels good makes routines something people strive to preserve. Stable food routines also provide a sense of comfort. A woman whose family had just returned from a trip described their eating while away as "off balance" and getting back to normal as "a relief."

Although routines that work well persist and provide stability, they are also modifiable as a person's circumstances and schedule changes. Job changes may cause changes in food routines. For example, one woman said, "I was eating better when I had a long commute to work. I'd pack a sandwich to eat on the way. And now that I work close to home, I don't do that and wind up missing my breakfast most days."

Disruptions to family or school schedules may also mean modified food routines. Food routines organized around children's schedules change as the children's activities change, such as school year to summer vacation, or fall sports to winter sports. Parents may develop new routines for eating when the children are away or leave home. A father whose son was away at summer camp explained, "My eating schedule is all off this week… now that [my son] isn't there."

Viewing food routines through the framework of eating episodes allows the nature of the repetition and changes to be identified. Repetition in particular dimensions of an eating episode may be essential for the existence of a routine, while other dimensions can vary. For example, eating out together on Friday nights at the same family restaurant may be a routine for some families but the foods consumed may vary.

People reflect on their food routines and sometimes develop an identity from them. People often think about and evaluate their food routines. Reflections can be negative, such as a person who states, "It's the same old routine…it's pathetic." In contrast, another person with a positive evaluation might say proudly, "We have a great evening meal routine. The kids take turns choosing the vegetables."

People also compare their eating routines to those of others, often using cultural ideals as the basis for what they view as "normal." One single mom reflected that her friends had to be home to cook dinner for a husband who expected to eat at a certain time. Her life did not include that structure and she said "with just me and [my son] to think about, our routine is very different."

Comparisons help people make sense of their routines for themselves and others. "I don't eat the same food at the same time each day. I eat when I feel hungry. I'm just not a scheduled eater like my sister."

Work by other researchers (e.g. Giddens 1991) supports the connections between a person's identity and routine behavior patterns that make up an individual's daily world. Bisogni et al. (2002) described the influence of one's identity on eating practices as well as the opposite, the influence of food behavior on identity formation. A person who values health in food choice and repeatedly emphasizes healthy foods in their eating episodes may proudly consider herself as a "healthy eater" or "the healthiest eater I know" (Bisogni et al. 2002). A person who is proud to be a gourmet may have difficulty incorporating healthy eating practices into her routines because she must revise her identity. The strong link between food routines and identities must be considered when asking people to change their food behaviors.

65.7 Applications

The Food Choice Process Model provides a way for organizing the many different factors and processes involved in food behavior. It enables researchers and practitioners to be mindful of the overall complexity and dynamic nature of a person's thoughts, feelings, and actions related to food, while allowing them to focus on particular parts of the model in their professional work.

Developed using data from samples of free-living individuals in the USA, the model has a number of limitations (Sobal et al. 2006; Sobal and Bisogni 2009). It may not apply well to people living in other cultures, historical times, places, or food systems. It organizes an array of factors and processes involved in food choice based on people's perspectives into broad categories, but does not elaborate on all components in a systematic way. The model is not intended to direct health promotion interventions, although it provides useful insights into why and how people behave the way that they do and how both structure and agency are potentially involved in adopting and maintaining new behaviors for health promotion.

The concept of eating episodes underscores how important it is to take a detailed look at how people experience eating situations. Those who wish to study or modify a person's food behaviors must recognize that the person may experience eating situations as much more than involving food and drink. Traditional 24-h recalls focus on the nutritional quality of the foods consumed and typically pay less attention to the surrounding details, even though these details may help understand the barriers and opportunities to change. The concept of eating episodes with multiple dimensions suggests ways for researchers and practitioners to ask about and summarize the details of the situation in which food behaviors occur.

Food scripts demonstrate how to conceptualize linkages between cognitions and behavior that depict the complex constructions people may hold for a single eating episode. Evening meal scripts highlight important individual similarities and differences in the conceptualization of a single eating episode. The study of food scripts may provide a valuable set of conceptual tools for dietary assessment, nutrition counseling, message tailoring and targeting, and program design and evaluation. People develop scripts for food and eating behaviors as ways to provide predictability and simplicity in decision making (Connors et al. 2001). However, when a particular eating episode is encountered repeatedly, parts of the episode script may begin to function automatically and may even be used in episodes where it is inappropriate (Baldwin 1992). Asking people to add, modify, or delete a given food or way of eating may require them to adjust many aspects of their scripts including the values, expectations, strategies, and procedures for several different food behaviors.

The concept of food routines reminds researchers and practitioners that regularity of many food behaviors is linked to many other elements of a person's life. Asking a person to change the way that they eat requires them to alter individual episodes and sequences of episodes that have been established over a long period of time to fit the person's food choice values and particular life circumstances, such as work and family schedules. Incorporating new food behaviors into existing routines requires mental attention and persistence because the person may have to resolve new food choice value conflicts or negotiate with other people. The person may have to lose the comfort and security of long established behaviors. Time and trial and error are required to develop a new satisfactory routine. Some changes in food behavior may be impossible to achieve until structural factors change, such as a person's employment, family responsibilities, or access to food.

65.8 Conclusions

To advance health promotion, researchers and practitioners need concepts and models that will enable them to better understand how people adapt their food-related behaviors to their needs, preferences, and environments both situationally and over time. The Food Choice Process Model and the concepts of eating episodes, food scripts, and food routines provide insight about how people experience food choice and ways for researchers and practitioners to consider the many factors and processes that are involved. The concepts of eating episodes, food scripts, and food routines provide ways to understand how individuals construct situational and recurring food behaviors. Additional studies are needed to extend and elaborate upon how these concepts can advance research and practice.

Summary Points

- People construct their thoughts, feelings, and actions related to food and eating in individual ways based on their life course experiences, ideals, personal factors, resources, social setting, and contexts. The inductive Food Choice Process Model portrays these factors and the processes involved in food choice from people's perspectives.
- People develop personal food systems, the cognitive processes for food choice that include developing food choice values, negotiating and balancing food choice values, classifying foods, and developing and revising strategies, scripts, and routines.
- People experience eating as involving more than just food and beverage consumption. The concept of multidimensional eating episodes helps capture the surrounding details in which eating behavior occurs by recognizing the dimensions of time, location, social setting, mental processes, physical conditions, and other activities.
- Food scripts represent the complex cognitions that people develop to guide behavior in specific situations and include their values, strategies, and detailed behavioral plans.
- People construct food routines consisting of recurring eating episodes or repeating sequences of eating episodes that match work and family schedules, reflect their food choice values, and provide stability and predictability for daily life.
- Understanding eating episodes, food scripts, and food routines will help practitioners effectively work with clients toward the adoption and maintenance of healthy eating practices.

Definitions and Explanations of Key Terms

Eating episodes: Any acts of eating or drinking with the surrounding situational details.

Eating episode dimensions: Categories of characteristics used to describe the situational aspects of an eating episode from people's perspectives: of food/drink, time, location, activities, social setting, mental processes, physical condition.

Food behavior: All actions related to food (includes acquiring, preparing, serving, eating/drinking, storing, giving away, and cleaning-up).

Food choice: Thoughts, feelings, and actions related to food and eating.

Food choice values: Important considerations a person constructs and weighs in food choice.

Food routines: Recurrent eating episodes and sequences of eating episodes a person uses.

Food scripts: Mental processes that guide food behavior in specific situations including expectations about the situations and plans for acting.

Food strategies: Heuristics, guidelines, and rules that people develop to help them achieve food choice values in food behavior.

Personal food system: The mental processes that people construct to interpret and manage the many factors that shape their food behavior including construction of food choice values, negotiation values, classification of foods, development of strategies, development of food scripts, and development of food routines.

Schema: Generalized collections of knowledge stored in long-term memory and constructed from past experience that contain organized and related categories that guide behavior in subsequent familiar situations.

Script flexibility: Adaptability of scripts to accommodate the day-to-day variations in dimensions of eating episodes.

Script scope: Includes the starting and ending points of a script as well as the details of the plan.

Situational eating: Acts of eating/drinking including the specific surrounding details (i.e. time, place, activities, people present, activities, physical and mental conditions).

Value negotiation: Process of setting priorities and making tradeoffs among food choice values.

24 hour situational recall: Retrospective recall of all food and beverages consumed on the previous day along with the surrounding details of the situations in which the consumption occurred, such as where food was consumed, who was present, time of day, physical conditions, mental processes, activities coinciding with eating and reoccurrence of the episode.

References

Abelson RP. The psychological status of the script. Am Psychol. 1981;36:715–29.

Axelson M, Brinberg D. The measurement and conceptualization of nutrition knowledge. J Nutr Educ. 1992;24:239–46.

Baldwin MW. Relational schemas and the processing of social information. Psychol Bul. 1992;112(3):461–84.

Betsch T, Fiedler K, Brinkmann J. Behavioral routines in decision making: the effects of novelty in task presentation and time pressure on routine maintenance and deviation. Eur J Soc Psychol. 1998;28:861–78.

Bisogni CA, Connors M, Devine C, Sobal J. Who we are and how we eat: a qualitative study of identities in food choice. J Nutr Educ Behav. 2002;34:128–39.

Bisogni CA, Falk LW, Madore E, Blake C, Jastran M, Sobal J, Devine CM. Dimensions of everyday eating and drinking episodes. Appetite 2007;48(2):218–31.

Blake CE. Individual differences in the conceptualization of food across eating contexts. Food Qual Pref. 2008;19:62–70.

Blake CE, Bisogni CA. Personal and family food choice schemas of rural women living in Upstate New York. J Nutr Educ Behav. 2003;35(6):282–93.

Blake CE, Bisogni CA, Sobal J, Devine CM, Jastran M. Classifying foods in contexts: how adults categorize foods for different eating settings. Appetite 2007;49(2):500–10.

Blake CE, Bisogni CA, Sobal J, Jastran M, Devine CM. How adults construct evening meals. Scripts for food choice. Appetite 2008;51:654–62.

Bove C, Sobal J. Foodwork in newly married couples: making family meals. Food Culture Soc. 2006;9(1):69–89.

Connors M, Bisogni CA, Sobal J, Devine CM. Managing values in personal food systems. Appetite (June) 2001:189–200.

Denham S. Relationships between family rituals, family routines, and health. J Fam Nurs. 2003;9(3):305–30.

Devine CM. The life course perspective: understanding food choices in time, social location, and history. J Nutr Educ Behav. 2005;37(3):121–8.

Devine CM, Connors M, Bisogni CA, Sobal J. Life-course influences on fruit and vegetable trajectories: a qualitative analysis of food choices. J Nutr Educ. 1998;31(January–February):361–70.

Devine CM, Wolfe WS, Frongillo EA, Bisogni CA. Life-course events and experiences: association with fruit and vegetable consumption in 3 ethnic groups. J Am Diet Ass. 1999;99:303–14.

Devine CM, Farrell TJ, Blake CE, Jastran M, Wethington E, Bisogni CA. Work conditions and the food choice coping strategies of employed parents. J Nutr Educ Behav. 2009;41:365–70.

Falk LW, Bisogni CA, Sobal J. Food choice processes of older adults. J Nutr Educ. 1996;28:257–65.

Falk LW, Bisogni CA, Sobal J. Personal, social, and situational influences associated with diet changes of participants in an intensive heart program. J Nutr Educ. 2000;32:251–60.

Falk LW, Connors M, Sobal J, Bisogni CA, Devine CM. Managing healthy eating: definitions, classifications and strategies. Health Educ Behav. 2001;28(4):425–39.

Fiese BH, Foley KP, Spagnola M. Routine and ritual elements in family mealtimes: contexts for child well-being and family identity. In: Larson RW, Wiley AR, Branscomb KR, editors. Family mealtime as a context of development and socialization. San Francisco: Jossey-Bass; 2006. p. 67–90.

Furst TM, Connors M, Bisogni CA, Sobal J, Falk LW. Food choice: a conceptual model of the process. Appetite 1996;26:247–65.

Furst TM, Connors M, Sobal J, Bisogni CA, Falk LW. Food classifications: levels and categories. Ecol Food Nutr. 2000;39:331–55.

Gallimore RE, Lopez M. Everyday routines, human agency and eccocultural context: construction and maintenance of individual habits. Occ Ther J Res. 2002;22 (Proceedings of habits conference):70S–7S.

Giddens A. Modernity and self identity. Cambridge: Polity; 1991.

Gillman M, Rifas-Shiman S, Frazier A, Rockett H, Camargo C, Berkey C, Golditz G. Family dinner and diet quality among older children and adolescents. Arch Fam Med. 2000;9(3):235–40.

Holmberg D, MacKenzie S. So far, so good: scripts for romantic relationship development as predictors of relational well-being. J Soc Pers Rel. 2002;19(6):777–96.

Ilmonen K. Sociology, consumption and routine. In: Gronow J, Warde A, editors. Ordinary consumption. London: Routledge; 2001. p. 9–24.

Jabs J, Devine CM, Bisogni CA, Farrell TJ, Jastran M, Wethington E. Trying to find the quickest way: employed mothers' constructions of time for food. J Nutr Educ Behav. 2007;39(1):18–25.

Janas BG, Bisogni CA, Campbell CC. Conceptual model for dietary change to lower serum cholesterol. J Nutr Educ. 1993;25:186–92.

Jastran M, Bisogni CA, Sobal J, Blake C, Devine CM. Eating routines: embedded, value based, modifiable, and reflective. Appetite 2009;52:127–36.

Khare A, Inman JJ. Habitual behavior in American eating patterns: the role of meal occasions. J Consum Res. 2006;32(4):567–75.

Lakshmi-Ratan R, Iyer E. Similarity analysis of cognitive scripts. J Acad Mark Sci 16(2):36–42.

Lewin K, Heider F, Heider GM. Principles of topological psychology. New York: McGraw-Hill; 1936.

Magnusson D, Torestad B. Individuals as interactive agents. In: Wals WB, Craik KH, Price RH, editors. Person-environment psychology: models and perspectives. Hillsdale: Erlbaum;1992. p. 89–126.

Markus H. Self-schemata and processing information about the self. J Person Soc Psychol. 1977;35(2):63–78.

Meiselman H. The contextual basis for food acceptance, food choice and food intake. In: Meiselman HL, editor. Food choice, acceptance and consumption. London: Blackie; 1996. p. 239–63.

Nishida H. A cognitive approach to intercultural communication based on schema theory. I JIR 1999;23(5):753–77.

Olson JC. The importance of cognition processes and existing knowledge structures for understanding food acceptance. In: Solms J, Hall RL, editors. Criteria of food acceptance. Zurich: Forester; 1981. p. 69–81.

Rumelhart DE. Schema and the cognitive system. In: Wyer JR, Siwl TK, editors. Handbook of social cognition. Hillsdale: Erlbaum; 1984. p. 161–88.

Schank R, Abelson R. Scripts, plans, goals, and understanding. Hillsdale: Erlbaum; 1977.

Smart LR, Bisogni CA. Personal food systems of male college hockey players. Appetite 2001;36(August):57–70.

Sobal JS, Bisogni CA, Devine CM, Jastran M. A conceptual model of the food choice process over the life course. In: Shepherd R, Raats MM, editors. Psychology of food choice. Oxfordshire: CABI; 2006. p. 1–18.

Sobal JS, Bisogni CA. Constructing food decision making. Ann Behav Med. 2009;38(1):37–46.

Sparks P, Shepherd R. Self-identity and the theory of planned behavior: assessing the role of identification with "Green Consumerism." Soc Psych Q 1992;55(4):388–99.

Spradley JP. Culture and cognition: rules, maps, and plans. Prospect Heights: Waveland; 1972.

Strauss AL, Corbin J. Basics of qualitative research: grounded theory procedures and research. Newbury Park: Sage; 1990.

Trzebinski J. Action-oriented representations of implicit personality theories. J Person Soc Psych. 1985;48(5):1266–78.

Wagner SA. Understanding green consumer behaviour: a qualitative cognitive approach. New York: Routledge; 2005.

Zisberg A, Young HM, Schepp K, Zysberg L. A concept analysis of routine: relevance to nursing. J Adv Nurs. 2007;57(4):442–53.

Chapter 66
Endogenous Opioids, Opioid Receptors, and Incentive Processes

Mauricio R. Papini and Leonardo A. Ortega

Abbreviations

cE	Consummatory extinction
CNS	Central nervous system
cSNC	Consummatory successive negative contrast
DOR	Delta opioid receptor
EFF	Escape from frustration
iE	Instrumental extinction (operant lever pressing)
iSNC	Instrumental successive negative contrast
KOR	Kappa opioid receptor
MOR	Mu opioid receptor
ORL-1	Opioid-receptor-like receptor
pE	Pavlovian extinction (autoshaped lever pressing)

66.1 Introduction

Endogenous opioid peptides and their receptors are involved in the modulation of a variety of behavioral functions because of their relatively diffuse distribution in the CNS. Recent research suggests that endogenous opioids modulate incentive processes. Incentives are environmental resources that motivate the organism to behave. Incentive motivation is activated by expectancies which, in turn, are the result of learning and memory processes. Thus, the study of endogenous opioids in relation to incentive processes encompasses behavioral topics including motivation, emotion, learning, and memory (Table 66.1).

66.2 Opioid Peptides and Receptors

Endogenous opioid peptides consist of short sequences of amino acids synthesized from precursor polypeptides. There are five major groups of opioid peptides, and their precursors are known for four of them (Table 66.2). A model example of the posttranslational changes that result in the sequential

M.R. Papini (✉)
Department of Psychology, Texas Christian University, Fort Worth, TX 76129
e-mail: m.papini@tcu.edu

Table 66.1 Key features of opioid system and incentive processes

1. The four types of opioid receptors are diffusely distributed in the mammalian brain, thus playing a role in many different behavioral processes.
2. Opioid peptides and their receptors have significant functions in relation to incentive processes, i.e., the attribution of hedonic value to environmental resources such as food and fluids.
3. Incentive value can be viewed in an absolute (e.g., food palatability) or relative manner (e.g., incentive contrast effects).
4. Food palatability, also known as food liking (as different from food wanting), depends on the degree of opioid activation during consummatory behavior.
5. Endogenous opioids are naturally released during episodes involving the unexpected omission or devaluation of food reinforcers (incentive contrast).
6. The initial reaction to incentive contrast involves DORs, whereas the recovery from incentive contrast involves KORs.

This table lists the key facts about the relationship between endogenous opioids, opioid receptors, and incentive processes

Table 66.2 Precursors and products

Precursor	Peptide
Pro-opiomelanocortin	γ-MSH (melanocyte stimulating hormone)
	ACTH (adrenocorticotropic hormone)
	α-MSH (melanocyte stimulating hormone)
	γ-LPH (lipotropin hormone)
	β-LPH (lipotropin hormone)
	β-endorphin
Pro-enkephalin	Met-enkephalin
Pro-dynorphin	Dynorphin A
	Dynorphin B
	Neoendorphin
Pro-nociceptin	Nociceptin/orphanin
(Unknown)	Endomorphin-1
	Endomorphin-2

This table illustrates the polypeptide precursors and their opioid and nonopioid products
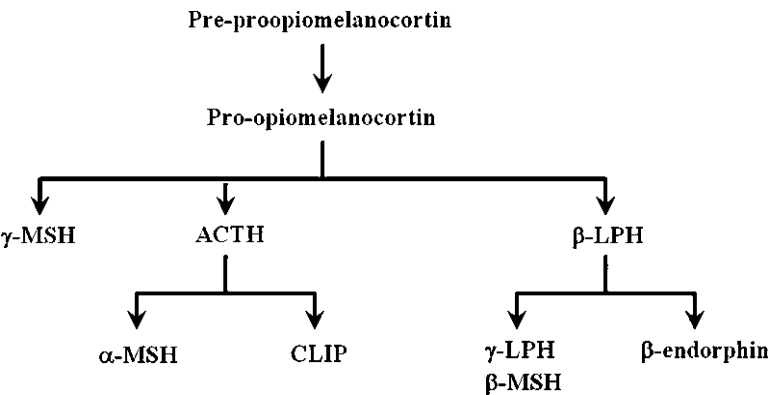
Fig. 66.1 Gene products of pre-proopiomelanocortin. Cleavage of opioid and nonopioid peptide products from the pre-proopiomelanocortin gene

cleavage from an opioid precursor is provided by proopiomelanocortin (POMC) in Fig. 66.1. The pre-proopiomelanocortin gene codes for the precursor POMC. This gene contains 7,665 bp in three exons and two introns (Raffin-Sanson et al. 2003). The resulting polypeptide, consisting of 241 amino acids, is processed and, depending upon the enzymes present, cell-specific patterns of cleavage

generate the opioid peptides β-endorphin and β-lipotropin, as well as nonopioid peptides such as the adrenocorticotropic hormone (ACTH), other lipotropins (LPH), corticotropin-like intermediate peptide (CLIP), and different types of melanocyte-stimulating hormones (MSH).

Opioid receptors are G-protein-coupled receptors that exhibit a high degree of structural similarity (Lord et al. 1977; Sim-Selley et al. 2003). Four opioid receptors have been identified and are known as MOR, KOR, DOR, and ORL-1 (also known as nociceptin opioid peptide receptor). These receptors are distributed throughout the CNS, with somewhat differential concentrations of each receptor across brain areas (Fig. 66.2) (Mansour et al. 1995; Sim-Selley et al. 2003). They have been described in mammals, birds, reptiles, amphibians, and teleost fish, but not in chondrichthyes (sharks), cephalochordates (lancelets), urochordates (tunicates), or arthropods (fruit fly) (Dreborg et al. 2008;

CNS Compartment	Receptor and CNS Areas

MOR: Presubiculum
      Basolateral amygdala
      Cortical amygdaloid N
DOR: External plexiform layer
      Anterior olfactory N
      Caudate-putamen   ORL-1: Cingulate cortex
      N accumbens   Insular cortex
      Olfactory tubercle   Perirhinal cortex
KOR: N accumbens   Piriform cortex
      Olfactory tubercle   Hippocampus
      Medial amygdaloid N   Amygdala

Telencephalon

MOR: Thalamus   ORL-1: Thalamus
KOR: Preoptic area

Diencephalon

MOR: Superiorcolliculus
      Inferior colliculus

Mesencephalon

MOR: Interpeduncular N
      N ambiguous
      N tractus solitarius

Rhombencephalon

MOR: Substantia gelatinosa
KOR: Substantia gelatinosa

Spinal cord

Fig. 66.2 Distribution of opioid receptors in the mammalian CNS. CNS areas with very high density of receptor binding (Region data from Mansour et al. 1995; Sim-Selley et al. 2003; Yaster et al. 2003)

Table 66.3 Selective ligands for opioid receptors

Function	MOR	DOR	KOP	ORL
Agonist	DAMGO	DPDPE	U50,488H	Nociceptin
	Endomorphin-1	SNC 80	U69595	
	Endomorphin-2			
Antagonist	CTAP	Naltrindole	Nor-binaltorphimine	(Unknown)

A variety of ligands have been developed that, unlike endogenous opioids, bind selectively to specific opioid receptors. These compounds play a key role in identifying opioid receptors that are selectively involved during specific behavioral processes

Stevens 2009). Although the amino acid sequences of opioid receptors are very similar across species and within species, nonmammalian opioid receptors are more similar to each other than are mammalian opioid receptors (Stevens et al. 2007).

In mammals, endogenous opioid peptides bind differentially, but not exclusively, to each opioid receptor. The exception is the ORL-1 receptor, which does not bind endogenous opioids. For instance, β-endorphin and enkephalins have a higher affinity for the MOR and the DOR, than for the KOR. In turn, dynorphins bind preferentially to the KOR and nociceptin binds to the ORL-1 receptor. Finally, endomorphin-1 and endomorphin-2 bind specifically to the MOR. In addition to these endogenous opioids, a number of receptor-selective ligands have been developed (Table 66.3).

66.3 Opioid Receptors and Absolute Incentive Value

One strategy used to clarify the role of the opioid system in behavior has been to study the opioid effects in combination with the stimulation of specific brain areas. Following this rationale, it has been proposed that opioid receptors located in the hindbrain may be involved in sensory and metabolic functions, opioid receptors located in the amygdala may regulate the hedonic (i.e., appetitive or aversive) properties of food, and opioid receptors in the hypothalamus may control energetic needs. In addition, opioid receptors located in the basal ganglia may be involved in the modulation of motor patterns (Aubert et al. 2007). This section emphasizes opioid modulation of food incentives.

The role of the opioid system on taste palatability was suggested by the reduction of drinking behavior in animals exposed to solutions of saccharine, sucrose, saline, and hydrochloric acid while under the influence of the nonselective opioid antagonist naloxone (Levine et al. 1982). Similar results were reported using sweetened or unsweetened food and manipulating the food deprivation states. Levine et al. (1995) found that naloxone reduced consumption of sweet food, when compared to unsweetened food, independently of the type of deprivation. In addition, naloxone reduced sucrose preference in two-bottle tests (sucrose vs. water) for wild-type and β-endorphin knockout mice, but it had no effect on enkephalin and dynorphin knock-out strains (Hayward et al. 2006). Naloxone blockage of opioid receptors seems to devalue the palatability of sucrose solutions, rather than the postingestional effects of sucrose. This is suggested by two series of experiments using naloxone-induced suppression of sucrose in a preparation of feeding by open gastric fistula. In the first series of experiments, naloxone reduced sucrose consumption on rats exposed to sham drinking (Rockwood and Reid 1982). In the second series of experiments, naloxone reduced sucrose intake in rats exposed to 10% and 20% sucrose to a level similar to that of saline controls exposed to 5% and 10% sucrose (Kirkham and Cooper 1988).

Following an incentive-motivation framework, Berridge (2004) suggested a distinction between "liking" and "wanting." Liking is defined as the hedonic reaction triggered by the immediate presentation

of a reward, whereas wanting refers to the incentive significance of the reward. This distinction is consistent with Craig's (1918) classification of behavior in terms of consummatory (i.e., liking) and appetitive components (i.e., wanting), and it was proposed to reconcile the effects of some physiological manipulations on behavior supported by access to incentives. For example, dopamine antagonists that disrupt the effects of the mesolimbic dopaminergic system reduce wanting, thus decreasing motivation to seek incentives. However, when incentives are delivered passively (e.g., intraoral sucrose infusions), animals show normal liking responses (e.g., lip licking, tongue protrusion). Conversely, naloxone blockage of opioid receptors in key areas of the reward system (e.g., nucleus accumbens, ventral pallidum) eliminates orofacial liking responses, whereas microinjections of endogenenous opioids increase them.

Endogenous opioid and cannabinoid mechanisms in the nucleus accumbens are critical for the orofacial responses to sweetness used as an index of liking (i.e., consummatory-like responses; Berridge 2004). Administration of DAMGO (a selective MOR agonist) in the medial accumbens shell increases these orofacial liking responses (Peciña and Berridge 2005). Additional studies with opioids shed light on the functional connection between the nucleus accumbens and the posterior ventral pallidum. For example, the enhancing effects of DAMGO administered in the posterior ventral pallidum on liking responses were blocked by microinjections of naloxone in the nucleus accumbens. Moreover, opioid activation in any of the two areas causes an increase in Fos protein expression in the other area, an effect suppressed by naloxone (Smith et al. 2009). Thus, opioid release in the nucleus accumbens, amygdala, and ventral pallidum are intimately involved in incentive palatability.

66.4 Opioid Receptors and Relative Incentive Value

Incentive relativity involves a comparison process, usually between present and remembered incentives. Behavioral preparations used to study incentive relativity typically involve some type of unexpected reward devaluation or reduction that triggers the comparison (Flaherty 1996). The role of the opioid system in incentive relativity has been studied in several preparations (Table 66.4; Papini 2009).

Table 66.4 Effects of opioid manipulations on incentive relativity

Preparation	Drugs	Dose	Administered	Reference
cSNC	Morphine	0.5–16.0 mg/kg	Pretrial	Rowan and Flaherty (1987)
	DPDPE	24 µg/kg	Pretrial	Wood et al. (2005)
	DPDPE	24 µg/kg	Post-trial	Daniel et al. (2009)
	U50,488H	1–10 mg/kg	Pretrial	Wood et al. (2008)
	U50,488H	1–3 mg/kg	Post-trial	Wood et al. (2008)
	Naloxone	0.25–1.0 mg/kg	Pretrial	Rowan and Flaherty (1987)
	Naloxone	2 mg/kg	Pretrial	Pellegrini et al. (2005)
	Naloxone	2 mg/kg	Post-trial	Daniel et al. (2009)
	Naltrindole	1 mg/kg	Pretrial	Pellegrini et al. (2005)
	Naltrindole	1 mg/kg	Post-trial	Daniel et al. (2009)
iSNC	FK33–824	0.3 mg/kg	Pretrial	Lynch and Clark (1983)
	Naloxone	1–10 mg/kg	Pretrial	Lynch and Clark (1983)
cE	Naloxone	2 mg/kg	Pretrial	Norris et al. (2008)
iE	Naloxone	2 mg/kg	Pretrial	Norris et al. (2009)
pE	Naloxone	2 mg/kg	Post-trial	Daniel et al. (2009)
EFF	Naloxone	2 mg/kg	Pretrial	Norris et al. (2009)

This table summarizes research on the effects of opioid drugs on situations involving unexpected incentive devaluations. Opioid administration was intraperitoneal, except in Lynch and Clark (1983), who used subcutaneous administration

Most of the information originates in the consummatory successive negative contrast (cSNC) situation, in which the consummatory behavior of a group exposed to a downshift in sucrose concentration (e.g., from 32% to 4% sucrose) is compared to that of an unshifted control group only exposed to the lower concentration (e.g., 4% sucrose). The incentive downshift leads to a sharp and transient suppression of consummatory behavior and opioid drugs modulate the degree of suppression. The use of an unshifted control allows an assessment of the extent to which opioids effects are selective to the incentive downshift experience. For example, morphine attenuated consummatory suppression (i.e., attenuated cSNC), whether administered before the first or before the second downshift trial (Rowan and Flaherty 1987). Naloxone reversed the effects of morphine (Rowan and Flaherty 1987) and also enhanced cSNC (Pellegrini et al. 2005). Except for the highest morphine dose (16 mg/kg), neither morphine nor naloxone affected the consummatory behavior of unshifted controls, suggesting that the effect was selective to the downshift experience and therefore unrelated to potential opioid effects on motor, sensory, or palatability aspects of the task. Naloxone acts by distorting the normal process of detection of the incentive downshift, which involves a ratio comparison between pre- and postshift sucrose concentrations (Papini and Pellegrini 2006). Opioid blockage shifts the incentive comparison from a ratio to an absolute difference comparison (Daniel et al. 2009). However, neither naloxone nor naltrindole (selective DOR antagonist) affects the course of cSNC when administered immediately after the first downshift trial.

Naloxone also leads to similar results in other training situations. For example, naloxone increases behavioral suppression in the iSNC situation (Lynch and Clark 1983), facilitates instrumental extinction of lever-press responses acquired by pairings with food or sucrose pellets (Norris et al. 2009), and promotes consummatory extinction of licking responses paired with sucrose solutions (Norris et al. 2008). Naloxone also eliminates the escape-from-frustration effect in which rats exposed to appetitive extinction have the opportunity to "escape" to a neutral compartment by jumping over a barrier (Norris et al. 2009). However, as in the cSNC situation, posttrial naloxone administration during appetitive extinction leads to no detectable effects on lever-press responses (Daniel et al. 2009). All together, these results suggest that: (1) opioid receptors are normally engaged during exposure to incentive downshifts; (2) their role is to attenuate the emotional impact of the downshift; and (3) they probably play no direct role in the consolidation of the emotional memory of the downshift event.

Opioid modulation of cSNC is also quite selective with respect to the amount of downshift experience. For example, the DOR agonist DPDPE reduces cSNC on the first downshift trial, but has no effect on the second downshift trial (Wood et al. 2005). Similarly, the DOR antagonist naltrindole enhances cSNC selectively on the first downshift trial (Pellegrini et al. 2005). Thus DORs are engaged during the initial response to the incentive downshift, but are less relevant as the animal learns about the situation with more extended practice. Interestingly, the KOR agonist U50,488H has the opposite profile. It attenuates cSNC when administered on the second downshift trial, but has no effect when administered on the first downshift trial (Wood et al. 2008). Because both morphine (Rowan and Flaherty 1987) and naloxone (Pellegrini et al. 2005) influence cSNC on both the first and second downshift trials, and because these drugs have greater affinity for the MOR, it is tempting to conclude that the MOR is not trial selective in the cSNC situation. The picture emerging from these results is that different combinations of opioid receptors are engaged as a function of the amount of experience with the downshifted incentive. A MOR–DOR combination is active during the early stages of downshift detection, whereas a MOR–KOR combination becomes active as the animal interacts further with the downshifted solution. Such combinations await further research with selective MOR opioids, but it is intuitively consistent with heterodimerization of MOR–DOR complexes. MOR–DOR heterodimers have been postulated to underlie enhanced hypoalgesia after spinal cord administration of morphine (Gomes et al. 2004; Snook et al. 2008).

66.5 Applications to Areas of Health and Disease

The experiments reviewed in the previous section demonstrate that endogenous opioids are normally activated by an episode of incentive downshift. Thus, further activation by opioid agonists (e.g., morphine, DPDPE, U50,488H) reduced cSNC, whereas interference by antagonists (e.g., naloxone, naltrindole) enhanced cSNC. But, like most behavioral phenomena, recovery from incentive downshift is a variable process, with individuals exhibiting behavioral phenotypes ranging from very fast recovery (i.e., normal consummatory levels after a single exposure to the downshifted solution) to very slow recovery (i.e., little or no evidence of recovery after five trials, the usual length of the postshift phase in cSNC experiments). Even rats that show very similar consummatory suppression on the first downshift trial can differ dramatically in the speed of recovery from cSNC (Pellegrini et al. 2005). Interestingly, if these individual differences in recovery were related to differences in some property of the opioid system, one would predict a direct correspondence between recovery from reward downshift and general sensitivity to opioid treatments.

MORs are known to exhibit allelic variation in rodents and humans (e.g., Mayer and Höllt 2001; Zimprich et al. 1995). MORs are important for health-related reasons because they are one site of action for morphine and naloxone, two drugs with extensive clinical applications. Allelic variations differ in the efficacy with which the MOR interacts with opioid agonists and have clinical implications for addiction and pain treatments (Drews and Zimmer 2010; Klepstad 2007). Thus, if individual differences in opioid receptor efficacy and recovery from cSNC are related, then slow recovery animals should differ from fast recovery animals in terms of sensitivity to opioid blockage. Consistent with this hypothesis, rats that recovered more slowly from incentive downshift exhibited greater sensitivity to naloxone treatment in an activity test than rats that recovered faster (Pellegrini et al. 2005). Slow- and fast-recovery animals did not differ in their level of suppression during the first downshift trial, as well as in terms of growth rates or water intake. However, siblings were significantly more likely than chance to be assigned to the same recovery group.

The opioid system (receptors and endogenous neuropeptides) participates in a wide variety of behaviorally relevant processes. The role of this neurochemical system in nutrition relates to its ability to modulate incentive value, both absolute and relative. As a result of this incentive function, it is not surprising that the area of influence of opioid modulation extends beyond that of food reinforcement processes. For example, in addition to the well-established role in pain and analgesia, opioids participate in fear conditioning, social stress, drug tolerance and drug dependence, drug abuse, gastrointestinal function, and mental disorders among others (Bodnar in press).

Summary Points

- Opioid receptors and endogenous peptides play a role in a wide variety of behavioral and physiological processes.
- Four types of opioid receptors have been identified: mu (MOR), delta (DOR), kappa (KOP), and opioid-receptor-like receptor (ORL-1).
- A variety of endogenous opioids have been identified, including β-endorphin, met-enkephalin, dynorphins, and nociceptin, among others.
- Several receptor-selective compounds are available for research (e.g., DAMGO, DPDPE, and U50,488H selectively agonize MOR, DOR, and KOR, respectively).
- Opioid receptors and neuropeptides modulate the absolute (palatability) and relative (incentive contrast) value of incentives.

- Incentive value refers to the hedonic dimension of stimuli such as food and fluids, that is, to their appetitive or aversive value.
- Opioid peptides and receptors modulate food palatability and so-called liking orofacial responses.
- Endogenous opioids are released during events involving unexpected incentive devaluations.
- Different opioid receptors affect behavior at different points in the process of adjustment to incentive devaluation.

Key Terms

Endogenous opioids: Gene products expressed in the vertebrate CNS, acting on membrane receptors to modulate synaptic transmission.

Opioid receptors: Gene products of the G-protein-coupled type, expressed in the vertebrate CNS, sensitive to a variety of endogenous and exogenous opioid peptides, and modulating synaptic transmission.

Absolute incentive value: The direct hedonic (i.e., appetitive–aversive) dimension of environmental resources such as food and fluids.

Relative incentive value: The hedonic value of a current incentive in relation to the incentive expected on the basis of prior experience.

Negative incentive contrast: Greater rejection of a small incentive in animals previously exposed to a large incentive, relative to animal always exposed to the small incentive.

References

Aubert I, Guigoni C, Li Q, Dovero S, Bioulac BH, Gross CE, Crossman AR, Bloch B, Bezard E Biol Psych. 2007; 61:836–44.

Berridge KC. Physiol Behav. 2004;81:179–209.

Bodnar RJ Peptides. in press.

Craig W. Biol Bull. 1918;34:91–107.

Daniel AM, Ortega LA, Papini MR Neurobiol Learn Mem. 2009;92:439–50.

Dreborg S, Sundström G, Larsson TA, Larhammar D Proc Nat Acad Sci USA. 2008;105:15487–92.

Drews E, Zimmer A. Prog Neurobiol. 2010;90:1–5.

Flaherty CF. Incentive relativity. Cambridge: Cambridge University Press; 1996.

Gomes I, Gupta A, Filipovska J, Szeto HH, Pintar JE, Devi LA. Proc Nat Acad Sci USA. 2004;101:5135–9.

Hayward MD, Schaich-Borg A, Pintar JE, Low MJ Pharmacol Biochem Behav. 2006;85:601–11.

Kirkham TC, Cooper SJ Physiol Behav. 1988;44:491–4.

Klepstad P. Curr Anaesth Crit Care. 2007;18:149–56.

Levine AS, Murray SS, Kneip J, Grace M, Morley JE Physiol Behav. 1982;28:23–5.

Levine AS, Weldon DT, Grace M, Cleary JP, Billington CJ. Am J Physiol. 1995;268:R248–52.

Lord JA, Waterfield AA, Hughes J, Kosterlitz HW Nature. 1977;267:495–9.

Lynch WC, Clark S Life Sci. 1983;32:2801–7.

Mansour A, Fox CA, Akil H, TINS. 1995;18:22–9.

Mayer P, Höllt V. Pharmacol Ther. 2001;91:167–77.

Norris JN, Daniel AM, Papini MR Learn Motiv. 2008;39:296–312.

Norris JN, Perez-Acosta AM, Ortega LA, Papini MR Pharmacol Biochem Behav. 2009;94:81–7.

Papini MR. Int J Comp Psychol. 2009;22:170–87.

Papini MR, Pellegrini S Learn Motiv. 2006;37:357–78.

Peciña S, Berridge KC J Neurosci. 2005;25:11777–86.

Pellegrini S, Wood M, Daniel A, Papini MR Behav Brain Res. 2005;164:239–49.

Raffin-Sanson ML, Keyzer Y, Bertagna X Eur J Endocrinol. 2003;149:79–90.

Rockwood GA, Reid LD Physiol Behav. 1982;29:1175–8.

Rowan GA, Flaherty CF Psychopharmacology. 1987;93:51–8.

Sim-Selley LJ, Vogt LJ, Childers SR, Vogt BA Neuropharmacology. 2003;45:220–30.

Smith KS, Tindellb AJ, Aldridge JW, Berridge KC Behav Brain Res. 2009;196:155–67.

Snook LA, Milligan G, Kieffer BL, Massotte D J Neurochem. 2008;105:865–73.

Stevens CW. Front Biosci. 2009;14:1247–69.

Stevens CW, Brasel CM, Mohan S Neurosci Lett. 2007;419:189–94.

Wood MD, Daniel AM, Papini MR Behav Neurosci. 2005;119:446–54

Wood MD, Norris JN, Daniel AM, Papini MR Behav Brain Res. 2008;193:28–36.

Yaster M, Kost-Byerly S, Maxwell LG In: Schechter NL, Berde CB, Yaster M, editors. Pain in infants, children, and adolescents. 2nd ed. Philadelphia: Lippincott Williams & Wilkins; 2003. p. 181–224.

Zimprich A, Simon T, Höllt V FEBS Lett. 1995;359:142–6.

Part IX
General and Normative Aspects: Appetite

Chapter 67
Central Regulation of Appetite and Satiety Behavior

Edward B. Lee and Rexford S. Ahima

Abbreviations

3v	Third ventricle
AGRP	Agouti related protein
Arc	Arcuate nucleus
CART	Cocaine-and amphetamine regulated transcript
CCK	Cholecystokinin
CCK-1R	Cholecystokinin-1 receptor
CN	Cranial nerve
CNS	Central nervous system
CNTF	Ciliary neutrotrophic factor
CRH	Corticotropin-releasing hormone
DMV	Dorsal motor nucleus of the vagus
LHA	Lateral hypothalamic area
MCH	Melanin concentrating hormone
α-MSH	α-Melanocyte stimulating hormone
NAc	Nucleus accumbens
NPY	Neuropeptide Y
NTS	Nucleus of the solitary tract
OB-Rb	Leptin receptor b (longest isoform)
OXY	Oxytocin
POMC	Proopiomelanocrotin
PVN	Paraventricular nucleus
STAT	Signal transducers and activators of transcription
TRH	Thyrotropin-releasing hormone
VMN	Ventromedial nucleus
VTA	Ventral tegmental area

———————————————
R.S. Ahima (✉)
Institute for Diabetes, Obesity and Metabolism, School of Medicine, University of Pennsylvania School of Medicine, 712A Clinical Research Building, 415 Curie Boulevard, Philadelphia, PA 19104
e-mail: ahima@mail.med.upenn.edu

67.1 Introduction

Energy homeostasis is the process whereby an organism regulates food intake, energy expenditure, and energy stores. Many aspects of energy homeostasis are regulated by the central nervous system. Appetite and satiety are the subjective feelings of hunger or adequacy generated by the central nervous system in order to regulate food intake. Towards this end, the CNS serves as an integrator of several peripheral signals, including those generated by nutrient intake and adiposity (Fig. 67.1). Integration of these peripheral signals triggers the expression of neurotransmitters and neuropeptides with orexigenic or anorexic effects. Several brain circuits will be discussed within the context of peripheral signals which influence their activity. Although appetite and satiety primarily affect food intake, they are inexorably intertwined with a complex network of homeostatic and nonhomeostatic processes which regulate energy homeostasis.

67.2 Gut–Brain Axis

The primary role of the gastrointestinal tract is to digest and absorb nutrients. Secondarily, the gut plays a role in energy homeostasis via mechanoreceptors and chemosensors which detect the volume and quality of food intake. The vagus nerve extensively innervates the gut, carrying afferent mechanical and chemical signals from the gut to the dorsal vagal complex in the medulla, terminating primarily on the medial and dorsomedial parts of the nucleus of the solitary tract (NTS; Schwartz 2000,
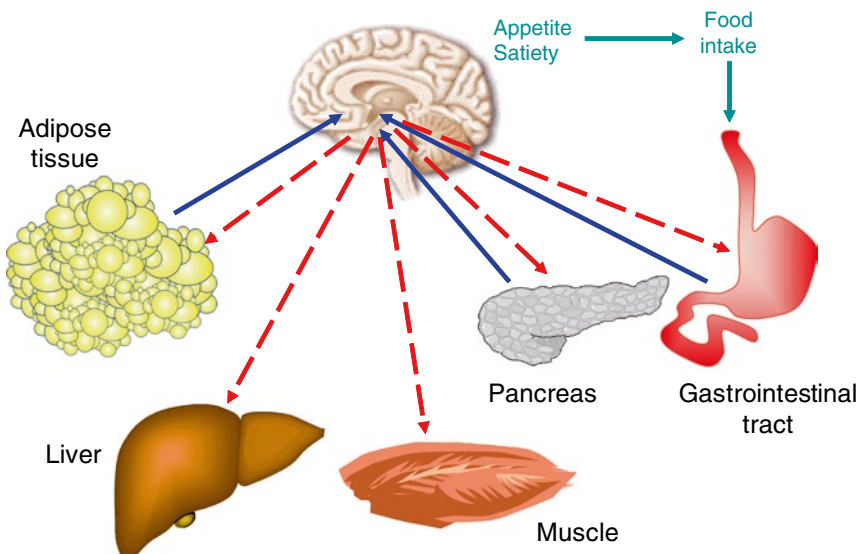
Fig. 67.1 Cross-talk between the brain and peripheral organs. Several organs communicate with the central nervous system via signals reflective of energy input (food intake) and energy storage levels (adiposity). The gastrointestinal system is the source of nutrient and hormonal signals that act through the vagus nerve to regulate neuronal circuits in the brainstem, and ultimately the forebrain. Adipose tissue secretes adipokines such as leptin and adiponectin which act in the hypothalamus and other brain areas. Insulin is secreted by the pancreas and has pleotrophic effects on metabolism in the periphery, but also can act centrally to influence appetite and feeding behavior. The brain in turn sends efferent neuronal and hormonal signals to liver, gut, muscle, and adipose tissue to regulate energy homeostasis

Fig. 67.2 Neuronal connections of the nucleus of the solitary tract. The nucleus of the solitary tract (NTS), located in the medulla, receives visceral sensory information from the gut via the vagus nerve, and taste information from the facial, glossopharyngeal, and vagus nerves. NTS neurons project to the dorsal motor nucleus of the vagus, hypothalamus, thalamus, and limbic regions (amygdala and cingulate gyrus)
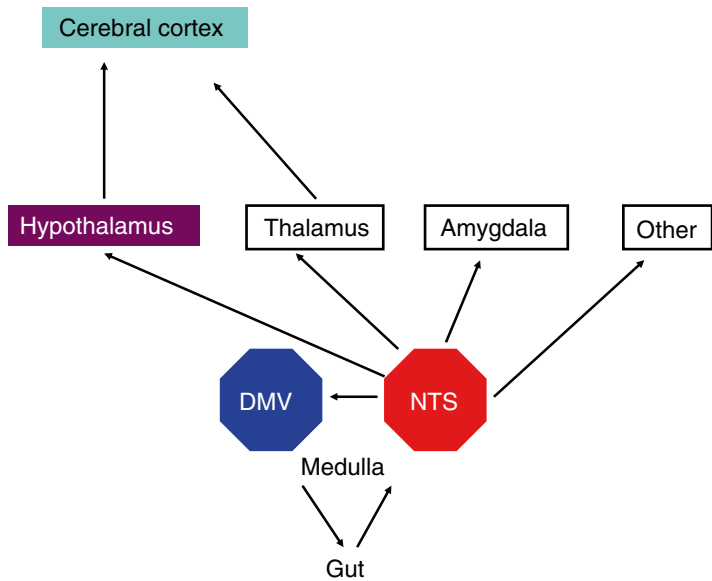
2006). There is also a small projection to the area postrema, a circumventricular organ which lies in the rhomboid fossa in the floor of the fourth ventricle. Multiple projections from the NTS are known (Fig. 67.2). Signals are carried forward to motor nuclei such as the dorsal motor vagal nucleus, which then project back out via the vagus nerve to peripheral targets including the gut and liver, forming a viscera–brain–viscera loop. Aside from its role in appetite and satiety, these gut–brain–viscera circuits regulate other metabolic parameters. For example, gastrointestinal infusion of long chain fatty acids results in signals via the vagus nerve from the gut to the hindbrain, which then signals back to the liver via the vagus to regulate glucose production (Wang et al. 2008). NTS neurons also project to higher brain regions such as the visceral sensory thalamus, which in turn projects to the visceral sensory neocortex, thereby forming the conscious feeling of fullness and satiety. NTS projections are also sent to several other brain regions including the hypothalamus, parabrachial nucleus, amygdala, and insular cortex.

The regulation of feeding behavior through vagal afferents from the gut has been well studied. Satiety can be induced by direct vagal stimulation, mechanical stimulation by balloon distension, and chemical stimulation via infusion of solutions rich in fat, carbohydrates, and proteins (Schwartz 2000, 2006). These effects are inhibited by blocking the vagal afferent signal, either by vagotomy or by peripheral application of capsaicin, a sensory neurotoxin (Smith et al. 1985; South and Ritter 1988). These peripheral manipulations of vagal signaling also increase meal size and duration. Centrally, blocking *N*-methyl-d-aspartate receptor glutamatergic transmission in the brainstem also increases meal size, probably by inhibiting the neurons which integrate vagal afferent signals (Treece et al. 1998). These findings demonstrate a potent negative-feedback mechanism whereby signals of food intake generated in the gut are transmitted via the vagus nerve to the brain, thereby inducing satiety and inhibiting food intake.

The hormonal signals which affect the gut–brain axis can also be mediated by autonomic signals via the vagus nerve. In response to food intake, the gut responds to nutrient intake by secreting hormones such as cholechystokinin (CCK), some of which act on the nervous system to regulate appetite and satiety (Liebling et al. 1975). CCK is secreted by the duodenum and ileum in response to luminal lipid or protein, resulting in the release of digestive enzymes and bile. CCK also has effects on satiety, inhibiting eating behavior and meal size (Gibbs et al. 1973; Kraly et al. 1978). This is
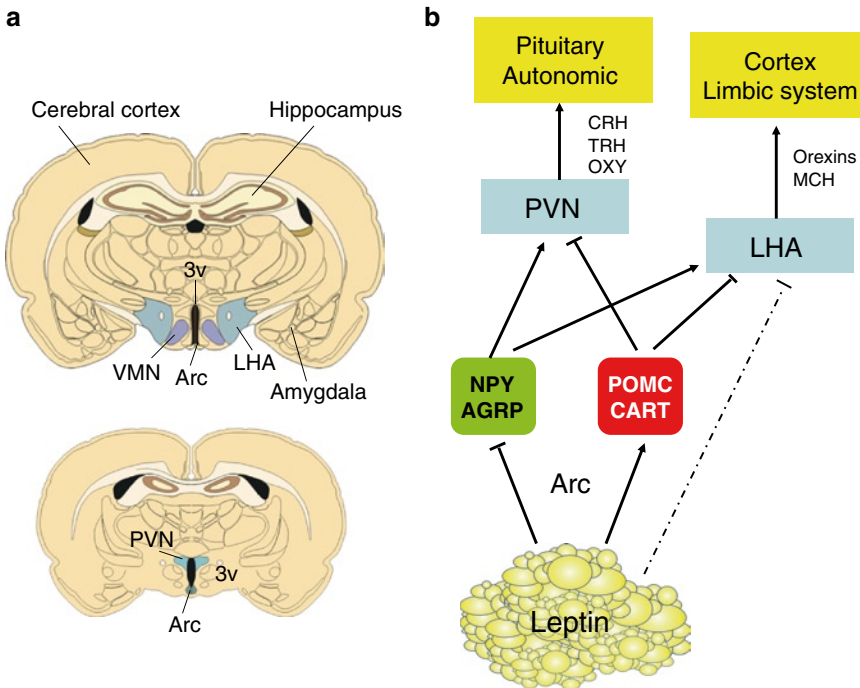
Fig. 67.3 Hypothalamic circuits involved in feeding behavior. (**a**) Coronal sections of mouse brain showing the locations of key nuclei involved in regulation of feeding behavior and energy homeostasis. (**b**) The arcuate nucleus is an important integrator of peripheral metabolic signals such as leptin and insulin. Neurons coexpressing NPY and AGRP are directly inhibited by leptin, whereas neurons expressing POMC (precursor of α-MSH) and CART are stimulated by leptin. Arcuate neurons project to the hypothalamus including the lateral hypothalamic area (*LHA*) and the paraventricular nucleus (*PVN*). Rising leptin levels in the fed state inhibit feeding by suppressing NPY/AGRP and stimulating POMC/CART. Recent evidence suggests that leptin is able to directly inhibit LHA neurons. Conversely, the fall in leptin levels during fasting potently stimulates feeding. Arcuate projections indirectly regulate the neuroendocrine axis, as well as limbic and higher cortical functions, thereby enabling feeding to be integrated with metabolism, sleep–wake cycles, and complex behaviors

consistent with the finding that CCK receptor antagonists increase feeding behavior and postpone satiety (Dourish et al. 1989). CCK exerts its satiety-inducing effects by modulating afferent autonomic signals to the CNS. CCK binds to CCK-1 receptors (CCK-1R) on vagal sensory afferent terminals, thereby transmitting a satiety signal via the vagus nerve to the NTS (Schwartz 2000, 2006). Thus, blocking the vagal afferent signal either chemically or by vagotomy abolishes the effect of CCK on satiety (Smith et al. 1985; South and Ritter 1988). Furthermore, rats lacking functional CCK-1R are hyperphagic and obese when exposed to a high fat diet (Bi et al. 2007). However, in mice, absence of CCK signaling has no effect on long-term body weight maintenance (Kopin et al. 1999), indicating that CCK signaling is likely a short-term satiety signal that does not play a major role in long-term energy homeostasis. Additional gut hormones with satiety-inducing effects have been identified, including glucagon-like peptide 1, oxyntomodulin, peptide YY, and amylin.

In contrast with the satiety-inducing effects of CCK, ghrelin is an appetite-inducing factor synthesized predominantly by fundic cells in the stomach with a relatively small amount generated by the pancreas (Tschop et al. 2000; Wiedmer et al. 2007). Ghrelin levels rise prior to meals and in periods of fasting, and exogenous administration of ghrelin results in increased feeding behavior (Tschop et al. 2000). Ghrelin signals through the growth hormone secretagogue receptor, a G protein-coupled receptor

expressed in several neuronal populations including the arcuate and ventromedial nuclei in the hypothalamus (Guan et al. 1997; Bailey et al. 2000). Neurons expressing the ghrelin receptor also express both neuropeptide Y (NPY) and agouti-related protein (AGRP). By activating these hypothalamic neurons, an orexigenic signal is generated which leads to increased appetite and feeding behavior (see Fig. 67.2 and the section below on the adipose-brain axis for a more detailed description of the arcuate-hypothalamic circuit). Extra-hypothalamic ghrelin signaling may also affect appetite. Ghrelin activates the mesolimbic reward system, and thereby may stimulate appetite behaviors by enhancing the hedonic response to food intake (see Fig. 67.3; Naleid et al. 2005; Abizaid et al. 2006). Effects on learning, memory, anxiety, and depression have also been identified, although the connection between these effects and the induction of appetite are yet poorly understood (Diano et al. 2006; Lutter et al. 2008).

67.3 Adipose–Brain Axis

The major energy store in mammals is in the form of adipose tissue. The regulation of adiposity, therefore, is critical to maintenance of energy homeostasis. It is not surprising, therefore, that there are signals related to adiposity which are integrated by the CNS which affect appetite and satiety. Adipose tissue generates several secreted factors called adipokines which regulate appetite and satiety in part by signaling to the brain. The best understood adipokine is leptin. Leptin is secreted primarily by adipose tissue and is transported into the brain to effect neuronal signaling (Ahima and Flier 2000; Ahima et al. 2000). Of the five leptin receptor splice variants, only the longest isoform, OB-Rb, results in downstream intracellular signaling via a Jak (janus kinase)-STAT (signal transducers and activators of transcription) signal transduction pathway. This signaling cascade is critical to the central effects of leptin on eating behavior and energy homeostasis.

Leptin concentrations correlate with adiposity, and the absence of leptin or OB-Rb results in a constellation of phenotypes which include hyperphagia and severe obesity (Zhang et al. 1994; Chua et al. 1996). Although originally thought to be an antiobesity hormone, high endogenous levels of leptin in obese individuals does not inhibit overeating and obesity. Therefore the concept of leptin-resistance has emerged in which leptin-responsive circuits do not respond adequately to prolonged hyperleptinemia (Myers et al. 2008). Conversely, low concentrations of leptin are a signal of fasting, which triggers a compensatory response, including stimulation of appetite, activation of the hypothalamic–pituitary–adrenal axis, and suppression of thyroid and reproductive function (Ahima et al. 1996).

There are numerous central targets of leptin including OB-Rb-expressing neurons within the arcuate nucleus, ventromedial hypothalamus, dorsomedial hypothalamus, ventral premammilary nucleus, preoptic area, periaqueductal grey, dorsal raphe, parabrachial nucleus, and NTS (Myers et al. 2008). Although these diverse neuronal groups are thought to respond to leptin due to their expression of OB-Rb, the effect of leptin signaling in most of these neurons is largely unknown, and the projections from these leptin-responsive neurons is obscure. Of these diverse neuronal groups, the effects of leptin signaling on hypothalamic arcuate neurons are best understood (Fig. 67.3, Elias et al. 1999; Ahima et al. 2000). Low leptin levels due to fasting results in activation of neurons which express the orexigenic neuropeptides NPY and AGRP, with a concomitant inhibition of neurons expressing anorexic neuropeptides proopiomelanocortin (POMC, precursor to α melanocyte-stimulating hormone α-MSH) and cocaine and amephetamine-regulated transcript (CART). As is the general rule in CNS circuits, arcuate neurons likely project to multiple second-order neurons. However, there is a strong projection to several hypothalamic nuclei including the paraventricular nucleus (PVN) and the lateral hypothalamic area (LHA). PVN neurons synthesize neuropeptides with anorexic effects when administered centrally including corticotropin-releasing hormone (CRH), thyrotropin-releasing hormone

(TRH), and oxytocin. LHA neurons express the orexigenic neuropeptides, melanin concentrating hormone (MCH), and orexins. Again, the arcuate-hypothalamus circuit projects to many regions including the NTS (Myers et al. 2008, 2009). As already mentioned, NTS neurons also express OB-Rb and thus may respond directly to leptin signals. In doing so, the nutrient intake signals associated with vagal signaling from the gastrointestinal system (described above) and the energy storage signals from leptin secretion by adipose tissue converge, and activate or deactivate higher order circuits which produce the subjective feelings of appetite and satiety. Perhaps it is this convergence of signals which underlies the experimental finding that leptin and CCK can act in concert to decrease meal size (Emond et al. 1999).

Although the arcuate-hypothalamus circuit is a critical regulator of leptin-dependent appetite and satiety behavior, leptin signaling in extrahypothalamic regions may also influence feeding behavior. The mesolimbic reward system is a dopaminergic circuit in which ventral tegmental area (VTA) neurons project to the nucleus accumbens (ventral striatum), amygdala, hippocampus, and medial prefrontal cortex (Fig. 67.4). This circuit is involved in feelings of reward and is thought to be important in processing the hedonic aspects of appetite, particularly in terms of more palatable foods. Leptin can act on OB-Rb expressing neurons in the VTA and thus may modulate the mesolimbic reward circuit (Fulton et al. 2006; Hommel et al. 2006). Direct administration of leptin to the VTA decreased food intake, while downregulation of the leptin receptor in VTA neurons increased food intake (Fulton et al. 2006; Hommel et al. 2006). In human studies, leptin replacement therapy for individuals with congenital leptin deficiency results in increased activity in satiety centers (prefrontal neocortex) and decreased activity in hunger centers (ventral striatum; insular, parietal, and temporal neocortex, Baicy et al. 2007; Farooqi et al. 2007). Similarly, serial functional magnetic resonance imaging (fMRI) measurements in obese individuals at baseline and after weight loss reveals altered neuronal activation in numerous brain regions (Rosenbaum et al. 2008). These changes in neuronal activation are reversible after exogenous leptin treatment. It is unknown whether these changes in neuronal activation in humans are due to the direct action of leptin on these neuronal groups.
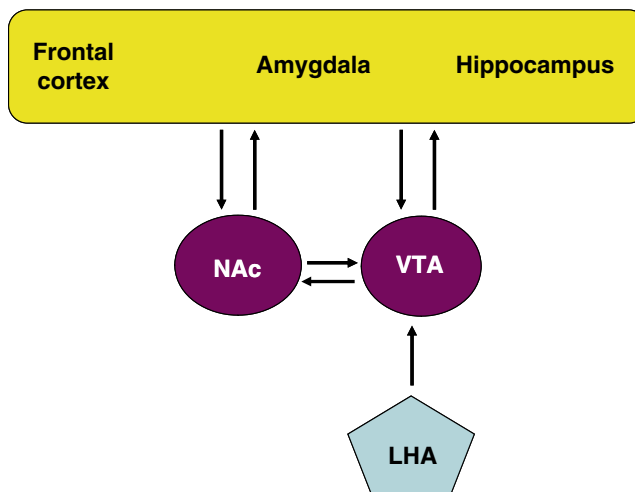
Fig. 67.4 Neuronal circuits mediating reward. The regulation of appetite and satiety by higher order brain regions is in part due to the activation of the mesolimbic reward system in response to palatable foods. The mesolimbic reward system comprises a dopaminergic pathway which activates feelings of reward or motivation. The circuit involves the ventral tegmental area of the midbrain, the nucleus accumbens (ventral striatum), and other limbic and cortical regions (amygdala, hippocampus, and medial prefrontal/orbitofrontal cortex)

Adiponectin is an adipokine which, in contrast to leptin, is inversely correlated with adiposity (Ahima and Lazar 2008). Thus, obesity results in low circulating adiponectin levels and fasting results in high adiponectin levels. Adiponectin is found in the periphery as a homotrimer, low-molecular weight hexamer, and higher molecular weight complexes, and the absence of adiponectin results in insulin resistance and hyperlipidemia (Ahima and Lazar 2008). Although high molecular weight species are unlikely to cross the blood–brain barrier, cerebrospinal fluid contains trimeric and low molecular weight adiponectin species (Spranger et al. 2006; Kusminski et al. 2007). Evidence of central effects of adiponectin stems from the inhibition of food intake and the potentiation of energy expenditure, secondary to intracerebroventricular administration of adiponectin (Qi et al. 2004). Adiponectin signals through one of two seven-transmembrane domain containing receptors, AdipoR1 and AdipoR2, which are widely expressed in the CNS and induce an AMP kinase phosphorylation signal transduction cascade (Kubota et al. 2007). The anorexic effects of central adiponectin are dependent on the presence of AdipoR1 (Coope et al. 2008). Although the site of central adiponectin signaling is not clear, intracerebroventricular adiponectin activates hypothalamic intraneuronal signal transduction cascade which overlaps with those of leptin and insulin (Coope et al. 2008). Adiponectin is also known to activate neurons in area postrema (a circumventricular organ which is exposed to the peripheral circulation) and inhibit oxytocin-expressing neurons in the PVN (Fry et al. 2006; Hoyda et al. 2007). Although adiponectin has effects on these neuron groups, it is not clear which neurons are responsible for adiponectin-dependent anorexia.

Insulin is another peripheral factor which increases in proportion to body fat. Insulin is secreted by the pancreas and regulates blood glucose concentration via pleotrophic effects in the periphery. However, insulin also has central effects on food intake behavior. Insulin crosses the blood–brain barrier via a receptor-mediated process, and direct infusion of insulin into the brain reduces both food intake and body weight (Woods and Porte 1983). Inhibition of insulin signaling has an opposite effect, increasing food intake and decreasing body weight (Niswender et al. 2003). Insulin receptors are widely expressed in the brain including the NPY/AGRP and POMC-expressing neurons in the arcuate nucleus. Consistent with its anorexic activity, insulin activates POMC neurons, and insulin deficiency results in decreased NPY expression (Niswender et al. 2003; Xu et al. 2005). Thus, insulin and leptin both act on the arcuate nucleus, consistent with the finding that insulin and leptin have additive effects on feeding behavior (Air et al. 2002). Insulin and leptin signaling pathways converge at the level of PI3 kinase, and pharmacologic inhibition of PI3 kinase inhibits the anorexic effects of insulin (Niswender et al. 2003; Xu et al. 2005). However, there are key differences between the effect of insulin and leptin on arcuate neurons. Although deletion of neuronal insulin receptors results in very mild obesity in female mice (Bruning et al. 2000), downregulation of insulin receptors or PI3 kinase in POMC and AGRP neurons does not affect feeding behavior or weight (Konner et al. 2007; Hill et al. 2008). Therefore, while the acute effects of insulin on feeding behavior are well documented, insulin signaling in the arcuate nucleus does not seem to play a major role in the long-term regulation of energy homeostasis.

67.4 Additional Peripheral Signals

Endocannabinoids also have effects on appetite and metabolism. Endocannabinoids signal through G-protein coupled cannabinoid receptors which are widely expressed in the brain and periphery (Kunos 2007). Endocannabinoids induce food intake while cannabinoid antagonists reduce food intake and increase energy expenditure. Furthermore, deletion of the cannaboid receptor 1 reduced caloric intake and decreased body fat through both peripheral and central mechanisms. Finally, overnutrition results

in activation of the endocannabinoid system, in concert with increased feeding, decreased energy expenditure, and obesity. Centrally, endocannabinoids may act through the arcuate–hypothalamic circuit, or via projections from the lateral hypothalamus to the mesolimbic reward system.

Excess glucocorticoids increase feeding behavior, total body weight and central adiposity. Administration of glucocorticoids in the brain increases NPY expression in the hypothalamus, and affects the mesolimbic reward system resulting in increased intake of palatable foods (Dallman et al. 2007). On the other hand, glucocorticoid deficiency secondary to adrenalectomy results in decreased food intake and weight, even in the markedly obese leptin or leptin receptor-deficient mice (Shimomura et al. 1987). Estrogen may also modulate feeding behavior, as peripheral and central estrogen administration enhances the anorexic effects of leptin and insulin (Clegg et al. 2006).

Proinflammatory cytokines such as tumor necrosis factor-α and interleukin-6 inhibit feeding and induce thermogenesis, and are largely responsible for the wasting and cachexia associated with infection and cancer. Although many of the effects of proinflammatory cytokines are certainly due to their many peripheral activities, their effect may be in part due to effects on the hypothalamus (Buchanan and Johnson 2007). For example, ciliary neutrotrophic factor (CNTF) inhibits food intake, increases energy expenditure, and reduces body weight (Buchanan and Johnson 2007). Although CNTF treatment can suppress NPY expression and therefore inhibit food intake, the anorexic effects of CNTF persist after cessation of treatment. This long-lasting effect may be due to enhanced hypothalamic neurogenesis in which newly generated neurons are responsive to leptin (Kokoeva et al. 2005). Integration of these neurons in the arcuate-hypothalamic circuit may therefore lead to the long-lasting effects of CNTF on feeding and metabolism.

67.5 Application to Other Areas of Health and Disease: The Hedonic Response to Food

Classic examples of brain diseases affecting feeding behavior include individuals with large pituitary tumors which encroached on the ventral forebrain, leading to voracious feeding, morbid obesity, and hypogonadism. Relatively crude rodent experiments involving lesions to the ventromedial hypothalamus (the so-called "satiety center") recapitulated these findings, whereas lesions to the lateral hypothalamus (the so-called "feeding center") resulted in anorexia and starvation (Hervey 1959). These findings led to the "dual center model." While we now know that these lesions resulted in more extensive damage to adjacent areas and axonal projections passing through the lesion, and that the "dual center model" is likely too simplistic, these experiments formed the basis of the central regulation of satiety and feeding behavior. However, while the hypothalamus and hindbrain is critical to the detection and integration of peripheral signals, it is unlikely to be the brain region ultimately responsible for hedonic responses to food and subjective feelings of satiety. Earlier, the impact of leptin on the mesolimbic reward system was outlined. There are brain disorders in which this circuit is dysfunctional and hedonic responses to food are dysregulated. One such example is frontotemporal dementia, the second most common dementia after Alzheimer's disease. Many individuals with frontotemporal dementia exhibit hyperphagia with episodes of binge eating and weight gain. Neuroanatomic analysis in affected individuals indicates that abnormalities of a right orbito-frontal–insular–striatal circuit are closely correlated with abnormal feeding behavior (Woolley et al. 2007). A lesion in this circuit can also lead to Gourmand's syndrome in which an individual becomes preoccupied by food, especially fine dining (Regard and Landis 1997). This circuit is also implicated in other disorders which feature feeding abnormalities including obsessive-compulsive disorder and bulimia. Interestingly, individuals with frontotemporal dementia may continue eating

despite feeling full, suggesting that dysfunctional reward circuits may induce appetite despite feelings of satiety (Woolley et al. 2007). In this regard, satiety is often described in terms of satisfaction and the physical sensation of fullness, whereas appetite is often described in terms of a hedonic drive for food.

These diseases highlight that feeding behavior is strongly influenced by pleasure and reward circuits. The peripheral signals discussed thus far are largely homeostatic signals related either to short-term factors (such as ingestion of food) or long-term factors (such as adiposity and energy stores). In contrast, hedonic responses to food are largely nonhomeostatic and can lead to imbalances in energy homeostasis, as evidenced by increasing obesity rates secondary to the overabundance of high calorie, palatable food. Aside from the mesolimbic reward system already discussed, the sensations of vision, taste, and smell are powerful signals which may induce appetite despite other signals of satiety. Taste information is carried via cranial nerves VII, IX, and X to the gustatory part of the NTS. These neurons then project to the medial parabrachial nucleus (in the pons), followed by projections to the ventral posteromedial nucleus of the thalamus, and then to the postcentral gyrus and insular cortex. Projections to the central nucleus of the amygdala and the LHA are also present, which may be responsible for the effects of taste sensation on appetite. There is cross-talk between peripheral metabolic signals and central pathways as leptin-deficient mice have a preference for sweet substances and leptin administration inhibits sweet taste sensation (Morley 1987; Kawai et al. 2000). CCK also reduces sucrose intake in fasted rats (Gibbs 1973).

Olfactory cues are first detected in the olfactory epithelium on the roof of the sinonasal passages. These primary sensory neurons project to the olfactory bulb, where second order neurons pass centrally via the olfactory tract. Axons in the olfactory tract terminate in numerous brain regions including the prepiriform area (primary olfactory cortex), amygdala, semilunar gyrus, ambient gyrus, septal (subcallosal) area, olfactory tubercle, and anterior olfactory nucleus. The olfactory system is the only sensory system which bypasses the thalamus en route to the CNS. Furthermore, the close association between the olfactory system and limbic regions (amygdala, septal area) provides a possible structural basis for the strong emotional responses invoked by olfactory cues. Olfactory information can also project to the hypothalamus, reticular formation, salivatory nuclei, and dorsal vagal nucleus via the medial forebrain bundle and the medullary striae of the thalamus. Again, it is clear that the gustatory and olfactory senses are strong modulators of appetite. However, the mechanisms and pathways whereby this modulation occurs are obscure.

67.6   Conclusions

Multiple steps are required in the central regulation of appetite and satiety behavior (Table 67.1). First, signals generated in the periphery are relayed to the brain. These signals are generated in response to short-term signals such as food intake into the gastrointestinal system. Long-term signals reflect the levels of energy storage in adipose tissue. Other signals are not homeostatic, but instead reflect non-homeostatic factors such as palatability and the hedonic response to food. These signals act on brain circuits including the NTS, arcuate hypothalamus, and mesolimbic reward system. The relative activation or inhibition of neuronal circuits results in appetite and satiety. The central control of appetite and satiety behavior is remarkably robust in most situations and for most organisms. Not until recent times of food abundance and relatively sedentary lifestyles are the mechanisms controlling appetite and satiety behavior becoming perturbed. Thus the basic understanding of the central regulation of feeding behavior under normal physiologic perturbation conditions provides a framework for elucidating the mechanisms underlying obesity and various disorders of energy homeostasis.

Table 67.1 Key central brain circuits in the regulation of appetite and satiety behavior

- Nucleus of the solitary tract (NTS)
  - Receives vagal afferents
  - Gut–brain axis (mechanical, cholecystokinin)
- Arcuate nucleus
  - Leptin signaling
  - Insulin signaling
  - Orexigenic peptides (NPY and AGRP)
  - Anorexic peptides (α-MSH and CART)
- Lateral hypothalamic area (LHA)
  - Catabolic pathway
  - Orexigenic peptides (MCH and orexins)
- Paraventricular nucleus (PVN)
  - Anabolic pathway
  - Anorexic peptides (CRH, TRH, OXY)
- Mesolimbic reward system, frontal neocortex, insular neocortex, ventral striatum
  - Ventral tegmental area, ventral striatum (nucleus accumbens), frontal neocortex, insular cortex, amygdala, hippocampus
  - Higher order processing such as hedonic response to food

Summary Points

- The central regulation of appetite and satiety behavior is one mechanism whereby an organism regulates its energy balance.
- The gastrointestinal tract sends short-term nutrient and humoral signals through the vagus nerve to the brainstem.
- Adipose tissue secretes leptin and other adipokines which serve as long-term hormonal signals of energy storage levels to the brain.
- Complex brain circuits such as the mesolimbic reward system integrate metabolic and nonhomeostatic signals to generate hedonic responses to food.
- Multiple brain circuits in the hypothalamus, other forebrain regions, and the brainstem integrate a variety of peripheral signals.
- In concert, numerous brain circuits are responsible for generating the feelings of appetite or satiety, which ultimately serve to regulate food intake.

Definitions and Explanations of Key Terms

Adipokine: Adipose-secreted hormones, many of which may regulate energy homeostasis. Although derived from the words adipose and cytokine, the term adipokine is generally used for any adipose-derived hormone, and not only adipose-derived cytokines (the latter specifically acting on the immune system).

Anorexigenic: Causing decreased feeding.

Appetite: Subjective desire to eat food.

Energy homeostasis: The processes whereby an organism regulates feeding behavior, energy storage, and energy expenditure to maintain a relatively constant metabolic profile. In environments in which food is in abundance, nonhomeostatic factors may overcome homeostatic factors, leading to obesity and other metabolic derangements.

> **Gut–brain axis:** Signals from the gastrointestinal system in response to food intake, transmitted to the brain via the autonomic nervous system or hormones.
> **Orexigenic:** Causing increased feeding.
> **Satiety:** Subjective feeling of adequate food intake.

References

Abizaid A, Liu ZW, Andrews ZB, Shanabrough M, Borok E, Elsworth JD, Roth RH, Sleeman MW, Picciotto MR, Tschop MH, Gao XB, Horvath TL J Clin Invest. 2006;116:3229–39.

Ahima RS, Flier JS Annu Rev Physiol. 2000;62:413–37.

Ahima RS, Lazar MA Mol Endocrinol. 2008;22:1023–31.

Ahima RS, Prabakaran D, Mantzoros C, Qu D, Lowell B, Maratos-Flier E, Flier JS Nature. 1996;382:250–2.

Ahima RS, Saper CB, Flier JS, Elmquist JK Front Neuroendocrinol. 2000;21:263–307.

Air EL, Benoit SC, Clegg DJ, Seeley RJ, Woods SC Endocrinology. 2002;143:2449–52.

Baicy K, London ED, Monterosso J, Wong ML, Delibasi T, Sharma A, Licinio J Proc Natl Acad Sci USA. 2007;104:18276–9.

Bailey AR, Von Englehardt N, Leng G, Smith RG, Dickson SL J Neuroendocrinol. 2000;12:191–7.

Bi S, Chen J, Behles RR, Hyun J, Kopin AS, Moran TH Am J Physiol Regul Integr Comp Physiol. 2007;293:R55–63.

Bruning JC, Gautam D, Burks DJ, Gillette J, Schubert M, Orban PC, Klein R, Krone W, Muller-Wieland D, Kahn CR Science. 2000;289:2122–5.

Buchanan JB, Johnson RW Neuroendocrinology. 2007;86:183–90.

Chua SC, Jr., Chung WK, Wu-Peng XS, Zhang Y, Liu SM, Tartaglia L, Leibel RL Science. 1996;271:994–6.

Clegg DJ, Brown LM, Woods SC, Benoit SC Diabetes. 2006;55:978–87.

Coope A, Milanski M, Araujo EP, Tambascia M, Saad MJ, Geloneze B, Velloso LA FEBS Lett. 2008;582:1471–6.

Dallman MF, Warne JP, Foster MT, Pecoraro NC J Physiol. 2007;583:431–6.

Diano S, Farr SA, Benoit SC, McNay EC, da Silva I, Horvath B, Gaskin FS, Nonaka N, Jaeger LB, Banks WA, Morley JE, Pinto S, Sherwin RS, Xu L, Yamada KA, Sleeman MW, Tschop MH, Horvath TL Nat Neurosci. 2006;9:381–8.

Dourish CT, Rycroft W, Iversen SD Science. 1989;245:1509–11.

Elias CF, Aschkenasi C, Lee C, Kelly J, Ahima RS, Bjorbaek C, Flier JS, Saper CB, Elmquist JK Neuron. 1999;23:775–86.

Emond M, Schwartz GJ, Ladenheim EE, Moran TH Am J Physiol. 1999;276:R1545–9.

Farooqi IS, Bullmore E, Keogh J, Gillard J, O'Rahilly S, Fletcher PC Science. 2007;317:1355.

Fry M, Smith PM, Hoyda TD, Duncan M, Ahima RS, Sharkey KA, Ferguson AV J Neuroscience. 2006;26:9695–702.

Fulton S, Pissios P, Manchon RP, Stiles L, Frank L, Pothos EN, Maratos-Flier E, Flier JS Neuron. 2006;51:811–22.

Gibbs J, Young RC, Smith GP J Comp Physiol Psychol. 1973;84:488–95.

Guan XM, Yu H, Palyha OC, McKee KK, Feighner SD, Sirinathsinghji DJ, Smith RG, Van der Ploeg LH, Howard AD Brain Res Mol Brain Res. 1997;48: 23–9.

Hervey GR. J Physiol. 1959;145:336–52.

Hill JW, Williams KW, Ye C, Luo J, Balthasar N, Coppari R, Cowley MA, Cantley LC, Lowell BB, Elmquist JK J Clin Invest. 2008;118:1796–805.

Hommel JD, Trinko R, Sears RM, Georgescu D, Liu ZW, Gao XB, Thurmon JJ, Marinelli M, DiLeone RJ Neuron. 2006;51:801–10.

Hoyda TD, Fry M, Ahima RS, Ferguson AV J Physiol. 2007;585:805–16.

Kawai K, Sugimoto K, Nakashima K, Miura H, Ninomiya Y Proc Natl Acad Sci USA. 2000;97:11044–9.

Kokoeva MV, Yin H, Flier JS Science. 2005;310:679–83.

Konner AC, Janoschek R, Plum L, Jordan SD, Rother E, Ma X, Xu C, Enriori P, Hampel B, Barsh GS, Kahn CR, Cowley MA, Ashcroft FM, Bruning JC Cell Metab. 2007;5:438–49.

Kopin AS, Mathes WF, McBride EW, Nguyen M, Al-Haider W, Schmitz F, Bonner-Weir S, Kanarek R, Beinborn M J Clin Invest. 1999;103:383–91.

Kraly FS, Carty WJ, Resnick S, Smith GP J Comp Physiol Psychol. 1978;92:697–707.

Kubota N, Yano W, Kubota T, Yamauchi T, Itoh S, Kumagai H, Kozono H, Takamoto I, Okamoto S, Shiuchi T, Suzuki R, Satoh H, Tsuchida A, Moroi M, Sugi K, Noda T, Ebinuma H, Ueta Y, Kondo T, Araki E, Ezaki O, Nagai R, Tobe K, Terauchi Y, Ueki K, Minokoshi Y, Kadowaki T Cell Metab. 2007;6:55–68.

Kunos G. Am J Med. 2007;120:S18–24; discussion S24.

Kusminski CM, McTernan PG, Schraw T, Kos K, O'Hare JP, Ahima R, Kumar S, Scherer PE Diabetologia. 2007;50:634–42.

Liebling DS, Eisner JD, Gibbs J, Smith GP J Comp Physiol Psychol. 1975;89:955–65.

Lutter M, Sakata I, Osborne-Lawrence S, Rovinsky SA, Anderson JG, Jung S, Birnbaum S, Yanagisawa M, Elmquist JK, Nestler EJ, Zigman JM. Nat Neurosci. 2008;11:752–3.

Morley JE. Endocr Rev. 1987;8:256–87.

Myers MG, Cowley MA, Munzberg H Annu Rev Physiol. 2008;70:537–56.

Myers MG, Jr., Munzberg H, Leininger GM, Leshan RL Cell Metab. 2009;9:117–23.

Naleid AM, Grace MK, Cummings DE, Levine AS Peptides. 2005;26:2274–9.

Niswender KD, Schwartz MW Front Neuroendocrinol. 2003;24:1–10.

Qi Y, Takahashi N, Hileman SM, Patel HR, Berg AH, Pajvani UB, Scherer PE, Ahima RS Nat Med. 2004;10:524–9.

Regard M, Landis T Neurology. 1997;48:1185–90.

Rosenbaum M, Sy M, Pavlovich K, Leibel RL, Hirsch J J Clin Invest. 2008;118:2583–91.

Schwartz GJ. Nutrition. 2000;16:866–73.

Schwartz GJ. Philos Trans R Soc Lond B Biol Sci. 2006;361:1275–80.

Shimomura Y, Bray GA, Lee M Horm Metab Res. 1987;19:295–9.

Smith GP, Jerome C, Norgren R Am J Physiol. 1985;249:R638–41.

South EH, Ritter RC Peptides. 1988;9:601–12.

Spranger J, Verma S, Gohring I, Bobbert T, Seifert J, Sindler AL, Pfeiffer A, Hileman SM, Tschop M, Banks WA Diabetes. 2006;55:141–7.

Treece BR, Covasa M, Ritter RC, Burns GA Brain Res. 1998;810:34–40.

Tschop M, Smiley DL, Heiman ML Nature. 2000;407:908–13.

Wang PY, Caspi L, Lam CK, Chari M, Li X, Light PE, Gutierrez-Juarez R, Ang M, Schwartz GJ, Lam TK Nature. 2008;452:1012–6.

Wiedmer P, Nogueiras R, Broglio F, D'Alessio D, Tschop MH Nat Clin Pract Endocrinol Metab. 2007;3:705–12.

Woods SC, Porte D, Jr. Adv Metab Disord. 1983;10:457–68.

Woolley JD, Gorno-Tempini ML, Seeley WW, Rankin K, Lee SS, Matthews BR, Miller BL Neurology. 2007;69:1424–33.

Xu AW, Kaelin CB, Takeda K, Akira S, Schwartz MW, Barsh GS J Clin Invest. 2005;115:951–8.

Zhang Y, Proenca R, Maffei M, Barone M, Leopold L, Friedman JM Nature. 1994;372:425–32.

Chapter 68
Role of the Gastrointestinal Tract in Peptide Hormone Release and Appetite

Joan Khoo, Christopher K. Rayner, Christine Feinle-Bisset, and Gary Wittert

Abbreviations

BBB	Blood–brain barrier
CB1	Cannabinoid-1
CCK	Cholecystokinin
CCK1R	Cholecystokin-1 receptor
CNS	Central nervous system
DPP-4	Dipeptidyl peptidase-4
GLP-1	Glucagon-like peptide-1
LCFA	Long-chain fatty acid
MCH-1	Melanin-concentrating hormone-1
OXM	Oxyntomodulin
PP	Pancreatic polypeptide
PYY	Peptide YY

68.1 Introduction

The gastrointestinal tract, in addition to its primary functions of digestion and absorption, plays an important part in the regulation of appetite, triggering processes that initiate food intake, and leading to satiation and satiety after meals. "Satiation" refers to the processes that terminate food intake (feeling of "fullness") and limit meal size, while "satiety" refers to the suppression of hunger in between meals that reduces the frequency of eating. The role of the vagus nerve in conveying signals that induce satiation has been known for decades, but there is increasing recognition of the importance of gut hormones in the regulation of food intake. Ingested food causes satiation by gastric distension and secretion of peptide hormones from the stomach and small intestine, which act locally on vagal nerve endings and in the brain to prevent the overconsumption of nutrients and maintain energy homeostasis. Vagal and hormonal signals also influence appetite regulation centers in the hindbrain and hypothalamus to control feeding behavior in a complex network of gut–brain interactions.

C.K. Rayner (✉)
Discipline of Medicine, Royal Adelaide Hospital, Adelaide,
South Australia, Australia
e-mail: chris.rayner@adelaide.edu.au

68.2 Responses of the Gastrointestinal Tract to Ingested Food

The gastrointestinal tract responds to a meal in three integrated and overlapping phases: cephalic, gastric, and intestinal, which are dependent on parasympathetic vagal nerve transmission (Camilleri 2006) (Fig. 68.1). In the cephalic phase, meal-induced stimuli and anticipation trigger gastrointestinal secretory and motor processes that aid digestion by gastric acid, pancreatic enzymes, and bile. Vagal signaling is integral to the cephalic phase: gustatory and other visceral afferents project to the nucleus tractus solitarius in the brainstem to activate these digestive processes via vagal efferents from motor nuclei in the brainstem, with acetylcholine, cholecystokinin, and gastrin being the main neurotransmitters. The cephalic phase constitutes approximately 50% of the prandial motor and secretory responses (Camilleri 2006). Subsequently, the gastric and intestinal phases are activated by transit of nutrients through the stomach and small intestine. The gastric phase involves relaxation of the proximal stomach, and load-dependent regulation of gastric emptying. During this process, solids empty in an overall linear pattern after an initial lag phase, while the emptying of liquids is dependent on caloric content and varies from an exponential to a linear pattern as the caloric content increases, with lipids having the greatest inhibitory effect (Ritter 2004). In response to meal ingestion, there is a switch from the cyclical migrating motor complex of the fasting state to intermittent irregular phasic contractions that characterize the fed state, which serve to slow transit of nutrients through the small intestine and facilitate mixing and absorption. The duration of this postprandial pattern is prolonged by increased caloric content (Camilleri 2006). Neural and hormonal signals are transmitted in the gastric and intestinal phases to slow transit food through the gastrointestinal tract and induce satiation. Impulses travel through networks of neurons (submucosal and myenteric nerve plexuses) collectively known as the enteric nervous system, which are present throughout the gastrointestinal tract, while gut hormones

Cephalic phase

VAGAL parasympathetic fibres in the brainstem transmit signals to mediate gut motility

Brainstem

Anticipation of meals and sensory stimuli trigger vagal impulses in the brain

FOOD

Gastric phase

VAGAL afferents in the gut convey information about distension and luminal nutrient type and content to the brain

Intestinal phase

➢ Gastric relaxation and accommodation
➢ Slowed gastric emptying
➢ Suppressed ghrelin secretion
➢ Increased leptin secretion

➢ Change to intermittent, irregular phasic contractions
  → slowing of intestinal transit
➢ Secretion of gut peptides (CCK, GLP-1, OXM, PYY)
  → satiation

Fig. 68.1 Responses of the gastrointestinal tract to a meal. This figure illustrates the neural and hormonal responses of the brain and gut to a meal. These responses facilitate digestion and nutrient absorption, and limit food intake (*CCK* cholecystokinin, *GLP-1* glucagon-like peptide-1, *OXM* oxyntomodulin, *PYY* peptide YY)

Table 68.1 Key features of neural and hormonal satiation signaling in the gastrointestinal tract

1. The *enteric nervous system* consists of submucosal and myenteric nerve plexuses in the stomach and intestine, which function as the "brain" of the gut.
2. *Vagal and spinal sensory afferents* in the stomach respond to stretch, volume and tension, and communicate with appetite centers in the brain.
3. *Enteroendocrine cells* (e.g., *I and L cells*) in the small intestine respond to nutrients in the intestinal lumen by secreting gut hormones which induce satiation
4. *Intestinal taste receptors* on apical surface of enterocytes detect chemical properties of "sweet" or "bitter" nutrients.

This table lists the components of neural and hormonal satiation signaling, which connect the gastrointestinal tract to the brain and limit feeding when nutrients are detected in the stomach and small intestine

are secreted from specialized gastric and intestinal mucosal cells in response to nutrients. The various forms of signaling will be discussed in subsequent sections (Table 68.1).

68.3 Satiation Signaling in the Gastrointestinal Tract

68.3.1 Gastric Satiation Signaling

Vagal signaling is central to the mediation of gastric satiation by distension of the stomach. The stomach wall contains receptors for tension, stretch, and volume, which relay signals to the brain through dense networks of vagal and spinal sensory afferents (Ritter 2004). Intramuscular arrays in the circular and longitudinal muscle layers, which serve as stretch and volume receptors for generating negative feedback from gastric distension, are capable of sustained impulse transmission during prolonged stretch in a full stomach during feeding, despite reduced gastric wall tension during accommodation (Berthoud 2008). Distension of the antrum, as compared to the proximal stomach, tends to provoke nausea and bloating (Ladabaum et al. 1998), and may explain the observation that satiation and satiety are directly related to antral width (Sturm et al. 2004), i.e. satiation is induced more readily by the presence of food in the distal stomach than the fundus.

68.3.2 Small Intestinal Satiation Signaling

The perception of gastric distension is greatly increased by concomitant intraduodenal lipid or carbohydrate infusions, inducing a sensation of "meal-like" fullness (Feinle et al. 1997). This highlights the importance of nutrients in the small intestine as a stimulus for terminating food intake. Infusion of nutrients directly into the small intestine rapidly reduces food intake due to satiation signals produced within the gut. Many of these signals, which include gut peptides secreted from enteroendocrine cells in the small intestine, slow nutrient emptying from the stomach and thus prolong gastric distension, but infusions of carbohydrates, amino acids, and fatty acids into the small intestines of rats in sham feeding experiments have shown that slowing of emptying is not necessary for satiation to occur (Fig. 68.2) (Ritter 2004).

There are four criteria that define a satiating factor (Geary 2004): (1) it is released in response to ingested nutrients; (2) infusion of physiological doses produces satiation and limits food intake; (3) cessation of eating occurs soon after secretion, and (4) blockade or absence of its receptor reverses the satiating effects and/or increases meal size. These criteria are satisfied by several gut hormones
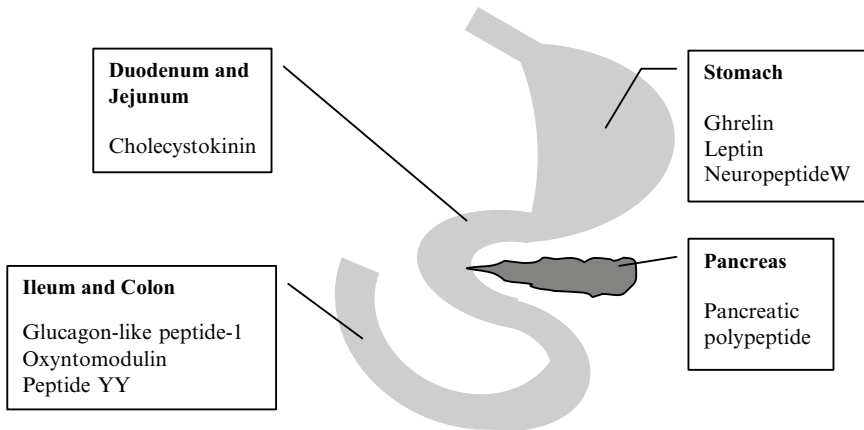
Fig. 68.2 Sites of secretion of peptide hormones involved in appetite regulation and food intake in the gastrointestinal tract. This figure is an overview of the sites of release of gut hormones which regulate appetite

including, but not limited to, cholecystokinin, glucagon-like peptide-1, oxyntomodulin, peptide YY, and pancreatic polypeptide.

In response to nutrients, gut peptides are secreted from specialized enteroendocrine cells in the proximal and distal small intestine. These exert local and systemic effects by diffusing through interstitial fluid to stimulate vagal and spinal sensory nerve fibers in their vicinity, and may also circulate in the bloodstream and cross the blood–brain barrier to influence feeding and appetite directly or indirectly (Banks 2008). In the small intestine, gut peptide secretion and satiation is dependent on the caloric load (Pilichiewicz et al. 2007), macronutrient composition (Seimon et al. 2009), and the length of intestine exposed (Meyer et al. 1998). Digestion is required for nutrient–gut interactions, as shown by studies in which inhibition of lipase attenuated the satiating effect of oral fat ingestion in healthy subjects (O'Donovan et al. 2003). Within the small intestine, the site of contact with nutrients also influences peptide hormone secretion: the duodenum and jejunum release cholecystokinin (CCK), while glucagon-like peptide-1 (GLP-1), and peptide YY (PYY) are secreted predominantly in the distal small intestine and colon. These gut peptides are major satiation signals, acting both peripherally within the gastrointestinal tract, and in the appetite centers of the hindbrain and hypothalamus, to reduce food intake.

68.4 Gut Peptides Involved in Satiation Signaling

This section will briefly discuss cholecystokinin, gastric leptin, glucagon-like peptide-1, oxyntomodulin, peptide YY, pancreatic polypeptide, neuropeptide W, the endocannabinoids, and ghrelin (Table 68.2).

68.4.1 Cholecystokinin

Cholecystokinin (CCK), the first satiating gut peptide described, is secreted from I-cells in the duodenum and jejunum, primarily in response to the presence of luminal lipids (especially fatty acids) and proteins, with less stimulation by carbohydrate. CCK also regulates the digestion of fat

Table 68.2 Effects of peptide hormones secreted by the gastrointestinal tract and pancreas

Gut hormone	Site of secretion	Appetite	Other major effects
Cholecystokinin (CCK)	Duodenum, jejunum	↓	Slows gastric emptying
Gastric leptin	Stomach	↓ (↑ CCK secretion)	↑ biliary and pancreatic secretion
Ghrelin	Stomach	↑	↑ protein absorption
Neuropeptide W	Stomach	↓	↓ carbohydrate and fat absorption
Glucagon-like peptide-1 (GLP-1)	Distal small intestine, colon	↓	?appetite suppression, weight loss via effects in the brain
Oxyntomodulin (OXM)	Distal small intestine	↓	Accelerates gastric emptying
Peptide YY (PYY)	Distal ileum	↓	↑ insulin secretion in response to oral glucose load, weight loss
Pancreatic polypeptide	Pancreas	↓*	Weight loss

*Increases appetite when injected into the central nervous system of rodents

This table shows the effects of gut hormones on appetite and on processes in the gastrointestinal tract which aid digestion and absorption of nutrients

and protein in the small intestine by coordinating the delivery of nutrients with the secretion of pancreatic enzymes and bile salts in reflex pathways involving the vagus. The satiating effects of CCK are mediated via CCK1 (previously known as CCK-A) receptors (CCK1R), as evident from the increase in food intake in rats lacking CCK1R, and in humans given CCK1 receptor antagonists (Cummings and Overduin 2007). CCK1R are present in the hindbrain and hypothalamus, and on vagal afferents and efferents in the stomach, intestine, and pancreas. Injection of CCK into hypothalamic nuclei increases satiation in rodents by stimulating CCK1R in the hypothalamus and hindbrain, while administration of physiological doses of CCK in rodents and humans reduces meal size in a dose-dependent fashion (Little et al. 2005).

In humans, gastric distension augments the anorexigenic effects of exogenous CCK, suggesting that slowing of gastric emptying contributes to CCK-induced satiation (Kissileff et al. 2003). The vagus is important for CCK signaling, as vagotomy in rodents has been found to reduce the satiating effects of peripherally administered CCK (Moran et al. 1997). CCK may also influence the ability of vagal afferent neurons to respond to other neurohormonal signals through the expression of G-protein coupled receptors and regulation of the release of peptide neurotransmitters (Dockray 2009). When plasma CCK is low during fasting, expression of cannabinoid-1 (CB1) and melanin-concentrating hormone-1 (MCH-1) receptors, which are associated with stimulation of feeding, is increased. Conversely, postprandial release of CCK downregulates CB1 and MCH-1 receptors, but increases expression of Y2 receptors in gastric afferent neurons, which are stimulated by peptide YY, a satiating gut hormone (Dockray 2009). Although CCK reduces individual meal size, body weight does not change due to increased frequency of eating; furthermore, the anorexigenic effect is of short duration, being undetectable if CCK is injected more than 30 min before meals, and disappearing after 24 h of continuous infusion (Little et al. 2005). Hence, the importance of CCK in long-term body weight regulation appears modest.

68.4.2 Gastric Leptin

Although adipose tissue is known to be the primary source of the peptide hormone leptin, which reduces appetite and increases energy expenditure, chief cells in the gastric fundic mucosa of humans and rodents secrete leptin postprandially in response to vagal stimulation or hormonal factors (primarily CCK) (Guilmeau et al. 2004). In rats, gastric leptin binds to soluble leptin receptors in gastric juice to form high molecular weight complexes that are resistant to digestion by gastric acid and bind

to basolateral receptors in the small intestinal mucosa to exert paracrine effects in the gastrointestinal tract (Cammisotto and Bendayan 2007). Leptin stimulates intestinal secretion of CCK to form a positive feedback loop which slows gastric emptying, increases biliary and pancreatic secretion, and induces satiation (Guilmeau et al. 2004). Leptin also reduces the absorption of fat and carbohydrate in the jejunum (Cammissotto and Bendayan 2007), which, in addition to its central effects to suppress appetite by activation of satiety centers in the hypothalamus and hindbrain, serves to reduce caloric intake.

68.4.3 Glucagon-like Peptide-1

Glucagon-like peptide-1 (GLP-1) is derived from proglucagon, synthesized in L-cells predominantly located in the distal small intestine and colon, and is cosecreted with oxyntomodulin and peptide YY. The concentration of GLP-1 rises in response to the presence of lipids and carbohydrates in the small intestine, but its active metabolites GLP-1 (7–36) and GLP-1 (7–37) are rapidly inactivated by the enzyme dipeptidyl peptide 4 (DPP-4). Fat is the most potent secretagogue for GLP-1 (Feinle et al. 2003), followed by carbohydrate and protein hydrolysates (but not intact proteins). The mechanisms by which ingested nutrients stimulate GLP-1 secretion are not completely understood. In humans, direct infusion of glucose into the small intestine only results in GLP-1 release if glucose is allowed access beyond the proximal 60 cm (Little et al. 2006). Although a threshold load of glucose delivery of ~1.4 kcal/min to the small intestine has been suggested to be necessary to induce GLP 1 release, intraduodenal glucose infusions of 1.0 kcal/min have been shown to produce an early but transient rise in GLP-1 levels (Kuo et al. 2008), which is not seen with lipids, suggesting that lipids and glucose stimulate GLP-1 secretion by different mechanisms, or that GLP-1 release is delayed by the time required for intraluminal digestion of lipids. Possibly, the intestinal L-cell exposure to glucose stimulates the initial rise in GLP-1 secretion, and GLP-1 then slows further delivery of glucose downstream. Alternatively, this early transient release of GLP-1 could be due to a duodeno–jejunoileal "loop", in which glucose in the duodenum indirectly triggers distal GLP-1 release by neural or hormonal means, though the mediator of such a loop in humans is unclear at present.

The satiating effects of GLP-1 are mediated by receptors (GLP1R) which are present in the stomach, small intestine, colon, pancreatic islet cells, and brain (especially neurons in the hypothalamus around the satiety centers), as shown by the absence of the satiating effect of exogenous GLP-1 in GLP1R-knockout mice, and in rats and humans given the GLP1R antagonist, exendin 9–39 (Williams et al. 2009). GLP-1-induced satiation is also abolished by vagal transection or deafferentiation in rats (Abbott et al. 2005), underscoring the importance of the vagus in brain–gut communication for appetite suppression during feeding. Although intravenous infusions of physiological doses of GLP-1 (7–36) reduce food intake, its short half-life (1–2 min due to inactivation by DPP-4) necessitates continuous subcutaneous or intravenous administration for anorexigenic effects (Cummings and Overduin 2007) and renders native GLP-1 impractical for clinical use. GLP-1 also has an insulinotropic effect, and as one of the two known "incretin" hormones, plays an important role in many aspects of glucose metabolism. Long-acting GLP-1 analogs that are resistant to inactivation by DPP-4 (such as exenatide and liraglutide) were developed for the treatment of type 2 diabetes, but have also been shown to reduce appetite and weight (Drucker and Nauck 2006). Exogenous administration of GLP-1 also reduces gastroduodenal motility, increases gastric accommodation, and inhibits gastric and pancreatic secretion in a dose-dependent fashion (Drucker and Nauck 2006), which is likely to contribute to the satiating properties of GLP-1 by prolonging the duration of exposure of the small intestine to luminal nutrients.

68.4.4 Oxyntomodulin

Oxyntomodulin (OXM) is derived from proglucagon in L cells of the distal small intestine, and is cosecreted with GLP-1 and peptide YY, in proportion to the calorie content of ingested carbohydrates and fats (Cummings and Overduin 2007). Administration of OXM induces satiation in rodents (Dakin et al. 2004). Animal studies suggest that the satiating effects of OXM are likely to be exerted via GLP1R, since injection of the GLP1R antagonist, exendin 9–39, into the hypothalamus prevents intestinal OXM-induced satiation in rats (Dakin et al. 2004), and OXM does not affect feeding in GLP1R-knockout mice (Maida et al. 2008). The appetite-suppressing effects of OXM may be caused by reduction in secretion of ghrelin, an orexigenic hormone (Dakin et al. 2004; Cohen et al. 2003). Like GLP-1, OXM is inactivated by DPP-4 and has the capacity to stimulate insulin secretion (Maida et al. 2008).

68.4.5 Peptide YY and Pancreatic Polypeptide

Peptide YY (PYY) is a 36-amino acid peptide, which is co-secreted with GLP-1 by L-cells in the distal ileum in response to a nutrient load. Lipids are the most potent stimulus for PYY release, followed by carbohydrates and proteins (Pilichiewicz et al. 2007). Concentrations of PYY are low in the fasting state, but rise rapidly and in a biphasic pattern during feeding, with initial neural stimulation via cholinergic vagal afferents, followed by release in proportion to the caloric load, composition, and consistency of the food (Karra et al. 2009). In humans, postprandial PYY levels are positively correlated with satiety scores (Guo et al. 2006), suggesting a physiological role for PYY in appetite regulation. PYY is metabolized to the active form PYY (3–36) by the enzyme DPP-4, and binds to Y receptors in the G-protein coupled receptor superfamily in a variety of sites in the central nervous system (CNS), including the hindbrain, hypothalamus, and amygdala, which regulate satiation and energy balance, and to peripheral gastrointestinal vagal afferents. The satiating effect of intraperitoneal PYY injection is blocked by pharmacological Y2 receptor (Y2R) blockade and abolished in Y2R-knockout mice (Batterham et al. 2002), demonstrating the importance of Y2R activation for inhibiting feeding. There has been some inconsistency in data from different researchers as to the effects of intravenous administration of PYY (3–36) on appetite, and although plasma PYY concentrations in humans increase in proportion to the ingested calorie load, inhibition of food intake by exogenous PYY infusion is significant only at pharmacologic plasma concentrations of PYY (3–36), at which there is a tendency for nausea to occur (Degen et al. 2005).

Pancreatic polypeptide (PP), which shares structural features with PYY (3–36), is secreted from cells in the periphery of pancreatic islets in a biphasic manner (similar to PYY) in proportion to caloric load, under vagal nerve regulation. The effects of PP on appetite regulation are predominantly mediated by Y4, and, to a lesser extent, Y1 receptors (Cummings and Overduin 2007). In humans, peripheral PP administration results in acute and sustained (>24 h) reductions in appetite and food intake (Batterham et al. 2003). Previous reports that the anorexigenic effect of PP might be mediated by slowed gastric emptying were not reproduced in later studies which used human rather than bovine PP (Batterham et al. 2003).

68.4.6 Neuropeptide W

Neuropeptide W (NPW), a peptide hormone involved in the regulation of energy, thyroid, and adrenal homeostasis, was first discovered in the hypothalamus and brainstem of rodents, but has since

been demonstrated in rat, mouse, and human gastric antral mucosa (Caminos et al. 2008). NPW binds to the G-protein coupled receptors GPR7 and GPR8, and is thought to have a modulatory role in appetite regulation. Intracerebroventricular administration of NPW reduced food and water intake, reduced weight gain, and increased energy expenditure, suggesting that NPW is a catabolic signal in the brain (Mondal et al. 2003). Gastric NPW gene expression was decreased by fasting and restored with refeeding; moreover, increased feeding in pregnant rats is likely to be due to downregulation of NPW (Caminos et al. 2008). The role of NPW in humans remains to be established.

68.4.7 Ghrelin

Ghrelin, an acylated 28-amino acid peptide secreted by X/A cells in the stomach and duodenum, stimulates appetite and gastrointestinal motility (Cummings 2006). Plasma levels of ghrelin rise markedly just before expected meal times and are associated with an increase in meal frequency but not meal size. This preprandial surge is thought to be stimulated by the sympathetic nervous system as part of the cephalic phase of digestion, and can be entrained to regularly scheduled feeding (Mundinger et al. 2006), thereby suggesting a role in preparing for food intake and digestion. Endogenous ghrelin secretion is suppressed by food, with carbohydrates being more potent than proteins and lipids, but gastric distension or exposure of the stomach to nutrients is not required; rather, this negative feedback process is mediated by intestinal signaling and postabsorptive events such as increased plasma insulin, osmolarity of intestinal luminal contents, and nonvagal enteric neural signaling (Cummings 2006).

68.4.8 Endocannabinoids

The endocannabinoids are endogenous lipid mediators that regulate energy intake, primarily by activating cannabinoid receptors in the limbic system and hypothalamus to stimulate appetite. However, endocannabinoids also act to reduce excitatory transmission in the enteric nervous system, leading to slowing of gastric emptying and small intestinal transit (Izzo and Camilleri 2008). These effects on digestion and gut motility are mediated by CB1 receptors (CB1R) in cholinergic nerves in the myenteric and submucosal plexuses, circular and longitudinal muscle layers, and in crypt epithelial cells. Increased intestinal transit has been observed in rodents that are CB1-deficient or are administered the CB1-antagonist, rimonabant, while administration of CB1-agonists, or inhibitors of endocannabinoid inactivation, delay gastric emptying, slow small intestinal transit, and reduce phasic and tonic colonic motor responses to meal ingestion (Izzo and Camilleri 2008). The role of peripheral CB1R activation in humans remains unclear, though it is possible that endocannabinoid activation functions as an additional physiological "brake", in similar fashion to the slowing of gastrointestinal motility seen with GLP-1 and PYY.

68.5 Mechanisms of Nutrient Detection: Taste Receptors in the Gut

Until recently, the mechanisms of nutrient detection by the small intestine were almost completely unknown. There is now strong evidence that nutrient signaling can occur by stimulation of 'taste'

receptors on the apical microvilli of intestinal epithelial cells, which detect the chemical properties of food, analogous to taste-receptors on the tongue (Fig. 68.3). These might then induce the release of gut peptides such as GLP-1, PYY, and CCK, or mediators such as serotonin, from the basolateral surface of the cell to stimulate nearby vagal, enteric, and spinal afferents, or enter the circulation to exert central effects on appetite (Cummings and Overduin 2007). Examples of the small intestinal "taste" apparatus include the T1R2/T1R3 sweet taste receptor (Young et al. 2009), T2-family bitter taste receptors, and the taste-specific G protein, Gα-gustducin (Rozengurt 2006). While carbohydrate and protein could potentially be detected by the sweet and bitter taste receptors respectively, fatty acids can activate the G-protein-coupled receptors GPR120 and GPR119, a process that is linked to GLP-1 secretion in rats (Lauffer et al. 2009).
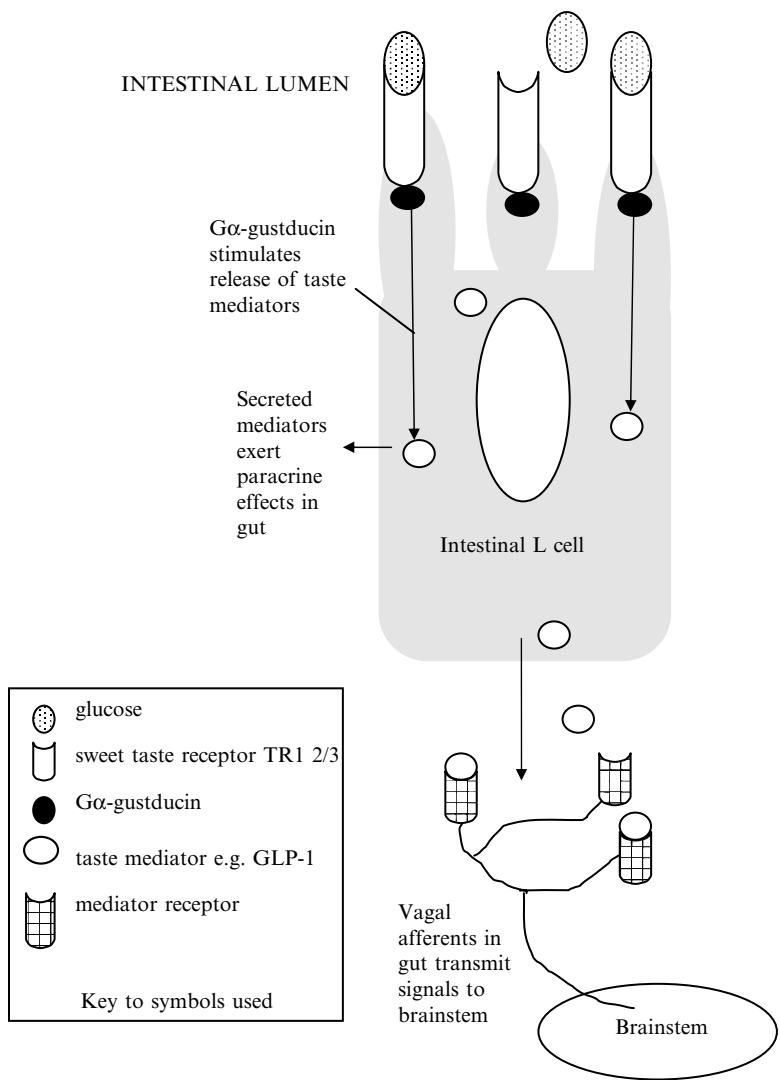
Fig. 68.3 Sensing of glucose in the small intestine by sweet taste receptors on L cells and mucosal vagal afferents to brainstem and hypothalamus. This figure illustrates the mechanisms by which intestinal sweet taste receptors detect ingested glucose and transmit sensory impulses via the vagus nerve to appetite centers in the brainstem. Diagram is not drawn to scale

68.6 Nonvagal Communication in the Gut–brain Axis

In addition to the importance of the vagus in mediating the effects of gut hormones, nonvagal mechanisms of gut–brain communication have been elucidated for ghrelin, CCK, PYY (3–36) and GLP-1. These include direct transfer of gut peptides across the blood–brain barrier (BBB) and alteration of endothelial cell function in the BBB (Banks 2008). Insulin, GLP-1, ghrelin, and pancreatic polypeptide are known to cross the BBB via specialized transporters and bind to receptors within the CNS. However, the central actions of these hormones may oppose their peripheral effects, such as with pancreatic polypeptide, which increases food intake in rats when injected intraventricularly, and reduces appetite when administered intraperitoneally (Asakawa et al. 2003), suggesting that central and peripheral Y4 receptors are differentially involved in appetite regulation. Insulin is a well-studied example of a hormone that influences appetite by altering endothelial function in the BBB: it increases the transport rate of the amino acid, tryptophan (which is required for the synthesis of serotonin), and thus stimulates feeding (Banks 2008). More studies are required to clarify the processes by which peripheral gut hormones exert their effects on appetite and metabolic regulatory centers in the hindbrain and hypothalamus.

68.7 The Ileal Brake

The negative feedback mechanisms, by which the transit of nutrients to the proximal small intestine stimulates the release of satiating gut peptides and vagal signaling to slow gastric emptying and reduce food intake (as discussed in the preceding sections), have been termed the "duodenal" and "jejunal" brakes; similarly, exposure of the ileum to nutrients inhibits proximal gastrointestinal motility and secretion to optimize nutrient digestion and absorption (Read et al. 1984). In particular, gastric and proximal intestinal motility in rats and dogs is markedly reduced by carbohydrate and fat infusions into isolated loops of ileum, but not duodenum, suggesting that passage of nutrients to the distal small intestine is necessary to generate strong inhibitory feedback (Maljaars et al. 2008), while the length of small intestine exposed to nutrient correlates with the degree of inhibition of motility induced by each class of macronutrient (Fig. 68.4) (Meyer 1998).

The chief mediators of the ileal brake are thought to be GLP-1 and PYY (Maljaars et al. 2008); as discussed earlier, these are stimulated by the presence of carbohydrates and lipids in the ileum and colon. Rats with a jejuno-ileal bypass, which leads to rapid exposure of the ileum to nutrients, exhibit raised concentrations of these gut hormones, in association with reduced food intake and weight loss, compared with sham-operated controls (le Roux et al. 2006). Transposition of an isolated segment of ileum to the jejunum, resulting in an intestinal tract of normal length but greater proximal density of enteroendocrine L-cells, produces an earlier and greater inhibitory response to feeding in rats, associated with reduced food intake and marked weight loss (Strader et al. 2005). In summary, there is strong evidence that activation of the ileal brake is an important inhibitory mechanism for food intake in animal models. Although there is a paucity of human studies, the ileal brake may be a potential target for appetite regulation and weight management. For example, rapid access of nutrients to the distal small intestine after Roux-en-Y gastric bypass surgery with concomitant release of "distal" gut peptides seems likely to contribute to the greater efficacy of this procedure over gastric banding in terms of weight loss (Morinigo et al. 2006).
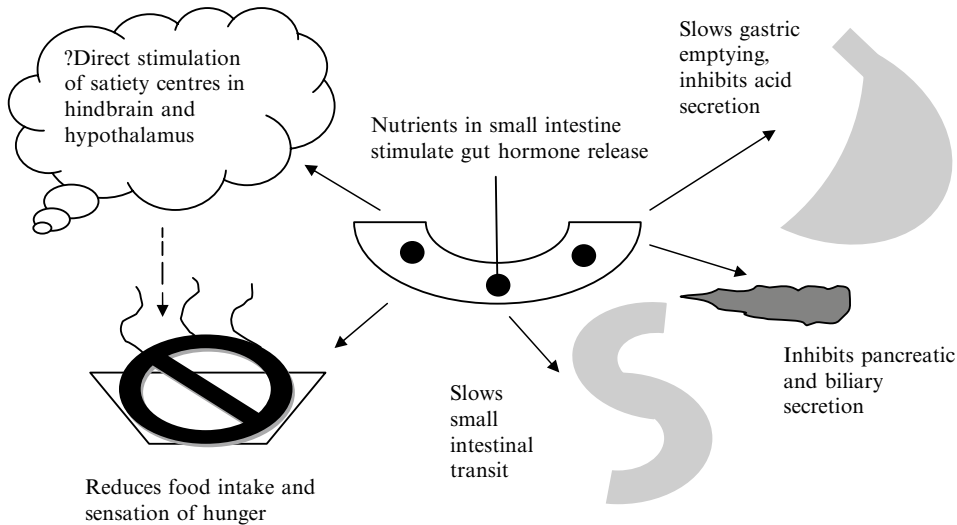
Fig. 68.4 Effects of the ileal brake on appetite and gastrointestinal secretory and motor function. This figure is an overview of the processes involved in the ileal brake. The ileal brake is thought to limit nutrient intake by inhibiting gastrointestinal motility and secretion, and stimulating the brain to reduce appetite

68.8 The Gut–Brain–Liver Neural Axis

Neural circuits activated in the intestine in response to ingested nutrients, which connect the gut, brain, and liver, and contribute to the maintenance of glucose homeostasis by regulating insulin sensitivity, have recently been described in rats (Wang et al. 2008). A metabolite of long-chain fatty acids (LCFA), LCFA-CoA, formed from enzymatic cleavage of intraduodenally-infused triglycerides is detected by intestinal sensor cells, and a vagally mediated circuit through the nucleus tractus solitarius in the hindbrain leads to reduced glucose production in the liver. Interruption of this circuit by vagotomy or gut vagal deafferentiation abolishes the insulin-sensitizing effects of intestinal lipid infusion, but does not affect peripheral glucose metabolism. LCFA-CoA also activates satiety centers in the hypothalamus to reduce appetite, and CNS pathways that increase hepatic insulin sensitivity (Obici et al. 2003). Exposure of the small intestine to fatty acids thus stimulates counter-regulatory mechanisms in the brain, gut, and liver that prevent hyperglycemia and limit caloric intake. The presence of glucose in the small intestine similarly signals to reduce hepatic VLDL production (Lam et al. 2007). Circulating amino acids derived from ingested proteins, such as leucine, activate hypothalamic neurons involved in energy and nutrient sensing in the hypothalamus in rats via vagal afferents, and may also influence hepatic glucose production by stimulating amino acid sensors in the liver (Potier et al. 2009). The presence and importance of these elegant regulatory circuits in humans and their role in obesity and related metabolic disorders remain to be determined (Table 68.3).

68.9 Therapeutic Applications to Other Areas of Health and Disease

Strategies to modify secretion of peptide hormones in the stomach and small intestine may have a number of therapeutic applications. Antiobesity therapies targeted at gut hormones are in various

Table 68.3 Key features of the gut–brain–liver axis

1. Vagal afferent nerves in the small intestine respond to the presence of nutrients, such as long-chain fatty acids and amino acids.
2. These nerves connect to the brain and to the liver to form a circuit known as the gut–brain–liver axis.
3. Activation of this axis reduces appetite and hepatic insulin sensitivity through central effects, and reduces glucose and lipid production from the liver.
4. The presence of nutrients in the small intestine therefore stimulates the brain, gut, and liver to prevent hyperglycemia and reduce food intake.
5. Physical interruption of this circuit prevents lipids in the intestine from causing insulin sensitization, and leads to overproduction of hepatic glucose.

This table lists the key features of the gut–brain–liver axis, which serves as a counter-regulatory mechanism to prevent hyperglycemia and excessive calorie intake after feeding in rats

stages of development. In rodents, parenteral PYY (3–36) and Y2 receptor agonists are effective when used as monotherapy, or in combination with GLP-1 or leptin (Karra et al. 2009), for reducing food intake and weight. In healthy human subjects, orally active forms of GLP-1 and PYY were shown to increase plasma GLP-1 and PYY levels, and to reduce ghrelin, without major adverse effects (Beglinger et al. 2008), but there are no long-term data for the effects of these formulations on appetite and weight at present. The endocannabinoid CB1 receptor inverse agonist, rimonabant, was approved in 2006 by the European Agency for the Evaluation of Medical Products for weight reduction and improvement of metabolic profile in obesity, but was withdrawn in 2008 over concerns about the increased risk of depression and suicide. Bariatric surgical procedures in common use, such as Roux-en-Y gastric bypass, which lead to earlier exposure of the ileum to ingested nutrients, are associated with elevated postprandial levels of GLP-1 and PYY, and reduced ghrelin levels; GLP-1 and PYY concentrations rise progressively for months after bypass surgery, in association with sustained weight loss and rapid improvement of glycemic control (Vincent and le Roux 2008).

Long-acting GLP-1 analogs and pharmacological inhibitors of DPP-4, which utilize the insulinotropic effects of GLP-1 to lower blood glucose concentrations without the risk of hypoglycemia and, in the case of the GLP-1 agonists, with the benefit of modest weight reduction (Drucker and Nauck 2006), are potentially useful therapies for type 2 diabetes, especially in obese and elderly patients. Similarly, agonists of the small intestinal sweet taste or fatty-acid G-protein-coupled receptors could potentially be useful for augmenting endogenous GLP-1 release, although studies of the artificial sweetener, sucralose, in humans have not confirmed that it releases GLP-1, as reported for in vitro experiments, suggesting specific additional requirements of sugar-receptor binding (Ma et al. 2009).

Ghrelin, which increases gastric motility and energy storage through adipogenesis, in addition to its orexigenic effects, has been shown to increase dietary intake and functional status in peritoneal dialysis and cancer patients, as well as elderly patients with anorexia of aging (Davidson and Smith 2007). In critically ill patients with cardiac, renal, and hepatic failure, administration of ghrelin and ghrelin agonists improve appetite, reduce muscle and adipose tissue catabolism, and have anti-inflammatory effects (Kamiji and Inui 2008). Ghrelin receptor agonists have shown promise in treating gastroparesis by accelerating gastric emptying, and are currently in phase 1 trials in humans (Table 68.4) (Wargin et al. 2009).

Table 68.4   Therapeutic applications of gut hormones

Drug/procedure	Basis of action	Application
Rimonabant	Endocannabinoid CB1 receptor inverse agonist	Anti-obesity
Bariatric surgery e.g., gastric bypass	↑ endogenous GLP-1 and PYY production	Anti-obesity
GLP-1 analog e.g., exenatide, liraglutide	Activate GLP-1 receptors	Treatment of type 2 diabetes
DPP-4 inhibitor e.g., sitagliptin, vildagliptin	Inhibit degradation of GLP-1	Treatment of type 2 diabetes
Ghrelin, ghrelin receptor agonist e.g., TZP-101	Stimulate ghrelin receptors	Anorexia of cancer, critical illness and aging
		Gastroparesis

This table lists interventions which utilize the effects of gut hormones in the management of conditions such as obesity, type 2 diabetes mellitus, cachexia, and gastroparesis

Summary Points

- The gastrointestinal tract communicates with the brain to regulate appetite by neurohormonal signaling via the vagus nerve, and by gut hormones secreted in response to meals.
- "Gastric" satiation signaling is mediated by mechanical distension, particularly of the antrum, which stimulates vagal afferents, but requires concomitant 'intestinal' signals in order to be perceived as "meal-like" fullness.
- "Intestinal" satiation signaling by gut peptides is mediated by luminal exposure to nutrients, which is dependent on caloric load, macronutrient composition, and length of intestinal exposure.
- Satiating gut peptides, secreted by specialized cells in the small intestine and colon, include cholecystokinin (CCK), glucagon-like peptide-1 (GLP-1), oxyntomodulin, peptide YY (PYY), and neuropeptide W.
- These hormones act by slowing gastric emptying, and inhibiting appetite centers in the brainstem and hypothalamus.
- The stomach secretes leptin, which potentiates the effects of CCK, and ghrelin, which opposes the actions of the satiating gut peptides.
- Delivery of nutrients to the ileum inhibits secretion and motility in the stomach and proximal small intestine by the "ileal brake", which is mediated by GLP-1 and PYY.
- Nutrient detection in the small intestine appears to be mediated by "taste" receptors, analogous to those on the tongue, which detect macronutrients and are linked to secretion of peptide hormones such as GLP-1.
- Modulation of the gastrointestinal mechanisms involved in appetite regulation has potential therapeutic application to obesity, diabetes mellitus, nutrition in critically ill patients, and gastroparesis.

Glossary

Satiety: The suppression of hunger in between meals that reduces the frequency of eating.
Satiation: The processes that terminate feeding and limit meal size i.e. the feeling of "fullness" after ingestion of food.
Orexigenic: Appetite-stimulating (contrasts with *anorexigenic* = appetite suppressing)
Enteric nervous system: The network of neurons in the gastrointestinal tract (collected into submucosal and myenteric nerve plexuses), which control gut motility, secretion, and immune function.

Migrating motor complex(es): Waves of activity which pass down the intestines in regular cycles during fasting, and which facilitate transport of nutrients and other substances from proximal to distal parts of the gastrointestinal tract.

Enteroendocrine cells: Specialized cells in the gastrointestinal tract (e.g., L cells) that secrete hormones such as cholecystokinin, glucagon-like peptide-1, and peptide YY in response to luminal nutrients.

Incretin: An endocrine transmitter produced by the gastrointestinal tract which stimulates insulin secretion in response to postprandial hyperglycemia.

Ileal brake: Negative feedback mechanisms, by which the transit of nutrients to the ileum stimulates vagal signaling and the release of satiating gut peptides to inhibit gastric, duodenal, and jejunal motility and secretion.

Bariatric surgery: Surgical therapy for obesity, to restrict gastric capacity with intestinal malabsorption (e.g., Roux-en-Y gastric bypass) or without it (e.g., laparoscopic adjustable gastric banding).

Gastroparesis: A clinical disorder characterized by delayed gastric emptying, in the absence of mechanical obstruction, most frequently presenting with upper gastrointestinal symptoms such as nausea and vomiting.

References

Abbott CR, Monteiro M, Small CJ, Sajedi A, Smith KL, Parkinson JR, Ghatei MA, Bloom SR. Brain Res. 2005;1044:127–31

Asakawa A, Inui A, Yuzuriha H, Ueno N, Katsuura G, Fujimiya M, Fujino MA, Niijima A, Meguid MM, Kasuga M. Gastroenterology. 2003;124:1325–36.

Banks WA. Regul Pept. 2008;149:11–4

Batterham RL, Cowley MA, Small CJ, Herzog H, Cohen MA, Dakin CL, Wren AM, Brynes AE, Low MJ, Ghatei MA, Cone RD, Bloom SR. Nature. 2002;418:650–4

Batterham RL, le Roux CW, Cohen MA, Park AJ, Ellis SM. J Clin Endocrinol Metab. 2003;88:3989–92

Beglinger C, Poller B, Arbit E, Ganzoni C, Gass S, Gomez-Orellana I, Drewe J. Clin Pharm Ther. 2008;84:468–74

Berthoud HR. Regul Pept. 2008;149:15-25.

Camilleri M. Gastroenterology. 2006;131:640–58.

Caminos JE, Bravo SB, García-Rendueles ME, Ruth González C, Garcés MF, Cepeda LA, Lage R, Suárez MA, López M, Diéguez C. Regul Pept. 2008;146:106–11.

Cammisotto PG, Bendayan M. Histol Histopathol. 2007;22:199–210.

Cohen MA, Ellis SM, le Roux CW. J Clin Endocrinol Metab. 2003;88:4696–701.

Cummings DE, Overduin J. J Clin Invest. 2007;117:13–23.

Cumming DE. physiol Behav. 2006;89:71–84

Dakin CL, Small CJ, Batterham RL, Neary NM, Cohen MA. Endocrinology. 2004;145:2687–95.

Davidson I, Smith S. Proc Nutr Soc 2007;66:346–50.

Degen L, Oesch S, Casanova M, Graf S, Ketterer S, Drewe J, Beglinger C. Gastroenterology. 2005;129:1430–6.

Dockray GJ. Regul Pept. 2009;155:6–10.

Drucker DJ, Nauck MA. Lancet. 2006;368:1696–705.

Feinle C, Grundy D, Read NW. Am J Physiol. 1997;273:G721–6.

Feinle C, O'Donovan DG, Doran S, Andrews JM, Wishart J, Chapman I, Horowitz M. Am J Physiol Gastrointest Liver Physiol. 2003;284:G798–807.

Geary N. Physiol Behav. 2004;81:719–33.

Guilmeau S, Buyse M, Bado A. Curr Opin Pharmacol. 2004;4:561–6.

Guo Y, Ma L, Enriori PJ, Koska J, Franks PW, Brookshire T, Cowley M, Salbe AD, Delparigi A, Tataranni PA. Obesity (Silver Spring). 2006;14:1562–70.

Izzo AA, Camilleri M. Gut. 2008;57:1140–55.

Kamiji MM, Inui A. Curr Opin Clin Nutr Metab Care. 2008;11:443–51.

Karra E, Chandarana K, Batterham RL. J Physiol. 2009;587:19–25.

Kissileff HR, Carretta JC, Geliebter A, Pi-Sunyer FX. Am J Physiol Regul Integr Comp Physiol. 2003;285:R992–8.

Kuo P, Chaikomin R, Pilichiewicz A, O'Donovan D, Wishart JM, Meyer JH, Jones KL, Feinle-Bisset C, Horowitz M, Rayner CK. Regul Pept. 2008;146:1–3.

Ladabaum U, Koshy SS, Woods ML, Hooper FG, Owyang C, Hasler WL. Am J Physiol. 1998;275:G418–24.

Lam TKT, Gutierrez-Juarez R, Pocai A, Bhanot S, Tso P, Schwartz GJ, Rossetti L. Nat Med. 2007;13:171–80.

le Roux CW, Aylwin JBS, Batterham RL, Borg CM, Coyle F, Prasad V, Shurey S, Ghatei MA, Patel AG, Bloom SR. Ann Surg. 2006;243:108–14.

Little TJ, Horowitz M, Feinle-Bisset C. Obes Rev. 2005;6:297–306.

Little TJ, Doran S, Meyer JH, Smout AJPM, O'Donovan DG, Wu KL, Jones KL, Wishart J, Rayner CK, Horowitz M. Am J Physiol Endocrinol Metab. 2006;291:E647–55.

Lauffer LM, Iakoubov R, Brubaker PL. Diabetes. 2009;58:1058–66.

Ma J, Bellon M, Wishart JM, Young R, Blackshaw LA, Jones KL, Horowitz M, Rayner CK (2009) Am J Physiol Gastrointest Liver Physiol. 296:G735–739

Maida A, Lovshin JA, Baggio LL, Drucker DJ. Endocrinology. 2008;149:5670–8.

Maljaars PWJ, Peters HPF, Masclee AAM. Physiol Behav. 2008;95:271–81.

Meyer JH, Tabrizi Y, DiMaso N, Hlinka M, Rayboud HE. Am J Physiol. 1998;275:R1308–19.

Mondal MS, Yamaguchi H, Date Y, Shimbara T, Toshinai K, Shimomura Y, Mori M, Nakazato M. Endocrinology. 2003;144:4729–33.

Moran TH, Baldessarinin AR, Salorio CF, Lowery T, Schwartz GJ. Am J Physiol. 1997;272:R1245–51.

Morínigo R, Moizé V, Musri M, Lacy AM, Navarro S, Marín JL, Delgado S, Casamitjana R, Vidal J. J Clin Endocrinol Metab. 2006;91:1735–40.

Mundinger TO, Cummings DE, Taborsky GJ. Endocrinology. 2006;147:2893–901.

O'Donovan D, Feinle-Bisset C, Wishart J, Horowitz M. Br J Nutr. 2003;90:849–52.

Obici S, Feng Z, Arduini A, Conti R, Rossetti L. Nature Med. 2003;9:756–61.

Pilichiewicz AN, Papadopoulos P, Brennan IM, Little TJ, Meyer JH, Wishart JM, Horowitz M, Feinle-Bisset C. Am J Physiol Regul Integr Comp Physiol. 2007;293:R2170–8.

Potier M, Darcel N, Tomé D. Curr Opin Clin Nutr Metab Care. 2009;12:54–8.

Read NW, McFarlane A, Kinsman Ri, Bates TE, Blackgall NW, Farrar GB. Gastroenterology. 1984;86:274–80.

Ritter RC. Physiol Behav. 2004;81:249–73.

Rozengurt E. Am J Physiol Gastrointest Liver Physiol. 2006;291:G171–7.

Seimon RV, Feltrin KL, Meyer JH, Brennan IM, Wishart JM, Horowitz M, Feinle-Bisset C. Am J Physiol Regul Integr Comp Physiol. 2009;296:R912–20.

Strader AD, Vahl TP, Jandacek RJ, Woods SC, D'Alessio DA, Seeley RJ. Am J Physiol Endocrinol Metab. 2005;288:E447–53.

Sturm K, Parker B, Wishart J, Feinle-Bisset C, Jones KL, Chapman I, Horowitz M. Am J Clin Nutr. 2004;80:656–67.

Vincent RP, le Roux CW. Clin Endocrinol. 2008;69:173–9.

Wang PYT, Caspi L, Lam CKL, Chari M, Li X, Light PE, Gutierrez-Juarez R, Ang, Schwartz GJ, Lam TKT. Nature. 2008;452:1012–6.

Wargin W, Thomas H, Clohs L, St-Louis C, Ejskjaer N, Gutierrez M, Shaughnessy L, Kosutic G. Clin Drug Invest. 2009;29:409–18.

Williams DL, Baskin DG, Schwartz MW. Endocrinology. 2009;150:1680–7.

Young RL, Sutherland K, Pezos N, Brierley SM, Horowitz M, Rayner CK, Blackshaw LA. Gut. 2009;58:337–46.

Chapter 69
Manipulation of Diet to Alter Appetite

Joanne A. Harrold and Jason C.G. Halford

Abbreviations

AGRP   Agouti gene related peptide
AP   Area postrema
ARC   Arcuate nucleus
CART   Cocaine and amphetamine related transcript
CCK   Cholecystokinin
DMH   Dorsomedial hypothalamic nucleus
GLP-1   Glucagon-like peptide 1
g   Gram
kcal   Kilocalorie
LHA   Lateral hypothalamic area
Nac   Nucleus accumbens
NPY   Neuropeptide Y
NTS   Nucleus of the solitary tract
POMC   Pro-opiomelanocortin
PVN   Paraventricular nucleus
PYY   Peptide YY
VAS   Visual analogue scales
VMH   Ventromedial hypothalamic nucleus

69.1 Introduction

With enhanced prevalence of overweight and obesity, it is important to identify properties of food that promote increased energy intake and thus contribute to a positive energy balance. The effects of manipulating the macronutrient composition of the diet on appetite have been widely examined. More recently energy density and the portion size of foods have been identified as important environmental factors influencing appetite control.

Despite the considerable scientific input into this field, numerous anomalies and unanswered questions remain. For example, whilst it has become generally accepted that certain macronutrients exert

J.A. Harrold (✉)
Kissileff Laboratory for the Study of Human Ingestive Behavior, School of Psychology,
University of Liverpool, Liverpool, UK
e-mail: harrold@liverpool.ac.uk

stronger influences on postingestive appetite (per kcal consumed), e.g., protein verses fat, the number of studies demonstrating macronutrient-induced changes in subsequent ad libitum intake are more limited. Moreover, less satiating nutrients like fat paradoxically often provoke greater changes in biomarkers of appetite (gastrointestinal motility and gut peptide release), than their more satiating equivalents such as protein. Additionally, in experimental designs it is often not clear whether the incorporation of one nutrient, or the removal of another, drives any subsequent change in appetite, energy intake, or weight change. Finally, the heterogeneity of proteins, carbohydrates, fats, and fibers, and the consequent effects on sensory experience and energy density of food still provide clear obstacles to our ability to manipulate diet to control spontaneous appetite expression and manage body weight. These issues will be addressed in the chapter along with an examination of the nature of appetite expression, the structure of the appetite system, the consequences of energy restriction, the role of macronutrients, energy density, and portion size in appetite expression – and finally the implications of these for weight management.

69.2 Appetite Expression

Appetite can be defined as the tendency to seek and consume food. Typically, this consummatory behavior is characterized by discrete eating events (meals and snacks) which are under the control of a wealth of peripherally generated factors. Both episodic and tonic factors contribute to the control of feeding behavior (Halford and Blundell 2000). They differ in terms of their duration of effect. Episodic factors are generated by recent consumption and influence intake in the short term. Tonic factors provide influence over the long term and are generated by metabolism and the storage of energy. Both classes of peripheral factors provide input to hypothalamic CNS neurones which are key to the long-term control of body weight.

The regulatory components so far discussed (peripheral factors and hypothalamic CNS neurones) underpin the homeostatic expression of appetite. Their collective action maintains the body's energy stores. Eating is driven by need (hunger) as the energy stores are depleted. Once this need is met negative feedback signals are generated to bring the period of eating to an end (satiation). These signals ultimately lead to a state of satiety in which the hunger drive and eating behavior are inhibited (Blundell 1991). The satiety cascade depicts the events which stimulate eating along with the processes triggered by the ingestion of food which terminate intake (Fig. 69.1).

When food is freely available this homeostatic appetite system defends well against energy deficit. However, as demonstrated by the current obesity pandemic, defense against energy excess is less potent, resulting in an asymmetrical regulatory system more sensitive to under- than overconsumption. In turn, hedonic neuronal systems in the brain can stimulate overconsumption by signaling the sensory pleasure derived from food. Pairing the regulation of food intake with pleasure and reward in this way can lead to the less potent homeostatic energy-surplus defense mechanisms being overridden, promoting hyperphagia and obesity.

69.2.1 Episodic Factors

Episodic signals are predominantly generated by the gastrointestinal tract in response to the physical and/or chemical presence of food. As a consequence their levels tend to rise and fall in coordination with periods of eating. Many of these factors, including cholecystokinin (CCK) and glucagon-like peptide (GLP)-1, are sensitive to the presence of specific macronutrients (fats, protein, and carbohydrate). When released in response to macronutrients, they indicate the fullness of the stomach to the CNS and estimate the caloric content of the ingested food. Table 69.1 shows some key peripheral episodic signals as well as tonic and CNS regulatory factors.
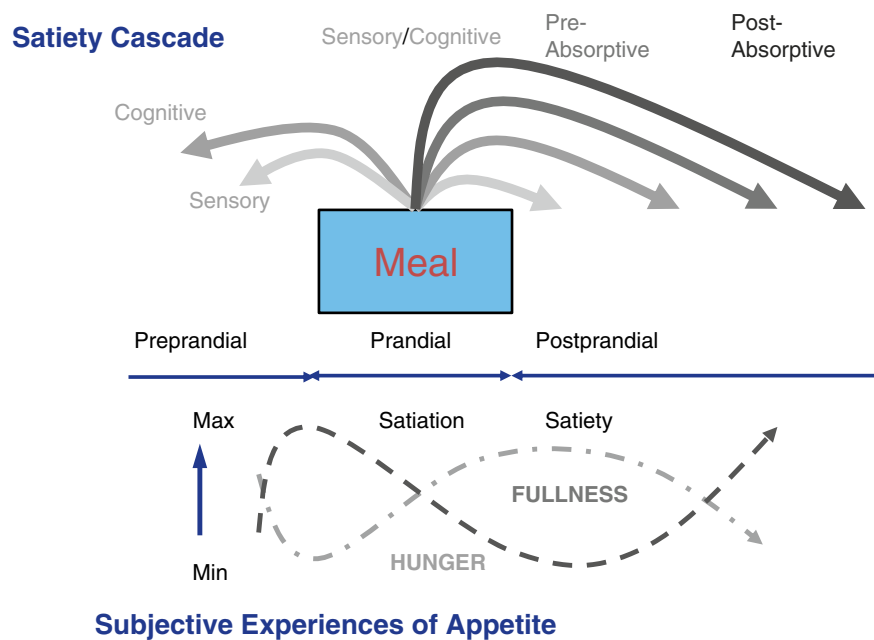
Fig. 69.1 The satiety cascade demonstrates a series of behavioral and physiological events that stimulate eating, occur during food intake and follow food intake to inhibit further eating until the return of hunger signals

Table 69.1 Peripheral and central systems underpinning the expression of appetite

	Peripheral		Central	
	Episodic	Tonic	Homeostatic	Hedonic
Orexigenic	Ghrelin	Progesterone	NPY	Opioids
			Orexins (A and B)	Endocannabinoids
			MCH	Dopamine
			AgRP	
Anorexigenic	CCK	Leptin	Melanocortins	
	GLP-1	Estrogens	CART	
	PYY		5-HT	
	Amylin			
	Obestatin			

Major peripheral episodic and tonic signals along with CNS orexigenic and anorexigenic regulatory factors. Key: *CCK* cholecystokinin, *GLP-1* glucagon-like peptide-1, *PYY* peptide YY, *NPY* Neuropeptide Y, *MCH* melanin concentrating hormone, *AgRP* agouti-gene-related peptide, *CART* cocaine- and amphetamine-related transcript, *5-HT* serotonin

69.2.2 Tonic Factors

Appetite not only relates to daily food intake and eating behavior but must also respond to the long-term (tonic) energy status of the individual. Tonic signals arise from tissue stores, the metabolic status of which provides a signal to indicate the status of the stores and drive intake if energy reserves are low. Organs implicated in energy storage include the liver, pancreas, and adipose tissue. They secrete various circulatory factors known to act as potent determinants of food intake, e.g., leptin and insulin. In addition, there is evidence to suggest that metabolites produced by the metabolism of nutrients, e.g., adipsin and the interleukins, also play a role in influencing the long-term expression of appetite.

69.3 Structure of the Appetite System

The control of energy balance depends critically on the CNS. The brain integrates multiple biological signals in order to determine the energy requirement of the body and to modify the experience of hunger and initiate the relevant behavioral actions in response to this. The CNS regions that control energy homeostasis are accessible to numerous circulating hormones and other factors. Information reaches the CNS via three main routes:

1. The central control of appetite is guided by the peripheral signals already discussed. These include signals derived from receptors in the gut (mechanoreceptors and chemoreceptors) and from metabolic changes in the liver. They are sent via afferent vagal signals to the Nucleus of the Solitary Tract/Area Postrema (NTS/AP) complex in the brainstem.
2. Regulatory signals are also derived from receptors within the CNS, particularly the brainstem. These detect circulating levels of nutrients, metabolites, and other regulatory factors.
3. Specific substances, e.g. glucose and neurotransmitter precursors, have the ability to cross the blood–brain barrier and enter the brain. Here they alter neurochemical activity in key appetite-regulating sites.

Within the CNS itself are specific neuronal populations that recognize these signals and act in a network to integrate the multiple inputs, and help determine energy intake and expenditure. The primary location involved in the regulation of food intake in mammals is the hypothalamus (Fig. 69.2); others include the amygdala and nucleus accumbens of the forebrain and also structures in the brainstem.

69.3.1 Brainstem

The NTS/AP are adjacent areas in the medulla of the brainstem which are key sites for integration of various afferent signals. Vagally transmitted gustatory signals (including gastric distension and portal vein glucose levels) are relayed from the periphery. There is evidence to indicate that the levels of
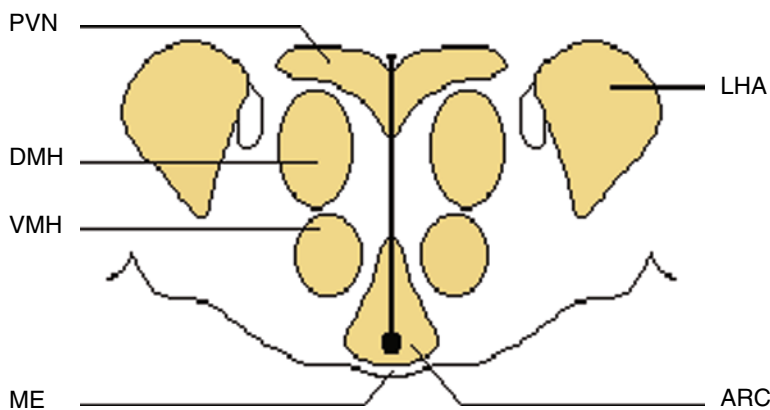
Fig. 69.2 This image shows the relative positions of the key hypothalamic appetite regulating nuclei with respect to each other. Key: *DMH* dorsomedial hypothalamic nucleus, *PVN* paraventricular nucleus, *VMH* ventromedial hypothalamic nucleus, *ARC* arcuate nucleus, *LHA* lateral hypothalamic area, *ME* median eminence

circulating nutrients can also be detected by receptors located in these brainstem areas. Finally, afferent sensory information from the mouth, including taste, also converges on this region.

69.3.2 Hypothalamus

Hypothalamic nuclei play key roles in the control of hunger and satiety (Fig. 69.2). For example, injection of various substances into the paraventricular nucleus (PVN) influences intake (either increases or decreases it); lesions in this region result in hyperphagia (increased intake), reduced energy expenditure, and obesity (Shor-Posner et al. 1986). Other key hypothalamic sites include the Arcuate Nucleus (ARC), Dorsomedial Hypothalamic Nucleus (DMH), Lateral Hypothalamic Area (LHA), and the Ventromedial Hypothalamic Area (VMH). The ARC is readily accessible to peripherally generated signals (both episodic and tonic) indicating nutritional status. It contains functionally discrete populations of neurones including the orexigenic (stimulatory) neuropeptide Y and agouti-gene-related peptide (NPY-AgRP) containing neurones and the anorexigenic (inhibitory) pro-opiomelanocortin and cocaine and amphetamine-related transcript (POMC–CART) containing neurones. The ARC also has extensive reciprocal connections with the other hypothalamic appetite-regulating regions. In addition they receive afferent information via the NTS/AP.

69.3.3 Forebrain

Other key limbic sites identified as playing critical roles in appetite regulation include the Nucleus Accumbens (Nac) and Amygdala of the forebrain. These sites contain an extensive neural system that processes appetitive and rewarding aspects of food intake; palatability and pleasure are arguably the most powerful motivators of food intake. The Nac contains both dopaminergic and opiodergic neuronal pathways and thus acts as an interface between motivation and actual feeding behavior. Reciprocal connections have also been identified between the Nac and the LHA (Stratford et al. 1999). These connections offer a means of interaction between homeostatic and nonhomeostatic regulatory pathways. The amygdala is also an important component of reward circuitry, with several subnuclei of the amygdala influencing reward-related food intake.

Whilst this chapter provides only a brief overview of the complex CNS neuropeptide and neurotransmitter systems that integrate the numerous metabolic and gut signals that drive appetite, Lee and Ahima's chapter (Central regulation of appetite and satiety behavior) provides a more comprehensive review of current understanding in this field.

69.4 The Consequences of Energy Restriction

Fundamentally, to reduce body weight, individuals must reduce caloric intake and increase their energy expenditure. This principle is universally accepted as the only appropriate approach to weight control. However, theoretically whilst small adjustments to behavior should reverse weight gain, increasing levels of obesity clearly demonstrate that losing weight by reducing calorie intake and changing lifestyle remains difficult. Protective metabolic mechanisms which evolved to cope with periods of food shortage become reactivated during the self-imposed reduction in intake of dieting, thus making weight loss more difficult.

Reduced dietary energy intake has a number of positive effects in humans including lower cholesterol, fasting glucose, and blood pressure and improved memory. However, dietary restriction can also produce negative consequences, some of which are particularly relevant when the aim of the restriction period is the reduction of weight. Weight loss is characterized by numerous metabolic and/or endocrine adaptations which could in turn affect appetite in the reduced weight state. Weight loss has been shown to reduce sympathetic nervous system activity, plasma leptin, and insulin, all of which would normally act to inhibit food intake and energy expenditure. Furthermore, weight loss improves glycemic control resulting in reduced fasting glucose, which has been shown to trigger episodes of feeding (Campfield and Smith 1900).

69.4.1 Weight Loss and Appetite

The Minnesota experiment (Keys 1950), a clinical study performed at the University of Minnesota between November 1944 and December 1945, is a powerful indicator of the effects of caloric restriction on appetite. It consisted of a 12-week control phase during which the 36 male participants ate normally, a 24-week "semi-starvation" phase when participants were restricted to half of their normal daily intake and a 3–9-month rehabilitation phase during which the men were gradually refed. Although described as a semi-starvation phase it is important to note that the level of caloric restriction employed during this period of the study was comparable to that used currently to define "conservative" treatments for obesity. A number of physical and psychological changes were observed during this phase. In terms of attitude and behavior towards food, one of the most striking changes reported by the study participants was a considerable increase in preoccupation with food. Relentless thoughts of food and eating inhibited concentration on usual daily activities. Furthermore, participants reported serious difficulties in adhering to the diet when confronted with unlimited access to food. This was reflected during the refeeding phase by a loss of control over appetite demonstrated by the majority of the participants. Similar to preclinical studies, the Minnesota study also indicates the profound adaptive capacity of the body in terms of maintaining a relatively constant body weight. Although the participants regained their original weight plus approximately 10% during the refeeding period, this gradually declined to pre-experimental levels by the end of follow-up.

More recently, Doucet et al. (2000) have directly examined the impact of weight loss on appetite. In this study the impact of a standardized breakfast on subjective appetite scores (as measured by visual analog scales, VAS; Table 69.2) was measured in the control state, following a 15-week drug-treatment (fenfluramine) phase and after an additional 18-week low fat diet and exercise follow-up. Following both treatment phases, an increase in the fasting desire to eat, hunger and prospective consumption were observed, although the effect was greater following the low fat diet and exercise follow-up. These results suggest that weight loss is accompanied by an increase of baseline appetite.

Pasman, Saris, and Westerterp-Plantenga drew similar conclusions from their 1999 study. Following an initial weight loss induced over 2 months by a low calorie diet, hunger (as measured by the Three-Factor Eating Questionnaire) was found to be a significant predictor of weight regain over a 14-month period.

69.4.2 Weight Loss and Leptin

Given the appetite-suppressing effects of leptin, it has been speculated that lower leptin levels, occurring as a consequence of weight and specifically adipose tissue loss, may be responsible for stimulating appetite and thus limiting diet-induced weight loss in humans (Boden et al. 1996). Mars and

Table 69.2 Key features of Visual Analogue Scales (VAS)

1. Visual Analogue Scales (VAS) use self-report methodology to measure the motivation to eat.
2. VAS measure subjective appetite sensations and provide a quantifiable objective measure from these subjective sensations.
3. A series of experimental studies have demonstrated that VAS have within subject reliability and validity in experimental conditions.
4. VAS take the form of a 100 mm horizontal line, unbroken and unmarked and with the two extreme states (minimum and maximum) anchored at either end (Fig. 69.3).
5. VAS are flexible in that the questions and anchor labels can be altered to suit the manipulation being examined.
6. VAS are typically completed immediately before and after an eating episode and periodically at intervals (typically 1 h) between eating episodes, providing a diurnal profile of subjective appetite sensations.

This table lists the key features of visual analogue scales including the aspects they are designed to measure, the form they take, and the standard procedure via which they are administered

colleagues (2006) reported a positive correlation between self-reported appetite (assessed using a 10-point likert scale) and serum leptin levels during a 4-day diet containing 36% of estimated energy requirements. During the diet period leptin levels progressively fell by 39.4% and self-reported appetite increased. This suggests that falling leptin levels have an important role in restoring negative energy balances by stimulating appetite and signaling the need for increased food intake.

The relationship between appetite and plasma leptin has also been examined by Heini et al. (1998) who induced controlled weight loss in the form of a low calorie (800 kcal) diet for a 5-week period. During this period only changes in plasma leptin were found to be associated with appetite ratings such that higher leptin levels correlated with greater feelings of fullness.

Doucet et al. (2000) also identified a link between weight loss-induced changes in appetite and plasma leptin levels, with changes in fullness being reported to be associated with changes in fasting leptin levels, but only in their male participants. However, in this study, the most consistent predictor of weight loss-induced changes in appetite, in both men and women, was changes in fasting plasma cortisol levels. As glucocorticoids play a role in glucose homeostasis and weight loss reduces fasting glucose levels, it has been proposed that changes in cortisol may reflect an attempt to restore glucose levels by increasing energy intake.

To conclude, weight loss is always accompanied by a compensatory increase in appetite. Despite a need for greater understanding of the biological mechanisms underlying these changes in appetite, these human data concur strongly with anecdotal evidence from both dieters and clinicians that caloric restriction increases appetite. For human appetite control this has clear implications: (1) diet induced changes in appetite in turn make the process of controlling eating behavior difficult during the weight loss process and (2) the psychological consequences of these aversive appetite experiences predict post-treatment weight regain (consequences that may undermine further weight loss attempts).

69.5 The Influence of Macronutrient Composition on Appetite

In recent years interest has increased in the influence of food composition on energy intake and appetite.

69.5.1 Fats

For decades dietary fat has been considered a key contributor to the development of obesity. Obesity can reliably be induced in various animal models utilizing diets of 30% or more of energy from fat.

INSTRUCTIONS FOR PARTICIPANTS:
Please read each question and then put a mark through the line that best represents
how you are feeling in relation to that particular sensation at this moment.

EXAMPLE:

How **TIRED** do you feel **at this moment?**
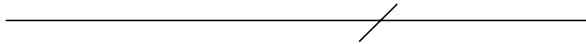
Not at all   Extremely
tired   tired

PLEASE ANSWER THE FOLLOWING QUESTIONS:

How **HUNGRY** do you feel **at this moment**?

Not at all   Extremely
hungry   hungry

How **FULL** do you feel **at this moment**?
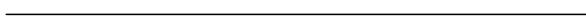
Not at all   Extremely
full   full

How **STRONG** is your desire to **eat at this moment**?
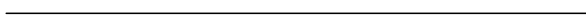
Not at all   Extremely
strong   strong

How **MUCH FOOD** do you feel you could eat **at this moment**?

None   A large
at all   amount

THANK YOU

Fig. 69.3 The commonly used questions to assess the motivation to eat and the appropriate anchor labels for each of these are incorporated into this example of a visual analogue scale. The questions assess subjective states and reflect the intensity of each state at the time of completion

Similarly, humans report higher caloric intake and higher BMI when consuming high fat compared to low fat diets (Ballard-Barbash et al. 1996).

The obesogenic properties of dietary fat are attributed to a phenomenon known as passive overconsumption. This refers to the unintentional ingestion of excess calories as a consequence of ineffective satiety signals thus undermining the normal regulation of food intake. Several

mechanisms are proposed for the stimulation of energy intake by energy dense foods, including high fat foods. Typically higher palatability ratings are assigned to energy dense foods (Nasser 2001) and palatability is positively associated with energy intake (McCrory et al. 2000). Additionally, energy dense foods tend to lack volume. Consequently, they can be rapidly consumed before satiety mechanisms such as stomach distension, which contribute to the feeling of fullness, can be activated.

Initially studies examining the influence of dietary fat on energy intake reported that reductions in fat content decreased energy intake even when palatability did not vary (Lissner et al. 1987; Kendall et al. 1991). In the study by Lissner and colleagues 24 women were exposed to three 2-week treatments in which 15–20%, 30–35%, or 40–45% of the energy was derived from fat. Compared to energy intake on the medium fat diet, subjects consumed an 11.3% deficit on the low fat diet and a 15.4% surplus on the high fat diet. However, whilst palatability was not a confounding variable in these studies, they were flawed by the inability to moderate fat content without altering energy density. It was thus impossible to attribute any observed changes in intake to one particular variable. Yet, it is possible to separate these effects by diluting food or by adding water-rich vegetables. When such approaches are employed to maintain energy density even large variations in the fat content of the diet (20–60%) had no significant impact on body weight (Stubbs et al. 1995; Saltzman et al. 1997; Rolls et al. 1999).

Despite this apparent lack of effect of fat content on energy intake, dietary fat remains a potential contributor to the obesity pandemic. Evidence indicates a potential genetic contribution to determining an individual's susceptibility to gain weight upon exposure to a high fat diet. Whilst normal weight subjects respond to increased fat intake with the enhanced oxidation of fats, this may not be the case for obese individuals. Some studies report an appropriate compensation for fat intake in obese individuals (Maffeis 1995) whilst others suggest that fat oxidation does not increase with intake in this population resulting in a vulnerability to weight gain (Thomas et al. 1992). Obese individuals also appear to differ from their lean counterparts in terms of preference for high fat foods (Reed et al. 1997). Obesity and preference for high fat foods are positively associated. Furthermore, it has been suggested that the disproportionally weak control over appetite offered by high fat foods is further weakened in obese individuals such that they are even less responsive to satiety signals triggered by fat intake.

To conclude, the apparent relationship between intake of dietary fat and obesity appears to be explained by the impact of enhanced fat content on energy density. However, not all individuals react equally to dietary fat, with genetics contributing to susceptibility to weight gain with fat intake. Particularly in susceptible individuals, the palatability of energy dense high fat foods stimulates passive and active overconsumption. Whilst advising people to moderate their dietary fat may assist in avoiding passive overconsumption, such advice will probably do little to overcome active overconsumption promoted by high palatability.

69.5.2 Carbohydrate

Total carbohydrate is composed of various nutrients with those of particular interest being sugars and fiber. As carbohydrates are less energy dense than fats and so result in lower intake when compared to higher fat diets (Kennedy and Bowman 2001) they appear to protect against overconsumption and the development of obesity. However, the different nutrient components of carbohydrate have quite different effects on energy intake.

69.5.2.1 Fiber

The link between dietary fiber and reduced appetite and energy intake is clearly established in the literature. Fibers possess distinct sensory, physiological, and metabolic properties which give rise to their effects on appetite and physiological responses to food. They may be distinguished by their solubility, viscosity, and fermentablity. Viscosity and fermentation in particular are likely to affect appetite through distinct within- and postmeal mechanisms. While most research emphasizes post-prandial mechanisms, viscous fibers may also affect satiation. Viscosity appears to be a key factor influencing slowing eating rate and the emergence of fullness during a meal (Mattes and Rothacker 2001). The effects of viscous fibers on appetite may also arise from postprandial delays in blood glucose response, prolonged gastric emptying, and altered intestinal transit times. Viscosity slows oral processing time, reducing intake by slowing the rate of ingestion and facilitating meal-generated satiating signals, alters palatability (Hoad et al. 2004), and may increase an individual's estimate of a food's satiating potency. Additionally, viscous fibers may increase sensations of fullness through delayed gastric emptying and/or increase in gastric volume "bulk." Increasing dietary fiber reduces postprandial glucose and insulin responses; particularly with insoluble fibers relating to their impact on glycaemic index of foods (Wolever 1990). Similarly, the literature indicates that various soluble fibers can alter the release of gut hormones, increasing glucagon-like peptide (GLP)-1 and peptide YY (PYY) and suppressing ghrelin release, providing potential mechanisms for the stimulation of satiety and later suppression of hunger (Adam and Westerterp-Plantenga 2005; Greenway et al. 2007). Another route by which (particularly nonviscous soluble) fibers may influence appetite is through microbial fermentation of fibers producing short-chain fatty acids (SCFA) in the proximal colon (Gibson et al. 1995). Increased availability of SCFA (acetate, propionate, and butyrate) may also stimulate GLP-1 and PYY release.

A systematic review of the available literature reveals 114 publications (117 studies) examining fiber manipulation and appetite in various experimental designs. Effects on appetite (hunger and satiety) are consistently reported (but only reach significance in 80 publications). Effects on intake are reported in a number of studies (Howarth et al. 2001) with intake being reduced upon consumption of high fiber regime, even when controlling for dietary fat, palatability, and energy density (Fig. 69.4.).
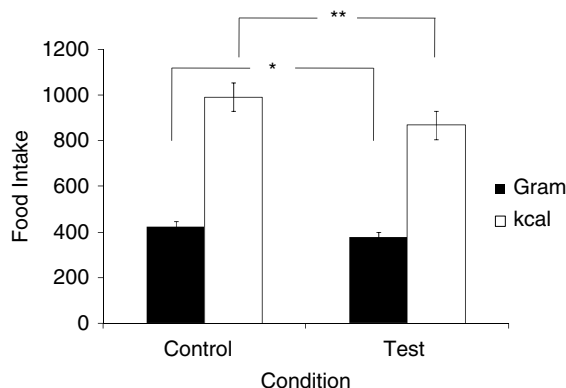
Fig. 69.4 Both protein and fibers have a documented role in appetite reduction by decreasing hunger and increasing fullness feelings, but not necessarily reducing food intake. However, when served as a breakfast meal and a mid-morning snack, a yoghurt enriched with protein and viscose fiber reduced energy intake (g and kcal) at an ad-libitum lunch compared to an equicaloric load of an unenriched yoghurt matched for taste and palatability. Results are expressed as mean ± SEM, $n= 24$ lean unrestrained female volunteers. $*p < 0.012$; $**p < 0.002$

69.5.2.2 Simple Carbohydrates

Links between carbohydrates and enhanced energy intake are established in studies employing refined and simple carbohydrates. Such carbohydrates are more rapidly absorbed into the circulation than other macronutrients or complex carbohydrates. This rapid glucose entry may prompt excess insulin release, consequently lowering blood sugar levels dramatically. According to glucostatic theory rapid falls in blood sugar will prompt a powerful hunger drive.

The general consensus from a review of 16 controlled experimental studies examining this concept is that high glycemic index foods (characterized by a high content of refined and simple carbohydrates) trigger the release of high insulin levels, promoting intake (Ludwig et al. 1999). As anticipated, intake of low glycemic index foods is associated with enhanced satiety and reduced intake (Ludwig et al. 1999). However, these findings remain controversial with methodological approaches being questioned and the short-term nature of the studies seen as a major limitation; studies investigating the long-term association between glycemic index and appetite have had inconsistent results (Vermunt et al. 2003; Raben et al. 2003).

To conclude, when considered as a whole, carbohydrates appear to reduce energy intake. However, not all carbohydrates are alike. Simple carbohydrates tend to promote overconsumption via an exaggerated insulin response. Conversely, fiber reduces energy intake, although the mechanism via which this is achieved depends on the nature and properties of the fiber employed.

69.5.3 Protein

It is generally accepted that proteins exert the greatest influence of the macronutrients on satiety (Blundell and Macdiarmid 1997). From this it can be predicted that elevated protein intake will impact upon appetite (increasing fullness and reducing hunger ratings) and reduce intake at the next meal (Fig. 69.4).

Halton and Hu (2004) provide a comprehensive review of controlled experimental studies investigating the predicted effects of high protein diets on appetite and intake. Of 14 studies examining protein's effects on appetite, 11 report that subjective ratings of satiety were significantly increased following a protein preload compared to at least one other macronutrient. However, many of these studies are methodologically flawed, with it being impossible to distinguish the influence of protein on appetite from other influences on satiety such as palatability, energy density and the reduction in the levels of other macronutrients resulting from elevation of protein levels. Of 15 studies examining the effect of protein on energy intake (Halton and Hu 2004), 8 found that energy intake was significantly decreased following higher protein preloads. However, in addition to the methodological problems identified above, the ecological validity of some of these studies can be questioned. For example, two were conducted in whole body calorimeter chambers, and two used anesthesia and/ or nose clips in order to remove taste of the protein preloads.

Despite some evidence to support an elevated satiating value of protein, other evidence points toward a potential contribution of elevated protein intake to the development of obesity. High protein diets are reported to induce hyperphagia in rodents (Rolland-Cachera et al. 1995). Furthermore, an association has been identified between high protein intake early in life and an increased risk of childhood obesity (Rolland-Cachera et al. 1995).

To conclude, there is evidence to suggest that high protein diets impact positively on appetite. However, reports of accompanying reductions in intake are inconsistent. Additionally, animal studies produce conflicting results, indicating an association between protein intake and the development

of obesity. Furthermore, similar relationships have been identified in humans when protein intake is elevated at critical times in development. It is possible that protein intake has a beneficial impact on appetite and intake over a specific range, with protein intake in excess of this maximum promoting the development of obesity.

Overall, a satiety hierarchy has been established amongst the macronutrients with protein > carbohydrate > fat. This hierarchy is established on the basis of differences in palatability and energy density of the macronutrients. Studies of the effects of macronutrients can be particularly misleading if they do not consider the energy density of the diet under investigation.

69.6 The Influence of Energy Density on Appetite

Energy density is the amount of energy (kilocalories or kilojoules) in a given amount of food (typically measured in grams, g). Thus, the energy density of a food is related to its macronutrient composition. Dietary fat and water exert the most significant impact on energy density. Dietary fat has a higher caloric density compared to protein or carbohydrate, whilst water contributes to the weight of a food without the addition of calories.

There is considerable evidence to indicate that the energy density of food, independent of macronutrient composition, is a key determinant of short-term energy intake in humans. From the results of controlled experimental studies and the examinations of self-reported intakes of free-living individuals, it would appear that individuals tend to consume a constant weight of food regardless of variation in energy density (Seagle et al. 1997). Consumption of energy dense foods will thus result in intake of additional calories. Bell and colleagues (1998) demonstrated this in a study manipulating energy density (low, medium, and high energy density conditions) within a given portion size. Over a 2-day period participants were served all of their meals (three per day). They ate a similar weight of food in all conditions despite the variation in energy density. Consequently intake was reduced by approximately 30% in the low energy dense condition compared to the high energy dense condition. However, ratings of fullness and satisfaction were not significantly altered despite reductions in energy intake. Importantly, ratings of palatability were also not altered by the modification to energy density.

69.6.1 Impact of Weight Status on Response to Energy Density of Foods

Rolls et al. (1999) confirmed this finding in lean and obese participants when manipulating the energy density of only a portion (50%) of the usual daily intake across a 4-day period. All participants reduced energy intake by approximately 16% when comparing low and high energy dense conditions. Ratings of hunger did not vary between diets. Nor was any compensation for reduced energy intake observed over the testing period.

Bell and Rolls (2001) also examined for lean and obese differences in the impact of varying energy density on intake. In this study the energy density of the main component of each meal (breakfast, lunch, and dinner) was manipulated across three percentages of dietary fat (25%, 35%, and 45%). Again, energy density was found to influence intake across all fat content in both lean and obese women, with approximately 20% lower energy intake in the low compared to the high energy-dense condition. Despite this, only small differences in hunger and fullness ratings were reported.

69.6.2 *Impact of Age on Response to Energy Density of Foods*

Whilst studies examining the impact of modifying energy density on intake have not identified a relationship with weight status there is evidence to indicate that the control of energy intake varies with age. It has been suggested that young children can respond to energy density of foods better than adults. This rationale is based on studies employing a preload design, with preschool children being found to compensate for increased energy density of preloads by reducing intake of a main course resulting in a constant total energy intake across both meals (Birch and Deysher 1985, 1986; Hetherington et al. 2000). However, these findings remain controversial as other preload studies report incomplete (both over- and under-) compensation (Birch et al. 1993; Cecil et al. 2005). Furthermore, ad libitum studies indicate that children, similar to adults, consume a consistent weight of food despite manipulations of energy density (Fisher et al. 2007; Leahy et al. 2008a) an effect found to persist beyond single meal studies to manipulation of the three daily meals consumed over a 2-day period (Leahy et al. 2008b)

Whilst dietary energy density impacts upon intake, it has been argued that decreases in energy intake associated with reductions in energy density will be shortlived with compensation occurring over time. This is based on the assumption that the weight of food consumed impacts initially upon pre-absorptive mechanisms associated with short-term satiety. However, it is not expected to have a persistent impact on post-absorptive mechanisms more orientated to reacting to the energy content of food. Few studies have tested this hypothesis. The influence of energy density independent of changes in macronutrient composition has been shown to persist for 4 days (Rolls et al. 1999) and 14 days (Stubbs et al. 1998) although the latter was an extremely small scale study recruiting six individuals.

To conclude, the consumption of low energy dense foods generally results in a reduction in energy intake with this effect being observed within a single meal and over a period of days. Whilst this finding has significance in terms of the development of dietary strategies for weight management, more long-term studies are required to identify whether changes in energy density can modulate intake in the long term or whether compensatory mechanisms limit the impact of this dietary manipulation on appetite.

69.7 The Influence of Portion Size on Appetite

The portion sizes of numerous foods have increased over recent years, occurring in parallel with the increased prevalence of obesity. Despite this, the average portions of food consumed by young children appear to have remained stable; suggesting that portion size appears to exert little influence over intake in this population (Westerterp-Plantenga 2004). This indicates that young children respond more to internal physiological intake cues such as hunger and satiety rather than food cues such as portion size. However, the observation that intake is increased with portion size in older children (Rolls et al. 2000) suggests that external factors appear to exert a greater influence in later years. It is possible that early eating experiences in children lead to the development of behaviors that result in them ignoring or overriding hunger and satiety signals. For example, it has been demonstrated that 4-year old children rewarded for clearing their plate increase energy intake (Birch et al. 1987). These learned responses along with heightened attention to food and environmental cues prompt overconsumption.

Adults respond in a similar way to older children with intake increasing with portion size. This effect has been observed with a variety of foods in both controlled laboratory environments (e.g.. Rolls et al. 2002) and the more naturalistic eating settings offered by cafeterias and restaurants (Dilberti et al. 2004). Observations of a lack of compensation for the increased intake at the next meal, an effect found to persist for 11 days (Rolls et al. 2007) indicate how this influence of portion size could potentially increase body weight.

Evidence from experimental studies suggest that this consistently observed increased intake with portion size in adults, as in older children, appears to relate to the ignoring or overriding of hunger and satiety signals. For example, in single meal studies it has been reported that fullness ratings do not increase despite the consumption of significantly greater portions of food (Rolls et al. 2002, 2004a). Furthermore, in studies with multiple meals, despite reporting enhanced feelings of fullness following consumption of larger portion size, compensation at the next or subsequent meals is not observed (Rolls et al. 2002, 2004a). It is possible that inappropriate eating behaviors learnt in childhood, e.g., eating in the absence of hunger, may persist into adulthood (Fisher and Birch 2002).

To conclude, both laboratory-based and free-living studies demonstrate that increasing the amount of food supplied as a snack or at a meal can lead to an increased intake. This effect applies to different types of food and is sustained beyond a single meal. Furthermore, the response to portion size is robustly demonstrated by individuals of various ages and body sizes. In fact, evidence suggests that cues indicating the amount of food consumed have a greater influence on intake than that offered by the energy density of the food consumed. Thus the "super size" portions offered in the modern eating environment place consumers at high risk of overconsumption and ultimately the development of overweight and obesity.

69.8 Combined Effects of Energy Density and Portion Size on Appetite

When both energy density and portion size are increased simultaneously within a meal, their effects are independent and additive in terms of increases in energy intake. Kral and colleagues (2004) demonstrated this relationship by manipulating energy density (high and low) across three portion sizes. They reported 56% greater energy consumption in the high energy-dense largest portion-size condition compared to the low energy-dense smallest portion-size condition.

By contrast, consumption of large portions can decrease energy intake across a meal if the food is of low energy density. For example, in a 7-week study of 33 women, Rolls et al. (2004b) demonstrated that consumption of a low energy-dense salad first course reduced intake at the main course, compared to consumption of no first course. Furthermore, whilst a small portion of the low energy-dense salad reduced intake by 7%, a large portion reduced intake by a greater extent (12%).

This additive effect of manipulations of energy density and portion size has been shown to persist beyond the single meal. In a 2-day study a 30% reduction in energy density was found to decrease daily intake by 23%, whilst a 25% reduction in portion size produced a 12% decrease in daily energy intake. These reductions in intake were not accompanied by significant differences in hunger and fullness ratings across the 2 days. However, longer term studies are required to determine whether these additive effects persist for extended periods. Such studies will need to consider the challenges faced by consumers, with low energy-dense foods often being more expensive than their high energy counterparts. This may impact upon the effectiveness and success of weight control strategies aimed at enhancing satiety and moderating intake through manipulation of a combination of energy density and portion size

69.9 Applications to Other Areas of Health and Disease

Irrespective of obesity the literature clearly demonstrates that childhood diet predicts adult health outcomes. Moreover, the role of body weight and more specifically abdominal fat mass

in obesity related disease is well understood. As epidemiologically studies have demonstrated the link between habitual diet and obesity, so they have also linked obesity to both the risk factors for (blood glucose and insulin, blood lipids and cholesterol, hypertension) and the occurrence of cardio metabolic disorders (diabetes, cardiovascular disease, and stroke) and other obesity related non-communicable diseases. Longitudinal data also clearly demonstrate that where the prevalence of obesity has spread, this has in time clearly been followed by increases in diabetes, and then cardiovascular diseases. However, even in the obese state, relatively small reductions in body mass appear to reduce both the risk factors for, and possible even the occurrence of obesity related disease. This strongly indicates effective changes in diet, reducing energy intake, and maintaining a negative energy balance, can yield positive health outcomes if sustained.

Summary

- A variety of nutritional scenarios exist (energy restriction, macronutrient composition, energy density, and portion size) whereby the manipulation of diet can lead to enhanced intake and the development of obesity.
- Variation in susceptibility to these different dietary inputs may be explained by genetics, adaptation, or nutrient-gene interactions.
- Energy restriction is always accompanied by a compensatory increase in appetite. This diet induced change in appetite in turn makes the process of controlling eating behavior difficult during the weight loss process.
- In terms of macronutrient composition, the heterogeneity of proteins, carbohydrates, and fats and the consequent effects on palatability and energy density provide obstacles to the manipulation of diet to control appetite.
- Increased intake promoted by an elevated dietary fat content can be explained by the impact of enhanced fat content on energy density.
- Fibers possess distinct sensory, physiological, and metabolic properties responsible for their reported effects on appetite (enhanced satiety) and physiological responses to food (reduced intake).
- Refined and simple carbohydrates are rapidly absorbed into the circulation producing an exaggerated insulin response. The resulting falls in blood sugar trigger hunger and promote overconsumption.
- High protein diets impact positively on appetite by enhancing satiety. However, an association between protein intake and the development of obesity has been demonstrated, particularly when protein intake is elevated at critical times in development.
- The energy density of food, independent of macronutrient composition, is a key determinant of short-term energy intake in humans. The consumption of low energy dense foods results in a reduction in energy intake.
- Increasing portion size can lead to an increased intake. This response to portion size applies to different types of food and is demonstrated by individuals of various ages and body sizes.
- The effects of energy density and portion size on intake are independent and additive.
- The manipulation of diet to alter appetite yields potential weight control strategies aimed at enhancing satiety and moderating intake.

Key Words

Energy density: The amount of energy (kilocalories or kilojoules) in a given weight of food (grams).

Energy intake: Total number of calories consumed daily.

Episodic factors: Peripheral signals generated by the recent consumption of food and which can influence intake in the short term, e.g., ghrelin and CCK.

Hedonic control: Reward based pathways that can override homeostatic regulation. They stimulate energy intake by increasing the desire to consume highly palatable foods.

Homeostatic control: The control of energy balance achieved by increasing the motivation to eat following depletion of the body's energy stores.

Hunger: The motivation to seek and consume food. It is often the initiator of a feeding event.

Hyperphagia: Increased appetite for and excessive intake of food.

Macronutrient: Nutrients (protein, carbohydrate, or fat) required by the body in relatively large amounts.

Palatability: A combination of attributes (taste, texture) of food which determine its acceptability and attractiveness for consumption.

Passive overconsumption: The unintentional ingestion of excess calories when signals for satiation do not function effectively to control meal size.

Satiety: The end point of the process of satiation. It begins at the end of one meal and continues until the start of the next, thus determining the intermeal interval. It is characterized by a lack of drive to consume as well as feelings of fullness.

Satiation: Begins within a meal and generates negative feedback signals designed to terminate food intake. In doing so satiation determines meal size.

Tonic factors: Peripheral signals generated by the metabolism and storage of energy which influence intake over the long term, e.g., leptin and insulin.

References

Adam TC, Westerterp-Plantenga MS. Br J Nutr. 2005;93:845–51.
Ballard-Barbash R, Graubard I, Krebs-Smith SM, Schatzkin A, Thompson FE. Eur J Clin Nutr. 1996;50:98–106.
Bell EA, Rolls BJ. Am J Clin Nutr. 2001;73:1010–8.
Bell EA, Castellanos VH, Pelkman CL, Thorwart ML, Rolls BJ. Am J Clin Nutr. 1998;67:412–20.
Birch LL, Deysher M. Learn Motiv. 1985;16:341–55.
Birch LL, Deysher M. Appetite. 1986;7:323–31.
Birch LL, McPhee LS, Shoba BC, Steinberg L, Krehbiel R. Learn Motiv. 1987;18:301–17.
Birch LL, McPhee LS, Bryant JL, Johnson SL. Appetite. 1993;20:83–94.
Blundell JE. Trends Pharm Sci. 1991;12:147–57.
Blundell JE, Macdiarmid JI. J Am Diet Assoc. 1997;97:S63–9.
Boden G, Chen X, Mozzoli M, Ryan I. J Clin Endocrinol Metab. 1996;81:3419–23.
Campfield LA, Smith FJ. Int J Obes. 1990;14 Suppl 3:15–31.
Cecil JE, Palmer CN, Wrieden W, Murrie J, Bolton-Smith C, Watt P, Wallis DJ, Hetherington MM. Am J Clin Nutr. 2005;82:302–8.
Considine RV, Sinha MK, Heiman ML, Kriaucinas A, Stephens TW, Nyce MR, Ohannesian JP, Marco CC, McKee LJ, Bauer TL. N Engl J Med. 1996;334:292–5.
Dilberti N, Bordi PL, Conklin MT, Roe LS, Rolls BJ. Obes Res. 2004;12:562–8.
Doucet E, Imbeault P, St-Pieree S, Almeras N, Mauriege P, Richard D, Tremblay A. Int J Obes Relat Metab Disord. 2000;24:906–14.
Gibson GR, Beatty ER, Wang X, Cummings JH. Gastroenterology. 1995;108:975–82.

Greenway F, O'Neil CE, Stewart L, Rood J, Keenan M, Martin R. J Med Food. 2007;10:720–4.

Fisher JO, Birch LL. Am J Clin Nutr. 2002;76:226–31.

Fisher JO, Liu Y, Birch LL, Rolls BJ. Am J Clin Nutr. 2007; 86:174–9.

Halford, JCG, Blundell JE. Ann Med. 2000;32:222–32.

Halton Tl, Hu FB. J Am Coll Nutr. 2004;23:373–85.

Heini AF, Lara-Castro C, Kirk KA, Considine RV, Caro JF, Weinsier RL. Int J Obes Relat Metab Disord. 1998;22:1084–7.

Hetherington M, Wood C, Lyburn SC. Nutr Neurosci. 2000;3:321–9.

Hoad CL, Rayment P, Spiller RC, Marciani L, Alonso Bde C, Traynor C, Mela DJ, Peters HP, Gowland PA. J Nutr. 2004;134:2293–300.

Howarth NC, Saltzman E, Roberts SB. Nutr Rev. 2001;59:129–39.

Kendall A, Levitsky DA, Strupp BJ, Lissner L. Am J Clin Nutr. 1991;53:1124–9.

Kennedy E, Bowman S. J Am Diet Assoc. 2001;101:455–60.

KEYS A. Science. 1950;112:371–733.

Kral TVE, Roe LS, Rolls BJ. Am J Clin Nutr. 2004;79:962–8.

Leahy KE, Birch LL, Fisher JO, Rolls BJ. Obesity. 2008a;16:1559–65.

Leahy KE, Birch LL, Rolls BJ. Am J Clin Nutr. 2008b;88:1459–68.

Lissner L, Levitsky DA, Strupp BJ, Kalkwarf HJ, Roe DA. Am J Clin Nutr. 1987;37:763–7.

Ludwig DS, Pereira MA, Kroenke C, Hilner JE, Van Horn L, Slattery ML, Jacobs DR. JAMA. 1999;282:1539–46.

Maffeis C. J Pediatr. 1995;126:15–20.

Mars M, de Graaf C, de Groot CP, van Rossum CT, Kok FJ. Int J Obes (Lond). 2006;30:122–8.

Mattes RD, Rothacker D. Physiol Behav. 2001;74:551–7.

McCrory MA, Fuss PJ, Saltzman E, Roberts SB. J Nutr. 2000;130:276S–9S.

Nasser J. Obes Rev. 2001;2:213–8.

Pasman WJ, Saris WH, Westerterp-Plantenga MS. Obes Res. 1999;7:43–50.

Raben A, Agerholm-Larsen L, Flint A, Holst JJ, Astrup A. Am J Clin Nutr. 2003;77:91–100.

Reed DR, Bachmanov AA, Beauchamp GK, Tordoff MG, Price RA. Behav Genet. 1997;27:373–87.

Rolland-Cachera MF, Deheeger M, Akrout M, Bellisle F. Int J Obes Relat Metab Disord. 1995;19:573–8.

Rolls BJ, Bells EA, Castellanos VH, Chow M, Pelkman CL, Thorwart ML. Am J Clin Nutr. 1999;69:863–71.

Rolls BJ, Engell D, Birch LL. J Am DieT Assoc. 2000;100:232–4.

Rolls BJ, Morris EL, Roe LS. Am J Clin Nutr. 2002;76:1207–13.

Rolls BJ, Roe LS, Kral TVE, Meengs JS, Wall DE. Appetite. 2004a;42:63–9.

Rolls BJ, Roe LS, Meengs JS. Obesity. 2007;15:1535–43.

Rolls BJ, Roe LS, Meengs JS. J Am Diet Assoc. 2004b;104:1570–6.

Saltzman E, Dallal GE, Roberts SB. Am J Clin Nutr. 1997;66:1332–9.

Seagle HM, Davy BM, Grunwald G, Hill JO. Obes Res. 1997;5:78S.

Shor-Posner G, Azar AP, Insinga S, Leibowitz SF. Physiol Behav. 1986;35:883–90.

Stratford TR, Kelley AE, Simansky KJ. Brain Res. 1999;825:199–203.

Stubbs RJ, Ritz P, Coward WA, Prentice AM. Am J Clin Nutr. 1995;62:330–7.

Stubbs RJ, Johnstone AM, O'Reilly LM, Barton K, Reid C. Int J Obes. 1998;22:980–7.

Thomas CD, Peters JC, Reed GW, Abumrad NN, Sun M, Hill JO. Am J Clin Nutr. 1992;55:934–42.

Vermunt SHF, Pasman WJ, Schaafsman G, Kardinaal AFM. Obesity Rev. 2003;4:91–9.

Westerterp-Plantenga MS. Br J Nutr. 2004;92 Suppl 1:S35–9.

Wolever TM. Am J Clin Nutr. 1990;51:72–5.

Chapter 70
Disinhibition, Appetite, and Weight Regulation in Adults

Eleanor J. Bryant

Abbreviations

BED	Binge eating disorder
BMI	Body mass index
BN	Bulimia nervosa
HD	High Disinhibition
HR	High Restraint
HDHR	High Disinhibition, high Restraint
HDLR	High Disinhibition, low Restraint
LDHR	Low Disinhibition, high Restraint
LDLR	Low Disinhibition, low Restraint
TEF	Thermic effect of food
TFEQ	Three Factor Eating Questionnaire
VLCD	Very low calorie diet
WHO	World Health Organisation

70.1 Introduction

The current rise in overweight and obesity in the Western world is associated with many health risks. Not only is the increase in body weight having an impact at an individual level, with increased risk of obesity related illnesses such as coronary heart disease (World Health Organization 2009), but it is also having an impact at a societal level. For example, the economic burden, with regard to the cost of health service, for treating obesity-related illness are estimated to be up to 6% of the total health care expenditure in the countries of the WHO's European Region (Knai et al. 2007), a cost which is expected to rise with the increase in prevalence of overweight and obesity.

It is clear that the susceptibility of some individuals to gain weight in an obesigenic environment (see list of definition) is an important issue. However, obesity and weight gain are not an inevitable consequence of living in an obesigenic environment; some individuals are more susceptible to weight

E.J. Bryant (✉)
Centre for Psychology Studies, Social Sciences and Humanities, Richmond House,
University of Bradford, West Yorkshire, BD7 1DP, UK
e-mail: e.j.bryant@bradford.ac.uk

gain than others (Blundell et al. 2005). Susceptibility implies the presence of particular dispositions to create a positive energy balance. Here susceptibility refers to behavior (as opposed to metabolism), and is related to the tendency to increase energy intake (eating) or reduce energy expenditure (physical activity). Conversely, the obesigenic environment also increases the susceptibility of some individuals to develop disturbed eating behavior. The conflict between the obesigenic environment and societal demands to be lean can be argued to be responsible for the current trends for increased prevalence of eating disorders (Fairburn and Harrison 2003). Therefore, the identification of markers and eating behavior dispositions which are associated with an individual's susceptibility to weight gain, or to develop disturbed eating behavior, would be extremely useful.

Disinhibition, as measured by the Three Factor Eating Questionnaire (TFEQ: Stunkard and Messick 1985), is one factor which is becoming increasingly evident as a useful trait. It is not only associated with weight gain and obesity, but also with mediating variables, such as food choice, physical activity levels, and psychological and physical health. However, Disinhibition is also associated with disturbed eating behavior and eating disorders. The following sections will explore the relationship between disinhibition, eating behavior, appetite regulation, and weight in relation to the satiety cascade (Blundell 1991). It is probable that Disinhibition exerts its influence on the appetite regulation through both homeostatic and hedonic processes. Homeostatic regulation of appetite concerns the biological systems and processes in place which attempt to control our eating behavior, such as appetite related peptides. This system is primarily aimed at regulating energy balance. Whereas hedonic processes are related to the reward individuals gain from consuming food, and how this influences subsequent food intake. These systems interact to regulate appetite and food consumption (Lutter and Nestler 2009). Furthermore, an exploration of the usefulness of utilizing Disinhibition for predicting success at weight loss and managing Disinhibition within weight loss interventions will be addressed.

70.1.1 What Is Disinhibition?

Primarily, it is important to define exactly what is meant by Disinhibition. Trait Disinhibition is one of three eating behavior traits measured by the TFEQ (Stunkard and Messick 1985); these traits are Disinhibition, Restraint and Hunger. Restraint refers to concern over weight control and strategies which are adopted to restrict food intake or prevent overeating. For instance, avoiding fattening foods, eating small portions, and stopping eating before reaching satiation are strategies typically used to limit food intake. Disinhibition reflects a habitual tendency towards overeating and eating opportunistically in an obesigenic environment. This can include, eating in response to negative affect, overeating in the presence of others eating, overeating in response to the palatability of food, and not being able to resist temptation to eat. The factor of Hunger is concerned with the extent to which hunger feelings are perceived and the extent to which such feelings induce food intake. For example, feeling so hungry an individual finds it difficult to stop eating during a meal, eats more than three times per day, or feels so hungry that their stomach feels like a bottomless pit.

Further developments of the original TFEQ have been carried out, which have identified several subscales existing within the three factors. Bond et al. (2001), using factor analysis, identified that the three scales could be further broken down into several subscales; these are presented in Table 70.1. In addition, a more recent factor analysis of Disinhibition, revealed the existence of two subscales, which closely map onto those previously identified by Bond et al. (Niemeier

Table 70.1 Summary of key evidence of how Disinhibition influences the satiety cascade at each point of the satiety cascade

Eating phase	Hedonics vs. homeostasis	Influence of high Disinhibition
Cephalic phase	Hedonics	• Responsive to food cues. • Increased liking of food groups. • Eating in response to mood (reward from eating). • Personality factors (e.g. novelty seeking, extravagance, sensory stimulation, impulsiveness).
	Homeostasis	• Increased salivation.
Eating episode	Hedonics	• Responsive to the palatability of food. • Increased sensory sensitivity to the fat content of food. • Larger meal size.
	Homeostasis	• Decreased sensitivity to appetite related peptides (e.g. ghrelin & leptin). • Larger meal size.
Satiation	Hedonics	• Reduced alliesthetic response to food when sated.
	Homeostasis	• Reduced thermic effect of food. • Reduced satiety to high fat food.
Satiety	Hedonics	• Increased liking of food groups. • Increased wanting of high fat food. • Eating in response to mood. • Increased snacking.
	Homeostasis	• Eating in the absence of hunger. • Decreased sensitivity to appetite related peptides (e.g., ghrelin & leptin).

This table highlights the key mechanisms, both homeostatic and hedonic, through which Disinhibition influences the operational domain of the satiety cascade

et al. 2007). Despite the usefulness of these subscales, relatively few studies have examined the influence of these subscales, thus an in depth consideration of them is not included here.

Thus within this chapter, Disinhibition is considered as a trait which infers susceptibility to weight gain and eating disturbance. This chapter will regard Disinhibition as a general eating behavior trait as it is associated with an enduring set of characteristics which influence several aspects of an individual's life (Bryant et al. 2008). However, it is pertinent here to make a crucial distinction between trait Disinhibition and the term "disinhibition effect." The term "disinhibition effect" refers to transient episodes of overeating due to a weakening of Restraint. However, trait Disinhibition refers to a habitual tendency towards overeating, which is independent of Restraint. The focus of this chapter will be on trait Disinhibition, as a persistent set of characteristics associated with an individual's susceptibility to weight gain and disturbed eating behavior.

70.2 Disinhibition and Body Weight

Due to Disinhibition being characterised by a readiness to eat and a habitual tendency to eat opportunistically, it is not surprising that individuals characterised by a high level of Disinhibition are more susceptible to gain weight. This has been demonstrated in both cross-sectional and prospective studies. A positive association between BMI and Disinhibition scores has been

reported to exist across different BMI categories. For instance, individuals who are overweight and obese exhibit higher levels of Disinhibition (Provencher et al. 2003; Boschi et al. 2001). In addition, individuals within the lean BMI range (19–25 kg/m^2) are more likely to have higher BMIs than individuals with a low level of Disinhibition (Lawson et al. 1995; Bryant et al. 2010). Individuals with varying weight histories (e.g. where an individual was either overweight/obese as a child or adolescent or not), where formerly overweight/obese individuals maintained a higher Disinhibition score, despite a lower current weight (Bellisle et al. 2004), show how Disinhibition is also related to weight in the lower BMI categories. However, this raises an issue of causality: is Disinhibition driving the increase in weight or is it weight increase per se which drives up Disinhibition?

Similarly to the cross-sectional studies, two prospective studies showed how Disinhibition predicted weight gain over several years and predicted current BMI (Hays et al. 2002a), with the strongest predictor of weight gain being habitual susceptibility to Disinhibition (Hays and Roberts 2008). However, it should be noted that Drapeau et al. (2003) found that although changes in eating behavior traits were associated with changes in weight over 6 years; surprisingly, there was little difference between high- and low-Disinhibition individuals in their weight gain over this time period. This highlights the important issue that Disinhibition may not act in isolation, but frequently exerts its effect in interaction with the level of the TFEQ factors Restraint and Hunger. It has been suggested that when high Disinhibition is combined with a high level of Restraint, the relationship between Disinhibition and weight is weakened (Hays et al. 2002a, b 2004). Evidence for this suggestion comes from studies which demonstrate that a higher body weight is associated with a high Disinhibition coupled with a low Restraint. Conversely, when a high Disinhibition is associated with a high Restraint a somewhat lower body weight is evident (e.g. Dykes et al. 2004; Bryant et al. 2008, 2010). Therefore, to gain an accurate prediction of the influence of Disinhibition upon body weight, the other two TFEQ factors should be considered.

Given the evidence indicating a clear relationship between Disinhibition and weight, it is important to understand the mechanisms which may mediate or moderate this relationship. It is likely that Disinhibition influences both the homeostatic and hedonic control of eating, and that it is through these pathways which Disinhibition mediates appetite regulation and weight status. Thus the following sections examine evidence which may elucidate some of the mechanisms, both homeostatic and hedonic, linking Disinhibition and body weight.

70.3 Disinhibition and Food Intake Regulation

To examine the quality of food intake regulation in individuals with a high Disinhibition level the evidence can be considered within the framework of the satiety cascade (Blundell 1991). The satiety cascade details the temporal stages involved in appetite regulation, from cognitive processes to physiological and neurological processes involved in food intake from before food enters the mouth (cephalic phase), to the postabsorption stages of ingestion. This model is complex and a detailed account of all aspects of this model is beyond the scope of this chapter. Here, each temporal stage of the operational domain of the satiety cascade will be addressed, and evidence regarding food regulation in high Disinhibition individuals will be presented. Figure 70.1 presents a model outlining the role of Disinhibition in appetite regulation, through the homeostatic and hedonic processes. In addition, Table 70.2 summarises evidence relating to how Disinhibition influences appetite regulation at each temporal stage of food consumption.
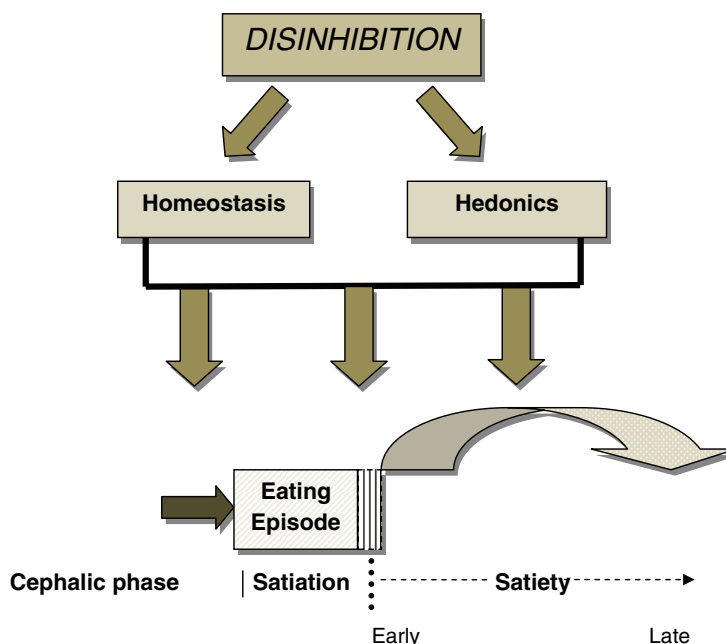
Fig. 70.1 A schematic diagram outlining how Disinhibition could moderate satiety and satiation through homeostatic and hedonic processes. The model shows how Disinhibition (an enduring set of eating behavior characteristics) acts through both homeostatic and hedonic processes, to influence eating behavior at each stage of the operational domain of the satiety cascade. High Disinhibition individuals possess vulnerabilities (both hedonic and homeostatic) which facilitate a dysregulated appetite. These vulnerabilities exert their influence before eating (cephalic phase), during eating (satiation) and following a meal (satiety). Collectively these processes explain how HD individuals are more susceptible to weight gain and disturbed eating behavior

70.4 Meal Initiation

Inherent to the trait of Disinhibition is eating in response to habit and frequent overeating (Habitual Susceptibility), eating in response to emotion (Emotional Susceptibility and Internal Disinhibition), and eating in response to external cues (Situational Susceptibility and External Disinhibition). Eating episodes are not always driven by physiological appetite sensations, but rather psychological and external cues which could eventually lead to a dysregulated appetite response. Indeed, evidence suggests that eating episodes are not driven by feelings of hunger and fullness in obese participants with a high level of Disinhibition (Barkeling et al. 2007), thus other factors are contributing to the initiation of eating episodes. Therefore, what leads to the initiation of an eating episode? The following sections outline factors which could exacerbate the opportunistic eating pattern of individuals with a high level of Disinhibition.

70.4.1 Food Reward: Eating in Response to Negative Affect

The intensity of pleasure derived from eating and the amount food is liked could be a strong factor in the initiation of an eating episode. In terms of the hedonic dimension of food, individuals are likely to differ in the extent to which they derive pleasure from eating. Indeed, sensitivity to reward may reflect an innate characterological trait (Davis and Woodside 2002) which causes some individuals

Table 70.2 Subfactors of the original TFEQ factors

TFEQ factor	Subfactor	Definition
Bond et al. (2001)		
Restraint	*Strategic Dieting Behavior*	Specific behaviors which may be used to control weight (e.g. taking small helpings & stopping eating before being full).
	Attitude to Self Regulation	This assesses the individual's overall attitude to weight control and eating (e.g. counting calories & dieting to lose weight).
	Avoidance of Fattening Foods	This factor relates mainly to behavioral items (e.g. shopping for low calorie foods).
Disinhibition	*Habitual Susceptibility to Disinhibition*	This seems to be the core component, items loading on this factor relate to situations which may predispose an individual to recurrent episodes of overeating (e.g. binge eating and frequent weight fluctuations).
	Emotional Susceptibility	This describes situations where negative affect prompts an eating episode (e.g. eating when feeling down, anxious, or stressed).
	Situational Susceptibility	This factor is related to situations where environmental cues initiate an episode of eating (e.g. overeating when others do, and overeating in social occasions).
Hunger	*Internal Locus*	This refers to hunger which is interpreted and regulated internally (e.g. feeling so hungry their stomach feels like a bottomless pit).
	External Locus	This refers to hunger which is prompted by external cues (e.g. feeling hungry enough to eat when observing another person eating).
Niemeier et al. (2007)		
Disinhibition	*Internal*	This is related to eating episodes which are prompted by affect (e.g., eating in response to anxiety and feeling low).
	External	This factor refers to the influence external cues have on initiating eating episodes (e.g. the presence of others eating).

This table outlines the subfactors which have been indentified from the original Three factor Eating Questionnaire by two authors. These subfactors were derived using factor analysis, and they outline with more specificity what each factor measures

to seek reward from activities such as eating. Research has highlighted that genetically determined differences exist in dopamine availability in areas of the brain associated with reward, and that a lower availability is linked to a higher risk of addiction (Sabol et al. 1999). Some individuals are proposed to suffer from a deprivation of the brain's reward chemicals, an idea known as the "reward deficiency syndrome" (Blum and Nobel 1997). Here a person is likely to seek out compensatory behaviors as a way of self-medicating negative affective states (e.g. Carton et al. 1994: see list of definitions). On this basis, it is assumed that food can be used, in a similar fashion to addictive drugs, as a way to stimulate brain dopamine levels (Blundell et al. 2006). Therefore, it is hypothesized that individuals with a high level of Disinhibition may be particularly susceptible to the rewarding effects of consuming food, especially for alleviating negative affect.

Studies have demonstrated that high Disinhibition (HD) individuals do indeed eat in response to negative affect and stress (e.g. Weinstein et al. 1997; Haynes et al. 2003; Yeomans and Coughlan 2009). Interestingly, Haynes et al. (2003) reported that HD individuals were the most affected by a stress induction manipulation as they reported the highest levels of negative affect (& lowest positive affect) before taking part in the stress condition and were more responsive to the stress manipulation than the low Disinhibition (LD) individuals. This indicates that HD individuals may be more likely to eat in response to their emotional state as a way of self-medicating negative affect. Indeed, Carmody et al. (1995) suggested a relationship between aspects of coping and food intake among

overweight individuals. Their findings suggest that there are possible links between the experience and expression of emotions, dieting and eating behaviors, which can be influenced by Disinhibition.

The degree to which HD individuals eat in response to negative affect is moderated by Restraint. Both Haynes et al. (2003) and Yeomans and Coughlan (2009) have demonstrated that individuals with a high Disinhibition and low Restraint (HDLR) consumed the most food; high Disinhibition, high Restraint (HDHR) and low Disinhibition, low Restraint (LDLR) women increased their food consumption in response to stress and negative affect while the low Disinhibition, high Restraint (LDHR) women's intake remained unaffected by stress and negative affect.

These findings therefore suggest that HD individuals gain some reward from food consumption, as food intake can be initiated by negative affect and stress. In addition, the type of food that is usually chosen to alleviate negative mood is highfat and/or sugar (e.g. Oliver and Huon 2001). This poses a threat to maintaining energy balance and could lead these individuals to be susceptible to weight gain.

70.4.2 Hedonics: Disinhibition and Food Choice

A further hedonic aspect of food intake for high Disinhibition individuals is the degree of liking and wanting of food these individuals possess. A greater 'liking' for foods has been found to correlate positively with Disinhibition scores (Lahteenmaki and Tuorila 1995; Bryant et al. 2006) and a greater "wanting" of high fat foods has also been demonstrated experimentally in this group (Bryant et al. 2006). The level of liking and wanting HD individuals have for food is associated with actual intake. Individuals with high Disinhibition have been found to have a tendency to select more high fat foods, butter, high salt foods, sweet foods, ice-cream, sweets, fruit and vegetables, processed meat, coffee and sweet, carbonated drinks (Lahteenmaki and Tuorila 1995; Borg et al. 2004), whereas a negative correlation between Disinhibition and intake of some fruit and vegetables and high fibre bread has been documented (Borg et al. 2004). In addition, higher alcohol consumption has been reported by high Disinhibition women (Contento et al. 2005; Higgs and Eskenazi 2007) and men (Borg et al. 2004).

These studies clearly demonstrate that individuals with a high Disinhibition score are more likely to make less healthful food choices, which could have a detrimental influence on their body weight and general health. There is some evidence to suggest that mothers' Disinhibition scores were related to their own intake and their children's. Mothers' Disinhibition scores were positively correlated with their children's overall intake of calories, fat, cholesterol, protein, and sodium and correlated negatively with intake of some vegetables (Contento et al. 2005). This clearly raises issues for childhood weight management.

70.4.3 Responsivity to Food Cues

Disinhibition provides an indication of a person's higher responsiveness to cues to eat. This is illustrated well in the aforementioned studies where the hedonic aspect of food and reward gained from food could, at least in part, explain reasons for a HD individual's responsiveness. In addition, evidence revealed that HD individuals also have a tendency to show a heightened salivary response before food consumption (Brunstrom et al. 2004), suggesting that HD individuals have an increased biological, as well as psychological, response to food. It is important to note here that highly Restrained individuals in this study produced a stronger salivary response to food than the HD individuals. This highlights the importance of considering the influence of these eating behavior traits in combination, as the level of one trait may moderate the expression of the other.

Table 70.3 Summary of the influence of Disinhibition on meal initiation

1. HD individuals are likely to initiate an eating episode in the absence of hunger.
2. HD individuals show a heightened physiological response to food (increased salivary response).
3. HD individuals are likely to initiate an eating episode in response to their experience of negative affect.
4. HD individuals are responsive to the hedonic aspects (pleasure-derived) of eating food, making them more vulnerable to eat opportunistically.
5. HD individuals have a higher liking and wanting of food groups, particularly high fat, sweet foods.

This table summarises the key points from the section detailing the influence Disinhibition has on meal initiation, through both homeostatic and hedonic processes

Furthermore, in terms of HD individuals being responsive to cues to eat, evidence suggests that, in a sample of normal weight individuals, Disinhibition is associated with novelty seeking, impulsiveness and extravagance (Gendall et al. 1998; Yeomans et al. 2008). These traits are strongly associated with poor impulse control, excitability and the desire for sensory stimulation, thus it seems plausible that this combination of personality traits would be counterproductive to the maintenance of successful control over food intake and lead to a higher responsiveness to cues to eat. In support of this, Carmody et al. (1995) report that a high Disinhibition score is related to higher dietary helplessness.

In summary, the above sections give some indication of the factors which could lead to the opportunistic eating pattern expressed by HD individuals. They also highlight how HD individuals are susceptible to respond to a plethora of factors, other than their physiological drive, to initiate eating episodes. This not only increases their vulnerability toward overweight, but also towards problematic eating behaviors (e.g. binging) (Table 70.3).

70.5 During the Eating Episode: Homeostasis Versus Hedonics

70.5.1 Homeostasis

After the onset of an eating episode, HD individuals are vulnerable to a number of factors which make them more susceptible to overeating. These factors exert their influence during the meal and during meal cessation. Biologically, a number of systems and processes exist which attempt to control food intake and to terminate an eating episode. These processes include both tonic and episodic signals from the gastrointestinal tract, adipose tissue, and neurochemical processes. It is reasonable to purport that the dysregulated eating patterns displayed by high Disinhibition women could be influenced by differing levels of hunger or satiety related peptides. Two peptides which show a relationship with Disinhibition are ghrelin and leptin. Ghrelin levels are lower in obese than lean people and there is a negative relationship between BMI and ghrelin concentrations within an obese group (Schindler et al. 2004; Levin et al. 2004). However, St-Pierre et al. (2004) showed that ghrelin levels were not correlated with Disinhibition scores in a sample of lean women. Moreover, a positive relationship between leptin concentrations and Disinhibition in obese women, after controlling for BMI has also been demonstrated (Blundell et al. 2008). The significant relationship between Disinhibition scores and two peptides (ghrelin and leptin) known to play significant roles in energy homeostasis (Klok et al. 2007) suggest that the behavioral trait Disinhibition plays a role in the physiological processes of energy homeostasis. Therefore, it is possible that differing levels of, and sensitivity to, these peptides could contribute to the opportunistic and overeating behavior seen in HD individuals.

70.5.2 Hedonics

Alongside the homeostatic control over eating during a meal, the role of hedonics also influences eating behavior for HD individuals. This was well demonstrated in a study by Yeomans et al. (2004) where the palatability of food was manipulated. It was evident that HD individuals were highly responsive to the palatability of food, leading to a higher consumption. The responsivity of HD individuals to the palatability of the food was however moderated by the level Restraint: HDLR women were more responsive to the palatability of the food, as they consumed more food in the palatable than the bland condition. The HDHR and LDLR groups also increased their intake in the palatable condition, but LDHR did not increase intake in response to palatability.

The vulnerability of HD individuals to the palatability of foods could, in part, be as a result of the hedonic reward of food being closely linked to the sensory perceptions of food in the mouth; for many individuals this is the main drive to eat (Drenowski 1997). Support for this notion comes from a study by DelParigi et al. (2005) who demonstrated an abnormal brain response to the sensory experience of a liquid meal following a prolonged period of fasting, in a group of obese individuals, for whom Disinhibition was strongly correlated with BMI. A greater sensitivity to the fat content and/or texture of the liquid meal was apparent from an increased activity in the insular cortex (a sensory area). However, what the authors regarded as an abnormal brain response could actually be a normal brain response for HD individuals. This brain response could provide at least a partial explanation for the preference for sweet and high fat foods, shown in high Disinhibition individuals. As a result of this higher sensitivity, it is more likely that HD individuals will increase their food consumption and therefore their energy intake within a meal. This notion is supported by evidence which shows HD individuals do have a higher energy intake within meals (e.g. Lawson et al. 1995; Ouwens et al. 2003) and a higher vulnerability towards binging behavior (d'Amore et al. 2001).

70.5.3 Weak Satiation

HD individuals are susceptible to overeating due to experiencing a blunted response during the termination of a meal. A meal is usually terminated by feelings of fullness and reduced, perceived palatability of the food being consumed (alliesthesia: see list of definitions). It has, however, been demonstrated that individuals with a high level of Disinhibition display a blunted alliesthesia response following a meal, as they retain a higher liking and wanting of food, even in a sated state (Bryant 2006). This persistent vulnerability to the hedonic aspects of food, can lead to larger meal sizes and frequent episodes of overeating (e.g. Lawson et al. 1995), which will eventually result in weight gain.

Furthermore, Blundell et al. (2005) demonstrated that individuals who are susceptible to weight gain, and characterized by a high level of Disinhibition, show a weak satiety response to fatty meals and a strong hedonic attraction to palatable foods and to eating per se. This has been confirmed by Barkeling et al. (2007), who also found that obese women, with a high level of Disinhibition, also showed a weak satiety response to a high fat meal. This increases the likelihood of these individuals overconsuming during a meal, and entering positive energy balance.

Furthermore, Disinhibition has been shown to be associated with a metabolic process involved in energy balance. A blunted thermic effect of food (TEF) response has been demonstrated in HD individuals (Lawson et al. 1995). The TEF relates to the energy utilized for the digestion, absorption, and disposal of ingested nutrients. Some authors argue that a blunted TEF is associated with weight gain and obesity (see Granata and Brandon 2002 for a review). More importantly, however, TEF has been suggested to be associated with the satiating effect of food, whereby an increased TEF is associated

Table 70.4 Summary of the influence of Disinhibition during the eating episode

1. HD individuals may have differing levels of, and sensitivity to, appetite-related peptides which influence their control over eating.
2. HD individuals show a heightened response to the fat content of food, which could in part explain their higher energy intake within a meal.
3. HD individuals show a weakened alliesthetic response to food and blunted TEF, which could explain their weakened satiety response, leading to more frequent episodes of overeating.

This table is a summary of the homeostatic and hedonic processes through which Disinhibition influences food intake during an eating episode

with an increased satiation (Crovetti et al. 1997). Therefore, the blunted TEF response shown in high Disinhibition individuals could be related to their experience of a weaker satiety response to a meal (Table 70.4).

70.5.4 Satiety

Following a meal, HD individuals are susceptible to a number of factors which induce the initiation of the next eating episode more swiftly than other individuals. Once a meal has ended, a number of biological signals occur to stop an individual consuming more food until biologically necessary (the satiety cascade). In the postingestive stage, these signals (peptides and neural pathways) promote feelings of fullness and reduce feelings of hunger, whereas in the postabsorptive stage feelings of hunger will begin to return and the perception of fullness will decrease. Evidence indicates, however, that HD individuals have a reduced sensitivity to these signals, making them susceptible to opportunistic eating. Due to the differing levels of satiety peptides found in HD individuals (e.g. Schindler et al. 2004; Levin et al. 2004), a lack of sensitivity to these peptides can be hypothesized. This is particularly highlighted by a study in which obese individuals who reported that their eating episodes were unrelated to fluctuations in hunger and satiety (fullness), were characterized by a high Disinhibition (Barkeling et al. 2007). Eating in the absence of hunger is characteristic of opportunistic eaters, who show a readiness to eat.

The biological expression of Disinhibition is further supported by evidence which suggests that Disinhibition is, to some degree, genetically determined. Estimates of the genetic heritability of Disinhibition do however show large variation with ranges varying from 40%, to 45%, 17.5% and 0% (Steinle et al. 2002; Neale et al. 2003; Provencher et al. 2005; de Castro and Lilenfeld 2005). Authors have also suggested specific chromosomal locations for TFEQ eating behavior traits in proximity to genes encoding for peptides which control eating behavior and body weight. For instance, Bouchard et al. (2004) found four trait loci for Disinhibition and Hunger. A missense polymorphism (p.T73T) was significantly associated with Disinhibition and Hunger but not with Restraint. This variant is associated with body fat, where increased body weight and body fat were seen in individuals homozygous for T73T. On the chromosome areas related to Disinhibition and Hunger, the candidate genes identified were aryl-hydrocarbon receptor nuclear translator 2, which is known to be responsible for a monogenetic form of obesity (Michaud et al. 2000). Also associated was the thyroid hormone associated protein, which is known to modulate energy expenditure (al-Adsani et al. 1997), growth hormones 1 and 2 associated with metabolic syndrome, including abnormal obesity (Perusse et al. 2001) and also neuromedin B which modulates behaviors and food intake in many species (Oeffner et al. 2000; Johnston and Merali 1998).

Table 70.5 Summary of the influence of Disinhibition on satiety

1. HD individuals show a weaker satiety response, which can help to explain their opportunistic eating behavior.

2. HD individuals can continue to eat even in a sated state, leading to a higher energy intake. This can increase the vulnerability of these individuals entering positive energy balance.

3. Evidence suggests that Disinhibition is to some degree inherited and is associated with chromosomal loci in proximity to genes encoding for peptides which influence eating behavior and body weight.

This table provides a summary of the processes which Disinhibition influences food intake and appetite regulation during satiety

In addition, Steinle et al. (2002) have also proposed four regions of suggested linkage for Disinhibition and Hunger in proximity to leptin and plasminogen activator inhibitor (PAI-1) genes. PAI-1 plays a role in coronary heart disease and obese individuals may have higher concentrations along with those who have insulin resistance and type-II diabetes (Ito et al. 1996), whereas leptin exerts anorexigenic effects. Restraint on the other hand, was in proximity to genes encoding for glucagon-like peptide-1 (GLP-1), which is secreted following a meal, and stimulates the release of insulin, lowers blood glucose and decreases food intake (Flint et al. 1998). Therefore, chromosomal linkages for the TFEQ eating behaviors have been observed in proximity to some important genes which encode for peptides which influence eating behavior and body weight and could influence appetite regulation or dysregulation (as displayed in HD individuals). However, further research is required to confirm these genetic associations.

Taken together, the evidence outlined above describes an eating behavior trait, which at high levels leads to an individual to be susceptible to weight gain and overeating, through vulnerabilities in their eating behavior control. These vulnerabilities involve both hedonic and homeostatic processes, and contribute to HD individuals being more susceptible to initiate eating episodes in the absence of any homeostatic drive to eat, and continue to eat, even in a sated state (Tables 70.5 and 70.1).

70.6 Applications to Other Areas of Health and Diseases

Due to the intricate association of Disinhibition with eating behavior and body weight, there are obvious associations with health related issues. Not only has Disinhibition been implicated in weight gain and obesity, which is associated with a poorer physical and psychological health, it is also related to the level of success during weight loss interventions, and within eating disorders. The sections below will address the importance of managing Disinhibition levels within the management of weight and disordered eating.

70.6.1 Weight Loss and Weight Maintenance

There is a large body of evidence detailing the relationship of Disinhibition with weight loss in weight loss treatment programs. These treatment programs tend to look at administering low energy diets, dietary advice, behavioral treatment, and some prescribed physical activity. There is a consensus in the data that over the period of a weight loss regime, reductions in Disinhibition and Hunger and an increase in Restraint are associated with weight loss.

In studies which investigated weight loss with very low calorie diets (VLCD) (Foster et al. 1998; Westerterp-Plantenga et al. 1998; Karlsson et al. 1994; Pekkarinen et al. 1996; Foster et al. 1996;

LaPorte and Stunkard 1990; Wadden et al. 2004), all but one study (La Porte and Stunkard 1990) reported that over the duration of treatment, ranging from 10 to 120 weeks, Disinhibition and Hunger scores decreased, while Restraint scores increased. However, this change was not seen in all participants, for example Westerterp-Plantenga et al. (1998) in their 120 week dietary weight loss intervention, split their sample into successful weight maintenance (<50% of weight loss), partially successful (where <50% loss had occurred once, followed by some weight regain), and unsuccessful (a regain of >50% of weight lost). In the successful weight maintenance group there was a positive relationship between Disinhibition and Restraint and an increase in Restraint score. Whereas in the partially successful group, there was no correlation between Disinhibition and Restraint, yet in the unsuccessful group there was a negative correlation between Disinhibition and Restraint. This demonstrates how the relationship between Disinhibition and Restraint is complex and not always readily related to the success of weight loss and maintenance.

Further studies have explored the role of TFEQ factors in the relationship between a combination of diet and exercise on weight loss (Bjorvell et al. 1994; Clark et al. 1994; Richman et al. 1996; Fogelholm et al. 1999; Cuntz et al. 2001; Kiernan et al. 2001; Chaput et al. 2005). Again, there was a robust finding that following treatment, which ranged from 10 weeks to 1 year, Disinhibition and Hunger scores decreased and Restraint scores increased. Most of these studies also included behavioral therapy in their protocol, aimed at regulating eating behavior (Bjorvell et al. 1994; Clark et al. 1994; Richman et al. 1996; Fogelholm et al. 1999; Cuntz et al. 2001). The main aim of this behavior therapy varied between the studies: while most authors targeted the increase of Restraint, one group included decreasing Disinhibition in their therapy. Cuntz et al. found that Disinhibition could be reduced by enhancing self-control without increasing restrained eating. This was mainly achieved through the reduction of dysfunctional emotional influences on eating behavior, thus endorsing the use of behavioral therapy in obesity treatment, particularly for those with high Disinhibition scores.

Disinhibition has also been associated with weight loss maintenance. Two prospective studies found that individuals who had higher Disinhibition, were not as successful at weight loss, and found that higher Disinhibition was associated with weight regain (McGuire et al. 1999; Carmody et al. 1995). A further two prospective studies have identified that higher baseline Internal Disinhibition scores (a subscale of Disinhibition), are predictive of less successful weight loss and predictive of weight regain (Niemeier et al. 2007). Furthermore, Butryn et al. (2009) found that change in Internal Disinhibition was predictive of weight loss and weight loss maintenance, whereby the greater the decrease in Internal Disinhibition, the greater the loss in weight and the higher success in weight loss maintenance. This clearly shows that management of Disinhibition, particularly Internal Disinhibition, would be beneficial for improving weight loss.

However, recent evidence also suggests that a high Disinhibition level is associated with more successful weight loss (Bryant et al. 2009). Here an exercise only methodology was adopted with no additional behavioral or dietary intervention. Participants expended 500 kcal/day in a supervised exercise intervention for 12 weeks, Disinhibition, and particularly Internal Disinhibition, were found to predict better weight loss. Participants who had a higher baseline Disinhibition and experienced the greatest decrease in Disinhibition and Internal Disinhibition, also showed the greatest weight loss. Low attrition rates and the mandatory exercise sessions could explain why these data contradict previous findings. Therefore, structured and supervised weight loss intervention could benefit HD individuals, which has implications for the subsequent design and implementation of weight loss interventions. It is possible that HD individuals require a higher amount of external motivation and intervention structure to achieve optimal success within a weight loss program.

Furthermore, when weight is managed through gastric surgery (e.g. Karlsson et al. 1998; Burgmer et al. 2005), or through pharmacological treatment (e.g. Lejeune et al. 2003; McElroy et al. 2004; Hainer et al. 2004) a decrease in Disinhibition and Hunger and increase in Restraint scores are

Table 70.6 Summary of the influence of Disinhibition on weight loss:

1. A decrease in Disinhibition and Hunger and an increase in Restraint are seen with successful weight loss (through diet and behavioral interventions and through surgical and pharmacological treatment).

2. Some evidence suggests that a higher Disinhibition is related to less success at weight loss within a structured weight loss intervention.

3. High Disinhibition individuals are more vulnerable to regain weight they have lost following a weight loss intervention.

This table provides a summary of the key points relating to the influence Disinhibition has upon weight loss

observed. This highlights the influential role of these eating behavior traits within a variety of weight management interventions and the importance of considering these traits in relation to one another.

Therefore, two main conclusions can be drawn from these data: primarily Disinhibition scores tend to decrease as weight is lost. Secondly, Disinhibition appears to counteract body weight maintenance following weight loss (when the intervention is not highly structured) and favor weight gain. Further research examining more structured weight control interventions in HD individuals would be highly beneficial (Table 70.6).

70.6.2 Eating Disorders

Several studies have identified a relationship between TFEQ factors, eating disturbance and clinical eating disorders. These studies have tended to focus on Binge Eating Disorder (BED), but associations with bulimia nervosa (BN) have also been found. Disinhibition seems to play a key role in determining the severity of eating disturbances.

The evidence highlights a positive association between in both BED (e.g. Adami et al. 1995) and BN (e.g. Ardovini et al. 1999 see Bryant et al. (2008a, b) for a review) patients with Disinhibition. Perhaps one of the most interesting findings is that Disinhibition is associated with the severity of binge eating episodes (e.g. Ardovini et al.) and with a more problematic psychological health profile, including lower self esteem and higher neuroticism (Brown et al. 2006). Due to the relationship between Disinhibition and disordered eating behavior, it is proposed that the management of Disinhibition would be beneficial within eating disorder treatment.

It is, however, important to note that eating disorder pathology is also related to a (very) high Restraint score. Of particular interest is that evidence suggests the combination of a concurrent high Disinhibition and a high Restraint level, appears to dysregulate eating control in clinical (eating disordered) and nonclinical individuals. The conflict between the ardor to restrain intake (high Restraint) and the desire to eat (high Disinhibition), can lead to a cyclical pattern of food restriction and overeating. It is suggested, therefore, that a high Disinhibition (particularly when coupled with a high Restraint) could be used as a way to identify those who will be susceptible to disturbed eating behaviors and express high eating disorder symptomatology. Indeed, in a nonclinical sample of women a HDHR has been found to be associated with a higher vulnerability towards disturbed eating behavior (Lawson et al. 1995; Bryant et al. 2010). Furthermore, in a clinical sample, those with a HDHR have been shown to exhibit higher eating disorder pathology (Bryant 2006).

This evidence suggests that Disinhibition not only has the potential to be used as a psychomarker to predict for those more susceptible to disturbed eating behavior, but also that management of the Disinhibition trait could be utilized within eating disorder treatment to reduce disorder symptomatology and possibly to reduce relapse (Table 70.7).

Table 70.7 Summary of the influence of Disinhibition on eating disorder

1. A combination of a high Disinhibition and a high Restraint is related to eating disorder severity in a clinical sample and with eating disturbance in a nonclinical sample.

2. High levels of Disinhibition are associated with both BED and BN.

3. Management of Disinhibition levels could help to improve success within eating disorder treatment.

This table provides a summary of the key points of the influence Disinhibition has eating disorders

Table 70.8 Key points about Disinhibition

Key points

1. Disinhibition is a pervasive and dynamic eating behavior trait which influences an individual's body weight, food choice, and lifestyle choices.

2. The evidence suggests that high Disinhibition individuals are susceptible to a number of homeostatic and hedonic factors which facilitate a dysregulated appetite system. These influences exert their influence before, during and after a meal.

3. Evidence suggests high Disinhibition negatively impacts on weight loss in response to interventions and is associated with weight regain following weight loss. Therefore, Disinhibition management and intervention structure are important for optimum weight loss in this group of individuals.

4. Individuals with a high Disinhibition have a higher preference and intake of foods in general, but particularly high fat and sweet foods.

5. Disinhibition is related to disturbed eating behavior and eating disorders (e.g. BN and BED). High levels of Disinhibition are related to the severity of eating disorder pathology (e.g. binging severity).

6. Disinhibition does not act independently; a concurrent high level of other eating behavior traits (e.g., Restraint), moderate its influence. HDHR is associated with a more problematic eating behavior, higher levels of smoking, alcohol consumption and higher neuroticism. Whereas HDLR is associated with a higher body weight and increased sedentary behavior.

This table outlines the key messages within this chapter, including how trait Disinhibition is expressed, how Disinhibition is associated with other eating behavior issues such as eating disorders and food choice, and how Disinhibition influences weight loss

70.6.3 General Health

High levels of Disinhibition have been related to lower levels of general health, poor health behaviors (such as higher smoking rates and levels of alcohol consumption; Bryant et al. 2010), and adverse psychological symptoms (Kensinger et al. 1998). Cross-sectional studies have revealed that high levels of Disinhibition were associated with a lower health related quality of life (Marchesini et al. 2000), including a higher incidence of diseases associated with the metabolic syndrome (Hainer et al. 2006), whereby some of these associations have been shown to be independent of weight status (Hays et al. 2002b). Furthermore, high levels of Disinhibition have been found to be detrimental to glycaemic control in Type I and II diabetic patients (Balfour et al. 1993; Straub et al. 1996). It is probable that the opportunistic eating pattern and less healthy food choices of HD individuals can exacerbate any problems with maintaining glycaemic control in these individuals.

Thus it can be surmised that the association of high Disinhibition with lower levels of physical health could in part be due to their lower levels of physical activity, poorer quality diet, and higher adiposity. It is therefore apparent that trait Disinhibition is a pervasive trait, which not only influences eating behavior but has an overarching influence on the person as a whole (Table 70.8).

Summary

- Disinhibition is an influential, pervasive and dynamic eating behavior trait which exerts its influence to effect body weight, eating episode initiation, satiation and satiety.
- The mechanisms through which Disinhibition exerts its influence are both homeostatic and hedonic and serve to dysregulate an individual's eating pattern.
- Individuals with a high Disinhibition are characterized by a set of psychological and physiological traits which predispose that individual towards opportunistic eating, eating in response to negative affect (as opposed to physiological satiety signals), frequent eating episodes and overeating, and having a high preference and intake of high fat and sweet foods. All these factors can lead

---

Key Definitions

Alliesthesia: When an individual's ratings of an object (e.g., food) are sometimes pleasant, sometimes unpleasant, depending upon their internal state (e.g. being in a hungry or in a sated state).

Food cue: Any type of food associated signal can be considered as a food cue. For example, a food advertisement, the sight and/or smell of food (e.g., in a bakery or cafeteria), or simply talking about food.

Obesigenic: An environment which facilitates sedentary behavior and overconsumption due to the availability of energy dense foods. In essence, one which promotes a positive energy balance.

Negative affect: Experience of negative emotions (e.g., feeling low, or experiencing stress).

Satiety cascade: A model which summarizes the biopsychology of appetite regulation. It incorporates psychological, physiological, and neuronal elements of appetite control.

Satiation: Intrameal satiety. A point within a meal when an individual begins to experience feelings of fullness and less hunger, leading to the cessation of the eating episode.

Satiety: Postngestive satiety. The time interval in between eating episodes.

Taste test: An experimental procedure whereby participants rate the food for pleasantness and palatability; for example, when the primary focus is the amount of food being consumed. Usually, taste tests are carried out following a manipulation of mood, or following consumption of a preload, for instance.

---

an individual to be susceptible to weight gain, weight regain following weight loss, poor general health, and disturbed eating behavior.
- Disinhibition does not act in isolation; the levels of the other TFEQ factors moderate the influence of Disinhibition upon eating behavior and body weight. For instance, evidence highlighted how when a level of high Disinhibition was coupled with a high Restraint score, a problematic eating behavior profile was apparent (Bryant et al. 2010; Lawson et al. 1995), together with a higher alcohol consumption and a higher smoking rate (Bryant et al. 2010).
- When a high Disinhibition score was coupled with a low Restraint score, a higher sedentary behavior pattern emerged, alongside a higher susceptibility to weight gain (Bryant et al. 2010; Lawson et al. 1995).

- The utilization of strategies to manage high Disinhibition levels in weight management and eating disorder programmes, could prove to be useful in increasing their level of success.

References

Adami GF, Gandolfo P, Bauer B, Scopinaro N. Int J Eat Disord. 1995;17(1):45–50.
al-Adsani H, Hoffer L, Silva J. J Clin Endoc & Metab. 1997;82:1118–25.
Ardovini C, Caputo G, Todisco P, Grave R. Eur Eat Disords Rev. 1999;7:299.
Balfour L, White D, Schiffrin ADG, Dufresne J. Health Psyc. 1993;12:33–8.
Barkeling B, King NA, Naslund E, Blundell JE. Int J Obes. 2007;31:435–9.
Bellisle F, Clement K, Le Barzic M, Le Gall A, Guy-Grand B, Basdevant A. Obes Res. 2004;12:2023–30.
Bjorvell B, Aly A, Langius A, Nordstrom G. Int J Obes. 1994;18(8):521–5.
Blum K, Nobel E. Handbook of psychiatric genetics. CRC Press: Boca Raton, Florida; 1997. pp. 311–27.
Blundell JE, Stubbs RJ, Golding C, Croden F, Alam R et al. Physiol Behav. 2005;86:614–22.
Blundell J. Trends Pharmacol Sci. 1991;12:147–57.
Blundell J, King N, Bryant E. Interactions among physical activity, food choice, and appetite control: health messages in physical activity and diet. In: Cameron N, editor. Childhood obesity: contemporary issues. NET Morgon Taylor and Francis: London; 2006. pp. 135–47.
Blundell JE, Levin F, King NA, Barkeling B, Gustafson T, Hellstrom PM, Holst JJ, Naslund E. Reg Peptides. 2008;149:32–38.
Bond MJ, McDowell AJ, Wilkinson JY. Int J Obes Relat Metab Disord. 2001;25:900–6.
Borg P, Fogelholm M, Kukkonen-Harjula K. Int J Obes Relat Metab Disord. 2004;28:1548–54.
Boschi V, Iorio D, Margiotta N, D'Orsi P, Falconi C. Ann of Nutr & Metab. 2001;45(2):72–7.
Bouchard L, Drapeau V, Provencher V, Lemieux S, Chagnon Y et al. Am J Clin Nutr. 2004;80:1478–86.
Brown K, Bryant E, Naslund E, King N, Blundell J. Obes Rev. 2006;7:330.
Brunstrom JM, Yates HM, Witcomb GL. Physiol Behav. 2004;81:85–90.
Bryant E. Understanding disinhibition and its influences on eating behaviour and appetite. PhD Thesis University of Leeds, UK; 2006.
Bryant E, Caudwell P, Hopkins M, King N, Blundell J. Obesity Facts: Eur J Obes. 2009;2(2):211.
Bryant E, Finlayson G, King N, Blundell J. Obes Rev. 2006;7:343.
Bryant E, Kiezebrink K, King NA, Blundell JE. Eating Weight Dis. 2010;15:43–51.
Bryant E, King N, Blundell J. Obes Revs. 2008;9:409–19.
Burgmer R, Grigutsch K, Zipfel S, Wolf AM, de Zwaan M et al. Obes Surg. 2005;15(5):684–91.
Butryn M, Thomas J, Lowe M. Obes Res. 2009;17:1101–3.
Carmody TP, Brunner RL, St Jeor ST. Int J Eat Disord. 1995;18:256.
Carton S, Jouvent R, Widlocher D. J Subst Abuse. 1994;6:67–76.
Chaput J, Drapeau V, Hetherington M, Lemieux S, Provencher V, Tremblay A. Physiol Behav. 2005;86:224–32.
Clark MM, Marcus BH, Pera V, Niaura RS. Int J Eati Disord. 1994;15:405.
Contento IR, Zybert P, Williams SS. Prevent Med: nt J Devoted Pract. Th. 2005;40:336.
Crovetti R, Porrini M, Santangelo A, Testolin G. Eur J Clin Nutr. 1997;52:488.
Cuntz U, Leibbrand R, Ehrig C, Shaw R, Fichter MM. Int J Obes. 2001;25Suppl 1:99–101.
d'Amore A, Massignan C, Montera P, Moles A, De Lorenzo A, Scucchi S. Intl J Obes. 2001;25:373–7.
Davis C, Woodside DB. Compr Psyc. 2002;43:189–94.
de Castro JM, Lilenfeld LR. Nutrition. 2005;21(4):446–55.
Delparigi A, Chen K, Salbe AD, Reiman EM, Tataranni PA. Neuroimage. 2005;24(2):436–43.
Drapeau V, Provencher V, Lemieux S, Despres J-P, Bouchard C, Tremblay A. Int J Obes. 2003;27:814.
Drenowski A. Ann Rev Nutr. 1997;17:237–53.
Dykes J, Brunner EJ, Martikainen PT, Wardle J. Int J Obes. 2004;28:262–8.
Fairburn C, Harrison P. Lancet. 2003;361:407–16.
Flint A, Raben A, Astrup A, Holst J. J Clin Investigation. 1998;101:515–20.
Fogelholm M, Kukkonen-Harjula K, Oja P. Int J Obes. 1999;23(2):203–10.
Foster GD, Wadden TA, Swain RM, Stunkard AJ, Platte P, Vogt RA. Int J Obes. 1998;22(8):778–85.
Foster GD, Wadden TA, Kendall PC, Stunkard AJ. J Consulting Clin Psyc. 1996;64:757.
Gendall KA, Joyce PR, Sullivan PF, Bulik CM. Int J Eat Disord. 1998;24(4):371–9.
Granata G, Brandon L. Nutr Rev. 2002;60:223–33.
Hainer V, Kunesova M, Bellisle F, Hill M, Braunerova R, Wagenknecht M. Int J Obes. 2004;29:208–16.

Hainer V, Kunesova M, Bellisle F, Parizkova J, Braunerova R et al. Int J Obes. 2006;30:830–6.

Haynes C, Lee MD, Yeomans MR. Eat Behav. 2003;4:369–83.

Hays NP, Bathalon GP, McCrory MA, Roubenoff R, Lipman R, Roberts SB. Am J Clin Nutr. 2002a;75(3):476–83.

Hays NP, Bathalon GP, Roubenoff R, Lipman R, Roberts SB. J Gerontology: Series A: Bio Sci Med Scis. 2002b;57A:M133.

Hays NP, Roberts SB. Obes Res. 2008;16:52–8.

Higgs S, Eskenazi T. Eat Behav. 2007;8:236–43.

Ito T, Okeda T, Sato Y, Ito M, Sakata T. Proc Soc Exper Bio Med. 1996;211:287–91.

Johnston S, Merali Z. Peptides. 1998;9:233–44.

Karlsson J, Hallgren P, Kral J, Lindroos A-K, Sjostrom L, Sullivan M. Appetite. 1994;23(1):15–26.

Karlsson J, Sjostrom L, Sullivan M. Int J Obes. 1998;22(2):113–26.

Kensinger GJ, Murtaugh MA, Reichmann SK, Tangney CC. J Am Dietetic Assoc. 1998;98(8):863–8.

Kiernan M, King AC, Stefanick ML, Killen JD. Obes Res. 2001;9(12):770–7.

Klok MD, Jakobsdottir S, Drent ML. Obes Rev. 2007;8:21–34.

Knai C, Suhrcke M, Lobstein T. Econ Hum Biol. 2007;5:392–408.

Lahteenmaki L, Tuorila H. Physiol Behav. 1995;57:81–8.

LaPorte DJ, Stunkard AJ. Int J Obes. 1990;14(3):197–206.

Lawson OJ, Williamson DA, Champagne CM, DeLany JP, Brooks ER et al. Obes Res. 1995;3:153–61.

Lejeune MP, Hukshorn C, Saris WH, Westerterp-Plantenga MS. Int J Obes. 2003;27:1494–9.

Levin F, King N, Barkeling B, Gustafsson T, Hellstrom P et al. Obes Res. 2004;12:444–9.

Lutter M, Nestler E. J Nutr. 2009;139:629–32.

Marchesini G, Solaroli E, Baraldi L, Natale S, Migliorini S et al.. Diabetes, Nutr & Metab Clin Exp. 2000;13(3): 156–64.

McElroy SL, Kotwal R, Hudson JI, Nelson EB, Keck P Jr. J Clin Psyc. 2004;65:56.

McGuire MT, Wing RR, Klem ML, Lang W, Hill JO. J Consult Clin Psyc. 1999;67:185.

Michaud J, DeRossi C, May N, Holdener B, Fan C. Mech Dev. 2000;90:253–61.

Neale BM, Mazzeo SE, Bulik CM. Twin Res. 2003;6:478.

Niemeier H, Phelan S, Fava J, Wing R. Obesity. 2007;15:2485–94.

Oeffner F, Bornholdt D, Ziegler A et al. Acta Diabetol. 2000;37:93–101.

Oliver KG, Huon GF. Int J Eat Disord. 2001;30(3):329–37.

Ouwens MA, van Strien T, van der Staak CP. Appetite. 2003;40:291–8.

Pekkarinen T, Takala I, Mustajoki P. Int J Obes. 1996;20:332–7.

Perusse L, Rice T, Chagnon Y et al.. Diabetes. 2001;50:614–21.

Provencher V, Perusse L, Bouchard L, Drapeau V, Bouchard C et al. Obes Res. 2005;13:1624–9.

Provencher V, Drapeau V, Tremblay A, Despres JP, Lemieux S. Obes Res. 2003;11(6):783–92.

Richman RM, Webster P, Salgo AR, Mira M, Steinbeck KS, Caterson ID. Int J Obes. 1996;20:413–9.

Sabol S, Nelson M, Fisher C. Health Psyc. 1999;18:7–13.

Schindler K, Prager G, Ballaban T, Kretschmer S, Riener R et al. Eur J Clin Invest. 2004;34(8):549–54.

St Pierre DH, Karelis AD, Cianflone K, Conus F, Mignault D et al. J Clin Endocrin & Metab. 2004;89(12):5993–7.

Steinle NI, Hsueh WC, Snitker S, Pollin TI, Sakul H et al. Am J Clin Nutr. 2002;75:1098–106.

Straub RH, Lamparter-Lang R, Palitzsch KD, Scholmerich J. Eur J Clin Invest. 1996;26(7):564–8.

Stunkard AJ, Messick S. J Psychosom Res. 1985;29:71–83.

Wadden TA, Foster GD, Sarwer DB, Anderson DA, Gladis M et al. Am J Clin Nutr. 2004;80(3):560–8.

Weinstein SE, Shide DJ, Rolls BJ. Appetite. 1997;28:18.

Westerterp-Plantenga MS, Kempen KP, Saris WH. Int J Obes. 1998;22(1):1–6.

World Health Organization. Obesity and overweight. http://www.who.int/mediacentre/factsheets/fs311/en/index.html; 2009.

Yeomans M, Coughlan E. Appetite. 2009;52:290–8.

Yeomans M, Leitch M, Mobini S. Appetite. 2008;50:469–76.

Yeomans MR, Tovey HM, Tinley EM, Haynes CJ. Int J Obes Relat Metab Disord. 2004;28:144–51.

Chapter 71
The Effects of Exercise on Appetite Control

Catia Martins, Denise Robertson, and Linda Morgan

Abbreviations

EB	Energy balance
EI	Energy intake
REI	Relative energy intake
EE	Energy expenditure
CCK	Cholecystokinin
TG	Total ghrelin
AC	Acylated ghrelin
DG	Desacyl ghrelin
PYY	Polypeptide YY
GLP-1	Glucagon-like peptide-1
PP	Pancreatic polypeptide
PA	Physical activity
AUC	Area under the curve
HEP	High-energy preload
LEP	Low-energy preload
VO_2max	Maximal oxygen consumption

71.1 Introduction

Obesity is a global epidemic with huge public health implications (World Health Organization 2006). Despite its complex etiology, it is widely accepted that obesity results from a state of long-term positive energy balance (EB), with energy intake (EI) exceeding energy expenditure (EE) (World Health Organization 2003). It has been suggested that a large reduction in PA levels, driven by dramatic changes in lifestyle, together with an inability of the organism to downregulate EI to a similar extent to match the reduced EE, are the dominant factors in promoting obesity in industrialized countries (Moore 2000). This uncoupling between EI and EE is likely to result from a breakdown in the normal mechanisms that regulate appetite and eating behavior.

———————————————

C. Martins (✉)
Department of Cancer Research and Molecular Medicine, Faculty of Medicine,
Norwegian University of Science and Technology, Trondheim, Norway
e-mail: catia.martins@ntnu.no

Appetite is under the control of the brain, together with multiple hormonal and metabolic signals released by the periphery. The hypothalamus, in particular the arcuate nucleus, is constantly receiving and processing neural, metabolic, and endocrine signals from the periphery, enabling it to maintain energy homoeostasis by adjusting not only EI but also EE. Two types of peripheral signals can be described: firstly, episodic signals, which are periodically released, mainly from the gastrointestinal tract, in response to feeding or fasting, signaling the acute nutritional state; secondly, tonic signals, which are constantly released, mainly by the adipose tissue, in proportion to the amount of stored lipids, signaling the chronic nutritional state (Blundell 2006). To the first category of peripheral gastrointestinal signals belongs ghrelin, an orexigenic hormone released in response to fasting, and several satiety hormones such as glucagon-like peptide-1 (GLP-1), polypeptide YY (PYY), and pancreatic polypeptide (PP), which are released in response to feeding. The second category of peripheral signals includes leptin, released mainly by the adipose tissue, and insulin, released by the pancreas, whose secretion is directly proportional to the amount of body fat.

Apart from the potential for physical inactivity to deregulate the appetite-regulatory system, thus contributing to positive EB and obesity, it is also important to understand how exercise impacts on appetite control. When individuals start an exercise program, weight loss is neither inevitable nor consistent (King et al. 2008). This is probably related to the fact that in some individuals exercise upregulates hunger and food intake thus offsetting any beneficial impact exercise might have on EB (King et al. 2008). It is likely that the impact of exercise on EB and body weight is mediated through changes in the plasma levels of appetite-regulating hormones. In the face of current widespread levels of physical inactivity (Varo et al. 2003), it is extremely important to determine how both inactivity and exercise (short- and long-term) impact on appetite control. A better understanding of the role of exercise on appetite control will lead to more effective ways of incorporating exercise into weight management programs.

71.2 Effects of Exercise on the Coupling Between EI/EE and Energy Compensation

The impact of physical activity (PA) on the coupling between EI and EE has been extensively studied. EI and energy requirements seem to be very well coupled, but only for moderate-to-high levels of PA. At low levels of PA, however, EI and EE are uncoupled, so that a reduction in EE is not followed by a proportional reduction in EI, leading to a net positive EB and weight gain (Mayer et al. 1956). This clearly suggests first, that inactivity is linked to a disruption of the homeostatic mechanisms involved in appetite control and, second, that exercise has the ability to "fine tune" those physiological mechanisms. More recently, it has been shown that the adoption of a sedentary lifestyle is not followed, at least in the short- to medium-term, by a compensatory decrease in EI, with consequent positive EB (Murgatroyd et al. 1999; Stubbs et al. 2004).

Interestingly, inactivity seems to impair not only the coupling between EI and EE (as described above), but also short-term appetite control, usually described as "energy compensation." If this process is not tightly regulated it can lead to energy imbalance in the long-term. Energy compensation is measured using the "preload test meal paradigm." This paradigm has been systematically used in appetite research and consists of manipulating the energy content of a preload in order to alter EB and then investigating the homeostatic feedback control of appetite by measuring EI later on with an ad libitum test meal.

Cross-sectional studies have shown better accuracy in energy compensation in active versus sedentary normal-weight individuals, both acutely at a test meal (Long et al. 2002) and over the course of a day (van Walleghen et al. 2007). Whilst sedentary individuals are unable to adjust subsequent EI in response to preload energy manipulation, active individuals significantly decrease their EI following a high-energy preload (HEP) compared with after a low-energy preload (LEP) (Long et al. 2002; van Walleghen et al. 2007). These studies suggest that exercise improves short-term appetite control by leading to a more sensitive eating behavior in response to previous EI. Moreover, we have recently shown that a 6-week exercise program improves the sensitivity of compensation in response to previous EI, over a 24-h period, in normal-weight individuals (Martins et al. 2007b). Similar findings have been more recently observed after a 12-week exercise intervention in overweight/obese individuals (Fig. 71.1) (C. Martins, B. Kulseng, N.A. King, and J.E. Blundell, unpublished results).

The improvement in energy compensation observed in response to exercise is likely to result from changes at the level of the appetite regulatory system, in particular episodic signals released by the gastrointestinal tract in response to feeding. It can be hypothesized that, in a sedentary individual, there are no differences in the postprandial release of anorexigenic peptides (such as PYY and GLP-1) and/or suppression of orexigenic peptides (ghrelin) after high- and low-energy preloads (denoting an abnormal response), whereas after an exercise intervention the postprandial release of appetite hormones is sensitive to the energy content of the preload, resulting in an improved compensatory response. Although this is just hypothetical and research in this area is lacking, a large body of evidence has been accumulating regarding the impact of exercise on appetite regulating hormones.
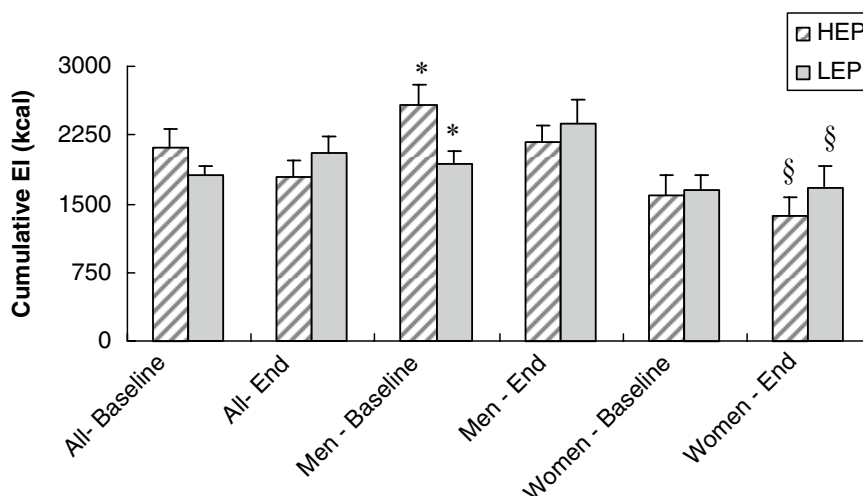
Fig. 71.1 Effects of chronic exercise on energy compensation in overweight/obese individuals. Cumulative energy intake (EI) (kcal), for the rest of the day, after a high- (HEP) and low-energy preload (LEP), at baseline and end of a 12-week exercise intervention in all individuals ($n = 15$), men ($n = 8$), and women ($n = 7$) (C. Martins, B. Kulseng, N.A. King, and J.E. Blundell, unpublished results). Results are expressed as mean ± SEM. A 2-way ANOVA showed a significant effect of gender ($P < 0.01$) and an exercise*preload interaction ($P = 0.011$), but no effects of exercise, preload or other interactions. Histograms sharing the same symbol denote a trend towards significant differences between conditions: *$P = 0.030$, §$P = 0.047$. In men, ANOVA revealed also a significant exercise*preload interaction ($P = 0.027$), but no effect of preload or exercise. In woman no significant effects or interactions were observed on cumulative EI

71.3 Effects of Exercise on Appetite-Regulating Hormones

The impact of both acute and chronic exercise, on circulating levels of hormones involved in appetite control is an area that has received considerable attention over the last decades, particularly with respect to leptin and ghrelin.

71.3.1 Effects of Exercise on Leptin Plasma Levels

The effects of exercise on leptin plasma levels were extensively discussed in a review by Kraemer and collaborators (2002). They concluded that, in the absence of weight loss, no significant changes on fasting leptin plasma levels are observed in response to exercise (Kraemer et al. 2002). However, a significant reduction in plasma leptin levels was reported after an intense, prolonged exercise period (25 km swimming race) in highly trained individuals (Karamouzis et al. 2002) and also after a 1-year exercise intervention, even after adjusting for BMI and fat mass (Reseland et al. 2001). However, in the study where participants underwent a 25 km swimming race (Karamouzis et al. 2002), a huge negative EB was imposed and the subjects were not in a fasting state, therefore allowing the release of insulin, which is known to exert a negative feedback over leptin secretion. It has been proposed that an exercise intervention that improves insulin sensitivity would have the ability to alter leptin levels independently of any changes in fat mass, due to changes in insulin and cortisol levels, known modulators of leptin secretion (Considine 1997).

   Although acute exercise, when performed in the fed state, does not seem to impact on leptin plasma levels in normal weight individuals (Zoladz et al. 2005), extreme exercise (until exhaustion) in healthy normal-weight men was reported to significantly increase plasma leptin concentrations (Sliwowski et al. 2001).

71.3.2 Effects of Exercise on Gut Peptides

71.3.2.1 Acute Exercise

Effects of Acute Exercise on Ghrelin Plasma Levels

The majority of the studies show that total ghrelin (TG) plasma levels are unaffected by a single exercise session regardless of the exercise mode (running vs. cycling), intensity (50%, 70%, and 90% VO_2max), or metabolic state (fasting or postprandial) in normal-weight individuals (Dall et al. 2002; Kraemer et al. 2004a; Martins et al. 2007; Schmidt et al. 2004; Zoladz et al. 2005). There are a few studies, however, that report either a reduction or an increase in TG plasma levels in response to acute exercise. TG has been shown to be reduced for up to 2 h after the end of a maximal exercise test till exhaustion (Vestergaard et al. 2007), immediately and 15 min after moderate (80% maximal) resistance exercise with concentric, but not eccentric muscle contractions (Kraemer et al. 2004b), and immediately after a single bout of circuit resistance exercise (at 60% 1-RM) (Ghanbari-Niaki 2006). However, none of the three studies had a resting/control condition. In a study by Malkova and collaborators (2008), despite there being no difference in TG plasma levels between an exercise (cycling at 90% of the lactate threshold for a duration required to expend 200 kcal) and a control condition, when a meal was served 2 h after the end of exercise, postprandial TG plasma levels were

significantly lower after exercise compared with the control condition (Malkova et al. 2008). Moreover, several studies have reported an increase in TG in response to acute maximal exercise (6,000-m rowing ergometer test ~19 min) (Jürimäe et al. 2007), and prolonged moderate- to high-intensity rowing (~20 km/2 h) (Jürimäe et al. 2009), and cycling (3 h at 50% maximal aerobic power) (Christ et al. 2006) in elite athletes.

The above studies showing an increase in TG plasma levels in response to exercise have all been performed in elite athletes and involved high intensity and/or prolonged endurance training resulting in a large overall energy deficit (Christ et al. 2006; Jürimäe et al. 2007, 2009; Malkova et al. 2008). Studies that have not found any effect of acute exercise on TG plasma levels have included more sedentary individuals and employed exercise protocols using fewer muscle groups for shorter periods of time (Dall et al. 2002; Kraemer et al. 2004a; Martins et al. 2007; Schmidt et al. 2004; Zoladz et al. 2005) resulting, therefore, in limited negative EB. This suggests that changes in EB may drive the TG response; the TG concentration following exercise is therefore a direct result of exercise-induced EE and a threshold of energy imbalance may be needed for acute exercise to induce a compensatory increase in TG plasma levels. This is supported by the fact that TG plasma levels immediately after exercise were positively correlated with rowing distance during a 2-h training session (Jürimäe et al. 2009) and by the fact that when exercise is performed in EB (by upregulating food intake) no significant impact on fasting TG is observed (Hagobian et al. 2008).

Acylation of ghrelin is thought to be essential for ghrelin to bind to the growth hormone-secretagogue receptor and cross the blood–brain barrier and, therefore, to exert its effects on appetite control. For this reason, the isolated measurement of TG can mask important changes in AG. To date, relatively few studies have looked at the impact of acute exercise on AG plasma levels. One study investigated the impact of 1 h of vigorous treadmill running followed by 8 h of rest (exercise condition), performed in the fasting state, on the plasma levels of AG for a period of 9 h (with a meal being presented 3 h after the start of each trial) in normal-weight active men. The authors described a significant suppression in AG in the exercise compared with the control condition, which was sustained for up to 8 h after the end of the exercise session. Moreover, these suppressed levels of AG were shown to be correlated with suppressed hunger during the first 3 h of the exercise trial (Broom et al. 2007). A recent study by Broom and colleagues (2009) investigated the effects of resistance (90 min weight lifting session followed by 6.5 h rest) and aerobic (60 min run followed by 7 h rest) exercise (compared with a control condition of 8 h rest) performed in fasting, on hunger feelings and circulating levels of AG and PYY. Participants were fed a test meal 2 and 5 h into each trial. They reported a significant suppression of hunger during and shortly after resistance and aerobic exercise, a suppression of AG during resistance and aerobic exercise and a significant increased in PYY plasma levels during and after aerobic exercise (Broom et al. 2009). Moreover, a recent study showed that a cycling test to exhaustion suppressed AG plasma levels but did not affect TG, both in normal-weight and obese individuals, despite the latter achieving a lower exercise output and performance. The authors concluded that acute exercise has no impact on TG but suppresses AG plasma levels independently of adiposity and exercise performance (Marzullo et al. 2008). These studies suggest, not only that AG responds differently to acute exercise compared with TG, but also that AG may play a role in the suppression of appetite observed during and shortly after moderate- to high-intensity aerobic and resistance exercise, a phenomenon known as "exercise-induced anorexia."

Effects of Acute Exercise on Satiety Gut Peptides Plasma Levels

In contrast to the large number of studies investigating the impact of acute exercise on the orexigenic hormone ghrelin, only a few have looked at the effects of acute exercise on anorexigenic (satiety)

hormones, such as PYY, GLP-1, cholecystokinin (CCK), and PP, and the majority has been performed in normal-weight individuals (Table 71.1). The available evidence suggests that acute exercise increases fasting plasma levels of GLP-1 (O'Connor et al. 1995) and fasting and postprandial levels of CCK (Bailey et al. 2001; Sliwowski et al. 2001) and PP (Greenberg et al. 1986; O'Connor et al. 1995; Sliwowski et al. 2001; Sullivan et al. 1984). However, appetite was not the primary outcome in any of the previous studies and, therefore, appetite sensations and food intake in the postexercise period were not recorded.

We have recently investigated the effects of acute exercise on postprandial plasma levels of TG, PYY, GLP-1, and PP in normal-weight individuals. Participants were given a 500 kcal breakfast and 1 h later, cycled for 60 min, at 65% of their maximal heart rate or rested. A significant increase in postprandial plasma levels of PYY, GLP-1, and PP were observed, in the absence of significant changes in TG, suggesting that exercise triggers physiological changes in hormone secretion toward a more satiating state (Martins et al. 2007a).

All the studies previously described were run in normal-weight individuals. A recent study by Ueda and colleagues (2009) showed that exercise, performed 1 h after breakfast, lead to a significant transient increase in PYY and a significant sustained increase in GLP-1 plasma levels, compared

Table 71.1 Studies looking at the effect of acute exercise on satiety gut peptides

References	Subjects	Intervention	Outcome[a]
Hilsted et al. (1980)	Healthy men	Three hours of exercise (cycle ergometer) at 40% of VO_2max vs. resting	Sig.↑ in fasting PP plasma levels
Sullivan et al. (1984)	Male athletes	Marathon running	Sig. ↑ in fasting PP plasma levels
Greenberg et al. (1986)	Nonobese healthy men and women	Forty-five min of exercise (cycle ergometer) at 50% VO_2max, 30 min after a 425 kcal breakfast vs. resting	Significant increase in postprandial plasma levels of PP
O'Connor et al. (1995)	Athletes (men and women)	Marathon running	Sig. ↑ in fasting GLP-1 and PP plasma levels
Bailey et al. (2001)	Physically active normal-weight men	Cycling test to exhaustion vs. resting	Sig. ↑ in fasting CCK plasma levels
Martins et al. (2007a)	Normal-weight men and women	Sixty minutes of exercise (cycle ergometer) at 65% max HR, 1 h after a 500 kcal breakfast vs. resting	Sig. ↑ in PYY, GLP-1 and PP plasma levels
Broom et al. (2009)	Physically active normal-weight men	Resistance exercise (90 min weight lifting) vs. aerobic exercise (60 min at 70% VO_2max) vs. resting (performed in fasting)	Sig. ↑ in PYY plasma levels during aerobic exercise
Ueda et al. (2009)	Normal-weight and obese men	Exercise (60 min at 50% VO_2max) performed 1 h after breakfast vs. resting	Sig. ↑ in PYY and GLP-1 plasma levels in both groups

The majority of the studies show that acute exercise increases the release of satiety gut peptides

Sig. significant, ↑ increase, ↓ reduction, *CCK* cholecystokinin, *PP* pancreatic polypeptide, *PYY* polypeptide YY, *GLP-1* glucose like peptide-1, *VO_2max* maximal oxygen uptake, *HR* heart rate

[a]In comparison with a control (resting) condition

with a resting condition, but no changes in TG, both in normal-weight and obese men (with no differences between groups). This pattern is identical to the findings previously reported by us in a mixed sample of normal-weight men and women (Martins et al. 2007a). For an overview on the effects of acute exercise on the plasma levels of hormones involved in appetite control, in both normal-weight and overweight/obese individuals, see Table 71.2.

Overall, the majority of the evidence suggests that acute exercise has a beneficial impact on the appetite regulatory system by increasing the release of satiety gut peptides and reducing the secretion of AG (Fig. 71.2).

71.3.2.2 Chronic Exercise

Studies on the impact of chronic exercise on appetite-regulating hormones are summarized in Table 71.3.

Table 71.2 Effects of acute exercise on appetite-regulating hormones in normal-weight and overweight/obese individuals

Gut hormones	Normal-weight	Overweight/obese
– TG	No change	NA
– AG	↓	NA
– GLP-1	↑ (fasting, postprandial)	↑ (postprandial)
– PYY	↑ (fasting, postprandial)	↑ (postprandial)
– PP	↑ (fasting and postprandial levels)	NA
– CCK	↑ (fasting)	NA

Acute exercise seems to have a neutral or negative impact (reduction) on hunger hormones (TG and AG) and a positive impact (increase) on satiety hormones (GLP_1, PYY, PP, and CCK)

NA not available, ↑ increase, ↓ reduction, *TG* total ghrelin, *AG* acylated ghrelin, *GLP-1* glucose like peptide-1, *PYY* polypeptide *YY*, *PP* pancreatic polypeptide, *CCK* cholecystokinin
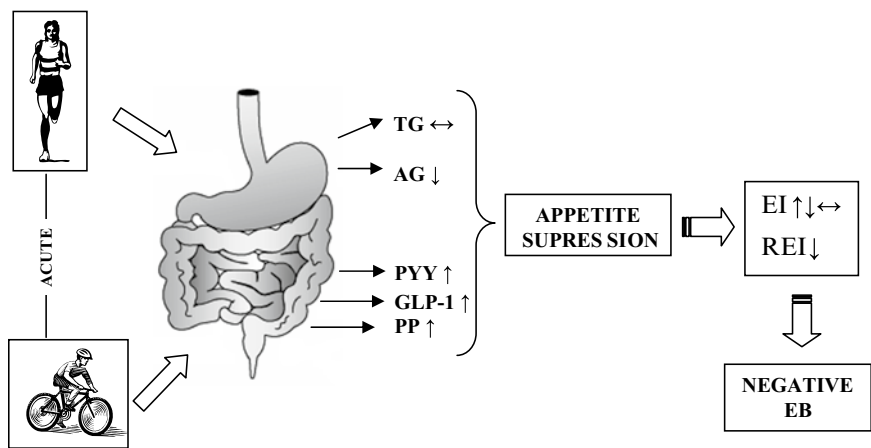
Fig. 71.2 Effects of acute exercise on appetite-regulating hormones. Acute exercise has a beneficial impact on the appetite regulatory system by reducing the secretion of hunger hormones and increasing the secretion of satiety hormones. This, if sustained, can lead to negative EB in the long-term. *TG* total ghrelin, *AG* acylated ghrelin, *PYY* polypeptide YY, *GLP-1* glucagon like peptide-1, *PP* polypeptide YY, *EI* energy intake, *REI* relative energy intake, *EB* energy balance, ↑ increase, ↓ decrease, ↔ no change

Table 71.3 Studies looking at the effect of chronic exercise on appetite-regulating hormones

References	Subjects	Intervention	Outcome
Medium-term studies			
Mackelvie et al. (2007)	Normal-weight (NW) and overweight (OW) male adolescents	Five consecutive days of aerobic exercise (1 h/day)	No sig. change in body weight. No sig. change in fasting/postprandial TG or DG, but a sig. ↑ in fasting AG and postprandial AG AUC. The ↑ in fasting AG was sig. higher in NW compared with OW. DG AUC ↓ in NW but ↑ in OW
Chanoine et al. (2008)	Normal-weight and overweight male adolescents	Five consecutive days of aerobic exercise (1 h/day)	No sig. change in body weight. No sig. change in fasting GLP-1 plasma levels, but a sig. ↑ in GLP-1 response in the first 30 min postprandially, in both groups
Long-term studies (>2 weeks)			
Hurley et al. (1991)	Sedentary normal-weight men	Ten-week jogging program (20 min at 70% VO_2max, three times/week)	No sig. change in body weight, but sig. ↓ in % body fat. Slight ↑ in fasting and postprandial peak PP plasma levels
Bailey et al. (2001)	Physically active Normal-weight men	Four-week cycling program (three times/week with incremental duration and	No sig. change in body weight. No sig. change in fasting CCK plasma levels
Ravussin et al. (2001)	Seven pairs of monozygotic male twins (borderline overweigh)	Ninety-three days of exercise in a residential facility inducing a 53,000 kcal energy deficit	Sig. weight loss (average 5 kg). Trend toward an ↑ in fasting TG plasma levels
Leidy et al. (2004)	Normal-weight women	Three-month exercise intervention (five times/week) in negative EB or in EB (by providing extra calories to maintain body weight) vs. a control condition	Sig. ↑ in TG plasma levels in weight-loss exercisers (negative EB group – average weight loss 3.2 kg), but no difference in weight stable exercisers (EB group) or controls. Positive correlation between changes in TG and weight loss

Foster-Schubert et al. (2005)	Obese postmenopausal women	One-year exercise intervention (in the absence of dietary changes)	Sig. weight loss (average 1.4 kg) Sig. ↑ in fasting TG (positively correlated with weight loss)
Kim et al. (2008)	Overweight 11-year old boys	Twelve-week supervised exercise program (aerobic and resistance training, without energy restriction) vs. a control condition	Sig. ↓ in body weight (average 2 kg) compared with control No sig. change in fasting AG, but ↑ in DG and TG Weight loss was associated with increased DG
Jones et al. (in press)	Overweight sedentary adolescents	Eight months supervised exercise intervention (45 min, three times/week between 60–85% VO$_2$max)	No sig. change in body weight, but a sig. ↓ in % body fat Sig. ↑ in fasting PYY plasma levels No sig. change in fasting AG

Chronic exercise does not seem to have an independent effect on TG plasma levels, but exercise-induced weight loss may result in a compensatory increase in TG plasma levels. The impact of chronic exercise on AG seems to be dependent on body weight and a larger increase can be expected in normal-weight individuals. The few available studies on the impact of chronic exercise on satiety peptides seem to suggest an increase in their secretion

Sig. significant, ↑ increase, ↓ reduction, *TG* total ghrelin, *AG* acylated ghrelin, *DG* des-acyl ghrelin, *EI* energy intake, *EB* energy balance, *PP* pancreatic polypeptide, *PYY* polypeptide YY, *GLP-1* glucose like peptide-1, *VO₂max* maximal oxygen uptake, *NW* normal weight, *OW* overweight

Effects of Chronic Exercise on Ghrelin Plasma Levels

The effects of chronic exercise on TG plasma levels have been extensively studied. Foster-Schubert and colleagues (2005) showed that a 1-year exercise intervention (in the absence of dietary changes), leading to an average weight loss of 1.4 kg, resulted in a significant increase in fasting TG in obese postmenopausal women (Foster-Schubert et al. 2005). Moreover, they reported that the increase in fasting TG plasma levels was positively correlated with weight loss and that physical fitness per se did not appear to have an independent effect on TG independently of its impact on body weight. Ravussin and colleagues (2001), in a very elegant study, reported a trend toward an increase in fasting TG plasma levels after exercise-induced weight loss (average 5 kg) (Ravussin et al. 2001). This study was run under extremely controlled conditions in a research facility over a 93-day period where food intake was held constant and monitored over time and a 53.000 kcal energy deficit was induced through supervised exercise. The small sample size (seven pairs of borderline overweight monozygotic twins) may have prevented the detection of a significant change in TG in this study. In another well designed study, Leidy and colleagues (2004) compared the TG responses to a 3-month exercise intervention in normal-weight individuals, where participants were either in negative EB (by providing fewer calories than required to maintain body weight) or in EB (by providing extra calories to maintain body weight) versus a control condition. They reported a significant increase in TG plasma levels in the weight-loss exercisers (average weight loss of 3.2 kg), but no difference in the weight-stable exercisers or controls, and a significant positive correlation between changes in TG and changes in body weight (Leidy et al. 2004). Interestingly, they also reported that changes in body weight preceded changes in TG plasma levels. The above studies indicate first, that exercise does not have an independent effect on TG plasma levels in the absence of weight loss and second, that exercise-induced weight loss results in a compensatory increase in TG plasma levels, in both normal-weight and overweight/obese individuals, in order to up-regulate hunger and food intake and, therefore, restore EB.

However, changes in TG plasma levels in response to exercise provide limited information as to whether exercise leads to a stimulation or inhibition of appetite and food intake. Although desacyl ghrelin (DG) has traditionally been seen as devoid of any endocrine activities, recent studies suggest that the effects of ghrelin on EB are mediated through both AG and DG and that the latter induces a negative EB by reducing food intake and delaying gastric emptying in an inverse manner to AG (Soares and Leite-Moreira 2008). Therefore, the overall impact of exercise on appetite should be ascertained not only by changes in TG, but by relative changes in its components (AG and DG). Mackelvie and colleagues (2005) measured the impact of 5 days of supervised aerobic exercise on TG, AG, and DG plasma levels, in normal-weight and overweight male adolescents. They reported no change in TG or DG plasma levels, but a significant increase in fasting and postprandial AG and a positive correlation between changes in AG and markers of subjective appetite (Mackelvie et al. 2007). However, several interactions were reported so that the increase in AG observed with exercise was higher in the normal-weight group, both in fasting and postprandially, and exercise was associated with a decrease in postprandial DG in normal-weight, but an increase in overweight adolescents (Mackelvie et al. 2007). These preliminary results seems to suggest that the impact of chronic exercise on AG is body-weight dependent and that a larger increase may be expected in normal-weight, compared with overweight/obese individuals, in order to quickly restore EB and avoid weight loss.

Although the previous study suggests a limited effectiveness of exercise in inducing a sustained negative EB, particularly in the normal-weight group, since associated with an increase in AG plasma levels, it is limited by its short duration and the fact that EI was not controlled. A recent paper examined the impact of a 12-week supervised exercise program (without energy restriction), versus a control condition, on TG, AG, and DG in overweight children. The authors reported a significant

weight loss, no change in fasting AG plasma levels, but a significant increase in fasting TG and DG plasma levels after the exercise intervention (Kim et al. 2008). Based on the available evidence (Kim et al. 2008; Mackelvie et al. 2007) it can be hypothesized that as exercise duration increases, its impact on EB becomes more favorable by increasing DG without changing AG, thus creating an appetite inhibitory state which favors weight loss.

More importantly, weight loss in response to exercise was shown to be correlated not only with changes in TG but also with DG (much strongly and with higher significance level) and the increase in TG and DG observed after 12 weeks of exercise was also preceded by weight loss (Kim et al. 2008). This new evidence suggests that the increase in TG plasma levels reported by previous studies in response to exercise-induced weight loss (Foster-Schubert et al. 2005; Leidy et al. 2004) does not necessarily mean an increase in AG and is likely to reflect instead an increase in DG. Although more studies are needed in this area, the increase in TG reported after exercise-induced weight loss is unlikely to be part of a counter-regulatory mechanism to restore EB, particularly because chronic exercise has also been shown to increase the release of satiety peptides (see Section 71.3.2.2.2). In fact, the changes in appetite-regulating hormones following exercise are likely to, not only help in weight loss by inhibiting hunger/increasing satiety, but more importantly (since weight loss seems to precede the increase in DG) (Kim et al. 2008) prevent weight regain.

This argument is supported by the fact that high levels of PA have been shown to be a stronger predictor of long-term weight loss maintenance compared with dietary restriction (Catenacci et al. 2008), probably because diet-induced weight loss leads to counter-regulatory adaptations at the level of the appetite regulatory system which ultimately stimulate appetite and food intake (Doucet and Cameron 2007), which does not seem to occur is response to exercise. We propose that the critical role of exercise on long-term weight loss maintenance can, in fact, be attributed to an improved appetite control.

Effects of Chronic Exercise on Satiety Gut Peptides Plasma Levels

Evidence regarding the impact of chronic exercise on the plasma levels of satiety-gut peptides is relatively scarce. One study showed no change in fasting CCK plasma levels after a 4-week exercise program in active men (Bailey et al. 2001) and other a slight increase in both fasting and postprandial peak PP plasma levels, in previously sedentary men, after a 10-week exercise intervention (in the absence of weight loss) (Hurley et al. 1991). A recent study in normal-weight and overweight male adolescents measured fasting and postprandial GLP-1 plasma levels in response to five consecutive days of exercise (1 h/day). They reported no change in fasting GLP-1 but a significant increase in GLP-1 response in the first 30 min postprandially, independently of the weight group (Chanoine et al. 2008). Another recent investigation in overweight adolescents showed that an 8-month supervised exercise intervention (45 min, three times/week, between 60–85% VO_2max), in the absence of dietary restriction, increased fasting PYY plasma levels, and had no impact on AG. A significant reduction in fat mass (%) was observed with the exercise program, but no significant changes in body weight (Jones et al. 2009).

For an overview on the effects of chronic exercise, with and without weight loss, on the plasma levels of hormones involved in appetite control, see Table 71.4.

Overall, the available evidence seems to suggest that chronic exercise leads to changes in appetite-regulating hormones toward an appetite-inhibited state (Fig. 71.3). Unfortunately, no long-term studies have looked at the impact of exercise on the postprandial release of satiety-gut-peptides and how changes in these hormones correlate with changes in food intake and weight loss. More research is urgently needed in this area.

Table 71.4 Effects of chronic exercise, with or without weight loss, on appetite-regulating hormones

Gut hormones	Exercise with weight loss	Exercise without weight loss
– TG	↑ (fasting)	↔
– AG	↔ (fasting)	↑ (fasting and postprandial)[a]; ↔
– DG	↑ (fasting)	↓ in NW, ↑ in OW
– GLP-1	NA	↑ (postprandial)[b]
– PYY	NA	↑ (fasting)
– PP	NA	↑ (fasting and postprandial)

Chronic exercise alone increases TG but does not impact on AG. Chronic exercise with weight loss has no impact on TG, but may increase AG, and increases the release of satiety hormones (GLP-1, PYY, and PP)

NA not available, ↑ increase, ↓ reduction, ↔ no change, *NW* normal-weight, *OW* overweight

[a]Larger ↑ in NW compared with OW

[b]In the first 30 min postprandially
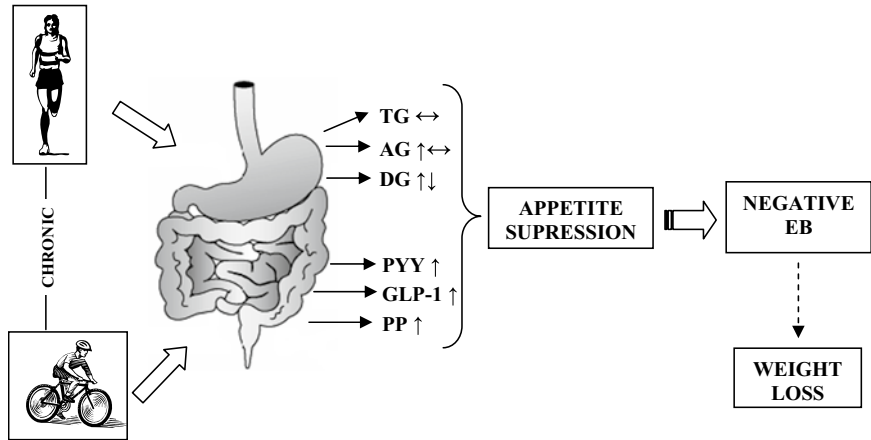
Fig. 71.3 Effects of chronic exercise on appetite-regulating hormones. Chronic exercise leads to changes in appetite-regulating hormones towards an appetite inhibited state. This can help to create a negative EB and, in the long-term, weight loss. *TG* total ghrelin, *AG* acylated ghrelin, *PYY* polypeptide YY, *GLP-1* glucagon like peptide-1, *PP* polypeptide YY, *EI* energy intake, *REI* relative energy intake, *EB* energy balance, ↑ increase, ↓ decrease, ↔ no change

71.3.3 Gender Differences in the Effects of Exercise on Appetite-Regulating Hormones

Several studies have suggested that gender may modulate the impact of exercise on the release of appetite regulating hormones. A training session consisting of 60–90 min of exercise at 80% VO_2max was reported to induce a significant reduction in TG plasma levels in male, but not female athletes (Sartorio et al. 2008). Although this study only measured TG (and not AG) and subjective feelings of appetite were not recorded, the suppression of TG during exercise in men, but not in women, can help to explain why the phenomenon of "exercise induced anorexia" is usually only experienced by men (Martins et al. 2008). More recently, Hagobian and colleagues (2009), using a crossover design, allocated overweight and obese men and women to three trials: (1) no exercise with subjects in EB, (2) 4 days of daily exercise with energy added to the baseline diet to maintain EB (EEB), and (3) 4 days of daily exercise without added energy to induce energy deficit (EED). In men, AG AUC was

not different between trials. In women, AG AUC was higher after the EED (+32%) and EEB (+25%) compared with the control condition. In men, but not in women, appetite was inhibited after EEB relative to EED and control (Hagobian et al. 2009). Another study also showed that serum leptin concentration decreased significantly in females after 12 weeks of aerobic exercise training (4 days/week, 30–45 min/day), but was not significantly reduced in males, despite no changes in fat mass after training in either group (Hickey et al. 1997). This suggests that exercise has the ability to down-regulate the production of leptin by the adipose tissue, in a gender-dependent manner.

The above studies suggest that exercise in women, but not in men, leads to changes in appetite-regulating hormones in a direction expected to stimulate appetite. This may help to explain why exercise has no effect on subsequent EI in men, whereas in women, an increase in EI is usually observed, either decreasing or abolishing the effects of exercise on EB (Stubbs et al. 2002a, b).

Although no study has investigated the differential effects of chronic long-term exercise on appetite-regulating hormones in men and women, the available evidence suggests an identical pattern to that already described for acute- and medium-term exercise. Long-term exercise was shown to increase TG in overweight postmenopausal women (Foster-Schubert et al. 2005) and young women (Leidy et al. 2004), but not in men (Ravussin et al. 2001), even though the exercise-induced energy deficit was much higher in the last study. Unfortunately all the studies on the impact of chronic exercise on AG and DG were done in males. Although a strong correlation seems to exist between TG and AG plasma levels, changes in one cannot be used to predict the other, and some studies have in fact reported changes in TG in the absence of changes in AG plasma levels or the other way around. Despite this limitation, the available data suggests that exercise has a more favorable impact on the release of appetite-regulating hormones in men compared with women and this can help to explain why exercise is a more successful strategy for weight loss in men (Donnelly et al. 2003).

71.4 Effects of Exercise on Appetite Sensations and Prospective Food Intake

71.4.1 Acute Exercise

The impact of acute exercise on hunger/fullness sensations and subsequent food intake is conflicting and seems to be dependent on the intensity and duration of exercise and on the time interval between exercise and meal intake. However, the majority of the evidence suggests that acute exercise has no impact or suppresses hunger and, although absolute EI after a bout of exercise is variable, a reduction in relative EI (REI) is usually observed (Martins et al. 2008). It was recently shown that while short-duration high-intensity (30 min/100 W = 170 kcal energy deficit) and low-intensity aerobic exercise (30 or 60 min at 50 W = 85–170 kcal energy deficit) have no effect on hunger sensations or EI at a test meal presented 15 min after the end of the exercise bout, long-duration low-intensity exercise (inducing 340 kcal energy deficit) significantly increases food intake without a concomitant increase in hunger levels (Erdmann et al. 2007). Interestingly, an increase in TG plasma levels was observed during low-intensity (for all durations: 30, 60, and 120 min), but not high-intensity exercise (Erdmann et al. 2007). This study suggests that the impact of acute exercise on food intake is probably dependent on the energy deficit induced by exercise and that TG is unlikely to be the only determinant in postexercise food intake.

Acute exercise (60 min at 50% VO_2max) has also been described to reduce EI and REI, at a test meal presented 1 h after the end of the exercise bout, when compared with a control condition, in the absence of changes in hunger, fullness, or desire to eat. Moreover, no change was observed in TG plasma levels in response to acute exercise, but a significant increase in PYY and GLP-1 was reported

(Ueda et al. 2009). In a recent study we reported a significant increase in absolute EI, but a reduction in REI, at a test meal presented 1 h after the end of an exercise bout (60 min at 65% max HR), compared with a control resting condition. Although a significant hunger suppression was observed during and shortly after exercise, no significant differences in hunger sensations, or circulating appetite-regulating hormones (TG, GLP-1, PYY, and PP) were observed between the exercise and the control leg, immediately before the buffet meal was presented (Martins et al. 2007a). It can be hypothesized that the increase in absolute EI observed in response to acute exercise was the result of cognitive factors such as the belief that exercise increases hunger or the common behavior of using food as reward for exercising. Although we reported an inverse temporal pattern, during and shortly after exercise between hunger feelings (which were suppressed) and PYY, GLP-1, and PP levels (which were increased), no significant correlations were observed between hunger feelings and the plasma levels of any of the satiety hormones measured (Martins et al. 2007a).

The previous studies suggest that changes in the plasma levels of appetite-related hormones following exercise underpin changes in the subjective measures of appetite (suppression of hunger) during the same period. However, the specific hormones involved in this phenomenon are unknown. Although changes in AG were shown to be correlated with hunger suppression in the postexercise recovery period in one study (Broom et al. 2007), others have found no correlations between suppressed hunger and AG (Broom et al. 2009), TG (Martins et al. 2007a), PYY (Broom et al. 2009; Martins et al. 2007a) or GLP-1 (Martins et al. 2007a) plasma levels. Appetite control is a complex process. It is likely that the impact of exercise on hunger feelings and prospective food consumption results from the combined action of both orexigenic and anorexigenic hormones, and not of the isolated action of a specific hormone, and other factors, both physiological and psychological, may also contribute to this process.

The effect of exercise timing, relative to meal consumption, on hunger feelings and appetite-regulating hormones was recently investigated by Cheng and colleagues (2009). They measured subjective feelings of hunger and plasma levels of PYY_{3-36} and TG in moderately active young men for a period of 7 h during three trials: (1) meal consumption, (2) exercise two hours after a meal, and (3) exercise 1 h before a meal, in random order using a crossover design. Exercise consisted of 50-min cycling at 60% VO_2max. They reported that exercise performed after a meal extended the appetite suppressant effect of food intake much more than when exercise was performed before a meal. Exercise, either before or after a meal, tended to increase PYY_{3-36} compared with meal consumption only (control trial). Only exercise performed before a meal increased TG plasma levels and this may help to explain the absence of a prolonged suppression of hunger in this trial (Cheng et al. 2009). However, other studies have shown no impact of acute exercise on TG plasma levels independently of the exercise bout being performed in the fasting (Dall et al. 2002; Kraemer et al. 2004a; Schmidt et al. 2004; Zoladz et al. 2005) or in the postprandial state (Martins et al. 2007a). More studies are needed in this area to clearly establish whether the impact of acute exercise on subjective feelings of appetite, prospective food intake and appetite-regulating hormones plasma levels is dependent upon the metabolic state (fasting vs. postprandial).

71.4.2 Chronic Exercise

In the long-term, very few studies have looked at the impact of chronic exercise, as the sole intervention, on motivation to eat. A significant increase in EI (corresponding to a partial 30% compensation relative to the energy deficit created by exercise) and a significant but small increase in hunger feelings has been described in women after 1 week of exercise (with either two or three 40 min

exercise session/day) (Stubbs et al. 2002b). However, no significant effects were observed on EI or subjective feelings of hunger/fullness after the same protocol in men (Stubbs et al. 2002a), suggesting that the impact of chronic exercise on appetite feelings and food intake is gender dependent. Unfortunately appetite-regulating hormones were not measured in these two studies. In a recent study, no significant changes in the sensations of hunger, desire to eat, or prospective food consumption, either in fasting or postprandially, were reported in normal-weight and overweight male adolescents after 5 days of supervised aerobic exercise, despite a tendency toward a decrease in fullness. Interestingly, the reduction in fullness 30 min after a meal was correlated with changes in AG. Another study consisting of a 6-week intervention of fixed, reduced dietary intake and 6 h a day of skill-based PA in obese children resident in a weight loss camp showed a significant increase in diurnal profiles of hunger and a reduction in fullness, together with a significantly lower suppression of hunger in response to a test meal at the end of the intervention (King et al. 2007). However, this intervention resulted in a substantial weight loss (8.4 kg) and consisted of both exercise and dietary restriction. Therefore, it is impossible to ascertain whether the increase in hunger was due to exercise or to diet.

A recent study consisting of a 12-week supervised exercise intervention in overweight/obese individuals showed that the impact of long-term exercise on subjective feelings of hunger and food intake is variable and can, at least to some extent, explain the magnitude of exercise-induced weight loss. King and colleagues (2008) reported that those who lost less weight than predicted after an exercise intervention (according to the energy expended during the exercise program) experienced an increase in hunger and EI, while those who lost more weight than predicted experienced no change in hunger feelings and a reduction in EI (King et al. 2008).

Despite the limited number of studies in this area, the available evidence seems to suggest that exercise has little or no impact on subjective feelings of hunger/fullness in the medium-term, in the absence of weight loss. However, in the long-term some individuals may experience an increase in hunger feelings which drives up food intake and offsets the magnitude of weight loss.

71.5 Conclusions and Future Directions

There is a large body of evidence supporting a beneficial role for exercise on appetite control. Acute exercise does not seem to impact on TG plasma levels, but increases the release of satiety hormones. Some studies also suggest that acute exercise may, in fact, suppress AG plasma levels, independently of body weight or exercise performance. However, there is some evidence for a compensatory increase in TG plasma levels in response to large volumes of acute exercise in athletes. This is likely to be a protective mechanism to prevent weight loss in athletes. Chronic exercise, per se, also does seem to increase TG plasma levels and there is some evidence for an increase in the release of satiety gut peptides.

The available findings clearly reinforce the importance of incorporating exercise in all weight management programs for several reasons. First, exercise improves the coupling between EI and EE in the long-term, so that changes in EE are quickly followed by proportional changes in EI in the opposite direction, thus ensuring the maintenance of a constant body weight over time. Second, exercise improves energy compensation, so that changes in EI at a particular meal are detected and compensated for at the following meal, leading to an improved appetite control in the short-term. Third, exercise does not seem to induce physiological adaptations at the level of the appetite regulatory system toward increased hunger or EI. However, the impact of exercise

on the release of appetite-regulating hormones is likely to be more favorable in men than in women.

The data discussed in this chapter is, nevertheless, limited by the fact that most studies on the impact of exercise on appetite-regulating hormones, have measured total hormone plasma levels and not their active components. More research is needed to clarify the impact of both, acute and chronic exercise, on the active components of the different hormones involved in appetite control and how that relates to changes in subjective feelings of appetite, food intake, and body weight.

71.6 Applications to Other Areas of Health and Disease

The more detailed evidence now available regarding the role exercise plays in appetite control is likely to contribute to the design of exercise programs that are more effective in creating an appetite suppressant environment and, therefore, in inducing a negative EB and weight loss. Moreover, a better understanding of the contribution that exercise-induced changes in the release of appetite-regulating hormones make on interindividual variation in exercise-induced weight loss will allow a better management of available resources by directing people to appropriate treatment regimes.

Apart from obesity management, other areas of research such as sports physiology and nutrition are likely to benefit from an increased knowledge in this area.

71.7 Key Facts on Exercise and Appetite Control (see Table 71.5)

Table 71.5 Key features on exercise and appetite control

1. Aerobic exercise consists of moderate intensity physical activity that requires the heart and lungs to work harder to meet the body's increased oxygen demand. Examples of aerobic exercise include running, swimming, and cycling.
2. Resistance exercise is any exercise where muscles contract against an external resistance with the objective of increasing strength, tone, mass, and/or muscular endurance. Is performed at high intensity and for very short periods of time.
3. Appetite is a range of parameters that can predict normal eating behavior, such as sensations of hunger and fullness, food preferences, and craving for certain foods.
4. Leptin is a hormone produced by fat cells, in proportion to body fat levels, which provides information to the brain about the state of energy stores. It plays a key role in long-term energy balance by reducing food and increasing energy expenditure.
4. Ghrelin is a hormone which increases hunger feelings and prompts us to eat.
5. GLP-1, PYY, PP, and CCK are satiety hormones that make us feel full and stop eating.

This table lists the key facts on exercise and appetite control including types of exercise, the basic concept of appetite, and the function of several hormones involved in appetite control

CCK cholecystokinin, *PYY* polypeptide YY, *GLP-1* glucagon like peptide-1, *PP* pancreatic polypeptide

Summary Points

- Exercise improves energy compensation, by leading to a more sensitive eating behavior in response to previous EI.
- Acute exercise does not change TG plasma levels, but may suppress AG and increase the release of satiety hormones (PYY, GLP-1, and PP). This is likely to underpin changes in subjective feelings of appetite during the same period.
- There is some evidence that resistance exercise may suppress TG but that if a large energy deficit is created by exercise, a compensatory increase in TG may occur, particularly in athletes.
- Chronic exercise per se independently of weight loss, does not increase TG plasma levels and seems to upregulate the release of satiety hormones, creating an appetite inhibitory state which favors weight loss and prevents weight regain.
- Exercise seems to have a more favorable impact on the release of appetite-regulating hormones in men compared with women.

Key Terms

Energy compensation: The ability to distinguish between two preloads (meals) with different energy content and to compensate for that afterward by eating more after a low-energy preload compared with after a high-energy preload. It is calculated as the difference in EI following preload consumption divided by the difference in preload energy content and expressed as a percentage.

"Exercise-induced anorexia": Suppression of hunger experienced during and shortly after exercise (particularly moderate- to high-intensity exercise).

VO$_2$max: The maximum capacity of an individual's body to transport and utilize oxygen during incremental exercise; it represents the physical fitness of an individual.

Lactate threshold: The exercise intensity at which lactic acid starts to accumulate in the bloodstream.

Relative energy intake: The difference between absolute EI at a test meal and the energy expended during exercise.

References

Bailey DM, Davies B, Castell LM, Newsholme EA, Calam J. J Appl Physiol. 2001;90:105–13.

Blundell JE. Obesity. 2006;14:160S–3S.

Broom D, Batterham RL, King JA, Stensel DJ. Am J Physiol Regul Integr Comp Physiol. 2009;296:29–35.

Broom DR, Stensel DJ, Bishop NC, Burns SF, Miyashita M. J Appl Physiol. 2007;102:2165–71.

Catenacci VA, Ogden LG, Stuht J, Phelan S, Wing RR, Hill JO, Wyatt HR. Obesity. 2008;16:153–61.

Chanoine J-P, Mackelvie KJ, Barr SI, Wong ACK, Meneilly GS, Elahi DH. Obesity. 2008;16:202–4.

Cheng MH-Y, Bushnell D, Cannon DT, Kern M. Appetite. 2009;52:193–8.

Christ ER, Zehnder M, Boesch C, Trepp R, Mullis PE, Diem P, Decombaz J. Eur J Endocrinol. 2006;154:397–403.

Considine RV. J Appl Physiol. 1997;83:3–4.

Dall R, Kanaley J, Hansen TK, Moller N, Christiansen JS, Hosoda H, Kangawa K, Jorgensen JO. Eur J Endocrinol. 2002;147:65–70.

Donnelly JE, Kirk EP, Jacobsen DJ, Hill JO, Sullivan DK, Johnson SL. Am J Clin Nutr. 2003;78:950–6.

Doucet E, Cameron J. Appl Physiol Nutr Metab. 2007;32:523–32.

Erdmann J, Tahbaz R, Lippl F, Wagenpfeil S, Schusdziarra V. Regul Pept. 2007;143:127–35.

Foster-Schubert KE, McTiernan A, Frayo RS, Schwartz RS, Rajan KB, Yasui Y, Tworoger SS, Cummings DE. J Clin Endocrinol Metab. 2005;90:820–5.

Ghanbari-Niaki A. Clin Biochem. 2006;10:966–70.

Greenberg GR, Marliss EB, Zinman B. Horm Metab Res. 1986;18:194–6.

Hagobian TA, Sharoff CG, Braun B. Metabolism. 2008;57:393–8.

Hagobian TA, Sharoff CG, Stephens BR, Wade GN, Silva JE, Chipkin SR, Braun B. Am J Physiol Regul Integr Comp Physiol. 2009;296:R233–42.

Hickey MS, Houmard JA, Considine RV, Tyndall GL, Midgette JB, Gavigan KE, Weidner ML, McCammon MR, Israel RG, Caro JF. Am J Physiol. 1997;272:E526–66.

Hilsted J, Galbo H, Sonne B, Schwartz T, Fahrenkrug J, Schaffalitzky de Muckadell OB, Lauritsen KB, Tronier B. Am J Physiol. 1980;239:G136–40.

Hurley RS, Rossetti BM, O'Dorisio TM, Tenison EB, Welch MA, Rice RR. J Sports Med Phys Fitness. 1991;31:52–6.

Jones TE, Basilio JL, Brophy PM, McCammon MR, Hickner RC. Obesity. 2009;17:1189–95.

Jürimäe J, Jürimäe T, Purge P. Exp Biol Med. 2007;232:904–9.

Jürimäe J, Rämson R, Mäestu J, Purge P, Jürimäe T, Arcieiro PJ, Von Duvillard SP. Med Sci Sports Exerc. 2009;41:137–43.

Karamouzis I, Karamouziz M, Vrabas IS, Christoulas K, Kyriazis N, Giannoulis E, Mandroukas K. Clin Chem Lab Med. 2002;40:132–6.

Kim HJ, Lee S, Kim TW, Kim HH, Jeon TY, Yoon YS, Oh SW, Kwak H, Lee JG. Clin Endocrinol (Oxf). 2008;68:416–22.

King NA, Hester J, Gately PJ. Int J Obes. 2007;31:334–9.

King NA, Hopkins M, Caudwell P, Stubbs RJ, Blundell JE. Int J Obes. 2008;32:177–84.

Kraemer RR, Chu H, Castracane VD. Exp Biol Med. 2002;227:701–8.

Kraemer RR, Durand RJ, Acevedo EO, Johnson LG, Kraemer GR, Hebert EP, Castracane VD. Exp Biol Med. 2004a;229:240–6.

Kraemer RR, Durand RJ, Hollander DB, Tryniecki JL, Hebert EP, Castracane VD. Endocrine. 2004b;24:93–8.

Leidy HJ, Gardner JK, Frye BR, Snook ML, Schuchert MK, Richard EL, Williams NI. J Clin Endocrinol Metab. 2004;89:2659–64.

Long SJ, Hart K, Morgan LM. Br J Nutr. 2002;87:517–23.

Mackelvie KJ, Meneilly GS, Elahi D, Wong ACK, Barr SI, Chanoine J-P. J Clin Endocrinol Metab. 2007;92:648–54.

Malkova D, McLaughlin R, Manthou E, Wallace AM, Nimmo MA. Horm Metab Res. 2008;40:410–5.

Martins C, Morgan L, Truby H. Int J Obes. 2008;32:1337–47.

Martins C, Morgan LM, Bloom SR, Robertson MD. J Endocrinol. 2007a;193:251–8.

Martins C, Truby H, Morgan LM. Br J Nutr. 2007b;98:834–42.

Marzullo P, Salvadori A, Brunani A, Verti B, Walker GE, Fanari P, Tovaglieri I, De Medici C, Savia G, Liuzzi A. Clin Endocrinol (Oxf). 2008;69:970–1.

Mayer J, Roy P, Mitra KP. Am J Clin Nutr. 1956;4:169–75.

Moore MS. Proc Nutr Soc. 2000;59:193–8.

Murgatroyd PR, Goldberg GR, Leahy FE, Gilsenan MB, Prentice AM. Int J Obes. 1999;23:1269–75.

O'Connor AM, Johnston CF, Buchanan KD, Boreham C, Trinick TR, Riddoch CJ. Int J Sports Med. 1995;16:283–7.

Ravussin E, Tschop M, Morales S, Bouchard C, Heiman ML. J Clin Endocrinol Metab. 2001;86:4547–51.

Reseland JE, Anderssen SA, Solvoll K, Hjermann I, Urdal P, Holme I, Drevon CA. Am J Clin Nutr. 2001;73:240–5.

Sartorio A, Morpurgo S, Cappielo V, Agosti F, Maraki M, Giordani C, Rigamonti A E, Muller EE, Spada A. J Sports Med Phys Fitness. 2008;48:97–101.

Schmidt A, Maier C, Schaller G, Nowothy P, Bayerle-Eder M, Buranyi B, Luger A, Woizt M. Horm Metab Res. 2004;36:174–7.

Sliwowski Z, Lorens K, Konturek SJ, Bielanski W, Zoladz JA. J Physiol Pharmacol. 2001;52:53–70.

Soares JB, Leite-Moreira AF. Peptides. 2008;29:1255–70.

Stubbs RJ, Hughes DA, Johnstone AM, Horgan GW, King N, Blundell JE. Am J Clin Nutr. 2004;79:62–9.

Stubbs RJ, Sepp A, Hughes DA, Johnstone AM, Horgan GW, King N, Blundell J. Eur J Clin Nutr. 2002a;56:129–40.

Stubbs RJ, Sepp A, Hughes DA, Johnstone AM, King N, Horgan G, Blundell JE. Int J Obes. 2002b;26:866–9.

Sullivan SN, Champion MC, Christofides ND, Adrian TE, Bloom SR. Phys Sportsmed. 1984;12:77–82.

Ueda SY, Yoshikawa T, Katsura Y, Usui T, Nakao H, Fujimoto S. J Endocrinol. 2009;201:151–9.

van Walleghen EL, Orr JS, Gentile CL, Davy KP, Davy BM. Int J Obes. 2007;31:1277–85.

Varo JJ, Martinez-Gonzalez MA, De Irala-Estevez J, Kearney J, Gibney M, Martinez JA. Int J Epidemiol. 2003;32:138–46.

Vestergaard ET, Dall R, Lange KHW, Kjaer M, Christiansen JS, Jorgensen JOL. J Clin Endocrinol Metab. 2007;92:297–303.

World Health Organization. Global strategy on diet, physical activity and health - obesity and overweight; 2003. http://www.who.int/hpr/NPH/docs/gs_obesity.pdf

World Health Organization. Obesity and overweight - Fact sheet Nº 311; 2006. http://www.who.int/mediacentre/factsheets/fs311/en/print.html.

Zoladz JA, Konturek SJ, Duda K, Majerczak J, Sliwowski Z, Grandys M, Bielanski W. J Physiol Pharmacol. 2005;56:63–85.

Chapter 72
Whey Protein and Satiety: Implications for Diet and Behavior

Sylvia M.S. Chung Chun Lam and Paul J. Moughan

Abbreviations

VAS	Visual analogue scales
GMP	Glycomacropeptide
BCAAs	Branched chain amino acids
β-lg	β-Lactoglobulin
α-la	α-Lactalbumin
BSA	Bovine serum albumin
Ig	Immunoglobulins
CCK	Cholecystokinin
GLP-1	Glucagon-like peptide-1
PYY	Peptide YY
DIT	Diet-induced thermogenesis

72.1 Introduction

In recent years, the prevalence of obesity and overweight has increased rapidly in various populations and across all age groups, but particularly among the young. Consequently, the risk of diseases associated with obesity such as type-2 diabetes, cardiovascular disease, hypertension, and stroke has also risen dramatically and this is a major health concern (Bjorntorp 2001).

The regulation of food intake has been the subject of intensive study driven by the need to understand the problem of overweight and obesity. It is well established that the satiating effect of foods is an important part of overall food intake regulation. Satiety is defined as the feeling of fullness and suppression of hunger feelings after a meal resulting from the ingestion of food. Foods that maximize satiety are promising as they help to reduce the amount of food consumed at the next eating episode and increase the time interval between two meals (Van Itallie and Vanderweele 1981; Kissileff and Van Itallie 1982; Blundell et al. 1996).

Various satiety-inducing food ingredients have been investigated (Kissileff et al. 1984; Rolls et al. 1990; Holt et al. 1995). It would appear that energy density (Stubbs et al. 2000) and fiber content

S.M.S.C.C. Lam (✉)
Riddet Institute, Massey University, Private Bag 11-222, Palmerston North, New Zealand
e-mail: s.m.chungchunlam@massey.ac.nz

(Burton-Freeman 2000; Howarth et al. 2001) of a food are important factors modulating food intake and satiety. Consumption of low energy-dense foods and/or high-fiber foods is directly related to lower energy intake and increased satiety. Although there is some evidence that simple carbohydrate and fat may have an effect on satiety, there is increasing data indicating that protein is the most satiating macronutrient independent of its calorific value (Eisenstein et al. 2002; Anderson and Moore 2004; Halton and Hu 2004).

72.2 Dietary Protein, Food Intake, and Satiety

In many human studies protein appears to be more satiating than the other macronutrients (available carbohydrate, fat, or alcohol). Marmonier et al. (2000) convincingly demonstrated that a high-protein meal delayed the request for food for 60 min compared with 34 min for carbohydrate and 25 min for fat. Eisenstein et al. (2002) reviewed ten preload studies that included measurement of food intake as well as satiety ratings, and found that eight out of the ten studies showed a lower energy intake at the subsequent meal with a high protein preload than with a low protein preload. More direct evidence regarding the effect of high-protein meals in reducing food energy intake and increasing feelings of satiety comes from studies by Booth et al. (1970), Porrini et al. (1995), Poppitt et al. (1998), and Latner and Schwartz (1999) (see Table 72.1). In the study of Poppitt et al. (1998) where the satiating effect of the four dietary components (fat, carbohydrate, protein, and alcohol) was investigated, subjects reported feeling less hungry and more satiated throughout the study period and ate less food at lunch following a protein preload relative to the other macronutrients. In the Latner and Schwartz (1999) study, subjects consumed 31% more energy at dinner after a high-carbohydrate lunch and 20% more energy after a mixed carbohydrate and protein lunch compared to a high-protein lunch. The latter condition suppressed hunger more relative to the other two diets. Porrini et al. (1995) found that when twelve normal-weight men consumed a carbohydrate-rich meal, their subsequent food intake was higher versus consuming a protein-rich meal. Ratings of fullness and satiety were also increased after the high-protein preload compared to the high-carbohydrate preload. In a study of nine subjects who ate a protein-rich or a protein-poor lunch, Booth et al. (1970) found that energy intake at a meal 2–3 h later was lower after consumption of the protein-rich lunch compared to the low-protein lunch.

A few studies found suppression of food intake at a subsequent meal but no change in feelings of satiety after a high-protein meal (Table 72.1). Johnson and Vickers (1993) showed that a smaller amount of food and fewer calories were consumed after a high-protein meal compared with a high-carbohydrate or high-fat meal in 14 normal-weight subjects. However, there was no difference between carbohydrate and protein on feelings of satiety as both carbohydrate and protein were rated as more satiating than fat. Although Barkeling et al. (1990) did not find any change in subjective ratings of satiety between a high-protein meat casserole and a high-carbohydrate vegetarian casserole, they showed a decrease in food intake at the subsequent meal when subjects ate the high-protein meat casserole compared to when they ate the high-carbohydrate vegetarian casserole.

With respect to subjective ratings of satiety, studies by Stubbs et al. (1996), Vandewater and Vickers (1996), Crovetti et al. (1998), and Smeets et al. (2008) have shown that protein is more satiating than carbohydrate or fat (Table 72.1). Stubbs et al. (1996) reported that energy intake at a lunch test meal was similar for all the breakfast treatments but there was a greater suppression of the feeling of hunger after a high-protein meal compared to a meal high in carbohydrate or fat. Similar findings were observed by Crovetti et al. (1998) who studied intake at a test meal and satiety feelings by means of a satiety rating questionnaire in ten normal-weight women. There was no difference between the

Table 72.1 Compilation of recorded effects of dietary protein on food intake and subjective ratings of satiety in humans

References	Subjects	Diets	Measure	Results: food intake	Results: satiety
Barkeling et al. (1990)	Twenty normal-weight women	High-protein meat casserole (64.5 g P, 43% of E from P, 21% F, 36% C) High carbohydrate vegetarian casserole (15.5 g P, 10% of E from P, 21% F, 69% C)	Food intake 4 h after casserole lunch was measured using a universal eating monitor and subjective feelings of satiety were also rated.	Subjects consumed 12% fewer calories after the high-protein meal compared to the high-carbohydrate meal.	No change in subjective ratings between treatments.
Booth et al. (1970)	Nine normal-weight subjects (no further specification)	Protein-rich lunch Protein-poor lunch	Food intake 2–3 h after lunch	Energy intake was lower after consumption of the protein-rich lunch compared to the protein-poor lunch.	Not measured
Crovetti et al. (1998)	Ten normal-weight women	High-protein meal (68.1% of E from P, 19.2% F, 12.6% C) High carbohydrate meal (69.1% of E from C, 20.7% F, 10.1% P) High fat meal (70.1% of E from F, 21.3% C, 8.6% P)	Food intake 7 h later and satiety feelings were rated using a satiety rating questionnaire.	No difference on total test meal intake.	Subjects felt fuller after the high-protein meal over the 7 h test period than after the high carbohydrate or high fat meals.
De Graaf et al. (1992)	Twenty-nine normal-weight women	Ten liquid breakfasts: A zero condition (0.03 MJ) and the nine other preloads varied in energy levels (0.42, 1.05, and 1.67 MJ) and macronutrient content.	Food intake after breakfast was recorded in a diary. Satiety ratings were also assessed after consumption of breakfast.	No difference in energy intake for the remainder of the day.	The rated responses to satiety for the macronutrients did not differ.
Geliebter (1979)	Twelve normal-weight men	Protein load (egg albumin) Fat (corn oil) Carbohydrate (corn starch)	Test meal was presented 70 min after the preload and satiety ratings were measured.	No difference in energy intake during test meal.	Ratings of satiety did not differ.

(continued)

Table 72.1 (continued)

References	Subjects	Diets	Measure	Results: food intake	Results: satiety
Johnson and Vickers (1993)	Nine normal-weight women and six men	High-protein meal High-carbohydrate meal High-fat meal	A mini buffet lunch was served 90 min following the preload and subjects rated their hunger, stomach fullness, and prospective consumption 2 and 90 min after the preload.	A smaller amount of food and fewer calories were consumed after the high-protein meal compared to the high-carbohydrate or high-fat meals.	The high-carbohydrate and high-protein preloads decreased hunger and prospective consumption and increased stomach fullness more than the high-fat preload.
Latner and Schwartz (1999)	Twelve normal-weight women	High-Protein Lunch (80 g of whey protein, 71.5% of E from P) High Carbohydrate Lunch (113 g of polycose supplement 99% of E from C) Mixed Lunch (62 g C & 40 g P, 55.1% of E from C & 35.7% P)	Buffet-style dinner served 4.5 h after lunch consumption. Pre- and postmeal satiety ratings were assessed.	Thirty-one percent more energy was consumed at dinner following the high-carbohydrate lunch and 20% more following the mixed lunch than following the high-protein lunch.	Hunger was less in the high-protein condition than for the high-carbohydrate and mixed treatments. The mixed lunch also reduced hunger more than the high-carbohydrate lunch.
Poppitt et al. (1998)	Twelve normal-weight women	1 MJ baseline meal and drink to which 1MJ of carbohydrate, protein, fat and alcohol was added	Food intake 90 min after treatment and prior to, and at 30, 90, and 120 min, subjective feelings of hunger and satiety were measured.	Energy intake was statistically significantly lowest after the protein treatment relative to the other macronutrients.	Subjects reported feeling less hungry and more satiated throughout the test period on the protein meal compared to the other macronutrients.
Porrini et al. (1995)	Twelve normal-weight men	High-Protein meal (56% of E from P, 25% F, 19% C) High Carbohydrate meal (17% of E from P, 27% F, 56% C)	Food intake at an ad libitum meal was measured and subjects rated their feelings of satiety.	Subsequent food intake was lower for the high-protein meal compared with the high-carbohydrate meal.	Ratings of fullness and satiety were higher following ingestion of high-protein meal compared with the high-carbohydrate meal.
Raben et al. (2003)	Nineteen normal-weight women and 10 men	Breakfasts differed by percentage E contributed by each macronutrient: 1. P (32%) 2. C (65%) 3. F (65%) 4. Alcohol (23%)	Food intake 5 h after breakfast meals and subjective satiety ratings were measured before, after and every 30 min until 5 h after the test meals.	No difference in subsequent energy intake.	No difference in satiety sensations after the four meals.

Smeets et al. (2008)	Nineteen normal-weight women and 11 men	High-Protein lunch (25% of E from P, 45% C, 30% F) Adequate-Protein lunch (10% of E from P, 60% C, 30% F)	Satiety ratings were measured immediately, at 30, 60, 120, 180, and 240 min following the meal.	Not measured	The ratings for hunger and satiety were higher 30 and 120 min after the high-protein lunch than after the adequate-protein lunch.
Stubbs et al. (1996)	Six men	High-Protein breakfast (59% of E from P) High-Carbohydrate breakfast (18% of E from P) High-Fat breakfast (22% of E from P)	Energy intake at a test meal lunch and throughout the rest of the day was assessed and subjective hunger, fullness, and appetite was measured hourly.	Lunch and after lunch energy intakes were similar following all the breakfast treatments.	The high-protein breakfast produced greater suppression of hunger between breakfast and lunch and over 24 h than the High-Carbohydrate or High-Fat treatments.
Vozzo et al. (2003)	Sixteen normal-weight men	High-Protein yoghurt (29% of E from P, 44% C, 24% F) High-Carbohydrate yoghurt (60% of E from C, 24% F, 14% P) High-Fat yoghurt (40% of E from F, 14% P, 42% C)	Food intake for the remainder of the day (7 h) was measured. Subjective rating scales assessing hunger and fullness were used at 15 min intervals for the duration of the study.	Subsequent food intake least but statistically non-significantly after the High-Protein yoghurt than High-Carbohydrate and high-fat yoghurts.	No difference in ratings of satiety.

The weight of the evidence suggests that dietary protein induces satiety more strongly than available carbohydrate, fat, or alcohol in humans as indicated by objective and subjective measures. Meals high in protein decrease food intake at a subsequent meal and subjective ratings of satiety also showed that protein is more satiating than carbohydrate, fat, or alcohol

h hour, MJ megajoules, min minutes; E energy, P protein, C carbohydrate, F fat

diets on test meal intake but subjects felt fuller after the high-protein meal over the 7-h test period than after the high-carbohydrate or high-fat meals. In the Smeets et al. (2008) study, the visual analogue scales (VAS) for hunger and satiety were higher after the high-protein lunch than after the adequate-protein lunch. In addition, results from a study by Vandewater and Vickers (1996) showed that protein-rich meals produced a greater feeling of satiety. The high-protein versions of yoghurt or sandwich induced a greater decrease in hunger and increase in stomach fullness ratings than the low-protein versions.

Contrary to the above discussed results, however, Geliebter (1979), de Graaf et al. (1992), Raben et al. (2003), and Vozzo et al. (2003) found that protein did not affect food intake or subjective responses to satiety (Table 72.1). There was no difference in ratings of satiety and energy intake at a test meal presented 70 min after equicaloric loads of protein (egg albumin), fat (corn oil), and carbohydrate (corn starch) (Geliebter 1979). In the de Graaf et al. (1992) study, energy intake at a test meal, energy intake for the remainder of the day, and satiety feelings did not differ with preloads that varied in macronutrient content. Raben et al. (2003) showed no change in subsequent energy intake or satiety feelings after meals rich in one of the four macronutrients; protein, carbohydrate, fat, or alcohol. In the Vozzo et al. (2003) study, spontaneous food intake and ratings of satiety did not differ significantly after preloads high in protein, carbohydrate, or fat. Subsequent food intake tended to be suppressed 29% by the high-protein preload, 20% by the high-fat preload, and 17% by the high-carbohydrate preload.

Several trials have investigated the relationship between high dietary protein intake and reduced body weight as well as long-term weight maintenance as summarized in Table 72.2. In a 6-month study, Skov et al. (1999) compared the effects of diets varying in percentage energy from protein (25% vs. 12%) on body weight and body composition in 65 otherwise healthy overweight and obese subjects. Weight loss after 6 months was 5.1 kg in the low-protein group vs. 8.9 kg in the high-protein group and fat loss was 4.3 and 7.6 kg, respectively. Subjects spontaneously limited their food intake on the high-protein diet which may have been associated with an enhanced satiety of the high-protein diet. In another study, when 19 subjects increased the proportion of dietary energy supplied by protein from 15% to 30% for 12 weeks, they reported greater feelings of satiety, a larger decrease in spontaneous energy intake, and lost more body weight and body fat on the high-protein diet (Weigle et al. 2005). Layman et al. (2003) monitored the weight management progress of 24 overweight women, who were either on a carbohydrate to protein ratio of 3.5 (68 g protein/day) or a ratio of 1.4 (125 g protein/day). Participants in both groups lost 7–7.5 kg after 10 weeks but women on the low carbohydrate to protein ratio diet reported feeling more satiated compared to the women that were on the high carbohydrate to protein ratio diet. A 4-week study (Baba et al. 1999) of 13 obese hyperinsulinemic normoglycemic men on a hypoenergetic diet that provided 80% of their resting energy expenditure found that those who consumed a high-protein diet (45% protein, 25% carbohydrate, and 30% fat as a percentage of dietary energy) lost more weight (8.3 vs. 6.0 kg) compared to those who consumed a high carbohydrate diet (12% protein, 58% carbohydrate, and 30% fat).

The weight of the evidence suggests that protein is more satiating than the other macronutrients. Preload studies looking at differences in food intake at the subsequent meal and/or feelings of satiety report an increased satiety value of protein. However, some studies did not find any change in subsequent intake or subjective ratings of satiety. Discrepancies in observations from preload studies may be affected by preload volume and composition and the time interval between preload and test meal (Rolls and Hammer 1995). In a recent study by Bellissimo et al. (2007), when the time interval between preload and test meal was increased from 30 to 60 min, the effect of carbohydrate preload decreased whereas the effect of whey protein increased. Carbohydrates and proteins have different post-ingestional consequences. The satiating effect of protein may improve over time

Table 72.2 Summary of results of studies that investigated the long-term effects of high-protein diets in overweight and obese humans

References	Subjects	Diets	Duration	Effects
Baba et al. (1999)	Thirteen men	High-Protein diet (45% of E from P, 25% C, 30% F) Low-Protein diet (12% of E from P, 58% C, 30% F)	Four weeks	Greater weight loss with the High-Protein diet than with the Low-Protein, High-Carbohydrate diet.
Layman et al. (2003)	Twenty-four women	High-Protein diet, carbohydrate to protein ratio of 1.4 (125 g protein/day; 30% of E from P, 41% C, 29% F) Low-protein diet, carbohydrate to protein ratio of 3.5 (68 g protein/day; 16% of E from P, 58% C, 26% F)	Ten weeks	Decrease in body weight in both diets but the ratio of fat/lean loss was found to be greater in the High-Protein diet compared with the Low-Protein, High-Carbohydrate diet. Greater satiety with the High-Protein diet was demonstrated than with the Low-Protein diet.
Skov et al. (1999)	Sixty-five subjects; 19 women and 6 men on each treatment diet	High-protein diet (25% of E from P, 45% C, 30% F) Low-protein diet (12% of E from P, 58% C, 30% F)	Six months	Greater body weight loss and body fat loss with the High-Protein diet compared to the Low-Protein diet. Subjects also spontaneously reduced their total food intake on the High-Protein diet.
Weigle et al. (2005)	Sixteen women and 3 men	High-protein diet (30% of E from P, 50% C, 20% F) Low-protein diet (15% of E from P, 50% C, 35% F)	Twelve weeks	Decreased spontaneous energy intake, body weight, and body fat on the High-Protein diet. Subjects on the High-Protein diet also reduced their spontaneous energy intake and reported greater feelings of satiety.

The effects of high-protein intake on body weight and body composition in overweight and obese humans
E energy, *P* protein, *C* carbohydrate, *F* fat

(after 30 min) but the effect may become less precise as the duration to the next meal increases up to 3 h. The effect of the time interval between the ingestion of protein and subsequent food intake on the measurement of satiety appears to be critical and deserves more investigative attention. Nonetheless, consumption of high-protein meals in the long term may reduce body weight and body fat; effects that may be useful in the treatment of obesity. The short-term effects of protein on satiety may be an important factor.

72.3 Mechanism of Action of Protein on Satiety

Dietary protein may influence food intake and satiety via a number of mechanisms. Firstly, higher dietary protein intakes influence the plasma concentrations of amino acids which in turn may influence satiety-related hormones. Proteins have a high thermic effect and bioactive peptides released during digestion in the gut may also play a role (Rutherfurd-Markwick and Moughan 2005; refer to Fig. 72.1).
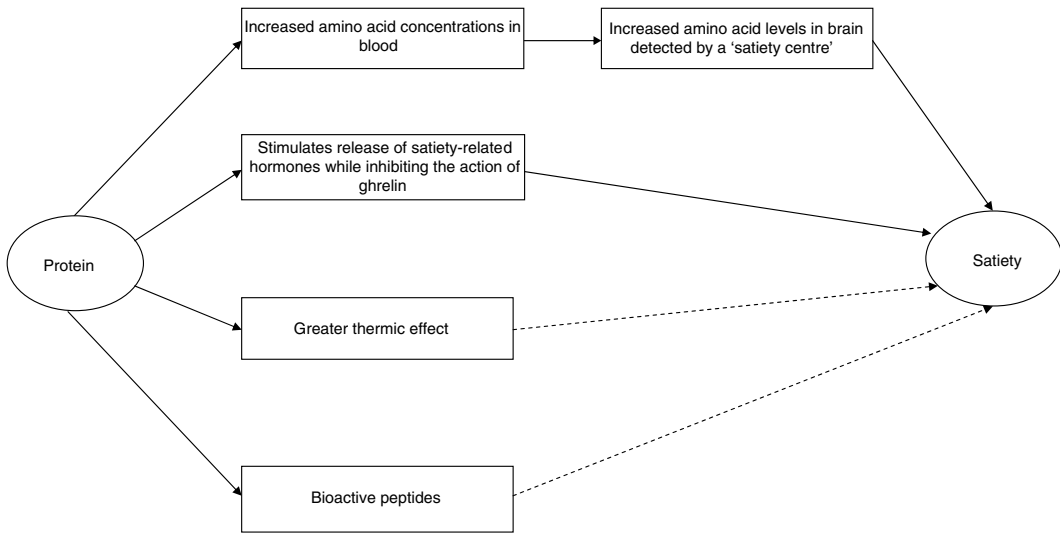
Fig. 72.1 Mechanisms of action of dietary protein. This figure illustrates the mechanisms whereby dietary protein may exert its effect on satiety. Protein ingestion results in the release of amino acids and small peptides. The circulating levels of amino acids rapidly increase and this may contribute to satiety through increased amino acid concentrations in the brain. Amino acids may also stimulate the release of satiety-related hormones including cholecystokinin, glucagon-like peptide-1, and peptide YY while inhibiting the action of ghrelin, a hormone known to stimulate feeding. Part of the satiety effect of dietary protein may be due to the higher thermic effect of protein and the bioactive peptides released during protein digestion. → proven mechanism, --> probable mechanism

72.3.1 Amino Acids

The aminostatic hypothesis of feeding put forward by Mellinkoff et al. (1956) suggests that plasma amino acid concentration is inversely related to fluctuations in appetite. Studies in rats fed amino-acid-imbalanced diets indicate that low plasma concentrations of certain amino acids may lead to increases or decreases in food intake. The changes in plasma amino acid concentrations result in changes in amino acid concentrations in the brain, which are sensed by a "satiety centre" in the brain. The rise in plasma amino acids elicited by protein ingestion may assist in the suppression of food intake and the onset of satiety (Mellinkoff et al. 1956). Specific amino acids may have different effects on the satiety centre, which could explain differences among protein sources in inducing satiety.

72.3.2 Satiety Hormones

A number of studies show that dietary protein intake is correlated to the release of a number of satiety-related hormones such as cholecystokinin (CCK), glucagon-like peptide-1 (GLP-1), peptide YY (PYY) and to a decrease in ghrelin, a hormone known to stimulate feeding. In the study by Hall et al. (2003), the suppression of food intake by whey was shown to be associated with increases in CCK and GLP-1. Compared with whey or casein, carbohydrate consumption decreased ghrelin and increased CCK to a lesser extent (Bowen et al. 2006b). However, no difference in ghrelin, GLP-1, and PYY was found between a high-protein (25% of energy from protein) and an adequate-protein diet (10% of energy from protein) (Smeets et al. 2008). Further, in a metabolic trial in which the energy

from protein was increased from 10% to 30%, plasma ghrelin remained unchanged, but after dinner GLP-1 concentrations were higher on the high-protein diet compared with the adequate-protein diet (Lejeune et al. 2006).

72.3.3 Thermic Effect of Protein

The higher thermic effect of dietary protein may be partly responsible for its satiating effect. Consuming high-protein diets results in greater levels of heat production, partly related to increased energy expenditure, compared to carbohydrate and fat, which is referred to as the thermic effect of protein or diet-induced thermogenesis (DIT). Karst et al. (1984) studied the thermic effect of three protein sources (egg white, gelatine, and casein), two carbohydrates (starch and hydrolyzed starch), and two fats (sunflower oil and butter) in 12 healthy men for 6 h. While fat produced no observed thermic effect, the thermic effect of protein was three times larger than that of carbohydrate. A review of data from 19 trials revealed that for each 1% change in energy from protein, the thermic effect of the meal increased by 0.22% (Westerterp 2004). Crovetti et al. (1998) argued that the greater thermic effect of protein relative to carbohydrate or fat might be related to satiety. Similar conclusions were made by Westerterp-Plantenga et al. (1999), Lejeune et al. (2006), and Smeets et al. (2008). In the Westerterp-Plantenga et al. (1999) study, a high-protein meal (29% of energy from protein, 61% from carbohydrate and 10% from fat) increased DIT more than that for a high fat meal (9% of energy from protein, 30% from carbohydrate, and 61% from fat). They concluded that satiety assessed by VAS was associated with the thermic effect of the diets.

The higher thermic effect of protein is believed to be related to satiety and might explain at least in part why high-protein meals promote body weight loss. The role of dietary protein in body weight regulation and underlying mechanisms has been the subject of recent reviews (Halton and Hu 2004; Moughan 2008; Westerterp-Plantenga et al. 2009). High-protein diets seem to be effective in sustaining or increasing fat-free body mass. The preservation of a higher lean mass has an added energy cost and appears to have a significant effect on resting energy expenditure. Consumption of dietary protein above the required level will increase protein turnover by increasing protein synthesis and protein breakdown in the body. All of the processes associated with high-protein diets result in a lower metabolic efficiency of energy utilization that may contribute to weight loss.

72.4 Protein Source and Food Intake and Satiety

The source of dietary protein appears to be a factor in the suppression of food intake. Some evidence indicates that consumption of milk proteins, particularly whey protein may increase satiety in animals and humans.

72.4.1 Animal Studies

Studies in animals indicate that whey protein consumption may reduce food intake more than other protein sources. Yu et al. (2009) investigated the effects of whey, soy, and gluten proteins on inter-meal interval, meal number, meal size, and meal duration in male mice. Mice fed the whey protein

diet showed the greatest reduction in energy intake over seven days and gained less weight than those fed the other protein diets. The decrease in energy intake in mice fed the whey protein diet was attributed to a low meal number and a long intermeal interval rather than a decrease in meal size. Using obese minipigs, Ferrari et al. (2005) and Dunshea et al. (2007) compared the effects of whey or soy proteins on food intake and body weight. Both studies found that obese pigs fed the high whey protein diet reduced their food intake to a greater extent than pigs fed the high soy protein diet. Furthermore, pigs fed the high-protein diets experienced less weight and fat gain than pigs fed the low-protein diets, with the greater effect demonstrated by whey protein than soy protein.

72.4.2 Human Studies

The evidence regarding a stronger effect of whey protein compared to other protein sources on satiety in humans is limited (Table 72.3). In one study, food intake at a test meal 60 min later was reduced to a greater extent after consumption of whey protein than after soy protein or egg albumen (Anderson et al. 2004). In another study, although food intake at lunch 180 min after consumption of the treatments did not differ, whey protein had a greater effect in suppressing hunger than either casein or soy (Veldhorst et al. 2009a). Within milk protein types, Hall et al. (2003) reported that whey suppressed food intake at a buffet meal 90 min later more than casein. Subjective ratings of satiety were also greater following consumption of the whey preload.

However, not all studies have found whey to have an effect on food intake and satiety. In one study, Bowen et al. (2006b) investigated the role of whey and casein proteins, relative to lactose or glucose in energy intake and satiety and in a second study, Bowen et al. (2006a) compared the effects of whey, soy, gluten, and glucose. In both studies, energy intake at a buffet lunch 3 h later was 10% higher after the glucose treatment compared with all the other preloads. There was no difference in subjective ratings for hunger, satiety, emptiness, or desire to eat between the treatments. Although the researchers observed a greater reduction in food intake after consumption of the high-protein meals than the high carbohydrate meals, they did not find any significant effect of protein source (whey, soy, gluten, and casein). The time interval of 180 min between preload and test meal may have been too long for the effect of the different protein sources on food intake to be detected.

Several studies have compared the effect of different dietary proteins on satiety but it remains unclear whether whey protein has a stronger effect on satiety than other protein sources. There is evidence for an effect of whey protein, but the situation is not definitive.

72.5 Composition of Whey Protein

It is of interest to enquire as to what properties of whey protein could lead to the purported satiety effect. Is it related to the amino acid composition of whey, peptides released upon digestion or some other attribute?

Cow's milk contains approximately 3.3% protein, and milk proteins fall into two main categories: caseins and whey proteins, as illustrated in Fig. 72.2. Caseins represent ~80% while whey proteins represent the rest (~20%) of the total milk proteins (Walstra et al. 2006). During cheese making, whey is the soluble component of milk that is separated from the casein curd. For years, whey was considered as a waste product of the cheese making process but recently, whey has become a valuable ingredient in numerous food products, particularly in protein fortified products (Walzem et al. 2002).

Table 72.3 Compilation of research studies that investigated the effects of protein source on satiety in humans

References	Subjects	Treatments	Measure	Results: food intake	Results: satiety
Anderson et al. (2004)	Thirteen normal-weight men	Fifty grams of egg albumen, whey and soy protein were placed in sweet and flavored beverages in addition to water control.	Food intake 1 h after the treatments	Whey and soy protein decreased food intake relative to the control, whereas egg protein did not.	Not measured
Bowen et al. (2006a)	Seventy-two overweight men	Liquid preloads (1.1 MJ) containing 50 g whey, soy, gluten or glucose	An ad libitum buffet lunch was served 3 h after consuming the liquid breakfast and ratings of satiety were measured after preload consumption.	Energy intake after glucose was statistically significantly higher compared to the other preloads.	No effect of treatment on subjective ratings
Bowen et al. (2006b)	Nineteen over-weight men	Liquid breakfasts (1 MJ) consisting of 50 g of whey, 55 g of casein, 56 g of lactose or 50 g of glucose	An ad libitum buffet lunch was served 180 min after consuming the liquid breakfast and ratings of satiety were measured after preload consumption.	Energy intake after glucose was statistically significantly higher compared to the other preloads and there was no difference between protein sources.	Satiety ratings did not differ significantly between the four treatments.
Hall et al. (2003)	Eight lean women and 8 men	Liquid preloads (1,700 kJ) containing 48 g of whey or casein protein	A buffet meal was served 90 min after consumption of the preloads	The whey preload reduced energy intake at buffet meal by 829 kJ or 18% compared with the casein preload.	No difference in subjective satiety ratings.
Hall et al. (2003)	Eight lean women and 1 man	Liquid preloads (1,700 kJ) containing 48 g of whey or casein protein	A fixed lunch was offered at 42 g/kg 90 minutes after preload and ratings of hunger, satiety and desire to eat were measured.	Not measured	Greater fullness and reduced desire to eat followed the whey test meal over 180 minutes.

(continued)

Table 72.3 (continued)

References	Subjects	Treatments	Measure	Results: food intake	Results: satiety
Veldhorst et al. (2009a)	Fourteen normal-weight women and 11 men	Custard breakfasts with either casein, soy or whey protein at two different energy levels (Normal Protein, 10% of E from P, 55% C, 35% F or High Protein, 25% of E from P, 55% C, 20% F)	Satiety ratings were recorded for 4 h and an ad libitum lunch was offered 180 min after the preload.	No difference between protein source and protein concentration for food intake at lunch.	There was no difference in satiety ratings between protein sources when the protein level was high (25% P). At 10% P, whey decreased hunger compared to casein or soy.

Protein source may determine the satiating effect of protein, but the evidence from studies in humans is limited. Whey protein derived from milk has been suggested as a potential protein that may contribute more strongly than other protein sources to short-term satiety in humans

h hour, min minutes, MJ megajoules, kJ kilojoules, g grams, kg kilograms; E energy, P protein, C carbohydrate, F fat
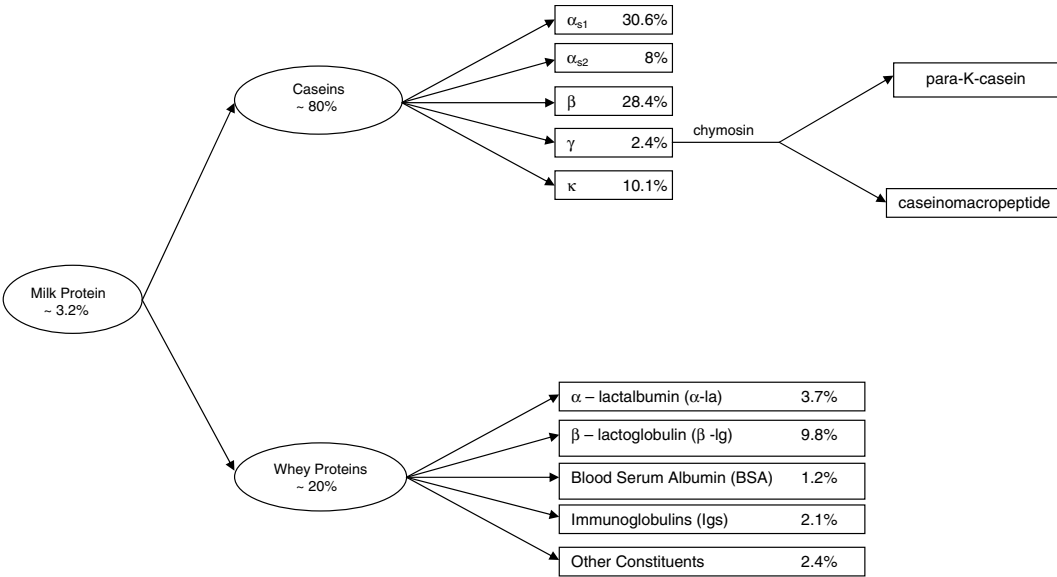
Fig. 72.2 Protein composition of bovine milk. Bovine milk contains about 3.3% protein. The two major fractions of milk proteins are casein and whey protein, which comprise about 80% and 20% of the total milk proteins. Casein and whey protein are divided into other components. During cheese making, the enzyme chymosin breaks down κ-casein into para-κ-casein and caseinomacropeptide. The latter is water-soluble and becomes part of the whey fraction (Adapted from Walstra et al. 2006, with permission. ~ = approximately; α = alpha; β = beta; γ = gamma; κ = kappa)

The nutritive value of whey protein is related to its amino acid composition as well as the high bioavailability of these amino acids. Whey protein has a very high concentration of branched chain amino acids (BCAAs). These BCAAs are thought to be beneficial to athletes and individuals looking to achieve optimal lean muscle mass as they help to increase the bioavailability of carbohydrate in the muscles and prevent muscle protein breakdown during exercise (Walzem et al. 2002). The most important components of whey proteins are β-lactoglobulin (β-lg), α-lactalbumin (α-la), bovine serum albumin (BSA), and immunoglobulins (Ig). Other nitrogenous constituents include lactoferrin, lactoperoxidase, and many other bioactive factors and enzymes. They also contains caseinomacropeptide, a polypeptide of 64 amino acid residues, formed from the action of the enzyme chymosin on κ-casein. Glycomacropeptide (GMP), the glycosylated fragment of caseinomacropeptide has been shown to stimulate the secretion of the gut hormone cholecystokinin (CCK) (Beucher et al. 1994), which may induce satiety. Glycomacropeptide would appear to be a prime candidate for explaining a satiating effect of whey. Having said this, the empirical evidence for an effect of glyco-macropeptide on satiety is not overwhelming (refer to Table 72.4).

72.6 Effect of Glycomacropeptide on Food Intake and Satiety in Humans

Caseinomacropeptide, the unglycosylated form of GMP, at doses of 0.4 and 20 g did not show any effect on food intake or subjective ratings of satiety over 1 h in a clinical trial (Gustafson et al. 2001). In our own work and with a carefully controlled study, we did not find any difference in energy intake at a cafeteria meal offered 30 min after administration of whey preloads without GMP, or with naturally present GMP or with added GMP (Chung Chun Lam et al. 2009). However, Veldhorst et al. (2009b)

Table 72.4 Compilation of human studies assessing the effects of whey protein and glycomacropeptide on food intake and subjective ratings of satiety

References	Subjects	Diets	Measure	Results: food intake	Results: satiety
Burton-Freeman (2008)	Ten normal-weight men and 10 women	Preload milkshakes (1 MJ): 1. Whey; Whey Protein isolate (44% of E from P) 2. Whey-GMP; whey protein without GMP (44% P) 3. Control; low protein (2% P) 4. GMP; GMP isolate (3% P)	Food intake 75 min after the preloads and satiety ratings recorded before and after preload consumption	No difference between preloads for food intake at the lunch test meal.	Greater satiety with Whey and Whey-GMP preloads compared to the Control preload in women. However, no difference in satiety ratings observed in men. No difference between the GMP and control preloads on subjective satiety in participants.
Chung Chun Lam et al. (2009)	Thirty-one normal-weight women and 19 men	Preload milkshakes (1.3 MJ): 1 Whey; Whey Protein isolate (8.4 g GMP) 2. Whey + GMP; Whey with added GMP (24.2 g GMP) 3. Whey-GMP; Whey without any GMP 4. Carbohydrate (maltodextrin)	A buffet lunch was served 30 min after preload administration and ratings of satiety were measured before and after preload consumption.	Equal suppression of food intake by protein preloads compared with carbohydrate.	Whey induced a greater feeling of fullness immediately after consumption of the preload compared to the other treatments.
Gustafson et al. (2001)	Thirty-two normal-weight women and 20 men	Preloads (34 J) were prepared by dissolving 0.4 or 2.0 g of CMP in a noncaloric fruit-flavored beverage vehicle.	Food intake 1 h after consuming the beverage. Participants assessed their feelings of satiety pre- and post preload and test meal and every hour until bedtime on 100 mm VAS.	No difference in food intake during test meal.	No effect of treatment on subjective ratings of satiety.
Veldhorst et al. (2009b)	Fourteen normal-weight women and 11 men	Custard breakfasts (2.5 MJ) with either whey or whey without GMP at two different energy levels (Normal Protein, 10% of E from P, 55% C, 35% F or High Protein, 25% of E from P, 55% C, 20% F).	Satiety ratings were recorded for 4 h and an ad libitum lunch was offered 180 min after the preload.	Protein concentration did not have an effect on food intake at lunch. However, there was a greater reduction in energy intake after the Whey breakfast than after the breakfast with Whey without GMP.	There was no difference in satiety ratings between protein sources but satiety ratings were higher after the normal protein breakfasts than after the high-protein breakfasts.

The presence of glycomacropeptide may be a determinant of the satiating effect of whey protein but the limited evidence from studies in humans is not strong

MJ megajoules, min minutes, J joules, E energy; P protein, GMP glycomacropeptide, WPI whey protein isolate, SMP skim milk powder

found that the presence of GMP as part of whey protein in a breakfast meal reduced energy intake at lunch, 180 min later. To test the effects of a preload containing GMP alone on food intake, feelings of satiety, and CCK release, Burton-Freeman (2008) fed 20 adults either a low-protein preload, or a whey protein preload with GMP, or a whey protein preload without GMP, or a GMP preload. Test meal intake 75 min later, subjective satiety or CCK release was not affected by whey protein or GMP. Contradictory findings on the effect of GMP on satiety may be related to differences in the dose of whey protein used and the time interval between preload and test meal. Human trials looking at the long term effect of GMP and whey protein are limited. In a 12-month randomized trial, Keogh and Clifton (2008) compared the effects of GMP-enriched whey powder versus skim milk powder meal-replacements in 127 overweight and obese subjects. Subjects who consumed the GMP-enriched whey protein meal replacement had greater weight loss after 12 months than those who consumed skim milk meal-replacements (9.9 vs. 10.8 kg), but the difference was not statistically significant. The role of GMP on CCK release and CCK-mediated satiety requires further work.

72.7 Applications to Other Areas of Health and Disease

The need to understand the regulation of food intake and the termination of eating is essential to the understanding and effective treatment of obesity and eating disorders. Obese people or individuals with eating disorders such as anorexia nervosa, bulimia nervosa, or binge eating disorder may exhibit different hunger and satiety mechanisms compared to normal-weight people or people not suffering from eating disorders. Binge eating is a central characteristic of bulimia nervosa and binge eating disorder and is defined as the consumption of a very large amount of food until the person feels uncomfortably full (American Psychiatric Association 1994).

People with bulimia nervosa and binge-eating disorder exhibit distorted satiety responses and tend to overeat throughout the day (Rossiter et al. 1992) and during binge episodes (Yanovski et al. 1992). Individuals who binge-eat were found to consume a higher proportion of energy from fat and a lower percentage of intake from protein. Hetherington et al. (1994) showed that the percentage of dietary energy from protein intake during the day was lower for women with bulimia nervosa compared with controls. Similarly, women with binge-eating disorders ate a lower proportion of energy from protein than controls when asked to binge-eat (Yanovski et al. 1992). Consumption during binge episodes in subjects suffering from binge-eating disorders was shown to be high in carbohydrates but during non-binge days, a greater amount of protein was consumed (Rossiter et al. 1992). Protein intake may assist eating-disordered and obese individuals from overeating or binge-eating.

For individuals who binge-eat, the satiating effect of different macronutrients may be a factor in the loss of control over eating. There is strong evidence that protein, in comparison with other macronutrients, is more effective in promoting satiety and suppressing food intake (Table 72.5). Latner and Wilson (2004) investigated the effect of protein on binge eating, food intake at a test meal and rated satiety in subjects with bulimia nervosa or binge-eating disorder. Over the course of 2 weeks, eighteen women with bulimia nervosa or binge eating disorder ingested a high-protein or a high-carbohydrate supplement three times daily. Food intake at test meals was reduced and subjects felt less hungry and fuller after protein supplementation compared with carbohydrate supplementation. Subjects experienced less binge eating episodes during protein supplementation than during carbohydrate supplementation. Dietary protein may in part correct the satiety impairment in people with bulimia nervosa and binge eating disorders. The role of protein in inducing satiety and reducing binge eating episodes may have some implications for the long-term treatment of eating disorders.

Table 72.5 Key features of satiety

1. Satiety is defined as the feeling of fullness that determines the time interval between two meals (the intermeal interval) and the amount of food consumed at the next eating event.
2. Foods that increase satiety offer promise to encourage an individual to prolong the intermeal interval and reduce food intake. This is useful for the overweight and people on energy-restricted diets that have difficulty achieving satiety while complying with the energy restriction.
3. Many dietary factors affect satiety including the energy density, fiber content and macronutrient composition of a food. It is widely believed that protein is the most satiating macronutrient independent of its caloric value. Whey protein derived from milk may be more effective than other protein sources in inducing satiety.
4. Three main approaches used to measure satiety:
   ▪ The time taken to request food after a test meal.
   ▪ Rating scales are used to measure subjective feelings of satiety. The most common is the visual analogue scales which are usually 100 mm long lines labeled at each end with extremes of the subjective feeling.
   ▪ Food intake at a subsequent meal.

This table lists the key features underlying the concept of satiety including the definition of satiety, why satiety is important, the dietary factors affecting satiety and the measurement of satiety

Summary

- Satiety is related to the time interval between meals and the amount of food eaten at the next eating occasion.
- Dietary protein appears to be more satiating and suppresses food intake more than carbohydrate or fat**.**
- The effect of protein on food intake and satiety may be source-dependent with whey protein derived from milk, potentially having an effect on food intake suppression and increased satiety.
- Glycomacropeptide, found in whey protein, is a peptide claimed to induce satiety by stimulating the release of the hormone cholecystokinin involved in the control of food intake.
- The mechanisms of action of protein related to food intake suppression and satiety include increased secretion of satiety-related hormones, a greater thermic effect of protein, the plasma concentration of amino acids, and possibly bioactive peptides released during digestion.
- Dietary protein may play a role in the long-term treatment of eating disorders by promoting satiety and reducing binge-eating episodes.

Key Terms

Amino acids: The building blocks of proteins.

Binge eating: The uncontrollable consumption of an excessive amount of food.

Bioactive peptides: Peptides which are active either locally in the gut or systemically to impact on a range of physiological functions, including modifying nutrient absorption and excretion, immunoregulatory effects, and antihypertensive activity. Some are released from foods during digestion.

Branched chain amino acids: Three out of the nine essential amino acids that cannot be produced by the body. They are leucine, isoleucine, and valine.

Casein protein: The major fraction of milk protein comprising of 80% of the total protein.

Energy density: The energy content in kilojoules or Calories per unit of weight or volume.

Fiber: Plant materials which are resistant to digestion by alimentary enzymes.

Glycomacropeptide: The glycosylated fragment of caseinomacropeptide, a polypeptide of 64 amino acid residues. When milk is treated with the enzyme chymosin during the formation of

cheese curd, caseinomacropeptide is released from bovine kappa-casein and moves out of the curd with the whey fraction.

Peptide: Two or more amino acids chained together by a bond. Peptides can serve as messengers within the body such as enzymes, hormones, antibodies, and structural components.

Satiety: The feeling of fullness that occurs after eating a meal.

Visual analogue scales: A subjective measure of satiety. The scale is usually 100 or 150 mm long labeled at each end with extremes of the subjective feeling to be quantified.

Thermic effect of food or diet-induced thermogenesis: Levels of heat produced during the absorption and metabolism of ingested nutrients and partly related to energy expenditure.

Whey protein: The soluble component of milk that is separated from the casein curd during cheese making and represents 20% of the total milk protein.

References

American Psychiatric Association. Diagnostic and statistical manual of mental disorders. Washington: American Psychiatric Association; 1994.

Anderson GH, Moore SE. J Nutr. 2004;134:974S–9S.

Anderson GH, Tecimer SN, Shah D, Zafar TA. J Nutr. 2004;134:3011–5.

Baba NH, Sawaya S, Torbay N, Habbal Z, Azar S, Hashim SA. Int J Obes. 1999;23:1202–6.

Barkeling B, Rössner S, Björvell H. Int J Obes. 1990;14:743–51.

Bellissimo N, Desantadina MV, Pencharz PB, Berall GB, Thomas SG, Anderson GH. Int J Obes. 2007;32:362–71.

Beucher S, Levenez F, Yvon M, Corring T. J Nutr Biochem. 1994;5:578–84.

Bjorntorp P. International textbook of obesity. New York: Wiley; 2001.

Blundell JE, Lawton CL, Cotton JR, Macdiarmid JI. Annu Rev Nutr. 1996;16:285–319.

Booth DA, Chase A, Campbell AT. Physiol Behav. 1970;5:1299–1302.

Bowen J, Noakes M, Clifton PM. J Clin Endocrinol Metab. 2006a;91:2913–9.

Bowen J, Noakes M, Trenerry C, Clifton PM. J Clin Endocrinol Metab. 2006b;91:1477–83.

Burton-Freeman B. J Nutr. 2000;130:272S–5S.

Burton-Freeman B. Physiol Behav. 2008;93:379–87.

Chung Chun Lam SMS, Moughan PJ, Awati A, Morton HR. Physiol Behav. 2009;96:162–8.

Crovetti R, Porrini M, Santangelo A, Testolin G. Eur J Nutr. 1998;52:482–8.

de Graaf C, Hulshof T, Weststrate JA, Jas P. Am J Clin Nutr. 1992;55:33–8.

Dunshea FR, Ostrowska E, Ferrari JM, Gill HS. Aust J Exp Agric. 2007;47:1051–9.

Eisenstein J, Roberts SB, Dallal G, Saltzman E. Nutr Rev. 2002;60:189–200.

Ferrari JM, Ostrowska E, Muralitharan M, Tatham BG, McCauley I, Cox ML, Eason PJ, Kerton DJ, Dunshea FR. FASEB J. 2005;19:A1478.

Geliebter AA. Physiol Behav. 1979;22:267–73.

Gustafson DR, McMahon DJ, Morrey J, Nan R. Appetite. 2001;36:157–63.

Hall WL, Millward DJ, Long SJ, Morgan LM. Br J Nutr. 2003;89:239–48.

Halton TL, Hu FB. J Am Coll Nutr. 2004;23:373–85.

Hetherington MM, Altemus M, Nelson ML, Bernat AS, Gold PW. Am J Clin Nutr. 1994;60:864–73.

Holt SH, Miller JC, Petocz P, Farmakalidis E. Eur J Nutr. 1995;49:675–90.

Howarth NC, Saltzman E, Roberts SB. Nutr Rev. 2001;59:129–39.

Johnson J, Vickers Z. Appetite. 1993;21:25–39.

Karst H, Steininger J, Noack R, Steglich HD. Ann Nutr Metab. 1984;28:245–52.

Keogh JB, Clifton P. Am J Clin Nutr. 2008;87:1602–5.

Kissileff HR, Gruss LP, Thornton J, Jordan HA. Physiol Behav. 1984;32:319–32.

Kissileff HR, Van Itallie TB. Ann Rev Nutr. 1982;2:371–418.

Latner JD, Schwartz M. Appetite. 1999;33:119–28.

Latner JD, Wilson GT. Int J Eat Disord. 2004;36:402–15.

Layman DK, Boileau RA, Erickson DJ, Painter JE, Shiue H, Sather C, Christou DD. J Nutr. 2003;133:411–7.

Lejeune MPGM, Westerterp KR, Adam TCM, Luscombe-Marsh ND, Westerterp-Plantenga MS. Am J Clin Nutr. 2006;83:89–94.

Marmonier C, Chapelot D, Louis-Sylvestre J. Appetite. 2000;34:161–8.

Mellinkoff SM, Frankland M, Boyle D, Greipel M. J Appl Physiol. 1956;8:535–8.

Moughan PJ. In: Thompson A, Boland M, Singh H, editors. Milk proteins: from expression to food. London: Academic; 2008. pp. 483–99.

Poppitt SD, McCormack D, Buffenstein R. Physiol Behav. 1998;64:279–85.

Porrini M, Crovetti R, Testolin G, Silva S. Appetite. 1995;25:17–30.

Raben A, Agerholm-Larsen L, Flint A, Holst JJ, Astrup A. Am J Clin Nutr. 2003;77:91–100.

Rolls BJ, Fedoroff IC, Guthrie JF, Laster LJ. Appetite. 1990;15:115–26.

Rolls BJ, Hammer VA. Am J Clin Nutr. 1995;62:1086S–95S.

Rossiter EM, Agras WS, Telch CF, Bruce B. Int J Eat Disord. 1992;11:111–20.

Rutherfurd-Markwick KJ, Moughan PJ. J AOAC Int. 2005;88:955–66.

Skov AR, Toubro S, Rønn B, Holm L, Astrup A. Int J Obes. 1999;23:528–36.

Smeets AJ, Soenen S, Luscombe-Marsh ND, Ueland O, Westerterp-Plantenga MS. J Nutr. 2008;138:698–702.

Stubbs J, Ferres S, Horgan G. Crit Rev Food Sci Nutr. 2000;40:481–515.

Stubbs RJ, Van Wyk MC, Johnstone AM, Harbron CG. Eur J Clin Nutr. 1996;50:409–17.

Van Itallie TB, Vanderweele DA. In: Howard AN, editor. Recent advances in obesity research. London: Newman; 1981. pp. 278–88.

Vandewater K, Vickers Z. Physiol Behav. 1996;59:579–83.

Veldhorst MAB, Nieuwenhuizen AG, Hochstenbach-Waelen A, van Vught AJAH, Westerterp KR, Engelen MPKJ, Brummer R-JM, Deutz NEP, Westerterp-Plantenga MS. Physiol Behav. 2009a;96:675–82.

Veldhorst MAB, Nieuwenhuizen AG, Hochstenbach-Waelen A, Westerterp KR, Engelen MPKJ, Brummer R-JM, Deutz NEP, Westerterp-Plantenga MS. Appetite. 2009b;52:388–95.

Vozzo R, Wittert G, Cocchiaro C, Tan WC, Mudge J, Fraser R, Chapman I. Appetite. 2003;40:101–7.

Walstra P, Wouters JTM, Geurts TJ. Dairy science and technology. Boca Raton: CRC; 2006.

Walzem RL, Dillard CJ, German JB. Crit Rev Food Sci Nutr. 2002;42:353–75.

Weigle DS, Breen PA, Matthys CC, Callahan HS, Meeuws KE, Burden VR, Purnell JQ. Am J Clin Nutr. 2005;82:41–8.

Westerterp K. Nutr Metab. 2004;1:1–5.

Westerterp-Plantenga MS, Rolland V, Wilson SA, Westerterp KR. Eur J Clin Nutr. 1999;53:495–502.

Westerterp-Plantenga MS, Nieuwenhuizen A, Tome D, Soenen S, Westerterp KR. Annu Rev Nutr. 2009;29:21–41.

Yanovski SZ, Leet M, Yanovski JA, Flood M, Gold PW, Kissileff HR, Walsh BT. Am J Clin Nutr. 1992;56:975–80.

Yu Y, South T, Huang X-F. Appetite. 2009;52:372–9.

Part X
General and Normative Aspects: Fatty Acids

Chapter 73
Dietary n-3 Polyunsaturated Fatty Acids and Brain Lipid Fatty Acid Composition

Gudrun V. Skuladottir

Abbreviations

ALA	α-Linolenic acid (18:3n-3)
DHA	Docosahexaenoic acid (22:6n-3)
DPA	Docosapentaenoic acid (22:5n-3)
EPA	Eicosapentaenoic acid (20:5n-3)
PC	Phosphatidylcholine
PE	Phosphatidylethanolamine
PI	Phosphatidylinositol
PL	Phospholipids
PS	Phosphatidylserine
PUFA	Polyunsaturated fatty acids
SM	Sphingomyeline

73.1 Introduction

In the mammalian brain, the major polyunsaturated fatty acids (PUFA) in neuronal membrane lipids are the n-3 PUFA docosahexaenoic acid (DHA, 22:6n-3) and the n-6 PUFA arachidonic acid (20:4n-6) (Sastry 1985). The main source of both these PUFA is the diet. The n-3 PUFA found in the diets are α-linolenic acid (ALA, 18:3n-3), eicosapentaenoic acid (EPA, 20:5n-3), and DHA, and the n-6 PUFA is linoleic acid (18:2n-6) and 20:4n-6. Metabolic studies on healthy humans have shown that in contrast to EPA, ALA is not efficiently converted to DHA. ALA is more rapidly oxidized than the 20- and 22-carbons n-3 PUFA, which decreases the availability of ALA for conversion to the EPA and DHA in liver (reviewed in Burdge and Calder 2005; Pawlosky et al. 2001). It has been suggested that the metabolism of n-3 PUFA in the brain depends both on the diet and the liver (Rapoport et al. 2007). The limited conversion of dietary ALA into EPA and DHA in the body might lead to an amount in brain lipids that is not sufficient to meet physiological needs.

—————————————
G.V. Skuladottir (✉)

Department of Physiology, Faculty of Medicine, School of Health Sciences, University of Iceland, Vatnsmyrarvegi 16, IS-101 Reykjavik, Iceland
e-mail: gudrunvs@hi.is

Phospholipids (PL) are the fundamental building blocks of cell membranes, and the PL bilayers of the membrane form a stable barrier between two aqueous compartments and represent the basic structure of all biological membranes. The DHA and 20:4n-6 incorporated into the cell membrane PL of the central nervous system increase the fluidity of the membranes, which is an important feature for normal functioning of the central nervous system (reviewed in Horrocks and Farooqui 2004).

The ratio of n-6/n-3 PUFA in the human diet has changed from being ~1 in preagricultural times to 15–16.7:1 in the modern Western diet (Simopoulos 2006). This change is attributed both to increased intake of n-6 PUFA and to decreased intake of n-3 PUFA, particularly n-3 long chain (C ≥ 20) PUFA. The balance of the different types of dietary PUFA is important to fetal and postnatal development, and for beneficial health outcomes throughout life. In the present chapter an attempt is made to give an overview of the fatty acid composition in healthy mammalian brain lipids associated with balanced dietary n-6 PUFA and n-3 PUFA, gender, and aging.

73.2 n-3 Polyunsaturated Fatty Acids (PUFA)

PUFA are chains of 18 carbons or more in length, with hydrogens attached and with two or more double bonds between the carbons in the chain. PUFA are designated by the number of their carbons and double bonds. The location of the first carbon, where the first double bond appears, is counted from the methyl (n-) end of fatty acid. The n-3 PUFA have the first double bond at carbon number three, counted from the methyl end (Fig. 73.1): α-linolenic acid (ALA, 18:3n-3) with 18 carbons and three double bonds, and docosahexaenoic acid (DHA, 22:6n-3) with 22 carbons and six double bonds. PUFA with the first double bond at carbon number six from the methyl (n-) end are termed n-6 PUFA.
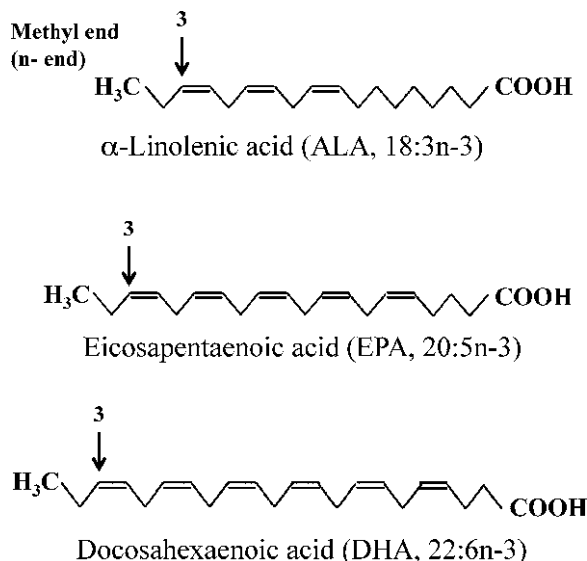
Fig. 73.1 Structure models of the n-3 polyunsaturated fatty acids (PUFA) α-linolenic acid (ALA, 18:3n-3) and its derivatives, the eicosapentaenoic acid (EPA, 20:5n-3) and docosahexaenoic acid (DHA, 22:6n-3). PUFA are designated by the number of their carbons and double bonds. The location of the first carbon, where the first double bond appears, is counted from the methyl (n-) end of fatty acid. The n-3 PUFA have the first double bond at carbon number three, counting from the methyl end. Neither carbon nor hydrogen is shown in the fatty acid chains

73.2.1 Essential Fatty Acids

The major PUFA in mammalian brain are the n-3 PUFA DHA and the n-6 PUFA arachidonic acid (20:4n-6). Mammals lack the necessary enzymes to synthesize the precursors ALA and linoleic acid (18:2n-6) of DHA and 20:4n-6 respectively. ALA is an essential nutrient for mammals in growth and development throughout the life span. Liver and brain of mammals have an enzyme system that desaturates and elongates ALA to make its longer-chain derivatives EPA and DHA. However, the liver is the primary site for essential fatty acid metabolism, where the first part of this pathway takes place in the endoplasmic reticulum and consists of sequential alternating elongation and desaturation steps catalyzed by fatty acid elongases and desaturases (Nakamura et al. 2001). The mechanism of the final conversion to DHA occurs via the so-called Sprecher pathway (Fig. 73.2) (Sprecher et al. 1995).

Both the precursors ALA and 18:2n-6 are essential fatty acids, since mammals have to obtain them from food. ALA is mainly found in green leafy vegetables, soybean, flax seed, and canola oil. Many studies indicate that the conversion of ALA to DHA is limited in the human body, and it is debated whether dietary ALA can fulfill the needs of the human body or whether dietary intake of preformed DHA is necessary. EPA and DHA are found in seafood. The solar energy (photosynthesis) and the necessary enzymes enable the phytoplankton to synthesize ALA, EPA, and DHA. These n-3 PUFA ascend the food chain, in zooplanktons, pelagic fish (such as herring, capelin, and tuna), and benthic fish (such as halibut and cod). Then n-3 PUFA ascend in the tissue of terrestrial animals when farmers manipulate animal feed in an attempt to increase n-3 PUFA content of meat, milk, and eggs (Fig. 73.3) (Enser et al. 1996; Kris-Etherton et al. 2000; Sanders, 2000). Specific 18:2n-6
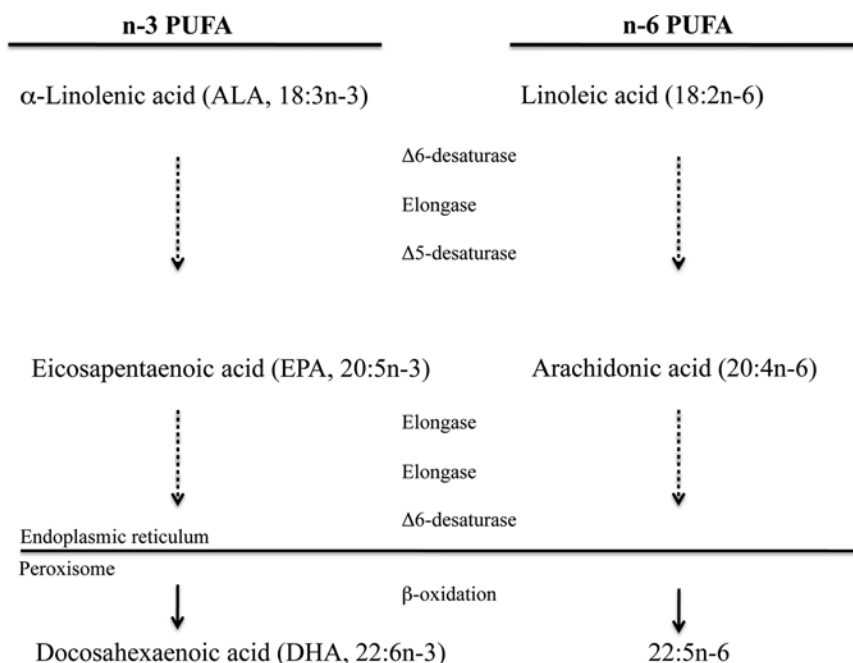
Fig. 73.2 A schematic representation of the biosynthetic pathways for the n-3 polyunsaturated fatty acids (PUFA) and n-6 PUFA. The same enzyme system desaturates and elongates the essential n-3 PUFA and n-6 PUFA, α-linolenic acid (ALA, 18:3n-3) and linoleic acid (18:2n-6) to their longer chain derivatives: eicosapentaenoic acid (EPA, 20:5n-3), docosahexaenoic acid (DHA, 22:6n-3), and arachidonic acid (20:4n-6). Sprecher et al. (1995) re-evaluated the pathways for the biosynthesis of n-3 and n-6 PUFA and demonstrated that the final step for n-3 PUFA takes place in peroxisome, where C24:6n-3 is converted to DHA in one step of β-oxidation
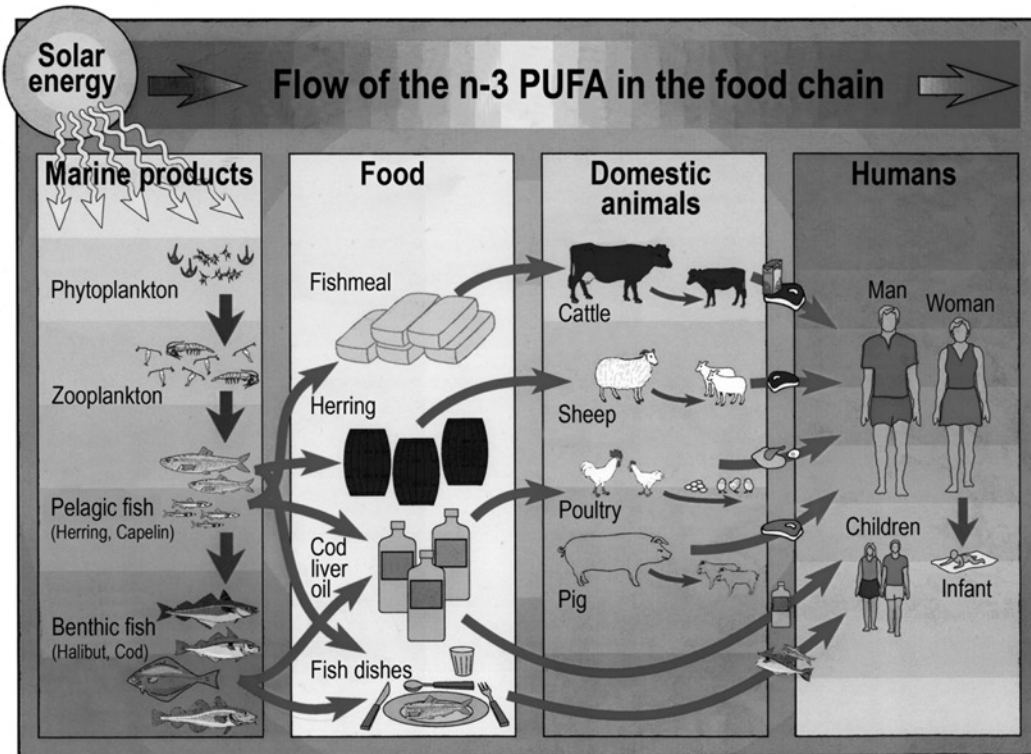
Fig. 73.3 A schematic flow of n-3 polyunsaturated fatty acids (PUFA) in the food chain. Marine products: The solar energy (photosynthesis) and the necessary enzymes enable the phytoplankton to synthesize α-linolenic acid (ALA, 18:3n-3), eicosapentaenoic acid (EPA, 20:5n-3), and docosahexaenoic acid (DHA, 22:6n-3). These n-3 PUFA ascend the food chain in zooplankton, pelagic fish (such as herring, capelin and tuna), and benthic fish (such as halibut and cod). Food: Marine products include: fishmeal produced from herring and capelin, cod liver oil, and fish. Domestic animals: Dietary n-3 PUFA of cattle, sheep, poultry, and pigs are reflected in blood, muscle, and other tissues of the domestic animals when farmers manipulate animal feed with fishmeal and/or fish oil in an attempt to increase n-3 PUFA content of meat, milk, and eggs. Humans: Dietary n-3 PUFA intake is reflected in blood plasma lipids and in cell membrane lipids of tissues and organs of the human body

deficiency does not seem to occur in the human body, since it is present in variable quantities in many plant oils. In the mammalian body, 18:2n-6 is converted to 20:4n-6 (Fig. 73.2) (Sprecher et al. 1995), and 20:4n-6 is also found in meat and eggs.

73.3 Brain DHA Sources

In humans, during growth, development, and aging, the brain DHA content is largely determined by dietary fatty acid composition. Most DHA accumulation in the brain takes place during brain development from the beginning of the last trimester of gestation to 2 years after birth (Dobbing and Sands 1979; Martinez 1992). Therefore, the supply of DHA has to be substantial in order to meet the demands of human growth during the last trimester of gestation and postnatal (Clandinin et al. 1980a,b). At birth, the DHA status in the human infant brain reflects maternal n-3 PUFA status during pregnancy (van Houwelingen et al. 1995). The DHA sources of neonates are DHA in adipose

tissue (Van Duyne and Havel 1959) and breast milk DHA or milk with preformed DHA (Makrides et al. 1994). Neonates that are not breast fed need a diet containing preformed DHA, since the DHA stores at birth will be used up within the first 2 months after birth (Farquharson et al. 1993). After weaning, the sources for DHA in brain membrane lipids are derived from the diet, from liver conversion of the respective dietary precursors ALA and EPA (Fig. 73.2), or from body stores (Spector 2001; Lefkowitz et al. 2005; Chen and Cunnane 1992).

73.4 Brain Lipids

In the mammalian brain, about 50% of the dry weight consists of lipids (Sastry 1985). A variety of complex lipids exist in the brain, and the composition and metabolism of these lipids change with development, age, and diet. Phospholipids (PL) are the major components of the neuronal membranes of the gray matter of the brain. PL is highly polar, with its two fatty acids being hydrophobic, and the water-soluble head group consisting of phosphorus and either choline, ethanolamine, inositol, or serine (Fig. 73.4). The PL classes are phosphatidylcholine (PC), phosphatidylethanolamine (PE), phosphatidylinositol (PI), or phosphatidylserine (PS). This polar nature of PL confers on the property of forming bilayer membranes in aqueous media: the hydrophobic fatty acids face inward toward the core of the membrane, and the head groups face outward toward the water. The fatty acids of most natural PL have one or more double bonds, which introduce kinks into the hydrocarbon chains and make them difficult to pack together. The long hydrocarbon chains of the fatty acids therefore move freely in the interior of the membrane, the membrane itself is flexible, which is an important feature of the physical properties of all cell membranes.

The PL classes PC, PI, PS, PE, which contain two fatty acids each, and sphingomyeline (SM), which contains only one fatty acid, are asymmetrically distributed between the two leaflets of the membrane bilayer. It has been established that PC and PE are the major classes of PL in human brain, and that PS and PI make up the balance (Söderberg et al. 1991). The outer leaflet of the membrane consists mainly of PC and SM, whereas PE, PI, and PS are the predominant PL of the inner leaflet.
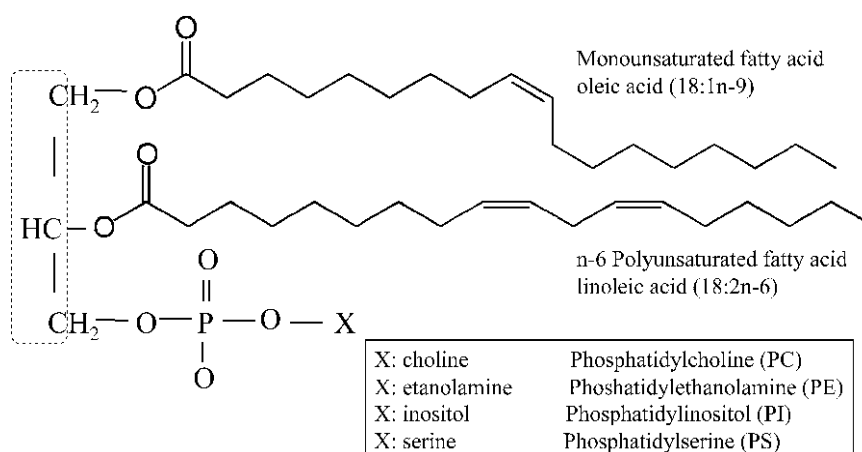
Fig. 73.4 A structural form of phospholipids (PL), the major components of cell membranes in gray matter of the brain. The three-carbon backbone glycerol has attached fatty acids at the first and second carbons. A phosphorus is attached to the third carbon, and a water-soluble head group consisting either of choline (phosphatidylcholine, PC), ethanolamine (phoshatidylethanolamine, PE), inositol (phosphatidylinositol, PI), or serine (phosphatidylserine, PS) is attached to the other side of the phosphorus

73.4.1 Fatty Acid Composition

The brain PL of the grey matter are particularly rich in DHA and 20:4n-6. No ALA and only a trace amount of EPA are detected in brain PL. SM contains mostly saturated fatty acids and rarely 20:4n-6 and DHA. The analysis of fatty acid composition of human and animal brain lipids has been performed either in total lipids, total PL, or separate PL classes from whole brain or brain regions. In animals it has been demonstrated that the DHA levels in brain are different, both between regions (Chung et al. 2008; Levant et al. 2006; Xiao et al. 2005; Diau et al. 2005; Carrié et al. 2000) and between PL classes (Petursdottir et al. 2007; Söderberg et al. 1991). Chung et al. (2008) studied the fatty acid composition of total lipids in five brain regions from 4.7-month-old Sprague-Dawley rats fed a control diet. They demonstrated that the levels of DHA and 20:4n-6 in total lipids were region-specific, ranging from 11.1–17.7% and 8.3–13.5% of total fatty acids, respectively (Fig. 73.5). Petursdottir et al. (2007) studied the fatty acid composition of PC, PS, PI, and PE in hippocampus and amygdala in 4-month-old male senescence-accelerated prone mice (SAMP8) that were fed a control diet (Fig. 73.6). They found that both in hippocampus and amygdala, PS and PE contained the highest
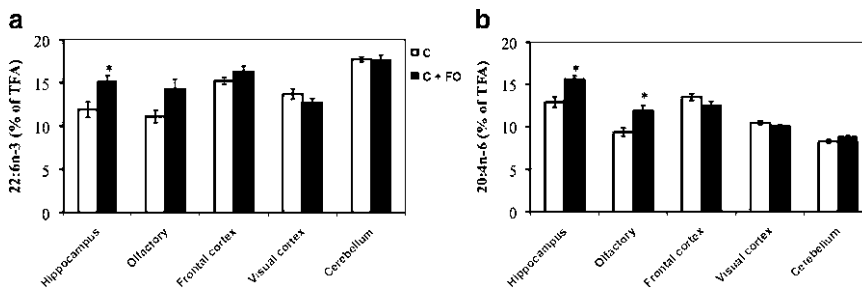
Fig. 73.5 Effects of dietary n-3 polyunsaturated fatty acids (PUFA) on the levels (% of total fatty acids [TFA]) of docosahexaenoic acid (DHA, 22:6n-3) (**a**), and arachidonic acid (20:4n-6) (**b**) in total lipids of brain regions from 4.7-month-old male Sprague-Dawley rats. The rats were fed a control diet containing fish oil (C+FO group; dietary n-6 PUFA/n-3 PUFA = 0.13, where 23.7% EPA, 22:5n-3, and DHA were included), or a control diet (C group; dietary n-6 PUFA/n-3 PUFA = 8, where 1.8% EPA and DHA were included). Values are mean ± SEM, n = 9–11. *$P < 0.05$, compared to rats fed the control diet (Based on data from Chung et al. 2008)
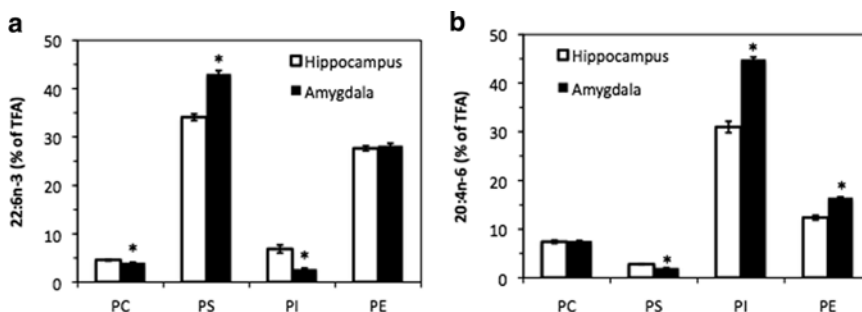
Fig. 73.6 The levels (% of total fatty acids [TFA]) of docosahexaenoic acid (DHA, 22:6n-3) (**a**) and arachidonic acid (20:4n-6) (**b**) in phosphatidylcholine (PC), phosphatidylserine (PS), phosphatidylinositol (PI), and phosphatidylethanolamine (PE) of hippocampus and amygdala from 4-month-old male senescence-accelerated prone mice (SAMP8). The mice were fed a control diet (n-6 PUFA/n-3 PUFA = 7.3) with trace amounts (0.6%) of EPA and DHA. Values are mean ± SEM, n = 8–10 preparations. *$P < 0.05$, compared to hippocampus (Based on data from Petursdottir et al. 2007)

levels of DHA (34.0% ± 0.69% and 43.03% ± 0.69%, 27.63% ± 0.51%, and 28.2% ± 0.48%, respectively) compared to the other PL classes, and that PI in amygdala contained the highest level (44.88% ± 0.49%) of 20:4n-6 compared to that in the hippocampus and the other PL classes. Furthermore, the level of DHA was higher in PS and lower in PI of the amygdala than in the hippocampus (43.03% ± 0.69% versus 34.0% ± 0.69%, 2.71% ± 0.2% and 6.87% ± 0.84%, respectively).

73.4.2 Dietary n-6/n-3 PUFA Ratio

As modern Western diet contains much more 18:2n-6 than ALA, most of the PUFA products in liver are 20:4n-6, since high levels of 18:2n-6 compete with ALA for the Δ6 desaturase (Fig. 73.2) (Rahm and Holman 1964). Nutritional interventional trial designed to determine whether in vivo conversion of dietary ALA is influenced by the 18:2n-6/ALA ratio or by the absolute amounts of 18:2n-6 or ALA in the human diet demonstrated that the dietary 18:2n-6/ALA ratio is not a determinant of the n-3 PUFA conversion (Goyens et al. 2006). It was reported that an increase in EPA synthesis can be obtained by lowering the amount of 18:2n-6 in the diet, whereas an increase in DHA synthesis is achieved by increasing the amount of dietary ALA. Recently, a study reported that higher DHA content was found in PE, PS, and PC of frontal cortex from piglets when fed a diet providing 1.1% energy from 18:2n-6 with a dietary 18:2n-6/ALA ratio close to 1 compared to that from piglets fed a diet providing 10.7% energy from 18:2n-6 with a dietary 18:2n-6/ALA ratio close to 10 (Novak et al. 2008). The elevated levels of DHA in PE, PS, and PC were compensated for by lower levels of 20:4n-6.

In rats and mice whose brains grow postnatally, studies have shown that diets, which are nutritionally adequate but differ in the fatty acid composition, can modify the fatty acid composition of the adult brain. When studying the dietary PUFA effect on fatty acid composition of these animal brain lipids, the control diet during development corresponded to the 18:2n-6/ALA ratio of 6–7 (Bourre et al. 1990). Chung et al. (2008) studied in rats the effect of fish oil supplementation (dietary n-6/n-3 PUFA ratio=0.13, with 23.7% total of EPA, 22:5n-3 and DHA) on the fatty acid composition of total lipids in five brain regions during development and adulthood. They found that the total lipids of hippocampus and olfactory bulb accumulated more DHA and 20:4n-6 in the fish oil supplemented rats than in those of the control rats (dietary n-6 PUFA/n-3 PUFA=7.97, with 1.8% total of EPA and DHA) (Fig. 73.5). The fish oil supplementation did not affect the total lipid levels of DHA and 20:4n-6 in frontal cortex, visual cortex, and cerebellum. However, studies have shown that dietary DHA competes with 20:4n-6 for incorporation into brain PL classes (Gamoh et al. 1999; Suzuki et al. 1998). A study on 10-month-old mice fed high-DHA diet for 8 weeks has demonstrated that PC, PI, and PE in hippocampus and amygdala contained higher DHA levels, and that PC, PS, PI, and PE contained lower 20:4n-6 levels than when mice were fed low-DHA diet (Fig. 73.7) (Petursdottir et al. 2008). The reason the DHA levels of PS in both hippocampus and amygdala were not affected by the high-DHA diet could be that PS contains the highest level of DHA compared to the other PL classes, and that an upper threshold for the incorporation of dietary n-3 PUFA has been reached (Venkatraman et al. 1992). The n-6/n-3 PUFA ratio was 0.1 (26% EPA and DHA included) and 7.4 (0.6% of EPA and DHA included) in the high-DHA diet and the low-DHA diet, respectively.

73.4.3 Gender

It has been suggested that gender has an important influence on DHA content of tissues, and this has been explained by the role of estrogen on DHA biosynthesis (Childs et al. 2008; Giltay et al. 2004). Studies have shown that when the dietary precursor ^{13}C labeled ALA is given to healthy adults,
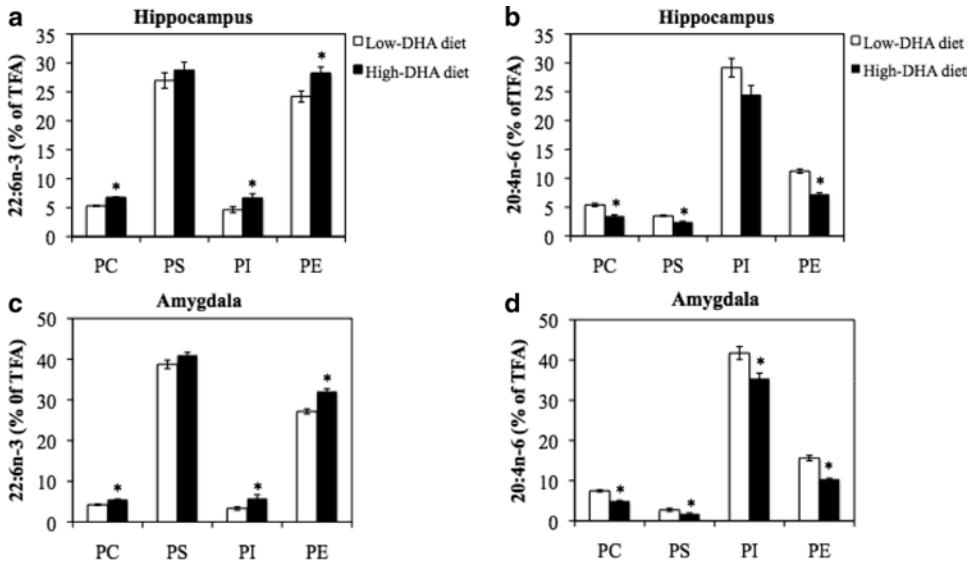
Fig. 73.7 Effects of dietary n-3 polyunsaturated fatty acids (PUFA) on the levels (% of total fatty acids [TFA]) of docosahexaenoic acid (DHA, 22:6n-3) and arachidonic acid (20:4n-6) in phosphatidylcholine (PC), phosphatidylserine (PS), phosphatidylinositol (PI), and phosphatidylethanolamine (PE) of hippocampus (**a** and **b**), and of amygdala (**c** and **d**) from 12-month-old male senescence-accelerated prone mice (SAMP8). The 10-month-old mice were fed low-DHA diet (n-6 PUFA/n-3 PUFA=7.4) for 8 weeks with trace amounts (0.6%) of EPA and DHA included, or a high-DHA diet (n-6 PUFA/n-3 PUFA = 0.1, where 26% EPA and DHA were included). Values are mean ± SEM, n = 8–10 preparations. *$P < 0.05$, compared to mice fed a low-DHA diet (Based on data from Petursdottir et al. 2008)

endogenous biosynthesis of DHA from ALA is higher in women than men (reviewed in Burdge and Calder, 2005; Pawlosky et al. 2003), and that women exhibit greater circulating plasma DHA than men under similar dietary conditions (Crowe et al. 2008; Bakewell et al. 2006; Giltay et al. 2004). Recently, preliminary data have shown that the AA/DHA ratio in postmortem prefrontal cortex from humans was greater in adolescent males than females irrespective of cause of death (McNamara et al. 2009). This preliminary data support the hypothesis of hormonal regulation of PUFA metabolism.

73.4.4 Aging

A direct comparison between data on age-related effects on brain lipid fatty acid composition is impossible, because the analysis of fatty acid composition in brain has been performed either in total lipids, total PL or in separate PL classes from whole brain or brain regions, and secondly, the n-6/n-3 PUFA ratio of the subjects diet might be variable throughout the life. And last but not at least, when studying age-related effects on lipid content and fatty acid composition of postmortem brain, one has to take in account the effects of postmortem storage conditions, such as time and temperature.

A study on the membrane lipid composition of frontal and temporal cortices and white matter in human subjects (20–100 years) who had died suddenly and unexpectedly demonstrated that total PL content began to decrease as early as ~20 years of age in both frontal and temporal cortices (Svennerholm et al. 1994). On the other hand, human study on normal subjects (33–92 years) reported that age had no influence on the fatty acid compositions of PE and PC from frontal gray matter, frontal white matter, hippocampus, and in the pons (Söderberg et al. 1991). Another study on

young (13–19 years) normal subjects reported that the 20:4n-6/DHA ratio in total lipids of frontal cortex was negatively correlated with age at death (McNamara et al. 2009). Rhesus monkeys fed the same control diet (18:2n-6/18:3n-3 ratio 53.1:7.7) as their mothers during pregnancy had higher levels of DHA and lower levels of 20:4n-6 and 22:5n-6 in frontal cortex PE and PS after two to three postnatal years than at birth (Anderson et al. 2005). Compared to 2-month-old male rats fed the control diet (18:2n-6/18:3n-3 ratio 18.2:3.0), the hippocampus of 18-month-old rats contained lower levels of DHA in PE and PS (Favreliére et al. 2003). This age-related decrease in DHA levels of PE and PS was replaced by the monounsaturated fatty acid oleic acid (18:1n-9) at 18 months. The levels of DHA and 18:1n-9 persisted at 21 months compared to 18-month-old rats. Human and animal studies on age-related changes in fatty acid composition in the brain lipids are inconsistent, and the main reason for this is probably the different PUFA composition of the subject diets. On the other hand, the data from these age-related studies on the fatty acid composition of brain lipids indicate that fatty acid analysis of PL classes, rather than total lipids, will produce more reliable data on the modification of fatty acids in cell membrane phospholipids during aging.

73.5 Applications to Other Areas of Health and Disease

In mammals, DHA content in the brain is largely determined by type and content of dietary PUFA during growth, development, and aging (Fig. 73.8). Studies on dietary PUFA and PUFA in brain lipids associated with development and diseases indicate that dietary DHA is important for fetal and postnatal development (Innis 2009), and for health outcomes during aging (Calder and Yaqoob
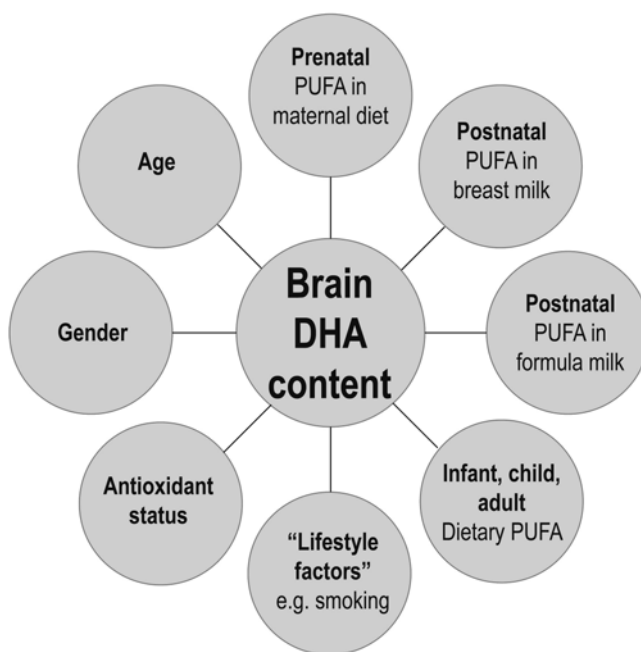
Fig. 73.8 Key features on the factors that can affect docosahexaenoic acid (DHA, 22:6n-3) content in mammalian brain lipids. Brain DHA content can be affected by dietary fatty acid composition during intrauterine and extrauterine growth, development and aging, other lifestyle factors such as smoking, the antioxidant status in the body, gender, and aging

2009). Low DHA content in brain lipids has been linked to a variety of neurological disorders, such as impaired cognitive and sensory functions, psychiatric disorders, cardiovascular disease, diabetes, cancer, and degenerative diseases. Fortunately, several studies in young and aged animals have demonstrated that DHA deficiency in brain regions is reversible. However, due to the high content of DHA in brain relative to other organs, lipid peroxidation is thought to be one of the major outcomes of free radical-mediated injury to brain (Montine et al. 2002). Although healthy organisms possess an efficient antioxidant defense system, they might need nutritional compounds with antioxidant defense (such as lipoic acid, vitamin E, and vitamin C) to minimize lipid peroxidation in the body.

In summary, the data demonstrate that the n-3 PUFA content of lipids in mammalian brain regions is differently affected by type and content of dietary PUFA, gender, and age, which might contribute to changes in neuronal functions. Further studies are needed to estimate the dietary balance of n-3 and n-6 PUFA needed at different age stages to provide the conditions for normal neurological development and beneficial health outcomes.

Summary Points

- DHA is the major n-3 PUFA in neuronal membrane lipids in mammalian brain.
- DHA incorporated into cell membrane PL of the central nervous system increase the fluidity of membranes, which is an important feature for normal functioning of the central nervous system.
- Dietary n-3 PUFA are essential for mammals.
- Dietary n-3 PUFA maternal intake is especially important during gestation and breastfeeding for pre- and postnatal development of the offspring.
- DHA content of lipids in different brain regions is affected by dietary PUFA, gender and age.
- Relatively low DHA content in brain lipids is associated with disturbed neurological functions.

Definitions

α-Linolenic acid (ALA, 18:3n-3): An n-3 polyunsaturated fatty acid (PUFA) with 18 carbons and three double bonds. ALA is an essential fatty acid, and is mainly found in green leafy vegetables, soybean, flax seed, canola oil, and marine plants (phytoplankton). In animals, ALA is the precursor of the longer chain (C ≥ 20) n-3 PUFA eicosapentaenoic acid (EPA, 20:5n-3), docosapentaenoic acid (22:5n-3) and docosahexaenoic acid (DHA, 22:6n-3).

Arachidonic acid (20:4n-6): An n-6 polyunsaturated fatty acid (PUFA) with 20 carbons and four double bonds. It is found in meat and eggs. In animals, 20:4n-6 is synthesized from the linoleic acid (18:2n-6). The phospholipids (PL) of the grey matter in brain are particularly rich in 20:4n-6, as well as in DHA.

Docosahexaenoic acid (DHA, 22:6n-3): An n-3 polyunsaturated fatty acid (PUFA) with 22 carbons and six double bonds. DHA is mainly found in marine products. In animals, DHA is synthesized from α-linolenic acid (ALA, 18:3n-3) and eicosapentaenoic acid (EPA, 20:5n-3). DHA represents the longest and the most unsaturated fatty acid commonly found in biological systems.

Eicosapentaenoic acid (EPA, 20:5n-3): An n-3 polyunsaturated fatty acid (PUFA) with 20 carbons and five double bonds. EPA is mainly found in marine products. In animals, EPA is synthesized from α-linolenic acid (ALA, 18:3n-3).

Essential fatty acids: Animals lack the necessary enzymes to synthesize α-linolenic acid (ALA, 18:3n-3) and linoleic acid (18:2n-6) and have to obtain them from the diet. Those two fatty acids are essential because they are the precursors of the longer chain n-3 polyunsaturated fatty acid (PUFA) eicosapentaenoic acid (EPA, 20:5n-3) and docosahexaenoic acid (DHA, 22:6n-3), and the n-6 PUFA 20:4n-6, respectively. In humans, EPA and DHA are considered essential fatty acids, since the conversion of ALA to EPA and DHA is limited in the human body.

Linoleic acid (18:2n-6): An n-6 polyunsaturated fatty acid (PUFA) with 18 carbons and two double bonds. Linoleic acid is an essential fatty acid and is found in many plant oils. In animals, linoleic acid is converted into the longer chain n-6 PUFA arachidonic acid (20:4n-6).

Monounsaturated fatty acid: A monounsaturated fatty acid is a chain of carbons with hydrogens attached and only one double bond between the carbons in the chain. The most common monounsaturated fatty acid in mammals is oleic acid with eighteen carbons and the only double bond located at carbon number nine counted from the metyl (n-) end of the chain (18:1n-9).

Phospholipids (PL): PL are highly polar with two fatty acids being hydrophobic, and the water-soluble head group consisting of phosphorus and either choline, ethanolamine, inositol, or serine. The PL classes are phosphatidylcholine (PC), phosphatidylethanolamine (PE), phosphatidylinositol (PI), or phosphatidylserine (PS). PL are the major components of the neuronal membranes of the gray matter of the brain, and they are particularly rich in docosahexaenoic acid (DHA, 22:6n-3) and 20:4n-6.

Polyunsaturated fatty acids (PUFA): PUFA are chains of 18 carbons or more in length with hydrogens attached and with two or more double bonds between the carbons in the chain. PUFA are designated by the number of their carbons and the location of the first carbon, where the first double bond appears in a position counting from the methyl (n-) end of the chain (e.g., 18:3n-3, 22:6n-3, 20:4n-6).

n-3 polyunsaturated fatty acids (PUFA): n-3 (or omega-3) PUFA have the first double bond located at carbon number three, counting from the methyl (n-) end of the chain. The essential n-3 PUFA, α-linolenic acid (ALA, 18:3n-3), is the precursor of the longer chain n-3 PUFA eicosapentaenoic acid (EPA, 20:5n-3) and docosahexaenoic acid (DHA, 22:6n-3).

n-6 polyunsaturated fatty acids (PUFA): n-6 (or omega-6) PUFA have the first double bond located at carbon number six, counted from the methyl (n-) end of the chain. The essential n-6 PUFA linoleic acid (18:2n-6) is the precursor of the arachidonic acid (20:4n-6).

Saturated fatty acid: Saturated fatty acid is a chain of carbons with hydrogens attached and with only single bonds between carbons in the chain. The most common saturated fatty acids in mammals are palmitic acid with 16 carbons (16:0) and stearic acid with 18 carbons (18:0).

References

Anderson GJ, Neuringer M, Lin DS, Connor WE. Pediatr Res. 2005;58:865–72.

Bakewell L, Burdge GC, Calder PC. Br J Nutr. 2006;96:93–9.

Bourre JM, Piciotti M, Dumont O, Pascal G, Durand G. Lipids. 1990;25:465–72.

Burdge GC, Calder PC. Reprod Nutr Dev. 2005;45:581–97.

Calder PC, Yaqoob P. Biofactors. 2009;35:266–72.

Carrié I, Clément M, de Javel D, Francès H, Bourre JM. J Lipid Res. 2000;41:465–72.

Chen ZY, Cunnane SC. Pediatr Res. 1992;31:47–51.

Childs CE, Romeu-Nadal M, Burdge GC, Calder PC. Proc Nutr Soc. 2008;67:19–27.

Chung W-L, Chen J-J, Su H-M. J Nutr. 2008;138:1165–71.

Clandinin MT, Chappell JE, Leong S, Heim T, Swyer PR, Change GW. Early Hum Dev. 1980a;4:128–9.

Clandinin MT, Chappell JE, Leong S, Heim T, Swyer PR, Change GW. Early Hum Dev. 1980b;4:131–8.

Crowe FL, Skeaff CM, Green TJ, Gray AR. Br J Nutr. 2008;99:168–74.

Diau GY, Hsieh AT, Sarkadi-Nagy EA, Wijendran V, Nathanielsz PW, Brenna JT. BMC Med. 2005;3:11.

Dobbing J, Sands J. Early Hum Dev. 1979;3:79–83.

Enser M, Hallett K, Hewitt B, Fursey GAJ, Wood JD. Meat Sci. 1996;42:443–56.

Farquharson J, Cockburn F, Patrick WA, Jamieson EC, Logan RW. Arch Dis Child 1993;69:589–93.

Favreliére S, Perault MC, Huguet F, De Javel D, Bertrand N, Piriou A, Durand G. Aging. 2003;24:233–43.

Gamoh S, Hashimoto M, Sugioka K, Shahdat Hossain M, Hata N, Misawa Y, Masumura S. Neuroscience. 1999;93:237–41.

Giltay EJ, Gooren LJ, Toorians AW, Katan MB, Zock PL. Am J Clin Nutr. 2004;80:1167–74.

Goyens PL, Spilker ME, Zock PL, Katan MB, Mensink RP. Am J Clin Nutr. 2006; 84:44–53.

Horrocks LA, Farooqui AA. Prostaglandins Leukot Essent Fatty Acids. 2004;70:361–72.

Innis SM. J Pediatr Gastroenterol Nutr. 2009;48:S16–24.

Kris-Etherton PM, Taylor DS, Yu-Poth S, Huth P, Moriarty K, Fishell V, Hargrove RL, Zhao G, Etherton TD. Am J Clin Nutr. 2000;71 Suppl:179S–88S.

Lefkowitz W, Lim S-Y, Lin Y, Salem N Jr. Pediatr Res. 2005;57:157–65.

Levant B, Ozias MK, Jones KA, Carlson SE. Lipids. 2006;41:407–14.

Makrides M, Neumann MA, Byard RW, Simmer K, Gibson RA. Am J Clin Nutr. 1994;60:189–94.

Martinez M. J Pediatr. 1992;120:S129–38.

McNamara RK, Jandacek R, Rider T, Tso P, Dwivedi Y, Roberts RC, Conley RR, Pandey GN. Prostaglandins, Leukot Essent Fatty Acids. 2009;80:19–26.

Montine TJ, Neely MD, Quinn JF, Beal MF, Markesbery WR, Roberts LJ, Morrow JD. Free Radic Biol Med. 2002;33:620–6.

Nakamura MT, Cho HP, Xu J, Tang Z, Clarke SD. Lipids. 2001;36:961–4.

Novak EM, Dyer RA, Innis SM. Brain Res. 2008;1237:136–45.

Pawlosky RJ, Hibbeln JR, Novotny JA, Salem N Jr. J Lipid Res. 2001;42:1257–65.

Pawlosky RJ, Hibbeln JR, Lin Y, Goodson S, Riggs P, Sebring N, Brown GL, Salem N Jr. Am J Clin Nutr. 2003;77:565–72.

Petursdottir AL, Farr SA, Morley JE, Banks WA, Skuladottir GV. Neurobiol Aging. 2007;28:1170–8.

Petursdottir AL, Farr SA, Morley JE, Banks WA, Skuladottir GV. J Gerontol A Biol Sci Med Sci. 2008;63:1153–60.

Rahm JJ, Holman RT. J Nutr. 1964;84:15–19.

Rapoport SI, Rao JS, Igarashi M. Prostaglandins Leukot Essent Fatty Acids. 2007;77:251–61.

Sanders TA. Am J Clin Nutr. 2000;71 Suppl:176S–8S.

Sastry PS. Prog Lipid Res. 1985;24:69–176.

Simopoulos AP. Biomed Pharmacother. 2006;60:502–7.

Söderberg M, Edlund C, Kristensson K, Dallner G. Lipids. 1991;26:421–5.

Spector AA. J Mol Neurosci. 2001;16:159–65.

Sprecher H, Luthria DL, Mohammed BS, Baykousheva SP. J Lipid Res. 1995;36:2471–7.

Suzuki H, Park SJ, Tamura M, Ando S. Mech Ageing Dev. 1998;101:119–28.

Svennerholm L, Boström K, Jungbjer B, Olsson L. J Neurochem. 1994;63:1802–11.

Van Duyne CM, Havel, RJ. Proc Soc Exp Biol Med. 1959;102:599–602.

van Houwelingen AC, Sørensen JD, Hornstra G, Simonis MM, Boris J, Olsen SF, Secher NJ. Br J Nutr. 1995;74:723–31.

Venkatraman JT, Toohey T, Clandinin MT. Lipids. 1992;27:94–7.

Xiao Y, Huang Y, Chen ZY. Br J Nutr. 2005;94:544–50.

Chapter 74
Mother–Child Long Chain Polyunsaturated Fatty Acid Relationships: Implications for Diet and Behavior

S.A. van Goor, D.A.J. Dijck-Brouwer, and F.A.J. Muskiet

Abbreviations

EFA	Essential fatty acids
LCP	Long chain polyunsaturated fatty acids
LA	Linoleic acid
ALA	Alpha-linolenic acid
FADS1	Fatty acid desaturase 1 (delta-5 desaturase)
FADS2	Fatty acid desaturase 2 (delta-6 desaturase)
AA	Arachidonic acid
EPA	Eicosapentaenoic acid
DHA	Docosahexaenoic acid
SAFA	Saturated fatty acids
MUFA	Monounsaturated fatty acids
PPAR	Peroxisome proliferator activated receptor
CVD	Cardiovascular disease
RCTs	Randomized controlled trials
RBC	Red blood cells
GDM	Gestational diabetes mellitus

74.1 Introduction

The maternal diet prior to conception and during pregnancy and lactation, as well as infant nutrition during early postnatal life, are important for child growth and development and for the maintenance of good health at adult age (Barker 2007). Dietary fat and especially its constituents, such as essential fatty acids (EFA; see Table 74.1) and fat soluble vitamins, are among the many nutrients that are involved. This chapter describes the role of EFA and their chain-elongated and desaturated metabolites, named long-chain polyunsaturated fatty acids (LCP, ≥20 carbon atoms and ≥3 methylene-interrupted cis-double bonds; see Table 74.2). After an introduction into the (patho)biochemistry and (patho)physiology of EFA we focus at the role of LCP during pregnancy and in early postnatal life and discuss the currently recommended LCP intakes by pregnant mothers and infants.

———————————————
S.A. van Goor (✉)
University Medical Center Groningen, Nijlandspark 26, 9301 BZ Roden, The Netherlands
e-mail: saskiavangoor@yahoo.com

Table 74.1 Key facts of essential fatty acids, or EFAs

- EFA are fatty acids that cannot be synthesized within the human body.
- EFA are essential for the proper functioning of humans.
- EFA should be obtained from the diet to prevent disease.
- Linoleic acid (LA) and alpha-linolenic acid (ALA) are the parent EFA for humans.
- LA and ALA are obtained from vegetable oils; LA notably from safflower oil and sunflower oil and ALA from linseed oil and soy bean oil.
- EFA are used for energy generation but are also building blocks of membranes of all cells, thereby influencing the functions of membrane-bound receptors, transporters, ion channels, enzymes, and other membrane-dependent functions.
- LA is a building block of ceramides in our skin; ceramides function as barriers to limit water loss from our skin.
- LA can be stored in our adipose tissue.
- ALA is mostly degraded to acetyl-CoA for the generation of energy and for the synthesis of other fatty acids and cholesterol.
- ALA and LA are precursors of long-chain polyunsaturated fatty acids (LCP); they compete for the enzymes in the LCP synthetic pathway.

This table lists the key facts of Essential Fatty acids, including their function and sources

Table 74.2 Key facts of long-chain poly-unsaturated fatty acids or LCP

- LCP are fatty acids with at least 20 carbon atoms and at least 3 (methylene-interrupted *cis-*) double bonds.
- There are two LCP classes: the n-3 series (synthesized from ALA) and the n-6 series (synthesized from LA).
- The most important n-3 LCP are EPA (eicosapentaenoic acid) and DHA (docosahexaenoic acid); the most important n-6 LCP is arachidonic acid (AA).
- Endogenous EPA and notably DHA synthesis is considered insufficient.
- EPA and DHA can be obtained from the diet, notably from (fatty) fish.
- AA can be synthesized from LA with little difficulty.
- AA can also be obtained from the diet, notably from meat and eggs.
- AA, EPA, and DHA are precursors of eicosanoids, leukotrienes, neuroprotectins, and resolvins, which are hormone-like substances with a wide variety of actions.
- AA is an important building block of the brain, but also of all other organs. AA has functions in cell signal transduction and in the initiation and resolution of inflammatory processes.
- DHA is a building block of the brain, but also of all other organs. DHA in membranes is necessary for appropriate receptor functioning (e.g. in the retina), while EPA and DHA are important for the resolution of inflammatory processes.
- EPA and DHA are important for a healthy heart and blood vessels.
- High EPA+DHA intake from fish is beneficial for brain development, and the prevention of cardiovascular disease, depression, and other psychiatric diseases in which low-grade inflammation may be a common denominator.

This table lists the key facts of long-chain poly-unsaturated fatty acids or LCP, including their function and sources

74.2 EFA and LCP Dietary Origins and Synthesis

Linoleic acid (18:2n-6, LA, precursor of the so called omega-6 or n-6-series fatty acids) and alpha-linolenic acid (18:3n-3, ALA, precursor of the omega-3 or n-3-series) are the parent EFA for humans. They can be converted into LCP by microsomal desaturation by delta-6 and delta-5 desaturase (also referred to as FADS2 and FADS1, respectively), microsomal chain elongation and peroxisomal chain shortening (Fig. 74.1). Both LA and ALA are predominantly derived from vegetable oils. Important LCP are arachidonic acid (20:4n-6, AA) from LA, and eicosapentaenoic acid (20:5n-3, EPA) and docosahexaenoic acid (22:6n-3, DHA) from ALA. Synthesis of DHA from ALA is limited in humans and DHA is therefore considered to be conditionally essential (Muskiet et al. 2004). "Conditionally essential" refers to the necessity of a dietary source at circumstances during which
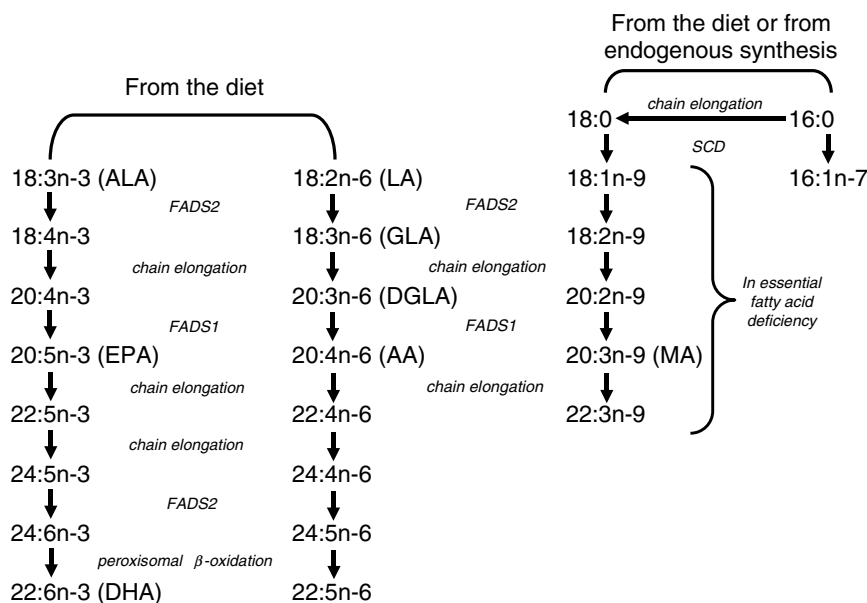
Fig. 74.1 Pathways of fatty acid chain elongation and desaturation. ALA and LA are the parent EFA for humans, and can be converted into LCP by microsomal desaturation by FADS2 and FADS1, microsomal chain elongation, and peroxisomal chain shortening. *ALA* alpha-linolenic acid, *LA* linoleic acid, *GLA* gamma-linolenic acid, *DGLA* dihomo-gamma-linolenic acid, *EPA* eicosapentaenoic acid, *AA* arachidonic acid, *MA* Mead acid, *DHA* docosahexaenoic acid, *FADS1* fatty acid desaturase 1, delta-5 desaturase, *FADS2* fatty acid desaturase 2, delta-6 desaturase, *SCD* stearoyl-CoA desaturase, delta-9 desaturase

the need exceeds endogenous synthesis. Meat, eggs, and poultry are rich sources of AA, while EPA and DHA are derived notably from fish, especially fatty fish.

The order of substrate affinity of FADS2 is ALA>LA>oleic acid (18:1n-9). Consequently, deficiency of parent EFA (i.e., of both LA and ALA) gives rise to the accumulation of Mead acid (20:3n-9), because of the action of the chain elongation/desaturation system on the competing oleic acid (Fig. 74.1). The sharing of the elongating and desaturating enzymes by n-6 and n-3 fatty acids causes these fatty acids to compete for conversion into the various LCP. The n-3 and n-6 fatty acids also compete in many other processes, such as transport, beta-oxidation, incorporation into lipids, release from lipids, conversion into highly active metabolites, and binding to receptors. The regulation of LCP synthesis is complex and notably targets FADS1 and FADS2. Both enzymes are widely expressed in human tissues with the highest contents in liver. The liver seems the major origin of endogenously synthesized LCP from LA and ALA. Dietary LCP downregulate LCP synthesis by negative feedback inhibition (Nakamura and Nara 2004). Insulin stimulates the expression of both enzymes, while it also stimulates expression of delta-9 desaturase (stearoyl-CoA desaturase) (Jump 2008). The latter is the third important desaturase that is notably associated with de novo fatty acid synthesis and is, e.g., induced in adipose tissue during insulin resistance. The strong feedback control of LCP on LCP synthesis predicts that the dietary supply of either LCPn-6 or LCPn-3 may shut off synthesis of both LCP series (Nakamura and Nara 2004). This seems especially important in the context of our currently high intake of LA from vegetable oils, which inhibits the synthesis of EPA from ALA (Angela Liou and Innis 2009). The complex interrelationships between the two EFA series put emphasis on the need of dietary "n-3/n-6 balance" to reach "homeostasis." The dietary composition producing this balance is as yet unknown, but it may be postulated that this balance is part of our Paleolithic diet on which our genes have evolved (Muskiet et al. 2006).

74.3 EFA and LCP (Patho)Biochemistry and (Patho)Physiology

Most of the dietary LA and ALA is used for energy generation, converted to other compounds or used for structural purposes. LA especially, can be stored to reach high levels in adipose tissue. LA and LCP (especially AA, EPA, and DHA) are the building blocks of the membrane phospholipids of all cells. They contribute to the membrane's physico-chemical properties and thereby to the functions of membrane-bound receptors, transporters, ion channels, enzymes, and other membrane-bound biochemical processes, such as those involved in signaling pathways. LA also acts as building block of ceramides in the skin and thereby contributes to the skin's barrier function. In contrast to LA, ALA gets stored in our body to only a limited extent. ALA is largely degraded to acetyl-CoA for the generation of energy or de novo synthesis of saturated fatty acids (SAFA), monounsaturated fatty acids (MUFA), and cholesterol.

Brain dry weight contains about 6% AA and 8% DHA, whereas brain levels of LA and ALA are low. DHA and AA are notably located in the synaptosomes, where AA is of special importance as a second messenger in (synaptic) signal transduction, and DHA provides the needed membrane fluidity for appropriate neurotransmitter receptor activity. DHA's role in neurodevelopment has been grouped into effects on gene expression, monoaminergic neurotransmission, protection against apoptotic cell death, and neurite outgrowth from the cell body (Innis 2007a). LCP are precursors of eicosanoids, resolvins, and protectins, which are highly potent metabolites that are involved in various signaling processes. The eicosanoids from EPA are believed to be less potent than those of AA. Eicosanoids from AA are widely considered to be proinflammatory, whereas those from EPA are weakly inflammatory or even anti-inflammatory. This must however be viewed upon as a generalization, since newly identified mediators of AA are not only involved in the initiation, but also in the resolution of inflammatory reactions (Serhan and Chiang 2008). Brain regions differ in AA and DHA contents at different ages, which may imply age- and region-specific regulation. Especially the membrane lipids of the visual elements of the infant retina contain high amounts of DHA and AA (Makrides et al. 1994), whereas at a later age, the retina contains a high amount of DHA but not AA. In nonhuman primates, brain grey matter contains the highest amounts of DHA as well as AA (Diau et al. 2005).

Together with their eicosanoid products and other fatty acids, LCP are firmly implicated in gene expression. For example, dietary LCP are ligands of peroxisome proliferator-activated receptors (PPARs). PPARs are among our bodily "lipid sensors" and, importantly, they constitute a link between lipid and glucose metabolism and inflammation (Jump 2008). They are also involved in growth and development. Because of their strategic role in many metabolic and signaling routes PPARs are logical targets for drugs. For instance, the fibrates for serum triglyceride lowering are agonists of PPAR-alpha, while the insulin sensitivity increasing properties of the thiazolidinediones (glitazones) are based on their agonistic action towards PPAR-gamma. In addition, PPARs are also likely to constitute a link between dietary fatty acids and one-carbon metabolism and thereby epigenetics, since folic acid supplementation of dietary protein-restricted pregnant rats corrected the overexpression of the PPAR-alpha gene in the fetal liver (Lillycrop et al. 2008). Folic acid-stimulated methylation of CpG dinucleotides in the PPAR-alpha gene promoter was found to be the underlying mechanism. These methylation patterns persisted into adulthood (Lillycrop et al. 2008) and were passed on to the next generation (Burdge et al. 2007). Modifiable PPAR-alpha expression by maternal dietary protein and folic acid might be expected to confer different sensitivities of the offspring to PPAR-alpha natural ligands, such as the LCP and their metabolites. Little is as yet known on the influence of nutrient–nutrient interaction in (patho)biochemistry and (patho)physiology, including the many possible interactions of different nutrients with LCP.

Clinically apparent EFA deficiency (i.e., of both n-6 and n-3 fatty acids) in Western countries is rare. The sporadic cases are mostly based on heritable or acquired diseases that cause, or are accompanied by, poor gastrointestinal fat absorption. A-betalipoproteinemia, cystic fibrosis, and chronic intestinal disorders causing malabsorption (e.g., Crohn's disease) are examples of such diseases. Growth retardation, reproductive failure, fatty liver, and a dry scaly skin that is characterized by augmented transdermal water loss are attributed to n-6 fatty acid shortage. Deficiency of n-3 fatty acids is related to dysfunction of the central nervous system, including cognitive dysfunction and impaired vision. Imbalances between AA, EPA, and DHA may change the ratio between their eicosanoids, resolvins, and protectins with concomitant pathophysiological effects, such as those associated with chronic low grade inflammation (Serhan and Chiang 2008). Higher intakes of EPA and DHA from fish are firmly implicated in cardiovascular and neuro-psychiatric health benefits. It is nowadays widely recognized that insulin resistance and its sequelae associated with the metabolic syndrome (such as diabetes type 2, cardiovascular disease (CVD), certain pregnancy complications and cancer types), neurodegenerative disorders (like Alzheimer's and Parkinson's disease), and depression may find a common origin in a state of chronic low-grade inflammation that is intimately related to the current high dietary intakes of SAFA, *trans* fatty acids, and n-6 fatty acids, and the low intakes of n-3-fatty acids, notably those abundant in fish (Warnberg et al. 2009). The presently advised dietary intake of about 450 mg LCPn-3/day confers virtually maximum antiarrhythmic effects, but is below the estimated dosages that confer maximum benefits for other CVD risk factors responding favorably to fish oil, such as hypertension, dyslipidemia, and thrombosis (Mozaffarian and Rimm 2006), suggesting that each of the many LCPn-3 functions has its own optimal intake and that the function least sensitive to dietary intervention may define the requirement.

Low perinatal frontal cortex DHA accretion is associated with suboptimal development of the dopaminergic system and is therefore considered to be a risk factor for attention-deficit/hyperactivity disorder (ADHD) and schizophrenia. There is good evidence to show that DHA is accrued in rodent, primate, and human brain during active periods of perinatal cortical maturation, and that DHA plays an important role in neuronal differentiation, synaptogenesis, and synaptic function (McNamara and Carlson 2006). Low intake of EPA and DHA is implicated in the high incidence of depression in Western countries and there is a strong inverse correlation between national dietary fish intakes and rates of postpartum depression (Hibbeln 2002). Randomized controlled trials (RCTs; see Table 74.3 for explanation) with LCPn-3, especially EPA, have shown favorable outcomes in depression (Ross et al. 2007).

74.4 LCP in Pregnancy

74.4.1 Maternal and Fetal LCP Metabolism and Transplacental Transport

Fetal EFA/LCP status is dependent on maternal EFA/LCP status and on fetal LCP synthesis from transplacentally transferred parent EFA. Several human studies demonstrated relationships between maternal and fetal EFA/LCP status in compartments such as red blood cells (RBC) and plasma (Al et al. 1990, 1995; Rump et al. 2001; Vlaardingerbroek and Hornstra 2004). Differences in maternal dietary DHA and AA ratios were shown to influence offspring brain LCP composition (van Goor et al. 2008a; Wainwright et al. 1997), while maternal erythrocyte LCP content was shown to correlate with fetal brain LCP content (van Goor et al. 2008a) (Fig. 74.2), at least in mice. Although, in general, conversion of ALA to EPA and especially to DHA is low in humans, women show a higher

Table 74.3 Key facts of randomized controlled trials or RCT

- An RCT is a scientific experiment of high standards that is most commonly used for testing the efficacy or effectiveness of a healthcare service (such as nursing) or health technologies (such as drugs, nutrients, medical devices or surgery).
- RCTs involve the random allocation of different interventions (treatments or conditions) to subjects.
- A Placebo-controlled study is a way of testing a medical therapy in which, in addition to a group of subjects that receives the treatment to be evaluated, a separate control group receives "placebo" treatment which is specifically designed to have no real effect.
- The purpose of the placebo group is to account for "placebo effects," which are effects from treatment that are not caused by the treatment itself. Such effects may originate from the knowledge of who receives real treatment, attention from health care professionals, and the expectations that the real treatment is effective by those who conduct the study. Without a placebo group for comparison there is no proof of "causality," that is, it is not possible to know whether the real treatment had any effect.
- If the RCT is double-blinded, patients and investigators are unaware of which treatment (real or placebo) is given to an individual patient.
- As long as the numbers of subjects are sufficient, randomization is an effective method for balancing confounding factors between treatment groups.

This table lists the key facts of randomized controlled trials
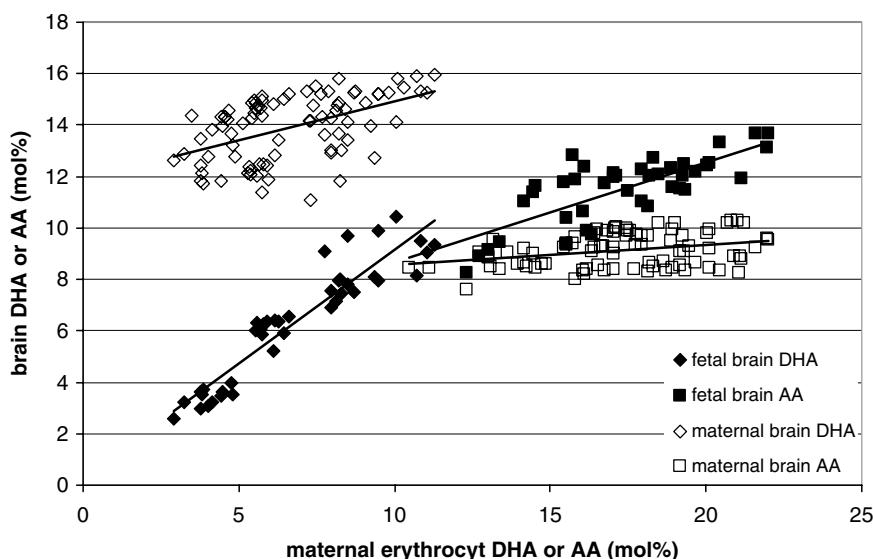
Fig. 74.2 Correlations between maternal erythrocyte LCP, and maternal and fetal brain LCP. Maternal erythrocyte DHA and AA correlates with fetal brain DHA and AA in mice. *AA* arachidonic acid, *DHA* docosahexaenoic acid. Diets varying in parent essential fatty acids (EFA), AA and DHA were administered from day 3 prior to conception till day 15 of pregnancy at which samples were taken (Adapted from van Goor et al. (2008a) with permission from Elsevier (modified figure))

conversion compared to men. A possible explanation may lay in the action of estrogen, and it is possible that the increasing estrogen concentrations upregulate ALA conversion during pregnancy (Burdge 2006). This higher efficiency in women might be important, but is unlikely to compensate fully for the fetal and newborn needs. Transplacental fatty acid transport is selective for LCP, as concluded from the relatively higher LCP contents in the fetal circulation, compared with maternal circulation, while the transfer of LA and ALA is nonselective. The underlying mechanism of LCP transplacental transfer, causing what is called "biomagnification" (Crawford et al. 1976) (Fig. 74.3), is probably by a combination of many mechanisms, including selective hydrolysis of LCP from
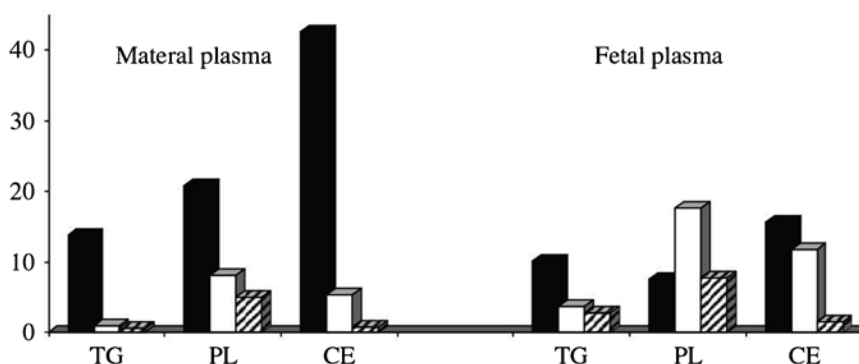
Fig. 74.3 Essential fatty acid contents (g/100 g fatty acids) in maternal plasma lipids (*left*) and cord plasma lipids (*right*). The higher DHA and AA in fetal lipids compared to maternal lipids has been named "biomagnification." ■ Linoleic acid; □ arachidonic acid (AA); docosahexaenoic acid (DHA); *TG* triglycerides, *PL* phospholipids, *CE* cholesterol esters (Adapted from Innis (2005) with permission from Elsevier)

maternal triglycerides, increasing maternal free fatty acids with advancing gestation in combination with higher fetal albumin, placental fatty acid binding proteins and fatty acid transfer proteins, and the trapping of the transferred LCP in the fetal circulation by albumin and alpha-fetoprotein or by esterification to lipids (Duttaroy 2009). The placenta contains both FADS1 and FADS2 activities which suggests that placental LCP synthesis may contribute to fetal LCP status, although the extent to which this occurs is unknown (Innis 2005). The outcome of the various mechanisms is that fatty acids are transferred from mother to child with an order of preference of DHA>AA>ALA>LA (Duttaroy 2009).

There is reasonable evidence to show that in Western countries, the maternal body becomes somewhat depleted from LCP, notably DHA, during pregnancy and subsequent breastfeeding. The following characteristics of LCP physiology have been derived from the courses of the plasma phospholipids and RBC fatty acid compositions during pregnancy in Western countries: maternal AA increases in early pregnancy and subsequently falls below prepregnancy levels, DHA increases in early pregnancy and subsequently decreases but remains above prepregnancy levels, the EFA/non-EFA ratio [(sum n-3 + sum n-6)/(sum n-7 + sum n-9)] decreases while the DHA deficiency index (22:5n-6/22:4n-6) increases with gestational age. Maternal and fetal LCP (notably DHA) status is correlated, normalization of maternal DHA status after delivery is retarded by breastfeeding, and maternal plasma DHA is higher in primigravidae than multigravidae (Hornstra 2000).

In general, EPA + DHA intakes in Western countries are low compared to the recommendation to consume about 450 mg LCP n-3/day. An EFA deficiency initiated three days prior to conception in female mice, caused biochemical signs of DHA depletion in maternal brain, but severely impaired accretion of DHA in the fetal brain. This implies that, at least in mice, the growing fetal brain is more sensitive to low LCP status than maternal brain (van Goor et al. 2008a), as illustrated by the steeper slopes of the relation between maternal erythrocyte LCP and fetal brain LCP, compared to the relations between maternal erythrocyte LCP and maternal brain LCP (Fig. 74.2). Extreme models with long term ALA-deficiency in female rats showed that maternal brain DHA is vulnerable to depletion, which becomes aggravated by pregnancy and lactation and affects specific brain regions differently (Levant et al. 2008). Thus, because of the high fetal demands, it seems likely that the marginal LCP status in Western countries causes maternal brain to lose LCP, notably DHA, during pregnancy, while declining brain DHA is associated with increasing AA turnover and neuroinflammation (Orr and Bazinet 2008). Declining maternal DHA status was suggested to be involved in the compromised

selective attention, which is a key component of cognition, during pregnancy (de Groot et al. 2004) and although unproven in RCTs with LCPn-3 (Ross et al. 2007), a relation between declining maternal DHA status and postpartum depression was observed (Hibbeln 2002).

Positive as well as negative associations between fish intake and fetal growth have been observed. A meta-analysis of LCPn-3 supplementation studies during pregnancy indicated an increased length of gestation (1.57 days) and a trend towards an increased head circumference (0.26 cm). Supplementation did not influence the percentage of preterm deliveries, the rate of low-birth-weight infants, the rate of preeclampsia or eclampsia, and birth weight and birth length (Szajewska et al. 2006).

Both maternal and fetal LCP status are compromised by gestational diabetes mellitus (GDM), types 1 and 2 diabetes mellitus, and preeclampsia. This might be of growing importance because affluent countries experience increasing prevalence of overweight and obesity in pregnancy, while a high maternal BMI is a well established risk factor for GDM, diabetes mellitus type 2, preeclampsia and fetal defects. Umbilical vessels at term (Muskiet et al. 2006) and erythrocytes of newborns up to 0.2 years (Fokkema et al. 2002) contain relatively high amounts of Mead acid. Umbilical arteries contain higher Mead acid than umbilical veins. Both in the umbilical artery and umbilical vein, Mead acid correlates inversely with AA and LA levels, and positively with oleic acid levels, suggesting that the intrauterine environment is characterized by low EFA status. The abundant intrauterine synthesis of Mead acid is a consequence of the high de novo synthesis of oleic acid from the ample glucose that crosses the placenta in the third trimester (Fig. 74.4). In contrast, relatively little maternal LA becomes trapped in the fetal circulation. The resulting high fetal oleic acid/LA ratio directs fetal FADS2 to synthesize Mead acid from oleic acid (Fig. 74.1), at the expense of AA synthesis from LA. Compromised glucose homeostasis in maternal diabetes mellitus and GDM may cause higher transplacental glucose flux with concomitantly increased fetal de novo fatty acid synthesis, while the insulin resistance in both (gestational) diabetes and preeclampsia may cause increased de novo fatty acid synthesis in the maternal liver with subsequent transfer of these de novo synthesized fatty acids to the fetus. The outcome is a fetal state of "relative EFA/LCP deficiency," rather than an absolute deficiency, with as yet unknown consequences.

Taken together, it seems that both maternal and fetal DHA status and to a lesser extent AA status are at risk in current Western societies because of the low maternal intake of fish and the increasing prevalence of maternal insulin resistance and compromised glucose homeostasis. The crucial importance of the fetal LCP status seems, however, clear from the well established fetal preference of LCP, notably DHA, as compared with their parent EFA precursors, while there is ample evidence that the DHA and AA intakes from our ancient diet have been much higher compared with contemporary intakes (Muskiet et al. 2006).

74.4.2 *LCP in Pregnancy and Neurodevelopment*

Several studies indicated the importance of DHA in pregnancy and neurodevelopment. A large observational study showed that 6 months to 8 years old children from mothers with seafood consumption below 340 g/week had lower verbal IQ and an increased risk of suboptimal outcomes for prosocial behavior, fine motor skills, communication and social development scores, compared with children from mothers eating more than 340 g/week (Hibbeln et al. 2007). A higher cord plasma DHA was associated with a more optimal cognitive development at 6 months and at 11 months, and a higher cord plasma DHA/AA was associated with a more optimal visual development at 6 months, cognitive development at 6 months, and motor development at 11 months (Jacobson et al. 2008).
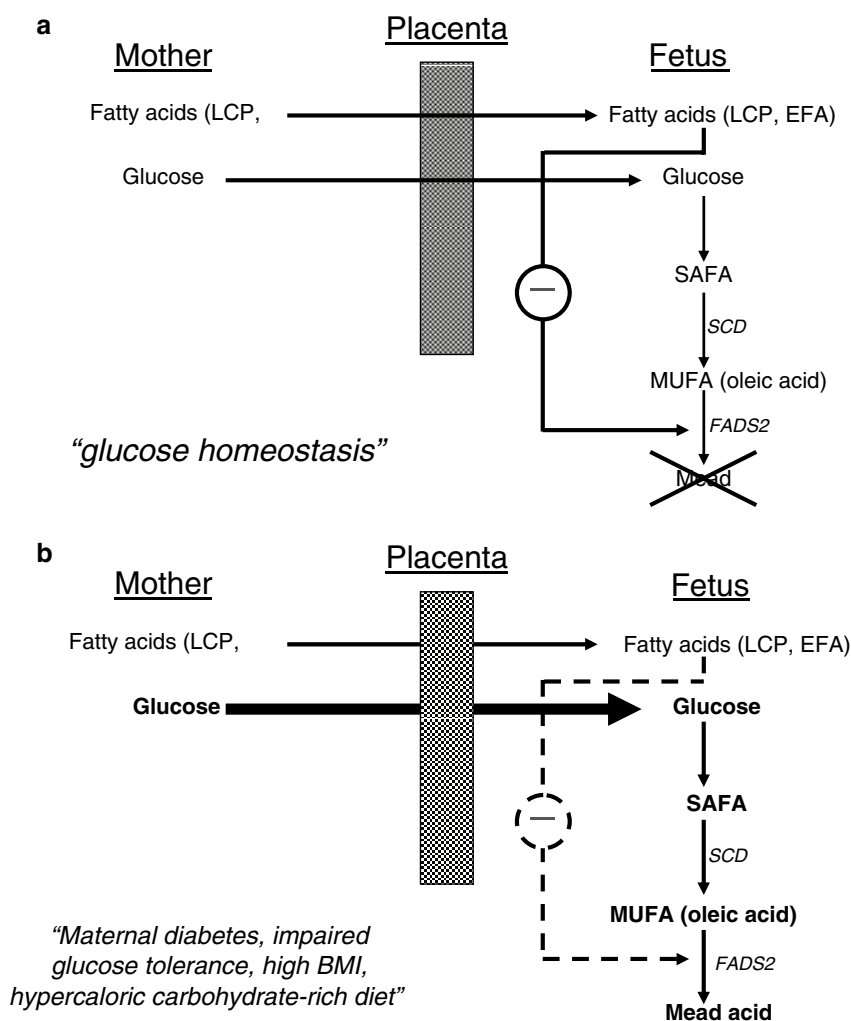
Fig. 74.4 Fetal essential fatty acid (EFA) and long chain polyunsaturated fatty acid (LCP) status at "normal" (**a**) and augmented (**b**) transplacental glucose transport. Increased transplacental glucose fluxes may occur in maternal diabetes, impaired glucose tolerance, high body mass index (BMI), and a hypercaloric carbohydrate-rich diet. Increased de novo synthesis of fatty acids from glucose in the fetus by stearoyl-CoA desaturase (SCD, delta-9 desaturase) causes augmented accretion of saturated (SAFA) and monounsaturated (MUFA) fatty acids, notably 16:0, 16:1n-7, and 18:1n-9 (oleic acid). Oleic acid may compete with linoleic acid for fetal delta-6 desaturase (FADS2) causing formation of Mead acid (20:3n-9) at the expense of the synthesis of arachidonic acid (20:4n-6) from linoleic acid. Accretion of de novo synthesized fat gives rise to dilution of fetal EFA and LCP status, causing a state of 'relative' EFA/LCP deficiency, rather than absolute deficiency (Adapted from Muskiet et al. (2006) with permission from Elsevier)

Umbilical cord plasma DHA was also associated with lower internalizing problem behavior at 7 years (Krabbendam et al. 2007), whereas AA showed no significant relations. Others showed that maternal plasma phospholipid DHA was related to more mature sleep patterns in their neonates, while the n-6/n-3 ratio was negatively associated (Cheruku et al. 2002). Infants of mothers with high RBC DHA performed better on psychophysiological measures (4, 6, and 8 months) and on free play attention and distractibility paradigms (12 and 18 months) (Colombo et al. 2004), while maternal DHA intake during pregnancy was associated with better stereo acuity of their children at 3.5 years

(Williams et al. 2001). Also, AA was found to be important to neurodevelopment. For instance, a positive association was found between umbilical vessel DHA as well as AA and the neurological optimality score at 2 weeks (Dijck-Brouwer et al. 2005), and between umbilical venous AA and general movement quality at 3 months (Bouwstra et al. 2006b) and the neurological optimality score at 18 months (Bouwstra et al. 2006a). Maternal AA intake during pregnancy was related to shorter brainstem auditory-evoked potentials of their infants at 1 month (Parra-Cabrera et al. 2007). Another study revealed no relation between umbilical blood DHA or AA status with child cognition at 4 years (Ghys et al. 2002) and 7 years (Bakker et al. 2003). Taken together, these studies indicate the importance of not only DHA during pregnancy, but also of AA and the DHA/AA balance.

Maternal DHA supplementation studies during pregnancy or during pregnancy and subsequent lactation with doses ranging from 200 to 3,300 mg DHA/day resulted in improved visual acuity at 4 months (Judge et al. 2007a), enhanced problem solving at 9 months (Judge et al. 2007b), improved eye–hand coordination at 2.5 years (Dunstan et al. 2006) or a higher IQ at 4 years (Helland et al. 2003), whereas other developmental parameters showed no benefits (Hadders-Algra 2008). Some studies showing no effect, reported associations similar to those noted in observational studies (Hadders-Algra 2008). The positive effects of maternal DHA supplementation may first become expressed after early infancy, but the discrepancy may also relate to a complex interplay between a ceiling effect in the dose–outcome relationship, benefits to those with suboptimal baseline status only, and interindividual differences in developmental potential (Innis and Friesen 2008). A high variety in developmental tests, differing in functional background, has been employed in the various studies. Various brain regions differ in fatty acid composition, which may imply region-specific regulation of brain LCP contents. It might therefore be that DHA supplementation influences some brain regions, but not all, and thereby fails to influence the outcomes of each of the various tests. In addition, the relation between DHA status and neurodevelopment may be nonlinear.

Preliminary data from our group indicate a U-shaped relation between especially the erythrocyte DHA/AA ratio and the quality of general movements as a parameter of brain development. U- or bell-shaped curves similar to ours were also reported by others. Variation in rat brain DHA content by dietary means caused sex-specific alterations in locomotor activity, with males being most affected notably at postadolescent age. The observed DHA intake-effect curve proved bell-shaped, with both low and high DHA intakes giving rise to lower locomotor activities compared with control and medium low DHA intakes (Levant et al. 2006). Although uncommented by the authors, a U-shaped relation was shown between cord plasma phospholipid DHA and the Bayley Scales Psychomotor Development Index (PDI) at 11 months in breastfed Inuit infants with high DHA intakes living in the Arctic region (Jacobson et al. 2008). In addition, excess as well as deficient n-3 fatty acid intakes during pregnancy and lactation cause impaired neural transmission in rats (Church et al. 2008). In human infants, negative associations between higher DHA intakes and verbal skills have been reported (Lauritzen et al. 2005; Scott et al. 1998). U-shaped dose–response curves are not uncommon (Calabrese and Baldwin 2003). Of these, the effect of alcohol consumption on CVD risk is probably best known, while also micronutrient dose–response curves are classical examples (Hayes 2008). The pathophysiological effects in U-shaped curves in the descending (i.e., deficient) and ascending (i.e., toxicological) parts usually reflect different underlying mechanisms leading to the common denominator of "unfavorable effects." It is possible that the descending and ascending parts of U-shaped dose–response curves of DHA or the DHA/AA ratio in neurodevelopment indicate different neurodevelopmental trajectories in which the descending part indicates DHA shortage, while the effects in the ascending part may not necessarily be unfavorable in the long term.

74.5 LCP in Early Postnatal Life

74.5.1 Importance of LCP in Neonatal Nutrition

Generally, breastfeeding is associated with better brain development, at least partly because breast-feeding is related to socioeconomic background. A higher socioeconomic background is associated with better brain development, and it is known that mothers with a higher socioeconomic status tend to breastfeed their children more frequently compared to those with a lower socioeconomic background. In addition, the nutrient composition of breast milk is also widely presumed to be superior for brain development, compared to that of infant formula. For example, important brain constituents such as LCP are available in breast milk, whereas many formulas up till now do not provide LCP. Numerous studies have shown a decline of DHA and AA in plasma and RBC of children receiving infant formula without preformed LCP, as compared to breastfed counterparts. A few autopsy studies on brain LCP levels have been conducted (Clandinin et al, 1980a, b; Farquharson et al. 1992; Jamieson et al. 1999; Makrides et al. 1994; Martinez and Mougan 1998). Infants receiving formula without DHA and AA had lower DHA in brain, but their AA was normal or somewhat higher. Brain DHA levels increased with age in breastfed infants, which was largely an effect of length of feeding, while the accretion of AA was dependent on age but not diet (Makrides et al. 1994). The lower DHA in frontal cortex phosphatidylethanolamine, with concomitantly higher AA, 22:4n-6 and 22:5n-6, suggested low DHA status with compensatory chain elongation/desaturation of n-6 fatty acids (Innis 2003). In other words, the occasionally higher AA and consistently lower DHA in the brain of formula-fed infants seem rather caused by DHA shortage with corresponding dominance of LCPn-6 synthesis, notably of 22:5n-6, than by competition of DHA and AA for incorporation. The consequences in humans are as yet unclear, but the decrease in brain DHA in animals is accompanied by altered developmental parameters (Innis 2003).

Brain accretion of DHA and AA primarily occurs during the last trimester of pregnancy and the first year of life (Clandinin et al. 1980b). Consequently, prematures are likely to benefit most from postnatal DHA and AA supplementation. However, a Cochrane meta-analysis based on RCT with relatively mature and healthy preterm infants showed: (i) that most studies did not find differences in visual acuity over the first year; (ii) that there was no effect on neurodevelopment at 12 or 18 months; and (iii) that there were no effects on growth (weight, length, or head circumference) at 12 and 18 months. It was concluded that there are no clear long-term benefits for infants receiving formula supplemented with LCP and that there is no evidence that formulas with LCPn-3 and LCPn-6 impair the growth of preterm infants (Simmer et al. 2008b). In a recent study, mothers of preterm infants were supplemented with DHA from enrolment until term corrected age in order to achieve a 1 wt% DHA in their milk. Compared to controls receiving milk with 0.3 wt% DHA, infants receiving milk with 1 wt% DHA showed improved visual evoked potential acuity at 4 months corrected age, although not at 2 months (Smithers et al. 2008), and improved Bayley Scales of Infant Development-Mental Development scores at 18 months corrected age in girls only (Makrides et al. 2009).

A Cochrane meta-analysis on postnatal LCP supplementation with term infants showed: (i) that data for visual acuity up to 3 years are inconsistent; (ii) that there are no benefits on mental or psychomotor developments through the first 2 years; and (iii) that there are neither beneficial nor harmful effects on growth through the first three years of life. The final conclusion was that there are no beneficial effects of LCP supplementation of formula milk on visual, physical, and neurodevelopmental outcomes for infants born at term, and that LCP supplementation cannot be recommended on the basis of current evidence (Simmer et al. 2008a).

In contrast to the inconsistency of human studies, animal experiments with induced DHA deficiency have shown consistent abnormalities in various cognitive and behavioral tests, while also the beneficial effects of DHA in other human life stages (e.g., in CVD and neuro-psychiatric diseases) cannot be ignored. It was suggested that differences in sensitivity of global tests and of tests targeted at more specific neural domains may account for the mixed results of the currently completed RCTs. Other possible explanations include inadequate amounts of supplemental DHA in formulas, poor study quality, the ability of term infants receiving formulas without LCP to synthesize their own DHA, an absence of cognitive deficits when differences in brain concentrations of DHA are small because of brain plasticity (i.e., the ability of the brain to adapt), or the inability of the performance tests to detect subtle differences in performance resulting from relatively small differences in brain concentrations of DHA (McCann and Ames 2005). Also of importance might be that in the majority of studies neurodevelopmental outcome was assessed at 6–24 months, which is an age of "latency" in the expression of neurological dysfunction (Hadders-Algra et al. 2007).

74.6 Recommendations for Infant Formula

Despite inconsistent beneficial results of LCP supplementation of formula, many recommendations for infant formula have been issued by various nutritional boards and advisory committees. These recommendations are based on studies with LCP contents as encountered in breast milk of mothers living in Western countries. This approach does not take into account that milk DHA and to a lesser extent AA are highly variable among different countries with different dietary habits (Kuipers et al. 2007) (Fig. 74.5). Western mothers have low intakes of ALA, a high dietary LA/ALA ratio and a limited consumption of fish, which relates to CVD, postpartum depression, and suboptimal neurodevelopment as outlined earlier. Criticizing their diet in relation to these conditions is inherent to criticizing the milk content of DHA and AA (and other fatty acids), since both milk DHA and AA are to a large extent dependent on long-term dietary habits, with the majority of the LCP deriving from maternal stores (van Goor et al. 2009).

In view of their derivation from Western observations, it is not surprising that the current recommendations for DHA in infant formula are inconsistent with the human milk DHA contents of women who have lifetime dietary DHA intakes according to current recommendations for adults or those for pregnant and lactating women (van Goor et al. 2008b). For instance, the recent guidelines for the LCP contents of infant formulas, as endorsed by the World Association of Perinatal Medicine, the Early Nutrition Academy and the Child Health Foundation recommend to add at least 0.2 g DHA/100 g fatty acids (0.2 wt%) to formula for term infants. DHA should not exceed 0.5 wt% and the minimum amount of AA should be equivalent to DHA (Koletzko et al. 2008). The basis of this recommendation is that at least 0.2 wt% DHA is necessary to achieve benefits on functional endpoints, but that systematic evaluation of levels above 0.5 wt% DHA has not been published. The recommendations acknowledge that "breast is best," that pregnant and lactating women should aim at dietary intakes of at least 200 mg DHA/day, and that higher intakes up to 1 g DHA and 2.7 g LCPn-3 have been studied without significant adverse effects. This new advice on formula DHA is not in line with current recommendations for the general public to consume 450 mg LCPn-3/day (about 170 mg DHA) or with the recommendations of the International Society for the Study of Fatty Acids and Lipids (ISSFAL) to consume 300 mg DHA/day during pregnancy and lactation (ISSFAL 2009). Women adhering to these recommendations will have mature milk DHA contents ranging from 0.43–0.79 wt%, but likely above 0.5 wt% (van Goor et al. 2008b) (Fig. 74.6). We constructed dose–response curves for the mature milk DHA contents of women with known lifetime DHA
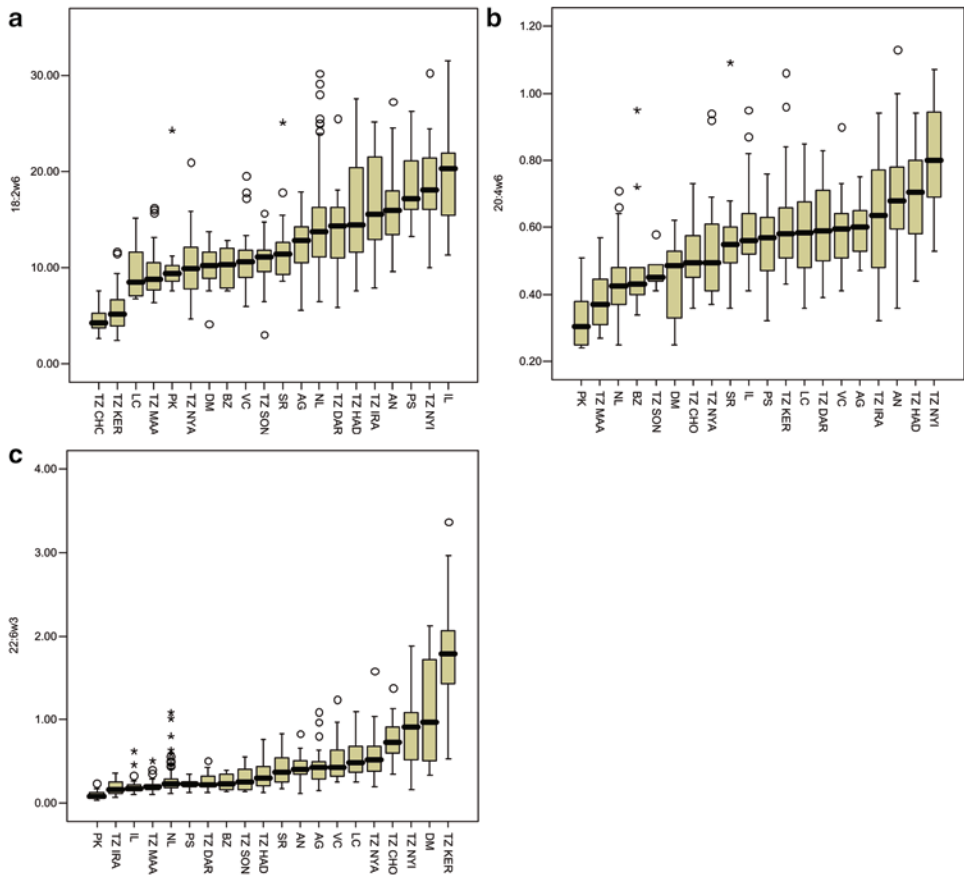
Fig. 74.5 Linoleic acid (LA, panel **a**), arachidonic acid (AA, panel **b**), and docosahexaenoic acid (DHA, panel **c**) in the milk of Tanzanian tribes and locations, as compared with countries in our world data set. Data [in wt%] are indicated as box plots, showing medians [black bar], interquartile range [box length], minimum and maximum of the sample or smallest and largest values inside a 1.5 box length distance from the end of the box [crossbars at the far ends of whiskers], values between 1.5 and 3 box lengths from either end of the box [outliers, indicated by *], and values >3 box lengths from either end of the box [extremes, indicated by *]. *AG* Antigua, *BZ* Belize, *DM* Dominica, *IL* Jerusalem–Israel, *LC* St. Lucia, *AN* Curaçao–Netherlands Antilles, *NL* The Netherlands, *PK* Pakistan–Islamabad, *PS* Jerusalem–Palestine, *SR* Surinam, *TZ-CHO* Chole, *TZ-DAR* Dar-es-Salaam, *TZ-HAD* Hadzabe, *TZ-IRA* Iraq, *TZ-KER* Kerewe, *TZ-MAA* Maasai, *TZ-NYA* Nyakius, *TZ-NYI* Nyarimba, *TZ-SON* Sonjo, *VC* St. Vincent (Adapted from Kuipers et al. (2007) with permission from Elsevier)

intakes (Innis 2007b) and for milk of women who were supplemented with various DHA dosages for 12 weeks (Makrides et al. 1996). The estimate from women with lifetime intakes indicates that a recommendation of 170 mg DHA/day corresponds with 0.43 wt% DHA in mature milk and that this figure increases up to 0.79 wt% DHA if the women would comply with the consumption of 300 mg DHA/day during pregnancy and lactation. The slope of the dose–response curve for a short-time supplementation is less steep compared with that of a lifetime intake, probably because milk DHA derives mostly from maternal stores that are unlikely to reach an equilibrium in 12 weeks.

DHA has been found to reach the highest contents in milk from traditionally eating Tanzanian populations living along the shores of the Indian Ocean (i.e., Chole) and freshwater lakes (i.e., Kerewe and Nyakius) (Fig. 74.5). Their milk AA was in the median range whereas their milk LA was among the lowest. Especially the milk fatty acid composition from Chole was suggested to closely reflect the diet on which *Homo sapiens* has evolved. Their milk DHA content of 0.73 wt% is
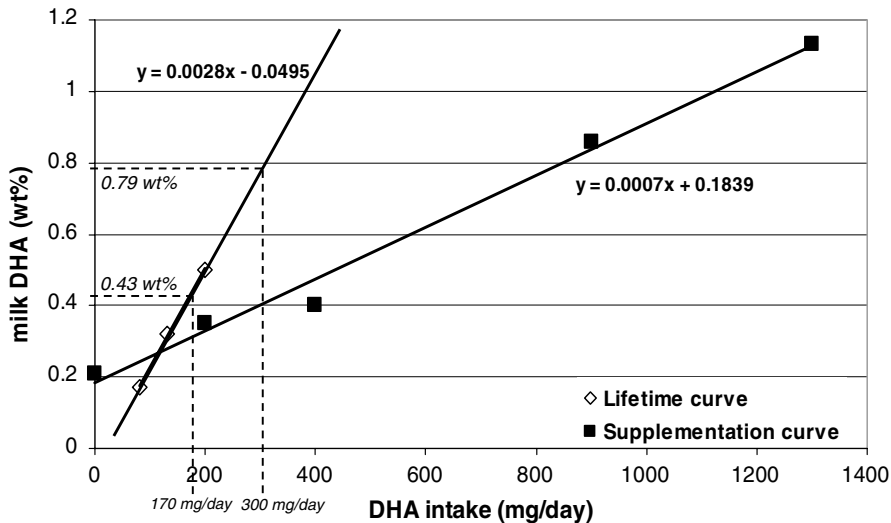
Fig. 74.6 Dose–response curves for dietary DHA and mature milk DHA. Data are depicted for a lifetime DHA intake and a 12 weeks supplementation. The estimated lifetime curve (Innis 2007b) shows that the current recommendation of 170 mg DHA/day (450 mg LCPn-3) for adults results in 0.43 wt% DHA in mature milk. Milk of women complying with the recommendation of 300 mg DHA/day during pregnancy and lactation will have a milk DHA content in between 0.43% and 0.79 wt%. The supplementation curve (Makrides et al. 1996) is less steep compared to the lifetime curve, probably because milk DHA derives mostly from maternal stores that will not reach equilibrium during 12 weeks supplementation

at the upper range of the milk DHA of women complying to lifetime intakes of 170–300 mg DHA/ day (Fig. 74.6). Whether this composition supports optimal homeostasis is currently unknown. However, the apparent lack of adverse effects in the children living in Tanzanian land–water ecosystems, seems to argue against the validity of recommendations that are solely based on the milk composition of Western mothers (Kuipers et al. 2007).

74.7 Epilog

Western diets are characterized by low fish intakes and consequently low DHA and EPA intakes. Maternal dietary LCP status is correlated with fetal and neonatal brain LCP status, which implies that also the fetal and neonatal DHA status in Western countries is low. In addition, the increasing incidence of maternal insulin resistance and compromised glucose homeostasis may cause a state of relative fetal EFA/LCP deficiency. It is generally accepted that both DHA and AA are important for brain development and that the members of the LCPn-3 and LCPn-6 families exhibit as yet incompletely understood relationships of competition, but also of collaboration and synergy (Horrobin et al. 2002; Orr and Bazinet 2008). Taken together, this raises the question whether the current Western EFA/LCP status of the fetus and newborn is optimal.

Apart from our currently low dietary LCPn-3 intake, we have also decreased our ALA intake, while our LA intake has increased 2–3-fold. At present, both high intakes of LCPn-3 and LA are advocated to diminish the risk of cardiovascular disease, which translates into a recommended intake of 450 mg EPA + DHA per day and of 5–10 energy% LA (about 17 and 12 g/day for men

and women) (Harris et al. 2009), respectively. The problem with the LA recommendation is that such high LA intakes have never occurred in the past (Kuipers et al. 2007) and that the resulting EFA/LCP status may impose new challenges to our health. For instance, a high LA intake is known to inhibit the synthesis of 20:3n-6 and EPA (Angela Liou and Innis 2009) which, together with AA and DHA, are precursors of eicosanoids, resolvins, and protectins. These signaling molecules are involved in both the initiation and resolution of inflammatory reactions (Serhan and Chiang 2008). The recommended higher intake of EPA + DHA may on its turn inhibit the conversion of LA to AA by feedback inhibition and thereby increase our dependence on a dietary AA source. Whatever the underlying mechanisms, it has become clear that plasma phospholipid LA contents correlate positively with the AA/20:3n-6 and AA/EPA ratios (Liou and Innis 2009), suggesting that a higher LA intake contributes to the chronic low grade inflammation that is characteristic for the current Western lifestyle, while a higher EPA + DHA intake may be favorable.

It should be noted that RCTs show only small effects on brain development at best, whereas association studies indicate clear relations between LCP status and neurodevelopment. Since cognitive development is related to socioeconomic status and DHA status might be no more than a proxy for socioeconomic background, healthy lifestyle factors, or both (Hibbeln et al. 2007), the genuine lesson here might be that RCTs with single ("magic bullet") nutrients are unlikely to provide us with the proper information to restore the homeostasis on which our genes have evolved. RCTs basically ignore the many possible interactions with other nutrients and the many changes in our lifestyle that have occurred, while they usually rely on dose choices from poorly investigated dose–response relations. Heterodimerization of nuclear receptors, that each require the binding of a certain nutrient or one of its metabolites, is illustrative for the many poorly understood nutrient–nutrient interactions (Nakamura and Nara 2004). It is therefore possible that the only genuine overall conclusion from the negative meta-analyses on LCP supplementation and neurological development might be that "no evidence of effect is not evidence of no effect" and that we are still distant from the definition of a balanced diet and a healthy lifestyle in general.

It seems that the current recommendations based on the milk LCP contents of Western mothers are likely to create a vicious circle: low LCP intakes by Western mothers cause low LCP contents in their breast milk and, correspondingly, low recommendations for infant formulas, while both the consumption of LCP-poor breast milk and formula will cause maintenance of low infant LCP status. The sole reliance on RCTs for "evidence-based" therapies in patient care and recommendations in health care are increasingly criticized (Rawlins 2008). Combinations of intervention studies, observational studies, historical data, knowledge of underlying mechanisms, toxicological considerations, and others might add to the strength of a recommendation and each of these pieces of evidence cannot contribute by introducing standardized weight factors that are compiled from a consensus hierarchy of scientific strength. For instance, higher intakes of EPA and DHA in the past, positive outcomes of RCTs with fish oil in CVD (Lee et al. 2008) and of EPA in depression (Ross et al. 2007), and knowledge of the underlying (patho)physiological mechanisms in inflammation, gene expression, and others, are together strong arguments for LCPn-3 recommendations for adults and consequently for all humans across the life cycle, infants included.

We conclude that, given the difficulty to prove beneficial effects of LCP in infants, current recommendations for pregnancy and early infancy are not to be based on negative meta-analyses and also not on data of milk from mothers with Western lifestyles. While more attention should be paid to the interaction of other nutrients with LCP, such as the interaction between folate and LCP, until further notice, a combination of data from milk of mothers eating traditional diets from the land–water ecosystem, and milk from mothers adhering to evidence-based recommended LCP intakes for adults may constitute the basis for LCP recommendations for infants.

Summary Points

- The maternal diet prior to conception and during pregnancy and lactation, as well as infant nutrition during early life, are important for child growth and development
- The long-chain polyunsaturated fatty acids (LCP), docosahexaenoic acid (DHA), and arachidonic acid (AA) are important for brain development.
- The positive meta-analyses of RCTs with LCPn-3 in cardiovascular disease and depression add to the contention that LCPn-3 is important across the entire life cycle.
- The DHA contents of infant formula should not be based on DHA contents in breast milk from mothers living in Western countries, since these mothers have low fish intakes.
- Studies on the relation between LCP status and brain development are positive, while meta-analyses of RCTs with prenatal as well as postnatal LCP supplementation are inconclusive.
- No evidence of LCP effects is not evidence of no effects.
- RCTs with single nutrients ignore the many possible interactions with other nutrients. Their outcomes are therefore unlikely to provide the proper information to restore the homeostasis on which our genes have evolved.
- Milk from mothers eating traditional diets from the land–water ecosystem and mothers adhering to evidence based recommended LCP intakes, may set the basis for LCP recommendations for infants.

Definitions of Key Terms

Essential fatty acids: EFA, fatty acids that cannot be synthesized and must be obtained from the diet to prevent deficiency disease. "Conditionally essential" refers to the necessity of a dietary source at circumstances during which the need exceeds endogenous synthesis.
Long chain polyunsaturated fatty acids: LCP, fatty acids with 20 or more carbon atoms, and 3 or more methylene-interrupted double-bonds in the *cis* configuration.
DHA, **docosahexaenoic acid:** an important LCP that is considered conditionally essential since its synthesis from precursors is limited. DHA is an important structural component of membrane phospholipids, a modulator of gene expression, and a precursor of resolvins and (neuro) protectins.
AA, **arachidonic acid:** an important LCP. AA is an important structural component of membrane phospholipids and a precursor of eicosanoids and resolvins.
Relative EFA/LCP deficiency: a deficiency of EFA/LCP that is not caused by low absolute amounts, but rather by an increase of other fatty acids, causing EFA/LCP dilution.

Key areas of this chapter

Essential fatty acids (EFA) and long chain polyunsaturated fatty acids (LCP)
    EFA and LCP metabolism
    EFA and LCP function
LCP in pregnancy
    Maternal and fetal LCP metabolism and transplacental transport
    LCP during pregnancy and neurodevelopment
LCP in early postnatal life
    Importance of LCP in neonatal nutrition
Recommendations for pregnant women and newborns
Epilog

References

Al MD, Hornstra G, van der Schouw YT, Bulstra-Ramakers MT, Huisjes HJ. Early Hum Dev. 1990;24:239–48.

Al MD, Van Houwelingen AC, Kester AD, Hasaart TH, de Jong AE, Hornstra G. Br J Nutr. 1995;74:55–68.

Angela Liou Y, Innis SM. Prostaglandins Leukot Essent Fatty Acids. 2009;80:201–6.

Bakker EC, Ghys AJ, Kester AD, Vles JS, Dubas JS, Blanco CE, Hornstra G. Eur J Clin Nutr. 2003;57:89–95.

Barker DJ. J Intern Med. 2007;261:412–7.

Bouwstra H, Dijck-Brouwer DA, Decsi T, Boehm G, Boersma ER, Muskiet FA, Hadders-Algra M. Pediatr Res. 2006a;60:334–9.

Bouwstra H, Dijck-Brouwer DA, Decsi T, Boehm G, Boersma ER, Muskiet FA, Hadders-Algra M. Pediatr Res. 2006b;59:717–22.

Burdge GC. Prostaglandins Leukot Essent Fatty Acids. 2006;75:161–8.

Burdge GC, Slater-Jefferies J, Torrens C, Phillips ES, Hanson MA, Lillycrop KA. Br J Nutr. 2007;97:435–9.

Calabrese EJ, Baldwin LA. Annu Rev Pharmacol Toxicol. 2003;43:175–97.

Cheruku SR, Montgomery-Downs HE, Farkas SL, Thoman EB, Lammi-Keefe CJ. Am J Clin Nutr. 2002;76:608–13.

Church MW, Jen KL, Dowhan LM, Adams BR, Hotra JW. Neurotoxicol Teratol. 2008;30:107–17.

Clandinin MT, Chappell JE, Leong S, Heim T, Swyer PR, Chance GW. Early Hum Dev. 1980a;4:131–8.

Clandinin MT, Chappell JE, Leong S, Heim T, Swyer PR, Chance GW. Early Hum Dev. 1980b;4:121–9.

Colombo J, Kannass KN, Shaddy DJ, Kundurthi S, Maikranz JM, Anderson CJ, Blaga OM, Carlson SE. Child Dev. 2004;75:1254–67.

Crawford MA, Hassam AG, Williams G. Lancet. 1976;1:452–3.

de Groot RH, Adam J, Jolles J, Hornstra G. Prostaglandins Leukot Essent Fatty Acids. 2004;70:41–7.

Diau GY, Hsieh AT, Sarkadi-Nagy EA, Wijendran V, Nathanielsz PW, Brenna JT. BMC Med. 2005;3:11.

Dijck-Brouwer DA, Hadders-Algra M, Bouwstra H, Decsi T, Boehm G, Martini IA, Boersma ER, Muskiet FA. Prostaglandins Leukot Essent Fatty Acids. 2005;72:21–8.

Dunstan JA, Simmer K, Dixon G, Prescott SL. Arch Dis Child Fetal Neonatal Ed. 2008 Jan;93(1):F45–50. Epub 2006 Dec 21.

Duttaroy AK. Prog Lipid Res. 2009;48:52–61.

Farquharson J, Cockburn F, Patrick WA, Jamieson EC, Logan RW. Lancet. 1992;340:810–3.

Fokkema MR, Smit EN, Martini IA, Woltil HA, Boersma ER, Muskiet FA. Prostaglandins Leukot Essent Fatty Acids. 2002;67:345–56.

Ghys A, Bakker E, Hornstra G, van den Hout M. Early Hum Dev. 2002;69:83–90.

Hadders-Algra M. J Perinat Med. 2008;36:101–9.

Hadders-Algra M, Bouwstra H, van Goor SA, Dijck-Brouwer DA, Muskiet FA. J Perinat Med. 2007;35 Suppl 1:S28–34.

Harris WS, Mozaffarian D, Rimm E, Kris-Etherton P, Rudel LL, Appel LJ, Engler MM, Engler MB, Sacks F. Circulation. 2009;119:902–7.

Hayes DP. Am J Clin Nutr. 2008;88:578S–81S.

Helland IB, Smith L, Saarem K, Saugstad OD, Drevon CA. Pediatrics. 2008;111:e39–e44.

Hibbeln JR. J Affect Disord. 2002;69:15–29.

Hibbeln JR, Davis JM, Steer C, Emmett P, Rogers I, Williams C, Golding J. Lancet. 2007;369:578–85.

Hornstra G. Am J Clin Nutr. 2000;71:1262S–9S.

Horrobin DF, Jenkins K, Bennett CN, Christie WW. Prostaglandins Leukot Essent Fatty Acids. 2002;66:83–90.

Innis SM. J Pediatr. 2003;143:S1–S8.

Innis SM. Placenta. 2005;26 Suppl A:S70–5.

Innis SM. J Nutr. 2007a;137:855–9.

Innis SM. Proc Nutr Soc. 2007b;66:397–404.

Innis SM, Friesen RW. Am J Clin Nutr. 2008;87:548–57.

ISSFAL. http://www.issfal.org.uk/adequate-intakes.html. 2009.

Ref Type: Internet Communication

Jacobson JL, Jacobson SW, Muckle G, Kaplan-Estrin M, Ayotte P, Dewailly E. J Pediatr. 2008;152:356–64.

Jamieson EC, Farquharson J, Logan RW, Howatson AG, Patrick WJ, Weaver LT, Cockburn F. Lipids. 1999;34:1065–71.

Judge MP, Harel O, Lammi-Keefe CJ. Lipids. 2007a;42:117–22.

Judge MP, Harel O, Lammi-Keefe CJ. Am J Clin Nutr. 2007b;85:1572–7.

Jump DB. Curr Opin Lipidol. 2008;19:242–7.

Koletzko B, Lien E, Agostoni C, Bohles H, Campoy C, Cetin I, Decsi T, Dudenhausen JW, Dupont C, Forsyth S, Hoesli I, Holzgreve W, Lapillonne A, Putet G, Secher NJ, Symonds M, Szajewska H, Willatts P, Uauy R. J Perinat Med. 2008;36:5–14.

Krabbendam L, Bakker E, Hornstra G, van OJ. Prostaglandins Leukot Essent Fatty Acids. 2007;76:29–34.

Kuipers RS, Smit EN, van der Meulen J, Dijck-Brouwer DA, Boersma ER, Muskiet FA. Prostaglandins Leukot Essent Fatty Acids. 2007;76:221–33.

Lauritzen L, Jorgensen MH, Olsen SF, Straarup EM, Michaelsen KF. Reprod Nutr Dev. 2005;45:535–47.

Lee JH, O'Keefe JH, Lavie CJ, Marchioli R, Harris WS. Mayo Clin Proc. 2008;83:324–32.

Levant B, Ozias MK, Carlson SE. Physiol Behav. 2006;89:196–204.

Levant B, Ozias MK, Davis PF, Winter M, Russell KL, Carlson SE, Reed GA, McCarson KE. Psychoneuroendocrinology. 2008;33:1279–92.

Lillycrop KA, Phillips ES, Torrens C, Hanson MA, Jackson AA, Burdge GC. Br J Nutr. 2008;100(2):278–82.

Makrides M, Gibson RA, McPhee AJ, Collins CT, Davis PG, Doyle LW, Simmer K, Colditz PB, Morris S, Smithers LG, Willson K, Ryan P. JAMA 2009;301:175–82.

Makrides M, Neumann MA, Byard RW, Simmer K, Gibson RA. Am J Clin Nutr. 1994;60:189–94.

Makrides M, Neumann MA, Gibson RA. Eur J Clin Nutr. 1996;50:352–7.

Martinez M, Mougan I. J Neurochem. 1998;71:2528–33.

McCann JC, Ames BN. Am J Clin Nutr. 2005;82:281–95.

McNamara RK, Carlson SE. Prostaglandins Leukot Essent Fatty Acids. 2006;75:329–49.

Mozaffarian D, Rimm EB. JAMA 2006;296:1885–99.

Muskiet FA, Fokkema MR, Schaafsma A, Boersma ER, Crawford MA. J Nutr. 2004;134:183–6.

Muskiet FA, van Goor SA, Kuipers RS, Velzing-Aarts FV, Smit EN, Bouwstra H, Dijck-Brouwer DA, Boersma ER, Hadders-Algra M. Prostaglandins Leukot Essent Fatty Acids. 2006;75:135–44.

Nakamura MT, Nara TY. Annu Rev Nutr. 2004;24:345–76.

Orr SK, Bazinet RP. Curr Opin Investig Drugs. 2008;9:735–43.

Parra-Cabrera S, Moreno-Macias H, Mendez-Ramirez I, Schnaas L, Romieu I. Early Hum Dev. 2008;84(1):51–7. Epub 2007 Apr 16.

Rawlins M. Lancet. 2008;372:2152–61.

Ross BM, Seguin J, Sieswerda LE. Lipids Health Dis. 2007;6:21.

Rump P, Mensink RP, Kester AD, Hornstra G. Am J Clin Nutr. 2001;73:797–806.

Scott DT, Janowsky JS, Carroll RE, Taylor JA, Auestad N, Montalto MB. Pediatrics.1998;102(5):E59.

Serhan CN, Chiang N. Br J Pharmacol. 2008;153 Suppl 1:S200–15.

Simmer K, Patole SK, Rao SC. Cochrane Database Syst Rev. 2008a; CD000376.

Simmer K, Schulzke SM, Patole S. Cochrane Database Syst Rev. 2008b; CD000375.

Smithers LG, Gibson RA, McPhee A, Makrides M. Am J Clin Nutr. 2008;88:1049–56.

Szajewska H, Horvath A, Koletzko B. Am J Clin Nutr. 2006;83:1337–44.

van Goor SA, Dijck-Brouwer DA, Fokkema MR, van der Iest TH, Muskiet FA. Prostaglandins Leukot Essent Fatty Acids. 2008a;78:159–69.

van Goor SA, Dijck-Brouwer DA, Hadders-Algra M, Doornbos B, Erwich JJ, Schaafsma A, Muskiet FA. Prostaglandins Leukot Essent Fatty Acids. 2009;80:65–9.

van Goor SA, Smit EN, Schaafsma A, Dijck-Brouwer DA, Muskiet FA. J Perinat Med. 2008b;36:548–9.

Vlaardingerbroek H, Hornstra G. Prostaglandins Leukot Essent Fatty Acids. 2004;71:363–74.

Wainwright PE, Xing HC, Mutsaers L, McCutcheon D, Kyle D. J Nutr. 1997;127:184–93.

Warnberg J, Gomez-Martinez S, Romeo J, Diaz LE, Marcos A. Ann NY Acad Sci. 2009;1153:164–75.

Williams C, Birch EE, Emmett PM, Northstone K. Am J Clin Nutr. 2001;73:316–22.

Chapter 75
Genetic Markers, Weight Reduction, and Behavioral Changes in Lifestyle

Thomas Reinehr and Anke Hinney

Abbreviations

BMI	Body mass index
BMR	Basal metabolic rate
ENPP1	Nucleotid pyrophosphatase/phosphodiesterase-1 gene
FTO	Fat mass and obesity associated gene
INSIG2	Insulin-induced gene 2
MC4R	Melanocortin 4 receptor gene
POMC	Pro-opiomelanocortin gene
SDS-BMI	Standard deviation of BMI
TCF7L2	Transcription factor 7-like-2 gene

75.1 Introduction

The prevalence of obesity is increasing in adults and children worldwide caused by changes in lifestyle and environment (Ebbeling et al. 2002). Since obesity is associated with increased morbidity and mortality, effective preventive and therapeutic approaches are urgently needed. Already, obese children suffer from features of metabolic syndromes such as dyslipidemia, impaired glucose tolerance, and hypertension (I'Allemand et al. 2008), which all lead to atherosclerosis (Reinehr et al. 2006b). Early vascular changes as demonstrated by increased intima-media thickness have already been reported in obese children and were reversible after weight loss. Additionally, childhood obesity affects both the children's quality of life and social integration (Ebbeling 2002). Furthermore, obese children tend to become obese adults (Ebbeling 2002). In conclusion, early intervention in obese children seems necessary.

Guidelines concerning treatment of childhood obesity recommend long-term outpatient training programs for both children and parents consisting of a combination of physical exercise, nutrition education, and behavior therapy, although few programs have been run or evaluated (Ebbeling 2002; http: and www.a-g-a.de/Leitlinie.pdf 2008; Summerbell 2007).

T. Reinehr (✉)
Department of Paediatric Nutrition Medicine, Vestische Hospital for Children and Adolescents,
University of Witten/Herdecke, Dr. F. Steiner Str. 5, 45711 Datteln, Germany
e-mail: T.Reinehr@kinderklinik-datteln.de

Furthermore, the effect of lifestyle intervention varied widely between different studies. Probably, a different degree of motivation, socioeconomic status, and/or genetic background may influence the outcome. In the following chapter these potential influence factors are discussed after introducing the training program Obeldicks, which is an example of a long-lasting successful lifestyle intervention in obese children and adolescents (Reinehr et al. 2005).

75.1.1 Lifestyle Intervention "Obeldicks"

Obeldicks, a lifestyle intervention program addresses obese children and adolescents aged 8–14 years. Briefly, this outpatient intervention program is based on physical activity, nutrition education, and behavior therapy, including the individual psychological care of the child and his or her family (Reinehr et al. 2005, 2006a). An interdisciplinary team of pediatricians, diet-assistants, psychologists, and exercise physiologists is responsible for the training. The children are divided into groups according to their sex and age. The 1-year training program is divided into three phases (see Fig. 75.1): In the intensive phase (3 months), the children take part in the nutritional course and in the eating-behavior course in six group-sessions each lasting for 1.5 h. At the same time, the parents are invited to attend six parents' evenings. In the establishing phase (6 months), individual psychological family therapy is provided (30 min/month). In the last phase of the program, accompanying the families back to their everyday lives (3 months), further individual care is possible, if and when necessary. The exercise therapy takes place once a week during the whole year through and consists of ball games, jogging, trampoline jumping, and instructions in physical exercise as part of everyday life and in a reduction in the amount of time spent watching television. The nutritional course is based on the prevention concept of the "Optimized mixed diet." Here the present scientific recommendations are translated into food-based dietary guidelines, while also considering the dietary habits of children and families in Germany. In contrast to the present-day diet of children in Germany with a fat content of 38% of energy intake, 13% proteins, and 49% carbohydrates including 14% sugar (Kersting et al. 1998), the "Optimized mixed diet" is both fat and sugar reduced and contains 30%
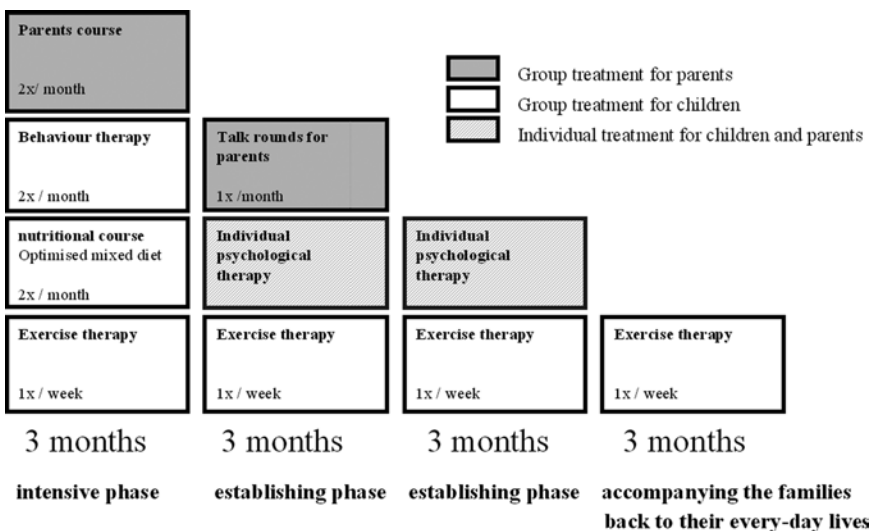
Fig. 75.1 Structure of the lifestyle intervention "Obeldicks." Components of the lifestyle intervention Obeldicks

fat, 15% proteins, and 55% carbohydrates including 5% sugar. The children follow a "traffic-light system" when selecting their food. In this system, the foods and drinks available in Germany are separated according to their fat and sugar contents into "red = stop," "orange = consider the amount," and "green = o.k. when hungry or thirsty." Three-day weighed dietary records demonstrated a reduction of the mean energy content of 1,459 (standard deviation (SD) 379) kcal per day before intervention to a median of 1,250 (SD 299) kcal per day at the end of intervention and a reduction of percentage fat from 36.3 (SD 5.0)% to 30.4 (SD 7.1)% (17). Furthermore, we have demonstrated an increase of physical activity during intervention (Reinehr et al 2005; Sousa et al 2009).

75.1.1.1 Long-Term Outcome After Intervention

More than 1,000 children and adolescents participated in this lifestyle intervention program, and in contrast to a control group, demonstrated long-term success (Reinehr et al. 2005). The success rate based on the "intention-to-treat" approach was 79% with a dropout rate of 17%. The mean reduction of SDS-BMI was 0.40, approximately a mean reduction of 2 kg/m² in BMI. A subgroup of 227 children was evaluated three years after the end of the intervention (Reinehr et al. 2007). In these children the mean SDS-BMI reduction was greater as compared to end of intervention (see Fig. 75.2).

Long-term multidisciplinary lifestyle interventions for children and their parents based on nutrition, exercise, and behavior therapy can lead to long-term weight loss. However, it is unclear which children profit from this intervention.

The achieved weight loss was clinically relevant as demonstrated by a decrease of blood pressure, triglycerides, impaired glucose tolerance, and prevalence of metabolic syndrome in contrast to a control group (Reinehr et al. 2006a) (Fig. 75.3). Furthermore, the intima-media thickness as a predictive factor for atherosclerosis decreased (Wunsch et al. 2006). The achieved weight loss was also relevant from the perspective of the participants as demonstrated by improved quality of life (Reinehr et al. 2005).
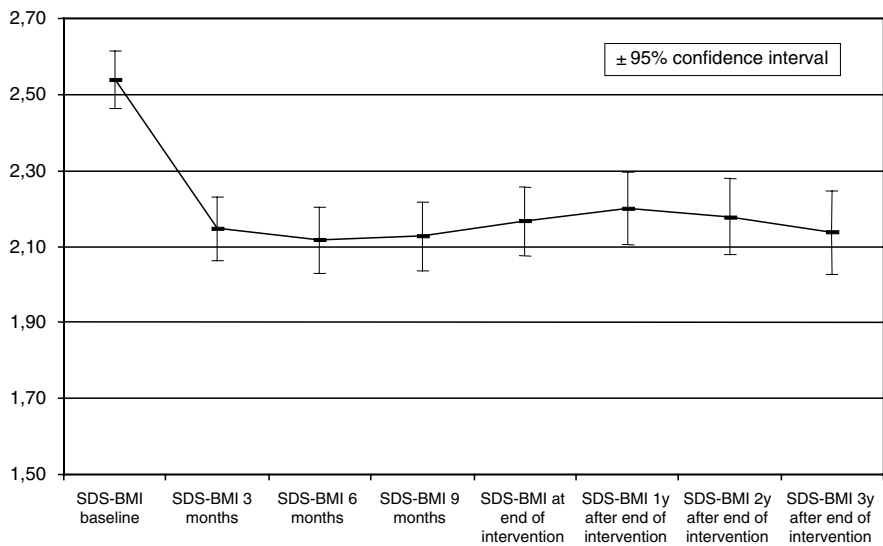
Fig. 75.2 Degree of overweight as standard deviation score of BMI (SDS-BMI) in a 4-year follow-up of 227 participants in the lifestyle intervention program Obeldicks (intention-to-treat analysis, data as mean and 95% confidence interval) (adapted from Reinehr et al. 2007). The participants in the lifestyle intervention program Obeldicks reduced their extent of overweight and this achieved weight loss was sustained over 3 years
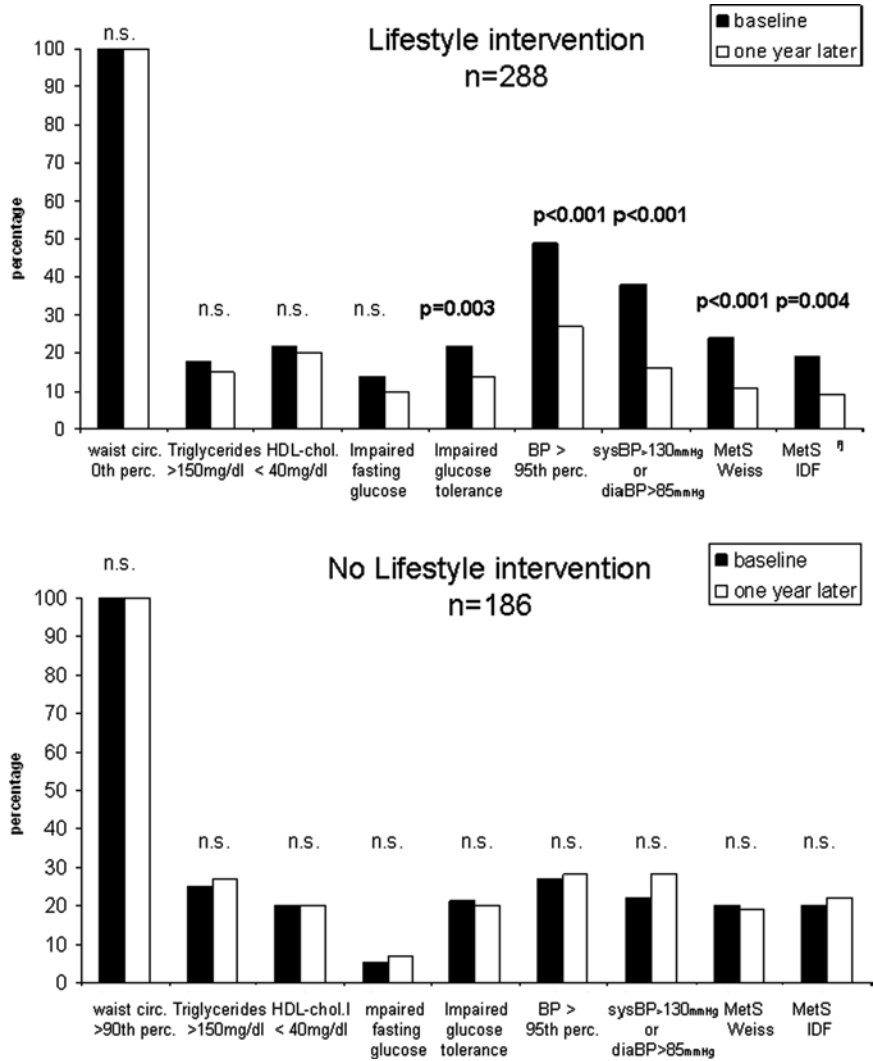
Fig. 75.3 Change of prevalence of the metabolic syndrome and its components in 288 obese children with lifestyle intervention and 186 obese children without lifestyle intervention in the course of 1 year (*p*-value derived from paired *t*-test; *perc.* percentile; *chol.* cholesterol, *sys* systolic, *dia* diastolic, *BP* blood pressure, *MetS* Metabolic syndrome). Participating in the lifestyle intervention program Obeldicks was associated with a reduction in the prevalence of metabolic syndrome in contrast to a control group

The achieved weight loss in lifestyle intervention for obese children even when only small is sufficient to improve the cardiovascular risk factor profile.

75.1.2 Motivation and Socioeconomic Status

The motivation and willingness to change dietary habitual intake and exercise habits are very likely decisive for success in lifestyle intervention (Ebbeling et al. 2002; http: and www.a-g-a.de/Leitlinie.pdf 2008; Summerbell 2007). Subjective estimates of the degree of motivation shown by the children

and their families are only of limited use. The desire to decrease weight does not always correspond with the willingness to change behavior. A questionnaire on the degree of motivation before the treatment showed that those obese children who were extremely well-motivated achieved worse results (Kirschenbaum et al. 1984).

Therefore, it is still not clear how the obese children's motivation to reduce weight can be proven. Suggestions have been a previous weight reduction, payment for the treatment by the patient himself, or psychological tests. It is problematic to demand weight reduction before the treatment since the children and their families want to take part in the training for the very reason that they are not able to achieve weight reduction on their own. Furthermore, there is the danger that weight loss is achieved due to a short-term hypocaloric diet which then leads to the yo-yo effect. If the parents have to pay for their children's training this would mean that the lower social classes (where obesity is more often found (Gortmaker et al. 1993)) would be unable to take part in the intervention. One disadvantage of using psychological tests to determine the degree of motivation is the necessarily long time and number of personnel involved. Studies on adults showed that psychological tests could not predict the rate of success after schooling (Fontaine et al. 1997).

To identify potential prediction factors for therapy success, we characterized the participants in our outpatient training "Obeldicks" and their families at the beginning of the treatment according to their dietary and physical habits, somatic characteristics, socioeconomic status, and the quality of their 3-day-weighes records (Reinehr et al. 2003).

The children who successfully reduced weight through the Obeldicks program differed from the unsuccessful children in the following ways (see Table 75.1): their mothers had a slightly higher BMI, they lived more seldom in single parent families, they had more often participated in therapy trials to reduce weight, and they had more often taken part in the exercise groups for the obese offered at the clinic before beginning of the training. Multiple logistic regression analysis showed that the previous participation in the exercise groups for the obese was an independent factor that was the strongest predictor for success in the training (Reinehr et al. 2003).

Therefore, families' motivation to change lifestyle during a training program and success in a lifestyle intervention may be predicted by participation in exercise groups before the beginning of the intervention.

In our experience an advantage of exercise groups for obese children before intervention is that the families are confronted with the difficulties involved when attending training regularly (time expenditure, means of transport, caring for other family members). Furthermore, these obese children can make contact with other obese children who have already finished their training and who can report on what they experienced. The children usually enjoy the exercise therapy which is often not the case for them when doing school sports. Conventional sport clubs are often unsuitable for obese children since they strive to achieve high sporting results. The difficulties for obese children being accepted within a conventional sports club can be estimated by the fact that no child in our sample actually became a member of such a club.

In our sample, the somatic characteristics of participants and their families (age, sex, and weight status) had no influence on the success of the treatment corresponding to other studies (Golan et al. 1998), while some others report on a better success rate with younger children, and a negative correlation between the success of the treatment and the degree of overweight (Epstein et al. 1990). Obesity in the parents has been described as a negative predictor of success (Epstein et al. 1990). Beside genetic influence factors, obese parents are said to have worse control over their children's nutrition, have less physical exercise, and are thus negative role models (Fogelholm et al. 1999).

The family's socioeconomic status (level of education of the children and their parents, working mother, marital status) had no influence on the success of the treatment in our sample. However, there was a tendency, though not significant, that children from single-parent families who were also

Table 75.1 Characteristics of successful and unsuccessful participants at the beginning of training program

	Successful	No success	*p*-Value
Willingness to change behavior			
Changes in SDS-BMI over the last 3 months	+0,0 (-0,4–+0,3)	+0,0 (-0,3–+0,2)	0.79**
Number of therapy trials	1 (0–4)	1 (0–3)	0.05**
Participation exercise groups before training	46%	4%	00002*
Somatic characteristics			
Age in years	11,6 (7,8–15,3)	11,8 (7,0–15,2)	0.95**
Gender	46% girls	52% girls	0.62*
Weight status (BMI)	28,8 (21,2–47,2)	30,4 (20,9–41,5)	0.99**
Weight status (SDS-BMI)	+2,5 (+1,9–+3,4)	+2,7 (+1,9–+3,8)	0.71**
BMI mother	26,7 (20,6–47,9)	25,3 (18,3–36)	0.02**
BMI father	27,3 (19,6–40,0)	28,2 (22,5–49,2)	0.25**
Number of obese siblings	1 (0–3)	0 (0–2)	0.33*
Socioeconomic status			
Type of schooling of children			0.91*
Hauptschule	23%	22%	
Realschule	17%	11%	
Gymnasium Gesamtschule	15%	11%	
Grundschule	13%	15%	
	33%	41%	
Mother's schooling level			0.08*
Hauptschule	48%	74%	
Realschule Hochschulreife	29%	11%	
	22%	15%	
Father's schooling levels			0.06*
Hauptschule	56%	78%	
Realschule Hochschulreife	25%	4%	
	19%	19%	
Single parent family	10%	30%	0.03*
Working mother	75%	74%	0.92*
Others involved in take care of child except parents	17%	33%	0.11*
Exercise habits			
average amount of physical exercise (hours per week)	0,0 (0,0–6,0)	0,0 (0,0–6,0)	0.81**
average amount of watching TV/ playing computers (hours per day)	3,0 (0,5–6,0)	4,0 (0,5–6,0)	0.19**
Dietary intake			
Reported energy intake MJ/Tag	6,4 (4,0–16,5)	6,6 (3,6–9,2)	0.86**
Reported energy intake/predicted basal metabolic rate	0,93 (0,38–2,00)	0,95 (0,48–1,59)	0.60**

Data as median and range, *: Chi-square-test, **: Mann-Whitney *U* test, *SDS-BMI* Standard deviation Score of Body Mass Index (Reinehr et al. 2003) in Germany, Grundschule is a primary school for all children in the first 4 years of school and Gesamtschule includes all types of secondary schools (Hauptschule, Realschule, and Gymnasium). Hauptschule refers to the lowest level of school education among the secondary schools compared to Realschuleand Gymnasium. Hochschulreife means qualification for university

Demonstrating that participating in sports groups predicts success in the lifestyle intervention Obeldicks in contrast to all other analyzed parameters

cared for by other people apart from their parents, had difficulties in losing weight. Another study, though on much smaller numbers, also showed that children from malfunctioning families had worse results (Kirschenbaum et al. 1984). If children regularly have meals elsewhere than in their family the chances of success decrease (Epstein et al. 1990). Strict adhesion to nutrition and dietary and exercise rules is made more difficult if different people like home helps, day care nurses, or grandparents are all responsible for the child.

In our sample, the quality of dietary recording as indicators of self-reflection and motivation demonstrated no association with the success of the intervention. We used several indices for quality of dietary recording:

- Number of recorded days.
- The quality of recording by percentage of weighed versus estimated food items per record.
- The validity of reported energy intake. For that purpose, the ratio of reported energy intake (EI) and predicted basal metabolic rate (BMR) was used. BMR was calculated using equations of Schofield (Schofield 1985), including measured height and weight of the individuals.
- Percentage of valid records was calculated based on sex and age-dependent cut-offs for EI/BMR calculated for children to identify underreporting (Sichert-Hellertet al. 1998). In both groups (successful and nonsuccessful participants) the percentage of nonplausible dietary records was high. In the ongoing observational DONALD-Study (DOrtmund Nutritional and Anthropometric Longitudinally Designed Study), conducted in the neighborhood at the Research Institute of Child Nutrition Dortmund, using the same recording method, only 5% of dietary records from normal weight children were identified as nonplausible (Sichert-Hellert et al. 1998). However, it is well known, that underreporting increases with increasing overweight (Golan et al. 1998; Sichert-Hellertet al. 1998).

Negative predictive factors of success in lifestyle interventions in children are

- Single-parent families
- Age >14 years
- Extreme obesity
- Obese parents

Since obesity in parents seems to influence the outcome in a lifestyle intervention program, genetic background may influence the success in lifestyle intervention.

75.1.3 Genetic Background

Twin studies clearly demonstrated a genetic predisposition in obesity (Hebebrand et al. 2001, 2003). The initially detected (until 2009) human genetic variants associated with polygenic obesity in multiple studies are summarized in Table 75.2. These variants have a relatively small effect size, but they are frequent and thus relevant in a substantial number of obese individuals. In 2009 the number of polygenic variants increased to 17 (Hinney and Hebebrand 2009); additionally, there is a small number of

Table 75.2 Variants with a polygenic effect on the human body weight detected until 2009 (adapted from Hinney and Hebebrand 2009)

Nearest gene	SNP	Approx. frequency of the risk allele (risk allele)	Sample size in the original publication	Effect on BMI in the original publication	Reference
INSIG2	rs7566605	37% (C)	9,881	+1.0 kg/m² for CC genotype	Herbert et al. (2006)
FTO	rs9939609	40% (A)	38,759	+0.40 kg/m² per A allele	Dina et al. (2007)
MC4R	rs2229616 (Val103Ile)	2% (103I)	7,713	−0.48 kg/m² per 103I allele	Geller et al. (2004)

Demonstrating the frequencies and effects on BMI of different SNPs

monogenic forms of obesity. The latter is characterized by a major effect of the respective mutation on the development of obesity. However, the frequency of these mutations is (extremely) low and can thus only explain the obese phenotype in a small fraction of obese individuals.

75.1.3.1 MC4R Mutations and Polymorphisms

Studies in mice and humans have pointed out the critical importance of the central melanocortinergic pathway in the control of energy homeostasis and, in particular, the pivotal role of the melanocortin 4 receptor gene (*MC4R*) (Hinney et al. 2006). Previous studies in humans have shown that the prevalence of functionally relevant *MC4R* mutations ranges from 0.5% to 5.8% in obese children and adolescents ascertained for molecular genetic studies (Hinney et al. 2006). More than 90 different obesity-associated mutations in the *MC4R*, most of which are nonsynonymous mutations leading to either total or partial loss of function, have so far been reported (Hinney et al. 2006; Tao and Segaloff 2003). The phenotype of carriers with mutations leading to a reduced receptor function considerably varies in their effect on body weight (Hinney et al. 2006). These mutations within the coding region are assumed to have a major effect on body weight, averaging approximately 4.5 and 9 kg/m² in adult males and females, respectively (Dempfle et al. 2004). Interestingly, two nonsynonymous polymorphisms, Val103Ile and Ile251Leu, that occur in 1–3% of the examined populations, respectively, are both associated with a slightly decreased BMI (Geller et al. 2004; Heid et al. 2008).

Recently, two genome-wide association studies (GWAS) showed that two variants located downstream of the *MC4R* are associated with obesity and related traits (Chambers et al. 2008; Loos et al. 2008). The C-allele of rs17782313 was associated with obesity as detected in more than 60,000 individuals (adults and children) of European descent (Loos et al. 2008). Each copy of this allele conferred odds of approximately 1.30 for severe childhood obesity. Chambers et al. (2008) showed that the variant rs12970134 was additionally associated with waist circumference and insulin resistance (Chambers et al. 2008).

75.1.3.2 FTO Polymorphisms

Several studies have demonstrated an association between variants in the "fat mass and obesity associated gene" (*FTO)* and obesity in both adults and children (Dina et al. 2007; Hinney et al. 2007; Muller et al. 2008). The biological function of *FTO* is largely unknown. However, *FTO* is expressed in multiple tissues throughout the brain and the periphery with high expression in the pituitary and adrenal glands and the hypothalamus. It has thus been suggested that *FTO* might play a role in the hypothalamic–pituitary–adrenal axis. Recently, a knockout mouse model for *Fto* showed that lack of *Fto* protects from obesity (Fischer et al. 2009). *FTO* knockout mice showed postnatal growth retardation and a significant reduction in adipose tissue and lean body mass. The leanness of *Fto*-deficient mice developed as a consequence of increased energy expenditure and systemic sympathetic activation, despite decreased spontaneous locomotor activity and relative hyperphagia. In summary, these data show that *FTO* is functionally involved in energy homeostasis by the control of energy expenditure (Fischer et al. 2009). Additionally, it was shown that *FTO* mRNA levels were reduced by 60% in the arcuate nucleus of wild-type mice following food deprivation, and that this decrease of *Fto* mRNA was independent of the fasting-induced decrease of leptin levels (Gerken et al. 2007). Further analyses revealed that *FTO* shares sequence motifs with Fe(II)- and 2oxoglutarate (2OG)-dependent oxygenases and that murine *FTO* catalyzes the Fe(II)- and 2OG-dependent demethylation of 3-methylthymine in single stranded DNA with concomitant production of succinate, formaldehyde, and carbon dioxide. Localization of *FTO* to

the nucleus in transfected cells is consistent with this potential role of *FTO* in nucleic acid demethylation. Additionally, allelic variation of *FTO* has been shown to be associated with a reduced cerebrocortical insulin effect on beta activity. It is therefore possible that impaired cerebrocortical insulin response at least partly accounts for the implication of *FTO* variants on obesity (Tschritter et al. 2007).

75.1.3.3 INSIG2 Polymorphism

An SNP located ~10 kb upstream of the insulin-induced gene-2 *INSIG2* (rs7566605) was shown to be associated with increased obesity risk for CC-homozygotes in a cross-sectional study of adults and children (Herbert et al. 2006). However, the influence of this SNP on obesity risk is uncertain: It has been genotyped in another 25,166 individuals of different ethnic backgrounds (Rosskopf et al. 2007). In 8,197 of these, an association with obesity could not be detected. However, a meta-analysis of case-control and family-based approaches comprising 16,969 individuals confirmed an association of rs7566605 and obesity (Lyon et al. 2007).

The mechanisms by which *INSIG2* influences body weight are unclear. *INSIG2* encodes a protein of the endoplasmic reticulum (ER) that blocks proteolytic activation of sterol regulatory element binding proteins and membrane-bound transcription factors that activate synthesis of cholesterol and fatty acids in animal cells. These proteins also restrict lipogenesis in mature adipocytes and block differentiation of preadipocytes (Gong et al. 2006).

75.1.3.4 Other Mutations and Polymorphisms Associated with Obesity

The extremely rare autosomal recessive genetic disorders leptin or leptin receptor deficiency, and loss of function mutations in the pro-opiomelanocortin gene (*POMC*) are well-established monogenic causes of obesity (Hinney and Hebebrand 2009). Moreover, several polymorphisms are discussed to influence the weight status such as, for example, variants in nucleotid pyrophosphatase/phosphodiesterase-1 gene (*ENPP1*) or the transcription factor 7 like-2 gene *(TCF7L2)* (Bottcher et al. 2006; Grant et al. 2006). The relevance of these variants is unclear and large confirmation studies are lacking so far. Variations in *TCF7L2* also contribute to insulin sensitivity and resistance. *TCF7L2* encodes a transcription factor and thereby regulates blood glucose homeostasis through regulation of proglucagon gene expression. The single nucleotide polymorphism (SNP) rs7903146 in *TCF7L2* is associated with an increased risk of type 2 diabetes mellitus and a slightly reduced risk for obesity.

75.2 Impact of Genetic Variants on Outcome of a Lifestyle Intervention

If all of the above mentioned genetic variants and mutations had an impact on body weight, one might speculate that they may influence the success in a lifestyle intervention program. Therefore, we analyzed the genetic background concerning mutations and/or variants in *MC4R*, *INSIG2*, *FTO*, and *TCF7L2* in the participants of the lifestyle intervention program Obeldicks and correlated them to the achieved weight loss.

The degree of overweight reduction in relation to genetic variants is demonstrated in Table 75.3 and Figs. 75.4 and 75.5. We did not find an increased risk for dropping out of lifestyle interventions for carriers of the obesity risk alleles of the polymorphisms in *INSIG2*, *TCF7L2*, and *FTO*, or *MC4R* mutations.

In concordance with a small previous report comprising four children with *MC4R* mutations (Hainerova et al. 2007), our children with *MC4R* mutations that lead to a reduced receptor function

Table 75.3 Mean change of SDS-BMI after the lifestyle intervention Obeldicks related to genetic variants

	Mean change of SDS-BMI	References
All participants	−0,40 *	Reinehr et al. (2003, 2005, 2006a)
Recessive model	Homozygotes[$]
INSIG2	−0,24 *,[$]	Reinehr et al. (2008b)
FTO	−0,27 *	Reinehr et al. (2009b)
TCF7L2	−0,47 *	Reinehr et al. (2008a)
Dominant model	Carrier of variants	
MC4R- deficiency-mutations	−0,18 *,[$]	Reinehr et al. (2009a)
MC4R polymorphisms (Val103Ile&Ile251Leu)	−0,45 *	(Reinehr et al. (2009a)

[$]Homozygotes refers to homozygous carriers of risk alleles at the following genes: CC-carriers in *INSIG2,* AA-carrier in *FTO,* and TT-carrier in *TCF7L2*;* nominal $p < 0,05$ comparison of carriers of wildtype alleles and heterozygotes (recessive model) or comparison between mutation carrier and nonmutation carrier (dominant model); [$]$p < 0.05$ adjusted for age, gender, and SDS-BMI at baseline

Demonstrating the effect of different genetic variants on the degree of overweight reduction in the lifestyle intervention program Obeldicks
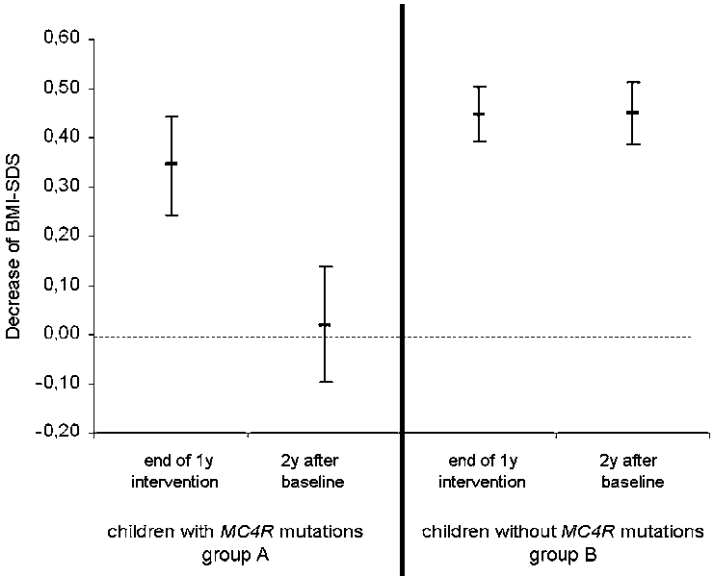
Fig. 75.4 Decrease of BMI-SDS (mean and standard deviation of the mean) in children with *MC4R* mutations that leads to a reduced receptor function (group A) and age- and gender- matched children without *MC4R* mutations (group B) at the end of a 1-year lifestyle intervention and 1 year after end of intervention compared to baseline BMI-SDS, *$p < 0.05$ (adapted from Reinehr et al. 2009a). Children with MC4R mutations were able to lose weight in the lifestyle intervention but failed to sustain this weight loss after the end of intervention

decreased their weight at the end of the intervention (Reinehr et al. 2009a). However, 1-year after the end of the lifestyle intervention, children with these *MC4R* mutations demonstrated a similar degree of overweight as at baseline, while children without these mutations had sustained their degree of weight loss (see Fig. 75.4) (Reinehr et al. 2009a). These findings support the impact of *MC4R* mutations on weight status. Since carriers of the *MC4R* mutations can lose body weight but have difficulties in maintaining this weight loss, longterm lifestyle interventions seem to be necessary for these children.

   MC4R-deficient obese children can lose weight in a lifestyle intervention but have great difficulties in maintaining weight loss.
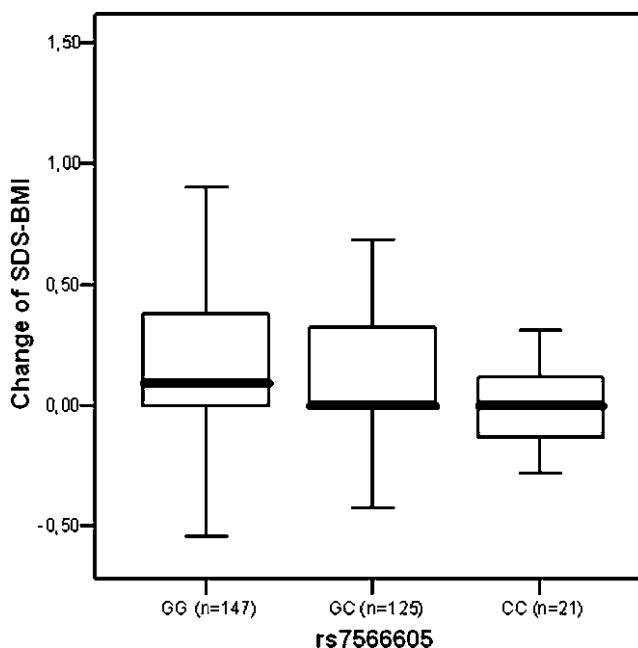
Fig. 75.5 INSIG2: rs7566605 genotypes and change of weight status (SDS-BMI) compared to baseline in 293 children after participation in the 1-year intervention based on an intention-to-treat analysis (data as median and interquartile range) (adapted from Reinehr et al. 2008b). CC carrier in *INSIG2* demonstrated a significant lower overweight reduction as compared to the wildtype or heterozygotes

Homozygotes for the C-allele of rs7566605, located approximately 10 kb upstream of *INSIG2*, showed a slightly increased risk to become obese. After the 1-year obesity intervention, children with the CC-genotype had reduced their BMI-SDS to a lower extent than obese children with GC- or GG-genotypes (recessive model P = 0.007) (Reinehr et al. 2008b). However, we have to keep in mind that it is unlikely that rs7566605, located 10 kb upstream of the transcriptional start site of the gene, is itself functional, but rather a variant elsewhere within the gene (Smith et al. 2007).

CC-homozygotes at SNP rs7566605 in the vicinity of *INSIG2* lost less weight in this lifestyle intervention. However, the effect was very moderate and replication studies are necessary to prove if a causal correlation really exists.

Children homozygous for the obesity risk-A-allele in *FTO* lost weight in the intervention, but to a lesser extent than children heterozygous or homozygous for the wildtype allele, while there was no significant difference with respect to SDS-BMI (Reinehr et al. 2009b). After adjusting for age, gender, baseline BMI, and the analyzed gene polymorphisms, this quantitative association between A-alleles in *FTO* and BMI change was not significant. Also, TT-carriers in *TCF7L2* did not differ in their overweight reduction as compared to heterozygotes or the wildtype carriers (Reinehr et al. 2008a).

Polygenic mechanisms are relevant in obesity; we therefore analyzed potentially aggravating effects of obesity risk alleles on weight loss. Our data revealed that obese children with a combination of the *INSIG2* CC-genotype and the *FTO* AA-genotype had no decrease of BMI and SDS-BMI within the Obeldicks lifestyle intervention (Reinehr et al. 2009b). The interaction term between the allele frequencies was significant ($p = 0.02$ for BMI as response and $p = 0.003$ for SDS as response variable (Reinehr et al. 2009b). One previous study in adults showed that homozygosity for both polymorphisms in *FTO* and *INSIG2* as well as the combination of *FTO/INSIG2* homozygosity/

heterozygosity leads to increased BMI (Chu et al. 2008). Conversely, yet another study showed no interaction between *INSIG2*, *MC4R* mutations, and *FTO* (Andreasen et al. 2008).

Since the combination of *INSIG2* CC-genotype and *FTO* AA-genotype was significantly associated with the lowest degree of overweight reduction, this finding suggests that the effects of *INSIG2* and *FTO* aggravate each other. Therefore, this finding provides a hint toward gene–gene interactions for weight loss during a lifestyle intervention program lasting 1 year.

Some important limitations of our studies have to be considered. First, the mechanisms of the genetic variants that influence overweight reduction are unclear. It is also possible that an interaction between polymorphism, mutations, and environmental factors such as diet may influence the change of weight status. Obesity occurs due to gene–gene and gene–environment interactions that vary across individuals. However, dietary records in obese children are difficult to interpret due to underreporting. Furthermore, our study only considered one polymorphism per gene; but especially for *FTO* the a priori evidence is so compelling that the analysis of a single SNP can be viewed as sufficient for an initial analysis (Hinney et al. 2007; Muller et al. 2008). With regard to the validity of our findings and the moderate study size, subsequent replication studies are necessary. However, longitudinal studies in overweight children undergoing a lifestyle intervention are difficult to perform and data are currently scarce.

Apart from the potential influence of genetic markers on the degree of weight loss, genetic polymorphisms may influence the improvement of cardiovascular risk factors in weight loss. In our study samples, most genetic variants such as *INSIG2, FTO,* or *MC4R* mutations did not influence the change of cardiovascular risk factor profile and insulin resistance (Reinehr et al. 2008b, 2009a, b). However, the T-allele at rs7903146 in *TCF7L2* was associated with a significant negative dosage effect per allele on the improvement of insulin resistance and sensitivity indices such as HOMA-IR and QUICKI after the lifestyle intervention independently of degree of weight loss, age, and gender (Reinehr et al. 2008a). Linear regression with gender, age, puberty, insulin, and glucose levels at baseline, as well as change of BMI-SDS as covariates, demonstrated a significant relationship between genotypes of rs7903146 and changes of HOMA-IR, HOMA-B%, and QUICKI (Table 75.4). The estimated effects adjusted for age, gender, pubertal stage, and change of BMI-SDS were +0.68 ± 0.01 for HOMA-IR per additional T-allele and −0.010 ± 0.004 for QUICKI per additional T-allele. However, the variance explained by these models was low (only 6.5% for HOMA-IR and 6.8% for QUICKI).

This finding is in line with the study of Florez and colleagues (Florez et al. 2006) demonstrating in a longitudinal study that the T-allele at rs7903146 is associated with impaired β-cell function. Further experimental and longitudinal studies are necessary to clarify the role of the *TCF7L2* gene variants in the progression to type 2 diabetes mellitus in humans.

Genetic background also influences changes in cardiovascular risk factors in lifestyle intervention programs independent of change in weight status.

Table 75.4 Tests for association of *rs7903146* in *TCF7L2* with changes of BMI-SDS, insulin, glucose, HOMA-IR, HOMA-B%, and QUICKI in the course of a 1 year lifestyle intervention in 236 overweight children

	Homozygous CC	Heterozygous TC	Homozygous TT	*p*-value
Number	121	97	18	–
Change of BMI-SDS	−0.30 ± 0.03	−0.28 ± 0.03	−0.33 ± 0.08	0.999
Change of glucose [mmol/l]	+0.04 ± 0.05	−0.04 ± 0.05	+0.10 ± 0.08	0.441
Change of insulin [mU/l]	−2.9 ± 1.3	+0.64 ± 1.4	+3.5 ± 2.6	0.014
Change of QUICKI	+0.008 ± 0.003	+0.002 ± 0.004	−0.020 ± 0.013	0.001

Data as mean and SE except *: median and interquartile range since variable is not normally distributed; *p*-values derived from linear regression analyses under allele-dosage model adjusted for gender, age, pubertal stage, baseline insulin and glucose levels, as well as change of weight status (BMI-SDS) except for change of BMI-SDS (adapted from Reinehr et al. 2008a)

The TT carriers in *TCF7L2* demonstrated a significantly lower improvement of insulin resistance as compared to the wildtype, and heterozygous carries independently of overweight reduction

75.3 Applications to Other Areas of Health and Disease

Lifestyle intervention is effective in motivated obese children to reduce weight and improve the cardiovascular risk factor profile. Therefore, whenever possible all diseases related to obesity should be treated with lifestyle intervention in this age group. Since genetic variations influence outcome with respect to both overweight reduction and improvement of cardiovascular risk factors, unsuccessful children should not be blamed. Putting together genetic research and clinical intervention studies represents a new promising field to prove the impact of genetic variants on body weight and to understand the different outcomes

Summary points

- Guidelines concerning treatment of childhood obesity recommend long-term outpatient training programs for both children and parents consisting of a combination of physical exercise, nutrition education, and behavior therapy, although few programs have been run or evaluated.
- Long-term multidisciplinary lifestyle interventions for children and their parents based on nutrition, exercise, and behavior therapy can lead to long-term weight loss.
- The families' motivation to change lifestyle during a training program and success in lifestyle intervention may be predicted by participation in exercise groups before the beginning of the intervention.
- Negative predictive factors of success in lifestyle interventions in children are single parent families, age >14 years, extreme obesity, obese parents.
- The achieved weight loss in lifestyle intervention for obese children is only small but sufficient to improve the cardiovascular risk factor profile.
- *MC4R*-deficient obese children can lose weight in a lifestyle intervention but have great difficulties in maintaining their weight loss.
- CC-homozygotes at SNP rs7566605 in the vicinity of *INSIG2* lost less weight in this lifestyle intervention.
- The effects of *INSIG2* and *FTO* on the effect of a lifestyle intervention seem to aggravate each other (gene–gene interactions)
- Genetic background also influences the changes in cardiovascular risk factors in lifestyle intervention independent of change in weight status.

Definitions

Socioeconomic status: Social class depending on income and education of an individual
Somatic characteristics: Weight, height, body circumferences of individuals
Genetic predisposition: Genetic part of the variance of a given phenotype or disease, usually determined by heritability estimates derived from, e.g., twin studies.
Polygenic: The combined action of alleles of more than one gene leads to a phenotype/disease. Body weight is an example of a polygenic trait. Presumably, the effect sizes of most gene variants predisposing to obesity are quite small (polygenic inheritance).
Mutation: The original human genetic definition is "**g**enetic variants (heritable changes in the nucleotide sequence in a gene or a chromosome) that occur in *less* than 1% of the normal population." Some authors suggest that "mutation" should relate to variants that are causal for/associated with a phenotype/disease. For this definition it is important that reference to the caused/associated phenotype/disease is given.

Polymorphism: Again the original human genetic definition is "**g**enetic variants that occur in *more* than 1% of the normal population." Some authors suggest that "polymorphism" should relate to variants that are *not* causal for/associated with a phenotype/disease. For this definition it is important that reference to the analyzed phenotype/disease is given. However, for complex traits this definition might not be useful.

Key Features of Single Nucleotide Polymorphisms (SNPs)

1. Single nucleotide polymorphisms (SNPs) are DNA sequence variations that occur when a single nucleotide (A, T, C, or G) in the genome sequence is altered.
2. Frequency of the minor allele above 1% in the general, unselected population.
3. SNPs make up approximately 90% of all human genetic variation.
4. They occur every 100–300 bases along the three billion base human genome.
5. SNPs can occur in coding (gene) and noncoding regions of the genome.
6. Many SNPs have no (direct) effect on function, but could predispose individuals to disease or influence their response to a drug.
7. A total of 6,573,789 validated SNPs in introns, exons, and intergenic regions can currently be found in the database (*dbSNP web query for build 129:Apr 14, 2008*).
8. Approximately 100,000–300,000 SNPs are presumed to be related to disease (associated to a phenotype).
9. SNPs are valuable for biomedical research and for developing pharmaceutical products or medical diagnostics.

Key Facts of Obeldicks

1. Lifestyle Intervention for obese children and adolescents aged 6–15 years
2. One-year intervention based on physical activity, nutrition education, and behavior therapy, including the individual psychological care of the child and his or her family.
3. An interdisciplinary team of pediatricians, diet-assistants, psychologists, and exercise physiologists is responsible for the training.
4. The children are divided into groups according to their sex and age.
5. The 1-year training program is divided into three phases:

   • In the intensive phase (3 months), the children take part in the nutritional course and in the eating-behavior course in six group-sessions each lasting for 1.5 h. At the same time, the parents are invited to attend six parents' evenings.
   • In the establishing phase (6 months), individual psychological family therapy is provided (30 min/month).
   • In the last phase of the program (accompanying the families back to their everyday lives) (3 months), further individual care is possible, if and when necessary.

• The exercise therapy takes place once a week during the whole year through and consists of ball games, jogging, trampoline jumping, and instructions in physical exercise as part of everyday life and in reduction of the amount of time spent watching television.
• The nutritional course is based on the prevention concept of the "Optimized mixed diet." Here the present scientific recommendations are translated into food-based dietary guidelines.

References

Andreasen CH, Mogensen MS, Borch-Johnsen K, Sandbaek A, Lauritzen T, Sorensen TI, Hansen L, Almind K, Jorgensen T, Pedersen O, Hansen T. PLoS.ONE. 2008;3:e2872.

Bottcher Y, Korner A, Reinehr T, Enigk B, Kiess W, Stumvoll M, Kovacs P. J Clin Endocrinol Metab. 2006;91:4948–52.

Chambers JC, Elliott P, Zabaneh D, Zhang W, Li Y, Froguel P, Balding D, Scott J, Kooner JS. NatGenet. 2008;40:716–8.

Chu X, Erdman R, Susek M, Gerst H, Derr K, Al-Agha M, Wood GC, Hartman C, Yeager S, Blosky MA, Krum W, Stewart WF, Carey D, Benotti P, Still CD, Gerhard GS. Arch Surg. 2008;143:235–40.

Dempfle A, Hinney A, Heinzel-Gutenbrunner M, Raab M, Geller F, Gudermann T, Schafer H, Hebebrand J. J Med Genet. 2004;41:795–800.

Dina C, Meyre D, Gallina S, Durand E, Korner A, Jacobson P, Carlsson LM, Kiess W, Vatin V, Lecoeur C, Delplanque J, Vaillant E, Pattou F, Ruiz J, Weill J, Levy-Marchal C, Horber F, Potoczna N, Hercberg S, Le Stunff C, Bougneres P, Kovacs P, Marre M, Balkau B, Cauchi S, Chevre JC, Froguel P. Nat Genet. 2007;39:724–6.

Ebbeling CB, Pawlak DB, Ludwig DS. Lancet. 2002;360:473–82.

Epstein LH, Valoski A, Wing RR, McCurley J. JAMA. 1990;264:2519–23.

Fischer J, Koch L, Emmerling C, Vierkotten J, Peters T, Bruning JC, Ruther U. Nature. 2009;16:458(7240):894–8. E Pub 2009 Feb 22.

Florez JC, Jablonski KA, Bayley N, Pollin TI, de Bakker PI, Shuldiner AR, Knowler WC, Nathan DM, Altshuler D. N Engl J Med. 2006;355:241–50.

Fogelholm M, Nuutinen O, Pasanen M, Myohanen E, Saatela T. Int J Obes Relat Metab Disord. 1999;23:1262–8.

Fontaine KR, Cheskin LJ. Addict Behav. 1997;22:567–70.

Geller F, Reichwald K, Dempfle A, Illig T, Vollmert C, Herpertz S, Siffert W, Platzer M, Hess C, Gudermann T, Biebermann H, Wichmann HE, Schafer H, Hinney A, Hebebrand J. Am J Hum Genet. 2004;74:572–81.

Gerken T, Girard CA, Tung YC, Webby CJ, Saudek V, Hewitson KS, Yeo GS, McDonough MA, Cunliffe S, McNeill LA, Galvanovskis J, Rorsman P, Robins P, Prieur X, Coll AP, Ma M, Jovanovic Z, Farooqi IS, Sedgwick B, Barroso I, Lindahl T, Ponting CP, Ashcroft FM, O'Rahilly S, Schofield CJ. Science. 2007;318:1469–72.

Golan M, Weizman A, Apter A, Fainaru M. Am J Clin Nutr. 1998;67:1130–5.

Gong Y, Lee JN, Brown MS, Goldstein JL, Ye J. Proc Natl Acad Sci U.S.A. 2006;103:6154–9.

Gortmaker SL, Must A, Perrin JM, Sobol AM, Dietz WH. N Engl J Med. 1993;329:1008–12.

Grant SF, Thorleifsson G, Reynisdottir I, Benediktsson R, Manolescu A, Sainz J, Helgason A, Stefansson H, Emilsson V, Helgadottir A, Styrkarsdottir U, Magnusson KP, Walters GB, Palsdottir E, Jonsdottir T, Gudmundsdottir T, Gylfason A, Saemundsdottir J, Wilensky RL, Reilly MP, Rader DJ, Bagger Y, Christiansen C, Gudnason V, Sigurdsson G, Thorsteinsdottir U, Gulcher JR, Kong A, Stefansson K. Nat Genet. 2006;38:320–3.

Hainerova I, Larsen LH, Holst B, Finkova M, Hainer V, Lebl J, Hansen T, Pedersen O. J Clin Endocrinol Metab. 2007;92:3689–96.

Hebebrand J, Friedel S, Schauble N, Geller F, Hinney A. Obes Rev. 2003;4:139–46.

Hebebrand J, Sommerlad C, Geller F, Gorg T, Hinney A. Int J Obes Relat Metab Disord. 2001;25 Suppl 1:10–8.

Heid IM, Vollmert C, Kronenberg F, Huth C, Ankerst DP, Luchner A, Hinney A, Bronner G, Wichmann HE, Illig T, Doring A, Hebebrand J. Obesity (Silver.Spring). 2008;16:369–76.

Herbert A, Gerry NP, McQueen MB, Heid IM, Pfeufer A, Illig T, Wichmann HE, Meitinger T, Hunter D, Hu FB, Colditz G, Hinney A, Hebebrand J, Koberwitz K, Zhu X, Cooper R, Ardlie K, Lyon H, Hirschhorn JN, Laird NM, Lenburg ME, Lange C, Christman MF. Science. 2006;312:279–83.

Hinney A, Hebebrand J. Obes Facts. 2009;2(1):3–8. Epub 2009 Feb 16.

Hinney A, Bettecken T, Tarnow P, Brumm H, Reichwald K, Lichtner P, Scherag A, Nguyen TT, Schlumberger P, Rief W, Vollmert C, Illig T, Wichmann HE, Schafer H, Platzer M, Biebermann H, Meitinger T, Hebebrand J. J Clin Endocrinol Metab. 2006;91:1761–9.

Hinney A, Nguyen TT, Scherag A, Friedel S, Bronner G, Muller TD, Grallert H, Illig T, Wichmann HE, Rief W, Schafer H, Hebebrand J. PLoS ONE. 2007;2:e1361

http: and www.a-g-a.de/Leitlinie.pdf; 2008

I'Allemand D, Wiegand S, Reinehr T, Muller J, Wabitsch M, Widhalm K, Holl R. Obesity (Silver.Spring). 2008;16:1672–9.

Kersting M, Sichert-Hellert W, Lausen B, Alexy U, Manz F, Schoch G. Z Ernahrungswiss. 1998;37:47–55.

Kirschenbaum Harris ES, Tomarken AJ. Behav Ther. 1984;15:266–72.

Loos RJ, Lindgren CM, Li S, Wheeler E, Zhao JH, Prokopenko I, Inouye M, Freathy RM, Attwood AP, Beckmann JS, Berndt SI, Jacobs KB, Chanock SJ, Hayes RB, Bergmann S, Bennett AJ, Bingham SA, Bochud M, Brown M, Cauchi S, Connell JM, Cooper C, Smith GD, Day I, Dina C, De S, Dermitzakis ET, Doney AS, Elliott KS, Elliott P, Evans DM, Sadaf FI, Froguel P, Ghori J, Groves CJ, Gwilliam R, Hadley D, Hall AS, Hattersley AT, Hebebrand J, Heid IM, Lamina C, Gieger C, Illig T, Meitinger T, Wichmann HE, Herrera B, Hinney A, Hunt SE, Jarvelin MR, Johnson T, Jolley JD, Karpe F, Keniry A, Khaw KT, Luben RN, Mangino M, Marchini J, McArdle WL, McGinnis R, Meyre D, Munroe PB, Morris AD, Ness AR, Neville MJ, Nica AC, Ong KK, O'Rahilly S, Owen KR, Palmer CN, Papadakis K, Potter S, Pouta A, Qi L, Randall JC, Rayner NW, Ring SM, Sandhu MS, Scherag A, Sims MA, Song K, Soranzo N, Speliotes EK, Syddall HE, Teichmann SA, Timpson NJ, Tobias JH, Uda M, Vogel CI, Wallace C, Waterworth DM, Weedon MN, Willer CJ, Wraight YX, Zeggini E, Hirschhorn JN, Strachan DP, Ouwehand WH, Caulfield MJ, Samani NJ, Frayling TM, Vollenweider P, Waeber G, Mooser V, Deloukas P, McCarthy MI, Wareham NJ, Barroso I, Jacobs KB, Chanock SJ, Hayes RB, Lamina C, Gieger C, Illig T, Meitinger T, Wichmann HE, Kraft P, Hankinson SE, Hunter DJ, Hu FB, Lyon HN, Voight BF, Ridderstrale M, Groop L, Scheet P, Sanna S, Abecasis GR, Albai G, Nagaraja R, Schlessinger D, Jackson AU, Tuomilehto J, Collins FS, Boehnke M, Mohlke KL. Nat Genet. 2008;40:768–75.

Lyon HN, Emilsson V, Hinney A, Heid IM, Lasky-Su J, Zhu X, Thorleifsson G, Gunnarsdottir S, Walters GB, Thorsteinsdottir U, Kong A, Gulcher J, Nguyen TT, Scherag A, Pfeufer A, Meitinger T, Bronner G, Rief W, Soto-Quiros ME, Avila L, Klanderman B, Raby BA, Silverman EK, Weiss ST, Laird N, Ding X, Groop L, Tuomi T, Isomaa B, Bengtsson K, Butler JL, Cooper RS, Fox CS, O'Donnell CJ, Vollmert C, Celedon JC, Wichmann HE, Hebebrand J, Stefansson K, Lange C, Hirschhorn JN. PLoS Genet. 2007;3:e61

Muller TD, Hinney A, Scherag A, Nguyen TT, Schreiner F, Schafer H, Hebebrand J, Roth CL, Reinehr T. BMC Med Genet. 2008;9:85

Reinehr T, Brylak K, Alexy U, Kersting M, Andler W. Int J Obes Relat Metab Disord. 2003;27:1087–92.

Reinehr T, de SG, Andler W. Obes Res. 2005;13:1824–33.

Reinehr T, de SG, Toschke AM, Andler W. Am J Clin Nutr. 2006a;84:490–6.

Reinehr T, Friedel S, Mueller TD, Toschke AM, Hebebrand J, Hinney A. Int J Obes (Lond). 2008a;32:1521–4.

Reinehr T, Hebebrand J, Friedel S, Toschke AM, Brumm H, Biebermann H, Hinney A. Obesity (Silver.Spring). 2009a;17:382–9.

Reinehr T, Hinney A, Nguyen TT, Hebebrand J. Diabetes. 2008b;57:623–6.

Reinehr T, Hinney A, Toschke AM, Hebebrand J Arch Dis Child. 2009b.

Reinehr T, Kersting M, Wollenhaupt A, Alexy U, Kling B, Strobele K, Andler W. Klin Padiatr. 2005;217:1–8.

Reinehr T, Kiess W, de SG, Stoffel-Wagner B, Wunsch R. Metabolism. 2006b;55:113–8.

Reinehr T, Temmesfeld M, Kersting M, de SG, Toschke AM. Int J Obes (Lond). 2007;31:1074–7.

Rosskopf D, Bornhorst A, Rimmbach C, Schwahn C, Kayser A, Kruger A, Tessmann G, Geissler I, Kroemer HK, Volzke H. Science 2007;315:187.

Schofield WN. Hum Nutr Clin Nutr. 1985;39(1):5–41.

Sichert- Hellert G, Kersting M, Schöch G. Z Ernährungswiss. 1998;37:242–51.

Smith AJ, Cooper JA, Li LK, Humphries SE. Int J Obes (Lond). 2007;31:1753–5.

Sousa GD, Hussein A, Trowitzsch E, Andler W, Reinehr T. Klin Padiatr. 2009;221:237–240.

Summerbell CD. Obesity (Silver Spring). 2007;15:1341–2.

Tao YX, Segaloff DL. Endocrinology. 2003;144:4544–51.

Tschritter O, Preissl H, Yokoyama Y, Machicao F, Haring HU, Fritsche A. Diabetologia. 2007;50:2602–3.

Wunsch R, de Sousa G, Toschke AM, Reinehr T. Pediatrics. 2006;118:2334–40.

Chapter 76
The Role of Gene Polymorphisms in Susceptibility to Anorexia Nervosa and Bulimia Nervosa

Palmiero Monteleone and Mario Maj

Abbreviations

5-HT	Serotonin
5-HTT	Serotonin Transporter
AN	Anorexia Nervosa
ANBP	Anorexia Nervosa Binge-Eating/Purging Subtype
ANR	Anorexia Nervosa restricting Subtype
BDNF	Brain-Derived Neurotrophic Factor
BMI	Body Mass Index
BN	Bulimia Nervosa
BNNP	Bulimia Nervosa Nonurging Subtype
BNP	Bulimia Nervosa Purging Subtype
BW	Body Weight
CLOCK	Circadian Locomotor Output Cycles Kaput
COMT	Cathecol-O-Methyltransferase
DAT	Dopamine Transporter
ED	Eating Disorder
FAAH	Fatty Acid Amide Hydrolase
KCNN3	Small-Conductance Calcium-Activated Potassium Channel-3
MAOA	Monoamino Oxydase A
NAAA	N-Acylethanolamine-Hydrolyzing Acid Amidase
NET	Noradrenaline Transporter
NPY	Neuropeptide Y
SNP	Single Nucleotide Polymorphism
SSRI	Selective Serotonin Reuptake Inhibitor
TPH-1	Tryptophan-Hydroxylase-1
UCP	Uncoupling Protein
VNTR	Variable Number of Tandem Repeats

P. Monteleone (✉)
Department of Psychiatry, University of Naples SUN, Largo Madonna delle Grazie, 80138 Naples, Italy
e-mail: monteri@tin.it

76.1 Introduction

Anorexia nervosa (AN) and bulimia nervosa (BN) are eating disorders (EDs) characterized by pathological concerns about body weight (BW) and body shape and abnormal patterns of feeding behavior and energy expenditure. Specifically, AN is characterized by the obsessive fear of being fat and the voluntary pursuit of thinness; despite increasing emaciation and a BW below the 85% of the ideal, individuals with AN are dissatisfied with the perceived size and shape of their body, and engage in unhealthy behaviors to perpetuate BW loss or prevent BW gain. In the Diagnostic and Statistical Manual of Mental Disorders – IV edition (American Psychiatric Association 1990), AN is classified into two subtypes: AN binge-eating/purging subtype (ANBP), where patients engage in binge-purging behaviors, and AN-restricting subtype (ANR), where patients exclusively restrict their food intake. BN is characterized by recurrent episodes of uncontrolled binge eating coupled with inappropriate compensatory behaviors, such as vomiting, laxative abuse, food restriction, and/ or excessive exercising, in order to prevent BW gain, because of the patient's pathological fear of becoming fat. Similarly to AN, BN is classified into two subtypes: BN purging subtype (BNP), where patients provoke vomiting, abuse laxatives and/or diuretics as compensatory behaviors, and BN nonpurging subtype (BNNP), where patients engage in excessive exercise and/or food restriction to prevent BW gain.

The etiopathogenesis of EDs is thought to be multifactorial with psychological, social, and biological factors being allegedly involved, although the exact role played by each of them is not yet completely known. At present, it is widely accepted that genetic factors are responsible for the transmission of a biological vulnerability to the disorders, as clearly demonstrated by epidemiological, family, and molecular genetic studies.

Molecular genetic studies aiming to identify chromosomal regions and genes of vulnerability in EDs use two methodologies: linkage and association (i.e., case–control or within family) designs.

Linkage study is an approach without an a priori hypothesis for the genes possibly involved in the disease. By screening the whole human genome with genetic markers in a cohort of affected families, it examines the transmission and segregation of polymorphic markers to identify chromosomal regions rather than specific genes likely linked to the disorder. This strategy needs a large recruitment of families including probands and affected and unaffected relatives, which represents a major limitation for rare disorders such as EDs.

Association study uses a different approach based on a priori hypotheses, which rely on biochemical, physiological, or pharmacological evidence suggesting the involvement of specific endogenous substances in the etiopathogenesis of a disorder; therefore, the genes involved in the physiology of those substances are identified as "candidate genes" contributing to the heritable susceptibility to the disorder. Association study compares the frequency of polymorphic alleles and genotypes between two groups, controls and patients (Table 76.1). A higher or a lower frequency in patients would suggest that the gene may be associated to the disorder with predisposition or protection, respectively. A disadvantage of this design is the risk of yielding false positive results due to population stratification. However, an association study can also be performed in family trios (affected proband and both biological parents) by using the transmission disequilibrium test (TDT). In this design, the transmission versus nontransmission of marker alleles to affected offspring is compared. This method eliminates population stratification effects completely.

The purpose of this review is to critically appraise the extant literature on association studies of candidate gene polymorphisms in AN and/or BN.

Table 76.1 Key features of polymorphisms.

- A single-nucleotide polymorphism (SNP) is a DNA sequence variation occurring when a single nucleotide in the genome differs between members of a species (or between paired chromosomes in an individual). In this case two *alleles* are identified: the wild type allele and the polymorphic (or mutant) allele.
- SNPs may fall within coding sequences of genes, noncoding regions of genes, or in the intergenic regions between genes.
- SNPs within a coding sequence will not necessarily change the amino acid sequence of the protein that is produced, due to degeneracy of the genetic code. A SNP in which both alleles lead to the same polypeptide sequence is termed *synonymous.*
- An SNP which induces a different polypeptide sequence is termed *nonsynonymous*. The nonsynonymous SNP leads to changes in protein structure and/or function.
- SNPs that are not in protein-coding regions may still have consequences for gene splicing, transcription factor binding, or the sequence of noncoding RNA.
- The greatest importance of SNPs in biomedical research is for comparing regions of the genome between cohorts (such as with matched cohorts with and without a disease) in order to identify polymorphic variants of genes that could be involved in the genetic susceptibility to human disease.
- There are variations between human populations; so an SNP allele that is common in one geographical or ethnic group may be much rarer in another.
- The nomenclature for SNPs can be confusing: several variations can exist for an individual SNP and consensus has not yet been achieved.

76.2 Central Regulators of Eating Behavior

In the last 20 years, central neurotransmitters, hormones, and peptides have been identified to regulate eating behavior and, in some cases, psychopathological dimensions associated to EDs (Monteleone et al. 2008). Regulators of feeding that have been of interest for the genetics of AN and BN include central neurotransmitters and peptides such as serotonin (5-HT), dopamine (DA), noradrenaline (NA), endocannabinoids, opioids, the brain-derived neurotrophic factor (BDNF), neuropeptide Y (NPY), and the agouti-related protein. Therefore, the genes involved in the biosynthesis and/or degradation of those substances and their receptors have been selected as candidate genes, and mutations, variations, and polymorphisms of those genes appear of particular interest, especially if they affect either the protein structure/function or expression.

76.2.1 Serotonin

Genes coding the 5-HT transporter (5-HTT) protein, 5-HT receptors, and the biosynthetic enzyme tryptophan hydroxylase-1 have received a great deal of interest in association studies, since 5HT has been shown to be involved in the modulation of both food ingestion and psychopathological traits associated with EDs, such as depression, anxiety, impulsivity, and obsession (Lucki 1998). Moreover, 5-HT has been supposed to modulate harm avoidance, a human personality dimension that is disturbed in ED patients (Cloninger et al. 1993).

76.2.1.1 Serotonin Transporter

The human *5-HTT* gene is located on chromosome 17q11.1–17q.12. A polymorphism in the promoter region of the *5-HTT* gene (*5-HTTLPR*) has been described (Heils et al. 1999). It consists of a

44-base pair deletion (short or S variant) or insertion (long or L variant), which is endowed with functional consequences as the S form is associated with a lower transcriptional activity and a reduced 5-HT reuptake efficiency than the L isoform (Greenberg et al. 1999). A nominal association of the S allele with AN has been detected in two studies (Fumeron et al. 2001; Matsushita et al. 2004), but not confirmed in five others (Hinney et al. 1997a; Di Bella et al. 2000; Sundaramurthy et al. 2000; Urwin et al. 2003a; Rybakowski et al. 2006) (Table 76.2). In particular, the positive study of Matsushita et al. (2004) reported that the S allele was more frequent in AN patients who had a stable AN diagnosis for at least 3 years. A meta-analysis including four of the cited association studies concluded that the S allele of the *5-HTTLPR* polymorphism may represent a moderate but significant risk factor for AN (Gorwood 2004).

As for BN, one study showed a positive association between the S allele of the *5-HTTLPR* polymorphism and BN (Di Bella et al. 2000), one other found a higher frequency of the L allele in BN female patients (Monteleone et al. 2006a), and two studies did not report any significant association (Lauzurica et al. 2003; Matsushita et al 2004) (Table 76.3).

The possibility that the *5-HTTLPR* polymorphism is not directly associated with EDs, but linked to phenotypic aspects of AN and BN has been also explored. Indeed, the S allele was found to be associated with comorbid borderline personality disorder, affective instability, and insecure attachment in women with binge-purging syndromes (Steiger et al. 2005), and to higher levels of drive for thinness and body dissatisfaction in patients with AN and BN (Frieling et al. 2006). Moreover, two studies found that BN patients carrying at least one S allele had lower values of BMI and body fat mass and higher levels of harm avoidance and anxiety than those with the LL genotype (Monteleone et al. 2006a; Ribasès et al. 2008).

The 5-HTT represents the prime target of Selective Serotonin Reuptake Inhibitors (SSRIs) and the S allele of the 5-*HTTLPR* has been associated with poorer SSRI response in major depression (Serretti and Artioli, 2004). Similarly, one study showed that the S form of the 5-*HTTLPR* was associated with a poorer outcome of SSRI therapy in BN women undergoing a 12-week naturalistic treatment with different SSRIs plus nutritional counselling (Monteleone et al. 2005a). Indeed, as compared to patients with LL genotype, bulimic subjects carrying at least one copy of the S allele had a 23.33-fold reduced probability of a response (defined as a >50% decrease in the weekly frequency of binge-purging episodes) and a 10.66-fold decrease in the probability of remission (defined as a complete absence of binge-purging episodes). These results disagree with those of Erzegovesi et al. (2004) who found no association between the 5-*HTTLPR* polymorphism ant treatment outcome in BN individuals undergoing a 6-week treatment with one of four different SSRIs or placebo plus a standardized intensive cognitive behavioral treatment program. However, in this study, the efficacy of drug treatment was evaluated as the percent improvement in the Yale-Brown-Cornell Eating Disorders Scale, which assesses food-related obsessions and compulsions and does not provide any specific measure of bulimic symptomatology. Therefore, differences in the study designs, duration of SSRI treatments, and measurements of the outcome may explain the inconsistency between the two studies. In line with Monteleone et al.'s results (2005a), Steiger et al. (2008) found that women with bulimia-spectrum EDs carrying the 5-HTTLPR low functional allele (or the low function allele of the -1438G/A SNP of the $5\text{-}HT_{2A}$ receptor gene) showed smaller reduction in binge-eating and anxiety symptomatology after a multimodal intervention strategy.

It has been recently shown that the L allele consists of two main different variants, one of which has the same activity as the S allele (Nakamura et al. 2000); hence, studies taking into account the 5-*HTTLPR* triallelic model need to be performed to clarify the role of 5-*HTTLPR* polymorphism in the genetic susceptibility to EDs and in the response prediction in BN.

Table 76.2 Association studies of genes coding central regulators of feeding in anorexia nervosa

Candidate gene	Analyzed polymorphism	Statistical significance	Note	References
5-HT transporter	44 bp Del/Ins (promoter)	S	A meta-analysis (Gorwood 2004) concluded that the S allele may represent a moderate but significant risk for AN	Fumeron et al. (2001); Matsushita et al. (2004)
		NS		Hinney et al. (1997a); Di Bella et al. (2000); Sundaramurthy et al. (2000); Urwin et al. (2003a); Rybakowski et al. (2006)
5-HT$_{2A}$ receptor	−1438G/A (promoter)	S	The A allele was associated specifically to ANR	Collier et al. (1997, 1999); Sorbi et al. (1998); Enoch et al. (1998); Nacmias et al. (1999); Ricca et al. (2002, 2004)
		NS		Hinney et al. (1997b); Campbell et al. (1998); Ziegler and Gorg (1999); Ando et al. (2001a); Nishiguchi et al. (2001); Kipman et al. (2002); Gorwood et al. (2002); Rybakowski et al. (2006)
	Thr25Asn	NS		Hinney et al. (1997b); Nacmias et al. (1999)
	His452Tyr	NS		Hinney et al. (1997b); Nacmias et al. (1999)
	102T/C	NS		Nacmias et al. (1999)
	516T/C	NS		Nacmias et al. (1999)
5-HT$_{2C}$ receptor	Cys23Ser	S	The Ser23 allele was suggested to predispose to a general proneness of young women to experience weight loss through reducing food intake	Westberg et al. (2002); Hu et al. (2003)
		NS		Nacmias et al. (1999)
5-HT$_{1D\beta}$ receptor	Phe124Cys	NS		Hinney et al. (1999a)
	−1,123T>C	NS		Bergen et al. (2003)
	−628T>C	NS		Bergen et al. (2003)
	1,080C>T	NS		Bergen et al. (2003)
	2,190A>G	NS		Bergen et al. (2003)
	rs652783	NS		Brown et al. (2007)
	rs604030	NS		Brown et al. (2007)
	rs674386	S		Brown et al. (2007)
	rs856510	S		Brown et al. (2007)
5-HT$_7$ receptor	Pro279Leu	NS		Hinney et al. (1999a)
Tryptophan hydroxylase-1	T1095C	NS		Han et al. (1999)

(continued)

Table 76.2 (continued)

Candidate gene	Analyzed polymorphism	Statistical significance	Note	References
Dopamine transporter (DAT1)	VNTR	S		Shinohara et al. (2004)
Dopamine D2 receptor (DRD2)	−141 Indel-/C	NS		Bergen et al. (2005)
	2,730T>C	NS		Bergen et al. (2005)
	932C>G	NS		Bergen et al. (2005)
	939C>T	NS		Bergen et al. (2005)
	957C>T	NS		Bergen et al. (2005)
	725 bp 3' G>T	S	The association was statistically significant in ANBP but not in ANR	Bergen et al. (2005)
	10,620C>T	S		Bergen et al. (2005)
	TaqA1	NS		Nisoli et al. (2007)
Dopamine D3 receptor (DRD3)	Bal-I	NS		Bruins-Slot et al. (1998)
Dopamine D4 receptor (DRD4)	3-bp deletion	NS		Hinney et al. (1999b)
	48-bp repeat	NS		Hinney et al. (1999b)
	D4pr C(521)T	S		Bachner-Melman et al. (2007)
	D4pr C(616)G	NS		Bachner-Melman et al. (2007)
	D4pr A(809)G	NS		Bachner-Melman et al. (2007)
	D4pr 120 repeat	S	The association was statistically significant in ANBP but not in ANR	Bachner-Melman et al. (2007)
	D4 exon III repeat	NS		Bachner-Melman et al. (2007)
Noradrenaline transporter (NET)	4bp Del/Ins (promoter)	S	The association was statistically significant in ANR but not in ANBP patients	Urwin et al. (2002)
		NS		Hu et al. (2007)
β3-adrenergic receptor	Trp64Arg	NS		Hinney et al. (1997c); Miyasaka et al. (2006)
Catechol-O-methyltransferase (COMT)	Val158Met (472G/A)	S		Frisch et al. (2001); Michaelovsky et al. (2005); Micolajczyk et al. (2006)
		NS		Gabrovsek et al. (2004)
	−1,219A/G	NS		Michaekowsky et al. (2005)
	186C/T	NS		Michaekowsky et al. (2005)
	408C/G	S	The association was statistically significant in the ANR but not in the ANBP group	Michaekowsky et al. (2005)
ARVCF	826InsC	NS		Michaekowsky et al. (2005)
	659C/T	NS		Michaekowsky et al. (2005)

(continued)

Table 76.2 (continued)

Candidate gene	Analyzed polymorphism	Statistical significance	Note	References
	524T/C	S	The association was statistically significant in the ANR but not in the ANBP group	Michaekowsky et al. (2005)
Monoamino oxidase A (MAOA)	MAOA-uVNTR	NS		Urwin et al. (2003b)
Brain-derived neurotrophic factor (BDNF)	196G/A (Val66Met)	S	The Val66Met SNP of the *BDNF* gene was found quite consistently although not specifically linked to ANR	Ribasès et al. (2003, 2004, 2005a); Koizumi et al. (2004); Dmitrzak-Weglarz et al. (2007)
		NS		Friedel et al. (2005); Rybakowski et al. (2007); Dardennes et al. (2007)
	−270C/T	NS		Ribasès et al. (2003, 2004, 2005a); Koizumi et al. (2004); Dardennes et al. (2007)
Neurotrophic tyrosin kinase receptor 2 (NTRK2)	−69C>G	S	The association was statistically significant in the ANBP but not in the ANR group	Ribasès et al. (2005b)
	IVS2+40C>T	NS		Ribasès et al. (2005b)
	IVS13+40G>A	NS		Ribasès et al. (2005b)
	IVS17+125T>C	NS		Ribasès et al. (2005b)
	IVS18+13G>A	NS		Ribasès et al. (2005b)
	2,785–2,785insC	NS		Ribasès et al. (2005b)
Neuropeptide Y Y$_1$ receptor	*Pst*I	NS		Rosenkranz et al. (1998a)
Neuropeptide Y Y$_5$ receptor	Gly426Gly	NS		Rosenkranz et al. (1998a)
Agouti-related protein (AGRP)	G760A	S		Vink et al. (2001); Dardennes et al. (2007)
	G526A	S		Vink et al. (2001)
	C659T	NS		Vink et al. (2001)
Opioid receptor delta-1	80T>G	NS		Bergen et al. (2003)
	8,214T>C	NS		Bergen et al. (2003)
	23,340A>G	NS		Bergen et al. (2003)
	47,821A>G	S		Bergen et al. (2003)
	51,502A>T	NS		Bergen et al. (2003)
	rs569356	S		Brown et al. (2007)
	rs521809	S	The association was statistically significant in the ANR but not in the ANBP group	Brown et al. (2007)
	rs4654327	S	The association was statistically significant in the ANR but not in the ANBP group	Brown et al. (2007)

Table 76.2 (continued)

Candidate gene	Analyzed polymorphism	Statistical significance	Note	References
	rs204055	NS		Brown et al. (2007)
	rs204047	NS		Brown et al. (2007)
	rs2298896	NS		Brown et al. (2007)
Cannabinoid receptor 1 (CNR1)	AAT 7,9–15 repeats	S	The 13-repeat allele was preferentially transmitted in ANBP patients while the 14-repeat allele was preferentially transmitted in the ANR group	Siegfried et al. (2004)
		NS		Muller et al. (2008)
	−22,959A/G	NS		Muller et al. (2008)
	−6,274A/T	NS		Muller et al. (2008)
	−6,215T/G	NS		Muller et al. (2008)
	−5,489T/C	NS		Muller et al. (2008)
	−1,359G/A	NS		Muller et al. (2008)
Fatty acid amide hydrolase (FAAH)	−272G/A	NS		Muller et al. (2008)
	10,741C/A	NS		Muller et al. (2008)
	11,966G/A	NS		Muller et al. (2008)
	13,883G/A	NS		Muller et al. (2008)
	19,542C/A	NS		Muller et al. (2008)
N-acylethanolamine-hydrolyzing acid amidase (NAAA)	368A/G	NS		Muller et al. (2008)
	9,263A/T	NS		Muller et al. (2008)
	19,229G/T	NS		Muller et al. (2008)

This table lists published association studies of polymorphic variants of genes involved in the physiology of central regulators (neurotransmitters, neuropeptides and neurohormones) of feeding and energy homeostasis in anorexia nervosa

AN anorexia nervosa, *ANR* anorexia nervosa restricted subtype, *ANBP* anorexia nervosa binge-purging subtype, *5-HT* serotonin, *NS* not significant, *S* significant, *VNTR* variable number of tandem repeats, *ARVCF* armadillo repeat gene deleted in velocardiofacial syndrome, *MAOA-uVNTR* MAOA-upstream variable number of tandem repeats

76.2.1.2 Serotonin Receptors

5-HT_{2A} and 5-HT_{2C} receptors play a role in the serotonergic control of appetite, and polymorphisms of genes coding these two receptors have been identified. The -1438G/A polymorphism in the promoter region of the 5-HT_{2A} receptor gene is of particular interest, since functional activity of the promoter and 5-HT_{2A} receptor activation have been reported to be lower for the G allele and higher for the A allele (Shimizu et al. 2003; Parsons et al. 2004). A significantly higher frequency of both the AA genotype and the A allele of the -1438G/A polymorphism was found in AN by some studies (Collier et al. 1997; Collier 1999; Sorbi et al. 1998; Enoch et al. 1998; Nacmias et al. 1999; Ricca et al. 2002, 2004), but not confirmed by others (Hinney et al. 1997b; Campbell et al. 1998; Ziegler and Görg, 1999; Ando et al. 2001a; Nishiguchi et al. 2001; Kipman et al. 2002; Gorwood et al. 2002; Rybakowski et al. 2006) (Table 76.2). Four of the positive studies, all of the same research group (Sorbi et al. 1998; Nacmias et al. 1999; Ricca et al. 2002, 2004), reported that the -1438G/A polymorphism was specifically associated to ANR subtype. The A allele has been reported to be linked with some AN-related phenotypic traits such as an older age at onset, higher levels of weight

Table 76.3 Association studies of genes coding central regulators of feeding in bulimia nervosa

Candidate gene	Analyzed polymorphism	Statistical significance	Note	References
5-HT Transporter	44 bp Del/Ins (promoter)	S	One study reported a higher frequency of the S allele (Di Bella et al. 2000); the other one reported a higher frequency of the L allele (Monteleone et al. 2006a)	Di Bella et al. (2000); Monteleone et al. (2006a)
		NS		Lauzurica et al. (2003); Matsushita et al. (2004)
5-HT$_{2A}$ receptor	−1,438G/A (promoter)	S	One study (Nishiguchi et al. 2001) found a significant association with the G allele instead of the A allele	Nishiguchi et al. (2001); Ricca et al. (2002, 2004)
		NS		Enoch et al. (1998); Ziegler and Gorge (1999); Fuentes et al. (2004); Bruce et al. (2005)
	Thr25Asn	NS		Nacmias et al. (1999)
	His452Tyr	NS		Nacmias et al. (1999)
	102T/C	NS		Nacmias et al. (1999)
	516T/C	NS		Nacmias et al. (1999)
5-HT$_{2C}$ receptor	Cys23Ser	NS		Nacmias et al. (1999); Burnet et al. (1999)
5-HT$_{1D\beta}$ receptor	G861C	NS		Levitan et al. (2001, 2006)
Tryptophan hydroxylase-1	A218C	NS	The A allele was associated with a more severe bulimic symptomatology	Monteleone et al. (2007)
Dopamine Transporter (DAT1)	VNTR	NS		Shinohara et al. (2004)
Dopamine D2 receptor (DRD2)	TaqA1	NS		Nisoli et al. (2007)
β3-adrenergic receptor	Trp64Arg	NS		Miyasaka et al. (2006)
Catechol-O-methyltransferase (COMT)	Val158Met (472G/A)	NS		Micolajczyk et al. (2006)
Brain-derived neurotrophic factor (BDNF)	196G/A (Val66Met)	S		Ribasès et al. (2004)
		NS	In the study of Koizumi et al. (2004) a significant association was found in the BNNP group	Ribasès et al. (2003, 2005a); Koizumi et al. (2004); Monteleone et al. (2006b)
	−270C/T	NS		Ribasès et al. (2003, 2004, 2005a);
Neurotrophic tyrosin kinase receptor 2 (NTRK2)	−69C>G	NS		Ribasès et al. (2005b)
	IVS2+40C>T	NS		Ribasès et al. (2005b)
	IVS13+40G>A	S		Ribasès et al. (2005b)
	IVS17+125T>C	S		Ribasès et al. (2005b)

(continued)

Table 76.3 (continued)

Candidate gene	Analyzed polymorphism	Statistical significance	Note	References
	IVS18+13G>A	NS		Ribasès et al. (2005b)
	2,785–2,785insC	NS		Ribasès et al. (2005b)

This table lists published association studies of polymorphic variants of genes involved in the physiology of central regulators (neurotransmitters, neuropeptides, and neurohormones) of feeding and energy homeostasis in bulimia nervosa

BNNP bulimia nervosa nonpurging subtype, *5-HT* serotonin, *NS* not significant, *S* significant, *VNTR* variable number of tandem repeats

and shape concerns and total Eating Disorder Examination scores, lower levels of harm avoidance, and reward dependence (Kipman et al. 2002; Gorwood et al. 2002; Ricca et al. 2004; Rybakowski et al. 2006).

Three studies reported a significant association of the -1438G/A polymorphism of the promoter of the *5-HT$_{2A}$* receptor gene with BN (Nishiguchi et al. 2001; Ricca et al. 2002, 2004), whereas five others did not (Enoch et al. 1998; Ziegler and Görge 1999; Fuentes et al. 2004; Bruce et al. 2005) (Table 76.3). One of the positive studies performed in an Asian population (Nishiguchi et al. 2001) found a nominal association between BN and the GG genotype/G allele instead of the AA genotype/A allele as observed in the other two studies (Ricca et al. 2002, 2004). Interestingly, the GG genotype and the G allele were more frequent in the group with binge-purging phenotype (ANBP and BNNP), and BN patients with GG genotype were characterized by blunted prolactin response to meta-chlorophenylpiperazine and higher levels of impulsivity (Bruce et al. 2005), which suggests a reduced serotonergic activity of the wild type allele. Therefore, the higher 5-HT$_{2A}$ receptor activity associated to the A allele, could result in a potentiation of the anorectic 5-HT signal explaining the above-reported association of this allele with ANR and with reduced levels of harm avoidance, whereas the G allele could sustain binge eating behavior in BN because of lower 5-HT$_{2A}$ receptor activity.

The Thr25Asn, His452Tyr, 102T/C, and 516T/C SNPs of the *5-HT$_{2A}$* receptor gene were found not significantly associated with both AN and BN (Hinney et al. 1997b; Nacmias et al. 1999) (Tables 76.2 and 76.3).

The Ser23 allele of the Cys23Ser SNP of the *5HT2C* receptor gene is associated with a higher 5-HT$_{2C}$ receptor expression (Sodhi et al. 1999), and two out of three studies (Nacmias et al. 1999; Westberg et al. 2002; Hu et al. 2003) reported higher frequencies of the Ser23Ser genotype and the Ser23 allele in Caucasian AN patients (Table 76.2). Furthermore, in the study of Hu et al. (2003), including also 43 AN trios, the TDT showed a preferential transmission of the Ser23 allele, which was also associated with lower BMI. Therefore, the putative enhanced activity of 5-HT$_{2C}$ receptors in carriers of Ser23 allele would sustain the restrictive behavior of AN patients and could explain the lower BMI. Recently, a higher frequency of the Ser23 allele has been found also in teenage girls reporting weight loss but not affected by AN (Westberg et al. 2002), which suggests that this SNP might be not specifically associated with AN, but with a general proneness of young women to experience weight loss through reducing food intake. No association between the Cys23Ser SNP of the *5-HT$_{2C}$* receptor gene and BN has been detected (Nacmias et al. 1999; Burnet et al. 1999) (Table 76.3).

Some SNPs and the haplotypes -1123T>C/1080C>T and 1080C>T/2190A>G of the *5-HT$_{1D\beta}$* receptor gene were found significantly associated with AN or ANR (Bergen et al. 2003; Brown et al.

2007) (Table 76.2). These associations are intriguing, since the *5-HT$_{1D\beta}$* receptor gene is positioned under an observed linkage peak on chromosome 1 for ANR (Grice et al. 2002; Bergen et al. 2003). Therefore, the *5-HT$_{1D\beta}$* receptor gene certainly is worth of further investigation. The G861C SNP of the *5-HT$_{1D\beta}$* receptor gene has been investigated in BN patients (Levitan et al. 2001, 2006) (Table 76.3); although no significant association emerged between this SNP and BN, bulimic individuals with GG genotype had a minimum lifetime BMI significantly lower than GC and CC genotypes and a more severe comorbid obsessive-compulsive disorder.

No significant association has been detected between the Pro279Leu SNP of *5-HT$_7$* receptor gene and AN (Hinney et al. 1999a).

76.2.1.3 Serotonin Biosynthetic Enzyme

The A218C SNP of the *tryptophan-hydroxylase-1* (*TPH-1*) gene is endowed with functional effects, since the A allele has been found to be associated with lower cerebrospinal fluid 5-hydroxyindolacetic acid levels in healthy volunteers (Jonsson et al. 1997). Although no significant association was found between the A218C SNP of the *TPH*-1 gene and BN (Table 76.3), BN women with the AA genotype displayed a more severe bulimic symptomatology (as measured by the weekly frequency of binge-purging episodes and the Bulimia Investigation Test Edinburgh) and higher levels of harm avoidance as compared to AC and CC genotypes (Monteleone et al. 2007). Therefore, it could be hypothesized that BN individuals with the A variant of the *TPH*-1 A218C SNP have reduced concentrations of 5-HT at their central synapses, which would represent a vulnerability factor for binge eating behavior and higher harm avoidance.

No significant association between the Y1095C SNP of the *TPH-1* gene and AN was reported in a small sample study (Han et al. 1999) (Table 76.2).

76.2.2 Dopamine

Dopaminergic neurotransmission modulates feeding, thinking processes, motor activity, reward-motivated and drug-seeking behaviors. AN and BN patients, aside from their well-known disturbances of eating behavior, exhibit physical hyperactivity, distortion of thinking and body image, and obsessive–compulsive behaviors. Therefore, genes of dopamine transmission are candidate genes in EDs.

76.2.2.1 Dopamine Transporter

The dopamine transporter (DAT) protein is a critical regulator of synaptic dopamine. The *DAT1* gene, encoding the DAT protein, is polymorphic, and in most human beings occurs with greatest frequency in the 9- and 10-repeat forms. The 10-repeat variable number of tandem repeats (VNTR) polymorphism has been shown to be associated with an approximately 50% increase of DAT binding sites as compared to the 9-repeat allele (vanNess et al. 2005). One study investigated the VNTR polymorphism of the *DAT1* gene in small groups of ANBP and BN patients and found a higher frequency of short alleles (seven and nine repeats) as compared to long alleles (10 and 11 repeats) in ANBP but not in BN (Shinohara et al. 2004) (Tables 76.2 and 76.3).

76.2.2.2 Dopamine Receptors

Bergen et al. (2005) tested seven SNPs within the dopamine D2 receptor gene (*DRD2*) and found significant associations of the 725bp3'G>T and 10620C>T SNPs with ANBP (Table 76.2). Moreover, the haplotype Indel+939C>T was significantly associated with both AN and ANR; the haplotypes Indel +957C>T and 939C>T+725bp3'G>T were significantly associated with AN, and the haplotype 939C>T+10520C>T was significantly associated with ANR. Another variant of the *DRD2* gene is represented by the polymorphic Taq1A restriction endonuclease site that has been shown to reduce D2 receptor synthesis (Laakso et al. 2005). No association between the *DRD2* Taq1A polymorphism and AN or BN was detected in a very small sample of patients, including also obese individuals (Nisoli et al. 2007) (Tables 76.2 and 76.3), although it was found significantly associated with the Eating Disorder Inventory Subitems that characterize the drive for thinness and ineffectiveness, which suggests a possible role of this polymorphism in ED-related phenotypic traits.

SNPs of the dopamine D3 (*DRD3*) and D4 (*DRD4*) receptor genes have been investigated for association with AN and results were generally negative (Bruins-Slot et al. 1998; Hinney et al. 1999b; Bachner-Melman et al. 2007) (Table 76.2). A functional polymorphism of the *DRD4* gene is represented by the D4prC(521)T, where the C allele has been found to be responsible for less transcriptional activity of the *DRD4* gene (Okuyama et al. 2000). The recent study of Bachner-Melmam et al. (2007), who explored five SNPs of the *DRD4* gene, showed that the C allele of the D4pr C(521) T SNP was preferentially transmitted to AN individuals and that the D4pr C(521)T SNP, the D4pr 120 repeat, and several two, three, four, and five locus haplotypes were significantly associated with AN (with some differences between ANR and ANBP) and with the socially proscribed perfectionism subscale and/or the self-oriented perfectionism subscale of the Children and Adolescent Perfectionism Scale in AN. These findings suggest a possible involvement of *DRD4* gene in ED-related phenotypic traits such as perfectionism.

76.2.3 Noradrenaline

Decreased levels of norepinephrine have been detected in the blood and cerebrospinal fluid of long-term weight-restored patients with AN (Kaye et al. 1985), which supports an involvement of noradrenergic transmission in AN. A repeat polymorphism in the promoter region of the norepinephrine transporter (*NET*) gene (NETpPR), characterized by a 4bp deletion (NETpPR-S4) or insertion (NETpPR-L4), has been characterized. This polymorphism results in an alteration of a potential transcription factor binding site. In a sample of 101 AN Australian trios, including 14 ANBP trios and 87 ANR trios, a higher frequency of L4/L4 genotype and L4 allele was found in ANR patients. Moreover, the TDT showed a preferential transmission of the NETpPR-L4 allele from L4/S4 heterozygous parents to their ANR children (Urwin et al. 2002). This finding was not confirmed in a subsequent study (Hu et al. 2007) (Table 76.2).

In humans, the beta-3 adrenoceptor is primarily expressed in visceral fat and its activation by catecholamines promotes lipolysis. Recently, the Trp64Arg SNP of the beta-3 adrenergic receptor has been suggested to be a predisposing factor for abdominal obesity and metabolic alterations, especially in women (Kurabayashi et al. 1996); therefore, this SNP has been considered to be of interest also in EDs. However, no association between the Trp64Arg SNP of the *beta-3 adrenergic receptor* gene and AN or BN has been detected (Hinney et al. 1997c; Miyasaka et al. 2006) (Tables 76.2 and 76.3).

76.2.4 Monoamine Degrading Enzymes

Catechol-O-methyltransferase (COMT) and monoamine oxidase A (MAOA) are the two main enzymes involved in the degradation of brain monoamines. An SNP at position 472 (472G/A) of the *COMT* gene creates an amino acid change (158 Val>Met) leading to two forms of the mature protein: the 158Val protein is provided of high enzymatic activity, which is about 4 times greater than the 158Met protein (Lachman et al 1996). A nominal association of the ValVal genotype and the Val allele with AN has been shown in two studies (Frisch et al. 2001; Micolajczyk et al. 2006) but has not been confirmed in a large case-control study of individuals from six European countries (Gabrovsek et al. 2004) (Table 76.2). Similarly, a preferential transmission of the Val allele was detected in a sample of 66 ANR trios (Michaelovsky et al. 2005), but not confirmed in a larger study including 372 AN trios (Gabrovsek et al. 2004). Moreover, four SNPs of the COMT gene other than the Val158Met SNP were investigated together with two SNPs in the adjacent *armadillo repeat gene deleted in velocardiofacial syndrome* (*ARVCF*) gene, and the haplotype COMT-186C-408G-472G-ARVFC-659C-524T was identified as a "risk haplotype," whereas the haplotype COMT-186T-408C-472A-ARVFC659T-524C was identified as a "protective haplotype" for AN (Michaekowsky et al. 2005) (Table 76.2). Moreover, the TDT showed a preferential transmission of the C allele of the 408C/G and of the T allele of the 524T/C SNPs. Finally, the Met allele of the 158 Val>Met SNP of the COMT gene was found to be associated with ED-related phenotypic traits, such as higher scores on the subscales bulimia, ineffectiveness, interoceptive awareness, maturity fears, and impulse regulation of the Eating Disorder Inventory (Frieling et al. 2006).

The promoter of the *MAOA* gene has a functional MAOA-upstream VNTR (MAOA-uVNTR) polymorphism, which consists of 3 (3-allele) or 4 (4-allele) copies of a 30-bp sequence, or rarely 2 (2-allele) or three copies plus the first 18-bp of the same 30-bp sequence (3a-allele), or five copies (5-allele). The 3a-allele and 4-allele (MAOA-L) are transcribed more efficiently than the shorter 3-allele (MAOA-S) (Sabol et al. 1998). One study found no significant association between the MAOA-uVNTR polymorphism and AN (Urwin et al. 2003b) (Table 76.2). No study has been performed to assess specifically the association of SNPs of the *COMT* and *MAOA* genes with BN. Only Mikolajczyk et al. (2006) reported no significant association between the 472G/A SNP of the *COMT* gene and BN in a study including only 28 BN individuals.

76.2.5 Epistasis

Epistasis, that is gene–gene interaction, between the *5-HTTLPR* polymorphism and polymorphisms of the *NET* or the *MAOA* gene have been investigated in AN. No significant interaction between *5-HTTLPR* and a polymorphism within the *NET* gene promoter polymorphic region was found in a sample of 106 Australian trios (Urwin et al. 2003a). On the contrary, the same research group detected a significant synergistic epistatic interaction between the *5-HTTLPR* and a polymorphism in the *MAOA* gene, since the risk of developing AN was up to eight times greater that the risk imposed by the *MAOA* gene variant alone when the MAOA variant was transmitted together with the *5-HTTLPR* SS genotype (Urwin and Nunn 2005). Finally, an epistatic interaction between the MAOA-uVNTR and the NETpPR polymorphisms was identified, since receiving a MAOA-L allele was found to more than double the risk for developing ANR, conditional on an individual also being a NETpPR-L4 homozygote (Urwin et al. 2003b).

76.2.6 Brain-Derived Neurotrophic Factor

It has been widely demonstrated that BDNF has a role in the regulation of eating behavior, acting as a satiety factor in the experimental animal (Tsuchida et al. 2001). Moreover, in symptomatic patients with AN or BN, circulating levels of BDNF have been detected to be decreased (Monteleone et al. 2004, 2005b) and only partially restored after body weight rehabilitation in AN (Nakazato et al. 2006). The Val66Met (196G/A) SNP of the *BDNF* gene, which has an effect on the intracellular processing and secretion of BDNF, has been assessed for association with AN yielding somewhat conflicting, yet generally, promising results. Indeed, a small study and a large case-control study of individuals from five European countries showed that ANR and ANBP individuals had a higher frequency of the AA genotype and the A allele of the Val66Met (196G/A) SNP of the *BDNF* gene (Ribasès et al. 2003, 2004), and that patients carrying at least one copy of the A allele had lower values of lifetime minimum BMI (Table 76.2). In a subsequent study (Ribasès et al. 2005a) including 359 family trios recruited from seven European countries, the previously reported higher frequency of the AA/AG genotypes and the A allele in ANR was confirmed, but no preferential transmission of the A or G allele was detected, although in trios with ANR the A allele was transmitted with a significant lower minimum BMI than the G allele. An association between the Val66Met SNP and ANR or AN was reported by two further independent research groups (Koizumi et al. 2004; Dmitrzak-Weglarz et al. 2007). Three studies, instead, provided negative results (Friedel et al. 2005; Rybakowski et al. 2007; Dardennes et al. 2007); however, in one of them AN patients with the A allele of the Val66Met SNP had higher levels of harm avoidance than GG homozygotes (Rybakowski et al. 2007), suggesting an association between this SNP and personality traits in AN (Table 76.2).

As for BN, Ribasès et al. (2004) found a higher frequency of the AA/AG genotype and the A allele of the Val66Met SNP in 389 BN individuals recruited from three European countries, but this was not confirmed in their subsequent family trios study (Ribasès et al. 2005a) and in a small study including only 70 BN patients (Ribasès et al. 2003). Negative findings were also reported by Koizumi et al. (2004) in a sample of 118 BN patients; however, when patients were stratified into BNP and BNNP subtypes, a significantly higher frequency of the AG genotype was detected in BNP patients while the A allele was significantly associated with BNNP subtype (Table 76.3). Monteleone et al. (2006b) assessed the association of the Val66Met SNP with both BN and binge eating disorder, and results were negative; however, patients carrying the AA genotype displayed a higher severity of binge-eating (assessed by the weekly frequency of bingeing and the Bulimia Investigation Test Edinburgh symptom and total scores), which suggests a possible involvement of this SNP in the susceptibility to the aberrant eating behavior.

A second common SNP of the *BDNF* gene is represented by the -270C/T SNP. No significant association between the -270 C/T SNP and AN was founded in five studies (Ribasès et al. 2003, 2004, 2005a; Koizumi et al. 2004; Dardennes et al. 2007) (Table 76.2). However, in a study including 359 AN trios recruited from seven European countries and investigating also the Val66Met SNP, it was found that the -270C/T/Met66 haplotype was preferentially transmitted to the affected ANR offspring (Ribasès et al. 2005a) while Rybakowski et al. (2007) reported that AN patients with the T allele had higher levels of persistence and harm avoidance than CC homozygotes.

No significant association of the -270C/T SNP with BN has been detected (Ribasès et al. 2003, 2004, 2005a); however, BN individuals carrying the T allele exhibited an earlier age at onset of weight loss and higher maximum BMI (Ribasès et al. 2004) (Table 76.3).

Very recently, epistasis between the *BDNF* gene and the *DRD4* gene has been assessed in a sample of 162 female probands with BN (Kaplan et al. 2008). Probands carrying both the hypofunctional 7R allele of *DRD4* gene and the Met allele of *BDNF* gene had significantly higher maximum BMI than probands in the other gene–gene interaction groups.

76.2.6.1 BDNF Receptor

SNPs of the *NTRK2* gene, which encodes a BDNF receptor, have been investigated for association with AN and BN in a study that screened the entire NTRK2 gene and identified 14 SNPS (Ribasès et al. 2005b). The -69C >G SNP was found nominally associated with ANBP and the IVS13+40G>A and the IVS17+125T>C SNPs were found significantly associated with BN, whereas no significant association emerged between the IVS2+40C>T, IVS18+13G>A and 2784–2785insC with both AN and BN (Tables 76.2 and 76.3). Moreover, a strong association was detected between the C-A-insC haplotype and ANBP. Finally, BN patients carrying the C-A-insC haplotype showed higher scores in the harm avoidance dimension of the personality. These results need replication.

76.2.7 Neuropeptide Y and the Agouti-Related Protein

NPY is a highly potent stimulator of hunger in the hypothalamus, where it is co-secreted with another potent orexigenic peptide, the agouti-related protein, which is an inverse agonist at melanocortinergic receptors where melanocortins derived from proopiomelanocortin act as anorexigenic agonists. NPY exerts its effects in the regulation of food ingestion mainly through NPY 1 and NPY 5 receptors. No significant associations between SNPs of *NPY Y$_1$* and *Y$_5$* receptor genes and AN were detected in one study (Rosenkranz et al. 1998a), whereas the G760A and G526A, but not the C659T SNP of the *agouti-related protein* gene were found nominally associated to AN (Vink et al. 2001) (Table 76.2). The 760A and 526A alleles were in complete linkage disequilibrium and the mutant allele was preferentially transmitted to ANBP offspring in a family trios study (Dardennes et al. 2007). Finally, it was found that AN individuals carrying the mutant allele had a younger age at onset and lower sense of interpersonal distrust (Dardennes et al. 2007).

76.2.8 Opioids and Endocannabinoids

Opioid peptides and endocannabinoids have been demonstrated to be involved in the control of both quantitative and hedonic/rewarding aspects of food choice and consumption. In particular, endocannabinoids, such as anandamide and 2-arachidonylglycerol, control food intake at two levels. First, they tonically reinforce the motivation to find and consume food with a high incentive value, possibly by interacting with the mesolimbic pathway involved in reward mechanisms. Second, they are activated "on demand" in the hypothalamus after short-term food deprivation and transiently regulate the levels and/or action of other orexigenic and anorectic mediators to modulate appetite (Matias and Di Marzo 2007). Alterations in circulating levels of anadamide and opioid peptides have been detected in ED patients (Brambilla et al. 1991; Monteleone et al. 2005c); so the investigation of genes involved in the physiology of those substances seems to be promising in EDs.

Bergen et al. (2003) found that the 47821A>G SNP and the haplotypes 8214T>C/47821A>G and 80A>G/8214T>C/23340A>G/47821T>G/51502A>T of the *OPRD1* gene were associated to AN. Recently, Brown et al. (2007) found three other SNPs of the *OPRD1* gene to be associated with both ANR and/or ANBP (Table 76.2). It is of note that the *OPRD1* gene is positioned under the observed linkage peak on chromosome 1 for ANR close to the *5HTR1D* gene (Grice et al. 2002; Bergen et al. 2003).

Polymorphisms of the endocannabinoid CB1 receptor gene (*CNR1*) and of the gene coding the fatty acid amide hydrolase (FAAH) and the N-acylethanolamine-hydrolyzing acid amidase (NAAA), the major degrading enzymes of endogenous cannabinoids, have been studied for association with AN (Table 76.2). Specifically, it was demonstrated that the 13-repeat allele of the (AAT)n triplet repeat polymorphism of the *CNR1* gene was preferentially transmitted in ANBP patients while the 14-repeat allele was preferentially transmitted in the ANR group (Siegfried et al. 2004), but this was not confirmed in a larger study showing also no significant association or transmission of different SNPs of *CNR1*, *FAAH*, and *NAAA* genes with AN in 91 German AN trios (Muller et al. 2008).

76.3 Peripheral Regulators of Eating Behavior

A number of substances secreted by the gut, the pancreas, and the adipose tissue have been identified and characterized as modulators of food intake and/or energy expenditure. Alterations in circulating levels of those substances and/or change in their secretory responses to physiological stimuli have been detected in both AN and BN patients (Monteleone et al. 2008). At the moment, there are no conclusive data as to whether secretory alterations of feeding regulatory substances precede the appearance of an ED or are the consequence of the nutritional changes occurring with the disorder. However, it has been suggested, although not proved, that even if those alterations are secondary phenomena disappearing after the recovery from the ED, they may hypothetically contribute to the maintenance of both aberrant eating behaviors and/or other symptomatic changes, thus affecting the course and the outcome of the ED. Therefore, genetic association studies have been performed to evaluate the role of polymorphic variants of genes coding ghrelin, cholecystokinin, leptin, and their receptors, as well as adiponectin and resistin in the genetic susceptibility to AN and/or BN.

No significant associations between the Arg51Gln and/or the Gln90Leu SNPs of the *ghrelin* gene with AN have been reported in four independent studies (Ando et al. 2006; Cellini et al. 2006; Dardennes et al. 2007; Monteleone et al. 2006c) (Table 76.4); the Leu72Met SNP, instead, was found associated with ANBP in a family trios study reporting a preferential transmission of the Met allele and of the haplotype 90Gln/72Met to ANBP offspring (Dardennes et al. 2007). However, two case-control studies and a large family trios study did not confirm those results (Ando et al. 2006; Cellini et al. 2006; Monteleone et al. 2006c) (Table 76.4). No significant association was found between the Arg51Gln and the Gln90Leu SNPs of the *ghrelin* gene and BN (Cellini et al. 2006; Monteleone et al. 2006c), although the haplothype Gln90/Leu72/Arg51 was detected preferentially transmitted to BN offspring (Cellini et al. 2006). Similar negative findings were reported for the Leu72Arg SNP in two different BN samples (Cellini et al. 2006; Monteleone et al. 2006c) (Table 76.5). Ando et al. (2006), instead, reported a nominal association of the Leu72Met and 3056T>C SNPs with BNP and a higher frequency in this group of the haplotype Met72/3056C. Finally, the 171T/C SNP of the *ghrelin receptor* gene was found associated with BN, but not with AN in a Japanese population (Miyasaka et al. 2006).

Only the rs11129946 SNP of the *cholecystokinin* gene was found nominally associated with AN in a single study (de Krom et al. 2006) (Table 76.4). No associations were found between SNPs of the *cholecystokinin-A receptor*, *leptin*, *leptin receptor*, *adiponectin*, and *resistin* genes with AN and/or BN in single small case–control studies (Hinney et. 1998; Quinton et al. 2004; Dolinkova et al. 2006; Miyasaka et al. 2006) (Tables 76.3 and 76.4). The only interesting finding that emerged from those studies was that AN patients carrying the minor T allele of the 276G>T SNP of the *adiponectin* gene had increased cholesterol levels (Dolinkova et al. 2006), which might help to explain hypercholesterolemia of underweight AN patients.

Table 76.4 Association studies of genes coding peripheral regulators of feeding in anorexia nervosa

Candidate gene	Analyzed polymorphism	Statistical Significance	Note	References
Ghrelin	Arg51Gln	NS		Ando et al. (2006); Cellini et al. (2006); Monteleone et al. (2006b)
	Gln90Leu	NS		Ando et al. (2006); Cellini et al. (2006); Dardennes et al. (2007)
	Leu72Met	S	Significantly associated to ANBP	Dardennes et al. (2007)
		NS		Ando et al. (2006); Cellini et al. (2006); Monteleone et al. (2006b)
	3,056T>C	NS		Ando et al. (2006)
	3,083A>G	NS		Ando et al. (2006)
	3,615A>C	NS		Ando et al. (2006)
Growth hormone secretagogue receptor (GHSR, ghrelin Receptor)	171T/C	NS		Miyasaka et al. (2006)
Cholecystokinin (CCK)	rs11129946	S		De Krom et al. (2006)
	rs6791019	NS		De Krom et al. (2006)
	rs7611677	NS		De Krom et al. (2006)
	rs6809785	NS		De Krom et al. (2006)
	rs6801844	NS		De Krom et al. (2006)
CCK-A Receptor	−81A>G	NS		Miyasaka et al. (2006)
	−128G>T	NS		Miyasaka et al. (2006)
Leptin	−1,387 G/A	NS		Hinney et al. (1998)
Leptin receptor	Gln223Arg	NS		Quinton et al. (2004)
	Lys109Arg	NS		Quinton et al. (2004)
	Lys656Asn	NS		Quinton et al. (2004)
Adiponectin	45T>G	NS		Dolinkovà et al. (2006)
	276G>T	NS		Dolinkovà et al. (2006)
Resistin	62G>A	NS		Dolinkovà et al. (2006)
	180C>G	NS		Dolinkovà et al. (2006)

This table lists published association studies of polymorphic variants of genes involved in the physiology of peripheral regulators (peptides and hormones) of feeding and energy homeostasis in anorexia nervosa

ANBP anorexia nervosa binge-purging subtype, *NS* not significant; *S* significant

76.4 Other Candidate Genes

Other genes that have been supposed to be likely involved in the biological vulnerability to EDs are those coding uncoupling proteins (UCP), tumor necrosis factor-α, estrogen receptors, phospholipase A2, the small-conductance calcium-activated potassium channel-3 (KCNN3), and the circadian locomotor output cycles kaput (CLOCK).

UCP2 and UCP3 are ubiquitous proteins promoting thermogenesis and modulating metabolic adaptation during fasting. Allele 13 of the microsatellite marker D11S911 of the *UCP2/UCP3* gene was found associated with AN in one study (Campbell et al. 1999), but this was not confirmed by another research group (Hu et al. 2002). One study performed in an Asian population reported no

Table 76.5 Association studies of genes coding peripheral regulators of feeding in bulimia nervosa

Candidate gene	Analyzed polymorphism	Statistical significance	Note	References
Ghrelin	Arg51Gln	NS		Cellini et al. (2006); Ando et al. (2006); Monteleone et al. (2006b)
	Gln90Leu	NS		Ando et al. (2006); Cellini et al. (2006)
	Leu72Met	S	Significant association with BNP	Ando et al. (2006)
		NS		Cellini et al. (2006); Monteleone et al. (2006b)
	3056T>C	S	Significant association with BNP	Ando et al. (2006)
	3,083A>G	NS		Ando et al. (2006)
	3,615A>C	NS		Ando et al. (2006)
Growth hormone secretagogue receptor (GHSR, ghrelin receptor)	171T/C	S		Miyasaka et al. (2006)
CCK-A receptor	−81A>G	NS		Miyasaka et al. (2006)
	−128G>T	NS		Miyasaka et al. (2006)
Leptin	−1,387 G/A	NS		Hinney et al. (1998)

This table lists published association studies of polymorphic variants of genes involved in the physiology of peripheral regulators (peptides and hormones) of feeding and energy homeostasis in bulimia nervosa

BNP bulimia nervosa purging subtype, *CCK* colecystokinin, *NS* not significant, *S* significant

association between the -866G>A SNPs of the *UCP2* gene and the -55cT SNP of the *UCP3* gene with AN (Ando et al. 2004) (Table 76.6).

Tumor necrosis factor-α is a cytokine that decreases the activity of lipogenic enzymes including the intracellular phospholipase A2 enzyme and induces lipolysis-promoting cachexia. Four SNPs of the *tumor necrosis factor-α* gene and the intPla polymorphism of the *Phospholipase A2* gene were found not associated with AN in two case–control studies (Ando et al. 2001b; Slopien et al. 2004) (Table 76.6).

EDs occur predominantly in women with a female to male ratio of 9:1. This female predominance suggests a role for sex hormones, especially estrogens, in the etiopathogenesis of AN and BN. The genes coding estrogen receptor type 1 (*ESR1*) and estrogen receptor type 2 (*ESR2*) have been analyzed for their putative association with AN and BN. The 1082G>A SNP but not the 1730A>G SNP of the *ESR2* gene has been found nominally associated with AN in two independent case-control studies (Rosenkranz et al. 1998; Eastwood et al. 2002) (Table 76.6). The 1730A>G SNP of the *ESR2* gene, instead, has been found nominally associated with BN in one study (Nilsson et al. 2004), but not in another one (Rosenkranz et al. 1998) (Table 76.7). Finally, a statistically significant higher frequency of the mutant A allele of the ERβcx+56G>A polymorphism of the *ESR2* gene has been detected in a small sample of BN individuals including also patients with partial syndrome BN (Nilsson et al. 2004). No association of polymorphisms of the *ESR1* gene with AN was detected in a single case–control study (Eastwood et al. 2002).

The KCNN3 regulates ion flow through the NMDA-glutamate receptor and dampens neuronal excitability. An association between the CAG repeat polymorphism of the *KCNN3* gene and AN has

Table 76.6   Association studies of other candidate genes in anorexia nervosa

Candidate gene	Analyzed polymorphism	Statistical significance	Note	References
Uncoupling protein 2, 3 (UCP2/ UCP-3)	D11S911	S	Allele 13 of D11S911 microsatellite marker was significantly over represented in AN	Campbell et al. (1999)
		NS		Hu et al. (2002)
	D11S916	NS		Campbell et al. (1999); Hu et al. (2002)
	−866G/A (UCP-2)	NS		Ando et al. (2004)
	−55C/T (UCP-3)	NS		Ando et al. (2004)
Tumor necrosis factor-α (TNFα)	−1,031T>C	NS		Ando et al. (2001b)
	−863C>A	NS		Ando et al. (2001b)
	−857C>T	NS		Ando et al. (2001b)
	308G/A	NS		Slopien et al. (2004)
Phospholipase A2	*intPLA2*	NS		Slopien et al. (2004)
Estrogen receptor-1 (ESR1)	ESR1-PvuI	NS		Eastwood et al. (2002)
	ESR1-XbaI	NS		Eastwood et al. (2002)
	Dinucleotide repeat	NS		Eastwood et al. (2002)
Estrogen receptor-2 (ESR2 or ESR-β)	1,082G>A	S		Rosenkranz et al. (1998); Eastwood et al. (2002)
	1,730A>G	NS		Rosenkranz et al. (1998); Eastwood et al. (2002)
	Dinucleotide repeat	NS		Eastwood et al. (2002)
Calcium-activated potassium channel (KCNN3)	CAG repeat	S	Alleles longer than 19 repeats were more frequent in AN	Koronyo-Hamaoui et al. (2002, 2004)
Circadian Locomotor Output Cycles Kaput (CLOCK)	3,111T/C	NS	AN subjects with at least one copy of the C allele exhibited a minimum past BW significantly lower than those with T/T genotype	Tortorella et al. (2007)

This table lists published association studies of polymorphic variants of genes involved in the physiology of other regulators (peptides and hormones) of feeding and energy homeostasis in anorexia nervosa

AN anorexia nervosa, *BW* body weight, *NS* not significant, *S* significant

been recently investigated in two studies by the same group (Koronyo-Hamaoui et al. 2002, 2004) (Table 76.6). Patients with AN were more likely than controls to manifest genotypes with alleles longer than 19 CAG repeats (L alleles). The TDT showed a preferential transmission of the L alleles to AN offspring. Moreover, AN patients with comorbid obsessive-compulsive disorder had a higher frequency of L repeats than those without an obsessive–compulsive disorder (Koronyo-Hamaoui et al. 2004).

Feeding is subjected to circadian regulation; therefore, changes in the components of the endogenous oscillator regulating circadian rhythms may be involved in disordered rhythmicity of eating

Table 76.7 Association studies of other candidate genes in bulimia nervosa

Candidate gene	Analyzed polymorphism	Statistical significance	Note	References
Estrogen receptor-2 (ESR2 or ESR-β)	1,082G>A	NS		Rosenkranz et al. (1998); Nilsson et al. (2004)
	1,730A>G	S		Nilsson et al. (2004)
		NS		Rosenkranz et al. (1998);
	ERβ cx+56G>A	S		Nilsson et al. (2004)
Circadian Locomotor Output Cycles Kaput (CLOCK)	3,111T/C	NS	BN subjects with at least one copy of the C allele exhibited a minimum past BW significantly lower than those with T/T genotype	Tortorella et al. (2007)

This table lists published association studies of polymorphic variants of genes involved in the physiology of other regulators (peptides and hormones) of feeding and energy homeostasis in bulimia nervosa

BN bulimia nervosa, *BW* body weight, *NS* not significant, *S* significant

behavior as it occurs in EDs. Although several genes have been identified in the endogenous machinery modulating circadian rhythms, to date only the *CLOCK* gene has been investigated in EDs. No significant associations of the 3111T/C SNP of the *CLOCK* gene with AN or BN has emerged (Table 76.7); however, AN and BN subjects with at least one copy of the C allele exhibited a minimum past BW significantly lower than those with the T/T genotype, which suggests a possible involvement of the *CLOCK* gene in the regulation of BW (Tortorella et al. 2007).

76.5 Concluding Remarks

It is evident from the above that genetic association studies of AN and BN are in an early phase. Although in the last 10 years, polymorphic variants of different candidate genes have been assessed for an association with AN and BN, results have been often inconsistent. There are several reasons that may explain at least part of such an inconsistency. First of all, the majority of association studies has been performed on small subject samples (often in groups of less than 100 subjects) and suffered from insufficient statistical power and lack of correction for multiple testing. Second, differences in the ethnicity of populations included and the use of different criteria to diagnose AN and BN may further contribute to the discrepancies among the studies. Third, genetic heterogeneity and population stratification may provide false positive results. Furthermore, EDs have a high rate of comorbidity with other psychiatric conditions, including affective, anxiety, and personality disorders, which may further contribute to the clinical heterogeneity of studied samples and may partially account for current discrepant results. Finally, the effects of environmental risk factors on gene expression have been so far completely neglected in genetic association studies on EDs. Life events, nutrition, cultural, and social risk factors by acting through epigenetic mechanisms may influence the activation and/or deactivation of genes and modify the risk of developing an ED. As outlined by Moffitt et al. (2005), discrepancies among association studies may be the result of still unknown gene x environmental interactions, in which genes have a susceptibility role for an ED only in those patients who are exposed to those putative environmental risk factors.

Nonetheless, some intriguing conclusions can be drawn across association studies in AN and BN. The -1438G/A SNP of the *5-HT*$_{2A}$ receptor gene and the Val66Met SNP of the *BDNF* gene have been

found quite consistently although not specifically linked to ANR and/or to phenotypic traits associated with the disorder in large sample studies. Therefore, the *5-HT*$_{2A}$ receptor gene and the *BDNF* gene are promising candidates for genetic influences on AN. The second intriguing finding is that in both AN and BN SNPs have been found frequently associated with ED-related phenotypic traits rather that to the full syndromes as currently categorized in DSM-IV. Although these results need replication and confirmation in larger studies, they underline the importance of focusing on more homogeneous subgroups, either relying on specific ED traits or identifying endophenotypes. For instance, six quantitative phenotypic traits (obsessionality, age at menarche, anxiety, lifetime minimum BMI, concern over mistake, and food-related obsessions) have been characterized as specific traits to be used for both linkage analyses and association studies (Bulik et al. 2005), and future researches should consider them. An endophenotype, instead, is a measurable trait that may be physical (neurophysiological, biochemical, neuroanatomical), cognitive, or neuropsychological and that is associated with the related illness, is heritable, and primarily state-independent. The identification of endophenotypes in EDs will help to identify more homogenous subgroups of patients in order to reduce the potential obscuring effects of focusing on currently categorized complex syndromes.

It is clear that the genetics of EDs needs more and larger association studies with adequate sample sizes. To pursue this goal, multicenter collaborative studies should be encouraged. Moreover, a promising area for future research is to examine gene–gene interactions in light of the fact that biological susceptibility to EDs has a multigenic nature. Epistatic studies have produced some interesting findings, but the results are still too preliminary to draw any significant conclusion.

In summary, genetic association studies of EDs have produced a plethora of data but little conclusive knowledge. We are hopeful that, in the future, a more homogeneous characterization of clinical phenotypes and the promotion of multicenter collaborative studies will help to identify the genes likely involved in the heritable transmission of biological vulnerability to these serious and debilitating conditions.

76.6 Applications to Other Area of Health and Disease

Anorexia nervosa and bulimia nervosa are psychiatric disorders with physical consequences that often may threat the survival of the patients. The etiology of these conditions is not know, but it is commonly believed that a genetic predisposition to the disorders is transmitted to vulnerable individuals and may interact with personality and environmental risk factors to generate anorexia or bulimia nervosa. Some phenotypic aspects, such as low body weight, bingeing behavior and personality dimensions, seems to be more strictly associated with polymorphic gene variants. Moreover, preliminary evidence has been provided that polymorphisms of certain candidate genes may predict the outcome to treatments. Putting together genetic research and clinical intervention studies will help clinicians to improve the outcome of anorexia and bulimia nervosa and to organize adequate prevention.

Summary Points

- Epidemiological, family and molecular genetic studies suggest a strong genetic component in anorexia nervosa and bulimia nervosa.
- Association studies of candidate genes indicate the *5-HT*$_{2A}$ receptor gene and the *BDNF* gene as promising candidates for genetic susceptibility to AN.
- Association studies of candidate genes have provided inconsistent results in BN.

- The following reasons may explain at least part of discrepancies among the studies: a) the majority of studies has been performed on small subject samples and suffered from insufficient statistical power and lack of correction for multiple testing, b) different ethnic populations have been studied; c) different criteria to diagnose AN and BN have been used; d) genetic heterogeneity and population stratification could provide false positive results; e) comorbidity of AN and BN with other psychiatric conditions has been not taken into account; f) the interaction gene-environment has been completely neglected.
- Several intriguing associations have emerged between polymorphisms of candidate genes and eating disorder-related phenotypic traits.
- In the future, the identification of endophenotypes and the promotion of multicenter collaborative studies will lead to more consistent results.

Key Terms

Binge eating: An episode of binge eating is characterized by both of the following:
- o Eating, in a fixed period of time, an amount of food that is definitely larger than most people would eat under similar circumstances.
- o A lack of control over eating during the episode: a feeling that one cannot stop eating or control what or how much one is eating.

Candidate gene: gene coding a protein that is likely involved in the etiopathogenesis of a disease as supported by clinical, biochemical and other research data.

Compensatory behaviors: acts by which the person tries to compensate for the effects of overeating. Examples of such acts are purging (induced *vomiting* or *laxative* abuse), *fasting*, and heavy exercising.

Eating-disorder related phenotypic traits: clinical symptoms or personality characteristics that are typical of patients with anorexia nervosa or bulimia nervosa.

Epistasis: is the *interaction* between genes. Epistasis takes place when the effects of one *gene* are modified by one or several other genes.

Single-nucleotide polymorphism: is a *DNA sequence* variation occurring when a single *nucleotide* in the *genome* differs between members of a species (or between paired chromosomes in an individual). In this case two *alleles* are identified: the wild type allele and the polymorphic (or mutant) allele.

References

American Psychiatric Association. Diagnostic and statistical manual of mental disorders. Washington DC: American Psychiatric Press; 1990.

Ando T, Ishikawa T, Kawamura N, Karibe M, Oba M, Tatsuta N, Hara S, Takii M, Naruo T, Takei M, Kurokawa N, Nozoe S, Kubo C, Komaki G. Psychiatr Genet. 2001a;11:161–4.

Ando T, Komaki G, Karibe M, Kawamura N, Hara S, Takii M, Naruo T, Kurokawa N, Takei M, Tatsuta N, Ohba M, Nozoe S, Kubo C, Ishikawa T. Psychiatr Genet. 2001b;11:157–60.

Ando T, Kodama N, Ishikawa T, Naruo T, Tachikawa N, Nozaki T, Okabe K, Takeuchi K, Masuda A, Kawamura N, Komaki G. Psychiatr Genet. 2004;14:215–8.

Ando T, Komaki G, Naruo T, Okabe K, Takii M, Kawai K, Konjiki F, Takei M, Oka T, Takeuchi K, Masuda A, Ozaki N, Suematsu H, Denda K, Kurokawa N, Itakura K, Yamaguchi C, Kono M, Suzuki T, Nakai Y, Nishizono-Maher A, Koide M, Murakami K, Nagamine K, Tomita Y, Ookuma K, Tomita K, Tonai E, Ooshima A, Ishikawa T, Ichimaru Y. Am J Med Genet B Neuropsychiatr Genet. 2006;141:929–34.

Bachner-Melman R, Lerer E, Zohar AH, Kremer I, Elizur Y, Nemanov L, Golan M, Blank S, Gritsenko I, Ebstein RP. Am J Med Genet B Neuropsychiatr Genet. 2007;144:748–56.

Bergen AW, van den Bree MB, Yeager M, Welch R, Ganjei JK, Haque K, Bacanu S, Berrettini WH, Grice DE, Goldman D, Bulik CM, Klump K, Fichter M, Halmi K, Kaplan A, Strober M, Treasure J, Woodside B, Kaye WH. Mol Psychiatry. 2003;8:397–406.

Bergen AW, Yeager M, Welch RA, Haque K, Ganjei JK, van den Bree MB, Mazzanti C, Nardi I, Fichter MM, Halmi KA, Kaplan AS, Strober M, Treasure J, Woodside DB, Bulik CM, Bacanu SA, Devlin B, Berrettini WH, Goldman D, Kaye WH. Neuropsychopharmacology. 2005;30:1703–10.

Brambilla F, Ferrari E, Petraglia F, Facchinetti F, Catalano M, Genazzani AR. Psychiatry Res. 1991;39:115–27.

Brown KM, Bujac SR, Mann ET, Campbell DA, Stubbins MJ, Blundell JE. Biol Psychiatry. 2007;61:367–73.

Bruce KR, Steiger H, Joober R, Ng Ying Kin NMK, Israel M, Young SN. Am J Med Genet B Neuropsychiatr Genet. 2005;137:40–4.

Bruins-Slot L, Gorwood P, Bouvard M, Blot P, Adès J, Feingold J, Schwartz JC, Mouren-Siméoni MC (1998) Biol. Psychiatry 43: 76–78.

Bulik CM, Bacanu SA, Klump KL, Fichter MM, Halmi KA, Keel P, Kaplan AS, Mitchell JE, Rotondo A, Strober M, Treasure J, Woodside DB, Sonpar VA, Xie W, Bergen AW, Berrettini WH, Kaye WH, Devlin B. Am J Med Genet B Neuropsychiatr Genet. 2005;139:81–7.

Burnet PWJ, Smith KA, Cowen PJ, Fairburn CG, Harrison PJ. Psychiatr Genet. 1999;9:101–4.

Campbell DA, Sundaramurthy D, Markham AF, Pieri LF. Lancet. 1998;351:499.

Campbell DA, Sundaramurthy D, Gordon D, Markham AF, Pieri LF. Mol Psychiatry. 1999;4:68–70.

Cellini E, Nacmias B, Brecelj-Anderluh M, Badía-Casanovas A, Bellodi L, Boni C, Di Bella D, Estivill X, Fernandez-Aranda F, Foulon C, Friedel S, Gabrovsek M, Gorwood P, Gratacos M, Guelfi J, Hebebrand J, Hinney A, Holliday J, Hu X, Karwautz A, Kipman A, Komel R, Rotella CM, Ribases M, Ricca V, Romo L, Tomori M, Treasure J, Wagner G, Collier DA, Sorbi S; EC Framework V 'Factors in Healthy Eating' consortium. Psychiatr Genet. 2006;16:51–2.

Cloninger CR, Svrakic DM, Przbeck TR. Arch Gen Psychiatry. 1993;50:975–90.

Collier DA, Arranz MJ, Li T, Mupita D, Brown N, Treasure J. Lancet. 1997;350:412.

Collier DA, on behalf of all authors. Authors' reply. Lancet. 1999;353:929.

Dardennes RM, Zizzari P, Tolle V, Foulon C, Kipman A, Romo L, Iancu-Gontard D, Boni C, Sinet PM, Thérèse Bluet M, Estour B, Mouren MC, Guelfi JD, Rouillon F, Gorwood P, Epelbaum J. Psychoneuroendocrinology. 2007;32:106–13.

de Krom M, Hendriks J, Hillebrand J, van Elburg A, Adan R. Psychiatr Genet. 2006;16:239.

Di Bella DD, Catalano M, Cavallini MC, Riboldi C, Bellodi L. Mol Psychiatry. 2000;5:233–4.

Dmitrzak-Weglarz M, Skibinska M, Slopien A, Szczepankiewicz A, Rybakowski F, Kramer L, Hauser J, Rajewski A. Psychiatr Genet. 2007;17:245–6.

Dolinková M, Krízová J, Lacinová Z, Dolezalová R, Housová J, Krajícková J, Bosanská L, Papezová H, Haluzík M. Cas Lek Cesk. 2006;145:562–6.

Eastwood H, Brown KM, Markovic D, Pieri LF. Mol Psychiatry. 2002;7:86–9.

Enoch MA, Kaye WH, Rotondo A, Greenberg BD, Murphy DL, Goldman D. Lancet. 1998;351:1785–6.

Erzegovesi S, Riboldi C, Di Bella D, Di Molfetta D, Mapelli F, Negri B, Tenace M, Bellodi L. J Clin Psychopharmacol. 2004;24:680–2.

Friedel S, Horro FF, Wermter AK, Geller F, Dempfle A, Reichwald K, Smidt J, Brönner G, Konrad K, Herpertz-Dahlmann B, Warnke A, Hemminger U, Linder M, Kiefl H, Goldschmidt HP, Siegfried W, Remschmidt H, Hinney A, Hebebrand J. Am J Med Genet B Neuropsychiatr Genet. 2005;132:96–9.

Frieling H, Römer KD, Wilhelm J, Hillemacher T, Kornhuber J, de Zwaan M, Jacoby GE, Bleich S. Psychiatr Genet. 2006;16:205–8.

Frisch A, Laufer N, Danziger Y, Michaelovsky E, Leor S, Carel C, Stein D, Fenig S, Mimouni M, Apter A, Weizman A. Mol Psychiatry. 2001;6:243–5.

Fuentes JA, Lauzurica N, Hurtado A, Escartí A, Barrios V, Morandé G, Soriano J, Jáuregui I, González-Valdemoro MI, García-Camba E. Psychiatr Genet. 2004;14:107–9.

Fumeron F, Betoulle D, Aubert R, Herbeth B, Siest G, Rigaud D. Mol Psychiatry. 2001;6:9–10.

Gabrovsek M, Brecelj-Anderluh M, Bellodi L, Cellini E, Di Bella D, Estivill X, Fernandez-Aranda F, Freeman B, Geller F, Gratacos M, Haigh R, Hebebrand J, Hinney A, Holliday J, Hu X, Karwautz A, Nacmias B, Ribases M, Remschmidt H, Komel R, Sorbi S, Tomori M, Treasure J, Wagner G, Zhao J, Collier DA. Am J Med Genet B Neuropsychiatr Genet. 2004;124:68–72.

Gorwood P, Adès J, Bellodi L, Cellini E, Collier DA, Di Bella D, Di Bernardo M, Estivill X, Fernandez-Aranda F, Gratacos M, Hebebrand J, Hinney A, Hu X, Karwautz A, Kipman A, Mouren-Siméoni MC, Nacmias B, Ribasés M, Remschmidt H, Ricca V, Rotella CM, Sorbi S, Treasure J; EC Framework V 'Factors in Healthy Eating' consortium. Mol Psychiatry. 2002;7:90–4.

Gorwood P. Am J Pharmacogenomics. 2004;4:9–17.

Greenberg BD, Tolliver TJ, Huang SJ, Li Q, Bengel D, Murphy DL. Am J Med Genet. 1999;88:83–7.

Grice DE, Halmi KA, Fichter MM, Strober M, Woodside DB, Treasure JT, Kaplan AS, Magistretti PJ, Goldman D, Bulik CM, Kaye WH, Berrettini WH. Am J Hum Genet. 2002;70:787–92.

Han L, Nielsen DA, Rosenthal NE, Jefferson K, Kaye W, Murphy D, Altemus M, Humphries J, Cassano G, Rotondo A, Virkkunen M, Linnoila M, Goldman D. Biol Psychiatry. 1999;45:615–9.

Heils A, Teufel A, Petri S, Stöber G, Riederer P, Bengel D, Lesch KP. J Neurochem. 1999;66:2621–4.

Hinney A, Barth N, Ziegler A, von Prittwitz S, Hamann A, Hennighausen K, Pirke KM, Heils A, Rosenkranz K, Roth H, Coners H, Mayer H, Herzog W, Siegfried A, Lehmkuhl G, Poustka F, Schmidt MH, Schäfer H, Grzeschik KH, Lesch KP, Lentes KU, Remschmidt H, Hebebrand. J Life Sci. 1997a;61:295–303.

Hinney A, Ziegler A, Nöthen MM, Remschmidt H, Hebebrand J. Lancet. 1997b;350:1324–5.

Hinney A, Lentes KU, Rosenkranz K, Barth N, Roth H, Ziegler A, Hennighausen K, Coners H, Wurmser H, Jacob K, Römer G, Winnikes U, Mayer H, Herzog W, Lehmkuhl G, Poustka F, Schmidt MH, Blum WF, Pirke KM, Schäfer H, Grzeschik KH, Remschmidt H, Hebebrand J. Int J Obes Relat Metab Disord. 1997c;21:224–30.

Hinney A, Bornscheuer A, Depenbusch M, Mierke B, Tölle A, Middeke K, Ziegler A, Roth H, Gerber G, Zamzow K, Ballauff A, Hamann A, Mayer H, Siegfried W, Lehmkuhl G, Poustka F, Schmidt MH, Hermann H, Herpertz-Dahlmann BM, Fichter M, Remschmidt H, Hebebrand J. Mol Psychiatry. 1998;3:539–43.

Hinney A, Herrmann H, Löhr T, Rosenkranz K, Ziegler A, Lehmkuhl G, Poustka F, Schmidt MH, Mayer H, Siegfried W, Remschmidt H, Hebebrand J. Int J Obes Relat Metab Disord. 1999a;23:760–3.

Hinney A, Schneider J, Ziegler A, Lehmkuhl G, Poustka F, Schmidt MH, Mayer H, Siegfried W, Remschmidt H, Hebebrand J. Am J Med Genet. 1999b;88:594–7.

Hu X, Murphy F, Karwautz A, Li T, Freeman B, Franklin D, Giotakis O, Treasure J, Collier DA. Mol Psychiatry. 2002;7:276–7.

Hu X, Giotakis O, Li T, Karwautz A, Treasure J, Collier DA. Neuroreport. 2003;14:781–3.

Hu X, Karwautz A, Wagner G, Holliday J, Li T, Treasure J, Collier DA. Psychiatr Genet. 2007;17:247–8.

Jönsson EG, Goldman D, Spurlock G, Gustavsson JP, Nielsen DA, Linnoila M, Owen MJ, Sedvall GC. Eur Arch Psychiatry Clin Neurosci. 1997;247:297–302.

Kaplan AS, Levitan RD, Yilmaz Z, Davis C, Tharmalingam S, Kennedy JL. Int J Eat Disord. 2008;41:22–8.

Kaye WH, Jimerson DC, Lake CR, Ebert MH. Psychiatry Res. 1985;14:333–42.

Kipman A, Bruins-Slot L, Boni C, Hanoun N, Adès J, Blot P, Hamon M, Mouren-Siméoni M, Gorwood P. Eur Psychiatry. 2002;17:227–9.

Koizumi H, Hashimoto K, Itoh K, Nakazato M, Shimizu E, Ohgake S, Koike K, Okamura N, Matsushita S, Suzuki K, Murayama M, Higuchi S, Iyo M. Am J Med Genet B Neuropsychiatr Genet. 2004;127:125–7.

Koronyo-Hamaoui M, Danziger Y, Frisch A, Stein D, Leor S, Laufer N, Carel C, Fennig S, Minoumi M, Apter A, Goldman B, Barkai G, Weizman A, Gak E. Mol Psychiatry. 2002;7:82–5.

Koronyo-Hamaoui M, Gak E, Stein D, Frisch A, Danziger Y, Leor S, Michaelovsky E, Laufer N, Carel C, Fennig S, Mimouni M, Apter A, Goldman B, Barkai G, Weizman A. Am J Med Genet B Neuropsychiatr Genet. 2004;131:76–80.

Kurabayashi T, Carey DGP, Morrison NA. Diabetes. 1996;45:1358–63.

Laakso A, Pohjalainen T, Bergman J, Kajander J, Haaparanta M, Solin O, Syvälahti E, Hietala J. Pharmacogenet Genomics. 2005;15:387–91.

Lachman HM, Papolos DF, Saito T, Yu YM, Szumlanski CL, Weinshilboum RM. Pharmacogenetics. 1996;6:243–50.

Lauzurica N, Hurtado A, Escartí A, Delgado M, Barrios V, Morandé G, Soriano J, Jàurequi I, Gonzàles-Valdemoro MI, Garcià-Camba E, Fuentes JA. Neurosci Lett. 2003;352:226–30.

Levitan RD, Kaplan AS, Masellis M, Basile VS, Walker ML, Lipson N, Siegel GI, Woodside DB, Macciardi FM, Kennedy SH, Kennedy JL. Biol Psychiatry. 2001;50:640–3.

Levitan RD, Kaplan AS, Masellis M, Basile VS, Richter MA, Kennedy JL. Eur Neuropsychopharmacol. 2006;16:1–6.

Lucki I. Biol Psychiatry. 1998;44:151–62.

Matias I, Di Marzo V. Trends Endocrinol Metab. 2007;18:27–37.

Matsushita S, Suzuki K, Murayama M, Nishiguchi N, Hishimoto A, Takeda A, Shirakawa O, Higuchi S. Am J Med Genet B Neuropsychiatr Genet. 2004;128:114–7.

Michaelovsky E, Frisch A, Leor S, Stein D, Danziger Y, Carel C, Fennig S, Mimouni M, Klauck SM, Benner A, Poustka A, Apter A, Weizman A. Am J Med Genet B Neuropsychiatr Genet. 2005;139:45–50.

Mikolajczyk E, Smiarowska M, Grzywacz A, Samochowiec J. Neuropsychobiology. 2006;54:82–6.

Miyasaka K, Hosoya H, Sekime A, Ohta M, Amono H, Matsushita S, Suzuki K, Higuchi S, Funakoshi A. J Neural Transm. 2006;113:1279–85.

Moffitt TE, Caspi A, Rutter M. Arch Gen Psychiatry. 2005;62:473–81.

Monteleone P, Tortorella A, Martiadis V, Serritella C, Fuschino A, Maj M. Psychosom Med. 2004;66:744–8.

Monteleone P, Santonastaso P, Tortorella A, Favaro A, Fabrazzo M, Castaldo E, Caregaro L, Fuschino A, Maj M. Mol Psychiatry. 2005a;10:716–8.

Monteleone P, Fabrazzo M, Martiadis V, Serritella C, Pannuto M, Maj M. Psychol Med. 2005b;35:897–905.

Monteleone P, Matias I, Martiadis V, De Petrocellis L, Maj M, Di Marzo V. Neuropsychopharmacol. 2005c;30:1216–21.

Monteleone P, Santonastaso P, Mauri, Bellodi L, Erzegovesi S, Fuschino A, Favaro A, Rotondo A, Castaldo E, Maj M. Psychosom Med. 2006a;68:99–103.

Monteleone P, Zanardini R, Tortorella A, Gennarelli M, Castaldo E, Canestrelli B, Maj M. Neurosci Lett. 2006b;406:133–7.

Monteleone P, Tortorella A, Castaldo E, Di Filippo C, Maj M. Neurosci Lett. 2006c;398:325–7.

Monteleone P, Tortorella A, Martiadis V, Serino I, Di Filippo C, Maj M. Neurosci Lett. 2007;421:42–6.

Monteleone P, Castaldo E, Maj M. Regulat Peptides. 2008;149:39–50.

Muller TD, Reichwald K, Bronner G, Kirschner J, Nguyen TT, Scherag A, Herzog W, Herpertz Dahlmann B, Lichtner P, Meitinger T, Platzer M, Schäfer H, Hebebrand J, Hinney A. Child Adol Psychiatry Ment Health. 2008;2:33–9.

Nacmias B, Ricca V, Tedde A, Mezzani B, Rotella CM, Sorbi S. Neurosci Lett. 1999;277:134–6.

Nakamura M, Ueno S, Sano A, Tanabe H. Mol Psychiatry. 2000;5:32–8.

Nakazato M, Hashimoto K, Yoshimura K, Hashimoto T, Shimizu E, Iyo M. Prog Neuro-Psychopharmacol Biol Psychiatry. 2006;30:1117–21.

Nilsson M, Naessén S, Dahlman I, Lindén Hirschberg A, Gustafsson JA, Dahlman-Wright K. Mol Psychiatry. 2004;9:28–34.

Nishiguchi N, Matsushita S, Suzuki K, Murayama M, Shirakawa O, Higuchi S. Biol Psychiatry. 2001;50:123–8.

Nisoli E, Brunani A, Borgomainerio E, Tonello C, Dioni L, Briscini L, Redaelli G, Molinari E, Cavagnini F, Carruba MO. Eat Weight Disord. 2007;12:91–6.

Okuyama Y, Ishiguro H, Nankai M, Shibuia H, Watanabe A, Arinami T. Mol Psychiatry. 2000;5:64–9.

Parsons MJ, D'Souza UM, Arranz MJ, Kerwin RW, Makoff AJ. Biol Psychiatry. 2004;56:406–10.

Quinton ND, Meechan DW, Brown K, Eastwood H, Blakemore AI. Psychiatr Genet. 2004;14:191–4.

Ribasés M, Gratacòs M, Armengol L, de Cid R, Badía A, Jiménez L, Solano R, Vallejo J, Fernández F, Estivill X. Mol Psychiatry. 2003;8:745–51.

Ribasés M, Gratacòs M, Fernández-Aranda F, Bellodi L, Boni C, Anderluh M, Cavallini MC, Cellini E, Di Bella D, Erzegovesi S, Foulon C, Gabrovsek M, Gorwood P, Hebebrand J, Hinney A, Holliday J, Hu X, Karwautz A, Kipman A, Komel R, Nacmias B, Remschmidt H, Ricca V, Sorbi S, Wagner G, Treasure J, Collier DA, Estivill X. Hum Mol Genet. 2004;13:1205–12.

Ribasés M, Gratacòs M, Fernández-Aranda F, Bellodi L, Boni C, Anderluh M, Cristina Cavallini M, Cellini E, Di Bella D, Erzegovesi S, Foulon C, Gabrovsek M, Gorwood P, Hebebrand J, Hinney A, Holliday J, Hu X, Karwautz A, Kipman A, Komel R, Nacmias B, Remschmidt H, Ricca V, Sorbi S, Tomori M, Wagner G, Treasure J, Collier DA, Estivill X (2005a) Eur. J. Hum. Genet. 13:428–434.

Ribases M, Gratacos M, Badia A, Jimenez L, Solano R, Vallejo J, Fernandez-Aranda F, Estivill X. Mol Psychiatry. 2005b;10:851–60.

Ribasés M, Fernández-Aranda F, Gratacòs M, Mercader JM, Casasnovas C, Núñez A, Vallejo J, Estivill X. J Psychiatr Res. 2008;42:50–7.

Ricca V, Nacmias B, Cellini E, Di Bernardo M, Rotella CM, Sorbi S. Neurosci Lett. 2002;323:105–8.

Ricca V, Nacmias B, Boldrini M, Cellini E, di Bernardo M, Ravaldi C, Tedde A, Bagnoli S, Placidi GF, Rotella CM, Sorbi S. Neurosci Lett. 2004;365:92–6.

Rosenkranz K, Hinney A, Ziegler A, Hermann H, Fichter M, Mayer H, Siegfried W, Young JK, Remschmidt H, Hebebrand J. J Clin Endocrinol Metab. 1998;83:4524–7.

Rosenkranz K, Hinney A, Ziegler A, von Prittwitz S, Barth N, Roth H, Mayer H, Siegfried W, Lehmkuhl G, Poustka F, Schmidt M, Schäfer H, Remschmidt H, Hebebrand J. Int J Obes Relat Metab Disord. 1998;22:157–63.

Rybakowski F, Slopien A, Dmitrzak-Weglarz M, Czerski P, Rajewski A, Hauser J. Neuropsychobiology. 2006;53:33–9.

Rybakowski F, Dmitrzak-Weglarz M, Szczepankiewicz A, Skibinska M, Slopien A, Rajewski A, Hauser J. Neuroendocrinol Lett. 2007;28:153–8.

Sabol SZ, Hu S, Hamer D. Hum Genet. 1998;103:273–9.

Serretti A, Artioli P. Psychopharmacology. 2004;174:490–503.

Shimizu M, Kanazawa K, Matsuda Y, Takai E, Iwai C, Miyamoto Y, Hashimoto M, Akita H, Yokoyama M. Thromb Res. 2003;112:137–42.

Shinohara M, Mizushima H, Hirano M, Shioe K, Nakazawa M, Hiejima Y, Ono Y, Kanba S. J Psychiatry Neurosci. 2004;29:134–7.

Siegfried Z, Kanyas K, Latzer Y, Karni O, Bloch M, Lerer B, Berry EM. Am J Med Genet B Neuropsychiatr Genet. 2004;125:126–30.

Slopien A, Rybakowski F, Dmitrzak-Weglarz M, Czerski P, Hauser J, Komorowska-Pietrzykowska R, Rajewski A. Acta Neuropsychiatr. 2004;16:290–4.

Sodhi M, Kerwin R, Campbell I, Makoff A. Mol Psychiatry. 1999;4:94.

Sorbi S, Nacmias B, Tedde A, Ricca V, Mezzani B, Rotella CM. Lancet. 1998;351:1785.

Steiger H, Joober R, Israël M, Young SN, Ng Ying Kin NM, Gauvin L, Bruce KR, Joncas J, Torkaman-Zehi A. Int J Eat Disord. 2005;37:57–60.

Steiger H, Joober R, Gauvin L, Bruce KR, Richardson J, Israel M, Anestin AS, Groleau P. J Clin Psychiatry. 2008;69:1565–71.

Sundaramurthy D, Pieri LF, Gape H, Markham AF, Campbell DA. Am J Med Genet. 2000;96:53–5.

Tortorella A, Monteleone P, Martiadis V, Perris F, Maj M. Am J Med Genet B Neuropsychiatr Genet. 2007;144:992–5.

Tsuchida A, Nonomura T, Ono-Kishino M, Nakagawa T, Taiji M, Noguchi H. Int J Obes Relat Metab Disord. 2001;25:1286–93.

Urwin RE, Bennetts B, Wilcken B, Lampropoulos B, Beumont P, Clarke S, Russell J, Tanner S, Nunn KP. Mol Psychiatry. 2002;7:652–7.

Urwin RE, Bennetts BH, Wilcken B, Beumont PJ, Russell JD, Nunn KP. Neuropsychopharmacology. 2003a;28:1351–5.

Urwin RE, Bennetts BH, Wilcken B, Lampropoulos B, Beumont PJ, Russell JD, Tanner SL, Nunn KP. Eur J Hum Genet. 2003b;11:945–50.

Urwin R, Nunn K. Eur J Hum Genet. 2005;13:370–5.

VanNess SH, Owens MJ, Kilts CD. BMC Genet. 2005;6:55.

Vink T, Hinney A, van Elburg AA, van Goozen SH, Sandkuijl LA, Sinke RJ, Herpertz-Dahlmann BM, Hebebrand J, Remschmidt H, van Engeland H, Adan RA. Mol Psychiatry. 2001;6:325–8.

Westberg L, Bah J, Råstam M, Gillberg C, Wentz E, Melke J, Hellstrand M, Eriksson E. Neuropsychopharmacology. 2002;26:789–93.

Ziegler A, Görg T. Lancet. 1999;353:929.

Chapter 77
Changes in Brain Gene Expression in Nutrient Deficiencies: An Example with Iron

Erica L. Unger, Narasimha Hegde, and James R. Connor

Abbreviations

CSF	Cerebrospinal fluid
IF	Interstitial fluid
Tim-2	T-cell immunoglobulin and mucin domain-containing protein 2
IRP	Iron regulatory protein
IRE	Iron responsive element
UTR	Untranslated region
mTOR	Mammalian target of rapamycin
CamK2a	Calcium/calmodulin-dependent protein kinase II alpha
BDNF	Brain derived neurotrophic factor
ARA	Arachidonic acid
MBP	Myelin basic protein
MOG	Myelin-oligodendrocyte glycoprotein
MAL	Myelin and lymphocyte protein
MOBP	Myelin-associated oligodendrocytic basic protein
PMP22	Peripheral myelin protein 22
PLP	Proteolipid protein
DAT	Dopamine transporter
GABA	Gamma-aminobutyric acid
GAT1	Gamma-aminobutyric acid transporter type 1
VMAT2	Vesicular monoamine transporter 2
trkB	Tyrosine kinase B

77.1 Introduction

Iron is an indispensable element in biological systems and is responsible for the function of many prosthetic groups, including heme and iron–sulfur clusters. Cellular iron uptake, distribution, and export must be tightly regulated, as iron deficiency impairs the function of many proteins, and excess

E.L. Unger (✉)
Department of Nutritional Sciences, Pennsylvania State University,
University Park, PA 16802
e-mail: elu103@psu.edu

iron can oxidize and damage the protein, nucleic acid, and lipid content of the cell. A well-regulated feedback control functions to enhance iron absorption when the body is deficient and to limit excessive iron accumulation when iron is abundant. Major sites of iron regulation are the doudenum where dietary iron is absorbed, the bone marrow where red blood cells are produced, the liver where most excess iron is stored, and the spleen and reticuloendothelial system where red blood cells are catabolized and iron is extracted for reuse. The importance of iron homeostasis becomes clear when one considers that iron deficiency anemia is the most widespread nutritional disorder affecting over 30% of the world's population, and that iron overload can lead to diabetes and heart disease and is a contributing factor to neurodegenerative diseases. The proper distribution and sequestering of iron is a challenging task at both the cellular and organismic levels due to the involvement of many organs and their differential requirement for iron that differs by age and sex. In the brain, iron is required for a multitude of cellular processes; thus it is the organ most vulnerable to iron deficiency during critical periods of development, particularly during the last trimester of fetal life and during the period of brain growth spurt and differentiation. This chapter will discuss iron regulation in the brain and changes in gene expression in the condition of iron deficiency.

77.2 Iron Transport in the Brain

Iron is required as a cofactor in central nervous system metabolic processes such as oxygen transport, neurotransmitter production, nitric oxide metabolism, and oxidative phosphorylation (Ponka 2004). The neuronal need for iron is obvious considering the fact that about 20% of the oxygen consumption of the body relies on mitochondrial respiration in the brain. During development, embryonic and dividing neurons require iron to support the activity of the enzyme ribonucleotide reductase, which is critical for DNA replication. Further, the role of iron in neuroectodermal development was demonstrated by mutating the gene encoding the transferrin receptor, which provides transferrin-bound iron to the brain, resulting in nonviable embryos with severe malfunctions of the central nervous system (Levy et al. 1999).

Evidence over the last 2 decades suggests that mechanisms of iron transport across the blood–brain barrier involve a transferrin–transferrin receptor pathway. (Bradbury 1997; Malecki et al. 1999; Burdo and Connor 2003). Uptake of transferrin-bound iron by transferrin receptor-mediated endocytosis from the blood into the cerebral endothelial cells is similar to iron uptake by other cell types. This process involves binding, endocytosis, acidification, and dissociation, and finally translocation of iron across the endosomal membrane via a process that may involve divalent metal transporter 1 (Fleming et al. 1997). A second proposed mechanism of iron transport across the abluminal membrane involves astrocytes, through their endfoot processes on the capillary endothelium (Malecki et al. 1999; Oshiro et al. 2000). A small portion of transferrin–iron complex is also known to cross the blood–brain barrier by receptor-mediated transcytosis (Moos and Morgan 1998). In addition to these pathways, it has been proposed that the lactoferrin receptor-lactoferrin and glycosylphosphatidylinositol (GPI)- anchored p97-secreted pathways may play a role in iron transport across the blood–brain barrier (Faucheux et al. 1995).

When iron has been transported across the blood–brain barrier, it binds to transferrin that is secreted from the oligodendrocytes and epithelial cells of the choroid plexus (Bradbury 1997). Transferrin in cerebrospinal fluid (CSF) and interstitial fluid (IF) is fully saturated with iron under normal conditions, and several experiments suggest that the iron concentration exceeds that of the binding capacity of transferrin in the CSF and IF. The nontransferrin-bound iron in the brain is likely associated with citrate, ascorbate, albumin, lactoferrin, and secreted p97. The presence of nontransferrin-bound iron in brain extracellular fluids and the absence of transferrin receptors in astrocytes, oligodendricytes, and microglia show that glia acquire iron via mechanisms independent

of transferrin/transferrin receptor mediation (Moos 1996; Moos and Morgan 1998). For instance, oligodendrocytes express T-cell immunoglobulin and mucin domain-containing protein 2 (Tim-2), which binds and internalizes the iron storage protein H-ferritin. This interaction is likely the main mechanism for iron acquisition into oligodendrocytes (Todorich et al. 2008).

77.3 Iron Homeostasis

Given the fact that iron requirements far exceed the gastrointestinal absorption capacity, iron utilized on a daily basis is continuously recycled from internal storage. This process is regulated by the hepatocyte-derived peptide hepcidin, which maintains systemic iron homeostasis by regulating gastrointestinal iron absorption and iron release from reticuloendothelial stores via the plasma membrane iron exporter ferroportin (Nemeth et al. 2004). Ceruloplasmin maintains a rate of plasma iron oxidation sufficient for the continued release of this essential metal from the storage site (Harris et al. 1998). Iron levels in the blood are not static and are known to fluctuate with the diurnal cycle, which has been attributed to fluctuating iron release from reticuloendothelial cells (Scales et al. 1988; Uchida et al. 1983). The rationale for variations in plasma iron relative to fluctuations in tissue needs for iron is interesting but not elucidated by current theories of iron requirements.

Brain iron accounts for less than 2% of the total body iron content. Iron content in the brain is highest in basal ganglia, with substantia nigra, red nucleus, and hippocampus also having significant iron contents (Hill and Switzer 1984; Morris et al. 1992). Similar to peripheral iron levels, regional brain iron levels fluctuate with the diurnal cycle, with as much as 30% differences in ventral midbrain (substantia nigra/ventral tegmentum) iron between the light and dark phases of the diurnal cycle in several inbred strains of mice (Unger et al. 2009). This flux in iron levels has not yet been attributed to specific cell types and the mechanisms surrounding this observation remain unknown. This is a paradigm shifting observation that establishes a dynamic state of iron flux rather than the static concepts that are entrenched in the literature to date (Dallman and Spirito 1977).

In the developing brain, iron uptake is greatest during the prenatal period when the brain is undergoing rapid growth. Iron deficiency in infancy is now known to inhibit cognitive development and alter affective behavior. Iron supplementation is ineffective in correcting many of these deficits (Lozoff 2007; Lozoff et al. 2000; Pinero et al. 2001). Similar to humans, rodents that were iron deficient during gestation and early postnatal life show similar deficits in cognition and attention after iron repletion. Thus, an understanding of the effects of early iron deficiency on brain structure and function and of the inability of the brain to correct iron content during postnatal iron repletion has critical implications.

Iron regulatory proteins: Regulation of iron metabolism occurs through iron regulatory proteins (IRPs) and iron-responsive elements (IREs). IRP1 and IRP2 register cytosolic iron concentrations and posttranscriptionally regulate expression of iron metabolism genes. These two proteins are ubiquitously expressed mammalian members of the aconitase gene family (Gruer et al. 1997), and bind to IRE with high affinity when intracellular iron levels are low. The IRE is a highly conserved nucleotide hairpin (IRP binding regions) located in the untranslated region (UTR) in mRNAs encoding specific proteins of iron metabolism (Henderson et al. 1994). Among the genes known to take part in iron homeostasis, the mRNA for ferritin, ferroportin, and HIF2alpha contain IREs in the 5′ untranslated region while transferrin receptor 1 and DMT1 mRNA contain IREs in the 3′ untranslated regions. In states of iron depletion, each IRP responds by binding to IREs. When the IRE is located in the 3′ UTR, the binding of IRPs to IRE stabilizes the mRNA, and hence more protein is translated (Haile 1999). Alternatively, by binding to a single IRE located in the 5′ UTR of mRNA, the IRP prevents translation. In cells that are iron-repleted, IRPs do not bind IREs, and ferritin and other transcripts that have an IRE in the 5′UTR are freely translated (Klausner et al. 1993).

77.4 Effect of Dietary Iron on Gene Expression in the Brain

77.4.1 Iron Regulatory Proteins

Abnormal amounts of iron in the brain have been documented in a number of age-related neurode-generative disorders including Alzheimer's (Bishop et al. 2002; Connor et al. 1992a, b 1995) and Parkinson's diseases (Kaur and Andersen 2004). It is generally accepted that this excess iron catalyzes the formation of reactive oxygen species and induces oxidative damage to which the brain is sensitive (Robb and Connor 1998). Iron deficiency-related research conducted to date suggests that dietary iron deficiency during critical periods of development also adversely affects brain function (Beard et al. 2002, 2003a; Felt et al. 2006; Felt and Lozoff 1996). Although a large body of literature is available that focuses on dietary iron deficiency and cognitive and behavioral deficits, only recently have studies focused on gene expression profiling in the brain during prenatal and postnatal iron deficiency (Carlson et al. 2007; Clardy et al. 2006; Liu et al. 2007).

Alterations in gene expression of the iron transporter transferrin in brain in response to iron deficiency has been observed in several rodent models. Iron deficiency from early gestation to postnatal day 21 produces a downregulation in transferrin gene expression (Clardy et al. 2006), which was also observed in a postweaning animal model where iron deficiency continued for six weeks (Han et al. 2003 #184). These studies further indicate that transferrin receptor and divalent metal transporter 1 are upregulated by gestational/lactational iron deficiency, while transferrin receptor gene expression is not changed by postnatal iron deficiency (Carlson et al. 2007; Clardy et al. 2006; Han et al. 2003; Siddappa et al. 2002). In pre and postnatal models of iron deficiency, transferrin protein levels in the brain and periphery are typically upregulated, which is an indication that transferrin protein could be acquired from sources outside the brain (Clardy et al. 2006; Crowe and Morgan 1992; Han et al. 2003). In contrast to the previously mentioned studies, iron deficiency during gestation and during the first week of lactation followed by 1 week of iron repletion increases transferrin mRNA levels in hippocampus (Carlson et al. 2007). Oligodendrocytes are the predominant source of transferrin mRNA in the brain, suggesting that transferrin mRNA production by oligodendrocytes may be upregulated by small periods of adequate iron during early postanal life.

77.4.2 Energy Metabolism and Cell Growth

Since iron homeostasis is coupled to energy metabolism, it is expected that dietary iron deficiency would bring about changes in the expression pattern of genes involved in energy metabolism and cellular growth. Mammalian target of rapamycin (mTOR) is a serine/threonine protein kinase that integrates several pathways to regulate cell growth, differentiation and survival. Importantly, the expression of genes in the mTOR signaling cascade including *Fkbp 1a*, *Gltscr 2*, *Ddit4*, *and Tsc2* are altered in hippocampus from gestational and early lactational iron-deficient rats (Carlson et al. 2007). A significant upregulation of the gene *Slc2a1*, the major brain glucose (energy) transporter, is observed in this same animal model (Carlson et al. 2007). Altered regulation of genes involved in energy metabolism and cell growth suggests that neural dendritic growth and synaptic transmission may be affected by iron deficiency. Iron deficiency also induced an upregulation in the hippocampal expression of the calcium/calmodulin-dependent protein kinase II alpha (CamK2a) gene, which is regulated by brain derived neurotrophic factor (BDNF) through the mTOR pathway, further implies an altered density of glutamatergic synapses and changes in synaptic plasticity (Schratt et al. 2004).

These specific neuronal changes may underlie some of the disturbed spatial recognition and learning abilities in the iron-deficient animal models.

Genes involved in the cell division cycle are also responsive to iron depletion. Microarray analyses of the whole brain from rats that are iron deficient during early gestation until weaning show more than a 1-fold increase in the cyclin B1, cyclin D1, cyclin L, and cyclin-dependent kinase four genes, indicating that iron deficiency affects the cell cycle progression during this period. To date, there is no evidence as to which cell type(s) show more active cycling after this period of iron deficiency. Studies using isolated hippocampal cells cultured in iron-depleted conditions show altered mRNA levels of *Bs69*, *Pdcd5*, *Anapc8*, and *Ruvbl2* (Liu et al. 2007). These proteins function during cell cycle arrest and can lead to apoptotic events in the brain. The direct relationship, if any, between iron status of cells and cell cycle activity is not known. Does iron status drive cell division or is iron only important for the cell to meet metabolic needs during division? One possible direct mechanism is through IRP2 which has a phosphorylation site, Ser157, that is phosphorylated by cyclin-dependent kinase/cyclin B1 during G(2)M. Thus phosphorylation of this site provides a mechanism by which ferritin and transferrin receptor production can be regulated during the cell cycle (Wallander et al. 2008).

Microarray analyses of whole brain (Clardy et al. 2006) and hippocampus (Carlson et al. 2007) suggest that several genes involved in cellular signal transduction mechanisms are altered by prenatal/lactational iron deficiency. Both of these studies have reported nearly a 3-fold increase (highest among all the genes represented in the array) in the expression of arachidonate 12-lipoxygenase and arachidonate 15-lipoxygenase. These enzymes belong to the family of oxydoreductases and are iron-dependent. 12/15-lipoxygenases are the major source of oxidative stress during pathological conditions including Alzheimer's disease (Pratico et al. 2004), which suggests that upregulation of these two enzymes could be indicative of brain oxidative stress induced by dietary iron deficiency. Arachidonate 12-lipoxygenase and arachidonate 15-lipoxygenase also participate in arachidonic acid (ARA) metabolism. ARA is a polyunsaturated fatty acid that is present in the phospholipids of membranes and is abundant in the brain (Rapoport 2008). Functions of arachidonic acid in the brain include maintaining hippocampal cell membrane fluidity (Fukaya et al. 2007), protecting the brain from oxidative stress by activating perioxisomal proliferator-activated receptors (Wang et al. 2006), and activating syntaxin-3 that is involved in neuron growth and repair (Darios and Davletov 2006). The involvement of ARA in cellular signaling as a lipid second messenger and as an inflammatory intermediate has been well documented (Darios and Davletov 2006; Abe et al. 1992). It is worth mentioning at this point that upregulation of these oxydoreductases in the ARA pathway are a good indication of altered lipid synthesis during developmental iron deficiency. The brain has to depend on de novo synthesis of lipids and cholesterols for structural changes such as dendritic growth, synapse formation, and myelination, which reach their peak during early postnatal life (Brody et al. 1987). Changes in the structural composition of the brain are likely to alter many processes including synaptic neurotransmission between and within brain regions and cause potentially irreparable behavioral deficits.

77.4.3 Myelin-Related Genes

Oligodendrocytes produce myelin in the CNS and are the most robustly iron stained cells in the healthy adult brain (Benkovic and Connor 1993; Todorich et al. 2009). A deficiency in iron increases the latency of auditory brain stem responses in human infants, an indirect indication of hypomyelination (Roncagliolo et al. 1998). Moreover, gestational and lactational iron deficiency in rodents reduces myelin formation in the spinal cord and the presence of integral myelin proteins proteolipid protein and myelin basic protein isoforms in whole brain homogenates (Ortiz et al. 2004; Yu et al. 1986).

Table 77.1 Myelin-related genes downregulated by early iron deficiency in whole brain

Name	Known or proposed function
Myelin basic protein	Myelin compaction and stability
Myelin-oligodendrocyte glycoprotein	Myelin stability, maintenance
Myelin and lymphocyte protein	Myelin biogenesis, stabilization
Myelin-associated oligodendrocyte basic protein	Myelin sheath maintenance
Peripheral myelin protein 22	Myelin compaction
Proteolipid protein	Myelin compaction, oligodendrocyte maturation

Myelin is a fatty insulating sheath that is wrapped around the nerve process termed the axon. Mylein increases the speed at which signals are conducted within the brain. A reduction in myelin associated genes suggests that the myelin content of the brain is reduced, thus affecting the transmission of signals

Further, hindbrain CNPase and myelin basic protein levels, indicators of reduced myelin production, are reduced in rats only exposed to postweaning iron deficiency, indicating that sufficient iron is required by oligodendrocytes for maintenance of myelin even after the period of peak myelination from P8-P12 (Beard et al. 2003b).The question of whether these changes in myelination are due to posttranslational events in iron deficiency or whether gene expression is also altered was examined as part of a study that investigated gene responses to gestational and early postnatal iron deficiency in rats (Clardy et al. 2006). This model of early iron deficiency showed a downregulation of myelin basic protein (MBP) and myelin-oligodendrocyte glycoprotein (MOG) that are important in myelin stability, myelin and lymphocyte protein (MAL) that is involved in myelin biogenesis, and myelin-associated oligodendrocytic basic protein (MOBP) that may be important in myelin sheath maintenance. Other downregulated genes include peripheral myelin protein 22 (PMP22), proteolipid protein (PLP), fibroblast growth factor, and chimerin 2. The decrease in myelin-related gene expression is consistent with a delay in oligodendrocyte maturation or with a reduced number of oligodendrocytes in the iron-deficient brain (Clardy et al. 2006).

Importantly, iron supplementation from weaning until 6 months of age can correct the deficits in whole brain myelin gene expression (Clardy et al. 2006). Despite this normalization of gene expression, myelin deficits remain at 6 months of age, indicating that there is a critical time point during which iron is required for proper myelination in adulthood (Ortiz et al. 2004). Given these recent findings, future studies aimed at investigating the critical period during which iron supplementation is required for proper myelination are warranted. The peak period of myelination is P8-P12 in the rat, but the question remains as to how late in postnatal life that iron supplementation can begin to have proper myelin production (Table 77.1).

77.5 Iron Deficiency and Neurotransmitter Systems

77.5.1 Dopamine

Extensive studies during the last several decades have indicated that iron deficiency has deleterious effects on the dopamine neurotransmitter system. The nigrostriatal dopamine pathway that regulates movement and the mesolimbic pathway that mediates the reinforcing effects of drug addiction appear to be the most affected regions of the brain (Beard 2003; Beard et al. 2003a; Erikson et al. 2000; Pinero et al. 2001; Youdim et al. 1984; Youdim). The 12 transmembrane domain protein, the dopamine transporter (DAT), serves as a key regulator of dopamine neurotransmission and is encoded by the Slc6A3 gene. Importantly, the solute carrier (Slc) gene family encodes membrane transport

Table 77.2 Genes affected by iron deficiency that encode neurotransmitter transporters and receptors

Name	Period of ID	Brain region(s)
Upregulated genes		
Norepinephrine transporter	P21 – P63	Globus pallidus
GABA transporter type 1	P21 – P63	Substantia nigra
Serotonin transporter	G5 – P21	Whole brain
Vesicular monoamine transporter 2	G5 – P21	Whole brain
Downregulated genes		
Dopamine receptor 1A	G5 – P21	Whole brain
Norepinephrine transporter	P21 – P63	Locus ceruleus, substantia nigra, cerebellum
Norepinephrine alpha2 receptor	P21 – P63	Locus ceruleus, cerebellum
GABAA receptor delta	G5 – P21	Whole brain
GABAA receptor alpha6	G5 – P21	Whole brain
GABAA receptor	P21 – P63	Substantia nigra
GABAB receptor	P21 – P63	Substantia nigra

Many neurotransmitter systems including dopamine, serotonin, norepinephrine and GABA are altered by iron deficiency. The timing (postnatal versus gestational) and the extent of iron deficiency are likely important factors in producing these outcomes. Further, the effect of iron deficiency on the brain is region dependent, i.e. all brain regions are not affected equally by iron deficiency

Period of iron deficiency (ID); *G* gestational day; *P* postnatal day

proteins that regulate neurotransmitter and nutrient transport, and deficits in the expression of these genes have serious health implications. In most rodent models of iron deficiency, regional DAT protein expression is downregulated, but the limited studies to date do not indicate that there is a similar change in Slc6A3 gene expression (Carlson et al. 2007; Clardy et al. 2006). The protein levels of two subtypes of dopamine receptors, D1 and D2, are also affected by iron deficiency, although only a downregulation in dopamine receptor 1A has been described in whole brain. Gene expression of DAT and dopamine receptor subtypes have not been evaluated in brain regions that typically show the largest reductions in DAT protein (i.e., striatum and nucleus accumbens). Thus, studies evaluating dopamine-related gene expression within these regions are necessary to conclude that changes in protein levels are a consequence of posttranslational modifications and/or changes in gene expression in the iron-deficient brain (Table 77.2).

77.5.2 Norepinephrine

There is a large body of literature that implicates norepinephrine in the modulation of attention, memory, emotion, and drug addiction. Deficits in these behaviors have been linked to iron deficiency in humans and rodents (Unger et al. 2007; Lozoff et al. 2006; Lozoff and Brittenham 1987; Lozoff et al. 1991, 2007). Norepinephrine cell bodies project from the locus coeruleus in the pons to diverse regions in the forebrain (cortex, caudate putamen, and hippocampus) or to the hindbrain cerebellum. Regulation of norepinephrine signaling occurs via the norepinephrine transporter, a member of the Slc6 family of transporters that has a similar structure to the previously mentioned dopamine transporter, and two distinct classes of receptors, alpha and beta, that are further divided into subtypes. Iron depletion in the brain typically reduces regional norepinephrine transporter protein expression and intracellular and extracellular norepinephrine levels in striatum (Anderson et al. 2009; Beard et al. 2006b; Bianco et al. 2009).

Two studies have specifically investigated the effects of iron deficiency on norepinephrine transporter and receptor mRNA levels in the brain using a postweaning animal model (iron deficient from

postnatal day 21 to day 63). Iron deficiency causes a downregulation of norepinephrine transporter mRNA in locus ceruleus, substantia nigra, and cerebellum and produces an upregulation in globus pallidus compared to iron-sufficient rats (Anderson et al. 2009; Beard et al. 2006b). Likewise, alpha2 receptor expression is reduced in locus ceruleus and cerebellum. These changes in the norepinephrine neurotransmitter system are not surprising given the extensive changes in the dopamine system in iron deficiency and the anatomical connections between the dopaminergic and noradrenergic systems. There is mounting evidence that the locus ceruleus can mediate dopamine release in the nucleus accumbens via direct and indirect projections to the ventral tegmental area, and that dopamine afferents in the locus ceruleus originate in the ventral tegmental area (Guiard et al. 2008). These projections allow a communication between neurotransmitter systems that together modulate cognition, attention, affect, drug addiction, and many other behaviors. As research into the gene expression profile of iron deficiency continues, elucidating the response of key genes involved in these pathways will become increasingly important to understand the persistent effects associated with iron deficiency.

77.5.3 Serotonin

The serotonin neurotransmitter system is widely known for its involvement in anxiety- and depression-related disorders. Slc6a4 encodes the serotonin transporter, which moves serotonin into the presynaptic neuron to terminate the serotonin signal, and is the site of action of many antidepressant/antianxiety drugs. Gestational and early postnatal iron deficiency causes an upregulation of Slc6a4 in whole brain (Clardy et al. 2006). Several postweaning models of iron deficiency have indicated that regional serotonin transporter protein levels are reduced, which creates a potential disconnect between gene and protein data (Beard 2003; Burhans et al. 2005). It is likely that the effects of pre- versus postweaning iron deficiency on the serotonin neurotransmitter system are quite diverse. A more in depth study investigating regional serotonin-related gene expression during iron deficiency will facilitate our knowledge as to the impact of iron regulation on the serotonin neurotransmitter system, and perhaps offer clues as to the relationship between iron deficiency, serotonin, and affective disorders.

77.5.4 GABA

Gamma-aminobutyric acid (GABA) is the most abundant inhibitory neurotransmitter in the adult mammalian central nervous system. Similar to monoamine neurotransmitters, the action of GABA is terminated by uptake via a membrane transporter protein and transmitted via distinct transmembrane receptors. The GABA neurotransmitter system has 4 known subtypes of transporters named type 1 (GAT1), type 2, type 3, and type 4 GABA transporters that are located on neurons and glia (Beleboni et al. 2004). The receptors are divided into two classes, metabotropic and ionotropic receptors. GABAB receptors are metabotropic and characterized by their ability to produce a slow inhibitory response through activation of G proteins (G-protein coupled receptors) and subsequent opening of ion channels. GABAA and GABAC ionotropic receptors are directly coupled to transmembrane ion channels (ligand gated ion channels) and produce fast responses. An understanding of the effect of iron deficiency on the GABA neurotransmitter system has become increasingly important because of behavioral abnormalities that are characteristic of deficits in dopamine/GABA interactions in the substantia nigra, striatum, and nucleus accumbens (Beard et al. 2006a; Erikson et al. 2000, 2001;

Pinero et al. 2001). These brain regions have proven to be sensitive to iron loss and to dopamine system dysregulation in iron deficiency (Beard et al. 2007; Erikson et al. 1997; Unger et al. 2007).

GABA-related gene expression in iron deficiency has been investigated in gestational and postweaning animal models. Microarray analysis of whole brain from rats that were deficient in iron from gestational day 5 to postnatal day 21 indicates that GABAA receptor delta and GABAA receptor alpha 6 are downregulated after early iron deficiency (Clardy et al. 2006). Since this study was performed with whole brain samples, we are unable to pinpoint these changes to distinct brain regions. Importantly, it appears likely that long-term iron repletion can correct this deficit since 5 months of iron supplementation did restore whole brain GABA receptor mRNA to control levels.

Iron deficiency begun at postnatal day 21 and continuing for 6 weeks reduces substantia nigra GABAA and GABAB receptor expression compared to iron sufficient rats, with other regions including caudate and cerebellum not being significantly affected (Anderson et al. 2008). GAT-1 mRNA expression was increased 3-fold in substantia nigra, again with little affect in other brain regions. Protein concentrations of GAT-1 were decreased and GABAA were increased in the iron-deficient substantia nigra suggesting that the gene response is a mechanism aimed at maintaining normal levels of these proteins or that there is a change in transcription efficiency. There are GABAergic striatal neurons that project to the substantia nigra (striatonigral neurons) that act to inhibit dopaminergic output from the dopamine call body containing substantia nigra. Given the consistent changes in GABA gene and protein expression in the substantia nigra, this provides a mechanism by which GABA may be involved in regulating dopamine and the related behaviors observed in iron deficiency.

77.5.5 Other Transporters

Two additional solute carrier genes that are important in the regulation of neurotransmitter signaling, Slc18a2 and Slc7a1 are upregulated by gestational/lactational iron deficiency (Clardy et al. 2006). Slc18a2, or vesicular monoamine transporter 2 (VMAT2), accumulates cytosolic monoamines including dopamine, serotonin, and norepinephrine into synaptic vesicles via an ATP dependent mechanism for release into the synapse. As noted previously, neurotransmitter system functioning is compromised in iron deficiency, and altered VMAT2 expression may contribute to the observed deficits in iron-deficient rodents. The gene encoding Slc7a1, or cationic amino acid transporter 1, is also upregulated in the same iron deficiency model and is responsible for arginine, lysine, ornithine, and histidine transport in the brain. Its role in arginine transport has implications for cell proliferation and for the production of nitric oxide that is necessary for many biological processes and has detrimental effects if not present at appropriate levels (Lameu et al. 2009). The altered expression of these transporter genes further indicates that proper movement of molecules and ions in the iron-deficient brain cannot be maintained.

77.6 Iron Deficiency and Neurotrophic Factors

Neurotrophic factors are a family of proteins that promote the growth and maintenance of developing neurons and the survival of mature neurons. Probably the best studied class of neurotophic factors are the neurotrophins, that include brain derived neurotrophic factor (BDNF) and nerve growth factor (NGF) among others. Perinatal iron deficiency from gestational day 2 to postnatal day 7 reduces levels of BDNF transcript III and BDNF transcript IV mRNA at postnatal days 7, 15, and 30, and these effects persist through postnatal day 65 (Tran et al. 2008, 2009). The gene expression of the

primary binding site of BDNF, tyrosine kinase B (trkB) receptor, is also reduced at P65. The BDNF signaling mechanism has several downstream targets including the activity-dependent immediate early transcription factors that assist in the regulation of neurite outgrowth and synaptic plasticity. Similar to BDNF, these transcriptional targets, early-growth-response-gene 1 (ERG1) and 2 (ERG2), cfos, and 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMGCR), are reduced at P65. The literature suggests that a reduction in the expression of BDNF and activity dependent immediate early transcription factors in hippocampus can result in a loss of neuronal plasticity. Indeed, early iron deficiency in rats does produce long-term changes in the morphology of dendrites and alters synaptic function in the CA1 area of the hippocampal dendrites (Jorgenson et al. 2003, 2005).

These studies illustrate that perinatal iron deficiency reduces the action of BDNF through early adult life and perhaps throughout the lifespan. Importantly, peak import of iron into the hippocampus occurs between postnatal day 5 and postnatal day 15 (Siddappa et al. 2002), and dramatic changes in gene expression in the rat hippocampus occur during the first 2 weeks of postnatal life (Stead et al. 2006). This period also encompasses the stage of maximal neuron growth and differentiation. Detrimental neurochemical and behavioral outcomes resulting from altered BDNF gene expression have been revealed in several mouse models and include deficits in maintenance of long term potentiation (Barco et al. 2005; Patterson et al. 1996), learning (Gorski et al. 2003; Monteggia et al. 2004) and affective behaviors (MacQueen et al. 2001). These findings may have direct relevance to the prolonged and irreversible losses in hippocampal-based learning and memory functioning and emotional responses that have been observed in human infants with iron deficiency and iron-deficient rodent models (Felt et al. 2006; Lozoff 2007; Lozoff et al. 2006).

77.7 Applications to Other Areas of Health and Disease – Alzheimer's Disease

Dysregulation of iron homeostasis has been implicated in several disease states including Parkinson's and Alzheimer's diseases (Connor et al. 1992a, b). An upregulation of several genes known to be implicated in the etiology in Alzheimer's disease has been observed in the developing hippocampus of mice that were iron deficient during gestation and early lactation (Carlson et al. 2007). These genes include connective tissue growth factor, fibronectin 1, cystatin C, cathepsin B, cathepsin S, amyloid beta precursor-like protein 1, amyloid beta precursor protein-binding familyB member 1, clusterin, and NDRG2. These data suggest there could be iron deficiency in the Alzheimer's brain despite the reported increase in iron. The latter concept may not be contradictory; much of the elevated iron in the Alzheimer's disease brain may be bound to plaques and thus, not bioavailable (Connor et al. 1992a; Meadowcroft et al. 2009). Moreover, there is a similar pattern of expression in genes associated with oxidative stress in the hippocampus of iron-deficient rodents and brains from Alzheimer's patients. These data suggest that we should re-evalute the interpretation of some of these data to consider that iron deficiency could generate a gene/protein profile of oxidative stress

Summary Points

- The brain is the organ most vulnerable to iron deficiency during critical periods of development that include the stage of brain growth spurt and differentiation.
- Genes that are altered by brain iron deficiency are integral to processes including signal transduction, myelin formation, cell growth, energy metabolism, and neurotransmitter signaling.

- While the expression level of some genes can be corrected with iron supplementation, other genes may not be responsive to iron treatment strategies.
- Timing of iron deficiency is an important factor when considering treatment intervention strategies. Critical to this idea is to determine the point in development when iron supplementation is required such that the negative behavioral effects associated with early iron deficiency do not persist through adulthood.
- The novel concept that iron deficiency may generate a stress profile in the brain similar that that observed in Alzheimer's Disease is an area that warrants future studies.

Definitions of Key Terms and Words

Iron deficiency anemia: is a late stage of iron depletion characterized by low plasma iron levels, a low serum transferrin saturation, elevated transferrin receptor levels and low serum ferritin concentrations.

Transferrin: is a glycoprotein that binds ferric iron for transport to target tissues.

The **transferrin receptor:** is a carrier protein that binds transferrin for movement of iron across membranes. Transferrin receptor levels are regulated by iron content in the body via iron regulatory proteins and iron response elements.

An **oligodendrocyte:** in a type of glial cell located within the central nervous system that is responsible for myelination of axon processes.

Oxidative stress: is a condition defined by elevated levels of reactive oxygen species, including peroxidases and free radicals, which the body is not able to eliminate efficiently.

Dopamine: is an inhibitory neurotransmitter synthesized from the amino acid tyrosine. This neurotransmitter is the precursor of the neurotransmitter norepinephrine.

Dopamine transporter: is a 12 transmembrane domain protein that transports dopamine from the extracellular space into the cytoplasm of a presynaptic neuron.

Brain-derived neurotrophic factor: is a member of the neurotrophin family of growth factors that supports neuron growth and survival.

Key Points of Iron Deficiency

- The World Health Organization (WHO) recognizes iron deficiency as the most common and widespread nutrient disorder in the world. Iron deficiency is currently the only nutrient deficiency that is prevalent in both nonindustrialized and industrialized countries, where it is prevalent in mainly women and children.
- Iron deficiency is believed to be the most common cause of anemia, which afflicts more than two billion people worldwide. Anemia is a condition in which the number of red blood cells in the body is reduced or the ability of the red blood cells to carry oxygen is diminished and cannot meet the body's needs.
- Iron deficiency in infancy has been consistently associated with adverse changes in development and in behavior, including impaired motor skills and increased fearfulness and unhappiness. Many of these behavioral outcomes continue to be observed for years after iron status has been improved in these children.
- Iron deficiency anemia can have a significant impact on an individual's work capacity by causing severe fatigue and producing affective difficulties, decreased attention, and reduced cognitive abilities. These negative outcomes can have an economical impact, particularly in regions where iron deficiency anemia is rampant.
- There is considerable evidence that iron plays an important role in many processes in the brain including neurotransmitter metabolism, myelin formation, and brain energy metabolism. These physiological consequences have been linked to the behavioral and development observations in iron deficiency.

References

Abe K, Araki T, Kawagoe J, Aoki M, Kogure K. Adv Exp Med Biol. 1992;318:183–95.

Anderson JG, Fordahl SC, Cooney PT, Weaver TL, Colyer CL, Erikson KM. Neurotoxicology. 2008;29:1044–53.

Anderson JG, Fordahl SC, Cooney PT, Weaver TL, Colyer CL, Erikson KM. Brain Res. 2009;1281:1–14.

Barco A, Patterson S, Alarcon JM, Gromova P, Mata-Roig M, Morozov A, Kandel ER. Neuron. 2005;48:123–37.

Beard J. J Nutr. 2003;133:1468S–72S.

Beard J, Erikson KM, Jones BC. J Nutr. 2003a;133:1174–9.

Beard JL, Erikson KM, Jones BC. Behav Brain Res. 2002;134:517–24.

Beard JL, Felt B, Schallert T, Burhans M, Connor JR, Georgieff MK. Behav Brain Res. 2006a;170:224–32.

Beard JL, Unger EL, Bianco LE, Paul T, Rundle SE, Jones BC. J Nutr. 2007;137:1176–82.

Beard JL, Wiesinger JA, Connor JR. Dev Neurosci. 2003b;25:308–15.

Beard JL, Wiesinger JA, Jones BC. Brain Res. 2006b;1092:47–58.

Beleboni RO, Carolino RO, Pizzo AB, Castellan-Baldan L, Coutinho-Netto J, dos Santos WF, Coimbra NC. Cell Mol Neurobiol. 2004;24:707–28.

Benkovic SA, Connor JR. J Comp Neurol. 1993;338:97–113.

Bianco LE, Unger EL, Earley CJ, Beard JL. Chronobiol Int. 2009;26:447–63.

Bishop GM, Robinson SR, Liu Q, Perry G, Atwood CS, Smith MA. Dev Neurosci. 2002;24:184–7.

Bradbury MW. J Neurochem. 1997;69:443–54.

Brody BA, Kinney HC, Kloman AS, Gilles FH. J Neuropathol Exp Neurol. 1987;46:283–301.

Burdo JR, Connor JR. Biometals. 2003;16:63–75.

Burhans MS, Dailey C, Beard Z, Wiesinger J, Murray-Kolb L, Jones BC, Beard JL. Nutr Neurosci. 2005;8:31–8.

Carlson ES, Stead JD, Neal CR, Petryk A, Georgieff MK. Hippocampus. 2007;17:679–91.

Clardy SL, Wang X, Zhao W, Liu W, Chase GA, Beard JL, True Felt B, Connor JR. J Neural Transm Suppl. 2006;173–96.

Connor JR, Menzies SL, St Martin SM, Mufson EJ. J Neurosci Res. 1992a;31:75–83.

Connor JR, Snyder BS, Arosio P, Loeffler DA, LeWitt P. J Neurochem. 1995;65:717–24.

Connor JR, Snyder BS, Beard JL, Fine RE, Mufson EJ. J Neurosci Res. 1992b;31:327–35.

Crowe A, Morgan EH. Brain Res. 1992;592:8–16.

Dallman PR, Spirito RA. J Nutr. 1977;107:1075–81.

Darios F, Davletov B. Nature. 2006;440:813–7.

Erikson KM, Jones BC, Beard JL. J Nutr. 2000;130:2831–7.

Erikson KM, Jones BC, Hess EJ, Zhang Q, Beard JL. Pharmacol Biochem Behav. 2001;69:409–18.

Erikson KM, Pinero DJ, Connor JR, Beard JL. J Nutr. 1997;127:2030–8.

Faucheux BA, Nillesse N, Damier P, Spik G, Mouatt-Prigent A, Pierce A, Leveugle B, Kubis N, Hauw JJ, Agid Y, et al. Proc Natl Acad Sci U S A. 1995;92:9603–7.

Felt BT, Beard J, Schallert T, Shao J, Aldridge JW, Connor JR, Georgieff MK, Lozoff B. Behav Brain Res. 2006;171:261–70.

Felt BT, Lozoff B. J Nutr. 1996;126:693–701.

Fleming MD, Trenor CC, 3rd, Su MA, Foernzler D, Beier DR, Dietrich WF, Andrews NC. Nat Genet. 1997;16:383–6.

Fukaya T, Gondaira T, Kashiyae Y, Kotani S, Ishikura Y, Fujikawa S, Kiso Y, Sakakibara M. Neurobiol Aging. 2007;28:1179–86.

Gorski JA, Balogh SA, Wehner JM, Jones KR. Neuroscience. 2003;121:341–54.

Gruer MJ, Artymiuk PJ, Guest JR. Trends Biochem Sci. 1997;22:3–6.

Guiard BP, El Mansari M, Blier P. Mol Pharmacol. 2008;74:1463–75.

Haile DJ. Am J Med Sci. 1999;318:230–40.

Han J, Day JR, Connor JR, Beard JL. Nutr Neurosci. 2003;6:1–10.

Harris ZL, Klomp LW, Gitlin JD. Am J Clin Nutr. 1998;67:972S–7S.

Henderson BR, Menotti E, Bonnard C, Kuhn LC. J Biol Chem. 1994;269:17481–9.

Hill JM, Switzer RC, 3rd. Neuroscience. 1984;11:595–603.

Jorgenson LA, Sun M, O'Connor M, Georgieff MK. Hippocampus. 2005;15:1094–1102.

Jorgenson LA, Wobken JD, Georgieff MK. Dev Neurosci. 2003;25:412–20.

Kaur D, Andersen J. Ageing Res Rev. 2004;3:327–43.

Klausner RD, Rouault TA, Harford JB. Cell. 1993;72:19–28.

Lameu C, de Camargo AC, Faria M. Recent Pat CNS Drug Discov. 2009;4:137–42.

Levy JE, Jin O, Fujiwara Y, Kuo F, Andrews NC. Nat Genet. 1999;21:396–9.

Liu M, Xiao DS, Qian ZM. Mol Cell Biochem. 2007;300:139–47.

Lozoff B. Food Nutr Bull. 2007;28:S560–71.

Lozoff B, Beard J, Connor J, Barbara F, Georgieff M, Schallert T. Nutr Rev. 2006;64:S34–43; discussion S72–91.

Lozoff B, Brittenham GM. Hematol Oncol Clin North Am. 1987;1:449–64.

Lozoff B, Corapci F, Burden MJ, Kaciroti N, Angulo-Barroso R, Sazawal S, Black M. J Nutr. 2007;137:683–9.

Lozoff B, Jimenez E, Hagen J, Mollen E, Wolf AW. Pediatrics. 2000;105:E51.

Lozoff B, Jimenez E, Wolf AW. N Engl J Med. 1991;325:687–94.

MacQueen GM, Ramakrishnan K, Croll SD, Siuciak JA, Yu G, Young LT, Fahnestock M. Behav Neurosci. 2001;115:1145–53.

Malecki EA, Devenyi AG, Beard JL, Connor JR. J Neurosci Res. 1999;56:113–22.

Meadowcroft MD, Connor JR, Smith MB, Yang QX. J Magn Reson Imaging. 1999;29:997–1007.

Monteggia LM, Barrot M, Powell CM, Berton O, Galanis V, Gemelli T, Meuth S, Nagy A, Greene RW, Nestler EJ. Proc Natl Acad Sci U S A. 2004;101:10827–32.

Moos T. J Comp Neurol. 1996;375:675–92.

Moos T, Morgan EH. J Neurosci Res. 1998;54:486–94.

Morris CM, Candy JM, Oakley AE, Bloxham CA, Edwardson JA. Acta Anat (Basel). 1992;144:235–57.

Nemeth E, Tuttle MS, Powelson J, Vaughn MB, Donovan A, Ward DM, Ganz T, Kaplan J. Science. 2004;306:2090–3.

Ortiz E, Pasquini JM, Thompson K, Felt B, Butkus G, Beard J, Connor JR. J Neurosci Res. 2004;77:681–9.

Oshiro S, Kawahara M, Kuroda Y, Zhang C, Cai Y, Kitajima S, Shirao M. Biochim Biophys Acta. 2000;1502:405–14.

Patterson SL, Abel T, Deuel TA, Martin KC, Rose JC, Kandel ER. Neuron. 1996;16:1137–45.

Pinero D, Jones B, Beard J. J Nutr. 2001;131:311–8.

Ponka P. Ann N Y Acad Sci. 2004;1012:267–81.

Pratico D, Zhukareva V, Yao Y, Uryu K, Funk CD, Lawson JA, Trojanowski JQ, Lee VM. Am J Pathol. 2004;164:1655–62.

Rapoport SI. J Nutr. 2008;138:2515–20.

Robb SJ, Connor JR. Brain Res. 1998;788:125–32.

Roncagliolo M, Garrido M, Walter T, Peirano P, Lozoff B. Am J Clin Nutr. 1998;68:683–90.

Scales WE, Vander AJ, Brown MB, Kluger MJ. J Appl Physiol. 1988;65:1840–6.

Schratt GM, Nigh EA, Chen WG, Hu L, Greenberg ME. J Neurosci. 2004;24:7366–77.

Siddappa AJ, Rao RB, Wobken JD, Leibold EA, Connor JR, Georgieff MK. J Neurosci Res. 2002;68:761–75.

Stead JD, Neal C, Meng F, Wang Y, Evans S, Vazquez DM, Watson SJ, Akil H. J Neurosci. 2006;26:345–53.

Todorich B, Pasquini JM, Garcia CI, Paez PM, Connor JR. Glia. 2009;57:467–78.

Todorich B, Zhang X, Slagle-Webb B, Seaman WE, Connor JR. J Neurochem. 2008;107:1495–505.

Tran PV, Carlson ES, Fretham SJ, Georgieff MK. J Nutr. 2008;138:2495–501.

Tran PV, Fretham SJ, Carlson ES, Georgieff MK. Pediatr Res. 2009;65:493–8.

Uchida T, Akitsuki T, Kimura H, Tanaka T, Matsuda S, Kariyone S. Blood. 1983;61:799–802.

Unger EL, Paul T, Murray-Kolb LE, Felt B, Jones BC, Beard JL. J Nutr. 2007;137:118–24.

Unger EL, Earley CJ, Beard JL. J Appl Physiol. 2009;106:187–93.

Wallander ML, Zumbrennen KB, Rodansky ES, Romney SJ, Leibold EA. J Biol Chem. 2008;283:23589–98.

Wang ZJ, Liang CL, Li GM, Yu CY, Yin M. Chem Biol Interact. 2006;163:207–17.

Youdim MB, Ashkenazi R, Ben-Shachar D, Yehuda S. Adv Neurol. 1984;40:159–70.

Youdim MB, Ben-Shachar D. Isr J Med Sci. 1987;23:19–25.

Yu GS, Steinkirchner TM, Rao GA, Larkin EC. Am J Pathol. 1986;125:620–4.

Pathology and Abnormal Aspects: Sensory

Chapter 78
When Taste Triggers Sociophobia

Matthieu J. Guitton

Abbreviations

5-HT2C	Serotonin receptor 2C
CTA	Conditioned taste aversion
ER	Estrogen receptor
ISI	Interstimulus interval
mCPP	Meta-chlorophenylpiperazine
PTSD	Post-traumatic stress disorder
LiCl	Lithium chloride
WD	Water deprivation

78.1 Introduction

Taste perception, food ingestion behaviors, and social behaviors are intimately linked together in mammals. The search for comestible food is one of the principal behavioral drives for animals. Transmission of information related to food has a critical importance in strongly socially organized species. Accurate social perception – necessary to maintain hierarchical rankings and satisfying group cohesion – is by essence multimodal. If the influence of smell on interindividual communication is obvious, the involvement of taste-related information in the regulation of interindividual interaction appears somehow less direct. It is however not necessarily less important. In addition, these links are pertinent – and can be actualized – not only in normal physiological situations, but also in pathological ones.

Philogenetical and ecological considerations can explain why the gustatory modality deserves a particular treatment, compared to other sensory modalities. Taste and smell are the only two sensory modalities using chemodetection directed toward external stimuli; they thus are the heirs of the most archaic forms of perception. Taste-dependent learning differs from other forms of associative (classical or instrumental) learning in a critical point: the time interval separating the conditioned stimulus

M.J. Guitton (✉)
Centre de Recherche Université Laval Robert-Giffard (CRULRG), 2601 Chemin de la Canardière
F-6517, Québec, QC, G1J 2G3, Canada
and
Faculty of Pharmacy, Laval University, Quebec City, QC, Canada
e-mail: matthieu.guitton@pha.ulaval.ca

from the unconditioned stimulus (the interstimulus interval or ISI). Whereas in most cases the two stimuli must appear almost together in time in order to be correctly associated, taste-dependent learning tolerates incredibly long ISI, up to several hours. This is due in part to the fact that, in contrast to the vast majority of negative reinforcers, ingestion-induced malaises (which unfortunately represents one of the main ecological outcomes of taste experience) usually require some time to develop. Stimuli that are less closely associated with food (such as auditory, visual, or tactile cues) are not able to support the same long intervals than taste (Garcia et al. 1968). In the context of conditioning, socially oriented behavioral sequences represent conditioned responses much longer than the ones classically observed for other forms of learning. Thus, the very long ISI of taste-dependent learning could support associations with social behaviors.

In this text, we will focus on the alteration to social behavior which can be induced by presentation of a taste. We will describe whether presentation of taste can induce direct social withdrawal, how taste presented by a conspecific can socially transmit food-related information, and how taste can reactivate off-line negative emotional states to trigger marked social withdrawal. The implications of these findings for human eating disorders will be extensively discussed, as well as some promising topics such as the influence of sexual hormones and the exploration of alterations in hedonism.

78.2 Food Ingestion and Social Withdrawal

The search for food is one of the most basic motivational drives of animal behaviors. Indeed, the capacity of survival of the individual is a direct function of the amount of food which can be found – and successfully ingested. However, one of the inherent problems of ingestive behavior is the risk of absorbing toxic or poisonous food. But luckily enough for animals, toxic food does not necessarily have a lethal effect. In most cases, the ingestion of toxic food only translates into transient malaise, often characterized by visceral pain. If the toxicity is averred, the individual won't be able to efficiently react to challenging situations. Thus, intoxicated animals should, through their behavior, avoid encountering predators – even more than in normal conditions. One of the best ways not to be captured by a predator is for the individual to avoid being in the same location than other potential preys, i.e., other conspecifics.

However, the increased vulnerability to predators does not represent the only risk for poisoned individuals. In the context of social organization, the maintenance of hierarchized ranking is a dynamic process. Animals sickened by inadapted food are likely to be unable to fight to maintain their hierarchical position regarding their subordinates. After ingesting poisonous food, the animal may well survive, but to fully avoid subsequent problems, the process should not be accompanied by a loss of social status within the hierarchy. In the context of social groups based on hierarchical organization, weakened animals should thus not only avoid encountering predators, but also avoid encountering conspecifics (Fig. 78.1).

Isolation periods following toxic food ingestion could thus rely on at least two evolutionary justifications: first, directed toward nonconspecific – to avoid predators while unable to defend efficiently – second, directed toward conspecifics – to avoid losing social status in a highly hierarchized context. Worthy of note is that this global social withdrawal following food poisoning is very close to the general sickness-associated social isolation (Bluthé et al. 1991; Dantzer 2001). In the case of unknown food – i.e., food with "new" taste – postingestion social withdrawal may therefore represent a natural predisposition of ecological significance (Fig. 78.1). By actively avoiding unnecessary social contacts, the individual may secure recently acquired food and avoid putative risks linked to postingestion. This direct effect represents a first level of food related taste-triggered social withdrawal in animals.

Fig. 78.1 Social withdrawal provoked by poisoning. After ingestion of poisonous or toxic food, the animal (white animal) will experience delayed noxious effects (such as visceral pain), and will adapt its social behavior in order to actively decrease its social interactions with conspecifics (grey animal)
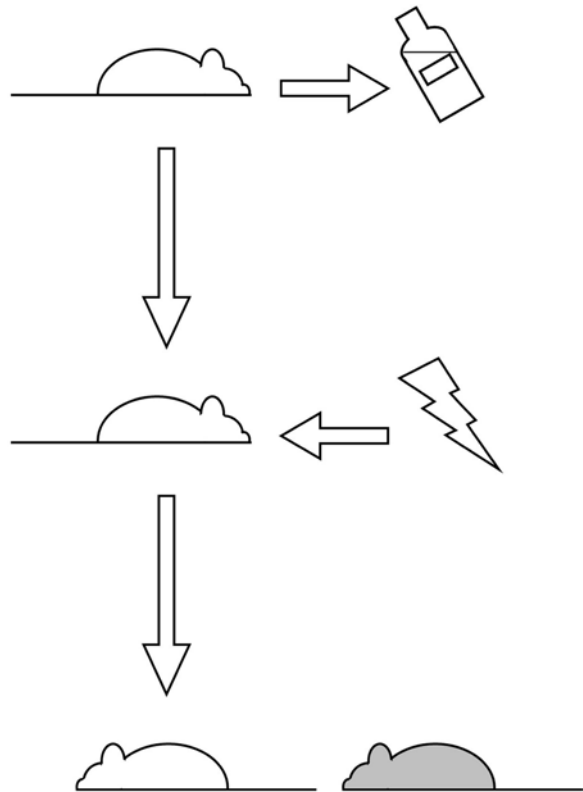
78.3 Socially Transmitted Food Preference

The social withdrawal triggered by absorption of toxic food represents a direct effect which can be associated with taste perception. Surprisingly, the effect that tastes can have on social behaviors go much further: in addition to effects on the social behavior of the animal which actually ate the food, passive information carried following food ingestion can trigger massive effect on the social behavior of other conspecifics as well (Galef and Wigmore 1983; Clipperton et al. 2008). Indeed, the taste of food attached to the animal can also carry information which will be socially transmitted to conspecifics (Galef and Wigmore 1983; Valsecchi and Galef 1989). This social transmission of information related to taste takes advantage of the fact that taste and smell can persist long time after their original cause (in this case, the food) disappeared.

Once an animal has eaten something, the smell of the food will stay on body parts surrounding the mouth. Actually, even the taste of the ingested food will stay and could be detected if another conspecific would be able to lick these body areas. While saying that may at first glance sound surprising, it is not. Indeed, most mammals do have interactions bringing into play these specific zones. For instance, in the case of rodents, whiskers represent one of the main organs used to investigate the world (Brecht et al. 1997). This also includes social interindividual exploratory behaviors – such as sniffing or grooming the partner (Guitton et al. 2008).

There are thus possibilities for direct exchange of taste related information between two animals during the process of social interactions. Generally speaking, alterations of perception can trigger clear modifications of social behavior. For instance, the occurrence of tinnitus – perception of sound in the absence of auditory stimulation – triggers in mice the full spectrum of social alterations

(Guitton 2009). As for other sensory modalities, such links exist between taste and social behavior, as it has been described here above. But, in contrast to other sensory information, taste can be directly transmitted from one individual to another. Due to the possibility of direct transmission of taste information between two individuals after physical contact, a same taste can elicit a second order, indirect effect in an individual which was not at first exposed to the original food.

As we mentioned above, one of the inherent problems of ingestive behavior is the risk to consume poisonous or toxic food. A major advantage for animals to live in a social context is the possibility for any given member of the group to use the experience of others. Taste information related to food can be transmitted without having to experience the real ingestion process; in contrast, effects of the food can be inferred by assessing the physical state of the "demonstrator" conspecific (Fig. 78.2). Thus, emerged the mechanism of social acquired food preference referred to as socially transmitted food preference (Galef and Wigmore 1983; Valsecchi and Galef 1989). The logic of this particular form of social learning is based on the principle that if an individual survived after ingesting a given food, then this food should not be so bad to eat (Fig. 78.2). On the other hand, for this mechanism to correctly work, if a newly ingested food is toxic, it is crucial for the poisoned individual not only to avoid taking it again, but also to transmit this information to its conspecifics by not letting them validate the food as putatively good by assessing its presence ("taste") on him. The obvious ecological advantage of acquiring food preferences from conspecifics is the possibility to somehow "bypass" the danger linked to the potential ingestion of toxic food (Galef and Wigmore 1983; Valsecchi and Galef 1989).

Thus, in addition to the two first ecological justifications underlying social withdrawal following the ingestion of toxic food, a third one would be not to transmit to other conspecifics the false information of the relative safety of the ingested food. Social withdrawal observed after the ingestion of toxic
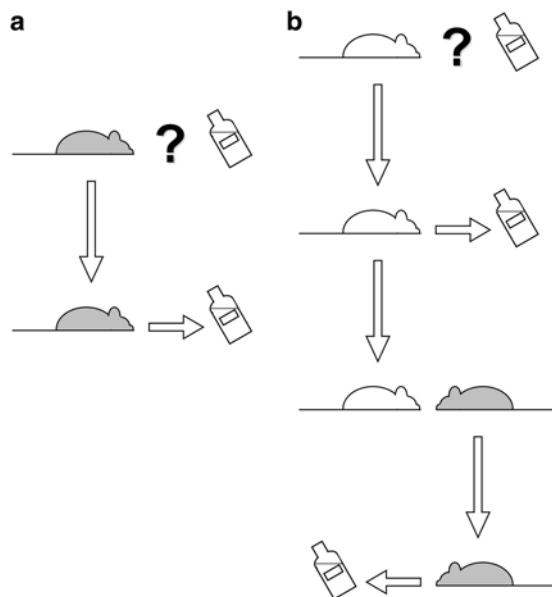
Fig. 78.2 Socially transmitted food preference. (**a**) When an animal is confronted with unknown food, it will hesitate before eating it (neophobia), since the new food may be potentially dangerous. (**b**) If a conspecific (white animal) has already eaten this food and "presents" the taste on its whiskers, the animal which was not confronted with the food (grey animal) will display a marked preference for this food when it encounters it. Indeed, the animal will "infer" from the fact that the demonstrator is still alive that the food can be ingested safely. This form of socially acquired knowledge is referred as socially transmitted food preference

food can therefore have at least three ecological reasons. As we will discuss below, the combination of these three postulated causes is highly interesting in the context of the ontogeny of food disorders observed in humans.

What we just discussed however only represents the most obvious part of taste-triggered social withdrawal. Indeed, in this case, the signals – both the taste (either directly from food, or indirectly via presentation of the taste by a conspecific) and the effects of food ingestion (either direct if the animal ate the food, or indirect if the animal is assessing the state of its conspecific) – are "on-line." But can taste trigger alterations of social behaviors if stimuli are not present, in other words "off-line" (Guitton et al. 2008)? The next paragraph will attempt to answer this question by examining how taste exposure and association with emotional states can produce long-term effects on social behaviors.

78.4 Taste-Dependent Social Withdrawal

Up to now, the effects described here where only "on-line" effects, meaning effects observed when the two stimuli (the taste and the effects of food) are still salient. The relationship between on-line taste information of social behavior is obvious, either in the case of immediate taste distress-provoked social withdrawal with direct taste detection and effect of the food, or in the case of immediate taste-dependent social learning with indirect presentation of the taste via a conspecific and evaluation of the health status of the individual. But in addition to these responses, taste can also trigger massive alterations of social behavior when the reinforcer is not there, i.e., when the original stimuli are "off-line" (Guitton et al. 2008).

When an animal is first exposed to a poisonous food, the odds that this animal will ingest this food if presented again are rather low. Indeed, the animal is likely to avoid it (Garcia et al. 1966; Berman and Dudai 2001; Guitton and Dudai 2004). This taste-dependent learning, in which the subject associates a conditioned stimulus (the taste) with a delayed unconditioned stimulus (visceral pain) is called a conditioned taste aversion (CTA, for a classical protocol used to induce CTA in rats, see Fig. 78.3) (Garcia et al. 1966; Bures et al. 1998). Following such a conditioning, the conditioned response will be a massive aversion for the food displaying the same taste. In the case of a classical CTA (while the new taste is associated with clear-cut visceral pain), there is no real need to engram the information necessary to trigger complex social withdrawal next time the taste will be presented, since once the taste will be recognized anew, the corresponding food will not be eaten again. And indeed, if animals present a CTA for a given taste, a subsequent presentation of this taste will not trigger any modification of their social behavior (Guitton et al. 2008). They will clearly avoid the food, but no further social effect will be observed (Fig. 78.4). However, the situation is drastically different if the food did not provoke massive visceral pain, but rather elicited a diffuse and vague emotional state. Anxiety and anxiety-like state result from situations that represent either real or imaginary danger for the individual (Marks 1987; LeDoux 1998). In contrast to visceral pain, anxiety is a rather diffuse internal state. But can anxiety act as unconditioned stimulus in the context of taste-dependent learning? This question was addressed using pharmacological tools to experimentally induce anxiety-like state in rats (Guitton and Dudai 2004). For instance, metachlorophenylpiperazine (mCPP), a serotoninergic agent acting as a 5-HT2C receptor agonist, is known to be able to provoke, both in humans and animals, anxiety-like state when injected (Bilkei-Gorzo et al. 1998; Guitton and Dudai 2004). Delayed anxiety provoked by intraperitoneal injection of mCPP was able to be specifically associated with taste information by rats, and this association was strong enough to be detected by behavioral measurements as a CTA (Guitton and Dudai 2004).
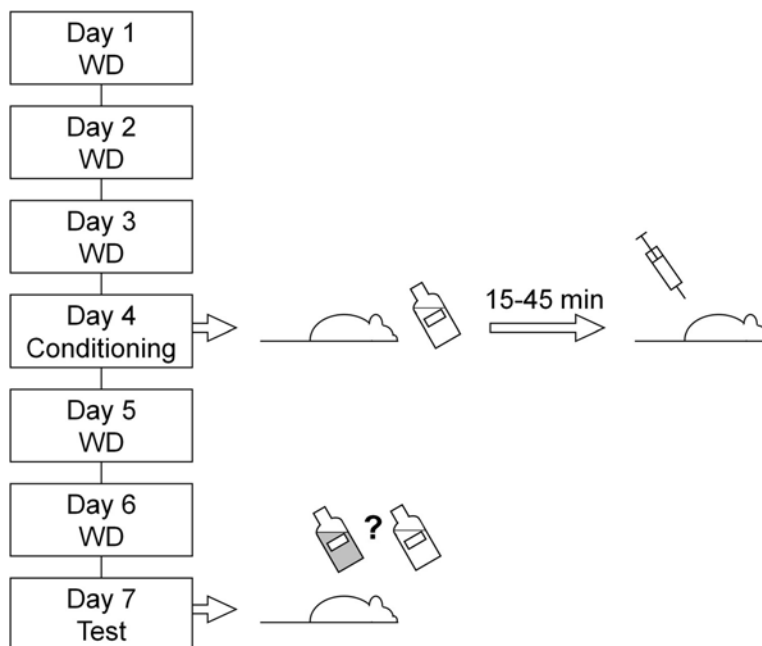
Fig. 78.3 A classical protocol to induce a CTA. Here is exemplified a "classical" protocol which can be used to induce conditioned taste aversion (CTA) in rats. During the time course of the protocol, animals are under water deprivation (WD), meaning that their access to water is restrained to 10 min per day (except the first day, for which the time allowed to access water is 30 min). At Day 4 (Conditioning), animals are allowed to drink a solution with a new taste instead of water for 10 min. About 15–45 min after the offset of the drinking period, animals are exposed to an agent inducing visceral pain (classically, a single intraperitoneal injection of LiCl, 0.15M, 2% of body weight). Three days after the conditioning (Day 7, Test), animals are given free choice between water and the conditioned taste during their 10 min daily drinking period. Conditioned animals are expected to massively display a behavioral preference toward water over the taste associated with visceral pain

Using a combination of anxiety-induced CTA (using mCPP injections as inductor of anxiety-like state) and social interaction measurements, we recently reported that taste-dependent conditioning procedure can trigger a marked impairment in social behavior – corresponding to a massive and active social withdrawal, or a "sociophobia" (Fig. 78.4) – in response to the conditioned taste (Guitton et al. 2008). When compared to control animals (or animals subjected to a classical CTA with visceral pain as unconditioned stimulus), animals treated with mCPP completely diverged concerning their behavioral outcomes when presented anew with the conditioned taste. Animals for which taste was initially paired with delayed anxiety presented a drastic decrease of the social events they displayed compared to any of the other experimental groups (Guitton et al. 2008). The number of behavioral escapes stayed very low for experimental animals whatever the group, except for the animals initially conditioned with mCPP-induced anxiety. In a phenotyping point of view, the modifications observed for the escape responses are of major importance to explain the deterioration of social interactions, since they confirm an active participation of the treated animal. Thus, the decrease of the number of social events was definitively not merely passive, but rather an active phenomenon. Therefore, this decrease of social interactions was really isomorphic to a social withdrawal (Guitton et al. 2008). The abnormal (anti)social behavior displayed by these animals is likely to affect the behavior of their naïve partner. And that is what actually occurred. Indeed, naïve partners strongly increased their following behaviors, mirroring the evolution of the escape behaviors
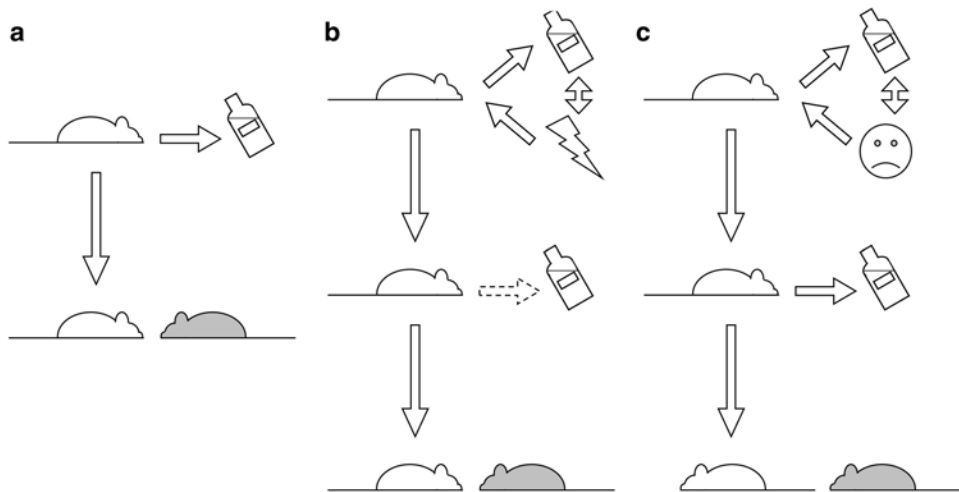
Fig. 78.4 Taste-dependent sociophobia. (**a**) Consumption of food does usually not induce any alteration of social behavior. (**b**) If an animal experiences the taste of a new food and is subjected later on to visceral pain (for instance using LiCl injection), the association of these two stimuli will produce a conditioned taste aversion (CTA). Such association will result in a strong avoidance of the conditioned taste (and so, food). However, if the animal eats this food again (which is unlikely to happen, discontinued arrow), the perception of this taste will not induce any modification of social behavior. (**c**) However, if the animal experiences a new taste followed by a delayed negative emotional state (such as anxiety-like state), the association will be more diffuse and the behavioral outcomes will be totally different. First, the animal may still want to eat the target food. However, after ingesting it, social behavior will be drastically affected. Indeed, the animal will actively avoid social contact (social withdrawal)

observed in mCPP-treated animals. However, since they were receiving less social inputs, naïve partners were ultimately also decreasing slightly their social activity in response to the sociophobic behavior displayed by mCPP-treated animals (Guitton et al. 2008) (Fig. 78.5). This behavioral response observed once the taste was presented again was clearly not a generalized avoidance, since almost no reduction in approach behavior of the spout, or in consumption was observed, translating the fact that anxiety was able to produce only a limited CTA (Guitton and Dudai 2004; Guitton et al. 2008). Furthermore, taste–anxiety associations are not generalized (Fig. 78.6): only the taste on which the association has been made can trigger social withdrawal, other tastes being unable to do so (Guitton et al. 2008).

Thus, if anxiety-like states have a relatively low power to induce CTA, this taste–emotion association has remarkable outcomes at the social behavior level (Guitton et al. 2008). The retrieval-induced "sociophobic" state lingers long after a single exposure to the nonreinforced taste. By predicting the unconditioned stimulus (which is in this case a purely emotional state), the gustatory cue appears to trigger a persistent emotional and social response. And that could be happening in the case of human beings. Indeed, taste could get associated with the emergence of a feeling, even unrelated. Since taste-dependent conditioning tolerates long ISI, the emotional feeling could well be associated with the taste. The association of taste with delayed negative internal states could generate conditioned response different from taste aversion, such as in this case active social withdrawal. It is clear that such forms of memory of association may contribute to the ontogenesis, reinforcement, and symptoms of some types of taste- and food-related disorders. The further association of a taste with social withdrawal might represent a conditioned augmentation of the natural predisposition of social withdrawal following ingestion of new food described in the beginning of this text.
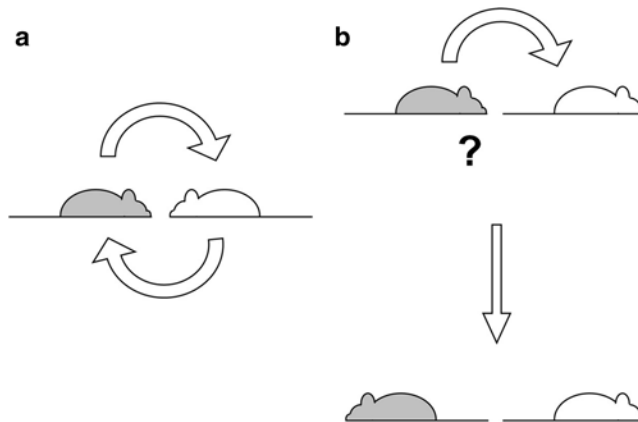
Fig. 78.5 Social interactions and social withdrawal. (**a**) Social interactions are active processes in which each of the two animals exhibits social behavior. In other words, there are interactions because each animal displays and initiates social events directed toward its partner – the events can be elicited either originally, or in response to the previous event emitted by the partner. (**b**) If one of the animal does not respond to the social stimuli sent by its partner (for instance, in the case of social withdrawal), there are no "interactions." So, the social dialog evolves toward a monolog. Finally, the partner will lose interest in the social communication with the unresponding animal, and will in turn also decrease the number of social behaviors emitted
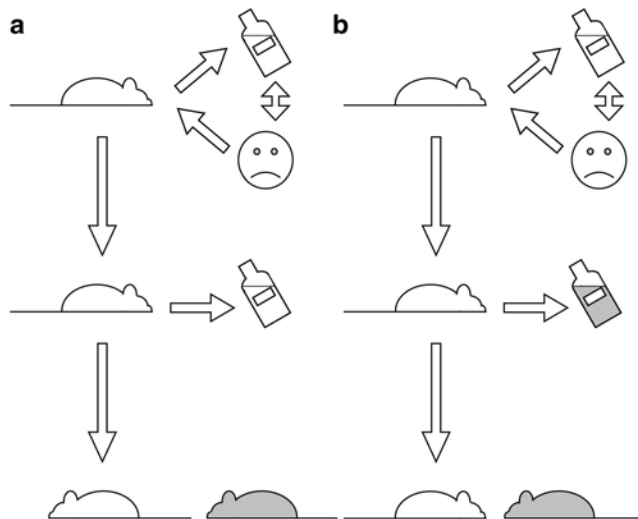
Fig. 78.6 Taste specificity in association leading to taste-dependent sociophobia. (**a**) Associations able to lead to a taste-dependent sociophobia (association between a new taste and a negative emotional state) are not generalized. Only the taste on which was made the association can potentially trigger alterations of social behavior such as social withdrawal. (**b**) In contrast, if another taste is presented to the animal, no alterations of social behavior will be assessed

78.5 Relevance for Human Eating Disorders

As we suggested above, this last effect of taste-triggered social withdrawal, described in animals, has significant implications for the understanding of ontogenesis and maintenance of human food disorders. Even if clearly based on abnormal and in adapted behaviors triggered by altered perception of food or food-related

elements (including body image – anorexic patients commonly present distortions in the perception of the size and shape of their own body), the social component of anorexia or bulimia is obvious and cannot be denied (Klein and Walsh 2004). According to current definitions, anorexia could be characterized by social withdrawal triggered by food consumption itself, or by the fact (averred or inferred) that others know that food was ingested. Numerous physiological, psychological, and social alterations are associated with eating disorders, and deciphering which are the factors predisposing or accelerating the apparition of the disorder is far to be an easy task (Klein and Walsh 2004). The ontogenesis of eating disorders is likely to be multifactorial, with massive interactions between internal (biological or psychological) and external (social or environmental) risk factors (Walsh and Devlin 1998; Klein and Walsh 2004).

Links between food disorders and alterations of social behavior clearly exist (Kaye et al. 2004; Guitton et al. 2008). Indeed, clinical studies demonstrated that both anorexia and bulimia nervosa present a significant comorbidity with social phobia (Kaye et al. 2004). A study performed during the Second World War on healthy conscientious war objectors showed that starvation provoked in humans increased irritability and diminished social interest (Franklin et al. 1948). Irritability is also one of the psychological symptoms frequently reported by anorexic patients in the acutely underweight state (Kaye 1997). Thus, progressive weight loss facilitates social avoidance. But since decrease of social interactions also oftenly triggers further weight loss, these two elements may well draw a vicious circle. Furthermore, food disorders have a strong co-occurrence with anxiety (Godart et al. 2000; Klein and Walsh 2004), with the onset of anxiety states often preceding the onset of anorexia or bulimia nervosa (Deep et al. 1995; Bulik et al. 1997; Godart et al. 2000). These privileged relations between negative emotions, taste perception, and social behavior may well represent a key element in the processes at the origin of food disorders. In this view, the taste–anxiety–sociophobia association described above may be highly relevant to eating disorders (Guitton et al. 2008).

Psychological stress may play some role in the initiation of the disorder. However, it is important to note that despite the high frequency of anxiety and mood alterations, purely antidepressant medications generally fail to help during the acutely underweight state of anorexia (Jones et al. 1991), suggesting that anxiety plays a role of reinforcer rather than being the real origin of the disorder. In the case of bulimia, negative emotions (such as feelings of anxiety, rejection, frustration, or low mood) often precede binges, which seem to become learned responses to negative emotional states (Abraham and Beumont 1982; Heatherton and Baumeoster 1991; Klein and Walsh 2004). A striking characteristic of eating disorders is the high persistence of disordered eating and/or abnormal dieting behavior once it has begun (Klein and Walsh 2004). This long-term persistence also strongly echoes the notion of strong association assessed in the particular form of memory that is a CTA (Bures et al. 1998; Berman and Dudai 2001; Guitton and Dudai 2004; Guitton et al. 2008).

Finally, in CTA, the context actualized when the subject tasted the food has also been shown to be able to act as a cue to elicit latter taste aversion (Desmedt et al. 2003), echoing the importance of the contextual environment in food disorders. In conclusion, association between food perception system and social behavior, and particularly the possibility of delayed social withdrawal triggered by taste, may be highly relevant for eating disorders (Table 78.1). An interesting possibility could be to consider anorexia as an epiphenomenon of social disturbance triggered by taste and food perception systems.

78.6 Influence of the Sex

In humans, eating disorders clearly affect disproportionately women (Klein and Walsh 2004), with a lifetime prevalence among women estimated at 1–3% for bulimia nervosa and at 0.5–2% for anorexia nervosa (Kendler et al. 1991; Favaro et al. 2003; Klein and Walsh 2004). Cultural reasons

Table 78.1 Key features of taste-dependent sociophobia

1. Social withdrawal occurs when an animal actively decreases the emission of social behaviors directed toward partners.
2. The regulation of social interactions and social ranking is dependent on sensory information.
3. Taste information related to food has clear ecological significance and can induce marked alterations of social behavior.
4. Social withdrawal can be triggered in mammals after association between taste and visceral pain or after retrieval of association between taste and negative emotional state.
5. The understanding of the links between taste and social behavior (especially taste-dependent social withdrawal) has significant implications for the understanding of ontogenesis and maintenance of human food disorders.
6. Eating disorders are associated with numerous physiological, psychological, and social alterations.
7. Anorexia and bulimia nervosa present a significant comorbidity with social phobia.
8. Anorexia may be characterized by social withdrawal triggered by food consumption, or by the fact (averred or inferred) that others know that food was ingested.

This table lists the key facts of taste-dependent sociophobia, including basic concept of social withdrawal, and how taste-dependent sociophobia evidenced in animals can be relevant for human food disorders

have often been mentioned to explain this situation. However, when considered with a sociobiological point-of-view – meaning, when considering that social behaviors are grounded by biological mechanisms – these sex-dependent differences observed in humans can find some elements of explanation at the molecular level. Indeed, estrogens are known to be able to modulate social learning. Both estrogen receptors alpha and beta have been demonstrated to be necessary for optimal social recognition in mice (Imwalle et al. 2002; Choleris et al. 2003, 2006).

This role of estrogens in social learning is particularly true for the social transmission of food preferences, and has been demonstrated using mice at various phases of the estrous cycle (Sánchez-Andrade et al. 2005; Clipperton et al. 2008). When tested immediately after socially acquired preference, the preference for the "unknown" food from which the taste was presented by a conspecific lasted longer in females in diestrus or proestrus females, than in females in estrus or ovariectomized (Clipperton et al. 2008). In addition to this effect on acquisition phase and short-term behavioral expression of this taste-dependent social learning, there is also an effect on the maintenance phase. Indeed, when compared to females in estrus or ovariectomized, females in proestrus and diestrus display a prolonged preference for the food targeted by the socially modulated taste-transmission (Clipperton et al. 2008). Finally, only mice in proestus clearly show a massive food preference when tested 24 h after the exposition to the taste through a conspecific having eaten the target food (Sánchez-Andrade et al. 2005).

A recent pharmacological study performed on animal model investigated more deeply the molecular basis of this modulation of taste-related social learning by estrogens, by focusing on the effects of selective agonists of the estrogen receptors (ERs) on socially transmitted food preferences. This study unveiled a differential role of ER alpha and ER beta in the acquisition and maintenance of socially transmitted food preference (Clipperton et al. 2008). When treated with the ER alpha selective agonist PPT (1,3,5-tris(4-hydroxyphenyl)-4-propyl-1H-pyrazole), ovariectomized mice are not able to acquire socially transmitted food preference – the alterations of this specific learning being neither due to the quality of interactions, nor to the food (Clipperton et al. 2008). In contrast, ovariectomized mice treated with the ER beta selective agonist WAY-200070 (7-Bromo-2-(4-hydroxyphenyl)-1,3-benzoxazol-5-ol) presented a massive increase of the duration of food preference (maybe partially through effects on submissive behavior), with the higher doses being able to trigger preferences similar to those observed in intact female mice during the proestrus and diestrus phases (Clipperton et al. 2008). This suggests the possibility of a balance between the activation of estrogen receptors – with ER beta activation countering ER alpha effects – in the modulation of taste-dependent

social learning. Further investigations may contribute to a better understanding of fine mechanisms of sexual regulation of taste-dependent withdrawal in human.

78.7 Perception of Hedonic Valence

Among the alterations of taste perception observed in humans suffering from eating disorders, those touching hedonism are highly interesting. In anorexic patients, hedonic self-rated perception of tastes are shifted toward a marked preference for sweetness, while high-fat solutions become aversive (Sunday and Halmi 1990). These alterations of hedonic valence do not seem however to stem from global disturbances of taste perception, since other dimensions of taste perception, such as taste intensity, are generally intact in anorexic patients (Klein and Walsh 2004). The mechanisms underlying these alterations in hedonism are still unknown. Some electrophysiological studies suggested that the brain processing of gustatory stimuli could be altered in anorexic patients (Tóth et al. 2004). Aversion to some particular kind of food (such as high-fat foods) might well reflect a form of conditioned aversion to "perceived" calories. Clearly, the "negative status" of some food is likely to relate at least to some extend to a learned association between the consumption of this food and subsequent disinhibition of eating behavior. Interestingly, the alterations of hedonism perception seem to somehow persist in anorexic patients, even following treatment (Sunday and Halmi 1990). Such, these shifts in hedonic perception could witness predisposing traits, rather than effects of the periods of self-imposed starvation.

Anorexic patients may present alterations of the reward value of food (Klein and Walsh 2004). However, food still represents a relevant stimulus for these patients, since food-related cues were demonstrated in neuropsychological experiments to be able to act as distractors (Sackville et al. 1998). Similarly, experiments realized with bulimic patients confirm this view, with cue reactivity demonstrated for taste, but also smell and sight, of typical binge foods (Staiger et al. 2000).

Such a role of hedonism seems to be also pertinent for animal models of food disorders. Actually, a recent work even suggests the possibility of a direct behavioral measure of hedonism in rats in the context of food disorders (Guitton et al. 2008). Indeed, once the conditioning has been performed using anxiety as unconditioned stimulus, consumption of beverage with the conditioned taste strongly correlates with the time of social interactions spent by the animal, following a linear regression with a different slope for each taste (Guitton et al. 2008). It has been suggested that the variation of the slope – which reflects at the individual level the relationship between active taste consumption and social behavior – could be a direct indicator of the hedonic valence of the considered taste (Guitton et al. 2008). In rats, food deprivation enhances the hedonic value of nonfood rewards, such as psychostimulants (Cabeza de Vaca and Carr 1998) and intracranial self-stimulation (Carr 2002). This suggests that starvation may have a "reward-potentiating effect," which may strongly reinforce abnormal behaviors in the case of human eating disorders. Further research is still needed to fully understand this phenomenon, but understanding the mechanisms underlying this process of reward-potentiation may further our knowledge on ontogeny of food disorders.

78.8 Conclusion

Either after a direct or indirect association between taste and on-line noxious state, or off-line retrieval of association between taste and negative emotional state, taste presentation can trigger social withdrawal in mammals. Even if clear demonstration of this phenomenon has been obtain on rats, these

properties of association between taste and social behavior have tremendous interest in the under-standing of eating disorders in humans (Table 78.1).

Modeling the cognitive aspects of eating disorders in animal clearly represents a highly challeng-ing issue – as it is the case for any psychiatric disorder. However, the use of adapted animal models unveils considerable promise as a mean to gain further insight into the molecular and biological mechanisms sustaining these abnormal eating behaviors. Further investigations will of course be needed, but the kind of behavioral approach described in this text on animal models may well con-tribute to the identification of new molecular targets, and to the development of innovative pharma-cological strategies to treat human patients suffering from food disorders.

Molecular regulation of the biological systems underlying this phenomenon is still far to be fully understood. However, understanding the fine regulation of the behaviorally observed forms of taste-dependent social withdrawal may well be one of the keys to understand the ontogeny of human food disorders.

78.9 Applications to Other Areas of Health and Disease

The main applications of research on taste-dependent sociophobia in animals are obviously the understanding of food and eating disorders, particularly anorexia nervosa and bulimia nervosa. However, applications to other areas of health, as well as to other specific diseases should not be neglected. In particular, working on this topic may help to understand some of the mechanisms modulating metabolic disorders such as diabetes.

By exploring complex conditioned responses different than the one classically analyzed in CTA, the interactions between taste detection, social behavior, and the association between these two com-ponents could help to further the analogies that several researchers have suggested between CTA and post-traumatic stress disorder (PTSD). Given the significance in terms of public health of PTSD, as well as the present lack of pharmacological agents to treat this pathology, the contribution of research performed on sociophobia induced following taste presentation may be crucial in the middle to long term.

Rats – like humans – are social animals and display a rich repertoire of social behaviors. In this view, testing social interactions in rats offers a possibility to test high-level behaviors, in addition to the simple aversive behavior classically observed with paradigms such as CTA. Such, investigation of social interactions in rodents (rats or mice) may represent an interesting tool to help further our understanding of pathologies strongly affecting behavior, and particularly psychiatric disorders. Finally, understanding how taste perception can influence social behavior and the maintenance of dynamic social ranking may account for a significant contribution in the research field of multimodal interactions in perception and cognition.

Summary Points

- Taste perception may have repercussions on social behaviors.
- Ingestion of poisonous or toxic food induces social withdrawal.
- Social withdrawal provoked by presentation of a taste is an active phenomenon.
- Food-related taste information can be transmitted from one animal to another conspecific.
- The social transmission of taste information between two animals can lead to a subsequent prefer-ence for the related taste in the animal which was not initially confronted to it.

- The association of a new taste and visceral pain results in a strong avoidance of the conditioned taste; however, if the animal detects this taste again, its perception will not induce modification of social behavior.
- In contrast, the association of a new taste and delayed anxiety-like state is more diffuse: the animal may have only a slight avoidance for the taste, but perceiving this taste anew will trigger massive alterations of social behavior, characterized by social withdrawal.
- The effects of this last form of association are rather specific to the conditioned taste and are not generalized.

Definitions of Key Terms

Anxiety-like state: Negative emotional state isomorphic to what is referred as anxiety in humans, the emotional state triggered by the perception of a potential danger (real or inferred).

Conditioned taste aversion: A particular form of associative learning between a new taste and an aversive delayed stimulus (usually visceral pain), which leads to a marked subsequent aversion for this taste and tolerates a very long interstimulus interval compared to other forms of associative learning.

Estrogen receptors: Endogenous receptors specifically activated by the binding with estrogenic hormones.

Neophobia: A form of novelty avoidance which occurs when an animal is confronted to an unknown taste, which reflects the inference of a putative toxicity of the food.

Poisonous or toxic food: Food which provokes deleterious effects when ingested by an animal; these effects can be either lethal or nonlethal (commonly provoking in this case transient malaise).

Socially transmitted food preference: Food preference acquired through social interactions with a conspecific which already tried this food without experiencing poisoning and display the taste on its whiskers. Socially transmitted food preference represents in rodents a socially acquired knowledge based on taste information.

Social withdrawal: Active (not a merely passive phenomenon) adaptation of behavior in order to decrease the occurrence and/or the duration of social interactions with conspecifics.

References

Abraham SF, Beumont PJ. Psychol Med. 1982;12:625–35.
Berman DE, Dudai Y. Science. 2001;291:2417–9.
Bilkei-Gorzo A, Gyertyan I, Levay G. Psychopharmacology. 1998;136:291–8.
Bluthé RM, Parnet P, Dantzer R, Kelley KW. Neurosci Res Commun. 1991;9:151–8.
Brecht M, Preilowski B, Merzenich MM. Behav Brain Res. 1997;84:81–97.
Bulik CM, Sullivan PF, Fear JL, Joyce PR. Acta Psychiatr Scand. 1997;96:101–7.
Bures J, Bermudez-Rattoni F, Yamamoto T. In: Bures J, Bermudez-Rattoni F, Yamamoto T, editors. Conditioned taste aversion, memory of a special kind. Oxford: Oxford University Press; 1998. pp. 1–25.
Cabeza de Vaca S, Carr KD. J Neurosci. 1998;18:7502–10.
Carr KD. Physiol Behav. 2002;76:353–64.

Choleris E, Gustafsson J-Å, Korach KS, Muglia LJ, Pfaff DW, Ogawa S. Proc Natl Acad Sci USA. 2003;100:6192–7.
Choleris E, Ogawa S, Kavaliers M, Gustafsson JÅ, Korach KS, Muglia LJ, Pfaff DW. Genes Brain Behav. 2006;5:528–39.
Clipperton AE, Spinato JM, Chernets C, Pfaff DW, Choleris E. Neuropsychopharmacology. 33:2362–75.
Dantzer R. Brain Behav Immun. 2001;15:7–24.
Deep AL, Nagy LM, Weltzin TE, Rao R, Kaye WH. Int J Eat Disord. 1995;1:291–7.
Desmedt A, Hazvi S, Dudai Y. J Neurosci. 2003;23:6102–10.
Favaro A, Ferrara S, Santonastaso P. Psychosom Med. 2003;65:701–8.
Franklin JC, Schiele BC, Brozek J, Key A. J Clin Psychology. 1948;4:28–45.
Galef BG Jr, Wigmore SW. Anim Behav. 1983;31:748–58.
Garcia J, Ervin FR, Koeling RA. Psychon Sci. 1966;5:121–2.
Garcia J, McGowan BK, Erzin FR, Koelling RA. Science. 1968;160:794–5.
Godart NT, Flament MF, Lecrubier Y, Jeammet P. Eur Psychiatry. 2000;15:38–45.
Guitton MJ, Dudai Y. Biol Psychiatry. 2004;56:901–4.
Guitton MJ, Klin Y, Dudai Y. Behav Brain Res. 2008;191:148–52.
Guitton MJ. J Psychosom Res. 2009; doi:10.1016/j.jpsychores.2008.10.017
Heatherton TF, Baumeoster RF. Psychol Bull. 1991;110:86–108.
Imwalle DB, Scordalakes EM, Rissman EF. Horm Behav. 2002;42:484–91.
Jones BP, Duncan CC, Brouwers P, Misrky AF. J Clin Exp Neuropsychol. 1991;13:711–28.
Kaye WH. Psychopharmacol Bull. 1997;33:335–44.
Kaye WH, Bulik CM, Thornton L, Barbarich N, Masters K. Am J Psychiatry. 2004;161:2215–21.
Kendler KS, MacLean C, Neale M, Kessler R, Heath A, Eaves L. Am J Pyschiatry. 1991;148:1627–37.
Klein DA, Walsh BT. Physiol Behav. 2004;81:359–74.
LeDoux JE. Biol Psychiatry. 1998;44:1229–38.
Marks I. Fears, phobias and rituals: panic, anxiety and their disorders. New York: Oxford University Press; 1987.
Sackville T, Schotte DE, Touyz SW, Griffiths R, Beumont PJ. Int J Eat Disord. 1998;23:77–82.
Sánchez-Andrade G, James BM, Kendrick KM. J Reprod Dev. 2005;51:54–558.
Staiger P, Dawe S, McCarthy R. Appetite. 2000;35:27–33.
Sunday SR, Halmi KA. Physiol Behav. 1990;48:587–94.
Tóth E, Túry F, Gáti A, Weisz J, Kondákor I, Molnár M. Int J Psychophysiol. 2004;52:285–90.
Valsecchi P, Galef BG Jr. Int J Comparat Psychol. 1989;2:245–56.
Walsh BT, Devlin MJ. Science. 1998;280:1387–90.

Chapter 79
Why Do We Dislike So Many Foods? Understanding Food Aversions

Christina L. Scott and Ronald G. Downey

Abbreviations

CR	Conditioned response
CS	Conditioned stimulus
UCS	Unconditioned stimulus
UCR	Unconditioned response

79.1 Introduction

Like breathing and drinking, eating is critical to our long-term survival. Given this fact, why do we avoid so many edible foods? This chapter will explore the major psychological factors that drive our eating behaviors (see Table 79.1). While there are clear physiological constraints to what we can eat (e.g., allergic reaction to peanuts or eating foods that contain large amounts of salmonella), this chapter will focus on why we avoid foods that we could eat with little danger to our health or survival. We will first focus on four major ways that these aversive behaviors develop (Passer and Smith 2007). These are:

- Classical conditioning
- Operant conditioning
- Observational learning
- Conscious choice

After briefly describing each of the four major ways that aversions to foods can develop, we will:

- Provide relevant examples of how aversive behaviors develop and are sustained over long period of time in our daily life, in spite of many efforts to change the behaviors
- Explain how our basic senses (e.g., vision, etc.) often drive learning
- Discuss how a variety of conscious choices impact out eating behaviors and
- Review the current methods that are used to try and change disruptive aversion behaviors

---

C.L. Scott (✉)
Whittier College, 13406 E. Philadelphia St. Whittier, CA 90608, USA
e-mail: cscott@whittier.edu

Table 79.1 Key features of food aversion

1. Food aversions develop quickly through the pairing of food with very negative events; e.g., foods that are too hot or foods that taste "bad."
2. Over time, we learn to seek out certain foods when we are reinforced by the positive nature of the food and we avoid those foods that produce a negative response.
3. We model our food preferences by observing other people; e.g., family, friends, etc.
4. Our senses of the smell, sight, feel (texture), and/or taste of food are all driving forces for eating or avoiding food.
5. We often consciously decide to avoid foods to obtain certain goals or avoid bad outcomes; e.g., a healthier lifestyle or manage health conditions.
6. Changing food aversions (or attractions) is enormously difficult.

This table lists the key facts of food aversion, including how they develop, interact with our basic senses, and affect our eating behaviors

79.2 Four Models of Food Aversion

79.2.1 Classical Conditioning

Classical conditioning is the most basic process of learning (Pavlov 1928). As is shown in Fig. 79.1, all living organisms have an innate response (e.g., approach or avoidance) when they encounter certain stimuli (e.g., heat, light, movement, taste), When babies are fed food that is too hot, they spit it out and cry. Thus, the association between the heat (unconditioned stimulus, UCS) and pain (unconditioned response, UCR) is established by the baby. Problems can occur when the baby pairs heat (UCS) and other properties of the food together (conditioned stimulus, CS) with the pain producing a conditioned response (CR). For example, if the food was strained carrots, the taste (or color, or texture, etc.) of carrots is now associated with heat/pain. When the baby eats carrots (hot or cold) in the future, the conditioned response is to spit them out.

79.2.2 Operant Conditioning

Operant conditioning is a more complex leaning process where the stimuli and responses are more complex, develop over a much more extended time, and involve reinforcement (positive or negative). Figure 79.2 outlines the basic process. Through operant conditioning we learn to effectively operate within a complex and ever changing environment through reinforcement (Skinner 1938). Simply put, when we are reinforced for a behavior, we are more likely to repeat the action, but when we are punished, we are less likely to repeat the behavior in the future. When offered a candy bar, a child is immediately reinforced with the sweet taste of milk chocolate and seeks to repeat the experience; however a bitter taste (a negative experience) of dark chocolate may serve as a disincentive and thus discourages the child from trying that food again.

79.2.3 Observational Learning

Observational learning occurs when we perceive and mirror the behaviors of others. No *immediate* reinforcement of the new behavior is required, but the perception exists that the modeled behavior will be rewarded in the future, either through social acceptance or direct reinforcement (Bandura 1969). A child who observes his father pushing away his plate with uneaten broccoli is more likely

Before Conditioning

Carrots   No fear, no anxiety

During Conditioning

Carrots

+

Hot food
Burns tongue.   Fear, anxiety,
                                                   and avoidance

After Conditioning
Carrots   Fear, anxiety,
                                                   and avoidance
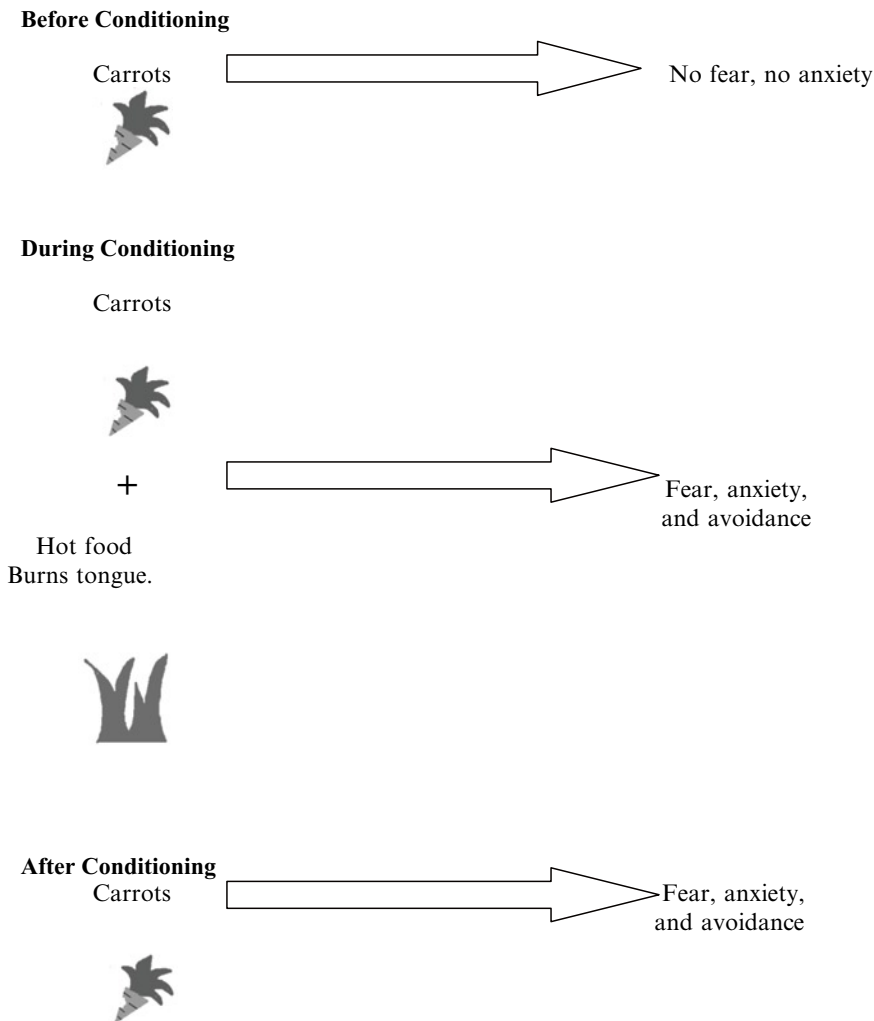
Fig. 79.1 Classical conditioning of food aversion. This figure illustrates how food aversions can develop by associating a negative event with a specific food

to emulate his father's behavior and push aside his/her own vegetables (see Fig. 79.3). This aversion to broccoli has not developed as a dislike for any specific properties of broccoli, but rather a desire to model the behavior of the father. Social learning plays a very powerful role in our eating behaviors, whether it is a toddler avoiding vegetables, or a teenager trying diet soda to "fit in" with the crowd. Social learning transcends a wide variety of situations and foods.

79.2.4 Conscious Choice

Finally, our eating behaviors can be directly influenced by our own judgments and decisions. Conscious choice influences us when we decide to avoid a food based on our own reasoning and when coupled with our past experience, and the outcomes we have witnessed in others (see Fig. 79.4). Suppose a teenage girl has a date planned for the following weekend and decides she wants to lose weight. Past

Fig. 79.2 Operant
conditioning of food
aversion. This figure
illustrates how reinforcement
creates a food preference and
punishment leads to a food
aversion.

REINFORCEMENT			
PROCESS	BEHAVIOR	CONSEQUENCE	RESULT
Positive	Response occurs ⟹ (milk chocolate is consumed)	Stimulus is presented ⟹ (sweet taste of milk Chocolate is enjoyed)	Response increases ⟹ (more milk chocolate is eaten)
PUNISHMENT			
Punishment	Response occurs ⟹ (dark chocolate is consumed)	Aversive stimulus is presented ⟹ (bitter taste is delivered)	Response increases ⟹ (dark chocolate is avoided)

Child observes father avoiding broccoli	⟹	Child wants to model father	⟹	Child avoids broccoli to model father
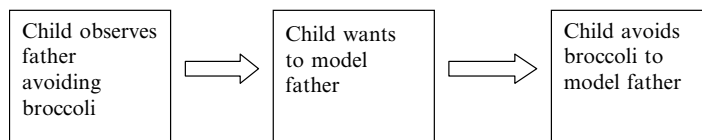
Fig. 79.3 Observational learning of food aversion. This figure illustrates how we avoid specific foods by observing other people

Wants to lose weight for upcoming date.	⟹	Recognizes that fatty foods will cause weight gain.	⟹	Makes conscious choice to avoid fatty foods.
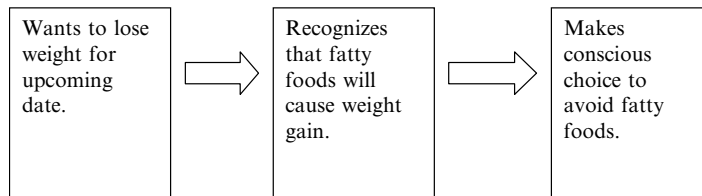
Fig. 79.4 Conscious choice model of food aversion. This figure illustrates how we consciously process information about our food choices

experience suggests that certain foods (e.g., fatty foods) may cause weight gain. Thus, the teenager makes a conscious choice to avoid fatty foods and opts for a garden salad. When choosing between foods we like, many of our food choices are determined by conscious decisions to select one food over another; sometimes even if we do not "like" the food we have chosen.

79.2.5 Summary of Learning Models

Thus, our responses to food are complex and determined by a variety of past events. Some of the responses (see Table 79.2) are very basic and almost instinctive (classical leaning). Others are acquired over a long time and require repeated experiences (operant learning). Equally complex

Table 79.2 Four models of food aversion. This figure outlines the four basic learning models associated with the development of food aversion

	Classical conditioning	Operant conditioning	Observational learning	Conscious choice
What behavior is required?	Accidently eat hot food (UCS) and pair it with the specific taste of carrots (CS).	Eat a piece of chocolate.	Based on watching other people, the same behaviors are replicated.	A decision is made to avoid a specific food.
How does learning occur?	Pairing of the UCS and CS leading to a conditioned response.	Reinforcement encourages future behavior and punishment discourages future behavior.	Observe behavior and motivated to replicate it.	Conscious motivation to avoid specific foods.
What is the sequence of events?	CS occurs before the CR.	Reward (punishment) occurs after the behavior.	Observation occurs before the behavior.	Conscious decision is made, behavior follows.
What is the outcome?	Strong negative reaction to specific foods due to unconscious pairing.	Strong positive or negative reaction to foods due to expected outcome.	Strong positive or negative response to specific foods based on prior observation.	Strong positive or negative response to specific foods based on a series of thought processes and decisions.

are the ways we learn from other individuals within our immediate environment (observational learning). Finally, as we grow and mature we make choices about what we do and do not want to eat and these choices may not be directly related to the sensory properties of the food. In the next sections we will discuss in detail how each of these processes can lead to potentially dysfunctional eating behaviors.

79.3 Sensory Processes and Eating

As will be outlined in the next sections, our sensory processes unconsciously determine many of our reactions. These include sight (appearance), smell, taste, and feel. While these will be discussed as separate senses, there is ample evidence (Martins and Pliner 2005) that they can be closely interconnected. For example, it is difficult for people to determine when taste and smell are different.

79.3.1 Smell

A food's aroma is one of the strongest signals we evaluate when facing an unfamiliar dish (Halpern 2002). If the scent "reminds" us of a similar food that we like, such as chicken or steak, we are more likely to respond favorably to the new dish. However, if the scent is strong and

unrecognizable, such as sauerkraut or fish, we tend to reject the new food without trying it. One of the strongest components of food aversion is the overlap between the way a food smells and its taste. If you've ever tried eating your favorite foods with a head cold, you quickly realized that the flavor of the food is diminished (Beauchamp and Bartohshuk 1997). Children, who are instructed to finish their vegetables, often plug their noses, to reduce the smell and, they assume, flavor of the offending vegetable. Memories of unpleasant smells in childhood are likely to follow us into adulthood and smells that remind us of disliked foods (such as Brussels sprouts) will be immediately rejected.

79.3.2 Sight (Appearance)

Go to a five star restaurant and you will be dazzled by the presentation of the food you are served, because "presentation is everything." Imagine two chicken dishes are placed before you; one features a plump, juicy, white chicken breast surrounded by colorful vegetables and a mound of mashed potatoes with a dollop of butter balanced on top; while the second dish features a dry, thin, graying chicken breast, next to a pile of green beans, and a baked potato wrapped in foil. The classical conditioning model suggests that we are immediately drawn to the more attractive meal because we associate good taste with attractive presentation that leads to satisfaction in our food choice. However, it is important to realize that our appreciation for the appearance of food is not innate. One look at the contents of baby food will remind us that as infants, our food preferences were mostly based on taste (and temperature) and not esthetics. However, as we grow older, we learn to value the appearance of our food. Toddlers find the round shape of Cheerios easy to grasp, which is reinforcing as they learn to manage finger foods, and in time, they will prefer whole crackers and cookies over broken pieces, even if the taste is identical.

79.3.3 Taste

From the time we are babies, we respond to food positively or negatively based on taste (Halpern 2002). The human tongue has approximately 9,000 taste buds that are devoted to recognizing the five elements of taste perception: sweet, sour, bitter, salty, and savory (Halpern 2002). Sweet tastes such as sugar are immediately reinforcing, while strong or bitter flavored foods such as cabbage and grapefruit are initially disliked. College students learn to consume large amounts of coffee by masking the bitter taste with sugar. Eventually many college students will desensitize to the bitter taste and they may require less sugar because the actual or perceived positive cognitive effect of the caffeine has become a stronger reinforcement.

79.3.4 Feel (Texture and Temperature)

As we demonstrated (Scott and Downey 2007) texture is strongly associated with food aversions and choice. On a hot summer's day nothing is more appealing that the cool creamy consistency of ice cream as it cools a burning throat. Although the flavor of the ice cream is important, the texture and

temperature are equally essential in our enjoyment. Melting ice cream loses its texture and although the taste remains the same, we may reject it. Foods that are not served at their ideal temperature are immediately judged as being less appealing. Cold coffee and warm white wine are immediately rejected as being unfit for human consumption. Tepid vegetables often remained untouched on a plate, as compared with the same vegetables served steaming hot. Anyone who has indulged in McDonald's French fries will attest to the fact that "fresh French fries" far outweigh the taste of lukewarm ones!

Foods with smooth even textures signal us at an unconscious level that what we are consuming is pure and consistent. Imagine eating a cup of yogurt or enjoying a fruit smoothie. Lumps or chunks produce an aversive response and we evaluate them as evidence that our food hasn't been blended properly. From our earliest experiences with food, we were served well-blended baby food, which featured a smooth and even consistency. We come to expect a certain texture from our food, such as creamy mashed potatoes and if we are served something outside of our expectations, we may find it aversive. A classic example would be the texture of soggy bread. As children we learn the ideal texture for bread by watching our parents. If it becomes too firm (stale) or too soggy (wet) we respond negatively and leave the bread untouched. Slimy and/or slippery foods such as oysters, mussels, and internal organs (e.g., liver) feature an unfamiliar and initially unappealing texture that results in most people avoiding these foods without trying them.

79.3.5 Summary of Sensory Processes and Eating

Our five senses play a critical role in our food preferences and aversions. While a large number of food choices, including avoidance of certain foods or types of foods can be traced back to sensory types of processes, a large number are related to the human processes of choice and decision making. The underlying processes determining these choices and decisions are complex and multidetermined. The next section will explore some of the major ways we *decide* to avoid certain foods. However, it should be noted that these decisions may be unconsciously associated with some of the sensory properties of the foods.

79.4 Applications of Food Aversions to Other Areas of Health and Wellness

While many food aversions are unconscious reactions to something unappealing, unfamiliar, or unpleasant, a large portion of our food choices are made based on conscious choice (see Table 79.3). We may be operating based on previous negative experience or observing the behaviors of others, but the outcome is the same, we avoid certain foods for the following reasons:

• Questionable or unsafe foods
• Temperature
• Media warnings
• Dietary restrictions (health)
• Dieting and diet fads
• Going organic: organic foods, vegetarians, and vegans budget

Table 79.3 Applications of food aversions to other areas of health and wellness. This figure outlines how we make a decision to avoid specific foods in order to achieve a healthier lifestyle

	Questionable or unsafe foods	Temperature	Media warnings	Dietary restrictions (health)	Dieting & diet fats	Going organic	Budget
What is the thought process?	That food doesn't look/smell familiar!	That temperature isn't appealing.	It's unsafe or unhealthy to eat that!	Eating that food may put my health at risk.	That food is too fattening.	Artificially grown foods aren't as healthy as organic foods.	That specific food is too expensive.
Food example	Oysters	Warm Beer	Corn syrup	Glutens or sugar	Pizza	Produce	Lobster
What is the outcome?	Avoidance	Temporary avoidance	Temporary avoidance	Temporary avoidance	Temporary avoidance	Temporary avoidance	Temporary avoidance

79.4.1 Questionable or Unsafe Foods

At the most basic level, we may choose to avoid specific foods because they appear questionable or unsafe, even though we have enjoyed similar foods in the past. Most of us have sampled milk that has begun to spoil or been taken aback at the green fuzzy mold growing on our cheese. Although we enjoy these foods on a regular basis, we detect that the foods may be "spoiled" or "unsafe" to consume and we avoid them for that one instance. The same might hold true if we are served an undercooked steak (although some people ask for **rare** steak) or we are served raw fish (however, many people like Sushi). This tendency may be enhanced by our previous experiences with undercooked foods, such as a case of food poisoning, but we might be equally reluctant to eat an undercooked piece of chicken if we saw a recent news report cautioning the dangers of salmonella or E Coli contamination. The texture of a food may enhance this concern. If we faced with slippery or slimy foods such as runny eggs or raw oysters, we may be more reluctant to try them than firmer textures such as steak or chicken.

79.4.2 Temperature

Although certain foods seem to taste better when served hot, such as fajitas, French fries or filet mignon, other foods, such as ice cream and shrimp seem to taste better cold. Many of these preferences for temperature are based on culture and develop through social learning. In the United States, we prefer our milk and dairy products to be ice cold, while in Europe consuming milk and yogurt served at room temperature is commonplace and milk straight from the cow is desired in many cultures (Rappoport 2003). Imagine you are served a bowl of leek soup and it arrives cold. Although this recipe is both valid and delicious, we may find the cold soup aversive and turn it away, because we expect soup to be served hot. In the Hofbrauhaus in Germany, warm beer is served intentionally to enhance the flavor of the beverage; however many American tourists would be offended if their beer was not served chilled: a *conscious choice*.

79.4.3 Media Warnings

Although many food aversions develop through direct experience (classical or operant conditioning) or direct observation (social learning), many food aversions are a conscious choice based on media warnings. With recent warnings about transfat, MSG, and other additives/preservatives in food, the public is more health conscious than ever. In the 1980s a media campaign warning about the dangers of high cholesterol suggested that consumption of eggs could cause serious health risks. Consumers made a *conscious choice* to cut back on their egg consumption in order to be health conscious and new food avoidance behavior was created. In the late 1990s, consumers were surprised to see a series of new commercials with a very different message advertising "The incredible, edible eggs!" as an excellent source of protein. For many consumers, the decision to avoid or enjoy eggs became a combination of the conflicting messages they received and a *conscious choice* based their own personal preference for eggs.

In 2008, commercials speaking out against products containing corn syrup surfaced featuring concerned mothers protecting their children from foods made from corn syrup. No specific claims were made about the possible health risks of corn syrup, but the commercials clearly suggested that giving your child a Popsicle containing unnatural chemicals such as red dye and corn syrup was an irresponsible decision. These commercials were followed almost immediately by a rebuttal campaign, using the same social learning technique featuring a mother correcting another woman's misconceptions about corn syrup arguing that it is produced naturally from corn and in moderation is "the same as sugar." As consumers, we have to determine which foods contain high fructose corn syrup (read the label) and make a conscious choice whether we want to give them up based on the media warnings, or decide to just enjoy them.

79.4.4 Dietary Restrictions (Health)

For people diagnosed with Diabetes, Celiac Disorder, or Food Allergies, the conscious choice to avoid specific foods is a necessary decision to protect overall health and wellness. Diabetics may watch the high fructose corn syrup debate with interest, but ultimately realize that any form of sugar, for their well being, will need to be monitored carefully. They may actively seek out foods with less sugar or sugar substitutes, such as Splenda or Equal, while restricting their intake of foods high in carbohydrates or sugars. There may be instances when they make a conscious choice to **not** restrict their dietary selections, which could result in higher blood sugar levels, and possible medical complications.

Food allergies can range from mild to severe and most appear in early childhood. Children and adults with Celiac Disorder are allergic to Glutens and therefore need to adhere to a strict Gluten-Free diet, which means no foods made with wheat. This would systematically eliminate most breads, pastas, and pizza from their diet, unless they were made with special Gluten-free ingredients. Wanting to enjoy a piece of cake at a classmate's birthday party or a slice of pizza with friends afterschool becomes increasingly more frustrating for children with Celiac Disorder as they may associate specific foods with "fitting in" and social acceptance. The conscious choice to avoid specific foods can be a matter of life and death. Individuals with peanut or chocolate allergies can find themselves suffering from migraines to severe anaphylactic shock depending on the level of their exposure and the severity of their allergies.

79.4.5 Dieting & Diet Fads

While we may be drawn to "comfort foods" such as sweets or starchy foods (Conner et al. 1988), many of us make a conscious choice for a limited period of time to avoid specific foods in order to lose weight. Freshmen college students, who have packed on the "freshmen fifteen" over the course of their first semester of college, may suddenly restrict their fried food intake and late night pizza binges in order to wear swimsuits over spring break. Although most dieticians suggest that "lifelong changes" are necessary to lose weight and maintain the weight loss, most Americans "crash diet" (Crow et al. 2006),which means a drastic restriction in calorie intake, combined with a long list of foods that must be avoided for quick weight loss. The promise of quick weight loss has led to an ever-increasing number of "fad diets" such as the SouthBeach and Atkins diets, which suggest a low-carbohydrate and high-protein regimen. Although both programs promise immediate results, most people prefer carbohydrates and find it difficult to avoid them for a prolonged period of time. Although most of us recognize that sugary foods are higher in calories, we don't want to give up the sweet taste we enjoy, so we make compromises such as switching to diet sodas or using sugar substitute products (Appleton and Conner 2001). We want the benefits of a lower calorie lifestyle, but are unwilling to sacrifice our preference for sweet tastes. A recent trend in wellness has been a detoxifying procedure, where people will consume only fruit juice or green tea; some people make the conscious choice to avoid *all foods* for 3–10 days in order to clear the impurities from their system (Glittleman 2006).

79.4.6 Going Organic: Organic Foods, Vegetarians, and Vegans

With the recent warnings about food chemicals leading to cancer, many Americans are turning to organic products. The decision to avoid foods grown with pesticides, growth hormones, or preservatives is becoming increasingly more popular, especially with parents seeking to protect their children (Burke 2007). Specialized grocery stores such as Whole Foods and Trader Joe's offer a variety of organic options, including dairy products and produce and most large grocery chains now have organic food sections. The only known downside to organic products is their higher cost, which means the availability of organic foods is restricted to those who can afford higher grocery bills.

The decision to avoid meat (vegetarians) or the decision to avoid all foods that contain either meat or dairy products (vegans) can be made for a variety of reasons. Some people may wish to avoid chemicals and preservatives and opt for organic fruits and vegetables, while others may wish to make a statement about the treatment of animals raised for food. The recent bestseller, *The Omnivore's Dilemma* (Pollan 2006), highlights the overcrowding and mistreatment of cattle raised for consumption, and led thousands to swear off meat in support of animal rights. Many such individuals report that although they enjoy the taste of a good steak, they are making a conscious choice not to support an industry that mistreats animals.

79.4.7 Budget

Although we may enjoy the "surf and turf" option at a five star restaurant, our budgets may restrict the foods we choose to eat. As any college student can tell you, the conscious choice to eat Top

Ramen, is not one made for taste preference, but generally due to the low cost. Dollar menus have become increasingly more common at fast food restaurants, including McDonald's, Taco Bell, and Burger King. Recognizing the need for lower priced offerings, establishments such as Applebee's and Chili's have started offering $7 menu items, or combination dinner specials which feature a shared appetizer, two entrees, and a dessert for a lower price. Senior menus and children's menus are often coveted for not only their smaller portions, but specifically their lower prices. Limited budgets required conscious choices to find lower priced food.

79.4.8 Summary of Conscious Choice

A conscious choice to avoid a specific food is made after considering a wide range of evidence. We may already have a negative association/experience with a specific food or we may we evaluating the health risks associated with a food we have enjoyed for many years. Our choice may be permanent, such as making a lifestyle change to promote better health or it may be temporary because we watching our budget or restricting our calories. We are constantly evaluating new evidence regarding our food choices and making conscious choices about the foods we consume.

79.5 Changing Food Aversion Behaviors

As most of us can attest, change is not easy. The older we are, the more likely we are to be set in our ways, which is why changes in food aversions are best introduced in infancy or early childhood (Chatoor and Ganiban 2003). Such changes are therefore most commonly introduced by parents and not based on the child's desire to overcome a food aversion. The most common methods of changing food habits in children include food pairings (classical conditioning), rewards for eating specific foods (operant conditioning), and food blending (masking foods within liked foods) and can be seen in Table 79.4.

Havermans and Jansen (2006) suggested a classical conditioning approach for introducing vegetables to young children. Parents paired a positive flavor (sweet taste of sugar) with a neutral flavor (vegetables) in order to help children develop a positive response to vegetables. It is important to note that the children in the study saw the vegetables as a neutral stimulus and had not developed a strong aversion to any of the vegetables they were asked to consume. The stronger and more long-term someone's aversion to a specific food is, the more difficult it is to override the initial negative response, no matter how strong the pairing. Brunstrom and Fletcher (2008) sought to explore the effects of flavor–flavor pairings with young adults (18–25 years), but discovered that the pairings were only successful when the participants were hungry, and therefore more motivated to eat.

Another approach to changing food aversions is through rewards, which utilizes an operant conditioning model. Hendy et al. (2005) rewarded elementary school children for eating fruits and vegetables in the cafeteria, by giving them tokens for each food consumed. Children exchanged tokens for small prizes and 2 weeks after the study, food preferences for fruits and vegetables increased. However, the effect was not long-lasting and when children were sampled seven months after the study, their interest in fruits and vegetables had returned to the baseline. Parents can encourage their children to eat less appealing foods through reinforcement; however the change is generally only

Table 79.4 Changing food aversion behaviors. This figure reviews the structure, process, and limitations of the four primary methods for changing food aversion behaviors

	Classical conditioning	Operant conditioning	Masking	Lewin's change theory model
What behavior is required?	Positive pairing is required. Sweet taste (UCS) is paired with vegetables (CS).	Reinforcement of desired behaviors is required. Receive rewards for eating vegetables.	Small amounts of a new food are hidden within an enjoyed food. (e.g., putting sweet potatoes in pancake batter).	Repeated exposure, time and commitment to adapt to a new food behavior.
How does learning occur?	Pairing of the UCS and CS leading to a new conditioned response.	Reinforcement encourages future behavior and punishment discourages future behavior.	Remember behavior and have motivation to replicate it.	Combination of classical, operant and observational learning, but increased conscious motivation to avoid or approach specific foods.
What is the sequence of events?	CS occurs before the CR.	Reward occurs after the behavior.	Increased exposure to new food hidden in preferred food.	Three stage process: *Unfreezing*–override aversion *Change*–consume new food *Freezing*–adopt food into permanent lifestyle.
What is the outcome?	Limited positive outcome if initiated early in infancy or childhood.	No permanent change, behavior terminates without reward.	Limited positive outcome if initiated early in infancy or childhood.	High level of psychological distress involved with limited positive outcome. Tendency to revert back to original behavior.

temporary. When the reinforcement is withdrawn, it is likely that children return to their original eating behaviors and the new foods are abandoned.

Another suggested technique for parents to change children's choices involves masking less appealing foods with preferred foods (Mueller et al. 2004). Recipes such as sweet potato pancakes, allow parents to "sneak in" a serving of vegetables into an already accepted food. In order to promote healthier eating habits, parents may switch to wheat bread when serving peanut butter and jelly sandwiches, or incorporate whole grain tortillas when serving burritos. Occasionally these pairings are successful with adults, such as the acceptance of green beans, when they are buried deep within a casserole, consisting of a sauce of mushroom soup and fried onions. However, most adults are fully conscious that undesirable foods, such as vegetables are being blended into their food preferences. For both adults and children, if we "know" a specific food is "in there" we may be unable to convince ourselves to try the new food, especially when strong aversions are present.

As we discussed previously, we may decide to make a conscious choice to change our food behaviors, but change does not come quickly or easily. In 1947, Kurt Lewin introduced his

"change theory" which specifically identified three major stages necessary for a change in food habits to occur. The initial step involved changing a person's current mindset, and bypassing their defense mechanisms; a process he called "unfreezing." Suppose a person has a strong aversion for tofu, but has recently starting dating a vegetarian and is trying to make a change in his food habits. Suppose he has promised to give up red meat in exchange for tofu burgers. Unfreezing would involve trying to override the initial aversion to tofu, including the texture, taste, and smell. Lewin's second stage was the "change" where the individual would begin eating tofu, even if their initial response was negative. Lewin notes that this stage requires a substantial amount of time because the new food is still unfamiliar and the person may find himself tempted to return to old habits, such as eating red meat. The final stage is "freezing" in which the new mindset is locked in place and a person's comfort level is restored once the new food has been accepted. Lewin's model would argue that with time, tofu would become more familiar and a part of the individual's eating routine.

Lewin's model requires repeated exposure, time, and a commitment to changing a specific food habit before a new behavior is adopted and the process is not without emotional consequences. Lewin notes that anxiety and discomfort are hallmarks of the second stage "change" when we are learning to accept unfamiliar foods. Although we may make a conscious choice to change our eating patterns, all three stages are limited by the very fact that food aversions often exist at a *basic level*. We know vegetables are good for us and that tofu is a health alternative to red meat, but we "just *don't like* the taste, texture, and/or smell" and whether it is food blending, food pairing, or trying to adopt a new food habit altogether, our aversions persist. Most adults can't articulate why they avoid specific foods, but despite our best efforts to reverse them, the long-term changes are minimal.

79.5.1 Summary Changing Food Aversion Behaviors

The older we are the more resistant we become to changing our food aversions. Although we may believe that our eating behaviors are predominantly a conscious choice, there are many unconscious influences that make certain foods unpalatable to us (see Table 79.4). Masking the flavor of disliked foods, such as putting cheese and butter on Brussel sprouts is only effective if we have a mild aversion. Unlike young children, it may not matter to us as adults how the food is masked or rewarded; we are still unlikely to eat it.

Overall Summary

It is almost always impossible to pinpoint the exact moment when food aversions develop for individuals. As we have discussed they can develop through a variety of learning and conscious choices. These include: classical conditioning, operant conditioning, and observational learning. Many aversions are driven by our sensory processes of smell, sight, taste, and texture. We can also make decisions to avoid specific foods whether they are for health, diet, or cost. Once we have developed these avoidance (or approach) behaviors, changing them is enormously challenging. Attempts to modify our food choices typically have not resulted in long-term changes in our eating behaviors. In essence, we are "what we eat" because our food preferences have become an ingrained and long-term part of who we are as unique individuals.

Definitions

Celiac disorder: A chronic nutritional disturbance, usually of young children, caused by the inability to metabolize gluten. The disorder can be controlled by a special diet that emphasizes the elimination of all foods containing gluten.

Classical conditioning: A neutral stimulus (the *conditioned stimulus*) is repeatedly presented in association with a neutral stimulus (the *unconditioned stimulus*) that elicits a natural response (the *unconditioned response*) until the neutral stimulus alone elicits the same response (now called the *conditioned response*).

Glutens: The tough, viscid, nitrogenous substance remaining when the flour of wheat or other grain is washed to remove the starch.

Diabetes: A medical condition in which the body is unable to control the level of sugar in the blood.

E. coli: A dangerous form of Escherichia coli, a bacterium that normally lives in the human colon.

Observational learning: Behavior occurs as a function of observing, retaining, and replicating behavior observed in others.

Omnivore: An organism that eats both plants and animals

Operant conditioning: A behavior is either reinforced or punished, which directly affects the likelihood of the behavior being repeated again.

Organic: Raised or conducted without the use of drugs, hormones, or synthetic chemicals.

Vegan: A person who does not eat meat, fish, or any animal products such as cheese, butter, etc.

Vegetarian: A person who does not eat meat or fish.

References

Appleton KM, Conner MT. Appetite. 2001;37:225–230.
Bandura A. New York: Holt, Rinehart, & Winston; 1969.
Beauchamp GK, Bartohshuk L (editors). Philadelphia: Academic Press; 1997.
Brunstrom JM, Fletcher HZ. Physiol. Behav. 2008;93:13–19.
Burke C. New York: Marlowe; 2007.
Chatoor I, Ganiban J. Cognitive Behav Practice. 2003;10:138–46.
Conner M, Haddon A, Pickering E, Booth D. J Appl Psychol. 1988;73(2):275–80.
Crow S, Eisenberg M, Story M, Neumark-Sztainer D. J Adoles Health. 2006;38:569–74.
Glittleman AL New York: Doubleday Broadway; 2006.
Halpern B. Taste. In: Pashler H, Yantis S, editors. 3rd ed. New York: Wiley; 2002.
Havermans RC, Jansen A Appetite. 2006;48:259–62.
Hendy HM, Williams KE, Camise TS. Appetite. 2005;45:250–63.
Lewin K. Washington, DC: National Research Council; 1943. pp. 35–65.
Martins Y, Pliner P. Appetite. 2005;45:214–24.
Muller MM, Piazza CC, Patel MR, Kelly ME, Pruett A. J Appl Behav Anal. 2004;37:159–70.
Passer MW, Smith RE. New York: McGraw-Hill; 2007.
Pavlov IP. New York: International Publishers; 1928.
Pollan M. New York: Penguin Press; 2006.
Rappoport L. Ontario: ECW Press; 2003.
Scott CL, Downey RG. J Psychol: Interdisciplinary Appl. 2007;141(2):127–34.
Skinner BF. New York: Aplleton-Century-Crofts; 1938.

Chapter 80
Influence of Cognitive Biases in Visual Evaluation of Food Amount in Patients Affected by Eating Disorders

Piergiuseppe Vinai

Abbreviations

AN	Anorexia nervosa
AW	Adjustable wedge
BED	Binge eating disorder
BMI	Body mass index
BN	Bulimia nervosa
FARS	Food amount rating scale
FFQ	Food frequency questionnaire
FPPB	Food portion photograph book
IPSAS	Interactive portion size assessment system
PSMA	Portion size measurement aids

80.1 Introduction

Accurate portion estimation is the key to controlling the amount of food ingested, a key element in the treatment of obesity and eating disorders (Dohm and Striegel-Moore et al. 2002), but it is a common clinical experience to find under-reporting of food intake among obese subjects and over-reporting among patients affected by anorexia nervosa (AN). Blundell (2000) provocatively affirmed that asking nutritionists to report information regarding their extramarital sexual encounters there would probably be a significant under-reporting, while asking on their donations to charity there would probably be an over-reporting.

Certainly, social acceptability contributes to food reporting but many other factors influence food amount estimation. Current levels of hunger/satiety (Beasley et al. 2004) and food palatability play a role in the evaluation as do the subjects' gender (Yuhas et al. 1989; Mac Diarmid and Blundell 1998), age (Frobisher and Maxwell 2003), and Body Mass Index (BMI) (Klesges et al. 1995). Children are less able to evaluate than adults; and women and overweight/obese subjects under-report their food intake more than men and normal-weight patients do.

P. Vinai (✉)
"GNOSIS" No Profit Research Group, V Langhe 64, 12060, Magliano Alpi, CN, Italy
e-mail: piervinai@tin.it; gnosis1@virgilio.it

Table 80.1 Factors influencing food amount evaluation among general population and subjects affected by eating disorders

- Cognitive biases
- Social acceptability
- Perceptive deficits
- Hunger and satiety
- Emotional states
- Reward sensibility
- Food palatability
- Eating disorders
- Subjects' age

Many factors influence food amount evaluation; among them cognitive biases and emotional states play a pre-eminent role in subjects affected by eating disorders. Moreover, perceptive biases affect the evaluation of subjects not affected by any eating disorder

In this chapter we will discuss how perceptive, cognitive, emotional, and social factors influence the evaluation of the amount of food consumed by patients affected by eating disorders. Moreover, the efficacy of proposed tools to improve the subjects' ability to evaluate their own food intake will be evaluated (Table 80.1).

80.2 Food Is Always Too Much. Food Amount Evaluation of AN Patients

Frequently, patients affected by AN claim to be unable to evaluate the amount of food served, engaging the therapists in endless Socratic debates regarding their real food intake, but the hypothesis that they really misperceive a food amount has been poorly studied.

More than 20 years ago, Yellowlees et al. (1988) surprisingly noted that in the many studies on AN only a minimal part was focused on food perception and little attempt was made to explain why they eat in such an unusual manner. So, they performed the first study regarding food perception in a sample of twenty patients affected by AN. Five items of food and four neutral objects of a similar size were video recorded. In the first experiment the objects were alternately placed in the middle of a dummy television screen, near a real TV screen. Each subject could compare the size of the real object with its image on the screen. The subjects were asked to manipulate the size of the object on the video screen until each image was, in their opinion, as close as possible to the size of the real object. No significant difference was found between AN patients and the control group in their ability to measure size. Both groups did, however, noticeably exaggerate the size of food, but patients with anorexia nervosa perceived it as 12% bigger overall than the control group members. The results did not change when the objects were placed in the dummy television screen for 10 s and then removed. The subjects were subsequently asked to adjust the video image from what they remembered.

To our knowledge no further research regarding food amount evaluation in patients affected by AN has been done in the subsequent 20 years. All of the studies on the perceptive abilities of these patients focused on their own body shape and weight estimation (Epstein et al. 2001). Their body size misperception seems to be more based on cognitive factors than by a perceptive bias (Skrzypek et al. 2001). Given that there is a tendency to a top-down process when judging food (Urdapilleta et al. 2005) and Stroop interference for food-related words (Overduin et al. 1995), cognitive factors could probably also influence their food amount evaluation. To test their ability in estimating food amount, thus avoiding these interferences, our research group (Vinai et al. 2007) carried out

a study in an experimental situation without any relation to food intake. Patients were informed that there was no effect on the therapy induced by their answer and particular attention was paid to avoid emotional and social influences on evaluation. We showed them subsequently a dish containing 27 high caloric and tasty yellow candies (A stimulus) and 27 plastic yellow LEGO® bricks of the same size and shape as the candies (B stimulus), placed in the same position on the plate to minimize the influence of shape, size, and disposition of the objects on number perception. Moreover, to avoid misperception through hunger on the evaluation, all the subjects had breakfast before being tested. No significant difference between AN patients and the control group in evaluating the number of the two stimuli has been found (both significantly underestimated the number of presented stimuli): 78% of AN patients and 78.6% of control subjects underestimated the number of candies, while 18.7% of the AN group and 21.4% of the control group overestimated them. Two AN patients (3.4%) and no control subjects guessed the correct number of candies. We found no correlation between the evaluation of number and the age of onset, or the duration of the illness, or the current or minimum BMI of the patients. The plastic bricks were evaluated in the same way as the candies (Fig. 80.1).

These results are apparently in contrast with the common clinical finding of overestimation of food intake among AN patients and with those of the study of Yellowlees et al. (1988), but the discrepancy can be explained by the differences between the experimental settings. In real life, as in the Yellowlees' experiment, the evaluation is not only the result of a flow of sensory information from periphery to brain, but also involves a *top-down* processing of a selection of inputs considered relevant by the subjects. In our study these processes have been minimized.

Summarizing, AN patients do not seem to be affected by a real perceptive deficit; they share the tendency of the general population to underestimate food amount. Top-down processes in
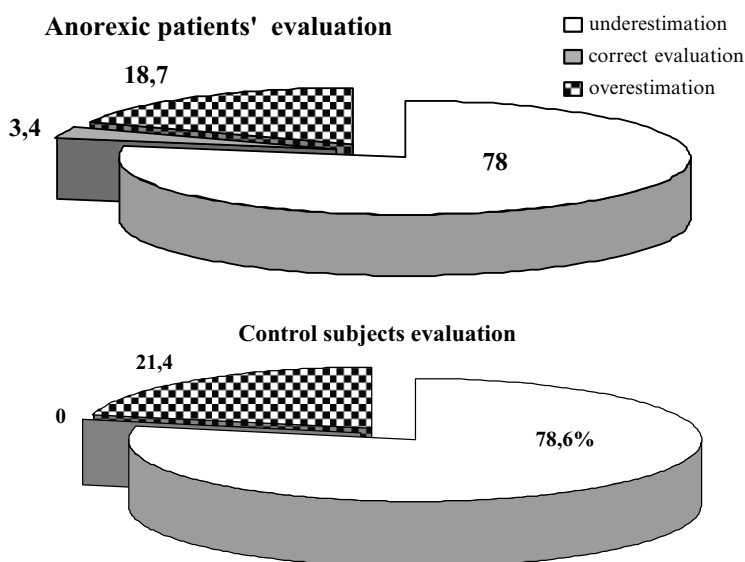
Fig. 80.1 Estimation of a number of tasty candies among patients affected by Anorexia Nervosa (AN) and control subjects. Seventy-eight percent of AN patients underestimate the number of tasty candies presented to them: 18.7% overestimated them and 3.4% correctly guessed the number. Patients affected by AN share the tendency to underestimate the amount of food with the general population. There are no significant differences between AN patients and control subjects in this evaluation. There is a general tendency among the normal weight population to underestimate the amount of food presented

judging food amounts seem to play a dominant role among them; e.g., when asked to categorize aliments, they cluster food on the basis of the consequences of ingestion (in terms of health, digestion, and weight gain), rather than on visual characteristics, as normal weight subjects do (Urdapilleta et al. 2005).

80.3 Surely I Have Eaten Too Much! Evaluation of Food in Patients Affected by Bulimia Nervosa

While there is a multitude of research about the eating behavior of patients affected by bulimia nervosa (BN), few studies focus on bulimics' perceptions of their peculiar eating behavior. Several findings led to the hypothesis that a distortion of what is a normal meal may represent a central cognitive mechanism of the disorder. Bulimic patients overrate the amount of food presented to them. This effect increases as caloric intake or actual amount increases at a greater rate than control subjects do (Gleaves et al. 1993). Overestimation of food amount could induce a more restrictive diet – the major risk factor for the onset of bulimic behavior. Moreover, the evaluation of caloric content of a food is subject to bias among these patients, worsening their tendency to reduce food intake. Their rating of the amount eaten is predicted by the estimate of the actual amount eaten, by the kind of food, and by mood level before eating (Keel et al. 2001). In a study including 165 females, those with bulimic behaviors and restrained eating were more likely to overestimate caloric content of the food presented (Stanton and Tips 1990).

Bulimic patients (Williamson et al. 1991) report overeating at a higher rate than control subjects, as they are affected by a bias distorting their perception of the amount of food eaten. Such cognitive biases could be the effect of an excessive concern about eating and dieting. As excessive weight is a threatening situation for these patients, they have interpretational biases toward foods that could induce weight gain (Williamson et al. 1991; Gleaves et al. 1993).

Caloric intake during binging episodes vary widely (Telch et al. 1990) and patients base their perceptions of having binged more on the type of food consumed than on the amount of food eaten (Rosen et al. 1985).

Bulimic individuals make cognitive attributions about different foods on a continuum from *safe* to *forbidden*, i.e., those high in calories and fat. The evaluation of an eaten food as forbidden, despite its caloric value, can trigger a binge episode in these patients and consumption of even small amounts of it may lead subjects to perceive their consumption as overeating (Herman and Polivy 1984; Rosen et al. 1985; Kales 1991). It has been reported (Kales 1990) that 69% of the episodes they evaluate as a binge contained *forbidden foods*, i.e., having a higher caloric density, whereas only 15% of the episodes defined as *nonbinge* contained them (Table 80.2).

Knight and Boland (1989) asked a group of women to consume either cottage cheese (nonforbidden food) or a chocolate milkshake (forbidden food) preload before tasting ice cream, informing participants that both foods contained the same number of calories. Highly restrained participants subsequently ate more ice cream when having first eaten the *forbidden* milkshake than they did after eating the cottage cheese. (Guertin and Conger 1999). Furthermore, these patients have perceptual distortions of their own body image in response to eating *forbidden* foods (Rosen et al. 1985) (Fig. 80.2).

Summarizing, subjective perceptions of overeating and binging are core factors in the onset of bulimic behavior; the perception of having overeaten and the self-reporting of having binged, rather than actual overeating, lead to disinhibition and binging (Polivy and Herman 1985). Given the lack of studies on the possibility of improving the ability of patients affected by BN to evaluate their food intake, further researches on this topic are needed.

Table 80.2 Key features of cognitive distortion regarding food intake among bulimic patients

- It is perceived as overeating, despite its caloric value.
- It can trigger a binge episode despite its caloric value.
- Most episodes they evaluate as binge eating contain *forbidden foods*.
- When they eat *forbidden foods* they have perceptual distortions of their own body image.

This table shows the effect of eating a *forbidden food* on patients affected by Bulimia Nervosa and its relationship with their eating behavior
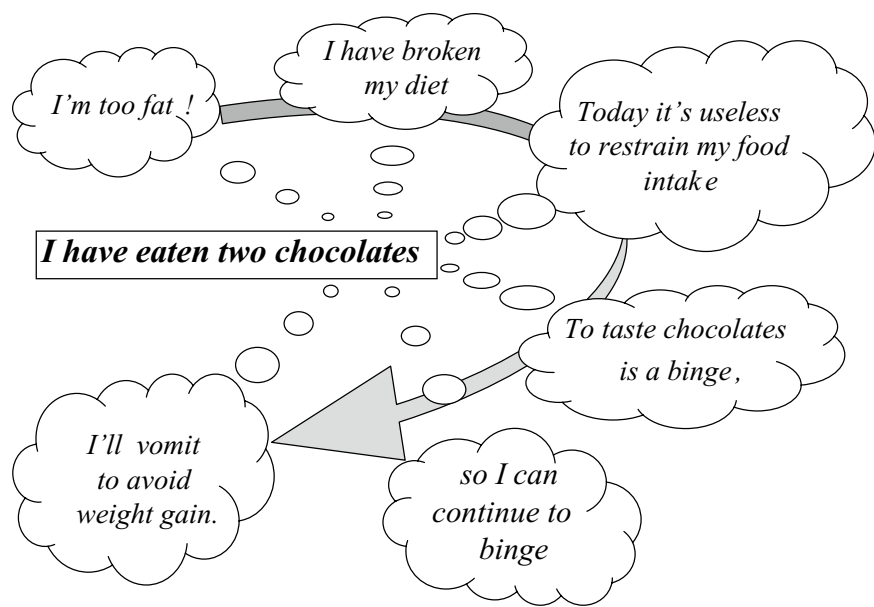
Fig. 80.2 Cognitive and behavioral consequences of the intake of a *forbidden food*. The picture shows the worry induced by *forbidden food* intake in a patient affected by Bulimia Nervosa. Cognitive biases regarding their own body image, the amount of eaten food, and the consequences of its intake frequently induce the patients to overeat and to vomit

80.4 Probably I Didn't Eat So Much. Visual Evaluation of Food in Patients Affected by Binge Eating Disorder

Patients affected by Binge Eating Disorder (BED) frequently fail in evaluating the quantity of food when introducing large quantities of food in a short time, but it is not yet clear whether this is due to either a perceptive or a cognitive bias. Greeno et al. (1999) tested whether BED patients have an altered perception of food. They asked obese women either affected or not by BED to report their *typical* and *largest-ever* portions of foods. Moreover, they had to report the minimum amount of each of eight foods they considered a binge. Neither evidence of cognitive distortions among BED patients, nor significant differences between the groups have been found. However, binge eaters reported that their *typical* and *largest-ever* portions of foods were larger in a very significant way, confirming the need for focus on the global eating behaviors of these patients even in the absence of perceptual distortions.

80.5 Eyes Are Bigger Than Stomach. Perceptive and Social Factors Influencing Evaluation of Food Amount in the General Population

The difficulty in evaluating the amount of a presented food is not a peculiar characteristic of eating disordered patients. Normal-weight subjects' ability to describe an amount of food they have just chosen, without the aid of measuring devices, is poor (Guthrie 1984) and both overweight and normal-weight subjects fail in estimating food portions (Blake et al. 1989). Many perceptive biases explain these results. It has been highlighted by Ginsburg in studies on general population since 1978 that the arrangement of the stimuli influences the evaluation of their amount. Using circular lighting dots he found that regularly arranged stimuli are overestimated while those randomly disposed are underestimated; these results have been confirmed using stimuli of different shapes (Ginsburg 1980). Usually food is randomly disposed into the dish so it gets underestimated. The area collectively occupied by dots also provides a basis for judging their numerousness: the larger the occupancy pattern, the higher the number estimated (Allik and Tuulmets 1991). Moreover, item size influences the evaluation: there is an inverse relation between item dimension and estimation of numerousness (Ginsburg and Nicholls 1988). In addition, form and energy density of food may affect its assessment; people have more difficulties in estimating the correct serving size for amorphous foods (e.g., apple sauce) compared to solid foods (Yuhas et al. 1989; Ayala 2006) (Table 80.3).

In a recent study our research group (Vinai et al. 2008) investigated the influence of socioeconomic factors and food palatability on food amount evaluation among children. We tested 94 ten- to fifteen-year old children living in Mali in western Africa, and 124 subjects comparable in age and gender in northern Italy. They were asked to evaluate an amount of palatable candies. Both Italian and Malian children significantly underestimated them. This characteristic could represent a protective factor against food shortage, but in regions with food abundance it could play a role in the onset and maintenance of an obesity epidemic (Fig. 80.3).

Subsequently we asked the same subjects to evaluate an amount of altered food (toffees dyed with ink and ammonia so as not to be palatable), and found a significant difference between the groups. African children do not underestimate the number of toffees presented to them while Italian children continued to underestimate them as palatable ones.

Food amount evaluation seems to be asymmetrically regulated. Food shortage influences the evaluation of nonedible food but current food abundance has no effect on the evaluation of palatable food. There is no downregulation caused by food abundance in evaluating the amount of tasty food. We can hypothesize that the few generations in which there has been food abundance in Italy are not enough to modify the tendency to underestimate a palatable food; a characteristic developed over centuries of shortage, while they are enough to reduce the emotional impact of seeing wasted food (Fig. 80.4).

Table 80.3 Factors inducing perceptive biases in food amount evaluation among general population

- Disposition (randomly/regularly)
- Dimensions
- Area occupied
- Form (solid/amorphous)
- Energy density
- Food disposability

When food is randomly disposed it is frequently underestimated, such as when it is cut in small pieces, or when occupies a small area. Subjects fail more frequently in evaluation of the amount of amorphous food and of aliments with a high energy density

Fig. 80.3 Evaluation of the number of tasty candies in different cultural contexts. Children living in different cultural contexts (Mali in Africa/Italy in Europe) with different food availability share a tendency to underestimate the number of tasty candies presented
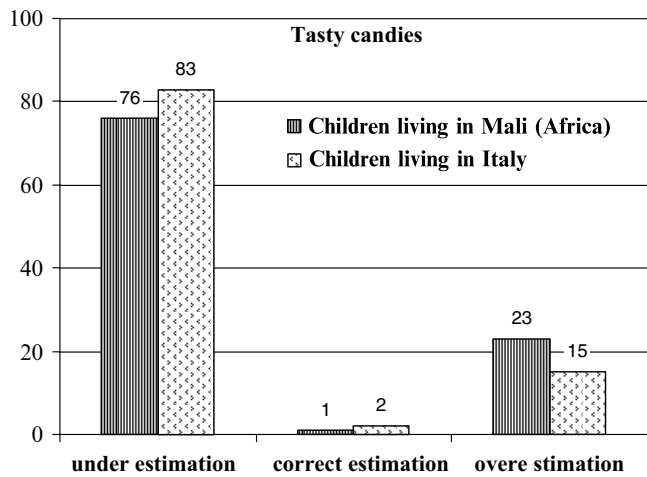
Fig. 80.4 Evaluation of the number of not edible candies in different cultural contexts. There are significant differences in evaluating an amount of altered, so no longer edible, candies between children living in different cultural contexts with different food availability. The 90% of the children living in Italy underestimate the number of candies. Only the 47% of the children living in Mali in Western Africa underestimate them
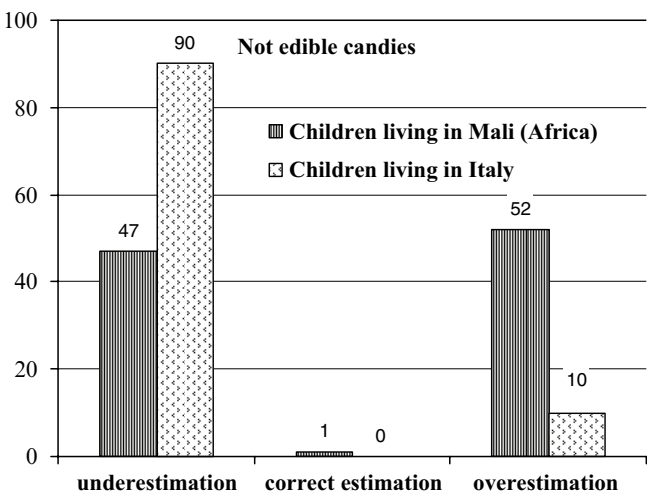
Summarizing cognitive and perceptive biases influence food amount evaluation among the general population inducing underestimation of food amount. In a context of food abundance they can represent a risk factor for overeating.

80.6 Applications to Other Areas of Health and Disease, Improving Food Amount Evaluation to Deal with an Obesity Epidemic

It is a common experience among people living in Europe to be surprised by the size of the portions as they enter a restaurant in the USA. The repeated exposure to extra-large portion sizes could have fostered the normalization of a high-energy intake. What was seen as an enormous portion 25 years ago may have down-sized to an 'average-sized' portion in the eyes of today's consumers (Dohm et al. 2005).

Table 80.4 Factors influencing food amount estimation among obese subjects

- Sensitivity to reward
- Large portions size
- Body Mass Index
- Preference for fatty foods
- Underestimation of portion size

Among factors influencing the food amount evaluation of obese subjects, the tendency to consider enormous amounts of food as normal, and the high caloric concentration of food seem to play a pre-eminent role

Mistakes in evaluating food intake have been reported by the Special Supplemental Food Program for Women, Infants, and Children (Webb and Yuhas 1988) and by several research programs focusing on obese subjects affected by type II diabetes (Rapp et al. 1986) or currently dieting (Howat et al. 1994). Obese persons generally under-report food intake and fail in estimating food quantity and calories more than normal-weight subjects do (Bandini et al. 1990); such mistakes are a barrier to the control of food intake (Davis et al. 2007). The largest miscalculation in reported caloric intake seems to be due to errors in portion-size estimation (Beasley et al. 2005), but it is still an open question whether obese patients actually have a perceptive bias needing specific training to accurately self-report their food intake during a weight loss program (Lansky and Brownell 1982), or intentionally under-report their food intake for social desirability reasons (Muhlheim et al. 1998). Moreover, they make great mistakes in converting food quantity to actual caloric values; indeed foods with the highest caloric density had the highest error level (Lansky and Brownell 1982).

Among obese women (Davis et al. 2007) an interesting interaction between obesity and *sensitivity to reward* on food amount ratings was found: high reward sensitivity was associated with the underestimation of food amounts. The authors hypothesize that a subject highly attuned to the rewarding properties of food will tend to have a biased perception of food amounts. In other words, larger portion sizes may be judged more *normal* by those who are easily rewarded in comparison to subjects with a more nonhedonic reaction to food. They also found that women with a strong preference for high-fat foods were more likely to underestimate the size of portions.

Reward sensitivity is positively associated with BMI and predisposes individuals to overeating (Loxton and Dawe 2001; Davis et al. 2004). Subjects' BMI seems to be a strong predictor of larger than recommended amounts of food. Individuals with a higher BMI may view a larger portion as *typical* and thus eat significantly larger portions of food (Burger et al. 2007). A strong preference for high-fat foods predisposes subjects to choose fast-food restaurants where portion sizes are typically larger than meals cooked at home (Briefel and Johnson 2004). Moreover, larger portion sizes tend to be underestimated more than smaller ones (Harnack et al. 2004) (Table 80.4).

The knowledge regarding food amount evaluation can be used in assessments of meal size and caloric intake of obese subjects and to develop psycho-educational programs to heighten awareness about correct portion sizes and to teach strategies for improving abilities to estimate food amounts (Davis et al. 2007) (Fig. 80.5).

80.7 Instruments to Improve Ability in Food Amount Evaluation Among Adults

Food diaries are widely used for dietary survey. One of the main problems of their use is to establish the size of consumed portions and the caloric value of food. Since 1984, Marilyn and Zegman found that 68% of a sample of 43 obese female subjects failed in evaluating calories using the *Handbook 456*, a
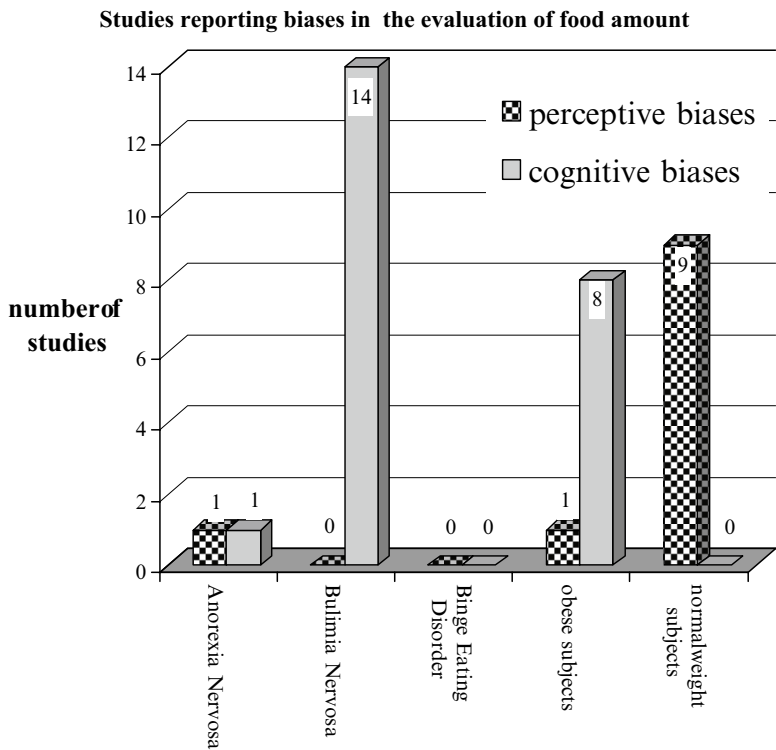
Fig. 80.5 Perceptive and cognitive biases in the evaluation of food amount. The graph reports the number of studies regarding food amount evaluation found in *Medline*® and their results. In the graph, the studies evaluating perceptive and cognitive biases are reported among patients affected by eating disorders, obesity, and normal-weight subjects. Several studies found perceptive deficits in the general population. Very few studies focus on food amount evaluation in BED and AN patients. Cognitive biases seem to play a primary role among patients affected by BN

small text showing caloric value of commonly used aliments. In the same year Guthrie (1984) suggested the use of tools to help patients in assessment of portion sizes. Given the importance of food amount evaluation in the assessment and therapy of ED and overweight patients, an objective measure that presents standard stimuli to assess an individual's judgment of food amounts is needed (Table 80.5).

Many instruments have been developed to improve subjects' ability in evaluating their own food intake. *Portion Size Measurement Aids* (PSMA) include two dimensional models: drawings of real foods, abstract shapes, household measures, food photographs, computer graphics, and package labels; and three-dimensional tools such as household measures, real samples, and models of food. Kircaldy et al. (1989) did not find any significant difference by comparing the accuracy of portion size estimates obtained with four different PSMA: color pictures of foods, abstract shapes, black and white drawings, preweighted amount of food. Their results were subsequently confirmed (Posner et al. 1992) comparing the effect of two-dimensional and three-dimensional models on evaluation. PSMA have been used separately and together but the validity of this tool is not yet clear (Cypei et al. 1997; Matheson et al. 2002).

The most common dietary assessment tool used in large epidemiologic studies of diet and health are the *Food Frequency Questionnaires* (FFQ); self-administered booklets asking participants to report the frequency of consumption and portion size of many foods over a period of time (Willet 2002). They contain sets of pictures of different portion sizes of foods. Each line item is defined by a series of foods or beverages (Table 80.6).

Table 80.5 Instruments to improve ability in food amount evaluation among adults

- Portion Size Measurement Aids (PSMA)
- Food Frequency Questionnaires (FFQ)
- Adjustable Wedge
- Food Portion Photograph Book (FPPB)
- Food Amount Rating Scale (FARS)
- Interactive Portion Size Assessment System (IPSAS)

Several instruments have been developed to improve subjects' ability in evaluating their food intake; among them photographs of food and a food amount rating scale seem to be the most effective. Among children, IPSAS and food photograph books adapted for children seem to be more effective than the instruments used for adults

Table 80.6 Key features of Food Frequency Questionnaires (FFQ)

FFQs ask participants to report the frequency of consumption and portion size of a series of foods and beverages (usually 100–150 items) over a defined period of time, e.g., the last month. Several questions on food preparation methods enable the researchers to further refine nutrient calculations. Food composition tables listing the average nutrient content of listed foods have been developed to estimate nutrient intake from SFFQ.

Food Frequency Questionnaires (FFQ) are self-administered booklets, commonly used in epidemiologic studies, developed with the purpose of obtaining a measure of usual diet

Kuehneman (1994) found no difference in the accuracy of food amount evaluation between subjects using PSMA and FFQ.

An *Adjustable Wedge* (AW) was proposed to assess wedge-shaped foods (e.g, pie, cake, and pizza) and tested by Godwin in 2006, among 320 subjects of both sexes, ranging from 18 to 65 years, using multiple sizes and types of wedge-shaped foods. The evaluation made with the AW was more accurate ($P < 0.05$) than the ruler in approximately one third of comparisons, but regardless of the aid used, some people have difficulty in estimating portions of wedge-shaped foods.

Photographs of food are useful instruments which are also widely used among people of different cultures, but despite the apparent simplicity of these tools, three skills are involved in their use: perception, memory, and cognitive functions. The subject has to be able to perceive the amount of eaten food, to remember it, to make a mental construction of an amount which is not currently present, and to relate it to the photograph. Any impairment in each of these skills can reduce the efficacy of the instruments. Regarding their efficacy, Nelson et al. (1994) found that photographs of small portions of food are overestimated while large ones are underestimated.

To assess individuals' estimation of food amounts Dohm and Striegel-Moore (2002) developed the *Food Amount Rating Scale* (FARS). It asks the subjects to rate 24 different portions of food described in the questionnaire (e.g., 1 bowl spaghetti, ½ cup tomato sauce, 1 bowl tossed green salad, 1/8 cup salad dressing, 2 pieces garlic bread) by checking via five definitions: *small amount, moderate amount, large amount, enormous amount, beyond enormous*, the definition which best describes each portion.

80.8 Food Amount Evaluation Among Children

Children also fail in estimating food amount and portion size and several research programmes tested the efficacy of the above described tools to improve their food amount evaluation. Matheson et al. (2002) evaluated errors associated with children's portion size estimates by means of 2 food portion measurement aids: the standard 2-dimensional food portion visuals and manipulative props.

Errors in quantitative estimates of gram weight of foods and energy intakes were large with both methods. Frobisher and Maxwell (2003) compared the ability of adults and children in evaluating portion size using food photographs and descriptions of portions. Forty-seven adults and 37 children were asked to describe a portion of nine food items using the terms small, medium, and large and to choose the photo in a photographic food atlas which best represented the portion size they had just served themselves. All subjects were asked to recall their food intake 3–4 days after the meal. There were very few differences in the estimation of portion sizes between the two testing periods but among children there was greater error than among adults. Children overestimate portions probably because they usually have smaller portion sizes than those depicted in the smallest portion size photograph in the food atlas. The findings suggested that for young subjects it was necessary to modify the tools for estimating portion sizes. Lillegaard et al. (2005) researching whether age influences the ability to estimate food portion sizes by viewing photographs of food did not find any age-related difference, but portion size was estimated more accurately when the actual served portion of food had exactly the same appearance as the foods on the photograph booklet. Foster et al. (2006) found that children's estimates of portion sizes were significantly more accurate (an underestimate of 1% on average) using age-appropriate food photographs than photographs designed for use with adults (an overestimate of 45% on average). Accuracy of children's estimates of portion size using age-appropriate tools was similar to that of adults; children overestimated a food weight by 18% on average and adults underestimated by 5%. In conclusion, providing children with food photographs depicting age-appropriate portion sizes greatly increases the accuracy of portion size estimates compared with estimates using photographs designed for use with adults.

New technologies have recently been used to help children's evaluation of the quantity of food. The *Interactive Portion Size Assessment System* (IPSAS) is a computer-based system to allow the child or interviewer to scroll through images of food depicting increasing portion size. These images are photographs of real foods that are used to indicate the portion served and any food left over. The system automatically records the portion size selected and stores this and related data, including the subjects' details. This data can easily be exported to a database or statistical software. Foster et al. (2008, 2009) assessed the accuracy of children's estimates of portion size using food photographs, food models, and the IPSAS. Significant differences were found between the accuracy of estimates using the three tools. Children of all ages performed better using the IPSAS and food photographs than when using food models. The authors suggest that IPSAS has potential for the assessment of dietary intake with children. Before its practical application it needs to be expanded to cover a wider range of foods and to be validated in a "real-life" situation. In conclusion, color food photography and the atlas seem to be useful tools for quantifying food portion size but new instruments are needed to improve food amount evaluation among children.

80.9   Transcultural Studies

Several studies assessed the utility of PSMA in different cultural contexts. Venter et al. (2000) developed the *Food Portion Photograph Book* (FPPB) in Southern Africa. Commonly eaten foods, preparation methods, recipes, and portion sizes were collected in a pilot study; then color photographs taken of foods prepared by the researchers and measured into three or four portion sizes were put together in the FPPB. One hundred and sixty-nine adult African volunteers were tested by presenting them with a portion of real food and asking them to estimate its size by matching it with one of the photographs. Of 2,959 portions tested, 68% were accurately estimated. The estimation was not affected by gender, age, or education of the participants.

In Italy, Turconi et al. (2005) developed a *color photographs food atlas* by weighing and taking digital photographs of three portion sizes of 434 foods and beverages typical of the Italian diet. They tested 448 volunteers ranging from 6 to 60 years old from a wide variety of social backgrounds, assessing 9,075 food portions eaten at lunch and dinner in relation to a set of color food photographs during 8 weeks of investigation. The results show that weights of portion sizes chosen from the set of photographs are significantly associated to weights of eaten portions and are regardless of age, gender, and BMI.

Huybregts et al. (2008) assessed the utility of photography in food recall after 24 h among women of Burkina Faso. Each photo album contains four photos for each item. Subjects were shown two previously weighed foods every morning, and another in the afternoon. The day after, the subjects were shown the pictures and had to choose the representative food of the day before. The use of images was effective for the estimation of food.

80.10 Conclusion

In conclusion, our findings suggest that assessment of what constitutes a binge or overeating, and judgment of food amounts in general, may be influenced by an individual's gender, ethnicity, dietary restraint status, level of depressive symptomatology, and current weight (Fig. 80.6).
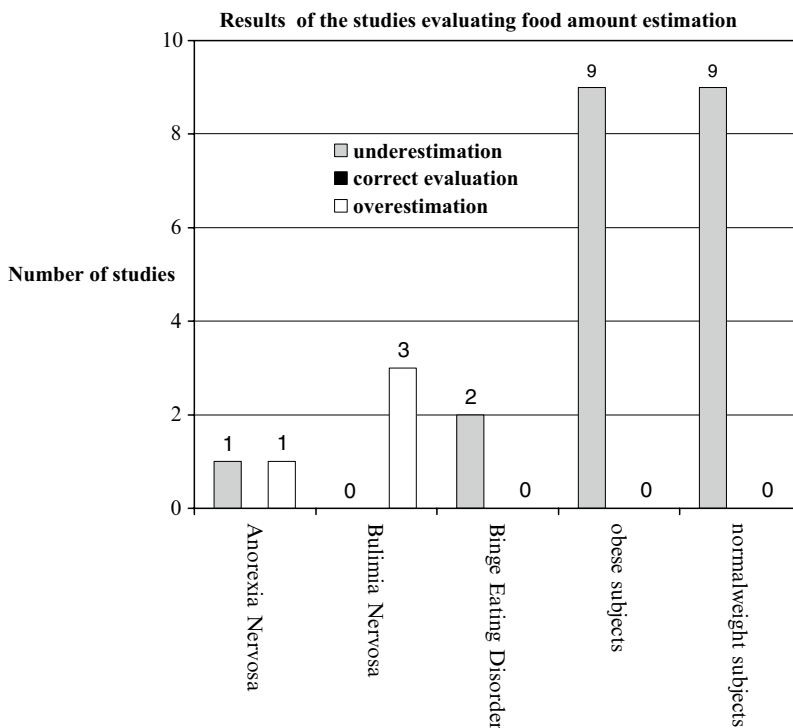
Fig. 80.6 Errors in food amount evaluation. The graph reports the number of studies regarding food amount evaluation found in *Medline*® and their results. There is a tendency to underestimate food amounts among the general population, obese subjects, and patients affected by BED. The studies involving bulimic subjects found an overestimation of food amount and the few researches regarding AN patients had controversial results

Researchers studying issues related to dietary intake (e.g., obesity) or disordered eating (e.g., binge eating) need to account and check for the possible confounding effects of these characteristics on self-reports of food intake. Furthermore, using this information to educate study participants and treatment clients about how their perceptions may be biased could improve future food reporting (Dohm et al. 2005). Future investigations should include an income measure to account for the effects of socioeconomic status on portion-size estimation. In addition, we suggest that interventions for preventing weight gain in young adults should focus on the importance of portion sizes for all foods, regardless of macronutrient content, and on increasing the awareness of eating habits in response to media messages and product packaging (Burger et al. 2007). It is noteworthy that training improves ability in estimating food. Yuhas et al. (1989) tested two groups of students in a nutrition course, dividing them into two groups: only one group (76 subjects) received training on estimating food quantities. The training consisted of 10-min sessions in which subjects passed around and viewed food models labeled with their portion sizes while one of the researchers verbally indicated the quantities. There were two solid foods (meat loaf and fish), two liquids (milk and soup), and two amorphous items (spaghetti and apple sauce). Immediately after, subjects individually estimated portion sizes of one food on a display. The second group of subjects, who had received no training, also estimated the same foods on the same displays. Training improved estimations and women tended to estimate more accurately than men. These results suggest the importance of using specific training in order for ED and obese subjects to evaluate their food intake better.

Summary Points

- Perceptive and cognitive biases influence food amount evaluation in the general population and among patients with eating disorders.
- The general population tends to underestimate food amounts.
- Patients affected by Anorexia Nervosa are not affected by perceptive deficit – it is cognitive and emotional factors which influence their evaluation of food amount.
- distortion of what is a normal meal represents a central cognitive mechanism of Bulimia Nervosa.
- Bulimic patients over-rate the amount of food presented to them; this can induce a more restrictive diet, a risk factor for the onset of bulimic behavior.
- Consumption of small amounts of *forbidden food* may lead bulimic patients to perceive their consumption as a binge.
- The perception of having overeaten rather than actual overeating leads to binging in BN.
- No evidence of perceptive distortion among BED patients has been found.
- It is possible to improve the subjects' ability in evaluating food amount.
- Food photographs are useful tools to train subjects in estimating their food intake.

Key Terms

Anorexia nervosa: An eating disorder characterized by markedly reduced weight and aversion to food.

Binge eating disorder: An eating disorder characterized by episodes of over-eating with a sensation of loss of control, not followed by purging behaviors.

Body mass index (BMI): An index for relating a subject's body weight to his/her height. It represents the subject's weight in kilograms divided by his/her height in meters squared.

Bulimia nervosa: An eating disorder characterized by episodes of binge-eating followed by purging behaviors, such as self-induced vomiting, abuse of laxatives or diuretics, or excessive physical exercise.

Cognitive biases: The tendency to make errors in judgment based on the processing of information, applying knowledge and changing preferences; it includes errors in statistical judgment, social attribution, and memory.

Downregulation of food: The process by which a subject underestimates a food amount in response to an external variable such as food abundance.

Food amount rating scale (FARS): A multiple choice questionnaire which asks for a rating by checking as: small, moderate, large, enormous, and beyond enormous – the amount of 24 different portions of food described in it.

Food frequency questionnaires (FFQ): Booklets asking participants to report the frequency of consumption and portion size of many foods over a period of time.

Malian: People living in Mali in Western Africa.

Perceptive biases: Mistakes in evaluation due to a sensorial deficit.

Portion size measurement aids (PSMA): Tools useful for improving accuracy in food amount evaluation. They include household measures, drawings, abstract shapes, photographs, package labels, real samples, and models of food.

Stroop interference: When a word such as green, red, blue etc. is printed in a color differing from the color expressed by the word's semantic value (e.g. the word *green* printed in red ink), naming the color of the word takes longer and is more prone to errors than when the meaning of the word is congruent with its ink color. Patients affected by Anorexia Nervosa show interference on the Stroop color naming task for food.

Type II diabetes: An illness characterized by high blood glucose due to the inability of body cells to respond appropriately to insulin, a hormone produced by the pancreas to reduce blood glucose levels. It is distinguished from type I diabetes due to reduced production of insulin by the pancreas.

References

Allik J, Tuulmets T. Percept Psychophys. 1991;49(4):303–14.

Ayala GX. Health Educ Res. 2006;21:133–45.

Bandini LG, Schoeller DA, Cyr HN, Dietz WH. Am J Clin Nutr. 1990;52:421–5.

Beasley LJ, Hackett AF, Maxwell SM, Stevenson L. J Hum Nutr Diet. 2004;17:219–25.

Beasley J, Riley WT, Jean-Mary J. Nutrition. 2005;21:672–7.

Blake AJ, Guthrie HA, Smiciklas-Wright H. J Am Diet Assoc. 1989;89:962–4.

Blundell JE. Am J Clin Nutr. 2000;71:3–5.

Briefel RR, Johnson CL. Annu Rev Nutr. 2004;24:401–31.

Brunstrom JM, Rogers PJ, Pothos EM, Calitri R, Tapper K. Appetite. 2008;51:296–301.

Burger KS, Kern M, Coleman KJ. J Am Diet Assoc. 2007;107:611–8.

Cypei YS, Guenthet PM, Petot GJ. J Am Diet Assoc. 1997;97:289–92.

Davis C, Levitan RD, Muglia P, Bewell C, Kennedy JL. Obes Res. 2004;12:929–35.

Davis C, Curtis C, Tweed S, Patte K. Eat Behav. 2007;8:170–6.

Dohm FA, Cachelin FM, Striegel-Moore RH. Obes Res. 2005;13:1061–9.

Dohm FA, Striegel-Moore RH. Obes Res. 2002;10:1173–9.

Epstein J, Wiseman CV, Sunday SR, Klapper F, Alkalay L, Halmi KA.. Eat Weight Disord. 2001;6:140–7.

Foster E, Matthews JN, Nelson M, Harris JM, Mathers JC, Adamson AJ. Public Health Nutr. 2006;9:509–14.

Foster E, Mattheews JN, Lloyd J, Marshall L, Mathers JC, Nelson M, Barton KL, Wrieden WL, Cornelissen P, Harris J, Adamson AJ. Br J Nutr. 2008;99:175–84.Foster E, Adamson AJ, Anderson AS, Barton KL, Wrieden WL. Eur J Clin Nutr. 2009;63:45–9.

Frobisher C, Maxwell SM. J Hum Nutr Diet. 2003;16:181–8.

Ginsburg N. J Gen Psychol. 1980;103:211–6.

Ginsburg N. Am J Psychol. 1978;91:267–73.

Ginsburg N, Nicholls A. Percept Mot Skills. 1988;67:656–8.

Gleaves DH, Williamson DA, Barker SE. Addict Behav. 1993;18:299-309.

Godwin S, Chambers E, Cleveland L, Ingwersen L. J Am Diet Assoc. 2006;106:1246–50.

Greeno CG, Wing RR, Marcus MD. Addict Behav. 1999;24:299–303.

Guertin TL, Conger AJ. Addict Behav. 1999;24:175–93.

Guthrie HA. J Am Diet Assoc. 1984;84:1440–4.

Harnack L, Steffen L, Arnett DK, Gao S, Luepker RV. J Am Diet Assoc. 2004;104:804–6.

Herman CP, Polivy J. Res Publ Assoc Res Nerv Ment Dis. 1984;62:141–56.

Howat PM, Mohan R, Champagne C, Monlezun C, Wozniak P, Bray GA. J Am Diet Assoc. 1994;94:169–73.

Huybregts L, Roberfroid D, Lachat D, Van Camp J, Kolsteren P. Public Health Nutr. 2008;11:581–7.

Kales EF. Physiol Behav. 1990;48:837–40.

Kales EF. Appetite. 1991;17:241–2.

Keel PK, Mayer SA, Harnden-Fischer JH. Int J Eat Disord. 2001;29:294–301.

Kirkcaldy-Hargreaves M, Lynch GW, Santor C. J Can Diet Assoc. 1989;41:102–10.

Klesges RC, Eck LH, Ray JW. J Consult Clin Psychol. 1995;63:438–44.

Knight LJ, Boland FJ. J Abnorm Psychol. 1989;98:412–20.

Kuehneman T, Stanek K, Eskridge K, Angle C. J Am Diet Assoc. 1994;94(5):548–51.

Lansky D, Brownell KD. Am J Clin Nutr. 1982;35:727–32.

Lillegaard IT, Overby NC, Andersen LF. Eur J Clin Nutr. 2005;59:611–17.

Loxton NJ, Dawe S. Int J Eat Disord. 2001;29:455–62.

Macdiarmid J, Blundell JE. Nutr Res Rev. 1998;11:231–53.

Marilyn AZ. Addictive Behav. 1984;9:347–50.

Matheson DM, Hanson KA, McDonald TE, Robinson TN. Arch Pediatr Adolesc Med. 2002;156:867–71.

Muhlheim LS, Allison DB, Heshka S, Heymsfield SB. Int J Eat Disord. 1998;24:259–66.

Nelson M, Atkinson M, Darbyshire S. Br J Nutr. 1994;72:649–63.

Overduin J, Jansen A, Louwerse E. Int J Eat Disord. 1995;18:277–85.

Polivy J, Herman CP. Am Psychol. 1985;40:193–201.

Posner BM, Smigelski C, Duggal A, Morgan JL, Cobb J, Cupples LA. J Am Diet Assoc. 1992;92:738–41.

Rapp SR, Dubbert PM, Burkett PA, Buttross Y. J Am Diet Assoc. 1986;86:249–51.

Robson Pj, Livingstone MB. Public Health Nutr. 2000;3:183–92.

Rosen JC, Leitenberg H, Gross J, Willmuth M. Adv Behav Res Ther. 1985;7:181–97.

Scagliusi FB, Polacow VO, Artioli GG, Benatti FB, Lancha AHJ. J Am Diet Assoc. 2003;103:1306–13.

Skrzypek S, Wehmeier PM, Remschmidt H. Eur Child Adolesc Psychiatry. 2001;10:215–21.

Stanton AL, Tips TA. Int J Eat Disord. 1990;9:387–93.

Telch CF, Agras WS, Rossiter EM, Wilfley D, Kenardy J. J Consult Clin Psychol. 1990;58:629–35.

Turconi G, Guarcello M, Berzolari FG, Carolei A, Bazzano R, Ruggeri C. Eur J Clin Nutr. 2005;59:923–31.

Urdapilleta I, Mirabel-Sarron C, Meunier JM, Richard JF. Encephale. 2005;31:82–91.

Venter CS, MacIntyre UE, Vorster HH. J Hum Nutr Diet. 2000;13:205–18.

Vinai P, Cardetti S, Ferrato N, Vallauri P, Carpegna G, Masante D, Luxardi G, Todisco P, Manara F, Ruggiero GM, Sassaroli S. Eat Behav. 2007;8:291–5.

Vinai P, Carpegna G, Cardetti S, Ferrato N, Vallauri P, Masante D, Meister A, Ruggiero GM, Sassaroli S. Eat Disord. 2008;16:128–35.

Webb CA, Yuhas JA. J Am Diet Assoc. 1988;88:601–2.

Willett WC. In: Willett WC, editor. Nutritional epidemiology. New York: Oxford University Press; 2002. pp. 74–100.

Yellowlees PM, Roe M, Walker MK, Ben-Tovim DI. Br Med J. 1988;296:1689–90.

Yuhas JA, Bolland JE, Bolland TW. J Am Diet Assoc. 1989;89:1473–7.

Williamson DA, Gleaves DH, Lawson OJ. J Psychopathol Behav Assess. 1991;13:257–68.

Chapter 81
Visual Processing, Food Cravings and Weight-Loss Dieters

Eva Kemps and Marika Tiggemann

Abbreviations

DVN   Dynamic visual noise
EM   Eye movements
ST   Spatial tapping
TS   Thought suppression

81.1 Introduction

The act of dieting involves the deliberate restriction of food intake in an attempt to achieve weight loss. Although moderate weight reduction in obese individuals can have clear health benefits, such as reduced risk of cardiovascular disease and increased aerobic and anaerobic aptitudes, the actual practice of weight-loss dieting is associated with a number of negative outcomes. For example, people who are on a diet often also exhibit mood swings, depression, lowered self-esteem and impaired cognition. Another unintended negative consequence of weight-loss dieting is the experience of unwanted food cravings. In fact, recurrent food cravings have the potential to disrupt and thwart dieting attempts. This highlights the need for effective techniques for reducing food cravings. However, contemporary intervention tools involving either suppression of craving-related thoughts or unreinforced exposure to food cues have shown only mixed success. This chapter describes a radically different approach to controlling food cravings based on converging evidence that mental imagery is a key component of the craving experience. Empirical data, which show that interfering with the cognitive processes that support craving-related mental images can suppress food cravings in dieters, are reviewed.

81.2 Food Cravings

The term "craving" refers to a motivational state whereby an individual feels compelled to seek and ingest a particular substance, usually cigarettes, alcohol or drugs (Baker et al. 1986). More recently, however, interest has fallen on *food* cravings. These have been described as an intense desire or urge to

E. Kemps (✉)
School of Psychology, Flinders University, GPO, Adelaide, SA 5001, Australia
e-mail: Eva.Kemps@flinders.edu.au

eat a specific food (Weingarten and Elston 1990). Food cravings are not to be equated with hunger, for they generally occur in the absence of hunger (Cornell et al. 1989). Hunger signals a physiological need to eat, which can be satisfied with any food. Cravings, however, are for a particular food, and can only be satisfied by eating that food. For example, one craves chocolate ice-cream, rather than something generically sweet. In particular, there is no substitute for chocolate when it is craved; other sweet foods, including white 'chocolate', cannot fully satisfy chocolate cravings (Michener and Rozin 1994).

Food cravings are a common and everyday experience (Lafay et al. 2001), with prevalence rates varying according to gender and age. Women tend to crave more than men (Weingarten and Elston 1991), and younger people crave more than older people (Pelchat 1997). Not surprisingly, there exist marked cross-cultural differences in the kind of foods craved (Hawks et al. 2003). For example, chocolate is the most commonly craved food in Western societies (Hetherington and Macdiarmid 1993), followed by chips, pizza, cake, and ice-cream. In Egypt, on the other hand, the most craved foods are vegetable dishes, some stuffed or cooked with meat (Parker et al. 2003).

The origin of food cravings has been attributed to a range of physiological and psychological factors. At a physiological level, food cravings have been linked to nutritional deficiencies (Wardle 1987), and in women to hormonal changes, such as menstrual-related changes (Dye et al. 1995) and pregnancy (Dickens and Trethowan 1971). At a psychological level, food cravings can be triggered by negative mood states, including feelings of boredom, loneliness, depression, anxiety, as well as stress (Hill et al. 1991). Food cravings can also by elicited by exposure to environmental cues, such as the sight or smell of tasty food (Fedoroff et al. 2003).

81.3 Food Cravings and Weight-Loss Dieting

Although food cravings are not invariably linked to dietary restraint, weight-loss dieting has been associated with an increased occurrence of cravings (Hetherington and Macdiarmid 1993; Pelchat 1997). Food cravings are thought to be part of the preoccupying cognitions concerning food, weight and body shape that accompany dieting behaviour (Green 2001). These dieting-related cravings can give rise to a range of negative consequences. In particular, food cravings have been implicated in the early dropout from weight-loss programs. For example, Sitton (1991) reported that attrition rates were almost three times higher for carbohydrate cravers than for non-cravers during the first month of a prescribed diet. Cravings for food can also lead to feelings of guilt and shame following consumption if dietary restriction fails (MacDiarmid and Hetherington 1995).

Importantly, dieting-related cravings are known to adversely affect cognitive processing. For example, dieters exhibit biased attentional processing of food and body shape words on the modified Stroop task (Green and Rogers 1993). Additionally, experimentally induced food cravings have been shown to slow responses on a simple reaction time task in highly restrained eaters and dieters (Green et al. 2000). This finding has important implications in that speeded responding to a visual probe (as in a reaction time task) is vital in vigilance tasks, such as inspecting items on an industrial production line, or manoeuvring through dense traffic. Slowed reaction times arising from food cravings could compromise performance of such everyday tasks, thereby reducing work efficiency or increasing accidents.

Finally, cravings triggered by chronic dietary restriction have been identified as a precursor to binge eating, particularly in the context of obesity (Schlundt et al. 1993) and eating disorders, such as bulimia nervosa (Mitchell et al. 1985). Obesity and eating disorders are themselves risk factors for the development of other serious medical and psychological problems, such as cardiovascular disease, Type 2 diabetes, depression and low self-esteem.

The incidence of such dieting-related food cravings is likely to be on the rise, fuelled by a continuing increase in obesity rates (Wadden et al. 2002) and body image concerns (Cash and Pruzinsky 2002). The advent of public health campaigns targeting the health risks associated with being overweight is intended to result in more people trying to lose weight. In parallel, the continual and pervasive presentation by the media of the thin ideal for women and the lean but muscular ideal for men can only serve to increase rates of body dissatisfaction, which many individuals attempt to resolve by dieting in an attempt to more closely approach the elusive societal ideal. As more people adopt food restriction (dieting) as the means for attempting weight loss in response to these messages, there will be a concomitant increase in accompanying levels of food craving. Thus the availability of a technique for curbing dieting-related food cravings is of considerable practical importance.

81.4 Reduction of Food Cravings

81.4.1 Thought Suppression and Cue Exposure Response Prevention

The techniques currently available for reducing food cravings involve either suppression of dieting-related thoughts or cue exposure response prevention. The rationale behind thought suppression is that people can avoid performing an unwanted behaviour by deliberately not thinking about it. Harnden et al. (1997) used this paradigm to investigate the effect of thought suppression on weight-related preoccupations in dieters. They instructed female dieters and non-dieters to either suppress or express thoughts about weighing themselves and to subsequently verbalise all thoughts that came to mind during a 5-min period. Although dieters mentioned more weight-related thoughts overall than did non-dieters, suppression reduced the frequency of such thoughts in both groups. The magnitude of suppression was, however, less for dieters than for non-dieters. Oliver and Huon (2001) further showed that women who reported high levels of disinhibited eating were more successful at suppressing thoughts about food and eating than were women low on disinhibition. However, high disinhibitors were more likely to use punishment and worry strategies to control their thoughts. These thought control strategies were themselves related to feelings of anxiety and distress (Table 81.1).

Table 81.1 Schematic representation of the craving reduction techniques of thought suppression and cue exposure response prevention

Thought suppression	Cue exposure response prevention
Period 1: Thought monitoring	Exposure *1* to craved food while resisting consumption, followed by a rating of food craving
Participants are instructed to think about anything they like, and to press a button if they think about the craved food	
Period 2: Thought suppression	Exposure *2* to craved food while resisting consumption, followed by a rating of food craving…
Participants are instructed to *not* think about the craved food, and to press a button if they do	
Period 3: Thought monitoring	Exposure *n* to craved food while resisting consumption, followed by a rating of food craving
Participants are again instructed to think about anything they like, and to press a button if they think about the craved food	

This table presents a step-by-step overview of the techniques of thought suppression and cue exposure response prevention as applied to the reduction of food cravings

Table 81.2 Mean pre- and post-imagery task food craving levels as a function of imagery task and dieting status (standard deviations in parentheses)

	Dieters		Non-dieters	
Imagery task	Pre	Post	Pre	Post
Visual	71.93 (24.11)	38.80 (26.32)	45.13 (29.95)	29.31 (25.02)
Auditory	49.40 (35.79)	35.96 (36.83)	28.93 (26.08)	21.11 (20.22)

This table shows that the visual imagery task reduced participants' level of food craving more than did the auditory imagery task, particularly for dieters. Craving was rated on a 100-point scale ranging from "no desire or urge to eat" to "extremely strong desire or urge to eat"

More generally, suppression of unwanted thoughts about food, eating or weight can paradoxically lead to an increase in such thoughts. For example, Johnston et al. (1999) showed that participants who had been instructed to suppress chocolate-related thoughts made fewer mentions of chocolate during a 5-min articulated thoughts task that involved planning a dessert menu for a dinner party than participants who had received no such instruction. However, those participants who engaged in thought suppression actually worked harder (performed better) on a subsequent task that yielded chocolate awards, indicating an *increase* in drive for chocolate. Although such a rebound effect is not necessarily always seen, ironic effects of thought suppression have been documented in a number of other areas, such as mood control, stereotyping and traumatic memories (Abramowitz et al. 2001). Furthermore, an increased occurrence of unwanted thoughts following attempts at suppression can itself lead to perceived loss of control over one's thoughts, and thereby give rise to feelings of failure and distress (Kelly and Khan 1994).

The second currently available technique, cue exposure response prevention, involves successive exposures to an appetitive target (food), with instructions to attempt to resist consumption. The elicited craving is expected to diminish across exposures because the appetitive cue is not reinforced by consumption. Tuomisto et al. (cited in Hetherington 2001) used this paradigm in an attempt to reduce food cravings in obese women. Following a baseline measurement of craving, the women were presented with warm pizza. They were asked to look at, smell and imagine eating the pizza, but not to eat it. Ratings of food craving were taken every 10 min. Although cravings decreased somewhat across exposures, they remained high compared to baseline. At a general level, cue exposure response prevention has been used with mixed success in the treatment of alcoholism (Conklin and Tiffany 2002), phobias and binge eating in patients with bulimia nervosa (Jansen 2001).

Thus, neither thought suppression nor cue exposure response prevention holds much promise as a technique for reliably reducing dieting-related food cravings. We reasoned that in order to develop a different (and potentially more successful) kind of craving-reduction technique, we first need to gain insight into the nature of the actual craving experience (Table 81.2).

81.4.2 The Nature of Food Cravings: A Role for Mental Imagery

There is accumulating evidence from a number of different sources pointing to a role for mental imagery in craving episodes. First, anecdotal accounts describe the experience of desire-related images in naturally occurring cravings (Salkovskis and Reynolds 1994). These accounts have now been corroborated by more formal surveys about everyday food cravings that show that respondents readily use imagery terms to describe their cravings. For example, Tiggemann and Kemps (2005) reported that 30% of their undergraduate student sample used phrases such as 'I could picture the pizza in my mind, picture eating it' when asked to write a short paragraph describing a previous food craving episode. In addition, when presented with a list of descriptive statements, respondents

strongly endorse imagery-based descriptors as characteristic of their cravings. Imagery descriptors in the visual modality (e.g. 'I am visualising it') in particular are rated highly; in contrast, auditory descriptors (e.g. 'I imagine the sound of myself having it') are not highly rated. Furthermore, when asked to assign specific percentages to each of the five sensory modalities involved in an imagined food craving experience, as shown in Fig. 81.1, the visual modality was the highest. These findings indicate that the imagery basis of food cravings is predominantly visual in nature (Table 81.3).

Second, instructing participants to imagine urge-related scenarios can induce cravings in the laboratory. For example, using a methodology derived from cigarette craving research, Green et al. (2000) reported a positive correlation between latency on a simple reaction time task following instructions to imagine a food scenario ('Imagine you are eating your favourite food') and self-reported desire to eat. Harvey et al. (2005) subsequently showed that craving levels increased following instructions to imagine a food scenario, but not a nonfood scenario. They also noted a positive correlation between participants' self-reported vividness of the image of the food scenario and their level of craving, indicating that stronger food cravings are associated with more vivid images.

Finally, a recent theoretical account of cravings, the elaborated intrusion theory of desire, proposes that sensory images are a central feature of any craving experience (Kavanagh et al. 2005).

Table 81.3 Key facts of food cravings

1. A food craving is an intense desire or urge to eat a *specific* food
2. The most commonly craved food in Western society is chocolate, followed by chips, pizza, cake and ice cream
3. Food cravings are a common, everyday experience, particularly in women and younger adults
4. Food cravings generally occur in the absence of hunger; they are instead triggered by hormonal changes, negative mood states and exposure to environmental food cues
5. Food cravings have been associated with a number of negative outcomes (particularly in weight-loss dieters), such as early dropout from weight-loss programs, feelings of guilt and shame, poor cognitive task performance and binge eating
6. Mental imagery is a key component of food cravings; specifically, when people crave they have vivid images of the craved food

This table lists the key characteristics of food cravings, including the various causes of food cravings, the potential consequences of food cravings, and the role of mental imagery in the experience of food cravings

Fig. 81.1 Mean percentages of sensory modalities involved in craving-related food images. This figure shows the relative involvement of each of the five sensory modalities in craving-related images of food. These are in order: visual (sight), gustatory (taste), olfactory (smell), tactile (touch) and auditory (hearing)
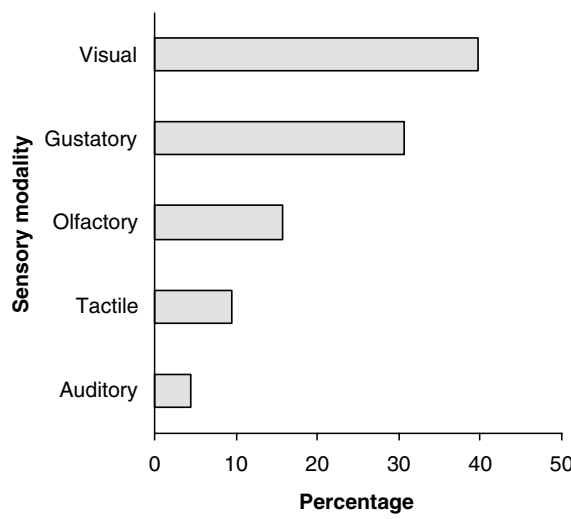
81.4.3 A Working Memory Approach to Reducing Food Cravings

In recent years, cognitive psychologists have adopted a working memory approach to conceptualise the phenomenological experience of mental imagery (Richardson 1999). A widely used and successful account of working memory is that originally proposed by Baddeley and Hitch (1974). The working memory model has undergone revision and elaboration over time but in its current version comprises an overarching central executive responsible for coordinating the activities of a number of modality-specific slave systems and an episodic buffer, a multimodal interface with long-term memory (Baddeley 2000).

The two initially proposed slave systems, which have attracted the most research attention, are the visuo-spatial sketch pad and the phonological loop. The visuo-spatial sketch pad maintains visual and spatial material and is involved in visual imagery. The phonological loop analogously maintains verbal material and is involved in auditory imagery. These slave systems are argued to have limited capacity. Thus a concurrent visual (or verbal) task will interfere with the content of the visuo-spatial sketch pad (phonological loop) by competing for the limited visual (verbal) storage capacity. In support, Baddeley and Andrade (2000) employed dual-task methodology to show that the vividness of visual imagery was reduced by tasks that selectively loaded the visuo-spatial sketch pad, whereas the vividness of auditory imagery was reduced by tasks that specifically utilised the phonological loop.

Inspired by recent developments in cigarette-craving research (Panabokke 2004), we (Harvey et al. 2005) applied this analysis to investigate whether interference from a competing task that requires the same working memory resources as those used to create and maintain craving-related images could suppress food cravings in dieters. As questionnaire data on the subjective experience of cravings have shown that craving-related food images involve visual rather than auditory content, we predicted that a competing visual task (loading the visuo-spatial sketch pad) would reduce food cravings relative to a comparable auditory task (loading the phonological loop). In our study, undergraduate women (self-identified dieters and non-dieters) underwent an imaginal food craving induction procedure and subsequently rated their level of craving. They were then cued to vividly imagine a series of nonfood items. A random half of each group formed visual images of common objects and scenes (e.g. a rainbow), whereas the other half formed auditory images of everyday sounds (e.g. a siren). Following the imagery task, all participants again rated their level of food craving. As predicted, the visual imagery task was superior to the auditory task in reducing the women's food cravings. Moreover, as can be seen in Table 18.2, dieters reported stronger cravings overall, and the magnitude of craving reduction was greater for them than for non-dieters. Thus visual imagery techniques offer potential scope for reducing dieting-related food cravings.

While forming a series of visual images and holding them in mind constitutes an excellent laboratory technique for investigating cravings, it is not only an elaborate, but also a cognitively effortful, procedure and therefore unlikely to be an effective craving reduction technique in a practical sense. Instead, we need to find a simple and relatively undemanding visual task. Fortunately, the working memory literature boasts several simple tasks known to load the visuo-spatial sketch pad. These include saccadic eye movements (visually tracking a rapidly moving stimulus; Idzikowski et al., cited in Baddeley 1986), dynamic visual noise (watching a flickering pattern of random black and white dots, similar to snow on an untuned television screen; Quinn and McConnell 1996) and spatial tapping (tapping four keys arranged in a square pattern; Farmer et al. 1986).

To investigate the craving reduction capacity of such simple repetitive tasks, we (Kemps et al. 2004) adopted a paradigm derived from experimental analogues of post-traumatic stress disorder (Table 81.4). These have shown that concurrent visual processing in the form of simple eye or arm movements, or watching a flickering pattern of random black and white dots, reduced the vividness and consequent emotional impact of distressing images (Andrade et al. 1997; Kavanagh et al. 2001). Accordingly, in view of the association between imagery vividness and food craving intensity,

Table 81.4 Key features of visual working memory based craving reduction

1. The visual component of working memory (i.e. visuo-spatial sketch pad) is involved in the generation and maintenance of visual images
2. Food cravings involve primarily images in the visual sensory modality
3. In working memory terms, food cravings engage the visuo-spatial sketch pad
4. The visuo-spatial sketch pad has limited storage capacity
5. Loading the visuo-spatial sketch pad with a concurrent task when experiencing a food craving reduces the intensity of the craving, because the task and the visual imagery associated with the craving compete for the same limited storage capacity
6. The intensity of a food craving is related to the vividness with which the craved food is imagined, such that stronger food cravings are associated with more vivid images of the craved food
7. Concurrent visual processing has its specific craving reducing effect by diminishing the vividness of craving-related food images

This table outlines the theoretical rationale behind the utility of visual working memory-based techniques for reducing food cravings, with emphasis on the visual imagery basis of food cravings, the mutual competition between food cravings and concurrent visual tasks for limited visuo-spatial sketch pad storage capacity, and the relationship between imagery vividness and craving intensity
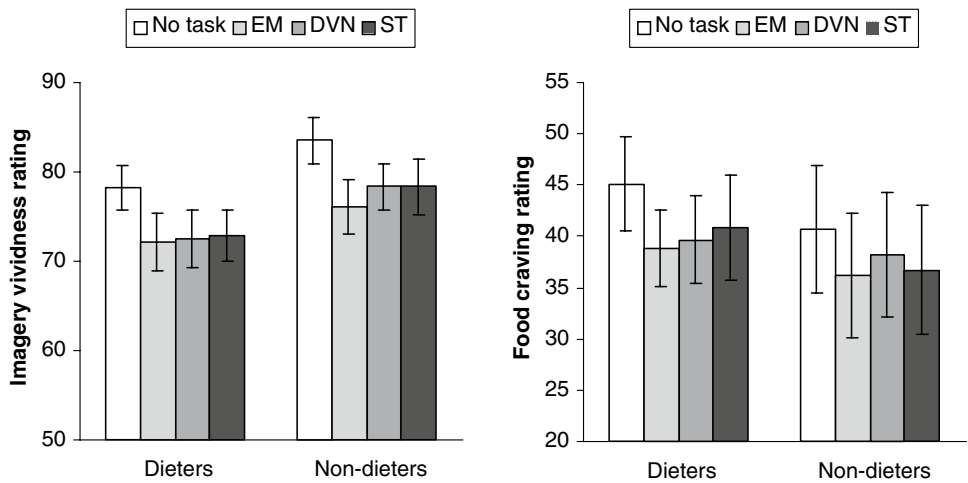
Fig. 81.2 Mean imagery vividness and food craving levels (with standard errors) for dieters and non-dieters in each of the concurrent task conditions. This figure shows that the concurrent visual tasks of eye movements, dynamic visual noise and spatial tapping made food images less vivid and food cravings less intense for both dieters and non-dieters. Imagery vividness and craving were rated on a 100-point scale ranging from "no image at all" to "image perfectly clear and vivid", and from "no desire or urge to eat" to "extremely strong desire or urge to eat", respectively. *EM* eye movements, *DVN* dynamic visual noise, *ST* spatial tapping

we investigated whether engaging in relatively effortless visual activity could reduce food cravings in dieters (via the analogous mechanism of decreasing the vividness of the accompanying images).

In our investigations, dieting and non-dieting female undergraduate students formed and maintained images of commonly craved foods (e.g. chocolate, cake, ice-cream) elicited by pictures or verbal cues, while performing one of the three aforementioned visual tasks: saccadic eye movements, dynamic visual noise or spatial tapping. Participants rated the vividness of their images and the intensity of their food cravings. As predicted, all three tasks made participants' food images less vivid. Importantly, as can be seen in Fig. 81.2, this reduction in imagery vividness was accompanied by a reduction in participants' level of food craving. Dieters and non-dieters showed the same pattern of results. Thus simple, repetitive visual tasks hold promise as a practical technique for controlling food cravings in dieters.
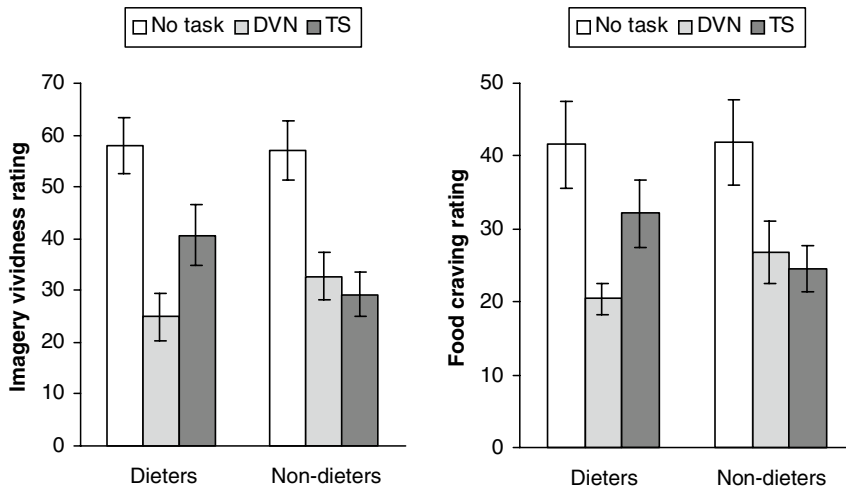
Fig. 81.3 Mean imagery vividness and food craving levels (with standard errors) for dieters and non-dieters in each of the concurrent task conditions. This figure shows that dynamic visual noise was a more effective technique than thought suppression for reducing the vividness of food images and the intensity of food cravings in dieters; however, the techniques were equally effective for non-dieters. Imagery vividness and craving were rated on a 100-point scale ranging from "no image at all" to "image perfectly clear and vivid", and from "no desire or urge to eat" to "extremely strong desire or urge to eat", respectively. DVN = Dynamic visual noise; TS = Thought suppression

In a subsequent study, we (Kemps et al. 2008) examined whether these findings in dieting samples of normal weight university students extended to community samples of overweight people who are actively trying to lose weight. Overweight women following a prescribed weight-loss diet and non-dieting controls formed and maintained images of highly desired foods (e.g. chocolate, chips, pizza) while watching the dynamic visual noise display or suppressing thoughts about food. Both techniques successfully reduced food cravings for dieters as well as non-dieters. However, as shown in Fig. 81.3, their relative effectiveness differed markedly depending on the women's dieting status. While both techniques reduced cravings equally well for non-dieters, dynamic visual noise was clearly the more effective technique for dieters. Thus the utility of visually based tasks for curbing dieting-related food cravings clearly extends to overweight individuals who are trying to lose weight.

81.5 Conclusion

The working memory approach outlined here presents a radically different strategy for reducing dieting-related food cravings, one that is based on the visual imagery nature of food cravings. According to working memory theory, food cravings engage the visuo-spatial sketch pad, and can thus be reduced by loading this component with a concurrent task. Specifically, concurrent visual tasks have their craving reducing effect by diminishing the vividness of desire-related food images held in the limited capacity visuo-spatial sketch pad. Unlike thought suppression and cue exposure response prevention, concurrent visual processing does not focus directly on the craved food. As a result, it is likely to be found less aversive, making it not only an effective but also an attractive technique for reducing dieting-related food cravings.

81.6 Applications to Other Areas of Health and Disease

The next challenge is to see how well these techniques involving concurrent visual activity generalize outside the laboratory, how well they are able to control unwanted and problematic food cravings in clinically overweight and obese individuals, as well as in patients diagnosed with binge eating disorder and bulimia nervosa. These techniques may also have utility beyond the food domain, to cravings for other substances, such as nicotine, caffeine, alcohol and drugs. Deprivation of these substances, like food restriction, can lead to cravings. Such cravings are also imagery based, and involve, primarily, visual images (May et al. 2004; Kemps and Tiggemann 2009). In fact, emerging evidence shows that visual imagery tasks can similarly suppress cigarette cravings in smokers (Versland and Rosenberg 2007) and caffeine cravings in habitual coffee drinkers (Kemps and Tiggemann 2009). Future research could determine whether simple visual tasks, like dynamic visual noise, could also reduce these cravings, as well as cravings for alcohol and other drugs.

More generally, mental imagery has been shown to play a role in the development and maintenance of a variety of psychological disorders, including post-traumatic stress disorder, agoraphobia, body dysmorphic disorder and mood disorders. Imagery-based interventions have been used successfully in the treatment of these psychopathologies (Hackman and Holmes 2004). More recently, Lilley et al. (in press) showed that making simple eye movements while imagining a traumatic event reduced the vividness and emotional impact of distressing, intrusive images in a clinical sample with post-traumatic stress symptoms.

Summary Points

- Dieting to lose weight is associated with a number of negative outcomes, including the experience of unwanted food cravings.
- Although food cravings are a common everyday experience, dieting-related cravings can give rise to a range of negative consequences, such as binge eating, early dropout from weight-loss programs, feelings of guilt and shame and poor cognitive task performance.
- The prevalence of dieting-related cravings is likely to increase, because of increasing rates of obesity and body image concerns, highlighting the need for effective craving reduction techniques.
- The currently available techniques for reducing dieting-related food cravings involving either thought suppression or cue exposure response prevention have not proven very successful.
- Based on converging evidence pointing to mental imagery as a key component of the craving experience, recent findings show that interfering with the cognitive processes that support craving-related images reduces food cravings in weight-loss dieters.
- As food cravings involve images primarily in the visual sensory modality, engaging in a concurrent visual task is most effective in reducing dieting-related cravings.

Definitions and Explanations of Key Terms

Binge eating: The consumption of an excessively large amount of food in a single sitting, accompanied by feelings of lacking control over one's eating.

Cue exposure response prevention: A psychological intervention derived from conditioning models of psychopathology that involves successive exposures to an appetitive target, with instructions to attempt to resist consumption.

Food craving: A strong urge or desire to eat a specific food.

Mental imagery: The mental representation of stimuli that are not physically present.
Preoccupying cognitions: A chronic preoccupation with personally relevant or motivationally salient thoughts.
Thought suppression: A cognitive control strategy whereby an individual avoids thinking about a behaviour in order to prevent performing that behaviour.
Weight-loss dieting: The deliberate restriction of food intake in an attempt to lose weight.
Working memory: A system for the temporary storage of information in the face of ongoing processing.

References

Abramowitz JS, Tolin DF, Street GP Clin Psychol Rev. 2001;21:683–703.

Andrade J, Kavanagh D, Baddeley A Brit J Clin Psychol. 1997;36:209–23.

Baddeley A. Trends Cogn Sci. 2000;4:417–23.

Baddeley AD. Working memory. Oxford: Oxford University Press; 1986.

—Baddeley AD, Hitch GJ In: Bower G, editor. The psychology of learning and motivation. London: Academic; 1974. p. 47–90.

Baddeley AD, Andrade J J Exp Psychol Gen. 2000;129:126–45.

Baker TB, Morse E, Sherman JE In: Rivers PC, editor. The Nebraska symposium on motivation: alcohol use and abuse. Lincoln: University of Nebraska Press; 1986. p. 257–323.

Cash TF, PruzinskyT editors. Body image: a handbook of theory, research and clinical practice. New York: Guilford; 2002.

Conklin CA, Tiffany ST Addiction 2002;97:155–67.

Cornell CE, Rodin J, Weingarten H Physiol Behav. 1989;45:695–704.

Dickens G, Trethowan WH J Psychosom Res. 1971;15:259–68.

Dye L, Warner P, Bancroft J J Affect Disorders. 1995;34:157–64.

Farmer EW, Berman JVF, Fletcher YL Q J Exp Psychol. 1986;38A:675–88.

Fedoroff IC, Polivy J, Herman CP Appetite 2003;41:7–13.

Green MW, Rogers PJ Int J Eat Disorder. 1993;14:515–7.

Green MW, Rogers PJ, Elliman NA Int J Eat Disorder. 2000;27:419–27.

Hackmann A, Holmes EA Memory 2004;12:389–402.

Harnden JL, McNally RJ, Jimerson DC Int J Eat Disorder. 1997;22:285–90.

Harvey K, Kemps E, Tiggemann M Brit J Health Psych. 2005;10:49–56.

Hawks SR, Madanat HN, Merrill RM, Goudy MB, Miyagawa T Health Promot Int. 2003;18:153–62.

Hetherington MM. Food cravings and addiction. Surrey: Leatherhead; 2001.

Hetherington MM, Macdiarmid JI Appetite 1993;21:233–46.

Hill AJ, Weaver CF, Blundell JE Appetite 1991;17:187–97.

Jansen AIn: Hetherington MM, editor. Food cravings and addiction. Surrey: Leatherhead; 2001. p. 549–65.

Johnston L, Bulik CM, Anstiss V Int J Eat Disorder. 1999;26:21–7.

Kavanagh D, Andrade A, May J Psychol Rev. 2005;112:446–7.

Kavanagh DJ, Freese S, Andrade J, May J Brit J Clin Psychol. 2001;40:267–80.

Kelly AE, Khan JH J Pers Soc Psychol. 1994;66:998–1006.

Kemps E, Tiggemann M (2009) Exp. Clin. Psychopharm. 17: 43–50

Kemps E, Tiggemann M, Woods D, Soekov B Int J Eat Disorder. 2004;36:31–40.

Kemps E, Tiggemann M, Christianson R J Behav Ther Exp Psy. 2008;39:177–86.

Lafay L, Thomas F, Mennen L, Charles MA, Eschwege E, Borys J, Basdevant A Int J Eat Disorder. 2001;29:195–204.

Lilley SA, Andrade J, Turpin G, Sabin-Farrell, Holmes E, Brit. J. Clin. Psychol. 2009;48:309–321.

Macdiarmid JI, Hetherington MM Brit J Clin Psychol. 1995;34:129–38.

May J, Andrade J, Panabokke N, Kavanagh D Memory 2004;12:447–61.

Michener W, Rozin P Physiol Behav. 1994;56:419–22.

Mitchell JE, Hatsukami D, Eckert ED, Pyle RL Am J Psychiat. 1985;142:482–5.

Oliver KG, Huon KG Int J Eat Disorder. 2001;30:329–37.

Panabokke N. The role of visual imagery in craving. PhD University of Sheffield; 2004.

Parker S, Kamel N, Zellner D Appetite 2003;40:193–5.

Pelchat ML. Appetite 1997;28:103–13.

Quinn JG, McConnell J Q J Exp Psychol. 1996;49A:200–15.

Richardson JTE. Imagery. Hove: Psychology; 1999.

Salkovskis PM, Reynolds M Behav Res Ther. 1994;32:193–201.

Schlundt DG, Virts KL, Sbrocco T, Pope-Cordle J Addict Behav. 1993;18:67–80.

Sitton SC. Psychol Rep. 1991;69:683–6.

Tiggemann M, Kemps E Appetite 2005;45:305–13.

Versland A, Rosenberg H Addict Res Theory. 2007;15:177–87.

Wadden TA, Brownell KD, Foster GD J Consult Clin Psych. 2002;70:510–25.

Wardle J. Brit J Clin Psychol. 1987;26:47–55.

Weingarten HP, Elston D Appetite 1990;15:231–46.

Weingarten HP, Elston D Appetite 1991;17:167–75.

Chapter 82
Abnormal Physiologic Responses to Touch in Feeding Difficulties

Donna Scarborough

Abbreviations

APIB   Assessment of Preterm Infants' Behavior
NBAS   Neonatal Behavioral Assessment Scale

82.1 Introduction

Development of early feeding skills in full-term infants is complex for a number of reasons:

- An infant undergoes a dramatic transformation during the first year of life in all aspects of development including: neurologic, anatomic, motor, sensory, physiologic, feeding/swallowing skills, communication, cognitive, social–emotional, and play. Each of these areas is interdependent, and, like the pieces of a jigsaw puzzle, can be viewed piece by piece or as a whole (Fig. 82.1).
- The transition of feeding behaviors from primarily physiologic responses to cognitively learned responses, or combinations of both.
- Infants and young children are dependent upon others during the feeding process and express themselves by indirect, nonverbal means. Thus, successful feeding interactions and development are dependent upon appropriate interpretations of behavior.

One aspect of feeding development that reflects this complexity is the ability of an infant to appropriately respond to touch input (Table 82.1). This section will examine early infant development, identify behaviors related to touch processing during the earliest stages of development, and examine long-term feeding complications and clinical applications related to an interruption of these early stages.

82.2 Early Developmental Levels

Since the 1950s, a number of researchers have described the childhood maturation process as proceeding in a sequential manner. Many of the early developmental theories proposed by Piaget (1952), Mahler et al. (1975), Greenspan and Lourie (1981), and Kopp (1982) have historically been important

D. Scarborough (✉)
Department of Speech Pathology and Audiology, Miami University, 26 Bachelor Hall, Oxford, OH 45056, USA
e-mail: scarbod@muohio.edu

Fig. 82.1 The complex puzzle of development. For a child to successfully develop each individual component must cohesively connect
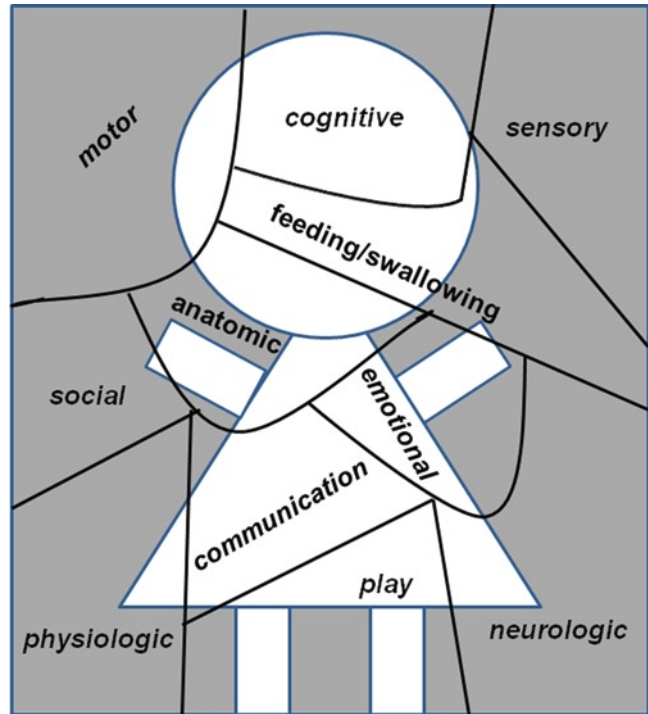
Table 82.1 Key features of touch (Henricson et al. 2008; Pihko and Lauronen 2004; Jean 2001; Hendry et al. 1999)

- Touch or mechanoreception is only one component of the somatosensory system (Fig. 82.2)
- Touch includes perception of pressure, texture, form, and vibration
- Touch receptors are found at varying depths below the skin, and include Pacinian corpuscles, Ruffini corpuscles, Meissner corpuscles, and Merkel cells
- Each type of touch receptor responds differently to varying types of input
- Touch information from the body and limbs is carried to the dorsal root ganglia cells of the spinal cord, through the dorsal column–medial lemniscus pathway to the thalamus. From the thalamus, the information is then carried to the cortex.
- Touch from the face, oral cavity, and pharynx is carried from the trigeminal, glossopharyngeal, and vagus nerves to the thalamus. From the thalamus the information is then carried to the cortex.
- Touch is organized throughout each level with a clearly defined map of the body
- As early as the seventh month of pregnancy, touch pathways are intact enough to produce cortical responses
- The speed of processing and timing of processing improves as mylenation occurs
- Sleep stages impact processing of touch input in newborns
- The touch of firm pressure has a calming effect on the sympathetic nervous system

for classifying feeding behaviors. For the purpose of this section, a compilation and summary of these four theories targeting the first year of development is described utilizing the nomenclature of Greenspan and Lourie (1981) and Kopp (1982) (Fig. 82.3):

- The period of "homeostasis" or "neurophysiologic maturation," is a critical period from birth to 3 months of life when an infant's biological functions stabilize as a result of autonomic nervous system maturation. Examples of stabilizing biologic functions include temperature regulation, respiratory rhythms, sleep–wake cycles, and feeding and excretion patterns. Touch processing during the beginning of this stage involves generalized autonomic system responses, such as startling,
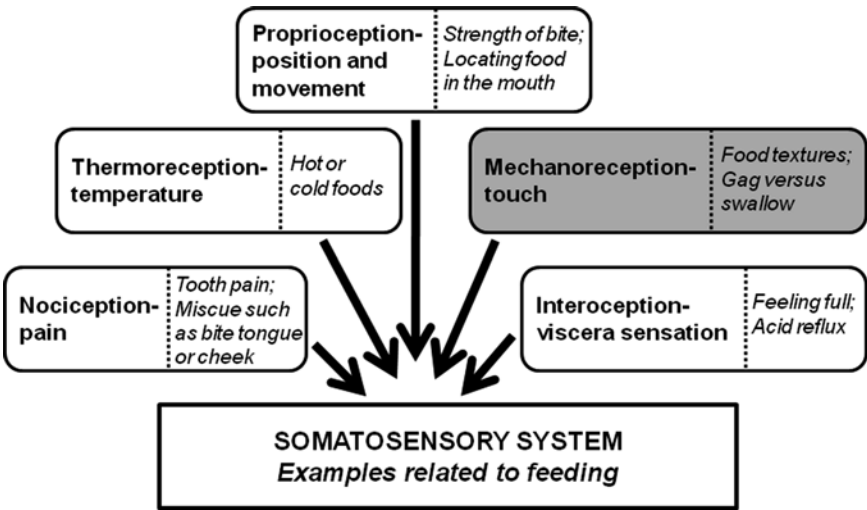
Fig. 82.2 Somatosensory system and feeding. The somatosensory system is very complex and critical for successful feeding. Touch or mechanoreception is only one component of this system and will be the focus of this section
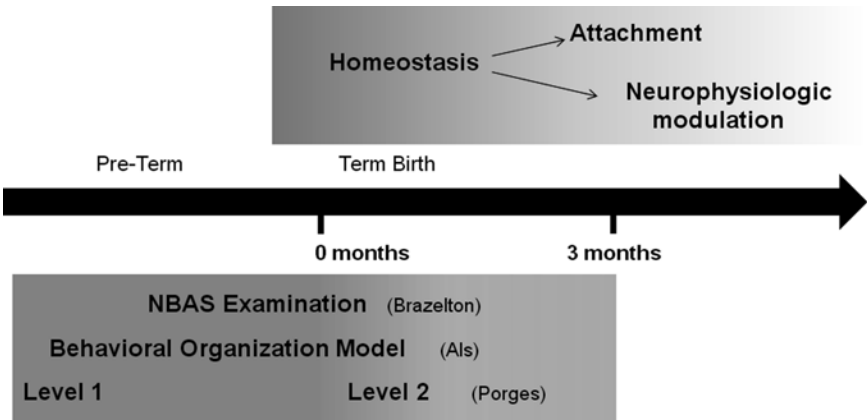
Fig. 82.3 Developmental levels for feeding. Homeostasis is the first developmental level for term infants. In typical development, this stage flows into the concurrent stages of attachment and neurophysiologic modulation. Preterm development is assessed through the NBAS (which highlights state behavior changes) and other models of preterm development

gagging, or state behavior changes. As the child progresses through this period of development touch responses become more appropriate such that an infant begins to differentiate between the soothing touch of being swaddled and the painful touch of a needle (Scarborough et al. 2006).

• The periods of "attachment" and "sensorimotor modulation" follow "homeostasis." During the period of *attachment* infants respond to the outside world, thus beginning the process of forming relationships and differentiating between caregivers. Concurrent with the period of attachment is the period of *sensorimotor modulation*. During this period of development the infant begins to utilize multiple sensory systems (i.e., touch, vision, balance) during interactions in order to modulate motor responses such that movements become voluntary rather than reflexive. An important component of this stage is that children will repeat behaviors or modulate movements without purposeful or conscious reflection. By the end of the first year of life, these periods of development should be complete.

82.3 Understanding Infant Behaviors During the Period of "Homeostasis"

Successful interpretation of infant behavior is one of the greatest challenges for developmental feeding specialists, particularly in very young infants. Although the period of "homeostasis" is considered the first stage of development for full-term infants, we know that development is on a continuum, thus later behaviors are dependent on successful achievement of previous neurologic maturation. Therefore, much of our understanding of behaviors of very young-term infants may be extrapolated from the healthy preterm infant population. In the 1970s, Brazelton published the Neonatal Behavioral Assessment Scale (NBAS) that classified infant behaviors while experiencing periods of stimulation or stress (Brazelton 1973) (Fig. 82.3). As part of this original research, it was postulated that the baby's state of consciousness or *state behavior* was the single most important element of the NBAS examination. State behaviors are seen as reflections of autonomic nervous system maturation, as well as reactions to incoming stimuli (Brazelton and Cramer 1990). Since that time, seven distinct states behaviors have emerged in infants older than 36 weeks gestational age (Brazelton 1984; Prechtl 1987). Furthermore, it is recognized that only in an alert, bright state does the newborn orient to external sources of input and takes in information (Brazelton 1990; Kaufmann-Hayoz 1987).

The "*behavioral organization" model* was proposed in the 1980s (Fig. 82.3). This model separates infant behavior according to distinct but interdependent neurologically based subsystems. Such subsystems included not only state behavior organization, but also autonomic, motor, attention, interaction, self-regulation, and balance systems (Als 1982, 1986; Als et al. 2005). The behavioral organization model also assumes that neurologic maturation will occur with increasing gestational age, which in turn, allows for improved interaction between systems. Although this model has primarily been applied to infants through 42 weeks gestation, we know that the modulation these subsystems continue through the period of homeostasis, which should be complete by 3 months of age (Chatoor et al. 1984; Porges 1996; Greenspan 1990). As a result of the behavioral organization model, an Assessment of Preterm Infants' Behavior (APIB) was developed, which allows clinicians to observe and score unique physiologic behaviors related to disorganization from each of the specific subsystems. Gagging, for example, is considered a sign of autonomic stress, whereas changes in posture and muscle tone are reflective of motoric stress (Als et al. 2005). Understanding which specific subsystems are disorganized allows clinicians and caregivers to provide the appropriate support to assist the infant in regulation.

82.4 Autonomic Homeostasis, Impact on Emotional and Behavioral Development

The *Polyvagal Theory* describes two distinct types of vagal responses that infants may present to stressors: the mammalian system and the reptilian vagal system (Porges et al. 1996). A mammalian response system is considered the optimal means for an infant to maintain physiologic homeostasis in response to stress by means of an increased arousal state. However, if this system is regularly challenged (i.e., medical interventions such as gavage feeding) then the heightened physiologic response pattern could become detrimental to the developing infant. The second type of vagal response has been deemed as the reptilian vagal system. Basically with this type of response pattern to stress, the autonomic nervous system shuts down. Clinical observations of infants who are utilizing reptilian strategies in response to stress can involve potentially lethal bradycardia (slow heart rate) and/or apnea. Therefore, depending upon the vagal system that an

Fig. 82.4 Infant stress responses. Basic representation of the Polyvagal theory, which indicates that two distinct types of vagal response patterns will evoke a heightened or reduced physiologic state

infant uses to respond to stress, either heightened or reduced physiologic states will be observed (Porges 1996, 2009) (Fig. 82.4).

Based on the Polyvagal Theory, a hierarchical model was developed that identified the importance of neural regulation of autonomic homeostasis as a precursor to emotional, cognitive, and behavioral regulation (Porges 1996). At the foundation of this model (Level 1), infants must be able to achieve internal physiologic homeostasis through autonomic regulation between the brainstem and peripheral organs, before attempting to cope with external factors. Once infants are able to successfully regulate single physiologic systems, the infants can then begin to coordinate multiple systems and respond to external challenges (Level II) (Fig. 82.3). Thus, the successful completion of a complex activity (such as feeding), which requires an infant to both negotiate internal homeostasis and with external demands, are dependent on regulation of autonomic system. Further, this model also has provided a means for studying long-term effects of abnormal autonomic nervous system functioning particularly related emotional dysregulation in preschool to adolescence (Beauchaine et al. 2007) Thus, the polyvagal theory has been ground-breaking for providing a means to identify autonomic nervous system regulation as an integral part of healthy cognitive, emotional, and behavioral development and for showing that difficulties with physiologic homeostasis can persist well beyond the first year of life.

82.5 Touch and Feeding and Interruption of the Period of "Homeostasis"

The behavioral response pattern of neonates and full-term infants younger than 3 months of age includes a variety of autonomic nervous system responses. For example, it is not uncommon to observe gagging and/or "state" behavior changes (such as uncontrolled crying, fussiness, drowsiness, or falling asleep) in young infants while processing touch input. Touch input refers both to touch to the body such as general physical handling and/or oral touch associated with feeding. Over time as the infant develops beyond the period of "homeostasis" (3 months of life) these autonomic nervous system
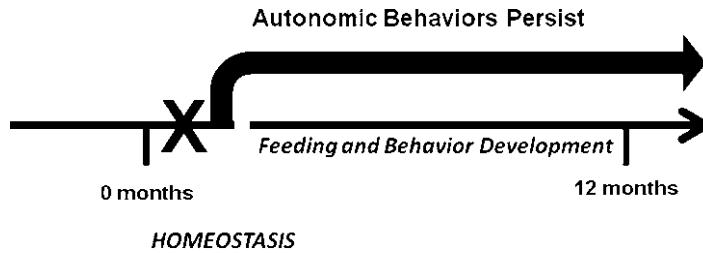
Fig. 82.5 Interrupting homeostasis. If normal development is interrupted at any point during the period of homeostasis (including the preterm period) then aberrant autonomic behaviors during feeding may persist well beyond the first year of life

responses become less generalized and more appropriate to environmental situations. For instance, gagging is a normal protective reflex when elicited by touch to the posterior oral regions; however, gagging to anterior oral touch or touch to more peripheral areas of the body is seen as a sign of immature physiological (autonomic) processing. Thus, in typical infants older than 3 months of age autonomic nervous system responses to touch are unusual (Scarborough et al. 2002, 2006).

Full-term infants and children who have had an interruption of oral feeding during at least 2 weeks during the period of "homeostasis" (first 3 months of life) have been found to respond to graded tactile input with signs of poor autonomic regulation (such as gagging and major state changes) (Fig. 82.5). In particular, these aberrant autonomic responses have been documented from touch to both nonoral body regions (i.e., shoulders) and to regions in the anterior portion of the mouth and are not evident in age matched healthy peers. Further, these aberrant autonomic behaviors have been observed in children as old as 18 months of age and tend to persist even with behavioral intervention (Scarborough et al. 2006).

82.6 Clinical Application

Like many areas of pediatrics, one of the challenges for the professional is making clinical judgments based on observed behaviors that could be the result of more than one etiology. As an example, a "hypersensitive" gag reflex is a regularly observed behavior within the pediatric feeding population (Fig. 82.6). A *hypersensitive gag reflex* will be defined for the purpose of this section as triggering a gag reflex from nonoral regions of the body or within the anterior 2/3 of the oral cavity regardless of the strength of the motor response (Scarborough et al. 2008). In the case of a hypersensitive gag reflex, obtaining the child's past medical history is a critical component to determining the cause of the behavior. For instance, a hypersensitive gag reflex observed in premature and full-term medically fragile infants who have a history of tube feedings during the period of homeostasis is likely the result of abnormal autonomic nervous system development (Scarborough and Isaacson 2006; Scarborough et al. 2006). In contrast, children who have a history of traumatic brain injury, specifically involving bilateral corticobulbar tracts demonstrate a "hypersensitive" gag reflex due to the loss of upper motor neuron inhibition (Schulze-Delrieu and Miller 1997). In other children, a hypersensitive gag reflex has been reported as a result of maladaptive parent–child interactions through conditioned negative responses (Byars et al. 2003). Therefore, when a hypersensitive gag reflex is observed during a feeding trial, it is critical that the clinician not assume an underlying cause of this behavior regardless of the age of the child without a complete medical history. Once the cause(s) of the hypersensitive gag reflex is found, then a targeted treatment plan can be developed
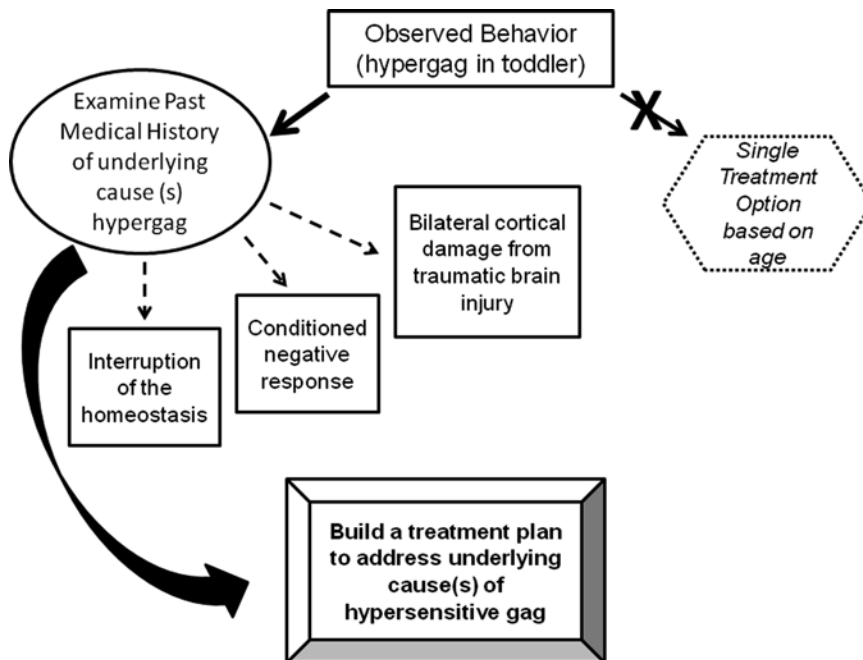
Fig. 82.6 Clinical decision flow chart. Clinical decisions for treatment need to look beyond age-related behaviors. This is to ensure that the underlying cause of a behavior is addressed

that appropriately remediates or offsets this negative feeding behavior. Further, if a single treatment technique is not effective for correcting the behavior, other treatments should be explored that target different levels of development.

Summary Points

The period of "homeostasis" is critical for modulation of touch responses through the autonomic nervous system.

- Normal early infant behaviors (under 3 months of age) related to general physical handling or oral touch during feeding may involve state behavior changes or gagging. These autonomic responses modulate to more appropriate behavioral patterns during the first 3 months of life in healthy infants.
- Developmental theories of preterm infants can provide valuable information regarding full-term infant behavior.
- Interruption of normal oral tactile input (i.e., tube feedings) in full-term infants during the period of homeostasis and earlier can lead to abnormal processing of touch and persistent behaviors such as gagging and extreme state behavior changes.
- Behaviors related to autonomic regulation can persist well past the first year of life.
- The same negative feeding behavior observed in older children may be the result of more than one cause acquired during early childhood. Therefore, assessment of feeding behaviors, such as the hypersensitive gag reflex, should include a comprehensive past medical history of the child.
- Treatment techniques should be geared to remediate the underlying cause(s) of an observed feeding behavior.

Explanation of Key Terms

Homeostasis: A critical developmental period of neurophysiologic modulation from birth to approximately 3 months of life when an infant's biological functions stabilize as a result of autonomic nervous system maturation.

Attachment: The developmental period following homeostasis when infants respond to the outside world, thus beginning the process of forming relationships and differentiating between caregivers.

Neurophysiologic modulation: The period of development that is concurrent with attachment when an infant begins to utilize multiple sensory systems to modulate motor responses such that movements become voluntary rather than reflexive without purposeful or conscious reflection.

Polyvagal theory: Proposes that successful adaptation of mammals is dependent on systematic and reliable withdrawal and reengagement of the vagus nerve as a mechanism to respond to environmental demands (Porges et al. 1996). This theory describes two distinct types of vagal responses that infants may present to stressors, the mammalian system and the reptilian vagal system. For a detailed review of this theory, see Porges 1996 and Porges et al. 1996.

Behavioral organization model: Separates infant behavior according to distinct but interdependent neurologically based subsystems. Such subsystems included not only state behavior organization, but also autonomic, motor, attention, interaction, self-regulation, and balance systems. The behavioral organization model also assumes that neurologic maturation will occur with increasing gestational age, which in turn, allows for improved interaction between systems. For a detailed review, see Als 1982, 1986; and Als et al. 2005.

State behaviors: Different levels of infant alertness that are considered as reflections of autonomic nervous system maturation, as well as reactions to incoming stimuli. For a detailed review of state behaviors, see Brazelton 1973, 1984.

Hypersensitive gag reflex: Triggering a gag reflex from nonoral regions of the body or within the anterior 2/3 of the oral cavity regardless of the strength of the motor response.

References

Als H. Inf Mental Health J. 1982;3:229–43.

Als H. Phys Occup Ther Pediatr. 1986;6:3–55.

Als H, Butler S, Kosta S, McAnulty G. Ment Retard Dev D R. 2005;11:94–102.

Beauchaine TP, Gatzke-Kopp L, Mead HK. Biol Psychol. 2007;74:174–84.

Brazelton TB. Clin Dev Med. 1973;50:1–66.

Brazelton TB. Clinics in developmental medicine. Philadelphia: J.B. Lippencott; 1984.

Brazelton TB. Child Dev. 1990;61:1661–71.

Brazelton TB, Cramer BG. The earliest relationship: parents, infants, and the drama of early attachement. Reading: Addison-Wesley; 1990.

Byars KC, Burklow KA, Ferguson K, OFlaherty T, Santoro K, Kaul A. J Pediatr Gastr Nutr. 2003;37:473–80.

Chatoor I, Schaefer S, Dickson L, Egan J. Pediatr Ann. 1984;13:829–43.

Greenspan SI. In: Shonkoff M, editor. Handbook of early childhood intervention. New York: University Press; 1990. pp. 150–72.

Greenspan SI, Lourie RS. Am J Psychiat. 1981;138:725–35.

Hendry SHC, Hsiao SS, Bushnell MC. In: Zigmond MJ, Bloom FE, Landis SC, Roberts JL, Squire LR, editors. Fundamental neuroscience. San Diego: Academic; 1999. pp. 761–89.

Henricson M, Berglund A-L, Maatta S, Ekman R, Segesten K. J Clin Nurs. 2008;17:2624–33.

Jean A. Physiol Rev. 2001;81:929–69.

Kaufmann-Hayoz R. In: GEV Stelmach PA, editor. Advances in psychobiology: psychobiology and early development. North-Holland: Elsevier Science; 1987. pp. 117–27.

Kopp CB. Dev Psychobiol. 1982;18:199–214.

Mahler M, Pine F, Bergman A. The psychological birth of the human infant. New York: Basic Book; 1975.

Piaget J. The origins of intelligence in children. New York: International Universities Press; 1952.

Pihko E, Lauronen L. Exp Neurol. 2004;190:S2–S7.

Porges SW. Dev Psychopathol. 1996;8:43–58.

Porges SW. Clev Clin J Med. 2009;76:S86–S90.

Porges SW, Doussard-Roosevelt JA, Portales AL, Greenspan SI. Dev Psychobiol. 1996;29:697–712.

Prechtl H. In: HS Rauh HC, editor. Psychobiology and early development. North-Holland: Elsevier Science; 1987. pp. 231–8.

Scarborough DR. Consequences of interrupting normal neurophysiologic development: Impact on prefeeding skills. (Dissertation) University of Cincinnati; 2002.

Scarborough DR, Boyce S, McCain G, Oppenheimer S, August A, Strinjas J. Dev Med Child Neurol. 2006;48:460–4.

Scarborough DR, Isaacson LG. Clin Anat. 2006;19:640–4.

Scarborough DR, Bailey-Van Kuren M, Hughes M. J Am Dent Assoc. 2008;139:1365–72.

Schulze-Delrieu K, Miller RM. In: Perlman AL, Schulze-Delrieu K, editors. Deglutition and its disorders. San Diego: Singular; 1997. pp. 144–5.

Chapter 83
Gut Peptides and Enteral Feeding in Critically Ill Patients: Implications for Gastric Dysmotility and Appetite

N.Q. Nguyen and R.H. Holloway

Abbreviations

ICU   Intensive care unit
CCK   Cholecystokinin
PYY   Peptide YY
GLP-1 Glucagons-like peptide 1
IPPW   Isolated pyloric pressure wave
MMC   Migrating motor complex
IL   Interleukin

83.1 Introduction

Nutritional deprivation or malnutrition in critically ill patients have been shown to be associated with impairment of immunological function, prolongation of mechanical ventilation, increased length of intensive care unit (ICU) and hospital stay, increased infective complications, and ultimately higher mortality (Harrington 2004). Although the practice of nutritional support by either enteral or parenteral routes has now become standard treatment, for many years it was frequently either not provided routinely (Berger et al. 1997) or inadequately delivered to meet metabolic requirements (Heyland et al. 1995, 2003). Previously, the incidence of malnutrition amongst long-stay critically ill patients has been as high as 50% (Quirk 2000). Currently, enteral nutrition is the preferred mode of nutritional delivery in critically ill patients due to the ease of administration, reduced health-care costs, lower rate of sepsis, lack of requirement for central venous access, and enhancement of gastrointestinal barrier function with the potential reduction in bacterial translocation (Heyland et al. 1998, 2003).

Adequate delivery of enteral feeds to critically ill patients, however, is frequently hampered by a variety of factors; the most frequent is gastric dysmotility. A number of factors including mechanical ventilation, drugs (especially opiates and catecholamines), hyperglycemia, shock, circulating inflammatory cytokines, and the admission diagnosis have been implicated in the etiology of slow gastric emptying in critically ill patients. However, the majority of these factors were inferred from studies

N.Q. Nguyen (✉)
Department of Gastroenterology and Hepatology, Royal Adelaide Hospital, North Terrace, Adelaide, SA, 5000, Australia
e-mail: quoc.nguyen@health.sa.gov.au

performed in either animals (Dubois et al. 1975) or a non-critically ill population (Yuan et al. 1998). More recently, there is evidence to suggest that gastric dysmotility of critical illness may relate to disturbance of the complex interaction between enteral nutrition and gastrointestinal hormones that involved in the enterogastric feedback regulation. The aim of this chapter is to review the gastrointestinal motor and hormonal responses to enteral nutrition in critically ill patients, and how the complex interactions between these factors can potentially give insights into the pathogenesis of impaired gastric motor function in this population.

83.2 The Role of Enteral Nutrition in Critically Ill Patients

The impact of nutritional support on patients' outcomes has been examined extensively over last two decades. While many studies have documented that nutritional support changes metabolic outcomes, such as amino acid profile and nitrogen balance, the impact of this intervention on clinically important end points such as infection, length of stay, and mortality is less clear-cut. There are a number of methodological reasons that might explain the discrepancies among the reported studies. First, over 60% of trials that have examined this issue lacked sufficient statistical power (Heyland 1998; Heyland et al. 2003; Doig et al. 2005). This is further confounded by the heterogeneity of the critically ill population and differences in the mix of patients between the studies (Doig et al. 2005). In addition, the quality of many trials was suboptimal with a lack of randomization, controls, and blinding (Doig et al. 2005). Meta-analyses that have examined only high-quality randomized–controlled (level 2) trials suggest that, compared with patients who received standard care (i.e., IV fluid support only), nutritional support via either the enteral or parenteral route is associated with a 5–12% reduction in mortality (Heyland et al. 1995, 2003; Doig and Simpson 2005). In surgical and multitrauma patients, nutritional support improves wound healing, decreases the catabolic response to injury, and reduces infective complications (Kudsk et al. 1992; Heyland 1998; Heyland et al. 1998, 2003). Similar reductions in septic complications and a shorter length of stay in ICU and hospital have also been demonstrated in medical critically ill patients (Heyland et al. 1995, 2003; Doig and Simpson 2005).

The optimal time to start nutritional support in critical illness, however, is unknown. It is recognized that patients should not be deprived of nutrients for more than 5 days as earlier studies have demonstrated a higher mortality in surgical patients who had been deprived of nutrition for longer than this (Thomas and Robert 1979). In animals, nutrient deprivation for durations as short as 24 h may lead to intestinal mucosal atrophy and malabsorption (Alpers 2002). These abnormalities can be reversed or prevented by the early introduction of luminal nutrients (Alpers 2002). In a more recent randomized–controlled study, patients with nutrient deprivation for a mean duration of 4 days had a significant reduction in the villous height and crypt ratio and an increased gut permeability as assessed by the lactulose–mannitol test (Hernandez et al. 1999), compared those who received enteral feed within 24 h of admission.

Until recently, the concept of early aggressive feeding was not universally accepted by many critical care staff. Despite recognizing the importance of early feeding, a number of nutritional surveys in intensive care units have reported that less than 50% of eligible patients received enteral nutrition within 48 h of admission (McClave et al. 1999; Montejo 1999; Heyland et al. 2003), placing these patients at risk of intestinal mucosal atrophy, increase gut permeability, and malnutrition (Alpers 2002). As the integrity of the gastrointestinal tract is thought to be important for the prevention of bacterial translocation and subsequent infective complications (Alpers 2002), these findings suggest that delayed enteral nutrition may increase the risk of sepsis.

The impact of early enteral nutrition on outcomes in critically ill patients has been investigated in a number of randomized controlled trials (Minard et al. 2000; Artinian et al. 2006). These have produced conflicting results possibly due to a lack of adequate statistical power. A meta-analysis using

these data has also given an inconclusive answer with only a trend toward a reduction in infective complications and mortality, and no difference in length of stay (Heyland et al. 2003). Most recently, Artinian et al. (2006) conducted a large study that included 4,049 medical critically ill patients. This study showed that early enteral nutrition was associated with a 20% reduction in ICU mortality and a 25% reduction in hospital mortality. The benefit to mortality was most pronounced among patients with the highest Acute Physiology and Chronic Health Evaluation II (APACHE II) scores (Artinian et al. 2006), although a higher incidence of ventilated associated pneumonia was reported in patients who had received early feeding. The reason for this finding is unclear but may relate to the more prolonged exposure to nasogastric feeds, a known risk factor for gastroesophageal reflux and aspiration (Montejo 1999; Mentec et al. 2001). Based on current evidence, a number of international working committees have published guidelines for nutritional support in critically ill patients (Heyland et al. 2003; Doig and Simpson 2005). Of these, the Canadian Clinical Practice guideline is best known and has been most widely adopted (Heyland et al. 2003). Although there are minor variations among these guidelines, common themes include (Heyland et al. 2003):

- Nutritional support, either in the form of total parenteral nutrition or enteral nutrition, should be considered in all patients who are admitted to critical care.
- Enteral nutrition is the preferred modality of nutritional support in critically ill patients, particularly in those with intact gastrointestinal tract.
- In patients whom enteral nutrition is indicated, it should be commenced within 24–48 h of admission.

83.3 Regulation of Gastric Emptying and Enterogastric Feedback in Health

In order to appreciate the potential significances of gastric dysmotility and hormonal abnormalities in response to enteral nutrition in critically ill patients, an understanding of gastric emptying regulation in health, especially those related to "enterogastric" feedback mechanisms, is required. After ingestion of a meal, the rate of gastric emptying is tightly regulated by the presence of intraluminal nutrients in the duodenum and small intestine, a process known as the enterogastric reflex (Lin et al. 1989). This feedback response is important in preventing excessive dumping of gastric contents into the small intestine and allows nutrients to enter the small intestine at a rate of 2–3 kcal/min (Lin et al. 1989).

83.3.1 Gastric Motor Responses of Enterogastric Feedback

After ingestion of nutrients, the proximal stomach relaxes and acts as a reservoir. Subsequently, the fundus undergoes slow sustained contractions to distribute contents distally and is believed to have a major role in controlling emptying of liquids (Kelly 1980). In contrast, motor activity in the distal stomach is characterized by irregular contractions, which aid mixing and propagation of nutrient along the gastrointestinal tract. Mixing is due to intermittent isolated antral waves contracting against a closed pylorus. Gastric emptying of nutrient occurs predominantly in a pulsatile fashion when peristaltic wave activity continues through an open pylorus, aiding movement of contents into the duodenum (White et al. 1981). The peristaltic wave is dependent on the integration of motor activity in the proximal and distal stomach, as well as in the proximal small intestine (Horowitz et al. 1994). The rate of transpyloric flow is tightly regulated by the "enterogastric" feedback (Brener et al. 1983), whereby duodenal nutrient triggers a neurohumoral response that reduces antral waves, increases basal pyloric pressure and increases frequency of isolated pyloric pressure waves (IPPWs).

83.3.2 Humoral Response of Enterogastric Feedback

A large number of hormones, including cholecystokinin (CCK), peptide YY (PYY), motilin, GLP-1, and ghrelin, are involved in the "humoral" regulation of the enterogastric feedback responses (King et al. 1985; Horowitz et al. 1994). Of these, CCK and PYY are the best studied. The best-characterized CCK in humans is cholecystokinin-octapeptide (CCK-8) (Liddle et al. 1986). This peptide hormone is secreted by cells in the duodenum and upper jejunum in response to duodenal acid and nutrients, particularly lipids and proteins (Liddle et al. 1986). In humans, exogenous CCK-8 infusions that mimic plasma concentrations in the postprandial range induce significant fundic relaxation (Straathof et al. 1998), inhibit antral motility, increase basal pyloric pressure, and stimulate IPPWs (Fraser et al. 1993). These responses are abolished by coadministration of a CCK antagonist, loxiglumide (Mesquita et al. 1997). The effects of CCK on gastric emptying in humans are, however, conflicting. Although intravenous administration of both exogenous CCK-8 and CCK-3 at physiological concentrations is associated with a decrease in gastric emptying of both liquid and semisolid meals (Moran and McHugh 1982; Liddle et al. 1986), data on the impact of specific CCK antagonists on gastric emptying in humans remain controversial, which may be related to the different formulation of the CCK antagonists used among the studies. All studies that have used the intravenous form of the specific CCK antagonists, loxiglumide and lintitript, have reported an accelerated gastric emptying of both liquid and solid meal, as well as nutrient and nonnutrient meal (Fried et al. 1991; Kreiss et al. 1998). On the other hand, the two studies that used the orally administered CCK antagonists, such as MK-320 and loxiglumide, have failed to demonstrate a change in the gastric emptying rate of either solid or liquid meals, despite a positive effect on gallbladder motility (Liddle et al. 1989; Corazziari et al. 1990).

Peptide YY, also known as the "ileal-brake" hormone that regulates both gastric emptying and intestinal transit, is secreted by the endocrine L cells of the small and large bowel (Adrian et al. 1985). After an intraduodenal meal, plasma PYY increases even before nutrients reach the PYY-containing cells in the ileum, suggesting that PYY release is neurally mediated, probably via the vagus (Greeley et al. 1989). In humans, PYY 3-36 has been consistently reported to inhibit gastric emptying of liquids in a dose-dependent manner (Pironi et al. 1993). In contrast, there are limited data regarding the effects of PYY antagonists on gastric emptying in humans. Unlike CCK, the motor mechanisms underlying the slowing of gastric emptying of PYY 3-36 are less well studied. The impact of PYY on proximal gastric motor activity has not been examined. In humans, elevated fasting PYY concentrations are associated with less frequent phase 3 activity of the MMC arising from the antroduodenal region (Naslund et al. 1998), a reduction in the frequency of antroduodenal contractions (Ledeboer et al. 1999) and an increase in IPPW (MacIntosh et al. 1999). Currently, there are no studies that have examined the impact of PYY antibody on gastric motility in humans.

83.4 Upper Gastrointestinal Motility During Critical Illness

Disturbances in gastrointestinal motor activity occur in up to 70% of the critically ill patients who require mechanical ventilation (Heyland et al. 1996; Kao et al. 1998; Ritz et al. 2001; Nguyen et al. 2007b, d, 2008a, b). Delayed gastric emptying occurs in 40–80% of patients, and the prevalence depends on factors such as admission diagnosis as well as the techniques used to assess gastric emptying (Heyland et al. 1996; Kao et al. 1998; Ritz et al. 2001; Nguyen et al. 2007d, 2008a). Using gastric scintigraphy, up to 80% of critically ill patients admitted with head injury have slow gastric emptying (Kao et al. 1998; Nguyen et al. 2008a). In contrast, delayed gastric emptying occurs in only 40–60% of patients in unselected cohort, when assessed by either the paracetamol absorption test or ^{13}C-octanoic

Table 83.1 Gastric motor abnormalities reported during critical illness

Region of stomach	Gastric motor abnormalities
Proximal stomach	• Delayed and prolonged fundal relaxation
	• Reduced fundic volume waves
	• Greater proximal meal retention
Distal stomach	• Persistent MMC during feeding
	• Reduction in antral contractions and antral motility index
	• Increased isolated pyloric contractions and pyloric tone
	• Inverse correlation between pyloric motor activity and gastric emptying
Integration between gastric regions	• Lack of fundoantral motor association
	• Antral contractions frequently occur in close association with pyloric contractions
Duodenum	• Disorganized duodenal contractions
	• Increased number of retrograded duodenal contractions
Enterogastric feedback responses	• Increased fasting plasma CCK and PYY levels
	• Increased nutrient-stimulated plasma CCK and PYY levels
	• Plasma CCK and PPY inversely correlated with rate of gastric emptying

acid breath test (Heyland et al. 1996; Tarling et al. 1997; Ritz et al. 2001; Nguyen et al. 2007d, 2008b). Delayed gastric emptying of critical illness is associated with impaired motor function in all regions of the stomach during both fasting and fed state (Dive et al. 1994; Chapman et al. 2005; Nguyen et al. 2006a, 2007a, 2008c; Chapman et al. 2008) (Table 83.1). Clinical indicators of upper gut dysmotility include high gastric residual volumes (GRV), vomiting, reflux, and aspiration (Montejo 1999).

83.4.1 Fasted State

During fasting, the gastric phase of the migrating motor complex (MMC) in the antroduodenal region is significantly shorter in mechanically ventilated, critically ill patients than in controls (32 vs. 101 min) (Bosscha et al. 1998). In part, this appears to be related to a virtual absence of phase 2 of the MMC and a marked reduction in antral pressure waves (Dive et al. 1994; Bosscha et al. 1998; Chapman et al. 2005), whereas the lengths of phase 1 and 3 do not differ significantly from those of healthy volunteers (Bosscha et al. 1998). Although proximal gastric volume, pyloric tone, and the frequency of IPPWs are similar between critically ill patients and healthy subjects, the frequency of fundic volume waves is significantly lower in critically ill patients (Dive et al. 1994; Chapman et al. 2005; Nguyen et al. 2006a, 2007a).

83.4.2 Intragastric Nutrient Stimulation

During intragastric feeding, there is persistence of the gastric and small intestinal interdigestive pattern but less than 10% of the phase 3 activity fronts of MMC originate in the stomach (Bosscha et al. 1998). In a small observational study, a persistent fasting pattern was observed in one half of the patients and a mixed pattern of fasting and postprandial motility was seen in the other half (Bosscha et al. 1998). The number of antral pressure waves (Dive et al. 1994; Chapman et al. 2005) and the antral motility index (Bosscha et al. 1998) are also markedly reduced in critically ill patients during gastric meal, and there is a negative correlation between the antral motility index and gastric retention during gastric feeds (Bosscha et al. 1998).

83.4.3 Intraduodenal Nutrient Stimulation

More marked gastrointestinal motor abnormalities are observed during direct small intestinal feeding (Chapman et al. 2005). Relaxation of the proximal stomach is delayed although the magnitude of the relaxation is normal. Fundic slow wave activity is reduced and the recovery of proximal gastric volume to prestimulation levels is delayed. Antral motility is also reduced (Chapman et al. 2005) and is associated with an increase in isolated pyloric activity (Chapman et al. 2005). There is an inverse correlation between pyloric motor activity and gastric emptying (Chapman et al. 2005), suggesting that the increase in localized pyloric motor activity may contribute to the slowing of gastric emptying in critical illness. More importantly, these adverse motor changes are still observed in the critically ill patients even when the infusion rate is as low as 1 kcal/min, which does not alter distal gastric motor activity in healthy subjects (Chapman et al. 2005). These findings suggest that the gastrointestinal tract of critically ill patients responds to small intestinal nutrients differently from normal and the sensitivity of enterogastric feedback response to small intestinal nutrients in critical illness is enhanced.

83.4.4 Antrofundic Motor Integration

In addition to the generalized gastric dysmotilities, the association between the two gastric regions (i.e., antrofundic motor integration) has been shown recently to be disturbed. Antral contractions frequently occur in close association with pyloric contractions, particularly during infusion of a high nutrient load (2 kcal/min) (Nguyen et al. 2008c). Given the importance of this gastric regional association to the redistribution of proximal gastric content distally, the disruption to this antrofundic integration is likely to provide an explanation for the significantly greater meal retention in the proximal stomach in these patients (Nguyen et al. 2008a), especially in those with delayed gastric emptying.

83.4.5 Duodenal Motility

Although duodenal activity usually persists, the organization of the waves is abnormal with an increased proportion of retrograde contractions (Chapman et al. 2008). This has been reported to be associated with impaired transpyloric flow and slowing of gastric emptying (White et al. 1981). Disruption of the organization of duodenal contractions may also contribute to duodenogastric reflux and thereby, bile-induced esophagitis (Dive et al. 1999), which is common in these patients.

83.5 Hormonal Responses to Enteral Nutrition in Critically Ill Patients

Given the known abnormalities of gastric motor activity and enterogastric feedback responses in critically ill patients, it is not surprising that the gastrointestinal hormonal responses that regulate gastric motility through the enterogastric feedback mechanisms are also significantly disturbed (Nguyen et al. 2006b, 2007c, 2008b). Compared to healthy volunteers, both fasting and duodenal nutrient-stimulated plasma CCK and PYY concentrations are significantly elevated (Fig. 83.1) (Nguyen et al. 2006b, 2007c, 2008b). More importantly, plasma concentrations of CCK and PYY are greatest in patients with delayed gastric emptying (Fig. 83.2) and who do not tolerate enteral feeding (Fig. 83.3),

Fig. 83.1 Plasma CKK (**a**) and PYY (**b**) concentrations during fasting and 60 min after duodenal nutrient infusion at 1 and 2 kcal/min in healthy subjects (□) and critically ill patients (■). *$P < 0.05$, and **$P < 0.001$, vs. healthy subjects (Data adapted from Nguyen et al. 2006b, 2007c)
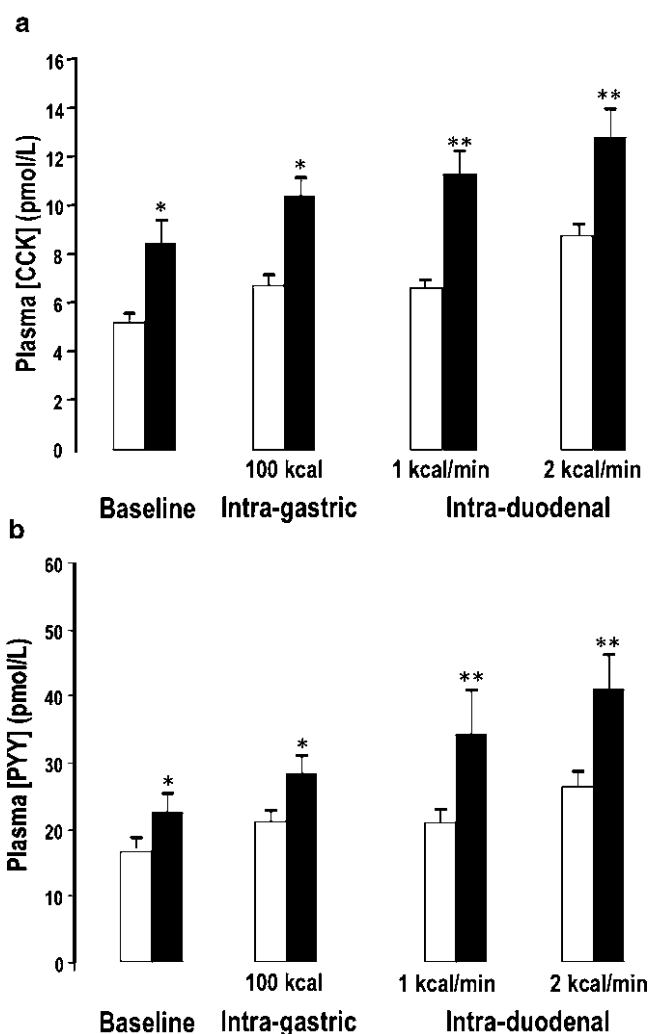
a clinical manifestation of slow gastric emptying (Nguyen et al. 2006b, 2007c, 2008b). As observed in healthy subjects (Nguyen et al. 2006b, 2008b), the elevation of plasma PYY concentration is observed within 20 min of nutrient stimulation in critically ill patients (Nguyen et al. 2006b), suggesting that the elevated PYY concentrations are most probably mediated by factors in the proximal small intestine rather than direct nutrient stimulation of the distal ileum (Adrian et al. 1985). CCK is likely to be an important "proximal" mediator given its known stimulatory effect on the release of PYY in the small intestine (Lin et al. 2000) and a positive correlation between the hormones have been demonstrated in these patients (Fig. 83.4) (Nguyen et al. 2006b, 2008b). More importantly, the elevated fasting plasma PYY concentrations in these patients during the first week of admission have been shown to normalize 3 weeks after discharge from the ICU (Nematy et al. 2005).

Preliminary data also suggest that plasma concentration of ghrelin, an enterogastrone that stimulates gastric motility and increases gastric emptying (Murray et al. 2005), is also disturbed in these patients with a reduced fasting level during critical illness and returned to normal level as the patient recovers from their illness (Nematy et al. 2005).
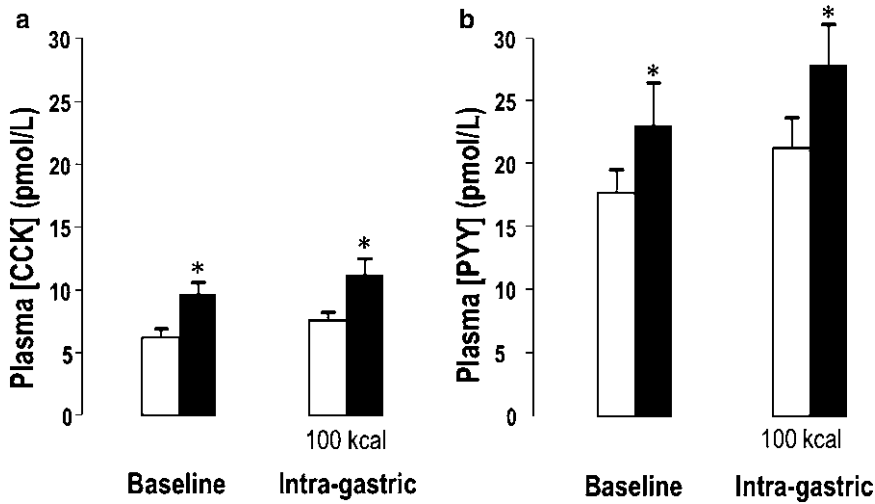
Fig. 83.2 Plasma concentrations of CCK (**a**) and PYY (**b**) during fasting and 120 min after an intragastric feed (100 kcal) in critically ill patients with normal (□) and delayed (■) gastric emptying (GE). *$P < 0.05$, vs. patients with normal GE (Data adapted from Nguyen 2008b)
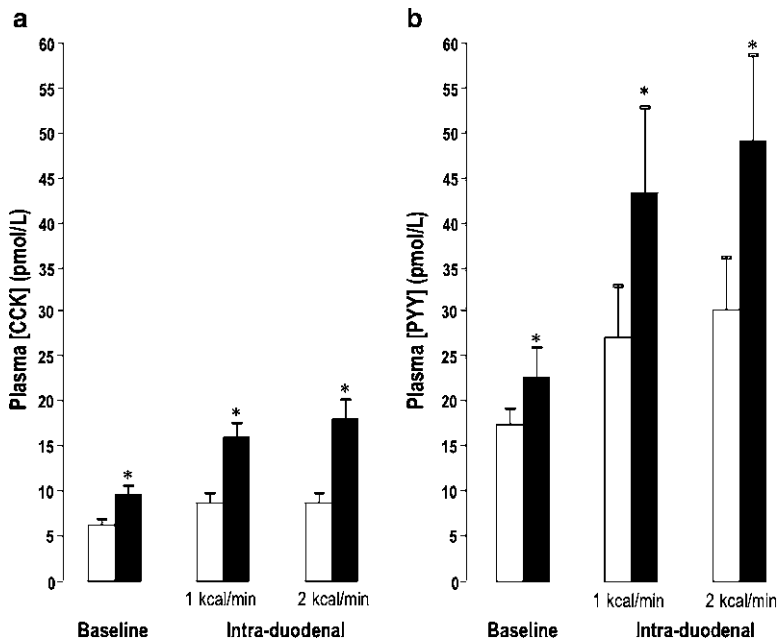
Fig. 83.3 Plasma CCK (**a**) and PYY (**b**) concentrations 60 min after intraduodenal nutrient infusions, at rate of 1 and 2 kcal/min, in critically ill patients who tolerated (□) and did not tolerate (■) enteral feeding. *$P < 0.01$ vs. feed tolerance (Data adapted from Nguyen et al. 2006b, 2007c)

The mechanisms responsible for the abnormally high plasma CCK and PYY concentrations during fasting and in response to small intestinal nutrient infusion in critically ill patients remain unclear. Recent data suggest that the presence of inflammation may have a role in the regulation of entero-endocrine cells in the small intestine (McDermott et al. 2006). In a mouse model, upper gut inflammation has been reported to increase plasma CCK concentrations and reduce energy intake, via an
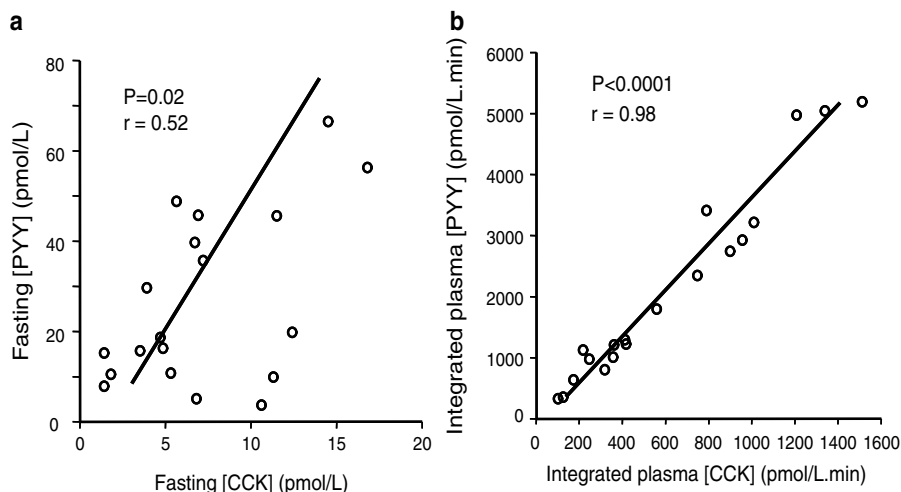
Fig. 83.4 Relationship between plasma PYY and CCK concentrations in critically ill patients during (**a**) fasting and (**b**) duodenal nutrient stimulation (expressed as integrated plasma levels (AUC $_{(0-180min)}$, pmol/L min)) (Data adapted from Nguyen et al. 2006b)

effect on CD_4 T-lymphocytes, and the related inflammatory cytokines (IL-3 and IL-4), can upregulate CCK-expressing cells (McDermott et al. 2006). Systemic inflammation with elevated inflammatory cytokines is common in critically ill patients (Souba 1994) and this could result in increased CCK responses to intestinal nutrients in these patients. Although nutritional deprivation has been shown to be associated with slow gastric emptying and elevated plasma CCK concentrations in non-critically ill subjects (Corvilain et al. 1995), these effects have not been observed in critically ill patients who had enteral nutritional delayed for the first 4 days of admission as compared to those who had been fed within 24 h of admission (Nguyen et al. 2008b).

Common factors in critical illness such as mechanical ventilation, and drugs like sedatives, and inotropic therapy may also contribute, at least in part, to the abnormal PYY and CCK responses. Apart from inducing splanchnic hypoperfusion, mechanical ventilation with high-end inspiratory pressure may also increase pulmonary and systemic cytokine release (Mutlu et al. 2001), with a secondary effect on small intestinal enteroendocrine cell function (McDermott et al. 2006). There is a trend for plasma PYY concentrations to be higher in patients who received inotropic therapy but it is unclear whether this elevation is a physiological response to shock, or a direct consequence of the inotropic drugs. In animals, PYY infusion causes intestinal vasoconstriction and a rise in systemic arterial blood pressure (Lundberg et al. 1982).

83.6 Relationship Between Gut Peptides and Gastric Emptying in Critical Illness

There are several findings that support a potential role for enhanced enterogastric feedback in the pathogenesis of slow gastric emptying in critical illness, and the underlying mechanism may relate to abnormal humoral factors such as gut hormones. First, the motor abnormalities in both proximal and distal regions of the stomach in response to small intestinal nutrient stimulation are consistent with enhanced enterogastric inhibitory effects (Chapman et al. 2005; Nguyen et al. 2008c). Second,

plasma levels of the two major gastrointestinal hormones that mediate this enterogastric feedback are significantly elevated in critically ill patients (Nguyen et al. 2006b, 2007c, 2008b). In a recent study (Nguyen et al. 2008b), although there were no differences in gastric emptying and gastrointestinal hormones between critically ill patients who were randomized to receive enteral feeds on either day 1 or day 4, both fasting and nutrient-stimulated plasma concentrations of CCK and PYY were higher in the subset of patients who had delayed gastric emptying compared to those with normal gastric emptying. Third, there is an inverse relationship between the rate of gastric emptying and both the plasma levels as well as the integrated changes in the plasma levels of CCK and PYY (Fig. 83.5) (Nguyen et al. 2008b).

Together, these findings suggest that although only a small amount of nutrients is delivered into the duodenum in patients with delayed gastric emptying, the "increased sensitivity" of the duodenal receptors leads to a greater hormonal release for the same nutrient load, and that there is a complex interaction between gastric emptying, intestinal nutrients and hormonal release in critically ill patients. However, according to Grossman (1974), the physiological role of these hormones in critically ill patients can only be established if they suffice all three criteria: (i) there is a rise in plasma levels of the hormone in association with the stimulus; (ii) exogenous administration of the hormone at a "physiological" concentration produces a similar motor response; and (iii) the response is blocked by specific hormone antagonists (Grossman 1974). So far, there are no
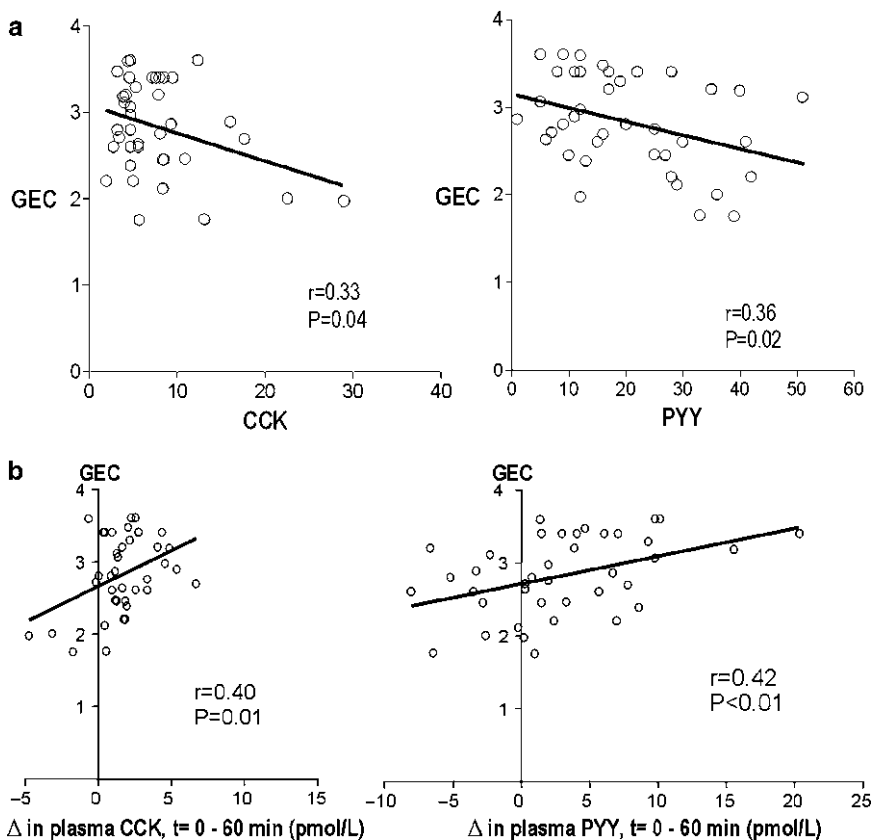
Fig. 83.5 The relationship between plasma PYY and CCK concentrations during (**a**) fasting and (**b**) from baseline to 60 min, and the rate of gastric emptying assessed by gastric emptying coefficience (GEC) in critically ill patients (Data adapted from Nguyen et al. 2008a)

studies that have examined the role of CCK or PYY antagonists in critically ill patients, an area that warrants further evaluation.

83.7 Relationship Between Gut Peptides and Feeding Behavior During Critical Illness

An impaired conscious state, from either the underlying disease(s) or sedation for mechanical ventilation, is almost universal in critically ill patients. Oral intake is often not possible, and should be avoided due to the risk of aspiration, which make the assessment of appetite or feeding behavior difficult, if not impossible. Thus, it is not surprising that there are only very limited data in this area.

In non-critically ill, hospitalized patients, appetite and feeding behavior are significantly impaired, and are characterized by a premature feeling of fullness and loss of hunger (McWhirter and Pennington 1994; le Roux et al. 2005). More importantly, anorexia and the associated cachexia from cardiac failure in patients with severe pulmonary hypertension have been shown recently to be associated with an exaggerated and early PYY response to a test meal when compared to control subjects (le Roux et al. 2005). A marked reduction in appetite and oral intake was also noted recently in a small group of conscious, non-mechanically ventilated critically ill patients (Nematy et al. 2005), which resulted in poor nutritional status prior to and during ICU stay. In this study, appetite and food intake were positively associated with percentage increase in ghrelin and negatively with decrease in PYY. Although the appetite scores increased significantly after discharge from ICU, the mean daily energy intake remained lower than estimated energy requirements 4 weeks after discharge from hospital (Nematy et al. 2005). This prolonged suppression of appetite after critical illness may explain why malnutrition continues to be a persistent problem several months after ICU admission. There are no data on the relationship between CCK and appetite or feeding behavior in critically ill patients. Given the known effect of PYY and ghrelin on appetite and oral intake, however, these preliminary findings suggest a potential role for deranged plasma levels of gut peptides in the mediation of anorexia during critical illness.

83.8 Conclusions

Enteral nutrition undoubtedly improves the outcomes of critically ill patients, especially when it is delivered within the first 24 h of admission. In response to enteral nutrition, the humoral response of enterogastric feedback inhibition is abnormal, and both fasting and duodenal nutrient-stimulated plasma CCK and PYY concentrations are significantly elevated in critically ill patients. More importantly, plasma concentrations of CCK and PYY are greatest in patients with delayed gastric emptying or feed intolerance, a clinical manifestation of slow gastric emptying. Overall, an inverse relationship exists between the rate of gastric emptying and both fasting and postprandial plasma CCK and PYY concentrations after a gastric liquid meal. In view of the enhanced enterogastric inhibitory feedback on both proximal and distal gastric motility during critical illness, these findings strongly support the potential role of plasma CCK and PYY in the pathogenesis of gastric dysmotility in these patients. However, demonstration of a causal relationship requires the use of specific antagonists. As currently available prokinetic agents have major limitations, further evaluation of hormonal agents, especially CCK-A antagonists, may potentially provide alternative avenues for the treatment of feed intolerance in critically ill patients.

83.9 Applications to Other Areas of Health and Disease

Impaired gastric motility and appetite, leading to reduced oral intake and malnutrition, are common in many non-critically ill, hospitalized patients. The potential role of gut peptides, such as CCK and PYY, which mediate enterogastric feedback inhibition as well as appetite and oral intake should be explored in these patients. With the current availability of antagonists against CCK and PYY, the therapeutic implications of these agents for "*anorexia of the sick*" are potentially enormous if the role of gut peptides is to be proven.

Summary

- Adequate administration of enteral nutrition improves the outcomes of critically ill patients, but is frequently hampered by gastric dysmotility.
- Delayed gastric emptying of critical illness is associated with impaired motor function in all regions of the stomach during both fasting and fed state.
- In response to enteral nutrition, enterogastric feedback inhibition is abnormally heightened during critical illness.
- Both fasting and duodenal nutrient-stimulated plasma CCK and PYY concentrations are significantly elevated in critically ill patients, and are greatest in patients with delayed gastric emptying or feed intolerance.
- There is an inverse relationship between the rate of gastric emptying and both fasting and postprandial plasma CCK and PYY concentrations after a gastric liquid meal.
- There is an inverse relationship between fasting plasma concentrations of PYY and appetite and oral intake during critical illness.

Keywords and Definitions

Enteral nutrition: A method of giving nutritional support into the gastrointestinal tract via a feeding tube to subjects who cannot have oral intake.

Gastrointestinal hormones: A group of hormones or peptides secreted by cells of the gastrointestinal tract that regulates satiety, oral intake, and gastrointestinal motor function via their central and/or peripheral actions.

Critical illness: Medical condition(s) that lead to death rapidly if there is no provision of life support or organ support systems.

Gastric dysmotility: Disturbance of gastric motor activities that leads to impaired gastric function and delayed gastric emptying.

Enterogastric feedback inhibition: A physiological feedback process in which exposure of nutrients in the small intestine leads to slowing of gastric emptying, so that nutrition enters the small intestine at a controlled rate of 2–3 kcal/min.

Feed intolerance: The inability to tolerate nasogastric feeding due to impaired gastric emptying that leads to large gastric residual volume.

References

Adrian TE, Ferri GL, Bacarese-Hamilton AJ, Fuessl HS, Polak JM, Bloom SR. Human distribution and release of a putative new gut hormone, peptide YY. Gastroenterology. 1985;89:1070–7.

Alpers DH. Enteral feeding and gut atrophy. Cur Op Clin Nutr Metab Care. 2002;5:679–83.

Artinian V, Krayem H, DiGiovine B. Effects of early enteral feeding on the outcome of critically ill mechanically ventilated medical patients. Chest. 2006;129:960–7.

Berger MM, Chiolero RL, Pannatier A, Cayeux MC, Tappy L. A 10-year survey of nutritional support in a surgical ICU: 1986–1995. Nutrition. 1997;13:870–7.

Bosscha K, Nieuwenhuijs V, Vos A, Samsom M, Roelof J, Akkermans L. Gastrointestinal motility and gastric tube feeding in mechanically ventilated patients. Crit Care Med. 1998;26:1510–17.

Brener W, Hendrix TR, McHugh PR. Regulation of the gastric emptying of glucose. Gastroenterology. 1983;85:76–82.

Chapman M, Fraser R, Vozzo R, Bryant L, Tam W, Nguyen N, Zacharakis B, Butler R, Davidson G, Horowitz M. Antro-pyloro-duodenal motor responses to gastric and duodenal nutrient in critically ill patients. Gut. 2005;54:1384–90.

Chapman MJ, Fraser RJ, Bryant LK, Vozzo R, Nguyen NQ, Tam W, Zacharakis B, Davidson G, Butler R, Horowitz M. Gastric emptying and the organization of antro-duodenal pressures in the critically ill. Neurogastroenterol Motil. 2008;20:27–35.

Corazziari E, Ricci R, Biliotti D, Bontempo I, De Medici A, Pallotta N, Torsoli A. Oral administration of loxiglumide (CCK antagonist) inhibits postprandial gallbladder contraction without affecting gastric emptying. Dig Dis Sci. 1990;35:50–54.

Corvilain B, Abramonwicz M, Fery Y, Schoutens A, Verlinden M, Balase E, Horowitz M. Effect of short term starvation on gastric emptying in humans: relationship to oral glucose tolerance. Am J Physiol. 1995;269:G512–7.

Dive A, Moulart M, Jonard P, Jamart J, Mahieu P. Gastroduodenal motility in mechanically ventilated critically ill patients: a manometric study. Crit Care Med. 1994;22:441–7.

Dive A, Michel I, Galanti L, Jamart J, Vander Borght T, Installe E. Gastric acidity and duodenogastric reflux during nasojejunal tube feeding in mechanically ventilated patients. Intensive Care Med. 1999;25:574–80.

Doig AK, Simpson F. Evidence-based guidelines for nutritional support of the critically ill: results of a bi-national guideline development conference. www.EvidenceBased.net; 2005.

Doig AK, Simpson F, Delaney A. A review of the true methodological quality of nutritional support trials conducted in the critically ill: time for improvement. Anaesth Analg. 2005;100:527–33.

Dubois A, Henry DP, Kopin IJ. Plasma catecholamines and postoperative gastric emptying and small intestinal propulsion in the rat. Gastroenterology. 1975;68:466–9.

Fraser R, Fone D, Horowitz M, Dent J. Cholecystokinin octapeptide stimulates phasic and tonic pyloric motility in healthy humans. Gut. 1993;34:33–7.

Fried M, Erlacher U, Schwizer W, Lochner C, Koerfer J, Beglinger C, Jansen JB, Lamers CB, Harder F, Bischof-Delaloye A, et al. Role of cholecystokinin in the regulation of gastric emptying and pancreatic enzyme secretion in humans. Studies with the cholecystokinin-receptor antagonist loxiglumide. Gastroenterology. 1991;101:503–11.

Greeley GH, Jr., Jeng YJ, Gomez G, Hashimoto T, Hill FL, Kern K, Kurosky T, Chuo HF, Thompson JC. Evidence for regulation of peptide-YY release by the proximal gut. Endocrinology. 1989;124:1438–43.

Grossman MI. Candidate hormones of the gut. Gastroenterology. 1974;67:730–55.

Harrington L. Nutrition in critically ill adults: key processes and outcomes. Crit Care Nurs Clin N Am. 2004;16:459–65.

Hernandez G, Velasco N, Wainstein C, Castillo L, Bugedo G, Maiz A, Lopez F, Guzman S, Vargas C. Gut mucosal atrophy after a short enteral fasting period in critically ill patients. J Crit Care. 1999;14:73–7.

Heyland D. Nutritional support in the critically ill patients. A critical review of the evidence. Crit Care Clin. 1998;14:423–40.

Heyland D, Cook DJ, Winder B, Brylowski L, Van demark H, Guyatt G. Enteral nutrition in the critically ill patient: a prospective survey. Crit Care Med. 1995;23:1055–60.

Heyland D, Dhaliwal R, Drover JW, Gramlich L, Dodek P. Canadian Critical Care Clinical Practice Guidelines. Canadian clinical practice guidelines for nutrition support in mechanically ventilated, critically ill adult patients. JPEN J Parenter Enteral Nutr. 2003;27:355–73.

Heyland DK, Tougas G, King D, Cook DJ. Impaired gastric emptying in mechanically ventilated, critically ill patients. Intensive Care Med. 1996;22:1339–44.

Heyland DK, MacDonald S, Keefe L, Drover JW. Total parenteral nutrition in the critically ill patient: a meta-analysis. JAMA. 1998;280:2013–9.

Horowitz M, Dent J, Fraser R, Sun W, Hebbard G. Role and integration of mechanisms controlling gastric emptying. Dig Dis Sci. 1994;39:7S–13S.

Kao C, Changlai S, Chieng P, Yen T. Gastric emptying in head-injury patients. Am J Gastroenterol. 1998;93:1108–12.

Kelly KA. Gastric emptying of liquids and solids: roles of proximal and distal stomach. Am J Physiol. 1980;239:G71–6.

King PM, Heading RC, Pryde A. Coordinated motor activity of the human gastroduodenal region. Dig Dis Sci. 1985;30:219–24.

Kreiss C, Schwizer W, Borovicka J, Jansen JB, Bouloux C, Pignol R, Bischof Delaloye A, Fried M. Effect of lintitript, a new CCK-A receptor antagonist, on gastric emptying of a solid-liquid meal in humans. Regul Pept. 1998;74:143–9.

Kudsk K, Croce MA, Fabian TC. Enteral versus parenteral feeding: effects on septic morbidity after blunt and penetrating abdominal trauma. Ann Surg. 1992;215:503–11.

le Roux CW, Ghatei MA, Gibbs JS, Bloom SR. The putative satiety hormone PYY is raised in cardiac cachexia associated with primary pulmonary hypertension. Heart. 2005;91:241–2.

Ledeboer M, Masclee AA, Coenraad M, Vecht J, Biemond I, Lamers CB. Antroduodenal motility and small bowel transit during continuous intraduodenal or intragastric administration of enteral nutrition. Eur J Clin Invest. 1999;29:615–23.

Liddle RA, Gertz BJ, Kanayama S, Beccaria L, Coker LD, Turnbull TA, Morita ET. Effects of a novel cholecystokinin (CCK) receptor antagonist, MK-329, on gallbladder contraction and gastric emptying in humans. Implications for the physiology of CCK. J Clin Invest. 1989;84:1220–5.

Liddle RA, Morita ET, Conrad CK, Williams JA. Regulation of gastric emptying in humans by cholecystokinin. J Clin Invest. 1986;77:992–6.

Lin HC, Doty JE, Reedy TJ, Meyer JH. Inhibition of gastric emptying by glucose depends on length of intestine exposed to nutrient. Am J Physiol. 1989;256:G404–11.

Lin HC, Chey WY, Zhao X. Release of distal gut peptide YY (PYY) by fat in proximal gut depends on CCK. Peptides. 2000;21:1561–3.

Lundberg JM, Tatemoto K, Terenius L, Hellstrom PM, Mutt V, Hokfelt T, Hamberger B. Localization of peptide YY (PYY) in gastrointestinal endocrine cells and effects on intestinal blood flow and motility. Proc Nat Acad Scie USA. 1982;79:4471–5.

MacIntosh CG, Andrews JM, Jones KL, Wishart JM, Morris HA, Jansen JB, Morley JE, Horowitz M, Chapman IM. Effects of age on concentrations of plasma cholecystokinin, glucagon-like peptide 1, and peptide YY and their relation to appetite and pyloric motility. Am J Clin Nutr. 1999;69:999–1006.

McClave SA, Sexton LK, Spain DA, Adams JL, Owens NA, Sullins MB, Blandford BS, Snider HL. Enteral tube feeding in the intensive care unit: factors impeding adequate delivery. Crit Care Med. 1999;27:1252–6.

McDermott JR, Leslie FC, D'Amato M, Thompson DG, Grencis RK, McLaughlin JT. Immune control of food intake: enteroendocrine cells are regulated by CD4+ T lymphocytes during small intestinal inflammation. Gut. 2006;55:492–7.

McWhirter JP, Pennington CR. Incidence and recognition of malnutrition in hospital. BMJ. 1994;308:945–8.

Mentec H, Dupont H, Bocchetti M, Cani P, Ponche F, Bleichner G. Upper digestive intolerance during enteral nutrition in critically ill patients: frequency, risk factors, and complications. Crit Care Med. 2001;29:1955–61.

Mesquita MA, Thompson DG, Troncon LE, D'Amato M, Rovati LC, Barlow J. Effect of cholecystokinin-A receptor blockade on lipid-induced gastric relaxation in humans. Am J Physiol. 1997;273:G118–23.

Minard G, Kudsk KA, Melton S, Patton JH, Tolley EA. Early versus delayed feeding with an immune-enhancing diet in patients with severe head injuries. JPEN J Parenter Enteral Nutr. 2000;24:145–9.

Montejo JC. Enteral nutrition-related gastrointestinal complications in critically ill patients: a multicenter study. The Nutritional and Metabolic Working Group of the Spanish Society of Intensive Care Medicine and Coronary Units. Crit Care Med. 1999;27:1447–53.

Moran TH, McHugh PR. Cholecystokinin suppresses food intake by inhibiting gastric emptying. Am J Physiol. 1982;242:R491–7.

Murray CD, Martin NM, Patterson M, Taylor SA, Ghatei MA, Kamm MA, Johnston C, Bloom SR, Emmanuel AV. Ghrelin enhances gastric emptying in diabetic gastroparesis: a double blind, placebo controlled, crossover study. Gut. 2005;54:1693–8.

Mutlu GM, Mutlu EA, Factor P. GI complications in patients receiving mechanical ventilation. Chest. 2001;119:1222–41.

Naslund E, Gryback P, Backman L, Jacobsson H, Holst JJ, Theodorsson JJ, Hellstrom PM. Distal small bowel hormones: correlation with fasting antroduodenal motility and gastric emptying. Dig Dis Sci. 1998;43:945–52.

Nematy M, O'Flynn J, Wandrag L, Brynes A, Brett S, Patterson M, Ghateir M, Bloom S, Frost G. Changes in appetite related gut hormones in intensive care unit patients: a pilot cohort study. Crit Care. 2005;10:R1–10.

Nguyen NQ, Fraser RJ, Chapman M, Bryant LK, Holloway RH, Vozzo R, Feinle-Bisset C. Proximal gastric response to small intestinal nutrients is abnormal in mechanically ventilated critically ill patients. World J Gastroenterol. 2006a;12:4383–8.

Nguyen NQ, Fraser RJ, Chapman M, Bryant LK, Wishart J, Holloway RH, Horowitz M. Fasting and nutrient-stimulated plasma peptide-YY levels are elevated in critical illness and associated with feed intolerance: an observational, controlled study. Crit Care. 2006b;10:R175.

Nguyen NQ, Fraser RJ, Bryant LK, Chapman M, Holloway RH. Proximal gastric motility in critically ill patients with type 2 diabetes mellitus. World J Gastroenterol. 2007a;13:270–5.

Nguyen NQ, Fraser RJ, Bryant LK, Chapman MJ, Wishart J, Holloway RH, Butler R, Horowitz M. The relationship between gastric emptying, plasma cholecystokinin, and peptide YY in critically ill patients. Crit Care. 2007b;11:R132.

Nguyen NQ, Fraser RJ, Chapman MJ, Bryant LK, Holloway RH, Vozzo R, Wishart J, Feinle-Bisset C, Horowitz M. Feed intolerance in critical illness is associated with increased basal and nutrient-stimulated plasma cholecystokinin concentrations. Crit Care Med. 2007c;35:82–8.

Nguyen NQ, Ng MP, Chapman M, Fraser RJ, Holloway RH. The impact of admission diagnosis on gastric emptying in critically ill patients. Crit Care. 2007d;11:R16.

Nguyen NQ, Chapman MJ, Fraser RJ, Bryant LK, Burgstad C, Ching K, Bellon M, Holloway RH. The effects of sedation on gastric emptying and intra-gastric meal distribution in critical illness. Intensive Care Med. 2008a;34:454–60.

Nguyen NQ, Fraser RJ, Bryant LK, Burgstad C, Chapman MJ, Bellon M, Wishart J, Holloway RH, Horowitz M. The impact of delaying enteral feeding on gastric emptying, plasma cholecystokinin, and peptide YY concentrations in critically ill patients. Crit Care Med. 2008b;36:1469–74.

Nguyen NQ, Fraser RJ, Bryant LK, Chapman M, Holloway RH. Diminished functional association between proximal and distal gastric motility in critically ill patients. Intensive Care Med. 2008c;34:1246–55.

Pironi L, Stanghellini V, Miglioli M, Corinaldesi R, De Giorgio R, Ruggeri E, Tosetti C, Poggioli G, Morselli Labate AM, Monetti N, et al. Fat-induced ileal brake in humans: a dose-dependent phenomenon correlated to the plasma levels of peptide YY. Gastroenterology. 1993;105:733–9.

Quirk J. Malnutrition in critically ill patients in intensive care units. Br J Nursing. 2000;9:537–41.

Ritz MA, Fraser R, Edwards N, Di Matteo AC, Chapman M, Butler R, Cmielewski P, Tournadre JP, Davidson G, Dent J. Delayed gastric emptying in ventilated critically ill patients: measurement by 13 C-octanoic acid breath test. Crit Care Med. 2001;29:1744–9.

Souba WW. Cytokine control of nutrition and metabolism in critical illness. Curr Prob Surg. 1994;31:577–643.

Straathof JW, Mearadji B, Lamers CB, Masclee AA. Effect of CCK on proximal gastric motor function in humans. Am J Physiol. 1998;274:G939–44.

Tarling MM, Toner CC, Withington PS, Baxter MK, Whelpton R, Goldhill DR. A model of gastric emptying using paracetamol absorption in intensive care patients. Intensive Care Med. 1997;23:256–60.

Thomas L., Robert D. Nutritional status and body composition in critically ill patients. Relationship between results and mortality. Am J Clin Nutr. 1979;32:510–11.

White CM, Poxon V, Alexander-Williams J. A study of motility of normal human gastroduodenal region. Dig Dis Sci. 1981;26:609–17.

Yuan C, Foss J, O'Connor M, Roizen M, Moss J. Effects of low-dose morphine on gastric emptying in healthy volunteers. J Clin Pharmacol. 1998;38:1017–20.

Chapter 84
The Brain and Leptin Resistance and Implications for Food-Related Disorders

Nina Eikelis and Gavin Lambert

Abbreviations

ob	The gene that encodes leptin protein
ob/ob	Obese mouse with a mutation in the leptin gene
db	The gene that encodes leptin receptor
db/db	Obese mouse with a recessive mutation in the leptin receptor gene
Ob-Rb	Splice variant of the leptin receptor gene
BBB	Blood–brain barrier
CSF	Cerebrospinal fluid
BMI	Body mass index
Jak	Janus Kinase, implicated in signaling by leptin
STAT	Signal transducer and activator of transcription protein
SOCS	Suppressor of cytokine signaling

84.1 Introduction

Obesity is a complex multifactorial disease involving environmental, genetic, behavioral, and psychological components. Despite its increasing prevalence and our improved understanding of the disease, only limited effective obesity management plans are in place. The discovery of leptin, an appetite-suppressing hormone principally produced in adipocytes, rejuvenated the field and initially generated great hopes for the treatment of obesity. Leptin was discovered through positional cloning in 1994 by Friedman's group at the New York's Rockefeller University (Zhang et al. 1994). Researchers soon demonstrated that administration of leptin to genetically obese mice (*ob/ob*) resulted in these animals losing weight dramatically. The weight loss was attributed to both suppression of appetite and increased metabolism. Leptin appeared to act via a negative feedback loop: when an animal overeats and is starting to gain weight, the increase in body weight leads to the increase in leptin expression and secretion, which stimulates energy expenditure and suppresses appetite, which in turn leads to the animal losing weight (Fig. 84.1). Unfortunately, the *ob/*ob mice did not turn out to be the model of

N. Eikelis (✉)
Human Neurotransmitters Laboratory, Vascular and Hypertension Division, Baker IDI Heart and Diabetes Institute, Melbourne, Victoria 8008, Australia
e-mail: nina.eikelis@bakeridi.edu.au
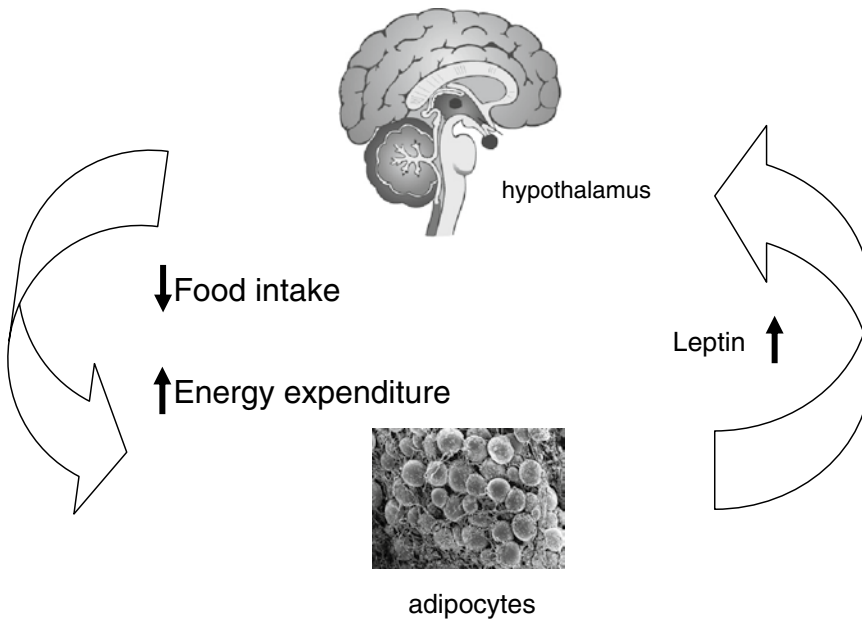
Fig. 84.1 Negative feedback of leptin regulation: as body weight increases so does leptin synthesis and secretion by adipocytes. Within the central nervous system (hypothalamus) leptin acts to decrease food intake and increase energy expenditure, thereby reducing body weight

common human obesity and the hopes for leptin to be an antiobesity drug soon dimmed after it was established that overweight and obese humans are not leptin deficient at all. In contrast, their circulating leptin levels are extremely high and are in proportion to the level of adipose tissue.

84.2 Regulation of Food Intake

There are many physiological and psychological mechanisms that are known to be involved in the regulation of food intake and body weight. For many years the brain, and in particularly the hypothalamus, was considered to be the center that integrates peripheral signals in the control of appetite and body weight. Early studies provided an anatomical basis to suggest that central mechanisms must operate to regulate food intake. The first evidence came from the experimental studies in rats where lesions of the lateral area of the hypothalamus led to animals losing weight, while lesions to the ventromedial hypothalamus resulted in animals overeating and becoming obese (Hennessy and Grossman 1976). Experimental evidence of this type led to the widely held view that food intake was controlled by two opposing hypothalamic nuclei (or centers): namely, one which initiates feeding and the second that brings about satiation.

More recently, a feedback system for the regulation of food intake and body weight has been proposed. This feedback is dependent upon not only the amount and the quality of the ingested food but also on the nutrient content. A number of investigations have provided evidence of a variety of hormonal systems and other mechanisms that can shape the central response to nutritional stimuli. For example, the gastrointestinal tract is known to be lined with a number of different sensory receptors responsible for "sensing" shape and texture of food. This information is sent to the brainstem via the vagus nerve (Sclafani et al. 2003), so that activation of the vagal nerve leads to satiation.

The concept that humoral factors generated in proportion to energy stores provide feedback to the central nervous system was first suggested by Kennedy in the 1950s (Kennedy 1953). Moreover, the gastrointestinal–brain axis has long been viewed important in meal termination, with gastrointestinal peptides such as cholecystokinin (CCK) and peptide YY (3–36) as examples. More recently, ghrelin (which is primarily produced by stomach) has challenged this notion. Ghrelin is a unique hormone that was found to stimulate food intake (Strader and Woods 2005). Injections of ghrelin, both centrally and intravenously, result in increased feeding and generation of adiposity (Hashimoto et al. 2007). Ghrelin levels peak in both humans and animals in anticipation of food intake.

Insulin is another key player that signals to the central nervous system about body adiposity. Insulin has been found in cerebrospinal fluid (CSF) where its concentration is increased following the infusion of glucose (Kontoyannia et al. 1974). Moreover, when insulin was infused into the lateral ventricle of baboons, a dose-dependent suppression of food intake and body weight was recorded (Porte and Woods 1981).

Another satiety factor which is the focus of this chapter is leptin. Leptin is synthesized primarily by adipocytes (fat cells) and is then secreted into the bloodstream. Leptin primarily acts in the hypothalamus on leptin receptors and initiates signals to stop eating and increase energy expenditure. Plasma levels of leptin follow body fat content closely: as body weight increases, so does the leptin concentration in blood. In addition, injections of leptin into obese animals with leptin gene mutations result in animals losing weight, both through reduction in food intake and increase in energy expenditure.

84.3 Obesity

Obesity is defined as excess in body weight that often results in significant impairment of health. It is a known factor for a number of chronic conditions including heart disease, hypertension, diabetes, kidney disease, and some forms of cancer. Obesity, including being moderately overweight, is also associated with a significant increase in odds of mood and anxiety disorders. An expert panel, convened by the National Institutes of Health in 1998, recommended that Body Mass Index (BMI), the ratio of weight to height (kg/m^2), be used to classify overweight and obesity. A person's BMI correlates significantly with risk of disease and death; for example, the risk of heart disease increases with increasing BMI in all population groups.

Maintaining a stable body weight requires that the food intake matches energy expenditure. Therefore obesity can only present when energy intake (food) exceeds energy expenditure (Fig. 84.2). Although at first sight it might seem that obesity is simply the result of changes to our diet and a reduction in physical activity, efforts to attribute obesity to a high level of energy intake (food intake) or to a low level of energy expenditure have been unsuccessful. Studies show that obesity is a multifactorial
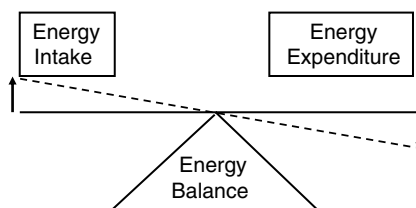
Fig. 84.2 Energy balance is the difference between calorie intake (food) and energy expended through metabolism and daily activities. Finding the right balance of energy intake and expenditure allows one to achieve and maintain a healthy body weight

disease and is caused by more than one factor. One such factor that has come under examination over the past 15 years is the role of genetics, with a particular focus on the leptin gene and genes that are involved in leptin regulation.

84.4 Leptin Genetics

Earlier theories describing appetite and energy expenditure were suggestive of an adipose-derived circulating factor that sends signals to the central hunger and satiety centers in the brain to modulate food intake and body weight. However, the experimental techniques to validate such hypotheses were lacking at the time. Two strains of obese mutant mice, the *ob/ob* and *db/db*, proved invaluable in the study of food intake, energy expenditure, and body weight regulation.

84.4.1 The Leptin Gene

Leptin was discovered through positional cloning using the leptin-deficient mouse (Zhang et al. 1994). Leptin was initially found to be expressed in white adipose tissue (Zhang et al. 1994), however, further studies found leptin to be synthesized in a wider variety of tissues than originally thought, including placenta, stomach, mammary gland, heart, and brain (Bado et al. 1998; Eikelis et al. 2004; Morash et al. 1999). The *ob* gene encodes a 4.5 kilobase messenger RNA with a highly conserved 167 amino acid open reading frame. Leptin in humans has been localized to chromosome 7 and consists of three exons separated by two introns (Zhang et al. 1994). A nonsense mutation in codon 105 has been identified in the *ob/*ob mouse (Zhang et al. 1994). A C→T mutation results in a change of amino acid and a premature stop codon. Overexpression of the leptin gene has been found in both subcutaneous and visceral tissues of overweight and obese individuals (Lonnqvist et al. 1995).

In humans, the first research investigating mutations in the leptin gene failed to identify any individuals with a mutation in the coding region of the leptin gene (Considine et al. 1995; Maffei et al. 1996). A mutation in the leptin gene in humans was first reported in two children in 1997 (Montague et al. 1997). The mutation was a deletion of a single nucleotide in the codon 133 of the leptin gene. This deletion caused a frameshift mutation and a premature stop codon resulting in a nonfunctional protein (Montague et al. 1997). In a separate report, a mutation in codon 103 has been reported in three members of a Turkish family (Strobel et al. 1998), also resulting in the leptin protein to be generated with no biological activity. The phenotype of leptin-deficient individuals is similar to that seen in *ob/ob* and *db/db* mice and is characterized by early onset obesity, hyperphagia, and hypothalamic hypogonadism.

84.4.2 The Leptin Protein

Human leptin is synthesized as a 167-amino acid precursor protein that includes a 21 amino acid signal sequence that is cleaved upon secretion from the cell. Mature leptin is 146 amino acids in length, and under reducing conditions migrates as a band at approximately 16 kDa on sodium dodecyl sulfate–polyacrylamide gel electrophoresis**.** The sequence of amino acids is highly conserved between species. The largely hydrophilic amino acid sequence of leptin has no notable structure

motifs or membrane spanning domains other than an *N*-terminal signal sequence (Zhang et al. 1994). In addition, the leptin protein contains a disulfide chain that appears to be important for its biological function (Grasso et al. 1997). Human leptin is 84% homologous to mouse and 83% homologous to rat leptin. The extensive homology of the *ob* gene product among species suggests that its function is also highly conserved. Structural analysis indicates that it is similar to the cytokine family of proteins and as such consists of four alpha-helicies (Madej et al. 1995).

84.4.3 The Leptin Receptor

The leptin receptor is encoded by the *db* gene. Tartaglia et al. were the first to describe the leptin receptor in a mouse (Tartaglia et al. 1995). It belongs to the interleukin 6 receptor family of cytokine receptors. There are a number of leptin receptor isoforms that result from alternative messenger RNA splicing as well as proteolytic processing of the subsequent leptin products (Chua et al. 1997). In all species, leptin receptor isoforms can be divided into three classes: secreted, short, and long (Fig. 84.3). The secreted leptin receptor only contains the extracellular domain but it binds leptin with the same affinity as the membrane-bound receptor. The secreted leptin receptor perhaps modulates circulating leptin levels by delaying its clearance and determines the amount of free versus bound leptin. In obese individuals, a significantly larger proportion of leptin circulates in the free form compared to lean individuals (Sinha et al. 1996). In addition, the amount of free leptin increases in proportion to BMI, which perhaps suggests that leptin-binding protein (soluble leptin receptor) is saturated in obesity.

Short forms and a long form of the leptin receptor contain identical extracellular and transmembrane domains, but then differ in intracellular sequence because of alternative splicing. The long form of the leptin receptor, often referred to as *Ob-Rb*, is the only leptin receptor that contains all
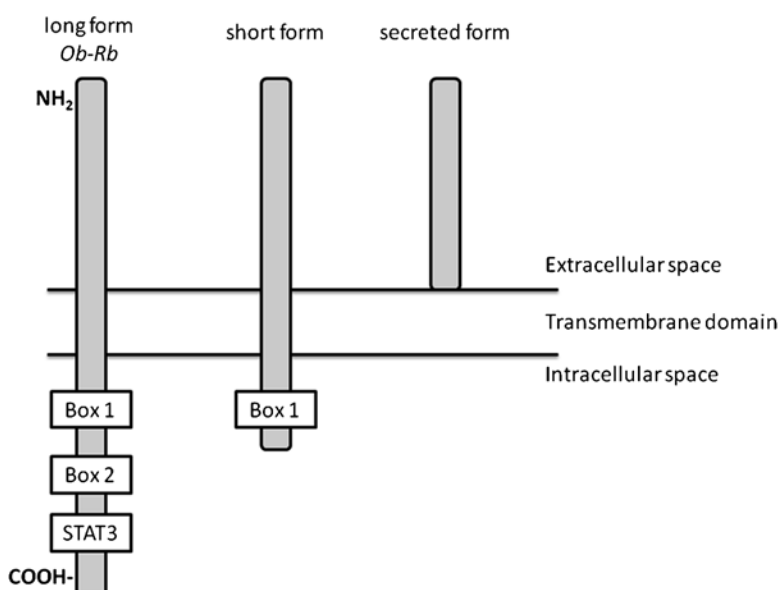
Fig. 84.3 Schematic representation of leptin receptor isoforms. All leptin receptors share an identical extracellular domain (ligand-binding domain), but differ in their carboxy terminus. Only the long isoform, *Ob-Rb*, has all the intracellular motifs required for signal transduction via Jak-STAT3 pathway

intracellular motifs required for signal transduction (Tartaglia et al. 1995). Indeed, the originally described *db/db* mice lack only the long form of the leptin receptor, but have the same phenotype as mice lacking all leptin receptor isoforms as well as leptin-deficient mice (*ob/ob*) (Chua et al. 1997; Tartaglia et al. 1995). While the role of the short-form and secreted leptin receptors are less clear, they have been suggested to be involved in leptin transport across the blood–brain barrier (BBB; El-Haschimi et al. 2000).

Ob-Rb is highly expressed in the hypothalamus in both the human and rodent brain. Experimental studies identified the hypothalamic arcuate, dorsomedial, paraventricular, ventromedial, and lateral nuclei as the principal sites of leptin receptor expression in the central nervous system (Fei et al. 1997; Mercer et al. 1996). Interestingly, all of these nuclei have previously been implicated in the regulation of body weight. Indeed the ablation of these centers results in increased feeding and other neuroendocrine abnormalities that mimic the phenotypes of *db/db* and *ob/ob* mice, which indicates that these hypothalamic nuclei are crucial for leptin signaling (Elmquist et al. 1999). Outside the hypothalamus, the leptin receptor is also found in the thalamus and cerebellum (Guan et al. 1997; Mercer et al. 1998).

Similar to the *ob* gene, mutations in the *db* gene are extremely rare in humans. The first demonstration of a leptin receptor mutation in humans was reported by Clement (Clement et al. 1998). In these patients, a single G A substitution in exon 16 resulted in a nonfunctional leptin receptor lacking both transmembrane and intracellular domains. As a result of this mutation, the truncated leptin receptor is unable to activate the signal transduction pathway. Similar to the *ob* gene mutation in humans, a mutation in the leptin receptor gene causes hyperphagia and early onset obesity.

84.4.4 Leptin Signaling Pathway

Binding of leptin to *Ob-Rb* causes a rapid activation of receptor-associated Janus kinase-2 (Jak2), a tyrosine kinase, which in turn leads to leptin receptor phosphorylation (Bjorbaek et al. 1997). This initial activation of Jak2 is a crucial step in leptin signaling as the leptin receptor does not have enzymatic activity on its own. Activated Jak2 tyrosine phosphorylates itself as well as a number of tyrosine residues in the intracellular domain of *Ob-Rb*, and in particular Tyr_{985}, Tyr_{1077}, and Tyr_{1138} (for review see Villanueva and Myers 2008). Each of these tyrosine residues recruits a specific set of downstream signaling proteins when phosphorylated. For example, phosphorylated tyrosine at residue 1,138 binds and mediates activation of signal transducer and activator of transcription 3 (STAT3), which in turn activates transcription of suppressor of cytokine signaling 3 (SOCS3). Phosphorylated STAT3 is a second messenger for the long-form leptin receptor. Not surprisingly, mutations at Tyr_{1138} abolish STAT3 signaling by the leptin receptor (Baumann et al. 1996).

84.5 Leptin Resistance Phenomenon

As briefly mentioned in the Introduction, early results of clinical investigations clearly demonstrated that overweight and obese humans are not deficient in leptin. In fact, there are only a few reported cases of obesity caused by the mutation in the *ob* or *db* gene (Clement et al. 1998; Montague et al. 1997; Strobel et al. 1998). Therefore, despite promising results of leptin replacement therapy in obese leptin-deficient mice, endogenous leptin is ineffective in reducing appetite or increasing energy expenditure in overweight and obese humans. Consequently, it soon became apparent that neither

endogenous hyperleptinemia nor leptin replacement even at supraphysiological doses would be effective in the clinical setting. This failure of elevated leptin levels to suppress feeding and initiate weight loss was termed "leptin resistance."

A number of mechanisms have been proposed to contribute to the development of leptin resistance and consequently obesity. Animal models of obesity provided excellent systems to explore how leptin functions and to identify which central mechanisms or signaling pathways might be compromised. The delivery of leptin into the brain seems to represent the crucial step in the regulation of food intake and energy balance given that leptin exerts its effects in the hypothalamus.

Although leptin administration has been reported to reduce food intake and normalize body weight in leptin-deficient mice, the relevance of this genetic model to the treatment of obesity remains to be determined. On the contrary, the diet-induced model of obesity may more adequately reflect the physiology of the obese human than does the leptin-deficient *ob/ob* mouse. For example, diet-induced obese mice exhibit resistance to peripherally administrated leptin, while they retain sensitivity to leptin after intracerebroventricular infusion (Van Heek et al. 1997). These observations perhaps suggest that some overweight and obese humans, who appear to be unresponsive to elevated circulating endogenous leptin, may respond to a leptin analogue delivered directly into the central nervous system. To overcome the multitude of barriers that stand in the way of potential therapeutic agents reaching the central nervous system, numerous drug delivery strategies have been developed, which generally aim at either manipulating drugs or disrupting the BBB (for review see Misra et al. 2003).

In a study conducted by Wilsey and colleagues (Wilsey et al. 2003), leptin resistance in rats was caused by 100 days of high fat feeding. After the establishment of obesity, the animals received a single central injection of recombinant adeno-associated virus particle encoding leptin. Lean chow-fed control counterparts responded robustly to such treatment, as evident by significant weight loss. In contrast, rats fed a high-fat diet were completely unresponsive to central leptin overexpression (Wilsey et al. 2003). Furthermore, central leptin treatment caused a significant increase in the STAT3 signaling pathway in lean rats, but failed to do so in obese animals fed a high-fat diet. The authors concluded that central overexpression of leptin is not a potent strategy to reverse diet-induced obesity.

Although leptin was thought initially to be synthesized primarily by adipocytes, there are a number of studies demonstrating leptin production in sites other than adipose tissue (Bado et al. 1998; Eikelis et al. 2004; Esler et al. 1998). Previous observations from our laboratory of leptin overflow in the internal jugular vein were suggestive of leptin production in the brain itself (Eikelis et al. 2004; Esler et al. 1998; Wiesner et al. 1999). Simultaneous sampling of arterial and venous blood across a range of organs is a useful tool to identify which organ releases leptin (or other hormones, transmitters, etc.) to or removes it from plasma. The central venous catheter was used to sample blood from the internal jugular vein. Using this method, we investigated the capacity of the human brain to extract leptin from plasma to test whether this was reduced in obesity as might be predicted by the leptin resistance model. Our expectations were that measurable leptin uptake into the brain from plasma might be present in lean but not obese people. Surprisingly, our initial findings indicated a net efflux of leptin from the brain (Eikelis et al. 2004; Esler et al. 1998; Wiesner et al. 1999). Even more surprising was the observation that leptin release was greater in overweight compared to lean men. The leptin efflux from the brain may well have derived from brain production and/or uptake from plasma. The production of leptin in the brain has implications for the prevailing idea of leptin resistance in obesity, as it has been proposed that the primary flaw in obesity may be a reduction in leptin transport to the brain. Our demonstration of leptin production by the brain itself contradicts this idea.

To verify this observation, we have used human donor tissue to directly examine leptin gene expression in the human hypothalamus (Eikelis et al. 2007). The source of the obtained tissue included a mix of male and female donors, of different age and BMI. Leptin was detected in hypothalamic tissue of some donors. However, we found no relation of leptin gene expression in the

hypothalamus to the BMI or gender (Eikelis et al. 2007). Interestingly, in our studies leptin gene expression was only evident in donors who died suddenly and unexpectedly, as opposed to if deaths were from suicide or illicit drug use. Therefore, we can speculate that contrasting nutritional state, with possibly poor nutrition just prior to death with suicide or drug use, may have lead to different levels of leptin gene expression in the brain. Interestingly, in a separate study while arterial leptin concentration in patients with major depressive disorder and healthy volunteers was not different, leptin release from the brain into the jugular vein in patients with major depressive disorder was reduced (Eikelis et al. 2006). These two observations of reduced leptin release by the brain of depressed patients and the fact that leptin was only seen in the brains of the donors who died of natural causes (as opposed to death by suicide) suggest that leptin may play a role beyond appetite control. Indeed, leptin has also been linked to depression, in at least rats, and implicated as a neurotrophic factor. In an elegant study by Pinto et al. (2004), leptin was demonstrated to act as a neurotrophic factor in a mouse hypothalamus. Leptin-deficient mice were found to have reduced numbers of synapses in the arcuate nucleus of the hypothalamus, the defect which was rapidly normalized and detectable within several hours of treatment (Pinto et al. 2004).

As mentioned earlier, leptin resistance may arise as a result of the transport of leptin into the brain may become compromised, the end result being the inability of leptin to reach its target in the hypothalamus (Banks and Farrell 2003). The blood–brain barrier (BBB) plays an important role in the communication between the brain and the peripheral tissues, by controlling the entry of major hormones into the brain from blood. The blood–CSF barrier at the choroid plexus and BBB at the cerebral endothelium are two major controlling sites for entry of circulating proteins into the brain. It has been suggested that leptin receptors in the choroid plexus (Devos et al. 1996; Tartaglia et al. 1995) and at the BBB (Bjorbaek et al. 1998; Golden et al. 1997) may mediate leptin transport into the brain. Interestingly the short form of the leptin receptor has been found to be expressed in the choroid plexus and has been suggested to act merely as a leptin transporter (Tartaglia 1997).

The study by Zlokovic et al. (2000) used an in situ brain perfusion model to determine simultaneously the rates of leptin transport across the blood–CSF barrier, into the hypothalamus, and at the BBB in lean rats with the assumption that radiolabeled leptin behaves in a manner similar to unlabeled endogenous leptin. They reported a rapid and high-affinity transport system that mediated leptin entry into the hypothalamus and across the blood–CSF barrier. In contrast, low-affinity transport was found at the BBB outside the hypothalamus (Zlokovic et al. 2000). Leptin transport across the blood–CSF barrier appears to be saturated at higher plasma leptin levels, therefore suggesting that the choroid plexus may serve a rate-limiting function to avoid increases in CSF leptin concentrations. In obese individuals, increases in circulating leptin levels are not accompanied by increases in the CSF leptin concentration (Caro et al. 1996). Analysis of leptin concentration in the CSF of obese individuals was reported to be similar to those found in nonobese matched controls (Schwartz et al. 1996). These observations do suggest that impairment in the transport of leptin across the blood–CSF barrier may underlie leptin resistance, at least in part, in some obese individuals.

Another possible mechanism that may explain leptin resistance in some cases of obesity involves a defect in the leptin receptor itself. When we have examined the full-length leptin receptor expression in the human hypothalamus across a wide range of adiposites, we have found no relation between the level of *Ob-Rb* expression and BMI (Eikelis et al. 2007). These results do suggest that the leptin resistance phenomenon cannot be simply explained on the basis of leptin receptor down-regulation in obesity. In addition, as discussed earlier, while leptin receptor mutations have been reported in humans, they are very rare.

Since most cases of human obesity are not associated with leptin deficiency or mutations in the leptin receptor, a defect may lie in the signaling cascade. Whereas a large body of evidence suggests that central leptin resistance contributes to the development of diet-induced obesity, the molecular
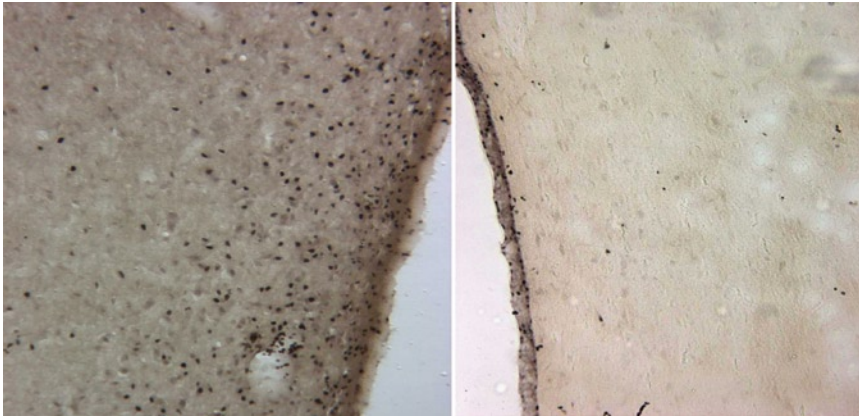
Fig. 84.4 Representative photomicrographs of c-fos positive nuclei in the periventricular nucleus of the hypothalamus. Shown are the sections from a lean and obese rabbits given 100 μg leptin intracerebroventricular 90 min before the perfusion. In the lean rabbit (*left*), central leptin injection resulted in many c-fos positive cells being present in the periventricular nucleus. The central injection of leptin in an HFD animal (*right*) caused only few fos-immunoreactive cells in the corresponding nuclear cells

mechanisms behind this resistance are not clearly understood. Intracerebroventricular leptin administration to lean rabbits indicated that leptin activates specific nuclei in the hypothalamus, as indicated by c-fos immunoreactivity (Fig. 84.4, unpublished observations). However, rabbits fed a high-fat diet for 3 weeks were unresponsive to central leptin injections as evidenced by minimal c-fos activation (Fig. 84.4, unpublished observations).

This demonstration excludes the possibility that leptin resistance in the overweight rabbits induced by diet was due to impaired transport of leptin, as leptin was given intracerebroventricularly and therefore bypassed the BBB. Therefore, in this case, diet-induced obesity may have had an effect on the downstream signaling pathways. Given that signaling through STAT3 second messenger system appears critical in the leptin signaling cascade, a major focus has been on identifying whether STAT3 is in fact impaired in diet-induced obesity. Accordingly, a defect in STAT3 activation by leptin in the arcuate nucleus of the hypothalamus was reported in diet-induced obese mice (El-Haschimi et al. 2000).

84.6 Eating Disorders

There exist many theories and much data indicating that in obesity there exists a strong biological component underlying hunger and eating behavior. What about people with eating disorders? What are the mechanisms underlying hunger and eating for people with such disorders? While emotional, behavioral, and environmental factors play a significant role in the onset of eating disorders, a great deal of research also points to the possibility of a genetic component.

In general terms, there are mainly three kinds of eating disorders: binge eating, anorexia nervosa, and bulimia. Binge eating is characterized by one eating a very large amount of food until she or he feels uncomfortably full. This binge eating is done when one is not hungry. According to the DSM-VI, anorexia nervosa has two types; a restricting type and a binge-eating/purging type (American Psychiatric Association 1994). Anorexia nervosa restricting type is when one extremely restricts food intake, and it is not followed by binge-eating or purging behavior. On the other hand, anorexia nervosa binge-eating/purging type is described as a person who is engaged in purging and binge-eating regularly. A common symptom of

anorexia is one putting her or himself on self-starvation to avoid feeling fat or gaining weight. Although people with this disorder weigh far below normal, they still have the perception of being overweight. Eventually they are at risk of losing their lives due to malnutrition. To fulfill the diagnostic criteria for bulimia, the binge eating habits and compensatory behavior have to occur at least twice a week for 3 months. Despite their excessive concern about body weight, bulimics are usually of normal weight.

Research shows that eating disorders are characterized by abnormalities in central neurotransmitter levels. For example, it has been shown that eating disorders are associated with elevated concentrations of serotonin (Kaye et al. 1998). Numerous other hormones and neurotransmitters in the brain have been linked to eating disorders. Stress triggers the production and secretion of cortisol, and chronically elevated levels of this stress hormone have been observed in patients with anorexia and bulimia. The results of clinical studies show that pharmacological doses of glucocorticoids (such as cortisol) can increase circulating plasma leptin in the short term (Newcomer et al. 1998). Furthermore, these cortisol-induced increases in leptin concentration suggest a mechanism that may contribute to anorexia and weight loss associated with this condition.

Given that eating disorders are associated with abnormal eating behavior and dysregulation of the endocrine axis, extensive research has been carried out to understand the role of leptin in the pathophysiology of eating disorders. Anorexia and bulimia are both associated with altered eating patterns and purging behaviors, malnutrition, and/or denutrition with consequent metabolic changes that, in turn, are responsible for several organic alterations, including abnormalities in reproductive hormone activity and neuroendocrine functions.

It is known that when body fat mass and weight drop past a certain point, leptin levels also drop, which leads to the stimulation of appetite. While under normal conditions of unrestrained food intake leptin serves as a measure of the available energy stored in the adipose tissue, under conditions of acute changes in energy intake as seen in eating disorders, leptin secretion varies independent of the available fat stores and may be affected by a macronutrient content (Kolaczynski et al. 1996). Indeed, the study by Monteleone et al. also suggested that factors other than body weight changes may affect leptin synthesis and secretion (Monteleone et al. 2002). In this study, the assessment of leptin dynamics was done in untreated patients with bulimia and matched healthy volunteers during the acute fasting and refeeding. While patients with eating disorders did exhibit low leptin levels at baseline compared to healthy individuals, they did not respond to short-term fasting; however, leptin levels increased after refeeding (Monteleone et al. 2002). Therefore, while even at low plasma values, leptin still holds its function as a sensor of body weight mass, its function as an index of acute changes in energy balance is lost.

84.6.1 Leptin in Anorexia Nervosa

Anorexia nervosa is an illness characterized by a chronically low body weight and distorted body image with an extreme fear of gaining weight. Individuals diagnosed with anorexia nervosa control their body weight through starvation and, in some cases, increased exercise (Klein et al. 2007). The patients lose their weight by reducing their total food intake. Since anorexia nervosa is at the opposite end of the spectrum from obesity, an attempt has been made to determine whether a correlation exists between leptin concentration in anorectic patients and BMI, percent body weight, and duration of illness.

A study by Eckert et al. reported low leptin levels in patients with anorexia during starvation and subsequent increase in leptin concentration following refeeding (Eckert et al. 1998). While low leptin levels are strongly associated with the increase in energy intake, this physiological stimulus is perhaps overridden in patients with anorexia nervosa by a morbid fear of food. The fact that leptin levels increased upon nutritional rehabilitation in these patients does suggest that there is a normal physiological response of leptin to body weight increase in anorexia. In the same study, it

was demonstrated that while there was a strong correlation between body weight and leptin concentration in healthy female control subjects, that correlation was absent in anorectic women during starvation (Eckert et al. 1998). Interestingly, the linear correlation appeared in anorectic females during refeeding, suggesting perhaps that at very low BMI there is a threshold below which leptin cannot be lowered any further (Eckert et al. 1998). This concept is consistent with data indicating sources of leptin aside from adipose tissue.

The fact that leptin rose dramatically during refeeding raises the question as to whether weight-induced increase in leptin levels during rehabilitation limit further weight gain. Longitudinal studies have also demonstrated that in patients with anorexia nervosa undergoing recovery, circulating leptin levels rise progressively and reach values disproportionate to those measured in stable-weight healthy individuals (Hebebrand et al. 1997). This observation further suggests that hyperleptinemia in anorexia nervosa patients during refeeding may be one of the factors making it difficult for patients to reach and to maintain their weight. Furthermore, a too rapid gain in weight with concomitant high circulating leptin levels in these patients was found to be associated with poor prognosis (Remschmidt et al. 1990). In another study, leptin concentration was measured in CSF of patients with anorexia nervosa and control individuals. While the leptin concentration in the CSF of the anorectic patients was lower compared to healthy individuals, the ratio of CSF to plasma was significantly elevated (Mantzoros et al. 1997). Furthermore, leptin levels in these patients increased, or were comparable, to the control levels after treatment (refeeding) even though they had not reached their desired body weight. Altogether, these results do suggest that the rapid restoration of leptin levels before reaching the desired body weight could contribute to resistance of these patients to increase weight and recovery.

84.6.2 Leptin in Bulimia Nervosa

Bulimia is a psychological eating disorder characterized by intermittent episodes of binge eating behavior followed by episodes of restricted eating. Bulimia was first diagnosed as an eating disorder on its own in the 1980s. Bulimia patients generally exhibit normal body weight (as indicated by their BMI) but their eating habits are far from normal. People with bulimia most often present with normal weight while some may be even overweight. It is often difficult to determine whether one has bulimia because bulimic patients tend to have their binging and food restriction episodes in secret. Bulimia is most common in adolescents and young, adult women.

Studies of eating behavior in patients with bulimia nervosa have demonstrated a diminished responsiveness in satiety-related pathways involving serotonin and other neurotransmitters (Wolfe et al. 1997). Excessive eating during the binge in these patients may potentially affect leptin synthesis and secretion. On the other hand, decreased leptin function may also contribute to reduced satiety responses and large meals in this group of patients. Alteration in leptin function may also contribute to abnormalities in other neuroendocrine systems. It is also worth mentioning that there is some discrepancy in published data with regard to leptin levels in patients with bulimia nervosa, ranging from very low anorexic-like leptin levels to normal plasma concentrations. One possibility is that within the bulimia nervosa group there exists a subset of patients who may hypersecrete leptin.

To test the hypothesis that decreased leptin function may contribute to abnormalities associated with eating patterns in bulimia nervosa patients, Jimerson et al. compared leptin levels in well-characterized outpatients with bulimia and matched control subjects (Jimerson et al. 2000). They reported that bulimic patients had significantly reduced serum leptin concentrations compared to age- and weight-matched controls. An additional finding from this study was that patients who recovered from bulimia still had significantly lower circulating leptin levels (Jimerson et al. 2000). The latter observation perhaps indicates that decreased leptin function in bulimia may be a stable biological trait.

84.7 Future Directions and Applications to Other Areas

Apart from its involvement in the regulation of body weight, leptin appears to be associated with cardiovascular disease. Using data from the West of Scotland Coronary Prevention Study (WOSCPS), researchers investigated whether plasma leptin levels are associated with the risk of a coronary event and if it was independent of BMI, age, lipids, blood pressure, and C-reactive protein, which is a marker of inflammation and a predictor of coronary heart disease (Wallace et al. 2001). Leptin levels were found to be significantly higher in individuals who experienced a cardiac event compared to age- and BMI-matched controls. Leptin also strongly correlated with C-reactive protein levels (Wallace et al. 2001). Based on this set of results, leptin would appear to be an independent risk factor for coronary heart disease.

It is clear that a link exists between obesity and hypertension which may involve leptin. This link is suggested by the observation that mice deficient in leptin have reduced blood pressure, whereas the mice overexpressing leptin have elevated blood pressure (Mark et al. 1999). Furthermore, leptin administered peripherally and, to a greater extent, centrally has been demonstrated to increase the sympathetic outflow to the kidneys, adipose tissue, skeletal muscles, and adrenals (Dunbar et al. 1997; Haynes et al. 1997).

Leptin has been also implicated in neurogenesis. In a study by Pinto published in Science (Pinto et al. 2004), leptin was demonstrated to affect both the architecture and function of neural circuits in the brains of mice: in response to leptin the cells were shown to create new connections. In addition, the researchers found that leptin alters the electrical activity of these connections. The capacity for change of these neural circuits by leptin suggests the possibility that the brain's wiring may differ between lean and obese individuals. Therefore, learning more about the hormone's mechanism of action could be critically important in understanding not only obesity but also other conditions.

Despite the recent advances in our knowledge of the physiology and pathophysiology of leptin, many important questions remain. Regardless of whether leptin has a place in the therapeutic treatment of the twenty-first century, studies on leptin are contributing greatly to our knowledge of the physiology of energy homeostasis and, on this basis, may lead to the development of novel therapeutic approaches to obesity.

Table 84.1 Key features of leptin resistance

1. Leptin is a 167-amino acid protein hormone secreted predominantly by adipocytes into the bloodstream and is present in circulation in direct proportion to the amount of adipose tissue
2. Leptin acts in the central nervous system, particularly in hypothalamus, where it signals satiety
3. Laboratory mice that have mutation in leptin gene become morbidly obese. Leptin administration to these mice normalizes their body weight as well as other metabolic parameters
4. Peripheral administration of leptin to overweight/obese humans has little effect on weight loss in these people. In fact human obesity is characterized by high circulating levels of leptin. As such, humans are thought to be resistant to leptin's weight-reducing effects
5. Several mechanisms may contribute to leptin resistance, including failure of leptin to enter the brain, defects in leptin receptor or leptin signaling pathways
6. Although animals models of obesity and diet-induced obesity are important in understanding how the system works, the differing results from leptin administration studies do suggest that detailed action of leptin in appetite and energy metabolism are different in humans and rodents for instance

This table lists the key facts of leptin resistance

Table 84.2 Key features of leptin discovery

1. *1994*: Leptin gene discovery (Zhang et al. 1994)
2. *1995*: Discovery of leptin receptor (Tartaglia et al. 1995)
3. *1996*: Biotechnology company (Amgen) announces that it began large clinical trials of leptin in humans. This trial fails to demonstrate weight-reducing effect of leptin in overweight individuals dashing hopes that the hormone could treat obesity
4. *1996*: Demonstration of reduced leptin transport into the brain of obese individuals, suggesting a possible mechanism for leptin resistance (Caro et al. 1996)
5. *1997*: First reported case of leptin gene mutation in humans
6. *1997*: First demonstration of an extra-adipocyte source of leptin (Hassink et al. 1997)
7. *1997*: Demonstration of leptin gene mutation in humans (Montague et al. 1997)
8. *1998*: First report suggesting brain as a source of leptin in humans (Esler et al. 1998)
9. *1998*: Demonstration of leptin receptor mutation in humans (Clement et al. 1998)
10. *2004*: Demonstration of leptin-mediated neuroplasticity (Pinto et al. 2004)

This table summarizes key discoveries of leptin

Key Terms

Body mass index: A measure of someone's weight in relation to height (kg/m^2). It is used as an indicator of body fatness for most people and to screen for weight categories that may lead to health problems.

Blood brain barrier: A protective mechanism that serves to separate blood from the central nervous system. The main function of this barrier is to protect the brain from sudden changes in the levels of ions, amino acids, and other substances and as such a key element in the normal functioning of the brain.

Cerebrospinal fluid: Produced by the brain and surrounds and circulates throughout the central nervous system.

Hyperleptinemia: High circulating leptin levels characteristic of obesity.

Leptin resistance: In common obesity leptin loses the ability to signal the brain to inhibit food intake and increase metabolism.

References

Bado A, Levasseur S, Attoub S, Kermorgant S, Laigneau JP, Bortoluzzi MN, Moizo L, Lehy T, Guerre-Millo M, Le Marchand-Brustel Y, Lewin MJ. Nature 1998;394(6695):790–3.

Banks WA, Farrell CL. Am J Physiol Endocrinol Metab. 2003;285(1):E10–5.

Baumann H, Morella KK, White DW, Dembski M, Bailon PS, Kim H, Lai CF, Tartaglia LA. Proc Natl Acad Sci U S A. 1996;93(16):8374–8.

Bjorbaek C, Uotani S, da Silva B, Flier JS. J Biol Chem. 1997;272(51):32686–95.

Bjorbaek C, Elmquist JK, Michl P, Ahima RS, van Bueren A, McCall AL, Flier JS. Endocrinology 1998;139(8):3485–91.

Caro JF, Kolaczynski JW, Nyce MR, Ohannesian JP, Opentanova I, Goldman WH, Lynn RB, Zhang PL, Sinha MK, Considine RV. Lancet 1996;348(9021):159–61.

Chua SC, Jr., Koutras IK, Han L, Liu SM, Kay J, Young SJ, Chung WK, Leibel RL. Genomics 1997;45(2):264–70.

Clement K, Vaisse C, Lahlou N, Cabrol S, Pelloux V, Cassuto D, Gourmelen M, Dina C, Chambaz J, Lacorte JM, Basdevant A, Bougneres P, Lebouc Y, Froguel P, Guy-Grand B. Nature 1998;392(6674):398–401.

Considine RV, Considine EL, Williams CJ, Nyce MR, Magosin SA, Bauer TL, Rosato EL, Colberg J, Caro JF. J Clin Invest 1995;95(6):2986–8.

Devos R, Richards JG, Campfield LA, Tartaglia LA, Guisez Y, van der Heyden J, Travernier J, Plaetinck G, Burn P. Proc Natl Acad Sci U S A. 1996;93(11):5668–73.

Dunbar JC, Hu Y, Lu H. Diabetes 1997;46(12):2040–3.

Eckert ED, Pomeroy C, Raymond N, Kohler PF, Thuras P, Bowers CY. J Clin Endocrinol Metab. 1998;83(3):791–5.

Eikelis N, Lambert G, Wiesner G, Kaye D, Schlaich M, Morris M, Hastings J, Socratous F, Esler M. Am J Physiol Endocrinol Metab. 2004;286(5):E744–52.

Eikelis N, Esler M, Barton D, Dawood T, Wiesner G, Lambert G. Mol Psychiatry. 2006;11(9):800–1.

Eikelis N, Wiesner G, Lambert G, Esler M. Regul Pept. 2007;139(1–3):45–51.

El-Haschimi K, Pierroz DD, Hileman SM, Bjorbaek C, Flier JS. J Clin Invest. 2000;105(12):1827–32.

Elmquist JK, Elias CF, Saper CB. Neuron 1999;22(2):221–32.

Esler M, Vaz M, Collier G, Nestel P, Jennings G, Kaye D, Seals D, Lambert G. Lancet 1998;351(9106):879.

Fei H, Okano HJ, Li C, Lee GH, Zhao C, Darnell R, Friedman JM. Proc Natl Acad Sci U S A. 1997;94(13):7001–5.

Golden PL, Maccagnan TJ, Pardridge WM. J Clin Invest. 1997;99(1):14–8.

Grasso P, Leinung MC, Ingher SP, Lee DW. Endocrinology 1997;138(4):1413–8.

Guan XM, Hess JF, Yu H, Hey PJ, van der Ploeg LH. Mol Cell Endocrinol. 1997;133(1):1–7.

Hashimoto H, Fujihara H, Kawasaki M, Saito T, Shibata M, Otsubo H, Takei Y, Ueta Y. Endocrinology 2007;148(4):1638–47.

Hassink SG, de Lancey E, Sheslow DV, Smith-Kirwin SM, O'Connor DM, Considine RV, Opentanova I, Dostal K, Spear ML, Leef K, Ash M, Spitzer AR, Funanage VL. Pediatrics 1997;100(1):E1.

Haynes WG, Morgan DA, Walsh SA, Mark AL, Sivitz WI. J Clin Invest. 1997;100(2):270–8.

Hebebrand J, Blum WF, Barth N, Coners H, Englaro P, Juul A, Ziegler A, Warnke A, Rascher W, Remschmidt H. Mol Psychiatry. 1997;2(4):330–4.

Hennessy JW, Grossman SP. Physiol Behav. 1976;17(1):103–9.

Jimerson DC, Mantzoros C, Wolfe BE, Metzger ED. J Clin Endocrinol Metab. 2000;85(12):4511–4.

Kaye W, Gendall K, Strober M. Biol Psychiatry. 1998; 44(9):825–38.

Kennedy GC. Proc R Soc Lond B Biol Sci. 1953;140(901):578–96.

Klein DA, Mayer LE, Schebendach JE, Walsh BT. Psychoneuroendocrinology 2007;32(5):539–47.

Kolaczynski JW, Considine RV, Ohannesian J, Marco C, Opentanova I, Nyce MR, Myint M, Caro JF. Diabetes 1996;45(11):1511–5.

Kontoyannia P, Katsilambros N, Theophanides C, Dragines E. Eur Neurol. 1974;11(2):128–32.

Lonnqvist F, Arner P, Nordfors L, Schalling M. Nat Med. 1995;1(9):950–3.

Madej T, Boguski MS, Bryant SH. FEBS Lett. 1995;373(1):13–8.

Maffei M, Stoffel M, Barone M, Moon B, Dammerman M, Ravussin E, Bogardus C, Ludwig DS, Flier JS, Talley M, et al. Diabetes 1996;45(5):679–82.

Mantzoros C, Flier JS, Lesem MD, Brewerton TD, Jimerson DC. J Clin Endocrinol Metab. 1997;82(6):1845–51.

Mark AL, Shaffer RA, Correia ML, Morgan DA, Sigmund CD, Haynes WG. J Hypertens. 1999;17(12 Pt 2):1949–53.

Mercer JG, Hoggard N, Williams LM, Lawrence CB, Hannah LT, Trayhurn P. FEBS Lett. 1996;387(2–3):113–6.

Mercer JG, Moar KM, Hoggard N. Endocrinology 1998;139(1):29–34.

Misra A, Ganesh S, Shahiwala A, Shah SP. J Pharm Pharm Sci. 2003;6(2):252–73.

Montague CT, Farooqi IS, Whitehead JP, Soos MA, Rau H, Wareham NJ, Sewter CP, Digby JE, Mohammed SN, Hurst JA, Cheetham CH, Earley AR, Barnett AH, Prins JB, O'Rahilly S. Nature 1997;387(6636):903–8.

Monteleone P, Martiadis V, Colurcio B, Maj M. Psychosom Med. 2002;64(6):874–9.

Morash B, Li A, Murphy PR, Wilkinson M, Ur E. Endocrinology 1999;140(12):5995–8.

Newcomer JW, Selke G, Melson AK, Gross J, Vogler GP, Dagogo-Jack S. Arch Gen Psychiatry. 1998;55(11):995–1000.

Pinto S, Roseberry AG, Liu H, Diano S, Shanabrough M, Cai X, Friedman JM, Horvath TL. Science 2004;304(5667):110–5.

Porte D Jr., Woods SC. Diabetologia 1981;20(Suppl):274–80.

Remschmidt H, Schmidt MCG. Prediction of long-term outcome in anorectic patients from longitudinal weight measurements during inpatient treatment: a cross validation study. Child and youth psychiatry: Europen perspectives, vol. 1. Anorexia Nervosa. Toronto: Hogrefe & Huber; 1990. p. 150–67.

Schwartz MW, Peskind E, Raskind M, Boyko EJ, Porte D Jr. Nat Med. 1996;2(5):589–93.

Sclafani A, Ackroff K, Schwartz GJ. Physiol Behav. 2003;78(2):285–94.

Sinha MK, Opentanova I, Ohannesian JP, Kolaczynski JW, Heiman ML, Hale J, Becker GW, Bowsher RR, Stephens TW, Caro JF. J Clin Invest. 1996;98(6):1277–82.

Strader AD, Woods SC. Gastroenterology 2005;128(1):175–91.

Strobel A, Issad T, Camoin L, Ozata M, Strosberg AD. Nat Genet. 1998;18(3):213–5.

Tartaglia LA. J Biol Chem. 1997;272(10):6093–6.

Tartaglia LA, Dembski M, Weng X, Deng N, Culpepper J, Devos R, Richards GJ, Campfield LA, Clark FT, Deeds J, et al. Cell 1995;83(7):1263–71.

Van Heek M, Compton DS, France CF, Tedesco RP, Fawzi AB, Graziano MP, Sybertz EJ, Strader CD, Davis HR Jr. J Clin Invest. 1997;99(3):385–90.

Villanueva EC, Myers MG Jr. Int J Obes (Lond). 2008;32(Suppl 7):S8–12.

Wallace AM, McMahon AD, Packard CJ, Kelly A, Shepherd J, Gaw A, Sattar N. Circulation 2001;104(25):3052–6.

Wiesner G, Vaz M, Collier G, Seals D, Kaye D, Jennings G, Lambert G, Wilkinson D, Esler M. J Clin Endocrinol Metab. 1999;84(7):2270–4.

Wilsey J, Zolotukhin S, Prima V, Scarpace PJ. Am J Physiol Regul Integr Comp Physiol. 2003;285(5):R1011–20.

Wolfe BE, Metzger E, Jimerson DC. Psychopharmacol Bull. 1997;33(3):345–54.

Zhang Y, Proenca R, Maffei M, Barone M, Leopold L, Friedman JM. Nature 1994;372(6505):425–32.

Zlokovic BV, Jovanovic S, Miao W, Samara S, Verma S, Farrell CL. Endocrinology 2000;141(4):1434–41.

Chapter 85
The Role of Bile Acids in Gut-Hormone-Induced Weight Loss After Bariatric Surgery: Implications for Appetite Control and Diabetes

Rachel E. Roberts, Jamsaid Alaghband-Zadeh, and Carel W. Le Roux

Abbreviations

ARC	Arcuate nucleus
AUC	Area under the curve
BND	Gastric banding
BPD	Biliopancreatic diversion
D2	Type 2 iodothyronine deiodinase
FGF-19	Fibroblast growth factor-19
FXRα	Farnesoid X receptor α
GBP	Gastric bypass
GI	Gastrointestinal
GK	Goto Kakizaki rats
GLP-1	Glucagon-like peptide 1
HbA1C	Hemoglobin A1C
HOMA-IR	Homeostasis model assessment for insulin resistance
MAPK	Mitogen-activated protein kinase
mM	Millimolar
OGTT	Oral glucose tolerance test
PI3K	Phosphoinositide 3-kinase
PYY	Peptide YY
RYGBP	Roux-en-Y gastric bypass
T2DM	Type 2 diabetes mellitus
TGR5	G-protein-coupled receptor TGR5

85.1 Introduction

Obesity is a growing problem, which the World Health Organization predicts will affect 700 million people by 2015 (WHO 2006). The impact of obesity on national health services is unparalleled when considering its cardiovascular, metabolic, neoplastic, reproductive, musculoskeletal,

R.E. Roberts (✉)

Discipline of Medicine, School of Medicine, King's College London, 2nd Floor, Henriette Raphael House, Guy's Campus, London Bridge, London, SE1 1UL, UK

email: rachel.roberts@kcl.ac.uk; rachelroberts100@googlemail.com

and psychosocial complications. Bariatric surgery has become an increasingly popular option in the management of obesity and obesity-related complications. Proposed mechanisms for the success of weight loss post bariatric surgery include gastric restriction, mild malabsorption, alterations in neural signals, duodenal exclusion, and early delivery of nutrients to the distal small intestine (Moo and Rubino 2008). These changes may alter secretion of metabolically active gastrointestinal (GI) hormones ghrelin, peptide YY (PYY), and glucagon-like peptide-1(GLP-1) (Korner et al. 2005; Chan et al. 2006). In addition to the success of bariatric surgery in inducing weight loss there is also substantial evidence supporting its efficacy in controlling type 2 diabetes mellitus (T2DM), even before substantial weight loss has occurred. Increased concentrations of GLP-1 may account for the improved glycemic control via its incretin action. The mechanisms of increased PYY and GLP-1 concentrations post bariatric surgery are not clear. Altered anatomy following bariatric surgery accelerates the delivery of nutrient-dense chyme to the distal intestine to stimulate increased secretion of gut hormones. It is possible that co-delivery of bile acids within the chyme enhances the stimulation of gut hormone release.

85.2 Roux-en-Y Gastric Bypass Surgery

Roux-en-Y gastric bypass (RYGBP) is the most frequently performed gastric bypass (GBP) surgery. It involves division of the stomach into a small proximal pouch (which holds about 15–30 mL) and a larger distal portion, which is bypassed (Fig. 85.1). The small pouch is anastomosed to the distal part of the jejunem, which is divided 30–75 cm from the ligament of Treitz. The remaining distal portion of the stomach, the duodenum, and proximal jejunem are reattached to the GI tract at a variable distance from the gastrojejunostomy, usually 75–150 cm, to allow for excretion of GI and pancreatic juices. This results in food bypassing 95% of the stomach, the entire duodenum, and a section of the jejunum (Saber et al. 2008). More than 70% of the small bowel remains in continuity and thus malabsorption of calories does not usually occur. RYGBP results in an initial weight loss of 20–40%, which is largely maintained over at least 15 years (Cummings et al. 2004).

85.3 Mechanisms of Weight Loss and Diabetes Reversal After Bariatric Surgery

The mechanisms of weight loss following GBP surgery are incompletely understood. Several hypotheses have been put forward. Reduced gastric capacity post-RYGBP certainly results in early symptoms of satiety and consequently patients eat smaller meals (Trostler et al. 1995). However, if this were the sole cause of weight loss a compensatory mechanism would come into effect to increase food intake and reduce energy expenditure in response to the weight loss, and patients would increase energy intake by eating more frequently and choosing energy-dense foods (Tadross and le Roux 2009). Instead, it has been found that after RYGBP surgery patients typically eat fewer meals and snacks per day (Halmi et al. 1981; Kenler et al. 1990). Furthermore purely restrictive surgeries, such as gastric banding (BND), require production of smaller gastric pouches than RYGBP before significant weight loss occurs, and BND is less successful in terms of weight loss and appetite control compared with GBP surgery (Biertho et al. 2003). Malabsorption of nutrients has also been proposed as a mechanism of weight loss after RYGBP (Brolin et al. 2002). Although initially this is true once
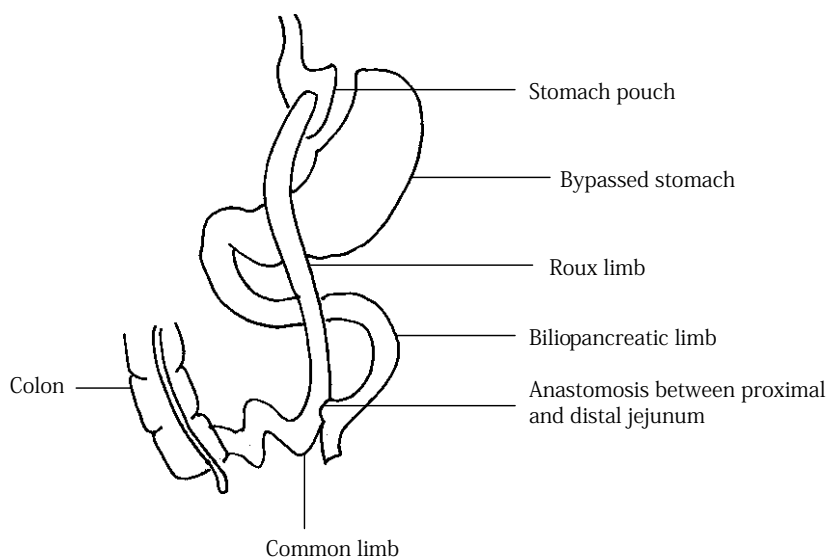
Fig. 85.1 Schematic representation of the Roux-en-Y gastric bypass (RYGBP). Roux-en-Y gastric bypass (RYGBP) involves division of the stomach into a small proximal pouch and a larger distal portion, which is bypassed. The small pouch is anastomosed to the distal part of the jejunem and the larger distal portion is reattached further down the gastrointestinal (GI) tract to allow for excretion of GI and pancreatic juices

the gut has adapted clinically significant malabsorption measured by serum markers of nutritional status such as albumin, prealbumin, and fecal fat, is not observed (Faraj et al. 2001; MacLean et al. 2001; Brolin 2002). The "dumping syndrome," which is a physiological response to consuming simple sugars, is also a possible mechanism of weight loss post-RYGBP. Following high-carbohydrate meals sugars are rapidly "dumped" into the small intestine, causing an osmotic load, which results in a fluid shift from the blood into the intestine. In some patients, this can cause symptoms of nausea, bloating, colic, diarrhea, lightheadedness, sweating, and palpitations (Hertz 1913). These unpleasant symptoms can promote avoidance of high-sugar foods, which may contribute to weight loss. However, the dumping syndrome is not universally experienced by patients following RYGBP and the severity of dumping correlates poorly with the efficacy of RYGBP (Cummings et al. 2004). It is therefore unlikely that dumping plays a major role in weight loss following RYGBP. Perhaps the most important factor in determining weight loss post-RYGBP is the profound loss of appetite which ensues (Brolin 2002). There is also a significant change in feeding behavior following GBP with patients reporting less frequent episodes of hunger, overeating, guilt about eating, or food preoccupation than morbidly obese control subjects (Rand et al. 1987). Gut hormones are important regulators of appetite and energy expenditure and several studies have shown that changes in gut hormone profiles following bariatric surgery favor an anorectic state, facilitate weight loss, and improve metabolic parameters (Korner et al. 2005).

In addition to the weight loss achieved following bariatric surgery it has also been widely observed that dramatic improvements in glycemic control in subjects with T2DM occur, specifically following RYGBP (Pories et al. 1995). It is estimated that bariatric surgery resolves T2DM in 76% of patients (Buchwald et al. 2004). Weight loss plays an important role in the reversal of T2DM following bariatric surgery but many patients with T2DM have significant improvement in glycemic control, discontinuing all antidiabetic medication and even achieving normal fasting plasma glucose

concentrations before significant weight loss has occurred (Clements et al. 2004). It has been proposed that these immediate improvements in diabetic control may be the result of altered gut hormone profiles following bariatric surgery.

85.4 Contribution of Gut Hormones to Weight Loss and Reversal of T2DM Post Bariatric Surgery

A number of peptides released from the GI tract have been shown to play an integral role in appetite control and food intake. Ghrelin is the only known gut hormone to stimulate appetite while PYY, glucagon-like peptide-1 (GLP-1), cholecystokinin, and oxyntomodulin suppress appetite. These hormones work at the level of the arcuate nucleus (ARC) in the hypothalamus to exert their orexigenic and anorexigenic effects (Schwartz and Morton 2002). The improvements in glycemic control, reduction in appetite, and weight loss following GBP surgery may be the result of changes in circulating gut hormone concentrations.

Several prospective studies of RYGBP have shown an exaggerated postprandial response of PYY compared to placebo (Vincent and le Roux 2008). Both peak and area under the curve (AUC) postprandial PYY concentrations have been found to be increased following RYGBP (Korner et al. 2009). The increased PYY response post-RYGBP is to concentrations previously shown to have appetite-reducing effects in humans (Batterham et al. 2003). The increase in postprandial PYY has been reported to occur as early as 2 days after bypass suggesting that the exaggerated response is secondary to the intervention per se and not to weight loss (Chaikomin et al. 2005). However, once substantial weight loss has occurred after RYGBP, the PYY response to the oral glucose tolerance test (OGTT) is significantly higher than in controls, demonstrating that changes in PYY concentrations following RYGBP persist after weight loss occured (Borg et al. 2006). Interestingly the postprandial response of PYY following RYGBP is strikingly greater than that after BND, perhaps accounting for the greater weight loss seen in RYGBP compared to BND (Korner et al. 2006). A study of matched RYGBP and BND subjects demonstrated that inhibition of gut hormone release by administration of octreotide (a somatostatin analogue) increased appetite and food intake in the RYGBP subjects by 87% but not in the BND patients, further implicating gut hormones in the regulation of food intake after RYGBP (le Roux et al. 2007).

In addition to raised postprandial plasma PYY concentrations, postprandial GLP-1 concentrations are also increased following RYGBP (Borg et al. 2006) although no differences have been found in fasting GLP-1 concentrations (Clements et al. 2004). Furthermore, in a cross-sectional analysis of patients post-RYGBP, AUC of PYY and GLP-1 was greater in "good" compared with "poor" responders (le Roux et al. 2007). GLP-1 concentrations are also raised after jejunoileal bypass (Naslund et al. 1997). Increased concentrations of GLP-1 are thought to contribute to increased insulin sensitivity and improvement in glycemic control as well as to increased satiety following RYGBP (Naslund et al. 1997).

RYGBP was initially shown to suppress serum concentrations of the orexigenic hormone ghrelin compared with stable weight individuals, despite significant weight loss (Cummings et al. 2002). However, subsequent studies have found inconsistent results regarding ghrelin concentrations post-GBP (Copeland et al. 2003; Faraj et al. 2003; Fruhbeck et al. 2004; Couce et al. 2003; Geloneze et al. 2003; Holdstock et al. 2003; Leonetti et al. 2003; Tritos et al. 2003; Vidal et al. 2003; Stoeckli et al. 2004; Vendrell et al. 2004) indicating it is unlikely that ghrelin has a major role in weight loss post-RYGBP.

85.5 Why Do PYY and GLP-1 Concentrations Rise Post-GBP Surgery?

The mechanism of increased PYY and GLP-1 concentrations post-GBP is not entirely understood. PYY and GLP-1 are predominantly secreted by L-cells of the distal gut following nutrient ingestion (Anini et al. 1999). L-cells are the most abundant endocrine cell type in the colon and ileum (Bryant et al. 1983). Altered anatomy post-GBP results in rapid transit of nutrients to the distal gut. This may increase nutrient-dependent stimulation of L-cells and thus greater secretion of GLP-1 and PYY. In addition to nutrients, Bile acids also stimulate PYY and GLP-1 release. In RYGBP surgery, the anastomosis of the bypassed stomach, duodenum, and proximal jejunem to the distal small intestine allows GI and pancreatic juices to be directly excreted into the distal small intestine, bypassing a significant proportion of the GI tract, resulting in increased exposure of L-cells to bile acids, which may represent a second mechanism by which concentrations of PYY and GLP-1 increase following RYGBP.

85.5.1 Hindgut Theory

The "hindgut hypothesis" was first described by Mason (Mason 1999) and proposes that the rapid transit and greater exposure of nutrients to the distal terminal ileum (a common feature of GBP and biliopancreatic diversion (BPD)) is responsible for the improvement in glycemic control after surgery and for the enduring effects on glucose metabolism (Patriti et al. 2004a,b; Patriti et al. 2004, 2005). It has been suggested that increased postprandial GLP-1 concentrations are responsible for the metabolic success of the hindgut hypothesis (Mason 1999; Cummings et al. 2004; Patriti et al. 2004). Ileal transposition (IT) is a surgical manipulation designed to allow assessment of the exclusive role of ileal activation as a mediator of surgically induced weight loss. The procedure involves resecting a 10–20 cm portion of the distal ileum, and then transposing it into the proximal jejunum. Following IT there is premature delivery of nutrient-rich chyme to the ileum, as in jejunoileal bypass, but the total length of the bowel is unaffected and malabsorption is absent. Strader et al. (2005) performed ITs in rats and found that they lost more weight and consumed less food than control rats with intestinal transections and reanastomosis without transposition. Rats with IT also had increased synthesis and release of GLP-1 and PYY. To avoid the effects of postoperative weight loss on insulin resistance and GLP-1 and insulin secretion, Patriti et al. (2005) used a model of nonobese diabetic Goto-Kakizaki (GK) rats, whose weight is not affected by IT. This study showed that glucose tolerance improved during an OGTT 30 days after IT without any effect on weight or food intake. A possible mechanism for the improvement in glycemic control could be the incretin effect of GLP-1 as GLP-1 concentrations were significantly higher in the IT diabetic group compared with the sham-operated rats. Patriti et al. later showed that GLP-1 secretion in GK IT rats was characterized by a more sustained response during OGTT and increased pro-glucagon mRNA expression in the ileum compared with sham-operated or nonoperated controls. However, they found no effect on glucose-stimulated GLP-1 concentrations by 6 months postsurgery (Patriti et al. 2007). Clinically performed IT in patients with T2DM and a mean BMI of 30.1 kg/m^2 showed promising results with mean weight loss of 22% (postsurgery BMI 24.9 kg/m^2) and adequate glycemic control in 86.9% with decreased HbA1C (by 28%), fasting glucose (by 44.6%), postprandial glucose (by 45.3%), and HOMA-IR (by 50%), heralding it as a promising procedure for the control of T2DM (DePaula et al. 2008). Unfortunately, GLP-1 concentrations were not measured in this study.

85.5.2 Bile Acid Theory

Bile consists of bile acids, cholesterol, phosphatidylcholine, and bilirubin. Bile is synthesized in the liver and secreted from hepatocytes into the bile canaliculi. Bile acid synthesis from cholesterol is the principal pathway for cholesterol catabolism. Bile acids constitute a large family of molecules composed of a steroid structure with four rings and a five or eight carbon side-chain terminating in a carboxylic acid. Each bile acid has a specific number and orientation of hydroxyl groups (-OH). The principal primary bile acids in humans are cholic acid and chenodeoxycholic acid. Before bile acids leave the liver they are conjugated to either glycine or taurine, forming bile salts, such as glycocholic acid and taurochenodeoxycholic acid. Bile salts have an enhanced amphipathic nature to enable greater emulsifying activity for more effective dietary lipid absorption in the GI tract. Once in the GI tract intestinal flora can remove glycine or taurine from the bile salts, regenerating primary bile acids. Intestinal flora can then convert some of the primary bile acids into secondary bile acids by removing a hydroxyl group, for example cholic acid becomes deoxycholic acid and chenodeoxycholic acid becomes lithocholic acid. Bile is stored in the gallbladder. When a meal is ingested bile flows via the common bile duct into the duodenum. Ninety-five percent of bile salts are reabsorbed in the terminal ileum. Blood from the ileum flows directly to the hepatic portal vein and returns to the liver where the hepatocytes reabsorb the bile salts and return them to the bile ducts to be re-used (Fig. 85.2). Each bile acid can complete 4–12 cycles between the liver and intestine each day (Cohen 2003). Owing to this efficient recycling of bile salts only a small proportion of the bile acid pool is derived from de novo bile acid synthesis (Champe et al. 2005).

In addition to their role in lipid metabolism and cholesterol homeostasis bile acids act as signaling molecules. Three main signaling pathways activated by bile acids have been described: bile acids activate mitogen-activated protein kinase (MAPK) pathways (Gupta et al. 2001; Qiao et al. 2003), are ligands for the G-protein coupled receptor TGR5 (Maruyama et al. 2002; Kawamata et al. 2003), and activate nuclear hormone receptors such as farnesoid X receptor α (FXRα) (Mangelsdorf et al. 1995; Makishima et al. 1999; Parks et al. 1999), a ligand-activated transcription factor (Mangelsdorf et al. 1995). By activation of these pathways bile acids can regulate their own enterohepatic circulation, as well as cholesterol, triglycerides, energy, and glucose homeostasis, giving bile acids an important systemic endocrine function (Houten et al. 2006).

Bile acids have been shown to prevent high-fat-diet-induced obesity and development of insulin resistance (Ikemoto et al. 1997). Administration of bile acids to mice increases energy expenditure in brown adipose tissues, thus preventing obesity and insulin resistance via induction of the cyclic-AMP-dependent thyroid hormone activating enzyme type 2 iodothyronine deiodinase (D2) (Watanabe et al. 2006). This study also showed that *in vitro* treatment of brown adipocytes and human skeletal myocytes with bile acid increases D2 activity and oxygen consumption. These effects are medicated by increased cAMP production resulting from the binding of bile acids with TGR5. In addition bile acid stimulation of FXRα may also mediate the effects of bile acids on energy homeostasis via fibroblast growth factor-19 (FGF-19) induction, which activates a signaling pathway culminating in improved metabolic rate and decreased adiposity (Tomlinson et al. 2002; Holt et al. 2003; Inagaki et al. 2005).

Bile acids play a significant role in glucose metabolism. In humans, circulating bile acid concentrations correlate with measures of insulin sensitivity (Shaham et al. 2008). Modulation of bile acid homeostasis using bile acid sequestrants has been shown to have an effect on glucose metabolism. An assessment of the efficacy and tolerability of cholestyramine in patients with T2DM and dyslipidemia unexpectedly revealed it to also improve glycemic control (Garg and Grundy 1994). More recent clinical trials have shown a similar effect of the bile acid sequestrant colesevelam in
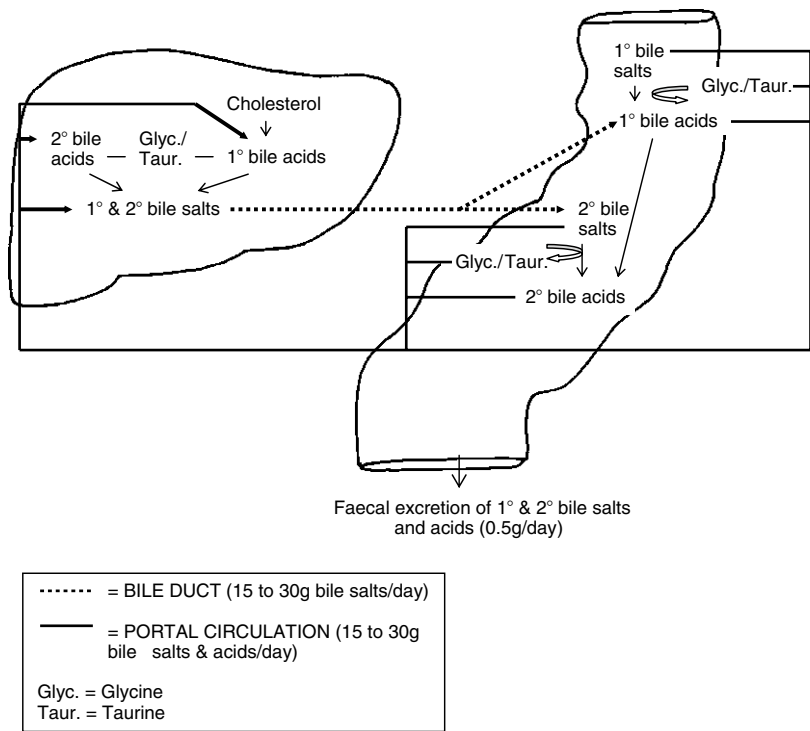
Fig. 85.2 Enterohepatic circulation of bile salts and bile acids. Primary (1°) bile acids are synthesized from cholesterol in the liver. Bile acids enter a complex pathway in the liver and gastrointestinal (GI) tract in order for effective dietary lipid absorption to take place. Ninety-five percent of bile salts are recycled and re-used via this pathway

improving glycemic control (Fonseca et al. 2008; Goldberg et al. 2008). The mechanisms by which bile acids improve glycemic control are likely to be multifactorial. They are largely thought to be FXRα-independent and are instead mediated by binding to TGR5, leading to cAMP generation and activation of the intracellular type 2 thyroid hormone deiodinase (Yamagata et al. 2004). Bile acids also act via the phosphoinositide 3-kinase (PI3 kinase)/AKT pathway, directly promoting insulin signaling and glycogen synthase activation, thus aiding insulin-dependent control of glucose metabolism in the liver (Han et al. 2004). It is also thought that bile acids affect glucose metabolism indirectly via their influence on body weight. As outlined above, bile acids increase energy expenditure in brown adipose tissues and stimulate FGF-19-dependent metabolic control. In addition bile acid activation of TGR5 has been found to stimulate GLP-1 production *in vitro*, which promotes insulin secretion, thus improves glucose metabolism (Katsuma et al. 2005).

A role of bile acids in appetite suppression was proposed as early as 1968 (Bray and Gallagher 1968). Bile acids are known to be strong stimulators of PYY and GLP-1 release with direct infusion of deoxycholate into the colon increasing secretion of enteroglucagon (proglucagon-derived peptide products of the L-cell including GLP-1) and PYY in humans (Adrian et al. 1993). Bile acids also promote GLP-1 release *in vitro* (Katsuma et al. 2005). Several studies have demonstrated the importance of bile acids, in combination with fatty acids, in the stimulation of PYY release. Infusion of fatty acid oleic acid alone was not found to stimulate PYY or GLP-1 release (Soper et al. 1990; Adrian et al. 1993), whereas infusion of a high dose of oleic acid (24%) emulsified with 10 millimolar (mM) of bile acid deoxycholic acid did cause significant PYY and GLP-1 release (Adrian et al. 1993). In isolated perfused rabbit colon, graded doses of oleic acid (0.22–22 mM)

suspended in 10 mM of deoxycholic acid did not cause a concentration-dependent increase in PYY concentrations whereas graded doses of deoxycholic acid (1–25 mM) alone did cause a concentration-dependent release of PYY in the portal circulation (Ballantyne et al. 1989). In canines, intraileal infusion of oleic acid (56.6 mM) alone failed to stimulate a PYY response (Wen et al. 1995), whereas oleic acid combined with taurocholate did stimulate PYY release in dogs (Aponte et al. 1985). These observations indicate that bile acids deoxycholic acid and taurocholic acid combined with fatty acids are more significant than fatty acids alone in stimulating PYY release in the ileum. Bile acid infusions of taurocheodeoxycholate and deoxycholate at 1–25 mM in the isolated perfused rabbit ileum and colon have been shown to increase serum PYY concentrations to more than 400 pmol/L (Ballantyne et al. 1989; Armstrong et al. 1993). In addition, deoxycholate infusion at 1–30 mM in the human colon stimulates PYY release in a dose-dependent manner (Adrian et al. 1993). Importantly, the concentrations of bile acids used in these studies are consistent with the physiological concentrations bile acids found in the intestinal lumen postprandially (Dietschy 1968), supporting a physiological role of bile acids in the stimulation of PYY release. However, not all bile acids have been found to stimulate PYY release. Taurocholic acid and deoxycholic acid, as mentioned, are effective in stimulating PYY release, whereas hyodexycholate (Plaisancié et al. 1996) and ursodeoxycholate (Ballantyne et al. 1989) have shown no effect on PYY release. The reason for differences found in specific bile acid stimulation of PYY release is not clear. It is likely that increased GLP-1 and PYY release is a contributory mechanism of bile acid-dependent appetite suppression.

The multifactorial mechanisms promoting weight loss and improved glycemic control following RYGBP are incompletely understood. As discussed, bile acids can mediate energy homeostasis, glucose metabolism, and appetite by several mechanisms including activation of the G-protein-coupled receptor TGR5 and type 2 thyroid hormone deiodinase enzyme, stimulation of FGF-19, and promotion of PYY and GLP-1 release. It has been proposed that altered upper intestinal tract anatomy post-GBP surgery may affect the enterohepatic circulation of bile acids, resulting in increased serum bile acid concentrations which may contribute to the improved carbohydrate and lipid metabolism observed in patients post-GBP surgery. Total serum bile acid concentrations are demonstrated to be more than twice as high in individuals 2–4 years after GBP surgery than in overweight or severely obese individuals who have not had bariatric surgery (Patti et al. 2009). The increased bile acids included both primary and secondary bile acids, and reached statistical significance for glycochenodeoxycholic (more than a fourfold increase), glycodeoxycholic, glycocholic, and taurodeoxycholic acids. In this study, total bile acid concentrations post-GBP correlated significantly with several key parameters of lipid and glucose metabolism. Total bile acid concentrations positively correlated with plasma adiponectin, a marker of insulin sensitivity, and postprandial peak concentrations of GLP-1 and total bile acid concentrations inversely correlated with 2-hour postprandial glucose concentrations and fasting glucose (Patti et al. 2009). It may be inferred from these data that the resolution of T2DM seen after GBP may be the result of improved insulin sensitivity (as indicated by increased concentrations of adiponectin) and incretin-mediated insulin secretion (as indicated by increased concentrations of GLP-1) although none of the subjects had T2DM before GBP, this needs further investigation. Unfortunately, PYY concentrations were not measured in this study. However, as both PYY and GLP-1 are secreted from the same L-cells in the distal intestine and release of both PYY and GLP-1 is stimulated by bile acids, it is likely that the rise in postprandial concentrations of GLP-1 would be mirrored by rises in PYY. It is therefore likely that bile acid-dependent increases in postprandial GLP-1 and PYY concentrations are partly responsible for the success of GBP surgery in terms of both weight loss and glycemic control.

One cited limitation of this study was that it measured only peripheral serum concentrations of bile acids (Patti et al. 2009). Although serum bile acid concentrations are correlated with portal

venous concentrations (Angelin et al. 1982), they cannot provide direct information about the complex enterohepatic circulation of bile acids. Therefore, it is uncertain whether the increase in bile acid concentration is the result of increased synthesis and secretion by the liver, increased active and passive reabsorption from the small intestine, increased return to the liver via the portal vein, or by more efficient hepatic uptake.

85.6 Conclusion

It is possible that the mechanisms involved in increasing GLP-1 and PYY concentrations post-GBP (increased bile acid concentrations and the hindgut hypothesis) are not mutually exclusive. Together with the rapid transit and greater exposure of nutrients to the distal small intestine, GBP surgery also delivers a more rapid load of bile acids to the distal intestine. Both nutrients and bile acids are known stimulators of endocrine L-cells, which are concentrated in the terminal ileum (Fig. 85.3). Therefore, it may be the cumulative effect of greater bile acid and nutrient delivery to the distal small intestine that causes the rise in gut hormones PYY and GLP-1, and consequent weight loss and reversal of T2DM, which is so well documented after bariatric surgery (Fig. 85.4).

Fig. 85.3 Schematic diagram to show proposed mechanism of increased L-cell stimulation after Roux-en-Y gastric bypass (RYGBP). Following Roux-en-Y gastric bypass (RYGBP) there may be greater exposure of both nutrients and bile acids to the distal terminal ileum resulting in increased PYY and GLP-1 secretion from endocrine L-cells

Fig. 85.4 Summary figure showing the proposed model for mechanisms of type 2 diabetes mellitus (T2DM) remission after GBP. It is likely that there are multiple mechanisms in which gastric bypass (GBP) may improve T2DM. These mechanisms can either work via weight loss or independent of weight loss

85.7 Applications to Other Areas of Health and Disease

Understanding the mechanism of weight loss and improved glycemic control after bariatric surgery has important implications for the future treatment of obesity and type 2 diabetes mellitus (T2DM).

The National Institute for Clinical Excellence (NICE) currently recommends bariatric surgery in patients with a BMI > 40 kg/m² without comorbidities or between 35 and 40 kg/m² in patients with significant comorbidities. In view of its beneficial effects in improving glycemic control, it may be appropriate to offer bariatric surgery to patients with lower BMIs who have comorbid T2DM, especially in cases of significant insulin resistance or when simple weight-loss methods and pharmacological treatment have proved ineffective.

In future pharmacological approaches that mimic the physiological changes seen after bariatric surgery could prove beneficial in treating patients with obesity and T2DM. For example, therapeutic agents based on targeted bile acid delivery to the distal small intestine may reduce appetite, stimulate weight loss, and improve glycemic control in patients with obesity and T2DM. Pharmacological agonists of receptors activated by bile acid-dependent pathways, for example TGR5 and FXRα could be successful in improving glycemic control. Activation of TGR5 increases energy expenditure *in vivo* and in cultured cells (Watanabe et al. 2006) and increases GLP-1 in cell lines (Katsuma et al. 2005). Further work *in vivo* is required to determine whether such agents are efficacious in humans.

One limitation of many studies that demonstrate increased gut hormone concentrations after bariatric surgery is that they have been conducted on nondiabetic subjects. These results have then been used as a possible explanation for the mechanisms of improved glycemic control in diabetic patients after bariatric surgery. Therefore, further research needs to be done directly on diabetic subjects to validate this mechanism in the diabetic population and to investigate the role that duration and severity of diabetes may play in determining the success of treating T2DM with bariatric surgery.

Summary Points

- Gut hormones play an integral role in appetite control and food intake. PYY and GLP-1 act in the hypothalamus to suppress appetite. GLP-1 also has an important incretin effect, thereby improving glycemic control.
- PYY and GLP-1 are both secreted by endocrine L-cells predominantly found in the distal small intestine. Both nutrients and bile acids are known stimulators of PYY and GLP-1 secretion.
- Roux-en-Y gastric bypass (RYGBP) is the most frequently performed and most successful surgery to treat obesity. It results in food bypassing 95% of the stomach, the entire duodenum, and a section of the jejunum. The mechanisms of weight loss following RYGBP are incompletely understood.
- RYGBP can dramatically improve glycemic control in subjects with T2DM. These improvements occur before significant weight loss has occurred. It has been proposed that these immediate improvements in diabetic control may be the result of altered gut hormone profiles following bariatric surgery.
- Following RYGBP PYY and GLP-1 concentrations are increased. It is likely that altered intestinal anatomy following RYGBP enables quicker transit and greater exposure of both nutrients and bile acids to the distal terminal ileum resulting in increased L-cell stimulation and PYY and GLP-1 secretion.
- Understanding the mechanism of weight loss and improved glycemic control after bariatric surgery has important implications for the future treatment of obesity and T2DM. Pharmacological compounds that stimulate bile acid-dependent pathways are a possible therapeutic option in improving metabolic conditions such as T2DM.

Definitions and Explanations of Key Terms and Words

Anorexigenic: Decreasing or inhibiting appetite.

Bariatric surgery: Surgical intervention for the treatment of morbid obesity.

Bile acids: Steroid acids found predominantly in bile. The two major bile acids are cholic acid and chenodeoxycholic acid. The main function of bile acids is to facilitate the formation of micelles, which promotes processing of dietary fat.

Bile salts: Bile acids conjugated to glycine or taurine. In humans, taurocholic acid and glycocholic acid (derivatives of cholic acid) represent approximately 80% of all bile salts. Bile salts have an enhanced amphipathic nature to enable greater emulsifying activity for more effective dietary lipid absorption in the GI tract.

Ghrelin: A 28-amino acid peptide produced predominantly by X/A-like cells of the mucosal layer in the fundus of the stomach. Ghrelin is the only known orexigenic hormone, and plays a role in regulating premeal hunger and meal initiation as well as long-term energy balance. Ghrelin also stimulates growth hormone release, lactotroph and corticotroph secretion, gastric motility and has cardiovascular effects.

Glucagon-like peptide-1: A 30-amino acid peptide, which is cleaved from its precursor preproglucagon. GLP-1 inhibits gastric motility, reduces gastric emptying, and inhibits gastric acid secretion. GLP-1 also has an important incretin effect and suppresses glucagon secretion, enhances glucose disposal, and inhibits food intake.

Incretins: A group of GI hormones that enhance glucose-dependent insulin secretion from beta cells of the islets of Langerhans after eating, thereby improving glucose tolerance.

L-cells: The most abundant endocrine cell type in the distal small intestine. The apical surface of L-cells has microvilli, which are in contact with the intestinal lumen allowing them to sense nutrients.

The basal surface of L-cells is rich in endocrine granules allowing secretion of hormones into the circulation. L-cells secrete peptide YY (PYY), proglucagon-derived peptides such as glucagon-like peptide 1 (GLP-1), glucagon-like peptide 2 (GLP-2), glicentin, and oxyntomodulin (OXM).

Orexigenic: Increasing or stimulating appetite.

Peptide YY: A 36-amino acid GI hormone, where Y depicts the abbreviation for tyrosine. It is a member of the pancreatic polypeptide family and mediates its effects through G-protein linked NPY receptors. PYY has an important role in appetite control. It stimulates satiety and reduces food intake. It also inhibits transit through the proximal small intestine, delays gastric emptying, and inhibits gallbladder emptying.

Roux-en-Y gastric bypass: Division of the stomach into a small proximal pouch and a larger distal portion, which is bypassed. The small pouch is anastomosed to the distal jejunem. The remaining distal portion of the stomach, the duodenum, and proximal jejunem are reattached to the GI tract distal to the gastrojejunostomy to allow for excretion of GI and pancreatic juices. It is a type of bariatric surgery.

Type 2 diabetes mellitus: A disorder characterized by high blood glucose in the context of insulin resistance and relative insulin deficiency.

Key Facts About PYY

- PYY is a 36-amino acid GI hormone, where Y depicts the abbreviation for tyrosine. PYY exists in two forms – the full-length peptide PYY1-36, which is truncated to the biologically active PYY3-36 by dipeptidyl peptidase-IV. PYY3-36 is the predominant form.
- PYY is a member of the pancreatic polypeptide family, which includes pancreatic polypeptide (PP) and neuropeptide Y (NPY), which mediate their effects through G-protein-linked NPY receptors of which there are several subtypes (Y1R, Y2R, Y4R, and Y5R represent fully defined subtypes).
- PYY is secreted by L-cells of the distal gut, together with glucagon-like peptide and oxynto-modulin. Peripheral neurons, especially enteric neurons, also express PYY, as do a restricted set of central neurons.
- Secretion of PYY in the GI tract is primarily stimulated by the presence of nutrients (mainly lipids and protein) in the gut lumen, and is proportional to the caloric density of the meal ingested. Other stimulants of PYY release include intraluminal bile acids, gastric acid, and cholecystokinin. Peak plasma concentrations of PYY occur in the second hour following food ingestion.
- PYY reduces food intake, inhibits transit through the proximal small intestine, delays gastric emptying, and inhibits gallbladder emptying.
- PYY secretion stimulates vagal and somatosensory afferent fibers arising in the GI tract and terminating at the nucleus tractus solitarius (NTS) of the brainstem, which transmit information pertaining to recent food intake. Neurons from the NTS can then relay this information to the ARC of the hypothalamus, a key component of the forebrain pathway involved in appetite control. PYY can also act directly in the brain via the blood, entering at areas where the blood–brain barrier is deficient.
- In obese humans, plasma concentrations of PYY are reduced. Genetic variations in PYY and NPY receptor Y2R genes may contribute to obesity and are associated with the severe obesity of Pima Indian men.
- In contrast, PYY concentrations have been found to be increased in disease states characterized by significant weight loss, such as anorexia nervosa, celiac disease, inflammatory bowel disease, and cardiac cachexia.

References

Adrian TE, Ballantyne GH, Basson MD, Bilchik AJ, Graham S, Longo WE, Modlin IM, Tierney RP Gut 1993;34:1219–24.

Angelin B, Björkhem I, Einarsson K, Ewerth S J Clin Invest. 1982;70:724–31.

Anini Y, Chariot J, Cuber JC, Fu-Cheng X, Kervran A, Roz C Pflugers Arch. 1999;438:299–306.

Aponte GW, Fink AS, Meyer JH, Tatemoto K, Taylor IL Am J Physiol. 1985;249:G745–50.

Armstrong DN, Ballantyne GH, Krenz HK, Modlin IM Gut 1993;34:483–8.

Ballantyne GH, Adrian TE, Bilchik AJ, Longo WE, Modlin IM, Savoca PE, Sussman J, Vukasin AP Am J Physiol. 1989;257:G715–24.

Batterham RL, Bloom SR, Cohen MA, Ellis SM, Frost GS, Ghatei MA, le Roux CW, Withers DJ N Engl J Med. 2003;349:941–8.

Biertho L, Gagner M, Herron D, Horber FF, Inabnet WB, Pomp A, Ricklin T, Steffen R J Am Coll Surg. 2003;197:536–44.

Borg CM, Aylwin SJB, Bloom SR, Ghatei MA, le Roux CW, Patel AGBr J Surg. 2006;93:210–5.

Bray GA, Gallagher TFJ Lancet. 1968;1:1066–7.

Brolin RE. JAMA 2002;288:2793–96.

Brolin RE, Cody RP, Kenler HA, LaMarca LB J Gastrointest Surg. 2002;6:195–203.

Bryant MG, Bloom SR, Demling L, Domschke S, Domschke W, Hobbs S, Mitznegg P, Polak JM, Ruppin H Gut 1983;24:114–9.

Buchwald H, Avidor Y, Braunwald E, Fahrbach K, Jensen MD, Pories W, Schoelles K JAMA 2004;292:1724–37.

Chaikomin R, Doran S, Feinle-Bisset C, Horowitz M, Jones KL, O'Donovan D, Rayner CK Am J Physiol Endocrinol Metab. 2005;289:E504–7.

Champe PC, Harvey RA, Ferrier DR In: Champe PC, Harvey RA, editors. Biochemistry. Philadelphia: Lippincott Williams & Wilkins; 2005. p. 217–42.

Chan JL, Goldfine AB, Mantzoros CS, Mun EC, Stoyneva V Obesity (Silver Spring) 2006;14:194–8.

Clements RH, Gonzalez QH, Laws HL, Long CI, Wittert G Am J Surg. 2004;70:1–4.

Cohen DE. In: Zakim D, Boyer TD, editors. Hepatology: a textbook of liver disease. Philadelphia: Saunders; 2003. p. 1713–43.

Copeland P, Davis P, Kaplan L Obes Res. 2003;11:A17.

Couce M, Burguera B, Cottam D, Esplen J, Schauer PR, Teijeiro R Obes Res. 2003;11:A35.

Cummings DE, Breen PA, Dellinger EP, Frayo RS, Ma MK, Purnell JQ, Weigle DS N Engl J Med. 2002;346:1623–30.

Cummings DE, Foster-Schubert KE, Overduin J J Clin Endocrinol Metab. 2004;89:2608–15.

DePaula AL, Halpern A, Macedo AL, Machado CA, Rassi N, Schraibman V, Silva LQ Surg Endosc. 2008;22:706–16.

Dietschy JM. J Lipid Res. 1968;9:297–309.

Faraj M, Cianflone K, Jones P, Sniderman AD J Lipid Res. 2001;42:571–80.

Faraj M, Blank D, Cianflone K, Havel PJ, Phelis S, Sniderman AD J Clin Endocrinol Metab. 2003;88:1594–602.

Fonseca VA, Jones MR, Rosenstock J, Truitt KE, Wang AC Diabetes Care. 2008;31:1479–84.

Fruhbeck G, Diez CA, Gil MJ N Engl J Med. 2004;350:308–9.

Garg A, Grundy SM Ann Intern Med. 1994;121:416–22.

Geloneze B, Geloneze SR, Pareja JC, Pilla VF, Repetto EM, Tambascia MA Obes Surg. 2003;13:17–22.

Goldberg RB, Fonseca VA, Jones MR, Truitt KE Arch Intern Med. 2008;168:1531–40.

Gupta S, Dent P, Hylemon PB, Stravitz RT J Biol Chem. 2001;11:276.

Halmi KA, Falk JR, Mason E, Stunkard A Int J Obes. 1981;5:457–64.

Han SI, Dent P, Fang Y, Grant S, Gupta S, Hylemonm PB, Li W, Qiao L, Studer E Hepatology 2004;39:456–63.

Hertz AF. Ann Surg. 1913;58:466–72.

Holdstock C, Engstrom BE, Karlsson FA, Lind L, Obrvall M Sundbom M J Clin Endocrinol Metab. 2003;88:3177–83.

Holt JA, Billin AN, Bisi J, Donahee M, Goodwin B, Jones SA, Kliewer SA, Kozarsky KF, Luo G, Mansfield TA, McNeill YY, Wang DY Genes Dev. 2003;17:1581–91.

Houten SM, Auwerx J, Watanabe M EMBO J. 2006;25:1419–25.

Ikemoto S, Ezaki O, Higuchi M, Itakura H, Kawanaka K, Maruyama K, Tabata I, Takahashi M, Tange T, Tsunoda N, Yamamoto TT Am J Physiol. 1997;273:E37–45.

Inagaki T, Choi M, Cummins CL, Gerard RD, Goodwin B, Jones SA, Kliewer SA, Luo G, Mangelsdorf DJ, McDonald JG, Moschetta A, Peng L, Repa JJ, Richardson JA Cell Metab. 2005;2:217–25.

Katsuma S, Hirasawa A, Tsujimoto G Biochem Biophys Res Commun. 2005;329:386–90.

Kawamata Y, Fujii R, Fujino M, Fujisawa Y, Fukusumi S, Habata Y, Harada M, Hinuma S, Hosoya M, Itoh T, Miwa M, Shintani Y, Yoshida H J Biol Chem. 2003;278:9435–40.

Kenler HA, Brolin RE, Cody RP Am J Clin Nutr. 1990;52:87–92.

Korner J, Bessler M, Cirilo LJ, Conwell IM, Daud A, Restuccia NL, Wardlaw SL J Clin Endocrinol Metab. 2005;90:359–65.

Korner J, Bessler M, Conwell IM, Daud A, Inabnet W, Olivero-Rivera L, Restuccia NL, Taveras C Obesity 2006;14:1553–61.

Korner J, Inabnet W, Febres G, Conwell IM, McMahon DJ, Salas R, Taveras C, Schrope B, Bessler M Int J Obes. 2009;33:786–95.

Leonetti F, Bacci V, Basso MS, Basso N, Di Mario U, Lacobellis G, Lannucci CV, Perrotta N, Ribaudo MC, Silecchia G, Tiberti C, Zappaterreno A J Clin Endocrinol Metab. 2003;88:4227–31.

le Roux CW, Bloom SR, Fandriks L, Ghatei MA, Kokkinos A, Laurenius A, Lonroth H, Olbers T, Osborne A, Welbourn R, Werling M Ann Surg. 2007;246:780–5.

MacLean LD, Nohr CW, Rhode BM J Gastrointest Surg. 2001;5:525–30.

Makishima M, Hull MV, Learned RM, Luk A, Lustig KD, Mangelsdorf DJ, Okamoto AY, Repa JJ, Shan B, Tu H Science 1999;284:1362–5.

Mangelsdorf DJ, Beato M, Blumberg B, Chambon P, Evans RM, Herrlich P, Kastner P, Mark M, Schutz G, Thummel C, Umesono K Cell 1995;83:835–9.

Maruyama T, Itadani H, Miyamoto Y, Nakamura T, Okada H, Tamai Y, Tanaka K, Sugiyama E Biochem Biophys Res Commun. 2002;298:714–9.

Mason EE. Obes Surg. 1999;9:223–8.

Moo TA, Rubino F Curr Opin Endocrinol Diabetes Obes. 2008;15:53–8.

Naslund E, Backman L, Gryback P, Hellstrom PM, Holst JJ, Jacobsson H, Theodorsson E Int J Obes Relat Metab Disord. 1997;21:387–92.

Parks DJ, Blanchard SG, Bledsoe RK, Chandra G, Consler TG, Kliewer SA, Lehmann JM, Moore DD, Stimmel JB, Willson TM, Zavacki AM Science 1999;284:1365–8.

Patriti A, Donini A, Facchiano E Ann Surg. 2004a;240:388–9.

Patriti A, Donini A, Facchiano E, Gulla N, Sanna A Obes Surg. 2004b;14:840–8.

Patriti A, Annetti C, Aisa MC, Donini A, Facchiano E, Fanelli C, Galli F Obes Surg. 2005;15:1258–64.

Patriti A, Aisa MC, Annetti C, Donini A, Ferri I, Galli F, Gullà N, Sidoni A Surgery 2007;142:74–85.

Patti ME, Houten SM, Bianco AC, Bernier R, Larsen PR, Holst JJ, Badman MK, Maratos-Flier E, Mun EC, Pihlajamaki J, Auwerx J, Goldfine AB. Obesity 2009; Epub ahead of print.

Plaisancié P, Chayvialle JA, Cuber JC, Dumoulin V J Endocrinol. 1996;151:421–9.

Pories WJ, Barakat HA, Brown BM, deRamon RA, Dolezal JM, Israel G, Long SB, MacDonald KG, Morris PG, Swanson MS Ann Surg. 1995;222:339–50.

Qiao L, Amorino G, Dent P, Engelhardt JF, Fang Y, Gilfor D, Grant S, Gupta S, Han SI, Hylemon PB, Park JS, Sealy L, Valerie K Mol Cell Biol. 2003;23:3052–66.

Rand CS, Hankins GC, Macgregor AM South Med J. 1987;80:961–4.

Saber AA, Elgamal MH, McLeod MK Obes Surg. 2008;18:121–8.

Schwartz MW, Morton GJ Nature 2002;418:595–7.

Shaham O, Carr SA, Gerszten RE, Lewis GD, Mootha VK, Ricciardi C, Thadhani R, Vasan RS, Wang TJ, Wei R Mol Syst Biol. 2008;4:214.

Soper NJ, Brown ML, Chapman NJ, Go VL, Kelly KA, Phillips SF Gastroenterology 1990;98:111–6.

Stoeckli R, Chanda R, Keller U, Langer I Obes Res. 2004;12:346–50.

Strader AD, D'Alessio DA, Jandacek RJ, Seeley RJ, Vahl TP, Woods SC Am J Physiol Endocrinol Metab. 2005;288:E447–53.

Tadross JA, le Roux CW Int J Obes. 2009;33:S28–32.

Tomlinson E, French D, Fu L, Huang X, Hultgren B, John L, Powell-Braxton L, Renz M, Stephan JP, Stewart TA, Tsai SP Endocrinology 2002;143:1741–7.

Tritos NA, Bertkau A, Goldfine A, Grayson R, Maratos-Flier E, Mun E Obes Res. 2003;11:919–24.

Trostler N, Avinoach E, Charuzi II, Mann A, Zilberbush N Obes Surg. 1995;5:39–51.

Vendrell J, Broch M, Gómez JM, Gutiérrez C, Molina A, Richart C, Simón I, Soler J, Vilarrasa N Obes Res. 2004;12:962–71.

Vidal J, Casamitjana R, Gomis R, Moize V, Morinigo R Obes Res. 2003;11:A9.

Vincent RP, le Roux CW Clin Endocrinol (Oxf). 2008;69:173–9.

Watanabe M, Auwerx J, Bianco AC, Christoffolete MA, Ezaki O, Harney JW, Houten SM, Kim BW, Kodama T, Mataki C, Messaddeq N, Sato H, Schoonjans K Nature 2006;439:484–9.

Wen J, Holst JJ, Kost LJ, Phillips SF, Sarr MG Am J Physiol Gastrointest Liver Physiol. 1995;269:G945–52.

WHO. Obesity and overweight: fact sheet No 3111. 2006.http://www.who.int/mediacentre/factsheets/fs311/en/index.html.

Yamagata K, Daitoku H, Fukamizu A, Hirota K, Ishida J, Matsuzaki H, Shimamoto Y J Biol Chem. 2004;279:23158–65.

Chapter 86
Orlistat and the Influence on Appetite Signals

Mark Ellrichmann

Abbreviations

AgRP	Agouti-related peptide
Alpha-MSH	Alpha-melanocyte-stimulating hormone
Apo A-IV	Apolipoprotein A-IV
BMI	Body mass index
BNRP	Bombesin/bombesin-related peptide
CART	Cocaine- and amphetamine-regulated transcript
CCK	Cholecystokinin
CCK1R	CCK-1 receptor
CNS	Central nervous system
CRF	Corticotropin-releasing factor
DPP-4	Dipeptidyl-peptidase-4
FFA	Free fatty acid
GHRH	Growth hormone-releasing hormone
GHS	Growth hormone secretagogue
GI	Gastrointestinal
GIP	Gastric inhibitory polypeptide
GIPR	Gastric inhibitory polypeptide receptor
GLP-1	Glucagons-like peptide 1
GLP-2	Glucagon-like peptide 2
kJ	Kilo joule
MCH	Melanin-concentrating hormone
MG	Monoglyceride
NPY	Neuropeptide Y
OLETF	Otsuka-Long-Evans-Tokushima-Fatty rat
OXM	Oxyntomodulin
PP	Pancreatic polypeptide
POMC	Pro-opiomelanocortin
PYY	Peptide YY

———————————————

M. Ellrichmann (✉)
Department of Medicine I, University Hospital Schleswig Holstein, Campus Kiel,
Schittenhelmstr 12, 24105 Kiel, Germany
e-mail: mark.ellrichmann@rub.de

THL	Tetrahydrolipstatin
TG	Triglyceride
VAS	Visual analogue scales

86.1 Introduction

Over the past decades, the prevalence of overweight and obesity worldwide has reached epidemic proportions. This has been correlated with various comorbidities, the most relevant ones being diabetes mellitus, arterial hypertension, and cardiovascular diseases. The management of obesity has become a modern challenge since nonpharmacological methods have demonstrated only short-term efficacy. Current obesity guidelines recommend that drug therapy should be considered in conjunction with nonpharmacological strategies for patients with a body mass index (BMI) greater than 30 kg/m^2 or a BMI of 25–30 kg/m^2 with one or more obesity-related disorders (Pi-Sunyer 1998). Antiobesity drugs can be classified into two categories: (1) drugs that suppress appetite, increase satiety or thermogenesis, primarily by modifying central nervous system (CNS) neurotransmitters; and (2) inhibitors of intestinal fat absorption.

86.2 Orlistat

Orlistat, also known as tetrahydrolipstatin (THL), is a covalent inhibitor of digestive lipases derived from lipstatin, a natural product from *Streptomyces toxytricini*. It is an active site-directed inhibitor that reacts with the nucleophilic serine residue from the catalytic center of intestinal lipases. By covalently blocking the active site of lipases, orlistat inhibits the hydrolysis of dietary triglycerides (TG) and thus reduces the intestinal absorption of the lipolysis products monoglycerides (MG) and free fatty acids (FFAs) (Lucas et al. 2001) (Fig. 86.1). The formulation of the drug was licensed by the European Union in 1998 and in the United States in 1999 for the treatment of morbid obesity. At the standard prescription dose of 120 mg three times daily before a meal, orlistat prevents approximately 30% of dietary fat from being absorbed (Zhi et al. 1999). Historically, orlistat has been available by prescription only, whereas nowadays certain formulations of orlistat at a dose of 60 mg have been approved in Australia, the European Union, and the Unites States (Table 86.1). The primary side effects of the drug are gastrointestinal (GI)-related, and include steatorrhea, fecal incontinence, frequent or urgent bowel movements, and flatulence. Side effects are most severe when beginning therapy and may decrease in frequency with time. This is supported by the XENDOS study, which showed that only 36% of people had GI adverse effects during their fourth year of taking orlistat, whereas 91% of the study population had experienced at least one GI-related side effect within the first month of treatment (Torgerson et al. 2004).

A recent meta-analysis by Padwal et al. included 11 orlistat studies with a follow-up period of at least 1 year. These trials comprised a total of 6,021 participants with an average BMI of 35.7 kg/m^2. The dose of orlistat used in all studies was 120 mg t.i.d. according to the recommended standard dose in clinical practice. In all reported studies a greater weight loss was reported in the orlistat group compared to placebo. Pooled results revealed a weight loss of 2.7 kg (95% CI: 2.3–3.1 kg; 11 studies) or 2.9% (95% CI: 2.3–3.4%; ten studies) with orlistat treatment (Padwal et al. 2003).
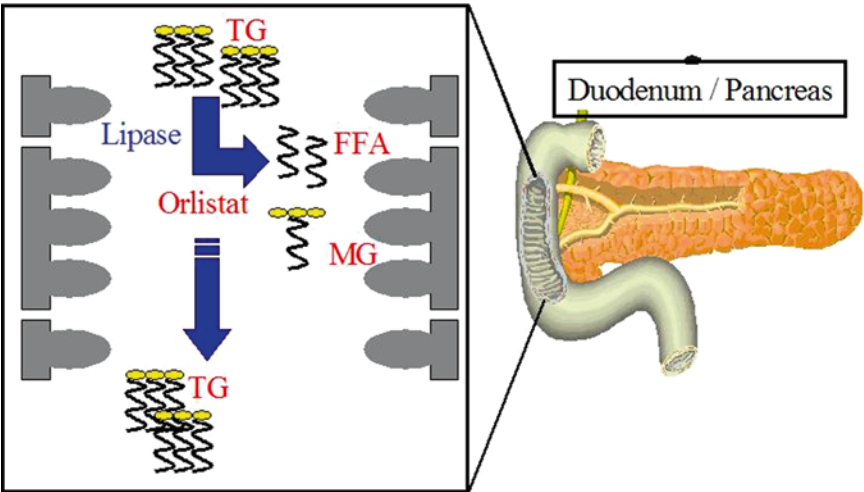
Fig. 86.1 Orlistat – mode of action. Oral administration of orlistat inhibits intestinal lipase and thus prevents dietary triglycerides (TG) from being hydrolyzed in absorbable free fatty acids (FFA) and monoglycerides (MG). About 30% of dietary TG are excreted undigested

Table 86.1   Key facts of orlistat

Orlistat
• Tetrahydrolipstatin
• Antiobesity drug
• Covalently blocks intestinal lipases
• Reduces hydrolysis of TG in MG and FFA by 30%
• 120 mg t.i.d. prescription dose
• 60 mg t.i.d. over-the-counter dose
• Negligible bioavailability
• Approved in the EU in 1998, in the US 1999

TG triglycerides, *MG* monoglycerides, *FFA* free fatty acids

86.3 Orlistat and Satiety

The regulation of body weight is precisely controlled by a variety of gut hormones and peripheral as well as central signals that influence hypothalamic, limbic, and brainstem circuits controlling appetite and energy expenditure. These include cholecystokinin (CCK), glucagon-like peptide (GLP)-1, insulin, and ghrelin among others (Wren et al. 2007). These and various other hormones contributing to the regulation of hunger and satiety are presented in Table 86.2.

While CCK, YY, and GLP-1 have been shown to enhance satiety and reduce the amount of caloric intake, ghrelin has been identified as an endogenous orexigenic factor (Wren et al. 2007). The hypothalamus also receives mechanical signals indicating distension of the stomach, and signals transmitting smell, sight, and social context of food. In addition, velocity of gastric emptying, pyloric pressure, and antro-pyloro-duodenal motility have been shown to modify appetite and satiety (Chaudhri et al. 2006). The secretion of the GI hormones from enteroendocrine cells is primarily controlled by the absorption of nutrients from the gut and can be modulated by variations in the velocity of gastric emptying (Meier et al. 2005). Therefore, inhibition of intestinal lipase would be expected to have extensive effects on GI hormone levels and gastric emptying. However, there has

Table 86.2 Overview of hormones and peptides regulating energy intake

Hormones/peptides involved in hunger	Hormones/peptides involved in satiety
Ghrelin	CCK
Orexin A and B	PP
NPY	PYY
AgRP	GLP-1
MCH	Leptin
Galanin	OXM
Noradrenalin	Amylin
ß-Endorphin	Enterostatin
Dynorphin	Somatostatin
GHRH	BNRP
	Apo A-IV
	Thyrotropin-releasing hormone
	Calcitonin-gene-related peptide
	Serotonin
	Alpha-MSH
	CART
	POMC
	CRF
	Urocortins

Hormones levels that are attenuated by orlistat administration according to the current data are underlined

NPY Neuropeptide Y, *AgRP* Agouti-related peptide, *MCH* Melanin-concentrating hormone, *GHRH* Growth hormone-releasing hormone, *CCK* Cholecystokinin, *PP* Pancreatic poly-peptide, *PYY* Peptide YY, *OXM* Oxyntomodulin, *GLP-1* Glucagon-like peptide 1, *BNRP* Bombesin/bombesin-related peptide, *Apo A-IV* Apolipoprotein A-IV, *Alpha-MSH* Alpha-melanocyte-stimulating hormone, *CART* Cocaine- and amphetamine-regulated transcript, *POMC* Pro-opiomelanocortin, *CRF* Corticotropin-releasing factor

been some controversy regarding the influence of orlistat treatment on the postprandial levels of CCK, PYY, and GLP-1, with some studies reporting significant reductions in the respective hormone levels and others showing normal or even increased concentrations. In a similar way, the effects of intestinal lipase inhibition on appetite control, food intake, and GI motility have been widely debated within the literature. The reasons underlying these discrepancies are yet unclear.

In our own tudy, 25 healthy volunteers were examined with a solid–liquid test meal following oral administration of 120 mg orlistat or placebo in a randomized fashion. Visual analogue scales (VAS) were used to assess feelings of hunger, satiety, fullness, and prospective food consumption over a period of 2 h after meal ingestion. As shown, the feelings of satiety and fullness rose significantly after ingestion of the test meal and declined during the subsequent study period ($p < 0.0001$). Both satiety and fullness were significantly reduced by orlistat administration from 15 to 120 min after the test meal (Fig. 86.2). The mean reduction of satiety by orlistat treatment was 15% ($p < 0.0001$), whereas fullness was lowered by 12% ($p < 0.0001$). Conversely, appetite and prospective food consumption were lowered immediately after meal ingestion and increased subsequently throughout the observation period ($p < 0.0001$). Orlistat significantly increased the mean ratings for appetite and prospective food consumption by 24% or 31%, respectively ($p < 0.0001$) (Ellrichmann et al. 2008). Previous studies have also examined the effects of orlistat on appetite sensations and the corresponding secretion of GI hormones, but conflicting results have been reported. Feinle et al. could show that lipase inhibition prevented the reduction in scores for prospective food consumption and hunger induced by duodenal fat infusion and increased energy intake at a free buffet meal (Feinle et al. 2003). These findings are
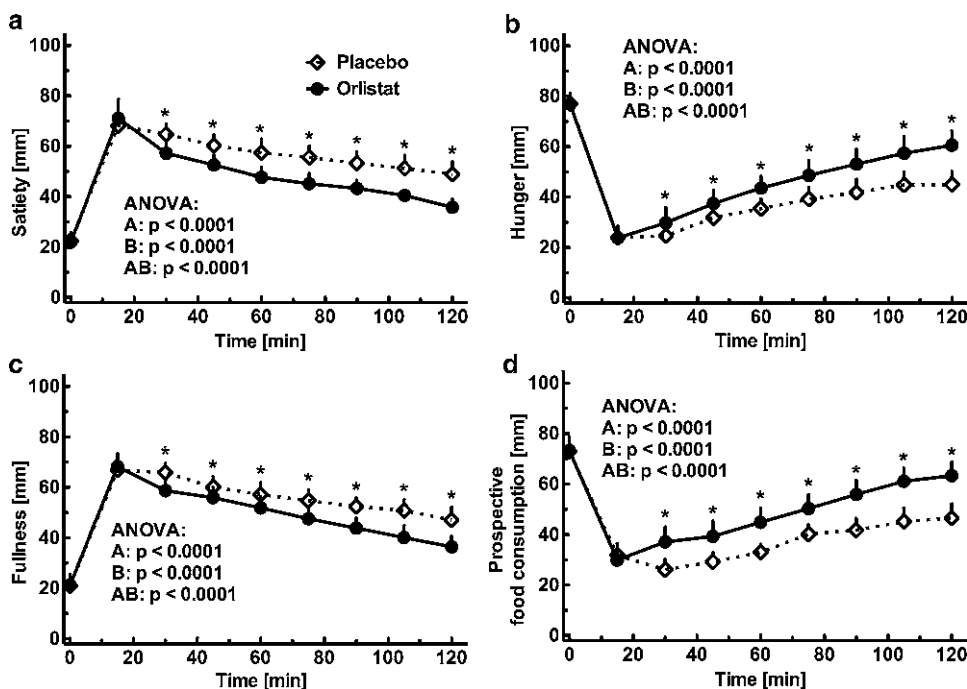
Fig. 86.2 Mean ratings for satiety (**a**), hunger (**b**), fullness (**c**) and prospective food consumption (**d**), as determined by visual analogue scales (VAS), after ingestion of a solid–liquid test meal following oral administration of 120 mg orlistat or placebo in 25 healthy volunteers. Data are presented as means ±SEM. *p*-Values were calculated using paired repeated measures ANOVA and denote A: difference between the experiments, B: differences over time and AB: differences due to the interaction of experiment and time. Asterisks indicate significant difference ($p < 0.05$) versus placebo at individual time points (one-way ANOVA)

consistent with other observations that the decrease in hunger and increase in fullness induced by gastric distension are diminished by lipase inhibition (Feinle et al. 2001). Moreover, these data are in line with other studies indicating that the suppression of food intake by duodenal infusion of olive oil is attenuated when fat digestion is inhibited, underlining the importance of the products of fat digestion in the regulation of appetite perception and food intake (Matzinger et al. 2000) (Table 86.3).

In contrast, Goedecke and colleagues found no effect of orlistat treatment on appetite ratings in healthy male subjects. Orlistat did not alter the ratings of hunger, satiety, and prospective food consumption, when examining changes over time in response to a high-fat meal. In addition, there were no differences in post-test meal intake between orlistat and placebo trials. The reasons underlying the discrepant results of some of these studies are difficult to explain, but certainly methodological issues need to be considered. In particular, different meal compositions and the respective routes of nutrient administration (direct intraduodenal infusions versus oral meal ingestion) might have had an impact on the conflicting results (Goedecke et al. 2003). Nevertheless, the majority of studies support the notion that appetite is acutely increased by orlistat treatment, most likely as a consequence of impaired secretion of anorexigenic GI hormones. The significant increase in appetite and prospective food consumption observed in our as well as previous studies (O'Donovan et al. 2003) may counteract the primary therapeutic indication of orlistat, i.e., the treatment of morbid obesity. Against this, intestinal lipase inhibition has proven to efficiently lower body weight in obese patients over chronic treatment durations (Kelley et al. 2002). Furthermore, in a recent prospective trial over 3 years eating behavior was not affected in a negative way by orlistat

Table 86.3 Effects of orlistat administration on gastrointestinal (GI) hormone regulation

Hormone	Study author (year)	Test meal	Change in hormone release	Comment
CCK	Ellrichmann et al. (2008)	Oral administration	↓	25 healthy volunteers, inverse correlation with hunger scores
	Feinle et al. (2001)	Intraduodenal infusion	↓	Intraduodenal infusion of lipids
	Borovicka et al. (2000)	Intraduodenal infusion	↓	Acceleration of gastric emptying, increase in postprandial gastric acidity
	Hildebrand et al. (1998)	Intraduodenal infusion	↓	Intraduodenal infusion of fat, significant CCK suppression by orlistat
GLP-1	Ellrichmann et al. (2008)	Oral administration	↓	Orally ingested test meal, significant suppression postprandial GLP-1 levels by orlistat
	O'Donovan et al. (2004)	Oral administration	↑	Only 8 patients with type 2 diabetes
	Damci et al. (2004)	Oral administration	↑	Increased GLP-1 plasma levels, decreased food intake
	Feinle et al. (2003)	Intraduodenal infusion	↓	Significantly attenuated GLP-1 levels by orlistat
	Pilichiewicz et al. (2003)	Oral administration	↓	Reduced GLP-1 levels after orlistat administration in type 2 diabetes
PYY	Ellrichmann et al. (2008)	Oral administration	↓	Signification attenuation of PYY by orlistat
	Degen et al. (2007)	Intraduodenal infusion	↓	CCK1R blockade reduced postprandial PYY concentrations
	Feinle et al. (2005)	Intraduodenal infusion	↓	Fat digestion required for PYY secretion
	Feltrin et al. (2006)	Oral administration	↓	CCK-8 infusions stimulate PYY concentrations
PP	Feinle et al. (2005)	Intraduodenal infusion	↓	Fat digestion required for PP secretion
GIP	Enc et al. (2009)	Oral administration	↓	Attenuation of GIP, no significant changes of GLP-1, PYY by orlistat
	Pilichiewicz et al. (2003)	Oral administration	↓	Only 7 patients with type 2 diabetes, attenuation of GIP
Leptin	Sahin et al. (2008)	Oral administration	unchanged	No effect of single dose of orlistat on serum leptin levels, 34 patients
	Dimitrov et al. (2005)	Oral administration	↓	Long-term therapy with orlistat reduces leptin leves, mediated by weight loss
Ghrelin	Ellrichmann et al. (2008)	Oral administration	unchanged	Ghrelin unchanged, due to accelerated gastric emptying
	Degen et al. (2007)	Intraduodenal infusion	↑	Effect mediated indirectly via CCK1R
	Feinle et al. (2005)	Intraduodenal infusion	↑	Elevated ghrelin levels by orlistat, intraduodenal lipid infusion
	Mohlig et al. (2002)	Intraduodenal infusion	↑	Elevated ghrelin levels by orlistat, intraduodenal lipid infusion

Overview of current studies evaluating the effect of orlistat on postprandial hormone levels, i.e., cholecystokinin (CCK), glucagon-like peptide (GLP)1, peptide YY (PYY), pancreatic polypeptide (PP), gastric inhibitory polypeptide (GIP), leptin, and ghrelin

treatment, although hunger ratings were still significantly increased at the end of the observation period. Over 300 obese subjects with a mean BMI of 37.5 ± 4.1 kg/m^2 were randomized to either 120 mg t.i.d or placebo. The scores for hunger were significantly increased in the orlistat group compared to placebo in male subjects after 33 months of treatment. Similar tendencies were observed in women, but did not achieve statistical significance (Svendsen et al. 2008). The acute and long-term effects of orlistat on satiety are mediated by several satiety signals, i.e., GI orexigenic and anorexigenic hormones.

86.4 Orlistat and CCK

Gibbs et al. first demonstrated a dose-dependent effect of exogenous CCK on reducing food intake in rats. This effect was specific to food intake, with CCK having no effect on water intake in water-deprived rats (Gibbs et al. 1973). This finding was subsequently confirmed in humans, in whom an intravenous infusion of the terminal octapeptide of CCK reduced meal size and duration. It has been proposed that the inhibitory effect of CCK on gastric motility might contribute to its inhibitory actions on feeding. CCK may promote excitation of gastric mechanoreceptors, and thus evoke a neural feedback from the gut to appetite centers of the brain (Moran et al. 1988). Similarly, gastric distension in humans was found to augment the reduction of nutrient intake effected by intravenous CCK-8 (Kissileff et al. 2003). CCK also alters food intake through pathways that are independent of its effect on the stomach. While the induction of satiety at higher doses of CCK may be attenuated by surgical removal of the pyloric sphincter, lower doses continue to be effective in inhibiting food intake. Lesioning of the vagus nerve abolishes the effects of CCK (Moran and Kinzig 2004). The induction of satiety by CCK at physiological concentrations may therefore rely on direct activation of vagal afferent fibers. In addition, CCK-1 receptors (CCK1Rs) were found on afferent fibers of the vagus nerve, and also in the brainstem and dorsomedial nucleus of the hypothalamus. The use of specific CCK-1 and CCK-2 receptor antagonists has implicated the CCK1R in the reduction of food intake (Moran et al. 1992). The Otsuka-Long-Evans-Tokushima Fatty (OLETF) rat, which lacks CCK1R, is both hyperphagic and obese, supporting the role of CCK in regulating energy balance (Schwartz et al. 1999).

CCK is released by intestinal I-cells in response to adequate hydrolysis of dietary TG. Hildebrand et al. showed in human studies that endogenous CCK release depends on adequate digestion of dietary fat by pancreatic lipase in the intestinal lumen (Hildebrand et al. 1998). As noted, administration of orlistat covalently inhibits the hydrolysis of dietary TG into MG and FFAs. We have recently established that orlistat significantly impairs CCK release, thereby accelerating gastric emptying and altering ratings of satiety and hunger. In our experiments healthy volunteers were investigated on two occasions, either with orlistat or placebo. Meal ingestion elicited an immediate and pronounced rise in CCK concentrations in the placebo experiments, whereas the increase in CCK levels was largely delayed and significantly blunted after orlistat treatment ($p < 0.0001$). Correlation analysis revealed a positive correlation between integrated CCK serum levels and hunger ratings, and an inverse correlation to satiety levels (Fig. 86.3). We also demonstrated a strong correlation between CCK serum levels and gastric emptying (Ellrichmann et al. 2008).

Borovicka et al. (2000) showed that intragastric administration of orlistat with a stable emulsion of TG, which reduced lipolysis by 75%, inhibited plasma CCK release. When administered intraduodenally, orlistat attenuated the CCK response to a triglyceride emulsion (Hildebrand et al. 1998). These studies are consistent with our findings that intragastric and intraduodenal administration of orlistat attenuates CCK release, via its inhibitory effects on lipolysis.

Fig. 86.3 (**a**) Plasma concentrations of cholecystokinin (CCK) after ingestion of a solid–liquid test meal following oral administration of 120 mg orlistat or placebo in 25 healthy volunteers. Data are presented as means ± SEM. *p*-Values were calculated using paired repeated measures ANOVA and denote A: difference between the experiments, B: differences over time and AB: differences due to the interaction of experiment and time. Asterisks indicate significant difference (*p* < 0.05) versus placebo at individual time points (one-way ANOVA). (**b**, **c**) Linear regression analysis between the integrated incremental plasma concentration of CCK and mean ratings for hunger (**b**) and satiety (**c**) as determined using visual analogue scales (VAS) (*n* = 50). Dashed lines indicate the respective upper and lower 95% confidence interval. r^2 = correlation coefficient squared, *p* < 0.05 statistically significant
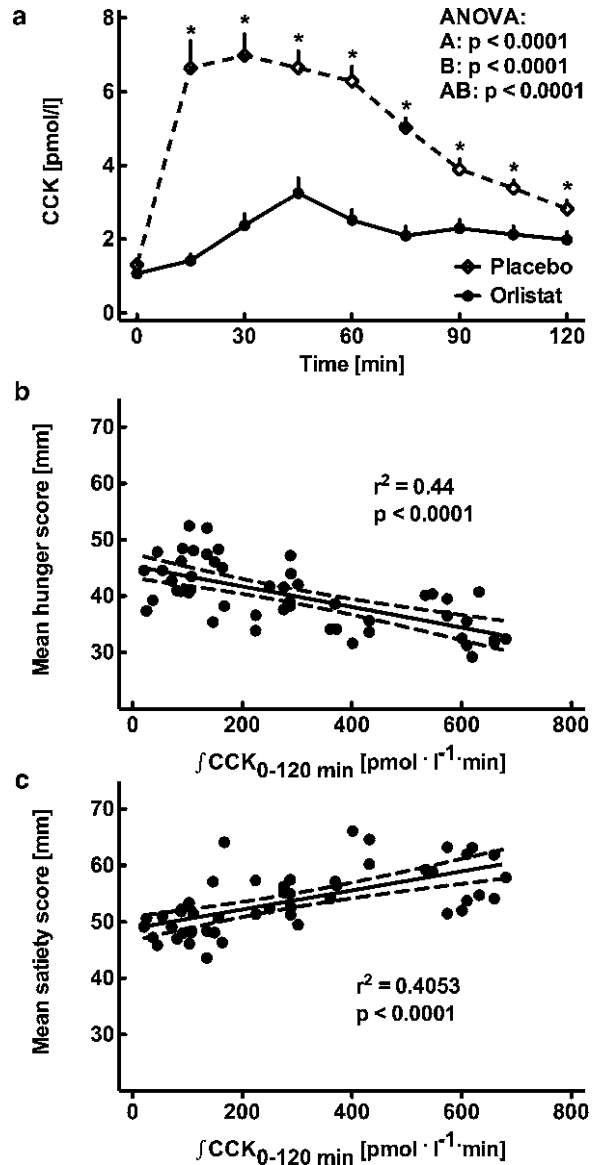
86.5 Orlistat and GLP-1

Glucagon-like peptide (GLP)-1 is cleaved from preproglucagon within the intestine, where it is co-localized in the endocrine L-cells of the distal gut with OXM, PYY, and GLP-2. GLP-1 mediates glucose-dependent insulinotropic effects in a number of species, inhibits gastric acid secretion and gastric emptying, as well as suppresses glucagon release and promotes an increase in pancreatic β-cell mass (Meier and Nauck 2005). Consistent with its role as an incretin, GLP-1 is released into the circulation in response to a meal in proportion of calories ingested (Orskov et al. 1994). In common with other gut peptides, GLP-1 works as a neurotransmitter within the CNS. It is present within the dorsovagal complex, the thalamus, and the pituitary, in key areas of the hypothalamus involved

in appetite regulation GLP-1-immunoreactive neurons were found (Larsen et al. 1997). Food intake data from human studies are concordant with animal studies. GLP-1 dose-dependently decreases appetite and caloric intake in lean and obese subjects and in patients with type 2 diabetes (Gutzwiller et al. 1999). A meta-analysis by Verdich et al. concluded that infusion of GLP-1 reduces both appetite and food intake with the magnitude of this reduction being similar in lean and obese men (Verdich et al. 2001).

The impact of orlistat administration on postprandial GLP-1 secretion has been debated in the literature. Damci et al. found that lipase inhibition stimulates the meal-mediated secretion of GLP-1. In this study, only a single blood sample was obtained 60 min after a meal in diabetic patients (Damci et al. 2004). O'Donovan et al. revealed that orlistat administration may exacerbate postprandial glycemia as a result of accelerated gastric emptying (O'Donovan et al. 2004). These observations need to be critically considered. In a study conducted by Feinle et al., the effect of lipase inhibition by orlistat on gastric emptying, antro-pyloro-duodenal motility, satiety, and GLP-1 levels was investigated. Healthy volunteers were given a TG emulsion via 120 min duodenal infusion either with orlistat or placebo. Immediately after the duodenal infusion, food intake at an ad libitum buffet was quantified. Lipase inhibition with orlistat resulted in significantly reduced postprandial GLP-1 levels. In addition, administration of orlistat was associated with markedly higher scores of prospective food consumption and hunger and greater food intake at the subsequent buffet. They conclude that GLP-1 secretion depends on adequate hydrolysis of TG into MG and FFA in the upper part of the small intestine (Feinle et al. 2003). In patients with type 2 diabetes, the ingestion of orlistat together with a liquid meal containing oil and glucose also accelerates gastric emptying and attenuates the postprandial rise in GLP-1 (Pilichiewicz et al. 2003). Furthermore, Beysen et al. demonstrated differential stimulation of GLP-1 release by different types of oral fat (monounsaturated, olive oil; polyunsaturated, softflower oil; saturated, palm stearin). The greatest increase in GLP-1 was observed after fat containing monounsaturated fatty acids (Beysen et al. 2002). These findings are in line with our own data showing that in healthy volunteers peak GLP-1 levels following orlistat treatment were 20% lower compared to placebo. Likewise, the integrated concentrations of GLP-1 were significantly lower following orlistat administration. These lowered GLP-1 levels were associated with reduced satiety ratings (Fig. 86.4).

86.6 Orlistat and PYY

Peptide YY (PYY) is released into the circulation in response to a meal from L-cells of the GI tract in proportion to the calories ingested and in relation to the meal composition (Wren et al. 2007). Higher plasma levels are seen following isocaloric meals of fat compared to meals consisting of protein or carbohydrate. The release of PYY in response to fat in the proximal intestine is atropine-sensitive, raising the possibility that a neural reflex involving the vagus nerve may mediate PYY release (Lin and Taylor 2004). Other stimulants of PYY release include intraluminal bile acids, gastric acid, and CCK (Onaga et al. 2002). PYY3-36 has a central role in the control of appetite in humans as supported by a number of observations. In disease states characterized by weight loss PYY3-36 levels are elevated (Le Roux et al. 2005). Conversely, in obese humans fasting plasma levels of PYY3-36 are reduced in overweight patients having a relative deficiency of postprandial PYY3-36 release associated with reduced satiety (Batterham et al. 2003b).

Degen et al. used orlistat to determine whether inhibition of fat hydrolysis affects the release of PYY. In their study, PYY secretion in response to intraduodenal fat in the small intestine was completely abolished by orlistat administration (Degen et al. 2007). The data are in line with previous

Fig. 86.4 (**a**) Plasma concentrations of glucagon-like peptide (GLP)1 after ingestion of a solid–liquid test meal following oral administration of 120 mg orlistat or placebo in 25 healthy volunteers. Data are presented as means ± SEM. *p*-Values were calculated using paired repeated measures ANOVA and denote A: difference between the experiments, B: differences over time and AB: differences due to the interaction of experiment and time. Asterisks indicate significant difference ($p < 0.05$) versus placebo at individual time points (one-way ANOVA). (**b**, **c**) Linear regression analysis between the integrated incremental plasma concentration of GLP-1 and mean ratings for hunger (**b**) and satiety (**c**) as determined using visual analogue scales (VAS) ($n = 50$). Dashed lines indicate the respective upper and lower 95% confidence interval. r^2 = correlation coefficient squared, $p < 0.05$ statistically significant
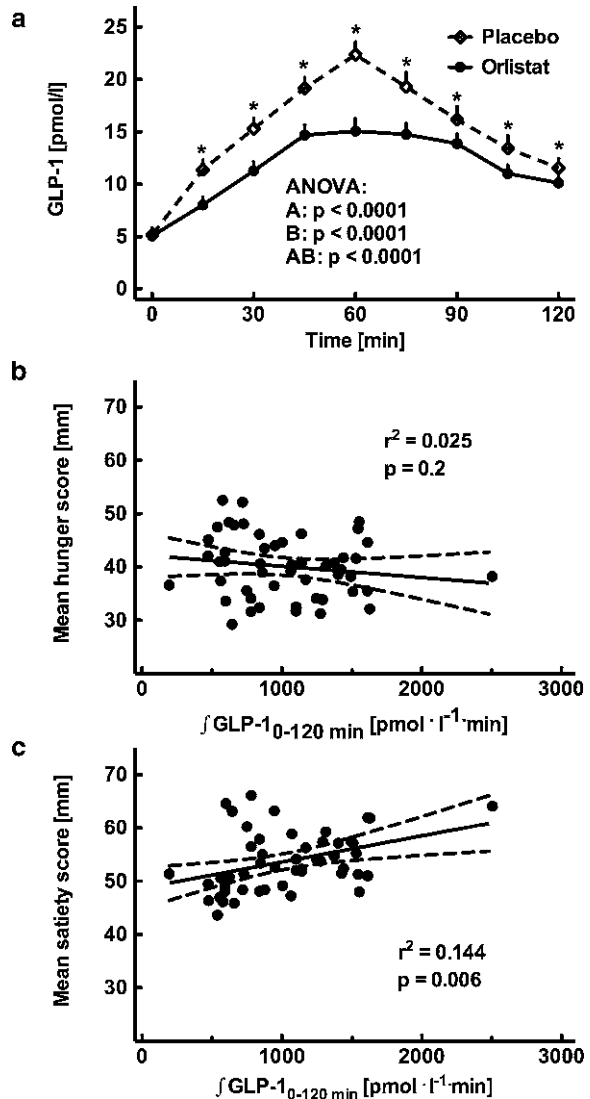
studies: suppression of fat hydrolysis by orlistat inhibits the release of PYY (Feinle et al. 2005). The crucial importance of fat hydrolysis on digestive functions is illustrated by the effects of these products on exocrine pancreatic responses in animals and humans. Only duodenal infusion of long-chain FFAs can stimulate maximal pancreatic enzyme secretion, whereas undigested long-chain TG are ineffective (Lin and Taylor 2004). Inhibition of lipolysis by orlistat reduces the amount of FFAs in the small intestine with a subsequent reduction in PYY release. The reduction in PYY release attenuates inhibitory appetite circuits resulting in further food intake. This hypothesis was confirmed by our work. Meal ingestion elicited a significant rise in PYY levels in both experiments, but the increase in PYY levels was significantly attenuated by orlistat treatment. The reduction in PYY responses resulted in increased ratings for hunger compared to control, though correlation analysis failed to reach statistical significance (Fig. 86.5) (Ellrichmann et al. 2008). This indicates that PYY may play a minor role in enteroendocrine appetite regulation.

Fig. 86.5 (**a**) Plasma concentrations of peptide YY (PYY) after ingestion of a solid–liquid test meal following oral administration of 120 mg orlistat or placebo in 25 healthy volunteers. Data are presented as means ± SEM. *p*-Values were calculated using paired repeated measures ANOVA and denote A: difference between the experiments, B: differences over time and AB: differences due to the interaction of experiment and time. Asterisks indicate significant difference (*p* < 0.05) versus placebo at individual time points (one-way ANOVA). (**b**, **c**) Linear regression analysis between the integrated incremental plasma concentration of PYY and mean ratings for hunger (**b**) and satiety (**c**) as determined using visual analogue scales (VAS) (*n* = 50). Dashed lines indicate the respective upper and lower 95% confidence interval. r^2 = correlation coefficient squared, *p* < 0.05 statistically significant

PYY secretion is initiated either directly via luminal contact of nutrients to the endocrine cells or indirectly through neurohumoral signals such as CCK. Since a CCK1R antagonist (Dexlox) completely abolished PYY response to intraluminal FFAs, it is conceivable that the products of fat digestion stimulate CCK release, which in turn regulates PYY secretion via CCK1Rs (Degen et al. 2007).

86.7 Orlistat and PP

Pancreatic polypeptide (PP) is produced largely not only in the PP-cells of the endocrine pancreas, but also in the exocrine pancreas, colon, and rectum. Like PYY, PP is released into the circulation in response to a meal in proportion to the caloric intake. Low levels of PP have been found in obese

patients (Glaser et al. 1988), and high levels in patients with anorexia nervosa (Fujimoto et al. 1997). Both basal and postprandial PP release is subject to control by the vagus nerve as proved by truncal vagotomoy. Both truncal vagotomy and atropine have been shown to reduce meal-induced PP release in humans (Meguro et al. 1995). PP secretion is also controlled by other gut hormones, including ghrelin, motilin, and secretin, all of which stimulate PP release, and somatostatin, which potently inhibits (Gomez et al. 1997).

A recent study evaluating the effects of duodenal infusion of a long-chain TG infusion with or without 120 mg THL revealed that lipase inhibition completely abolishes the postprandial PP release. In response to a subsequent free buffet meal, PP levels were stimulated in both groups with and without application of THL. In addition, the THL group consumed significantly more food at the buffet than the control group. This may suggest that, in contrast to PYY, gastric distension, enhanced by the greater amount of food eaten, may be a more potent stimulus for PP (Feinle-Bisset et al. 2005). Moderate gastric distension with a 600 mL balloon has been shown to cause a substantial increase in PP secretion in healthy volunteers (Koop et al. 1990). Alternatively, it is possible that other macronutrients, carbohydrate and protein, are more potent stimuli than fat. Batterham et al. demonstrated that PP infusion reduces both appetite and food intake in healthy subjects. In addition, inhibition of food intake was sustained, such that energy intake, assessed by food diaries, was significantly reduced both in the evening of the study and the following morning. Plasma levels of PP remain elevated for up to 6 h postprandially suggesting that PP may regulate meal-to-meal intervals (Batterham et al. 2003). Conversely, reduced PP levels induced by orlistat treatment may shorten meal-to-meal intervals and increase food uptake per meal by attenuating satiety signals. Further studies are required to establish these potential mechanisms.

86.8 Orlistat and GIP

The first incretin hormone to be identified was isolated from porcine small intestine and was initially named gastric inhibitory polypeptide (GIP), based on its ability to inhibit gastric acid secretion in dogs. Since the inhibitory effect on gastric acid secretion was only observed at pharmacological doses, whereas its incretin action occurred at physiological levels, GIP was renamed as glucose-dependent insulinotropic polypeptide (Meier et al. 2002). In accordance with its role as an incretin hormone, GIP is released from K-cells of the small intestine in response to glucose and fat ingestion, and thus potentiates glucose-stimulated insulin secretion. While the effects of GIP on insulin secretion have been studied extensively, only limited information is available about its effects on lipid homeostasis. The potent stimulation of GIP secretion after high-fat meals, as well as the observation of increased GIP plasma levels in obesity, suggested a role of GIP as an anabolic regulator of fat metabolism. The anabolic effects of GIP in fat include stimulation of fatty acid synthesis, enhancement of insulin-stimulated incorporation of fatty acids into TG, upregulation of lipoprotein lipase synthesis, and reduction of glucagon-stimulated lipolysis (Meier et al. 2002). Ob/ob mice with a GIP receptor (GIPR) knock-out are resistant to diet-induced obesity and exhibit reduced adipocyte mass. GIPR-/- mice expend more energy and use fat as preferred energy substrate, thereby preventing the accumulation of fat in adipocytes. Food intake is comparable in GIPR-/- and wild-type mice (Miyawaki et al. 2002). In humans, no direct links between GIP and obesity as well as appetite regulation have been demonstrated. Since GIP is released into the circulation in response to fat ingestion, the role of lipase inhibition on postprandial GIP response was investigated by several groups. According to Enc et al., orlistat administration induced profound attenuation of postprandial GIP response. With ingestion of the control mixed meal, plasma GIP levels increased significantly and

remained elevated throughout the experimental period. Orlistat significantly lowered GIP response as expressed by integrated areas under the curve (Enc et al. 2009). Pilichiewicz et al. evaluated the effect of orlistat on gastric emptying and plasma GIP response in patients with type 2 diabetes. This study also showed reduced postprandial GIP secretion and accelerated gastric emptying by orlistat treatment (Pilichiewicz et al. 2003). It is therefore likely that orlistat by its ability to inhibit intestinal lipid absorption attenuates postprandial GIP release. Despite the well-characterized effects of GLP-1 on appetite and food intake, the role of GIP in feeding regulation remains unclear. Peripheral infusion of GIP at a rate shown to elicit supraphysiological plasma concentrations increases feelings of hunger in healthy lean volunteers ($p < 0.05$). Comparing hunger responses between healthy lean subjects and obese patients with type 2 diabetes during GIP infusion, a trend for higher hunger scores was observed in lean subjects, though this trend failed to reach statistical significance ($p > 0.05$). Despite these findings, ad libitum food intake during a buffet lunch at the end of the infusions was similar in the GIP and placebo group (Daousi et al. 2008). Whether these potential effects of GIP on appetite regulation are relevant under physiological conditions remains questionable.

86.9 Orlistat and Leptin

Adipose tissue, once considered to be a relatively passive site of lipid storage, is known to carry a number of complex metabolic and endocrine functions. One important hormonal factor is the protein leptin, which was isolated and synthesized following positional cloning of the gene responsible for obesity in the ob/ob mouse strain. Leptin is synthesized and released from white adipose tissue and circulates to the brain where it binds to its receptor. It acts to decrease weight and adipose tissue mass through reduction in appetite and food intake. Detected synthesis of leptin within the gastric mucosa raised the possibility that it may also play a role in meal termination (Peters et al. 2005). Markedly elevated leptin levels have been shown in obese humans compared to nonobese, conversely leptin levels markedly decline in underweight patients compared to normal-weight subjects (Haluzik et al. 1999). Only two studies have investigated the effect of lipase inhibition on serum leptin levels. Sahin et al. studied the acute effects of orlistat on postprandial leptin levels in nondiabetic obese patients. Although serum leptin levels showed a more horizontal and delayed increase after a mixed meal in patients in the orlistat group than they had in the placebo group, there were no statistical differences between these two groups (Sahin et al. 2008). A long-term, 3-month prospective study was conducted in 40 patients with clinical features of metabolic syndrome either with or without coexisting type 2 diabetes. In addition to a hypocaloric diet, these patients were given orlistat t.i.d. They observed beneficially enhanced weight loss by orlistat accompanied by decreased serum leptin concentrations (Dimitrov et al. 2005). These changes cannot be regarded as direct effects by lipase inhibition but as indirect effects due to the significant weight loss.

86.10 Orlistat and Ghrelin

Ghrelin acts as the endogenous ligand for the growth hormone secretagogue (GHS) receptor secreted primarily by the stomach to the circulation although ghrelin mRNA is present throughout the whole GI tract. Ghrelin is a peripherally active appetite-stimulating gut hormone. Ghrelin levels rise in the fasting state and fall upon eating, which has led to the suggestion that ghrelin may be involved in meal initiation. The postprandial suppression of ghrelin does not require the vagus nerve, but vagal

afferents are necessary for the rise of ghrelin in the fasted state (Wren et al. 2007; Cummings et al. 2001). The exact mechanisms responsible for postmeal suppression of ghrelin are not known. Both carbohydrate and fat, when ingested orally, suppress ghrelin secretion, whereas protein may stimulate ghrelin release or may have no effect (Greenman et al. 2004). Postprandial decline of ghrelin levels significantly depends on the caloric load of the meal: a larger caloric load produces a lower nadir in ghrelin levels after a meal than a smaller one of similar volume (Callahan et al. 2004). Recent evidence in humans suggests that both PYY and oxyntomodulin (OXM) suppress concentrations of ghrelin when given peripherally, PP having no effect (Batterham et al. 2003).

Feinle et al. documented that duodenal infusion of a long-chain TG emulsion potently suppresses ghrelin secretion in healthy young man. This emulsion given with THL completely abolished ghrelin suppression, indicating that ghrelin secretion is sensitive to digested fat, an effect apparently not mediated by an increase in blood FFAs (Feinle et al. 2005). These findings are consistent with the data obtained by Degen et al. Intraduodenal infusion of fat induced a significant inhibition in ghrelin levels ($p < 0.01$) and a significant increase in PYY concentrations ($p < 0.02$). Inhibition of lipolysis by orlistat completely abolished both effects. In addition, administration of a specific CCK1R antagonist together with intraduodenal infusion of fat abolished the effect of long-chain fatty acids on ghrelin and PYY secretion. These authors conclude that fat hydrolysis in the proximal small intestine plays a crucial role for digestive processes. Free fatty acids stimulate the release of CCK, which in turn acts on CCK1Rs thereby initiating a series of digestive functions, including modulation of CCK-1-dependent ghrelin secretion (Degen et al. 2007). The data are contrasted by our own results showing no effect of orlistat on postprandial ghrelin concentrations (Ellrichmann et al. 2008). The size, composition, and route of administration of the respective test meals might explain these inconsistencies.

86.11 Applications to Other Areas of Health and Disease

CCK does not only regulate appetite sensation and gastric emptying but also regulates gallbladder contraction and emptying of bile during the postprandial state by binding to G-protein-coupled CCK-A-receptors on the smooth muscle of the gallbladder thereby mediating gallbladder emptying. As already mentioned, CCK is released by intestinal I-cells in response to an adequate hydrolysis of dietary TG. In addition to the previous studies, we assessed whether oral administration of orlistat inhibits CCK release in response to a test meal. In the same setting, healthy volunteers were given a test meal with 120 mg orlistat or placebo visualizing gallbladder volume by abdominal ultrasound. Orlistat administration resulted in significantly reduced gallbladder emptying through meal-mediated CCK release (Ellrichmann et al. 2008) (Fig. 86.6). Since reduced gallbladder contractility leading to bile stasis is one of the major risk factors for the development of cholesterol gallstones, in a 1-year follow-up Mathus-Vliegen et al. investigated the risk of gallstone occurrence by orlistat administration. After 1 month of diet, obese patients were treated with either placebo or 60 or 120 mg orlistat t.i.d. One month and 12 months after randomization, gallbladder kinetics and CCK levels were assessed. In the 60-mg group, no significant changes of the gallbladder motility were observed, whereas 120 mg orlistat resulted in a significant decrease in gallbladder emptying. The residual gallbladder volumes and percentage of gallbladder emptying are comparable to our findings. After 1 year of treatment, disturbed gallbladder emptying persisted, 16.7% of patients in the placebo group developed gallstones, whereas only 7.1% of gallstone formation was seen in the 60 mg orlistat group. In contrast, no gallstone formation was observed in the 120 mg orlistat group (Mathus-Vliegen et al. 2004). These results were rather unexpected and might indicate that altered gallbladder kinetics is outweighed by other factors, such as a reduction of cholesterol supernaturation and nucleation factors (Fig. 86.7).
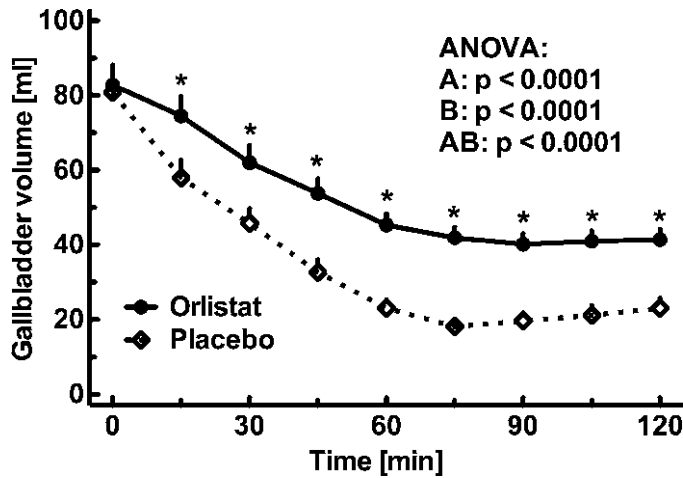
Fig. 86.6 Gallbladder volume after ingestion of a solid–liquid test meal following oral administration of 120 mg orlistat or placebo in 25 healthy volunteers. Data are presented as means ± SEM. *p*-Values were calculated using paired repeated measures ANOVA and denote A: difference between the experiments, B: differences over time and AB: differences due to the interaction of experiment and time. Asterisks indicate significant difference ($p < 0.05$) versus placebo at individual time points (one-way ANOVA). (**b, c**) Linear regression analysis between the integrated incremental plasma concentration of PYY and mean ratings for hunger (**b**) and satiety (**c**) as determined using visual analogue scales (VAS) ($n = 50$). Dashed lines indicate the respective upper and lower 95% confidence interval. r^2 = correlation coefficient squared, $p < 0.05$ statistically significant

Fig. 86.7 Effects of orlistat administration on postprandial gastrointestinal (GI) hormone levels. Orlistat reduces leptin levels secreted by the adipose tissue. In addition, the secretion of cholecystokinin (CCK), glucagon-like peptide (GLP)1, peptide YY (PYY), pancreatic polypeptide (PP), and gastric inhibitory polypeptide (GIP) from pancreas and the small intestine is attenuated. Ghrelin levels, primarily secreted by the stomach, are elevated. The changes in these GI hormone concentration lead to increased appetite sensation in the central nervous system (CNS) and thus to increased food intake

86.12 Conclusion

In conclusion, intestinal lipase inhibition by orlistat accelerates gastric emptying and markedly reduces the postprandial secretion of the anorexic hormones CCK, GLP-1, PYY, PP, and GIP, whereas ghrelin levels are elevated. Taken together, these alterations in GI hormone concentrations can increase appetite sensations leading to greater food consumption. These findings underline the importance of GI hormones in the central nervous control of energy homoeostasis. Increased appetite sensations, a potentially increased risk of developing gallbladder stones, and alterations in postprandial glucose regulation should be considered as potential side effects when applying lipase inhibitors for the treatment of morbid obesity.

Summary Points

- Orlistat inhibits intestinal lipases and thus reduces hydrolysis of dietary TG in MG and FFAs.
- Orlistat leads to a marked acceleration of gastric motility and to an inhibition of gallbladder emptying.
- Lipase inhibition significantly attenuates appetite ratings and increases food intake.
- Increased appetite induced by orlistat is mediated by changes in GI hormone levels, especially CCK, GLP-1, PYY and ghrelin.
- Changes in enteroendocrine hormone levels regulating appetite counteract the weight-lowering effect of the drug and the treatment of morbid obesity.

Definitions and Explanations of Key Terms

Cholecystokinin (CCK): CCK is derived from a 115-amino acid precursor, pro-CCK. Selective cleavage results in several circulating isoforms; the major forms in man are CCK-58, -33, -22, and -8. Biological activity resides in the amidated C-terminus of the peptide; all active species of CCK share a C-terminal heptapeptide sequence including O-sulfated tyrosine. CCK physiologically mediates gallbladder contraction and inhibits gastric emptying and gastric acid secretion. In addition, CCK induces satiating effects in the CNS.

Glucagon-like peptide (GLP)1: Post-translational processing of preproglucagon in enteroendocrine L-cells yields the peptides glicentin, OXM, GLP-2, and GLP-1. Multiple forms of GLP-1 are secreted in vivo, including GLP-1(1–37) and GLP-1(1–36)NH_2, which are thought to be inactive, and GLP-1(7–37) and GLP-1(7–36), which are biologically active. In humans, the majority of GLP-1 in the circulation is GLP-1(7–36)NH_2. GLP-1 possesses a variety of physiological properties comprising increase in insulin secretion, decrease of glucagon secretion, inhibition of gastric emptying, and attenuation of food intake.

Peptide YY (PYY): PYY is a 36-amino acid linear peptide and is a member of the pancreatic peptide family. The main of PYY is stored and secreted to the circulation as PYY(3–36), which is the N-terminally truncated form of the peptide. PYY is secreted from the endocrine L-cells of the small and large bowel, with high concentrations at the terminal ileum and colon and maximum concentration in the rectum. PYY exerts its action through NPY receptors thereby inhibiting gastric motility and pancreatic secretion. Furthermore, PYY has been shown to reduce to appetite and prospective food consumption via NPY receptor within the CNS.

Pancreatic polypeptide (PP): PP is a 36-amino acid peptide and as well a member of the pancreatic peptide family. It is produced in the endocrine type F cells located in peripheries of the pancreatic islets in response to food ingestion, hypoglycemia, and exercise. The physiological mechanisms of PP still remain unclear. Several studies suggest that vagal nerve activity can be estimated by PP serum levels.

Gastric inhibitory peptide (GIP): GIP is the first incretin hormone to be identified isolated from porcine intestine. Based on its ability to inhibit gastric acid secretion it was named "gastric inhibitory polypeptide." Subsequent studies demonstrated a glucose-dependent stimulation of insulin secretion by GIP. Accordingly, the term "glucose-dependent insulinotropic polypeptide" was proposed to more accurately define the acronym GIP. GIP is synthesized in K-cells of the upper small intestine. The mature bioactive 42-amino acid form of GIP is cleaved from its 153-amino acid proGIP precursor via post-translational processing. GIP is known to stimulate insulin secretion from the endocrine pancreas. It is also thought to have significant effects on fatty acid metabolism by stimulation of lipoprotein lipase in adipocytes.

Leptin: Leptin is a 16 kDa protein that plays a key role in regulating energy intake and expenditure. The ob gene located on chromosome 7 in humans is expressed in adipose tissue and encodes for leptin. In addition for being a biomarker for body fat composition, serum leptin levels reflect individual energy balance. By binding to NPY neurons in the arcuate nucleus leptin induces satiety in the CNS.

Ghrelin: Ghrelin has a 28-amino acid structure, with an octanoylated serine residue at position 3. This unique side chain appears to be essential for the effects on appetite regulation and GH release. The X/A-like cells in the fundus of the stomach are the major source of circulating ghrelin. To date, ghrelin is the only endogenous peripheral hormone that has been show to induce hunger and increase food intake.

References

Batterham RL, Cowley MA, Small CJ, Herzog H, Cohen MA, Dakin CL, Wren AM, Brynes AE, Low MJ, Ghatei MA, Cone RD, Bloom SR. Gut hormone PYY(3-36) physiologically inhibits food intake. Nature 2002;418:650–4.

Batterham RL, Cohen MA, Ellis SM, Le Roux CW, Withers DJ, Frost GS, Ghatei MA, Bloom SR. To eat or not to eat - how the gut talks to the brain. N Engl J Med. 2003;349:926–8.

Batterham RL, Le Roux CW, Cohen MA, Park AJ, Ellis SM, Patterson M, Frost GS, Ghatei MA, Bloom SR. Pancreatic polypeptide reduces appetite and food intake in humans. J Clin Endocrinol Metab. 2003;88:3989–92.

Beysen C, Karpe F, Fielding BA, Clark A, Levy JC, Frayn KN. Interaction between specific fatty acids, GLP-1 and insulin secretion in humans. Diabetologia. 2002;45:1533–41.

Borovicka J, Schwizer W, Guttmann G, Hartmann D, Kosinski M, Wastiel C, Bischoff-Delaloye A, Fried M. Role of lipase in the regulation of postprandial gastric acid secretion and emptying of fat in humans: a study with orlistat, a highly specific lipase inhibitor. Gut. 2000;46:774–81.

Callahan HS, Cummings DE, Pepe MS, Breen PA, Matthys CC, Weigle DS. Postprandial suppression of plasma ghrelin level is proportional to ingested caloric load but does not predict intermeal interval in humans. J Clin Endocrinol Metab. 2004;89:1319–24.

Chaudhri O, Small C, Bloom S. Gastrointestinal hormones regulating appetite. Philos Trans R Soc Lond B Biol Sci. 2006;361:1187–209.

Creutzfeld W, Ebert R, Willms B, Frerichs H, Brown JC. Gastric inhibitory polypeptide (GIP) and insulin in obesity: increased response to stimulation and defective feedback control of serum levels. Diabetologia. 1978;14:15–24.

Cummings DE, Purnell JQ, Frayo RS, Schmidova K, Wisse KE, Weigle DS. A preprandial rise in plasma ghrelin levels suggests a role in meal initiation in humans. Diabetes. 2001;50:1714–19.

Damci T, Yalin S, Balci H, Osar Z, Korugan U, Ozyazar M, Ilkova H. Orlistat augments postprandial increases in glucagon-like peptide 1 in obese type 2 diabetic patients. Diabetes Care. 2004;27:1077–80.

Daousi C, Wilding JP, Aditya S, Durham BH, Cleator J, Pinkney JH, Ranganath LR. Effects of peripheral administration of synthetic human glucose-dependent insulinotropic peptide (GIP) on energy expenditure and subjective appetite sensations in healthy normal weight subjects and obese patients with type 2 diabetes. Clin Endocrinol. 2009;71:195–201.

Degen L, Drewe J, Piccoli F, Gräni K, Oesch S, Bunea R, D'Amato M, Beglinger C. Effect of CCK-1 receptor blockade on ghrelin and PYY secretion in men. Am J Physiol Regul Integr Comp Physiol. 2007;292:R1391–9.

Dimitrov D, Bohchelian H, Koeva L. Effect of orlistat on plasma leptin levels and risk factors for the metabolic syndrome. Metab Syndr Relat Disord. 2005;3:122–9.

Ellrichmann M, Kapelle M, Ritter PR, Holst JJ, Herzig KH, Schmidt WE, Schmitz F, Meier JJ. Orlistat inhibition of intestinal lipase acutely increases appetite and attenuates postprandial glucagon-like peptide-1-(7-36)-amide-1, cholecystokinin, and peptide YY concentrations. J Clin Endocrinol Metab. 2008;93:3995–8.

Enc FY, Ones T, Akin HL, Dede F, Turoglu HAT, Ulfer G, Bekiroglu N, Haklar G, Rehfeld JF, Holst JJ, Ulusoy NB, Imeryüz N. Orlistat accelerates gastric emptying and attenuates GIP release in healthy subjects. Am J Physiol Gastrointestinal Liver Physiol. 2009;296:G482–9.

Feinle C, Rades T, Otto B, Fried M. Fat digestion modulates gastrointestinal sensations induced by gastric distention and duodenal lipid in humans. Gastroenterology 2001;120:1100–7.

Feinle C, O'Donovan D, Doran S, Andrews JM, Wishart J, Chapman I, Horowitz M. Effects of fat digestion on appetite, APD motility, and gut hormones in response to duodenal fat infusion in humans. Am J Physiol Gastrointest Liver Physiol. 2003;284:G798–807.

Feinle-Bisset C, Patterson M, Ghatei MA, Bloom SR, Horowitz M. Fat digestion is required for suppression of ghrelin and stimulation of peptide YY and pancreatic polypeptide secretion by intraduodenal lipid. Am J Physiol Endocrinol Metab. 2005;289:E948–53.

Figlewicz DP, Nadzan AM, Sipolis AJ, Green PK, Liddle RA, Porte D Jr, Woods SC. Intraventricular CCK-8 reduces single meal size in the baboon by interaction with type-A CCK receptors. Am J Physiol. 1992;263:R863–7.

Flint A, Raben A, astrup A, Holst JJ. Glucagon-like peptide 1 promotes satiety and suppresses energy intake in humans. J Clin Invest. 1998;101:515–20.

Fujimoto S, Inui A, Kiyota N, Seki W, Koide K, Takamiya S, Uemoto M, Nakajima Y, Baba S, Kasgua M. Increased cholecystokinin and pancreatic polypeptide responses to a fat-rich meal in patients with restrictive but not bulimic anorexia nervosa. Biol Psychiatry. 1997;41:1068–70.

Gibbs J, Young RC, Smith GP. Cholecystokinin decreases food intake in rats. J Comp Physiol Psychol. 1973;84:488–95.

Glaser B, Zoghlin G, Pienta K, Vinik AI. Pancreatic polypeptide response to secretin in obesity: effects of glucose intolerance. Horm Metab Res. 1988;20:288–92.

Goedecke JH, Barsdorf M, Beglinger C, Levitt NS, Lambert EV. Effects of a lipase inhibitor (Orlistat) on cholecystokinin and appetite in response to a high-fat meal. Int J Obes Relat Metab Disord. 2003;27:1479–85.

Gomez G, Udupi V, Greeley GH Jr. Comparison of somatostatin and pancreastatin on secretion of gastrin, pancreatic polypeptide, and peptide YY. Proc Soc Exp Biol Med. 1997;215:165–7.

Greenman Y, Golani N, Gilad S, Yaron M, Limor R, Stern N. Ghrelin secretion is modulated in a nutrient- and gender-specific manner. Clin Endocrinol. 2004;60:382–8.

Gutzwiller JP, Drewe J, Göke B, Schmidt H, Rohrer B, Lareida J, Beglinger C. Glucagon-like peptide-1 promotes satiety and reduces food intake in patients with diabetes mellitus type 2. Am J Physiol. 1999;276:R1541–4.

Haluzik M, Papezova M, Nedvidkova J, Kabrt J. Serum leptin levels in patients with anorexia nervosa before and after partial refeeding, relationships to serum lipids and biochemical nutritional parameters. Physiol Res. 1999;48:197–202.

Hildebrand P, Petrig C, Burckhardt B, Ketterer S, Lengsfeld H, Fleury A, Hadvary P, Beglinger C. Hydrolysis of dietary fat by pancreatic lipase stimulates cholecystokinin release. Gastroenterology. 1998;114:123–9.

Kelley DE, Kuller LH, McKolanis TM, Harper P, Mancino J, Kalhan S. Effects of moderate weight loss and orlistat on insulin resistance, regional adiposity, and fatty acids in type 2 diabetes. Diabetes Care. 2004;27:33–40.

Kissileff HR, Carretta JC, Geliebter A, Pi-Sunyer FX. Cholecystokinin and stomach distension combine to reduce food intake in humans. Am J Physiol Regul Integr Comp Physiol. 2003;285:R992–8.

Koop I, Ruppert-Seipp G, Koop H, Schafmayer A, Arnold R. Cholecystokinin release by gastric distension--an atropine-sensitive mechanism. Digestion. 1990;46:220–7.

Larsen PJ, Tang-Christensen M, Holst JJ, Orskov C. Distribution of glucagon-like peptide-1 and other preproglucagon-derived peptides in the rat hypothalamus and brainstem. Neuroscience. 1997;77:257–70.

Le Roux CW, Ghatei MA, Gibbs JS, Bloom SR. The putative satiety hormone PYY is raised in cardiac cachexia associated with primary pulmonary hypertension. Heart 2005;91:241–2.

Lin HC, Taylor IL. Release of peptide YY by fat in the proximal but not distal gut depends on an atropine-sensitive cholinergic pathway. Regul Pept. 2004;117:73–6.

Lucas KH, Kaplan-Machlis B. Orlistat--a novel weight loss therapy. Ann Pharmacother. 2001;35:314–28.

Mathus-Vliegen EM, Van Ierland-van Leeuwen ML, Terpstra A. Lipase inhibition by orlistat: effects on gall-bladder kinetics and cholecystokinin release in obesity. Aliment Pharamcol Ther. 2004;19:601–11.

Matzinger D, Degen L, Drewe J, Meuli J, Duebendorfer R, Ruckstuhl N, D`Amato M, Rovati L, Beglinger C. The role of long chain fatty acids in regulating food intake and cholecystokinin release in humans. Gut. 2000; 46: 688-93.

Meguro T, Shimosegawa T, Kikuchi Y, Koizuma M, Toyota T. Effects of cisapride on gallbladder emptying and pancreatic polypeptide and cholecystokinin. J Gastroenterol. 1995;30:237–43.

Meier JJ, Nauck MA. Glucagon-like peptide 1(GLP-1) in biology and pathology. Diabetes Metab Res Rev. 2005;21:91–117.

Meier JJ, Nauck MA, Schmidt WE, Gallwitz B. Gastric inhibitory polypeptide: the neglected incretin revisite. Regul Pept. 2002;107:1–13.

Meier JJ, Kemmeries G, Holst JJ, Nauck MA. Erythromycin antagonizes the deceleration of gastric emptying by glucagon-like peptide 1 and unmasks its insulinotropic effect in healthy subjects. Diabetes 2005;54:2212–8.

Miyawaki K, Yamada Y, Ban N, Ihara Y, Tsukiyama K, Zhou H, Fujimoto S, Oku A, Tsuda K, Toyokuni S, Hiai H, Mizunoya W, Fushiki T, Holst JJ, Makino M, Tashita A, Kobara Y, Tsubamoto Y, Jinnouchi T, Jomori T, Seino Y. Inhibition of gastric inhibitory polypeptide signaling prevents obesity. Nat Med. 2002;8:738–42.

Moran TH, Kinzig KP. Gastrointestinal satiety signals II. Cholecystokinin. Am J Physiol Gastrointestinal Liver Physiol. 2004;286:G183–8.

Moran TH, McHugh PR. Gastric and nongastric mechanisms for satiety action of cholecystokinin. Am J Physiol. 1988;254:R628–32.

Moran TH, Ameglio PJ, Schwartz GJ, McHugh PR. Blockade of type A, not type B, CCK receptors attenuates satiety actions of exogenous and endogenous CCK. Am J Physiol. 1992;262:R46–50.

Murakami N, Hayashida T, Kuroiwa T, Nakahara K, Ida T, Mondal MS, Nakazato M, Kojima M, Kangawa K. Role for central ghrelin in food intake and secretion profile of stomach ghrelin in rats. J Endocrinol. 2002;174: 283–8.

O'Donovan D, Feinle-Bisset C, Wishart J, Horowitz M. Lipase inhibition attenuates the acute inhibitory effects of oral fat on food intake in healthy subjects. Br J Nutr. 2003;90:849–52.

O'Donovan D, Horowitz M, Russo A, Feinle-Bisset C, Murolo N, Gentilcore D, Wishart JM, Morris HA, Jones KL. Effects of lipase inhibition on gastric emptying of, and on the glycaemic, insulin and cardiovascular responses to, a high-fat/carbohydrate meal in type 2 diabetes. Diabetologia. 2004;47:2208–14.

Onaga T, Zabielski R, Kato S. Multiple regulation of peptide YY secretion in the digestive tract. Peptides 2002;23:279–90.

Orskov C, Rabenhoj L, Wettergren A, Kofod H, Holst JJ. Tissue and plasma concentrations of amidated and glycine-extended glucagon-like peptide I in humans. Diabetes 1994;43:535–9.

Padwal R, Li SK, Lau DC. Long-term pharmacotherapy for overweight and obesity: a systematic review and meta-analysis of randomized controlled trials. Int J Obes Relat Metab Disord. 2003;27:1437–46.

Peters JH, McKay BM, Simasko SM, Ritter RC. Leptin-induced satiation mediated by abdominal vagal afferents. Am J Physiol Regul Integr Comp Physiol. 2005;288:R879–84.

Pilichiewicz A, O'Donovan D, Feinle C, Lei Y, Wishart JM, Bryant L, Meyer JH, Horowitz M, Jones KL. Effect of lipase inhibition on gastric emptying of, and the glycemic and incretin responses to, an oil/aqueous drink in type 2 diabetes mellitus. J Clin Endocrinol Metab. 2003;88:3829–34.

Pi-Sunyer X, Kissileff HR, Thornton J, Smith GP. C-terminal octapeptide of cholecystokinin decreases food intake in obese men. Physiol Behav. 1982;29:627–30.

Sahin M, Tanaci N, Yucel M, Kutlu M, Tutuncu NB, Pamuk B, Guvener ND. Acute effects of orlistat on postprandial serum leptin levels in nondiabetic obese patients. Minerva Endocrinol. 2008;33:169–73.

Schwartz GJ, Whitney A, Skoglund C, Castonguay TW, Moran TH. Decreased responsiveness to dietary fat in Otsuka Long-Evans Tokushima fatty rats lacking CCK-A receptors. Am J Physiol. 1999;277:R1144–51.

Svendsen M, Rissanen A, Richelsen B, Rössnr S, Hansson F, Tonstad S. Effect of orlistat on eating behavior among participants in a 3-year weight maintenance trial. Obesity (Silver Spring). 2008;16:327–33.

Torgerson JS, Hauptman J, Boldrin MN, Sjöström L. XENical in the prevention of diabetes in obese subjects (XENDOS) study: a randomized study of orlistat as an adjunct to lifestyle changes for the prevention of type 2 diabetes in obese patients. Diabetes Care. 2004;27:155–61.

Track NS, McLeod RS, Mee AV. Can J Physiol Pharmacol. 1980;58:1484–9.

Verdich C, Flint A, Gutzwiller JP, Näslund E, Beglinger C, Hellström PM, Long SJ, Morgan LM, Holst JJ, Astrup A. A meta-analysis of the effect of glucagon-like peptide-1 (7-36) amide on ad libitum energy intake in humans. J Clin Endocrinol Metab. 2001;86:4382–9.

Williams DL, Grill HJ, Cummings DE, Kaplan JM. Endocrinology 2003;144:5184–7.

Wren AM, Bloom SR. Gut hormones and appetite control. Gastroenterology 2007;132:2116–30.

Zhi J, Melia AT, Guerciolini R, Chung J, Kinberg J, Hauptman JB, Patel NJ. Retrospective population-based analysis of the dose-response (fecal fat excreation) relationship of orlistat in normal and obese volunteers. Clin Pharmacol Ther. 1994;56:82–5.

Zhi J, Mulligan TE, Hauptman JB. Long-term systemic exposure of orlistat, a lipase inhibitor, and its metabolites in obese patients. J Clin Pharmacol. 1999;39:41–6.

Pathology and Abnormal Aspects: Neurological

Chapter 87
Gastrointestinal Disorders in Neurologically Impaired Children

Alja Gössler and Karel Krafka

Abbreviations

GER	Gastroesophageal reflux
GERD	Gastroesophageal reflux disease
NIP	Neurologically impaired patients
PEG	Percutaneus endoscopic gastrostomy

87.1 Introduction

There is a saying "Liebe geht durch den Magen" – "The way to a man's heart is through his stomach." In neurologically impaired patients (NIPs), often eating or being fed something gustatorily pleasant is one of the highlights of their life. Despite this need for autonomic or assisted nutrition, problems and disorders of the gastrointestinal tract exist in a high percentage in this special group of patients, reducing their and their caregivers' quality of life.

Motility of the gut is controlled both by extrinsic inputs from the dorsal motor nucleus of the vagus and paravertebral sympathetic ganglia and by local reflexes mediated by intrinsic neurons of the enteric nervous system. Motility of the gastrointestinum results from interplay of a few fundamental mechanisms, including myogenic mechanisms, neurogenic propulsive mechanisms, and migrating neurogenic motor activity. This complex interplay can be interrupted or disturbed by abnormalities of one or more of these mechanisms.

Severe neurologic impairment affects both children and adults considerably. In many cases, severe gastrointestinal problems accompany these children throughout their life (Moore 2008). Failure to thrive, difficulties in oral nutrition, recurrent vomiting, and respiratory tract infections caused by aspiration as well as loss of appetite and abdominal pain are results of frequent associated conditions. Dysphagia is present in 60% of NIPs, gastroesophageal reflux (GER) in 77%, resulting in chronic pulmonary aspiration in 41%; 74% of NIPs suffer from chronic obstipation (Del Giudice et al. 1999).

A. Gössler (✉)
Department of Pediatric and Adolescent Surgery, General Hospital Klagenfurt,
St.Veiter Str. 47, 9020 Klagenfurt, Austria
e-mail: alja.goessler@lh-klu.at

It is difficult for NIPs to express the pain and discomfort caused by gastrointestinal disorders to their caregivers. Thus, the interpretation of behavior indicating pain experience is a challenge for parents and health care professionals, resulting in late diagnosis.

This chapter attends to the pathogenesis, diagnosis, and treatment of dysphagia, GER, and constipation as three of the main gastrointestinal problems in severe NIPs. Knowledge and understanding of these disorders will lead the way to earlier, timely diagnosis and treatment, thus preventing pain and further damage to the gastrointestinum as well as to the pulmonary system and improving the quality of life in this special group of patients.

87.2 Dysphagia

87.2.1 Background

87.2.1.1 Physiology of Normal Swallowing

The act of swallowing is a complex process and requires the coordination of cranial nerves, the brain stem, cerebral cortex, and 26 muscles of the mouth, pharynx, and esophagus. The main cranial nerves that influence swallowing include the trigeminal (V), the facial (VII), glossopharyngeal (IX), vagus (X), and hypoglossal (XII). These nerves mediate the sensation and movement related to swallowing. Any abnormalities affecting these nerves, the cerebral cortex, mid brain, or cerebellum may have a negative impact on the individual's ability to swallow.

Four phases of swallowing can be distinguished: the oral-preparatory, the oral, the pharyngeal, and the esophageal phases. Dysphagia is characterized by a dysfunction in the sequential oral, pharyngeal, and esophageal phases of the swallowing process. The presence of abnormal movement patterns, for example tongue thrust in children with cerebral palsy, disrupts the normal movement of food from the anterior to the posterior regions of the mouth. Children with dysphagia have trouble in tongue control and bolus manipulation, problems with movement of food from the mouth to the pharynx as well as delayed pharyngeal swallow. Delayed or lack of initiation of the swallowing reflex results in increased risk of aspiration from an unprotected airway.

87.2.1.2 Causes of Dysphagia

Dysphagia can be caused by acute onset of intracranial hemorrhage, cerebral infarction, or traumatic injuries (Schaller et al. 2006). Alternatively, it can be the result of congenital and chronic disorders resp. diseases: intracranial tumors, cerebral palsy, genetic disorders, encephalopathy, or neuropathy.

As can be observed, dysphagia from chronic causes may worsen progressively or remain static. Worsening dysphagia will lead to deterioration of feeding and swallowing skills. In static dysphagia, swallowing skills will remain stable, or there may be a slow improvement.

87.2.2 Signs and Symptoms

Difficulties in swallowing or transporting a food bolus may result in frequent aspirations, especially in fluid intake. Thus, it may eventually lead to pulmonary infections. Refusal of food, pain in swallowing, and inpatient or aggressive behavior of the children can be observed frequently. In some

children, dystrophy might be present. Food intake or feeding can show enormous duration. Excessive drooling, signs of fatigue, and respiratory distress during feeding are often found. Notable oral hypersensitivity to touch with spoon, food, or finger is sometimes present and should lead to further investigation considering dysphagia.

87.2.3 Diagnostics

An understanding of normal and abnormal swallowing patterns as well as other developmental characteristics unique to children is essential for assessment. Identification and assessment of dysphagia is complex and requires the expertise of a multidisciplinary team. A multidisciplinary team can use various assessment methods including the following.

87.2.3.1 History of Feeding

A feeding history obtained from parents or caregivers helps assessing severity of dysphagia considering preferred texture of meals, duration of feeding, and eventually occurring signs of aspiration.

87.2.3.2 Physical Assessment

Physical examination should include clinical bedside evaluation by the speech pathologist and oral motor examination. Look for structural abnormalities of the tongue, palate, and jaw, difficulties in any of the four phases of swallowing or abnormalities in oral, laryngeal, or pharyngeal movement. A neurological examination for presence of dystonia, which might affect the ability to feed, as well as for any indices of other neurological or neuromuscular disorders should be performed.

Upper motor impairments are common in children with neurogenic dysphagia and may affect the ability to control their head, neck, and trunk and thereby the subsequent ability to swallow and ability to self-feed. Presence of dystonia and dyskinesia will affect the patient's ability to chew, manipulate the bolus in the mouth, and swallow. Those suffering from muscular hypotonus may experience poor coordination of posterior tongue resulting in difficulties with the pharyngeal phase of swallowing.

The child's hydration and nutritional status and its growth and development must be assessed. Since GER can be associated with dysphagia, the signs and symptoms of this disorder need to be investigated.

87.2.3.3 History of Medications

Some neuroleptics and medications used to control seizures may reduce alertness and ability to swallow. Muscle relaxants administered to patients suffering from spasticity may affect their ability to swallow.

87.2.3.4 Radiological Examinations

A videofluroscopic modified contrast swallow study may be helpful to assess the type of dysphagia and the individual risk of aspiration.

87.2.4 Therapy

Dysphagia often occurs parallel with many other streams of abnormal or delayed development. This may include impaired cognitive, oral motor, and fine and gross motor skills. A child's developmental age and current level of functional swallowing skills, for example the ability to chew, and/or control and manipulate a bolus, should be considered in any management program. Management of dysphagia requires the expertise and cooperation of a multidisciplinary team. Members of this team include a medical practitioner, a speech therapist, a physiotherapist, an occupational therapist, a dietitian, and nurses as well as pediatric surgeons.

87.2.4.1 Monitoring Nutrition and Hydration

In oral motor dysfunction there may exist an inadequate nutritional intake. This sometimes is even worsened due to difficulties in communicating desire for food and food preferences, inability to self-feed, coexisting GER, and aspiration.

Assessment of the diet may help in maintenance of nutrition. This includes fluid and food intake and loss with consideration of supplemental nonoral feeding. To get a better understanding of this disorder and to find possible ways to improve symptoms, duration of meal times has to be observed.

87.2.4.2 Positioning the Patient

Children with poor head control and poor trunk stability will require appropriate and individualized positioning techniques. The aim of positioning is to maintain a central body alignment.

In children with severe cerebral palsy and feeding problems, feeding position can be dependent on degree of dysphagia and on its occurrence in the oral or pharyngeal phase. The chin tuck and 30° reclining position and flexed hips may be effective in eliminating aspiration in children with major oral phase swallowing problems. In children with minor oral phase but greater pharyngeal phase swallowing difficulties, the erect position with flexed neck and hips was recommended.

87.2.4.3 Diet

Children with dysphagia may have difficulties managing different bolus sizes, flavors, and textures. Modifications will vary according to the needs of each child. Barium swallow studies may be used to determine the safest textures for each child with dysphagia. Children with neuromuscular disorders and weakened or uncoordinated swallowing may swallow a semi-solid consistency more easily as a single bolus.

Thickened fluids are recommended as they assist in reducing the risk of aspiration.

87.2.4.4 Prevention of Complications

Patients must be observed for signs of aspiration (coughing, choking, and respiratory distress). If aspiration is suspected, oral feeding should be stopped until the cause is investigated.
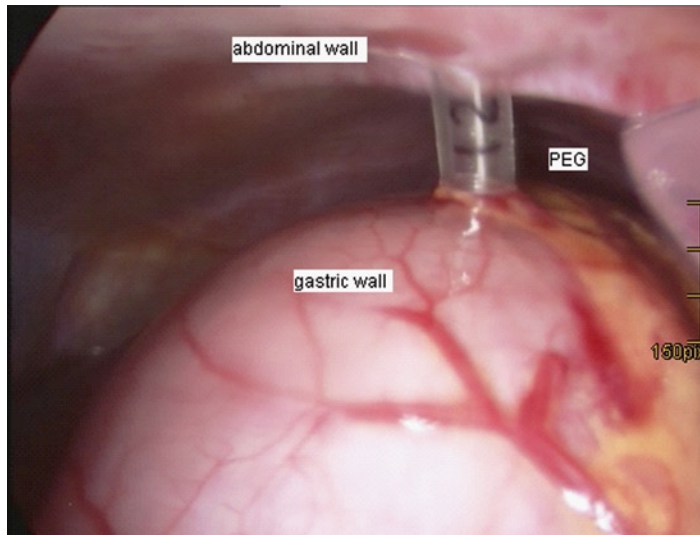
PIC 87.1   Laparoscopic view of a percutaneus endoscopic gastrostomy probe (PEG). The PEG penetrates the skin and the gastric wall to ensure endogastrical feeding

87.2.4.5 Nonoral Feeding

In severe dysphagia, oral feeding can not only become extremely exhausting both for patients as well as for caregivers but can endanger the health of the patients by recurrent pulmonary aspirations. In these cases, enteral feeding through a percutaneous endoscopic gastrostomy (PEG) probe or a button, to which the gastrostomy feeding probe can be fixed is preferred. In severe cachexia, continuous feeding through jejunal tube can be a good answer to this problem (Valletta and Angelini 2004) (PIC 87.1).

87.3 Summary Points

- Dysphagia can be caused by acute onset of intracranial hemorrhage, cerebral infarction, or traumatic injuries. Alternatively, it can be the result of congenital and chronic disorders and diseases: intracranial tumors, cerebral palsy, genetic disorders, encephalopathy, or neuropathy.
- Caring for children with dysphagia is stressful and to some degree exhausting for patients as well as for caregivers or parents.
- Information should be provided to assist caregivers to manage the child's swallowing and feeding difficulties. These include strategies for oral feeding, preparation of nutritious meals, adaptive equipment, positioning techniques, positive interactive behaviors, and child's progression in regaining swallowing skills.
- A multidisciplinary approach with parental involvement in assessment and management of their child's dysphagia is important. In severe dysphagia, enteral feeding through a PEG can be an extremely helpful approach.

(Adapted with the permission of the publisher from The Joanna Briggs Institute. Identification and management of dysphagia in children with neurological impairment. *Best Practice: Evidence Based Practice Information Sheets for Health Professionals*. 2000;4(3):1–6.)

87.4 Gastroesophageal Reflux

87.4.1 Background

Gastroesophageal reflux is defined as the return of gastric content into the esophagus. Up to some amount, this condition is normal and is found in each healthy individual. In this healthy context, there are mechanisms preventing an acid or pepsin refluat to overwhelm the intact epithelium: the antireflux barrier and functioning clearance mechanisms of the esophagus.

The antireflux barrier as the first line of mucosal defense consists of the lower esophageal sphincter and the crural diaphragm as well as of the angle of HIS. The latter is formed between the cardia at the entrance to the stomach and the gastric fundus, thus providing a valve which prevents reflux of gastric content from entering into the esophagus. The angle of His is created by the collar sling fibres and the circular muscles around this gastro-oesophagal junction.

The second line of defense consists of the esophageal clearance function, which limits the time of contact between refluate and esophageal mucosa by eliminating esophageal content into the stomach. Salivary secretions from the esophageal glands as well as gravitation in an upright position support this clearing function.

If these mechanisms are not sufficient, cellular defense, or mucosal resistance is discussed as the last line of defense against aggressive refluat (Boix-Ochoa and Ashcraft 2005).

A malfunctioning of these barrier or clearance mechanisms as well as a delayed gastric emptying leads the way to pathologic GER.

When the lower esophageal sphincter shows disturbed function, transient relaxations occur. These relaxations are not associated with swallows, a clearing wave of peristalsis, thus leading to regurgitation of gastric contents (Kawahara et al. 1997). In NIPs, the dysfunction of the esophageal motility causes longer contact of the acid gastric content with the esophageal mucosa leading to esophagitis and gastroesophageal reflux disease (GERD). Additionally these patients often lack upright positioning. Thus, gravity fails to support esophageal clearance function. Another cause for the high occurrence of GER in NIPs is considered the high incidence of epilepsy or spastic disorders elevating the muscular tonus and thereby increasing the intra-abdominal pressure.

To prevent further damage to the esophageal mucosa and the pulmonary system, to ease the pain and discomfort caused by pathologic GER, early diagnosis and treatment is mandatory. Therefore, health care professionals should pay attention to typical signs of GER as well as to behavioral alterations in children with neurological impairment and evaluate the possible causes including GER.

87.4.2 Signs and Symptoms

The diagnosis of GER is based on typical symptoms such as vomiting and regurgitation but is often diagnosed late, especially when symptoms like chronic pulmonary disease, recurrent pulmonary infections, and changes in behavior mislead the diagnosis.

Dental erosions, recurrent laryngitis, and esophagitis reveal the aggressive character of gastric content on extragastric tissue.

Recurrent episodes of uncontrollable singultus, belching, or acid foetor ex ore represent frequently existing and often underestimated symptoms.

In some cases a sudden rotation of the head and neck to one side and the legs to the opposite side in a spastic dystonic mode, typically appearing in the postprandial period may be present. This condition is called the Sandifer syndrome and is associated with GER.

Symptomatic GER presents as GERD and may be associated with recurring pain, thus impairing health-related quality of life (Madisch et al. 2003).

GER and GER-related esophagitis is often detected late due to severe deficits in communication – thus challenging the parents and caregivers abilities to interpret behavior indicating pain experience. It is difficult for NIPs to express the pain caused by acid reflux and esophagitis to their caregivers.

This reflux-related pain in neurologically impaired children has in many cases a significant influence on the behavior of these patients, as it may lead to increased agitation with increased undirected movements, moaning, crying, and difficulties to pacify as well as auto-aggressive behavior. Special attention should be given to changes in behavior indicating pain experience (Figs. 87.1 and 87.2).

In neurologically normal children the prevalence of symptoms associated with GER has been shown to peak at 4 months of age (67%) but decreases to 5% at 12 months of age (Nelson et al. 1997). In contrast, in children with neurological impairment pathological GER is a often lifelong condition.
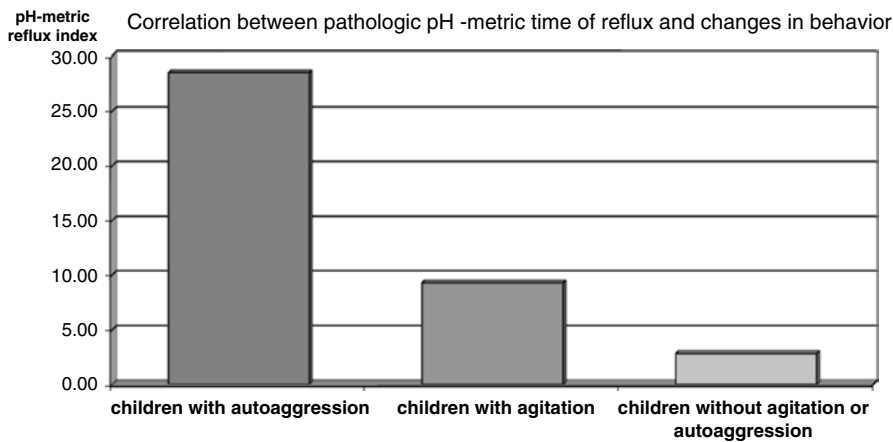
Fig. 87.1 Correlation of pH-metric time of reflux and changes in behavior. Children with behavioral changes, represented by increased agitation and auto-aggression, showed highly pathologic levels of gastroesophageal reflux here measured in RI with a sign difference to those without behavioral changes
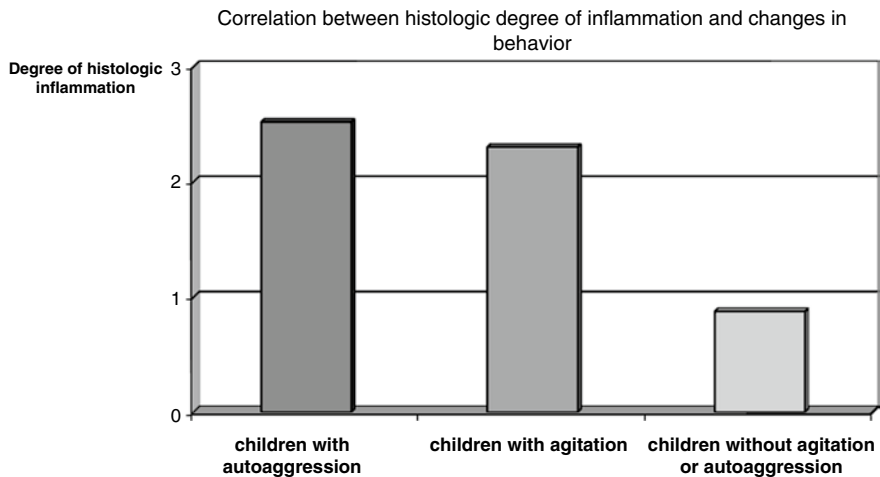
Fig. 87.2 Correlation of degree of inflammation of the esophageal mucosa and changes in behavior. Children with agitation and auto-aggressive behavior showed higher degrees of inflammation (grading after Savary Miller) and thus more severe inflammation than those without behavioral changes

The patients suffering from GER frequently haves difficulties with oral nutrition which may result in weight loss or failure to gain weight.

Delayed diagnosis of reflux and esophagitis not only results in difficult nutrition and recurrent pulmonary infections through aspirations, but also may finally result in mucosal damage leading to esophageal carcinoma arising from Barrett's epithelium.

Symptoms corresponding with pain for patients with severe neurological impairment were used to develop pain evaluation scales (Giusiano et al. 1995; Mc Grath et al. 1998). Despite the attempts to standardize the documentation of pain by medical professionals it has been shown that parents are best qualified to assess a typical behavior indicating that their child is feeling pain (Callery 1997). Therefore, medical professionals should respond to the caregivers' judgment of abnormalities in behavior even if otherwise typical symptoms are missing.

The clear correlation between auto-aggressive and agitated behavior and the severity of GERD shows that pathological GER may induce chronic pain in children with mental disabilities. Auto-aggressive or agitated behavior can be an indicator for GERD in neurologically impaired children and can be considered as a marker for reoccurring or first time diagnosed pathologic GER (Hunt et al. 2003).

Adapted with the permission from the publisher from. Gössler A, Schalamon J, Huber-Zeyringer A, Höllwarth ME, Gastroesophageal reflux and behavior in neurologically impaired children. J Pediatr Surg. 2007 Sep; 42(9):1486–90.

87.4.3 Diagnostics

87.4.3.1 Physical Assessment

A thorough examination of the patient should be performed to assess signs of GER or related conditions.

It is important to know if the patient is ambulatory or nonambulatory, if he prefers upright or prone position. Knowing this may lead to better understanding at which position the child suffers from more pathologic reflux and in which position each single child is feeling more comfortable. There is a healthy circulus, which is lacking in children who are bound to the wheel chair or the bed. The patient must be ambulatory, thus both increasing intestinal mobility and preventing obstipation. This is especially important, since the latter causes increased abdominal pressure which is associated with a higher incidence of GER.

Movement patterns should be observed as well as markers of auto-aggressive behavior like scratches or hematomas or bite marks.

Nutritional status as well as skin hydration should be examined; ideally, the development of weight and height should be stated.

Examination of the teeth to detect possible erosions from acid refluat should be included in the examination.

Auscultation, palpation, and percussion of the abdomen have to be performed to assess peristalsis, possible abdominal tumors, or hernias of the abdominal wall.

87.4.3.2 History

In most cases, a typical history of symptoms can be found. A thorough interview with patients and/ or caregivers is mandatory.

87.4.3.3 Sonography

Sonography is performed to investigate occurrence of GER, gastric emptying, and to exclude abdominal masses as the cause of increased abdominal pressure or barrier of intestinal movement.

87.4.3.4 Contrast Study

A contrast study of the upper gastrointestinal tract is performed to assess anatomy, gastric emptying, possible hiatal hernias, or esophageal strictures. In some patients, gastroesophageal reflux can be observed during this study, showing the heights of return of gastric content into the esophagus (PIC 87.2).

87.4.3.5 24-h pH Monitoring

pH is monitored to assess the total as well as the percentage time of acid refluat into the esophagus as well as the number and duration of occurring refluxes and the clearance function of the esophagus. Since this investigation monitors only acid refluat, a 24-h combined impedance and pH monitoring is now standard for investigation of acid and nonacid refluat (Del Buono et al. 2006) (PIC 87.3, PIC 97.4).

87.4.3.6 Endoscopy

Esophagogastroduodenal endoscopy is performed to assess or rule out mucosal damages. Esophagitis is assessed according to Savary and Miller. Ulcers, strictures, or Barrett mucosa can be found in

PIC 87.2 Upper gastrointestinal contrast study. Contrast study showing gastroesophageal reflux up to the upper half of the esophagus
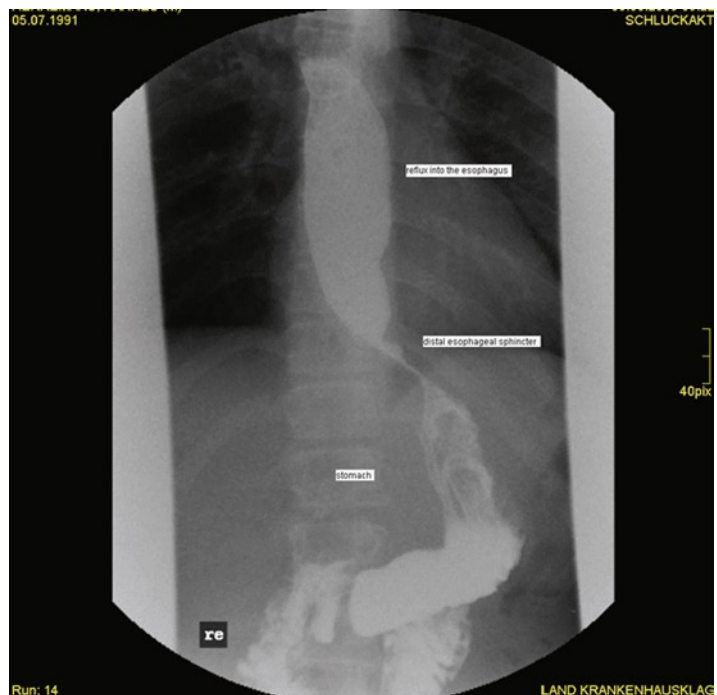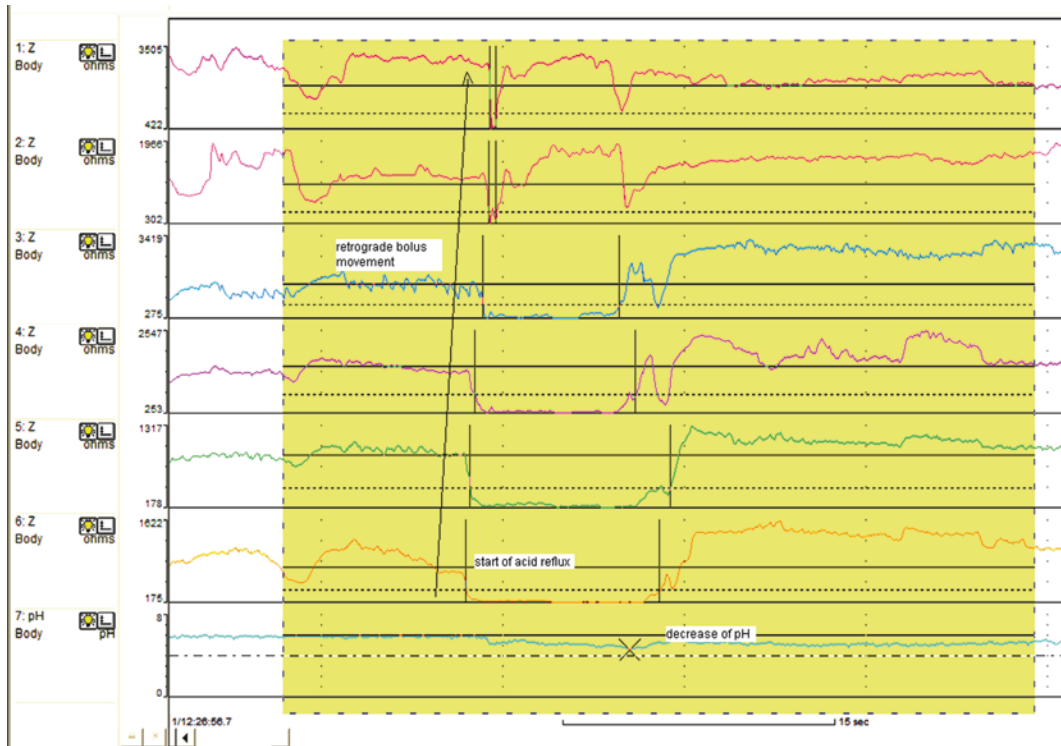
PIC 87.3 Measurement of gastroesophageal reflux by impedance pH monitoring. Impedance pH monitoring shows reflux of acid gastric content in the esophagus. Note drop of pH (lowest line) during reflux, the beginning and ending of which is marked with vertical lines

endoscopic examinations. Biopsies have to be taken, especially since in up to 48% of inflammation of the esophageal mucosa this has not been seen under macroscopic examination. During endoscopy, possibly occurring hiatal hernias can be observed.

87.4.3.7 Esophageal Manometry

Manometrically, the tonus, resting pressure, length, and transient as well as swallow-induced relaxations of the lower esophageal sphincter can be documented. The common cavity phenomenon with equalization of gastric and esophageal pressure is the manometric equivalence of reflux.

Esophageal peristalsis and occurrence of GER can be investigated.

87.4.4 Therapy

87.4.4.1 Conservative Treatment

A special diet which consists of less acid, low fat, and not too spicy food should be administered. Elevation of the head of the bed and, especially in children with frequent aspirations, thickened feedings will support gravity's part of esophageal clearance.
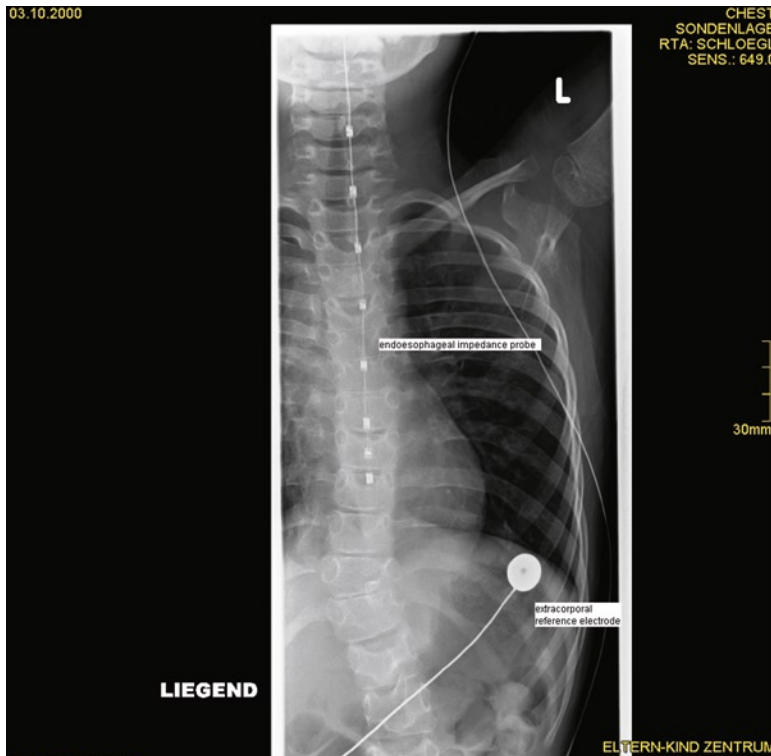
PIC 87.4 Positioning control of the impedance probe. Radiographic control of the endoesophageal position of the impedance probe

Reduction of acid refluat may permit healing of the esophageal mucosa in cases of mild to moderate GER. Thus both a better distal esophageal peristalsis and fewer transient lower sphincter relaxations may result, disrupting the circulus vitiosus of GER leading to esophagitis enhancing GER.

The superior efficacy and safety of proton pump inhibitors (PPIs) have changed the diagnostic and therapeutic recommendations. PPIs belong to a group of chemically related compounds whose primary function is the inhibition of acid production in the final common metabolic pathway of gastric parietal cells. The suppression of gastric acid secretion achieved with H2 receptor antagonists has proved to be suboptimal. PPIs have been shown to be more effective than them (Vandenplas, *Current Concepts in the Medical Therapy of GER in Children*).

In combination with mucosa protecting drugs like sucralfat, these mediations effectively may lead to healing of reflux-associated esophagitis.

In some cases motility enhancing, prokinetic drugs (cisapride, erythromycin) can be helpful. Cisapride is a prokinetic mainly acting via indirect release of acetylcholine from the myenteric plexus.

87.4.4.2 Surgery

How can the surgeon help?

GERD has been shown to occur with an increased incidence in neurologically impaired patients, representing a major factor in the long-term care and management and life in these patients.

Reduction of gastric acid production can improve symptoms of GERD. But while some improvement after healing of esophagitis may be present after some weeks or months of medication in mild GER, conservative therapy does not help with the natural history of development of gastroesophageal reflux disease. Reflux-depending symptoms and pathological oesophageal findings show recurrence in up to 80% within the first year. Thus, severe cases might require a long-term or even lifelong administration of medications (Stanghellini 2003).

In cases of severe GER, anatomic anomalies, failure to thrive, and recurrent pulmonary infections, fundoplication will lead to an impressive overall improvement of symptoms, health, and quality of life (Ceriati et al. 2006; Spitz and McLeod 2003).

87.5 Summary Points

- Pathologic GER is the result of malfunction of the barrier function and of the esophageal clearance.
- If left untreated or unrecognized, GERD can lead to damage of the esophageal mucosa or the pulmo by recurrent infections, failure to thrive, and changes in behavior like auto-aggression and agitation.
- Treatment includes special diet, acid suppressing medications, and surgery in severe cases.

87.6 Obstipation

87.6.1 Background

87.6.1.1 Physiology

The function of the colon is modulated through several separate systems, including neural, endocrine, and luminal factors.

There are two kinds of nervous systems controlling the colon – the intrinsic colonic nervous system and the extrinsic colonic nervous system. While the intrinsic nervous system consists of nerve cell bodies and endings that are located between the circular and the longitudinal muscle coats in the submucosal ganglia (Meissner's plexus) and the myenteric ganglia (Auerbach's plexus), the extrinsic acts through sympathetic and parasympathetic functions.

Stimulation of parasympathetic fibers increases the overall activity of the gastrointestinal tract. It initializes peristalsis, increases local blood flow and intestinal secretion, and promotes the defecation reflex. The sympathetic innervations of the gastrointestinal tract show an inhibiting effect on noradrenalin on the enteric nerves. It is supposed to regulate the contraction of the internal anal sphincter.

The external sphincter is innervated via branches of the pudendal nerves, as is sensation from the perianal area and perineum, whereas tension and stretch in the rectal wall and proximal part of the anal canal is carried in the pelvic nerves.

Through mass movements of the distal colon, feces are pushed into the otherwise empty rectum prior to defecation. The resulting distension and filling of the rectum initiates the sensation of the need

to defecate. Now relaxation of the internal anal sphincter and voluntary relaxation of the external sphincter promote defecation.

Defecation can be delayed by voluntary contraction of the external anal sphincter and the urge to defecate gradually decreases in intensity over a period of minutes.

The central nervous system contributes to the regulation of bowel function, and is involved in the timing and initiation of defecation.

Asides from neurologic function, three elements are important for normal bowel function: dietary bulk, fluid intake, and exercise (Winge et al. 2003).

Any factor that influences neurologically induced peristalsis or these three elements may cause bowel dysfunction and chronic constipation.

Chronic constipation is a common problem in children. And it is particularly common in children with disabilities.

Other possible causes of constipation include the disregard of the impulse to defecate, emotional conflicts, overuse of laxatives, or prolonged dependence on enemas as well as it can result as a side effect of some commonly used medications, especially antiepileptic drugs or sedative.

There is frequently a delay in the recognition and adequate treatment of constipation in children. Difficulties in communication make it nearly impossible for neurologically impaired children to express the extreme discomfort caused by constipation. This leads to existence of problems and symptoms for months or years before their importance is understood.

87.6.2   Signs and Symptoms

Constipation is defined as small, infrequent, or difficult bowel movements. But what is infrequent? Constipation always must be regarded in relation to the single patient. When defecation costs extreme effort, hurts and produces hard stool, constipation is present.

In most cases, constipation might just be a minor annoyance. But sometimes it presents as an acute abdominal condition with massive pain and respiratory distress caused by extreme metoristic abdomen and elevation of the diaphragm.

Adequate treatment of constipation provides relief for the child and impressively leads to an improvement in appetite and sometimes behavior.

If left untreated, chronic constipation may lead to painful fecal impaction. It can result in hemorrhoids, fissures, and abdominal pain. Additionally, elimination of hardened stool can become extremely difficult and painful. Pseudo incontinence can occur, when only fluid or softened stool can pass around hard and impacted stool without possibility to control this.

Many patients loose their appetite and refuse their meal, caused by nausea, pain, or simply the feeling of metoristic and "full" abdomen and frequent episodes of abdominal cramping.

Chronic obstipation can lead to an acquired afunctional distention of the colon with reduced or poor colonic peristalsis. As a secondary result of excessive use of laxatives, in some patients fluid and electrolyte depletions occur.

Especially in the neurologically impaired, this discomfort without possibility to communicate their problems can lead to an increase in auto-aggressive behavior as well as in disquietness and aggression.

Chronic obstipation is frequently associated with gastroesophageal reflux. A possible cause for this is found in the increased abdominal pressure as well as in the frequently additionally delayed gastric emptying.

87.6.3 Diagnostics

87.6.3.1 Physical Assessment

Especially in the neurologically impaired, an entire physical examination should be performed.

The abdomen should be auscultated to determine absence or presence of peristalsis as well as to determine the kind of peristalsis. Check the patient's abdomen for visible signs of distension or abdominal wall hernias, which may interfere with the necessary amount of abdominal pressure during defecation.

Palpation of the abdomen can show masses of hardened stool as well as abdominal tumors. In many cases, left lower quadrant pain can be found in severe acute constipation.

In many patients, signs of healed or yet active anal fissures or hemorrhoids can be found. Less frequently, anal polyps or rectal prolapse may be present. To some amount, sonography can assist in determining the rectal distension in patients in whom a rectal examination cannot or can only be performed with difficulty.

A thorough neurologic examination concerning anal, cremasteric, and abdominal wall reflexes should be performed.

Labor chemistry should be performed with special regard to the electrolyte status and thyroid status to rule out hypothyroidism in patients whose symptoms proved to be refractory to dietary management.

87.6.3.2 Radiology

Always a screening sonography should be performed to evaluate peristalsis, exclude abdominal or retroperitoneal tumors, and show rectal distension (PIC 87.5).

An abdominal X-ray can be useful in both indicating the nature of the problem and assessing the degree of constipation and, hence, the appropriate treatment.
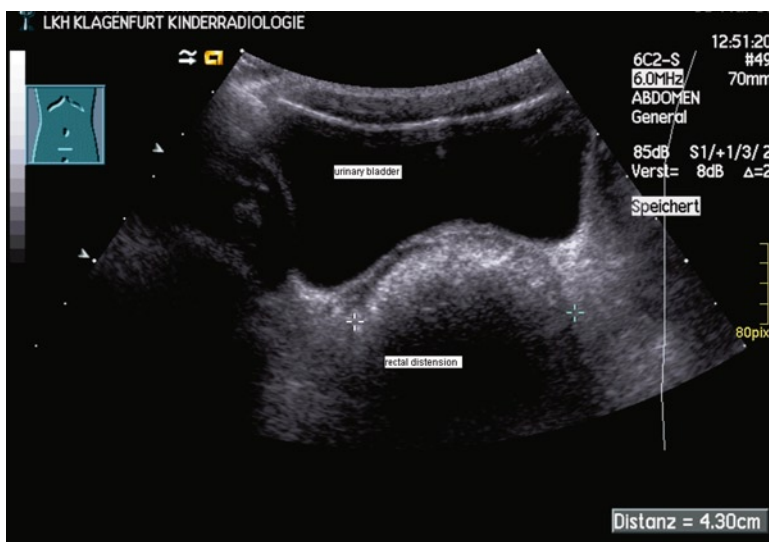
PIC 87.5 Transabdominal sonography of the rectum. Sonography showing rectal distension by stool masses

87.6.4 Therapy

The degree of neurologic involvement and abnormalities in defecation dynamics will guide in developing an appropriate management plan. A cleaning phase of the colon followed by medical and dietary management as well as changes in life style – if possible – is often successful. Since continence may not always be a realistic possibility in people with severe disabilities, the goal of therapy in these cases is to soften the stool so that it is painless to pass.

87.6.4.1 Treatment of Acute Constipation

To prevent abdominal cramping pain and to lead the way to an effective use of laxatives, the entire colon and rectum should first be emptied. This is achieved by use of enemas. In less severe cases, some suppositories can be used alternatively. These normally consist of CO_2-supps to achieve a sensation of filled rectum, which results in rectal peristalsis. Glycerin supp can soften the distal stool masses to assess easier passage. In severe cases, digital disimpaction under anesthesia by a physician may be necessary, including use of irrigation to clean the colon. It should not be performed ambulatory, since freedom of pain has to be assured during this otherwise hurting and unpleasant procedure. After this cleaning phase, oral medications are administered.

87.6.4.2 Management of Chronic Constipation

It should be aimed for frequent, at least each other day, effortless and – and this should not be underestimated – painless defecation. Especially in children with many physical and sometimes psychological problems, alleviation if not freedom of pain has to be achieved to improve their and consequently their caregivers' quality of life.

The need for patience has to be explained to caregivers, since sometimes medication and treatment can be necessary for several months to years.

Laxatives and fiber therapies may be effective in improving bowel movement frequency.

In less severe cases, adequate fluid and fiber intake alone may lead to adequate improvement. If the physical condition of the neurologically impaired child allows, some physical training should be performed.

Since some medications are known to worsen colonic peristalsis, anticholinergics, opiates, antacids, and antiepileptics as well as sedatives should be reduced as possible.

If these modifications alone fail to be effective, medication to ensure soft and easy-to-pass stool should be administered.

For a short period, lactulose can be useful. In cases of extreme dilatation of the colon caused by prolonged, sometimes yearlong delay in defecation and tailback of stool masses, we found dihydro-ergotamin to be a good choice.

Often used and very helpful is macrogol, which ensures the transport of softer, more voluminous stool masses. Medications such as pyridostigmin are also known to be effective in chronic constipation. Before administering these drugs, it has to be checked for contraindications.

Enemas and suppositories can relieve constipation temporarily. Still, they should be used only for a short period of time and not regularly. Inflammations, interfere with natural bowel muscle control and last, but not least, the discomfort caused for the patients should lead to an use only prior to oral antiobstipation medication.

When basic understanding of this training can be achieved, biofeedback techniques may be of some help in patients who initiate contraction of the external anal sphincter during the attempt to defecate. Biofeedback shows these children how they can change voluntarily the striated muscle contractions.

How can the surgeon help?

If changes in lifestyle, diet, and medication treatments fail to be effective, surgical therapy can improve bowel emptying and soften stress caused by this problem:

– Rectoscopy with anal dilatation or myotomy.
– Appendicostomy (Malone procedure) (Malone et al. 1990; Roberts et al. 1995; Zerhau et al. 2008) with antegrade continence enema (ACE).
– Colostomy.

87.7 Summary Points

- Obstipation is caused by immobility, inadequate fluid and fiber intake, and disturbed neuronal control of the colon as well as by some frequently used medications.
- If left untreated, it can lead to severe abdominal pain, anal fissures and refusal of food. The discomfort sometimes is shown by agitation and disquietness.
- Changes in diet, and physical training pave the way to improved colonic function.
- Laxatives, enemas, and stool softening medications help improve the symptoms and maintain regular stool passes.
- Surgical treatments like dilatation of the anal sphincter or, in severe cases, the Malone procedure may be very helpful treatments.

87.8 Surgical Therapy

87.8.1 PEG in Dysphagia

How can the surgeon help these patients?

Nutritional support is often an integral part of patient management in this group of children.

In patients where tube feeding is supposed to be of short duration, a nasogastric tube can be considered. There are three principal access routes used for nutrient delivery: oral, enteral, and parenteral. If oral intake is inadequate or contraindicated, then enteral tube feeding is preferable. Still, there are a number of problems associated with the use of the nasogastric tubes over the longer-term. A gastrostomy or jejunostomy is often the only way to secure the daily caloric need of the body in patients with a failure to thrive. Gauderer and Ponsky introduced a PEG 30 years ago. It is a safe and effective method for adequate enteral nutrition. The main indication for this is the inability to swallow or recurrent aspirations during the process of swallowing in children and adult patients with dysphagia as well as in extremely dystrophic or cachectic patients with GER. Their nutritional status as well as their quality of life improves sometimes impressively from the benefits of enteral feedings via gastrostomy or PEG (PIC 87.1).

Since neurologically impaired children pose the main indication and frequently suffer from additional GER, this condition has to be evaluated prior to gastrostomy.

Button: The major advantage of the PEG is that it allows a great number of patients to be discharged into family care. The simple button-gastrostomy tube is a next benefit in these cases.

87.8.1.1 Laparoscopy

Laparoscopy in pediatric surgical practice has become a reality. Laparoscopy in children requires a special care and provides a special caring.

Generally, low pressures about 6mmHg are used in children up to 8 years. We use instruments and ports no larger than 2 to 5 mm in diameter, thus providing very small wounds and minimal scarring.

Advantages of the laparoscopic approach are easily understood: there is a cosmetically better outcome, less tissue dissection, and disruption of tissue planes. Postoperatively, younger and older patients show less pain and overall there is a low intraoperative and postoperative complication rate.

Laparoscopic-assisted PEG: In patients with V-P shunt or generally in patients after another surgical procedure of the epigastric region a laparoscopy with 3mm camera is performed for visualization of the intraperitoneal part of the V-P shunt or for visualization of the adhesions between the stomach and the peritoneum (PIC 87.1).

Laparoscopic gastrostomy: Laparoscopic gastrostomy is indicated when a PEG cannot be performed or is contraindicated (obstruction of the esophagus, colon or omentum are overlaying the stomach). In these patients, the laparoscopic gastrostomy is the best opinion.

Laparoscopic jejunostomy eliminates the risk of aspiration associated with gastrostomy feeding. It will help assessing a healthier nutritional status in patients prior the further abdominal surgery.

In severely malnutrition, a jejunal tube can be inserted via the gastrostomy catheter for continuous enteral feeding in contrast to bolus feeding via the gastrostomy tube. It is posed under endoscopic surveillance into the jejunum.

87.8.1.2 Contraindications of PEG

Absolute contraindications for this procedure are:

Malignant obesity
Acute inflammation process of the abdominal wall
Peritoneal dialysis
Malignant ascites
Tumors of abdominal wall
Tumors of the left lobe of the liver with stomach dislocation
Peritonitis
Pancreatitis
Portal hypertension
Coagulation disorders
Relative contraindication: Displacement of the stomach (e.g., scoliosis).

87.8.1.3 Complications

Seldom, but possible complications are gastric and bowel perforation, gastric bleeding, migration of the gastric tube or wound infection, and abscess of the abdominal wall.

87.8.2 Fundoplication and Pyloroplasty in GERD

How can the surgeon help?

87.8.2.1 Pyloroplasty

In delayed gastric emptying, a pyloroplasty can be performed. In most cases, this surgery will be performed together with an antireflux procedure to ease emptying of the stomach.

When conservative treatment fails, or age, existing anatomic anomaly or severe symptoms make it necessary, surgery can present help against symptoms and GER-associated problems.

87.8.2.2 Fundoplication

In fundoplication, a complete or partial wrap of the fundus around the intra-abdominal esophagus is performed. Thus transient lower esophageal relaxations, which pose one major mechanism of pathologic GER, can be reduced successfully. Additionally the reconstruction of the angle of HIS prevents complete relaxation of the lower esophageal sphincter via elevation of the intragastric pressure. The diaphragmatic crura are narrowed to prevent the fundoplicate from slipping into the thorax as well as to reduce a hiatal hernia (PIC 87.6).

This surgery can be performed laparoscopically or in open access surgery.

The 360° wrap or Nissen fundoplication has been used much more frequently than other antireflux operations. For this wrap, the intra-abdominal esophagus is mobilized to assure an adequate length. Then a stomach cuff is created by passing the fundus dorsally around the distal esophagus. Anteriorly the left and right margins of this fundic wrap are sutured together in a "floppy" way. This wrap reacts as a valve, when gastric pressure is transmitted to the distal esophagus, raising the lower esophageal sphincter pressure (PIC 87.7).

In dorsal or ventral semifundoplications, the alternative surgical aim is to correct anatomic anomaly while permitting a physiologic amount of GER.

The wrap is created similarly. A partial – 180°–270° wrap is constructed and sutured to the esophageal wall.

Fundoplication can be a life-saving procedure in those patients who have severe manifestations such as recurrent aspiration or extreme failure to thrive.

PIC 87.6 Laparoscopic view of the narrowing of the diaphragmatic crura. Note the sutures to the diaphragmatic crurae which strengthen the distal esophageal sphincter and prevent the yet-to-be prepared fundoplicate from slipping into the thorax
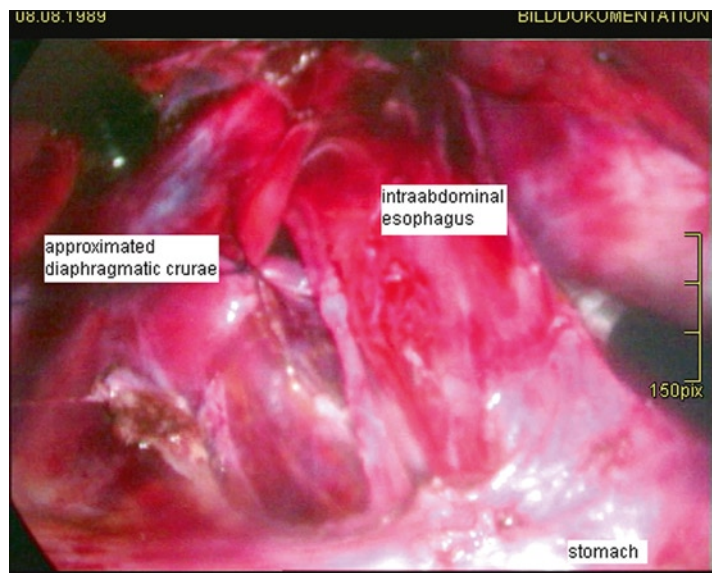
PIC 87.7 Laparoscopic view
of the fundoplicate.
Laparoscopic achieved
fundoplication after Nissen.
Note the 360° fundic wrap
around the distal esophagus
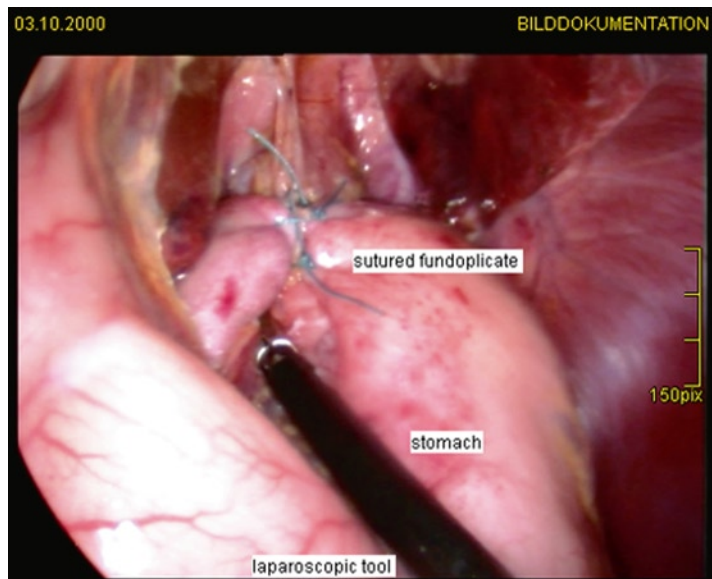
Antireflux surgery in the neurologically impaired carries a higher risk for wrap failure than in the neurologically normal patients. The most significant association of recurrent reflux in our own study was found with the state of preoperative dystrophy as an indicator of a catabolic status (Goessler et al. 2007).

An optimal, continuously anabolic preoperative nutritional status in NIP is important for the success of surgical treatment. This condition should be achieved by adequate enteral and/or parenteral therapy before any surgical procedure is planned (Falcão 2002; Kudsk et al. 2003).

The results of our own analysis showed that the surgical procedure results in significantly reduced GER-related symptoms and, as reported by the caregivers, a striking improvement of the quality of life (Teixeira et al. 2009) considering the often most difficult situation of caring and adequate feeding. Furthermore, an impressive reduction of agitation and auto-aggressive behavior was reported by the caregivers.

87.8.2.3 Complications

Seldom, but possible complications can be intraoperative injury to the gastric, intestine, or esophageal wall as well as lesions of liver or spleen. While performing the wrap, in cases with inadequate viability, the vagal nerve can be hurt, thus posing a risk for functioning gastric emptying. Other possible complications would be disruption of the fundoplicate, slipped fundoplicate, or to narrow wrap with postoperative need of bouginage or reoperation.

87.8.3 Anorectal Myectomy or Malone Procedure in Chronic Pbstipation

How can the surgeon help?

87.8.3.1 Anorectal Myectomy or Sphincter Dilatation

In some patients failing to correspond to the aforementioned conservative treatment of obstipation, the removal of a strip of rectal muscular wall can ease the process of defecation. This removal starts right below the dentate line and extends upwards to the level of the puborectalis muscle. The lowest part of the internal sphincter is not to be divided.

In less severe cases, anal sphincter dilatation during anesthesia can be a helpful procedure.

87.8.3.2 Malone Procedure

The Malone Procedure is easily understood when considering that it is just another way to administer an enema. In patients with neurological disorder, this can be extremely helpful not only because the enema runs through more efficiently when it is administered to Malone's site but also is easily accessible.

It consists of a special appendicostomy. The appendix is open or laparoscopically connected to the umbilicus or to the skin in right hypogastrium. The appendix is invaginated into the coecum or embedded submucosally after an incision of taenia libera. Thus, a valve mechanism is created.

If an appendectomy has been performed prior, a continent neo-appendicostomy can be created with a flap from the wall of the coecum.

The antegrade continence enema has met wide acceptance in the treatment of intractable fecal incontinence or for the use of repeated enemas in chronic intractable obstipation.

87.9 Summary Points

- In severe or distressing problems, surgery can be helpful, lead to less pain, and thus increase patients' and caregivers' quality of life.
- In dysphagia, gastral feeding via a PEG or jejunal continuous feeding via a jejunal tube can lead to a shortened duration of feeding and improvement of the nutritional status.
- In GER, a fundoplication or semi-fundoplication reduces the risk of damage to the esophagus and the pulmonary system and eases pain and reflux-associated symptoms.
- In obstipation, the Malone procedure is an easy access to perform frequent enemas.

87.10 Applications to Other Areas of Health and Disease

Dysphagia, GER, and obstipation present frequently existing conditions in neurologically impaired children. Understanding these conditions, knowledge of their signs and symptoms, especially of their tendency to lead to changes in behavior, will lead to earlier recognition and thus to earlier intervention and therapy. This poses extreme importance to caregivers, parents, nurses, doctors, and all therapists who perform training with this special group of patients.

Definitions

Dysphagia: In dysphagia, the transport of the fluid or food bolus from mouth to pharynx to esophagus is disturbed.

Gastroesophageal reflux: In GER, gastric content returns into the esophagus via a disturbed barrier function

Gastroesophageal reflux disease: Pathologic gastroesophageal reflux with damage to the esophageal mucosa or severe symptoms

Obstipation: Obstipation is characterized by chronic infrequent, difficult passage of hardened stool.

Key Facts of gastrointestinal problems in neurologically impaired patients (NIPs)

In 60% of NIPs, dysphagia is present

Up to 77% of NIPs suffer from pathologic gastroesophageal reflux, resulting in chronic pulmonary aspiration in 41%.

74% of NIPs show typical signs and problems of chronic constipation.

Due to deficits in verbal communication, the pain and discomfort resulting from these conditions is difficult to be expressed to caregivers and parents, resulting in late diagnosis and treatment.

Knowledge of signs and symptoms is mandatory to achieve earlier, timely diagnosis and therapy, thus
    improving quality of life of neurologically impaired children.

References

Callery P. Int J Nurs Stud. 1997;34:27–34.

Ceriati E, De Peppo F, Ciprandi G, Marchetti P, Silveri M, Rivosecchi M. Acta Paediatr Suppl. 2006;95:34–7.

Del Buono R, Wenzl TG, Rawat D, Thomson MJ. Pediatr Gastroenterol Nutr. 2006;43:331–5.

Del Giudice E, Staiano A, Capano G, Romano A, Florimonte L, Miele E, Ciarla C, Campanozzi A, Crisanti AF. Brain Dev. 1999;21:307–11.

Falcao MC, Tannuri U. Rev Hosp Clin Fac Med Sao Paulo. 2002;57:299–308.

Giusiano B, Jimeno MT, Collignon P, Chau Y. Methods Inf Med. 1995;34:498–502.

Goessler A, Huber-Zeyringer A, Hoellwarth ME. Acta Paediatr. 2007;96:87–93.

Hunt A, Mastroyannopoulou K, Goldman A, Seers K. Int J Nurs Stud. 2003;40:171–83.

Boix-Ochoa J, Ashcraft K. In: Ashcraft KW, Holcomb GW, Murphy JP editors. Pediatric surgery. Philadelphia: Elsevier Saunders; 2005. p. 383–404.

Kawahara H, Dent J, Davidson G. Gastroenterology. 1997;113:399–408.

Kudsk KA, Tolley EA, DeWitt RC, Janu PG, Blackwell AP, Yeary S, King BK. JPEN J Parenter Enteral Nutr. 2003;27:1–9.

Madisch A, Kulich KR, Malfertheiner P, Ziegler K, Bayerdörffer E, Miehlke S, Labenz J, Carlsson J, Wiklund IK. Z Gastroenterol. 2003;41:1137–43.

Malone PS, Rensley PG, Kiely EM. Lancet. 1990; 336(8725):1217–8.

McGrath PJ, Rosmus C, Canfield C, Campbell MA, Hennigar A. Dev Med Child Neurol. 1998;40:340–3.

Moore SW. Pediatr Surg Int. 2008;24:873–83.

Nelson SP, Chen EH, Syniar GM, Christoffel KK. Arch Pediatr Adolesc Med. 1997;151:569–72.

Roberts JP, Moon S, Malone PS. Br J Urol 1995;75:386–9.

Schaller BJ, Graf R, Jacobs AH. Am J Gastroenterol. 2006;101:1655–65.

Spitz L, McLeod E. Semin Pediatr Surg. 2003;12:237–40.

Stanghellini V. Drugs Today (Barc). 2003;39 Suppl A:15–20.

Teixeira JP, Mosquera V, Flores A. Hepatogastroenterology. 2009;56:80–4.

Valletta E, Angelini G. Pediatr Med Chir. 2004;26:112–8.

K Winge K, Rasmussen D, Werdelin LM. J Neurol Neurosurg Psychiatry. 2003;74:13–9.

Zerhau P, Husár M, T?ma J. Rozhl Chir. 2008;87:593–5.

Chapter 88
Dysphagia: Neurological and Behavioral Aspects

Dorianne Feldman and Marlís González-Fernández

Abbreviations

VFSS	Videofluroscopic swallow study
FEES	Fiberoptic endoscopic evaluation of swallowing
SLP	Speech-language pathologist
ALS	Amyotrophic lateral sclerosis
MS	Multiple sclerosis
TBI	Traumatic brain injury
PD	Parkinsons disease
PEG	Percutaneous endoscopic gastrostomy tube

88.1 Introduction

Swallowing dysfunction is a frequent complaint in older individuals (White et al. 2008), particularly if they have underlying dementia or a neurologic conditions (Easterling and Robbins 2008). Disordered swallowing or dysphagia can be classified as a primary (i.e., stroke) or secondary problem (i.e., radiation fibrosis) with many causes and complications. Age-related changes also accompany normal swallowing (Barczi et al. 2000; Humbert and Robbins 2008).

Dysphagia can significantly affect the health, quality of life, and nutritional status of those affected. The ramifications are serious and extremely concerning, especially in the elderly population, often overwhelmed by other medical conditions and social isolation and in whom swallowing difficulty is usually neurologically mediated (Humbert and Robbins 2008). There are many challenges when caring for these individuals. Changes in mental status, deficiencies in immunologic reserve, poor nutrition, and end-of-life issues increase medical complexity (White et al. 2008). As the population over age 65 increases, swallowing disorders and their impact on quality of life are of great importance.

M. González-Fernández (✉)
Department of Physical Medicine and Rehabilitation, School of Medicine,
Johns Hopkins University, Baltimore, MD
e-mail: mgonzal5@jhmi.edu

88.2 Epidemiology

In the United States, about 15% of community dwelling individuals over age 65 have some type of swallowing dysfunction; whereas in hospitals, the prevalence is around 13–14% (Humbert and Robbins 2008; Dray et al. 1998). In institutionalized settings, the rates rise; affecting up to half of all individuals (Easterling and Robbins 2008). Gilmore et al. (1995) evaluated 290 individuals residing in a nursing facility and demonstrated that of those eating less than half their meals, 30% had dysphagia and were unable to maintain adequate nutrition or an optimal weight with oral feeding. Groher and McKaig (1995) found that out of 740 individuals living in an institutionalized setting, 31% were receiving a modified meal. Of those studied, dementia was the most common underlying medical condition (53%) followed by stroke (25%).

88.3 Physiology of Swallowing

Swallowing is a finely regulated, intricate process that requires cortical and subcortical input from various regions of the brain to move food and/or liquid from the mouth to the stomach without compromising the airway (White et al. 2008). The physical act of swallowing can be divided into four discrete stages: oral preparatory, oral propulsive, pharyngeal, and esophageal (Matsuo and Palmer 2008). A normal swallowing videofluorographic sequence is described in Fig. 88.1.

In the oral phase, the bolus is prepared and then propelled under voluntary control with the assistance of the tongue to the back of the oral cavity and pharynx (Gonzalez-Fernandez and Daniels 2008). Once the bolus reaches the pharynx, the pharyngeal phase begins, consisting of a series of coordinated movements that drive the bolus to the upper esophageal sphincter. The esophageal stage starts as the bolus moves through the upper esophageal sphincter, esophagus, lower esophageal sphincter, and finally into the stomach. The pharyngeal and esophageal phases are not voluntarily controlled. Dysphagia can occur as a result of problems in one or more of these phases or locations (Matsuo and Palmer 2008). Key features of swallowing are detailed in Table 88.1.

88.4 Dysphagia

Many conditions can lead and/or increase susceptibility to dysphagia; making the identification process challenging, particularly in older individuals (Schindler and Kelly 2002). Nonetheless, neurologic disorders are the most common cause of swallowing disorders. Problems with sensation, muscle function/coordination, and behavioral issues are paramount and are usually related to a multifactorial rather than an isolated trigger (Easterling and Robbins 2008).

Oropharyngeal disorders are typically characterized by impairments in swallow initiation and food propulsion to the esophagus and are strongly linked to aging (Gleeson 1999; White et al. 2008). Associated findings include difficulty in chewing and manipulating the quantity of material consumed, sensation that the swallowed bolus is trapped (globus sensation), coughing, choking, dysphonia (wet-sounding vocalization), or passing of contents backwards through the nose or mouth (Schindler and Kelly 2002; White et al. 2008). Tongue pressure also declines with increased age contributing to disordered pharyngeal phase function (Schindler and Kelly 2002). In contrast, esophageal phase dysfunction is the result of esophageal pathologies which restrict or slow food entry or passage (i.e., esophageal strictures, carcinoma, and diverticulae; Dray et al. 1998).
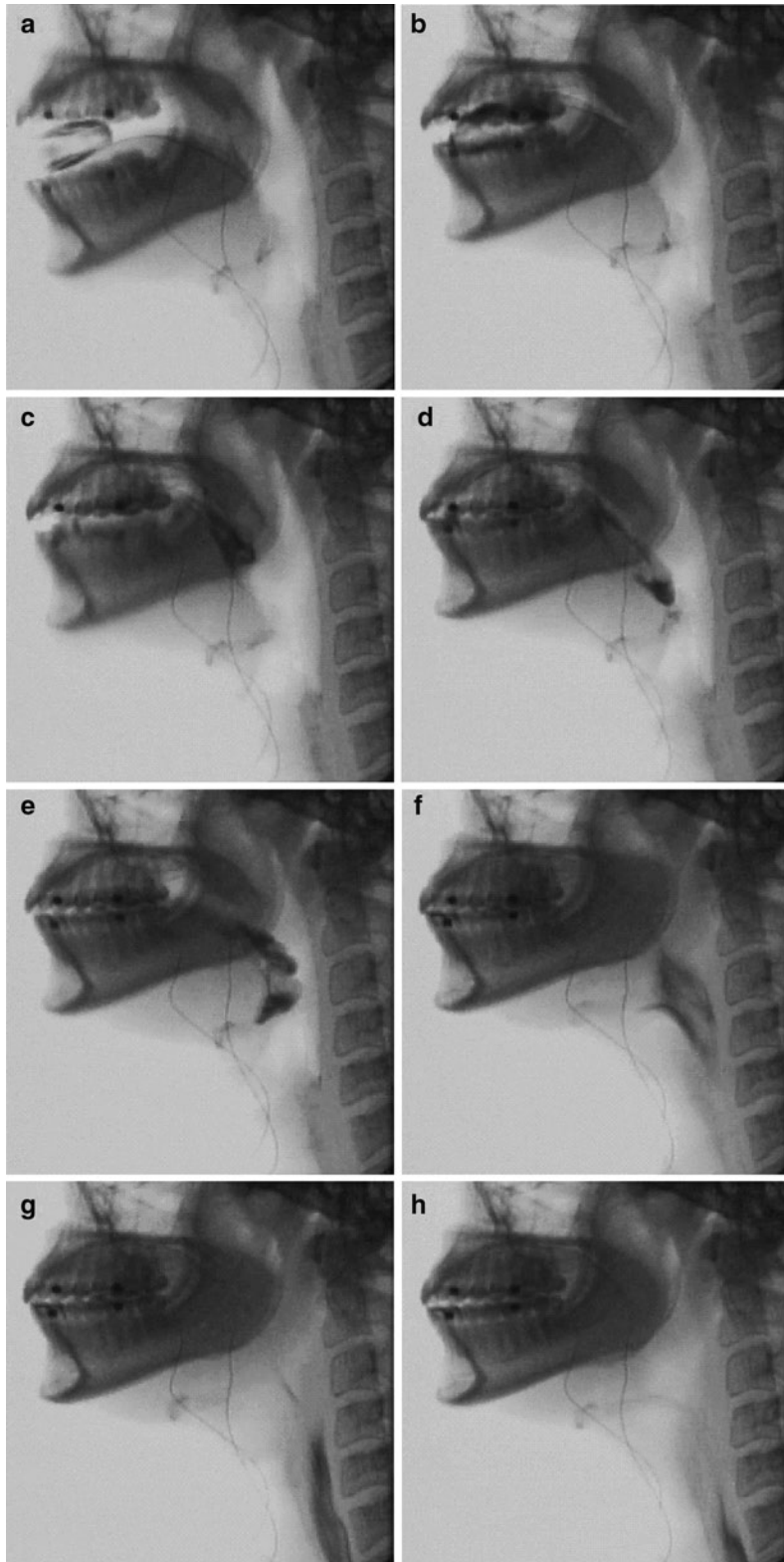
Fig. 88.1 Normal swallowing sequence eating a soft food (banana with a barium coating) on lateral projection videofluoroscopy. (**a**) Food is placed in the mouth. (**b**) Chewing starts. (**c**) Food that is of the appropriate size and consistency is moved posteriorly while chewing continues. (**d**) Food reaches the valleculae while chewing continues. (**e**) The remaining food from the mouth is moved posteriorly. (**f**) Swallowing ensues. (**g**) Upper esophageal sphincter opens to allow food passage. (**h**) Upper esophageal sphincter closes as food continues down in the esophagus

1. Swallowing is the basic process that allows passage of food from the mouth to the stomach.
2. Swallowing can be divided into four discrete stages: oral preparatory, oral propulsive, pharyngeal, and esophageal.
3. Normal swallowing requires cortical and subcortical input from various regions of the brain to move food and/or liquid from the mouth to the stomach.
4. Failure to protect the airway during swallowing may result in aspiration.
5. Gastroesophageal reflux can result in aspiration after the swallow.
6. Dysphagia rehabilitation can improve swallowing and may allow patients to continue oral feeding.

This table lists the key factors of swallowing including swallowing phases, neural control, and major consequences of swallowing dysfunction
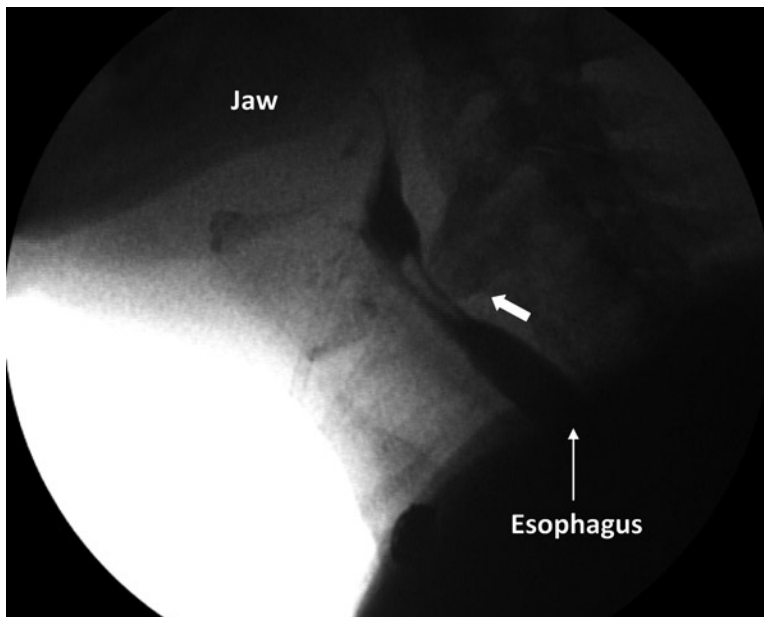
Fig. 88.2 Cervical spine osteophytes causing dysphagia. This lateral projection radiograph abstracted from a videofluorographic swallowing study illustrates a large cervical anterior osteophyte (bony prominence) causing mechanical obstruction of the foodway resulting in dysphagia. The dark black material is barium contrast passing by the obstruction

Orthopedic changes in the cervical spine associated with osteoarthritis (bony projections or osteophytes) cause decreased neck range of motion, thus hindering swallowing efficacy (Gleeson 1999; Achem and Devault 2005). Osteophytes in the cervical spine can push forward on the posterior pharyngeal wall creating a physical barrier to overcome in order to swallow (Fig. 88.2).

Other causes include polypharmacy and generalized age-related changes with breathing, gustation, sensation, and motor function of the tongue, face, neck, pharynx, and larynx (Gleeson 1999; Schindler and Kelly 2002; Leslie et al. 2005; Humbert and Robbins 2008).

In general, with aging, all processes operate at a reduced pace. In fact, studies have demonstrated a reduction in oropharyngeal and hypopharyngeal peristalsis along with a decline in the range of laryngeal movements (Leslie et al. 2005). Most importantly, and physiologically, vocal fold adduction secures the airway and must be coordinated with the speed of content passage in order to prevent aspiration (Fig. 88.3). If the sequencing of these processes is not timely, the airway can be compromised (Ren et al. 1993; Leslie et al. 2005).

Fig. 88.3 Aspiration of thin liquids. Lateral projection videofluoroscopy. Following administration of liquid barium contrast (*dark gray*) and a swallowing attempt, incomplete opening of the upper esophageal sphincter (*UES*) caused spillage of liquid into the pharyngeal vestibule (*open arrow*), through the vocal folds (*solid arrow*), and into the trachea (*white arrow*)
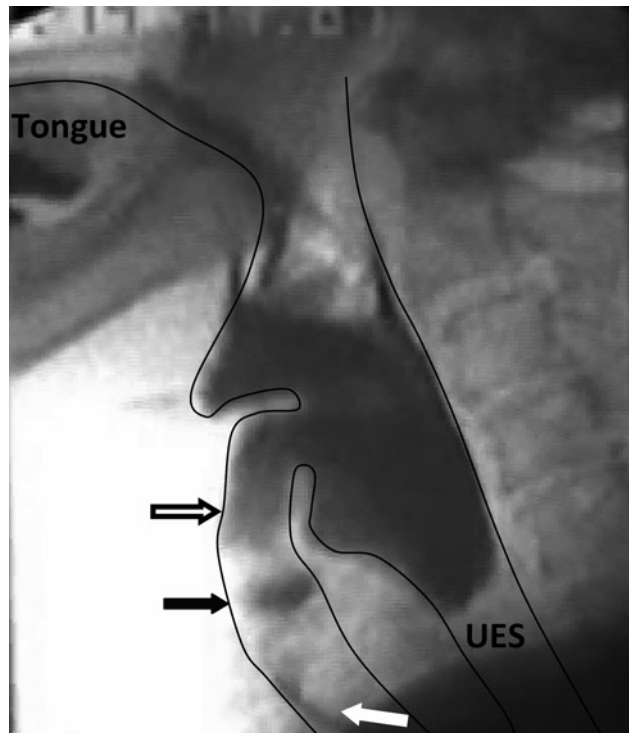
Swallowing safety is critical and is of utmost importance in preventing complications such as weight loss, fluid status deficits, malnutrition, and aspiration pneumonia (Easterling and Robbins 2008). Changes in mental capacity, diminished immune system function, and end-of-life issues amplify medical complexity and pose multiple care challenges in the elderly (White et al. 2008).

88.5 Neurologic Causes of Dysphagia

Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS), dementia, and traumatic brain injury (TBI) are neurologic conditions associated with swallowing dysfunction of which stroke is the most common (Easterling and Robbins 2008; Gonzalez-Fernandez and Daniels 2008; Miller et al. 2008; Ward et al. 2007).

In fact, neurologic disease accounts for three-quarters of dysphagia during the oropharyngeal phase (Ertekin and Aydogdu 2003). Incidence in stroke varies based on assessment methods, but can be as high as 90% (Gonzalez-Fernandez and Daniels 2008; Miller and Chang 1999). Stroke patients with dysphagia have longer duration of hospitalization and more difficulties with hydration and nutrition (Gordon et al. 1987; Axelsson et al. 1989; Kidd et al. 1995). A threefold increase in pneumonia has been documented in stroke patients with dysphagia (Martino et al. 2005); the risk is even higher in patients with confirmed aspiration (Teasell et al. 1996). Reports indicate that dysphagia in this population results from impairments in muscle control, tongue function, sensation (larynx and pharynx), and cough (Dray et al. 1998).

Dysphagia is also an important consideration in TBI and is associated with the severity of brain injury, time span for cognitive recovery, tracheostomy placement, and duration of mechanical

ventilation (Ward et al. 2007). Swallowing problems in this population are multifaceted and can be a result of impaired swallow response or lingual, pharyngeal, laryngeal, or cricopharyngeal dysfunction (Mayer 2004). Cognitive and executive dysfunctions, aberrant behavior, problems with speech production, and/or comprehension along with motor abnormalities are major constraints to intervention and airway protection (Mayer 2004). In TBI, these findings may be more problematic with regard to swallowing safety than the underlying pathologic swallow (Mayer 2004).

As opposed to PD and ALS in which the disease course continues to advance, stroke and head injury-induced swallowing problems usually improve or resolve (Dray et al. 1998; Broadley et al. 2005; White et al. 2008). In stroke, dysphagia resolves in up to 90% of patients (Broadley et al. 2005; White et al. 2008).

The rate of swallowing dysfunction in those with PD is variable (18–100%; Miller et al. 2008). Solid textures have been shown to be more challenging for these individuals (Edwards et al. 1992). Disordered swallowing usually occurs as a result of problems with mastication; most evident during the oral phase (Calcagno et al. 2002; Hartelius and Svensson 1994; Merson and Rolnick 1998; Thomas and Wiles 1999).

In MS, dysphagia occurs less frequently (33–43%) and often remains unrecognized by the individual until later in the disease course, despite acknowledgment by others (Dray et al. 1998; Gonzalez-Fernandez and Daniels 2008; Pasquinelli and Solaro 2008). For this reason, identification tends to be delayed (Schindler and Kelly 2002). Features include decreased bolus movement through the pharynx and inability to trigger a pharyngeal swallow response (Dray et al. 1998). As well, dysphagia for liquids and solids may be exacerbated by low energy levels, especially in the beginning phases (Dray et al. 1998).

ALS is a progressive neurodegenerative disease that destroys both upper and lower motor neurons specifically in the brainstem and spine along with the associated pathways. Dysphagia usually occurs at later stages of the disease but can be present at onset (Higo et al. 2004). Findings include protracted swallow responsiveness to the bolus and increased upper esophageal sphincter activity and pressure (Achem and Devault 2005). Oral phase difficulties, manifests soon after onset and in many cases, leads to increased time for food consumption and inability to tolerate textures that are not softened (Dray et al. 1998).

Dementia is a common cause of dysphagia and is likely the result of disease effects superimposed on age-related alterations in sensation, muscle function, and coordination (Easterling and Robbins 2008). Horner et al showed disordered swallowing in approximately 28% of those examined with Alzheimer's disease based on videofluoroscopic assessment (Horner et al. 1994). Another reason for disordered swallowing in this population is deterioration in olfaction (Easterling and Robbins 2008). Given the interdependence of smell and gustation, food tends to be less palatable and desirable; likewise nutritional status can become compromised (Easterling and Robbins 2008).

88.6 Swallowing in the Elderly

Growing old, in general, causes a host of changes – thinning of muscles, weakness, decline in bone quality, slower nerve conduction (loss of myelin) – and can affect virtually all bodily functions (Gleeson 1999). Global features include performing activities at a reduced pace, decrement in body processes, weakness, decreased stamina, and impairments in dexterity (Gleeson 1999). Swallowing is not exempt. In fact, Robbins et al demonstrated that swallowing velocity is reduced as early as 45 years of age and will continue insidiously thereafter so that by 70 years, the changes are more pronounced than those seen at 45 years (Robbins et al. 1992).

Adaptations in deglutition that are a result of the natural aging process are termed presbyphagia (Robbins et al. 1992; Leslie et al. 2005). While dysphagia refers to disordered swallowing, the alterations whether structural, instinctive, compensatory, and/or emotional are not considered to be pathologic (Humbert and Robbins 2008). For this reason, it is becoming increasingly more important to be able to make this distinction in order to manage these individuals appropriately (Humbert and Robbins 2008).

88.7 Nutritional Implications

Malnutrition is one of the major sequelae of dysphagia. If not promptly recognized, the clinical outcome may be significantly compromised (Curran 1990). Malnutrition can occur either as an early complication of swallowing dysfunction or late in progressive cases (Pasquinelli and Solaro 2008). Despite the cause or time of onset of dysphagia, elderly individuals are at risk because of social isolation, medical comorbidities, decreased mobility, fatigue, poor cognition, diminished awareness, impaired vision, and inability to cook, clean, and/or self-feed (Gariballa and Sinclair 1998; Leslie et al. 2005). Side effects of medications and mood disorders can also adversely impact nutritional status by retarding appetite (Cole et al. 2000). In addition, foods may be selected based on underlying swallowing impairments. For example, in PD softer foods are preferred (Lorefalt et al. 2006).

When the body is unable to maintain adequate nourishment and meet its inherent demands, the consequences can be devastating (Pasquinelli and Solaro 2008). Insufficient intake, malabsorption, and/or abnormal output are the usual culprits (Pasquinelli and Solaro 2008). Problems with olfaction (less palatable food) and memory (not remembering to eat) are major threats to sustaining sufficient intake (Easterling and Robbins 2008). Often, this is compounded by mealtime anxiety, general noncompliance, and an unwillingness to eat, especially in cases of dementia (Biernacki and Barratt 2001). More devastating are impairments in mastication and oral control, which necessitate adjustment in oral intake consistency, albeit not without drawbacks and/or nutritional risk (Easterling and Robbins 2008). In contrast, deglutition can also be worsened by malnutrition; inflicting further regression in an already impaired but safe swallow (Leslie et al. 2005).

Nutrition is an important factor not only for preservation of overall health and vigor, but also for convalescence (Gariballa and Sinclair 1998). Managing dysphagia appropriately can facilitate feeding in a situation that can be extremely stressful and complicated for caregivers who feel compelled to keep the patient alive. Consumption can be improved by providing food that is safe (from a swallowing standpoint), pleasurable, and/or self-selected on a frequent, yet, desired basis in addition to already scheduled times (Biernacki and Barratt 2001). Supervision and/or help with feeding may also be of benefit (Pasquinelli and Solaro 2008).

88.8 Management of Swallowing Dysfunction

A systematic and individualized approach is important in the management of swallowing dysfunction. In cases of dysphagia associated with neurological dysfunction it is important to consider the nature of the disease and the patient's wishes (Fig. 88.4).

The goal of dysphagia treatment is to ensure safe swallowing while concurrently avoiding complications; most worrisome being aspiration pneumonia. As a result, food and fluid consistencies
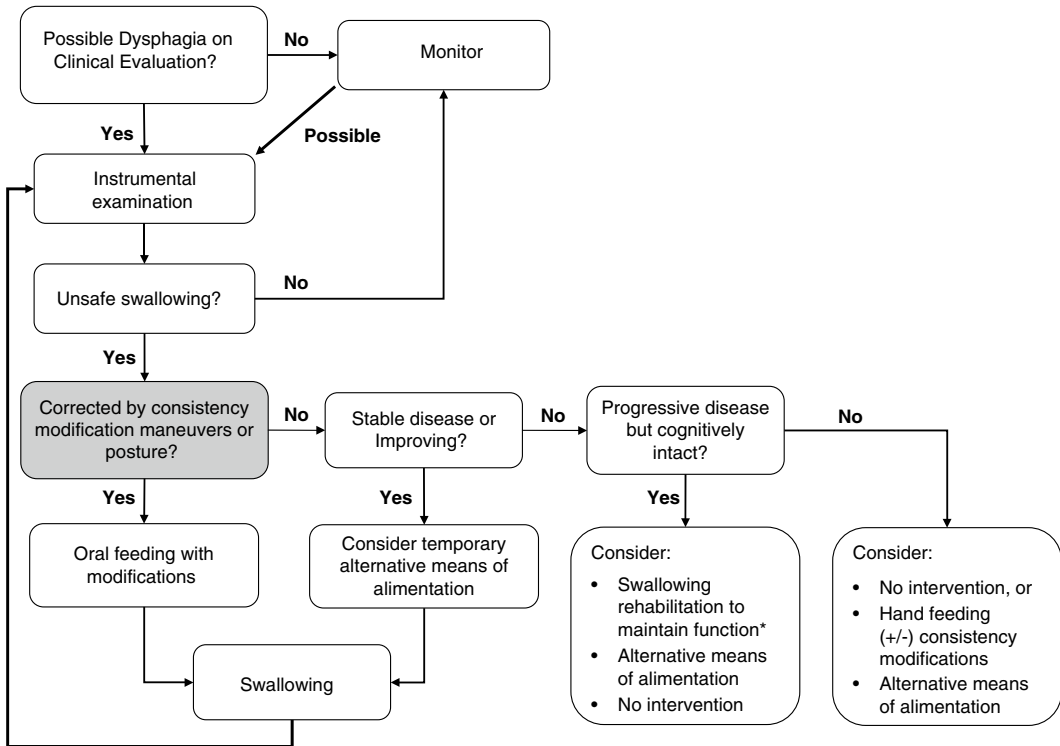
* Exercise might be contraindicated in certain diseases such as ALS.
Reprinted from Physical medicine and Rehabilitation Clinics of North America, 19(4), Gonzalez-Fernandez M, Daniels SK, Dysphagia in Stroke and Neurologic Disease, Pages 881, Copyright (2008), with permission from Elsevier.

Fig. 88.4 Dysphagia evaluation and management of the neurologic disease patient. *Exercise might be contraindicated in certain diseases such as ALS. (From Gonzalez-Fernandez and Daniels 2008). This algorithm describes the decision-making process in evaluation, management, and treatment of dysphagia in patients with neurologic disease

may be adjusted (Vivanti et al. 2009). Although consistency modification can be important to prevent passage of contents into the airway, these dietary restrictions can be rather displeasing (Humbert et al. 2009). In fact, this can cause more difficulty at mealtimes as intake, manipulation, and movement of food and fluid becomes more time consuming; and may result in nutritional or hydration problems (Vivanti et al. 2009).

It is extremely important that clinicians are able to identify swallowing dysfunction and coordinate appropriate treatment. Swallowing can be assessed clinically, with bedside screening tools such as the 3-oz water swallow test or the Mann assessment of swallowing ability, among others (Carnaby-Mann and Lenius 2008; DePippo et al. 1992; Easterling and Robbins 2008). Instrumental examination using videofluoroscopy (VFSS), in which X-ray beams are used to detect the course of specialized, contrast-labeled food products during swallowing and/or fiberoptic endoscopy is important to determine the underlying cause of dysphagia (Schindler and Kelly 2002). Although fiberoptic endoscopic evaluation of swallowing (FEES) is superior for direct evaluation of the pharynx and larynx, it is invasive and does not allow for visualization of the oral and esophageal phases. VFSS remains the most used method (Schindler and Kelly 2002).

The mainstay of dysphagia treatment includes compensatory and rehabilitative techniques (Table 88.2). Compensatory techniques (chin-up, chin tuck, head turn, head tilt, and reclining

Table 88.2 Common interventions for dysphagia management

Feeding modifications	Postural maneuvers	Rehabilitation[a]
Thickened liquids	Chin tuck	Oral exercises
Nectar thick liquids	Head tilt	Range of motion
Honey thick liquids	Head rotation	Strength exercises
	Neck extension	Lingual exercises
Processed solids	Reclining position	Masako maneuver
Pureed		Shaker exercises
Mechanical soft		Effortful swallow
		Glottal attacks
Volume control		Pushing and pulling exercises
Teaspoon feeding		EMG biofeedback
Special utensils		

[a]Lingual exercises – Aim is to augment multidirectional tongue movements, sucking and swallowing in order to improve oral control. Masako maneuver – Tongue-holding technique designed to facilitate tongue contact with the pharyngeal wall. Shaker exercises – Strengthening exercise for muscles located below the chin to facilitate upper esophageal sphincter opening and prevent pharyngeal food retention. Effortful swallow – A strategy in which a forceful swallow is encouraged increasing the oral/pharyngeal pressures to clear the bolus, from the vallecular space. Glottal attacks – Specialized adduction exercises in which the vocal folds are powerfully drawn toward midline prior to phonation increasing laryngeal muscular tension to enhance voice control. These can improve vocal cord adduction and closure during swallowing. EMG biofeedback – Adjunct therapy that allows visualization of muscle activity, in this case, visualization of submandibular or anterior neck muscles. It can allow greater control of those muscles and facilitate rehabilitation efforts

positioning, texture modification) serve to optimize bolus movement into the pharynx by altering head and/or chin positioning or improving bolus control (Logemann 2008). Rehabilitative efforts may include exercises to increase neck mobility and strengthen oral, lingual, pharyngeal, and laryngeal muscles and neuromuscular electrical stimulation (Logemann 2008). Postural maneuvers and texture modifications should be trialed during VFSS, FEES, and therapy sessions (Schindler and Kelly 2002). Other therapeutic strategies include sensory training, which targets gustation, and temperature accommodation (Logemann 2008).

When eating is not an option, enteral feeding can be considered via percutaneous endoscopic gastrostomy tube (PEG) or, for short-term purposes, with use of oral or nasogastric feeding tubes (Easterling and Robbins 2008). The underlying disease-causing swallowing dysfunction is critical in considering nonoral feeding. In cases with dementia, feeding through PEG tubes has not been associated with improved survival, functional status, patient comfort, or reduced complications (Finucane et al. 1999). The decision to use non-oral feeding requires the input of the patient (when possible), family, treating physicians, and speech language pathologists to determine if the benefits of nonoral feeding outweigh possible complications.

88.9 Application to Other Areas of Health and Disease

Eating is essential to the operation of virtually every body system; dysphagia can have a significant impact on an individual's ability to eat and meet its nutritional needs. As previously discussed, nutritional status can deteriorate with senescence; dysphagia can have an additional detrimental effect on nutrition. Malnutrition can have a major impact on overall functioning and disease susceptibility and can

Table 88.3 Key points of dysphagia

1. Neurologic disease is one of the most common causes of dysphagia.
2. Dysphagia associated with neurologic disease can affect any of the stages of swallowing.
3. Malnutrition is one of the most serious sequela of dysphagia.
4. Physical, cognitive, and behavioral changes can impact food preferences and contribute to swallowing difficulties in the elderly.
5. Age-related changes can increase the probability of developing dysphagia after neurologic events.
6. Early comprehensive dysphagia evaluation and treatment is essential for best outcomes.

This table lists the key facts of dysphagia including cause, swallowing stages, sequela, and age-related changes

result in growth and gonadotropic hormone insufficiency, decreased insulin uptake, hypothyroidism, immune system deficits, impaired gastrointestinal absorption, osteoporosis, psychiatric disorders, altered sleep hygiene, age-related and/or nutritional anemia, muscle mass loss, and vitamin deficiencies (Lytras and Tolis 2007; Carmel 2008)

Nutritional deficiencies can impair sensorimotor and cognitive functioning (Biernacki and Barratt 2001; Espeland and Henderson 2006). Endocrinologic and immune system alterations interfere with kidney output, nutrient uptake/processing, and generalized performance (Lytras and Tolis 2007). Physical impairments amplify associated medical risks leading to decubitus ulcers and pneumonia (Almirall et al. 2000; Gariballa and Sinclair 1998; Langmore et al. 2002). Thus, it is extremely important that clinicians understand the ramifications of malnutrition, its association with dysphagia, and other medical conditions/impairments in the aging population.

88.10 Final Points

Dysphagia is common, associated with neurologic disease and senescence. Depending on the primary pathology, the course is rather variable. However, when present, the complications can be extremely devastating substantiating the need for aggressive diagnosis, management, and treatment. With a better knowledge and awareness of the swallowing process including its relation to the existing disease state, complication risk, and importance of rehabilitation services, care can be coordinated effectively to improve overall health, wellbeing, and quality of life. Key points of this chapter are described in Table 88.3.

Summary Points

- Dysphagia is a common problem, particularly in older individuals and is primarily associated with dementia and neurologic disease.
- Depending on the primary pathology, the course of dysphagia is variable.
- Malnutrition, dehydration, weight loss, and aspiration pneumonia are frequent, yet serious complications associated with disordered swallowing.
- Older individuals are at greater risk for malnutrition due to medical comorbidities, decreased functional mobility, limited self-care capacity, and social isolation; which is exacerbated by underlying dysphagia.
- Proper diagnosis, management, and treatment are essential to the care of patients with disordered swallowing.
- Dysphagia therapy focuses on compensatory techniques and exercises for neck, facial, lingual, pharyngeal, and laryngeal muscles.
- Enteral feeding should be considered when safe oral feeding is not possible.

Key Terms

Dysphagia: Disordered swallowing.

Deglutition: The act of swallowing.

Presbyphagia: Age-related, nonpathologic changes in swallowing function.

Videofluoroscopic swallow study (VFSS): X-ray beams are used to detect the course of specialized, contrast-labeled food products during swallowing.

Fiberoptic endoscopic evaluation of swallowing (FEES): Passage of a small, flexible scope attached to a camera, through the nose and into the pharynx and larynx in order to visualize swallowing during the oral and esophageal phases.

Traumatic brain injury: Intracranial injury due to traumatic forces causing injury to the head.

References

Achem SR, Devault KR. Dysphagia in aging. J Clin Gastroenterol. 2005;39:357–71.

Almirall J, Bolibar I, Vidal J, Sauca G, Coll P, Niklasson B, Bartolome M, Balanzo X. Epidemiology of community-acquired pneumonia in adults: a population-based study. Eur Respir J. 2000;15:757–63.

Axelsson K, Asplund K, Norberg A, Eriksson S. Eating problems and nutritional status during hospital stay of patients with severe stroke. J Am Diet Assoc. 1989;89:1092–6.

Barczi SR, Sullivan PA, Robbins J. How should dysphagia care of older adults differ? Establishing optimal practice patterns. 2000;Semin Speech Lang. 21:347–61.

Biernacki C, Barratt J. Improving the nutritional status of people with dementia. Br J Nurs. 2001;10:1104–14.

Broadley S, Cheek A, Salonikis S, Whitham E, Chong V, Cardone D, Alexander B, Taylor J, Thompson P. Predicting prolonged dysphagia in acute stroke: the Royal Adelaide Prognostic Index for Dysphagic Stroke (RAPIDS). Dysphagia. 2005;20:303–10.

Calcagno P, Ruoppolo G, Grasso MG, De Vincentiis M, Paolucci S. Dysphagia in multiple sclerosis - prevalence and prognostic factors. Acta Neurol Scand. 2002;105:40–3.

Carmel R. Nutritional anemias and the elderly. Semin Hematol. 2008;45:225–34.

Carnaby-Mann G, Lenius K. The bedside examination in dysphagia. Phys Med Rehabil Clin N Am. 2008;19:747–68, viii.

Cole C, Bigando K, DeSutter S. Is altered nutritional status the root cause of your clients' negative outcomes? J Nurs Care Qual. 2000;14:41–56.

Curran J. Overview of geriatric nutrition. Dysphagia. 1990;5:72–6.

DePippo KL, Holas MA, Reding MJ. Validation of the 3-oz water swallow test for aspiration following stroke. Arch Neurol. 1992;49:1259–61.

Dray TG, Hillel AD, Miller RM. Dysphagia caused by neurologic deficits. Otolaryngol Clin North Am. 1998;31:507–24.

Easterling CS, Robbins E. Dementia and dysphagia. Geriatr Nurs. 2008;29:275–85.

Edwards LL, Quigley EM, Pfeiffer RF. Gastrointestinal dysfunction in Parkinson's disease: frequency and pathophysiology. Neurology. 1992;42:726–32.

Ertekin C, Aydogdu I. Neurophysiology of swallowing. Clin Neurophysiol. 2003;114:2226–44.

Espeland MA, Henderson VW. Preventing cognitive decline in usual aging. Arch Intern Med. 2006;166:2433–4.

Finucane TE, Christmas C, Travis K. Tube feeding in patients with advanced dementia: a review of the evidence. JAMA. 1999;282:1365–70.

Gariballa SE, Sinclair AJ. Assessment and treatment of nutritional status in stroke patients. Postgrad Med J. 1998;74:395–9.

Gilmore SA, Robinson G, Posthauer ME, Raymond J. Clinical indicators associated with unintentional weight loss and pressure ulcers in elderly residents of nursing facilities. J Am Diet Assoc. 1995;95:984–92.

Gleeson DC. Oropharyngeal swallowing and aging: a review. J Commun Disord. 1999;32:373–95; quiz 395–6.

Gonzalez-Fernandez M, Daniels SK. Dysphagia in stroke and neurologic disease. Phys Med Rehabil Clin N Am. 2008;19:867–88.

Gordon C, Hewer RL, Wade DT. Dysphagia in acute stroke. Br Med J (Clin Res Ed). 1987;295:411–4.

Groher ME, McKaig TN. Dysphagia and dietary levels in skilled nursing facilities. J Am Geriatr Soc. 1995;43:528–32.

Hartelius L, Svensson P. Speech and swallowing symptoms associated with Parkinson's disease and multiple sclerosis: a survey. Folia Phoniatr Logop. 1994;46:9–17.

Higo R, Tayama N, Nito T. Longitudinal analysis of progression of dysphagia in amyotrophic lateral sclerosis. Auris Nasus Larynx. 2004;31:247–54.

Horner J, Alberts MJ, Dawson DV, Cook GM. Swallowing in Alzheimer's disease. Alzheimer Dis Assoc Disord. 1994;8:177–89.

Humbert IA, Fitzgerald ME, McLaren DG, Johnson S, Porcaro E, Kosmatka K, Hind J, Robbins J. Neurophysiology of swallowing: effects of age and bolus type. Neuroimage. 2009;44:982–91.

Humbert IA, Robbins J. Dysphagia in the elderly. Phys Med Rehabil Clin N Am. 2008;19:853–66, ix-x.

Kidd D, Lawson J, Nesbitt R, MacMahon J. The natural history and clinical consequences of aspiration in acute stroke. QJM. 1995;88:409–13.

Langmore SE, Skarupski KA, Park PS, Fries BE. Predictors of aspiration pneumonia in nursing home residents. Dysphagia. 2002;17:298–307.

Leslie P, Drinnan MJ, Ford GA, Wilson JA. Swallow respiratory patterns and aging: presbyphagia or dysphagia? J Gerontol A Biol Sci Med Sci. 2005;60:391–5.

Logemann JA. Treatment of oral and pharyngeal dysphagia. Phys Med Rehabil Clin N Am. 2008;19:803–16, ix.

Lorefalt B, Granerus AK, Unosson M. Avoidance of solid food in weight losing older patients with Parkinson's disease. J Clin Nurs. 2006;15:1404–12.

Lytras A, Tolis G. Assessment of endocrine and nutritional status in age-related catabolic states of muscle and bone. Curr Opin Clin Nutr Metab Care. 2007;10:604–10.

Martino R, Foley N, Bhogal S, Diamant N, Speechley M, Teasell R. Dysphagia after stroke: incidence, diagnosis, and pulmonary complications. Stroke. 2005;36:2756–63.

Matsuo K, Palmer JB. Anatomy and physiology of feeding and swallowing: normal and abnormal. Phys Med Rehabil Clin N Am. 2008;19:691–707, vii.

Mayer V. The challenges of managing dysphagia in brain-injured patients. Br J Community Nurs. 2004;9:67–73.

Merson RM, Rolnick MI. Speech-language pathology and dysphagia in multiple sclerosis. Phys Med Rehabil Clin N Am. 1998;9:631–41.

Miller N, Allcock LM, Hildreth T, Jones D, Noble E, Burn D. Swallowing problems in Parkinson's disease: Frequency and clinical correlates. J Neurol Neurosurg Psychiatry. 2008. Electronic-publication doi: 10.1136/jnnp.2008.157701.

Miller RM, Chang MW. Advances in the management of dysphagia caused by stroke. Phys Med Rehabil Clin N Am. 1999;10:925–41, x.

Pasquinelli S, Solaro C. Nutritional assessment and malnutrition in multiple sclerosis. Neurol Sci. 2008;29 Suppl 4:S367–9.

Ren J, Shaker R, Zamir Z, Dodds WJ, Hogan WJ, Hoffmann RG. Effect of age and bolus variables on the coordination of the glottis and upper esophageal sphincter during swallowing. Am J Gastroenterol. 1993;88:665–9.

Robbins J, Hamilton JW, Lof GL, Kempster GB. Oropharyngeal swallowing in normal adults of different ages. Gastroenterology. 1992;103:823–9.

Schindler JS, Kelly JH. Swallowing disorders in the elderly. Laryngoscope. 2002;112:589–602.

Teasell RW, McRae M, Marchuk Y, Finestone HM. Pneumonia associated with aspiration following stroke. Arch Phys Med Rehabil. 1996;77:707–9.

Thomas FJ, Wiles CM. Dysphagia and nutritional status in multiple sclerosis. J Neurol. 1999;246:677–82.

Vivanti AP, Campbell KL, Suter MS, Hannan-Jones MT, Hulcombe JA. Contribution of thickened drinks, food and enteral and parenteral fluids to fluid intake in hospitalised patients with dysphagia. J Hum Nutr Diet. 2009;22:148–55.

Ward EC, Green K, Morton AL. Patterns and predictors of swallowing resolution following adult traumatic brain injury. J Head Trauma Rehabil. 2007;22:184–91.

White GN, O'Rourke F, Ong BS, Cordato DJ, Chan DK. Dysphagia: causes, assessment, treatment, and management. Geriatrics. 2008;63:15–20.

Chapter 89
Neuropsychological Aspects of Eating Disorders – A Focus on Diagnostic Criteria

Jennie C. Ahrén

Abbreviations

AN	Anorexia nervosa
BN	Bulimia nervosa
BED	Binge eating disorder
CSF	Cerebrospinal fluid
ED	Eating disorders
EDNOS	Eating disorders not otherwise specified
fMRI	Functional magnetic resonance imaging

89.1 Introduction

Eating disorders (ED) are severe psychiatric disturbances with psychosomatic complications, mainly affecting young women (Treasure 2008; Palmer 2008). The long-term effects of starvation and deviations in eating behaviors are devastating, from a psychological as well as a physiological perspective. ED is stated as one of the leading causes of disease burden in terms of years lost through disability or death in industrialized countries and recent work shows that they are increasing (Mathers et al. 2000; Hay et al. 2008). The mortality rate is higher than any other psychiatric disorder (Kaye et al. 2009).

The interest in neurological correlates of behavior has increased during the last decades. Modern neuropsychology assumes that intellectual capacities and cognitive processes are complex functions that depend on several interrelated systems in the brain. But even though our knowledge on neural networks and behavior has developed drastically, the classification in anatomical areas according to Brodmann in the early twentieth century is still frequently used and continually updated (Kandel 2000). The connection between brain and behavior as a key aspect of anorexia nervosa (AN) was introduced several years ago (Braun and Chouinard 1992) but new techniques have made it possible to evaluate and observe behaviors in ways that were not anticipated earlier. Functional magnetic resonance imaging (fMRI) is one of the latest methods in brain imaging, revealing patterns of neural activity and resulting in new insights on how the brain functions. fMRI is a specialized MRI scan

J.C. Ahrén

Center for Health Equity Studies, CHESS, Karolinska Institutet/Stockholm University, Sveavagen 160, 106 91, Stockholm, Sweden
e-mail: jennie.ahren@chess.su.se

where the neural activity in the brain or in the spinal cord is measured by the blood flow. It has come to dominate in the field of brain imaging, mainly due to the low radiation exposure.

The relationship between behavioral changes in ED on the one hand and alterations of the brain on the other can be divided into two categories as suggested by a recent review on AN (Kaye et al. 2009). The first one is based on the assumption that there is a genetic component involved; that premorbid traits make an individual more vulnerable to develop AN. Secondly, it is possible that malnutrition causes alterations in the brain and thereby reinforces and helps to maintain the behavior.

The overarching focus of this chapter was to describe subtypes of ED from a neuropsychological perspective. In order to establish how different functions are connected to behavior, definitions of ED will be presented rather detailed. The first section is a short overview of different subtypes of ED with a short description of the etiology of these conditions and comorbid symptoms. This is followed by a brief overview on neuropsychological functions in relation to ED. Furthermore, different parts of the brain involved in eating pathology are briefly described.

89.2 Etiology of ED

The etiology of ED remains unclear, multifactorial models are best applied to increase our understanding on how different factors interact in the development of disorders such as AN and bulimia nervosa (BN). An ED does not only involve deviations in eating behavior, but typically include somatic complications due to starvation and decreased psychosocial functioning. ED often occur during adolescence, a developmentally critical period. The functions of the brain are important clues in understanding behavioral changes in puberty, the relationship between genetic vulnerability, endocrine changes, and environment are overlapping (McAnarney 2008). The rapid change in body composition during this period requires flexibility in regulating weight and hunger; this may be associated with an increased vulnerability in the appetite regulation systems, including hypothalamic structures (Connan et al. 2003). The interaction between genetic, environmental, and psychological factors is complex and demands integrated perspectives (see Fig. 89.1).

Certain personality traits have been described as typical for different types of ED. AN is characterized by high constraint, constriction of affect, perfectionism, conformity, and obsessive-compulsive behavior (Bulik et al. 2003; Kaye 2008). One of the central traits in patients with ED is the need for control. Controlling food intake is sometimes described as a way of controlling a life situation that is overwhelming (Fairburn et al. 1999). For BN impulsivity, sensation seeking and low self-esteem are often stated as predisposing traits (Fairburn et al. 1999; Jacobi et al. 2004). The comorbidity between ED and personality disorders is high. A recent methodological review states that obsessive-compulsive personality disorder shares many of the same features as AN (Lilenfeld et al. 2006). Anxiety disorders are frequent in ED patients and previous research indicates that those might be interpreted as predisposing traits (Swinbourne and Touyz 2007).

Individual differences are likely to influence cognitive style and different aspects of problem-solving strategies. Certain traits that have been described as central for ED, such as obsessive or compulsive behavior, may actually be a result of neuropsychological impairments following the disorder. Starvation leads to a range of psychosocial consequences in the same way as physiological functions are affected. The well-known work by Keys et al. (1950) studied the effects of starvation in a group of healthy men during the mid-forties in Minnesota, USA. Thirty-sex men, described as intelligent, psychologically sound, and physically healthy had their food intake strictly limited during 6 months, resulting in significant weight loss. Interestingly, most of the men showed behavioral patterns similar to those described in patients with ED. Symptoms such as increased apathy, depression,
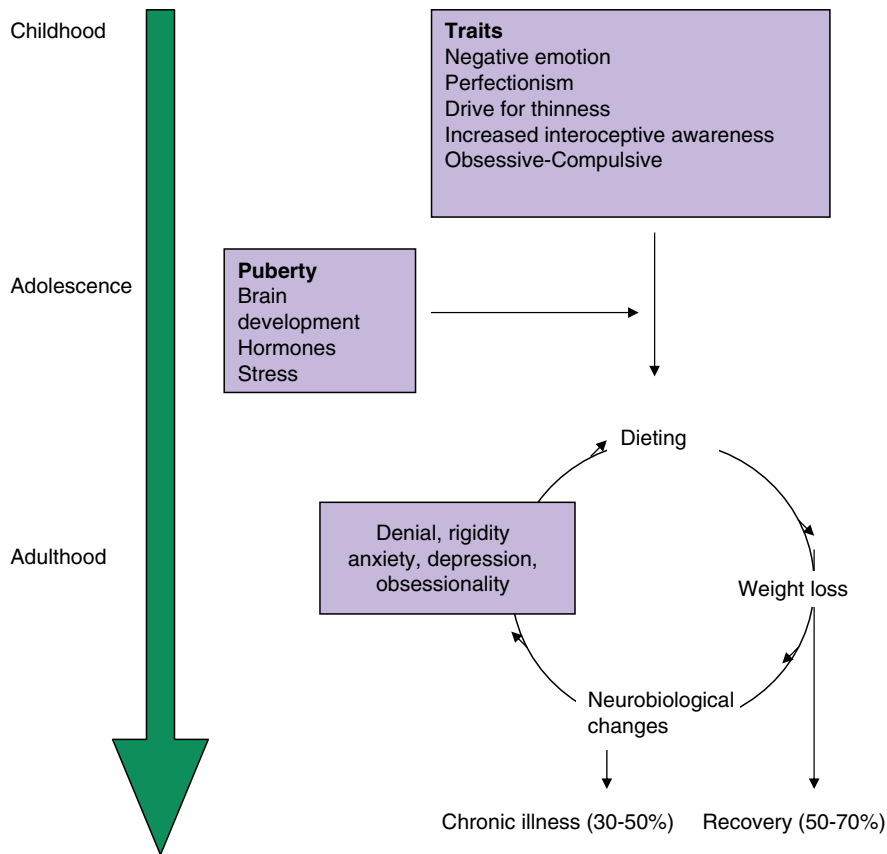
Fig. 89.1 The time course and phenomenology of anorexia nervosa (From Kaye et al. 2009)

and increased neuroticism were reported by most of the men. Furthermore, they showed an increased interest in food and were preoccupied with thoughts of food and became more socially withdrawn. They reported impaired concentration, comprehension, and bad judgment. Six months of semi-starvation also brought on other physical and cognitive problems, such as decreased motor control, impaired sleep, and visual disturbances.

The effects of starvation or binge-eating are obviously devastating from a physiological point of view, but neuropsychological aspects provide important clues in the development and maintenance of ED and need to be further explored.

89.3 Definitions of ED

According to DSM-IV (American Psychiatric Association 1994) ED are divided into the diagnoses AN, BN, eating disorders not otherwise specified (EDNOS), and binge-eating disorder (BED). The life-time prevalence in women for full and partial AN range from 0.9% to 4.3% (Hudson et al. 2007; Wade et al. 2006). Prevalence for full and partial BN range from 4% to 7% in women (Favaro et al. 2003). For BED the lifetime prevalence is 3.5%. The corresponding figures for men are 0.9% for AN, 0.5% for BN, and 2.0% for BED (Hudson et al. 2007). Most of the studies cited in this text are exclusively based on women, and the main perspective will therefore be on women.

It is commonly stated that AN and BN are modern phenomena, but a glance in historical descriptions shows that these conditions are not new. This particularly applies to AN, or "nervous consumption," as described by the British physician Richard Morton as early as in 1689. In 1868 Sir William Gull, physician to Queen Victoria, presented his three case studies under the title "Anorexia Nervosa" and the diagnose was given its name (Pearce 2006).

The essential feature of AN is low body weight and self-starvation. Diagnostic criteria according to the American Psychiatric Association (1994) are as follows (Table 89.1).

BN mainly refers to recurrent binge-eating and compensatory actions such as vomiting or using laxatives. The diagnosis was first applied in 1979 and was included in the psychiatric classification in 1980. Diagnostic criteria for BN according to DSM-IV (American Psychiatric Association 1994) are listed in Table 89.2.

The EDNOS category is for disorders of eating that do not meet the criteria for any specific ED. This does not imply that they are less severe; several features are the same as those stated in the diagnostic criteria for the other subtypes. Examples include the following (Table 89.3).

Table 89.1 Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria (APA 1994) for anorexia nervosa (AN*)*

(A) Refusal to maintain body weight at or above a minimally normal weight for age and height (e.g., weight loss leading to maintenance of body weight less than 85% of that expected; or failure to make expected weight gain during period of growth, leading to body weight less than 85% of that expected)
(B) Intense fear of gaining weight or becoming fat, even though underweight
(C) Disturbance in the way in which one's body weight or shape is experienced, undue influence of body weight or shape on self-evaluation, or denial of the seriousness of the current low body weight
(D) In postmenarchal females, amenorrhea – the absence of at least three consecutive cycles (a woman is considered to have amenorrhea if her periods occur only following hormone (e.g. estrogen) administration)

Types:
- Restricting type: During the current episode of anorexia nervosa, the person has not regularly engaged in binge-eating or purging behavior (i.e., self-induced vomiting or the misuse of laxatives, diuretics, or enemas)
- Binge-eating/purging type: During the current episode of anorexia nervosa, the person has regularly engaged in binge-eating or purging behavior (i.e., self-induced vomiting or the misuse of laxatives, diuretics, or enemas)

Table 89.2 Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria (APA 1994) for bulimia nervosa (BN)

(A) Recurrent episodes of binge-eating. An episode of binge-eating is characterized by both of the following: • Eating, in a discrete period of time (e.g., within any 2-h period), an amount of food that is definitely larger than most people would eat during a similar period of time and under similar circumstances • A sense of lack of control over eating during the episode (e.g., a feeling that one cannot stop eating or control what or how much one is eating)
(B) Recurrent inappropriate compensatory behavior in order to prevent weight gain, such as self-induced vomiting; misuse of laxatives, diuretics, enemas, or other medications; fasting; or excessive exercise
(C) The binge-eating and inappropriate compensatory behaviors both occur, on average, at least twice a week for 3 months
(D) Self-evaluation is unduly influenced by body shape and weight
(E) The disturbance does not occur exclusively during episodes of anorexia nervosa

Types:
- *Purging type*: during the current episode of bulimia nervosa, the person has regularly engaged in self-induced vomiting or the misuse of laxatives, diuretics, or enemas
- *Nonpurging type*: during the current episode of bulimia nervosa, the person has used other inappropriate compensatory behaviors, such as fasting or excessive exercise, but has not regularly engaged in self-induced vomiting or the misuse of laxatives, diuretics, or enemas

Table 89.3 Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria for eating disorder not otherwise specified (EDNOS)

(A) All diagnostic criteria for anorexia nervosa are met, except the menstrual cycle is normal
(B) All diagnostic criteria for anorexia nervosa are met, except weight is normal for height and age even after considerable weight loss
(C) All diagnostic criteria for bulimia nervosa are met, but the frequency of binges is less than twice weekly and for a duration of less than 3 months
(D) There are recurring efforts to compensate (such as self-induced vomiting) for eating only small amounts of food, but body weight is normal for height and age
(E) Regularly chewing and spitting out large quantities of food without swallowing
(F) Binge-eating disorder – regular episodes of binge eating, but with no recurring efforts to compensate, such as purging or excessive exercise

Table 89.4 Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria for binge eating disorder (BED)

(A) Recurrent episodes of binge-eating: an episode of binge-eating is characterized by both of the following:
(1) Eating, in a discrete period of time (e.g., within any 2-h period), an amount of food that is definitely larger than most people would eat in a similar period of time under similar circumstances
(2) The sense of lack of control over eating during the episode (e.g., a feeling that one cannot stop eating or control what or how much one is eating)
(B) Binge-eating episodes are associated with three (or more) of the following:
(1) Eating much more rapidly than normal
(2) Eating until feeling uncomfortably full
(3) Eating large amounts of food when not feeling physically hungry
(4) Eating alone because of being embarrassed by how much one is eating
(5) Feeling disgusted with oneself, depressed, or very guilty after overeating
(C) Marked distress regarding binge-eating is present
(D) The binge-eating occurs, on average, at least 2 days a week for 6 months
(E) The binge-eating is not associated with the regular use of inappropriate compensatory behavior (e.g., purging, fasting, excessive exercise, etc.) and does not occur exclusively during the course of anorexia nervosa or bulimia nervosa

BED was first described by Stunkard in 1959 (Mathes et al. 2009). Binge-eating refers to overeating to the extent that you have none or little control over your food intake. This is followed by feelings of disgust and guilt. People suffering from BED often eat alone or late at night to hide their behavior. BED is distinguished from BN by the absence of purging or compensatory after binge-eating. BED is more common in obese or overweight individuals. The criteria for BED are included for clarification of eating pathology, but will not be developed further in the text (Table 89.4).

89.4 Neuropsychological Functioning in ED

Earlier research proposes that neuropsychological deficits in various cognitive domains may serve as an underlying factor in the development of ED (Lena et al. 2004). A large study of women with AN showed that half of the patients studied had mild cognitive impairments and that more than one-third failed two or more neuropsychological tasks (Bayless et al. 2002). However, it is not clear whether malfunctions in cognitive processes are predisposing or stand as a consequence of the ED. In a review of cognitive functioning in patients with ED, Duchesne and co-workers (2004) reported that AN was associated with difficulties in executive functions, visuospatial abilities, and psychomotor

speed, BN was more connected to impairments in selective attention and executive functions. They conclude that ED in general is associated with neuropsychological dysfunctions, although there is no consensus on exactly what functions are affected. Executive functioning was studied in AN showing that performance worsened at the presence of obsessive behavior, depression, and starvation (Wilsdon and Wade 2006).

Neuropsychological assessment in a group of ED inpatients as compared with healthy controls showed that the performance level on tasks measuring attention demands and problem-solving abilities was impaired. Re-tests after recovery indicated that AN and BN were characterized by similar neuropsychological deficits, and that these malfunctions seemed to be reversible (Lauer et al. 1999). Gillbergs' research group did a follow-up study of AN patients 10 years after onset of the ED. They found no major neuropsychological deficits in the group (Gillberg et al. 2007).

It has been suggested that a weak central coherence is predisposing for AN. The focus on details and difficulties in assessing the "whole" are related to several core features of AN such as rigidity and impairments in cognitive flexibility (Gillberg et al. 1996; Tchanturia et al. 2004). Other studies have showed that people with ED have difficulties in global processing (Lopez et al. 2008a).

The inconsistency in these findings points at the need for identification of neuropsychological deficits, their relation to clinical symptoms, and potential relationships with personality and biological measures (Tchanturia et al. 2005). It also addresses issues of state versus trait, and shows the need for future studies assessing whether neurological abnormalities are predisposing in ED or if these dysfunctions are secondary to the condition (Kaye et al. 2009; Schmidt 2003).

89.5 Neurological Correlates of Eating Pathology

Recent neuro-imaging studies in AN have shown specific and persistent neuropsychological deficits associated with neurological abnormalities (Agrawal and Lask 2009). Earlier studies show that individuals with ED have reduced brain mass. Reductions in grey and white matter and increased levels of cerebrospinal fluid (CSF) has been found in both AN and BN subjects (Swayze et al. 2003; Giordano et al. 2001). A study on individuals who had recovered from their ED showed that both CSF and total volume of white and grey matter was restored (Wagner et al. 2006). This indicates that brain tissue abnormalities might be reversible after long-term recovery.

It has recently been suggested that a disconnection between structures in the brain leads to features typical for AN (Agrawal and Lask 2009). Nunn et al. (2008) suggest certain cortical structures in connection with AN; frontal, somatosensory and parietal cortices and sub-cortical amygdala, hippocampus, hypothalamus, and the striatum. Another study demonstrated a bilateral reduction in hippocampal volume in women with AN, although these were not associated with any impairments in cognitive functions (Connan et al. 2006). A medial prefrontal response to symptom-provoking stimuli was identified as a common feature in both AN and BN. Neural correlates thus indicate that there might be transdiagnostic features for ED (Uher et al. 2004).

Different parts of the brain have been put in connection with food intake. Two regions are located in the hypothalamus; one in the ventromedial part, and the other one in the lateral region. Further, the part of the cortex referred to as the insula, located in between the temporal lobe and the frontal lobe, is involved in regulation of appetite (Koh et al. 2003). Dieting is often stated as a major triggering factor in ED, even though the underlying reasons for this behavior can be multiple. The responses to taste stimuli in the insula and adjacent structures in the prefrontal cortex were stronger in the phase of fasting, especially in women as showed by Uher et al. (2006). Neurobiology of binge-eating has been compared to substance abuse behavior (Mathes et al. 2009). Dopaminergic neurons within the

nucleus accumbens, often described as an important part in the "reward system" in the brain, are stimulated by food intake. Repeated activation of this center in an attempt to relieve stress has been linked to binge-eating (Koob and Le Moal 2008).

Disgust and fear in response to images of food has been found in ED patients (Ellison et al. 1998). A study of changes in cerebral blood flow in BN patients showed that the right temporal lobe was activated after being exposed to images of the own body. This response was interpreted by the authors as caused by threat-related events (Beato-Fernandez et al. 2009). Similar results were found in a study on patients with AN. Body distortion was connected to activation of the amygdala, often stated as the brain's center for fear (Seeger et al. 2002). Uher et al. (2005) showed that patients with ED had less activity in neural networks connected to processing of female body shapes. The patients consistently rated body shapes in all categories as more aversive than did controls. This suggests an inability to evaluate the body in a realistic way. The authors conclude that illness duration most likely has an impact on body image disturbances.

89.6 Applications to Other Areas of Health and Disease

New insights into how the brain functions and develops have led to a better understanding on neurological aspects of eating pathology. This, in turn, renders new knowledge on how these conditions affect individuals, leading to better diagnoses and better opportunities for early treatment. Neuropsychological feedback has successfully been integrated in treatment suggesting that information-processing styles can be used for patients to develop a more balanced strategy in the relationship toward food and weight (Lopez et al. 2008b). For AN, impairments in cognitive flexibility have implications for rehabilitation, for example a focus on rigidity that goes beyond eating behaviors (Tchanturia et al. 2004). Older studies, pointing at deficiencies in visuospatial ability and difficulties in assessing the "whole" (Gillberg et al. 1996) are confirmed by recent work on information processing in AN strengthening the assumption that these patients often focus on details, indicating a weakness in central coherence (Southgate et al. 2008). Cognitive remediation therapy (CRT) which deals with processes rather than content of thoughts has been incorporated in the treatment of patients with AN (Agrawal and Lask 2009). Several studies on neuropsychological functions and neurological correlates of ED are currently ongoing. Insights into underlying mechanisms of disordered eating will evolve in the near future; this in turn will result in new perspectives on treatment and prevention of these severe disorders.

Summary Points

- ED are severe psychiatric disturbances resulting in impaired psychosocial functioning and physiological complications.
- AN, BN, and BED are the main diagnoses.
- The etiology of ED remains unclear; psychological, biological, and social perspectives need to be considered when assessing risk factors and clinical course.
- Neuropsychological functioning is impaired in patients with ED; chronic states of the disorder further complicate cognitive malfunctions.
- There are several inconsistencies in differences in cognitive ability between subtypes of ED and future studies need to assess how different functions in the brain are associated with deviations in eating behavior.
- The limbic system, insular cortex, and hypothalamus are the neurological structures that seem to be of most relevance in eating pathology.

Definitions

White matter (substantia alba): Composed of myelinated axons; nerve fibers.

Grey matter (substantia grisea): Tissue in the brain and the spinal cord that contains cell bodies.

Hypothalamus: Located above the brain stem under the thalamus and controls the autonomic system, endocrine, and motor functions. It also regulates food and water intake, body temperature, the sleep and wake cycle, and emotions. Involved in controlling behaviors such as hunger, thirst, sleep, and sexual response.

The insular cortex: Often referred to as the insula (the island in Latin), located between the temporal lobe and the parietal lobe. Involved in emotion, regulation of body homeostasis perception, motor control, and cognitive functioning.

Limbic system: The limbic system is often described as the center of emotions, learning, and memory. Included in this system are the cingulate gyri, hypothalamus, amygdala (emotional reactions), and hippocampus (memory).

References

Agrawal S, Lask B. Pediatric Health. 2009;3:209–121.

American Psychiatric Association. Diagnostic and statistical manual of mental disorders, 4th edition (DSM-IV). Washington: American Psychiatric Association; 1994.

Bayless JD, Kanz JE, Moser DJ, McDowell BD, Bowers WA, Andersen AD, Paulsen JS. Ann Clin Psychiatry. 2002;14:203–7.

Beato-Fernandez L, Rodriguez-Cano T, Garcia-Vilches I, Garcia-Vicente A, Poblete-Garcia V, Castrejon AS, Toro J. Psychiatry Res. 2009;171:129–37.

Braun CMJ, Chouinard M-J. Neuropsychol Rev. 1992;3:171–212.

Bulik CM, Tozzi F, Anderson C, Mazzeo SE, Aggen S, Sullivan PF. Am J Psychiatry. 2003;160:366–8.

Connan F, Lightman SL, Landau S, Wheeler M, Treasure J. Physiol Behav. 2003;79:13–24.

Connan F, Murphy F, Connor SE, Rich P, Murphy T, Bara-Carill N, Landau S, Krljes S, Ng V, Williams S, Morris RG, Campbell IC, Treasure J. Psychiatry Res. 2006;146:117–25.

Duchesne M, Mattos P, Fontenelle LF, Veiga H, Rizo L, Appolinario JC. Rev Bras Psiquiatr. 2004;26:107–17.

Ellison Z, Foong J, Howard R, Bullmore E, Williams S, Treasure J. Lancet. 1998;352:1192.

Fairburn CG, Cooper Z, Doll HA, Welch SL. Arch Gen Psychiatry. 1999;56:468–74.

Favaro A, Ferrara S, Santonastaso P. Psychosom Med. 2003;65:701–8.

Gillberg IC, Gillberg C, Råstam M, Johansson, M. Compr Psychiatry. 1996;37:23–30.

Gillberg IC, Råstam M, Wentz E, Gillberg C. J Clin Exp Neuropsychol. 2007;29:170–8.

Giordano GD, Renzetti P, Parodi RC, Foppiani L, Zandrino F, Giordano G, Sardanelli F. J Endocrinol Invest. 2001;24:510–4.

Hay PJ, Mond J, Buttner P, Darby A. PLoS ONE 2008;3 (2):e1541.

Hudson JI, Hiripi E, Pope HG Jr, Kessler RC. Biol Psychiatry. 2007;61:348–58.

Jacobi C, Hayward C, de Zwaan M, Kraemer HC, Agras WS. Psychol Bull. 2004;130:19–65.

Kandel ER. The brain and behavior. In: Kandel ER, Schwartz JH, Jessell TM editors. Principles of neural science, 4th edition. New York: McGraw Hill; 2000. p. 5–18.

Kaye W. Physiol Behav. 2008;94:121–35.

Kaye WH, Fudge JL, Paulus M. Nature Rev. 2009;10:573–84.

Keys A, Brozek J, Henschel A, Mickelsen O, Taylor HL. The biology of human starvation. Minneapolis: The University of Minnesota Press; 1950.

Koh M, Wilkins E, Bernsteins I. Behav Neurosci. 2003;117:1416–22.

Koob GF, Le Moal M. Annu Rev Psychol. 2008;59:29–53.

Lauer CJ, Gorzewski B, Gerlinghoff M, Backmund H, Zihl J. J Psychiatr Res. 1999;33:129–38.

Lena SM, Fiocco AJ, Leyenaar JK. Neuropsychol Rev. 2004;14:99–113.

Lilenfeld LRR, Wonderlich S, Riso LP, Crosby R, Mitchell J. Clin Psychol Rev. 2006;26:299–320.

Lopez C, Tchanturia K, Stahl D, Treasure J. Psychol Med. 2008a;38:1393–404.

Lopez C, Roberts ME, Tchanturia K, Treasure, J. Eur Eat Disord Rev. 2008b;16:411–20.

Mathes WF, Brownley KA, Mo X, Bulik CM. Appetite. 2009;52:5445–53.

McAnarney ER. J Adolesc Health. 2008;42:321–3.

Nunn K, Frampton I, Gordon I, Lask B. Eur Eat Disord Rev. 2008;16:355–60.

Pearce JMS. Eur Neurol. 2006;55:53–6.

Palmer B. Psychiatry. 2008;7:143–6.

Seeger G, Braus DF, Ruf M, Goldberger U, Schmidt MH. Neurosci Lett. 2002;326:25–8.

Schmidt U. Eur Child Adolesc Psychiatry. 2003;12:30–7.

Southgate L, Tchanturia K, Treasure J. J Psychiatr Res. 2008;160:221–7.

Swayze VW 2nd, Andersen AE, Andreasen NC, Arndt S, Sato Y, Ziebell S. Int J Eat Disord. 2003;33:33–44.

Swinbourne JM, Touyz SW. Eur Eat Disord Rev. 2007;15:253–74.

Tchanturia K, Anderluh MB, Morris RG, Rabe-Hesketh S, Collier DA, Sanchez P, Treasure, J. J Int Neuropsychol Soc. 2004;10:513–20.

Tchanturia K, Campbell IC, Morris R, Treasure J. Int J Eat Disord. 2005;37:S72–6.

Treasure J. Medicine. 2008;36:430–5.

Uher R, Murphy T, Brammer MJ, Dalgleish T, Philips ML, Ng VW, Andrew CM, Williams SCR, Campbell IC, Treasure J. Am J Psychiatry. 2004;161:1238–46.

Uher R, Murphy T, Friederich H-C, Dalgleish T, Brammer MJ, Giampietro V, Philips ML, Andrew CM, Ng VW, Williams SCR, Campbell EC, Treasure J. Biol Psychiatr. 2005;58:990–7.

Uher R, Treasure J, Heining M, Brammer MJ, Campbell IC. Behav Brain Res. 2006;169:111–9.

Wade TD, Bergin JL, Tiggemann M, Bulik CM, Fairburn CG. Austr NZ J Psychiatry. 2006;40:121–8.

Wagner A, Greer P, Bailer UF, Frank GK, Henry SE, Putnam K, Meltzer CC, Ziolko SK., Hoge J, McConaha C, Kaye WH. Biol Psychiatry. 2006;59:291–3.

Wilsdon A, Wade TD. J Psychiatr Res. 2006;40:746–54.

Chapter 90
Lexical-gustatory Synesthesia and Food- and Diet-related Behavior

Julia Simner

Abbreviations

Hz   Hertz
fMRI   Functional magnetic resonance imaging
DTI   Diffusion tensor imaging

90.1 Introduction

Synesthesia is a multivariant condition that gives rise to fundamental differences in sensory and cognitive functions. For people with synesthesia – known as synesthetes – everyday activities such as reading or listening to music, give rise to extraordinary experiences such as colors, tastes, smells, and other sensations. The condition is characterized by the co-activation of two (or more) functions when only one is stimulated. In other words, synesthetes experience two (or more) phenomenological sensations when only one would be felt by the average person. For example, when synesthete JW hears a 370-Hz single piano note, she experiences it not only as a sound, but also as a darkish off-yellow color (Ward et al. 2006). Synesthetic sensations often feel perceptually "real," and can be phenomenologically almost identical to real-world experiences. However, they are not considered hallucinations because the synesthete is almost always aware that these perceptions are not part of the outside world. For example, synesthete JS experiences letters and digits in color (and this is known as grapheme-color synesthesia), and those colors are seen projected onto the written typeface when he reads. However, JS is fully aware that the print itself is black on white. In other words, synesthetes are aware that their sensations are produced by their own mind, although they often assume that these sensations are experienced by all people.

Synesthesia has been a curiosity to psychologists for several hundred years, although the last decade has seen a considerable explosion of interest. Over 50% of all articles written on synesthesia during the last 100 years have been written within the last 5 years alone, and interest in the condition is higher now that at any previous time (see Fig. 90.1 for a statistical history of synesthetic reports over the last century).

J. Simner (✉)
School of Philosophy, Psychology and Language Sciences, University of Edinburgh,
7 George Square, Edinburgh, EH8 9JZ, UK
e-mail: j.simner@ed.ac.uk; psychology@ed.ac.uk
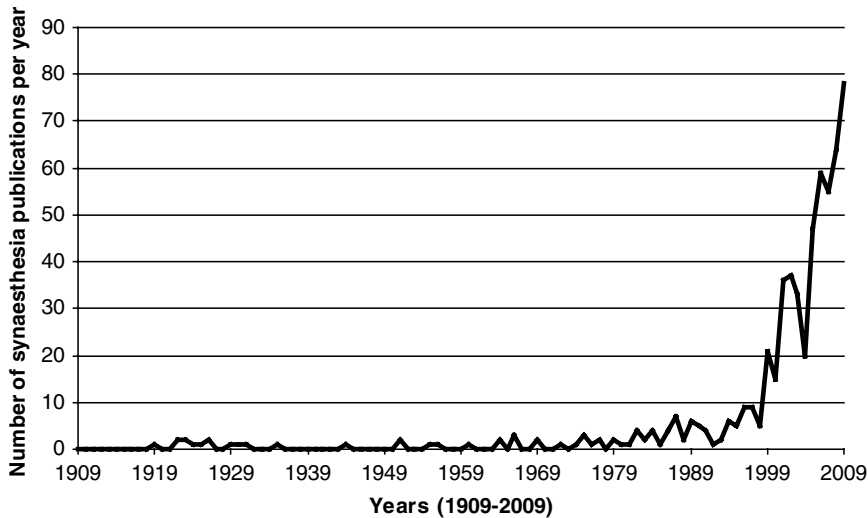
Fig. 90.1 History of synesthesia research. The number of research articles on the topic of synesthesia over the last 100 years, 1909–2009 (Web of Science; www.wos.mimas.ac.uk)

Very early treatments of synesthesia in the last century were hampered by the behaviorist movement in the psychological sciences which emphasized behavior over mental experience, and effectively knocked synesthesia out of scientific consciousness for almost 80 years. Public knowledge remained low, and this was compounded by the fact synesthetes rarely mention their unusual experiences, believing that everybody shares them. At the end of the twentieth century, however, improved methodologies and the advent of brain imaging (see next) re-introduced synesthesia into empirical study, and it has since found its way into the scientific main-stream. As a result, synesthesia studies no longer focus on simple tests of genuineness, as they did in the nineteenth and twentieth centuries, but instead, use a range of methodologies to reveal the complex system of cognitive, neurological, and sensory processes that underlie the condition. In turn, improvements in the public understanding of science, and the usefulness of the World Wide Web in bringing together large populations of synesthetes, have further transformed the field. Next, I give details of what has been learned about variants of synesthesia that involve food, taste, flavor, and diet, focusing particularly on *lexical-gustatory synesthesia*, the most well-understood food-related variant, in which flavor sensations are triggered by words. First, however, I give a brief overview of synesthesia, describing its prevalence, inheritance, genetic roots, and neurological basis.

90.2 Synesthesia: A Background

Synesthesia is an umbrella term that describes many different manifestations, according to the particular type of synesthetic *inducer* (i.e., triggering stimulus) and the particular type of synesthetic experience (or *concurrent*; Grossenbacher 1997). For synesthetes who experience synesthetic colors from sounds, for example, the inducer and concurrent are sound and color, respectively. However, at least 50 different variants have been attested to date (Day 2005). The most common type of synesthetic inducers are language units, such as letters, words, and digits, and these account for around 88% of all synesthesias identified in one recent large-scale assessment of prevalence (Simner et al. 2006).

For example, synesthetes may experience the word *Tuesday* as a pale yellow color, or the name *Phillip* as tasting of oranges. The fact that many variants are triggered by language units such as these shows that synesthesia can involve higher level processing, and is more than simply a "merging of the senses." Indeed, many studies now provide empirical evidence of a range of nonsensory synesthesias, involving personality constructs (e.g., Simner and Hubbard 2006), abstract word meanings (Simner and Ward 2006), and other language features (e.g., Simner et al. 2006a). Such nonsensory attributes are often acquired during childhood development (e.g., during literacy training), and this provides important evidence that synesthesia is sensitive to environmental influences. Next, we shall see that synesthesias involving taste are sensitive to the dietary environment of the synesthete.

The most common synesthetic concurrent is color, and so the most prevalent type of synesthesia overall is the involuntary and automatic pairing of linguistic units (such as days of the week, letters, and digits) with colors. In contrast, the chemical senses are comparatively *under*-represented (see Fig. 90.2, which shows the proportion of synesthesias whose inducer or concurrent involves the chemical senses, compared with other variants; Simner et al. 2006b). Nonetheless, there have been a number of reports of synesthesias involving gustation, olfaction, and flavor. Day (2005) describes a variant in which the flavor of foods in the mouth triggers the visual perception of color. These colored photisms appear in the visual field in response to the flavors of food in the mouth. Flavors in the mouth can also give rise to haptic sensations of touch against the skin. This particular variant was first described in detail by Richard Cytowic's *The Man who Tasted Shapes* (Cytowic 1993). His synesthete experiences geometric shapes triggered by flavors in the mouth, and these shapes can be felt against the skin, as well as seen in the mind's eye. As the taste develops on the tongue, the form of these shapes apparently changes (e.g., from round to pointed), and the case was verified by consistency over time, and by reduced cortical blood flow in Xenon SPECT imaging (Cytowic 1993; Cytowic and Wood 1982). Taste and flavor can also arise as the synesthetic concurrent, and one recent example has been attested by Beeli et al. (2005). Beeli and colleagues report a synesthete who experiences both pure tastants, and complex flavors when hearing musical tone intervals. For example, hearing a minor sixth interval triggers the sensation of cream, while hearing a major third triggers the pure sensation of sweetness. However, perhaps the most well-understood variants involving the chemical senses is known as lexical-gustatory synesthesia in which words trigger sensations of flavor in the mouth. This variant is described in detail in the present article, after further information about the general characteristics of synesthesia.
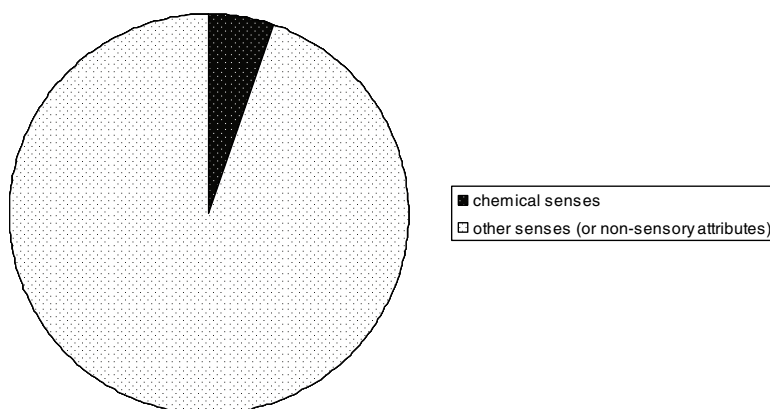
Fig. 90.2 Synesthesia and the chemical senses. The proportion of synesthesias identified in random sampling ($n = 500$) which involve the chemical senses as either inducer or concurrent, compared with other senses (including nonsensory variants involving language) (Data adapted from Simner et al. 2006)

Although synesthesia exists in many different forms, all variants have a number of characteristics in common. First, synesthesia appears to be typified by the consistency of the inducer-concurrent pairings over time. In other words, the type of synesthetic experience tied to any given trigger (e.g., the particular color of a letter) tends to remain constant throughout the synesthetes' life-time. For example, if the letter *a* is deep carmine red for any given synesthete, it will have been red for as long as that synesthete can remember, and will continue to be red throughout her life-time. (Some letters can have two colors, although again, these two colors are consistent over time.) This same consistency is found across synesthesias involving taste and flavor. For example, if hearing the name *Phillip* triggers the flavor of unripe oranges, it will always trigger that exact same association. The assumption of consistency has been a fundamental tool for synesthesia researchers, who use this characteristic as a diagnostic for the condition. Specifically, all studies tend to include an obligatory description of how the synesthete has been verified as genuine: the synesthete is first asked to provide her sensations for a set of stimuli (e.g., to list her colors for the letters of the alphabet), and is then given a surprise retest many months, or even years later. Synesthetes tend to perform at least 90% consistent over considerable time intervals, while non-synesthete control participants perform very badly. Controls are asked to invent comparable associations (e.g., to invent colors for letters) and then to recall these associations in a retest, which they do very poorly, even after a far shorter time interval. For example, synesthetes tested across a year will significantly out-perform controls tested after only a week, and this pattern remains even when controls (but not synesthetes) are prewarned about the retest, and even if controls are given financial incentives to perform well (Ward and Simner 2003). Due to its ubiquitous use, the test of consistency is now considered the "behavioral gold standard" test of genuineness for synesthesia (e.g., Rich et al. 2005). It may yet be possible that a small number of synesthetes have associations that are *not* consistent over time, and this may be most likely where their experiences are mediated in some way by emotion (e.g., some synesthetes report colors influenced by how they *feel*). However, there has been virtually no study of such synesthetes in the literature, perhaps given the difficulties encountered in establishing genuineness in the absence of the behavioral gold standard test of consistency.

Across all variants, synesthesia is found in at least 1 in 23 people, making a prevalence of at least 4%. Moreover, this figure is likely to be an underestimate, given that several novel variants of synesthesia have been identified since this seminal prevalence study took place (in 2005; reported in Simner et al. 2006b). For example, recently identified novel variants include *mirror-touch synesthesia*, in which tactile sensations are felt against the body in response to watching *others* being touched (Banissy and Ward 2007). The introduction of additional variants into the synesthesia literature means that a prevalence study carried out today would likely identify a yet higher proportion of synesthetes than was found previously. Another area that has seen development in recent studies is the estimate of female:male ratios among synesthetes. Older studies suggested that synesthesia was predominantly a female trait, because early methods for assessing prevalence found up to six times more female synesthetes than male synesthetes (e.g., Baron-Cohen et al. 1996). However, these studies relied on self-referral in their count of synesthetes, and it has since been shown that the self-referral methodology may artificially inflate the count for women (Simner et al. 2006b). This is because, across a range of different psychological phenomena, women are more likely to *report* atypical behavior than are men. Hence, female synesthetes may simply be more likely to identify themselves in self-report compared with male synesthetes. When prevalence was subsequently assessed without reliance on the self-referral method, approximately the same number of female and male synesthetes was found (Simner et al. 2006b). As such, the condition is likely to affect women and men in equal numbers (or perhaps women in only very moderately greater numbers; see Simner et al. 2006b).

Synesthesia is known to run in families (e.g., Ward and Simner 2005) and one recent whole genome scan of grapheme-color and music-color synesthetes found evidence of linkage to chromosomes 2q24, 5q33, 6p12, and 12p12 (Asher et al. 2009). Hence, the condition has a genetic basis which has now been identified, at least for some variants. This genetic inheritance is assumed to give rise to neuro-developmental differences in the brain maturation of synesthetes. The brains of adult synesthetes show increased structural connectivity, and this hyperconnectivity has been identified using a methodology known as diffusion tensor imaging (DTI; Rouw and Scholte 2007). The DTI technique identifies pockets of hyperconnectivity in the white matter of the brain, by tracking the movement of water molecules. Where white matter fiber bundles are more dense or more coherent, water moves in an anisotropic fashion (i.e., with restricted movement along some plane). In the brains of synesthetes, DTI imaging shows that pockets of hyperconnectivity are found in regions associated with the synesthesia. For example, synesthetes reporting colored letters showed increased connectivity (inter alia) in regions near to those implicated in the processing of letters and of colors (Rouw and Scholte 2007). Other areas implicated are those involved in the *binding* of features: i.e., areas responsible for the combing of featural information such as color and shape in the recognition of objects, for example. The role of these regions in synesthesia suggests that the condition may represent a type of *hyperbinding* – a propensity to combine features that are not present in the outside world. In addition to structural differences, synesthetes' brains also show functional differences, using functional magnetic resonance imaging (fMRI). The fMRI technique tracks oxygenated blood flow and indicates which brain regions are likely to be active in certain tasks. Studies using fMRI to identify the regions implicated in synesthetic experiences show that synesthetic sensations activate the same regions as those that support veridical perception. For example, synesthetes reporting color sensations (e.g., from graphemes) show activation in color-selective regions (e.g., human V4) when hearing or reading graphemes (e.g., Nunn et al. 2002; for a review of functional imaging data in synesthetes, see Hubbard and Ramachandran 2005). Put differently, imaging patterns showed evidence of color processing, where no color was present in the outside environment. Similar patterns are found in synesthesias involving flavor perceptions. Parslow et al. (unpublished, see Ward and Simner 2003 for report) generated fMRI data from a single lexical-gustatory (word-to-flavor) synesthete, and showed activation of Brodmann's area 43 when he listened to words (but not tones, while controls showed no such activity at all). This area is within the primary gustatory cortex, and provides strong evidence that the flavor experiences of lexical-gustatory synesthetes are, to some extent, perceptual in character.

In all imaging studies, synesthetes' patterns of neurological data are compared with those of the control participants, and these types of comparison show systematic differences in both structure and function across groups. But imaging studies have also shown differences *within* groups of synesthetes, and these differences correspond to the ways in which synesthetes experience their sensations. Dixon et al. (2004) identified a distinction between *projector* and *associator* synesthetes: projector synesthetes report that their synesthetic concurrents (e.g., colors) are experienced in a similar way to veridical perception, outside the body; for example, color may be seen superimposed onto the written type face. In contrast, associator synesthetes report that their sensations exist in "the mind's eye" only; for example, that colors are "seen" only on an "internal screen." This distinction is demonstrated not only in phenomenological reports and behavioral tasks, but is also seen in different patterns of fMRI activation. Hubbard et al. (2005) showed that both projector and associator synesthetes have significantly more activation in color-selective regions than control participants, but that projectors show most activation of all. These type of data provide neurological support for differences in the phenomenological reports of synesthetes, and validate the range of experiences they report. Next, we shall see that the same projector/associator distinction can be applied to synesthesias involving food, taste, flavor, and diet, and we turn to this subset of synesthesias now.

90.3 Lexical-gustatory Synesthesia

Previously we saw that each of the many different variants of synesthesia is characterized by the pairing of a particular type of synesthetic inducer with a particular type of synesthetic concurrent, and that taste/flavor can serve in either capacity. One of the best understood variants of the food-related synesthesias is lexical-gustatory synesthesia. In this variant, the inducer and concurrent are words and flavors, respectively. So for lexical-gustatory synesthetes, hearing, saying, or reading words gives rise to associated food experiences (Ward and Simner 2003; Ward et al. 2005; Simner and Ward 2006; Simner and Haywood 2009). For synesthete JIW, for example, the word *this* tastes of bread soaked in tomato soup, while the name *Philip* tastes of unripe oranges (Ward and Simner 2005). Equally, synesthete MM has sensations of flavor which flood her mouth whenever she hears proper names (e.g., *John* tastes of cornbread). Table 90.1 shows other examples of flavor sensations reported by lexical-gustatory synesthetes.

As in other variants of synesthesia, the condition is characterized by the consistency of inducer-concurrent pairings over time. Hence, the particular flavor associated with any given word tends to remain highly constant across the synesthete's life-time. In one extreme example, the consistency of word–food experiences of a lexical-gustatory synesthete was verified as being unchanged across almost 30 years. In this study, Simner and Logie (2007) presented a number of consistency tests to lexical-gustatory synesthete, JIW, including a retest of word–flavor associations first elicited in 1979. JIW was given a questionnaire in 2006 containing the target words from the original 1979 list in a randomized order, and was asked to write his synesthetic flavor associations, some 27 years after these had been initially elicited (by a third-party associate of JIW). JIW's performance in this task was compared with a group of ten non-synesthete age-matched controls. Control participants were given the same list of words and were asked to invent analogous associations (i.e., they were asked to pair each word with any food name of their choice). Controls were forewarned that they would be immediately retested as soon as they had generated the last of their word–taste pairings, and that they should make their associations as easy to recall as possible (e.g., if the target word were *Christmas*, they should write turkey). Controls were around 48% consistent in their immediate retest after only 10 s. JIW scored 100% consistent in his associations over 27 years. In other words, JIW significantly out-performed controls, notwithstanding the considerable difference in retest intervals. Simner and Logie concluded that JIW's performance was achieved by something other than the conscious, episodic retrieval of paired associations. Indeed, JIW reports that his score was simply the result of reporting exactly the flavors that flooded his mouth as he heard each word, and that these flavors simply do not change.

Lexical-gustatory synesthesia is rare, even within the rarity of synesthesia overall, although 10–15 cases have now been reported in the contemporary literature (Cytowic 1989; Ward and Simner 2003;

Table 90.1 Synesthetic flavors. Examples of flavor concurrents reported by lexical-gustatory synesthesia in a selection of historical and contemporary reports

Source	Inducer word	Concurrent description	Quality
Simner and Haywood (2009)	*Safety*	"Lightly buttered toast"	Food item
Simner and Ward (2006)	*Tambourine*	"Crumbly biscuit"	Food item including texture
Ward and Simner (2003)	*Jail*	"Cold, hard bacon"	Food item including texture and temperature
Pierce (1907)	*Ethel*	"A thimble on the tongue"	Texture only
Ferrari (1907, 1910)	*Alessandro*	"Taste of fried potato and smell of burnt wool"	Food items such as flavor and smell
Simner and Haywood (2009)	*Spluk*	"Yoghurt"	Food item from nonword
Ward et al. (2005)	*Beef*	"Overcooked, dried out beef"	Food item-matching inducer

Ward et al. 2005; Simner and Ward 2006; Simner and Haywood 2009) as well as four cases from historical sources (Ferrari 1907, 1910; Pierce 1907). The rareness of the condition is attested by the fact that no cases at all were found in the *n* = 500 population recruited for one recent prevalence study based on random sampling (Simner et al. 2006b), which otherwise found 38 different instances of synesthesia. This suggests that the prevalence of lexical-gustatory synesthesia is less than 0.2% of the population, and may be considerably lower. In investigating this unusual condition, we can consider in turn the nature of the concurrent experience, the nature of the inducing stimulus, and the processes by which these become associated, and we address each in turn in the following.

90.3.1   The Synesthetic Concurrent: Issues of Flavor, Food, and Taste

Previously we saw that synesthetes can be divided into projectors and associators, according to their phenomenological experience of the concurrent. We saw that projector grapheme-color synesthetes, for example, experience their colors as similar to veridical perceptions, subjectively located out in the word. In contrast, associator synesthetes see colors only in their "mind's eye," by association rather than with "real-world type" perception. The same projector/associator distinction has been made for lexical-gustatory synesthetes, who can be divided into the same two broad groups, this time according to the nature of their concurrent flavor experiences. For projector synesthetes, flavors are subjectively located in the mouth; synesthetic flavors are similar to veridical perceptual experiences and have the same reported phenomenology as those generated by food substances. For example, synesthete JIW reports that the only difference between his synesthetic flavors, and those he experiences while eating, comes from the fact that the former do not involve substances that can be rolled on the tongue. All other sensations, he reports, are phenomenologically identical (e.g., also see the subsequent part regarding texture and temperature). In a similar way, synesthete MM (Simner and Ward 2006) reports that her mouth is flooded with the taste of baked cornbread when she encounters the name *John*. In contrast, 'associator' lexical-gustatory synesthetes do not experience perceptual flavors in the mouth; instead, the food concurrent represents a type of cognitive association, a "mental link" to a food-type, which automatically enters into consciousness when the inducing word is encountered. Synesthete PS, for example, has the overwhelming notion of orange-flavored jelly when he hears, reads, or says the word *shoulder*. Although their subjective experiences differ, both associator and projector synesthetes represent the same, single type of synesthesia, with a shared cognitive basis, and with what is likely to be a shared neurological cause (see next).

In all cases of (projected/associated) lexical-gustatory synesthesia, food experiences are complex sensations, rather than generic tastes of bitter/sweet, etc. The flavors themselves are highly specific and extremely rich in detail, and the synesthetes often go to considerable trouble when describing them (Ward and Simner 2003). For synesthete JG for example, the name *Adrian* tastes of dressed salad, but not just any type of dressed salad: specifically, it is lettuce coated with Caesar salad dressing, and cannot (to her mind) be anything else. Equally, synesthete CS tastes the word *part* as a type of soup: specifically, chicken noodle soup and no other (Ward et al. 2005). Associations can incorporate temperature and texture as well as taste, and so the variant might be more properly described as "lexical-flavor" synesthesia (L.E. Marks, personal communication). For synesthete JIW for example, the word *jail* generates the experience of bacon that is cold and hard (Ward and Simner 2003), while *tambourine* is a biscuit with a crumbling texture. Some lexical-gustatory synesthetes have also reported olfactory experiences, although it is difficult to draw strong conclusions from this (Ward et al. 2005). Taste and smell are difficult to separate subjectively, and the rated intensity of taste sensations in the mouth is increased in the presence of olfactory cues (Murphy et al. 1977).
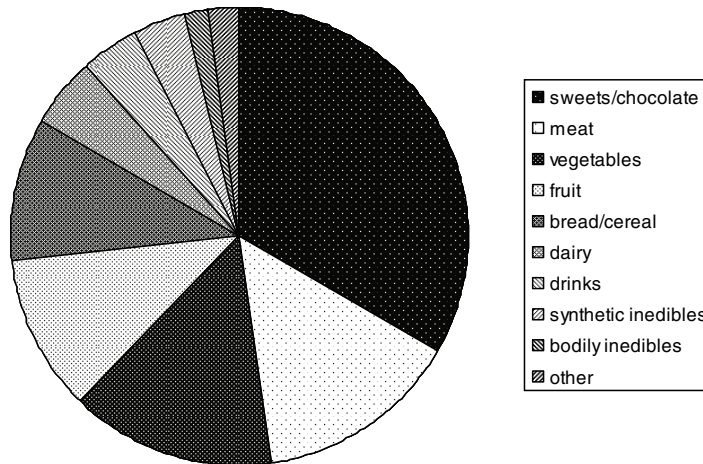
Fig. 90.3 Synesthetic flavor concurrents. Summary of synesthetic flavor associations of synesthete JIW, elicited by 1195 target words (Reproduced from Simner 2007)

However, in one historical case (Ferrari 1907) the lexical-gustatory synesthete reported that the same word triggered different food experiences in the gustatory versus olfactory domains (e.g., *Alessandro* gave the smell of burned wool, but tasted of fried potatoes). This historical report suggests that concurrents may indeed extend across both flavor and smell, and can do so independently.

Studies have shown the influence of diet and eating behavior in the nature of lexical-gustatory experiences. Analyses of synesthetic concurrents have shown that certain flavors tend to dominate, while others are conspicuous in their absence. In particular, common synesthetic flavors are for sweets (candy) and chocolate, while alcohol and other "adult tastes" tend to be absent. The synesthetic flavor concurrents of synesthete JIW are shown in Fig. 90.3, which illustrates that some flavors are present in greater proportions than others.

It is clear from Fig. 90.3 that certain food types dominate as synesthetic flavors, while others are less dominant, and studies have shown that these patterns are related to the dietary environment of the synesthete. The frequency of synesthetic flavors is correlated with the frequency with which the corresponding food is encountered in the synesthete's diet: commonly eaten foods are significantly more likely to occur as synesthetic concurrents (Ward and Simner 2003). Moreover, the dietary environment is most influential during development: synesthetic tastes are statistically more likely to reflect the diet eaten during childhood compared with adulthood. For instance, although the adult JIW is now a heavy coffee drinker, he did not drink coffee as a child, and consequently, coffee is almost entirely absent from his synesthetic flavors. Indeed, the only time it occurs is in "child-friendly" form, as coffee-flavored chocolates which he may have encountered at a young age. Ward and Simner (2003) confirmed this link between environment, development, and synesthetic experience, by administering dietary questionnaires to both JIW and to his mother; the former was questioned about foods in his current diet, and the latter, about foods in JIW's childhood diet. Both types of dietary information predicted his synesthetic flavors, although the most dominant influences came from his childhood eating patterns. Indeed, Simner (2007) points out that foods consumed during JIW's childhood are 10 times more likely to occur as synesthetic concurrents, compared with those encountered only in later life. This dominance of early foods suggests that synesthetic associations are formed during childhood development, and that they are resistant to change after adolescence. Figure 90.3 shows that a small number of synesthetic flavors are nonfoods. These include bodily inedibles such as earwax, and synthetic inedibles such as plastics. It is possible that these tastes were experienced as part of early exploratory eating behaviors in childhood.

90.3.2 The Synesthetic Inducer: Words, Phonology, and Meaning

Synesthetic flavors are triggered by words, and are influenced by phonemes (i.e., speech sounds), since similar sounding words tend to taste alike (e.g. for JIW, the words *message and college* both taste of sausage meat). Linguistic and statistical analyses show that each synesthetic flavor can be traced to a particular phoneme (or phonemes). For example, words containing the sound /k/ tend to taste of egg for synesthete JIW, and this is true whether the phoneme /k/ is spelt with a *k* (e.g., *York*), *c* (e.g., *accept*), *ck* (e.g., *chuck*), or *x* (e.g., *fax*) (Ward and Simner 2003). Some phoneme "triggers" have been shown to derive from food names. For example, for JIW, words containing the phonemes /I/, /n/, and /s/ (e.g., *prince*, *cinema*) trigger the flavor taste of mince, and the name of this food itself also contains these same three phoneme (*mince* = /mIns/). However, other phoneme relationships have less obvious roots: words containing the phoneme /f/ are significantly likely to taste of sherbet, although there is nothing in the name of this food to suggest why this particular phoneme might be important. However, the semantic associations to the word *fizz* /fIz/ may play a role, given the effervescence experienced in the mouth from sherbet food stuff, and given too, other semantic associations which are known to dictate the mappings. For example, for JIW, the word *blue* tastes "inky," the word *bar* tastes of "chocolate," and the word *newspaper* tastes of chips (French fries, which are traditionally served wrapped in newspaper in the United Kingdom). In other words, both the meaning of a word, and its sounds, can determine the nature of the synesthetic mapping between word and flavor.

It is known that synesthetic tastes can be triggered even when the synesthete is entirely unaware of how the word sounds. Simner and Ward (2006) placed lexical-gustatory synesthetes into *tip-of-tongue* states. Tip-of-tongue is the familiar experience in which a word is known but temporarily cannot be recalled from memory. This arises when the word's meaning, but not its spelling or phonemes, has been retrieved. Simner and Ward placed synesthetes in tip-of-tongue states by asking them to name pictures of uncommon objects (e.g., metronome, platypus). In tip of tongue, synesthetes began to taste the word before they could say it. One woman, for example, tasted Dutch chocolate while struggling to retrieve the word *phonograph*, which is her synesthetic flavor for that word. This study shows that synesthetic tastes can be triggered by word meaning alone, even when sound and spelling are temporarily inaccessible. Finally, synesthetes can taste foods from words they have never heard before, and from words that have no meaning at all. Simner and Haywood (2009; also Ward and Simner 2003; Ward et al. 2005) showed that synesthetes experiences tastes from nonsense words (e.g., *noik*), although these taste less intensely than real words. Figure 90.4 shows the self-rated intensity of synesthetic flavors from nonwords and real words, and illustrates the reduced strength of flavor in the former.

90.4 Applications to Other Areas of Health and Disease

Synesthesia is not recognized as a disease in any of its manifestations, but rather, as an alternative form of perception. Indeed, the widely held view is that synesthesia is something of an asset, which is known to be linked to improved memory, for example (e.g., Yaro and Ward 2007; Smilek et al. 2002). On closer inspection, however, the condition has a rather complex profile of costs and benefits, depending on the variant. In *sequence-space synesthesia*, for example, in which sequenced units such as numbers are seen projected into particular spatial arrays, synesthetes are significantly slower at certain aspects of mental calculation (known elsewhere to involve spatial processes; Ward et al. 2009). Other costs come in collateral experiences: synesthetes report a sense of malaise and discomfort when viewing perceptual objects that conflict with their synesthetic sensations. For example, a synesthete with a red letter *a* might feel discomfort when viewing the letter *a* printed in green
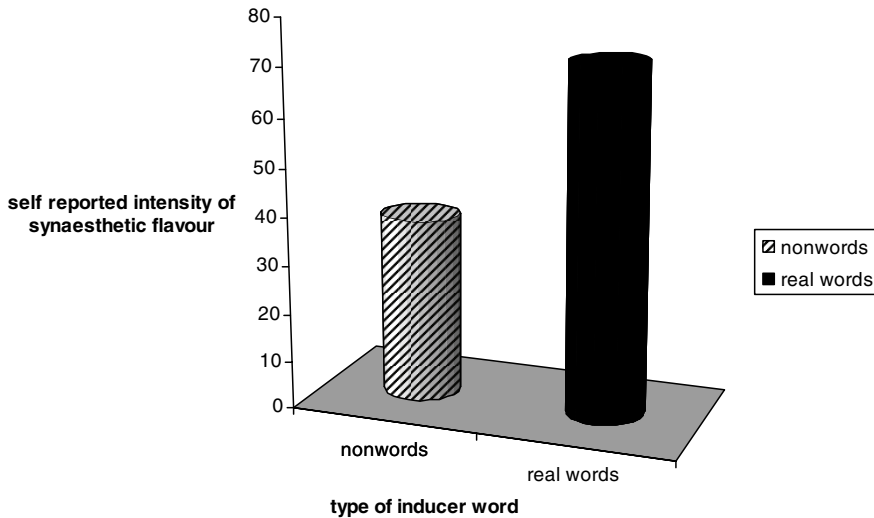
Fig. 90.4 Real words and nonwords. Self-rated intensity of synesthetic sensations of flavor from nonwords (e.g., noik) and real words (Data adapted from Simner and Haywood 2009)

(Callejas et al. 2007). These are fairly mild afflictions however, and overall, most synesthetes report positive experiences and even pleasure from their synesthetic sensations. One very notable exception, however, are those synesthetes who experience flavor in the mouth. Lexical-gustatory synesthete JIW, for example, has described his synesthesia as causing problems at both work and home. He has trouble concentrating during meetings or on the phone, since over half of every word he encounters every minute of every day triggers sensations of strong flavors that flood the mouth. Sometimes these flavors are distracting in their intensity, and other times they are distracting in their unpleasantness (e.g., tastes of earwax, vomit, and other bodily inedibles). Some flavors are particularly strong and persistent, and can last until overridden by a subsequent taste. For these reasons, projector lexical-gustatory synesthetes often regard their synesthesia as a source of irritation, and one that makes it difficult to concentrate. In contrast, associator lexical-gustatory synesthetes are more likely to find their experiences a source of interest of pleasure.

As in all variants of synesthesia, problems sometimes also arise in early childhood, when synesthetes first express their sensations to others, and are often met with disbelief and even ridicule (Day 2005). What is clear, however, is that synesthesias involving the chemical senses (especially in a projected form) appear in some way more noticeable to the synesthete, or more intrusive in daily life. First-person reports also suggest that taste-related synesthesias can have an impact on digestion and diet. Projector synesthetes have reported anecdotally that they encounter digestive discomfort, because their stomach is always anticipating foods that never arrive. Synesthetic tastes certainly appear to cause salivation, for example, and this may be tied to other physiological processes usually involved in food consumption. In addition, associator synesthetes have reported difficulties in maintaining a healthy weight. Associator synesthetes are constantly reminded of foods when speaking, hearing, or reading, and this, they suggest, triggers food-seeking behaviors. A common question from associator synesthetes is whether their condition has been linked to obesity, or weight-maintenance problems. However, no empirical work on this issue has yet been conducted.

Lexical-gustatory synesthesia is a condition of unique interest to neuroscientists and psychologists, but is yet to be explored in any detail by those in the dietary sciences. The gustatory and olfactory "reality" of synesthetic tastes, textures, temperatures, and odors allow us to see, in a very direct

Table 90.2   Lexical-gustatory synesthesia: key points

1	Inducer = heard, read, spoken, or subvocalized words
2	Concurrent = flavors, including taste, texture, temperature, and olfaction
3	Phenomenology = flavors are experienced either as veridical perceptions in the mouth (in projector synesthesia) or as an automatic cognitive association (in associator synesthesia).
4	Associations are automatic and cannot easily be repressed
5	Associations are highly consistent over time
6	Flavors are influenced by dietary experience, and frequently consumed foods generate the common synesthetic experiences. Childhood diet is particularly influential
7	Flavors can also include organic and synthetic inedibles, such as vomit, mucous, earwax, stones, plastics, and flowers. These were likely experienced at a young age through exploratory eating behaviors
8	Projector lexical-gustatory synesthetes report irritation, distraction, or sometimes discomfort from their experiences. Associator synesthetes report difficulties in weight maintenance

way, that the qualia of flavor perception are the result of internal processes, rather than external stimuli. Conditions such as lexical-gustatory synesthesias show us that flavor sensation is the product of a psychological reality which can be constructed in the absence of the usual external stimulation from food (Table 90.2).

Summary Points

- Synesthesia is a condition that gives rise to a merging of sensory and/or cognitive functions.
- Synesthetes experience two or more sensations when only one is stimulated.
- Synesthesia has a range of different manifestations, depending on the particular triggering stimulus (inducer) and the particular type of synesthetic experience (concurrent). The most common inducer is language and the most common concurrent is color.
- Taste and flavor can be either synesthetic inducers of synesthetic concurrents.
- The best understood variant of synesthesia involving flavor/taste is lexical-gustatory synesthesia, in which words trigger complex sensations of flavor.
- Lexical-gustatory synesthesia can produce flavor concurrents that are experienced as veridical sensations in the mouth (in projector synesthesia) or as automatic cognitive associations (in associator synesthesia).
- Synesthesia has a complicated profile of costs and benefits, although synesthesias involving tastes are most often reported as problematic.

Definitions and Explanations of Key Terms

Synesthesia: An inherited neurological condition that gives rise to the merging of sensory and/or cognitive functions.

Synesthete: A person with developmental or inherited synesthesia.

Phoneme: The minimal contrastive unit in the sound system of a language; substituting one phoneme for another changes the meaning of a word (e.g., /t/ vs /n/ because /bat/ differs in meaning to /ban/).

Grapheme: The minimal contrastive unit in the writing system of a language (e.g., *t* vs *n*).

Inducer: Stimulus that triggers the synesthetic sensation.

Concurrent: The particular sensation triggered during synesthesia, in addition to usual perceptions (e.g., in music-color synesthesia; music triggers the synesthetic concurrent of color, in addition to auditory perception).

References

Asher JE, Lamb JA, Brocklebank D, Cazier JB, Maestrini E, Addis L, Sen M, Baron-Cohen S, Monaco AP. Am J Hum Genet. 2009;84:279–85.

Banissy MJ, Ward J. Nat Neurosci. 2007;10:815–6.

Baron-Cohen S, Burt L, Smith-Laittan F, Harrison J, Bolton P. Perception. 1996;25:1073–9.

Beeli G, Esslen M, Jäncke L. Nature 2005;434:38.

Callejas A, Acosta A, Lupianez J. Brain Res. 2007;1127:99–107.

Cytowic RE, Wood FB. Brain Cognition. 1982;1:36–49.

Cytowic RE. Synaesthesia: A union of the senses. Springer, New York; 1989.

Cytowic RE. The man who tasted shapes. London: Abacus Books; 1993.

Day S. In: Robertson LC, Sagiv N editors. Synesthesia: perspectives from cognitive neuroscience. New York: Oxford University Press; 2005. p. 11–33.

Dixon MJ, Smilek D, Merikle PM. Cogn Affect Behav Ne. 2004;4:355–43.

Ferrari GC. Riv Psicologia. 1907;3:297–317.

Ferrari GC. Riv Psicologia. 1910;6:101–4.

Grossenbacher PG. In: Baron-Cohen S, Harrison JE editors. Synaesthesia: classic and contemporary readings. Oxford: Blackwell; 1997.

Hubbard EM, Ramachandran VS. Neuron. 2005;48:509–20.

Hubbard EM, Annan AC, Ramachandran VS, Boynton GN. Neuron. 2005;45:975–85.

Murphy C, Cain WS, Bartoshuk LM. Sens Process. 1977;1:204–11.

Nunn JA, Gregory LJ, Brammer M, Williams SCR, Parslow DM, Morgan MJ, Morris RG, Bullmore ET, Baron-Cohen S, Gray JA. Nat Neurosci. 2002;5:371–5.

Pierce AH. Am J Psychol. 1907;18:341–52.

Rich AN, Bradshaw JL, Mattingley JB. Cognition. 2005;98:53–84.

Rouw R, Scholte HS. Nat Neurosci. 2007;10:792–7.

Simner J. Trends in cognitive Sciences. 2007;11:23–29.

Simner J, Haywood SL. Cognition. 2009;110:171–81.

Simner J, Hubbard EM. Neuroscience. 2006;143:805–14.

Simner J, Ward J. Nature. 2006;444:438.

Simner J, Logie RH. Neurocase. 2007;13:358–65.

Simner J, Glover L, Mowat A. Cortex. 2006a;42:281–9.

Simner J, Mulvenna C, Sagiv N, Tsakanikos E, Witherby SA, Fraser C, Scott K, Ward J. Perception. 2006b;35:1024–33.

Simner J. In: Windhorst U, Binder M, Hirokawa N editors. Encyclopedia of neuroscience. GmbH, Heidelberg: Springer Verlag.

Smilek D, Dixon MJ, Cudahy C, Merikle PM. Psychol Sci. 2002;13:548–52.

Ward J, Simner J. Cognition. 2003;89:237–61.

Ward J, Simner J. Perception. 2005;34:611–23.

Ward J, Simner J, Auyeung V. Cogn Neuropsychol. 2005;22:28–41.

Ward J, Huckstep B, Tsakanikos E. Cortex. 2006;42:264–80.

Ward J, Sagiv N, Butterworth B. Cortex. 2009;45:1261–5.

Yaro C, Ward J. Q J Exp Psychol. 2007;60:682–96.

Chapter 91
Rethinking the Eating Disorder Continuum: A Categorical Approach to Abnormal Eating

Jessie L. Miller and Tracy Vaillancourt

Abbreviations

DSM   Diagnostic and Statistical Manual of Mental Disorders
Project EAT Project eating among teens
EDI   Eating disorder inventory
EAT   Eating attitudes test
EDNOS   Eating disorder not otherwise specified

91.1 Introduction

Do eating disorders exist on a continuum? This question has been debated theoretically and empirically in both the clinical and scientific domains for over four decades (Gleaves et al. 2004; Polivy and Herman 1987; Williamson et al. 2005). This debate is not specific to eating disorders; rather it resonates throughout much of the past and current scientific inquiries into the nature of all psychopathology (Gangestad and Snyder 1985; Watson and Clark 2006; Widiger and Samuel 2005). Nearly 100 years ago German psychiatrist Emil Kraepelin (1913) argued that while personality dimensions were the basic underlying constructs necessary for development of any psychological disorder, mental illness itself was qualitatively distinct from ordinary human behavior.

Kraepelin's (1913) fundamental theories on the etiology and diagnosis of psychiatric disorders in the 1900s formed the foundation for the classification system later devised by the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders (DSM) first published in 1952. With the inclusion of eating disorders as a diagnostic category in the third edition of the DSM (American Psychiatric Association 1980), controversy sparked over whether eating disorders should be considered along a continuum. Many theorists argued that eating disorders were best conceptualized as existing along a continuum of severity, ranging from 'healthy normals' (no weight preoccupation) to mildly weight-preoccupied individuals (with or without disordered eating behaviors), to subthreshold eating syndromes, and finally to the more severe clinical manifestations evidenced by those meeting diagnostic criteria for anorexia nervosa and bulimia nervosa (Button and Whitehouse 1981; Fries 1977; Garner et al. 1993, 1983; Polivy and Herman 1987; Rodin et al. 1984; Striegel-Moore et al. 1986).

J.L. Miller (✉)
Department of Psychiatry and Behavioural Neurosciences, Offord Centre for Child Studies, McMaster University, Chedoke Site, Central Building, 3rd Floor, 1200 Main Street West, Hamilton, Ontario, Canada, L8N 3Z5
e-mails: millej6@mcmaster.ca; jessie.miller@pearson.com

A continuum model of eating disorders presumes, in part, that abnormal eating is linearly related to normal eating and that differences are a matter of degree or severity. It also presumes that the individual features or symptoms of an eating disorder can be found across all groups to varying degrees, and are not specific to clinical populations. Furthermore, a continuum model assumes a range of variability in symptoms from least pathological in nonclinical populations to most pathological in clinical populations.

There are several problems with this logic however. First, weight preoccupied individuals may be on a continuum with individuals with an eating disorder with regards to the psychological symptoms, such as fear of fat, but they are not on a similar continuum with regards to the behavioral symptoms, namely, the bingeing, purging, and restricting behaviors of an eating disorder. In fact, most people who have some level of body shape/weight preoccupation are not engaged in any clinically relevant abnormal eating behaviors (Miller 2008). Second, not all abnormal eating behaviors found in clinical eating disorder populations are found among nonclinical populations. Purging behaviors are extremely rare in noneating disordered groups and found only infrequently among high risk or subclinical groups, as we will show later in this chapter. Third, not all eating disorder behaviors can be expressed on a continuum ranging from low pathology to extreme pathology. Extreme exercise, a compensatory behavior described in the DSM definition of anorexia nervosa restricting subtype, does not lend itself to a continuum very easily. Extreme exercise, a frequent and intense regimen of exercise, is not necessarily pathological. Consider elite athletes who would necessarily fall at the most extreme end of a continuum of exercise behaviors because of their profession, and yet for this very reason it would be difficult to consider this behavior to be pathological. Purging behaviors are another good example of an eating disorder behavior that does not conform to a continuum approach. At what point along a continuum would self-induced vomiting be considered normal and not pathological? Even at low frequencies, self-induced vomiting is abnormal and the distinction between normal and abnormal is very clearly drawn at the *onset* of vomiting behaviors. If purging behaviors can be classified as abnormal based on whether they are present or absent this is support for a categorical model of eating behaviors. In fact, some researchers and clinicians have disputed the notion of an eating disorder continuum all along and instead argued for fundamental differences in clinical eating disorders compared to the mild syndromes of weight preoccupation (Bruch 1973; Crisp 1965; Ruderman and Besbeas 1992). However over the last two decades, fewer research studies have been put forth in support of a discontinuous model of eating disorders. It seemed the field was making a shift toward a more continuous approach to understanding normal and abnormal eating behaviors.

More recently there have been a number of research studies using advanced statistical methods (i.e., taxometrics) which have reintroduced the notion of a categorical model of eating disorders. These studies do not contradict the prevailing theoretical perspective of an eating disorder continuum, but rather, they provide evidence for simultaneously employing a dimensional and a categorical model (Lowe et al. 1996; Gleaves et al. 2000a, b) as the two are not mutually exclusive (Wilfley et al. 2007).

Following the lead of recent taxometric studies, we present in this chapter an argument for a combined categorical-dimensional model of eating disorders. The focus of this model is on the relation between normal and abnormal populations for the *symptoms* of the eating disorder, but not the eating disorders as a whole. We propose a continuum of eating disorder thoughts (e.g., I am terrified of gaining weight, I think about vomiting after eating, I am dissatisfied with the shape of my body) and a discontinuum of eating disorder behaviors (severe and chronic restriction, vomiting, laxative abuse, bingeing, excessive exercise resulting in weight loss, etc.).

Toward this aim, we discuss three areas of eating disorder research that will (a) provide evidence to support a dimensional view of eating disorder thoughts and a categorical view of eating disorder behaviors (see Fig. 91.1); and (b) demonstrate the importance of distinguishing between psychological and behavioral symptoms in the assessment and measurement of eating disorders.
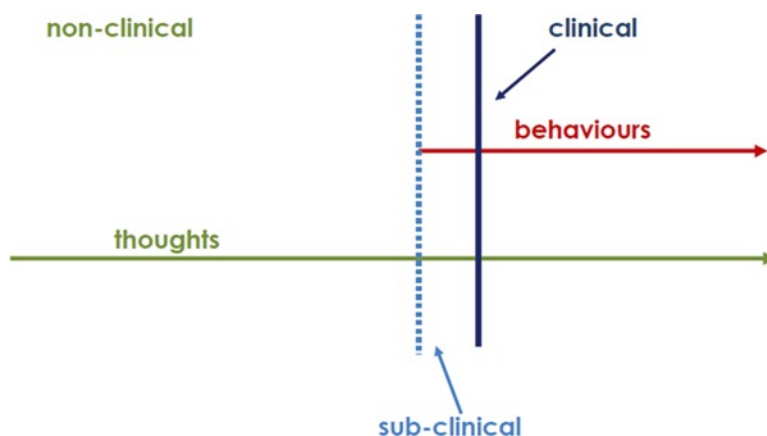
Fig. 91.1 A continuum/discontinuum model of eating disorders. What differentiates clinical from nonclinical groups is the presence of eating disordered behaviors and not extreme eating disordered thoughts. Once a person begins to engage in pathological compensatory behaviors (*broken vertical line* and *solid vertical line*) they are, in our opinion, at a subclinical or clinical level of an eating disorder

First, we discuss research indicating that many individuals (primarily females) in nonclinical populations experience the psychological symptoms of eating disorders and often at levels that closely approximate weight and shape concerns in clinical eating disorder groups. Yet the behavioral components of eating disorders are not necessarily present. In other words, it is possible to have elevated levels on the psychological criteria for an eating disorder with none of the behavioral features. Thus it seems that in nonclinical populations the psychological symptoms can present independent of an eating disorder. In contrast, while low levels of eating disorder behaviors may be present in nonclinical populations, they do not occur without psychological symptoms – suggesting that these groups may in fact be an undiagnosed subclinical or clinical population.

Second, we review recent studies that have tested the latent constructs of eating disorders using taxometric methods and draw attention to the fact that both categorical and dimensional models of eating disorders seem to fit the data, but these results vary depending on whether the targeted indicators are behavioral symptoms or psychological symptoms and also whether the composition of the sample is clinical or nonclinical.

Third, we examine the literature on treatment and recovery, and observe that behavioral recovery can often occur independent of psychological symptom recovery and recovery is most often defined by the absence of behavioral symptoms. The relevance of this literature is that it will highlight the fact that psychological symptoms of an eating disorder (i.e., the fear of fat and extreme body dissatisfaction) fail to clearly distinguish not only clinical and nonclinical populations, but also cannot clearly distinguish clinical and recovered populations.

We conclude this chapter with a summary of the implications for theory and research in the prevention and detection of eating disorders and offer recommendations for improving detection and diagnosis in epidemiological studies of eating disorders (Table 91.1).

91.2 The "Normative Discontent"

In 2004, Cash, Morrow, Hrabosky and Perry (2004), published a critical and systematic review of body image among college women and men using 22 studies – all published between 1983 and 2001. Using data from nonclinical samples they found 29% of white women, 17% of black women, and

Table 91.1 Key points in the argument for a categorical model of eating disorder behaviors

Main argument: The clinical behaviors of eating disorders are categorical ("I vomit after eating") while the cognitive/psychological symptoms are continuous ("I am terrified of being fat").

Evidence presented in this chapter:

1. Psychological symptoms of an eating disorder (body dissatisfaction, fear of being or becoming fat, or gaining weight) are present at both low and high levels in nonclinical and in clinical populations.
2. Behavioral symptoms of eating disorders are present at low and high levels in clinical populations only; when they are recorded in nonclinical samples they are accompanied by psychological symptoms of eating disorders and most likely reflect an undiagnosed subclinical or clinical subgroup.
3. Empirical studies of the latent factor structure of eating disorders show dimensional models when using psychological indicators, but categorical models when using behavioral indicators.
4. Psychological symptoms poorly discriminate between recovered and nonrecovered patients and it is the cessation of behavioral symptoms which most often defines recovery.

16% of white men reported *extreme* body dissatisfaction. Body dissatisfaction, which entails an intense disparagement toward specific body regions, as well as a general dissatisfaction with one's shape and weight (American Psychiatric Association 1994), is increasingly common among non-clinical populations and is often associated with significant psychopathology (Polivy and Herman 2002). In conjunction with the overvaluation of shape/weight and fear of fat, body dissatisfaction has been described as the most prominent risk and maintenance factor in pathological eating (Striegel-Moore et al. 1986; Polivy and Herman 2002), the most robust predictor of bulimic symptoms (Stice 2002); and the core psychopathology of both bulimia and anorexia nervosa (Fairburn et al. 2003). Yet despite the prominent role of these cognitions in clinical eating disorders, their increasing prevalence in nonclinical populations has reduced the specificity of these symptoms in identifying eating disorders in epidemiological research studies.

In the years following Cash et al.'s (2004) review of body dissatisfaction, a number of large epidemiological studies have demonstrated a similar level of discontent with weight and shape among females of varying ages. Approximately 46% of girls and 26% of boys are dissatisfied with their bodies according to recent statistics from Project EAT (Eating Among Teens), which to date is one of the largest ($N = 4746$), most comprehensive and ethnically diverse epidemiological studies of middle and high school students' eating behaviors (Ackard et al. 2007). In a review of epidemiological studies of partial syndrome eating disorders from 1980 to 2003, Chamay-Weber, Narring, and Michaud (2005) found 46–80% of adolescent girls in the United States reported intense body dissatisfaction. McVey, Tweed, and Blackmore (2004) sampled 2279 females, 10–14 years of age, from 42 Canadian schools and found 31.3% of the sample felt "too fat" and 29.3% stated they were currently trying to lose weight. Two epidemiological studies on the prevalence of disordered eating using a national Canadian sample (N=36 984), found 26% of women aged 15–24 responded "yes" to having a *strong fear* of being too fat in the past 12 months (Piran and Gadalla 2006). Extending this age range to women aged 15–65 years, Park and Beaudet (2007) found one in five women (19%) responded "yes" to the same question of having a strong fear of being too fat in the past 12 months and this fear was associated with negative self-esteem, body image preoccupation, and food obsession.

High weight preoccupation, however, is not necessarily associated with eating disorder behaviors. For example, Ackard et al. (2007) reported that 26.7% of girls and 20.4% of boys from Project EAT had severe body disparagement without any accompanying eating disorder behaviors (see Fig. 91.2). Bulik, Sullivan, and Kendler (2000) identified a subgroup of women who experienced preoccupied thoughts about weight and shape, but who had not engaged in behaviors associated with a clinical diagnosis of an eating disorder. Cooper and Goodyer (1997) found significant weight and shape concerns among 14.5% of 11–12 year olds, 14.9% of 13–14 year olds, and 18.9% of 15–16 year
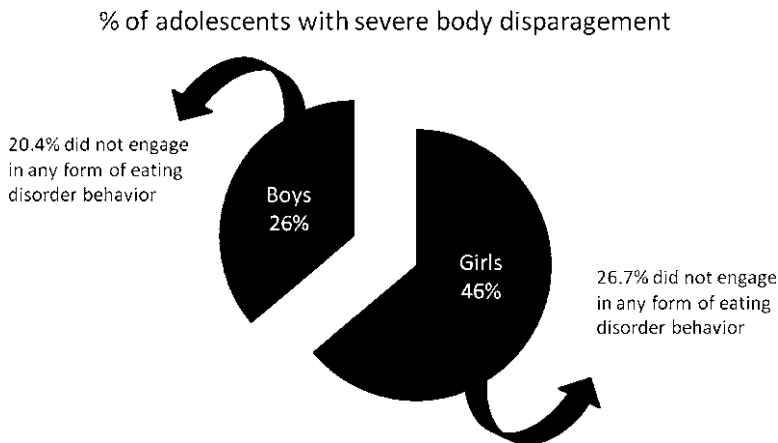
Fig. 91.2 Extreme body dissatisfaction among adolescent girls and boys in the USA. These statistics are based on Project EAT (Eating Among Teens), a large (N = 4746), and ethnically diverse epidemiological study of middle and high school students' eating behaviors (Ackard et al. 2007)

olds. However, only the 15–16 year olds showed any significant presence of behavioral pathology. Miller, Vaillancourt and Hanna (2009) compared eating-disordered thoughts to eating-disordered behaviors using items from the Eating Disorder Inventory (EDI; Garner et al. 1983) in a large sample of 1816 female university students and found that several of the items that tapped extreme body dissatisfaction were endorsed by over 50% of the sample whereas items that tapped eating disorder behaviors were rarely endorsed. Further comparing thoughts to behaviors, Miller et al. found that five groups could be identified on the basis of how often women worried about their weight and body image and how often they engaged in pathological compensatory behaviors such as vomiting or extreme food restriction. The most important finding from this study was that in general, behaviors did not occur without psychological symptoms, but psychological symptoms did occur without behaviors. Figure 91.3 illustrates that a significant number of women endorsed moderate to high levels of body dissatisfaction and fears of gaining weight (41%) without endorsing any restricting, binge eating, or purging behaviors. In contrast there were no individuals who endorsed moderate or high levels of restricting, binge eating, or purging behaviors without also endorsing the psychological symptoms. And while there was a sizeable group of women who endorsed moderate to high levels of eating disorder behaviors, it was always in conjunction with a parallel endorsement of the psychological symptoms of an eating disorder. Thus, these results highlight that pathological compensatory behavior is inextricably linked to fears of weight gain and body dissatisfaction, as indicated by the *absence* of a group characterized by eating disorder behaviors without psychological symptoms of an eating disorder. Importantly, these results were replicated in a national epidemiological sample of Canadian females aged 15–34 years (N = 1,627; Miller 2008).

Other studies have reported similar results. For example, Garner, Olmsted, Polivy, and Garfinkel (1984) compared patients with anorexia nervosa to weight-preoccupied and not-weight-preoccupied women drawn from a female college sample and a female sample of ballet students. The weight-preoccupied group displayed similar mean levels of body dissatisfaction and weight preoccupation as the patients with anorexia nervosa. However, only a portion of the weight-preoccupied women were engaged in clinical eating disorder behaviors. A cluster analysis of the weight-preoccupied group revealed one group of women who were elevated on all subscales of the EDI (Garner et al. 1983) and in fact scored as high as or higher than the anorexia nervosa group on dieting and weight preoccupation, but the second cluster was elevated only on scores of body dissatisfaction, drive for

Prevalence of Eating Disorder Symptoms by Type
(Behavioral or Psychological)
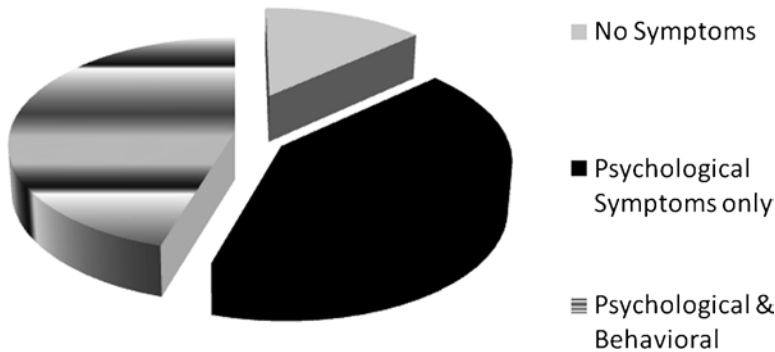
Fig. 91.3 Prevalence of eating disorder symptoms by type (behavioral or psychological). These data are based on results from Miller et al. (2009). No symptoms = 13.1%; Psychological symptoms only = 41%. This includes moderate to high levels of endorsement of body dissatisfaction and fears of gaining weight; Behavioral symptoms only = 0%; Psychological and Behavioral symptoms = 44%. This group includes individuals who endorsed moderate to high levels of psychological symptoms with moderate to high levels of behavioral symptoms. Note that only 2.2% of the sample endorsed both high levels of psychological and high levels of behavioral symptoms

thinness, and perfectionism. This weight-preoccupied-only group had low scores on all other EDI subscales including the bulimia subscale which contains items pertaining to binge eating and purging (core eating disorder behaviors).

Although these results by Garner et al. (1984) suggest that eating disorder behaviors were low or absent in this second cluster of weight-preoccupied women, it is important to note that binge eating and purging do not represent all eating disorder behaviors and these women may have been elevated on other eating behaviors, such as caloric restriction leading to weight loss. Indeed, both clusters of weight-preoccupied women scored high on the drive for thinness subscale which includes eating behaviors related to dieting and/or restriction of food intake. However, it is important to keep in mind that measures of dieting do not necessarily represent or capture the caloric restriction that leads to weight loss in anorexia nervosa. The relation between dieting and restriction is addressed in more detail at the end of this section.

Garner et al. (1984) concluded that their results supported the notion that some weight-preoccupied women resemble individuals with clinical eating disorders, and are likely a subclinical variant of a clinical syndrome, but that not all weight-preoccupied women resemble eating disorder populations. In fact, Garner and colleagues (1984) were the first to point out that the pursuit of thinness is not necessarily associated with psychopathology. The main difference between weight-preoccupied women who do and who do not resemble an eating disorder population is in whether or not they engage in clinical eating disorder *behaviors*. This is difficult to establish by examining existing research because measures of eating disorder symptoms have never clearly differentiated thoughts from behaviors. Even the studies by Garner et al. do not distinguish between behavioral and psychological factors since they measured symptoms using the EDI, where thought and behavior items are mixed within the same subscale.

Eating disorder behaviors do occur in non-clinical populations, albeit at low frequencies, and in conjunction with the psychological symptoms of an eating disorder. For instance, quoting the same research studies as before, statistics from Project EAT note 9.4% of girls and 13.5% of boys engage

Table 91.2   Key features of a continuous-discontinuous model of eating disorders

1. Subclinical and clinical eating disorders are on a continuum with one another with respect to the behavioral and psychological features of an eating disorder. In other words, they are different only in degree of symptoms but not in the kind of symptoms.
2. Subclinical and clinical eating disorders are discontinuous with nonclinical populations on the behavioral criteria of an eating disorder, but continuous with nonclinical populations with respect to the psychological symptoms of an eating disorder.
3. Subclinical and clinical eating disorders are discontinuous with partially recovered and recovered populations on the behavioral criteria of an eating disorder, but on a continuum with partially recovered and recovered populations with respect to the psychological symptoms of an eating disorder.

in recurrent purging behaviors such as vomiting, laxative abuse, or excessive exercise (Ackard et al. 2007); Chamay-Weber et al. (2005) report purging behaviors (vomiting, laxatives, and diuretics) between 5% and 16%; and McVey et al. (2004) found 3.9% of their sample endorsed binge eating and 1.5% endorsed self-induced vomiting. Importantly, while studies have reported high percentages of individuals who endorse the psychological symptoms of an eating disorder without the behavioral symptoms, there are no studies that have reported high percentages (or low percentages) of individuals who are engaged in eating disorder behaviors without the psychological symptoms. We would argue that the presence of these pathological eating disorder behaviors in the samples described by Ackard et al., Chamay-Weber et al., and McVey et al. are signaling an undiagnosed subclinical or clinical eating disorder.

According to Stice, Ziemba, Margolis, and Flick (1996), the discontinuity perspective of eating disorders would be supported if research were to show that the same variables that distinguish nonclinical groups from subclinical groups fail to distinguish between subclinical and clinical populations. There is ample research evidence to support behaviors failing to distinguish subclinical and clinical populations. Subclinical and clinical groups both engage in eating disorder behaviors, and even though they may differ in the frequency with which they engage in these behaviors, current research does not support evidence of any meaningful distinction between those engaged in behaviors once a week versus twice a week (Crow et al. 2002; Garfinkel et al. 1995). In fact, the accompanying pathology of those exhibiting subclinical symptoms of eating disorders has been shown to resemble the pathology observed in individuals with a full-blown eating disorder (Garfinkel et al. 1995; Fairburn et al. 2007; Zaider et al. 2000). And, the preponderance of those meeting criteria for a diagnosis of "eating disorder not-otherwise-specified" (EDNOS; approximately 60% of cases) suggests that the frequency level of eating disorder behaviors is less critical than *the actual presence of eating disorder behaviors* (Table 91.2) (Fairburn and Bohn 2005; Fairburn and Cooper 2007; Wade et al. 2006).

91.3 The Dieting Conundrum

We have argued that the behaviors outlined in the DSM criteria for eating disorders are the behaviors that are discrete – food restriction or food avoidance, binge eating, and compensatory or noncompensatory strategies. However, how these behaviors are defined and measured are critical aspects of understanding the continuous or discontinuous nature of these symptoms. Dieting and exercising are prime examples of the difficulty in applying a categorical framework to eating disorders. Dieting and exercising are both behaviors that are not necessarily pathological although they can be and the frequency of the behavior is not a good indicator of whether this behavior is pathological. Dieting, like exercise, does not necessarily increase in pathology the more you engage in the behavior and although

it is unhealthy to be constantly going on and off of a diet, it is not pathological unless it occurs with or leads to other clinical behaviors such as binge eating, significant weight loss, or other psychological aspects such as distress, dysfunction, or disability. Dieting is considered a clinically relevant behavior for two reasons; its role as a risk factor and its potential role as a restricting feature of an eating disorder, and often the distinction between the two becomes blurred by inconsistent definitions of what constitutes a "diet."

Both prospective and cross-sectional research indicates eating disorders commonly begin with behaviors that "resemble" normal dieting (Fairburn and Harrison 2003; Jacobi et al. 2004b). In longitudinal studies, dieting is most clearly demonstrable as a variable risk factor and maintenance factor to the onset of bulimia nervosa and anorexia nervosa binge-purge subtype because of its purported relation to binge eating (Jacobi et al. 2004b; Polivy and Herman 1985). The temporal precedence between dietary restraint and the onset of binge eating supports this assumption (Patton et al. 1990, 1999).

For the restricting type of anorexia, dieting is presumed to be a forerunner to the more severe caloric restriction and starvation that produces the abnormally low body weight exhibited by those with anorexia. But dieting is not synonymous with restriction nor is it sufficient in producing the abnormally low body weight typical of anorexia nervosa. If dieting were on a continuum with the restriction characteristic of an eating disorder, rates of anorexia nervosa would be higher, especially given the prevalence of self-reported dieting. In reality, anorexia restricting type is the rarest form of eating disorder (Hoek 2006). In addition, the majority of dieters do not go on to develop an eating disorder, offering support to the role of dieting as a risk factor, rather than a symptom/feature of an eating disorder (Patton et al. 1990, 1999).

The relation between dieting and restriction in the eating disorders depends on how dieting is defined. Chronic dieting resulting in consistent caloric restriction accompanied by weight loss is consistent with clinical features of anorexia nervosa, and thus, in this sense, dieting appears to be interchangeable with restriction. Research by Lowe et al. (1996) indicates that dieting is related to eating disorder behaviors (e.g., binge eating) only when accompanied by food restriction and weight loss. In contrast, dieting practices accompanied by "normative" body dissatisfaction may lead to emotional distress, but are not indicative of eating pathology (Lowe et al. 1996). The DSM definition of anorexia nervosa does not describe which eating behaviors are considered abnormal or clinically relevant in terms of what leads to the "refusal to maintain minimally normal body weight." Weight loss is referred to loosely as the result of a reduction in total food intake and this reduction is often preceded by the exclusion or restriction of certain foods from one's diet (American Psychiatric Association 2000).

Restriction in anorexia nervosa, by definition, always includes caloric deprivation and weight loss – in comparison, dieting can mean cognitive or behavioral deprivation, with or without weight loss. Dieting is most often defined and interpreted as a method of weight control, yet it is not always associated with weight loss (Brownell and Rodin 1994). In fact dieting is a notoriously ineffective means of achieving weight loss according to some researchers because 95% of those who lose weight will regain the weight within a few years and many will gain more than they originally lost (Grodstein et al. 1996; National Institutes of Health Technology Assessment Conference Panel 1993). The term dieting is also used in reference to cognitive restraint or the desire to lose weight and for this reason it seems clear why numerous research studies have found self-reported dieting to be negatively related to actual reductions in caloric intake or weight loss (Lowe 1993). Herman and Polivy (1984) have suggested that dieters may be best characterized by their *attempts* to lose weight than by actual weight loss.

It is possible that subjective measures of dietary restraint do not correspond well with objective measures of weight loss because the dieting attempts have failed. For instance, an individual may engage in dieting behaviors by restricting food intake or lowering caloric intake during the first half of the day, and this we would consider "engaging in dieting behavior." However, if in the latter half

of the day, when the food restriction has left the dieter feeling hungry and they begin to consume more calories than if they had eaten normally throughout the entire day, this overeating in the second half of the day compensates for the lowered food intake earlier in the day and in the end, the balance of the calories taken-in is either the same or possibly more. In this case, objective measures of weight, such as daily or weekly weighing of participants or even more precise assessments of caloric intake recorded during a single meal would fail to correlate with subjective reports of dietary restraint because overall, there has not been any weight loss. This is not the same as saying the individual is not dieting. They are engaged in dieting behaviors but these behaviors have failed to result in weight loss because they were not maintained. Thus if asked to complete a measure of dietary restraint these individuals would likely score high because from their perspective they are in fact dieting. What is not being accounted (objectively) in self-report measures of dieting is whether the dieter has suc-ceeded or failed in their dieting attempts.

Restriction in anorexia nervosa is unhealthy and pathological – but dieting is not necessarily unhealthy or pathological. Dieting is a heterogeneous term that includes both healthy (eating less fat, eating more fruits and vegetables, exercising) and unhealthy behaviors (e.g. skipping meals, fasting). According to Lowe and Timko (2004) dieting is neither beneficial nor harmful, but simply ineffec-tive for most individuals in the long-term. Dieting may have beneficial effects if the purpose of the diet is to counteract a predisposition to overeat or gain weight (Lowe and Timko 2004). Studies have found long-term low-calorie diets to be effective in decreasing binge eating in obese individuals with and without an eating disorder with length of follow-up varying from 3 to 24 months post-treatment (for a review, see Stice 2002). Even in a normal weight population, Presnell and Stice (2003) found that when college students lost a small amount of weight in a weight-loss program, their level of bulimic symptoms were reduced not increased after a 3 month follow-up. Lowe and Timko (2004) state that the merits of dieting are inconclusive without first clearly defining what is meant by the term, specifying the purpose of the diet, and toward which population it is intended.

These differences between the interpretation of and consequences to dieting versus restriction suggest the two are not synonymous with one another and that despite any overlap in behaviors across those who engage in normative dieting and those who engage in clinical restriction, dieting should not be used as a proxy for restriction unless the instruments used to measure dieting take into account cognitive versus behavioral restraint in conjunction with abnormally low body mass index or measured weight loss. If the purpose is to detect restrictors rather than dieters, it is necessary to separate out the small percentage of successful dieters – 5%, from the unsuccessful dieters – 95% (Grodstein et al. 1996).

91.4 Empirical Tests of the Latent Factor Structure of Eating Disorder Symptoms

Most research on the continuous–discontinuous debate of eating disorders has come from cross-sectional investigations using cluster analysis, latent class analysis, discriminant function analysis factor analysis, and most recently, a series of taxometric investigations (see Table 91.3).

Taxometric analyses specifically test for dimensional versus categorical constructs in a dataset (Waller and Meehl 1998). A taxon is an underlying entity that drives the relations between common indicators of a disorder, and while the common indicators are dimensional, similar to a latent vari-able in factor analysis, a taxon indicates a discrete category. Thus, a taxon does not preclude dimen-sional aspects; however it does indicate a qualitative difference between its underlying construct and other constructs. The utility of this analytic technique has spurred a number of taxometric investiga-tions in the field of eating disorders over the last 5 years.

Table 91.3 Summary of empirical studies on the continuum of eating disorders

Statistical test	Description	Published studies (peer reviewed)
Cluster analysis	• Assignment of a set of observations or objects into clusters/subsets • Requires an a priori assumption of the number of clusters/subsets in order to perform the statistical test • Distance between objects used to determine assignment to clusters	Garner et al. (1993), Hay et al. (1996), Stice and Agras (1999), Westen and Harden-Fischer (2001), Williamson et al. (1992)
Latent class analysis	• Assignment of a case or subject to a group (i.e., latent class) • There is an a priori assumption that the latent variables are discrete • Conditional probabilities are used to determine the likelihood that the set of observed, discrete variables or "cases" will fall into a particular latent class • Observed variables within a class are statistically independent	Bulik et al. (2000), Duncan et al. (2007), Keel et al. (2004), Striegel-Moore et al. (2005), Sullivan et al. (1998a, b), Sullivan and Kendler (1998), Wade et al. (2006)
Discriminant function analysis	• Purpose is to predict group membership or discriminate between two or more mutually exclusive groups from a set of predictors • The dependent variable is group membership	Stice et al. (1996), Lowe et al. (1996), Franko and Omori (1999), Goldner et al. (1999), Stice et al. (1998), Tylka and Subich (1999)
Factor analysis	• Determine the number of subsets (latent factors) that a set of variables can form • Subsets are largely independent of one another • Variables within a subset are related to one another	Gleaves and Eberenz (1993, 1995), Gleaves et al. (1993), Tobin et al. (1991), Vanderheyden et al. (1988), Williamson et al. (2002)
Taxometric analysis	• Determine whether the latent structure contains a taxon/a class in addition to its underlying dimension • There is no a priori assumption about the dimensional or categorical nature of the latent structure (see description in text)	Williamson et al. (2005), Gleaves et al. (2000a, b), Tylka and Subich (2003)

91.4.1 Taxometric Analysis in Clinical Samples

Williamson et al. (2002) examined three latent features of eating disorders derived through a series of exploratory and confirmatory factor analyses; binge eating, fear of fatness/compensatory behaviors, and drive for thinness. These latent scores were then used as indicators in a series of taxometric analyses comparing individuals with clinical eating disorders to obese persons without an eating disorder and to a normal weight comparison group. Binge eating disorder and bulimia nervosa were judged to be qualitatively distinct (taxonic) from both the normal-weight comparison group and the obese comparison group. In contrast, taxometric analyses did not reveal strong support for anorexia nervosa being qualitatively distinct from normalcy (i.e., not taxonic). Excluding noneating disorder groups, Williamson et al. went on to compare the categorical versus dimensional characteristics

within the eating disorders (i.e., anorexia nervosa, bulimia nervosa, and binge eating disorder) and concluded that while there was mixed support for a categorical model of eating disorder subtypes, some of the *features* appeared categorical and some appeared dimensional. Taken together, the taxometric results reported by Williamson et al. support bingeing and purging disorders being taxonic (i.e., categorical), especially when using a mixed sample (clinical and non-clinical), while anorexia nervosa appears to be more dimensional. These findings, that certain features of eating disorders are discrete from nonclinical populations while others are continuous and certain features within the eating disorders are discrete while others are continuous, are consistent with the three existing taxometric studies conducted on eating disorder populations to date (Gleaves et al. 2000a, 2000b; Tylka and Subich 2003).

How might we interpret these findings? If we examine these results from a framework of continuous eating disorder thoughts and discontinuous eating disorder behaviors we can make clearer the inconsistencies reported across taxometric studies. Bingeing and purging disorders (bulimia nervosa and anorexia nervosa binge-purge subtype) may appear taxonic especially in mixed samples because the central characteristic of these disorders are binge eating and purging which incidentally, occur at exceedingly low base rates in nonclinical populations. Bingeing and purging are extreme behaviors that are specific to eating disorder populations; thus when comparing clinical and nonclinical groups, rates of bingeing and purging will be very high in clinical populations and very low in normal populations, increasing the likelihood of detecting a taxon.

In contrast, restricting behaviors (anorexia-restricting subtype) are often measured using dieting items (e.g., Drive for Thinness subscale of the EDI) which are common among nonclinical populations (Chamay-Weber et al. 2005). In general, when restriction is measured in terms of dieting there will be more people in both clinical and nonclinical populations who will endorse items such as, I eat diet foods, than items related to bingeing or purging, (i.e., I vomit after I have eaten). The range of restricting behaviors will be reflected by a more continuous process in taxometric analyses compared to bingeing and purging where the limited variability will result in stronger evidence for a taxon. Williamson et al. (2005) proposed a three-dimensional model that argued for binge eating being taxonic while fear of fatness/compensatory strategies, and drive for thinness were continuous. However, these results may be an artifact of including restricting items that range from somewhat normative behaviors (skipping breakfast, periods of fasting, eating diet foods) to more extreme behaviors (prolonged periods of starvation and chronic lowering of caloric intake) in taxometric studies. We suspect that if Williamson et al. were to re-specify their model by only including extreme restricting items that reflect weight loss, they may find restricting behaviors to appear taxonic. In addition, the continuous nature of this fear of fatness-compensatory strategies may be confounded by the combination of thought and behavioral items in these analyses. For example, latent factors for fear of fatness have typically combined items pertaining to thoughts (preoccupation with weight and shape) with items of behaviors (caloric limitation) within the same latent class (e.g. Keel et al. 2004). Therefore, conclusions regarding the continuous nature of restricting behaviors may be premature.

91.4.2 Taxometric Analysis in Nonclinical Samples

Taxometric analyses on noneating disordered populations can also be understood within a thought-behavior framework. Tylka and Subich (2003) examined the latent structure of eating disorders by performing taxometric analyses on a sample of 532 college women. They included items representative of nonbehavioral features of eating disorders such as body dissatisfaction, and found five distinct factors, all indicative of a dimensional solution. Specifically, taxometric analyses revealed no presence of

a taxon in the data, although importantly, Tylka and Subich did not include *any* behavioral indicators of eating disorders in their model. These authors argue that much of the opposing findings in the literature surrounding the existence of a continuous versus a discontinuous model of eating disorders results from the fact that different indicators are used by different researchers. While some researchers use behavioral indicators (binge eating, purging, restricting) with nonbehavioral indicators (interoceptive awareness, maturity fears, or body dissatisfaction), other researchers use one but not the other. When researchers utilize more behavioral indictors of eating disorders than nonbehavioral indicators, results support categorical models of eating disorders (Gleaves et al. 2000a, b; Tylka and Subich 2003; Lowe et al. 1996), whereas studies that use more nonbehavioral indicators find more evidence for dimensional models of eating disorders (Tylka and Subich 1999, 2002, 2003).

Tylka and Subich (2003) argue that bingeing and purging should not be included in research aimed at uncovering the latent structure of eating disorders because these indicators may either inflate the notion of a categorical model or mask the presence of dimensional models of eating disorders. These authors suggest that one reason for this inflation may be that some researchers classify females in their sample as clinical or nonclinical based on bingeing and purging behaviors only to turn around and use these *same* behaviors as the criterion variable. Evidence in support of a taxon in the data may be artificial because of confounding indicators with the criterion (2003). However, while Tylka and Subich suggest excluding behavioral symptoms of eating disorders, behavioral indicators are fundamental attributes of individuals with eating disorders and must be considered in the continuum debate. Evidence for both categorical *and* dimensional models in taxometric studies are not conflicting findings; they are in fact telling us something critical about the nature of eating disorders.

91.5 Psychological Versus Behavioral Symptoms in Recovery from an Eating Disorder

A number of researchers have found the rate and timing of eating disorder recovery to vary depending on the presence or absence of psychological criteria in the definition of recovery (Cogley and Keel 2003; Couturier and Lock 2006; Fennig et al. 2002; Saccoman et al. 1989; Strober et al. 1997). In general, psychological recovery occurs more slowly, extending years beyond the cessation of behavioral symptoms and as a result, rates of recovery vary depending on the length of remission studied and the variables included in definitions. Saccoman et al. (1989) found that when only the physical aspects of an eating disorder (restricting, bingeing, purging) were considered, 79% of those with anorexia in their study had recovered. Yet when the psychological criteria were examined, this recovery rate fell to 48%. Strober et al. (1997), report recovery rates based on normal weight and regular menstruation to be 86% occurring on average 57.4 months from illness onset. But in the same study, recovery based on psychological criteria was only 76%; occurring an average of 79.1 months from illness onset. Similarly, Fennig et al. (2002) found the psychosocial recovery to take on average 6 years longer than the physical (i.e., behavioral) recovery from an eating disorder.

Bachner-Melman, Zohar, and Ebstein (2006) compared women behaviorally but not cognitively (i.e., lack of body image distortion or fear of weight gain) recovered from anorexia nervosa to a group of women recovered both cognitively and behaviorally and found that the symptoms and personality profile of the behaviorally recovered group showed residual features of anorexia whereas the cognitively and behaviorally recovered were indistinguishable from controls. It seems that while behavioral recovery is critical for initial symptom remission, psychological recovery is necessary for

Table 91.4   Key differences in behavioral versus psychological recovery from an eating disorder

1. Behavioral recovery occurs earliest.
2. Recovery rates are highest when recovery is defined by the absence of the behavioral symptoms (i.e., amenorrhea, bingeing, purging, restricting).
3. Psychological recovery (the absence of extreme weight and shape overevaluation and body dissatisfaction, and fears of weight gain/being fat) occurs slowly, and takes an average of 2 years longer than behavioral recovery.
4. One-third of those with anorexia nervosa will continue to struggle with the psychological symptoms for many more years post-treatment.
5. The presence of psychological symptoms at post-treatment is the best predictor of relapse.
6. Approximately 30–50% of those with bulimia nervosa will continue to struggle with a high degree of body shape and weight concerns following treatment.

longer-term maintenance of recovery from eating disorders (Couturier and Lock 2006; see Table 91.4). In a similar study, Cogley and Keel (2003) evaluated the concurrent validity of requiring remission of "undue influence of weight and shape on self-evaluation" in defining recovery from bulimia nervosa. Three groups were compared: 31 women fully recovered from bulimia, 28 women behaviorally recovered only, and 59 matched controls. Participants completed measures of mood, anxiety, psychosocial functioning, and body dissatisfaction. Results showed no differences between matched controls and the fully recovered individuals with bulimia on any measures, while the behaviorally recovered only group showed significant pathology across all reported measures.

Of particular importance in the distinction between behavioral and psychological recovery are the findings by researchers that body dissatisfaction and overvaluation are the *best* predictors of relapse. For instance, Fairburn, Peveler, Jones, Hope, and Doll (1993) and Freeman, Beach, Davis, and Solyom (1985) found the residual level of shape concern that remained at the end of "successful" treatment was the strongest predictor of relapse among patients with bulimia nervosa. These findings are disconcerting given the high rate of shape concern remaining among individuals who have completed treatment successfully; as many as 30–50% according to some estimates (Farrell et al. 2005). Keel, Dorer, Franko, Jackson, and Herzog (2005) found similar results in their prospective study of predictors of relapse. Specifically, Keel et al. report that body image disturbance was the best predictor of relapse at 9 years post-treatment across both bulimia and anorexia, and this was across a range of relapse predictors including behavioral, psychological, and Axis I and II comorbid conditions.

The overvaluation of shape and weight appears among individuals in nonclinical populations, clinical populations, and recovered or partially recovered populations. In contrast, behaviors are absent in nonclinical groups, acutely present in clinical groups, and absent or remitted in recovered or partially recovered groups. This ongoing battle for psychological recovery across the course of the eating disorder offers support for a continuum of psychological symptoms, while disordered behaviors are more specific to the active phase of the illness where individuals are still meeting diagnostic criteria for an eating disorder.

91.6 Summary

The aim of this review was to offer support toward the notion of a combined categorical-dimensional model of eating disorders by demonstrating that it is the psychological symptoms of eating disorders that are dimensional and the behavioral symptoms that are categorical. Three areas of research were reviewed to offer support for this hypothesis: (1) eating disorder thoughts are so prevalent that they

poorly discriminate between nonclinical and clinical groups; but behaviors are excellent markers of clinical groups because they are specific to clinical populations; (2) empirical studies of the latent factor structure of eating disorders show dimensional models when using psychological indicators, but categorical models when using behavioral indicators; (3) recovery rates for eating disorders are highest when defined by the absence of behavioral symptoms and lowest when defined by psychological symptoms, as the psychological symptoms fail to distinguish recovered individuals from ill or partially recovered individuals. Now we turn our attention to the potential implications of a categorical model of eating disorder behaviors.

91.7 Clinical and Research Implications

Advancing our understanding of the continuum of eating pathology has both research and clinical implications. First, understanding the nature of the relationship between disordered eating and eating disorders advances the theoretical underpinning of eating disorder research, as classification of mental illness is at the heart of all psychiatric diagnoses and subsequent treatment protocols. Establishing valid categories for eating disorders is clinically important as it enables accurate diagnostic instruments to be used and creates standards for diagnosis which is an essential part of interpretation and communication among clinicians and researchers. Addressing the question of continuity versus discontinuity in eating disorders will inform our measurement of eating disorder symptoms in at-risk groups. Improving our measurement in epidemiological research will help reduce the number of false positives in two-stage screening studies, increasing efficiency in research protocols, reducing costs from unnecessary testing, lessen participant burden incurred by lengthy interviews, and free up valuable professional resources that can be directed toward prevention and treatment (Miller 2008).

91.8 Applications to Other Areas of Health and Disease

91.8.1 Personality and Individual Differences in Eating Disorders

It is important to highlight that we are not suggesting eating disorder behaviors are the only difference between clinical and nonclinical populations, rather we would argue in a similar vein to Crisp (1965) and Bruch (1973), and as well Polivy and Herman (1987), that those with eating disorders have fundamental differences in personality, such as ego deficits or psychopathology such as comorbid mood disorder. Engaging in bingeing, purging, or restricting behaviors is both mentally and physically painful, and individuals who are able to engage in these aberrant behaviors likely have underlying personality features and/or brain neurochemistry that are very different from those who do not engage in these behaviors (e.g., Miller et al. 2006). For instance, impulsivity, characteristic of some individuals with bulimia (Bulik et al. 1995) may facilitate the disinhibited eating of a binge. Impulsivity is also associated with substance abuse, and the use of alcohol or other drugs among individuals with eating disorders has been linked to frequency of binges and purges (Davis and Claridge 1998). Concurrent mood disorder may facilitate restricting or bingeing behaviors as a result of changes to brain neurochemistry which can disrupt appetite and/or feelings of satiety (Halmi and Sunday 1991). Additionally, neuroticism has been linked to

symptoms of eating disorders (Davis and Claridge 1998; Miller et al. 2006), with the suggestion that fear of weight gain may enable the highly neurotic individual to restrict food intake more easily than those low in neuroticism.

Herman and Polivy's (1984) boundary model of eating behavior postulates that individuals with anorexia and bulimia have a lowered hunger boundary that allows them to tolerate greater degrees of food deprivation than normal. This "hunger boundary" may explain the ability of individuals with anorexia (restricting type) to maintain consumption at such stringent levels (Herman and Polivy 1984). Although, the authors concede that the degree to which this hunger boundary is imposed by environmental factors, a genetic predisposition, or both, is uncertain.

Individuals who purge may differ from those who restrict because of biological differences that may drive the choice of a particular coping mechanism (the behavior) in dealing with the shared psychopathology (the thoughts: overvaluation of shape and weight) of eating disorders. Thus, it may be beneficial to focus future research on understanding potential executive functioning deficits associated with the behaviors of an eating disorder. For example, reward deficiency syndrome has been put forth as an explanation for other compulsive, impulsive, and addictive disorders based on a common genetic deficiency in the dopamine D_2 receptor (Blum et al. 1996). Dopamine is not the only neurotransmitter implicated in the reward system, serotonin is also known to be involved (Blum et al. 1996) and there is already evidence to support the role of serotonin imbalances in the eating disorders, bulimia nervosa in particular (Steiger et al. 2003).

91.8.2 Measurement of Eating Disorders

Early identification of eating disorders is critical, as mortality rates increase linearly with duration of illness (Hoek 2006) and recovery rates are linked to symptom severity at the onset of treatment (Bulik et al. 1999). In general, recovery rates vary depending on the definition of recovery, but a substantial number of individuals, especially those with anorexia, will remain chronic, will relapse following treatment, or will continue to struggle with psychological symptoms (e.g., fear of weight gain, body dissatisfaction) despite achieving physical recovery (Strober et al. 1997). For these reasons, prevention and early detection is critical.

Detection of undiagnosed cases of eating disorders in community settings requires epidemiological research; however the usefulness of such studies is highly dependent on valid measures and clearly defined indicators of risk. The most rigorous method for identifying cases of eating disorders in those who do not seek medical treatment voluntarily is to employ a two-stage screening study. A two-stage screening study is considered the gold standard in epidemiological research on eating disorders (Jacobi et al. 2004a). The two-stage screen typically involves administering a questionnaire, such as the Eating Attitudes Test (EAT-26) to a large sample of at-risk individuals (e.g., adolescent females) and identifying the subset of individuals who score above a predetermined threshold on the questionnaire (e.g., 20 or above on the EAT-26) to return for the second stage of the screen: the clinical interview.

The EAT is the most widely used screen for detecting eating disorders in epidemiological studies, although its primary use has been for the detection of cases of anorexia nervosa, and not bulimia nervosa (Jacobi et al. 2004a). However, relying on screening measures such as the EAT for detecting undiagnosed eating disorders will be costly and time consuming because most existing screening tools, including the EAT, contain far more normative weight concern items and dieting items than clinically significant eating disorder behaviors and, importantly, it is the eating disorder behaviors which are pathognomonic. The presence of clinically significant eating

disorder behaviors is the best indicator that the disorder is present. While the psychological symptoms of an eating disorder will always identify all true cases of eating disorders, as long as the criteria for an eating disorder continues to be partially defined by disturbances in body image and fears of weight gain, the psychological symptoms will also identify far too many noncases because these symptoms are normative. Given the level of normative discontent concerning weight and shape in our culture it would seem prudent to examine other measures of eating pathology that have higher specificity.

91.9 Conclusion

The goal of this chapter was to introduce a new framework for understanding the inconsistent findings surrounding the continuous or discontinuous nature of eating disorders. If we scrutinize the many studies conducted over the last few decades that have found evidence in favor of either discrete or continuous models of eating disorders, we see that the competing results of most studies are accurate when we consider the sample composition and the features of eating disorders that were examined. Tylka and Subich (2003) argued that many studies find evidence for categorical models when using behavioral features of eating disorders and more dimensional models emerge when using nonbehavioral features; we would agree since it is precisely the behavioral features that appear categorical, not the disorder itself. When researchers examine clinical populations, or mixed samples, there will be more evidence for categorical models because the clinical groups will have more of the disordered behaviors, whereas a truly nonclinical population will mostly be comprised of a continuum of disordered thinkers who do not engage in disordered behaviors (Table 91.5).

Regardless of whether future research supports or refutes the notion of taxonicity in disordered behaviors and/or continuity in disordered thoughts, it is important to highlight the significance and utility of examining the role of psychological symptoms in the eating disorders independently from the behavioral symptoms, as this distinction holds both practical and theoretical implications to the field as a whole.

Table 91.5 Population-based screening of eating disorders: best practice recommendations

1. Body dissatisfaction, fear of fat, or other items that tap body image concerns (psychological symptoms) should not be used to screen for the presence of anorexia nervosa or bulimia nervosa given the high level of endorsement made by women who do not have an eating disorder. Screening with these psychological symptoms will result in too many false positives (poor specificity).

2. If psychological symptoms are included in population-based screening for eating disorders, an extreme threshold should be used as a cut-off point and they should be measured and interpreted separate from the eating disorder behaviors (i.e., psychological symptoms should have a separate total score form behavioral symptoms).

3. Items that assess pathological eating behaviors such as purging (vomiting, laxative/diuretic abuse), restricting, and binge eating will have the highest diagnostic accuracy (specificity and sensitivity).

4. Dieting questions should not be used to assess restricting behavior (e.g., "I eat diet foods" from the EAT-26) because it will increase the number of false positives.

5. Binge eating questions should include a definition of a "binge" (e.g., see the Eating Disorder Examination Questionnaire; EDE-Q) and be assessed along with relevant compensatory behaviors, given the subjective interpretation of binge eating. In the absence of compensatory behavior, such as in binge eating disorder, screening for binge eating behavior will be very difficult and requires further research to understand how and what to ask when screening for binge eating behaviors.

Summary Points

- Addressing the issue of a continuum of eating pathology is necessary because understanding the nature of the relation between disordered eating and eating disorders advances the theoretical underpinning of eating disorder research (i.e., the etiology of eating disorders).
- Understanding whether eating disorders exist on a continuum or are discontinuous informs our measurement and assessment of eating disorders.
- It is important to distinguish between psychological and behavioral symptoms in the assessment and measurement of eating disorders. Screening instruments that rely heavily on psychological indicators of eating disorders will yield high rates of false positives and will suffer a trade-off of low specificity for high sensitivity.
- The presence of clinically significant eating disorder behaviors is the best indicator that an eating disorder is present. It is the behavior which is pathognomonic.
- Because weight discontent is so normative in western culture, it is problematic, from a measurement standpoint, to use these normal features to screen for an abnormal syndrome.
- Screening for eating disorders using instruments such as the EDI or the Eating Attitudes Test (EAT-26) will be a costly and time-consuming effort because both measures contain far more normative weight concern items and dieting items than clinically significant eating disorder behaviors.

Definitions and Explanations

Behavioral symptoms: The behavioral symptoms of an eating disorder, as outlined in the DSM-IV include: a) binge eating and b) compensatory behaviors to prevent weight gain such as self-induced vomiting; misuse of laxatives, diuretics, enemas, or other medications; fasting; or excessive exercise.

Psychological symptoms: The psychological symptoms of an eating disorder, as outlined in the DSM-IV include intense fear of gaining weight or becoming fat, even though underweight; disturbance in the way in which one's body weight or shape is experienced, undue influence of body weight or shape on self-evaluation, denial of the seriousness of the current low body weight.

Population-based screening: Population-based screening for eating disorders is a method used in epidemiological research where a large and ideally representative sample of people from a nonclinical population are administered a short survey or interview that identifies those who are at-risk of having an eating disorder. Those who are determined to be at-risk are followed up with a more in-depth interview to determine whether they meet diagnosis for a clinical eating disorder.

Sensitivity: Sensitivity of an eating disorder measurement tool or diagnostic test refers to how good a test is at correctly identifying people who have an eating disorder.

Specificity: Specificity of an eating disorder measurement tool or diagnostic test refers to how good a test is at correctly identifying people who do not have an eating disorder.

Taxon: A taxon is like a category; it indicates a discrete group where in/out classifications can be made. However, the presence of a taxon does not mean there is no dimensional aspect. With eating disorders, if eating behaviors were taxonic, they could be measured on a continuum. The discrete part of the behavior comes when we compare clinical to nonclinical populations. A "dimension' of eating behaviors exits in the clinical sample (dimensional aspect), but this dimension is only present in the clinical sample; it is unique or specific to the clinical population. This is the categorical aspect.

References

Ackard DM, Fulkerson JA, Neumark-Sztainer D. Int J Eat Disord. 2007;40:409–17.

American Psychiatric Association. Diagnostic and statistical manual of mental disorders, 3rd edn. Washington, DC: APA; 1980.

American Psychiatric Association. Diagnostic and statistical manual of mental disorders, 4th edn. Washington, DC: APA; 1994.

American Psychiatric Association. Diagnostic and statistical manual of mental disorders, 4th edn., text revision. Washington, DC: APA; 2000.

Bachner-Melman R, Zohar AH, Ebstein RP. J Nerv Ment Dis. 2006;194:697–703.

Blum K, Sheridan PJ, Wood RC, Braverman ER, Chen TJH, Cull JG. J R Soc Med. 1996;89:396–400.

Brownell KD, Rodin J. Am Psychol. 1994;49:781–91.

Bruch H. Eating disorders. Basic Books, New York; 1973.

Bulik CM, Sullivan PF, Kendler KS. Am J Psychiatry. 2000;157:886–95.

Bulik CM, Sullivan PF, Joyce PR, Carter FA. J Nerv Ment Dis. 1995;183:593–8.

Bulik CM, Sullivan PF, Carter FA, McIntosh VV, Joyce PR. Int J Eat Disord. 1999;26:137–44.

Button EJ, Whitehouse A. Psychol Med. 1981;11:509–16.

Cash TF, Morrow JA, Hrabosky JI, Perry AA. J Consult Clin Psychol. 2004;72:1081–9.

Chamay-Weber C, Narring F, Michaud P. J Adolesc Health. 2005;37:417–27.

Cogley CB, Keel PK. Int J Eat Disord. 2003;34:200–10.

Cooper PJ, Goodyer I. Br J Psychiatry. 1997;171:42–4.

Couturier J, Lock J. Int J Eat Disord. 2006;39:550–5.

Crisp AH. Proc R Soc Med. 1965;11:509–16.

Crow SJ, Agras WS, Halmi K, Mitchell JE, Kraemer HC. Int J Eat Disord. 2002;32:309–18.

Davis C, Claridge G. Addict Behav. 1998;23:463–75.

Duncan AE, Bucholz KK, Neuman RJ, Agrawal A, Madden PAF, Heath A. Psychol Med. 2007;37:1097–107.

Fairburn CG, Bohn K. Behav Res Ther. 2005;43:691–701.

Fairburn CG, Cooper Z. Int J Eat Disord. 2007;40:S107–10.

Fairburn CG, Cooper Z, Bohn K, O'Connor ME, Doll HA, Palmer RL. Behav Res Ther. 2007;45:1705–15.

Fairburn CG, Cooper Z, Shafran R. Behav Res Ther. 2003;41:509–28.

Fairburn CG, Harrison PJ. Lancet. 2003;361:407–16.

Fairburn CG, Peveler RC, Jones R, Hope RA, Doll HA. J Consult Clin Psychol. 1993;61:696–8.

Farrell C, Shafran R, Lee M, Fairburn CG. Behav Cogn Psychother. 2005;33:189–200.

Fennig S, Fennig S, Roe D. Gen Hosp Psychiatry. 2002;24:87–92.

Franko DL, Omori M. J Adolesc. 1999;22:389–96.

Freeman RJ, Beach B, Davis R, Solyom L. Psychiatry Res. 1985;19:349–53.

Fries H. In: Vigersky R editor. Anorexia nervosa. New York: Raven; 1977. p. 163–176.

Gangestad S, Snyder M. Psychol Rev. 1985;92:317–49.

Garfinkel PE, Lin E, Goering P, Spegg C, Goldbloom DS, Kennedy S, Kaplan AS, Woodside DB. Am J Psychiatry. 1995;152:1052–8.

Garner DM, Garner MV, Rosen LW. Int J Eat Disord. 1993;13:171–85.

Garner DM, Olmsted MP, Garfinkel PE. Int J Eat Disord. 1983;2:11–20.

Garner DM, Olmsted MP, Polivy J, Garfinkel PE. Psychosom Med. 1984;46:255–66.

Gleaves DH, Brown JD, Warren CS. Behav Modif. 2004;28:739–62.

Gleaves DH, Eberenz K. J Psychopathol Behav Assess. 1993;15:141–52.

Gleaves DH, Eberenz KP. J Clin Psychol. 1995;51:181–9.

Gleaves DH, Lowe MR, Green BA, Cororve MB, Williams TL. Behav Ther. 2000;31:195–219.

Gleaves DH, Lowe MR, Snow AC, Green BA, Murphy-Eberenz KP. J Abnorm Psychol. 2000;109:56–68.

Gleaves DH, Williamson DA, Barker SE. J Abnorm Psychol. 1993;102:173–6.

Goldner EM, Srikameswaran S, Schroeder ML, Livesley WJ, Birmingham CL. Psychiatry Res. 1999;85:151–9.

Grodstein F, Levine R, Spencer T, Colditz GA, Stampfer MJ. Arch Intern Med. 1996;156:1302–6.

Halmi KA, Sunday SR. Appetite. 1991;16:219–37.

Hay PJ, Fairburn CG, Doll HA. Psychol Med. 1996;26:801–12.

Herman CP, Polivy J. In: Stunkard AJ, Stellar E editors. Eating and its disorders. New York: Raven Press; 1984. p. 141–156.

Hoek HW. Curr Opin Psychiatry. 2006;19:389–94.

Jacobi C, Abascal L, Taylor CB. Int J Eat Disord. 2004;36:280–95.

Jacobi C, Hayward C, de Zwaan M, Kraemer HC, Agras WS. Psychol Bull. 2004;130:19–65.

Keel PK, Dorer DJ, Franko DL, Jackson SC, Herzog DB. Am J Psychiatry. 2005;16:2263–8.

Keel PK, Fichter M, Quadflieg N, Bulik CM, Baxter MG, Thornton L, Halmi KA, Kaplan AS, Strober M, Woodside DB, Crow SJ, Mitchell JE, Rotondo A, Mauri M, Cassano G, Treasure J, Goldman D, Berrettini WH, Kaye WH. Arch Gen Psychiatry. 2004;61:192–200.

Kraepelin E. General Paresis. New York: Nervous and Mental Disease Publishing Company; 1913.

Lowe MR. Psychol Bull. 1993;114:100–21.

Lowe MR, Gleaves DH, DiSimone-Weiss RT, Furgueson C, Gayda CA, Kolsky PA, Neal-Walden T, Nelsen LA, McKinney S. J Abnorm Psychol. 1996;105:508–17.

Lowe MR, Timko CA. Br J Nutr. 2004;92:S19–22.

McVey G, Tweed S, Blackmore E. CMAJ. 2004;170:1559–61.

Miller JL. Measurement of eating pathology: Distinct roles of thoughts and behaviours in the assessment of risk and detection of eating disorders. Unpublished doctoral dissertation, McMaster University, Canada; 2008.

Miller JL, Schmidt LA, Vaillancourt T, McDougall P, Laliberté M. Eat Behav. 2006;7:69–78.

Miller JL, Vaillancourt T, Hanna SE. Eat Behav. 2009;10:89–96.

National Institutes of Health Technology Assessment Conference Panel. Ann Intern Med. 1993;199:764–70.

Park J, Beaudet MP. Eur Eat Disord Rev. 2007;15:311–20.

Patton GC, Johnson-Sabine E, Wood K, Mann AH, Wakeling A. Psychol Med. 1990;20:383–94.

Patton GC, Selzer R, Coffey C, Carlin JB, Wolfe R. BMJ. 1999;318:765–8.

Piran N, Gadalla T. Addiction. 2006;102:105–13.

Polivy J, Herman CP. Am Psychol. 1985;40:193–210.

Polivy J, Herman CP. J Consult Clin Psychol. 1987;55:635–44.

Polivy J, Herman CP. Annu Rev Psychol. 2002;53:187–213.

Presnell K, Stice E. J Abnorm Psychol. 2003;112:166–70.

Rodin J, Silberstein L, Striegel-Moore R. Nebr Symp Motiv. 1984;32:267–307.

Ruderman AJ, Besbeas M. J Abnorm Psychol. 1992;101:383–90.

Saccoman L, Savoini M, Naselli A, Cirrincione M, Matricardi A. Minerva Pediatr. 1989;41:5–10.

Steiger H, Israel M, Gauvin L, Ng YK, Young SN. Psychiatry Res. 2003;120:219–29.

Stice E. Psychol Bull. 2002;128:825–48.

Stice E, Agras WS. J Consult Clin Psychol. 1999;67:460–9.

Stice E, Killen JD, Hayward C, Taylor CB. J Consult Clin Psychol. 1998;66:784–90.

Stice E, Ziemba C, Margolis J, Flick P. Behav Ther. 1996;27:531–49.

Striegel-Moore R, Franko DL, Thompson D, Barton B, Schreiber GB, Daniels SR. Psychol Med. 2005;35:1563–72.

Striegel-Moore RH, Silberstein LR, Rodin J. Am Psychol. 1986;41:246–63.

Strober M, Freeman R, Morrell W. Int J Eat Disord. 1997;22:339–60.

Sullivan PF, Bulik CM, Kendler KS. Br J Psychiatry. 1998a;173:75–9.

Sullivan PF, Bulik CM, Kendler KS. Psychol Med. 1998b;28:599–610.

Sullivan PF, Kendler KS. Br J Psychiatry. 1998;173:312–9.

Tobin DL, Johnson C, Steinberg S, Staats M. J Abnorm Psychol. 1991;100:14–21.

Tylka TL, Subich LM. J Couns Psychol. 1999;46:268–76.

Tylka TL, Subich LM. J Couns Psychol. 2002;49:273–9.

Tylka TL, Subich LM. J Counsel Psychol. 2003;50:276–86.

Vanderheyden DA, Fekken GC, Boland FJ. Int J Eat Disord. 1988;7:321–9.

Wade TD, Crosby RD, Martin NG. Arch Gen Psychiatry. 2006;63:1377–84.

Waller NG, Meehl PE. Multivariate taxometric procedures: Distinguishing types from continua. Thousand Oaks: Sage Publications; 1998.

Watson D, Clark LA. Clin Psychol Sci Pract. 2006;13:210–5.

Westen D, Harnden-Fischer J. Am J Psychiatry. 2001;158:547–62.

Widiger TA, Samuel DB. J Abnorm Psychol. 2005;114:494–504.

Wilfley DE, Bishop ME, Wilson GT, Agras WS. Int J Eat Disord. 2007;40:S123–9.

Williamson DA, Gleaves DH, Savin SS. J Psychopathol Behav Assess. 1992;14:201–16.

Williamson DA, Gleaves DH, Stewart TM. Int J Eat Disord. 2005;37:1–10.

Williamson DA, Womble LG, Smeets MAM, Netemeyer RG, Thaw JM, Kutlesic V, Gleaves DH. Am J Psychiatry. 2002;159:412–8.

Zaider TI, Johnson G, Cockell SJ. Int J Eat Disord. 2000;28:58–67.

Chapter 92
Cued Overeating

Anita Jansen, Remco C. Havermans, and Chantal Nederkoorn

Abbreviations

WHO   World Health Organisation
CS   Conditioned stimulus (= cues)
US   Unconditioned stimulus
UR   Unconditioned response
CR   Conditioned response
CBT   Cognitive behaviour therapy

92.1 Introduction

Obesity, defined as an unhealthy amount of body fat, is a major health problem that is increasing dramatically worldwide; figures show a current overweight and obesity prevalence of more than 60% in the USA and UK, and comparable statistics are documented for many other countries in the world (Wadden et al. 2002). In 2005, it was estimated by the World Health Organisation (WHO) that at least 400 million adults were obese and 1.6 billion people of over the age of 15 were overweight (World Health Organisation 2009). WHO further predicts that by 2015, about 2.3 billion adults will be overweight and more than 700 million will be obese. WHO refers to these figures as the obesity epidemic.

The ultimate cause of obesity and overweight is an energy imbalance between calories consumed and calories expended. The main reasons for the energy imbalance are a shift in diet towards increased intake of energy-dense foods that are high in fat and sugars and decreased physical activity. Highly palatable energy-dense foods are widely available and difficult to resist. However, not everybody grows obese, so some people are better able to handle the temptations of the current environment than others. Understanding how people handle temptations is necessary to develop prevention strategies or to strengthen interventions for obesity. Why are some people better able to resist the "toxic" environment than others?

A difference between normal eaters and overeaters might be related to the automatic responding of one's body to appetitive cues as a consequence of learning. Overeating is associated with increased

A. Jansen (✉)

Department of Clinical Psychological Science, Maastricht University, P.O. Box 616, 6200 MD Maastricht, The Netherlands
e-mail: a.jansen@maastrichtuniversity.nl

cue reactivity, that is, increased appetitive responding to food cues (Jansen 1998; Jansen et al. 2003; Jansen et al. 2008). When overeaters are confronted with a diverse range of tasty food cues that are predictive of food intake – like the smell, taste, and sight of palatable high calorie foods – they show increased appetitive or cephalic phase responding, like salivation and the release of insulin, followed by increased food intake (Jansen 1998; Jansen et al. 2003; Wardle 1990; Woods 1991). Cephalic phase responses are responses that prepare for food intake: the greater the appetite, the more intense the response (Powley 1977). Signals that cause the cephalic phase response originate in the cerebral cortex, amygdala, and hypothalamus and are transmitted to the stomach. The cephalic phase or appetitive responding is believed to be experienced as an urge to eat, making it more difficult for people to refrain from eating. As a consequence, healthy eating in a "toxic" environment is much easier without than with these appetitive responses. Learning theory states that appetitive responses decrease and extinguish when exposure to foods remains *systematically* unreinforced, that is, when palatable high-calorie foods are seen or smelled but not eaten. In other words, being able to resist palatable high-fat food temptations and maintaining a regular and healthy diet even if exposed to the "toxic" environment, leads to a decrease and eventually extinction of the automatic urges to eat, which in turn makes it easier to refrain from eating high-fat foods for a longer period of time. In contrast, dieters who intermittently or always give in to the urge to eat, keep reinforcing the learned appetitive responding, ending up in increasingly stronger urges to eat the highly palatable foods (Jansen 1998). In the present chapter, it is argued and demonstrated that food cues might elicit almost reflex-like irresistible food cravings that could sabotage a healthy diet. It will also be shown that there are ways to decrease the abnormal food cue reactivity and overeating and it is suggested that cue exposure with response prevention should be used more often in the treatment of overeating.

92.2 Cue Elicited Eating

The intake of food activates physiological responses. A large number of studies show that the physiological responses brought about by food intake, e.g. insulin release, blood sugar increase, and salivation, can be brought under the control of any stimulus predictive of food intake, like odors, time of the day, eating-related situations, seeing, smelling, tasting, and even thinking of food (see for an overview Jansen 1998; Siegel 1972; Woods 1991). Any time food is ingested, there is an opportunity to associate the food with cues that are present at the time (Bouton et al. 2006; Havermans et al. 2007). The place where the food is eaten, the people with whom it is eaten, the food preparing rituals, the smell and taste of the foods – they may all become signals for eating and when this happens, classical conditioning occurs (see Fig. 92.1).

The conditioned responses (CRs) prepare the organism for food intake and contribute to the body's internal homeostatic regulation. Food intake may, in terms of classical conditioning, be considered an unconditioned stimulus (US), whereas its metabolic effects are unconditioned responses (URs). Cues that reliably signal food intake, such as the sight, smell, and taste of food, or even the context in which one eats, may start to act as conditioned stimuli (CSs) that easily trigger cue reactivity (CRs). In short, it is theorized that cues that are (nearly) always and almost exclusively present at the time of eating will, in the long run, acquire the ability to *predict* the eating and its effects. One might think of both proximal cues, e.g., the sight, smell, and taste of the food, intake rituals such as the preparation of food, and interoceptive cues (e.g., affective states or typical palatable food-related cognitions), but also distal cues like context cues (e.g., the room where usually is eaten, time of eating). From the very moment that these cues reliably signal food intake and classical conditioning occurs, the cues or conditioned stimuli (CS) acquire the ability to elicit special food intake related
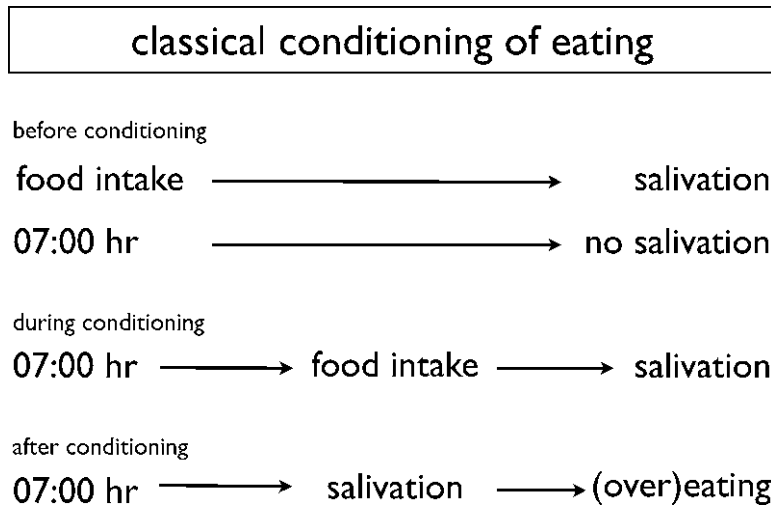
Fig. 92.1 The classical conditioning model of (over)eating. Any time food is ingested, the food intake is associated with the cues that are present at that time. For example, when breakfast is always eaten at 07:00, this time will be associated with food intake. At the moment 07:00 is a reliable predictor of food intake, the time alone elicits responses that prepare for intake, like salivation

responses in the organism, like insulin release, blood sugar decrease, and the subjective experience of food cravings or appetite. These responses are calledCRs or cue-reactivity. It is assumed that food cravings or appetite reflect the subjective experience of these learned responses (Jansen 1998).

The acquired responses (CRs) might have specific features. Deutsch (1974) showed that an initially neutral taste cue is able to elicit a glycometabolic effect in rats after pairing the taste with glucose administration in a classical conditioning paradigm; the rats learned that sugar would come and when they tasted the formerly neutral taste, they prepared for the glucose with a preparatory decline in blood sugar. In the same way, rats learned to respond with a decline in blood sugar to a placebo after they were repeatedly injected with glucose. Conditioned hypoglycemia was also demonstrated in dogs and humans after injections with intravenous glucose (Overduin and Jansen 1997; Overduin et al. 1997). Conversely, after repeated intravenous injections of insulin (which are usually followed by a decline in blood sugar level), rats learned to respond with a rise in blood sugar level to a placebo (Siegel 1972, 1983). Also eating behavior can be triggered by cues that were systematically associated with food consumption: rats that had already eaten till satiation were found to eat again when exposed to a tune that was previously associated with food consumption (Weingarten 1983). More recently, it was found that rats consumed significantly more (less palatable) chow when exposed to context cues that were earlier paired with the intake of highly palatable foods (Boggiano et al. 2009). Various context cues were used, e.g., different types of bedding or wallpaper. Boggiano et al. concluded that context-cues associated with palatable food intake might drive overeating in rats, even in sated rats and even when a less-preferred food (chow) was used in the test phase. The authors also report that the cue-conditioned overeating was quickly learned and appeared to be particularly strong when the taste of a palatable food was used to make cue-associations.

In humans, it has been found that the mere anticipation of food and sham feeding (i.e. the sight, smell, taste, chewing, or swallowing of food without it entering the gastrointestinal tract) as well as cognitive processes (such as the thought of food or even hypnotic suggestion of food) elicit responses which prepare the organism for the digestion of food, such as insulin release and salivary responses (Mattes 1997; Nederkoorn and Jansen 2002; Nederkoorn et al. 2000; Power and Schulkin 2008; Powley 1977; Rodin 1985).

In sum, it is well documented that exposure to food cues evokes cephalic phase responses. The cephalic phase responses gear up the body and serve the efficient use of nutrients. The classical conditioning model of food intake states that, after systematic association of cues (CS) and food intake (US), the cues will reliably signal the food intake effects. The moment the cues are good predictors of eating, they acquire the ability to elicit physiological responses that prepare for intake and are called cue reactivity. Appetite or craving is the subjective experience of cue reactivity. A main prediction flowing from this cued eating model is that the CRs or cue reactivity increase the likelihood of food intake and easily leads to overeating.

92.3 Cue Elicited Overeating

Imagine that you are in a wedding party: in that situation you will definitely eat more than when you are at home on a weekly day. Presumably, you will also eat more than you need to: you overeat. Overeating is quite normal; many people overeat once in a while, depending on the context or situation. But there are also people who do overeat on a regular basis, almost habitually. They will gain weight and might become overweight or obese. Some other people, mostly young females, are frequent binge eaters. Binge eating refers to the eating of an objectively large amount of food in a discrete period of time, while experiencing a loss of control over intake (APA 1994). Mostly, palatable high-calorie foods are eaten during a binge and the food usually is stuffed into the mouth. Binge eating occurs in the (sub)clinical eating disorders Bulimia Nervosa, Anorexia Nervosa, and Binge Eating Disorder (APA 1994), and it is also been found to occur in about 12% of a normal female population sample (Bruce and Agras 1992) as well as 15–50% of the obese participating in weight-control programs (Marcus et al. 1985). The obese usually do not compensate for the extra calories that they eat during a binge, whereas the underweight and normal weight binge eaters do compensate by e.g. self-induced vomiting, use of laxatives, exercising, and dieting.

The most frequently mentioned triggers of binge eating are negative emotions – like feeling depressed, hopeless, worried and dissatisfied – and appetitive cues that elicit craving – like the sight, smell, and taste of highly preferred foods (Jansen et al. 2008). Tasting or smelling palatable foods, being in a low mood, anxious or emotionally upset, thinking of eating; all these binge precursors could, hypothetically, be conditioned to the excessive intake of food. After systematic association of these cues with binge food intake, the cues reliably signal the food effects. The moment the cues are good predictors of intake, they will elicit physiological responses that are subjectively experienced as craving or appetite, which almost reflexively increase the likelihood of overeating.

This model hypothesizes that classically conditioned associations between cues that predict food intake and actual eating behavior are stronger in overweight than in normal-weight children since parents of overweight children more frequently prompt their children to empty their plate and overweight children show higher external eating styles, meaning that their intake is more often triggered by food cues like seeing or smelling food. Both increase the probability that a food cue is followed by food intake, which strengthens the bond between cues and intake and makes smell and taste more predictive of intake in overweight than in normal-weight children. In line with the model it was found that overweight and normal weight 8–12 year old children ate comparable amounts when they were not tempted by food cues (Jansen et al. 2003). However, when they were tempted by cues that signal eating, like the smell and taste of highly palatable foods, the overweight children overate. They ate more in response to food cues than without, whereas the normal weight children did the opposite: they ate less in response to food cues than without these cues. Cue reactivity (salivation) was related to food intake but only in the overweight children: they showed a highly significant correlation between

Table 92.1   Key points of cued overeating

1. The intake of food activates physiological responses
2. When food intake systematically is preceded by internal or external cues, classical conditioning occurs
3. During confrontation with the cue that predicts food intake, the body anticipates eating
4. Cues predictive of food intake are for example the smell, taste, and sight of palatable foods
5. These food cues bring about responses that prepare for intake, like salivation and the release of insulin
6. The anticipative appetitive responding increases appetite or the urge to eat
7. The anticipative appetitive responding increases intake

This table lists the key points of cued overeating including the required systematic association between cue and food intake that leads to a process of classical conditioning. Being confronted with a cue that predicts eating prepares the body for food intake by anticipative appetitive responding

caloric intake and salivary flow after food cue exposure ($r = 0.62$), whereas this relation was almost absent in the normal-weight group ($r = 0.05$).

The abovementioned study shows that overweight children eat normal amounts when tempting food cues are lacking. But when they are tempted by the taste or intense smell of palatable food, they fail to regulate their intake. This vulnerability to cued overeating in overweight children might follow from a learned association between the tempting cues and increased intake. The cue-elicited salivary response of the overweight sample was significantly related to their increased intake. Clearly, the cues elicited reactivity-related overeating in the overweight sample and not in the normal-weight sample, a finding that supports the idea that classically conditioned associations between cues that predict food intake (smell, taste) and actual eating behavior are stronger in overweight than in normal-weight children (Table 92.1).

92.4 The Role of Mood and Restraint

Risk factor models for eating disorders have put forward that negative mood states are key triggers of overeating in samples with eating disorders (Stice et al. 2008). In some recent studies, eating disorders were subtyped along dimensions of negative affect and these studies showed that increased negative affect signaled a stronger vulnerability to disinhibition (Stice et al. 2008). In our lab, we showed that a specific state-trait interaction facilitated overeating: the high negative affect overweight/obese subtype was more vulnerable to overeating in the presence of a disinhibiting cue (negative mood induction or food exposure) than the overweight/obese subtype that was low in negative affect (Jansen et al. 2008). The data show that individual differences might play a critical role in the way overweight/obese people handle the temptations of the current "toxic" environment: negative affect makes it more difficult for the overweight/obese to resist modern temptations (see Fig. 92.2).

Another trait that plays a role in the way people handle toxic temptations is restraint. Restrained eaters try to restrict their intake, mostly because they want to lose weight. But a substantial part of the restrained eaters usually alternates between restrained and overeating episodes: a very common eating pattern is that in the absence of tempting food cues, the so-called restrained eater succeeds in resisting highly palatable high calorie foods until a cued overeating episode announces itself. It should be noted that such an eating pattern facilitates classical conditioning: deprivation in the absence of cues and eating large amounts of high calorie palatable foods (strong USs) within a limited and specific range of cues (CSs) implies that the contingency between CS and US, and thus classical conditioning, will be strong (Bouton et al. 2006). Strong conditioning is reflected in strong CRs or cue reactivity including appetite or craving. Experimental studies indeed show that dieters overeat after exposure to cues that typically predict food intake, like tasting a priming dose (appetizer
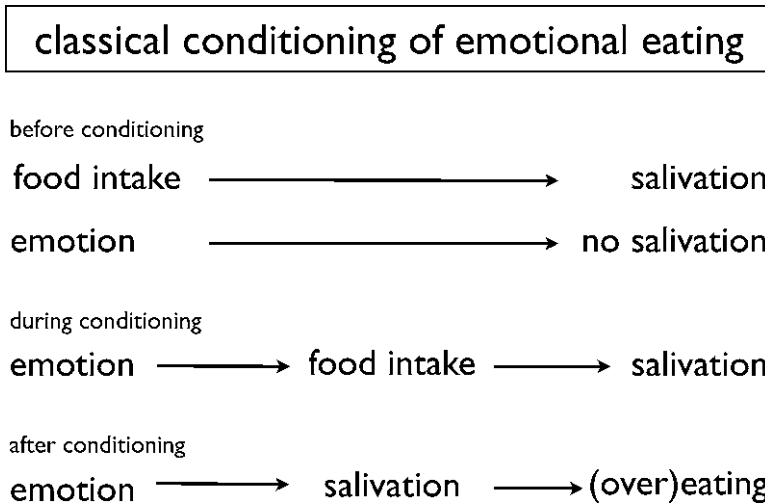
Fig. 92.2 The classical conditioning model of emotional eating. If snack foods are always eaten when emotionally upset, feeling upset will be associated with snack food intake. At the moment being emotionally upset is a reliable predictor of snack food intake, the emotion alone elicits responses that prepare for intake, like salivation

or preload; see for a classic experiment Herman and Mack 1975) and in other studies it was found that they overeat after mere exposure to the smell of binge food (e.g., Jansen and van den Hout 1991). The exposure to food cues (tasting, eating, or smelling the food) elicited a strong desire to eat in people that tend to alternate overeating and restrained eating.

92.5 Successful Dieting

Some dieters never overeat and they might be called successful dieters. Although it is not precisely clear how many people are successful in dieting, it is estimated that about 20% of the obese are capable of reducing to a normal weight and to maintain this reduced weight for at least a year (Wing and Phelan 2005). It is however not at all clear why some people are better able to stick to their diets for a long period of time in the context of a "toxic" environment than others. Successful dieters report to especially refrain from eating palatable high calorie fat foods; they say they are strict dieters who eat little fat and show little variety in their diets (Gorin et al. 2004; Raynor et al. 2005; Wing and Hill 2001). The classical conditioning model of cued overeating would predict that if exposure to tasty high fat foods remains unreinforced in successful dieters, this will lead to the extinction of cue reactivity (including craving) during confrontation with the cues. The extinguished cue reactivity makes it easier to maintain one's diet. In line with the cued overeating model, decreased salivary responding during exposure to palatable high fat food cues was found in postobese successful dieters, whereas unsuccessful obese dieters showed increased salivary responding during exposure to the same cues (Jansen et al. 2009). It was proposed that strict dieting extinguishes cue reactivity. In its turn, the extinction of cue reactivity will make dieting easier (see Fig. 92.3). Strict dieting is however quite difficult for many dieters, especially in the beginning of the dieting, and it might take much time before learned cue reactivity is extinguished. There are also dieters who do not expose themselves to high calorie foods but avoid them, for example because they only consume diet shakes for

Fig. 92.3 The relation between the way of dieting, food cue exposure, food cue reactivity, and extinction or the success of dieting. If exposure to tasty high fat foods remains unreinforced this will lead to the extinction of cue reactivity and makes dieting easier

Fig. 92.4 The relation between the way of dieting, food cue exposure, food cue reactivity, and extinction or the success of dieting. If the dieter avoids the exposure to tasty high fat foods, this will not lead to an extinction of cue reactivity and sabotages dieting

periods of time. They are expected to remain cue reactive, which makes it more difficult for them to maintain the lost weight (see Fig. 92.4). It was further argued that the extinction of cue reactivity is necessary for successful dieting. Dieters that avoid highly palatable food cues, like the dieters that follow a specific shake-diet or another limited diet, do not enable their cue reactivity to extinguish. Likewise, in dieters who intermittently keep overeating high-calorie high-fat palatable foods, cue reactivity will not disappear because the CS is followed repeatedly by the US, which makes it difficult to learn that the CS does not predict the US anymore (see Fig. 92.5). For successful dieting and a reduction of overeating it seems necessary that dieters enter a vicious circle of strict dieting and decreased cue reactivity (see Fig. 92.3). Dieting appears to be difficult. Can we help overeaters to decrease cue reactivity, to facilitate dieting? (Table 92.2).

Fig. 92.5 The relation between the way of dieting, food cue exposure, food cue reactivity, and extinction or the success of dieting. If the dieter intermittently overeats on tasty high fat foods, this will not lead to an extinction of cue reactivity and sabotages dieting

Table 92.2 Key points of successful dieting

1. When the body anticipates eating and prepares for consumption, appetite or the urge to eat is intense
2. When the cues are not followed by eating, the anticipative appetitive responding decreases and appetite or the urge to eat as well
3. After a series of nonreinforced exposures to the cues without eating, the cues do not predict eating anymore
4. When cues do not predict eating anymore, they will stop eliciting preparatory responses
5. Successful dieters confront themselves with the cues that predict food intake without eating
6. The preparatory responses in successful dieters are extinguished making it easier to refrain from foods

This table lists the key points of successful dieting including the required extinction of the systematic association between cue and food intake. Being confronted with a cue without eating extinguishes the anticipative appetitive responding and makes dieting easier

92.6 The Reduction of Cue Reactivity

The classical conditioning model of overeating states that cue reactivity follows from probabilistic CS (cues)–US (overeating) contingencies. Cues will elicit craving as long as they are reliable predictors of food intake or, to put it differently, as long as the CSs are systematically reinforced by the US. The model predicts that craving will extinguish when the CS–US bond is broken. This bond will be broken by prolonged and repeatedly nonreinforced exposure to the cues that predict overeating (CS). Strict dieting in the current "toxic" environment is a form of continuous nonreinforced exposure to palatable food cues. However, many dieters try to avoid the palatable food cues in order to make it easier to keep their diets. The toxic environment is however everywhere, so they will never succeed in always avoiding palatable food cues. The link between cues that indicate that overeating is forthcoming and the actual overeating might be eliminated by cue exposure with response prevention. During cue exposure with response prevention the subject is exposed to the craving-eliciting highly palatable food cues and eating is prevented. Individually customized sets of highly palatable food cues are the best to use; the more likeness the cues have to the favorite foods, the better the reactivity is. This means for the exposure to food cues, that all of the cues and contexts that play a part in the overeating should be included in the most perfect exposure: the exposure takes place at the customary overeating spot and with the most favorite foods for overeating. Special attention must be paid to
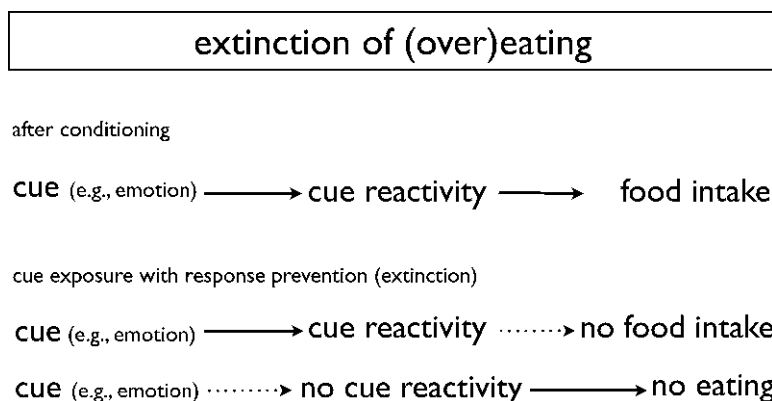
Fig. 92.6 The extinction of overeating through cue exposure with response prevention. The emotional eater is exposed to the emotion (e.g., by inducing emotions) and responds with cue reactivity including a strong desire to eat the foods (or craving). But the emotional eater is prevented from eating. After several sessions of exposure with response prevention, the emotion is no longer predictive of overeating. The cue reactivity including the desire for eating or craving is extinguished

moods and thoughts that accompany the overeating. For many overeaters, negative moods are important cues that elicit craving; inducing a negative mood might magnify the urge to eat. The goal of the exposure is to elicit a strong craving for the palatable high-calorie food. The overeater touches the food, feels around in it, grabs it, holds it to the nose and smells it – but never eats; the CS–US bond will be broken. Craving will increase until it is experienced as almost irresistible. But if the exposure lasts long enough, the craving for food will slowly die down despite all attempts to keep it as strong as possible; CRs (cue reactivity and craving) will extinguish (see Fig. 92.6).

Pilot studies show that cue exposure with response prevention elicits craving – the craving typically increases gradually until it is high, and then it extinguishes slowly in patients with bulimia nervosa (Jansen et al. 1989; Jansen et al. 1992; Toro et al. 2003; Martinez-Mallén et al. 2007). Extinction was found both within and between the exposure sessions (cue reactivity started lower each session). The exposure was not only highly effective in the reduction of cue reactivity and craving, also the binge frequency of the bulimia nervosa patients decreased significantly.

Another study was, however, less positive (Bulik et al. 1998; Carter and Bulik 1994). It was examined whether the effectiveness of short cognitive behavior therapy (CBT) could be increased through adding food cue exposure with response prevention. All bulimia nervosa patients were first treated with eight sessions of CBT, and then eight exposure sessions followed. The exposure did not improve the results of the short cognitive behavior therapy. However, CBT was already extremely effective; an 80% reduction of binge eating was reached and 40% of the sample was abstinent, i.e. did not binge eat anymore. These excellent results touch the sore spot; the cognitive behavior therapy reached a ceiling effect – the design of the study did not permit the exposures to be successful.

All in all, the positive findings from pilot studies suggest that cue exposure might be an effective treatment for binge eaters. Note, however, that although the data are promising, they were derived from pilot studies with small subject samples. The only large controlled clinical trial that was published is not positive about the contribution of cue exposure with response prevention to CBT in the treatment of binge eating. We pointed to several methodological shortcomings of that study. Further, as far as the authors know, the effects of cue exposure are yet only documented for bulimia nervosa patients. It remains to be seen whether nonbinging overeaters will also benefit from cue exposure with response prevention.

Apart from the extinction of cue reactivity that is strived for by the cue exposure to highly palatable food cues, the olfactory stimulation during the exposure to palatable food cues might have induced

olfactory sensory-specific satiety. A short period of olfactory stimulation (i.e., smelling) produced decreased pleasantness of the smell of the food, which is called olfactory sensory-specific satiety (Rolls and Rolls 1997). Thus, smelling foods may induce satiety. It was suggested by Jansen et al. (2003) that overeaters and people that show a tendency to overeat are characterized by a slowing down of the sensory-specific decrease in neural activity. Indirect evidence for this idea is given in studies on the extinction of craving in binge eaters; binge eaters show increased craving after they started smelling binge foods (without eating it), and the highest of their craving is after about 20 min, after which craving gradually declines. In normal eaters the highest of craving is reached earlier and craving extinguishes more rapidly.

Relating these findings to the cue reactivity model, it might be hypothesized that tasting or intense smelling of palatable food works as a prime that elicits cue reactivity especially in overeaters who are used to eat after being confronted with these cues. Normal eaters show sensory-specific satiety responses to the highly palatable foods. Note that the priming cues will elicit reactivity as long as they are reliable predictors of intake. The model predicts that the cue reactivity will lead to overeating until the cue–intake bond is broken by prolonged and repeated nonreinforced exposure to the cues. During cue exposure, the participant is exposed to the cues (smell, taste) and prevented from intake, leading to reduced reactivity and craving (Jansen 1998). Cue exposure with response prevention might be a promising new treatment intervention for overeaters. It might help to reduce cue reactivity and craving more quickly compared to when one is merely strict dieting. Thus, the first blow is half the battle; a successful start of the diet that frees the body of its cue reactivity will make dieting easier and more successful.

92.7 Applications to Other Areas of Health and Disease

The learning model of excessive consumption was originally formulated for addictive behaviors; many studies showed that the craving and substance intake of addicts is cue-controlled. Cue exposure with response prevention seems to be a useful therapy for addictive behaviors as well (see e.g., Havermans et al. 2007). Cue-elicited overeating might also be present in some anorexia nervosa patients, suggesting that cue exposure with response prevention is indicated for anorexia nervosa as well. Therapists are however strongly advised against using cue exposure with response prevention in anorexia nervosa. A main characteristic of anorexia nervosa is the low body weight and cue-induced (over)eating might be a mean to consume at least some calories. As long as they are underweight, anorexia nervosa patients should not be treated with strategies that do decrease intake.

92.8 Conclusions

The present model of cued overeating states that cues that reliably signal highly palatable food intake, such as the sight, smell, and taste of highly palatable foods, or even the context in which the overeating takes place, may start to act as conditioned stimuli that trigger cue reactivity and craving. It is assumed that learned cue reactivity increases the probability of overeating. Numerous experiments demonstrated that overeaters specifically overeat after confrontation with cues that predict the intake of highly palatable foods.

It was further argued that the extinction of cue reactivity is necessary for successful dieting. Dieters that avoid highly palatable food cues, like the dieters that follow a specific shake-diet or another limited diet, do not enable their cue reactivity to extinguish. Likewise, dieters who intermittently keep eating high-calorie high-fat palatable foods will remain cue reactive. Only dieters who expose themselves to highly palatable food cues without eating them are expected to show the desired

extinction of cue reactivity. This might however take a long time. The extinction of cue reactivity can be accelerated by cue exposure with response prevention. There have been a number of pilot studies suggesting that cue exposure with response prevention is an effective intervention to reduce binge eating. Whether cue exposure with response prevention is also suitable for overeaters and an effective intervention to reduce overeating remains to be studied.

Studies on the effectiveness of food cue exposure should be encouraged. Is cue exposure with response prevention beneficial to help people reaching the extinction sooner? Will dieting become easier and more successful when cue exposure with response prevention sessions are introduced quickly after or even before the start of the dieting? It would be highly relevant to find out how long it takes for learned cue reactivity to extinguish, in dieters who expose themselves to highly palatable high calorie foods without eating them and in dieters who do not expose themselves or to a lesser degree. The cued overeating model predicts that the first blow is half the battle. Experimental studies are needed to find out whether this is true.

Summary Points

- Obesity (partly) follows from overeating.
- Overeating follows from classically conditioned appetitive responding to food cues.
- The food cues elicit irresistible food cue reactivity including cravings that might sabotage a healthy diet.
- If overeating systematically follows negative emotions, the negative emotions will become cues for overeating.
- Cue exposure with response prevention decreases the abnormal food cue reactivity.
- Successful dieting requires the extinction of food cue reactivity.

Key Terms

Obesity: This refers to an unhealthy amount of body fat. Obesity usually is defined by a Body Mass Index (BMI = kg/m^2) of 30 or more.

Classical conditioning: It is a form of associative learning during which the organism learns that stimulus A predicts the occurrence of stimulus B, for example the smell of food (stimulus A) predicts eating (stimulus B).

Food cues: Cues that are predictive of food intake like the smell, taste, and sight of food, but also place, time, or emotions and thoughts if they are predictive of food intake.

Appetitive responding: Bodily responses that prepare for food intake, like salivation and insulin release, and the experience of appetite or urge to eat.

Cue reactivity: Increased appetitive responding to cues that predict food intake.

Extinction: The new learning that stimulus A does not predict stimulus B by presenting stimulus A without stimulus B.

Cue exposure with response prevention: A treatment procedure in which the cues that predict eating (e.g., the smell and taste of foods) are presented without the actual eating until the urge to eat is decreased. After several exposure sessions without eating it is learned that the cues do not predict food intake anymore and at that very moment they will not induce any appetitive preparatory responses and appetite anymore.

Successful dieting: The process by which dieters were successful in losing weight and in maintaining the weight loss.

References

American Psychiatric Association. Comittee on nomenclature and statistics: diagnostic and statistical manual of mental disorders. 4th ed. Washington, DC: American Psychiatric Association; 1994.

Boggiano MM, Dorsey JR, Thomas JM, Murdaugh DL. The Pavlovian power of palatable food: lessons for weight-loss adherence from a new rodent model of cue-induced overeating. Int J Obes. 2009;33:693–701.

Bouton ME, Woods AM, Moody EW, Sunsay C, Garcia-Gutierrez A. Counteracting the context-dependence of extinction: relapse and tests of some relapse prevention methods. In: Craske M, Hermans D, Vansteenwegen D, editors. Lear and fearning. From basic processes to clinical implications. Washington, DC: APA; 2006. p. 175–96.

Bruce B, Agras W. Binge eating in females: a population-based investigation. Int J Eat Disord. 1992;12:365–73.

Bulik CM, Sullivan FA, Carter FA, McIntosh VV, Joyce PR. The role of exposure with response prevention in the cognitive-behavioural therapy for bulimia nervosa. Psychol Med. 1998;28:611–23.

Carter FA, Bulik CM. Exposure treatments for bulimia nervosa: procedure, efficacy, and mechanisms. Adv Behav Res Ther. 1994;16:77–129.

Deutsch R. Conditioned hypoglycemia: a mechanism for saccharin-induced sensitivity to insulin in the rat. J Comp Physiol Psychol. 1974;86:350–8.

Gorin AA, Phelan S, Wing RR, Hill JO. Promoting long-term weight control: does dieting consistency matter? Int J Obes. 2004;28:278–81.

Havermans RC, Mulkens S, Nederkoorn C, Jansen A. The efficacy of cue exposure with response prevention in extinguishing drug and alcohol cue reactivity. Behav Interv. 2007;22:121–35.

Herman CP, Mack D. Restrained and unrestrained eating. J Pers. 1975;43:647–60.

Jansen A. A Learning model of binge eating: cue reactivity and cue exposure. Behav Res Ther. 1998;36:257–72.

Jansen A, van den Hout M. On being led into temptation: 'counterregulation' of dieters after smelling a 'preload'. Addict Behav. 1991;5:247–53.

Jansen A, van den Hout M, van Loof C, Zandbergen J, Griez E. A case of bulimia succesfully treated with cue exposure. Behav Ther Exp Psychiatry. 1989;20:327–32.

Jansen A, Broekmate J, Heymans M. Cue exposure vs self-control in the treatment of binge eating: a pilot study. Behav Res Ther. 1992;30:235–41.

Jansen A, Theunissen N, Slechten K, Nederkoorn C, Mulkens S, Roefs A. Overweight children overeat after exposure to food cues. Eat Behav. 2003;4:197–209.

Jansen A, Vanreyten A, van Balveren T, Roefs A, Nederkoorn Ch, Havermans R. Negative affect and cue-induced overeating in non-eating disordered obesity. Appetite 2008;51:556–62.

Jansen A, Stegerman S, Roefs A, Nederkoorn C, Havermans R. Decreased salivation to food cues in formerly obese successful dieters. Submitted for publication; 2009.

Marcus MD, Wing RR, Lamparski D. Binge eating and dietary restraint in obese patients. Addict Behav. 1985;10:163–8.

Martinez-Mallén E, Castro-Fornieles J, Lazaro L, Moreno E, Morer A, Font E, Julien J, Vila M, Toro J. Cue exposure in the treatment of resistant adolescent bulimia nervosa. Int J Eat Disord. 2007;40:596–601.

Mattes RD. Physiological responses to sensory stimulation by food: nutritional implications. J Am Diet Assoc. 1997;97:406–12.

Nederkoorn C, Jansen A. Cue reactivity and regulation of food intake. Eat Behav. 2002;3:61–72.

Nederkoorn C, Smulders F, Jansen A. Cephalic phase responses, craving and food intake in normal subjects. Appetite 2000;35:45–55.

Overduin J, Jansen A. Conditioned insulin and blood sugar responses in humans in relation to binge eating. Physiol Behav. 1997;61:569–75.

Overduin J, Dworkin BR, Jansen A. Introduction and commentary to: Mityushov, M.I. (1954): conditioned reflex secretion of insulin. Integr Physiol Behav Sci. 1954;32:228–46.

Power ML, Schulkin J. Anticipatory physiological regulation in feeding biology: cephalic phase responses. Appetite 2008;50:194–206.

Powley T. The ventromedial hypothalamic syndrome, satiety and a cephalic phase hypothesis. Psychol Rev. 1977;84:89–126.

Raynor HA, Jeffery RW, Phelan S, Hill JO, Wing RR. Amount of food group variety consumed in the diet and long-term weight loss maintenance. Obes Res. 2005;13:883–90.

Rodin J. Insulin levels, hunger, and food intake: an example of feedback loops in body weight regulation. Health Psychol. 1985;4:1–24.

Rolls ET, Rolls JH. Olfactory sensory-specific satiety in humans. Physiol Behav. 1997;61:461–73.

Siegel S. Conditioning of insulin-induced glycemia. J Comp Physiol Psychol. 1972;78:233–41.

Siegel S. Classical conditioning, drug tolerance and drug dependence. In: Israel Y, Smart FB, editors. Research advances in alcohol and drug problems, vol 7. New York: Plenum; 1983. p. 207–46.

Stice E, Bohon C, Fischer K. Subtyping women with bulimia nervosa along dietary and negative affect dimensions: further evidence of reliability and validity. J Consult Clin Psychol. 2008;76:1022–33.

Toro J, Cervera M, Feliu MH, Carriga N, Jou M, Martinez E, Toro E. Cue exposure in the treatment of resistant bulimia nervosa. Int J Eat Disord. 2003;34:227–34.

Wadden TA, Brownell KD, Foster GD. Obesity: responding to the global epidemic. J Consult Clin Psychol. 2002;70:510–25.

Wardle J. Conditioning processes and cue exposure in the modification of excessive eating. Addict Behav. 1990;15:387–93.

Weingarten H. Conditioned cues elicit feeding in sated rats: a role for learning in meal initiation. Science 1983;220:431–2.

Wing RR, Hill JO. Successful weight loss maintenance. Annu Rev Nutr. 2001;21:323–41.

Wing RR, Phelan S. Long-term weight loss maintenance. Am J Clin Nutr. 2005;82(suppl):222S–5S.

Woods SC. The eating paradox: how we tolerate food. Psychol Rev. 1991;4:488–505.

World Health Organisation (2009). http://www.who.int/topics/obesity/en/

Chapter 93
Frontal Behavioral Symptoms in Prader-Willi Syndrome

Kaeko Ogura, Toshikatsu Fujii, and Etsuro Mori

Abbreviations

PWS   Prader-Willi syndrome
OFC   Orbitofrontal cortex
MRI   Magnetic resonance imaging
PET   Positron emission tomography
FTD   Frontotemporal dementia

93.1 Introduction

Prader-Willi syndrome (PWS) is a neurodevelopmental disorder occurring in approximately one out of 15,000 live births and is the most well-known genetic cause of marked obesity. PWS is characterized by a distinctive behavioral phenotype, including food-related and food-unrelated behaviors. The first report of PWS, published in 1956 by pediatricians Prader, Labhart and Willi, described a syndrome characterized by obesity, short stature, lack of muscle tone during infancy, impaired sexual development, and mental retardation (Prader et al. 1956). Important contributions to the understanding of the clinical features of PWS were made over the following 20 years, and the physical characteristics (Hall and Smith 1972), clinical traits (Holm et al. 1993; Cassidy 1997), and behavioral patterns (Dykens et al. 1996; Dimitropoulos et al. 2001) were characterized better. Figure 93.1a and b show typical individuals with PWS. As for details of general clinical features and genetic background of PWS, please refer to other chapters relevant to PWS.

    In this chapter, we review behavioral features of PWS and discuss the symptoms of PWS in relation to the dysfunction of the frontal lobe, especially the orbitofrontal cortex (OFC) (Fig. 93.2).

K. Ogura (✉)
Department of Pediatrics, National Rehabilitation Center for Persons with Disabilities,
1, Namiki 4-chome, Tokorozawa, Saitama 359-8555, Japan
and
Department of Behavioural Neurology and Cognitive Neuroscience,
Tohoku University Graduate School of Medicine, Sendai, Japan
e-mail: ogura-kaeko@rehab.go.jp

An 1 year-and-9 months old girl with PWS.

Typical adults with PWS.
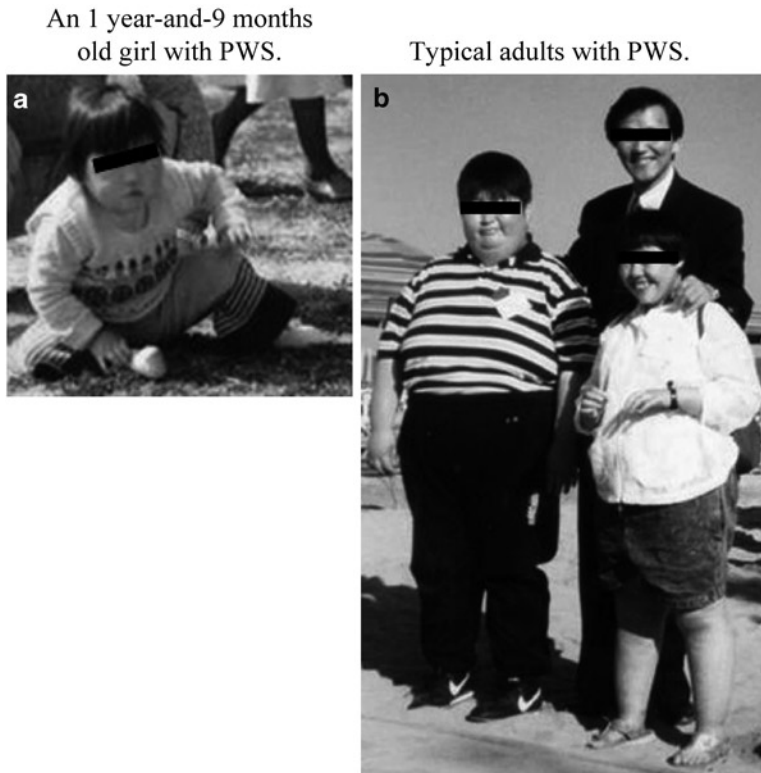
Fig. 93.1 Individuals with PWS. (**a**) An 1-year-and-9-month old girl with PWS. She cannot stand up yet, because she has muscular hypotonia for her age. (**b**) Typical adults with PWS. Two individuals standing in a front row are Japanese adults with PWS (a male pictured in the left and a female in the right) and a person in a rear rank is a healthy adult male. Two individuals with PWS have typical features: short stature, central obesity, low muscular volume, and typical facial feature with narrow bifrontal diameter, small appearing mouth with thin upper lip, and down turned corners of mouth. In addition, their hands and feet are small (Published with permission)

93.2 Eating Behavior in PWS

Abnormal eating behavior is the most striking feature of behavioral traits in PWS (Holm et al. 1993; Dimitropoulos et al. 2000). Persons with PWS show an intense preoccupation with food, hyperphagia, and incessant food seeking. Their fixation on foods sometimes strikes us as extraordinary. For instance, their families frequently report behavior such as food-stealing, scavenging, and eating raw or frozen food. The abnormal eating behavior is universal in children and adults with PWS, and the absence of it suggests an incorrect diagnosis (Holm et al. 1993; Dimitropoulos et al. 2000). The feature, however, is not present from birth. Individuals with PWS typically show failure to thrive in infancy, followed by the onset of obesity at the age of 18–36 months (Ehara et al. 1993). Infants with PWS are hypotonic, and have a poor suck, typically requiring tube feeding. During infancy they seem to have no interest in a feed. In early childhood, they develop an excessive interest in food and also in associated food seeking behavior, and they begin to gain weight excessively well above the 50th percentile for weight (Greenswag 1987). Hyperphagia and obesity are sustained into their adulthood. It is also shown that the abnormal body composition of those with PWS and their associated reduced energy-use contribute to their physical appearance and to the difficulty in preventing obesity they experience

Fig. 93.2 Schematic drawings of the brain. (**a**) The left cerebral hemisphere viewed from the lateral aspect and (**b**) The right cerebral hemisphere viewed from the medial aspect
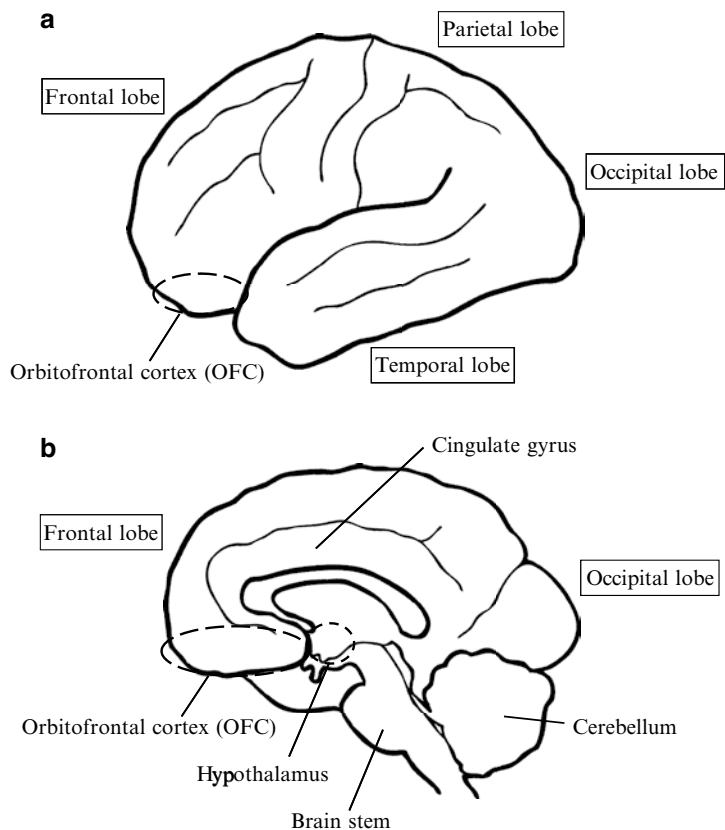
(Theodoro et al. 2006). Because the resulting obesity is highly likely to lead to serious health problems and untimely death, it is a major problem to be concerned about (Greenswag 1987).

It is generally stated that persons with PWS will continue to consume food as long as it is available and will search extensively for food when it is not available. In an experimental situation, individuals with PWS were shown to eat continuously, only a minority of them showing any reduction in their food intake over time (Zipf and Berntson 1987). Hyperphagia in PWS seems to be associated with an aberrant satiety response, particularly a delay in satiety (Holland et al. 1993). The food-related abnormal behavior have been attributed to a hormonal aberration caused by hypothalamic dysfunction, because those with PWS show other hypothalamic abnormalities, including growth-hormone deficiency, hypogonadism, and an inability to regulate their body temperature (Swaab 1997). Decreased numbers of oxytocin-secreting neurons were found in autopsy materials from individuals with PWS (Swaab et al. 1995).

In addition to hyperphagia, persons with PWS often show aberrant eating behaviors. Holm and Pipes (1976) reported that individuals with PWS have a propensity to consume products that are commonly considered as unappealing or unappetizing (e.g., dog food, garbage, sticks of butter, and decayed apples). Adults with PWS show a preference for sweet foods rather than salty, plain, or sour foods (Caldwell and Taylor 1983). Fieldstone et al. (1997) reported that individuals with PWS preferred high carbohydrate foods over high protein foods, and high protein foods over high fat foods. Anecdotal reports from parents and caregivers of persons with PWS suggest that those with PWS show a particular eating routine or ritualistic behavior during mealtime. These aberrant eating behaviors suggest that it is unlikely that eating behavior in PWS is simply attributable to the hypothalamic dysfunction.

93.3 Other Behavioral Features in PWS

Other behavioral characteristics in PWS are also distinctive, and they include temper tantrums, rigid thinking, uncontrollable impulse, aggressive behavior, lability of mood, and compulsive behavior (Holm et al. 1993; Dykens et al. 1996; Cassidy 1997; Dimitropoulos et al. 2001). Among them, the compulsive behavior has been of major interest to researchers investigating the PWS phenotype. The characteristic behaviors that are commonly seen in PWS include insistence on routines, repeating rituals, ordering and arranging objects, repetitive speech, and collecting behavior (Dykens et al. 1996). Repetitive behavior is common in early childhood among those with PWS. Children with PWS exhibit severer ritualistic behavior than typically developing children but not other children with developmental delays (Dimitropoulos et al. 2006). Older children and adults with PWS exhibit statistically significant elevations on the compulsivity subscale of the Yale-Broun Obsessive Compulsive Scale (Dykens et al. 1996). Dykens et al. (1996) found that individuals with PWS showed similar levels of symptom severity of compulsions when compared with those with obsessive-compulsive disorder who were matched for age and gender. They also found that the collecting behavior (see Table 93.1) was a salient symptom in PWS, and it was seen in more than half of the subjects. Recently, it is mentioned that compulsive manifestations is related to the severity of hyperphagia among individuals with PWS (Dimitropoulos et al. 2006).

93.3.1 Pathological and Neuroimaging Studies of the Brain in PWS

Despite the observation of serious neurobehavioral symptoms associated with PWS, little is known about the neurobiology and brain development of individuals with PWS. At present, there are only several case studies examining brain structures in individuals with PWS. Postmortem anatomical and histopathological studies have revealed enlarged lateral ventricles, cortical atrophy, abnormalities in cerebellar dentate nucleus, disorganization of neuronal cell layer, neuronal cellar loss, and neuronal heterotopia in the cerebral white matter and brain stem (Hattori et al. 1985; Hayashi et al. 1992; Stevenson et al. 2004). Structural magnetic resonance imaging (MRI) studies have also shown nonspecific morphological abnormalities including ventriculomegaly, cortical atrophy, asymmetry of the Sylvian fissures, a small brainstem, and an abnormal folding pattern of cerebral gyri (Leonard et al. 1993; Hashimoto et al. 1998; Yoshii et al. 2002; Titomanlio et al. 2006; Miller et al. 2007a).

Table 93.1 Key concepts of collecting behavior

- Collecting is the tendency to obtain and retain objects, and is commonly seen among both children and adults, in modern as well as primitive societies
- Abnormal collecting behavior is a symptom that involves acquiring things extensively, retaining objects even when they are of no immediate use, and resisting discarding the collected items even if they are excessive relative to the individual's circumstances or they are of little or no value
- The abnormal collecting behavior can appear as a manifestation of obsessive-compulsive disorder, autism, schizophrenia, anorexia, Tourette's syndrome and various types of dementia
- Little is known regarding its neurobiological mechanisms. It is deduced that the drive to collect would be initiated from subcortical and cortical mesolimbic structures involved in homeostatic regulation, and modulated by prefrontal and mesial temporal cortices
- Damage to prefrontal cortex has been associated with an inability to organize and carry out goal-directed behavior, decision-making, planning and anticipating future consequences, and this may contribute to the failure in normal discard behavior

This table lists the key concepts of abnormal collecting behavior and its neuronal substrates

Recently, some neuroimaging studies have reported that individuals with PWS had changes in regional activity in some brain regions. Shapira et al. (2005) reported a functional MRI study showing that, after glucose administration, three individuals with PWS showed delayed signal reduction in the hypothalamus, the OFC, and nucleus accumbens, with signal increase in the dorsolateral prefrontal cortex and insula. Other two functional MRI studies comparing individuals with PWS with healthy controls have also demonstrated increased activity in the medial prefrontal cortex, which involves the OFC in response to food stimuli (Holsen et al. 2006; Miller et al. 2007b). A positron emission tomography (PET) study showed that neural response to food intake in the OFC differed between a PWS group and a non-PWS group (Hinton et al. 2006). Kim et al. (2006) reported that cerebral glucose metabolism at rest differed in the OFC, middle and inferior frontal gyri, anterior cingulate gyrus, temporal pole, and uncus between PWS individuals and controls. Lucignani et al. (2004), using [^{11}C] flumazenil and PET, found possible functional changes of cerebral gamma-aminobutyric acid receptor in the insula, cingulate gyrus, and frontal and temporal neocortices in six adults with PWS. These findings suggest that there may be a specific relationship between neurobehavioral symptoms and functional abnormality in the OFC in persons with PWS.

93.3.2 Possible Relationship Between Behavioral Features in PWS and the Dysfunction of Orbitofrontal Regions

From a viewpoint of symptomatology, the behavioral features in PWS are strikingly similar to behavioral symptoms of patients with frontal pathologies affecting the OFC. For instance, patients with frontotemporal dementia (FTD), a progressive neurodegenerative disorder affecting the frontal and anterior temporal lobes, often show early alterations in behavior and personality (Neary et al. 1998). Behavioral symptoms in FTD include mental rigidity, impulsivity, mood changes, abnormal eating behavior, and compulsive behavior. The abnormal eating behavior and compulsive behavior are the factors that best distinguish FTD from other etiologies of dementia (Bozeat et al. 2000; Ikeda et al. 2002). Recent studies have highlighted the high prevalence of alterations in food preference (e.g., escalating desire for sweet food), appetite, and eating behaviors in FTD (Neary et al. 1998; Bozeat et al. 2000; Ikeda et al. 2002). A significant weight gain has been reported to occur in from 30% (Ikeda et al. 2002) to 70% (Bozeat et al. 2000) of patients with FTD. Stereotypic eating behaviors, such as wants to cook or eat exactly the same foods each day and tends to eat foods in the same order, were often observed in FTD (Ikeda et al. 2002). The compulsive behavior and collecting behavior are also often emerged in FTD. The compulsive behavior in FTD shows a spectrum of complexity, with simple motor mannerism and verbal repetitions at one end and complex behavioral routines and repetitive conversational themes at the other (Bozeat et al. 2000). For instance, Mendez et al. (1997) reported that patients with FTD showed repetitive checking, recurrent cleaning rituals, wearing clothes of specific colors only, compulsive self-injurious biting and hair-pulling, and collecting coupons entering multiple contests.

93.3.3 Frontal Behavioral Symptoms in PWS

We took particular note of behavioral similarities between PWS and FTD, which may be caused by shared neural dysfunction. To investigate how frequently individuals with PWS manifest frontal behavioral symptoms, we surveyed the prevalence of eating and noneating behavioral features in PWS by using assessment tools developed originally for patients with FTD and with frontal lobe

injury (Ogura et al. 2008). The questionnaire consisted of 35 questions related to three categories of behavior: eating behavior (with four domains: appetite, food preference, eating habits, and other oral behaivior), stereotyped behavior (with four domains: roaming, speaking, movements, and daily rhythm), and collecting behavior. It was administered in Japan to the parents of 250 individuals aged between 1–42 years with a clinical diagnosis of PWS. A parent was asked whether her/his child had the symptoms or not. If caregiver indicated that abnormal behavior was present, she/he was asked to rate its frequency and severity on a scale of one-to-three (where 1 is occasionally and 3 is frequently) and that of one-to-five (where 1 is slight and 5 is very marked), respectively. Then, a severity score was derived as the product of its frequency and severity. The results revealed that prevalence rates of all these behavioral categories were high for the individuals with PWS (Fig. 93.3 and Table 93.2). The overall prevalence rate was in good agreement with those in the previous reports for PWS (Caldwell and Taylor 1983; Holm et al. 1993; Dykens et al. 1996; Dimitropoulos et al. 2000), and it was comparable to those reported for FTD (Neary et al. 1998; Bozeat et al. 2000; Ikeda et al. 2002). Furthermore, the severity score of each domain in the eating behavior was significantly correlated with those in the stereotypy and the collecting behavior (Fig. 93.4).

The findings mentioned above suggest that the behavioral features in PWS are associated with a dysfunction of the frontal lobe, especially that of the OFC. The OFC is thought to play a crucial role
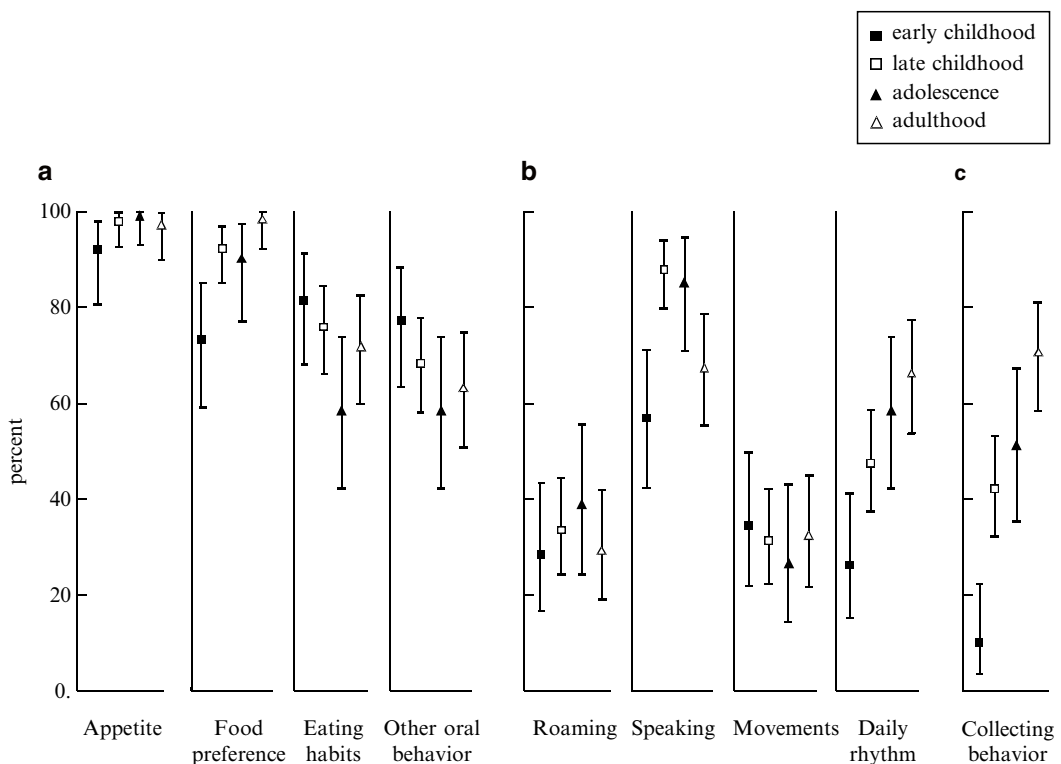
Fig. 93.3 The prevalence of symptom domains in each age group. The participating individuals were divided into four groups based on age: early childhood (aged 0–5 years), late childhood (aged 6–11 years), adolescence (aged 12–17 years), and adulthood (aged over 18 years). The overall prevalence of abnormal behaviors and the prevalence rates of each domain and of each item among the age bands were analyzed using the Chi-square test. (**a**) The prevalence of abnormal eating behaviors was extremely high in all age bands. (**b**) Stereotyped behaviors were also common, particularly stereotyped speaking and daily rhythm stereotypy. (**c**) The greatest group differences in prevalence were noted for collecting behaviors. Symbols indicate the prevalence and bars indicate 95% confidence intervals (Ogura et al. 2008: 472, Elsevier)

Table 93.2 Prevalence rates of items in the eating behavior

	Prevalence rate (95% confidence intervals) (%)				
	Early childhood	Late childhood	Adolescence	Adulthood	*p* value
	<6 years	6–11 years	12–17 years	>17 years	
Appetite					
Loss of appetite	2 (0–11)	5 (2–14)	7(2–20)	3 (0–10)	NS
Increase in appetite	53 (38–67)	60 (49–70)	71 (54–84)	72 (60–82)	NS
Seeks out food between meals	49 (34–64)	66 (56–76)	71 (54–84)	87 (76–94)	<0.001
Overeat at meal times	53 (38–67)	74 (64–83)	78 (62–89)	84 (73–92)	0.002
Reports hunger	71 (57–83)	83 (73–90)	80 (65–91)	87 (76–94)	NS
Reports being overfull	53 (38–67)	55 (45–66)	32 (18–48)	41 (29–54)	0.004
Food preference					
Prefers sweet foods or drinks more than before	67 (52–80)	91 (84–96)	90 (77–97)	97 (90–100)	<0.001
Drinks more tea/coffee	22 (12–37)	39 (29–50)	61 (45–76)	62 (49–73)	<0.001
Adds more seasoning to their food (e.g., adds more salt)	8 (2–20)	18 (11–28)	27 (14–43)	29 (19–42)	0.03
Hoards food	10 (3–22)	17 (10–27)	22 (11–38)	29 (19–42)	NS
Eating habits					
Wants to eat the same dishes or foods each days	31 (18–45)	30 (21–41)	34 (20–51)	35 (24–48)	NS
Buys exactly the same food each days	14 (6–27)	24 (16–34)	37 (22–53)	43 (31–55)	0.004
Wants to use the same sauce, the same seasoning or the same spice	6 (1–17)	13 (7–22)	17 (7–32)	46 (33–58)	<0.001
Eats with hands	61 (46–75)	37 (27–48)	14 (6–29)	19 (11–30)	<0.001
Takes a long time to eat	61 (46–75)	43 (33–54)	14 (6–29)	28 (18–40)	<0.001
Other oral behavior					
Tends to overfill mouth	59 (44–73)	49 (38–60)	37 (22–53)	49 (36–61)	NS
Chews or sucks on things (e.g., pens) without trying to eat them	18 (9–32)	28 (19–39)	22 (11–33)	15 (7–25)	NS
Eats non-edible foodstuffs or things not normally eaten	14 (6–27)	26 (17–36)	34 (20–51)	21 (12–32)	NS
Tends to snatch or grasp any food items within reach	43 (29–58)	26 (17–36)	15 (14–43)	19 (9–29)	0.003

The prevalence of each item related to abnormal eating behavior was analyzed. Because the domain of appetite included items for both increase of appetite and loss of appetite, we analyzed these items separately. The frequency of increased appetite was more than 50% in all age groups, whereas loss of appetite was less common (Ogura et al. 2008: 472, Elsevier)

NS not significant

in several neural networks, one of which is related to the integration of food-related sensory, visceral, and reinforcing information (Rolls 2005). Patients with damage to the OFC showed changes in eating habits and escalating desires for sweet food (Uher and Treasure 2005). Studies of patients with FTD have demonstrated that overeating and sweet-tooth were associated with atrophy involving the OFC region (Woolley et al. 2007). As noted earlier, recent neuroimaging studies have demonstrated that PWS subjects had a dysfunction of the satiety system in prefrontal areas, especially in the OFC (Shapira et al. 2005; Hinton et al. 2006; Holsen et al. 2006; Miller et al. 2007b). Visceral and other satiety-related signals reach the OFC and modulate the representation of food, resulting in an output that reflects the appetitive value of food. Food is a natural reinforcer, with reward value implicated in the risk for addiction (Volkow and Fowler 2000). Obesity in PWS, like drug addiction, seems to result from foraging for food and ingestion habits that are maintained and reinforced, despite the potentially serious health consequences. Furthermore, food intake in humans is not only regulated by

a

early childhood
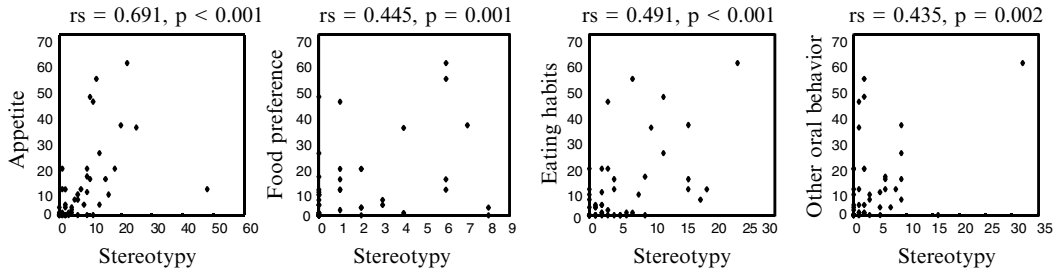
late childhood
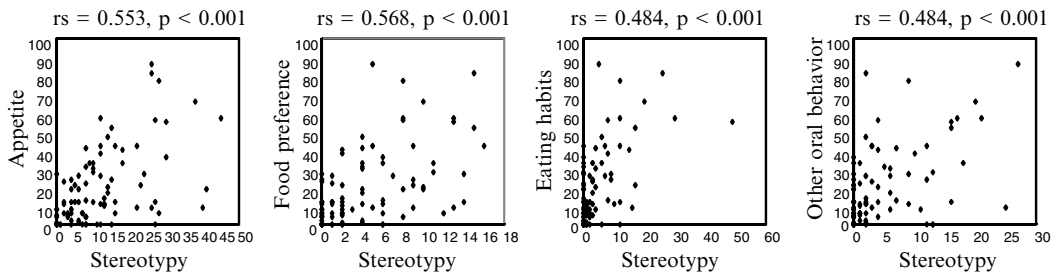
adolescence
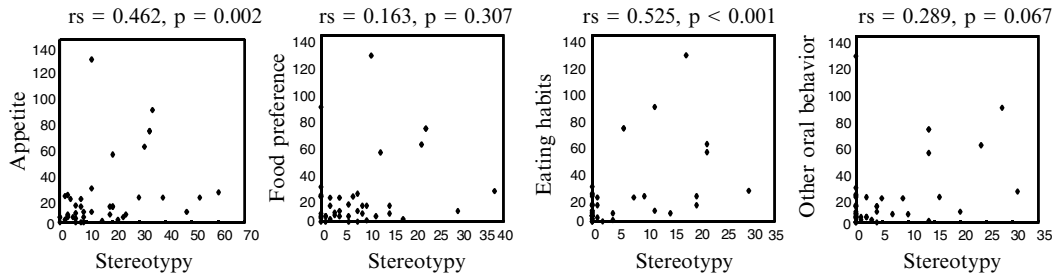
adulthood
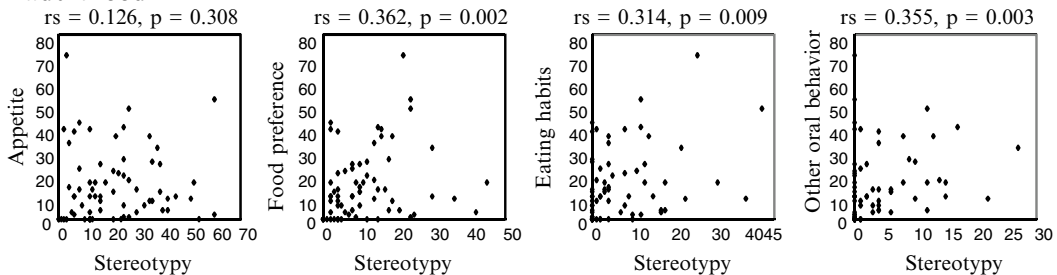
Fig. 93.4 (**a**) Correlations of stereotypy (severity score) with abnormal eating behaviors (severity score) for each age band and (**b**) correlations of collecting behavior (severity score) with abnormal eating behaviors (severity score) for each age band. Spearman's rs was used to test correlations between the domain scores included in abnormal eating behavior and the total score of the stereotypy or collecting behavior. The severity scores for all domains included in the abnormal eating behavior were significantly correlated with those for stereotyped behavior and collecting behavior (rs = 0.30–0.45, *p* < 0.001) when all the age bands were analyzed together. For each age band, although there were some exceptions, the severity scores for most of the abnormal eating behavior were significantly correlated with those for stereotypy and collecting behavior

b

early childhood

rs = 0.302, p = 0.035 | rs = 0.357, p = 0.012 | rs = 0.571, p < 0.001 | rs = 0.292, p = 0.042

late childhood

rs = 0.265, p = 0.011 | rs = 0.334, p = 0.001 | rs = 0.308, p = 0.003 | rs = 0.470, p < 0.001

adolescence

rs = 0.374, p = 0.016 | rs = −0.022, p = 0.890 | rs = 0.407, p = 0.008 | rs = 0.263, p = 0.096

adulthood

rs = 0.015, p = 0.904 | rs = 0.254, p = 0.036 | rs = 0.387, p = 0.001 | rs = 0.174, p = 0.155
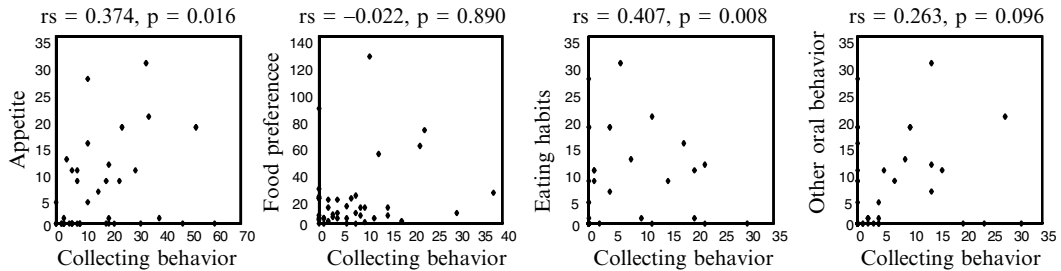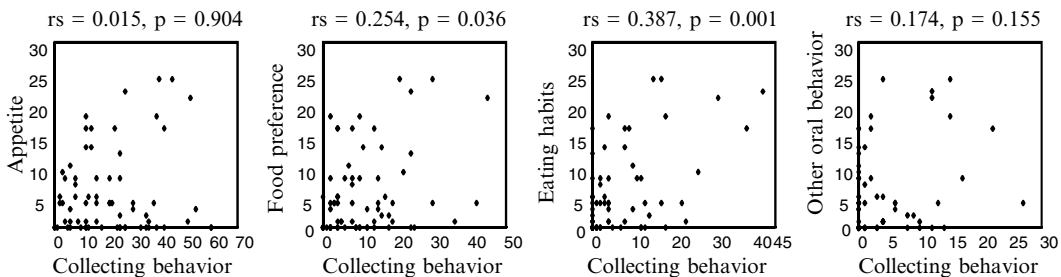
Fig. 93.4 (continued)

homeostatic processes, but also relies on interactions between homeostatic regulation and hedonic experience (Pecina et al. 2003). Thus, dysfunctioning of the OFC could lead individuals with PWS to both overeating and a propensity for detrimental food preferences such as overindulgence on sweet foods (Caldwell and Taylor 1983; Ogura et al. 2008).

In addition, a dysfunction of the OFC is likely to be involved in both compulsions and collecting behavior. One study showed that a patient with an infarction restricted to the OFC showed obsessive-compulsive symptoms such as ritualistic repetitive behavior (Kim and Lee 2002). Another study showed that patients with damage to ventromedial frontal regions including the OFC showed pathological collecting behavior, i.e., excessive extent of collecting, collection of useless items, and interference with normal daily functioning (Anderson et al. 2005). Hahm et al. (2001) reported on a patient who developed pathologic collecting behavior after a left OFC and caudate injury. It has become evident that collecting symptoms in the broader population are part of a discrete clinical syndrome that involves symptoms reminiscent of those associated with prefrontal damage, including difficulties in decision-making and organization (Saxena et al. 2004). As an alternative view, Kringelbach and Rolls (2004) argued that the lateral OFC is associated with the monitoring of punishment value, which may lead to an adjustment of current behavior. It is likely that maladaptive behaviors in PWS result from an impairment in making use of feedback to guide an appropriate behavior, which require controlling their impulse and monitoring outcomes to guide future decisions.

93.4 Applications to Other Areas of Diet and Behavior

The OFC is thought to be a part of the serotonergic system in the brain (Fig. 93.5). Serotonin, an important neurochemical messenger, plays an important role in impulse control and influences eating. Abnormalities in this system have been reported in individuals with PWS (Dimitropoulos et al. 2000) and FTD (Huey et al. 2006). Furthermore, psychopharmacological agents that act on the serotonergic system have been shown to reduce repetitive behavior in both disorders (Benjamin and Buot-Smith 1993; Moretti et al. 2003). Therefore, both the anatomical and neurochemical abnormalities associated with PWS could contribute to these behavioral features. The elucidation of the pathophysiological basis of the behavioral phenotype including food-related and food-unrelated behaviors in PWS would provide a clue to the treatment of the behavioral symptoms, as well as throw light on the mechanisms underlying the similar abnormal behavior involved in pathological overeating and obesity. Neuroimaging studies would also clarify the neural basis for behavioral traits in persons with PWS, and might allow us to understand the link between the neuroanatomical abnormalities and the genetic mechanism involved.

Fig. 93.5 Serotonergic system. The serotonergic system projects widely in the brain and influences multiple functions. This system is important for the control of emotion and behavior, and it modulates pain sensation as well as motor and autonomic functions

Raphe nuclei
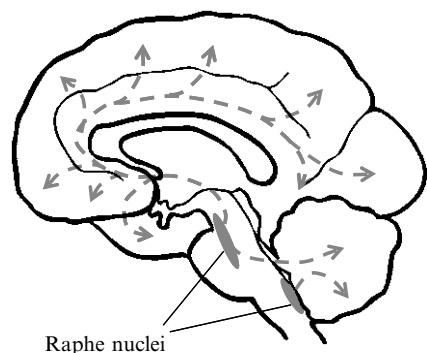
Summary Points

- PWS is generally regarded as a genetic model of obesity, and is characterized by a distinctive behavioral phenotype, including food-related and food-unrelated behaviors.
- The behavioral features in PWS are strikingly similar to behavioral symptoms of patients with frontal pathologies affecting the OFC.
- Our nation-wide survey along with those of some previous studies suggested that behavioral features in PWS are likely to be associated with the dysfunction of the OFC and its related areas.
- Recent neuroimaging studies showed that individuals with PWS had changes in regional activities in the OFC, although past studies focused on hypothalamic dysfunction.
- The elucidation of the pathophysiological basis of the behavioral symptoms of PWS would throw light on the mechanisms underlying the similar abnormal behaviors involved in pathological overeating and obesity.

Keywords and Their Explanations

Prader-Willi syndrome (PWS): Prader-Willi syndrome is a genetically determined neurodevelopmental disorder and is generally regarded as a genetic model of obesity. The syndrome is characterized by defects in cognitive and motor development, short stature, hypogonadism, hyperphagia with progressive obesity, and behavioral problems.

Hyperphagia: Hyperphagia is excessive eating behavior, also known as gluttony.

Compulsive behavior: This is abnormal comportment that a person does compulsively, not because she/he wants to behave that way, but irrespective of her/his will. The behavior shows a spectrum of complexity, with simple motor mannerisms and verbal repetitions at one end and complex behavioral routines and repetitive conversational themes at the other.

Abnormal collecting behavior: Abnormal collecting behavior is a symptom that involves acquiring things extensively, retaining objects even when they are of no immediate use, and resisting discarding the collected items. The behavior can appear as a manifestation of compulsive behavior.

Orbitofrontal cortex (OFC): The orbitofrontal cortex is a region of association cortex located within the frontal lobes, resting above the orbits of the eyes. The OFC is thought to have a role in adjusting behavior based on the social values of the outcomes of previous behavior.

Frontotemporal dementia (FTD): Frontotemporal dementia is a progressive neurodegenerative disorder affecting the frontal and anterior temporal lobes. Patients with FTD show a wide range of behavioral abnormalities, including mental rigidity, impulsivity, mood changes, and compulsive behaivior, and they share many behavioral and cognitive features with PWS individuals.

References

Anderson SW, Damasio H, Damasio AR. Brain 2005;128: 201–212
Benjamin E, Buot-Smith T. J Am Acad Child Adolesc Psychiatry. 1993;32:870–3.
Bozeat S, Gregory CA, Ralph MA, Hodges JR. J Neurol Neurosurg Psychiatry. 2000;69:178–86.

Caldwell ML, Taylor RL. J Ment Defic Res. 1983;27:45–9.

Cassidy SB. J Med Genet. 1997;34:917–23.

Dimitropoulos A, Feurer ID, Roof E, Stone W, Butler MG, Sutcliffe J, Thompson T. Ment Retard Dev Disabil Res Rev. 2000;6:125–30.

Dimitropoulos A, Feurer ID, Butler MG, Thompson T. Am J Ment Retard. 2001;06:39–51.

Dimitropoulos A, Blackford J, Walden T, Thompson T. Res Dev Disabil. 2006;27:90–202.

Dykens EM, Leckman JF, Cassidy SB. J Child Psychol Psychiatry. 1996;37:995–1002.

Ehara H, Ohno K, Takeshita K K. J Intellect Disabil Res. 1993;37:479–85.

Fieldstone A, Zipf WB, Schwartz HC, Berntson GG. Int J Obes Relat Metab Disord 1997;21:1046–52.

Greenswag LR. Dev Med Child Neurol. 1987;29:145–52.

Hahm DS, Kang Y, Cheong SS, Na DL. Neurology 2001;56:398–400.

Hall BD, Smith DW. J Pediatr. 1972;81:286–93.

Hashimoto T, Mori K, Yoneda Y, Yamaue T, Miyazaki M, Harada M, Miyoshi H, Kuroda Y. Pediatr Neurol. 1998;18:30–5.

Hattori S, Mochio S, Kageyama A, Nakajima T, Akima M, Fukunaga N. 1985; 37:1059–66.

Hayashi M, Itoh M, Kabasawa Y, Hayashi H, Satoh J, Morimatsu Y. Brain Dev. 1992;14:58–62.

Hinton EC, Holland AJ, Gellatly MS, Soni S, Patterson M, Ghatei MA, Owen AM. Int J Obes. 2006;30:313–21.

Holland AJ, Treasure J, Coskeran P, Dallow J, Milton N, Hillhouse E. Int J Obes Relat Metab Disord. 1993;17: 527–32.

Holm VA, Pipes PL. Am J Dis Child. 1976;130:1063–7.

Holm VA, Cassidy SB, Butler MG, Hanchett JM, Greenswag LR, Whitman BY, Greenberg F. Pediatrics 1993;91:398–402.

Holsen LM, Zarcone JR, Brooks WM, Butler MG, Thompson TI, Ahluwalia JS, Nollen NL, Savage CR. Obesity 2006;14:1028–37.

Huey ED, Putnam KT, Grafman J. Neurology 2006;66:17–22.

Ikeda M, Brown J, Holland AJ, Fukuhara R, Hodges JR. J Neurol Neurosurg Psychiatry. 2002;73:371–6.

Kim KW, Lee DY. J Neuropsychiatry Clin Neurosci. 2002;14:88–9.

Kim SE, Jin DK, Cho SS, Kim JH, Hong SD, Paik KH, Oh YJ, Kim AH, Kwon EK, Choe YH. J Nucl Med. 2006;47:1088–92.

Kringelbach ML, Rolls ET. Prog Neurobiol. 2004;72:341–72.

Leonard CM, Williams CA, Nicholls RD, Agee OF, Voeller KK, Honeyman JC, Staab EV. Am J Med Genet. 1993;46:26–33.

Lucignani G, Panzacchi A, Bosio L, Moresco RM, Ravasi L, Coppa I, Chiumello G, Frey K, Koeppe R, Fazio F. Neuroimage 2004;22:22–8.

Mendez MF, Perryman KM, Miller BL, Swartz JR, Cummings JL. J Geriatr Psychiatry Neurol. 1997;10:154–7.

Miller JL, Couch JA, Schmalfuss I, He G, Liu Y, Driscoll DJ. Am J Med Genet A. 2007a;143:476–83.

Miller JL, James GA, Goldstone AP, Couch JA, He G, Driscoll DJ, Liu Y. J Neurol Neurosurg Psychiatry. 2007b;78:615–9.

Moretti R, Torre P, Antonello RM, Cazzato G, Bava A. Eur Neurol. 2003;49:13–9.

Neary D, Snowden JS, Gustafson L, Passant U, Stuss D, Black S, Freedman M, Kertesz A, Robert PH, Albert M, Boone K, Miller BL, Cummings J, Benson DF. Neurology 1998;51:1546–54.

Ogura K, Shinohara M, Ohno K, Mori E. Brain Dev. 2008;30:469–76.

Pecina S, Cagniard B, Berridge KC, Aldridge JW, Zhuang X. J Neurosci. 2003;23:9395–402.

Prader A, Labhart A, Willi H. Schweiz Med Wochenschr. 1956;86:1260–61.

Rolls ET. Physiol Behav. 2005;85:45–56.

Saxena S, Brody AL, Maidment KM, Smith EC, Zohrabi N, Katz E, Baker SK, Baxter LR Jr. Am J Psychiatry. 2004;161:1038–48.

Shapira NA, Lessig MC, He AG, James GA, Driscoll DJ, Liu Y. J Neurol Neurosurg Psychiatry. 2005;76:260–2.

Stevenson DA, Anaya TM, Clayton-Smith J, Hall BD, Van Allen MI, Zori RT, Zackai EH, Frank G, Clericuzio CL. Am J Med Genet A. 2004;124:158–164.

Swaab DF. Acta Paediatr Suppl. 1997;423:50–4.

Swaab DF, Purba JS, Hofman MA. J Clin Endocrinol Metab. 1995;80:573–9.

Theodoro MF, Talebizadeh Z, Butler MG. Obesity 2006;14:1685–90.

Titomanlio L, De Brasi D, Romano A, Genesio R, Diano AA, Del Giudice E. Acta Paediatr. 2006;95:861–3.

Uher R, Treasure J. J Neurol Neurosurg Psychiatry. 2005;76:852–7.

Volkow ND, Fowler JS. Cereb Cortex. 2000;10:318–25.

Woolley JD, Gorno-Tempini ML, Seeley WW, Rankin K, Lee SS, Matthews BR, Miller BL. Neurology 2007;69:1424–33.

Yoshii A, Krishnamoorthy KS, Grant PE. Neurology 2002;59:644–5.

Zipf WB, Berntson GG. Am J Clin Nutr. 1987;46:277–81.

Chapter 94
Culture to Culture: Fat-Phobia and Somatization

Samir Al-Adawi, Sanjay Jaju, Ibrahim Al-Zakwani, and Atsu S.S. Dorvlo

Abbreviations

EAT-26 Eating Attitude Test-26
EDI   Eating Disorder Inventory
DSM   Diagnostic and Statistical Manual of Mental Disorders
ICD   International Classification of Disease
BSI   Bradford Somatic Inventory
BMI   Body mass index

94.1 Introduction

With the shift from infectious disease to nutritional and chronic lifestyle disorders in countries whose economies and cultures are in transition (Nasser et al. 2001), it has yet to be established whether disordered eating is triggered by recent affluence and changing lifestyles bringing newly acquired attitudes towards food consumption, or whether it is an inherent part of globalization and the maladjustment that the process may create (Lee 1996; Fedoroff and McFarlane 1998; Jackson et al. 2003), or whether it has an exclusive cultural component in spite of globalization. Studies show that younger women in non-Western societies in transition toward modern affluence may be embracing the body image dissatisfaction of Euro-Americans (Ford et al. 1990; Soomoro et al. 1995). Although the cultural dimension has occasionally been considered in the available literature (Littlewood 1995), one salient gap in the literature is sociocultural studies exploring whether there are inherent cultural features that may contribute to the idiom of distress central to the presentation of disordered eating outside the realm of Euro-American populations.

The first wave of research on this topic explored the presence of disordered eating in various populations. These studies shed light on whether rates of disordered eating in non-Western cultures are similar to Western populations. Emerging epidemiological studies suggest that rates of disordered eating in non-Western societies fluctuate in a complex and multifaceted way (Nasser 2006), but that there is indication that the rates are rapidly outpacing those reported in Western Europe and

S. Al-Adawi (✉)
Department of Behavioral Medicine, College of Medicine and Health Sciences, Sultan Qaboos University, Al-Khoudh 123, Muscat, Sultanate of Oman
adawi@squ.edu.om; samir1964@gmail.com; jimbo@omantel.net.om

North America (Wassenaar et al. 2000; Bhugra et al. 2000). Makino et al. (2004) synthesized the available literature in order to compare the rates of eating disorders in non-Western countries with those in 11 Western countries. These authors report that gender is significant for both Western and non-Western countries, with women aged 15–24 years appearing to be at increased risk of developing eating disorders. The study concludes that the rate of eating disorder in non-Western countries, though generally lower compared to Euro-American populations, is however rising at a significantly faster rate. Prevalence rates in Euro-American populations ranged from 0.1% to 5.7%, whereas they range between 0.46% and 3.2% in non-Western countries (Makino et al. 2004). This data indicates the need to open another research dimension, that is, whether dieting and disordered eating are culture-bound or culture-reactive phenomena. Further, it is unclear whether the literature takes into account the impact on the younger generations of aggressive media campaign in the form of TV, glossy magazines, and the Internet, which transcend geographic boundaries and influence the younger generations with respect to societal perception and expectations of what constitutes beauty and which type of body image is appreciated. The influence of movie stars and thin models cannot be underestimated. Similarly, it is difficult to disentangle whether dieting is in fact the conscious choice of young females who want to achieve, at any cost, those specific body characteristics that they hope will earn them appreciation and translate into riches if they get into a glamor business such as modeling. The presence of a great number of slimming centers in these neo-affluent societies, along with over-the-counter herbal preparations for slimming, and the acceptance of smoking by females to maintain weight also needs to be investigated. This consideration of conscious choice should help to decipher whether dieting and disordered eating are really a culture-bound phenomenon in the context of the last decade or two.

The second wave of research attempts to highlight the factors that influence the emerging trend of eating disorders in non-Western populations. The data are obtained mainly from comparative studies of non-European migrants and their children living in the West (Table 94.1). They have led to the view that cultural exposure may cause immigrants from cultures where thinness is not highly valued to adopt Western positive valuations of thinness, resulting in pathological preoccupation with body image and weight-loss behavior (Ford et al. 1990; Gunewardene et al. 2001). In other words, exposure to the Western ideal of beauty, the phenomenon of medicalization, and the stigmatization of the overweight have denigrated traditional features of body preference. Many traditional conceptions of female beauty tilt toward a voluptuous female form.

In some parts of the world, prior to marriage, adolescents are force-fed to achieve a highly favored plumpish figure (Al-Adawi et al. 2006). While modernity may have partly denigrated traditional features of body preference, the picture is not entirely clear. This is clearly shown in the phenomenon of *gavage* for girls before marriage. G*avage* means force-feeding and is an ancient practice that has largely disappeared in some parts of Oman, or, if it still exists, remains a furtive activity. The practice involves a nubile who is coerced into consuming a large amount of food or liquid deemed essential to increase one's weight (Resnikoff 1980; Gerteiny 1967). A voluptuous figure or, in modern parlance, obesity is equated with beauty, health, and wealth in such a cultural setting. This practice is deemed to constitute abuse, but the phenomena challenges the Western perception of beauty and health being characterized with thinness. This suggests that how obesity is conceived is dependent upon the sociocultural context.

Some studies have concluded that susceptibility toward disordered eating is related more to a traditional rather than a Westernized cultural orientation, possibly due to the stress of cultural adjustment, rather than to the influence of Western cultural values of femininity and beauty (Mumford et al. 1991a; Koneru et al. 2007; Reddy and Crowther 2007). Although many studies have explored disordered eating in cross-cultural populations (Cummins et al. 2005), most have generally employed a Western cultural microscope to glean the phenomenology of disordered eating among people of

Table 94.1 Demographic characteristics and variable relevant for eating disorder among Western and non-Western teenagers (Al-Adawi et al., in preparation)

Characteristic	All (*N* = 596)	European (*n* = 97)	Omani (*n* = 186)	Indian (*n* = 123)	Filipino (*n* = 190)
Age, years					
Mean (±SD)	15.1 ± 1.02	14.9 ± 0.78	15.3 ± 0.71	15.4 ± 1.03	14.8 ± 1.25
Median, (IQR)	15 (14 − 16)	15 (14 − 15)	15 (15 − 16)*	15 (15 − 16)*	14 (14 − 16)
BMI Class, n (%)					
Underweight (<18.5)	230 (39%)	53 (55%)	35 (19%)*	44 (36%)*	98 (52%)
Normal weight (18.5–25)	337 (57%)	44 (45%)	139 (75%)*	71 (58%)	83 (44%)
Overweight (25–30)	21 (4%)	0	7 (4%)*	5 (4%)#	9 (5%)*
Obese (> = 30)	8 (1%)	0	5 (3%)*	3 (2%)#	0#
Father education, n (%)					
High school or less	105 (18%)	0	54 (29%)*	9 (7%)*	42 (22%)#
College	232 (39%)	9 (9%)	72 (39%)*	67 (54%)*	84 (44%)*
Graduate school	259 (43%)	88 (91%)	60 (32%)*	47 (38%)*	64 (34%)*
Mother education, n (%)					
High school or less	210 (35%)	19 (20%)	59 (32%)*	71 (58%)*	61 (32%)*
College	255 (43%)	57 (59%)	86 (46%)*	32 (26%)*	80 (42%)*
Graduate school	131 (22%)	21 (22%)	41 (22%)	20 (16%)	49 (26%)
Daily regular breakfast, n (%)	344 (58%)	51 (53%)	85 (46%)	56 (46%)	152 (80%)*
Daily regular lunch, n (%)	475 (80%)	62 (64%)	141 (76%)*	113 (92%)*	159 (84%)*
Daily regular dinner, n (%)	459 (77%)	59 (61%)	111 (60%)	113 (92%)*	176 (93%)*
Daily between meal snacks, n (%)	259 (43%)	35 (36%)	48 (26%)	44 (36%)	132 (69%)*
Sought advice on eating/ dieting, n (%)	75 (13%)	7 (7%)	12 (6%)	9 (7%)	47 (25%)*
Slimming club member, n (%)	38 (6%)	10 (10%)	13 (7%)	8 (7%)	7 (4%)*
History of eating disorder, n (%)	77 (13%)	6 (6%)	22 (12%)	18 (15%)	31 (16%)*

Percents are column percentages; Statistical analyses were conducted using *Kruskal-Wallis test* and *univariate logistic regression* whenever appropriate

SD Standard deviation, *IQR* Interquartile range, *BMI* Body mass index

*Statistical significant result (p < 0.05) against the European control group

#Analyses not performed due to perfect prediction

diverse ethnic backgrounds whose conception of beauty and health may not parallel those in the Western world (Nasser et al. 2001; Casper 1998). Kleinman (1986) cautions that a view of human nature developed for one cultural group should not be uncritically applied to members of another group, for whom its validity has not been established. For both theoretical and clinical relevance, studies are needed to examine the interplay of culture and disordered eating. By exploring specific eating disorder symptoms, it would then be possible to determine whether ethnic and cultural variations in disordered eating are related to currently available algorithms for quantifying the presence of eating disorders.

In the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV) (American Psychiatric Association 1994) and International Classification of Disease (ICD) (World Health Organization 1993), disordered eating is characterized by significant weight loss, amenorrhea, distorted body image, and a relentless pursuit of thinness. Despite its centrality to the biomedical model, there are conflicting results on whether the relentless pursuit of thinness is a common occurrence among teenagers with a subclinical or clinical syndrome of disordered eating. In Western populations, manifestations of laparophobia have been shown to vary among various ethnic groups (Altabe 1998; Contento et al. 2003), with a notably low incidence among African-Americans in

some studies, but not in others (Duncan and Robinson 2004). In some of these studies, the rate varies from 15% to 20% in certain ethnic groups (Ramacciotti et al. 2002). Studies carried out in several Asian populations also reveal contradictory results. For example, a lack of laparophobia is shown to characterize the majority of patients with dieting disorders among a number of Chinese populations; however, this is not consistently confirmed in other Chinese populations (Ngai et al. 2000). In studies carried out among Arab populations, the trend indicates increasing presence of disordered eating, but without the presence of the explanatory construct pertinent to laparophobia (Kayano et al. 2008; Al-Adawi et al. 2004, 2002a). Such patterns are also observed in other cross-cultural populations (Khandelwal et al. 1995). It is possible that the concept of body image, as reported in Western populations, may not be applicable to some cross-cultural populations. Alternatively, there may be culture-specific manifestations of eating disorders that may not parallel those observed in Western adolescent populations. This issue has received scant treatment in the literature.

Despite the orthogonal manifestation to fat aversion found in Western teenagers, laparophobia is still not associated with a marked reduction in BMI and all the health consequences this may entail (Rieger et al. 2001). Within the context of conflicting findings on the prototypical conception of fear of fatness or laparophobia, more studies are needed. Comparative studies are needed to examine whether the lower incidence of a drive towards thinness, as one of the indices of nonlaparophobia in eating disorders, is not as common in non-Western populations, as has been alluded to in some studies (Ngai et al. 2000; Kayano et al. 2008). As distress is experienced in a sociocultural context, there is a strong rationale for undertaking such studies in order to shed light on pluralism within globalization. If cultural teaching does not encourage distress in the form of laparophobia, the question arises whether other idioms of distress are sanctioned. In various ethnic groups, numerous studies have suggested that some individuals tend to use somatopsychic idioms of distress rather than verbalize their distress in a psychological manner as is often reported in some populations in Western Europe and North America (Kleinman 1987). In some cross-cultural settings, women often come to health care settings for treatment of physical discomfort that has no apparent organic cause. There is empirical support, although not widely accepted, that in Western cultures there is a tendency to psychologize distress, which can be contrasted with the tendency in non-Western cultures to somatize it. Although the possibility remains that the somatizer may be suffering from, albeit hitherto unrecognized, unidentifiable physical illnesses, there are common denominators among somatizers to suggest that this may be a culturally specific idiom of distress. Al Lawati et al. (2000) report that somatizers tend to perceive themselves as sick despite repeated assurance to the contrary. As a clinical entity, somatization remains a chronic, disabling syndrome that, while presenting a physical facade, is associated with significant psychopathology that appears akin to affective and anxiety disorders. It is usually assumed that somatization occurs in response to psychological stresses on a background of predisposing personality factors, but by adopting the sick role, psychological equilibrium is achieved. Clinical and epidemiological surveys over the past decades suggest that acute forms of somatoform disorders are invariably present in all primary care settings (Ohaeri and Odejide 1994; Mumford et al. 1997). Naturalistic observations of somatization disorders reveal that the condition begins in adolescence. The disorder is inversely related to social position, occurs most often in communities with little urbanization and literacy, and affects more women than men. Ohaeri and Odejide (1994) and Mumford et al. (1997) find that the incidence of somatization ranges from 20% to 80% in various cultures among developing countries. Since the geography of somatization is in non-Western cultural groups, it has been speculated that physical symptoms are often seen as a more legitimate and morally acceptable manifestation of distress since the expression of negative feelings, and conflict of any kind, are generally seen as not acceptable (Eloul et al. 2009). Afflictive emotional states are not articulated due to cultural teaching that the expression of emotion is not only shameful

(Dwairy 2006) but also is perceived to be disruptive to group cohesion that is essential in group-oriented cultural setting. This has resulted in primarily somatic presenting complaints (Eloul et al. 2009). Such an idiom of distress has not received due attention in the literature on eating disorders. In order to fill this gap in the literature, studies are needed to examine whether there are ethnic variations in idiom of distress that may have relevance to eating disorders. Since the Western view of human nature is based on the concept of individualism, this begs the question: how could cross-cultural populations with a strong sense of collective identity develop disordered eating?

94.2 The Study in Oman

Due to their negative impact on health, the deliberate food restriction, and body image dissatisfaction, manifesting as anorexia nervosa, bulimia nervosa and their variant spectrum disorders, are now being recognized in many parts of the world (Nasser et al. 2001; Lee and Lee 2000), including Oman (Al-Adawi et al. 2002b). Oman is an Arab/Islamic country with distinct sub-cultural diversities. Its diverse society has experienced minimum acculturation until 2 decades ago. Oman is also characterized with a heterogenic mixture of various ethnicities because of the presence of a highly educated workforce and also a large number of contract laborers from many diverse foreign countries. Recent globalization and Westernization has endowed the country with economic development, technological, and educational advances and access to media similar to that seen in Western countries, and therefore this region provides fertile ground on which to examine the interplay between acculturation and social distress.

With emerging globalization, health care providers will encounter more clients with a wide range of cultural, social, regional, educational, and ethnic backgrounds. In this new medical environment, the viability of health care delivery will depend upon the medical community's ability to evolve and adjust to ethnic and cultural variations. Only through an awareness and appreciation of a patient's unique background can the modern health care provider delivering allopathic services decide on the best method to enhance health and the quality of life.

94.2.1 Culture to Culture: Deliberate Food Restriction

It has been suggested that, in the light of increasing Westernization/globalization, eating disorders in the non-Western world are taking on a Western pattern, in line with the suggestion that significant obsession with disordered eating such as in anorexia nervosa, bulimia nervosa and their variant spectra is a pathoplastic effect of globalization (Lai 2000; Barr and Garner 2001) due to the cult of thinness reinforced by the media (Abou-Saleh et al. 1998; Morant 2000) or obesogenic behaviors that is characterized by sedentary life but also complemented with a dietary habit that is rich in fat and calories (Mellor et al. 2009). Although acculturation may play a pivotal role in reinforcing the emerging trend of disordered eating in non-Western societies, sociocultural determinants must be identified to establish enlightened and culturally sensitive interventions. This issue is more complex than has been acknowledged in the available literature. For example, it is always taken for granted that thinness is the most desirable standard of beauty. However, there are some societies, including Oman, where the beauty preference would make mockery of the modern preoccupation with thinness. In traditional Omani society, beauty and wealth is equated with, in modern parlance, an obesity-like body silhouette. Society used to institute various methods to achieve a desirable weight as exemplified by the following vignettes.

Vignette 1

> *Buthaina is a 10 year old girl, growing up in an extended family in a semipastoral tribal region in the Southern region of Oman. She was brought to the primary health care in a comatose state. The accompanying family informed the attending medical team that she had spasms whenever she ingested any food or liquid. The clinical team noted that she was emaciated, dehydrated, cold intolerant, and had difficulty in maintaining core body temperature. Neither psychosocial nor medical history from the accompanying family revealed or suggested any clear trigger for her present predicament. She has normal developmental milestones. She attended school until a year ago, with insistence from her grandmother that she quit her education despite her performance being adequate. After inconclusive medical investigation, antiemetic and nutritional rehabilitation was instituted. She gradually became stable and was subsequently discharged. Three weeks later, she was brought back to the hospital in a similar state. It was noted by chance that Buthaina's distress coincided with the culturally sanctioned practice of forced overeating, akin to gavage. This furtive traditional practice aims to 'help' girls perceived as thin to transform themselves into much cherished voluptuous figures. Buthaina's family was counseled regarding the detrimental effect of such a practice. Initially, the grandmother resisted the suggestions and insisted that if Buthaina remains thin, she will be condemning herself to live the rest of her life as a spinster. Counter-arguments from other family members eventually moderated the view of the grandmother. Buthaina subsequently resumed her education and there was no relapse of the condition that brought her to the medical attention in the first instance.*

With the above-mentioned background, studies in Oman (Al-Adawi et al. 2002b, 2004; Kayano et al. 2008; Viernes et al. 2007) took advantage of the heterogeneous population to compare performance on indices of deliberate food restriction among teenage girls of diverse cultural and ethnic backgrounds living in Oman and the Philippines (for demographic characteristics, see Table 94.2).

The major themes emerging in the literature are, on the one hand, that the prevalence rates of deliberate food restriction in many non-Western populations sometimes exceed the trend previously reported among Westernized populations (Wassenaar et al. 2000). On the other hand, although it appears to be increasing, the overall rate of disordered eating in non-Western countries is lower than that of Western countries. Such a contradictory finding suggested the need for further study.

The comparison of Filipino, Indian, Omani, and Euro-American teenagers suggests that the four ethnic groups appear to have significant differences in their scores on dieting behavior and aberrant eating, derived from The *Eating Attitude Test (EAT-26)*. This is a 26-item, self-reporting questionnaire that measures symptoms implicated with deliberate food restriction and, at a pathological level, aberrant eating (Garner and Garfinkel 1979). Participants rate the frequency with which they experience each statement on dieting, bulimic behaviors, and self-control of eating behavior, using a six-point scale. Various authors report that EAT-26 is effective for assessing a wide range of attitudes and behavior characteristics of deliberate food restriction in both clinical and general populations (Nasser et al. 2001; Al-Subaie et al. 1996). While high scores on EAT-26 do not necessarily equate with clinical eating disorders, many of the characteristics represented constitute deliberate food restriction. EAT-26 is considered an appropriate screening device for eating disorders and has been widely translated. In the majority of studies in the Arab world and the Philippines, its cross-cultural application has been found to be acceptable (Nasser et al. 2001; Al-Subaie et al. 1996; Lorenzo et al. 2002).

On the whole, using EAT-26, Al-Adawi et al. (2006) have shown that non-Western teenagers have a greater tendency toward deliberate food restriction and dieting behavior than their Euro-American

Table 94.2 Criteria for diagnosis of deliberate food restriction, according to the Western psychiatric taxonomy (*Diagnostic and Statistical Manual of Mental Disorders* (DSM) and International Classification of Disease (ICD))

- Absence of a menstrual period in a woman of reproductive age.
- Disturbance in the way in which one's body weight or shape is experienced, undue influence of body weight or shape on self-evaluation, or denial of the seriousness of the current low body weight.
- Idiom of distress that primarily involves intense fear of gaining weight or becoming fat, even if underweight.
- Failure to make expected weight gain during the period of growth, leading to body weight less than 85% of that expected.

expatriate counterparts. This finding is seemingly consonant with earlier observations that in non-Western societies, preoccupation with food restriction and dieting behavior appears to be as common as those reported in Western countries (Hoek and van Hoeken 2003; Tsai 2000). The authors noted that the rate among non-Western teenagers is beginning to outpace the rate observed among Euro-American teenagers.

However, caution is needed in extrapolating the present findings with the background that a view of human nature developed for one cultural group should not be uncritically applied to members of another group for whom its validity has not been established. The utility of EAT-26 is a case in point. Al-Adawi et al. (2002a) have shown that although the EAT-26 is the most used screening instrument in cross-cultural studies, it does not appear to be reliable in identifying possible cases of anorexia among Omani adolescents. A previous study from Oman (2002), in which the cases identified using the EAT-26 were scrutinized with a gold standard structured interview and diagnostic criteria based on the Composite International Diagnostic Interview (World Health Organization 1993), the percentage of genuine positives was reduced from 29% to 9.5%. The authors opine that some available quick screening tools may give spurious results and hence in cross-cultural studies, qualitative interviews are likely to be more fruitful.

94.2.2 Culture to Culture: Fatphobia

With the realization that there is variation in the manifestation of eating disorders that may not be parallel to that observed in the Western adolescent population, the next step is to decipher performance on a core feature of eating pathology, namely, fear of fatness. Studies are needed to determine whether there is a difference in body dissatisfaction between Western and non-Western teenagers, in order to shed light on differences in idiom of distress. The diagnostic importance of laparophobia is testified to by the fact that it constitutes the central criterion in the diagnosis of anorexia nervosa for both DSM-IV (American Psychiatric Association 1994) and ICD-10 (World Health Organization 1993) (Table 94.3).

In Western populations, the manifestation of laparophobia is shown to fluctuate widely among various ethnic groups (Johnson et al. 2004; Williamson 1998). Similar variations are also observed in studies from some Asian countries (Ngai et al. 2000).

Finding an instrument that is appropriate for international comparison is essential, if not paramount, in this regard. Al-Adawi et al. (2004) have examined the presence of laparophobia using the drive for thinness, a subscale derived from one of the most widely used assessment measures of eating disorders, the *Eating Disorder Inventory* (EDI) (Garner et al. 1983). The EDI is a self-reporting measure, validated on both clinical and non-clinical populations (Garner et al. 1983). It has valid and reliable psychometric properties that were established in various ethnic groups, including the populations under scrutiny in the present study (Al-Subaie et al. 1996; Yates et al. 2004). The subscale utilized contains seven items that elicit information on the drive for thinness. Higher scores indicate greater levels of laparophobia, with a score of 15 or more on the composite scale suggesting a preoccupation with weight and/or body shape, or demonstration of a morbid fear of weight gain, an excessive concern with dieting or a strong desire for thinness (Garner et al. 1984).

Using this scale, Al-Adawi et al. (2002b) have shown that perceptions of fatness differed by ethnicity. The Euro-American students score significantly higher (more than twice the average) scores compared to the Omani, Filipino, and Indian groups. There is no difference in this perception between the Filipino and Indian groups, while the Omani and Euro-American students differed significantly from every other group. The Euro-Americans have significantly higher median composite EDI scores compared to the other groups. This evidence, along with other findings (Gupta et al. 2001), underscores the view that

constructs of laparophobia, an essential diagnosis for disordered eating, may be expressed differently from culture to culture and that this merits further investigation. First, many problems previously thought of as universal because of their shared attributes with similar latent manifestations in different parts of the world, are sometimes expressed in forms that are unique to particular cultures. As a result, many interventions tend to have only modest success because sociocultural factors often downgrade supposedly universal phenotypic presentations. One direct consequence of this is that many conditions are proliferating, not only because of acculturation, but also because of a lack of understanding of the contribution of sociocultural factors to these conditions. Secondly, and directly relevant to eating

Table 94.3 Comparison of criterion for diagnosis of deliberate food restriction according to available nomenclature as in the case of Anorexia Nervosa

	DSM IV	ICD 10	Comments
1.	Refusal to maintain body weight at or above a minimally normal weight for age and height (e.g., weight loss leading to maintenance of body weight less than 85% of that expected; or failure to make expected weight gain during period of growth, leading to body weight less than 85% of that expected)	There is weight loss or, in children, a lack of weight gain, leading to a body weight at least 15% below the normal or expected weight for age and height	Refusal component not addressed in ICD
2.	Intense fear of gaining weight or becoming fat, even though underweight	There is self-perception of being too fat, with an intrusive dread of fatness, which leads to a self-imposed low weight threshold.	Combining 2 and 4 of DSM column, denial of seriousness not addressed in ICD
3.		The weight loss is self-induced by avoidance of "fattening foods."	Avoidance of fatty foods not addressed in DSM
4.	Disturbance in the way in which one's body weight or shape is experienced; undue influence of body weight or shape on self-evaluation, or denial of the seriousness of the current low body weight		
5.	In post-menarchal females, amenor-rhea, i.e., the absence of at least three consecutive menstrual cycles. (A woman is considered to have amenorrhea if her periods occur only following hormone, e.g., estrogen, administration)	A widespread endocrine disorder involving the hypothalamic–pituitary–gonadal axis is manifest in women as amenorrhea and in men as a loss of sexual interest and potency. (An apparent exception is the persistence of vaginal bleeds in anorexic women who are on replacement hormonal therapy, most commonly taken as a contracep-tive pill)	Male component not addressed in DSM
6.		If onset is pre-pubertal, the sequence of pubertal events is delayed or even arrested (growth ceases; in girls the breasts do not develop and there is primary amenorrhea; in boys the genitals remain juvenile)	Pre-pubertal issue and male component not addressed in DSM

Table 94.3 (continued)

DSM IV	ICD 10	Comments
7. **Specify type**: **Restricting type**: During the current episode of anorexia nervosa, the person has not regularly engaged in binge eating or purging behavior (i.e., self-induced vomiting or the misuse of laxatives, diuretics, or enemas) **Binge eating/purging type**: During the current episode of anorexia nervosa, the person has regularly engaged in binge eating or purging behavior (i.e., self-induced vomiting or the misuse of laxatives, diuretics, or enemas)	The disorder does not meet criteria A and B for bulimia nervosa.Bulimia nervosa: A. Recurrent episodes of overeating (at least twice a week over a period of 3 months) in which large amounts of food arte consumed in short periods. B. Persistent preoccupation with eating and a strong desire or sense of compulsion to eat (craving). C. The patient attempts to counteract the "fattening" effects of food by one or more of the following: • Self-induced vomiting • Self-induced purging • Alternating periods of starvation • Use of drugs such as appetite suppressants, thyroid preparations or diuretics; when bulimia occurs in diabetic patients, they may choose to neglect their insulin treatment D. Self perception of being too fat, with an intrusive dread of fatness (usually leading to underweight)	• Specific subtypes not addressed explicitly in ICD 10. • Self-induced vomiting, self-induced purging, excessive exercise, use of appetite suppressants and/or diuretics SUPPORT diagnosis in DSM but not essential in ICD.
8.	ICD gives researchers ample scope to make their own decisions on the following: • Atypical anorexia nervosa • Atypical bulimia nervosa • Overeating associated with other psychological disturbances • Vomiting associated with other psychological disorders	Researchers have no scope for decisions in DSMIt is imperative from the ICD that culturally sensitive nomenclature ought to be established addressing the prevailing deficiency in coming to grip with the stated conditions

The above comparison between DSM and ICD suggest disordered eating is protean concept that differs from one nosological entity to another. The influences of sociocultural factors that critically play part in food and dietary habits including hospitality, generosity or simply altruism, often perceived as essential social modesty have received scant attention in the available nosology on disordered eating

disorders, unless nonlaparophobia progresses to advanced and irreversible pathology, such as overt emaciation, some sufferers of these debilitating disorders are likely to go unrecognized, since laparophobia is absent in the clinical presentation in some populations. According to Cummins et al. (2005), among psychiatric disorders, eating disorders are among the most fatal with mortality rates ranging from 0.3% to 20.0% and the situation is likely to be heightened among those who use different idioms of distress, and whose cultural practices place them outside the realm of diagnostic criteria based on Western norms. The following clinical vignette (Vignette 2) of an Omani teenager presenting with unacceptable low weight and amenorrhea highlights the dilemma of strictly relying on Western classification of distress.

Vignette 2

Nasra is a 14-year-old-girl who has grown up in rural Oman until her age of 12 years, attending an all girls secondary school in Muscat, urban metropolis of the country. Her father is a petroleum engineer working in the oil and gas sector while her mother is a homemaker with secondary school education. Nasra is the first born among 10 other siblings. Other than congenital mental disorder in one of her brothers, there is no history of adverse or delayed developmental milestones for Nasra or other siblings. Premorbidly, she was described by her mother as performing among the top percentile in her class. However, coinciding with the start of the new academic semester last year, Nasra was noted as being less enthusiastic during family dinner sessions, spending more time in front of the mirror to get ready and dress herself, besides spending more time seeing movies on TV. She performed poorly in academics. According to her accompanying mother, she also took a long time to finish her meals and unless prompted, she did not take any initiative on matters related to eating. Her mother praised all her other daughters as being beautiful and plumpish. She was worried that if Nasra remained skinny she might not attract a suitable husband.

Previous encounters assessment at hospital with health professionals did not result in any changes in Nasra's ever-increasing weight reduction. The family took her to a traditional healer to rule out if her current distress was due to evil eyes, a common idiom of distress in Oman. The traditional healer recommended some rituals but this did not increase her appetite. Opinion regarding mental health was sought as the last resort since the family did not perceive her to be 'crazy'. In the initial evaluation, she concurred to the mental health professional that her emaciation was due to nauseated feelings after consuming food, bloating and pain in the stomach. Despite unacceptably low weight and amenorrhea, she strongly rejected the idea that her distress was psychological in origin. Protracted examination using DSM-IV criteria for diagnosis of disordered eating was inconclusive.

Despite concerted psychotherapeutic and pharmacological intervention, her distress appeared to be impervious to psychiatric intervention. She insisted that she wanted to see a general physician, a view that was supported by her mother. Eventually her menses normalized and her weight returned to its premorbid level in the ensuing four to five months and this coincided with her completion of secondary school in which she performed outstandingly. The family attributed her 'cure' to selective serotonin reuptake inhibitors and tricyclic antidepressants dispensed from primary health doctors as well as unverified 'treatment' from the traditional healer.

94.2.3   Culture to Culture: Somatization

If the rate of disordered eating fluctuates differently from culture to culture and also if disordered eating may be expressed differently from culture to culture, the third dimension that would be necessary to contemplate is to shed light on whether idioms of distress, culturally specific experiences of expressing pain, suffering or social discontent, may partly contribute to variations in presentation and on what constitute core features of disordered eating. Although this does not amount to Rudyard Kipling's (Stedman 2005) conception of "East is East, and West is West, and never the twain shall meet", in general, Western societies are suggested to employ psychological language whereas other societies have a greater tendency to manifest the idiom of distress as somatization. This concept owes its origin to the view that some debilitating emotion is repressed, which, in turn, is converted into physical symptoms. In contrast to Vignette 2, which indicates a predominance of the somatic tendency, Vignette 3 suggests a Western idiom of distress that is compatible with Western diagnostic nosology.

Vignette 3

Sylvia, the only child in the family, is a 14-year-old girl who has been living in Oman for the last 4 years. Her father works in an international oil and gas company. Prior to the secondment to Oman, the father was working in the UK and USA. Sylvia attends an English-speaking school for the expatriate community in Muscat. According to the referral note from the school counselor, her school performance has been excellent. Sylvia has

keen interest and aptitude in sport. During her childhood, she participated in ballet school. More recently, she has also been keenly engaging in extra-school activities including swimming and volleyball. She has been a keen runner and she participates regularly in interschool competitions. She buys exercise videos that she uses in the family's private gym and swimming pools. In the last three years, Sylvia's mother has noted that her BMI appears to be 'too low'. Her mother concurred that she cuts her food into small pieces and takes longer to finish it. She also has been avoiding food items that are high in calories and she often reads about the content of the food eaten at the house. The relationship with her mother has been turbulent since she reached puberty, which the mother interpreted as 'typical adolescence turmoil' such as she once heard of in an Oprah Winfrey's talk show. Initial medical examination was not remarkable.

During the protracted psychiatric interview, Sylvia was cooperative. She concurred to the attending mental health specialist as having strong desire to be thin. She does want to look like her mother. A quick screening for the presence of eating pathology using EAT-26 suggests a presence of clinically significant pervasive and persistent anorexia nervosa. She appears to endorse all the clinical features including amenorrhea, distorted body image, intense fear of gaining weight and refusal to maintain minimal body weight. Due to the lack of multidisciplinary services for eating disorders in Oman, the family took her elsewhere for treatment.

Somatization in non-Western cultures have been explained in terms of the inability of some people to express emotional distress or simply not to have the words to describe certain emotions (Leff 1977). Although language may facilitate the expression of emotions, other psychosocial factors are suggested to have been involved. Somatization is reported even in those societies where psychological mindedness prevails (Mumford et al. 1991b); therefore, somatization may also serve as an adaptive social function rather than as a defense against anxiety. Various psychosocial factors are shown to play a part in increasing the tendency toward a somatic idiom of distress. Distress in a non-Western culture is not perceived to be precipitated by the trajectory of one's own behavior and one's own self. In a society where development of the self is not recognized, it is unlikely that a psychological façade would be endorsed. In reference to Chinese adolescents, Lee et al. (2001) remark that "Obligation to one's family is deeply ingrained in the Asian philosophy of life and is highly valued by all in the society. It is, therefore, not surprising that Asian-Americans reported extreme concerns about meeting high parental expectations… and achievement orientation and the consequent striving for perfection could possibly predispose these youngsters to the development of anorexia nervosa." (p. 229). In many non-Western societies, value systems have an affinity to the collective self. In these societies, from the time of birth, children are brought up in an environment that ushers them into a collective mindset, as the development of selfhood is generally discouraged. The development of the self, as conceived in Western psychology, is generally not lauded in a collective society (Al-Sinawi et al. 2008). According to Dwairy (2006), in the absence of a distinct domain for the self, somatic complaints are often the only channel to communicate any discomfort. It is worth noting that characteristics of somatopsychic culture are believed to have a lack of laparophobia (Kayano et al. 2008; Viernes et al. 2007; Al-Adawi et al. 2004). The lack of laparophobia, despite the presence of overt cachexia, is depicted as a tendency toward concealment or denial (Lee et al. 2001) or solely reflecting the traditional conception of beauty that often leans toward plumpness. Lee et al. (1993) suggest that laparophobia is predominantly characterized by subjective complaints involving abdominal pain, a bloated feeling, a lack of taste or diminished appetite, the presence of constipation, or being unable to consume adequate amounts of food. However, to date, no studies have examined whether the conception of somatization may partly contribute to the variation in pattern of disordered eating.

Viernes et al. (2007) have employed the *Bradford Somatic Inventory* (BSI) (Mumford et al. 1991b) to examine variation in the tendency for somatization. BSI is an inventory for psychosomatically expressed psychological distress which is relatively free of cultural bias (Al Lawati et al. 2000). The BSI enquires about a wide range of somatic symptoms during the prior month, and whether the subject has experienced a particular symptom on fewer or more than 15 days during that month (scoring 2 or 1, respectively). This study employs 12 items derived from the BSI. These items cover the parts of the body that are likely to be affected by eating and body image due to preoccupation with food.

The psychometric property of BSI is established for Arabic speaking populations (Zahid et al. 2001) as well as other cross-cultural populations (Havenaar et al. 1996; Al-Adawi et al. 2002a). A higher score suggests preoccupation with somatic attributes.

The study in Oman study suggests the preponderance of a somatopsychic idiom of distress and endorsement on indices of somatization among the cohorts from the Philippines, India and Oman. In these students, the tendency toward disturbed weight and dieting behavior increases along with the preoccupation with somatic attributes. The Euro-American counterparts however differ on the above counts. Here, the question arises whether the observed association between somatization and ethnicity implies that somatization is a predisposing factor, or simply a reaction to disturbed weight and dieting behavior. More studies that address this issue are imperative. On the other hand, the fact that the somatic metaphor is part of how particular cultural groups communicate distress gives rise to new ideas in the ongoing debate regarding core features of eating disorders. Despite the potential importance of this issue, no previous studies we reviewed have examined the idiom of distress in the context of disordered eating. It might be more constructive to explore different idioms of distress using assessment measures that have heuristic value for non-Western cultural groups.

94.3 Conclusion

Emerging global epidemiological trends suggest that the burden of noncommunicable disease has negative ramifications with direct bearing on the quality of life, in addition to a stifling of the contribution of much-needed human resources to sustainable development. In some non-Western societies, to complicate an already gloomy picture of poverty and rapid urbanization, diseases of affluence and a culture of affluence, with all the social and medical impacts they entail, are beginning to emerge (Al-Adawi 2006). These include eating disorders and body image disturbance, previously thought to be Euro-American culture-bound syndromes, diseases or a pet mental disturbance of modern affluent cultures (Swartz 1985; Halmi 1996).

Studies on diverse regional, cultural, and linguistic groups have yielded important insights into food and eating practices (Rozin et al. 1999; Lawton et al. 2008). As food is central to survival, disordered eating increases the risk of various medical, neurological, and psychiatric complications (Uher and Treasure 2005; Wong and Fielding 2008) and, when occurring during childhood and adolescence, it can affect physical and emotional development (Angold 2009). Golden and Meyer (2004) have summarized the factors associated with increased risk of disordered eating. The most notable is cachexia that manifests as loss of fat and muscle mass. Continued severe restrictive dietary habit could affect various organs that precipitate heart problems and, for that matter, sudden death. Emergency gastrointestinal problems, impaired reproductive health, osteoporosis, dermatological and dental problems are also common. Persistent and pervasive food restriction also affects cognitive, emotional, and behavioral functioning (see Fig. 94.1). This often makes it impossible to differentiate whether diminutions of higher function are causes or effects of disordered eating.

The present review has considered three interrelated themes among a cross-cultural population with reference to the unique situation in Oman. In this age of globalization and mass migration, health care services will require adjustment to ethnic and cultural variation to enhance health and the quality of life to be viable. Health-related behavior should be examined within its sociocultural context. With the ongoing globalization of the world community, the health care industry in many parts of the world will face an increasingly diverse and heterogeneous patient population, especially in urban areas. Health care providers will encounter more clients with a wide range of cultural, social,
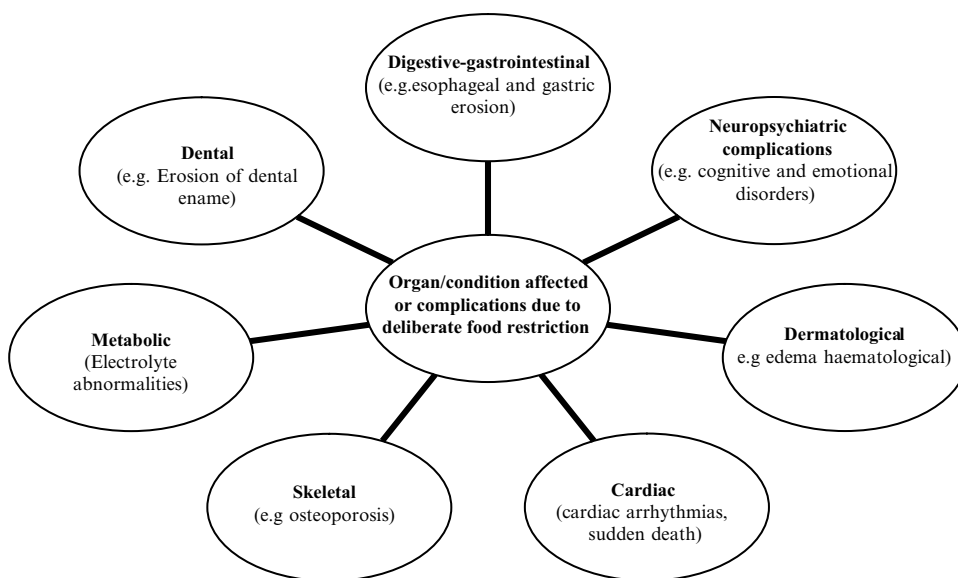
Fig. 94.1 Eating and associated increased the risk of various medical, neurological, and psychiatric complications. Many organs compromised and while medical, neurological, and psychiatric conditions are exacerbated due to chronically mal-nourished in individuals with deliberate food restrictions which in turn may cause life-threatening complications

regional, educational, and ethnic backgrounds. In this new medical environment, the viability of health care delivery will depend on the medical community's ability to evolve and adjust to ethnic and cultural variation. Only through an awareness and appreciation of each patient's unique background can a health care provider decide on the best method to enhance health and quality of life. Firstly, in comparing Western and non-Western teenagers, non-Western teenagers have a greater tendency toward deliberate food restriction and dieting behavior than their Euro-American counterparts do. The rate among non-Western countries appears to outpace the rate observed among Euro-American teenagers. Secondly, the studies in Oman have examined whether reliance on Western norms, on which diagnostic criteria are heavily based, are appropriate in cross-cultural populations. In one of the most employed diagnostic nomenclature such DSM and ICD-10, the core feature of disordered eating include amenorrhea, distorted body image, intense fear of gaining weight, and refusal to maintain minimal body weight. As would be expected, differences in culture tend to relate to differences in idiom of distress, and studies in Oman suggest that one example of a core feature of disordered eating, laparophobia, does not feature in non-Western population (see >Table 94.4).

Third, the quest of the present review was to ascertain whether somatopsychic idioms of distress would be common in the non-Western population. Previous studies have indicated that "psychological mindedness" is a sociocultural concept. The data points to the Western population tending to endorse cognitive metaphor in distress, while evidence suggests that non-Westerners tend to physical metaphor for their distress. Tables 94.4 and 94.5 the performances of indices of deliberate food restriction, laparophobia and somatization among Western and non-Western teenagers (Table 94.5).

Understanding cultural forces may help in devising preventive measures and, at a theoretical level, shed light on which are universal and which are culture-specific behaviors. The highly variable incidence of eating disorders found across ethnically diverse populations and geographies leads us to believe that sociocultural or ecological factors play a substantial role in the etiology of eating disorders.

Table 94.4 Performance of indices of deliberate food restriction, laparophobia and tendency toward utilizing psychosomatically expressed psychological distress in Western and non-Western population (*N* = 596) (Al-Adawi et al., in preparation)

Study cohort	Assessment measures	Kruskal's gamma	*p*-Value
Euro-American vs. Non-Western	Indices of deliberate food restriction and somatization	0.659	<0.001
	Indices of deliberate food restriction and laparophobia	−0.231	<0.001
	Indices somatization and laparophobia	−0.132	0.019

Non-Western teenagers having increased propensity toward deliberate food restriction and psychosomatically expressed psychological distress while Western teenagers show a greater tendency toward laparophobia. This suggests ethnicity and culture difference in food ingestion patterns and eating practices

Table 94.5 Performance of indices of deliberate food restriction, laparophobia and tendency toward utilizing psychosomatically expressed psychological distress in different ethnic groups (*N* = 596) (Al-Adawi et al., in preparation)

Study cohort	Assessment measures	Kruskal's gamma	*p*-Value
Indian	Indices of deliberate food restriction and somatization	0.556	<0.001
	Indices of deliberate food restriction and laparophobia	0.093	0.513
	Somatization and laparophobia	−0.615	<0.001
Omani	Indices of deliberate food restriction and somatization	0.648	<0.001
	Indices of deliberate food restriction and laparophobia	−0.187	0.083
	Somatization and laparophobia	0.412	<0.001
Euro-American	Indices of deliberate food restriction and somatization	0.804	0.160
	Indices of deliberate food restriction and laparophobia	−0.162	0.231
	Somatization and laparophobia	−0.651	0.167
Filipino	Indices of deliberate food restriction and somatization	0.679	<0.001
	Indices of deliberate food restriction and laparophobia	0.239	0.043
	Somatization and laparophobia	0.229	0.042

Non-Western teenagers were more likely to have propensity toward deliberate food restriction and somatization. In contrast, present defined Western teenagers show a greater tendency toward idiom of distress that primarily involves intense fear of gaining weight or becoming fat, even if underweight

94.4 Applications to Other Areas of Health and Disease

- Although eating disorders were initially perceived to be triggered by acculturation and modernization, their emergence in non-Western cultural groups may not necessarily hinge on pathoplastic globalization, since their expression stems from cultural patterning. This has implications for teasing out what is universal versus what is cultural in food ingestion patterns and eating practices.
- There are culturally specific patterns of expressing pain, suffering or social discontent that must be considered in cross-cultural studies, because illness and distress are experienced within sociocultural domains.
- Reliance on Western norms, on which diagnostic criteria are heavily based, may not always be appropriate in cross-cultural populations since there is no universal idiom of distress.
- In this age of globalization and mass migration, the viability of health care services will require adjustment to ethnic and cultural variation to enhance health and the quality of life.

Summary Points

- This study endeavors to determine whether well-known, culturally specific modes of expressing pain, suffering, or social discontent could also manifest as disordered eating.
- The study employs screening tools that bear directly on various aspects of idiom of distress, including a tendency to "psychologize" for Western populations and to "somatize" among non-Western populations, as well as a tendency toward deliberate food restriction.
- The rate of deliberate food restriction is higher among non-Western teenagers than their Western counterparts – a finding that is seemingly consonant with previous observations suggesting that eating disorders in non-Western societies are rapidly increasing or, to some extent, outpacing the trend in Western populations.
- Performance on indices of psychological distress and fat-phobia is higher among Western teenagers in this study. This supports the contention that Westerners tend to vocalize their distress in a language framed with psychological metaphor.
- Performance on indices of somatization is higher among non-Western groups, consonant with the view that, among these groups the expression of idiom of distress is commonly framed with somatic metaphor.
- These findings, as well as other reports amassed in the literature, have implications for further research as to what is universal vis-à-vis what is cultural, and the pathoplastic versus pathogenic viewpoints in disordered eating along with its consequences.

Definitions and Explanations

Idiom of distress: Culturally specific experiences of expressing pain, suffering or social discontent

Culture-bound: Pain, suffering, or social discontent that occurs only within a specific society or culture

Culture in transition: Traditional society that is acculturating and globalizing

Culture-reactive phenomena: Pain, suffering, or social discontent that is a pathoplastic effect of globalization

Fat-phobia: Idiom of distress that primarily involves intense fear of gaining weight or becoming fat, even if underweight. Fat-phobia has been predominantly reported in Western populations; also see laparophobia

Gavage: Practice involving a nubile who is coerced into consuming a large amount of food or liquid deemed essential to increase one's weight

Laparophobia: Idiom of distress that primarily involves intense fear of gaining weight or becoming fat, even if underweight. Laparophobia has been predominantly reported in Western populations; also see fat-phobia

Somatization: Idiom of distress that primarily involves presentation of somatic complaints as all forms of expressing pain, suffering, or social discontent

Psychologization: Idiom of distress that primarily involves presentation of psychological complaints as all forms of expressing pain, suffering, or social discontent

---

Key Facts

1. Diagnostic criteria and assessment measures are based on Western norms.
2. Based on the above, the cultural patterns noted to be prevalent are as follows:

Western population:	**Non-Western population:**
(a) Tendency to psychologize distress	Tendency to somatize distress
(b) Rate of food restriction is lower	Rate of food restriction comparatively higher and rapidly increasing
(c) Fat phobia higher	Fat phobia lower

3. Key confounders that must be addressed with respect to dietary habits: Global impact of media (TV, glossy magazines, Internet), movies (movie stars as role models), fashion and modeling industry, service industry (slimming centers), over-the-counter drugs (herbal slimming medicines), societal perception, and expectations of what constitutes beauty and which body image type is appreciated, and whether dieting is in fact the "preferred choice" of young females.

References

Abou-Saleh MT, Younis Y, Karim L. Int J Eat Disord. 1998;23:207–12.

Al-Adawi S. Sultan Qaboos University Med J. 2006;6:3–9.

Al-Adawi S, Dorvlo AS, Burke DT, Moosa S, Al-Bahlani S. Eat Weight Disord. 2002a;7:304–11.

Al-Adawi S, Dorvlo ASS, Burke D, Al-Bahlani S, Martin RG, Al-Ismaily S. J Am Acad Child Adolesc Psychiatry. 2002b;41:1124–31.

Al-Adawi S, Dorvlo ASS, Alexander PC, Martin RG, Yoishiuchi K, Kumano H, Kuboki T. Psicologia Conductual. 2004;12:429–46.

Al-Adawi S, Dorvlo ASS, Martin RG, Yoishiuchi K, Kumano H, Kuboki T. In: Swain P, editor. New developments in eating disorders research. New York: Nova Science; 2006. p. 65–91.

Al Lawati J, Al Lawati N, Al Siddiqui M, Antony SX, Al Naamani A, Martin RG, Kolbe R, Theodorsson T, Osman Y, Al Hussaini AA, Al Adawi S. J Sci Res: Med Sci. 2000;2:105–10.

Al-Sinawi H, Al-Adawi S, Al-Guenedi A. Transcult Psychiatry. 2008;45:695–704.

Al-Subaie A, Al Shammari S, Bamgboye E, Al Sabhan K, Al Shehri S, Bannah AR. Int J Eat Disord. 1996;20:321–4.

Altabe M. Int J Eat Disord. 1998;23:153–9.

American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4th ed. Washington, DC: American Psychiatric Association; 1994.

Angold A. J Am Acad Child Adolesc Psychiatry. 2009;48:3–4.

Barr DT, Garner ADM. Weight Disord. 2001;6:90–8.

Bhugra D, Bhui K, Gupta KR. Soc Psychiatry Psychiatr Epidemiol. 2000;35:86–93.

Casper RC. Int J Eat Disord. 1998;24:381–93.

Contento IR, Basch C, Zybert P. J Nutr Educ Behav. 2003;35:236–48.

Cummins LH, Simmons AM, Zane NWS. Am J Orthopsychiatry. 2005;75:553–74.

Duncan MC, Robinson TT. Quest. 2004;56:77–104.

Dwairy M. Counseling and psychotherapy with Arabs and Muslims: a culturally sensitive approach. New York: Teachers College Press; 2006.

Eloul L, Ambusaidi A, Al-Adawi S. Sultan Qaboos University Med J. 2009;9:123–30.

Fedoroff IC, McFarlane T. In: Kazarian SS, Evans DR, editors. Cultural clinical psychology: theory research and Practice. New York: Oxford University Press; 1998. p. 152–76.

Ford KA, Dolan BM, Evans C. J Psychosom Res. 1990;34:501–7.

Garner D, Olmsted M, Polivy J. Int J Eat Disord. 1983;2:15–34.

Garner DM, Garfinkel PE. Psychol Med. 1979;9:273–9.

Garner DM, Olmsted MP, Polivy J, Garfinkel PE. Psychosom Med. 1984;46:255–66.

Gerteiny AG. Historical dictionary of Mauritania. Mauritania: London Pall Mall; 1967.

Golden NH, Meyer W. Int J Adolesc Med Health. 2004;16:131–44.

Gunewardene A, Houon GF, Zheng R. Int J Eat Disord. 2001;29:289–93.

Gupta MA, Chaturvedi SK, Chandarana PC, Johnson AM. J Psychosom Res. 2001; 50:193–8.

Halmi KA. Ann NY Acad Sci. 1996;18:67–77.

Havenaar JM, Poelijoe NW, Kasyanenko AP, Van den Bout J, Koeter MW, Filipenko VV. Psychol Med. 1996;26:837–44.

Hoek HW, van Hoeken D. Eat Weight Disord. 2003;34:383–96.

Jackson RT, Rashed M, Saad-Eldin R. Int J Food Sci Nutr. 2003;54:1–11.

Johnson C, Crosby R, Engel S, Mitchell J, Powers P, Wittrock D, Wonderlich S. Eat Weight Disord. 2004;5:147–56.

Kayano M, Yoshiuchi K, Al-Adawi S, Viernes N, Dorvlo AS, Kumano H, Kuboki T, Akabayashi A. J Neuropsychiatry Clin. 2008;62:17–25.

Khandelwal SK, Sharan P, Saxena S. Int J Soc Psychiatry. 1995;41:132–46.

Kleinman A. Social origin of distress and disease. New Haven: Yale University Press,; 1986.

Kleinman A. Br J Psychiatry. 1987;151:447–54.

Koneru VK, Weisman de Mamani AG, Flynn PM, Betancourt H. Appl Prev Psychol. 2007;12:76–96.

Lai KYC. J Adolesc. 2000;23:561–68.

Lawton J, Ahmad N, Hanna L, Douglas M, Bains H, Hallowell N. Ethn Health. 2008;13:305–19.

Lee S. Soc Sci Med. 1996;42:21–34.

Lee S, Lee AM. Int J Eat Disord. 2000;27:317–27.

Lee S, Ho TP, Hsu LK. Psychol Med. 1993;23:999–1017.

Lee S, Lee AM, Ngai E, Lee DT, Wing YK. Int J Eat Disord. 2001;29:224–9.

Leff J. Cult Med Psychiatry. 1977;1:317–50.

Littlewood R. Br J Med Psychol. 1995;68:45–63.

Lorenzo CR, Lavori PW, Lock JD. Eat Weight Disord. 2002;7:202–9.

Makino M, Tsuboi K, Dennerstein L. Med Gen Med. 2004;6:49.

Mellor D, McCabe M, Ricciardelli L, Yeow J, Daliza N, Hapidzal NF. Body Image. 2009;6:121–8.

Morant H. Br Med J. 2000;320:1495.

Mumford DB, Bavington JT, Bhatnagar KS, Hussain Y, Mirza S, Naraghi MM. Br J Psychiatry. 1991a;158:379–86.

Mumford DB, Whitehouse AM, Platts M. Br J Psychiatry. 1991b;158:222–8.

Mumford DB, Saeed K, Ahmad I, Latif S, Mubbashar MH. Br J Psychiatry. 1997;170:473–8.

Nasser M. Psychiatry. 2006;51:392–5.

Nasser M, Katzman M, Gordon RA. Eating disorders and cultures in transition. New York: Taylor & Francis; 2001.

Ngai ES, Lee S, Lee AM. Acta Psychiatr Scand. 2000;102:314–7.

Ohaeri JU, Odejide OA. Am J Psychiatry. 1994;151:728–31.

Ramacciotti CE, Dell'Osso L, Paoli RA, Ciapparelli A, Coli E, Kaplan AS, Garfinkel PE. Int J Eat Disord. 2002;32:206–12.

Reddy SD, Crowther JH. Cultur Divers Ethnic Minor Psychol. 2007;13:45–53.

Resnikoff S. Med Trop Mars. 1980;4:419–23.

Ricciardelli LA, McCabe MP, Williams RJ, Thompson JK. Clin Psychol Rev. 2007;27:582–606.

Rieger E, Touyz SW, Swain T, Beumont PJ. Int J Eat Disord. 2001;29:205–15.

Rozin P, Fischler C, Imada S, Sarubin A, Wrzesniewski A. Appetite. 1999;33:163–80.

Soomoro GMM, Crisp AH, Lynch D, Tran D, Joughin N. Anorexia nervosa in non-white's populations. Br J Psychiatry. 1995;167:385–9.

Stedman EC, editor. A victorian anthology 1837 to 1895. London: Kessinger, LLC; 2005.

Swartz L. Soc Sci Med. 1985;20:725–30.

Tsai G. Eat Weight Disord. 2000;5:183–97.

Uher R, Treasure J. J Neurol Neurosurg Psychiatr. 2005;76:852–7.

Viernes N, Zaidan ZA, Dorvlo AS, Kayano M, Yoishiuchi K, Kumano H, Kuboki T, Al-Adawi S. Eat Behav. 2007;8:407–17.

Wassenaar D, Le-Grange D, Winship J, Lachenicht L. Eur Eat Disord Rev. 2000;8:225–36.

Williamson L. Health Care. 1998;28:61–73.

Wong WS, Fielding R. Acta Oncol. 2008;47:71–80.

World Health Organization. Composite international diagnostic interview (CIDI), Core version 1.1. Geneva: WHO; 1993.

Yates A, Edman J, Aruguete M. J Adolesc Health. 2004;34:300–7.

Zahid MA, Motaal MAA, Razik MA. Med Princ Pract. 2001;10:23–8.

Chapter 95
Examining the Relationship Between Binge Eating and Coping Strategies in Adolescents

Susana Sierra-Baigrie, Serafín Lemos-Giráldez, and Eduardo Fonseca-Pedrero

Abbreviations

APA	American Psychiatric Association
ACS	Adolescent Coping Scale
BED	Binge eating disorder
BITE	Bulimic Investigatory Test, Edinburgh
DSM-IV-TR	*Diagnostic and Statistical Manual of Mental Disorders*, fourth edition, text revision
SD	Standard deviation

95.1 Introduction

Binge eating, the consumption of large quantities of food accompanied by a sense of loss of control, is an essential symptom of two eating disorders – included in the fourth edition, text revision, of the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR) (American Psychiatric Association [APA] 2000) – Bulimia Nervosa (BN) and Binge Eating Disorder (BED), which is a provisional category included in the Appendix in need of further study. In addition, binge eating is also present in individuals with Anorexia Nervosa and subclinical eating disorders. Moreover, this behavior is not restricted to individuals with eating disorders, but it has also been reported in community samples (Williamson 1990; Beglin and Fairburn 1992; Spitzer et al. 1993; Vanderlinden et al. 2001; Croll et al. 2002; Ackard et al. 2003), being more frequent in obese populations, especially in those who are in weight-reduction programs (Amigo 2003; Didie and Fitzgibbon 2005).

According to the DSM-IV-TR (APA 2000), in order for an eating episode to be considered a binge, both a large amount of food in a discrete period of time and loss of control must be present. This is something important to keep in mind as binge eating is a concept widely used by both laypersons and professionals, yet the meaning attached to it may not be the same, thereby hindering proper communication between clinicians and patients in some cases (Beglin and Fairburn 1992). Consequently, it is important to further explore the variables which make up a binge eating episode to reach a more adequate definition of binge eating and therefore improve its assessment methods for both research purposes and clinical diagnosis. The key features of the definition of binge eating can be seen in Table 95.1.

S. Sierra-Baigrie (✉)
Department of Psychology, University of Oviedo, Plaza Feijoo, s/n, Oviedo 33003 Spain
e-mail: susisierrab@telecable.es; susisierrab@yahoo.com

Table 95.1 Key features of the definition of binge eating

- The diagnostic manuals describe binge eating as the consumption of large quantities of food (compared to what most people would eat) in a discrete period of time (for example 2 h), while experiencing a sense of loss of control.
- Therefore, three variables are taken into account in the definition: the amount eaten, the time it takes to eat the food, and loss of control.
- The presence of loss of control is important to distinguish overeating episodes form episodes of binge eating. Loss of control markers are for example eating much more rapidly than usual, eating when not hungry, eating until uncomfortably full, and feeling disgusted with oneself after the episode.

This table shows the key aspects of the definition binge eating described in the diagnostic manuals

Table 95.2 Problems associated to binge eating

- In the long run, binge eating is associated to weight gain and obesity.
- Binge eating is accompanied in some individuals by unhealthy compensatory methods to avoid weight gain which can be very physically and psychologically harmful, such as self-induced vomiting, misuse of laxatives, diet pills, over exercising, etc.
- Increased risk of developing a subthreshold or a full-blown eating disorder.
- Depression, anxiety, low self-esteem, body image disturbance.
- Higher risk of suicide.
- Social isolation and impaired social relationships.

This table summarizes the main psychological, physical, and social problems associated to regular binge eating

Binge eating is an unhealthy behavior present in a wide range of individuals associated with great distress as well as psychological, physical, and social problems (see Table 95.2). It is especially important to identify the factors associated with the development of this unhealthy eating behavior in young adolescents who have not yet developed an eating disorder in order to find ways of preventing this behavior from appearing.

95.2 Binge Eating in Adolescents

There is no question that adolescence is a particularly interesting period for the study of maladaptive eating behaviors which can be viewed as risk factors for the future development of eating pathology (Williams and McGillicuddy-De Lisi 2000). This is due to the diversity of physical, social, affective, and cognitive changes that take place during this developmental stage and its temporal proximity to the onset of the major eating disorders (Williams and McGillicuddy-De Lisi 2000; Liu et al. 2004). The literature has consistently shown that binge eating is a relatively frequent behavior in adolescents (e.g., Aljadir and Liprie 1999; Vanderlinden et al. 2001). Research studies have reported frequencies of binge eating which vary depending on the assessment method used, but, in general terms, it appears to be quite significant (Aljadir and Liprie 1999; Vanderlinden et al. 2001; Ackard et al. 2003; Sierra-Baigrie and Lemos-Giráldez 2008). For example, Ackard et al. (2003) examined the presence of binge eating in a sample of adolescents from public middle and high schools in Minnesota and found that this behavior was reported by 7.9% of the girls and 2.4% of the boys in their sample. Vanderlinden et al. (2001) found in their study that 41% of the women aged 14–25 who participated reported binge eating at least once with 15% of these women indicating that they had daily binges. Especially interesting was the high rate of binge eating in a nonclinical sample. Similarly, in another study (Aljadir and Liprie 1999), 51% of adolescents aged 10–15 who participated reported at least one episode of binge eating in the previous week. The authors were surprised by the high percentage of males (46%) who indicated binge eating, considering that most eating disorders are more frequent in females. Therefore, these

results highlight the importance of including males in the samples when studying binge eating in order to reach a better and more complete understanding of the phenomenon. They also found that binge eating was negatively correlated with age, with the highest rates in the 10-year-old group. Thus, this finding suggests that the onset of binge eating may be at an earlier age than was previously believed.

95.2.1   Binge Eating in Spanish Adolescents

With respect to binge eating in Spanish adolescents, research focused solely on this problem (and not only as a symptom of bulimia) is very scarce and, therefore, data are limited on the prevalence of binge eating in Spanish adolescent populations. One study by Rodriguez et al. (2001) examined the presence of eating disorders and altered eating behaviors in normal-weight Spanish adolescents. The sample consisted of 491 adolescents aged 14–18 from Cadiz, a city located in Southern Spain. The authors found that 42% of the adolescents reported "recurrent episodes of binge eating" with a sense of loss of control. More recently, we found in another study of 259 Spanish adolescents that 33.2% of these reported binge eating at least once in the last 6 months (Sierra-Baigrie and Lemos-Giráldez 2008). More epidemiological studies on binge eating in Spanish adolescents are needed in order to determine the prevalence of this behavior in this population and make comparisons with other cultures.

95.3   Factors Associated with Binge Eating and Theoretical Models

A great number of studies have attempted to determine the factors associated to binge eating (e.g., Stickney et al. 1999; McLaren et al. 2001; Vanderlinden et al. 2001; Ghaderi 2003; Fischer et al. 2004; Benjamin and Wulfert 2005). Among some of the factors identified, we find interpersonal stress, anxiety, body-weight concern, weight cycling, body dissatisfaction, boredom, depressive mood, avoidance coping, and restrictive dieting (Mayhew and Edelmann 1989; Stickney et al. 1999; Vanderlinden et al. 2001). Other studies have shown that stress is an antecedent to eating pathology in general (e.g., Bennett and Cooper 1999; Quiles Marcos and Terol Cantero 2008) and that individuals with eating disorders tend to view stressful situations as more stressful than those with no eating disorders (Hansel and Wittrock 1997; Bittinger and Smith 2003; Quiles Marcos and Terol Cantero 2008). However, most people are confronted with many stressful situations throughout their lives and do not develop an eating disorder. Hence, stress may be a possible antecedent to eating-disordered behavior mediated by other contributing factors in the development of disordered eating.

Over the years, researchers have proposed some interesting theories attempting to explain the mechanisms behind binge eating: for example, the restraint hypothesis, the binge–purge hypothesis, the set-point hypothesis, and theories that consider binge eating an affective disorder or an addiction (Beebe 1994; Fairburn 1995). Heatherton and Baumeister (1991) proposed an interesting explanation for binge eating with the escape model. These authors posit that binge eating acts as an escape from negative self-awareness. According to the authors, individuals who binge eat are very sensitive to not meeting their high standards, feeling an aversive negative state from which they wish to escape. For these individuals, binge eating is a way of focusing all the attention on immediate sensations, thus, turning attention away from themselves and the negative feelings they are experiencing. This model offers an interesting explanation for binge eating although perhaps it does not offer an explanation for this behavior in all individuals. In addition, more research is needed regarding many aspects of the underlying theory.

95.4 The relationship Between Coping and Binge Eating

Numerous studies have examined the relationship between the different coping strategies used and eating pathology (e.g. Mayhew and Edelmann 1989; Yager et al. 1995; Hansel and Wittrock 1997; Wolff et al. 2000; Ball and Lee 2002; Schwarze et al. 2003; García-Grau et al. 2004; Jáuregui Lobera et al. 2009). In one of these studies, Yager et al. (1995) compared the coping strategies used by recovered and nonrecovered women diagnosed with BN. The nonrecovered women with BN had a tendency to use less productive and fewer coping strategies than the recovered women (Yager et al. 1995). Moreover, another study (Garcia-Grau et al. 2004) found that Self-blame, which is a scale of the Intropunitive avoidance dimension in the ACS, was the strategy with the strongest link to the predisposition to eating disorders. Similarly, Mayhew and Edelmann (1989) also found that higher scores on the Eating Disorders Inventory (EDI) were associated to lower self-esteem, more irrational thinking, decreased use of cognitive and behavioral coping strategies, and increased use of avoidance coping. More recently, Quiles Marcos and Terol Cantero (2008) conducted a literature review regarding the role of coping in the eating disorders. They found that eating-disorder patients use avoidance and emotion-oriented coping more often and problem-oriented coping strategies less often than individuals with no eating disorders.

Regarding the relationship between coping and binge eating in particular, based on Heatherton and Baumeister's theory (1991), it may be considered that adolescents who do not have the appropriate skills to confront and deal with their daily problems in a constructive manner may try to escape from the negative feelings and thoughts surrounding the unresolved problems through an escape mechanism, such as binge eating. Therefore, we consider that adolescents with a greater tendency to use avoidance coping strategies would be more prone to binge eating. The individual´s coping style could be viewed as the mediating factor between the stressful situation and binge eating.

Research examining the link between coping strategies and binge eating has shown inconsistent results. Freeman and Gil (2004) found that distraction coping (which is part of avoidance coping) was related to the later risk of future binge eating. Similarly, Wolff et al. (2000) found in their study that the women who binge ate did not differ from the ones who did not binge eat in the number of coping strategies used, but did differ in that they used avoidance coping more frequently. Furthermore, in another study by Hansel and Wittrock (1997), the women who reported binge eating used positive and negative coping strategies more often than the nonbinge eating women. In another study we conducted to explore this relationship in Spanish adolescents, binge eating was found to be associated with avoidance coping (Sierra-Baigrie and Lemos-Giráldez 2008). The adolescents who had problems with binge eating used significantly more frequently avoidance coping and introversion in comparison to those adolescents with no binge eating problems.

On the other hand, several studies have failed to find an association between avoidance coping and binge eating (e.g., Paxton and Diggens 1997; Schwarze et al. 2003). Schwarze et al. (2003) found that the female undergraduate students in their study who reported problems with binge eating were more prone to using avoidance coping strategies than the women who did not binge eat. However, when depression was statistically controlled they did not find a significant difference between the two groups. In addition, Paxton and Diggens (1997) did not find a clear link between avoidance coping and binge eating in a sample of 149 undergraduate students. They also found a confounding effect of depression, that is, the relationship between binge eating and coping depended on the level of depression. Consequently, there is a need to clarify the role of coping strategies in the development and maintenance of binge eating in nonclinical adolescents, given that adolescence is a period of especial interest for the study of these types of subclinical symptoms.

95.5 Coping and Binge Eating in Spanish Adolescents

Recently our research team has conducted a study to further explore the relationship between coping and binge eating in Spanish adolescents. The main objective was to examine the relationship between the coping strategies used by adolescents and the presence of binge eating. Following Heatherton and Baumeister (1991), it was expected that the adolescents who used avoidance coping more often would be more likely to binge eat. Another objective was to examine the adolescents' definition of binge eating and compare it with the actual DSM-IV-TR (APA 2000) definition used by clinicians and researchers.

One thousand nine hundred and thirty-six adolescents from the Principality of Asturias, a northern region in Spain, participated in the study. The age of the participants ranged from 12 to 21 ($M = 14.72$; $SD = 1.73$), 50.3% males and 49.7% females. The participants completed the *Bulimic Investigatory Test, Edinburgh (BITE)* (Henderson and Freeman 1987), the *Adolescent Coping Scale* (ACS) (Frydenberg and Lewis 1993) and *three additional open-ended questions* to obtain more information about the binge eating episodes. The BITE (Henderson and Freeman 1987) is a self-report questionnaire used to evaluate the presence and severity of bulimic symptomatology. It is composed of 33 items divided into two different subscales: a 30-item symptom subscale and a three-item severity subscale. The minimum score on the symptom subscale is 0 and the maximum possible score is 30. The adolescents' coping strategies were measured using the ACS (Frydenberg and Lewis 1993), which is a self-report inventory for the assessment of general coping strategies in 12–18 year-old adolescents. It consists of a total of 80 items (one open-ended question) that reflect different ways of coping and that are rated on a 5-point Likert scale based on the frequency with which the adolescent feels that he/she uses that strategy (1 "It never happens to me or I never do it"; 5 "It happens very frequently or I very frequently do it"). The Spanish adaptation was employed for this study. According to the manual, these 18 coping strategies can be grouped into four different major coping dimensions: positive and effortful action (for example: "I ask a competent person for their advice"), hedonist-positive action (for example: "I do sports"), intropunitive avoidance (for example "I feel guilty") and introversion ("I avoid being with others"). Table 95.3 describes these coping dimensions in more detail.

Finally, to examine the adolescents' binge eating episodes, the participants completed three additional open-ended questions; one of these allowed them to define binge eating in their own words.

Table 95.3 Key Features of the dimensions of coping measured by the ACS

- The ACS is a useful instrument that can be used as a research tool for assessing adolescent coping strategies or as a practical tool for teaching adolescents constructive ways of coping.
- The ACS consists of 18 scales which refer to 18 different ways of coping. According to Frydenberg and Lewis (1993), these scales can be grouped into three different coping dimensions, namely: Solving problem, Reference to others, and Nonproductive coping.
- In the Spanish version of the ACS, the authors found four major coping dimensions which were used in this study. The *Positive* coping dimension refers to the effortful action of attempting to solve the problem, working hard, and achieving. The *Positive-hedonist* dimension refers to looking for healthy ways of distraction from the problem, wishful thinking, investing in close friends, and engaging in physical distraction. *Intropunitive avoidance* refers to not dealing with the problem, looking for ways of reducing the tension, and blaming oneself. Lastly, the *Introversion* dimension makes reference to keeping problems to oneself, not approaching others for help, avoiding professional help or social support.
- These dimensions are useful for comparing styles of coping in adolescents and for examining their relationship with different psychopathological variables.

This table describes the dimensions of coping measured by the ACS

ACS Adolescent Coping Scale

95.5.1 Rate of Binge Eating and Binge Eating Problems in Our Spanish Sample

To question 24 of the BITE *Have you ever binged on food?* 35.9% (688) of the adolescents answered yes (31.5% of the girls and 40.4% of the boys). In Table 95.4 the percentages of the participants who reported binge eating at least once are shown.

Regarding the presence of binge eating problems, the mean score on the BITE for the total sample was 5.22 (SD = 4.34) raging from 0 to 26 points. The mean score was 4.63 (SD = 3.75) for boys and 5.82 (SD = 4.79) for girls. The mean BITE score increased with age (χ^2 = 106.271, p < 0.001) and there were statistically significant differences between the genders (χ^2 = 16.430, p < 0.001) with females obtaining higher mean scores than males.

Consistent with findings from previous research (Aljadir and Liprie 1999; Rodriguez et al. 2001; Vanderlinden et al. 2001; Ackard et al. 2003), the results show that binge eating is a fairly common behavior in nonclinical adolescents. The rate of binge eating obtained in our sample of Spanish non-clinical adolescents (35.6%) is intermediate compared to rates reported in previous studies (e.g., 51% of adolescents in Aljadir and Liprie 1999; 41% in Vanderlinden et al. 2001; 5.15% in Ackard et al. 2003). One interesting finding of the present study was that the rate of binge eating was higher in males than in females, which is contrary to what has been found in other investigations (e.g., Aljadir and Liprie 1999; Ackard et al. 2003). Moreover, many studies do not include males in their samples when exploring eating pathology, such as binge eating. The high rate found in males in the present study, as well as in the study by Aljadir and Liprie (46%), suggest that it is important to include both males and females when studying binge eating in order to explore this behavior using representative samples.

95.5.2 Findings and Implications Regarding the Link Between Coping and Binge Eating

With respect to the link between coping strategies and binge eating, the results showed statistically significant differences in the mean scores on the four dimensions of coping between the adolescents who reported binge eating and those who reported no binge eating (Wilks' λ = 0.949, p < 0.001) (see Table 95.5).

The adolescents who reported at least one episode of binge eating obtained higher mean scores on the dimensions of Intropunitive avoidance (e.g., tension reduction, ignore problem) and Introversion (e.g., keep to oneself, avoid contact with others) and lower mean scores on the Positive dimension of coping (e.g., focus on the positive, concentrate on solving the problem) compared to the adolescents who

Table 95.4 Percentage of reported binge eating by age and gender

Age	Boys	Girls	Total
12–13 (n = 572)	67 (23.42%)	61 (21.32%)	128 (22.37%)
14–15 (n = 694)	139 (37.46%)	100 (30.12%)	239 (34.43%)
≥16 (n = 670)	180 (54.54%)	140 (41.17%)	259 (47.76%)

This table shows the percentages of the adolescents who answered affirmatively to question 24 on the BITE (have you ever binged on food?). As we can observe, this percentage increases with age (χ^2 = 106.271, p < 0.001). In addition, there are also statistically significant differences between males and females (χ^2 = 16.430, p < 0.001), with more males reporting binge eating

Table 95.5 ANOVA results comparing the mean scores (and standard deviations (SDs)) on the dimensions of coping

Coping dimension	Binges ($n = 677$)	No binges ($n = 1203$)	F	p	η^2
Positive	257.68 (40.02)	265.91 (44.97)	15.67	0.000	0.000
Avoidance	141.41 (38.18)	125.16 (35.52)	85.96	0.000	0.043
Positive-hedonist	447.83 (67.19)	442.45 (72.10)	2.53	n.s	0.000
Introversion	201.68 (41.80)	196.86 (42.97)	5.55	0.019	0.000

This table displays the ANOVA results comparing the adolescents who reported binge eating (i.e., those who answered affirmatively to question 24) and those who reported no binge eating (i.e., those who answered negatively) in the four dimensions of coping measured by the Adolescent Coping Scale (ACS)

n.s. non significant, *ANOVA* Analysis of Variance

Table 95.6 ANOVA results comparing the mean scores (and standard deviations (SDs)) on the four dimensions of coping between participants with high and low BITE scores

Coping dimension	High BITE score ($n = 252$)	Low BITE score ($n = 544$)	F	p	η^2
Positive	258.31 (41.10)	269.38 (48.11)	9.982	0.002	0.012
Intropunitive avoidance	163.65 (35.93)	114.29 (32.36)	373.34	0.000	0.320
Positive-hedonist	450.44 (63.95)	436.39 (74.24)	6.712	0.010	0.000
Introversion	205.85 (45.11)	195.97 (41.47)	9.229	0.002	0.011

This table shows the ANOVA results comparing the participants with a high BITE score (i.e., BITE ≥ 10) (indicating binge eating problems) and those with a low BITE score (BITE < 2) in the four dimensions of coping measured by the Adolescent Coping Scale (ACS)

BITE Bulimic Investigatory Test, Edinburgh, *ANOVA* Analysis of Variance

reported no binge eating. However, on the Positive-hedonist dimension the adolescents who reported binge eating obtained higher mean scores than the adolescents without binges, although this difference was not statistically significant. In order to control for the possible confounding effect of age, given that binge eating increased with age, the same analysis was conducted introducing age as a covariate. The analysis showed that age did not alter the results and, therefore, did not affect this relationship.

When this relationship was further explored by comparing the coping strategies used by the adolescents who have binge eating problems (BITE ≥ 10) and those who do not (BITE < 2), the results showed significant differences in all four dimensions of coping (Wilks' $\lambda = 0.673$, $p < 0.001$) (see Table 95.6).

As can be seen in Table 95.6, the group with binge eating problems obtained significantly higher mean scores in the Intropunitive avoidance and Introversion coping dimensions than the group with no binge eating problems. Therefore, the adolescents with binge eating problems use nonproductive coping strategies more frequently, such as not coping with the problem, keeping it to oneself, self-blame or seeking ways of reducing tension, in comparison to those with no binge eating problems. On the other hand, the adolescents with binge eating problems use positive strategies such as working hard and achieving and focusing on the positive less frequently.

The results are consistent with past research regarding the link between avoidance coping and binge eating and eating pathology in general (Hansel and Wittrock 1997; Wolff et al. 2000; Ball and Lee 2002; García-Grau et al. 2004; Sierra-Baigrie and Lemos-Giráldez 2008); however, other studies have found inconsistent results (Paxton and Diggens 1997; Schwarze et al. 2003). With respect to the Positive coping dimension, previous studies have found that the adolescents who report binge eating use positive strategies less frequently (Quiles Marcos and Terol Cantero 2008) whereas other studies have failed to support this association (e.g., Hansel and Wittrock 1997; Wolff et al. 2000). The adolescents in our sample who reported binge eating use positive-coping strategies, such as trying to solve the problem, focusing on the positive, or asking for help, less frequently than the adolescents who

reported not having binges. On the other hand, they reported using avoidance coping more frequently, perhaps due to the fact that they lacked the positive coping strategies needed to appropriately deal with stressful situations. These findings suggest that those adolescents who have a tendency to engage in binge eating may lack the proper skills to deal with daily problems or stressful situations, therefore, making use of less constructive ways of coping, such as avoidance coping. It would be interesting to determine which situations are associated with the use of avoidance-coping strategies in adolescents who binge eat and compare them to the strategies used by those who do not.

95.5.3 The Adolescents' Definition of Binge Eating: Analysis and Implications

With respect to the adolescents' definition of binge eating, there was a clear tendency to describe eating binges solely in terms of the large amount of food eaten. In our study, 76.23% of the participants' who answered ($n = 1662$) described binge eating solely in terms of amount eaten, 13.23% also mentioned time in their definition and only 9.40% described binge eating using the three variables included in the DSM-IV-TR (APA 2000) definition of binge eating (amount, time and loss of control). There were no significant differences in the variables mentioned by the adolescents who have problems with this behavior (BITE ≥ 10) and those who do not (BITE < 2) ($\chi^2 = 4.435$, $p = 0.218$). However, significant gender differences were found in the variables mentioned ($\chi^2 = 55.649$, $p < 0.001$) with a higher percentage of girls taking the three variables into account. On the other hand, there were no significant differences in the variables mentioned in the definitions by the different age groups ($\chi^2 = 9.006$, $p = 0.173$). Regarding the adequacy of the DSM-IV's definition of binge eating (APA 1994), a study was conducted at the University of Manitoba (Sierra-Baigrie 1997), which examined the effect of these three variables (amount eaten, time, and loss of control) in the identification of eating episodes as binges. There was a significant effect of amount eaten on the ratings with no effect found for time. Furthermore, loss of control interacted with both time and amount eaten. The results underscore the importance of loss of control in the identification of eating episodes as binges. However, in the present study there were very few adolescents who mentioned loss of control in their definition of binge eating. There are some possible explanations for this finding. On the one hand, the adolescents may have difficulties in verbalizing different behaviors or feelings thus focusing on the objective factors (such as amount) as opposed to the more subjective variables (such as loss of control). Perhaps when defining what a binge is, people take into account more objective variables with the more subjective variables being more important when rating one's own behavior.

95.6 Future Lines of Research

Some questions still remain regarding the relationship between coping and binge eating, such as why some studies have found that individuals who binge eat use more positive and negative coping strategies than those who do not engage in this behavior, that is, that binge eaters seem to use a greater number of strategies. More research is needed to clarify this relationship to further explore the types of avoidance-coping strategies used by the adolescents who binge eat before binge eating becomes a significant problem in order to gain understanding of the development of this eating problem. Longitudinal studies are needed to determine if those adolescents who have a tendency to use avoidance coping when confronted with stressful situations have a higher future risk of binge eating problems. Furthermore,

studies should also explore the circumstances under which binge eaters use avoidance coping more frequently as well as the factors associated with the use of avoidance coping in children and adolescents. Strategies for the prevention of binge eating problems could focus on these unproductive-coping strategies by helping children and adolescents find positive ways of dealing with stressors and, therefore, avoiding the development of unhealthy habits such as drug abuse or binge eating.

Regarding the adolescents' definition of binge eating, the findings of the study have important implications as well. The results suggest that the definition used by the adolescents and that used by clinicians and researchers may differ, which brings doubts about whether studies that measure binge eating without explicitly mentioning the three variables considered by the DSM-IV-TR (APA 2000) obtain a true measure of this behavior. Adolescents may be referring to overeating episodes as binge eating episodes which may falsely identify adolescents as binge eaters who in reality are not. It may be necessary to either explain what binge eating is according to the diagnostic manuals or formulate questions which explicitly consider the three variables mentioned in the definition. Another possibility is to use a two-stage procedure for the detection of individuals who binge eat, which has been shown to provide more accurate ratings as the interviewer in the second stage can explain more clearly what the questions mean, which significantly reduces the misunderstanding of questions (Peláez-Fernández et al. 2008). Future research could attempt to examine the variables which are taken into account by adolescents when rating their own eating episodes as binges.

In short, the review of the literature shows that binge eating is a fairly frequent behavior among adolescents and that it is associated to the use of avoidance coping strategies. These findings have important implications with respect to the prevention of binge eating and, consequently, of eating disorders and obesity, as well as contribute to the advancement in the understanding of this phenomenon in nonclinical adolescents. One possible means for the prevention of binge eating could be to focus on the adolescents' coping skills, helping them develop healthy and productive ways of coping with their problems. Moreover, it may be useful to identify when adolescents use avoidance coping strategies more often and show them ways of dealing with the feelings or the situations that trigger an escape mechanism.

95.7 Applications to Other Areas of Health and Disease

Regular binge eating has important consequences for the person's physical and psychological health. Binge eating has been found to be associated to a higher body mass index (BMI), lower self-esteem, depressive symptoms, decreased satisfaction with body image, and a higher risk of suicide attempts (Ackard et al. 2003). Individuals who engage in frequent binge eating episodes have a greater probability of developing a full-blown eating disorder in the future, such as BN or BED (Didie and Fitzgibbon 2005). On the other hand, binge eating is often associated to other pathological eating-related behaviors (such as fasting or extreme or unbalanced diets) and compensatory methods to prevent weight gain (such as vomiting, laxative misuse, etc.) which can also be very harmful. Moreover, frequent binge eating not accompanied by compensatory methods can lead to weight gain and obesity which also have important physical, psychological, and social consequences for the person. For example, it is well documented that obesity increases the risk for cardiovascular disease, sleep disorders, and Type II diabetes, among others (de la Serna 1998). Furthermore, obesity can be associated to a decrease in social relationships, difficulties in finding a partner, low self-esteem, depression, anxiety, and so on (de la Serna 1998). All these risks and consequences associated to binge eating clearly show the importance of its study, prevention, and treatment. Thus, the study of binge eating is important to prevent the onset of this behavior in young individuals who have not yet developed an eating-related disorder, and therefore, prevent the development of all the aforementioned associated risks.

With regards to coping strategies, numerous studies have shown that the use of avoidance coping is associated to a higher risk of developing other psychological problems, for example, depressive symptomatology, anxiety, or substance abuse (e.g., Liu et al. 2004; Figueroa et al. 2005; Ireland et al. 2005). Thus, showing children and adolescents healthy and constructive ways of coping with daily stressors can also prevent other mental problems in the future.

Summary Points

- The literature shows that binge eating is a fairly frequent behavior in adolescents.
- Binge eating is associated to considerable psychological, physical, and social impairment in some individuals and it is a symptom of two major eating disorders.
- It is important to study the variables associated to this maladaptive eating behavior in nonclinical samples to establish the mechanisms involved and find ways of preventing this behavior and, therefore, future eating problems.
- Numerous studies have found an association that avoidance coping is associated to binge eating; however, some studies have failed to find this association. Therefore, more research is needed to clarify this relationship.
- In our study of nonclinical Spanish adolescents, those who reported binge eating used avoidance coping and introversion strategies more frequently than those who reported no binge eating. On the other hand, they used positive coping strategies less frequently.
- Most of the Spanish adolescents in our study defined binge eating solely based on the amount eaten with very few adolescents mentioning loss of control. Therefore, there could be an overestimation of this behavior when using selfreport measures.
- Thus, the clinical definition of binge eating seems to differ from the nonprofessional understanding of the term, which could hinder proper communication between clinicians and patients.

Definitions and Explanations of Key Terms

Binge eating: This refers to eating a large amount of food in a relatively short period of time with a feeling of not being able to control how much one eats. The individual usually feels very distressed, uncomfortably full, and extremely upset with him/herself after the episode.
Coping strategies: This makes reference to the ways in which a person deals with daily stressors or stressful events. These can be behavioral, emotional, or cognitive approaches to deal with the problem.
Avoidance coping: It refers to unproductive or nonconstructive ways of coping with problems or problematic situations. Examples of avoidance coping are: not dealing with the problem, blaming oneself, or engaging in behaviors to reduce the associated tension, such as binge eating or alcohol consumption.
Compensatory methods: These refer to those behaviors eating-disordered individuals use to avoid gaining weight after overeating, such as vomiting, abusing laxatives, and excessive exercise. The most common compensatory method used by bulimics is self-induced vomiting.
Subthreshold or subclinical eating disorder: These are eating problems of clinical significance which do not meet the criteria for the diagnosis of a recognized eating disorder but that, nevertheless, are very distressing for the person.

References

Ackard DM, Neumark-Sztainer D, Story M, Perry C. Overeating among adolescents: prevalence and associations with weight-related characteristics and psychological health. Pediatrics. 2003;111:67–74.

Aljadir LP, Liprie ML . High rate of binge eating among young adolescents. J Am Diet Assoc. 1999;99:A50.

American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4th ed., Washington, DC: Author; 1994.

American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4th ed., text revision. Washington, DC: Author; 2000.

Amigo I. La delgadez imposible [The impossible thinness]. Barcelona: Paidos Ibérica S.A; 2003.

Ball K, Lee C. Psychological stress, coping, and symptoms of disordered eating in a community sample of young Australian women. Int J Eat Disord. 2002;31:71–81.

Beebe DW. Identification of "binge prone" women: An experimentally and psychometrically validated cluster analysis in a college population. Br J Clin Psychol. 1994;33:259–276.

Beglin SJ, Fairburn CG. What is meant by the term binge? Am J Psychiatry. 1992;149:123–124.

Benjamin SJ, Wulfert E. Dispositional correlates of addictive behaviours in college women: binge eating and heavy drinking. Eat Behav. 2005;6:197–209.

Bennett DA, Cooper CL. Eating disturbance as a manifestation of the stress process: a review of the literature. Stress Med. 1999;15:167–182.

Bittinger JN, Smith JE. Mediating and moderating effects of stress perception and situation type on coping responses in women with disordered eating. Eat Behav. 2003;4:89–106.

Croll J, Neumark-Sztainer D, Story M, Ireland M. Prevalence and risk and factors related to disordered eating behaviours among adolescents: relationship to gender and ethnicity. J Adolesc. 2002; Health 31:166–175.

De la Serna I. Comer no es un placer [Eating is not a pleasure]. Madrid: Litofinter, S.A.; 1998.

Didie ER, Fitzgibbon M. Binge eating and psychological distress: is the degree of obesity a factor? Eat Behav. 2005;6:35–41.

Fairburn CG. Overcoming binge eating. New York: Guilford; 1995.

Figueroa MI, Contini N, Betina Lacunza A, Levín M, Estévez Suedan A. Las estrategias de afrontamiento y su relación con el nivel de bienestar psicológico. Un estudio con adolescentes con nivel socioeconómico bajo de Tucumán (Argentina) [Coping strategies and its relation to the level of psychological wellbeing. A study with adolescents of low socioeconomic status from Tucumán (Argentina)]. An Psicol. 2005;21:66–72.

Fisher S, Anderson KG, Smith GT. Coping with distress by eating or drinking: role of trait urgency and expectancies. Psychol Addict Behav. 2004;18:269–274.

Freeman LM, Gil KM. Daily stress, coping and dietary restraint in binge eating. Int J Eat Disord. 2004;36:204–212.

Frydenberg E, Lewis R. ACS: Escalas de Afrontamiento para Adolescentes [ACS: Adolescent Coping Scale]. Madrid: TEA Editions; 1993.

García-Grau E, Fusté A, Miró A, Saldaña C, Bados A. Coping style and vulnerability to eating disorders in adolescent boys. Eur Eat Disord Rev. 2004;12:61–67.

Ghaderi A. Structural modeling analysis of prospective risk factors for eating disorder. Eat Behav. 2003;3:387–396.

Hansel Sl, Wittrock DA. Appraisal and coping strategies in stressful situations: a comparison of individuals who binge eat and controls. Int J Eat Disord. 1997;21:89–93.

Heatherton TF, Baumeister RF. Binge eating as an escape from self-awareness. Psychol Bull. 1991;110:86–108.

Henderson M, Freeman CP. A self-rating scale for bulimia. The "BITE". Br J Psychiatry. 1987;150:18–24.

Ireland JL, Boustead R, Ireland CA. Coping style and psychological health among adolescent prisoners: a study of young and juvenile offenders. J Adolesc. 2005;28:411–423.

Jàuregui Lobera I, Estébanez S, Santiago Fernández MJ, Álvarez Bautista E, Garrido O. Coping strategies in eating disorders. Eur Eat Disord Rev. 2009;17:220–226.

Liu X, Tein JY, Zhao Z. Coping strategies and behavioral/emotional problems among Chinese adolescents. Psychiatry Res. 2004;126:275–285.

Mayhew R, Edelmann J. Self-esteem, irrational beliefs and coping strategies in relation to eating problems in a non-clinical population. Pers Individ Dif. 1989;10:581–584.

McLaren L, Gauvin L, Steiger H. A two-factor model of disordered eating. Eat Behav. 2001;2:51–65.

Paxton SJ, Diggens J. Avoidance coping, binge eating and depression: An examination of the escape theory of binge eating. Int J Eat Disord. 1997;22:83–87.

Peláez-Fernández MA, Labrador FJ, Raich RM. Comparison of single- and double-stage designs in the prevalence estimation of eating disorders in community samples. Span J Psychol. 2008;11:542–550.

Quiles Marcos Y, Terol Cantero MC. Afrontamiento y trastornos de la conducta alimentaria: un estudio de revisión [Coping and eating disorders: a review study]. Rev Latinoam Psicol. 2008;40:259–280.

Rodríguez A, Novalbos JP, Martínez JM, Ruiz MA, Fernández JR, Jiménez D. J Adolesc Health. 2001;28:338–45.

Schwarze NJ, Oliver Jm, Handal PJ. J Coll Student Dev. 2003;44:644–52.

Sierra-Baigrie S. Judgements of videotaped eating episodes as binges: effects of DSM-IV criteria, size and duration of episode, and loss of control over eating (unpublished document). Winnipeg: University of Manitoba; 2003.

Sierra-Baigrie S, Lemos-Giráldez S. Span J Psychol. 2008;11:172–80.

Spitzer RL, Stunkard A, Yanovski S, Marcus MD, Wadden T, Wing R, Mitchell J, Hasin D. Int J Eat Disord. 1993;13:161–9.

Stickney MI, Miltenberger RG, Wolf G. J Behav Ther Exp Psychiatr. 1999;30:177–89.

Vanderlinden J, Grave RD, Vandereycken CN. Eat Behav. 2001;2:79–83.

Williams K, McGillicuddy-De Lisi A. J Appl Dev Psychol. 2000;20:537–49.

Williamson DA. Assessment of eating disorders. Elmsford: Pergamon; 1990,.

Wolff GE, Crosby RD, Roberts JA, Wittrock DA. Addict Behav. 2000;25:205–16.

Yager J, Rosty M, Rosotto E. J Nerv Ment Dis. 1995;183:86–94.

Chapter 96
Nutritional Influences on Antisocial Behavior

David Benton

Abbreviations

ADHD	Attention deficit hyperactivity disorder
DHA	Docosahexaenoic acid
EPA	Eicosapentaenoic acid
GI	Glycemic index
LCPUFA	Long chain poly-unsaturated fatty acids

96.1 Introduction

There have been a series of suggestions that what we eat may either increase or decrease irritability or the likelihood of displaying antisocial behaviour, even violence or criminality. Various possible mechanisms have been explored. It has been proposed that some individuals are sensitive to particular foods, so that their consumption leads to antisocial behaviour; in particular, sugar and food additives have attracted attention. Diets low in vitamin, minerals, and essential fatty acids have also been related to displays of violence. Finally the influence of the consumption of meals that result in low levels of blood glucose has received attention. This is an area where there has been relatively less research although there are a growing number of well-designed double-blind placebo-controlled trials. There is a need for studies that use this approach as it is clear that changing some aspects of the diet often produces a large placebo effect, a reflection of suggestion and expectation (Table 96.1).

96.2 Food Intolerance

Food intolerance or food hypersensitivity reflects an adverse physiological response to a food item by means other than that of the immune system. Although in the past, on occasions, an allergic reaction to food has been included as a form of food intolerance, more recently, the correct medical term has become nonallergic food hypersensitivity. Food allergy by definition reflects an immunological

---

D. Benton (✉)
Department of Psychology, University of Wales Swansea, Swansea SA2 8PP, Wales, UK
e-mail: d.benton@swansea.ac.uk;

Table 96.1 Key ways that diet influences antisocial behavior

Ways that diet may influence antisocial behavior:
- Food intolerance
- A lack of essential fatty acids
- Developing low blood glucose levels
- A diet low in minerals and vitamins

Diet had been suggested to influence behavior in various ways. The four most commonly proposed are listed

reaction that can be monitored by measuring the release of Immunoglobulin E. In contrast, food intolerance may reflect a pharmacological reaction, for example, to histamine, or alternatively a response to a toxin. Finally, a problem in the metabolism may also occur such as that associated with an enzyme deficiency; for example, lactase deficiency prevents the normal breakdown of the milk sugar lactose. As well as reacting adversely to food items, it is possible to respond to food additives; for example, a preservative, coloring, or artificial flavor. In particular it has been suggested that ADHD can be induced or at least exacerbated by diet.

As placebo effects can be substantial in this area, it is particularly important to consider double-blind trials. Children eat a "few-foods" diet, one that contains a limited number of items with a small chance of inducing an adverse reaction. Additional foods are then reintroduced that remain as part of the diet if there is no adverse reaction. Finally those foods to which there was an adverse reaction are tested using a double-blind procedure in which two similar meals are cooked that either do or do not contain the suspect food item. Benton (2007) subjected five such studies to meta-analysis and found an effect size of 0.8 of a standard deviation, i.e., a large response. The nature of the effect can be illustrated by the study of Egger et al. (1985). They found 48 foods to which at least one child responded adversely. Although, 79% of the children responded to the yellow artificial colour tartrazine and the preservative sodium benzoate, there was no child who did not in addition react to other food items. However, as there are many thousands of food additives and flavorings this cannot be generalized to other substances as each needs to be considered individually. The 8 most common problem foods are listed in Table 96.2. It is clear that an adverse response was not particularly associated with processed foods. There is an impression that many if not most foods can be a problem for at least a minority. Apparently "natural" and "healthy" items such as fruit were a problem for some. Sugar, that has attracted a great deal of negative attention, was less of a problem than 13 other foods. In fact the term "natural" has been frequently misused. Some of the most poisonous substances come from nature and similarly the chemist is capable of creating health-promoting molecules. In both instances we need to test the item to establish its safety in general and in particular whether there is a behavioral response. In this area it is not possible to offer general advice as each child has an individual pattern of response. No particular additive or food has been found to be a universal cause of problems.

Although these studies produce strong evidence that the behavioral problems of some children reflect a response to their diet, it should be remembered that this was a self-selected group whose parents believed prior to the study that they responded to what they ate. As such we cannot assume that a response to diet occurs in all children with a diagnosis of ADHD. In addition as the etiology of ADHD is known to be multifactorial, at the most, diet is one potential problem among many others.

At least among self-help groups, the ideas of Feingold (1975) continue to be advocated. Although his views were based on clinical observations rather than well-designed studies, he suggested that hyperactive behavior was stimulated by a diet containing salicylates (chemicals in food that have a similar structure to aspirin). Although it was not the purpose of the studies that used elimination diets

Table 96.2   Foods to which hyperactive children react

Cows milk	64%
Wheat	49%
Cows cheese	40%
Hens egg	39%
Beef	16%
Pork	13%
Chicken	11%
Potatoes	11%

The data are from the study of Egger et al. (1985) that studied children with ADHD whose parents prior to the study suspected that they responded adversely to their diet. They initially ate a "few foods" diet and then additional items were added one by one. If there was no adverse reaction the food item remained as part of the diet. Finally under double-blind conditions genuine adverse responses to diet were established. In total there were nearly 50 foods to which at least one child responded; the 20 most problematic foods and the percentage of children who responded are reported

Table 96.3   The number of children reacting to the Feingold diet

Tartrazine/sodium benzoate	79%	Fish	23%
Cows milk	64%	Oats	23%
Chocolate	59%	Pineapple	19%
Grapes	49%	Beef	16%
Wheat	49%	Sugar	16%
Oranges	45%	Malt	15%
Cows cheese	40%	Beans	15%
Hens egg	39%	Peas	15%
Peanuts	32%	Apples	13%
Maize	29%	Pork	13%

The Feingold diet proposes that a diet containing food items low in salicyclic acid will decrease hyperactive behavior and recommends the consumption of the above foods. These data taken from Egger et al. (1985) show the proportion of hyperactive children who responded adversely to the foods in the Feingold diet. The data do not support this approach

they are a powerful test of the Feingold hypothesis. It is clear in these double-blind trials that many children responded adversely to the foods low in salicyclates, which form the core of the Feingold diet (Table 96.3). Thus, although diet can be a problem for some children, the evidence from well-designed studies suggests that a diet low in natural salicylates is not helpful (Benton 2007).

There are isolated yet similarly convincing data from adults. For example Mackarness (1976) described a patient with a history of violence both toward her children and herself, who was being recommended for brain surgery to control her behavior. Similar to the study of children mentioned earlier, the test of a "few-foods" diet established the items to which she responded adversely. In this case they were then tested under double-blind conditions by introducing them via a tube directly into the stomach. When a new diet was developed the antisocial behavior ceased. Although it is unlikely that this is a unique case there is no way of knowing how frequently such a reaction occurs.

96.2.1 Additives

Repeated attention has been drawn to the suggestion that children may react adversely to food additives by displaying hyperactive-related behavior. Although the study of food intolerance produced evidence that some children react adversely to some additives, among other aspects of diet (Egger et al. 1985; Benton 2007), it is important to establish the extent of the problem. Schab and Trinh (2004) statistically integrated the findings of 15 well-designed studies that had examined the effect of artificial food colorings on those who displayed hyperactivity. They concluded that some additives adversely influenced behavior, however, to a greater extent in children whose parents, prior to the study, suspected that they did react to their diet. The influence of such food additives on the general population has been considered less than in those with ADHD. It has been suggested that younger children maybe more susceptible, in particular those with a general tendency to display an allergic reaction to many substances, for example, grass pollen.

Although data from samples of the general population are limited, an interesting study of 4-year-olds compared the reaction to a cocktail of food additives in those who either had or did not have a history of hyperactivity, and did or did not react to a series of allergens in a skin prick test. Based on parental ratings of activity, a reaction was found irrespective of whether there was a history of hyperactive behavior or an allergic tendency (Bateman et al. 2004). Similar findings were produced in a subsequent study of 3-year-old and 8/9-year-old children drawn from the general population (McCann et al. 2007). The use of a cocktail of five additives makes it unclear which substance was influential or whether combinations of additives rather than a single substance may be critical. It would be premature to draw conclusions from such limited data but the use of a community-based sample raised the possibility of a more general response to additives than had been suspected. However, when the European Food Standards Agency reviewed these studies they found the findings in this area to be inconclusive.

96.3 Fatty Acids

Two families of fatty acids, n-3 (omega-3) and n-6 (omega-6), have attracted an increasing amount of interest as it has been suggested that they are associated with a predisposition to depression, schizophrenia, anxiety, aggression, antisocial behavior, and ADHD. A review, however, concluded that "the evidence available is currently limited and highly inconsistent" (Appleton et al. 2008).

These two families of fatty acids are said to be "essential" as they form part of the diet as they cannot be manufactured by the body. Oily fish and some white fish are good sources of essential fatty acids although they are also found in flax; hemp; sunflower, pumpkin, and rape seeds; walnuts; and leafy vegetables.

As well as an effect on the brain these essential fatty acids have been suggested to help many dozens of physical ailments, in fact virtually all common diseases. Although we await confirmation of their influence, if these molecules affect so many seemingly unrelated biological phenomena then they must be acting at a fundamental level. These fatty acids play many important roles including the formation of eicosanoids that are signaling molecules involved in the control of inflammation and immunity as well as acting as messengers in the brain; they become cannabinoids (the endogenous molecules that act at the same neural sites as the active ingredients of cannabis); they influence protein activity directly and by influencing transcription. They have both a structural and a functional role in the brain and, in particular, attention has been directed to their influence as part of neuronal membranes. Cell membranes are a double layer of phospholipids, each of which contains two fatty acids

as part of their structure. Within the resulting phospholipid matrix are receptors and ion channels, so that the nature of the fatty acids will influence the structure of membrane-bound receptors and therefore the passage of information in and out of the cell (Stillwell and Wassall 2003).

Table 96.4 illustrates the sequence of n-3 and n-6 fatty acid metabolism. The essential fatty acids are α-linolenic acid, the beginning of the n-3 sequence; and linoleic acid, the starting point of n-6 metabolism. It is not, however, these genuinely essential substances that are important but rather some of their metabolites. From these two starting points the two metabolic pathways are illustrated with DHA being the finishing point in the case of n-3 metabolism, with the corresponding end point for n-6 being Docosapentaenoic acid. When considering the brain, attention should be paid to

Table 96.4   The synthesis of omega-3 and omega-6 fatty acids

Omega-3 FATTY ACIDS		Omega-6 FATTY ACIDS
Alpha-linolenic acid		Linoleic acid
↓	*Delta 6-desaturase*	↓
Octadecatetranoic acid		Gamma-linolenic acid
↓	*Elongase*	↓
Eicosatetraenoic acid		Dihommogamma linolenic acid
↓	*Delta 5-desaturase*	↓
Eicosapentaenoic acid (EPA)		**Arachidonic acid**
↓	*Elongase*	↓
Docosapentaenoic acid		Adrenic acid
↓	*Elongase*	↓
Tetracosapentaenoic acid		Tetracosatetraenoic acid
↓	*Delta 4-desaturase*	↓
Tetrahexaenoic acid		Tetacosapentaenoic acid
↓	*Beta-oxidation*	↓
Docosahexaenoic acid (DHA)		Docosapentaenoic acid

Omega-3 and omega-6 fatty acids are described as "essential" as they have to form part of the diet as they cannot be manufactured by the body. They are of particular interest as they are found in particularly high amounts in the brain and a relationship with many aspects of behavior, including depression, violence and intellectual development has been proposed. The metabolic pathways of these essential fatty acids are shown. Those in bold have attracted particular interest

Arachidonic acid and DHA as they play major structural roles, making up about 20% of the dry mass of the brain. High amounts of DHA are found in both synapses and photoreceptors. In addition, EPA has attracted attention as it has often been used in addition to DHA as a supplement.

Diets in industrialized countries are generally low in n-3 fatty acids and the DHA status of both the newborn and infants who are breast-fed, depends greatly on the diet of the mother. Human breast milk contains n-3 and n-6 fatty acids and during neonatal life these rapidly become part of the quickly growing brain. However, although there are many reports that the cognitive development of breast-fed infants is better than those who were bottle-fed, it is difficult to disassociate confounding factors such as the background and education of the mother. Fleith and Clandinin (2005), however, concluded that the "literature suggests that LCPUFA is important to the growth and development of infants".

96.3.1 Attention Deficit Hyperactivity Disorder

Although ADHD is known to be multifactorial in origin, Richardson and Puri (2000) reviewed the evidence that it is associated with a deficiency of essential fatty acids. For example Stevens et al. (1995) reported that those with ADHD had lower levels of fatty acids in plasma and red blood cells. In addition they were less likely to have been breast-fed and were more likely to suffer with allergies that are known to be associated with a deficiency of fatty acids. Other signs of deficiency were also found such as dry skin, dry hair, and drinking a lot. Interestingly, the dietary intake of poly-unsaturated fatty acids was greater in those with ADHD and did not differ in those with symptoms of deficiency, suggesting the possibility of a metabolic rather than dietary problem. Four out of five studies found low levels of n-3 fatty acids in those with ADHD and that there was a high n-6 to n-3 PUFA ratio (Appleton et al. 2008).

However, in three out of four intervention trials of children with a diagnosis of ADHD the consumption of n-3 fatty acid supplements failed to improve symptoms. In contrast, in four out of five studies of children with problems such as a lack or coordination, autism or self-harming, supplementation improved symptoms such as hyperactivity or impulsivity (Appleton et al. 2008). The area is, however, characterized by unsystematic results, where in a particular study one measure of hyperactivity-related behavior was influenced but others were not, or that significant findings were obtained from parental but not teachers ratings.

96.3.2 Aggression/Hostility

In a sample of nearly 5,000 American children, those with a total cholesterol concentration in the lowest quartile were almost threefold more likely to have been suspended or expelled from school (Zhang et al. 2005): it maybe that a low total cholesterol level is a risk factor for aggression. Although it has not been demonstrated that a diet-induced increase in serum cholesterol reduces antisocial behaviour in humans, monkeys fed a low fat diet have been found to be more aggressive (Kaplan et al. 1991). More specifically PUFA status has been considered. When examining risk factors for heart disease, young men who consumed fish rich in omega-3 fatty acids were found to be less likely to report feeling hostile (Iribarren et al. 2004). More specifically, in a sample of habitually violent and impulsive prisoners the level of dihomogammalinolenic acid and some subsequent n-6 acids were elevated (Virkkunen et al. 1987), perhaps indicating the importance of the n-3/n-6 ratio. However, although there is increasing epidemiological data that relates aspects of fat metabolism to aggressive and impulsive behavior, more easily interpreted data come from intervention studies.

Benton ([2007]) used meta-analysis to consider eight well-designed intervention studies that had given PUFA supplements and monitored the response using standard questionnaires to assess violence, hostility or aggression. He found that the incidence of aggression was significantly less in those taking PUFA supplements rather than a placebo. Six out of the eight studies had given a large dose of DHA combined with a smaller dose of EPA. The findings were obtained in a range of populations that varied in terms of age and pre-existing behavioral tendency, a consistency that suggested a fairly general influence on aggressiveness, although replications in specific populations will be necessary before making a recommendation.

In summary, fatty acids are essential dietary components that are found in high concentrations in the brain. Repeatedly, an association has been reported between PUFA levels found in biological samples and aggressive/impulsive behavior. Intervention studies have tended to find that n-3 fatty acid supplements decrease aggression although we need to further consider the composition of the supplements and the interaction with both individual differences in the ability to metabolize fatty acids and the pre-existing diet.

96.4 Hypoglycemia

In the general public there is a common assumption that a fall in blood glucose levels is associated with feelings of irritability, or even a predisposition to aggression. In turn, a fall in blood glucose has been popularly assumed to reflect the consumption of refined carbohydrate; in particular, sugar. Blood glucose levels rise progressively during the first half hour after eating a meal, as the carbohydrate in the meal is digested and released into the bloodstream. The rise in blood glucose stimulates the release of insulin that helps blood glucose levels to return to the optimal range for the body by causing glucose to be taken up by the liver and other cells. Figure 96.1 illustrates the phenomenon. On occasions, in susceptible individuals, the release of insulin is sufficient to cause blood glucose to
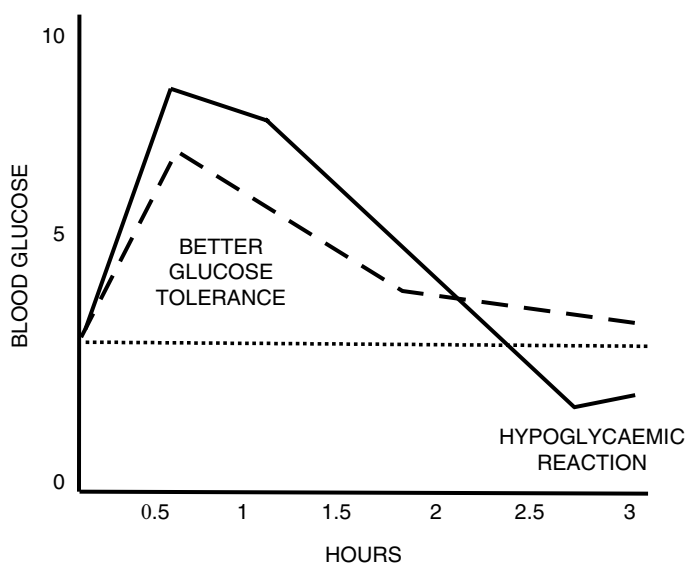
Fig. 96.1 Changes in blood glucose after consuming glucose. In a Glucose Tolerance Test blood glucose levels are monitored following the consumption of a glucose drink. In one individual after 2½ h the values are below the baseline. A tendency to develop low levels of blood glucose has been associated with a tendency to be aggressive. The data are mmol/L

fall to levels low enough to disrupt brain functioning. This marked fall in blood glucose was originally called spontaneous hypoglycemia but is also termed food-stimulated, reactive, functional, or postprandial hypoglycemia.

The brain is the most metabolically active organ in the body and unlike other organs, except under extreme conditions such as starvation, relies on a supply of glucose as its source of energy. As the stores of glucose in the brain are enough for only about 10 min, the supply of this basic fuel has to be continuous (Benton 2005). When glucose values fall to low levels the functioning of the brain is impaired causing confusion, blurred vision, and even violent outbursts. Under such circumstances counter-regulatory mechanisms increase blood glucose levels; these include the release of adrenaline (epinephrine) and glucagon that both cause the liver to release glucose into the blood. In turn other effects of adrenaline, such as stimulating heart rate, can be mistaken for anxiety.

Such has been the concern about this possible adverse reaction to our diet that various nutrition-related professional bodies issued a statement (Ad hoc committee 1973): "Valid evidence is lacking to support the hypothesis that reactive hypoglycemia is a common cause of violent behavior…." However, more recently there has been some evidence that a response to diet may play a role in antisocial behaviour, although it may occur with levels of blood glucose that are not sufficiently low to attract a diagnosis of clinical hypoglycemia.

Benton (2007) reviewed the evidence that individual differences in the ability to control the level of blood glucose may be important. In three very different samples a tendency to develop low levels of blood glucose was associated with hostility and violence: in Peruvian Indians, violent criminals, and undergraduates. Two intervention-studies were described in which consuming a glucose-containing drink, rather than a placebo, decreased the likelihood of behaving in an irritated manner. Donohoe and Benton (1999) gave a drink containing 50 g of glucose after fasting overnight and monitored changes in blood glucose. The lower that the levels of blood glucose fell after the initial rise the more likely it was that the subjects described themselves as aggressive. There was a cutoff, below a nadir of 60 mg/dL (3.3 mmol/L) in the Glucose Tolerance Test, where an aggressive tendency was more likely to be reported.

Throughout the day the level of blood glucose is usually maintained in the range 70–150 mg/dL (3.9–7.8 mmol/L). There is no commonly agreed value below which hypoglycemia is said to occur, although the lower limit of the normal range is variously said to be 60 or 70 mg/dL (3.3 or 3.9 mmol/L). The level of blood glucose below which the normal functioning of the brain is compromised will vary from individual to individual but is likely to be about 40 mg/dL (2.2 mmol/L) (Benton 2005). It is likely that few, if any, of the subjects reviewed by Benton (2007) had blood glucose levels low enough to attract a clinical diagnosis of hypoglycemia. Thus, it appears that an aggressive tendency occurs when blood glucose are low, yet higher than the levels needed to diagnose clinical hypoglycemia.

The question arises as to the frequency with which low blood glucose influences aggressiveness. The Glucose Tolerance Test monitors blood glucose levels for several hours after a glucose drink. Lev-Ran and Anderson (1981) found that the blood glucose levels of only 1 in 40 individuals fell to 40 mg/dl (2.2 mmol/L), the value at which hypoglycemic symptoms would begin to appear. However, the consumption of pure glucose by itself, after fasting overnight, is not typical of a normal diet. Benton (2007) after reviewing the topic concluded that when eating a normal diet throughout the day there is surprisingly little evidence of marked changes in blood glucose; rather there is a picture of blood glucose stability. The presence of both protein and fat alters the rate at which glucose is released into the blood stream, such that typical meals rarely stimulate reactive hypoglycemia.

It remains possible that there maybe an interaction between the composition of the diet and basic physiology; such that those with a tendency to release larger amounts of insulin might benefit from a low glycemic diet. The findings of an American study are consistent with this view. In a Florida institution,

those who did and did not report symptoms of hypoglycemia were distinguished (Fishbein 1982). Half ate their usual diet and half consumed meals designed to reduce the release of glucose into the blood. The scores on a questionnaire dealing with maladaptive behavior declined only in a quarter of those monitored; those with a history of hypoglycemic symptoms who had eaten the low glycemic diet.

96.4.1 Sugar Consumption

Sugar has had a particularly bad press as it has been suggested that it causes behavioral problems in children. As only double-blind intervention trials can offer evidence of a causal relationship, the meta-analysis of such data is critical. Based on 23 samples of children Wolraich et al. (1995) found that irrespective of the measure recorded, or the behavior monitored, sugar did not have an adverse influence. Benton (2008) considered a variety of suggestions made to account for these negative findings; for example, it may be only children with ADHD who react, or a reaction may be more likely to occur in younger children. Again, well-designed studies did not support such suggestions.

It has also been proposed that the incidence of violent behavior in prison can be decreased by reducing the level of sugar in the diet (Schoenthaler 1982). In the USA, a series of early studies claimed to have reduced the instance of antisocial behavior in prisoners when sugar in the diet was reduced. However, these were open trials and a wide range of changes in the diet inevitably altered several aspects of nutrition in addition to sugar intake. Benton (2008) discussed the three major mechanisms by which the level of sugar intake has been suggested to influence antisocial behavior; food intolerance, hypoglycemia or nutrient deficiency. Table 96.3 shows that sugar is by no means the most common cause of food intolerance. The influence of sugar consumption on micronutrient status is discussed below leaving the possible induction of hypoglycemia to be considered.

96.4.2 Glycemic Load

Although its use is controversial it is possible to classify foods by the calculation of the Glycemic Index (GI). The area under the curve created by plotting the changes in blood glucose for the 2 h following the consumption of a 50 g glucose drink is arbitrarily given a score of 100. On another day, sufficient of a test food is consumed to give 50 g of carbohydrate and the effect on blood glucose is expressed as a percentage of that obtained with glucose (Foster-Powell et al. 2002). Foods with a high-GI are rapidly digested and absorbed resulting in a rapid and marked increase in blood glucose levels. A low-GI food is slowly digested and causes more gradual changes in blood sugar. Table 96.5 gives a representative selection of foods that illustrates the phenomenon. It is apparent that many common assumptions about the influence of food items on blood glucose levels are mistaken.

Sucrose has only a moderate influence on blood glucose, not surprising as it is formed from the combination of a molecule of fructose and a molecule of glucose and the former does not influence blood glucose levels. Other foods such a bread and breakfast cereals have a greater impact. In addition, complex carbohydrates do not necessarily slowly release energy as much depends on food preparation. A baked potato has a GI of 85 that compares with a GI of 50 when they are boiled. Similarly the GI of rice varies greatly depending on the nature of starch. Chocolate illustrates one problem associated with the GI concept. There is an interaction between nutrients so chocolate has a low GI because the presence of fat and protein slows the release of glucose into the blood stream. It is clear that sucrose does not play a major role in inducing rapid swings in the level of blood glucose.

Table 96.5 The glycemic index (GI) of some common food items

High		Glucose	100
	>70	Low amylose white rice	88
		Baked potato	85
		Cornflakes	81
		White bread	70
Medium		Table sugar	65
	55–69	Honey	58
Low		Boiled potato	50
		Chocolate	49
	<55	High amylose rice	38
		Apple	38

The extent to which a food item causes the level of blood glucose to rise has been summarized by calculated the glycemic index. The change in blood glucose following the consumption of a 50 g glucose drink is arbitrarily given a score of 100. Then the change in blood glucose following the consumption of 50 g of carbohydrate from another food item is expressed as a percentage of that obtained with a glucose drink and is termed the glycemic index. A representative selection of foods are presented using data from Foster-Powell et al. (2002)

96.5 Micronutrient Status

One mechanism by which it has been proposed that a change in diet may affect the instance of antisocial behaviour is by influencing the levels of micronutrients consumed. Specifically it has been suggested that a diet high in refined carbohydrate, in particular sugar, may provide a marginal intake of micronutrients. There are two issues– whether a subclinical intake of micronutrients influences antisocial behaviour and if it does, whether it is associated with a particular dietary style.

Benton (2007) reviewed three well-designed published studies in which a multivitamin/ mineral supplement was administered and the incidence of antisocial behavior was found to decrease. As an example the disciplinary record of young offenders, over the age of 18 years, improved following supplementation. The taking of the supplements decreased violent incidents by 26% with a greater reduction in more serious offences (Gesch et al. 2002). An independent statistical reviewer, appointed by the UK Home Office, commented that it was "designed properly and with a good analysis" and there emerged "convincing scientific proof that poor nutrition plays a role in triggering aggressive behavior." The Dutch government responded to these findings by carrying out their own study. In prisoners who received a similar supplement to the British study, reports of violence decreased by 34% compared with a 13% increase in violence in those who received the placebo. The Dutch study was the fourth to report a beneficial response to micronutrient supplementation.

As the supplement in the British study offered 13 vitamins, 12 minerals, and fatty acids (Gesch et al. 2002) it is unclear which nutrients were influential. Were all the nutrients in the supplement important or alternatively did the response reflect the influence of a single or only a few nutrients? Were there synergistic interactions between nutrients? What is the optimal dose? These are questions that we have not begun to ask, never mind answer. As there are reports that supplementation with omega-3 fatty acids decreases violence (Benton 2007) they may have played a part. However, the report that a multivitamin/ mineral without fatty acids also reduced violence suggests that other nutrients are also important (Schoenthaler et al. 1997). We await the clarification that will be offered by future studies.

96.5.1 Micronutrient Status and Sugar Consumption

It has been proposed that particular dietary styles may predispose to a decreased intake of micronutrients. For example, according to the "empty calorie" hypothesis, sugar and other refined foods are said to provide energy stripped of micronutrients. However, those studies that have related sugar intake to micronutrient status have tended to conclude that there are no grounds for concern (Benton 2008). In fact one of the most extensive reviews concluded that a low rather than high intake of sugar tended to be associated with poor micronutrient status (Gibney et al. 1995). As micronutrient status is better predicted by total energy intake, rather than the level of sugar, it is likely that a low sugar intake was simply a predictor of a low energy intake. The key dimension in this area is the overall energy intake as in those who consume sufficient calories the level of micronutrient intake tends to achieve the recommended levels, irrespective of the sugar consumed.

96.6 Applications in Other Areas of Health and Disease

Given the serious consequences of antisocial behavior, any conclusive demonstration that diet was beneficial will have obvious public health implications. Both in specific situations, such as schools or prisons, but more generally in society, we would wish to decrease any predisposition to violence. However, although a number of well-designed trials have found that manipulating the diet can reduce antisocial behavior and violence, the available evidence is limited. We are, however, reaching the point where it is reasonable to suggest that the adequacy of diet should be added to the list of factors that predispose to the display of antisocial behavior. However, the body of knowledge is such that we are at present unable to readily distinguish those individuals who are nutritionally at risk. In addition we have only a sketchy idea of the nutrients that are important and therefore have not begun to establish the optimal intake.

   It is likely that the topic will raise questions for genetics and physiology. Rather than studying the diet in isolation it is probable that we will need to look at the interaction between the diet and individual differences in basic biology. It is a minority who display extreme food intolerance; we differ in our bodily need for micronutrients; glucose tolerance varies between individuals. One likely approach is the rapidly developing area of nutriomics, where the interaction between genetic differences and diet will be explored. In the future we may be able to screen for those who are likely to respond adversely to aspects of their diet. If this prediction is upheld then we will need to treat people as individuals such that general nutritional advice may be inappropriate.

   Yet even if causal mechanisms are satisfactorily demonstrated their significance will need to be kept in context. We should not too readily assume that diet is a major cause of antisocial behavior or that its modification is a simple means of solving difficult problems. Although there are examples of individuals where food intolerance has a dramatic impact (Mackarness 1976) a subtle response is more probable with many food-related approaches. By its nature our diet can only influence our basic biological functioning; that is it can only modify potential. Whether the potential to act in a peaceful or violent fashion is realized will depend on the interaction with the environment. The individual will need to be provoked and will or will not react depending on socialization, subcultural norms, and the current situation. Diet may change the basic biological predisposition but whether that predisposition is expressed will reflect the social situation and past history. At best, changes in diet are likely to be only one of several interventions that are required, although they may be influential in an appropriate psychological and social context.

Summary Points

- Although there is no suggestion that diet is the most common reason for children displaying ADHD, in well-controlled studies some children with the disorder have been shown to suffer with food intolerance. The pattern is individual to the child with a response being found to a wide range of foods.
- There is no support from well controlled studies for the suggestion of Feingold that hyperactive behavior was stimulated by a diet containing salicylates; chemicals in food that have a similar structure to aspirin.
- In double-blind trials supplementation with essential poly-unsaturated fatty acids has been found to decreased violence.
- Similarly there are reports that supplementation with multivitamins and minerals decrease aggressive behavior.
- There is an association between a tendency to develop low blood glucose and acting aggressively. The levels at which this occurs is higher than the levels required to produce a diagnosis of clinical hypoglycemia.
- The evidence is mainly of idiosyncratic responses to diet that prevent the offering of general rather than individual advice.
- The influence of diet must be kept in context as a biological predisposition will only be realized in an appropriate social and psychological environment.

Key Terms

Attention deficit hyperactivity disorder: This affects between 3% and 5% of children. It starts before the age of 7 and occurs more commonly in boys than girls. It is characterized by an inability to sustain attention, impulsive behavior, and hyperactivity.

Docosahexaenoic acid: It is found in high levels in the brain and the retina. It is the end point of the metabolic pathway that starts with the essential n-3 fatty acid alpha-linolenic acid.

Eicosapentaenoic acid: This is an n-3 fatty acid produced by the pathway that converts alpha-linolenic acid to docosahexaenoic acid.

Essential fatty acids: These cannot be created by the human body and therefore need to be part of the diet. In humans there are two families of essential long chain poly-unsaturated fatty acids, n-3 (omega-3) and n-6 (omega-6).

Food intolerance or food hypersensitivity: This is an adverse physiological response to a food item by a means other than the immune system. In contrast, food allergy by definition reflects an immunological reaction.

Glycemic index: The area under the curve created by plotting the changes in blood glucose following the consumption of a 50 g glucose drink is arbitrarily given a score of 100. The glucose response to consuming a test food that offers 50 g of carbohydrate is expressed as a percentage of that obtained with glucose. Foods with a high-GI result in a rapid increase in blood glucose while a low-GI food causes more gradual changes.

Hypoglycemia: This literally means a low level of glucose in the blood. When the levels of blood glucose fall to very low levels, the functioning of the brain can be compromised; resulting in slurred speech, blurred vision, and irritability. In some people the nature of the diet can induce a marked fall in blood glucose, a response called spontaneous, food-stimulated, reactive, or postprandial hypoglycemia.

References

Ad Hoc Committee on Hypoglycaemia. Statement of the ad hoc committee on hypoglycemia. Ann Int Med. 1973;78:301.

Appleton KM, Rogers PJ, Ness AR. (2008) Is there a role for n-3 long-chain polyunsaturated fatty acids in the regulation of mood and behaviour? A review of the evidence to date from epidemiological studies, clinical studies and intervention trials. Nutr Res Rev 2008;21: 13–41.

Bateman B, Warner JO, Hutchinson E, Dean T, Rowlandson P, Gant C, Grundy J, Fitzgerald C, Stevenson J. The effects of a double blind, placebo controlled, artificial food colourings and benzoate preservative challenge on hyperactivity in a general population sample of preschool children. Arch Dis Child. 2004;89:506–11.

Benton D. Diet, cerebral energy metabolism and psychological functioning. In: Lieberman HR, Kanarek R, Prasad C (ed) Nutrition, Brain & Behavior, Volume 3, Nutritional Neuroscience: Overview of an Emerging Field. Taylor and Francis, Boca Raton, pp. 2005;57–71.

Benton D. The impact of diet on anti-social behaviour. Neurosci Biobehav Rev. 2007;31:752–74.

Benton D. Sucrose and behavioural problems. Crit Rev Food Sci Nutr. 2008;48:385–401.

Donohoe RT, Benton D. Blood glucose control and aggressiveness in females. Personal Indi Diff. 1999;26:905–11.

Egger J, Carter CM, Graham PJ, Gumley D, Soothill JF. Controlled trial of oligoantigenic treatment in the hyperkinetic syndrome. Lancet 1985;1:540–5.

Feingold B. Why your child is hyperactive. Random House, New York:1975.

Fishbein DH. The contribution of refined carbohydrate consumption to maladaptive behavior. J Orthomol Psychiat. 1982;11:17–25.

Fleith M, Clandinin MT. Dietary PUFA for preterm and term infants: review of clinical studies Crit Rev Food Sci Nutr. 2005;45:205–29.

Foster-Powell K, Holt SH, Brand-Miller JC. International table of glycemic index and glycemic load values. Am J Clin Nutr. 2002;76:5–56.

Gesch CB, Hammond SM, Hampson SE, Eves A, Crowder MJ. Influence of supplementary vitamins, minerals and essential fatty acids on the antisocial behaviour of young prisoners. Randomised, placebo-controlled trial. Brit J Psychiatr. 2002;181:22–8.

Gibney M, Sigman-Grant M, Stanton JL, Keast DR. Consumption of sugars. Am J Clin Nutr. 1995;62 (1 Suppl):78S–193S.

Iribarren C, Markovitz JH, Jacobs DR, Schreiner PJ, Daviglus M, Hibbeln JR. Dietary intake of n-3, n-6 fatty acids and fish: relationship with hostility in young adults-the CARDIA study. Eur J Clin Nutr. 2004;58:24–31.

Kaplan R, Manuck SB, Shively C. The effects of fat and cholesterol on social behavior in monkeys. Psychosom Med. 1991;53:634–42.

Lev-Ran A, Anderson RW. The diagnosis of postprandial hypoglycemia Diabetes 1981;30:996–9.

Mackarness R. Not all in the mind. London: Pan Books; 1976.

McCann D, Barrett A, Cooper A, Crumpler D, Dalen L, Grimshaw K, Kitchin E, Lok K, Porteous L, Prince E, Sonuga-Barke E, Warner JO, Stevenson J. Lancet 2007;370:1560–7.

Richardson AJ, Puri BK. A randomized double-blind, placebo-controlled study of the effects of supplementation with highly unsaturated fatty acids on ADHD-related symptoms in children with specific learning difficulties. Prostaglandins Leukot Essent Fatty Acids. 2000;63:79–87.

Schab D, Trinh NH. Do artificial food colors promote hyperactivity in children with hyperactive syndromes? A meta-analysis of double-blind placebo-controlled trials. J Dev Behav Pediatr. 2004;25:423–34.

Schoenthaler SJ. The effect of sugar on the treatment and control of antisocial behavior: a double-blind study of an incarcerated juvenile population. Int J Biosoc Res. 1982;3:1–9.

Schoenthaler SJ, Amos S, Doraz W, Kelly MA, Muedeking G, Wakefield J. The effect of randomized vitamin-mineral supplementation on violent and non-violent anti-social behavior among incarcerated juveniles. J Nutr Environ Med. 1997;7:343–52.

Stevens LJ, Zentall SS, Deck JL, Abate ML, Watkins BA, Lipp SR, Burgess JR. Essential fatty acid metabolism in boys with attention-deficit hyperactivity disorder. Am J Clin Nutr. 1995;62:761–8.

Stillwell W, Wassall SR. Docosahexaenoic acid: membrane properties of a unique fatty acid. Chem Phys Lipids. 2003;126:1–27.

Virkkunen ME, Horrobin DF, Jenkins DK, Manku MS. Plasma phospholipid essential fatty acids and prostaglandins in alcoholic, habitually violent, and impulsive offenders. Biol Psychiat. 1987;22:1087–96.

Wolraich ML, Wilson DB, White JW. The effect of sugar on behavior or cognition in children. A meta-analysis J Am Med Assoc. 1995;274:1617–21.

Zhang J, Muldoon MF, McKeown RE, Cuffe SP. Association of serum cholesterol and history of school suspension among school-age children and adolescents in the United States. Am J Epidemiol. 2005;161:691–9.

Chapter 97
Disordered Eating and Mental Workload

Ethan E. Hull, Jennifer E. Phillips, and Dana L. Rofey

Abbreviations

APA	American Psychiatric Association
BED	Binge eating disorder
BN	Bulimia nervosa
CBT	Cognitive behavioral therapy
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders
EDI	Eating disorder inventory
EDNOS	Eating disorder not otherwise specified
EPQ-R	Eysenck personality scale-revised
FCQ-S	Food cravings questionnaire-state
LMS	Labeled magnitude scale
NASA-TLX	NASA task load index
NIH	National Institutes of Health

97.1 Introduction

Attempts at food restriction and dieting have become a way of life for many in search of the "ideal" body type. In the United States, the high prevalence of eating disorders among women suggests a preoccupation with thinness, yet obesity rates in the USA are among the highest across the globe. How are we to understand the contradiction between an increasingly overweight nation that is fixated upon the ideal of being thin? With a high demand for weight loss and thinness comes a surplus of messages and advertisements focused on dieting, body shape, weight, and attractiveness. Yet not everyone is adversely affected by these messages, and it may be that only certain individuals are predisposed to develop disordered eating when placed in a "weight-focused" environment. In this chapter, we approach this paradox from the perspective of "mental workload", or the ability to mentally process information pertaining to making food choices. Initially, we examine eating disordered eating and mental workload, and further explore factors that can impact this relationship, such as craving. We then discuss the demand that disordered eating places on cognitive processing

D.L. Rofey (✉)
Children's Hospital of Pittsburgh, 3414 Fifth Avenue, Room 128, Pgh, PA 15213, USA
e-mail: rofeydl@upmc.edu

capabilities, and then present empirical evidence to date that has examined this issue. Finally, we relay this information to the practitioner in an effort to continually advance the care given to individuals with eating disorders.

97.1.1 Eating Disorders

Disordered eating occurs in epidemic proportions in Western society; it is estimated that five to ten million women in the United States suffer from eating disorders (Crowther and Mizes 1992). Evidence indicates that women with a predisposition for disordered eating are at an increased risk when the environment promotes unhealthy thoughts or habits regarding food and weight (Bulik et al. 2004). Mainstream society sets high and often incompatible standards for women, and cultural pressure for women to be thin and have an ideal body is much greater than that for men (Mitchell and Eckert 1987). Women should have big breasts but small waists; they should be able to build-up stamina in an athletic manner, but not sweat; they should exercise daily, but not get too muscular (Brownell and Rodin 1994). Cultural pressure and the power of the media are implicated in the high prevalence for women to have an eating disorder.

The resultant morbidity associated with these disorders is considerable, and over the past 20 years societal attention, research, and clinical resources have increased alongside the prevalence of eating disorders (Fairburn and Brownell 2002). These disorders are marked by extremes, whether it is a severe disturbance in eating behavior (e.g., Bulimia Nervosa (BN)), such as reduction of food intake or overeating or significant feelings of distress about the shape of one's body.

Among women, the lifetime prevalence of BN is between approximately 1% and 3%; the rate of occurrence of this disorder in males is approximately one-tenth of that in females per the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV TR) (American Psychiatric Association (APA) 2000). Approximately 19% of female college students report symptoms of BN (Hoek 1993), an eating disorder characterized by recurrent episodes of binge eating, a sense of lack of control over food, and engagement in drastic compensatory measures, such as purging via vomiting, laxatives, or over-exercising (APA 2000). BN appears to have a chronic and sometimes episodic course in which periods of remission alternate with recurrences of binge/purge cycles. Eating disorders appear to be more common in college women, as a funtion of peer "enmeshment" and are confronted with adjustment difficulties and the challenges of newfound independence (Rand and Kuldau 1992).

Binge eating disorder (BED), currently categorized in DSM-IV-TR as an Eating Disorder Not Otherwise Specified (EDNOS), may be the most common of eating disorders, affecting approximately 3% of all adults in the United States, most of whom are women (NIH 2008). Although most obese people do not have BED, individuals with this problem are typically overweight or obese. BED is characterized by eating very rapidly until uncomfortably full, eating large amounts of food in the absence of hunger, eating alone because of embarrassment over the amount of food being consumed, and feeling disgust, guilt, or depressed after overeating. Binge episodes must occur, on average, at least two days a week for a period of at least six months to be clinically diagnosed as BED.

Despite the debate surrounding the assessment of "true" binge eating, considerable evidence supports the characterization of binge eating, whether in the context of BN or BED, as an impulse control disorder (McElroy and Kotwal 2006). The core feature of which is the failure to control a behavioral drive that may be detrimental to an individual (APA 2000). Some researchers suggest that binge eating is facilitated by a cognitive shift, wherein which the individual stops keeping track of

their food intake (Heatherton and Baumeister 1991). However, little is known about this cognitive shift or the mental effort expended to make food and weight decisions. If individuals are preoccupied with eating, they must constantly ignore food cues and suppress urges, requiring continual mental effort to control their behavior. Thus, a heightened "mental workload" may result when making food choices, especially in individuals with a predisposition toward disordered eating.

97.1.2 Mental Workload

Mental workload is the information processing load or resource demand imposed on a person by a specific task (Eggemeier 1988). Researchers, attempting to describe perceived mental workload, developed several theories describing characterizing the demand for processing capacity as "resources" (Wickens 1986). These theories suggest that when individuals are asked to perform several different tasks simultaneously, performances deteriorate as competition for mental resources or mental energy increase (Hirst and Kalmar 1987). That is, the more information a person is presented with, the more energy and mental resources they have to dedicate to processing that information, and the less energy and faculties they have in reserve. When individuals' attention is divided among two or more activities and they are not given the opportunity to rest, they will not fully replenish their "reserve" of mental energy. This view suggests that cognitive reserves are finite. Not only are a person's resources utilized for task performance and information processing, but they also regulate thoughts, emotions, and impulses (Baumeister et al. 2000). A further explanation of mental workload is presented in Table 97.1.

In the context of disordered eating, mental workload refers to the demand and the resulting ability of an individual to perform a particular task when presented with food cues. Because individuals with eating disorders may experience a "preoccupation" with certain foods, as well as difficulties with mood and personality characteristics that elicit distress (Strober 2000), they may have great difficulty managing all of the mental demands put on them. Thus, a young woman who has symptoms of disordered eating must resist temptation for a food substance and exert strong self-control to prevent her from carrying out an impulse she is attempting to suppress. If this same individual is presented with the sight or smell of a particular food, her performance on tasks requiring cognitive control will be impaired. This would result in the depletion of available resources due to the mental energy required to suppress thoughts and emotions pertaining to the food substances.

Table 97.1   Key points of mental workload

Mental workload is defined as the demand on the brain's resources as a function of the amount of task information being presented at a given moment.

Mental workload can be understood in terms of an economic model of supply and demand: The brain has a limited *supply* of mental resources while input can be thought of as the *demand* to which the brain must attend.

As more input occurs, greater attention is needed to attend to these stimuli. As more of the brain's resources are used, there are less in reserve and mental and physical performance can suffer

Mental workload is multidimensional and comprised of:

Mental Demand: The amount of mental or perceptual activity required (i.e., thinking, deciding, calculating, etc.)

Physical Demand: The amount of physical activity required (i.e., level of pushing, pulling, turning, etc.)

Temporal Demand: The amount of time pressure involved with the task (i.e., the pace of the task)

Performance: Success in accomplishing goals (i.e., how well one completed the objective)

Effort: How hard one had to work for the task (i.e., both mental and physical exertion)

Frustration: Level of discouragement at completing the task (i.e., level of stress, irritation, and contentedness)

This table provides a definition of mental workload along with its multiple components

97.1.3 Craving

Craving is an intense desire for a particular food or drug, also defined as a distinct state of especially urgent desire for a substance (Gendall et al. 1997). In typical cue reactivity paradigms, disordered eating individuals are presented with food-related cues without the opportunity to consume the substances. The sight and smell of a preferred substance with no opportunity for consumption have been shown to increase self-reported desire and autonomic arousal, such as increased heart rate (Cooney et al. 1997). Cravings can also be thought of as expectations for the pleasurable sensations that accompany consumption of a desired substance. Sights and smells are two food cues which tend to create a desire for a particular food or foods (Cornell et al. 1989). Thus, olfactory and visual exposure to food stimuli increase self-reported cravings. The combination of craving and disordered eating may amplify mental activity and increase sensation-seeking toward the food substance (Kambouropoulos and Staiger 2004). Conversely, if levels of craving are low in persons with symptoms of disordered eating, a lower desire for the food cues may occur (Perkins et al. 2003). As desire and craving appear to move in tandem, so also should the amount of mental energy necessary to process desirable food cues. This suggests that craving may moderate eating behavior, and is an important component of understanding the mental energy required of a person in the context of making food choices.

97.2 Mental Workload

Despite the prevalence of eating disorders in women, little is known about the effort expended to make food and weight decisions. If individuals are preoccupied with food choices, they must constantly ignore cues and suppress urges, requiring continual mental processing to control their behavior. Resource theories suggest that the more a person's mental energies are dedicated to decision making, the less energy they will have for other mental tasks. This infers that mental workload is associated with food choices, and this demand may be greater in those with eating disorders. Only one novel study has examined whether individuals with disordered eating feel more "mentally overwhelmed" by cues to eat.

This research exposed a sample of college women to food cues and then asked them to perform a challenging mental task related to food, on which they then rated the amount of "mental effort" expended by the task. The hypotheses for this study were that women with more disordered eating symptoms would rate the cognitive tasks as more mentally taxing compared with those with fewer symptoms of disordered eating. It was also thought that craving would operate as a moderating variable. Among women who endorsed high cravings, those high in disordered eating would rate the cognitive tasks as mentally more difficult than those low in disordered eating. Finally, it was hypothesized that women with high levels of Neuroticism and disordered eating would rate the cognitive tasks as more mentally taxing than those low in disordered eating. (A similar relation between disordered eating and mental workload was not predicted for individuals low in Neuroticism.)

97.2.1 Cue Reactivity and Craving in Women with Disordered Eating

Due to the high prevalence of eating disorders and symptoms in college women, undergraduate females are an ideal cohort. The study by Rofey et al. (2007) examined undergraduate women at a large Midwestern university (n = 175, ages 17–34 [mean age = 19.7 ± 1.9]). Most of the participants

were single (98.8%), Caucasian American (93.2%), and of freshman or sophomore status (89.2%). Racial/ethnic minority representation included African American (2.5%), Asian American (1.5%), Hispanic American (<1%), and others (1%). Participants completed several measures, including:

The Eating Disorder Inventory-2. The Eating Disorder Inventory-2 (EDI-2) is a self-report measure that assesses eating-disorder symptomatology (Garner 1991). Drive for Thinness, BN, and Body Dissatisfaction are the three subscales assessing attitudes and behaviors concerning eating. The Drive for Thinness scale measures the pursuit of thinness and the clinical manifestation of an intense fear of fatness, including excessive concern with dieting, preoccupation with weight, and fear of weight gain – all cardinal features of BN and anorexia nervosa (AN). Scores on the Drive for Thinness scale have been found to predict bulimic symptoms over a 10-year period (Joiner et al. 1997). The BN subscale measures the tendency to think about and engage in bouts of uncontrollable eating (binging), and has shown high convergent validity with other instruments assessing BN (Garner 1991). The Body Dissatisfaction subscale measures unhappiness with the shape and size of the regions of the body that are of greatest concern to those with eating disorders. Although every region of the body may be an area of concern, legs, buttocks, and stomach typically top the list.

Food Craving Questionnaire-State. The Food Cravings Questionnaire-State (FCQ-S) is designed to measure physiological and psychological motivation states that promote substance-seeking and ingestive behaviors (Cepeda-Benito et al. 2000). The FCQ-S is useful for measuring multiple dimensions of cravings such as anticipating positive feelings that may result from eating, relief from negative states as a result of eating, or an obsessive preoccupation with food or lack of control.

The Disorder Salient Stroop Task. The Stroop (1935) task has been used extensively by experimental psychologists to study attentional processes. In this task, participants are presented with words written in different colors of ink and are instructed to ignore the word and its meaning and instead indicate the color of the ink in which the word is printed. Stroop (1935) found that participants take longer to choose the color of the word when the word's meaning and ink color do not match (e.g., there is a longer color-naming latency when the word "blue" is written in red ink, verses when the word "blue" is written in blue ink). Researchers in the 1970s then began utilizing the Stroop test to examine cognitive processing and emotional disturbance. Instead of using color words, emotionally sensitive words were used. They found that emotionally sensitive words led to greater latency in color naming than did neutral words. This revised Stroop task, termed the disorder-salient Stroop, reveals that emotional sensitive words are selectively attended to by individuals with a particular disorder (Rofey et al. 2004). A recent meta-analysis of 27 studies using the disorder-salient Stroop task (with food and body-related words instead of color words) indicated that individuals with an eating disorder diagnosis exhibited greater delays in color naming compare to controls (Johansson et al. 2005). This infers that, for individuals with an eating disorder, there is an emotional connection to food-related words that may result in a delay in reaction times.

This emotion-connection view has extended to studying mood and affect as it pertains to disordered eating. Thus, research has examined how affect moderates the relationship between an eating disorder and reaction time. As Fig. 97.1 shows, individuals with higher bulimic scores who report low mood demonstrate slower response times to food cues than do bulimic women reporting more positive mood (Rofey et al. 2004).

The Labeled Magnitude Scale. The Labeled Magnitude Scale (LMS) is a scale of perceptual intensity used to rate pleasurable aspects of olfactory stimuli (Green et al. 1996). Pilot data show that the more pleasurable and more easily identifiable the olfactory cue, the higher the likelihood for craving (Rofey et al. 2004). Studies of eating-disordered women show that olfactory cues heighten eating-related cognitions (Staiger et al. 2000). Women suffering from BN like the smell and taste of high caloric foods as long as the possibility of ingestion is excluded (Drewnowski et al. 1987). Under a classical conditioning model, stimuli repeatedly associated with the consumption of a substance
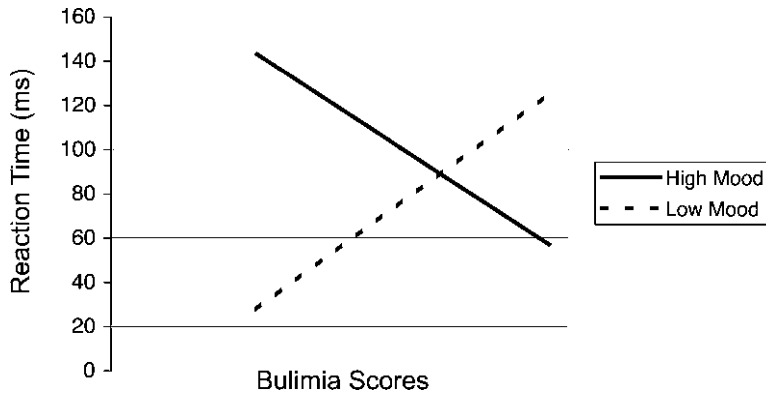
Fig. 97.1 Reaction time and Bulimia scores for high and low mood individuals. This figure shows a comparison of reaction times on a cognitive task using emotionally sensitive words, and Bulimia scores for individuals with high and low affect. As shown, women with low moods react faster when they have low levels of Bulimia, but as they score higher for Bulimic symptoms, they react slower to the cognitive task. Conversely, positive or high moods react faster as they have greater levels of bulimic symptoms. This shows that mood moderates the relationship between reaction time and Bulimia scores (Adapted from Rofey et al. 2004. With permission from Elsevier Ltd.)

(such as the sight and smell of food) are thought to elicit an increased desire to consume the food. Thus, presenting olfactory cues to persons predisposed to disordered eating may lead to heightened mental workload similar to that of visual cues on the disorder-salient Stroop task (Rofey et al. 2004). Therefore, if individuals with disordered eating are presented with olfactory cues related to pathological thoughts (i.e., the smell of peanut butter, graham crackers, chocolate, oatmeal, vanilla cookies, etc.), their ability to respond to a task without cognitive delay may be impaired.

NASA Task Load Index. The NASA Task Load Index (NASA-TLX) is a multidimensional rating procedure that provides a workload score based on a weighted average of six subscales: Mental Demand, Physical Demand, Temporal Demand, Performance, Effort, and Frustration. An overall workload score (0–100) and a paired comparison score (indicating which scale was rated the hardest) is obtained for each rated task by multiplying the weight by the individual dimension scale score, summing across scales and dividing by 15. The validation and sensitivity of the NASA-TLX has been demonstrated on a variety of multitask contexts (Hart and Staveland 1988).

Eysenck Personality Inventory – Revised. An issue neglected by existing workload research is the relationship between subjective performance and personality characteristics (Rose et al. 2002). The Eysenck Personality Questionnaire – Revised (EPQ-R) measures personality tendencies of Psychoticism (P), Extraversion (E), Neuroticism (N), and Lying. Studies that have been carried out with the EPQ-R and eating disorders suggest that BN is associated with high levels of Neuroticism and Psychoticism (Feldman and Eysenck 1986). This would infer that personality may affect the workload ratings of persons who experience disordered eating.

97.2.2 Review of Procedures

Methodological review shows that in the study by Rofey et al. (2007) participants completed questionnaires on troubled eating patterns and craving levels. Approximately two days after completing a self-report battery, participants were assessed for color blindness and given olfactory food cues, which they rated on a scale of "most pleasant" to "not pleasant." An intervening task occurred

between each cue to reduce carryover effects. Immediately following the sensory experience, the participants completed the LMS to assure that she was able to smell the substance.

After completing the LMS, the participant proceeded to the other side of a partition separating the laboratory and completed the disorder salient stroop task. A five minute computer program presented three groups of words: (1) color words (blue, green, red, and yellow); (2) neutral words: phone, bowl, shoe, watch, mouse, floor, violin, window, deer, elephant, falcon, coyote, crocodile, geese, raccoon, and mules, each matched to an appetitive or alcohol word; and (3) appetitive words: chips, caramel, pastry, chocolate, cake, spaghetti, pizza, and cookie (Stroop 1935; Israeli and Stewart 2001). After the Stroop task, the participants answered questions about levels of workload difficulty and craving.

97.2.3 An Analysis of Eating Disorders and Mental Workload

As shown in the Table 97.2, college women tended to score the highest on the Neuroticism and Drive for Thinness scales and lowest for Psychoticism and Bulimia. The greatest variability existed for Drive for Thinness and Bulimia, indicating that more women reported levels at opposite ends of the continuum.

Women rated each component of mental workload (first described in Table 97.1) immediately following the Stroop task. As shown, Mental Demand was the greatest contributing factor to workload while Physical Demand was the least influential component. This is not surprising since the Stroop task is designed as a measure of cognitive processing, and requires practically no physical movement except pushing a button. The Effort and Performance Scales were also important factors as the college women clearly indicated that they had to work hard and desired to perform well on the task. The time pressure or Temporal Demand along with Frustration did not appear to be as important as the demand placed on achievement and cognition in the food task. Interestingly, the Effort Scale was inversely associated with many of the other indices such that as the Mental Demand increased Effort subsided. This suggests that in certain individuals, as the task becomes more demanding and difficult there is a decrease in mental energy expenditure and a decline in desire to succeed.

This results show that individuals rate cognitive demands as the most difficult portion of mental workload. An important question is then if individuals with more disordered eating also have greater difficulty on factors such as Mental Demand and Performance scales when performing a food task.

Table 97.2 Shows means and standard deviations (SD) for disordered eating variables (Adapted from Rofey et al. 2007. With permission from Taylor & Francis Ltd.)

Variable	Mean	SD	Range
1. EDI-2 – Drive for Thinness	5.30	6.34	0–22
2. EDI-2 – Bulimia	2.33	5.81	0–32
3. EPQ-R – Psychoticism	2.49	1.83	0–8
4. EPQ-R – Neuroticism	5.64	3.30	0–12

This table shows descriptive data of college women for eating disorders and personality assessment. Of the eating disorders, women had a higher Drive for Thinness than for Bulimia. Of the personality characteristics, a greater level of Neuroticism was shown in these females.

EDI Eating Disorder Inventory, *EPQ-R* Eysenck Personality Scale-Revised; *SD* Standard Deviation

A multiple regression analysis showed that individuals with higher levels of disordered eating also had a more challenging time completing the food task. Interestingly, level of craving did not appear to impact this relationship (Rofey et al. 2007).

Additional factors that may be associated with mental workload include personality factors, such as Neuroticism, shown in Table 97.2. Broad personality traits such as Neuroticism and Psychoticism have been linked with performance goals, and have been associated with BN (Feldman and Eysenck 1986). For this reason, personality may impact mental workload, especially the performance component. As recently shown, a multiple regression analysis revealed that Neuroticism alters the strength of the relationship between Performance Workload and Drive for Thinness (Rofey 2005) (Table 97.3).

Individuals with higher levels of Neuroticism were more likely to be at greater risk of showing performance difficulties when they also had a higher Drive for Thinness. As shown in Fig. 97.2, workload scores differed between women with and without a strong Drive for Thinness, moderated by high and low levels of Neuroticism.

Among women who reported high levels of Neuroticism, those with a high Drive for Thinness reported the olfactory and Stroop tasks to be significantly more demanding on the Performance sub-scale than women who reported low Drive for Thinness and Neuroticism. High Neuroticism women with either high or low Drive for Thinness did not differ significantly on their rating of the tasks difficulty (Rofey et al. 2007).

Table 97.3 Key features of disordered eating and mental workload

1. Eating disorders affect 5–10 million women in the USA.
2. Mental workload is the demand placed on the brain's resources as a function of the amount of task information being presented at a given moment.
3. Individuals with eating disorders appear to be influenced by food cues (i.e., they have more difficulty processing food-relevant information).
4. As mental workload reaches capacity, less effort and energy appear to be expended.
5. Personality (e.g., Neuroticism) appears to influence mental workload as well as performance.

This table lists the key facts of disordered eating and mental workload as they pertain to the reviewed research in this chapter
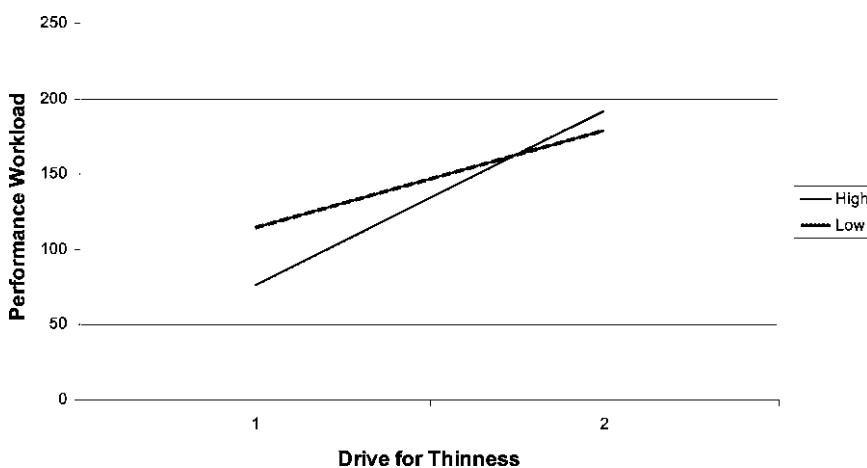
Fig. 97.2 Relation between Performance Workload and Drive for Thinness score for low and high levels of Neuroticism. This figure shows a comparison of slopes for Performance difficulty and Drive for Thinness. The slope is greater for women who are highly neurotic compared to those with low levels of Neuroticism. This shows that Neuroticism moderates the relationship between Performance difficulty and Drive for Thinness (Adapted with permission from Rofey 2005)

97.2.4 Summary of Analyses

To our knowledge, this is the first study to utilize the concept of mental workload to examine cognitive factors relevant to disordered eating. These analyses indicate that disordered eating symptoms appeared to directly influence participants' difficulty ratings on the olfactory and disordered salient Stroop tasks. For subscales on the NASA-TLX, disordered eating accounted for a significant portion of the variance in mental workload. While measures of food craving did not prove to be a significant moderator of the relationship between disordered eating, levels of bulimic symptoms were related to participants' difficulty ratings of olfactory and visual cues on measures of mental workload. For women who reported high Neuroticism, those with high disordered eating symptoms reported more difficulty in responding to salient cues than those with low disordered eating symptoms. Among women who reported low Neuroticism, women with high and low Drive for Thinness did not differ significantly on their ratings of task demand.

97.2.5 Interpretation of Hypotheses

Relationship between disordered eating and mental workload. Results revealed that disordered eating contributed to participants' rating the olfactory and Stroop tasks as being difficult. During these cognitive tasks, participants were asked to make continuous discriminations without rest, the nature of which prevented full replenishment of resources. Women who reported more symptoms of disordered eating found it more difficult to make appropriate responses on this demanding mental task. It is evident that Mental Demand and Performance subscales contributed most to overall workload ratings for women high in disordered eating on the disorder salient Stroop task and olfactory cues. Multiple, pertinent cues are being responded to simultaneously; consequently, women rate olfactory and Stroop tasks as more demanding. In other words, participants' limited mental resources are being expended to do many things at once; regulate thoughts, control emotions, and inhibit impulses (Baumeister et al. 2000). Theoretically, extension of these controlled laboratory findings into a "real-life" context suggests that an individual high in disordered eating must consistently resist dietary temptation and exert strong self-control to prevent the carrying out of a "forbidden" impulse, which may ultimately result in a depletion of resources necessary for suppression of substance food-related thoughts and emotions. At a certain point, these mental reserves may become depleted to the point where this individual no longer feels capable of self-restraint, and they may experience a "cognitive shift" toward more impulsive behavior (e.g., binge eating).

Craving as a moderator of the relationship between disordered eating and mental workload. Interestingly, craving did not appear to affect ratings of mental workload. Since 1955, there have been many articles debating the use of craving in science (Gendall et al. 1997; Kozlowski et al. 1989). The DSM-IV-TR (APA 2000) does not contain any discussion of the term, and cravings have generally been viewed as a motivational and individualistic state within the person. The existing literature on food has several limitations that may help explain the insignificant findings. First, the operational definition is still uncertain and the majority of studies rely on the participant's subjective understanding of the term (Kozlowski et al. 1989). For example, Marlatt and Gordon (1985) proposed that cravings be distinguished from urges by referring to the former as a subjective motivational state and the latter as an intention to engage in the behavior.

Second, studies examining the nature of food cravings are biased to certain groups within the population. Craving may have different implications for people on the low end of the disordered eating continuum within this normal population. For example, people who are experiencing hunger pains may rate craving as being present (e.g., I want a sandwich) whereas people high in disordered eating symptomatology may rate craving as present if it predisposes a binge (e.g., I need to go through the fast-food window and order four hamburgers).

There is also the issue of a subjective threshold. At which point does a desire for a food qualify as a craving? While psychophysiological indices (e.g., heart rate, salivation, skin conductance) have been proposed as objective measurements of craving, an individual's self-report may not follow with the physiology (Nirenberg and Miller 1982). Thus, utilizing varied measures of craving may be a more effective method to ascertain whether this threshold has been met.

Relationships between workload and Drive for Thinness and Neuroticism. Study findings indicated that among women who reported high Neuroticism, those with a high Drive for Thinness reported the olfactory and Stroop tasks to be significantly more demanding than those with low Drive for Thinness. Among women who reported low Neuroticism, women with high and low Drive for Thinness did not differ significantly on their mental workload ratings of the tasks. Ballard (1996) identifies personality as the most significant individual difference in human factors research. Studies have reported that individual differences in human factors experiments can be explained by personality traits such as field dependence (Moore and Gross 1973), Type A personality (Perry and Laurie 1992), and locus of control (Sanders et al. 1976). Neuroticism has also been found to be strongly associated with eating disorder symptom level (Diaz-Marsa et al. 2000), and has been predictive of subsequent bulimic symptomatology including future binge episodes and compensatory behavior (Leon et al. 1997).

An overarching finding of this study was that, in comparison with women low in disordered eating symptoms, participants with higher levels of disordered eating exerted less effort on the Stroop task as rated on the NASA-TLX Effort subscale. From a resource model of attention perspective, participants may have been affected by the emotionally sensitive food words because these cues are connected to things that are meaningful, and resources are being used to process these extraneous thoughts. As a coping mechanism, the women may have exerted less effort as the cognitive task becomes mentally taxing. Muraven et al. (1998) argue that similar to a limited supply of strength or energy, people have a limited capacity for self-regulation. Repeat exertion will diminish capacity to perform mental tasks. Thus, when individuals engage in repeated self-regulation of the visual and olfactory cues, they may show subsequent decrements of effort due to energy depletion (Muraven et al. 1998).

Overall, this chapter reviews research demonstrating that persons with eating disorders are expending more mental resources to suppress food urges and impulses. Personality characteristics can worsen task performance, and a person's available mental energy is depleted during and possibly after food cue exposure. Although understanding eating disorders can be a challenge for both researchers and clinicians, broad cognitive behavioral interventions targeting thought processes, possibly alongside personality characteristics, may be conducive in reducing mental demand and heightening ability to choose healthy behaviors.

Future areas of research would benefit from studying other human factors. Human factors researchers have spent decades studying vigilance and fatigue, two cognitively oriented facets that may lend themselves to achieving a better understanding of the underlying symptoms of eating disorders. While this is a new paradigm within clinical psychology, it may be advantageous to compare the NASA-TLX profiles with other human factors profiles (e.g., vigilance, memory, tracking, time estimation).

97.2.6 Applications

Media messages often convey unrealistic standards of appearance, perhaps leading to unhealthy attempts at food restriction (Harrison and Cantor 1997). When coupled with feelings of shame, low self-esteem, or other negative mood symptoms, these dieting behaviors may "backfire" and ultimately contribute to an eating disorder. The rise in prevalence of eating disorders over the past 20 years has been accompanied by heightened levels of attention from the clinical and research communities, along with society at large. Researchers and clinicians continue to search for ways to intervene upon existing patterns of disordered eating, and perhaps reduce individuals' overall susceptibility to eating disorders.

Cognitive-behavioral therapy is considered to be the treatment of choice for BN, particularly when used in combination with medications (Whittal et al. 1999), and the strategies for treatment of binge-eating disorder are similar to those for Bulimia (Wilfley et al. 1993). In addition to focusing on behaviors such as binge eating, purging, and ritualistic exercise, Cognitive Behavioral Therapy for Bulimia Nervosa (CBT-BN; Fairburn et al. 1993) involves a systematic series of interventions aimed at addressing the cognitive aspects of BN, such as the preoccupation with food, as well as one's body shape and weight. Initially, the goal of CBT-BN is to restore **control** over dietary intake, and avoid environments that "set up" opportunities to binge. To accomplish this, patients are asked to record their caloric intake while also noting environments or situations that may trigger bouts of disordered eating. Patients are then instructed in methods for coping with these challenging situations, which may include assertiveness training, ways to increase self-esteem, identifying mood states, and healthier alternatives for emotional expression.

The study presented here reveals an intriguing focus area for improving the treatment of disordered eating. If, in fact, individuals high in disordered eating symptoms become "overwhelmed" more easily in situations in which mental demands are high, they may be more at risk of shifting into a binge eating pattern in certain environments. This can be especially true when the environment promotes unhealthy thoughts or habits regarding food and weight. Evidence indicates that environmental factors can exacerbate a predisposition for disordered eating and can contribute to the onset and maintenance of an eating disorder (Bulik et al. 2004).

Although additional research in this area is needed, clinicians may advise patients being treated for an eating disorder to avoid certain "overstimulating" environments, particularly when patients are still in the vulnerable first stages of treatment. Of particular concern are "trigger foods" that enter the household from other members of the family. The patient must then the patient must then constantly attend to suppressing the urge to consume the food, and may dedicate large reserves of their mental energy to avoiding the substance. If their reserves are depleted to a low enough point, they may engage in a binge episode or sneak eating. Removal of these "trigger foods" from the environment may free the mental work associated with them, and will decrease the likelihood of unhealthy food behaviors.

Avoiding food-related stimuli may even extend to television, movies, or electronic media, especially in the context of eating a meal. One area for further study involves the possible link between mental workload and television viewing. If individuals are distracted when they are eating, they may consequently overeat due to the depletion of mental reserves necessary to suppress the urges to overeat. Further, food advertisements may spur additional urges to eat. Options may include replacing television viewing with a physical activity, or choosing chewing gum instead of high calorie snacks.

Although cognitive-behavioral therapy is the first-line treatment of choice for BN, its effectiveness is limited. Approximately 50% of patients who receive CBT-BN stop binge eating and purging, while some patients show partial improvement, and a small number do not benefit at all

(McGilley and Pryor 1998). A comorbid personality disorder is associated with a poorer response to cognitive-behavioral therapy. In reference to the study reviewed in this chapter, if attentional resources are finite, then individuals who exhibit higher trait Neuroticism and who also experience problematic eating may expend a great deal of available resources by attending to food stimuli. This could drain available resources and lower the ability to focus and suppress impulses, which could lead to a binge or overeating episode.

In clinical and research settings, routine screening for eating disorders in young women is another important implication of this research. It is possible that disordered eating symptoms often go undetected due to the sub-threshold clinical nature of many of these symptoms. When intervention is warranted, the results of the current study support a cognitive-behavioral treatment approach. Cognitive -behavioral therapies for eating disorders may be enhanced by targeting automatic food-related thoughts that underlie complex schemas related to coping with these pathological thoughts (Garner and Garfinkel 1997). The results reported here, as they pertain to emotionally sensitive olfactory and visual cues, also support the use of muscle relaxation with visual imagery or direct exposure to a series of situations that involve food cues. In using this technique, therapy would assist in lessening the emotional sensitivity of pertinent food cues. In addition, assisting individuals to identify and cope with food triggers may be critical in helping reduce the likelihood of disordered eating (Kozlowski et al. 1989).

Summary Points

- Having an eating disorder, such as BN, results in slower response times to tasks that include relevant food cues.
- This infers that there is an emotional connection to food-related words in individuals with an eating disorder.
- There are finite mental resources available, and when an individual has an eating disorder their thoughts may be consumed with eating-related stimuli.
- The brain of a person with an eating disorder processes food-related information differently than those without an eating disorder.
- Higher levels of craving do not appear to be associated with mental workload.
- This may be due to the inexact science of measuring craving, and a lack of understanding as to how craving differs along a continuum of eating disorders.
- Neuroticism, coupled with a Drive for Thinness, appears to be associated with greater Mental Demand and Performance difficulties.
- Personality characteristics appear to be linked with mental workload in the context of eating disorders.
- Individuals with higher levels of disordered eating report exerting less effort.
- As the task becomes more mentally taxing, less effort is exerted as a coping mechanism to resource depletion.

Definitions and Explanations

Cognition: This refers to the process of thought, the act of knowing, and applying knowledge. It is also related to abstract concepts such as reasoning, perception, and learning.

Craving: An intense, urgent, or abnormal desire or longing.

Disordered eating: An irregular behavior of food consumption often classified as either bulimia nervosa (BN), anorexia nervosa (AN), or eating disorder not otherwise specified (EDNOS).

Extraversion: A personality trait where gratification is obtained from outside the self. Extraverts tend to enjoy human interactions and are enthusiastic, talkative, and gregarious.

Mental workload: The information processing load or resource demands imposed by a task on an individual's mind.

Neuroticism: A personality trait where there is an enduring tendency to experience negative emotional states, such as anxiety, anger, guilt, and clinical depression.

Psychoticism: To display or have the propensity to display qualities commonly found among psychotics, such as recklessness, disregard for common sense, immaturity and inappropriate emotional expression. Higher Psychoticism scores have been reported among psychopaths and criminals.

References

American Psychiatric Association. *Diagnostic and statistical manual of mental disorders*. 4th ed., revised. Washington, DC; 2000.

Ballard JC. *Computerized assessment of sustained attention: A review of factors affecting vigilance performance*. J Clin Exp Neuropsychol. 1996;18:843–63.

Baumeister RF, Muraven M, Tice DM. *Ego-depletion: A resource model of volition, self-regulation, and controlled processing*. Soc Cogn. 2000;18:130–50.

Brownell KD, Rodin J. *Medical, metabolic, and psychological effects of weight cycling*. Arch Intern Med. 1994;154:1325–30.

Bulik CM, Klump KL, Thornton L, Kaplan AS, Devlin B, Fichter MM, Halmi KA, Strober M, Woodside DB, Crow S. (2004). *Alcohol use disorder comorbidity in eating disorders: A multicenter study*. J Clin Psychiatry. 2004;65:1000–6.

Cepeda-Benito A, Gleaves DH, Williams TL, Erath SA. *The development of the State and Trait Food Questionnaire*. Behav Ther. 2000;31:151–73.

Cooney NL, Litt MD, Morse PA, Bauer LO, Gaupp T. *Alcohol cue reactivity, negative-mood reactivity, and relapse in treated alcoholic men*. J Abnorm Psychol. 1997;106:243–50.

Cornell CE, Rodin J, Weingarten HP. *Stimulus-induced eating when satiated*. Physiol Behav. 1989;45:695–704.

Crowther JH, Mizes JS. *The etiology of BN: the Individual and familial context*. Washington, DC: Hemisphere; 1992.

Diaz-Marsa M, Carrasco J, Saiz J. *A study of temperament and personality in Anorexia Nervosa and Bulimia Nervosa*. J Pers Disord. 2000;14:352–9.

Drewnowski A, Halmi KA, Pierce B, Gibbs J, Smith GP. *Taste and eating disorders*. Am J Clin Nutr. 1987;46:442–50.

Eggemeier FT. *Properties of workload assessment techniques*. In: Hancock PA, Meshkati N editors. Human mental workload 1998 (pp. 41–62). Amsterdam: North-Holland.

Fairburn CG, Brownell KD editors. *Eating disorders and obesity*. 2002 New York: Guilford..

Fairburn CG, Marcus MD, Wilson GT In: Fairburn CG, Wilson GT, editors. Binge eating, nature, assessment, and treatment. New York: Guilford; 1993. p. 361–404.

Feldman J, Eysenck SB. *Addictive personality traits in bulimic patients*. Pers Individ Dif. 1986;7:923–6.

Garner DM. EDI-2 professional manual. Florida: Odessa; 1991.

Garner DM, Garfinkel PE Handbook of treatment for eating disorders. New York: Guilford; 1997.

Gendall KA, Joyce PR, Sullivan F (1997). *Impact of definition on prevalence of food cravings in a random sample of young women*. Appetite. 1997;28:63–72.

Green BG, Dalton P, Cowart B, Shaffer G, Rankin K, Higgins J (1996). *Evaluating the Labeled Magnitude Scale for measuring sensations of taste and smell*. Chem Senses. 1996;21:323–34.

Harrison K, Cantor J. *The relationship between media consumption and eating disorders*. J Commun. 1997;47:40–68.

Hart SG, Staveland LE (1988). *Development of NASA-TLX (Task Load Index): Results of empirical and theoretical research*. In: Hancock PA, Meshkati N editors. Human mental workload. Amsterdam: North-Holland; 1988. p. 139–83.

Heatherton TF, Baumeister RF *Binge eating as escape from self-awareness*. Psychol Bull. 1991;110:86–108.

Hirst W, Kalmar D (1987). *Characterizing attentional resources*. J Exp Psychol. 1987;116:68–81.

Hoek HW. *Review of the epidemiological studies of eating disorders*. Int Rev Psychiatry. 1993;5:61–74.

Israeli AL, Stewart SH 2001. *Memory bias for forbidden food cues in restrained eaters*. Cognit Ther Res. 2001;25:37–48.

Johansson L, Ghaderi A, Andersson G. *Stroop interference for food- and body-related words: a meta-analysis*. Eat Behav. 2005;6:271–81.

Joiner TE, Heatherton TF, Keel PK *Ten-year stability and predictive validity of five bulimia-related indicators*. Am J Psychiatry. 1997;154:1133–8.

Leon GR, Keel PK, Klump KL, Fulkerson JA. *The future of risk factor research in understanding the etiology of eating disorders*. Psychopharmacol Bull. 1997;33:405–11.

Kambouropoulos N, Staiger PK. *Reactivity to alcohol-related cues: Relationship among cue type, motivational processes, and personality*. Psychol Addict Behav. 2004;18:275–83.

Kozlowski LT, Mann RE, Wilkinson DA, Poulos CX. *Cravings: are ambiguous: Ask about urges or desires*. Addict Behav. 1989;14:443–5.

Marlatt GA, Gordon JR. Relapse prevention: maintenance strategies in the treatment of addictive behaviors. New York: Guilford; 1985.

McElroy SL, Kotwal R In: Hollander E, Stein DJ editors. *Clinical manual of impulse-control disorders*. Arlington: American Psychiatric Publishing; 2006. p. 115–48.

McGilley BM, Pryor TL. *Assessment and treatment of bulimia nervosa*. Am Fam Physician. 1998;57:2743–50.

Mitchell JE, Eckert ED. *Scope and significance of eating disorders*. J Consult Clin Psychol. 1987;55:628–34.

Moore SF, Gross SJ. *Influence of critical signal regularity, stimulus event matrix, and cognitive style on vigilance performance*. J Exp Psychol. 1973;99:137–9.

Muraven, M, Tice DM, Baumeister RF. *Self-control as a limited resource: Regulatory depletion patterns*. J Pers Soc Psychol. 1998;74:774–89.

National Institutes of Health. Binge eating disorder. NIH Publication No. 04–3589. http://www.win.niddk.nih.gov/publications/binge.htm

Nirenberg TD, Miller PM. *Salivation: An assessment of food craving?* Behav Res Ther. 1982;20:405–7.

Perkins KA, Ciccocioppo M, Jacobs L, Doyle T, Caggiula A. *The subjective and reinforcing effects of visual and olfactory stimuli in alcohol drinking*. Exp Clin Psychopharmacol. 2003;11:269–75.

Perry AR, Laurie CA. *Sustained attention and the Type A behavior pattern: The effect of daydreaming on performance*. J Gen Psychol. 1992;119:217–28.

Rand CS, Kuldau JM. *Epidemiology of bulimia nervosa and symptoms in a general population: Sex, age, race, and socioeconomic status*. Int J Eat Disord. 1992;11:37–44.

Rofey DL. Dissertation. Cincinnati: University of Cincinnati; 2005. p. 1–84.

Rofey DL, Corcoran KJ, Tran GQ. *Bulimic symptoms and mood predict food relevant interference in women with troubled eating patterns*. Eat Behav. 2004;5:35–45.

Rofey DL, Corcoran KJ, Tran GQ, Nabors LA, Matthews GD. *Demand on mental workload : Relation to cue reactivity and craving in women with disordered eating and problematic drinking*. Addict Res Theory. 2007;15:198–203.

Rose CL, Murphy LB, Byard, L, Nikzad K. *The role of the Big Five personality factors in vigilance performance and workload*. Eur J Personality. 2002;16:185–200.

Sanders MG, Halcomb CG, Fray JM, Owens JM. *Internal-external locus of control and performance on a vigilance task*. Percept Mot Skills. 1976;42:939–43.

Staiger P, Dawe S, McCarthy R. *Responsivity to food cues in bulimic women and controls*. Appetite. 2000;35:27–33.

Strober M. *Disorders of the self in AN nervosa*. In: Johnson C, editor. Psychodynamic treatment of AN nervosa and BN. New York: Guilford; 2000. p. 345–73.

Stroop JR. *Studies of interference in serial verbal reactions*. J Exp Psychol. 1935;18:643–61.

Whittal ML, Agras WS, Gould RA *Bulimia nervosa: a meta-analysis of psychosocial and pharmacological treatments*. Behav Ther. 1999;30:117–35.

Wickens CD, Hollands JG. Engineering Psychology and Human Performance, vol. 3. Upper Saddle River, New Jersey: Prentice Hall.

Wilfley DE, Agras WF, Telch CF, Rossiter EM, Schneider JA, Cole AG, Sifford K, Raeburn SD. J Consult Clin Psychol. 1993;61:296–305.

Chapter 98
Psychiatric Comorbidity in Eating Disorders

Tahany M. Gadalla

98.1 Introduction

Associations between eating disorders and other psychiatric disorders have been observed in samples drawn from treatment-seeking patients, high school/college students and the general populations. To date, the majority of these studies have been based on samples of women. Few studies included men and most of these did not report findings separately by gender. In addition, very few studies examined eating disorders and/or their psychiatric comorbidity in older women.

Researchers have proposed a few possible explanations for the observed high comorbidity rates in individuals with eating disorders. Although the exact mechanisms are yet to be determined, the importance of comorbidity studies cannot be over-emphasized. Examination of comorbid psychiatric disorders in individuals with eating disorders is important because studies have shown that those with multiple disorders tend to have a worse prognosis, longer episodes and are less responsive to treatment. Further, they tend to be at increased risk for engaging in parasuicidal behaviors and suicide attempts (Wildman et al. 2004).

Population-based studies are especially important in assessing the extent and nature of comorbidity (Dansky et al. 2000). Clinical-based studies are vulnerable to several sources of sampling bias especially when studying patients with multiple health problems since these patients may seek treatment for either problem and thus, are more likely than patients with one health problem to be found in clinical settings (Berkson 1946). Thus, comorbidity rates obtained in clinical studies may over estimate the actual comorbidity in the population. In addition, only in population-based samples can the whole range of symptom severity of psychiatric disorders be represented. Yet, few studies examined the comorbidity between disordered eating patterns and other psychiatric disorders in community-based samples.

98.2 Findings of Research Using Clinical Samples

Comorbidity studies conducted in clinical populations have suggested strong associations between eating disorders and other psychiatric disorders. For example, significantly high prevalence of major depression was found in samples of disordered eating adult patients (e.g. Blinder et al. 2006) and

T.M. Gadalla (✉)
Factor-Inwentash Faculty of Social Work, University of Toronto,
246 Bloor Street West, Toronto, Ontario, Canada, M5S 1V4
e-mail: tahany.gadalla@utoronto.ca

disordered eating adolescent patients (Geist et al. 1998). Additionally, in a sample of 135 male patients with eating disorders, 54% had lifetime diagnosis of major depression (Carlat et al. 1997). In a review of the literature on the comorbidity of mood disorders with eating disorders, Godart and colleagues (2007) found lifetime prevalence of major depression to range between 9.5% and 64.7% in restrictive anorexia nervosa patients and between 50% and 71.3% in anorexia nervosa with bulimic subtype patients.

Elevated prevalence of anxiety disorders were also found in women seeking treatment for eating disorders (Blinder et al. 2006; Carlat et al. 1997; Hinrichsen et al. 2004; Iwasaki et al. 2000; Milos et al. 2004) and vice versa (Roderiguez et al. 2004). For example, 43% of a sample of Japanese patients with eating disorders had a lifetime comorbidity of at least one anxiety disorder (Iwasaki et al. 2000), 54% of a sample of Swiss patients with eating disorders had lifetime anxiety disorders (Milos et al. 2004), and 56% of US female inpatients with eating disorders had anxiety disorders (Blinder et al. 2006). In general, reported lifetime prevalence of at least one anxiety disorder ranged from 25% to 75% in individuals with bulimia nervosa and from 23% to 54% in those with anorexia nervosa (Godart et al. 2002).

Although as a group, the reported prevalence of anxiety disorders does not differ across types of disordered eating, the reported prevalence of specific anxiety disorders varies widely across types of disordered eating (Blinder et al. 2006; Brewerton et al. 1995; Bulik 2003; Fornari et al. 1992; Jordan et al. 2008; Kaye et al. 2004). For instance, while social phobia has been indicated as the most common comorbid anxiety disorder in individuals with anorexia nervosa (Fornari et al. 1992; Jordan et al. 2008), high prevalence of obsessive-compulsive disorder has also been observed in people with anorexia nervosa (Bulik 2003; Kaye et al. 2004). In individuals with bulimia nervosa, however, the prevalence of specific anxiety disorders varied significantly across studies with some studies reporting high rates of prevalence of social phobia, simple phobia, and obsessive-compulsive disorder (e.g. Fornari et al. 1992), while others did not (Brewerton et al. 1995).

High rates of substance use have been found in clinical samples of women with eating disorders (e.g. Milos et al. 2004) and high rate of disordered eating patterns have been found in women with substance use diagnoses (e.g. Schuckit et al. 1996). The elevation in substance use has been found in women diagnosed with bulimia nervosa and bingeing and purging anorexia but not in restricting anorexia (Stock et al. 2002). In a sample of male patients treated for eating disorders, 37% were found to fulfill DSM-IV criteria for substance abuse (Carlat et al. 1997). More recently, measures of illicit drug abuse and dependence were significantly associated with disordered eating patterns in female inpatients with eating disorders (Blinder et al. 2006). Moreover, in a study of substance abuse patients, men and women reported similar levels of engagement in binge eating and compensatory behaviors, however, the women had higher disturbed attitudes toward body weight and shape (Jackson and Grilo 2002).

98.3 Findings of Research Using Community Samples

Elevated levels of mood and anxiety disorders in individuals with eating disorders have been found in community-based samples. In a national sample of US women, 36% of those meeting the criteria for BN, also met the criteria for a lifetime diagnosis of major depression (Dansky et al. 1998). Similar results were reported by Telch and Stice (1998), who found significantly higher rates for major depression in a community sample of women with binge eating disorder relative to control participants, and by Lewinsohn and colleagues (2000) who reported a high prevalence of psychiatric comorbidity in a sample of high school female students with eating disorders. Significant association

between eating disorders and mood disorders has been found for both men and women in other community samples (John et al. 2006; Schuckit et al. 1996). Reviewing the literature on the association of mood disorders and eating disorders, Godart and colleagues (2007) concluded that in community samples, the lifetime prevalence of mood disorders was 2.6–4 times higher in individuals with anorexia nervosa than those found in controls.

Kaye and colleagues (2004) found obsessive-compulsive disorder and social phobia to be the most common anxiety disorders among women with eating disorders. These authors found that anxiety disorders in general and obsessive-compulsive disorder in particular to be more prevalent in women with anorexia nervosa and bulimia nervosa compared with control women from the community. Significant associations between eating disorders and major depression, social phobia, agoraphobia, and panic disorder have been observed in men with eating disorders (Woodside et al. 2001). In another community-based sample of men and women, those who screened positive for binge eating disorder had significantly higher odds of depression, panic attacks, and generalized anxiety disorder (GAD) compared with controls (Grucza et al. 2007). Hudson and colleagues (2007) examined the association between threshold- and subthreshold-level eating disorders and a range of lifetime psychiatric comorbidities in a large, nationally representative sample of US men and women. The authors found high prevalence of lifetime comorbid psychiatric disorders in individuals with all eating disorders except subthreshold binge eating disorder. Specifically, the authors found individuals with bulimia nervosa or binge eating disorder to have elevated odds of having lifetime diagnosis of major depression, dysthymia, bipolar disorder, panic disorder, agoraphobia without panic, specific phobia, social phobia, post-traumatic stress disorder, obsessive-compulsive disorder, and separation anxiety.

Significant associations between disordered eating patterns and substance dependence were observed in community samples, regardless of the type of diagnostic assessment used (Bulik 2003; John et al. 2006; Woodside et al. 2001; Piran and Gadalla 2006). Measures of alcohol consumption, dependence, and interference were significantly associated with disordered eating attitudes and behaviors in a nationally representative sample of Canadian women (Piran and Gadalla 2006) and with bulimia nervosa in a nationally representative sample of US women (Dansky et al. 2000). Similar associations have been found in adolescents (e.g. Benjamin and Wulfert 2005) and in university students (e.g. Krahn et al. 2005). A few studies, however, did not find such association (Dunn et al. 2002).

Additionally, lifetime and 12-month measures of illicit drug abuse and dependence were significantly associated with disordered eating behaviors in a national sample of women (Piran and Gadalla 2006) and with disordered eating patterns in other community samples (e.g. von Ranson et al. 2002). Specifically, amphetamine use was found to be associated with the risk for eating disorders in both men and women while illicit drug use, dependence, and interference were associated with risk for eating disorders in women but not in men (Gadalla and Piran 2007). Associations between the use of illicit substances and disordered eating patterns have also been found in other community samples (e.g. von Ranson et al. 2002).

Gadalla (2008a) examined the associations between disordered eating symptomatology, defined as a score of 20 or more on EAT-26 (Garner et al. 1982), and measures of selected mood, anxiety, and substance use disorders as well as psychological distress in a nationally representative sample of Canadian men and women. Assessment of 12-month and lifetime prevalence of mood, anxiety, and substance use disorders were based on the short form of the Composite International Diagnostic Interview (CIDI-SF). Level of psychological distress during the 30 days previous to the interview was determined using the scale known as K10 (Kessler et al. 2002). As shown in Table 98.1, findings of this study indicated that while 12-month prevalence of major depression, manic disorder, panic disorder, agoraphobia, social phobia, and substance dependence were significantly associated with disordered eating symptomatology in women, only major depression, panic disorder, and social phobia were significantly associated with disordered eating syptomatology in men. A woman with

Table 98.1 Association between disordered eating symptomatology (EAT-26 score $\geq$ 20) and past 12-month measures of selected mood, anxiety, and substance disorders in Canadian men and women (Published with permission from Gadalla 2008a)

Disorder	Score on Eat-26	Odds ratio (95% CI)	
		Women	Men
Major depression	Score < 20	–	–
	Score $\geq$ 20	5.03 (4.08, 6.17)[***]	4.52 (2.48, 8.26)[***]
Manic episodes	Score < 20	–	–
	Score $\geq$ 20	4.76 (3.06, 7.41)[***]	1.69 (0.31, 9.09)
Panic disorder	Score < 20	–	
	Score $\geq$ 20	4.39 (3.14, 6.10)[***]	5.29 (2.02, 13.89)[**]
Agoraphobia	Score < 20	–	–
	Score $\geq$ 20	3.85 (2.44, 6.02)[***]	4.08 (0.69, 24.39)
Social phobia	Score < 20	–	–
	Score $\geq$ 20	4.20 (3.24, 5.49)[***]	3.80 (1.80, 8.06)[***]
Substance dependence	Score < 20	–	–
	Score $\geq$ 20	3.03 (2.02, 4.55)[***]	1.96 (0.90, 4.27)
Major depression/manic episodes	Score < 20	–	–
	Score $\geq$ 20	5.13 (4.18, 6.29)[***]	4.31 (2.40, 7.69)[***]
Any anxiety disorder	Score < 20	–	–
	Score $\geq$ 20	4.20 (3.37, 5.24)[***]	4.57 (2.47, 8.40)[***]
Any mood, anxiety or substance dependence	Score < 20	–	–
	Score $\geq$ 20	4.76 (3.98, 5.68)[***]	2.78 (1.66, 4.65)[***]

Data presented in this table indicate that both men and women with disordered eating symptomatology had significantly elevated odds for major depression, panic disorder, social phobia, and psychological distress. The 1-year prevalence of manic episodes, agoraphobia, and substance dependence were associated with disordered eating symptomatology for women but not for men

Assessment of 12-month prevalence of mood, anxiety, and substance use disorders were based on the short form of the Composite International Diagnostic Interview. Level of psychological distress was determined using the scale known as K10 (Kessler et al. 2002)

$*p < 0.05$, $**p < 0.005$, $***p < 0.0005$

disordered eating symptomatology was five times more likely to have at least one major depressive episode while a man with disordered eating symptomatology was more than four times more likely to have at least one such episode within the same year. As shown in Table 98.2, in women, disordered eating symptomatology was strongly associated with lifetime prevalence of manic episodes, panic disorder, agoraphobia, and social phobia. In men, it was strongly associated with lifetime prevalence of panic disorder and social phobia and moderately associated with agoraphobia. Disordered eating symptomatology was associated with a fivefold increase in women's odds of having panic disorder and fourfold increase in men's odds of having panic disorder. Data presented in Table 98.3 reveal a highly significant association between disordered eating symptomatology and concurrent psychological distress in both genders.

98.4 The Effect of Participants' Age on Comorbidity Rates

Research has shown that prevalence rates and illness duration of eating disorders and other psychiatric disorders are age dependent (Hudson et al. 2007; Kessler et al. 1994; Piran and Gadalla 2006). For example, Kessler and colleagues (1994) found lifetime and 12-month prevalence of DSM-III-R

Table 98.2 Association between Disordered Eating (EAT-26 score ≥20) and Lifetime Measures of Selected Mood, Anxiety and Substance Use Disorders in Canadian Men and Women (Published with permission, from Gadalla 2008a)

Disorder	Score on Eat-26	Odds ratio (95% CI)	
		Women	Men
Major depression	Score < 20	–	–
	Score ≥ 20	2.94 (2.45, 3.53)***	3.70 (2.31, 5.95)***
Manic episodes	Score < 20	–	–
	Score ≥ 20	3.98 (2.90, 5.46)***	2.22 (0.83, 5.71)
Panic disorder	Score < 20	–	–
	Score ≥ 20	4.15 (3.27, 5.29)***	4.98 (2.60, 9.52)***
Agoraphobia	Score < 20	–	–
	Score ≥ 20	4.15 (3.02, 5.71)***	3.19 (1.16, 13.16)*
Social phobia	Score < 20	–	–
	Score ≥ 20	3.07 (2.50, 3.77)***	4.40 (2.72, 7.14)***
Major depression/manic episodes	Score < 20	–	–
	Score ≥ 20	3.01 (2.52, 3.61)***	3.64 (2.29, 5.78)***
Any anxiety disorder	Score < 20	–	–
	Score ≥ 20	3.72 (3.12, 4.44)***	4.74 (3.03, 7.41)***
Any mood or anxiety disorder	Score < 20	–	–
	Score ≥ 20	3.88 (3.26, 4.61)***	3.30 (2.15, 5.05)***

Data presented in this table indicate that disordered eating symptomatology was significantly associated with lifetime depression, manic episodes, panic disorder, agoraphobia, and social phobia in women, and with lifetime depression, panic disorder and social phobia in men

Assessment of lifetime prevalence of mood, anxiety, and substance use disorders were based on the short form of the Composite International Diagnostic Interview (CIDI-SF). Level of psychological distress was determined using the scale known as K10 (Kessler et al. 2002)

*$p < 0.05$, **$p < 0.005$, ***$p < 0.0005$

Table 98.3 Association between disordered eating symptomatology (EAT-26 score ≥ 20) and psychological distress by gender (Published with permission, from Gadalla 2008a)

Measure of distress	EAT-26	Mean (sd)	
		Women	Men
K10	Score < 20	5.44 (5.45)***	5.04 (5.19)***
	Score ≥ 20	10.63 (7.78)	9.70 (9.02)

Data presented in the table reveal significant associations between disordered eating symptomatology and concurrent psychological distress in both men and women

Psychological distress was measured using the K10 scale (Kessler et al. 2002)

Significance levels were based on one-factor ANOVA comparing mean distress level for persons with EAT-26 score < 20 versus mean distress level for persons with EAT-26 score ≥ 20 for each gender

***$p < 0.0005$

psychiatric disorders to be age dependent with the highest lifetime prevalence in the 25–34 year age group and the highest 12-month prevalence in the 15–24 year age group.

The above findings highlight the importance of taking participants' age into consideration when examining the comorbidity of psychiatric disorders. One such study was carried out by Gadalla and Piran (2008) in which the authors examined the associations of disordered eating behaviors with selected mood, anxiety, and substance use disorders in a national sample of Canadian women in three different age groups, 25–24, 25–44 and 45 years or above. The authors found significant associations between disordered eating behaviors and major depression, substance dependence, and psychological distress for women in all three age ranges. Prevalence of specific classes of anxiety

disorders in women who reported disordered eating behaviors differed according to their age. Having disordered eating behaviors was significantly associated with both 12-month and lifetime prevalence of social phobia for women above 25 years of age. Lifetime prevalence of agoraphobia was associated with disordered eating behaviors in women 15–44 years old, and the 12-month prevalence was associated with disordered eating behaviors only in women 15–24 years of age. Disordered eating behaviors was significantly associated with lifetime prevalence of panic disorder in women in all three age ranges and with 12-month prevalence of panic disorder in women in two age ranges, 15–24 and 45 and above.

98.5 Psychological Comorbidity in Elderly Women with Eating Disorders

Eating disorders and their associated psychopathology in elderly individuals, especially those living in the community, have received limited attention. To date, research on eating disorders in the elderly have focused on under-nutrition and eating difficulty in institutionalized women (e.g. Chapman 2006). However, reports on body image have provided evidence that drive for thinness and body dissatisfaction in women do not decline with advancing age (Cosford and Arnold 1992; Gadalla 2008b; Mangweth-Matzek et al. 2006; Webster and Tiggemann 2003). For example, Webster and Tiggemann (2003) reported that there were no differences between groups of young, middle aged, or older women in body dissatisfaction and importance of body shape. These authors also found that body dissatisfaction was negatively related to self-concept and self-esteem of women of all ages. More recently, in a community sample of 60–70 year-old women, 80% practiced some form of weight control and 60.0% stated dissatisfaction with their bodies (Mangweth-Matzek et al. 2006). Furthermore, in a national sample of women, 15.9% of 50–60 year-old and 7.4% of those 65 years or older were strongly concerned about their weight or body shape (Gadalla 2008b). This author also reported that 2.6% of women 50–64 years old and 1.8% of women 65 years or older, exhibited disordered eating behaviors, such as elevated frequency of dieting behaviors and preoccupation with food intake and body shape. There as a significant negative association between disordered eating behaviors and women's physical health and a significant positive association with stress level.

Research reports provide evidence that eating disorders may also occur at any age throughout the lifespan. For example, Mangweth-Matzek and colleagues (2006) found that 3.8% of elderly women living in the community met the criteria for eating disorders. Eating disorders in older women could be new episodes occurring for the first time, relapsing or persistent episodes of earlier disorders that had occurred earlier in their lives (Cosford and Arnold 1992). Additionally, as the population ages and the idealized images presented by the media become progressively thinner, the prevalence of eating disorders in the elderly is expected to increase and hence, there is pressing concern for a careful consideration of disordered eating patterns and their associated psychiatric comorbidity in this population.

Gadalla (2008b) examined psychiatric comorbidity in women 50–64 years old and 65 years or older who exhibited disordered eating behavior using a large sample of women in the general population. Findings of this study indicated highly significant associations between disordered eating attitudes and behaviors and mood and anxiety disorders for women in both age groups. Women 50–64 years old who scored over 20 on EAT-26 (Garner et al. 1982) were 6.9 times more likely to have at least one mood disorder, 2.6 times more likely to have at least one anxiety disorder and 6.0 times more likely to be alcohol dependent compared to women who scored 20 or less. Women 65 years and older who scored above 20 on EAT-26 were 3.2 more likely to have at least one mood disorder and 5.6 more likely to have at least one anxiety disorders.

98.6 Discussion and Recommendations

Findings of previous research on prevalence of mood and anxiety disorders in individuals with eating disorders varied a great deal (Godart et al. 2002, 2007). Possible reasons for these variations include the use of different types of participants and sample selection and the use of different criteria for assessing both eating disorder patterns and psychiatric disorders. In addition, the reference time used for the diagnosis of disorders ranges from point-prevalence or concurrence rates to lifetime occurrence. Further, when authors report prevalence rates that had been collapsed over a number of anxiety or mood disorders, these rates will vary according to the number of specific disorders included in the collapsed rate (Wittchen 1996). These methodological differences make it difficult to compare findings across studies. Researchers are thus, encouraged to use standardized and validated instruments for the assessment of eating disorders and other psychiatric disorders and report prevalence rates separately for each disorder and each gender.

A central issue in comorbidity studies is the temporal sequence of the disorders. Knowledge of the temporal sequence of eating disorders and other psychiatric disorders is essential when examining possible explanations for their relationship. Very few studies examined the temporal sequence of eating disorders and other psychopathologies. One such study was carried out by Measelle and colleagues (2006) who found that initial depression predicted increases in eating disorders and substance abuse symptoms, while initial eating disorders' symptoms predicted an increase in substance abuse problems in a community sample of adolescent women. In addition, in a sample of women with anorexia nervosa or bulimia nervosa, the onset of obsessive-compulsive disorder, social phobia and generalized anxiety disorder preceded the development of eating disorders in the majority of them (Kaye et al. 2004). The chronology of eating disorders and other psychiatric disorders can only be examined in longitudinal studies.

Generational differences, with younger generations at higher risk of experiencing psychiatric comorbidity, have also been suggested (Gadalla and Piran, 2008). Hudson and colleagues (2007) found the risk of bulimia nervosa and binge eating disorders to increase with successive birth cohorts. Studies with longitudinal design can be used to separate the effects of age on women's susceptibility to psychiatric disorders from generational differences. It has also been suggested that developmental trajectories of these disorders might be gender-specific (Beato-Fernandez et al. 2007). Consequently, such studies should be carried out for men and women separately.

The age of onset and the duration of each disorder should be taken into account when studying comorbidity of multiple disorders. For instance, according to the Diagnostic and Statistical Manual of Mental Disorders (APA 1994), the average age onset of anorexia nervosa is 17 years and of bulimia nervosa is18 years while depression is usually observed later. Thus, if eating disorders are usually observed at younger age than depression, the chronology of these two disorders may be a result of their natural courses rather than a causal link between them (Godart et al. 2007).

A few conceptual explanations for the high comorbidity rates between eating disorders and other psychiatric disorders have been proposed. One possible explanation is that the comorbid disorders share common risk factors. A second possible explanation is that the presence of one disorder increases the risk for the development of the other. A further possible explanation is that comorbidity reflects a developmental process where one disorder is the early stage of the other disorder. Future gender-specific studies examining alternative conceptual models with regards to the multivariate comorbidity of eating disorders and other psychiatric disorders are needed.

There is also a need for better description of treatment strategies that would best help individuals suffering from them. Research findings suggest that women with disordered eating patterns should be screened for symptoms of depression, manic episodes, agoraphobia, social phobia, panic disorders,

substance dependence, and psychological distress, while men with disordered eating patterns should be screened for symptoms of depression, panic disorder, social phobia, and psychological distress. Men and women presenting with the above mentioned disorders should be screened for eating disorders. The high prevalence of depression in eating disordered men and women calls for special attention, especially in the light of data suggesting that disordered eating patients whose depression begins before their eating problem more often engage in parasuicidal behaviors (Wildman et al. 2004). The development of short screening instruments for assessing depressive symptoms as well as symptoms of specific classes of anxiety disorders could be proven useful. These screening instruments should be gender-specific, focusing on mood and anxiety disorders found to be more prevalent for each gender. It is also of importance to continue developing treatment and prevention programs, which take into consideration the psychological comorbidity specific to men and women with eating disorders.

98.7 Applications to Other Areas of Health and Disease

Comorbidity studies have an important role to play in the clinical management of disease as well as the understating of the etiology of different physical and psychological conditions. One other area in which comorbidity studies can prove extremely useful is the interplay of physical and mental health.

A burgeoning body of research has shown that mental disorders, such as mood and anxiety disorders are more prevalent in individuals with chronic physical illness compared to individuals with no such illness. A diagnosis of a disabling physical illness and the associated decline in physical health may cause enough distress to trigger a depressive episode or invoke anxiety in vulnerable persons. On the other hand, individuals with mental illness can develop physical symptoms and illnesses, such as weight loss and biological disturbances associated with eating disorders.

High prevalence of mental disorders among individuals with chronic physical conditions represents a significant burden to individuals and society. At the individual level, mental illness can affect individuals' response to the treatment of their physical illness and adversely affect the course of physical illnesses**. In addition, mental illness may interact with physical illness to amplify the disability associated with it, thus, leading to occupational impairment, disruption in interpersonal and family relationships, poor health, and suicide. At the national level, comorbid anxiety disorders can adversely affect the economy through reduced productivity and higher health care costs.

Summary Points

- Empirical research provides evidence of high prevalence of psychiatric disorders, such as mood, anxiety, and substance use disorders in disordered eating individuals. This comorbidity was observed for both genders and is highest between eating disorders and major depression.
- In contrast with the consistent pattern regarding the association of eating disorders and alcohol use disorders in women and men, research findings regarding illicit drug use are markedly different between genders.
- More research is needed to determine the temporal sequence of the occurrence of eating disorders and other psychiatric disorders and to explain their comorbidity.
- Emerging research indicates that disordered eating occur in men and older adults. However, few studies examined eating disorders and their psychiatric comorbidity in these populations.
- Future research is encouraged to use longitudinal data collected from population-based samples.

- The importance of taking into account the age of onset and the duration of each disorder when studying comorbidity of multiple disorders is highlighted.
- Generational differences in the prevalence of eating and other psychiatric disorders should also be considered when studying comorbidity of multiple disorders.

Definitions and Explanations of Key Terms

- **Anorexia nervosa:** Anorexia nervosa is a psychiatric diagnosis that describes an eating disorder characterized by low body weight and body image distortion with an obsessive fear of gaining weight.
- **Bulimia nervosa:** Bulimia nervosa is an eating disorder characterized by recurrent binge eating, followed by compensatory behaviors, such as self-induced vomiting and the use of laxatives, enemas, and diuretics.
- **Purging:** Purging refers to the act of using self-induced vomiting and the use of laxatives, enemas, or diuretics to get rid of ingested food.
- **Binge eating disorder:** Binge eating consists of episodes of uncontrollable overeating during which, a person rapidly consumes a large amount of food.
- **EAT-26:** Eating Troubles module was developed by Garner et al. (1982). A score of 20 or more indicates disordered eating attitude and behavior, suggesting that the person is at risk of having eating disorder.
- **Mood disorders:** Mood disorders include depressive disorders, of which the best known and most researched is major depressive disorder commonly called major depression, and bipolar disorder, formerly known as "manic depression" and described by intermittent periods of manic and depressed episodes.
- **Anxiety disorders:** Anxiety disorders include several conditions of pathological fears or anxieties, such as generalized anxiety disorder, panic disorder, agoraphobia, social anxiety disorder, obsessive-compulsive disorder, post-traumatic stress disorder, and separation anxiety.

Key Points

- Empirical research provides evidence of high comorbidity between disordered eating patterns and other psychiatric disorders, especially mood, anxiety and substance use disorders. This comorbidity is highest with depression.
- Several hypotheses have been proposed to explain the high prevalence of mood and anxiety disorders in individuals with eating disorders. These hypotheses have not been empirically tested. In addition, the temporal sequence of the occurrence of eating disorders and comorbid psychiatric disorders is not yet determined.
- Although there is evidence to suggest that disordered eating patterns occur in men and in older adults, few studies examined eating disorders and their comorbid psychopathologies in these populations.
- Comorbidity studies have important implications for understanding the etiology of mental disorders as well as the clinical management of patients.

References

American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4th ed., DSM-III-R. Washington, DC: APA; 1994.

Beato-Fernandez L, Roderiguez-Cano T, Pelayo-Delgado E, Calaf M. Child Psychiatr Hum Dev. 2007;37:193–203.

Benjamin L, Wulfert E. Eat Behav. 2005;6:197–209.

Berkson J. Biometrics Bull. 1946;2:47–53.

Blinder BJ, Cumella EJ, Sanathara VA. Am Psychosom Soc. 2006;68:454–62.

Brewerton TD, Lydiard RB, Herzog DB, Brotman AW, O'Neil PM, Ballenger JC. J Clin Psychiatr. 1995;56:77–80.

Bulik CM. Anxiety, depression and eating disorders. In: Treasure J, Schmidt U, van Furth E, editors. Handbook of eating disorders. Chichester: Wiley; 2003. p. 193–8.

Carlat DJ, Camargo CA, Herzog DB. Am J Psychiatr. 1997;154:1127–32.

Chapman IM. Med Clin North Am. 2006;90:887–907.

Cosford P, Arnold E. Int J Geriat Psychiatr. 1992;7:491–8.

Dansky BS, Brewerton TD, O'Neil PM, Kilpatrick DG. In: Widiger TA, Frances AJ, Pincus HA, First M, Ross R, Davis W editors. DSM-IV sourcebook, vol. IV. Washington, DC: American Psychiatric Press; 1998. p. 515–31.

Dansky BS, Brewerton TD, Kilpatrick DG. Int J Eat Disord. 2000;27:180–90.

Dunn EC, Larimer ME, Neighbors C. Int J Eat Disord. 2002;32:171–8.

Fornari V, Kaplan M, Sandberg DE, Mathews M, Skolnick N, Katz JL. Int J Eat Disord. 1992;12:21–9.

Gadalla TM. J Mens Health. 2008a;5:209–17.

Gadalla TM. Arch Womens Ment Health. 2008b;11:357–62.

Gadalla TM, Piran N. Eat Disord. 2007;15:189–203.

Gadalla TM, Piran N. Women Health. 2008;48:467–84.

Garner DM, Olmsted MP, Bohr Y, Garfinkel PE. Psychol Med. 1982;12:871–8.

Geist R, Davis R, Heinmaa M. Can J Psychiatr. 1998;43:507–12.

Godart NT, Flament MF, Lecrubier Y, Jeammet P. Eur Psychiatr. 2000;15:38–45.

Godart NT, Flament MF, Perdereau F, Jeammet P. Int J Eat Disord. 2002;32:253–70.

Godart NT, Perdereau F, Rein Z, Berthoz S, Wallier J, Jeammet PH. Flament MF. J Affect Disord. 2007;97:37–49.

Grucza RA, Przybeck TR, Cloninger CR. Compr Psychiatr. 2007;48:124–31.

Hinrichsen H, Waller G, van Gerko K. Eat Behav. 2004;5:285–90.

Hudson JI, Hiripi E, Pope HG, Kessler RC. Biol Psychiatr. 2007;61:348–58.

Iwasaki Y, Matsunaga H, Kiriike N, Tanaka H, Mastui T. Compr Psychiatr. 2000;41:454–60.

Jackson TD, Grilo CM. Eat Weight Disord. 2002;7:276–83.

John U, Meyer C, Rumpf HJ, Hapke U. Psychiatr Res. 2006;141:71–9.

Jordan J, Joyce PR, Carter FA, Horn J, McIntosh VW, Luty SE, McKenzie JM, Frampton CM, Mulder RT, Bulik CM. Int J Eat Disord. 2008;41:47–56.

Kaye WH, Bulik CM, Thornton L, Barbarich N, Masters K. Am J Psychiatr. 2004;161:2215–21.

Kessler RC, McGonagle KA, Zhao S, Nelson CB, Hughes M, Eshleman S, Wittchen H, Kendler KS. Arch Gen Psychiatr. 1994;51:8–19.

Kessler RC, Andrews G, Colpe LJ, et al. Psychol Med. 2002;32:959–76.

Krahn DD, Kurth CL, Gomberg E, Drewnowski A. Eat Behav. 2005;6:43–52.

Lewinsohn PM, Striegel-Moore RH, Seeley JR. J Am Acad Child Adolesc Psychiatr. 2000;39:1284–92.

Mangweth-Matzek B, Rupp CI, Hausmann A, Assmayr K, Mariacher E, Kemmler G, Whitworth AB, Biebl W. Int J Eat Disord. 2006;39:583–6.

Measelle JR, Stice E, Hogansen JM. J Abn Psychol. 2006;115:524–38.

Milos G, Spindler A, Schnyder U. Can J Psychiatr. 2004;49:179–84.

O'Brien KO, Vincent NK. Clin Psychol Rev. 2003;23:57–74.

Piran N, Gadalla TM. Addict 2006;102:105–13.

Schuckit MA, Tipp JE, Anthenelli RM, Bucholz KK, Hesselbrock VM, Nurnberger JI Jr. Am J Psychiatr. 1996;153:74–82.

Stock SL, Goldberg E, Corbett S, Katzman DK. J Adolesc Health. 2002;31:176–82.

Telch CF, Stice E. J Consult Clinic Psychol. 1998;66:768–76.

von Ranson KM, Iacono WG, McGue M. Int J Eat Disord. 2002;31:389–403.

Webster J, Tiggemann M. J Gen Psychol. 2003;164:241–52.

Wildman P, Lilenfeld LR, Marcus MD. Int J Eat Disord. 2004;35:190–7.

Wittchen HU. Br J Psychiatr. 1996;30:9–16.

Woodside DB, Garfinkel PE, Lin E, Goering P, Kaplan AS, Goldbloom DS, Kennedy SH. Am J Psychiatr. 2001;158:570–4.

Chapter 99
Cognitive Performance Deficits of Dieters

Michael W. Green

Deliberate restriction of food intake to control weight is one of the most common food choice-related behavior in the developed world. Indeed, over one third of the general US population is classed as obese (National Center for Health Statistics 2006), with an associated impact on health treatment resources (Bray 1996) (see Fig. 99.1).

Within the context of these rising obesity rates (Department of Health (DOH) 2008), an understanding of the psychological impact of undernutrition and weight loss assumes an increasing importance. Food deprivation is a situation which, to varying degrees, affects a large proportion of the world's human population. In economically developed countries, however, it is a comparatively rare phenomenon except during times of war. Indeed, most of the occurrences of food deprivation observed in such countries are the result of a self-initiated choice, such as that found with eating disordered psychopathology, weight loss dieting, or fasting for religious reasons (such as the Muslim festival of Ramadan). Aside from the obvious physiological consequences of prolonged periods of food deprivation, there is an increasing body of literature indicating that this activity is associated with a range of psychological effects. These range from effects on cognitive functioning to the range of dysphoric affective states associated with eating disordered psychopathology and dieting behavior. The current chapter will describe this literature, both in terms of the effects of dieting-related food deprivation on cognitive function and affective state, and to consider a number of mechanisms which may underlie these effects. In turn, the chapter will consider the effects of laboratory-based food deprivation on psychological function, the effects of naturalistic attempts at dieting on psychological function, the practical and conceptual differences between dieting and dietary restraint and possible mechanisms to account for these phenomena.

The difference between laboratory-based studies of imposed caloric restriction and studies of naturalistic dieting is an important distinction on a number of levels. First, there are obvious motivational differences separating those who volunteer to take part in laboratory-based studies of food deprivation and those individuals who are already dieting to lose weight at the time of testing in naturalistic studies of the psychological effects of dieting. Second, for ethical reasons, laboratory-based studies of the psychological effects of caloric restriction tend to examine participants who are already in the upper end of the body mass index distribution (e.g. Kretsch et al. 1997), whereas naturalistic studies have found dieting-related psychological effects in individuals within the normal or low body mass index range (Green and Rogers 1995a).

M.W. Green (✉)
Nutrition and Behaviour Laboratory, Psychology Department, School of Life and Health Sciences,
Aston University, Birmingham, UK, B4 7ET
e-mail: m.w.green@aston.ac.uk
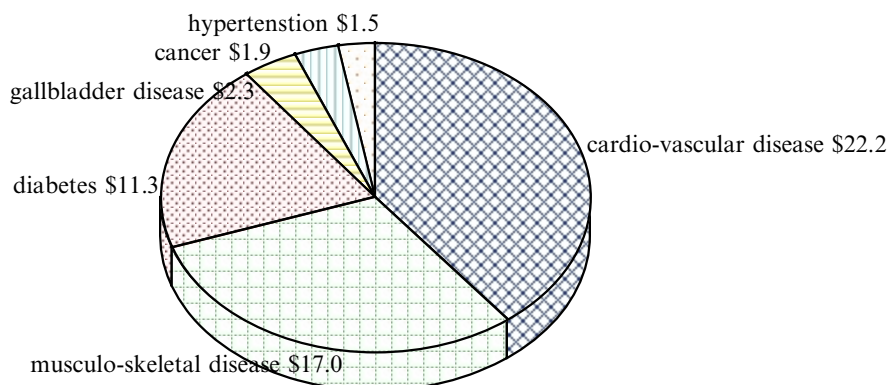
Fig. 99.1 Results of Bray (2006), showing US financial health costs ($US billion) of obesity-related diseases (total cost $US 56.2 billion)

99.1 Studies of Laboratory-Induced Food Deprivation

The main features of the studies which have examined the effects of laboratory-induced food deprivation are outlined below in Table 99.1.

The first systematic study of the effects of food deprivation was the famous Minnesota Study of Semi-Starvation (Keys et al. 1950). With a view to understanding the effects of starvation in order to determine refeeding strategies for malnourished refugees and prisoners of war following World War Two. In this study, participants were fed a diet comprising 50% of normal caloric intake for a period of 6 months, followed by a period of refeeding. Medical and psychological variables were measured at several time points over the course of the study. Over the course of the study, it was found that semistarvation resulted in increase in preoccupation with food and self-reported depression, in addition to self-reported problems with memory, concentration, alertness, and judgment. However, these effects were not borne out by objective performance measures. As there was no nonstarved control group for comparison, this lack of an effect of food deprivation on objective test performance could be interpreted in terms of a confounding practice effect. A more recent study has, however, partially replicated these findings (Sutker et al. 1992). It was found that, compared to nonstarved individuals, former prisoners of war with a history or malnutrition and body wasting (exceeding 35% of their precaptivity body weight) during captivity displayed poorer performance on a range of standardized tests of memory and learning. This study is important in two respects. First, it contained a nonstarved control group and so demonstrates that the results of the Minnesota Study may not be an experimental artefact. Second, effects on psychological function were observed several years after the period of food deprivation. It has to be remembered, however, that these studies examined the effects of relatively severe food deprivation, with roughly 25% of body mass being lost amongst participants in the Minnesota Study. Subsequent laboratory-based studies have not induced comparable degrees of food deprivation.

There are a number of studies which have examined the effects of laboratory-induced food deprivation of varying degrees on psychological function in a more controlled manner. In general, the results of these studies demonstrate that laboratory-induced food deprivation does not lead to significant impairments in psychological function (e.g. Shukitt-Hale et al. 1997; Corby et al. 2007), although there are methodological and procedural issues which need to be borne in mind when interpreting these data.

Table 99.1 Summary of studies investigating effects laboratory-induced food deprivation on cognition

Study	Participants	Deprivation	Findings
Corby et al. (2007)	Healthy adults (total N = 48)	4 conditions, ranging from normal feeding to 15% weight loss	No deprivation-related effects on cognition
Deijen et al. (1989)	Experimentally controlled dieting vs. nondieting controls (N = 10) per group	3 week weight loss diet	Dieting improved motor speed but impaired memory, but only when tested during morning
Green et al. (1995)	Healthy adults (N = 21)	Missing 1 meal to 24 h deprivation	No deprivation-related effects on cognition
Keys et al. (1950)	Healthy males (N = 36) No control group	24 weeks semi caloric intake	Impaired mood, attention, and memory (self reported)
Kretsch et al. (1997)	Obese women (N = 14) on diet, (N = 11) non- dieting controls	15 weeks of 50% caloric restriction	impaired reaction times No effect on other cognitive functions
Shukitt-Hale et al. (1997)	Healthy males (N = 17 per group)	30 days undernutrition vs. 30 days normal diet	No deprivation-related effects on cognition
Sutker et al. (1992)	Former POWs with history of malnutrition	Weight loss exceeding 35% of precaptivity weight	Range of impairments on various memory tasks
Wing et al. (1995)	Obese women (N = 21) No nondieting controls	Ketogeic vs. non- ketogenic diet	Ketogenic diet showed poorer spatial ability. Baseline differences make Clear interpretation difficult

The effects of prolonged experimentally-induced weight loss have been studied in a population of noneating-disordered obese individuals (Kretsch et al. 1997). During 15 weeks of 50% caloric restriction, obese subjects were regularly assessed on measures of sustained attention, immediate verbal free recall, distractibility, simple reaction time, and motor speed (2-finger tapping performance). Relative to nondieting control subjects, simple reaction times significantly slowed over the course of caloric restriction. However, there were no significant food deprivation-related deficits in the more complex measures of cognitive function. In fact, verbal recall was actually found to improve in the obese subjects, over the course of caloric restriction.

Other studies have examined the effects of experimentally-induced low energy diets on cognitive function. Wing, Vazquez and Ryan (1995) reported that the administration of a low carbohydrate diet (549 kcal/day) over 28 days amongst obese subjects was associated with impaired performance on a trail making task, relative to a group administered a low fat diet (590 kcal/day). There are, however, a number of problems with this study. Foremost of these is that, although beta-hydroxybutyrate levels (a metabolic indicator of starvation) rose significantly over the whole 28 days of the diet, trail making task performance was only significantly impaired at 7 days of dieting, compared to baseline. Subsequent measurements showed that trail making performance was actually better than baseline, with performance after 28 days of low carbohydrate dieting actually being better than at baseline. This was further confounded by marginally significant baseline differences between trail making performance (p = 0.06). Further support for the hypothesis that experimentally-induced weight loss per se does not significantly affect cognitive processing efficiency was provided by Deijen, Heemstra and Orlebeke (1989). This particular study found that, after a 3 week long, experimentally-induced weight loss diet, non-dieting subjects performed better than non-dieting subjects on a measure of motor speed (2-finger tapping). Although the dieting subjects performed more poorly than non-dieters on the Sternberg Memory Scanning Task, this difference was only apparent during morning test sessions, and not during the afternoon. There were no significant diet-related differences in

performance on a continuous performance task, pattern comparison task or the Symbol-Digit substitution sub-test of the Weschler Adult Intelligence Scale (WAIS). It has also been found that experimentally-induced food deprivation of up to 24 h in duration produced no significant performance decrements (Green et al. 1995).

The results of these studies raise the question of possible differences between food deprivation imposed as part of an experimental regime and weight loss spontaneously undertaken by the subject. Although such laboratory-based studies of food deprivation have the advantage of being able to study weight loss in tightly controlled conditions, they lack ecological validity of studies carried out on dieting "in the real world". This is because such spontaneously initiated dieting is often associated with swings in affective state (Tiggemann 1994), depression (Smoller et al. 1987), and self-reported stress (Beiner and Heaton 1995). It is also the case that such dieting frequently occurs within the context of a history of repeated failed attempts at weight regulation (French et al. 1995).

99.2 Spontaneous Dieting

In comparison to laboratory-induced food deprivation, there is consistent evidence that spontaneous dieting, undertaken as a response to dissatisfaction with current body shape or weight, is associated with impairments in cognitive function and mood. This is related to, but not necessarily the same as, the concept of dietary restraint. This can be defined as being "the self initiated tendency to control eating behavior in order to lose weight or maintain weight at a low, but stable level" (Tuschl 1990). Therefore, whilst high levels of dietary restraint are a prerequisite of dieting, it is possible to be a restrained eater without actually being a dieter. These studies are summarized in Table 99.2.

A series of studies has shown that individuals who report themselves as being currently dieting to lose weight at the time of testing display poorer performance on a range of performance measures, compared to nondieting restrained and nonrestrained eaters. For instance, Rogers and Green (1993) found that current dieters ($N = 13$) performed more poorly than nondieters on a 6 min long vigilance task. Replicating and extending this finding, it was found that current dieters also displayed poorer performance on measures of immediate verbal recall and simple reaction time (Green et al. 1994). Significantly, 2-finger tapping performance was not impaired in dieters, indicating that these findings cannot be explained in terms of a general impairment in motor performance or lowered motivation to complete the task battery amongst dieters. Both of these studies also found that nondieting, highly restrained eaters performed at a level intermediate to that of dieters and nondieting unrestrained eaters. This suggests that the phenomenon is fundamentally psychological, rather than physiological in nature, since nondieting, restrained eaters are not normally in a state of food deprivation. This hypothesis is supported by the finding that, whereas dieters reported a significantly lower caloric intake than unrestrained nondieters, there was no difference between the caloric intakes of restrained and unrestrained non-dieters (Green et al. 1994).

The hypothesis that this phenomenon represents an effect of dieting per se, rather than an epiphenomenon relating to pre-existing individual differences between subjects who happen to be dieting or not, at the time of testing has also been supported. It has been found that, within the same subjects, performance on the same cognitive task battery used in the first two studies in the series, was poorer when dieting than when not dieting (Green and Rogers 1995a). Three groups of current dieters were tested twice, 3 weeks apart. It was found that the two groups who were dieting on one session, but not the other displayed poorer performance on a vigilance task, slower simple reaction times and poorer immediate recall during the session on which they reported themselves as being "on a diet". It was also found that the dieting associated decrement in performance tended to be worse amongst the group who were dieting on the first

Table 99.2 Summary of studies investigating effects of spontaneous dieting on cognition

Study	Participants	Findings
Green et al. (1994)	Dieters ($N = 15$), nondieters ($N = 42$)	Dieters showed impaired ability to sustain attention, poorer immediate verbal memory, and slower reaction times
Green et al. (2005)	Unsupported dieters ($N = 25$), supported dieters ($N = 14$), non dieting controls ($N = 16$)	Unsupported dieters showed impaired ability to sustain attention, immediate verbal memory, and central executive function after 1 week of dieting. Results related to cortisol secretion
Green et al. (1997)	Dieters ($N = 21$), nondieters ($N = 48$)	Dieters poorer on measure of overall working memory capacity than nondieters, but no Differences in attentional focus. Task performance related to food-related preoccupations
Green et al. (2003)	Dieters ($N = 19$), nondieters ($N = 34$)	Dieting-related central executive Deficit. Related to preoccupying Cognitions, but not urinary 5-HIAA output
Green and Rogers (1995)	Dieters ($N = 19$ on first but not second session), ($N = 14$ on second session but not first), ($N = 28$ dieting on both)	Vigilance performance, verbal immediate memory, and reaction speed poorer in crossover groups on session in which they were dieting. Unrelated to weight loss
Green and Rogers (1998)	Dieters ($N = 19$), nondieters ($N = 52$)	Dieters poorer at tasks loading onto central executive and phonological loop components of working memory. Performance related to body shape-related preoccupations
Jones and Rogers (2003)	Dieters ($N = 20$)	memory performance poorer after consumption of sugary snack than before. Related to food preoccupations
Kemps and Tiggemann (2005)	Dieters ($N = 33$), nondieters ($N = 33$)	Dieting-related central executive impairment, mediated by preoccupying cognitions
Kemps et al. (2005)	Dieters (32), nondieters (N 32)	Dieters performed more poorly central executive tasks than other aspects of working memory. Mediated by food and body shape Preoccupations
Rogers and Green (1993)	Dieters ($N = 13$), nondieters ($N = 42$)	Dieters showed impaired ability to sustain attention
Shaw and Tiggemann (2004)	Dieters ($N = 19$), past dieters ($N = 29$), never dieters ($N = 44$)	Clear evidence of phological loop impairment in dieting. Less clear evidence of central executive impairment. Results mediated by preoccupying cognitions
Vreugdenburg et al. (2003)	Dieters ($N = 20$), nondieters ($N = 20$)	Dieters poorer at tasks loading onto central executive and phonological loop components of working memory. Performance related to food and body shape-related preoccupations

session (but not the second) than in the group who were dieting on the second session (but not the first). This is illustrated by their performance on the Bakan vigilance task (see Fig. 99.2), I addition to performance on tasks measuring immediate verbal memory and reaction speed.

It was concluded, therefore, that the decrement in performance was related to the stress of a change to habitual or preferred food intake, since this group had been dieting for a far shorter period of time.

Having demonstrated that this negative effect of dieting on cognitive function is a replicable effect, the next question relates to the precise nature of the cognitive deficit. Is it the case that dieting independently affects a number of cognitive domains or is there an overarching cognitive system affected by dieting which give the appearance of a relatively global deficit? There are a number of
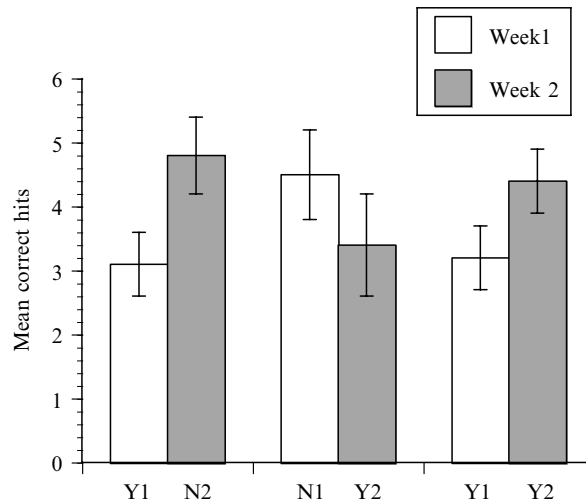
Fig. 99.2 Results of Green and Rogers (1995), showing Bakan task performance in three groups of dieters over the course of a 3 week attempt at weight loss (mean correct hits per minute; ± SE included). This shows performance on the Bakan vigilance task for three groups of dieters when either dieting (Y) or not dieting (N) on a first test session (1) and a second (2), 3 weeks later. In the two crossover groups, performance is poorer when dieting than when not dieting. The improvement in the Y1 Y2 group over time is attributed to practice

possible structures for this dieting-related cognitive impairment. Aside from the global deficit hypothesis, it is also possible that dieting is associated with a breakdown in the ability to attend to the task stimuli; the third possibility being a dieting-related reduction in cognitive processing (working memory) capacity (Baddeley 1986). The global deficit hypothesis is unlikely, since several studies show that performance is not affected on all cognitive tasks in a given performance battery (e.g. Green et al. 1994). Evidence regarding the second and third possible structures can be found in the results of the study of Green, Elliman and Rogers (1997). Dieting and nondieting subjects completed a measure of spatial and semantic distractibility and a measure of overall verbal working memory capacity, in addition to a number of self-report measures of somatic sensation and affective state. There were no dieting status-related differences on the flankers task. It was found, however, that current dieters exhibited smaller reading spans than nondieters and that this significantly covaried with self-reported "desire to eat". The data, therefore, supported the hypothesis that the deficit in cognitive processing associated with dieting is essentially one of a limitation in working memory capacity, rather than a failure in attentional focus. The data further indicated that this limitation is related to preoccupying cognitions concerning food.

Having established that spontaneously undertaken dieting is associated with impairment in working memory capacity, the next study in the series (Green and Rogers 1998) attempted to elucidate which of the sub-components of working memory are compromised in dieting. Processing Efficiency Theory (Eysenck and Calvo 1992) hypothesizes that preoccupying cognitions affect working memory capacity by means of subvocal worry, preferentially consuming the capacity of the Phonological Loop and Central Executive components of the system, these being the subsystems which deal with verbal information. The hypothesis that the working memory deficit associated with dieting bears similarity to deficits in the same system associated with the preoccupying cognitions accompanying anxiety and depression was the focus of an investigation by Green and Rogers (1998). Current dieters and nondieters completed computer-based measures of Central Executive capacity (Tower of London Task), Phonological Loop capacity (letter recall of visually presented material with/ without

articulatory suppression and with/ without phonological confusability) and Visuo-Spatial Sketchpad capacity (mental rotation). Consistent with the hypothesis that impaired cognitive processing in dieters is related to preoccupying cognitions, dieters displayed slower planning times on the Tower of London Task (four and five minimum move problems) and poorer performance on the letter recall task than nondieters. There were no dieting-related differences in performance on the mental rotation task. Further support for this hypothesis was found in the significant correlations between a self-report measure of body shape esteem and the two processing measures upon which dieters performed more poorly than nondieters.

The negative impact of current dieting status on working memory capacity is a finding which has been replicated several times. Vreugdenburg, Bryan and Kemps (2003) also found dieting-related impairments in central executive and phonological loop (but not visuo-spatial sketchpad) function which were related to a specific measure of food and body shape cognition. Other studies have broadly, but not consistently, also supported this conclusion. For instance, Shaw and Tiggemann (2004) investigated the precise nature of the phonological loop deficit associated with dieting and found that there was no dieting-related impairment in an auditory version of the phonological loop task used by Green et al. (1998), this measuring the storage capacity of the phonological loop. However, a dieting-related impairment in the articulatory control component of the phonological loop (the component resembling subvocal rehearsal), as measured by immediate recall for long and short words, presented via audio recording. This effect was significantly related to self-reported food-related preoccupations. Although the authors do not attempt to explain the discrepancy between their findings and those of Green and Rogers (1998), a possible explanation may lie in the differences between visual and auditory presentation of stimulus materials.

Other studies have found that the fundamental nature of the cognitive impairment associated with dieting is fundamentally related to central executive function, this being the overall attentional control and resource allocation component of working memory (Baddeley 1986). Kemps and Tiggemann (2005) found that spontaneous dieters performed more poorly on a measure of central executive capacity (combined verbal and spatial memory) than on measures of phonological loop or visuo-spatial, sketchpad capacity and that this is related to food-related preoccupying cognitions. The authors claim that the lack of effect on the phonological loop task was due to a comparative lack of cognitive loading, compared with the version of the task used by Green and Rogers (1998). However, the significant dieting-related impairment on what the authors claim is a central executive task could actually be due to a reduction in phonological loop capacity since a common way of increasing the cognitive load of a verbal recall task is to introduce distraction by means of concurrent motor activity. Stronger supporting evidence of a central executive impairment associated with spontaneous dieting has been found by Kemps, Tiggemann and Marshall (2005). This study employed a number of tasks previously validated as primarily loading onto central executive function (e.g. random number generation, task switching), in addition to phonological loop and visuo-spatial sketchpad function. It was found that current dieters displayed poorer performance on a number of central executive and phonological loop tasks, but not the visuo-spatial sketchpad task (Corsi block task). Further, these data support those of Green and Rogers (1998), by finding that these selective working memory impairments were partially mediated by food and body shape preoccupying cognitions.

It would appear then, that spontaneously undertaken dieting behavior, but not experimentally-induced food deprivation, is associated with selective impairments in cognitive function. Further, rather than being a global deficit or a breakdown in attentional focus, these deficits appear to be primarily due to a reduction in processing capacity of working memory. Specifically, it appears that the central executive and phonological loop components of the working memory system are affected by the attempt to lose weight, irrespective of whether the attempted weight loss is successful or not. Further evidence for the role of preoccupying cognitions in the dieting-related cognitive impairment

can be seen in the results of Jones and Rogers (2003). This study found that the dieting-related impairment in task performance was greater in dieters who had consumed a confectionary bar prior to the test session than in those who had not. This mitigates against a simple food/ glucose deprivation explanation. Although evidence suggests that this reduction in working memory capacity is the result of preoccupying cognitions relating to food, hunger, and body shape, there are still a number of other candidate biological mechanisms which could explain the dieting-related cognitive deficit.

99.3 Biological Mechanisms

As stated, there are a number of possible biological mechanisms which could account for the observed dieting-related impairment in cognitive function. These include food deprivation-induced impairments in neurotransmitter function, reduced iron metabolism, and the actions of cortico-steroid hormones. Each of these will be discussed.

99.3.1 Dieting-Related Alterations in Serotonergic Function

Although the studies relating to the effects of spontaneously undertaken dieting indicate that cognitive processing efficiency can be compromised even in the absence of any substantial weight loss (Green and Rogers 1995a), there is a body of research indicating that experimentally-induced weight loss can affect neurotransmitter function. Specifically, a number of studies have found that experimentally-induced weight loss compromises serotonergic function by lowering the relative availability of the serotonin (5-HT) precursor tryptophan and, therefore, levels of 5-HT (reviewed by Cowen et al. 1992). For instance, it has been found that a 3-week-long weight loss diet (1,000 kcal/day) lowered levels of plasma tryptophan in female subjects ($N = 12$) (Cowen et al. 1995).

A study which indicates that such tryptophan depletion may be responsible for the deficits in cognitive processing efficiency which accompany weight loss is that of Park, Coull, McShane, Young, Sahakian, Robbins and Cowen (1994). It was found that ingestion of an amino acid laden drink without tryptophan (vs. a control drink in which tryptophan was present) decreased the relative amounts of tryptophan available for 5-HT synthesis. Further, it was found that subjects in the tryptophan-deficient condition performed more poorly on a number of measures of cognitive processing efficiency. In particular, planning times on the Tower of London Task were longer in this group than in control subjects. However, there are research findings which indicate that it is unlikely that this mechanism mediates the working memory impairments associated with spontaneously undertaken dieting. Foremost of these is the finding that such impairment are present even in the absence of any substantial weight loss; although this does not preclude the nutritional composition of these diets may be deficient in certain micronutrients or indeed that they might lower 5-HT neurotransmission. Another method whereby tryptophan uptake to the brain may be affected is by alterations in the dietary carbohydrate (Wurtman and Wurtman 1989). It is hypothesized that the ingestion of carbohydrate causes the manufacture of insulin in the pancreas and, therefore, has the effect of increasing the relative concentration of tryptophan in the bloodstream, leading to increased uptake into the brain and increased 5-HT synthesis. The psychological impairments characteristic of dieting may, therefore, be due to a lack of sufficient dietary carbohydrate. Recent evidence (D'Anci et al. 2009), suggests that this relationship is not a simple one. It was found that, whilst low carbohydrate dieting over a period of weeks led to impairments in memory function (compared to a balanced, low-calorie diet), this regime actually led to an improvement in attentional function. The authors interpret their mixed finding in terms of the relative availability of glycogen

stores and the increased availability of protein during low carbohydrate dieting. These results are not congruent, however, with the results of studies which have found impairments in both of these cognitive domains in nutritionally balanced, low calorie dieters (e.g. Green et al. 1994) and may be explained in terms of a lack of statistical power (total sample size = 19).

It is possible, however, that neuro-endocrine imbalances are, at least in part, responsible for the deficits in brain function found in more severe states of starvation. There appears to be a complex relationship between neuro-endocrine function, depression, and severe starvation. In essence, this relationship is that clinical depression is frequently associated with both decreased levels of plasma tryptophan (Cowen et al. 1989) and loss of appetite (Cowen et al. 1992). In addition, weight loss (Green et al. 1997) and depression (Channon et al. 1993) and tryptophan depletion (Park et al. 1994) are associated with impairments in working memory capacity. The evidence for the role of tryptophan as a mediating variable in this relationship is further strengthened by the evidence indicating a comorbidity of depression with anorexic psychopathology (e.g. Laessle et al. 1987) and dieting behavior (Warren and Cooper 1988).

It is also possible that this relationship between tryptophan, affective state, and cognition may have some power as a means of explaining the information processing effects noted in less severe forms of food deprivation such as dieting. There is reliable evidence to indicate that the administration of diets specifically designed to alter the relative availability of tryptophan are associated with changes in affective state. For instance, tryptophan depletion has variously been associated with increased aggression (e.g. Cleare and Bond 1995) and depression (e.g. Benkelfat et al. 1994; Miller et al. 1992).

There are, however, a number of problems with this postulated relationship. First, impaired cognitive processing has been observed amongst dieters who do not display higher levels of self-rated depression than nondieting control subjects (Green et al. 1997). Second, it has been noted that the loss of appetite leading to weight loss in clinical depression is rarely severe (Casper and Beaton 1992). The causal direction of this hypothesized relationship must, therefore, be the subject of future research in this area. It has been found, however, that the effects of tryptophan depletion on affective state are related to the susceptibility of the subjects to depression (Benkelfat et al. 1994). In addition, there are a number of published studies which describe no effect of tryptophan depletion on affective state (Oldman et al. 1995, 1994).

Perhaps the strongest piece of experimental evidence against a serotonergic explanation for the impairment in cognitive function during dieting comes can be found in the study of Green et al. (2003). Using substantially the same methodology as Green and Rogers (1998), this study partially replicated these findings, with the demonstration of a significant dieting-related central executive impairment and a marginally significant phonological loop impairment in current dieters. In addition, 24 h urine collection over the course of the test day revealed no significant dieting-related differences in levels of the main serotonin metabolite, 5-HIAA. Whilst it could be argued that peripheral measures such as metabolite levels do not accurately reflect central serotonergic function, this study found a significant correlation between urinary 5-HIAA levels and self reported depression, indicating a relationship between central and peripheral measures of serotonin turnover. This study is a strong indicator that the impairments in working memory found during spontaneous dieting behavior are not related to compromised serotonin function/ metabolism.

99.3.2 Alterations in Iron Metabolism

Another possible nutritional factor which may mediate the effects of dieting on cognitive processing is that of iron status. Certainly, there is a body of research indicating that iron deficiency is associated with impairments in processing efficiency. For instance, a number of studies have found associations

between iron deficiency anemia amongst children and poor cognitive abilities (e.g. Pollitt and Leibel 1976; Pollitt and Kim 1988). Further, it has also been found that performance on the Bayley Scales of Infant Development (Bayley 1969) was poorer amongst iron deficient anemic children was poorer than that of iron-sufficient children both on baseline testing and after a 3 month intervention designed to normalize iron status (Lozoff et al. 1987). This finding is not unequivocally supported, however, since iron supplementation has also been found to improve the performance of non-anemic, iron-deficient children on the Bayley Scales of Infant Development (Oski et al. 1983).

Amongst adults, relationships have been found between serum ferritin levels and EEG readings, consistent with activation of the left cerebral hemisphere (Tucker et al. 1984). In addition, a significant negative correlation was found between ferritin levels and performance on a tonal memory backward span task and a significant positive correlation between ferritin levels and performance on a verbal fluency task. It was concluded that body iron stores are an important mediator of attentional function. Although statistically significant, the observed correlation coefficients were small ($r = 0.30$, $p < 0.05$ in both cases) and the conclusions drawn may, therefore, be subject to Type I error. In addition, no explanation is offered for the observed negative correlation between ferritin levels and performance on the memory span task. This interpretation of Tucker et al.'s data is supported by further evidence indicating the lack of a relationship between ferritin levels and cognitive processing efficiency (Fordy and Benton 1994). Low iron status in adults has, however, also been found to be significantly related to impairments in the function of the central executive in working memory and motor speed (Kretsch et al. 2006). The relationship between iron status and cognitive function, therefore, does not appear to be simple.

There is a small body of evidence suggesting that weight loss compromises iron status. It has been found that a 12 week long liquid formula very-low-energy diet (420 kcal/day) produced declines in transferrin saturation and increases in plasma ferritin concentration amongst obese subjects (Beard et al. 1997). Further, it has been found that decreasing hemoglobin concentrations resulting from an experimental weight loss program were significantly correlated with performance on a vigilance task (Kretsch et al. 1998).

A body of evidence exists, therefore, which suggests that impaired iron status is associated with impaired cognitive processing efficiency and, further, that iron status is compromised during weight loss. The obvious mechanism whereby iron status and cognition interact is that of cerebrovascular function, whereby low plasma iron levels may lead to inefficient oxygenation of the brain. Whether this can explain dieting-related cognitive impairments in the absence of any significant weight loss (e.g. Green and Rogers 1995a) is, however, a matter for debate.

99.3.3 Stress Hormones

While the evidence strongly suggests that spontaneous dieting is associated with working memory impairments, and that these are likely to be due to preoccupying cognitions concerning food, hunger, and body shape-related self esteem, these preoccupations may result in a concurrent effect on stress hormones. As stated earlier, self-initiated dieting is not without negative psychological consequences. For instance, dieting has been associated with increased depression and low self-esteem (e.g. Warren and Cooper 1988; French et al. 1995; Roncolato and Huon 1998). There is also evidence to show that dieting for short periods of time (6 days) is associated with an increased stress response (Johnstone et al. 2004). While the majority of published experimental evidence supports this relationship, dieting and depressed psychosocial status are not universally linked. Some studies have found that dieting leads to improved psychosocial status, although this appears to depend on the eventual success

of attempted weight loss and weight loss strategy adopted (Miller-Kovach et al. 1999) or whether an approach specifically designed to enhance self-esteem is adopted (e.g. Kenardy et al. 2001). Conversely, there are also a number of studies which show that successful weight loss is associated with a positive affective outcome (see Foster and Wadden 2002 for a review of this literature). The disparity between the findings of these studies can be attributed to a number of factors, such as the age and starting weight of the participants in each study. However, an important difference is that those studies which have found a positive effect of dieting concentrate on the eventual successful outcome of attempted weight loss whereas those which have found negative effects examine the active process of attempting weight loss.

Studies which have demonstrated a negative impact of dieting on psychological function have examined this phenomenon amongst individuals spontaneously dieting in an unsupported setting. As mentioned above, dieting-related cognitive impairments have even been found in the absence of any significant weight loss (e.g. Green and Rogers 1995a). There is evidence which suggests that supervised, supported weight loss promotes successful weight loss, results in a relatively better mood state, and avoids some of the potential negative health consequences of unsupported dieting (Blackburn 1993; Lowe et al. 1999) and a greater expectation of weight loss (Bagozzi and Edwards 1998). Unsupported dieting, however, is associated with a greater degree of eating disordered psychopathology and body dissatisfaction (Juda et al. 2004). The cognitive impairments associated with unsupported dieting may, therefore, be related to an elevated stress response during the early stages of attempted weight loss. There are a number of strands of evidence which support this hypothesis. The first is that acute cortico-steroid administration selectively impairs performance on working memory tasks and not on tasks which assess declarative memory or on vigilance tasks with a low working memory load (Lupien et al. 1999). Second, both urinary and salivary cortisol secretions are found to be higher in those with a high degree of dietary restraint than unrestrained eaters (restraint being the habitual tendency to restrict caloric intake to control weight) (McLean et al. 2001; Anderson et al. 2002). Green, Elliman and Kretsch (2005) provide further evidence to support this hypothesis. It was found that unsupported dieting was associated with working memory and vigilance impairments in the early stages of weight loss (within the first week) and that this was associated with elevated cortisol secretion. It was also found that dieting in a supported, group setting led to comparable weight loss, but no cognitive impairments or alterations in cortisol secretion or self-reported stress/arousal. These results, in terms of cortisol secretion and performance on a sustained attention task with a high working memory load (expressed in terms of mean correct hits per minute) are shown below in Fig. 99.3.

These impairments were structurally similar to those found with experimentally-induced mild stress (e.g. Lupien et al. 1999). From these and other data, it can be concluded that spontaneous, unsupported, dieting is associated with impairments in working memory resulting from preoccupying stressful cognitions relating to both body shape and thoughts of food/hunger.

99.4   Applications to Other Areas of Health

The impairment in psychological function found during unsupported spontaneous dieting is a function of preoccupying cognitions preferentially consuming working memory capacity. These impairments are structurally similar to those found in anxiety (Darke 1988) and depression (Channon et al. 1989) and, therefore, can be conceptualized as reflecting the effects of any preoccupation upon cognitive processing efficiency. In the case of dieting, however, the nature of this preoccupation is specific to body shape, food, and hunger. While dieting is primarily related to overweight, there are a
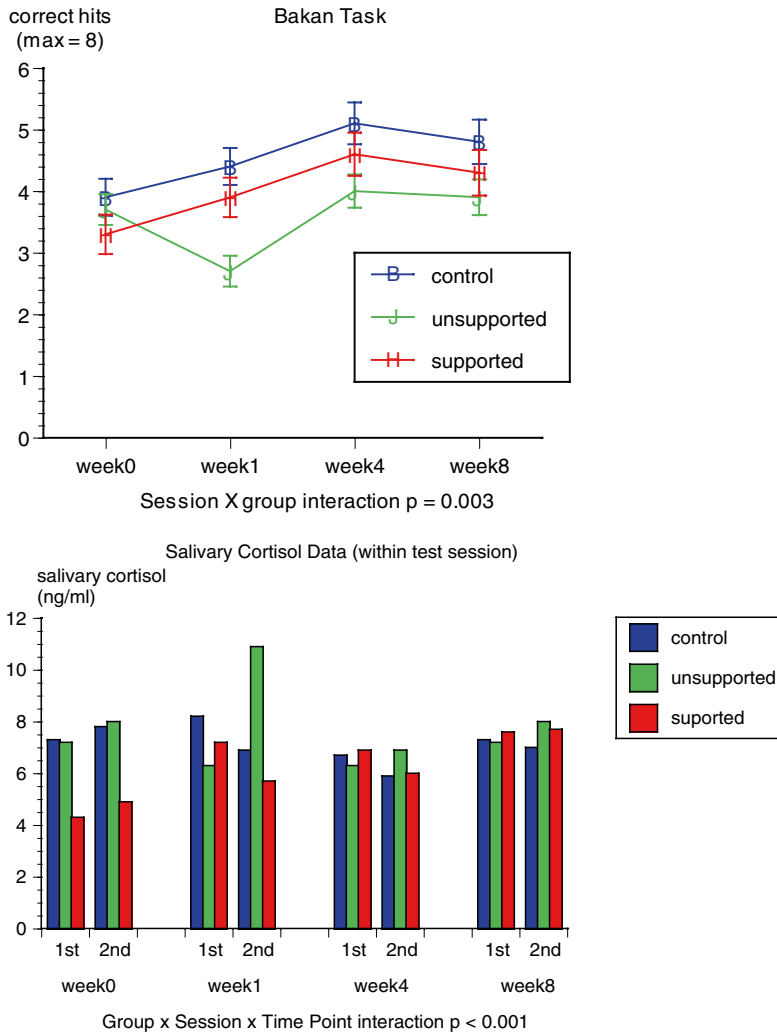
Fig. 99.3 Results of Green et al. (2005), showing salivary cortisol secretion and sustained attention task performance over the course of 8 weeks in supported dieters, unsupported dieters and nondieting control participants. Cortisol secretion rises over the course of the test session after 1 week of attempted weight loss in unsupported dieters only. Performance on Bakan task (mean hits per minute, ± SE included) is poorer in unsupported dieters after 1 week of dieting. There is a significant correlation between task performance and cortisol change during this session ($p < 0.001$)

number of other obesity-related health conditions in which dietary modification is recommended, including Type II Diabetes, atherosclerosis, hypercholesterolemia, and coronary heart disease. It is possible that dietary changes made in response to diagnosis with any of these conditions will be accompanied by the same psychological problems as is the case with dieting. Certainly, it has been found that cholesterol reduction (by means of statin drugs or dietary treatment) has been found to result in impaired performance on tasks sensitive to the effects of weight loss dieting (e.g. Wardle et al. 2000), shown in Fig. 99.4.

The studies reviewed here indicate that such dietary changes would be best attempted in a supported, group setting in order to minimize their possible negative psychological impact.
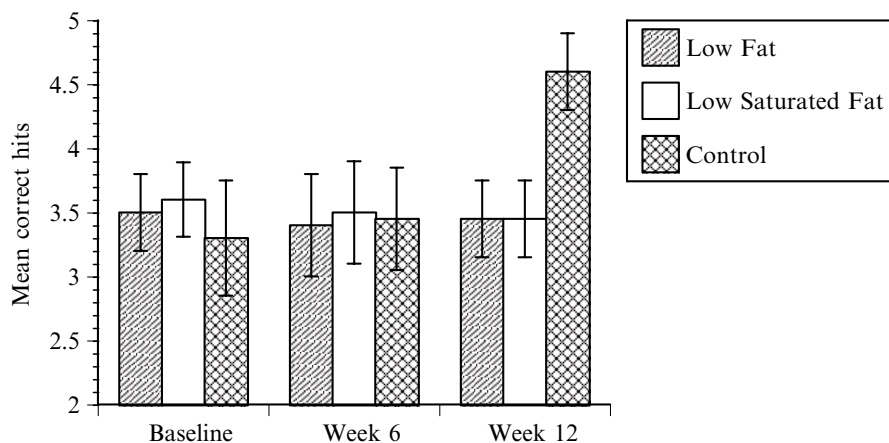
Fig. 99.4 Results of Wardle et al. (2000) showing Bakan task performance (mean correct hits per minute; ± SE included) in low fat diet, low saturated fat diet and non-intervention control groups over the course of a 12 week dietary intervention designed to lower cholesterol. Bakan task in nonintervention controls improves as a function of practice over 12 weeks improves in the nonintervention control groups. In the two cholesterol lowering diet groups, performance does not improve over 12 weeks, with performance significantly poorer than control group at the end of the intervention ($p < 0.05$). This significantly correlated with change in cholesterol levels

99.5 Conclusions

There are a number of clear conclusions that can be made concerning the work summarized in the current chapter. The first of which is that, under certain given circumstances, states of food deprivation outside of the severity of a fully diagnosed eating disorder are associated with impairments in psychological functioning. While a number of studies of severe, noneating disorder-related, starvation (e.g. Keys et al. 1950; Sutker et al. 1992) have shown that extreme induced food deprivation is associated with negative impacts on mood and the function of various cognitive domains. The evidence relating to mild, experimentally-induced food deprivation is, however, equivocal. A number of studies show that experimentally-induced mild food deprivation impairs psychological function, a number show that it has no effect and a number are subject to methodological difficulties which make clear interpretation of their data problematic. In addition, there seem to be study to study task-based inconsistencies in the cognitive domains affected which make clear interpretation of the results difficult.

Spontaneously undertaken dieting, however, is reliably associated with impaired cognitive function and that the nature of this deficit appears to be primarily due to a reduction in available working memory capacity. Given that working memory is the primary cognitive system which serves to allocate processing resources to ongoing cognitive operations and remember the moment to moment rules of action, this working memory impairment can give the appearance of a more global cognitive processing impairment. It can be further concluded that this phenomenon is the result of preoccupying concerns with body shape and food/hunger in the early stages of spontaneous dieting, acting in a manner similar to the role of preoccupying conditions typical of clinical depression and anxiety. There are, however, a number of other possible biochemical routes whereby dieting may affect cognition, but these are of varying plausibility.

Summary Points

- Chronic, severe caloric restriction, aside from anorexic psychopathology is associated with impaired mood and cognitive function.
- Experimentally-induced mild caloric restriction is less reliably associated with impaired psychological function and results are dependent on the methodology and psychological assessment tools employed.
- Spontaneous dieting is reliably associated with impaired psychological function, which is not necessarily related to weight lost or the success of the diet.
- Effects of spontaneous dieting on psychological function are most marked in the early stages of attempted weight loss and appear to be specific to unsupported dieting and not dieting within the context of an organized weight loss group.
- The effect of attempted weight loss on psychological function appears to be primarily a reduction in working memory capacity arising from preoccupying cognitions related to body shape, food, and hunger.
- There are a number of possible biological mechanisms underlying the effect, such as compromised iron or serotonin metabolism. The most likely biological correlate of these effects is a dieting-related increase in cortico-steroid levels resulting from the stress of attempted weight loss.

Key Facts

Bakan task: A highly sensitive cognitive performance task measuring the ability to sustain attentional focus for periods of time. Participants have to detect a number of series of three odd or three even numbers appearing on a display before responding. This task contains a high working memory and is sensitive to both nutritional and pharmacological manipulations.

Beta-hydroxybutyrate: A ketone body produced as the result of the metabolism of protein such as muscle tissue.

Body mass index: A measure of weight, adjusted for height. Calculated as mass (kg)/height $(m)^2$.

Cortico-steroid levels: Corticosteroids such as cortisol and DHA are steroid-based hormones which are involved in the regulation of arousal levels and the stress response. They have also been found to be associated with cognitive function and their metabolism is linked to body fat levels.

Ferritin: A compound which is involved in iron storage in the body.

Glycogen: A carbohydrate. The form in which glucose is stored in the body.

5-HIAA: The major metabolite of the neurotransmitter serotonin. Can be detected in blood or urine and is a reliable marker of serotonin turnover.

Sternberg memory scanning task: A memory task in which participants are presented with a list of numbers and then presented with a single number. They then have to decide whether this number was part of the original set or not, with response time being the dependent measure.

Tower of London task: A task involving mental movement of a series of objects which measures the capacity of the Central Executive component of working memory and the functioning of the brain's frontal cortex.

Transferrin: A compound found in plasma which is involved in the transport of iron to bodily tissues from the gut.

Tryptophan: The amino acid from which the neurotransmitter serotonin, or 5-HT is synthesized. This only comes from dietary sources and cannot be manufactured within the body.

Working memory: This can be regarded as *the* fundamental cognitive processing system, which serves to remember the moment-to-moment rules of action and allocate processing capacity to other, ongoing cognitive activities. It comprises three subsystems; these being the Central Executive (an overall attentional control and allocation system), the Phonological Loop (which serves to deal primarily with oral and written information), and the Visuo-Spatial Sketchpad (which primarily deals with spatial information).

References

Anderson DA, Shapiro JR, Lundgren JD, Spataro LE, Frye CA. Appetite 2002;38:13–7.
Baddeley A. Working memory. Oxford: Oxford University Press; 1986.
Bagozzi RP, Edwards E. Psychol Health. 1998;13:593–621.
Bayley N. Bayley scales of infant development manual. New York: Psychological Corporation; 1969.
Beard J, Borel M, Peterson FJ. Am J Clin Nut. 1997;66:104–10.
Beiner L, Heaton A. Am J Pub Health. 1995;85:714–7.
Benkelfat C, Ellenbogen MA, Dean P, Palmour RM, Young S. Arch Gen Psychiatr. 1994;51:687–97.
Blackburn GL. Ann Intern Med. 1993;119:714–8.
Bray G. Endocrin Metab Clin. 1996;25:907–19.
Casper RC, Beaton GH. In: Anderson GH, Kennedy SH, editors. The biology of feast and famine: relevance to eating disorders. San Diego: Academic; 1992. p. 269–84.
Channon S, Baker JE, Robertson MM. Psychol Med. 1993;23:87–91.
Cleare AJ, Bond AJ. Psychopharmacology. 1995;118:72–81.
Corby MK, Stephen AD, Hongmei H, York-Crowe E, Redman LM, Ravussin E, Williamson DA. Rejuv Res. 2007;10:179–89.
Cowen PJ, Parry-Billings M, Newsholme EA. J Affect Dis. 1989;16:27–31.
Cowen PJ, Anderson IM, Fairburn CG. In: Anderson GH, Kennedy SH, editors. The biology of feast and famine: relevance to eating disorders. San Diego: Academic; 1992. p. 269–84.
Cowen PJ, Clifford EM, William C, Walsh AES, Fairburn CG. Nature. 1995;376:557.
D'Anci KE, Watts KL, Kanarek RB, Taylor HA. Appetite. 2009;52:96–103.
Darke S. Cog Emot. 1988;2:145–254.
Deijen JB, Heemstra ML, Orlebeke JF. J Psychiat Res. 1989;23:275–83.
Department of Health. Healthy weight, healthy lives: a cross government strategy for England; 2008.
Eysenck MW, Calvo MG. Cog Emot. 1992;6:409–34.
Fordy J, Benton D. J Hum Nut Dietet. 1994;7:127–33.
Foster GD, Wadden TA. In: Fairburn CG, Brownell KD, editors. Eating disorders and obesity: a comprehensive handbook. New York: Guildford; 2002.
French SA, Perry CL, Leon GR, Fulkerson JA. J Adolesc Health. 1995;16:438–47.
Green MW, Rogers PJ. Psychol Med. 1995a;25:1003–10.
Green MW, Rogers PJ. Psychol Med. 1995b;28:1063–70.
Green MW, Rogers PJ, Elliman NA, Gatenby SJ. Physiol Behav. 1994;55:447–52.
Green MW, Elliman NA, Rogers PJ. J Psychiatr Res. 1995;29:245–53.
Green MW, Elliman NA, Rogers PJ. Br J Health Psychol. 1997;2:259–67.
Green, M.W., Rogers, P.J., 1998. Psych Med. 28, 1063–1070.
Green MW, Jones AD, Smith ID, Cobain MR, Williams JMG, Healy H, Cowen PJ, Powell J, Durlach PJ. Appetite. 2003;40:145–53.
Green, M. W., Elliman, N. A. & Kretsch, M. J. (2005). Psychoneuroendocrinology. 30, 908–918.
Johnstone AM, Faber P, Andrew P, Gibney ER, Elia M, Lobley G, Stubbs RJ, Walker BR. Eur J Endocrinol. 2004;150:185–94.
Jones N, Rogers PJ. Int J Eating Dis. 2003;33:185–92.
Juda MN, Campbell L, Crawford CB. Evol Hum Behav. 2004;25:200–208.
Kemps E, Tiggemann M. Br J Clin Psychol. 2005;44:357–66.
Kemps E, Tiggemann M, Marshall K. Appetite. 2005;25:287–94.
Kenardy J, Brown WJ, Vogt E. Eur Eat Disord Rev. 2001;9:242–54.

Keys A, Brozek J, Henschel A, Mickelsen O, Taylor HL. The biology of human starvation. Minneapolis: University of Minnesota Press; 1950.

Kretsch MJ, Green MW, Fong AKH, Elliman NA, Johnson HL. Int J Obesity. 1997;21:14–21.

Kretsch MJ, Fong AKH, Green MW, Johnson HL. Eur J Clin Nutr. 1998;52:512–8.

Kretsch MJ, Blanton CA, Green MW. FASEB J. 2006;20:A1003.

Laessle RG, Kittl S, Fichter MM, Wittchen HU, Pirke KM. Br J Psychiat. 1987;151:785–9.

Lowe MR. Psychol Bull. 1993;114:100–21.

Lozoff B, Brittenham GM, Wolf AW, McClish DK, Kuhnert PM. Pediatrics. 1987;79:981–95.

Lupien SJ, Gillin CJ, Hauger RL. Behav Neurosci. 1999;113:420–30.

McLean JA, Barr SI, Prior JC. Am J Clin Nutr. 2001;73:7–12.

Miller HL, Delgado PL, Salomon RM, Licinio J, Barr LC, Charney DS. J Clin Psychiat. 1992;53:28–35.

Miller-Kovach K, Hermann M, Winick M. J Women Health Gen B. 1999;8:477–82.

National Center for Health Statistics. Chartbook on trends in the health of Americans. Health, United States, 2006. Hyattsville, MD: Public Health Service; 2006.

Oldman AD, Walsh AES, Salkovskis P, Laver DA, Cowen PJ. J Psychopharmacol. 1994;1:8–13.

Oldman AD, Walsh A, Salkovskis P, Fairburn CG, Cowen PJ. Psychol Med. 1995;25:995–1001.

Oski FA, Honig AS, Helu B, Howanitz P. Pediatrics. 1983;71:877–80.

Park S, Coull JT, McShane RH, Young AH, Sahakian BJ, Robbins TW, Cowen PJ. Neuropsychopharmacology. 1994;33:575–88.

Pollitt E, Kim I. In: Youdin MBH, editor. Brain iron: neurochemical and behavioural aspects. London: Taylor & Francis; 1988. p. 115–44.

Pollitt E, Leibel RL. J Pediatr. 1976;88:372–81.

Rogers PJ, Green MW. Br J Clin Psychol. 1993;32:113–6.

Roncolato WG, Huon GF. Br J Health Psychol. 1998;3:375–86.

Shaw J, Tiggeman M. Br J Health Psychol. 2004;9:175–85.

Shukitt-Hale B, Askew EW, Lieberman HR. Physiol Behav. 1997;62:783–9.

Smoller JW, Wadden TA, Stunkard AJ. J Psychosom Res. 1987;31:429–40.

Sutker PB, Allain AN, Johnson JL, Butters NM. Arch Clin Neuropsychol. 1992;7:431–44.

Tiggemann M. Psychol Rep. 1994;75:1679–82.

Tucker DM, Sandstead HH, Penland MS, Dawson SL, Milne DB. Am J Clin Nutr. 1984;39:105–13.

Tuschl RJ. Appetite. 1990;14:105–9.

Vreugdenburg L, Bryan J, Kemps E. Apetite. 2003;41:291–300.

Wardle, J., Rogers, P. J., Judd, P., Taylor, M. A., Rapoport, L., Green, M. & Nicholson-Perry, K. (2000). Am J Med, 108, 547–553.

Warren C, Cooper PJ. Br J Clin Psychol. 1988;27:269–70.

Wing RR, Vazquez JA, Ryan CM. Int J Obesity. 1995;19:811–16.

Wurtman RJ, Wurtman JJ. Sci Am. 1989;260:50–7.

Chapter 100
Disturbed Growth in Early Life and Later Neurocognitive Development Associated with Psychiatric Disorders

Shiro Suda and Nori Takei

Abbreviations

AD	Alzheimer's disease
ADHD	Attention-deficit/hyperactivity disorder
AGA	Appropriate-for-gestational-age
ALA	α-linolenic acid
ASD	Autism Spectrum Disorder
BMI	Body mass index
CNS	Central nervous system
COMT	Catechol-O-methyl transferase
DHA	Docosahexanoic acid
DOHaD	Developmental origins of health and disease
DTI	Diffusion tensor imaging
EPA	Eicosapentaenoic acid
FA	Fractional anisotropy
IUGR	Intrauterine growth restriction
IQ	Intelligence quotient
LBW	Low birthweight
MRI	Magnetic resonance imaging
LC-PUFA	Long-chain polyunsaturated fatty acid
n-3 FA	Omega-3 family of long-chain polyunsaturated fatty acid
SGA	Small-for-gestational-age
SNAP-II	Score of neonatal acute physiology II
SNP	Single nucleotide polymorphism
VLBW	Very low birthweight

N. Takei (✉)
Research Center for Child Mental Development and United Graduate School of Child Development, Hamamatsu University School of Medicine, 1-20-1 Handayama, Higashi-ku Hamamatsu Shizuoka, 431-3192 Japan
and
Division of Psychological Medicine, Institute of Psychiatry, London, SE5 8AF, UK
e-mail: ntakei@hama-med.ac.jp

100.1 Introduction

Neurobiological and epidemiological studies provide evidence indicating that disturbed growth in early life may lead to the later development of physical problems as well as psychiatric disorders. Alterations in development at early stages of life (i.e., from the fetal stage through childhood) are known to determine the risk of development of various conditions later in life (e.g., obesity; type II diabetes; cardiovascular diseases; cognitive impairment; and psychiatric disorders such as autism spectrum disorders (ASDs), mood disorders, schizophrenia, and Alzheimer's disease) (Schlotz et al. 2009). The transitional phase from intra- to extra-uterine development is critically important in preparing for adjustments in adult life. During this adaptive period, fetuses and infants are particularly susceptible to environmental as well as genetic factors (i.e., epigenetic influences). Environmental factors include placental dysfunction, maternal malnutrition during pregnancy, psychological distress in pregnant mothers, and infections during both gestation and the postnatal period. Furthermore, the effects of these environmental factors have been associated with alterations in gene expression regulated by epigenetic factors such as DNA methylation and histone methylation/acetylation processes (Ross et al. 2008). Such alterations have been proposed to trigger permanent changes in the programming of physiological systems and predispose individuals to various abnormal conditions in adult life (Table 100.1); this conceptualization of the origin of certain conditions conforms to the notion suggested by the "Developmental Origins of Health and Disease" (DOHaD) model (Barker 2003). This transitional phase of development is pivotal for the development of the central nervous system (CNS), which includes neural cell programs such as cell proliferation and migration, neuronal extension and growth of dendrites, maintenance of the plasticity of synaptic connections, oligodendrocyte maturation, and myelination, all of which are vulnerable to the influences of exogenous modulating factors such as nutritional state, stress, endocrine disruption, exposure to chemical agents and drugs, maternal infections, and premature birth. Thus, along with genetic factors, environmental factors that exert a detrimental effect on CNS development during the pre-, peri-, and post-natal period are thought to be linked to neurodevelopmental disorders (Connors et al. 2008). In this chapter, we describe the mechanisms by which some early environments predispose individuals to adverse sequelae in adult life. Here, we will focus on the origins of health and disease, and in particular on nutritional factors or adverse events during early life that signal the emergence of neurocognitive impairments and psychiatric disorders later in life (Fig. 100.1).

Table 100.1 Key features of fetal programming

1. The transitional phase from intra- to extrauterine development is critically important in preparing for adjustments in adult life. For instance, during this transition, the brain is most vulnerable to nutritional deficiency or exposure to harmful environments.
2. During this phase, fetuses and infants undergo physical, metabolic, and hormonal adaptations for postnatal life.
3. Environmental factors (e.g., placental dysfunction, maternal malnutrition during pregnancy, psychological distress of pregnant mothers, and infections during both the gestational and postnatal period) have been associated with alterations in gene expression regulated by epigenetic factors.
4. Altered gene expression in response to the intra- and extrauterine environment has been proposed to trigger permanent changes in the programming of physiological systems and to predispose individuals to various adverse neuropathological conditions in adult life.

This table presents the concept of fetal programming and lists key features of this process
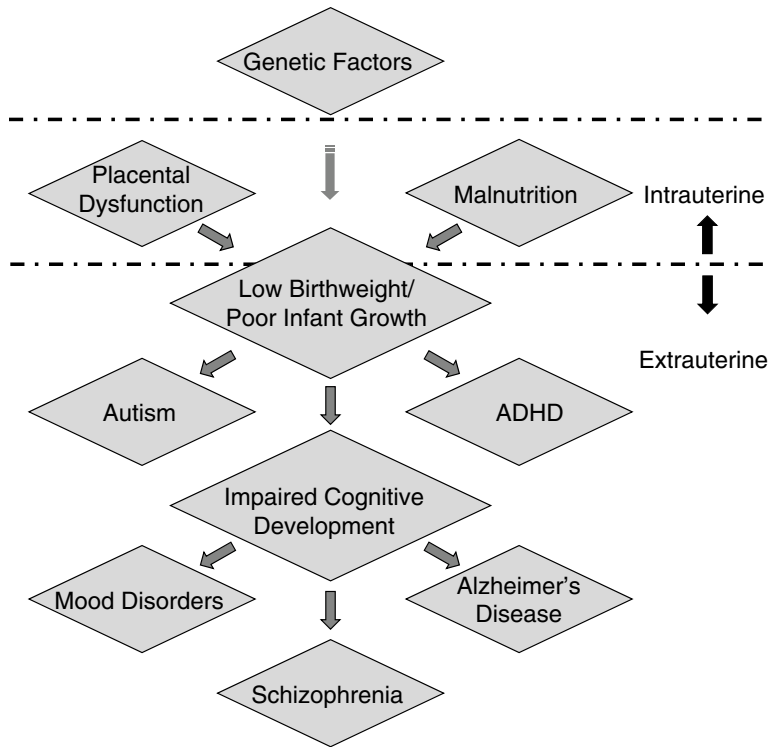
Fig. 100.1 Schema for the relationship between altered growth in early life and subsequent development of various neuropsychiatric disorders. Intrauterine environmental factors (e.g. placental dysfunction and malnutrition) and genetic factors predispose individuals to various psychiatric disorders in adult life. *Arrows* represent the relationship between risk factors and outcomes (disorders)

100.2 Spatially and Temporally Diverse Patterns of Development of the Central Nervous System (CNS)

In humans, CNS development is accomplished in a predetermined order, as exemplified by neurogenesis, cell migration (i.e., final "inside-out" positioning of cells in the cortex), molecular specification, synaptogenesis, and myelination. By the second trimester, most of the neurons in the human cerebral cortex have already been produced and have migrated to appropriate regions. However, delayed neuronal generation appears in some cortical areas such as the primary sensory area and the visual and/or auditory cortices, which form in very well-developed layers. In a similar manner, neurotransmitter systems (e.g., monoamines that originate in the brainstem) exhibit unique spatial and temporal patterns of development (Connors et al. 2008). At the beginning of the third trimester, synaptogenesis starts to accelerate, and a dramatic increase in synaptic formation continues until the individual reaches about 2 years of age (Connors et al. 2008). Myelination of the brain, which takes place in early infancy, is similarly a regional and temporally specific maturation process. The speed and timing of myelination vary in different areas of the CNS; that is, many parts of the cerebral hemispheres experience rapid, extensive myelination in individuals between ages 1 and 9 months old, whereas the frontal and temporal lobes continue myelinating even through the fifth decade of life (Bartzokis et al. 2001). Such diversity in CNS development may play a role in the emergence of

Fig. 100.2 Time frame for developmental processes in the human central nervous system (CNS). The time frame of developmental processes in the human CNS is outlined in this figure. The intrauterine period is scaled in trimesters, and the extrauterine period is shown in years

Table 100.2 Key points of neurocognitive development

1. Neurocognitive development incorporates multiple processes such as neurogenesis, neural cell migration, neuronal extension and growth of dendrites, synaptogenesis, oligodendrocyte maturation, and myelination.
2. Neurogenesis and neural cell migration are most prominent during the second trimester.
3. Synaptogenesis begins to accelerate at the beginning of the third trimester, and this dramatic increase in synaptic formation continues until the individual reaches about 2 years of age.
4. Myelination is most extensive between the ages of 1 month and 9 months.
5. The brain is vulnerable to nutritional deficiency and exposure to harmful environments while the individual is undergoing neurocognitive development.

This table presents the basic concepts of neurocognitive development in early life

various complicated characteristics of abnormalities and dysfunctions (e.g., the manifestation of particular neuropsychiatric disorders) that arise from abnormal neural development in specific brain regions and/or disturbed timing of developmental events (Fig. 100.2, Table 100.2).

100.2.1 Low Birthweight (LBW), Small-for-Gestational-Age (SGA), and Sequelae

Birthweight is a simple index of development, and yet it provides valuable information about disturbances in the in utero growth of the fetus, including CNS development. Low birthweight (LBW; <2,500 g) can arise as a result of preterm delivery or intrauterine growth restriction (IUGR), and can also be associated with being small-for-gestational-age (SGA; <10% percentile). Although the underlying pathobiology of IUGR is heterogeneous, it is primarily caused by maternal malnutrition or placental dysfunction (Table 100.3); the latter is characterized by a disturbance in placental-fetal circulation that maintains the supply of important nutrients such as oxygen, glucose, and amino acids (Cottrell et al. 2008). Moreover, IUGR has been shown to be associated with the development of adult diseases; this phenomenon is referred to as "fetal programming" (Ross et al. 2008). In response to poor nutritional states, the fetus undergoes metabolic and hormonal adaptations as a "thrifty phenotype" to maximize the chance of postnatal survival under conditions of deprivation. This "fetal programming" is partially beneficial in the prevention of adult diseases, provided that such poor conditions persist (Desai et al. 2007). However, when the postnatal environment provides plentiful nutrition, the "thrifty phenotype" will be turned into a risk factor for developing chronic diseases such as obesity, type II diabetes, and cardiovascular disease as a result of this early programming conflict (Cottrell et al. 2008).

Animal studies have demonstrated that IUGR induced by placental hypoperfusion results in structural and functional abnormalities in the CNS, including low total brain weight, reduced hippocampal formation with a decreased number of CA1 pyramidal neurons, and a reduction in the number of

Table 100.3 Causes of low birthweight

Preterm delivery
IUGR
Malnutrition
Essential nutrient deficiency
Placental dysfunction
Smoking
Maternal stress
Multiple birth

This table lists factors causative of low birthweight

IUGR intrauterine growth restriction

Purkinje neurons in the cerebellum (Mallard et al. 2000). Thus, IUGR and subsequent SGA have been considered to be associated with perinatal mortality and long-term morbidity, in addition to being risk factors for physiological, neurological, and behavioral deficits (Tolsa et al. 2004). In effect, epidemiological studies have shown significant associations between the presence of IUGR/SGA and impairments of subsequent neurocognitive development (O'Keeffe et al. 2003). For instance, a prospective study (Breslau et al. 1994) demonstrated that the mean IQ of LBW children at 6 years of age was 4.9 points lower than that of normal birthweight children, when adjustments were made for maternal IQ. Furthermore, a gradient relationship was observed between birthweight and IQ, with the largest IQ deficit in those born weighing ≤1,500 g, an intermediate deficit in those born weighing from >1,500 g to 2,000 g, and the least pronounced deficit in those born weighing >2,000 g, indicating that children born weighing 2,000 g or less bear the major burden of cognitive deficits (Breslau et al. 1994).

More recent studies have revealed that SGA children born at either term or preterm are associated with long-term developmental consequences. O'Keeffe et al. (2003) examined the relationships between full-term SGA and subsequent cognitive impairment, learning problems, and attentional deficits in adolescents. The authors found that adolescents who were born SGA at full-term exhibited the tendency to experience learning difficulties and attentional problems, with a higher prevalence of these problems in those with lower birthweight.

On the other hand, Tolsa et al. (2004) used volumetric magnetic resonance imaging (MRI) to study the brain tissue volume of 14 infants, aged only 2 weeks, who were born at preterm and SGA (mean and SD birthweight, 1,246 ± 299 g), and that of 14 infants matched for gestational age with appropriate-for-gestational-age (AGA) birthweight (1,843 ± 246 g). Premature infants with SGA were found to have both significantly reduced intracranial volume and cerebral cortical gray matter volume, compared with that of preterm AGA infants. The behavioral assessment revealed that compared with the scores of preterm AGA infants, those of preterm SGA infants indicated that the latter were significantly less mature in terms of attention-interaction availability; the reduced score of preterm SGA infants corresponded to a reduction in their cerebral cortical gray matter volume. Furthermore, a different research group (Feldman et al. 2006) found that preterm SGA infants exhibit a less organized state and have less mature neurobehavioral profiles in terms of their orientation and motor domains, and they also exhibit difficulties with the mother–infant relationship during infancy; these findings suggest that SGA infants are at higher risk for developmental and cognitive delays. In particular, SGA infants born weighing <1,000 g showed the poorest neonatal neurobehavioral maturation, social, and cognitive development, and these individuals were found to be at a twofold increased risk of cognitive deficits, compared with SGA infants born weighing >1,000 g.

The association between birthweight and subsequent cognitive development has been further highlighted by studies examining a population of very low birthweight infants (VLBW; ≤1,500 g). Although birthweight-related cognitive deficits are most prominent during infancy, they disappear

with age. However, cognitive impairments in VLBW infants have been found to persist later in life. For example, Kulseng et al. (2006) noted that adolescents with VLBW exhibit deficits in attention, executive function, working memory, and IQ, and over 70% of these individuals perform poorly (<2 SD) on tests of at least one of these measures of cognitive function. A recent MRI study using a diffusion tensor imaging (DTI) technique demonstrated a reduced fractional anisotropy (FA) value in the periventricular area (including the internal and external capsule; the corpus callosum; and the superior, middle superior, and inferior fasciculus) of adolescents born prematurely with VLBW; in general, low FA values are indicative of white matter damage (Skranes et al. 2007). That study also revealed an association between lower FA values and various clinical manifestations such as low IQ, a relatively high rate of ADHD-like symptoms, and mild social deficits. The results of the study by Skranes et al. (2007) suggest that infants born with VLBW are at high risk of perinatal white-matter injury in the periventricular areas, which has been associated not only with long-lasting perceptual, cognitive, and motor impairments, but also with mental health disturbances (Table 100.4).

In addition, most SGA infants with restricted growth during fetal life subsequently grow rapidly, exhibiting so-called "catch-up" growth within the first 2 years of life (Cottrell et al. 2008). One twin study addressed the effects of such catch-up growth, revealing that a larger gain in weight during the first 2 years of life is associated with lower IQ (Estourgie-van Burk et al. 2009), which implicated that catch-up growth is not a good sign in terms of development, or rather that such growth is a risk factor for impaired development.

100.2.2 Malnutrition in Early Life and Subsequent Development

Prenatal and postnatal nutritional deficiencies are major causes of disturbed growth in early life and have been postulated to play an important role in the etiology of neurodevelopmental disorders. Even as early as the 1950s, a relationship between prenatal malnutrition and the later risk of schizophrenia, one of the most devastating psychiatric disorders widely considered to be neurodevelopmental in origin, was postulated (Weinberger 1987; Murray et al. 1987); this nutritional hypothesis has until recently remained unchallenged due to the difficulty of conducting properly designed prospective studies. However, the Dutch famine was a "natural experiment" based on an unusual historical event known as the Dutch "Hunger Winter" of 1944–1945. During World War II, the Netherlands was invaded by the German army, and all food was rationed to a daily range of 1,500–2,000 kcal per person. However, at the end of 1944, a severe and pervasive food shortage occurred when the German army imposed an embargo on food transport. The famine reached its peak during the 4 weeks before

Table 100.4 Birthweight and cognitive deficits

Weight at gestational age		Birthweight	
AGA at term	-	LBW (>2,000 g)	±
SGA at term	±	LBW (<2,000 g)	+
AGA at preterm	±	VLBW (>1,000 g)	+
SGA at preterm	+	VLBW (<1,000 g)	++

The association between birthweight and later risk of cognitive deficits is summarized in this table

AGA appropriate-for-gestational-age, *SGA* small-for-gestational-age, <10% percentile, *LBW* low birthweight, <2,500 g, *VLBW* very low birthweight, <1,500 g, – no evidence, ± inconsistencies across studies, + significant evidence, ++ strong evidence

Table 100.5   Essential nutrients for CNS development in early life

Nutrient	Functional role in CNS development
Iron	Myelination, monoamine synthesis
Zinc	Neurotransmitter release, DNA and RNA synthesis
Copper	Neurotransmitter synthesis
LC-PUFAs	Synaptogenesis, myelination
Choline	Myelination, neurotransmitter synthesis, DNA methylation
Iodine	Cell energy metabolism
Folate	DNA and RNA synthesis, DNA methylation
Vitamin A	Signal transduction
Vitamin B6	Amino acid neurotransmitter synthesis
Vitamin B12	Myelination, DNA synthesis

This table lists the essential nutrients for CNS development and their respective functions

LC-PUFAs long-chain polyunsaturated fatty acids

the Liberation of early May 1945, and the daily ration yielded less than 1,000 kcal per person, per day. During the height of the famine, malnutrition was the leading cause of death (>22,000 deaths total). Unlike other famines, the Dutch "Hunger Winter" struck at a precisely circumscribed time and place, and is well-documented in terms of the timing and severity of nutritional deprivation and its effects on fertility and health. Utilizing the data from this unusual event, researchers have investigated the health sequelae of nutritional deficiencies, finding that prenatal exposure to severe malnutrition (especially in the first trimester of gestation, in which the most active neurogenesis takes place) was related to congenital anomalies of the CNS as well to a future risk for the development of schizophrenia and schizophrenia-spectrum personality disorders (Hoek et al. 1996; Susser et al. 1996). However, more recent studies (Georgieff 2007) have suggested that in the last third trimester of gestation and in the subsequent early postnatal stage, when rapid neuronal synaptogenesis and myelination are in full progress, the brain is most vulnerable to an inadequate diet. For example, an early-life deficiency of various micronutrients (e.g., iron; zinc; copper; long-chain polyunsaturated fatty acids [LC-PUFAs]; choline; iodine; folate; and vitamins A, B6, and B12) has been found to exert harmful and long-lasting effects on cognitive development (Georgieff 2007; Benton 2008) (Table 100.5).

100.2.3 Specific Clinical Syndromes as a Manifestation of Disturbed Growth in Early Life

Thus far, we have provided a general overview of the relationship between disturbed growth in early life and subsequently impaired development. We will now focus our attention on specific cognitive and/or behavioral consequences that are known to be linked to early-life disturbances such as nutritional deficiency and environmental exposure to toxins.

100.3 Autism Spectrum Disorders (ASDs)

Autism is a pervasive developmental disorder characterized by the behavioral traits of impaired social cognition and communication, as well as repetitive/obsessive behavior and interests. More broadly, ASDs include autism, Asperger's disorder, Rett's disorder, childhood disintegrative disorder, and not

otherwise-specified pervasive developmental disorder (American Psychiatric Association 2000). Earlier studies demonstrated that autism was associated with exposure to the preservative thimerosal, which contains ethylmercury, during early childhood (Bernard et al. 2002). However, recent epidemiological studies have failed to demonstrate any such association between exposure to ethylmercury in early life and the prevalence of autism (Schechter et al. 2008). Family studies, and especially twin studies, have generated primarily theories of ASDs that lean towards considering genetic factors causative (Bailey et al. 1995); however, recent research has provided evidence in support of the involvement of obstetric complications and adverse events in early life as risk-increasing factors. Kolevzon et al. (2007) systematically reviewed studies that examined the relationship between prenatal and perinatal events and the risk of autism. In their review, all seven epidemiological studies provided evidence that a history of obstetric events, including LBW and intrapartum hypoxia, is generally associated with an increased risk of ASDs, although the risk was not specific to the narrow condition of autism alone. On the other hand, Limperopoulos and colleagues (2008) carried out screening for early autistic features in children with a history of VLBW. They found that 26% of VLBW infants had at least one autistic feature. However, screening was conducted in children with a mean age of 21 months, an age at which instruments for identifying ASD features can be imprecise. Nonetheless, the authors also found that an elevated autistic-features score in their VLBW cohort was related to a history of chorioamnionitis and acute intrapartum hemorrhage. Such a history contributes greatly to the Score of Neonatal Acute Physiology II (SNAP-II; representing illness acuity) and is closely associated with abnormal findings on brain MRI (e.g., diffuse periventricular leukomalacia, periventricular hemorrhagic infarction, cerebellar hemorrhage, and ventriculomegaly).

Adverse conditions such as chorioamnionitis and placental hemorrhage are known to stimulate the ß2 adrenergic receptors; this mechanism is thought to be involved in the risk for autism. In fact, it has been shown that use of the ß2 adrenergic receptor stimulant with tocolytic action for preterm labor increases the risk for autism (Connors et al. 2008). A recent study (Field 2008) revealed that a potential risk factor for autism is a deficient supply of members of the omega-3 family of long-chain polyunsaturated fatty acids (n-3 FAs) (e.g., docosahexanoic acid [DHA], and eicosapentaenoic acid [EPA]), which are known to play an important role in CNS development (Georgieff 2007). An α-linolenic acid (ALA) can be converted to DHA in females, but not in males; this gender difference in the metabolism of fatty acids may contribute to the preponderance of autism among males.

However, obstetric complications and nutritional deficiencies may not necessarily be independent risk factors for autism. These variables need to be separately examined in large, population-based cohorts that provide sufficient statistical power for investigating each potential risk factor while at the same time allowing for various confounding factors.

100.4 Attention Deficit/Hyperactive Disorder

Attention-deficit/hyperactivity disorder (ADHD) is a disorder that affects children under 7 years of age and is characterized by a persistent pattern of inattention and/or hyperactivity-impulsivity (American Psychiatric Association 2000). Several case-control studies have reported that children born with SGA are at high risk of having attentional deficits (O'Keeffe et al. 2003; Tolsa et al. 2004). However, a population-based cohort study has shown that the presumed risk factors, including a history of pregnancy and delivery complications, LBW, and delivery of a twin birth, are not associated with ADHD (St. Sauver et al. 2004). Thus, the relationship between early events occurring around the time of birth and the development of ADHD remains controversial, and has yet to be determined.

Indredavik and colleagues (2005) explored the association between the presence of ADHD symptoms and cerebral MRI abnormalities in adolescents who had a history of LBW or VLBW, or had been

born SGA. Their results showed that when compared with control adolescents born at term, the VLBW group had an increased prevalence of ADHD symptoms, which was associated with white matter volume reductions, thinning of the corpus callosum, and white matter gliosis. Such an association between ADHD symptoms and brain abnormalities was not found in either the LBW or SGA group. Based on these findings, the researchers contend that a specific form of ADHD in VLBW children could be ascribed to perinatal events that impair white matter connectivity and brain development.

Furthermore, recent evidence points to the gene-environment interaction in the pathophysiology of ADHD. Catechol-O-methyl transferase (COMT) is an enzyme that catalyzes the degradation of dopamine in the prefrontal cortex, and it has been proposed to play a key role in prefrontal cortical function (Winterer et al. 2003). Val158Met (rs4680), a functional single nucleotide polymorphism (SNP) of the gene, has been shown to produce an amino acid substitution of methionine (Met) to valine (Val) at position 158 of the amino acid sequence, resulting in a significant change in enzyme activity. In fact, the Val allele is associated with approximately 40% higher enzyme activity than the Met allele (Chen et al. 2004). This SNP has been demonstrated to be related to prefrontal cognitive performance (e.g., working memory, executive function); the *met/met* genotype is associated with the best performance, whereas the *val/val* genotype is associated with the poorest performance (Malhotra et al. 2002). A family-based genetic study of children with ADHD has revealed that early-onset antisocial behavior, which has been shown to be linked to prefrontal cortical damage, in children with ADHD is associated with the *val/val* genotype (Thapar et al. 2005). Moreover, individuals with perinatal complications, as indexed by LBW, and with the *val/val* genotype have been shown to be more susceptible to ADHD.

100.5 Mood Disorders

Mood disorders are among the most common mental health problems in the general population. Whereas mood disorders cut across a wide range of age populations, predominantly women are affected. There are two major types of mood disorders: major depressive disorder and bipolar disorders. The etiology of mood disorders is considered to be heterogeneous, and the pathphysiological mechanisms underlying these disorders are still unknown. While earlier studies suggested an association between early life events (e.g., poor parent-child relationship) and a vulnerability to mood disorders (Brown 1966), there is increasing evidence that exposure to other hazardous environments in early life may play an important role in predisposing certain individuals to developing a mood disorder. The abovementioned Dutch Famine study provided the initial evidence indicating that exposure to malnutrition during the second trimester of gestation was associated with an increased risk of mood disorders later in life (Brown et al. 1995).

In Swedish large-scale cohort studies, Mittendorfer-Rutz et al. (2004) found an inverse relationship of birthweight to suicide, which predominantly occurs in patients with mood disorders. Intrigued by this report, other researchers further explored the postulated relationship. A gender-mediating effect was suggested in a study by Gale et al. (2004), who found an association of LBW with depression in females, but not in males; women in whom birthweight was less than 3,000 g were at higher risk of depression than those who weighed more than 3,500 g at birth. On the other hand, a retrospective study conducted in Helsinki demonstrated that being born at a weight appropriate for gestational age was not associated with depression. In contrast, VLBW participants born SGA were 2.5 times more likely to receive a diagnosis of depression than were controls born at standard birthweight (Raikkonen et al. 2008). Although further studies are needed to confirm the association, a tentative conclusion can be drawn based on these results, namely, that IUGR/SGA rather than birthweight per se may pose a risk of depression.

100.6 Schizophrenia

Schizophrenia is a complex neurodevelopmental disorder characterized by abnormalities in the perception of reality (i.e., delusions and hallucinations). Although the pathogenesis of schizophrenia is still poorly understood, accumulating evidence suggests that genetic, (early) environmental, and socio-psychological factors contribute to the etiology of the disorder. An involvement of gene(s) in the predisposition to schizophrenia is indisputable, as based on the results of family studies and, in particular, twin studies). Moreover, recent molecular biology studies have reported particular loci as responsible for the disorder, although the findings across studies have remained inconsistent. Nonetheless, there is a large body of evidence supporting an association between exposure to adverse environmental factors during the perinatal period and the subsequent development of schizophrenia. For instance, a meta-analysis of prospective population-based studies has shown that a history of obstetric complications is associated with schizophrenia later in life (Cannon et al. 2002). In analyses of individual complications of pregnancy, all of the following have been indicated to increase the risk of schizophrenia: bleeding, diabetes, rhesus incompatibility, pre-eclampsia, disturbed fetal growth (e.g., LBW), congenital malformations, reduced head circumference, and complications of delivery such as uterine atony, asphyxia, and emergency Cesarean section.

As noted above, studies of individuals who experienced the Dutch Famine have demonstrated that prenatal exposure to severe malnutrition, especially during the first trimester of gestation, is related to future risk for the development of schizophrenia (Susser et al. 1996). In a large population-based cohort study, Wahlbeck et al. (2001) examined whether nutritional factors in early life would have a risk-increasing effect. They found that a low late-pregnancy maternal body mass index (BMI), low placental weight, and LBW – each of which is postulated to be associated with intrauterine undernutrition – were related to an increased risk of schizophrenia. However, other studies have shown an inverted U-shaped association between birthweight and schizophrenia. For instance, Gunnell et al. (2003) demonstrated a sevenfold increased risk amongst individuals with LBW and a threefold increased risk for those with high birthweight (>4.0 kg). A similar pattern of the association has also been found for maternal BMI in our study (Kawai et al. 2004), showing that schizophrenia is linked to lower maternal BMI during late pregnancy, as well as to higher BMI during both early and late pregnancy.

More recently, a specific nutrient has attracted attention as a putative predisposing factor for schizophrenia. Iron is essential for the generation of hemoglobin, as well as for brain development and functioning. Emerging evidence has suggested that an iron deficiency in early life can lead to long-lasting neurocognitive deficits in infants and children (Georgieff 2007; Benton 2008). A population-based cohort study also revealed that a mean maternal hemoglobin concentration of 10.0 g/dL or less during the entire pregnancy was associated with a nearly fourfold increased rate of schizophrenia and schizophrenia-spectrum disorders in the offspring, when compared with a mean maternal hemoglobin concentration of 12.0 g/dL or higher (Insel et al. 2008). In addition, the findings of that study indicated a 27% decrease in the rate of the disorder for every 1 g/dL increase in the mean maternal hemoglobin concentration.

100.7 Personality Disorders

Personality disorder is defined as an enduring pattern of inner experience and external behavior that deviates markedly from the expectations of an individual's culture (American Psychiatric Association 2000). Little research has been done on possible associations between adverse events early in life and the risk of personality disorders, with the exception of one group who investigated the effects of

the Dutch Famine in 1944–1945 Hoek et al. (1996) investigated the association of prenatal malnutrition with the risk for personality disorders in a cohort affected by the famine, and found that prenatal nutritional deficiency was associated with a greater risk of schizoid personality disorder. The same group subsequently examined the relationship of severe prenatal nutritional deficiency to the risk for antisocial personality disorder, and found an increased risk only in men who had been prenatally exposed to the famine during the first and second trimester of pregnancy (Neugebauer et al. 1999).

100.8 Alzheimer's Disease

Alzheimer's Disease (AD) is the most common form of dementia among the elderly. The symptoms of AD include severe and progressive loss of memory and cognitive function (Hebert et al. 2003). A community-based case-control study examined the association between environment in early life and later risk for AD, and showed that the area of residence prior to reaching 18 years of age and the number of siblings were associated with the subsequent development of AD, indicating a possible involvement of early-life environment in the risk for AD (Moceri et al. 2000).

On the other hand, recent studies have shown a significant association between body size and risk for AD. Body size may reflect a difference in genetic background and varying environments to which individuals were exposed early in life. A study by Huang et al. (2008) has shown that greater knee height and a longer total arm span are associated with lower risk of AD among women. It was also found that women in the lowest quartile in terms of arm span were approximately at 1.5 times greater risk of AD than were other women studied. Among men, only longer arm span has been shown to be associated with lower risk of AD. Although no specific hypothesis has thus far been able to account for the possible involvement of early-life environment in the determination of future risk of AD, Sarter et al. (2004) speculated that ontogenetic abnormalities in the cortical cholinergic system, which is disturbed in subjects with AD, could mediate early-life cognitive limitations that later escalate to mild cognitive impairment and AD through the process of aging. Early-life cognitive limitations are presumed to begin with a disruption of the neurotrophic support of the cholinergic system, which is accompanied by subsequent dysregulation of cortical cholinergic function. The accelerating decline of the cholinergic system with age may be responsible for the clinical manifestation of AD.

100.9 Summary

In this chapter, we have expounded on the link between early-life growth disturbances, especially those associated with nutritional deficiencies, and subsequently impaired neurocognitive development. In general, it is well acknowledged that exposure to an adverse environment during a susceptible period, such as that in utero, is associated with physical illnesses in adulthood such as type II diabetes and cardiovascular disease. As noted above, early adverse events and associated altered growth early in life also contribute to the subsequent development of various neuropsychiatric disorders. Given that the time frame of susceptible (i.e., pre-, peri-, and postnatal) periods is also critical in terms of CNS development, it is not unreasonable to assume that early events with the potential to impair CNS development may in turn lead to subsequent disturbances in neurocognitive function, which can manifest as neuropsychiatric disorders.

Indeed, the accumulating evidence suggests that altered growth caused by malnutrition, placental dysfunction, or exposure to harmful environmental factors during early development is associated with clinical manifestations later in life such as pervasive developmental disorders (i.e., ASDs), major psychiatric disorders (i.e., mood disorders, schizophrenia), and Alzheimer's disease (AD).

The brain itself is a very complex organ; notably, its early development includes complicated processes of cell proliferation and migration, neuronal growth, synaptogenesis, and myelination. Furthermore, such processes are not uniform across brain regions. Any alteration or dysfunction in the brain that occurs at a particularly critical point in time in a specific location (or in a specific neurotransmitter system) may yield a wide range of pathological features as a consequence.

Although it will remain important to explore any associations between deviations from normal early developmental processes and subsequent disease-related consequences in adulthood, the need to elucidate the mechanisms underlying such associations should be emphasized, as such an emphasis is likely to enhance our understanding of the pathophysiology of a number of neuropsychiatric disorders.

100.10 Application to Other Health- and Disease-Related Issues

As overviewed above, several lines of evidence have suggested that disturbed growth in early life, in particular that caused by nutritional deficiency, is associated with the development of physical and psychiatric disorders later in life. In developing countries, food shortages remain a serious social issue, not least because they lead to malnutrition of pregnant women as well as their newborns. When the magnitude and persistence of nutritional deficiency in underdeveloped countries is taken into account, it is unfortunately not difficult to imagine that the consequences will be devastating. Infants exposed to severe malnutrition throughout gestation and early life will be predisposed to ill health, perhaps to a greater extent than even that described in this chapter. It should also be noted that young women of childbearing age in developed countries are likely to perceive slenderness as attractive, as they are often misguided by images in the media (e.g., fashion shows), which encourage them to lose weight. In some cases, even pregnant women may continue to smoke to achieve appetite reduction and to remain slim, in spite of abundant data demonstrating that tobacco smoking increases risk of premature birth. This is of great concern, since adequate nutrition in early life – in particular, a sufficient intrauterine nutritional supply that depends on maternal nutrition and health – is critically important for the healthy development of fetuses and infants. Therefore, providing nutritional assistance for individuals living in developing countries is an urgent issue, as is educating young women worldwide about body size and nutrition as they relate to both healthy pregnancy and the well-being of children.

Summary Points

- Disturbed growth in early life is known to determine the risk of physical and psychiatric disorders in adulthood.
- Environmental factors linked to altered development include placental dysfunction, maternal malnutrition during pregnancy, psychological distress in pregnant mothers, and infections during both the gestational and postnatal period.
- The effects of harmful environmental factors are thought to trigger permanent changes in the programming of physiological systems and to predispose individuals to various neuropathological conditions in adult life.
- The developing brain at early stages of life is quite vulnerable to nutritional deficiency and exposure to harmful environments.
- Altered CNS development caused by environmental factors is associated with cognitive impairments and various psychiatric disorders, including autism-spectrum disorders, ADHD, mood disorders, schizophrenia, and Alzheimer's disease.

Key Terms

Intrauterine growth restriction (IUGR): IUGR is attributed primarily to maternal malnutrition and placental dysfunction.

Small-for-gestational-age (SGA): SGA refers to a birthweight lower than the 10th percentile of newborns at a particular gestational age.

Low birthweight (LBW), very low birthweight (VLBW): Babies born weighing less than 2,500 g or 1,500 g are considered LBW or VLBW, respectively.

Fetal programming: Environmental factors in early life have been associated with alterations in gene expression, which are postulated to trigger permanent changes in the programming of physiological systems.

Thrifty phenotype: Under poor nutritional conditions, fetuses undergo metabolic and hormonal adaptations by which they survive, despite the lack of nourishment.

References

American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4th ed., Text revision. Washington, DC: American Psychiatric Association; 2000.

Bailey A, Le Couteur A, Gottesman I, Bolton P, Simonoff E, Yuzda E, Rutter M. Autism as a strongly genetic disorder: evidence from a British twin study. Psychol Med. 1995;25:63–77.

Barker DJ. The developmental origins of adult disease. Eur J Epidemiol. 2003;18:733–6.

Bartzokis G, Beckson M, Lu PH, Nuechterlein KH, Edwards N, Mintz J. Age-related changes in frontal and temporal lobe volumes in men: a magnetic resonance imaging study. Arch Gen Psychiatry. 2001;58:461–5.

Benton D. Micronutrient status, cognition and behavioral problems in childhood. Eur J Nutr. 2008;47(Suppl 3):38–50.

Bernard S, Enayati A, Roger H, Binstock T, Redwood L. The role of mercury in the pathogenesis of autism. Mol Psychiatry. 2002;7(Suppl 2):S42–3.

Breslau N, DelDotto JE, Brown GG, Kumar S, Ezhuthachan S, Hufnagle KG, Peterson EL. A gradient relationship between low birth weight and IQ at age 6 years. Arch Pediatr Adolesc Med. 1994;148:377–83.

Brown AS, Susser ES, Lin SP, Neugebauer R, Gorman JM. Increased risk of affective disorders in males after second trimester prenatal exposure to the Dutch hunger winter of 1944–45. Br J Psychiatry. 1995;166:601–6.

Brown F. Childhood bereavement and subsequent psychiatric disorder. Br J Psychiatry. 1966;112:1035–41.

Cannon M, Jones PB, Murray RM. Obstetric complications and schizophrenia: historical and meta-analytic review. Am J Psychiatry. 2002;159:1080–92.

Chen J, Lipska BK, Halim N, Ma QD, Matsumoto M, Melhem S, Kolachana BS, Hyde TM, Herman MM, Apud J, Egan MF, Kleinman JE, Weinberger DR. Functional analysis of genetic variation in catechol-O-methyltransferase (COMT): effects on mRNA, protein, and enzyme activity in postmortem human brain. Am J Hum Genet. 2004;75:807–21.

Connors SL, Levitt P, Matthews SG, Slotkin TA, Johnston MV, Kinney HC, Johnson WG, Dailey RM, Zimmerman AW. Fetal mechanisms in neurodevelopmental disorders. Pediatr Neurol. 2008;38:163–76.

Cottrell EC, Ozanne SE. Early life programming of obesity and metabolic disease. Physiol Behav. 2008;94:17–28.

Desai M, Gayle D, Babu J, Ross MG. The timing of nutrient restriction during rat pregnancy/lactation alters metabolic syndrome phenotype. Am J Obstet Gynecol. 2007;196, 555:e1–7.

Estourgie-van Burk GF, Bartels M, Hoekstra RA, Polderman TJ, Delemarre-van de Waal HA, Boomsma DI. A twin study of cognitive costs of low birth weight and catch-up growth. J Pediatr. 2009;154:29–32.

Feldman R, Eidelman AI. Neonatal state organization, neuromaturation, mother-infant interaction, and cognitive development in small-for-gestational-age premature infants. Pediatrics. 2006;118:e869–78.

Field SS. Omega-3 fatty acids, prematurity, and autism. Pediatrics. 2008;122:1416–7; author reply 1417.

Gale CR, Martyn CN. Birth weight and later risk of depression in a national birth cohort. Br J Psychiatry. 2004;184:28–33.

Georgieff MK. Nutrition and the developing brain: nutrient priorities and measurement. Am J Clin Nutr. 2007;85: 614S–20S.

Gunnell D, Rasmussen F, Fouskakis D, Tynelius P, Harrison G. Patterns of fetal and childhood growth and the development of psychosis in young males: a cohort study. Am J Epidemiol. 2003;158:291–300.

Hebert LE, Scherr PA, Bienias JL, Bennett DA, Evans DA. Alzheimer disease in the US population: prevalence estimates using the 2000 census. Arch Neurol. 2003;60:1119–22.

Hoek HW, Susser E, Buck KA, Lumey LH, Lin SP, Gorman JM. Schizoid personality disorder after prenatal exposure to famine. Am J Psychiatry. 1996;153:1637–9.

Huang TL, Carlson MC, Fitzpatrick AL, Kuller LH, Fried LP, Zandi PP. Knee height and arm span: a reflection of early life environment and risk of dementia. Neurology 2008;70:1818–26.

Indredavik MS, Skranes JS, Vik T, Heyerdahl S, Romundstad P, Myhr GE, Brubakk AM. Low-birth-weight adolescents: psychiatric symptoms and cerebral MRI abnormalities. Pediatr Neurol. 2005;33:259–66.

Insel BJ, Schaefer CA, McKeague IW, Susser ES, Brown AS. Maternal iron deficiency and the risk of schizophrenia in offspring. Arch Gen Psychiatry. 2008;65:1136–44.

Kawai M, Minabe Y, Takagai S, Ogai M, Matsumoto H, Mori N, Takei N. Poor maternal care and high maternal body mass index in pregnancy as a risk factor for schizophrenia in offspring. Acta Psychiatr Scand. 2004;110:257–63.

Kolevzon A, Gross R, Reichenberg A. Prenatal and perinatal risk factors for autism: a review and integration of findings. Arch Pediatr Adolesc Med. 2007;161:326–33.

Kulseng S, Jennekens-Schinkel A, Naess P, Romundstad P, Indredavik M, Vik T, Brubakk AM. Very-low-birthweight and term small-for-gestational-age adolescents: attention revisited. Acta Paediatr. 2006;95:224–30.

Limperopoulos C, Bassan H, Sullivan NR, Soul JS, Robertson Jr RL, Moore M, Ringer SA, Volpe JJ, du Plessis AJ. Positive screening for autism in ex-preterm infants: prevalence and risk factors. Pediatrics 2008;121:758–65.

Malhotra AK, Kestler LJ, Mazzanti C, Bates JA, Goldberg T, Goldman D. A functional polymorphism in the COMT gene and performance on a test of prefrontal cognition. Am J Psychiatry. 2002;159:652–4.

Mallard C, Loeliger M, Copolov D, Rees S. Reduced number of neurons in the hippocampus and the cerebellum in the postnatal guinea-pig following intrauterine growth-restriction. Neuroscience 2000;100:327–33.

Mittendorfer-Rutz E, Rasmussen F, Wasserman D. Restricted fetal growth and adverse maternal psychosocial and socioeconomic conditions as risk factors for suicidal behaviour of offspring: a cohort study. Lancet 2004;364:1135–40.

Moceri VM, Kukull WA, Emanuel I, van Belle G, Larson EB. Early-life risk factors and the development of Alzheimer's disease. Neurology 2000;54:415–20.

Murray RM, Lewis SW. Is schizophrenia a neurodevelopmental disorder? Br Med J (Clin Res Ed). 1987;295:681–2.

Neugebauer R, Hoek HW, Susser E. Prenatal exposure to wartime famine and development of antisocial personality disorder in early adulthood. JAMA 1999;282:455–62.

O'Keeffe MJ, O'Callaghan M, Williams GM, Najman JM, Bor W. Learning, cognitive, and attentional problems in adolescents born small for gestational age. Pediatrics 2003;112:301–7.

Raikkonen K, Pesonen AK, Heinonen K, Kajantie E, Hovi P, Jarvenpaa AL, Eriksson JG, Andersson S. Depression in young adults with very low birth weight: the Helsinki study of very low-birth-weight adults. Arch Gen Psychiatry. 2008;65:290–6.

Ross MG, Beall MH. Adult sequelae of intrauterine growth restriction. Semin Perinatol. 2008;32:213–8.

Sarter M, Bruno JP. Developmental origins of the age-related decline in cortical cholinergic function and associated cognitive abilities. Neurobiol Aging. 2004;25:1127–39.

Schechter R, Grether JK. Continuing increases in autism reported to California's developmental services system: mercury in retrograde. Arch Gen Psychiatry. 2008;65:19–24.

Schlotz W, Phillips DI. Fetal origins of mental health: evidence and mechanisms. Brain Behav Immun. 2009.

Skranes J, Vangberg TR, Kulseng S, Indredavik MS, Evensen KA, Martinussen M, Dale AM, Haraldseth O, Brubakk AM. Clinical findings and white matter abnormalities seen on diffusion tensor imaging in adolescents with very low birth weight. Brain 2007;130:654–66.

St Sauver JL, Barbaresi WJ, Katusic SK, Colligan RC, Weaver AL, Jacobsen SJ. Early life risk factors for attention-deficit/hyperactivity disorder: a population-based cohort study. Mayo Clin Proc. 2004;79:1124–31.

Susser E, Neugebauer R, Hoek HW, Brown AS, Lin S, Labovitz D, Gorman JM. Schizophrenia after prenatal famine. Further evidence. Arch Gen Psychiatry. 1996;53:25–31.

Thapar A, Langley K, Fowler T, Rice F, Turic D, Whittinger N, Aggleton J, Van den Bree M, Owen M, O'Donovan M. Catechol O-methyltransferase gene variant and birth weight predict early-onset antisocial behavior in children with attention-deficit/hyperactivity disorder. Arch Gen Psychiatry. 2005;62:1275–8.

Tolsa CB, Zimine S, Warfield SK, Freschi M, Sancho Rossignol A, Lazeyras F, Hanquinet S, Pfizenmaier M, Huppi PS. Early alteration of structural and functional brain development in premature infants born with intrauterine growth restriction. Pediatr Res. 2004;56:132–8.

Wahlbeck K, Forsen T, Osmond C, Barker DJ, Eriksson JG. Association of schizophrenia with low maternal body mass index, small size at birth, and thinness during childhood. Arch Gen Psychiatry. 2001;58:48–52.

Weinberger DR. Implications of normal brain development for the pathogenesis of schizophrenia. Arch Gen Psychiatry. 1987;44:660–9.

Winterer G, Goldman D. Genetics of human prefrontal function. Brain Res Brain Res Rev. 2003;43:134–63.

Chapter 101
Coronary Heart Disease, Diet and Neurocognitive Functioning

Colin R. Martin, Mick P. Fleming, and David R. Thompson

Abbreviation

CHD   Coronary heart disease

101.1 Introduction

Coronary heart disease (CHD) refers to disorders of circulation, which lead to a restricted supply of blood, oxygen and nutrients to the cardiac muscle. In most cases, this interruption is temporary but in some cases where the interruption is more prolonged this can lead to myocardial infarction and serious damage to the cardiac muscle. Atherosclerosis or the furring of the artery by fatty deposits causes blockages in the artery supplying blood to the heart. The main sign of CHD is chest pain caused by the restricted blood supply. Three different syndromes are categorised under the heading of CHD: unstable angina, myocardial infarction and heart/cardiac failure. Heart failure is seen as the end stage of hypertensive and valvular cardiovascular disease and has a mortality rate —four to eight times that of the general population (Kannel 2000). Nonspecific effects of CHD can include reduced activity, cognitive deficits, reduced quality of life, anxiety and depression (Lewin et al. 2002). Risk of cerebral vascular accident is much higher in people who have CHD, just over 55,000 people a year will die from stroke (BHF 2008). From an economic point of view, CHD costs the NHS in the UK £3.2 billion (BHF 2008).

101.2 Mortality/Morbidity

Measurements of how a disease is distributed across a population is usually categorised as incidence, which is a measure of new cases over a specific period of time, usually 1 year, and prevalence, the total number of cases when new cases are added to existing cases in a population over a specific time period, usually 1 year (Tandon et al. 2008).

C.R. Martin (✉)

School of Health, Nursing and Midwifery, University of the West of Scotland, Ayr Campus, Beech Grove,
Ayr KA8 0SR, UK
e-mail: colin.martin@uws.ac.uk

Mortality rates refer to the total number of deaths across a population over a given time period, usually 1 year. CHD is the most common cause of death in the UK, causing around 94,000 deaths in the UK each year, one in five men and one in seven women will die from CHD in the UK each year (BHF 2008). Around 19% of men and 10% of women will die prematurely as a result of CHD. Thirty-one thousand premature deaths were attributed to CHD in the UK in 2006 (BHF 2008).

Morbidity rates refer to the rate of illness within a population over a given time period, usually 1 year. There are gender differences with higher rates of CHD in men than women and the total number of myocardial infarctions range between 113,000–146,000 depending on the formula used to calculate the incidence. Four percent of men and 0.5% of women have had a heart attack. The incidence of CHD rises steeply with age, over 60% of all cardiovascular deaths in men and 80% in women occur after the age of 75 (Stanner 2009). The incidence rates for both angina and heart failure show gender differences with 52,000 new cases of angina per year in men and 43,000 in women and 38,000 new cases of heart failure in men versus 30,000 in women (BHF 2008). Again, there are variations in the prevalence of both angina and heart failure increasing with age (see Table 101.1).

The estimate is that 726,000 men and 393,000 women in the UK between the ages of 35–75 have had angina (BHF 2008).

An analysis of two studies found a prevalence of 393,000 men and 314,000 women have heart failure in the UK. Age differences show that the prevalence of heart failure rises sharply with age (see Table 101.1; BHF 2008).

Over the last 3 decades, trends have shown that deaths from CHD have been falling but morbidity statistics have not shown the same downward trend (BHF 2008; Jefferson 2008; Stanner 2009).
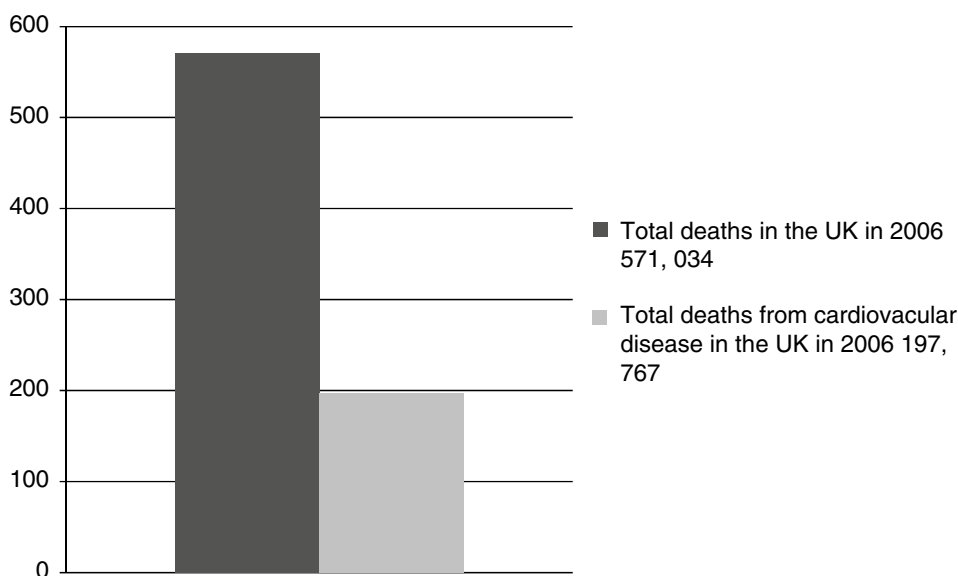
Fig. 101.1 Comparison of the total number of deaths in the UK in 2006 with the total number of deaths from cardiovascular disease in the UK in 2006. This figure compares the total number of those that died in the UK in 2006 with the total number of those that died from cardiovascular disease in the UK in 2006

Table 101.1 Measure of the prevalence of heart failure in the UK population by age range (BHF 2008)

Age range	Prevalence of heart failure in UK population (%)
65	1
75–84	6–7
85+	12–22

This table provides summary details in percentages of the prevalence of reported heart failure in the UK population across three significant age ranges (BHF 2008)

Fig. 101.2 The total number of deaths from all forms of circulatory disease in the UK in 2006 (BHF 2008). This figure compares the total number of people who died from the three main circulatory diseases including CHD in the UK in 2006

Total deaths from stroke in the UK
55, 098

Total deaths from CHD in the UK
94, 381

Total deaths from other forms of circulatory disease in the UK
48, 288
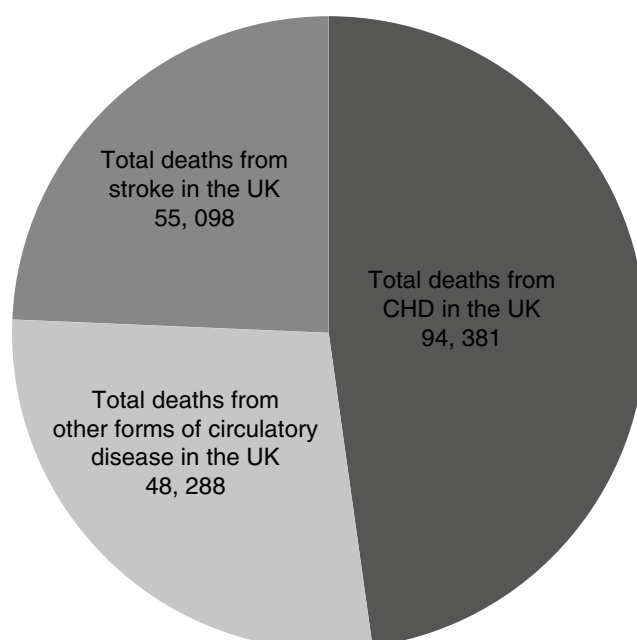
101.3   Modifiable Risk Factors

Several risk factors have been consistently recognised as contributing significantly to increasing the risk for CHD (Table 101.2). The consensus is that CHD is a hereditary condition, where people are predisposed to CHD through an inherited genetic vulnerability. Environmental risk factors further can precipitate the onset and contribute to the severity of CHD.

Smoking causes mortality from CHD, death rate from CHD was around 60–80% higher in smokers than in nonsmokers (BHF 2008). Exposure to second-hand smoke increases the risk of CHD by 25% (Law et al. 1997). Other studies have found that smoking cessation in people with CHD reduces the risk of death by 36% (BHF 2008).

Diet contributes significantly to CHD particularly where diet consists of high saturated fats raising cholesterol levels, high saturated fats and high sugar leading to weight gain and obesity, high sodium intake, which contributes to high blood pressure, and generally low intake of healthier food such as fresh fruit and vegetables. There is a strong correlation between higher systolic and diastolic blood pressure levels and CHD. Over 50% of CHD being linked to systolic blood pressure levels in

Table 101.2 Key facts of coronary heart disease (CHD)

1. The cause of CHD is a restricted flow of blood, which carries oxygen and nutrients to the heart muscle.
2. An interruption of blood flow to the heart is often caused by atherosclerosis, which is the blocking of the main arteries that lead to the heart by fatty deposits.
3. A prolonged interruption of blood flow can lead to myocardial infarction commonly known as a heart attack.
4. The term CHD refers to three different and distinct syndromes which are unstable angina, myocardial infarction and heart/cardiac failure.
5. The main signs of CHD are chest pain and tightness in the chest, tightness in the jaw, breathlessness, pain in the back of the legs, palpitations, and irregular heartbeat. The main signs of a myocardial infarction include tightness and severe pain in the chest, sweating, light headiness, breathlessness and nausea.
6. The death rate for CHD in the UK has been falling since the 1970s around 94,381 people died from CHD in the UK in 2006 (BHF 2008)

This table list's the key facts of CHD including the physiology, cause, the main signs and death rate

excess of 115 mmHg and 22% of heart attacks in Western Europe being attributed to a history of high blood pressure (BHF 2008). A link between increased systolic blood pressure of 10 mmHg and a 15% increase in risk for CHD has been noted by Turner et al. (1998).

Around 30% of CHD was due to deficiencies of fresh fruit and vegetables intake under 600 g/day or 7.5 portions (BHF 2008). As well as fruit and vegetables whole grains, soluble fibres, omega 3 fatty acids, plant sterols and stanols, folic acid and probiotics are considered to be important in improving cardiac functioning (Jefferson 2008). There is robust evidence that n-3 fatty acids have a beneficial effect on the cardiovascular system (Leaf 2008). A diet high in saturated fat and high sugar combined with a lack of physical activity will lead to increased weight gain and further increase the risk of CHD. Physical inactivity and a lack of exercise also contribute directly to CHD. The World Health Organization has calculated that taking less than 2.5 h of moderate intensity exercise/1 h of vigorous activity per week contributed to 20% of CHD (BHF 2008). Being overweight not only contributes to CHD directly but can lead to high blood pressure, raised cholesterol and diabetes. In their review, the BHF found evidence from the World Health Organization that being overweight accounted for 60% of high blood pressure in developed countries. They provide further evidence that suggests abdominal obesity (waist-to-hip ratio/waist circumference) contributed to 63% of heart attacks in Western Europe and that abdominal obesity was a more significant risk factor for heart attack than other types of obesity (BHF 2008). Type 2 diabetes has also been linked to the development of CHD. People with type 2 diabetes have a twofold increase in the risk for atheroma compared to the general population and for those aged between 40–50 years there is a twofold risk of death as a consequence of atheroma (Turner et al. 1998). It would be expected that the health issues relating to type 2 diabetes would be considered as causal risk factors for CHD, obesity, abdominal obesity, physical inactivity and raised insulin concentration but Turner et al. (1998) found in their sample that once type 2 diabetes had developed these risk factors for CHD became less predictive and that hypertension, increased concentrations of high-density lipoprotein cholesterol and hyperglycaemia become more significant as risk factors. High cholesterol level has been considered as a major risk factor for CHD and is influenced by the type of diet. Each 1% reduction in cholesterol leads to a 2% reduction in CHD risk (Jefferson 2008). Fatty foods increase the amount of lipid fat (cholesterol) produced by the liver and can cause hyperlipidemia. The transportation of these lipid fats is through the circulatory system via molecules known as lipoprotiens. Where there is a high level of cholesterol, this can cause a narrowing of the arteries (atherosclerosis) through the fatty deposits (plaques) left in the arteries, which reduce the amount of blood flow that carries oxygen and vitamins through the circulatory system and so is a precursor to CHD. The type and action of low-density lipoproteins in

carrying cholesterol from the liver to the cells for storage can be further influenced by the total amount of cholesterol. The density of low-density lipoproteins has been identified as a major risk factor for CHD (Turner et al. 1998). Where there is too much cholesterol or too much low-density lipoprotein for the cells to store and use then this leads to a harmful build up of cholesterol in the circulatory system. Over 60% of CHD in developed countries is linked to cholesterol levels above 3.8 mmol/L (WHO 2002). Blood cholesterol levels can vary and increase with age in both sexes. Men aged 45–64 are three times more likely to have a cholesterol level above 5.0 mmol/L than when they were aged between 16 and 24. Women aged 55–64 are more than twice as likely to have a cholesterol level above 5.0 mmol/L than when they were aged between 16 and 24 (BHF 2008) see Fig. 101.3. In order to reduce the risk for CHD the UK Government aim for a target of less than 5.0 mmol/L (DoH 2000).

The evidence linking alcohol intake and CHD is mixed. In his review, Marmot (2001) found evidence from heavy drinkers and an increased risk of CHD and this correlation was confirmed in data from 22 towns across the UK. Whereas the findings from international studies showed an inverse relationship between alcohol consumption and CHD. Comparative studies also found moderate drinkers to have a lower risk of CHD in comparison to abstainers (Marmot 2001). A positive relationship was found between women and their alcohol consumption and CHD. Alcohol consumption reduced the risk of CHD (BHF 2008).

In a systematic review, Hemingway et al. (2003) noted that four psychosocial factors, type A personality/hostility, depression and anxiety, psychosocial work characteristics, and social support, played an aetiological role in CHD. The same study found that psychosocial work characteristics, depression and anxiety and social support can also affect outcome and prognosis. Anxiety and minor and major depression has also been reported in people who have suffered a myocardial infarction (Rodgers et al. 2005) and people who have angina (Lewin et al. 2002).
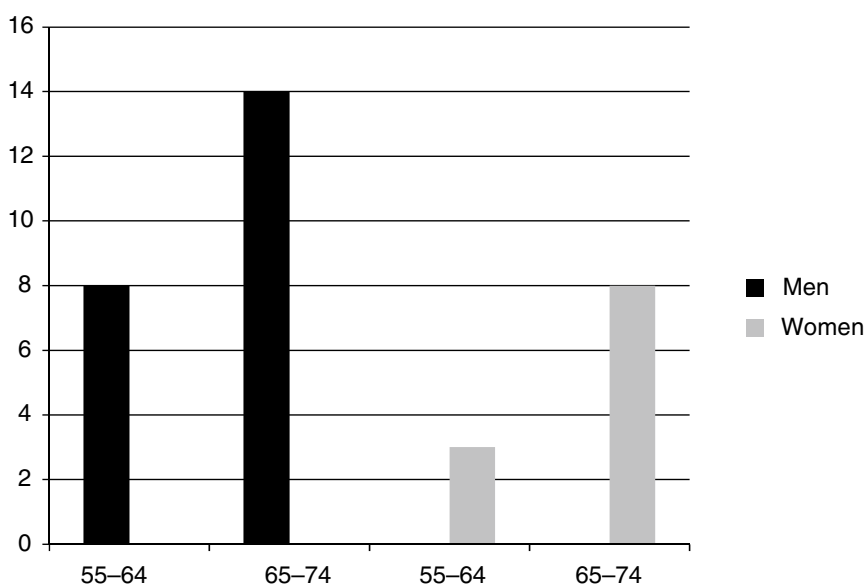
Fig. 101.3 Comparison of percentage age and gender differences in the prevalence of angina in the UK in 2006 (BHF 2008). This figure compares the number of people who have presented with angina in the UK in 2006 divided into two age ranges from both genders

101.4 Evidence for the Cardioprotective Properties of Dietary Interventions

101.4.1 Polyunsaturated Fatty Acids

N-3 fatty acids have been shown to have a beneficial effect in lowering the risk of CHD (Erkkila et al. 2008). Findings from a year cohort study comparing the CHD outcomes and the dietary intake of Green land Inuits with a sample from the USA and Denmark showed that the Greenland Inuits had only 10% mortality from CHD compared to the other two groups. The main difference in the diet of the Greenland Inuits compared to the other groups was that it is high in n-3 fatty acids primarily from fish fats (Bang et al. 1976). N-3 fatty acids are part of the long chain polyunsaturated fatty acids made up of eicosapentaenoic and docosahexaenoic acids. In his historical review of n-3 fatty acids and their effect on CHD Leaf (2008) found robust clinical evidence of the beneficial effects of n-3 acids. Benefits included a 29% reduction in fatal arrhythmias, reduction in cardiovascular mortality by 17–30%. The subjects in these studies had recently suffered myocardial infarction and were considered high risk. The cardioprotective action of n-3 fatty acids is unclear. The action influences arrhythmia, lipid concentrations, blood pressure, platelet aggregation, vascular relaxation, inflammation and arterial cholesterol delivery (Jung et al. 2008; Johnston 2009). Hypotheses about the nature of this action include the modulation of eicosanoid and other immune pathways that mediate inflammatory processes, modulation of enzymes associated with pathways that determine cell functioning and direct influence on gene expression (Jung et al. 2008). Evidence supporting these hypotheses suggests that chronic stimulation of inflammatory responses leads to lasting vascular reactivity, insulin resistance and hyperlipidemia. The suggestion is that fatty fish high in the n-3 acids eicosapentaenoic and docosahexaenoic acid interfere with the metabolic process that stimulate inflammation and protect against both the effects of chronic stimulation of inflammatory responses and arterial inflammation (Johnston 2009). In other words, the cardioprotective action of n-3 acids maybe anti-inflammatory.
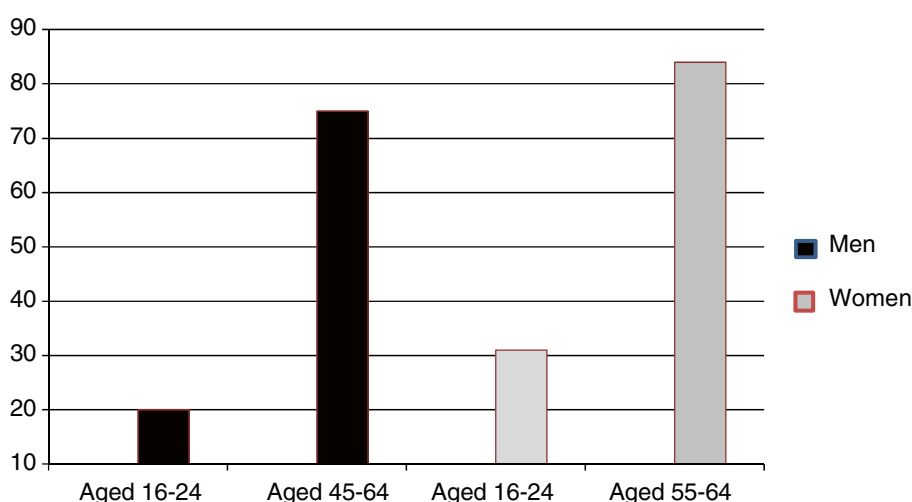
Fig. 101.4 Percentage age and gender differences in the numbers of people with cholesterol level above 5.0 mmol/L (BHF 2008). This figure compares the number of people who have recorded cholesterol level above 5.0 mmol/L in the UK in 2006 divided into two age ranges from both genders (BHF 2008)

Clinical trial evidence suggests that only a modest amount of n-3 fatty acid is required for effective protection. One to two servings of oily fish per week or an equivalent 250 mg/day of eicosapentaenoic and docosahexaenoic acids significantly reducing the risk of CHD and a 36% reduction in mortality (Mozaffarian 2008). Intake of lean fish four times per week was associated with reductions in both systolic and diastolic blood pressure in a small group of 12 participants (Erkkila et al. 2008).

101.5 Mediterranean Diet

Diets low in saturated fats, dairy products, and red meat but high in antioxidants such as plant foods, polyunsaturated fats, vegetables, fruit, nuts, beans and olive oil and that reflects the dietary patterns of the countries around the Mediterranean basin have been called the Mediterranean diet. This type of diet has been associated with a reduction of risk factors for CHD. 74,886 women between the ages of 38–63 years with no history of CHD were followed up over a 20-year period and those that adhered more strictly to a Mediterranean diet as determined by higher scores on the Mediterranean diet score were at lower risk for both CHD and stroke. Cardiovascular disease mortality was also significantly lower for those women who adhered more strictly to a Mediterranean diet (Fung et al. 2009). The evidence of the cardioprotective effects of the Mediterranean diet in terms is offered by Johnston (2009). She reviews evidence regarding its action on the markers of inflammation in high risk groups and its effects in reducing both cardiac mortality and overall mortality at 27 months (Johnston 2009). The study sample was made up of people who had survived myocardial infarction within the last 6 months rather than those with established CHD the effects cannot be generalised to this group of people.

101.6 Fibre

Water-soluble fibre found in fruits, vegetables, oats, barley, and dried peas/beans has a hypothesised action of decreasing the absorption of cholesterol from the gut, increasing the production of bile acids from cholesterol by increasing the amount of bile acids excreted in the faeces and inhibiting cholesterol synthesis in the liver (Coats 1998). There is robust evidence to link oat fibre and barley to reductions in plasma and low-density lipoprotiens and total cholesterol. In his review of 38 studies from 1963–1994 measuring the effects of oat fibre, oat meal and oat gum concentrate Truswell (2002) found total cholesterol was reduced by between 3–23% and low-density lipoprotien was reduced by between 3–9%. Two of the 38 studies showed no change in cholesterol levels and only one of the studies showed an increase in total cholesterol of 2%. In the majority of the 38 studies reviewed oat bran and oat fibre was given in the form of cereals which can have other potential cardioprotective ingredients such as nutrients and antioxidants and these may also help secondary prevention of CHD. A decrease of up to 15% in total cholesterol levels in a review of five studies using dietary fibre as the main intervention between 1988 and 1992 (Coats 1998).

101.7 Sodium

There is a strong correlation between the amount of sodium intake and hypertension and therefore CHD. Consequently, reductions in salt intake have been associated with lowering blood pressure in both people with hypertension and those who have blood pressure within normal limits. Based on the

findings of three studies including a meta-analysis He and MacGregor (2003) predict a reduction in dietary salt of 3 g a day would lead to a fall in blood pressure of 3.6–5.6 mmHg systolic and 1.9–3.2 mmHg diastolic. They also predict that doubling and then tripling the reduction would double and triple the effect on blood pressure and would reduce strokes by 13%, 26% and 39% and Ischaemic heart disease by 10%, 20% and 30%. Which they predict would reduce mortality from strokes by 20,500 and mortality from ischaemic heart disease by 31,400 in the UK. Sodium intake varies around the world but remains well above that required for physiological need in all areas of the world (Brown et al. 2009).

101.8 Fruits and Vegetables

Antioxidant nutrients such as vitamin C, which is found in fruits and vegetables, have been found to offer significant protection against cardiovascular and circulatory problems. The action is to protect cells of the body against the damage caused by free radicals through the process of oxidation and to prevent low-density lipoproteins from blocking arteries. Higher intake of fruit and vegetables was found to be cardioprotective in a sample of 832 men aged between 45–65 years in a 20 year longitudinal study (Gillman et al. 1995). Meta-analysis of nine cohort studies which included total sample sizes of 91,379 men and 129,701 women found that there was a 4% reduction in risk for CHD for every extra portion of fruit and vegetable or for each 7% increase of fruit alone (Dauchet et al. 2006). This reduction was particularly strong for the risk of cardiovascular mortality. The authors of the meta-analysis conclude that there was a publication bias which may mean the relative risks reported in the studies reviewed was overstated. There was no clue in the analysis as to the causal action of the fruit and vegetable on cardioprotection. One extra portion of fruit and vegetables was found to increase the forearm blood flow by 6.2% in a randomised trial of a fruit and vegetable intervention indicating an effect on endothelial functioning (McCall et al. 2009).

Dietary management is an essential part of secondary prevention of CHD.

101.9 Modifying the Risk Factors

Each of the risk factors for CHD mentioned above is based on a changeable lifestyle behaviour. Mediating factors such as illness beliefs, anxiety, depression and culture also influence the lifestyle behaviours that underpin these risk factors. Adapting these lifestyle behaviours would have significant impact on the severity, course and outcomes of CHD. Lifestyle behaviour changes such as dietary changes, smoking cessation and weight control have been recommended for the secondary prevention following myocardial infarction (NICE 2007).

101.10 Service Models/Delivery of Intervention to Modify Risk-Maintaining Lifestyle Behaviours

National health policy drivers within the UK have acknowledged the importance of interventions designed to modify lifestyle behaviours and other mediating factors that maintain the risk factors for CHD. Within UK health policy CHD is seen as a holistic concept; with a physical, psychological and behavioural component for both the patient and their family (DoH 2000). The National Service Framework for CHD recommends cardiac rehabilitation as a phase-specific intervention across the

four phases of treatment. Phase 1 – before discharge from hospital, Phase 2 – the early discharge period, Phase 3 – the formal rehabilitation programme, Phase 4 – long-term maintenance of the best possible health (DoH 2000).

There are various definitions of cardiac rehabilitation, and UK policy drivers base their recommendations for service models on the World Health Organization holistic definition: "¼the sum of activities required to influence favourably the underlying cause of the disease, as well as the best possible physical, mental and social conditions, so that they may, by their own efforts preserve or resume when lost as normal a place as possible in the community. Rehabilitation cannot be regarded as an isolated form or stage of therapy but must be integrated within secondary prevention services of which it forms only one facet" (DoH 2000, Chapter 7, p. 3).

Cardiac rehabilitation interventions should be tailored to individual need and aim to help the person understand their illness, provide psychological and emotional support, facilitate effective change in lifestyle behaviours and assisting with the transition back as normal life as possible (Thompson et al. 1996).

Specific interventions within cardiac rehabilitation include engagement strategies, health education and specific information about cardiac rehabilitation programmes and following these programmes in the home environment. Lifestyle advice is given about improving diet, controlling alcohol consumption, increasing activity levels with guidelines, smoking cessation and weight control.

Cardiac rehabilitation services should be integrated with other health services so specific help for increasing activity and smoking cessation is available. Stress-management interventions and other psychological support is also part of cardiac rehabilitation interventions (NICE 2007). This is understandable as anxiety and depression are consequences of CHD particularly after myocardial infarction. Although not recommended elements of more complex psychological interventions such as motivational enhancement, family management and cognitive behavioural therapy interventions are likely to be helpful.

In a combined systematic review and meta-analysis of 18 randomised controlled trials of home- versus centre-based cardiac rehabilitation interventions were found to be superior to routine care in terms of a 4 mmHg (95% CI 6.5, 1.5) greater reduction in systolic blood pressure, reduced relative risk of being a smoker (RR 0.71, 95% CI 0.51, 1.00), increased exercise capacity, decrease in total cholesterol and reductions in anxiety and depression (Jolly et al. 2006). The authors of the review recommend exercising caution when interpreting these results as the trials reviewed were clinically heterogeneous, small samples (less than 750 in total) and the quality was poorly reported.

Though effective, efficient and safe, cardiac rehabilitation service provision is suboptimal because of problems with referral, access and uptake and completion. Improving access to and equity of services is vital to improving cardiovascular health (Thompson and Clark 2009).

The EUROACTION model of cardiovascular disease prevention and rehabilitation (Wood et al. 2008) was effective in, for example, reducing saturated fat consumption and increasing fruit and vegetable and oily fish consumption in patients. A practice manual based on these principles (Jenning et al. 2009) is likely to be a useful aid to health-care professionals.

101.11   Application to Other Areas of Health and Disease

There is a commonality between the risk factors for type 2 (non-insulin-dependent) diabetes and CHD. Obesity, lack of exercise, high alcohol consumption and diet high in sugar and saturated fat are all modifiable risk factors for both diseases. Studies have found that people with type 2 diabetes have a two and threefold increased risk of death from CHD (Juutilainen et al. 2005) and myocardial infarction (Haffner et al. 1998).

Dietary interventions based on cardioprotective ingredients such as lean fish antioxidants, fresh fruit, plant foods, polyunsaturated fats, vegetables, nuts, beans and pulses. Are likely to reduce the incidence of both CHD and type 2 diabetes. Early dietary intervention and supporting education aimed people of high risk of developing type 2 diabetes may be preventative. Once the disease has been diagnosed delivery of cardioprotective dietary interventions may influence the course of the disease and may well protect against future CHD in people who may be candidates for this.

People who have serious mental health problems are at high risk of CHD compared to the general population (McCreadie 2003). This is partly as a consequence of poor diet as well as treatment. Some cardioprotective diets such as those diets high in N-3 polyunsaturated fatty acids and low in sugar, saturated fat and dairy products have also found to have a beneficial effect on the outcomes for people with serious mental health problems (Peet 2004). Dietary interventions may well have a twofold benefit in terms of psychotic symptoms and cardiac functioning. Perhaps a threefold benefit in terms of weight loss and reductions in the risk of type 2 diabetes in this vulnerable group.

Summary Points

- Blockages in the arteries caused by fatty deposits can restrict or interrupt the blood supply to the heart which can lead to myocardial infarction and serious damage to the cardiac muscle. This damage can reduce the efficient functioning of the heart and result in angina, myocardial infarction and heart failure. These three syndromes are all part of CHD.
- CHD is the most common cause of death in the UK, causing around 94,000 deaths in the UK each year in 2006, around 20% of men and 15% of women will die from CHD in the UK each year (BHF 2008).
- Between 113, 000–146, 000 people will suffer from a myocardial infarction. Around 4% of men and 0.5% of women will have a myocardial infarction each year. Angina and heart failure are more prevalent in men than women and the incidence both syndromes increases with age (BHF 2008).
- Environmental risk factors further can precipitate the onset and contribute to the severity of CHD. Smoking, obesity and being overweight, excessive alcohol, diet high in saturated fat, salt and sugar and a lack of exercise increase the likelihood of developing CHD. Other associated risk factors are high blood cholesterol level; high blood pressure and having type 2 (non-insulin-dependent) diabetes also significantly increase the risk for CHD.
- Certain types of foodstuffs such as fruit, beans, polyunsaturated fatty acids, lean fish, plant vegetables and diets low in saturated fats, red meat and salt have been found to protect cardiac functioning.
- Clinical trials of dietary interventions based on the introduction of cardioprotective foods and measuring the effects on cardiac functioning over time has confirmed the benefit of these dietary interventions on cardiac functioning.
- Cardiac rehabilitation programme based on tailoring programmes to individual need are recommended by national policy documents and clinical guidelines. These programmes include weight control and dietary interventions as well as interventions for changing lifestyle behaviours. In trials of cardiac rehabilitation programmes that include dietary and weight-control interventions, these have been found to have a beneficial effect on reduction in systolic blood pressure, reduced relative risk of being a smoker, increased exercise capacity, decrease in total cholesterol and reductions in anxiety and depression when compared to routine treatment (Jolly et al. 2006).

Definitions of Key Terms

Cardiac rehabilitation: This is the term used to describe treatment programmes that aim to improve recovery from cardiac events, help the person to manage their condition effectively prevent cardiac complications.

Cardioprotective: Anything that protects the heart and its functioning can include exercise, diet and medications.

Coronary Heart Disease (CHD): Diseases that are caused by disorders of the circulatory system, which lead to a reduction of blood supply to the heart. Three different syndromes are categorised under the heading of CHD, these are unstable angina, myocardial infarction and heart/cardiac failure.

Lifestyle: Patterns of social relationships, culture and consumption of material goods.

Mortality: The measured death rate from a syndrome over a specified time period, usually given as a unit of population, for example, 3 per 10,000.

Morbidity: The number of people or cases of a syndrome or illness over specified time period, usually given as a unit of population for example 3 per 10,000.

Polyunsaturated fatty acids: A group of unsaturated fatty acids where the carbon chain has two or more double or triple valence bond per molecule. These include omega 3 and omega 6 and occur as linolenic acid and arichidonic acid. These acids are found in vegetable, fish and seed oils.

Risk factors: Factors that mediate or influence the development of a disorder; in this case smoking may increase the risk of CHD. Modifiable risk factors are those mediating factors that are under the control of the person and can be altered through changes in behaviour.

Saturated fatty acids: A group of fatty acids that do not have the double or triple valence bond. Derived from animal fats or by the hydrogenation of unsaturated fatty acids.

References

Bang HO, Dyerberg J, Home N. Acta Med Scand. 1976;200:69–73.

BHF. British Heart Foundation statistics database. 2008. www.heartstats.org

Brown IJ, Tzoulaki I, Candeias V, Elliott P. Int J Epidemiol. 2009;38(3):791–813.

Coats AS. Postgrad Med J. 1998;74:391–4.

Dauchet L, Amouyel P, Hercberg S, Dallongeville J. J Nutr. 2006;136:2588–93.

DoH. National service framework. Coronary heart disease. London: Department of Health; 2000.

Erkkila AT, Schwab US, de Mekko VDF, Lappalainen T, Mussalo H, Lehto S, Kemi V, Lamberg-Allardt C, Uusitupa M. Eur J Nutr. 2008;47(6):319–28.

Fung TT, Rexrode KM, Mantzoros CS, Manson JE, Willett WC, Hu FB. Circulation. 2009;119:1093–100.

Gillman MW, Cupples LA, Gagnon D, Posner BM, Ellison RC, Castelli WP, Wolf PA. J Amer Med Assoc. 1995;273(14):1113–7.

Haffner SM, Lehto S, Ronnemaa T, Pyorala K, Laakso M. New Engl J Med. 1998;339:229–34.

He FJ, MacGregor GA. Hypertension 2003;42:1093–9.

Hemingway H, Kuper H, Marmot M. Psychosocial factors in the primary and secondary prevention of coronary heart disease: an updated systematic review of cohort studies. In: Yusuf S, Cairns JA, Camm AJ, editors. Evidence based cardiology. 2nd ed. London: BMJ Books; 2003. p. 181–218.

Jefferson A. J Comm Nurs. 2008;22(5):28–32.

Jennings C, Mead A, Jones J, Holden A, Connolly S, Kotseva K, Wood D. Principles of dietary intervention. In: Jennings C, Mead A, Jones J, Holden A, Connolly S, Kotseva K, Wood D, editors. Preventive cardiology: a practical manual. Oxford: Oxford University Press; 2009. p. 123–43.

Johnston C. Am J Lifes Med. 2009;3(Suppl 1):39s–43s.

Jolly K, Taylor RS, Lip GYH, Stevens A. Int J Cardiol. 2006;111:343–51.

Jung UJ, Torrejon C, Tighe AP, Deckelbaum RJ. Am J Clin Nutr. 2008;87(Suppl):2003s–9s.

Juutilainen A, Lehto S, Ronnemaa T, Pyorala K, Laakso M. Diabetes Care. 2005;28:2901–7.

Kannel WB. Heart Fail Rev. 2000;5(2):167–73.

Leaf A. Am J Clin Nutr. 2008;87(Suppl 6):1978s–80s.

Lewin R, Furze G, Robinson J, Griffith K, Wiseman S, Pye M, Boyle R. Brit J Gen Pract. March 2002.

Marmot M. Economic and social determinants of disease. Bull World Health Org. 2001;79:906–1004.

McCall DO, McGartland CP, McKinley MC, Patterson CP, Sharpe P, McCance DR, Young IS, Woodside JV. Circulation 2009;119:2153–60.

McCreadie RG. Brit J Psychiat. 2003;183:534–9.

Mozaffarian D. Am J Clin Nutr. 2008;87(Suppl 6):1991s–6s.

NICE. MI: secondary prevention in primary and secondary care for patients following a myocardial infarction. NICE clinical guideline 48. National Institute for Health and Clinical Excellence, London; 2007.

Peet M. Brit J Psychiat. 2004;184:404–8.

Rogers M, Fayter D, Richardson G, Ritchie G, Lewin R, Snowden AJ. The effects of psychosocial interventions in cancer and heart disease: a review of systematic reviews. Centre for Reviews and Dissemination, University of York; 2005.

Tandon R, Keshavan MS, Nasrallah HA. Schizophr Res. 2008;102:1–18.

Thompson DR, Clark AM. Cardiac rehabilitation: into the future. Heart 2009;95(23):1897–1900.

Thompson DR, Bowman GS, Kitson AL, de Bono DP, Hopkins A. Heart 1996;75:89–93.

Truswell AS. Eur J Clin Nutr. 2002;56:1–14.

Turner RC, Millns H, Neil HAW, Stratton IM, Manley SE, Matthews DR, Holman RR. Brit Mel J. 1998 (14th March);316:823–8.

Stanner S. Brit J Nurs. 2009;14(5):210–2.

WHO. The World Health Report. Reducing risks, promoting healthy life. Geneva: World Health Organisation; 2002.

Wood DA, Kotseva K, Connolly S, Jennings C, Mead A, Jones J, Holden A, De Bacquer D, Collier T, De Backer G, Faegerman O. on behalf of EUROACTION Study Group. Lancet 2008;371:1999–2012.

Chapter 102
Exercise, Appetite, and Energy Balance: The Interactions Between Energy Expenditure and Intake, and the Implications for Weight Management

Stephen Whybrow, Neil King, and James Stubbs

Abbreviations

DIT   Diet induced thermogenesis
NEAT   Non exercise activity thermogenesis
PAL   Physical activity level
RMR   Resting metabolic rate

102.1 Introduction

The continuing obesity epidemic of the past 3 decades is a result of economic and environmental changes that have affected both components of the energy balance equation (Table 102.1). Cheaper and more readily available foods, increased dietary energy density, and larger portion sizes are among the changes that have increased the possibility, and the probability, of ingesting more energy than required; at least for most people in developed and developing societies.

Although less well studied, and less easily quantified because of a lack of earlier good quality measurements, daily energy expenditure appears to have declined over the same period that has seen the rapid increase in obesity, and patterns of physical activity have changed. It is popularly believed, and often stated, that activity levels are currently lower than 30, or more, years ago, with increased television viewing (Prentice and Jebb 1995), mechanization of work (Tremblay and Doucet 1999), and increased reliance on mechanized transport (Haines et al. 2000) being cited to support this in the absence of good empirical data. The little evidence that is available suggests that, for many people, physical activity energy expenditure is about as low as it can be, and there is little scope to reduce it further.

Humans evolved under conditions where higher-than-current levels of activity were necessary to hunt and gather sufficient food. The PAL of preagricultural humans has been estimated at about 1.8, and for contemporary foragers with lifestyles similar to those assumed for our more recent ancestors, at 1.7–2.2 for males, and slightly less for females (Cordain et al. 1998). Furthermore, a re-evaluation of the methods used suggests that these may be underestimates (Leonard et al. 1997). An average PAL for modern, predominantly sedentary populations has been measured at 1.6 (Black et al. 1996). Moreover, only 15% of the 574 individuals in the meta-analysis conducted by Black et al. had PALs towards the

S. Whybrow (✉)
Faculty of Health and Medical Sciences, University of Surrey, Guildford, GU2 7XH, UK
e-mail: s.whybrow@surrey.ac.uk

Table 102.1 Key features of the energy balance equation

- The energy balance equation is often given as:
  Energy Intake = Energy Expenditure ± Energy Stores
- Energy balance can be thought of as a set of scales with intake on one side and expenditure on the other. The energy from food and drink needs to be balanced by the energy we expend in bodily functioning and physical activity
- When energy intake is greater than expenditure the excess if stored, mainly as fat, and body weight increases
- When energy intake is less than expenditure the deficit is supplied from fat stores, resulting in weight-loss
- When intake matches expenditure, body weight is stable
- People are rarely in energy balance in the short-term (over days). What is important (for body weight) is energy balance over the medium and longer-terms (weeks and months)
- One can be in energy balance at a low level of energy turnover (being sedentary but eating less), or a very high level of energy turnover (such as elite athletes), or anywhere between

This table gives the key features of the energy balance equation, and its implications for body weight maintenance

upper end of the normal range, above 2.0, and these were mainly individuals who regularly participated in active sports or active transport (Black et al. 1996). Obtaining our normal (from an evolutionary point of view) levels of activity has become a matter of choice rather than necessity, and one made by the atypical few.

It would be reasonable to suppose that energy expenditure is coupled to energy intake, such that increases or decreases in activity level would bring about compensatory changes in food intake through appetite and hunger mechanisms to realize energy balance. However, the sedentary are more likely to be overweight than the active (Martinez-Gonzalez et al. 1999), and adding an exercise program to an energy-restricted diet improves weight loss, and reduces weight regain (Miller et al. 1997), which would suggest otherwise. Conversely, individuals who frequently exercise, or participate in sports regularly, must be in long-term energy balance, as a prolonged energy deficit and continuing weight loss could not be maintained for long. It is likely that coupling between energy expenditure and intake will depend on whether the individual is in a transition of energy balance (i.e. dynamic) or in a steady state (i.e. static). Physically active individuals with high energy intakes, which match high expenditures, have been through a series of transitional periods to reach this steady state. Therefore, a new equilibrium at a higher level must be established eventually, although it appears to take several weeks at least for any adjustment to become detectable (Whybrow et al. 2008). The apparent contradiction in the interaction between energy expenditure and intake will be covered in this chapter by considering firstly whether exercise-induced increases in energy expenditure drive energy intake upwards undermining dietary approaches to weight management, and secondly whether sedentariness alters levels of energy intake or subsequent energy expenditure. Thirdly, if elevated levels of energy intake alter physical activity or exercise, and fourthly whether reduced energy intake (dieting and starvation) results in decreased energy expenditure. Finally, the implications of the links between energy expenditure and intake for achieving and maintaining weight loss, and preventing weight gain, will be considered.

102.2 Does Exercise/Increased Physical Activity Raise Energy Intake?

102.2.1 Exercise-Induced Energy Expenditure and Energy Balance

From a homeostatic perspective it is logical to assume that an exercise-induced increase in energy expenditure leading to an energy deficit is automatically followed by an equivalent increase in caloric intake. This assumption probably originates from empirical evidence that dietary-induced energy

deficits through food restriction induce marked increases in hunger and food intake (e.g. Hubert et al. 1998) and the theoretical approach that any perturbations in energy balance will be compensated for by compensatory adjustments (Mayer et al. 1956). Therefore, it is intuitive to expect food intake to increase in response to an exercise-induced energy deficit. Collectively, this leads to the belief that physical activity is a futile strategy for successful weight loss because the increase in energy expenditure will automatically drive up hunger and food intake. However, it should not be assumed that exercise will automatically exert the same effect as dieting or that the biological system is sensitive enough to detect acute increases in energy expenditure. The empirical evidence provides a positive view for the role of exercise in weight management.

102.2.2 What Does the Evidence Say?

Despite a minority of studies showing a compensatory increase in energy intake (e.g. Verger et al. 1992), most of the evidence shows that acute exercise-induced increases in energy expenditure generate little or no immediate effect on levels of hunger or daily energy intake. Therefore, the evidence points to a weak coupling between energy intake and acute activity-induced increases in energy expenditure (see Blundell et al. 2003).

It can be argued that the lack of compensatory increase in energy intake in response to acute and small increases in energy expenditure is not surprising. Accordingly, a series of seminal studies by Stubbs and colleagues provided evidence for the effect of increasing energy expenditure through exercise and extending the observation period of acute interventions to 7–14 days (Stubbs et al. 2002a, b). The results of these studies demonstrated that, despite a slight compensatory increase in energy intake in women, although not in men, energy intake did not fully compensate for relatively large increases in energy expenditure with an exercise intervention lasting 7 days. Extending the intervention to 14 days (Whybrow et al. 2008) and from a similar study of 52 days (Woo and Pi-Sunyer 1985) provided further evidence of partial compensation – approximately 30%. Therefore, although acute manipulations show no automatic compensatory increase in energy intake, after several days of imposed exercise-induced energy deficits intake does start to increase – but not sufficiently to fully compensate for the additional expenditure. From an energy balance perspective, the weak coupling between activity energy expenditure and intake generates an optimistic view of the role of exercise in weight management. It is worth noting that an increase in intake is not the only compensatory response that could potentially undermine the beneficial effect of exercise on weight control – other metabolic and behavioral compensatory barriers could occur (for a review, see King et al. 2007).

When considering the various ways in which energy intake could potentially increase (see Table 102.2) through changes in eating patterns, it is not surprising that there is some resistance to increasing food intake. It is important to remember that eating behaviors (food choice, meal frequency, etc.) have developed over many years and are heavily influenced by physiological limits (e.g. preabsorptive factors), psychological, and social factors (Blundell and King 1996).

Table 102.2 Changes in eating behavior changes that can increase in energy intake

1. Increased meal size (i.e. individual eating episodes)
2. Increased frequency of eating episodes (increased snacking)
3. Increased selection of energy dense (kcal/g) foods
4. Increased intake of energy-rich fluids

In addition to simply eating more food, energy intake can be increased through several behavioral changes, either independently or collectively

Some medium term exercise intervention studies also provide evidence for an orexigenic effect, which is exhibited as increases in fasting hunger (e.g. Doucet et al. 2000). However, it is important to note that this change is accompanied by significant reductions in body weight. It is not known whether the increase in the drive to eat is due to chronic exercise-induced physiological changes or in response to a significant reduction in body weight. Therefore, one of the problems when interpreting the appetite responses to chronic exercise interventions is whether any observed changes in appetite are independent of body weight or body composition changes.

102.2.3 Does Exercise Improve the Sensitivity of Appetite Control?

It is possible that exercise has the capacity to improve the sensitivity of appetite control, and to contribute to a better regulation of energy balance. Based on evidence that physically active individuals are leaner and have a lower BMI than sedentary individuals (Martinez-Gonzalez et al. 1999), and an isolated example of a strong coupling between energy expenditure and energy intake in Tour de France cyclists, albeit at very high levels of energy turnover (Saris et al. 1989) exercise could potentially promote better regulation. Data from two cross-sectional studies demonstrates that physical activity status influences the accuracy to compensate for covert manipulations in the energy content of meals or preloads. The evidence shows that physically active individuals have a better capacity to detect differences in energy in preloads compared to their sedentary counterparts (Long et al. 2002), and to adjust energy intake accordingly. There is some indication that the sensitivity of appetite regulation can be improved in sedentary individuals by raising energy expenditure (Martins et al. 2007). Data from a 12-week exercise intervention study revealed that exercise exerts two different processes on appetite sensitivity expressed as a function of fasting (pre-eating) and meal-induced states – which was partly dependent on the magnitude of weight loss (Caudwell et al. 2008). In individuals who did not experience substantial weight loss (nonresponders), exercise caused an increase in the drive to eat (see Fig. 102.1) compared with responders, who lost the amount of weight, or more, predicted from the planned energy deficit. In contrast, a fixed energy preload improved satiation and satiety (Fig. 102.2) after 12 weeks of exercise in both responders and nonresponders – hence the improvement in satiety was independent of weight loss. In essence, this latter effect suggests that 12 weeks of exercise raised the sensitivity of the physiological signaling system allowing a fixed amount of food to realize a greater suppression of hunger.

These novel data indicate the potential of exercise to exert effects on appetite regulation, which involves at least two processes: an increase in the orexigenic drive to eat and a concomitant increase in the satiating efficiency of a fixed meal. These data also provide evidence for interindividual variability in response to exercise (King et al. 2008) – such that these processes do not operate with the same intensity in all individuals who experience a chronic exercise-induced increase in energy expenditure.

102.3 Does Sedentariness Lower Energy Intake?

The previous section described a weak coupling between exercise-induced energy expenditure and energy intake. While this has positive implications for the role of increased physical activity in weight management, it provides a less optimistic scenario if the same phenomenon exists when exercise is reduced or stopped, and when people become more sedentary. Exercise is important in helping to achieve weight loss, and for maintaining the new lower body weight; of importance for limiting the development of obesity is how sedentariness, and changing from a high to a lower level of activity, affects energy
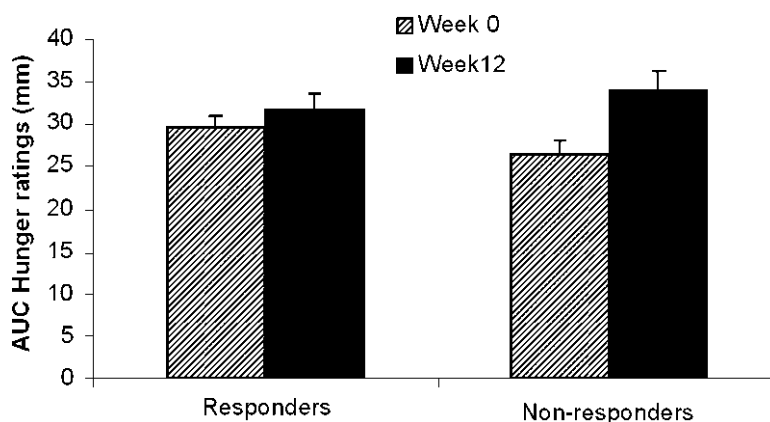
Fig. 102.1 Average daily hunger ratings before and after 12 weeks of supervised exercise in responders and nonresponders. Average daily hunger ratings expressed as the area under the curve (AUC) before (week 0) and after (week 12) the supervised exercise program. Individuals who lost less weight than predicted (nonresponders) showed an increased motivation to eat compared to responders who did lose weight
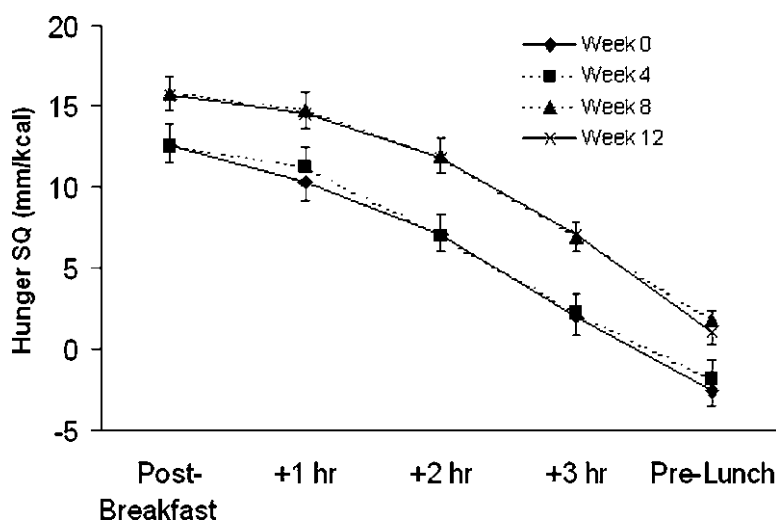
Fig. 102.2 Satiety responses to a fixed breakfast meal over a 12-week exercise program. Satiety responses, measured by the Satiety Quotient (SQ), to a fixed breakfast meal at weeks 0, 4, 8, and 12 in both responders and nonresponders (data pooled). After 12 weeks, satiation and satiety responses to a standardized breakfast were improved in both responders (who lost weight during the intervention) and nonresponders (who did not lose weight), suggesting that the improvement in satiety was independent of weight loss. SQ is calculated by dividing the difference between ratings of motivation to eat before and after the eating episode by the energy content of the test meal

intake to re-establish energy balance at a lower level of energy turnover. There is very little *direct* evidence to link sedentariness to the development of a positive energy balance. Instead a number of intuitively obvious arguments and proxies of physical activity have been used in (largely) cross-sectional comparisons, to suggest that a lowering of physical activity levels (PALs) in the population is predisposing us further to weight gain (Prentice and Jebb 1995). Despite the attractiveness of these arguments, it is remarkable that few studies have attempted to assess the impact on energy balance of imposing sedentary routines, within the normal range of activity, on healthy humans feeding ad libitum.

102.3.1 Evidence from Laboratory Studies

Murgatroyd et al. (1999) conducted 2-day experiments where subjects underwent active versus sedentary routines and consumed a high-fat or a low-fat diet, ad libitum, in a 2 × 2 design. Energy intake was the same on a given diet regardless of the level of energy expenditure. Similarly, decreased activity while resident in a whole body calorimeter for a day generated a positive energy balance in both lean and obese subjects (Shepard et al. 2001). However, the periods of enforced inactivity in both of these studies were very short and may not have provided sufficient opportunity to allow compensatory changes in intake to begin. In general, studies of this duration fail to produce a change in feeding behavior under a variety of conditions (King et al. 1997). The impact of a sedentary routine on energy balance has been assessed over a period that is long enough to allow compensatory changes in energy intake to be seen. Total daily energy expenditure was clamped at approximately 1.4 and 1.8 RMR in six male subjects who were continually resident in a whole body indirect calorimeter for seven consecutive days. The impact of this on subjective ratings of hunger and appetite, and energy intake was examined. Energy expenditure amounted to 9.7 and 12.8 MJ/day on the sedentary and active treatments respectively, while the corresponding energy intakes were not significantly different at 13.5 and 14.4 MJ/day. By day 7, cumulative energy balances for the sedentary and active treatments were 11.1 and 26.3 MJ respectively, with most of the excess energy being stored as fat (Fig. 102.3, Stubbs et al. 2004). Importantly, there were no time trends in either energy intake or expenditure over the 7 days this study, indicating no tendency to compensate for an acute decrease in physical activity energy expenditure over this time period.
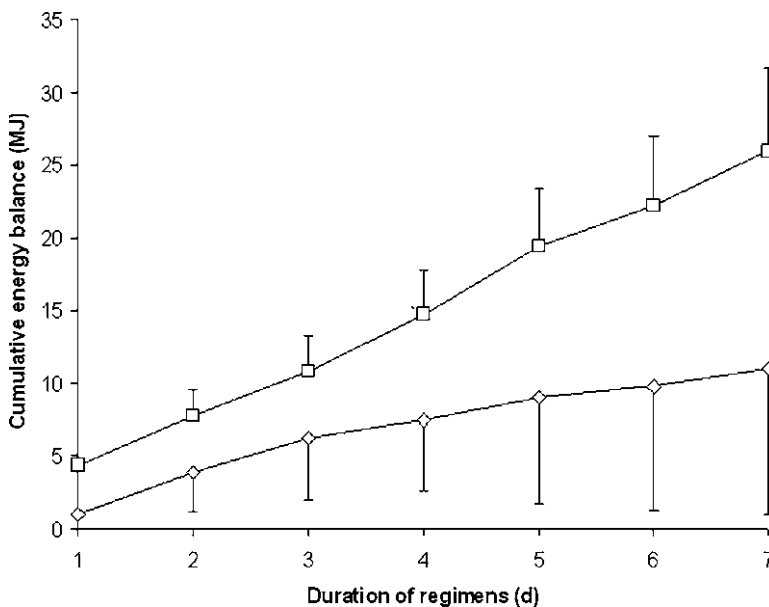
Fig. 102.3 Effects of imposed physical activity level on cumulative changes in energy balance in six men. Cumulative energy balance for six men during active (◊) and sedentary (□) regimes between days 1 and 7. Values are means (±SEM). Energy balance was calculated as energy intake minus energy expenditure. Energy balance became more positive from day 1 to day 7 on both treatments. Cumulative energy balance was 11.1 and 26.3 MJ by the end of day 7 on active and sedentary regimens, respectively. This was significantly different from zero on the sedentary treatment only ($P < 0.001$) (Stubbs et al. 2004)

It is possible to detect decreases in energy intake as a response to a sustained decrease in energy expenditure. For instance, in the experimental model of six-degree head-down tilt-bed rest, designed to simulate the energy expenditure during space flight, Ritz et al. (1999) have shown that energy intake does drop significantly as a consequence of long periods of extreme sedentariness; 6 weeks in this experiment. Energy intake fell by 17%, which was sufficient to place the eight male subjects in a negative energy balance, such that body weight fell by 3%. Subjects started to lose weight in the first week and continued to do so during the remainder of the period of sedentariness. Thus, the change in energy intake showed a fast response that was absent during the later calorimetry chamber experiment (Stubbs et al. 2004), where energy expenditure during the sedentary protocol (1.4 RMR) was similar to that during the head-down-tilt protocol (1.46 RMR) (Blanc et al. 1998). However, as the authors noted, the findings could have been an artefact of the experimental conditions associated with either the presentation of the food or some other aspect of the experiment.

102.3.2 Evidence from Studies in Free-Living People

Data from the NHANES series of studies suggest that, for most people, body weight tends to drift upwards at around 0.3–1.7 kg/year (Kant et al. 1995). A more recent study showed a similar increase in body weight in a sample of 6,406 individuals over an average follow-up period of 7.4 years (Williams and Thompson 2006). At baseline, body weight, BMI, and other indices of adiposity were inversely related to usual exercise levels (running distance). Furthermore, there was a dose-dependent effect of change in running distance on change in body weight, BMI, and other measures of adiposity over the observation period. Individuals who quit running between the baseline and followup assessments gained weight; the amount being proportional to the change in running distance, and up to 8 kg for those who reported running >48 km/week at baseline but who subsequently quit. Weight gain was considerably less at around 3 and 0.5 kg in those who took up running and who reported running <23 and >24 km/week respectively. Weight and BMI changes in people who were initially sedentary, and who remained sedentary, were in between the other two groups.

The difference in energy balance between those who quit, and those who started, running may well be greater than the changes in body weight alone suggest, as changes in weight are poor indicators of energy balance in the presence of changes in body composition. There is some evidence for body composition changes in the reported waist circumference measurements (Williams and Thompson 2006), which are consistent with increases and decreases in exercise levels and suggest proportionally greater losses and gains of lean tissue (muscle) respectively for those who quit and started running. However, the weight gain of the runners who quit was still considerably less than had there been no compensatory changes in energy intake or some other aspect of energy expenditure. Decreasing weekly running distance from 48 to 0 km would produce an initial positive energy balance of around 6 MJ a week, which could result in a weight gain in the order of 12 kg in the first year. Therefore, some compensatory adjustments, albeit incomplete, must have occurred.

The little evidence available suggests that abrupt decreases in activity energy expenditure, through training cessation or injury, leads to marked gain in body weight. Several life events, such as marriage (Jeffery and Rick 2002) and starting at university, that produce abrupt changes in lifestyle are associated with weight gain (Ogden et al. 2009), and it is possible that it is the change in habitual PAL per se and the time period needed to re-establish energy balance that are the risk factors for weight gain. Although it should be possible to achieve energy balance while maintaining a sedentary life style, a number of cross sectional studies provide evidence that this is unlikely in practice, as sedentariness is highly correlated with increased adiposity. For example, Martinez-Gonzalez et al. (1999) estimated the

association of leisure-time sedentary and nonsedentary, self-reported activities on BMI and the prevalence of obesity in 15,239 subjects across the European Union. They found that… "obesity and a higher body weight are strongly associated with a sedentary lifestyle and a lack of physical activity in the adult population of the European Union" (Martinez-Gonzalez et al. 1999). The more time people spent sitting the more likely they were to be obese; and the less active people were in their leisure time, the more likely they were to be obese. Furthermore, the two effects were additive.

102.3.3 Sedentary Lifestyle and Overeating

In addition to lowering daily energy expenditure, a number of studies suggest that the lifestyle correlates of a sedentary routine promote a positive energy balance through affording greater opportunities to overeat (Temple et al. 2007); for example time spent watching television is positively related to the consumption of energy-dense snack foods (Gore et al. 2003). There is however little evidence that a sedentary routine promotes greater levels of energy intake per se. Rather, people appear to continue to eat as they did when they were active, at least initially, and intake overshoots expenditure leading to weight gain.

These lines of evidence suggest that reduced activity energy expenditure is very weakly linked, through physiological signals, to energy intake and has little effect in reducing intake. Under these conditions it is likely that the rate of weight gain slows with time if energy requirements remain lowered. Whether the extent to which this occurs is due to changes in the components of expenditure, or to active cross-talk between reduced activity and intake is unclear at present. The evidence thus suggests an absence of any strong cross-talk between reduced activity energy expenditure and energy intake, resulting in a positive energy balance and a tendency to gain weight when activity is reduced and food is available ad libitum. Alternatively, a positive energy balance can be achieved by increasing energy intake, rather than decreasing expenditure, and this is probably of greater relevance to most Western consumers given that generally, PALs are already low, and where it is rare for food not to be available ad libitum. A series of studies has suggested that some people actively respond to overfeeding by elevating energy expenditure by increasing their ambulatory and positional movements; this has been termed the Non-Exercise Activity Thermogenesis (NEAT) phenomenon (Levine et al. 2000).

102.4 Does Overconsumption Raise Energy Expenditure?

102.4.1 Overconsumption and Energy Balance

It is well established that prolonged, and severe energy intake restriction (or underconsumption) leads to a decrease in energy expenditure, which is an attempt to prevent a continuing reduction in body weight (see following section). Therefore, overconsumption, in theory, should promote an increase in energy expenditure. However, energy balance is not necessarily symmetrical – the body will strongly defend attempts to lose weight, but weakly defend a positive energy balance. Indeed, it can be argued that this latter phenomenon exists naturally in today's environment in which overconsumption is easily promoted; especially through the passive overconsumption of high-fat and energy dense foods. Similar to the adaptations in RMR to underfeeding, any increases in total energy expenditure in response to overfeeding will be mainly due to changes in fat and fat-free mass associated with the energy demand of a greater body weight. Periodically through this chapter we have discussed several examples of

compensatory adjustments or adaptations to challenges to energy balance. The evidence indicates that, overall, adjustments to perturbations in energy balance will eventually "kick-in", although the intensity and time course of these adjustments tends to vary among individuals. This will depend on the direction (negative or positive) of interventions in energy expenditure or intake, and the magnitude or intensity of the perturbation. Furthermore, there is a large interindividual variability in the capacity to adjust or regulate the various components of energy balance. There is strong evidence to indicate that individuals vary in their resistance to lose or gain weight in response to increases or decreases in energy expenditure respectively. What about increases in energy intake? Do the same phenomena of resistance and variability to gain weight exist in response to overconsumption?

102.4.2 Overconsumption and Energy Expenditure

In effect, an overfeeding study is already taking place naturally in the habitual free-living environment. Whilst this provides a proxy indicator that overconsumption leads to weight gain, it does not quantify the contribution of increased energy intake to weight gain and obesity; neither does it provide information about the corresponding compensatory adjustments in energy expenditure that may attempt to counteract the food-induced positive energy balance. Carefully controlled studies that have attempted to measure the various components of energy expenditure provide some evidence of how imposed increased energy intake could be potentially offset by adaptations in energy expenditure. Problems with this type of study are associated with methodological constraints including practical implications of enforced overfeeding and monitoring, and the ability of measurement techniques to detect potentially small adjustments in energy expenditure. Furthermore, some of the conclusions are based on calculations of increases in body weight relative to the increment in energy intake, which estimate the proportion of weight gain relative to the amount of overfeeding.

To compound the problem further, there are very few available data that address the effects of imposed overconsumption on energy expenditure. Despite a majority of studies indicating that there is some evidence of proportional increases in energy expenditure in response to overconsumption, overall the evidence is equivocal. The most marked and least equivocal effect is the increase in RMR due to overfeeding. Harris et al. overfed subjects by 1,000 kcal/day (4.2 MJ/day) for 8 weeks and showed that there was a marked increase in RMR during the first 2 weeks that tended to plateau after approximately 5 weeks (Harris et al. 2006).

Given that DIT is related to the amount of digested and absorbed food, it is an ideal candidate for one component of energy expenditure that would automatically increase in response to overfeeding. Whilst some studies purported an increase in DIT (Levine et al. 1999) using more indirect measures, a majority of studies demonstrated no significant increases in DIT (e.g. Tremblay et al. 1992). There appears to be little evidence of adaptive thermogenesis, whereby weight gain is limited by upregulation of heat production to dispose of excess energy intake, during human overfeeding studies. The third component of energy expenditure, activity-induced energy expenditure, is unlike RMR and DIT in that it can be increased by volitional changes in behavior.

102.4.3 Non-exercise Activity Thermogenesis

It has been suggested that some people actively respond to overfeeding by increasing their ambulatory and positional movements, or NEAT (Levine et al. 1999). When 16 nonobese subjects were overfed by 4.2 MJ/day for 8 weeks fat gain was inversely related to change (increase) in NEAT,

which ranged from 0 to 3 MJ/day, and around 66% of the increase in daily energy expenditure was due to increased NEAT. This suggested that activation of NEAT dissipates excess energy to preserve leanness during overfeeding – at least in some people (Levine et al. 1999). However, a potential problem is that changes in energy balance were estimated assuming that all of the additional food was consumed. Any noncompliance with the aggressive overfeeding regimen in these lean subjects would be registered as NEAT, since NEAT was estimated by difference. The average energy cost of weight gain in this study was around 50% higher than expected from theoretical (Stubbs et al. 1998) and empirical (Forbes et al. 1986) sources. The possibility that subjects did not entirely comply with the overfeeding regime cannot be excluded.

Two key features of overfeeding experiments are the interindividual variability in weight gain and the proportion of energy intake that remains unaccounted for. One could infer from this that adaptations in energy expenditure are possible, and occur to differing degrees in different people, but current measurement methods lack the ability to detect them sufficiently well, and the phenomenon has yet to be clearly demonstrated.

102.5 Does Dieting Lower Energy Expenditure?

The effect of energy intake restriction on reducing activity has been less widely studied in humans than it has in animals but there is some evidence that it occurs.

Johnstone (2002) and Gibney (2001) examined the effect of three common regimens on the physical activity patterns of obese men (BMI 30–40) in a program of three studies (i) total fast (to lose a nominal 5% weight over 6 days); (ii) very-low-calorie diet (VLCD, 2.5 MJ/day to lose 10% weight over 3 weeks); (iii) low-calorie diet (LCD, 5.2 MJ/day to lose 10% weight over 6 weeks). Clearly, the energy deficit and rate of weight loss occurred in the order total fast > VLCD > LCD. Subjects rated their subjective feelings of fatigue every hour throughout the study. On both the total fast and the VLCD, fatigue ratings increased steadily throughout the weight-loss period. The increase in fatigue followed the same pattern as the dietary restriction, being greatest for subjects on the total fast, and unchanged compared to the prestudy period for those following the LCD (Johnstone 2007). At 5% weight loss PALs were significantly different at 1.38, 1.71 and 1.84 RMR for subjects on the fast, VLCD and LCD respectively (Stubbs et al. 2003). These data suggest that in obese subjects the more extreme the energy intake restriction, the greater the reduction in physical activity. These values amounted to daily energy expenditures of around 11.5, 13.5 and 13.9 MJ/day. The difference in physical activity between the total fast and LCD amounted to 2.4 MJ/day, while intake differed by 5.0 MJ/day. The decrease in physical activity therefore compensated for almost half of the difference in energy intake. Thus, there is evidence that an increased rate of weight loss through dietary restriction will produce a "compensatory" decrease in physical activity. This response may take a while to happen, at least in lean individuals, as subjective ratings of fatigue and tiredness were not affected by an acute fast of 36 h (Johnstone et al. 2002).

In Keys et al.'s classic 24-week semistarvation study, daily energy expenditure was 8.0 MJ/day lower at the end of the restricted energy intake period than at the beginning. The largest change in energy expenditure was a fall in physical activity (4.6 MJ/day), 64% of which was due to a decrease in volitional physical activity (Elia et al. 2003). Thus the greatest single response to prolonged semistarvation was a change in activity behavior. The remaining 36% was from several obligatory reductions in energy expenditure, resulting from changes in body weight and composition.

Dietary Induced Thermogenesis is proportional to the amount (and to a lesser extent composition) of ingested food, and will clearly be lower during food restriction. The energetic cost of movement will decrease as body weight decreases, as will the cost of maintenance, which results in a lower RMR.

Energy intake restriction, at least when it is more severe and for longer than is recommended for normal dieting and weight loss, does appear to lower energy expenditure, and therefore energy requirements. Some components are obligatory and are a direct consequence of the amount and composition of the weight lost, or through the decreased food intake per se. But there appears also to be a reduction in voluntary activity. During short-term total fasting, or when the energy intake restriction is around the maximum recommended for long-term weight-loss, there is little evidence of decreases in physical activity that would counter the diet-induced negative energy balance. Severe energy intake restriction, or "crash dieting", is not recommended as a solution for long-term weight loss for this reason, among others.

102.6 Pathology and Implications for Weight Control

A sedentary lifestyle is a risk factor for many chronic diseases, even after adjustment for the effects of obesity in their development. Regular moderately intense physical activity reduces the risk of developing a wide range of diseases, including type-2 diabetes, cardiovascular disease and some types of cancer (Warburton et al. 2006). A reduction in risk is seen with as little as 30 min moderately intense activity each day (Bassuk and Manson 2005). However, this level of activity may be insufficient to impact on energy balance, with much more activity being needed to prevent weight gain and to achieve weight loss.

102.6.1 How Much Exercise Is Needed to Prevent Weight Gain?

Hill et al. (2003) estimated the energy intake decrease, or energy expenditure increase, that would counter the 0.8–0.9kg average annual weight increase seen in two large epidemiological studies, NHANES and CARDIA. They concluded that 418 kJ/day of additional activity (approximately the cost of leisurely walking for 20-min) could prevent the gradual weight gain seen in 90% of the two cohorts. This is much less than the recommended 627–836 kJ/day (or 30 min moderately intense activity) to confer health benefits. However, the consensus from an IASO conference was that "… moderate intensity activity of approximately 45–60 min/day, or 1.7 PAL is required to prevent the transition to overweight or obesity" (Saris et al. 2003). This equates to almost 1,500 kJ/day additional activity depending on the person's body weight. Recently the American College of Sports Medicine updated its guidelines for physical activity, recommending that between 150 and 250 min/week (20–35 min/day) moderately intense activity to be effective at preventing weight gain (Donnelly et al. 2009).

Much of the data comes from retrospective studies that have looked at those who are more, or less, successful at maintaining a lower body weight rather than the more powerful prospective, and randomized, trials. The amount and intensity of exercise is often self-reported in epidemiological studies, and can be subject to an overreporting bias.

102.6.2 How Much Exercise Is Needed to Prevent Weight Regain?

It is generally agreed that exercise, or increased physical activity, is an important component in any weight maintenance program. Weight maintenance post weight-loss is more difficult to achieve than the initial weight loss, but maintenance programs that include exercise are more effective than those that rely on changing diet alone.

More exercise is recommended to prevent weight regain than to prevent the initial weight gain. This is partly because the composition of tissue increase during weight regain and weight gain is different. Weight regain is predominantly through the "re-filling" of depleted, existing adipose tissue with fat, whereas weight gain requires the accumulation of more lean tissue. As fat has a higher energy content than lean tissue, *per unit weight* a greater surplus of energy needs to be ingested to increase weight through (predominantly) fat accumulation than if the tissue deposition includes lean tissue. Furthermore, both dietary behaviors and patterns of activity and exercise tend to drift back towards those practiced preweight loss. Approximately 80-min/day physical activity, additional to a sedentary lifestyle, is estimated to be necessary for the prevention of weight regain (Saris et al. 2003). This is supported by evidence from members of the National Weight Control Registry; those who are successful at maintaining their weight-loss report undertaking about 60 min/day of moderate-intensity activity (Wing and Phelan 2005).

In a recent 2-year long diet and exercise intervention to achieve and maintain weight loss in 191 overweight and obese women, around a quarter achieved and maintained at least 10% reduction of their initial body weight, and did so by increasing their physical activity by 1,500 kcal/week (6,270 kJ/week) compared to that preweight loss, in addition to reducing their energy intakes. This corresponded to an additional 39 min exercise a day at the prescribed level (Jakicic et al. 2008). Figure 102.4 shows the dose effect of reported amount of physical activity on weight loss and maintenance.
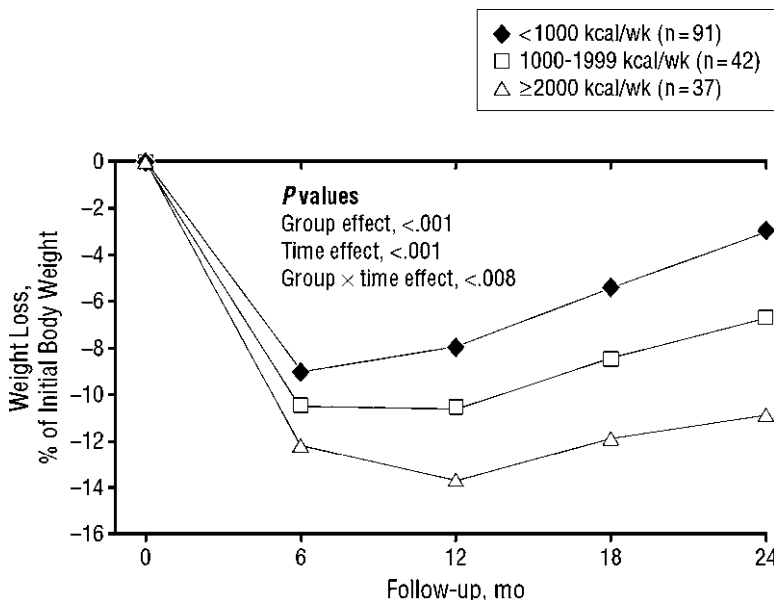
Fig. 102.4 Influence of physical activity on post-weight-loss weight-maintenance. Percentage weight loss by physical activity categories (kilocalories per week) in 170 overweight and obese women who increased physical activity energy expenditure, and reduced energy intake, for 24-months (Taken from Jakicic et al. 2008, with permission. Copyright © (2008) American Medical Association. All rights reserved)

102.6.3 How Much Exercise Is Needed to Achieve Weight-Loss?

A reduction in energy intake, rather than increasing physical activity alone, is the first choice for achieving weight-loss. The recommended rate of weight-loss is 0.5–1.0 kg a week, which equates to an energy deficit of 13–26 MJ a week (Stubbs et al. 1998). To achieve this through increasing energy expenditure alone would require exercising at a moderately intense level (expending around 1.5 MJ/h in addition to RMR) for 1¼–2½ h every day. Exercising to expend 2 MJ/day (over two, 40-min sessions) for 2-weeks is achievable for lean men and women who are not dieting (Whybrow et al. 2008); but the barriers for overweight and obese people in achieving this for short periods, and for maintaining it for the weeks needed to realize meaningful weight-loss, are considerable (Table 102.3).

It is important to note that overweight sedentary people have higher absolute levels of energy expenditure than lean, but physically active, people. A larger body mass requires a larger amount of metabolically active lean tissue; the obese therefore have higher absolute resting metabolic rates then the lean. The energy cost of movement, especially for weight-bearing activities, also increases with body size. However, the PAL of lean active people and overweight sedentary people tends to be similar (Jebb and Prentice 1995). Many overweight individuals already have energy expenditures towards the upper end of their ability to exercise, and there is limited scope to increase it further.

Overcoming the barriers to increasing physical activity and habituating people to activity is a considerable challenge. Regular brisk walking is an ideal form of exercise for the unfit. The level of energy expenditure can be increased steadily by increasing intensity and duration, or both, and by fitting it into people's daily routines can obviate the time-constraint barrier. Self-monitoring equipment, pedometers (or step counters) are inexpensive and readily available. For people who are very inactive, even 30 min extra activity each week has important health benefits, and as people become more active they become habituated to physical activity more.

Generally, intervention studies show that total daily energy expenditure increases by about the same amount as the exercise prescription (Stubbs et al. 2002a, b; Whybrow et al. 2008). Nonexercise activity does not appear to decrease substantially as a compensatory response to increased exercise (Racette et al. 1995; Whybrow et al. 2008), except in the elderly (Westerterp 1998), or when accompanied by severe energy intake restriction (Kempen et al. 1995).

Dietary-induced weight-loss, difficult to achieve though it is, is far more effective at producing prolonged negative energy balances than exercise alone. From a meta-analysis of published studies, weight-loss using diet, exercise, or diet plus exercise was 10.7, 2.9, and 11.0 kg respectively (Miller et al. 1997). Adding a component of moderate exercise to a weight-reducing diet is generally the most effective way of achieving weight-loss (Wu et al. 2009), and especially at limiting the weight regain (Miller et al. 1997).

Table 102.3 Barriers to exercising and becoming physically active

- The obese already have physical activity levels that are similar to those of the lean
- For some obese individuals, walking costs 50% of their maximum exercise ability
- Physical exertion can be uncomfortable for people who are unfit
- People often underestimate their energy expenditure in activity and overcompensate energy intake
- The average consumer does not know how much energy they expend – they cannot measure it
- Society does not encourage increased activity in our everyday lives. Exercise is largely a segregated activity
- Exercising is seen as time-consuming and difficult to incorporate into the daily routine.

Behavioral and physiological barriers make it difficult for individuals to start to become habitually physically active

102.7 Conclusions

This chapter has considered the relationship between energy intake and expenditure.

One belief is that physical activity increases food intake by increasing hunger, thereby rendering it futile as a method of weight control. There is, however, no evidence for such an immediate or automatic effect. Indeed it is apparent that, in the short-term, only a weak coupling between the two exists and that, on average, acute changes in one do not lead to compensatory changes in the other. In the longer-term physiological changes and behavioral adaptations re-establish energy balance at a new level of energy turnover. Individual variability produces a range in the degree of response to increases or decreases in energy intake or expenditure. Pooling data and reporting the mean conceals these individual responses, which in turn undermines the examination of the processes involved in the development of weight gain and obesity. There is emerging evidence that some individuals are more resistant, and others more susceptible, to a positive energy balance and weight gain in the free-living environment. Similarly, individuals vary in their resistance (and susceptibility) to interventions intended to promote weight loss. If we are to achieve a more successful reduction in obesity, more attention should be directed at targeting individuals and identifying individual responses to energy balance interventions.

Being physically active is important in reducing the risk of developing many chronic illnesses, and is a valuable component in helping to prevent weight gain, and in maintaining weight loss.

Summary Points

- We are far less physically active than our ancestors, with the majority being so sedentary that it has pathological consequences. Sedentariness increases the risk of weight gain and obesity, and independently, the risk of developing a range of chronic illnesses such as diabetes, coronary heart disease, and some types of cancer.
- Physically active individuals are leaner and have a lower BMI than sedentary individuals. Taking up regular exercise results in weight loss or maintenance, stopping results in weight gain.
- There is a lack of physiological coupling between acute changes in energy expenditure and energy intake. We are far more tolerant of positive energy balances (overeating and being sedentary) than of negative energy balances (dieting and unaccustomed exercise). This appears to promote weight gain and resist weight loss.
- In the long-term, both increases and decreases in activity bring about physiological and behavioral changes that re-establish energy balance. Weight loss reduces the energy cost of all activity, and changes in feeding behavior increase energy intake. Sedentariness results in weight gain and consequently higher energy expenditure.
- Behavioral changes in activity resulting from decreases in energy intake are too weak, and take too long to activate, to seriously threaten dietary approaches to weight management.
- More exercise is needed to prevent weight regain after dieting than is needed to prevent weight gain in the first place. Even more is needed to achieve weight loss through exercise alone.
- Individuals vary in their ability to adjust or regulate the various components of energy balance, and therefore in their resistance to lose or gain weight in response to increases or decreases in energy expenditure respectively.

Definitions and Explanations

Energy expenditure: In healthy adults in a normal environment, total energy expenditure is the sum of:

- RMR, which is the largest component, by far, for sedentary people.
- Diet Induced Thermogenesis (DIT), which is about 10% of an ingested meal's energy and is expended in digesting and processing the food.
- Exercise or volitional physical activity usually performed for recreation, health or fitness, such as sports. This is the most variable contribution to total energy expenditure component, both between and among individuals.
- NEAT the activities of everyday living and working, and including fidgeting (Levine et al. 2000).

Exercise intensity: Moderate intensity activities use between 14.5 and 29 kJ/min and includes activities such as brisk walking and leisurely cycling. Vigorous intensity activities use >29 kJ/min, and includes jogging, swimming, and cycling uphill.

Physical activity level: To account for differences in body size and composition it is often more informative to express energy expenditure relative to minimum energy requirements. An animal at complete rest, but awake, and under standardized conditions, would have a PAL of 1.0. PAL = Total Energy Expenditure/RMR.

Resting metabolic rate: The energy needed for basic physiological functioning (maintaining ion gradients across cell membranes, breathing, pumping blood, etc.).

References

Bassuk SS, Manson JE. J Appl Physiol. 2005;99:1193–204.

Black AE, Coward WA, Cole TJ, Prentice AM. Eur J Clin Nutr. 1996;50:72–92.

Blanc S, Normand S, Ritz P, Pachiauda C, Vico L, Gharib C, Gauquelin-Koch G. J Clin Endocrinol Metab. 1998;83:4289–97.

Blundell JE, King NA. Overconsumption as a cause of weight gain: behaviour-physiological interactions in the control of food intake (appetite). The origins and consequences of obesity. In: Chadwick DJ, Cardew G, editors. Chichester: Wiley; 1996. p. 138–58.

Blundell JE, Stubbs RJ, Hughes DA, Whybrow S, King NA. Proc Nutr Soc. 2003;62:651–61.

Caudwell P, King NA, Hopkins M, Stubbs RJ, Naslund E, Blundell JE. Int J Obes. 2008;32:S24.

Cordain L, Gotshall RW, Boyd Eaton S, Boyd Eaton III S. Int J Sports Med. 1998;19:328–35.

Donnelly JE, Blair SN, Jakicic JM, Manore MM, Rankin JW, Smith BK. Med Sci Sports Exerc. 2009;41:459–71.

Doucet E, Imbeault P, St-Pierre S, Alméras N, Mauriège P, Richard D, Tremblay A. Int J Obes Relat Metab Disord. 2000;24:906–14.

Elia M, Stratton R, Stubbs RJ. Proc Nutr Soc. 2003;62:529–37.

Forbes GB, Brown MR, Welle SL, Lipinski BA. Br J Nutr. 1986;56:1–9.

Gibney ER. The physical, psychological and metabolic effects of nutritional depletion and subsequent repletion. Cambridge: University of Cambridge; 2001.

Gore SA, Foster JA, DiLillo VG, Kirk K, Smith West D. Eat Behav. 2003;4:399–405.

Haines A, McMichael T, Anderson R, Houghton J. Br Med J. 2000;321:1168–9.

Harris AM, Jensen MD, Levine JA. Obesity 2006;14:690–5.

Hill JO, Wyatt HR, Reed GW, Peters JC. Science 2003;299:853–5.

Hubert P, King NA, Blundell JE. Appetite 1998;31:9–19.

Jakicic JM, Marcus BH, Lang W, Janney C. Arch Intern Med. 2008;168:1550–9.

Jebb SA, Prentice AM. Proc Nutr Soc. 1995;54:721–8.

Jeffery RW, Rick AM. Obes Res. 2002;10:809–15.

Johnstone AM. Weight loss in human obesity. Aberdeen: University of Aberdeen; 2002.

Johnstone AM. Obes Rev. 2007;8:211–22.

Johnstone AM, Faber P, Gibney ER, Elia M, Horgan G, Golden BE, Stubbs RJ. Int J Obes. 2002;26:1623–8.

Kant AK, Schatzkin A, Graubard BI, Ballard Barbash R. Int J Obes. 1995;19:468–74.

Kempen KPG, Saris WHM, Westerterp KR. Am J Clin Nutr. 1995;62:722–9.

King NA, Tremblay A, Blundell JE. Med Sci Sports Exerc. 1997;29:1076–89.

King NA., Caudwell P, Hopkins M, Byrne NM, Colley R, Hills AP, Stubbs JR, Blundell JE. Obesity 2007;15:1373–83.

King NA, Hopkins M, Caudwell P, Stubbs RJ, Blundell JE. Int J Obes. 2008;32:177–84.

Leonard WR, Galloway VA, Ivakine E. Am J Phys Anthropol. 1997;103:443–54.

Levine JA, Eberhardt NL, Jensen MD. Science 1999;283:212–4.

Levine JA, Schleusner SJ, Jensen MD. Am J Clin Nutr. 2000;72:1451–4.

Long SJ, Hart K, Morgan LM. Br J Nutr. 2002;87:517–23.

Martinez-Gonzalez MA, Martinez JA, Hu FB, Gibney MJ, Kearney J. Int J Obes. 1999;23:1192–201.

Martins C, Truby H, Morgan LM. Br J Nutr. 2007;98:834–42.

Mayer J, Roy P, Mitra KP. Am J Clin Nutr. 1956;4:169–74.

Miller WC, Koceja DM, Hamilton EJ. Int J Obes. 1997;21:941–7.

Murgatroyd PR, Goldberg GR, Leahy FE, Gilsenan MB, Prentice AM. Int J Obes. 1999;23:1269–75.

Ogden J, Stavrinaki M, Stubbs J. Psychol Health Med. 2009;14:239–49.

Prentice AM, Jebb SA. BMJ 1995;311:437–9.

Racette SB, Schoeller DA, Kushner RF, Neil KM, Herling-Iaffaldano K. Am J Clin Nutr. 1995;61:486–91.

Ritz P, Maillet A, Blanc S, Stubbs RJ. Clin Nutr. 1999;18:203–7.

Saris WHM, van Erp-Baart MA, Brouns F, Westerterp KR, ten Hoor F. Int J Sports Med. 1989;10:S26–31.

Saris WHM, Blair SN, van Baak MA, Eaton SB, Davies PSW, Di Pietro L, Fogelholm M, Rissanen A, Schoeller D, Swinburn B, Tremblay A, Westerterp KR, Wyatt H. Obes Rev. 2003;4:101–14.

Shepard TY, Weil KM, Sharp TA, Grunwald GK, Bell ML, Hill JO, Eckel RH. Am J Clin Nutr. 2001;73:703–8.

Stubbs RJ, Johnstone AM, O'Reilly LM, Barton K, Reid C. Int J Obes. 1998;22:980–7.

Stubbs RJ, Sepp A, Hughes DA, Johnstone AM, Horgan GW, King N, Blundell J. Eur J Clin Nutr. 2002a;56:129–40.

Stubbs RJ, Sepp A, Hughes DA, Johnstone AM, King N, Horgan G, Blundell JE. Int J Obes. 2002b;26:866–9.

Stubbs RJ, Hughes DA, Johnstone AM, Horgan GW, King N, Elia M, Blundell JE. Interactions between energy intake and expenditure in the development and treatment of obesity. In: Medeiro-Neto G, Halpern A, Bouchard C, editors. Progress in obesity research 9. Surrey: John Libbey Eurotext; 2003.

Stubbs RJ, Hughes DA, Johnstone AM, Horgan GW, King N, Blundell JE. Am J Clin Nutr. 2004;79:62–9.

Temple JL, Giacomelli AM, Kent KM, Roemmich JN, Epstein LH. Am J Clin Nutr. 2007;85:355–61.

Tremblay A, Doucet E. Proc Nutr Soc. 1999;58:99–105.

Tremblay A, Despres JP, Theriault G, Fourier G, Bouchard C. Am J Clin Nutr. 1992;56:857–62.

Verger P, Lanteaume MT, Louis-Sylvestre J. Appetite 1992;18:93–9.

Warburton DER, Nicol CW, Bredin SSD. CMAJ 2006;174:801–9.

Westerterp KR. Am J Clin Nutr. 1998;68:970S–4S.

Whybrow S, Hughes DA, Ritz P, Johnstone AM, Horgan GW, King N, Blundell JE, Stubbs RJ. Br J Nutr. 2008;100:1109–15.

Williams PT, Thompson PD. Obesity 2006;14:1975–84.

Wing RR, Phelan S. Am J Clin Nutr. 2005;82(suppl):222S–5S.

Woo R, Pi-Sunyer FX. Metab Clin Exp. 1985;34:836–41.

Wu T, Gao X, Chen M, van Dam RM. Obes Rev. 2009;10:313–323.

Chapter 103
Head Injury: Metabolic, Nutritional, and Energy Considerations

Christine Charrueau, Béatrice Morio, and Christophe Moinard

Abbreviations

ATP	Adenosine triphosphate
DNA	Deoxyribonucleic acid
GCS	Glasgow coma scale
HI	Head injury
IED	Immune-enhancing diet
IGF-1	Insulin-like growth factor-1
IL1	Interleukin-1
IL6	Interleukin-6
IL8	Interleukin-8
IL10	Interleukin-10
RMR	Resting metabolic rate
RNA	Ribonucleic acid
ROS	Reactive oxygen species
Sir2α	Mammalian silent information regulator
TNF$_\alpha$	Tumor necrosis factor-α
3-MH	3-methylhistidine

103.1 Introduction

Head injury (see Table 103.1) is recognized as an important public health problem. The incidence of head injury is highly variable from one country to another but it is estimated between 100 and 200 per 100,000 populations in Western Countries. In Europe, head injury is the leading cause of death between the ages of 15 and 44 years (Menon 2009). Worldwide, about 1.5 million people die from head injury per year (more than 90% in developing countries).

C. Moinard (✉)
Laboratoire de Biologie de la Nutrition EA 4466, Faculté des Sciences Pharmaceutiques et Biologiques, Université Paris Descartes, 4 avenue de l'Observatoire 75270 Paris Cedex 06, France
e-mail: christophe.moinard@parisdescartes.fr

Table 103.1 Key features of head injury

1. Head injury is the leading cause of mortality and morbidity in young adults.
2. Head injury can result from either a physical impact (motor vehicle accident, falls, bullet impact…) or sudden acceleration (shaken baby syndrome…).
3. Clinical severity of head injury is classically assessed by the Glasgow Coma Scale which ranges from 15 (fully conscious) to 3 (near death).
4. Head injury is caused by both primary and secondary injury mechanisms.
5. Primary injury results from mechanical lesions, which can kill neurons directly (rupture of membranes), or indirectly (ischemia following brain swelling and elevated intracranial pressure).
6. Secondary injury initiated by the primary insult is the sequence of cellular, neurochemical, and metabolic alterations that continue to develop over time.
7. Head injury leads not only to cerebral lesions but also to a systemic response of hypermetabolism and hypercatabolism.

This table lists the key features of head injury

Different approaches to head injury classification have been proposed and traditionally, it has been classified using either one of the following three systems: (1) causative physical mechanism (including impact loading, inertial loading and blast), (2) clinical indexes of severity (the Glasgow Coma Scale (GCS) being the most commonly used neurologic injury severity scale), (3) assessment of structural damages by neuroimaging. More recently an alternative approach has been to classify patients by prognostic risk (Maas et al. 2008).

The primary injury of head trauma typically occurs due to direct damage to the brain (diffuse axonal injury, intracranial hematoma, intracerebral hemorrhage…). The secondary injury occurs after the principal insult and exhibits hemodynamic instability, hypercapnia, and intracerebral hypertension. This phase is rapid and interventions aim to treat cranial hypertension and surgical evacuation of hematoma and hemorrhages (Cook et al. 2008). These cerebral lesions are accompanied by a systemic metabolic response, which is due to the proinflammatory cascade subsequent to brain damage: head injury stimulates the secretion of many cytokines (TNF$_\alpha$, IL1, IL6…) and hormones (glucagon, cortisol,…) that induce profound alterations of the intermediary metabolism, promote muscle wasting, and lead to energy depletion at tissue level (Loan 1999).

Hypermetabolism and massive protein wasting compromise clinical outcome and thereby increase morbidity and mortality. Hence, it has been suggested that protein depletion contributes to the impairment of the immune system often observed in catabolic states. This dysimmunity results in an increase of septic episodes (50–75% of patients sustaining severe head injury develop infectious complications after initial hospitalization) (Quattrocchi et al. 1990). These infections are due to catheter related blood stream infection, or linked to ventilatory support and bacteremia related to gut translocation. Finally, in this population, septic episodes are responsible for 10–25% of the observed mortality. In this context, nutritional therapy can play a major role in attenuating the catabolic response and limiting the deleterious effects of prolonged hypermetabolism in head injury patients.

Animal models of head injury are essential to address pathology and/or treatment providing that the injury is controlled, reproducible, quantifiable, and clinically relevant (Cernak 2005). These models can be broadly classified as impact acceleration models, inertial acceleration models, and direct brain deformation models. The latter include fluid percussion models, mainly in rodents, which produce well-controlled levels of localized injury rather than diffuse damage (Finnie and Blumbergs 2002). Fluid percussion models are highly valuable to optimize the nutritional intervention that follows head injury since they have been demonstrated to reproduce the profound alterations of the nutritional status (Moinard et al. 2005).

103.2 Metabolic Consequences of Head Injury (Fig. 103.1)

In clinical practice, head injury patients undergo rapid weight loss, with negative nitrogen balance and enhanced whole-body protein breakdown that rapidly leads to wasting syndrome and may compromise the patients' outcome. These metabolic disturbances are related to inflammatory response and the degree of disturbances is proportional to the severity of stress.

As observed in other catabolic states, head injury exhibits hormonal changes with a large increase of counterregulatory hormones (i.e., cortisol, glucagon, and catecholamines), hyperinsulinemia (associated to insulinoresistance), and a modification of growth hormone, prolactin, and vasopressin concentrations (Cook et al. 2008). Moreover, cytokine-mediated inflammatory responses are known to play a central role after head injury. Hence, TNF_α is detectable in the first hours after trauma, and IL1 and IL6 responses have been reported to peak between 4 and 48 h. In a second phase, anti-inflammatory mediators (like IL10) are detectable several days after head injury and are maintained up to several weeks (Maegele et al. 2007). The consequence of this huge inflammation is an increase of basal metabolism and of cellular energy requirement, which may promote energy failure.

All these alterations have functional consequences at tissue level as illustrated by gastrointestinal dysfunctions. Hence, head injury patients display intolerance to enteral feedings (correlated with the severity of head injury), increase of intestinal bleeding, prolonged gastric emptying, and proximal intestinal obstruction. Moreover, head injury reduces the intestinal barrier function, most likely mediated by open tight junctions (Feighery et al. 2008). This intestinal permeability then favors bacterial translocation and dissemination, which are responsible for sepsis, the leading cause of mortality after head injury. This phenomenon is also amplified by the dysimmunity associated to head injury. Hence, in rodents, head injury induces thymus atrophy and impairment in the lymphocyte CD25 receptor density responsiveness to stimulation (CD25 antigen is the IL2 receptor) (Belabed et al. 2006). In humans, severe head injury is also associated to a suppression in early helper T-cell activation and an alteration in CD25 receptor expression on lymphocyte membranes (Quattrocchi et al. 1990). These data may explain that despite improved diagnosis and
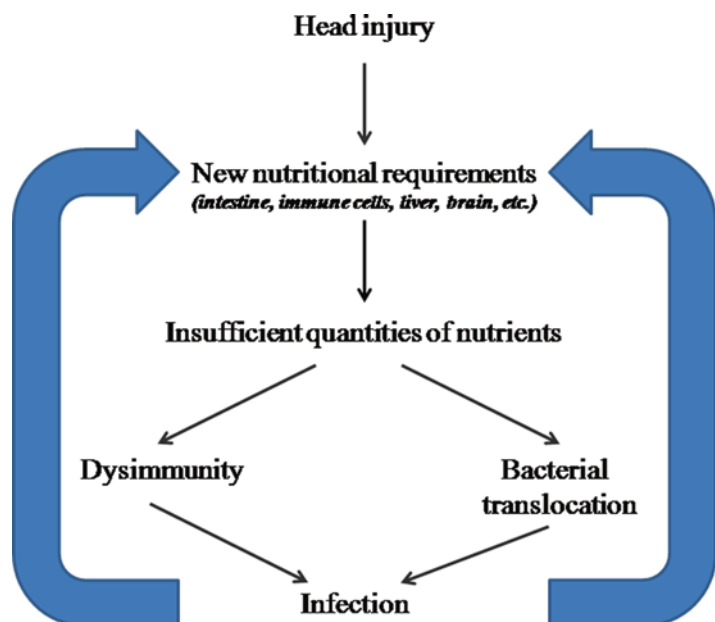
Fig. 103.1 Pathophysiology of the metabolic response following head injury. This figure represents the cascade of metabolic events, which are classically observed after traumatic brain injury: head injury is associated to denutrition, which favors dysimmunity and promotes infection

management, infection remains the most common complication in the head injury patients who survive the initial injury.

103.3 Nutritional Impairment Consecutive to Head Injury

103.3.1 Glucose Metabolism

After head injury, hyperglycemia is frequent, due to increased glucose production by the liver and overall increase in glucose flow through the extracellular compartment. As part of the acute-phase response, the elevation of counterregulatory hormones (catecholamines, glucagon, cortisol), stimulates hepatic glucose production (mainly by gluconeogenesis from amino acids), while insulin production and utilization are impaired (Loan 1999). In addition, insulin resistance is enhanced in the peripheral tissues (Fitzsimmons and Hadley 1991). Hyperglycemia is related to the severity of head injury and has detrimental effects on the neural cells through lactate accumulation and acidosis (Marie and Bralet 2009). However, insulin therapy to tightly control systemic glycemia has been associated with reduced cerebral glucose availability, increased brain energy crisis and enhanced mortality (Oddo et al. 2008).

103.3.2 Lipid Metabolism

Alterations of lipid metabolism in critically ill patients result from changes in the status of hormones and other mediators (for review see Carpentier and Scruel 2002). Fat metabolism is well known in injury and stress: since carbohydrate reserves are limited, endogenous fat progressively becomes the predominant energy source and elevated plasma concentrations of free fatty acids and glycerol following trauma illustrate the increased lipolysis (Nordenstrom et al. 1983). At brain level, deregulated lipid metabolism is of major importance in head injury, as this organ has the highest lipid concentration next to adipose tissue. Specific consequences of head injury on the lipid metabolism are little documented but a significant decrease of the whole-body lipolysis has been reported in multiple-trauma patients with severe head injury compared to multiple-trauma patients without severe head injury (Petersen et al. 1993). An aspect of lipid metabolism, i.e. apolipoprotein E and cholesterol metabolism, has held attention in head injury: indeed, apolipoprotein E is an important mediator of cholesterol and lipid transport in the brain and a novel therapeutic derived from apolipoprotein E has been shown to reduce brain inflammation and to improve outcome after closed head trauma (Adibhatla and Hatcher 2008).

103.3.3 Protein Metabolism

In clinical practice, head injury patients undergo rapid weight loss, an increase of whole-body protein synthesis and an enhanced whole-body protein breakdown. Usually, the patients exhibit a highly negative nitrogen balance due to an inappropriate activation of muscular proteolysis (as shown by enhanced urinary 3-methylhistidine (3-MH) excretion, which is an index of myofibrillar proteolysis). Mansoor et al. (1996) have determined the effect of head injury on the intracellular proteolytic

systems in the mammalian skeletal muscle (the lysosomal pathway, responsible for the soluble and extracellular protein degradation; the Ca^{2+}-dependent proteinases (calpains) responsible for the catabolism of cytoskeletal proteins and the ATP-ubiquitin-dependent pathway, which catalyzes the selective breakdown of the myofibrillar proteins). According to the literature, skeletal muscle myofibrillar protein breakdown has been confirmed to increase in head injury patients. Using muscular biopsies, authors have demonstrated that these metabolic adaptations correlate with enhanced expression of critical components of the lysosomal, Ca^{2+}-dependent, and ATP ubiquitin-dependent proteolytic pathways. Moreover, the mRNA levels for several proteinases or cofactors involved in protein breakdown are also increased (Table 103.2). This massive muscle proteolysis during the initial phase of injury allows the release of muscular amino acids used for inflammatory protein synthesis in the liver, for gluconeogenesis and as energy substrates (i.e., immune cells, enterocytes). In some patients, muscle weakness is so great that ventilation is inadequate to overcome the respiratory insufficiency associated with trauma. The consequence of this protein wasting is an increase in morbidity and mortality (Table 103.3).

Concerning the modification of protein synthesis in head injury patients, whole-body protein metabolism was assessed 48 h after head injury, and was found to have increased (Mansoor et al. 1997). However, this result is different according to the tissue considered: it was largely decreased in muscles whereas hepatic synthesis of fibrinogen (a positive acute-phase protein) was largely increased (Mansoor et al. 1997). In conclusion, these metabolic adaptations of protein metabolism can be considered as necessary for the liver to be supplied with large amounts of amino acids for sustaining the acute-phase hepatic response and gluconeogenesis; the amino acids are derived from increased protein breakdown and decreased protein synthesis in muscle.

Table 103.2 Protein turnover and muscle proteolytic pathways in control and head injury patients (Adapted and reprinted from Mansoor et al. 1996. Copyright 2009 by Proc Natl Acad Sci USA. With permission)

	Control	Head Trauma	p
Whole-body protein turnover (μmol/kg/min)	2.36 ± 0.15	3.52 ± 0.10	<0.01
Whole-body protein breakdown (μmol/kg/min)	1.38 ± 0.15	2.51 ± 0.09	<0.01
3-MH urinary excretion (μmol/kg/day)	3.40 ± 0.58	6.98 ± 0.08	<0.01
Muscle proteasome subunits mRNA (expressed as % of the control value)			
Ubiquitin	100%	225%	<0.05
14-kDa E2	100%	205%	<0.05
HC2 subunit	100%	271%	<0.05
HC8 subunit	100%	213%	<0.05

Whole-body protein kinetics and 3-methylhistidine (3-MH, myofibrillar protein breakdown marker) were determined in head injury patients (day 8 after trauma) and in control subjects

mRNA of ubiquitin, 14-kDa E2, and the proteasome HC2 and HC8 subunits were determined in *vastus lateralis* muscle biopsies from head trauma patients and control subjects. Mean ± SEM

Table 103.3 Consequences of protein deficiency at tissue level in head injury patients

Tissues	Complications
Skin	Delay of wound healing
Muscles	Wasting syndrome
Respiratory muscles	Respiratory insufficiency
Immune cells	Dysimmunity

Protein deficiency in head injury patients results in specific complications

103.3.4 Other Nutrients

Trauma patients have abnormal vitamin and trace element losses linked to their pathology. The metabolic consequences of head injury are characterized by an increase in specific micronutrient requirements. A zinc deficiency is observed in the blood following head injury while the excretion of zinc is increased in the urine (McClain et al. 1986). At brain level, the translocation of zinc from the presynaptic boutons to postsynaptic somata is a contributing factor that controls the death or survival of neurons after head injury. This is why zinc chelators are considered for neuroprotection after traumatic brain injury (Suh et al. 2000). Magnesium concentrations are altered following head injury and patients with low serum magnesium level (<1.3 mEq/L) and high cerebrospinal fluid magnesium level are most likely to have poor outcome after severe head injury (Stippler et al. 2007). Plasma selenium and vitamin E, recognized as antioxidant agents, are also depleted in the early period following experimental head injury (Kiymaz et al. 2007). In humans with moderate-to-severe head injury, plasma vitamin E levels are severely depressed on hospital admission and the second day after trauma (Braughler and Hall 1992).

103.4 Energy Metabolism Following Head Injury

103.4.1 Total Energy Expenditure

It is well known that traumatic injury causes hypermetabolism and hypercatabolism. Hypermetabolism is characterized by increased oxygen consumption, i.e. enhanced energy expenditure as measured by increased resting metabolic rate (RMR) (Table 103.4). The occurrence of hypermetabolism after trauma and injury has been investigated for almost a century and is well documented (for review see Frankenfield 2006). The degree of hypermetabolism is inversely correlated, although not in a linear fashion, with the score on the GCS that ranges from 15 (fully conscious) to 3 (near death) (Frankenfield 2006). RMR of head injury patients increases by 40–200% compared to healthy subjects (for review see Frankenfield 2006), the highest level being observed in patients with decerebrate/decorticate activity (Frankenfield 2006). The degree of elevation of energy expenditure after head injury has been shown to correlate with intracranial pressure (Bucci et al. 1988), muscle tone, and contraction (Robertson et al. 1984). It is also related to body temperature depending on GCS score. At score 4–5, RMR increased by 45% for each degree centigrade rise in body temperature but increased only 15% when GCS score was 6–7. No relationship was found between body temperature and RMR for GCS score higher than 8 (Robertson et al. 1984). Energy expenditure is reduced by sedative treatment; especially in barbiturate coma, it can be depressed

Table 103.4 Modification of energy expenditure according to the catabolic state considered

Pathology	Energy expenditure
Postoperative	+ 0–10%
Long bone fracture	+15–30%
Severe head trauma	**+25–55%**
Sepsis	+50–70%
Burn (20% of body surface)	+50%
Burn (70% of body surface)	+110%

Depending on the pathology considered, the level of hypercatabolism leads to increased energy expenditure

to a level lower than the RMR of healthy subjects (Dempsey et al. 1985). Several other medications can also reduce RMR. The most common ones are central nervous system agents (sedatives, analgesics, narcotics, hypnotics), autonomic agents (neuromuscular blocking agent), and cardiovascular agents (beta-adrenergic receptor antagonists) (for review see Dickerson and Roth-Yousey 2005).

103.4.2 Brain (Fig. 103.2)

The brain is the organ with the greatest oxygen consumption, contributing to 20% of the whole-body energy expenditure. Most of the energy is used by the neurons. Although glial cells account for almost half of the brain volume, they have a much lower metabolic rate and account for less than 10% of brain energy expenditure (Siesjo 1984). Fifty percent of the energy produced by the brain is required for synaptic activity; 25% is used for maintaining ionic gradients across cell membranes; the remaining energy is used for other processes necessary for cell functioning, such as macromolecule synthesis.

Brain cells must be continuously supplied with oxygen and glucose to produce the required energy. ATP is produced through aerobic metabolism, which involves the oxidative phosphorylation carried out by the mitochondria. Continuous cerebral blood flow, cerebral oxygen tension and delivery, and normal mitochondrial function are therefore of vital importance for the maintenance of brain function and tissue viability (for review see Verweij et al. 2007). If one or several parameters are altered, neuronal events and functional deficits occur.

Brain ischemia and hypoxia have been shown to be the most significant predictors of poor outcome in head injury (Verweij et al. 2007). As a main energy supplier, mitochondria are very sensitive
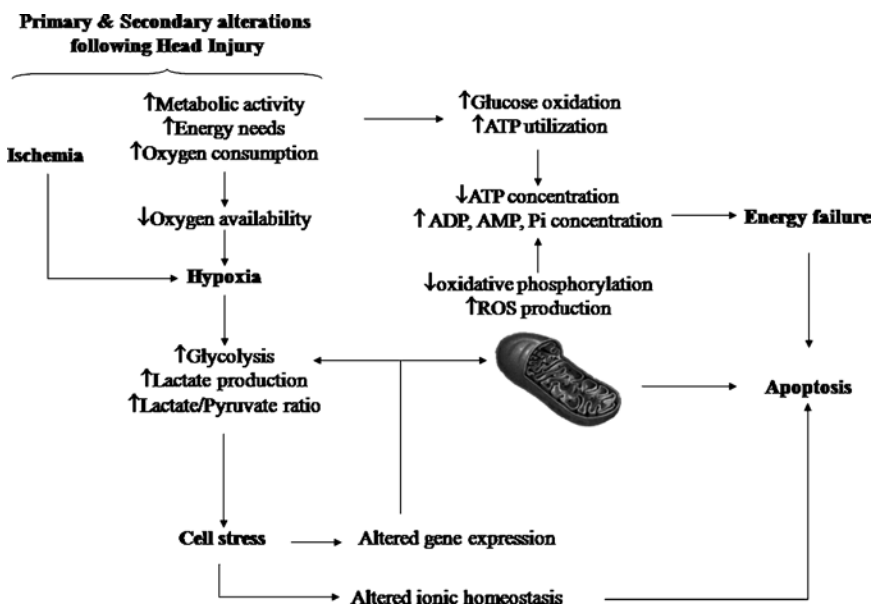
Fig. 103.2 Effect of head injury on cerebral energy homeostasis. Primary and secondary alterations following head injury induce energy consumption at the cerebral level, impairment of mitochondrial function, and finally induce neuronal apoptosis

to ischemia and hypoxia. Studies showed that mitochondria first positively adapt to head injury by enhancing ATP production in order to meet enhanced energy requirement (Vink et al. 1994). However, rapid detrimental effects of head injury on these organelles have been extensively documented (Dai et al. 2009). Mitochondrial alterations, which are characteristic of cerebral ischemia, result in reduced mitochondrial oxygen consumption (Levasseur et al. 2000) and depressed intracellular ATP level (Vagnozzi et al. 2005). Altered mitochondrial gene expression (Matzilevich et al. 2002) and reduced metabolic enzyme activity (Harris et al. 2001) have been reported a few hours after head injury. However, anaerobic glycolysis may compensate for oxidative phosphorylation deficiency (Matzilevich et al. 2002) and this is evidenced by increased production of lactate and increased lactate/pyruvate ratio (Hartley et al. 2008). This is also associated with decreased glucose availability (Stahl et al. 2001).

As it is intrinsically associated to alterations in energy metabolism, head injury promotes brain cell death through the induction of apoptotic pathways. Indeed, head injury is associated with intense intracellular ionic shifts (Hayes et al. 1992), compromised mitochondrial membrane potential (Ahmed et al. 2000), and enhanced production of reactive oxygen species (ROS) (Sullivan et al. 1999). Increased ROS production has been demonstrated directly and indirectly by lipid peroxidation and nucleic acid oxidation. Excess ROS production can oxidize macromolecules such as proteins, lipids, and DNA, the result being altered cell functioning. It may promote mitochondrial permeability transition pore opening and the release of proapoptotic proteins (Soustiel et al. 2008), thus inducing cell death. Finally, cell apoptosis may also be promoted by damage to the endoplasmic reticulum, which alters intracellular calcium buffering (Paschen and Doutheil 1999), enhancing glutamate concentration that activates *N*-methyl-d-aspartate receptors. This contributes to sustained pathological accumulation of calcium in brain-injured regions (Osteen et al. 2004).

103.4.3 Liver

Substantial alterations in liver energy metabolism have been observed as a consequence of secondary brain injury. Depletion of ATP and glycogen hepatic content has been reported, which demonstrates the development of distant organ failure (Moinard et al. 2008). These alterations are the result of a stress-induced impairment in liver energy metabolism. Depletion of ATP and glycogen content in the liver is an effect that may be related to head injury-induced anorexia or to head injury *per se*, or even both. Moinard et al. (2008) showed in rats that enteral nutrition was not able to restore hepatic ATP and glycogen content in head injury, thus demonstrating that anorexia is not the cause of energy depletion. Moreover, these authors underlined that head injury induced localized liver inflammation as assessed by histological examination (i.e., immune cell infiltration, edema, fibrosis, and necrosis). One may hypothesize that abnormal oxygen use, organ failure, or increased inflammatory response in the critically ill may impact on the mitochondrial function. Although energy requirements are strongly elevated in hypercatabolic situations, the measurement of mitochondrial and glycolytic enzyme activities showed that the oxidative capacity of the liver was not modified in head injury and enterally fed head injury rats. Therefore, if mitochondrial oxidative activity is not impaired after head injury, it cannot be excluded that the liver is not able to enhance mitochondrial energy production in order to respond to huge energy requirements and that an impairment of energy synthesis is occurring. Mitochondrial oxidative phosphorylation uncoupling may also occur. A decline in the mitochondrial membrane potential could also explain a reduction in ATP production and a decrease in intracellular ATP availability.

103.5 Nutritional Intervention

As research on potential treatments of head injury patients has progressed, more emphasis has been placed on determining the most appropriate nutritional intervention (Table 103.5). Nutritional management of head injury patients is challenging because of the extensive alterations in metabolic responses, immunity and the gastrointestinal function. The nutritional intervention following head injury has three aims: first, to prevent the loss of fat-free mass; second, to modulate the immune response; third, to promote gastrointestinal structure and function. In addition, the nutritional support may also improve neurological outcome to some extent.

The latest Cochrane review on nutritional support for head injury patients indicates that early feeding may be associated with fewer infections and a trend toward a better outcome in terms of survival and disability. However, the randomized–controlled trials included to determine the best

Table 103.5 Examples of beneficial effects of nutritional intervention in head injury

Diet/Nutrient	Route	Subject	Benefit	References
Carbohydrate-free diet	Enteral	Severely HI adults	↗ nitrogen balance without hyperglycemia	Ritter et al. (1996)
Creatin	*Per os*	HI children, adolescents	↗ clinical outcome	Sakellaris et al. (2006)
Glutamine + probiotics	Enteral	HI adults	↘ infection rate and ICU length of stay	Falcao de Arruda (2004)
IED (Stresson®)	Enteral	Severely HI children	↗ nitrogen balance	Briassoulis et al. (2006)
IED (Stresson®)	Enteral	Severely HI children	↘ IL8 level and gastric colonization	Briassoulis et al. (2005)
IED (Stresson®)	Enteral	Moderate HI in rats	↘ mucosal atrophy and bacterial translocation	Aydin et al. (2005)
IED (Crucial®)	Enteral	Moderate HI in rats	↗ thymus weight and stimulation of lymphocytes	Belabed (2006)
IED (Crucial®)	Enteral	Moderate HI in rats	↗ glutamine pools	Moinard (2006)
IGF-1	Enteral/ Parenteral	Severely HI adults	↗ nitrogen balance and survival	Hatton (1993, 1997)
IGF-1	Parenteral	Moderate–severe HI adults	↗ CD4/CD8 ratio	Hatton (1997)
IGF-1	s.c.	HI rats	↘ neurologic motor and cognitive outcome	Saatman et al. (1997)
L-arginine	Enteral	Moderate HI in rats	↗ cerebral blood flow	Dewitt et al. (1997)
Magnesium	i.v.	HI rats	↘ brain edema and neurologic impairments	Bareyre et al. (1999)
N-acetylcysteine	i.p.	HI rats	↘ cerebral inflammation	Chen et al. (2008)
Nicotinamide	i.p.	HI rats	Neuroprotection	Holland et al. (2008)
Omega-3 PUFAs	*Per os*	HI rats	Neuroprotection	Wu et al. (2007)
Zinc	Parenteral/ *Per os*	Severely HI adults	↗ GCS score	Young et al. (1996)

Experimental and clinical studies show that nutrition by itself and supplementation with specific nutrients can favorably influence outcome after head injury (HI)

i.p. intraperitoneal, *s.c.* subcutaneous, *i.v.* intravenous, *ICU* intensive care unit, *GCS* Glasgow coma scale, *PUFAs* polyunsaturated fatty acids

also been tested in clinical settings. The enrichment of an enteral diet with a combination of glutamine (to improve the nutrition of both the gut mucosa and immune cells) and probiotic bacteria (to favorably alter the intraluminal environment and compete with pathogenic bacteria) decreased the infection rate and shortened the stay in intensive care unit of head injury patients (Falcao de Arruda and Aguilar-Nascimento 2004). In children with severe head injury, immunonutrition significantly lowered IL8 levels and gastric colonization, but had no additional advantages over a standard enteral nutrition in terms of nosocomial infections, length of stay, length of mechanical ventilation, and survival (Briassoulis et al. 2006). It is still difficult to conclude on the efficacy of immunonutrition since the qualitative and quantitative composition of the commercialized IEDs is highly variable. Despite promising effects, IEDs are still not recognized as standard care and the best composition of an IED adapted to head injury patients remains to be determined.

103.5.3 Promotion of the Gastrointestinal Function

An increase in gut permeability, which is correlated with the severity of injury, is observed in head injury patients (Faries et al. 1998). It is generally recognized that the presence of enteral nutrients promotes mucosal health, maintains the intestinal absorption capacity, and preserves the gastrointestinal barrier function, better than the parenteral nutrition does (Suchner et al. 1996). Experimental data in head injury rats support the fact that immunonutrition significantly lowers intestinal apoptosis, mucosal atrophy, and bacterial translocation especially when it is implemented early following head injury (Aydin et al. 2005).

103.5.4 Improvement of Neurological Outcome

Nutrition by itself can favorably influence neurological recovery and better neurologic outcomes have generally been seen in the head injury patients who received the earliest and largest amounts of nutrients (Wilson et al. 2001).

In addition, the supplementation of head injury patients with specific nutrients may further improve neurological outcome. Hence, supplementation of patients suffering severe closed head injury with zinc during the immediate postinjury period led to significant improvement in GCS score (Young et al. 1996). The creatine kinase/phosphocreatine system exerts a central role in cellular bioenergetics, especially in neurons that are characterized by high and fluctuating energy requirements (Andres et al. 2008). In a prospective randomized study in children and adolescents suffering from head injury, administration of creatine (or *N*-aminoiminomethyl-*N*-methylglycine) significantly improved the clinical outcome in cognitive, personality/behavior, self-care, and communication aspects (Sakellaris et al. 2006).

Experimentally, magnesium appears to protect against neurological deficits after head injury by its effects on glycolysis, oxidative phosphorylation, and synthesis of DNA, RNA, and proteins (McIntosh et al. 1989). Magnesium administration has been shown to decrease brain edema and early neurologic severity score (Feldman et al. 1996) as well as delayed post-traumatic neurologic impairments in head injury rats (Bareyre et al. 1999). However, the issue of magnesium neuroprotection in humans with head injury has not been resolved yet and needs further investigations. Consistent with some negative preclinical studies, a recent clinical trial has shown that magnesium treatment did not improve outcome and may be harmful in some cases (Temkin et al. 2007). The decrease in

cerebral blood flow usually observed after head injury could be prevented by the enteral administration of L-arginine (Dewitt et al. 1997). IGF-1 has been shown to improve both neurologic motor and cognitive outcomes following experimental head injury in the rat (Saatman et al. 1997). Preclinical studies have demonstrated the strong neuroprotective abilities of nicotinamide or vitamin B3 in the injured brain and suggest that this nutrient may have therapeutic potential for head injury treatment (Holland et al. 2008). Head injury reduces mammalian silent information regulator (Sir2α) expression in the hippocampus, a cerebral region implicated in synaptic plasticity, learning and memory, in proportion to increased levels of protein oxidation. This reduction may increase the susceptibility of neurons to secondary damages. Dietary supplementation of omega-3 polyunsaturated fatty acids is effective to normalize levels of Sir2α, which are essential to maintain the cellular homeostasis required for neural plasticity following head injury (Wu et al. 2007). Finally, the secondary damages that occur in the brain following head injury can be attributed to three mechanisms that lead to neuronal death, i.e. glutamate excitotoxicity, Ca^{2+} overload, and oxidative stress. Some authors have suggested that decreasing oxidative stress would minimize the amount of secondary damage due to trauma. For that purpose, aggressive nutritional support may contribute to maximizing antioxidant defenses. Cysteine precursors such as *N*-acetylcysteine could be used to maintain the level of reduced glutathione, which plays a central role in scavenging peroxides (Chen et al. 2008). Flavonoids such as quercetin could be employed for their radical quenching, iron chelating, and anti-inflammatory properties (Juurlink and Paterson 1998).

103.6 Conclusion

For several decades, research in the management of head injury patients has focused on therapies aiming to preserve cerebral functions. A large number of randomized trials on neuroprotective intervention have been carried out. However, a significant part of delayed mortality does not result from initial cerebral lesions. It is caused by extensive adaptation at the systemic level such as inflammatory cascade, hypermetabolism, debilitation leading to dysimmunity. The latter ultimately triggers infections and compromises patients' outcome. In this context, nutritional management is clearly of major importance. Nonetheless, due to the lack of robust randomized–controlled trials aiming to demonstrate the clinical benefits of nutrition in head injury, consensual recommendations have not yet been stated.

Summary Points

- Head injury induces a protein wasting that contributes to the impairment of the immune system. This dysimmunity results in an increase of septic episodes, which compromise clinical outcome and thereby increase morbidity and mortality.
- Head injury is recognized to induce major gastrointestinal dysfunction including intolerance to enteral feeding, prolonged gastric emptying, increase of intestinal bleeding, and proximal intestinal obstruction.
- Head injury profoundly affects the liver function, in particular energy homeostasis (i.e., depletion of ATP and glycogen contents) and induces cellular inflammation (i.e., immune cell infiltration, edema, fibrosis, and necrosis).
- Head injury rapidly and deeply alters brain energy metabolism around the injured tissue. This is characterized by hypermetabolism, which can lead to cell death due to energy failure. Secondary

brain damages can also be caused by compensatory mechanisms that lead to increased intracranial pressure and hyperoxia in noninjured brain regions.

- The rationale for nutritional intervention following head injury is: (1) to prevent the wasting syndrome, (2) to restore the immune response, (3) to preserve the gastrointestinal function, and (4) to improve the neurological outcome.
- Nutrition by itself can favorably influence neurological recovery and better neurologic outcomes have generally been seen in the head injury patients who received the earliest and largest amounts of nutrients.
- Despite interesting experimental and clinical data, there are no sufficient clinical trials at present to make some nutritional recommendations in head injury patients (except that enteral nutrition is considered as the preferred way of feeding critically ill patients).

Definitions of Key Terms

Artificial nutrition: A therapy that prevents the deleterious effects of starvation in patients not fulfilling their nutritional requirements. It includes enteral nutrition administered in the digestive tract and parenteral nutrition, which is provided by the intravenous route.

Immune-enhancing diets: Specific enteral mixtures containing nutrients (i.e. arginine, glutamine, taurine, ω3 polyunsaturated fatty acids, messenger RNA, and certain vitamins and trace elements) able to modulate the immune response to stress.

Resistance to renutrition: The fact that malnutrition persists despite a nutrition covering the basal nutritional requirements.

Bacterial translocation and dissemination: Bacterial translocation corresponds to the passage of bacteria from the gastrointestinal tract to mesenteric lymph nodes. Subsequent dissemination may occur in other internal organs (i.e. lung, liver, spleen, etc.).

Wasting syndrome: This syndrome is characterized by rapid weight loss, negative nitrogen balance, and loss of lean body mass. In some patients, muscle weakness is so great that ventilation is inadequate to overcome the respiratory insufficiency associated with trauma. The consequence is an increase in morbidity and mortality.

References

Adibhatla RM, Hatcher JF. Subcell Biochem. 2008; 48:410–4.

Ahmed SM, Rzigalinski BA, Willoughby KA, Sitterding HA, Ellis EF. J Neurochem. 2000; 74:1951–60.

Andres RH, Ducray AD, Schlattner U, Wallimann T, Widmer HR. Brain Res Bull. 2008; 76:329–43.

Aydin S, Ulusoy H, Usul H, Yulug E, Cobanoglu U, Aydin K, Yenilmez E, Kutun S. Surg Today. 2005; 35:751–9.

Bareyre FM, Saatman KE, Helfaer MA, Sinson G, Weisser JD, Brown AL, McIntosh TK. J Neurochem. 1999; 73:271–80.

Belabed L, Charrueau C, Besson V, Gupta S, Walrand S, Marchand-Verrecchia C, Richon S, Nafziger J, Plotkine M, Chaumeil JC, Cynober L, Moinard C. Clin Nutr. 2006; 25:832–41.

Braughler JM, Hall ED. J Neurotrauma. 1992; 9 Suppl 1:S1–7.

Briassoulis G, Filippou O, Hatzi E, Papassotiriou I, Hatzis T. Nutrition. 2005; 21:799–807.

Briassoulis G, Filippou O, Kanariou M, Papassotiriou I, Hatzis T. Pediatr Crit Care Med. 2006; 7:56–62.

Bucci MN, Dechert RE, Arnoldi DK, Campbell J, McGillicuddy JE, Bartlett RH. Acta Neurochir (Wien). 1988; 93:133–6.

Carpentier YA, Scruel O. Curr Opin Clin Nutr Metab Care. 2002; 5:153–8.

Cernak I. NeuroRx. 2005; 2:410–22.

Chen G, Shi J, Hu Z, Hang C. Mediators Inflamm. 2008: ID716458 (8 pages).

Cook AM, Peppard A, Magnuson B. Nutr Clin Pract. 2008; 23:608–20.

Dai W, Cheng HL, Huang RQ, Zhuang Z, Shi JX. Brain Res. 2009; 1251:287–95.

Dempsey DT, Guenter P, Mullen JL, Fairman R, Crosby LO, Spielman G, Gennarelli T. Surg Gynecol Obstet. 1985; 160:128–34.

Dewitt DS, Smith TG, Deyo DJ, Miller KR, Uchida T, Prough DS. J Neurotrauma. 1997; 14:223–33.

Dickerson RN, Roth-Yousey L. J Am Diet Assoc. 2005; 105:835–43.

Falcao de Arruda, I, Aguilar-Nascimento JE. Clin Sci (Lond). 2004; 106:287–92.

Faries PL, Simon RJ, Martella AT, Lee MJ, Machiedo GW. J Trauma. 1998; 44:1031–5.

Feighery L, Smyth A, Keely S, Baird AW, O'Connor WT, Callanan JJ, Brayden DJ. J Trauma. 2008; 64:131–7.

Feldman Z, Gurevitch B, Artru AA, Oppenheim A, Shohami E, Reichenthal E, Shapira Y. J Neurosurg. 1996; 85:131–7.

Finnie JW, Blumbergs PC. Vet Pathol. 2002; 39:679–89.

Fitzsimmons L, Hadley SA. Dimens Crit Care Nurs. 1991; 10:4–12.

Frankenfield D. Nutr Clin Pract. 2006; 21:430–7.

Harris LK, Black RT, Golden KM, Reeves TM, Povlishock JT, Phillips LL. J Neurotrauma. 2001; 18:993–1009.

Hartley CE, Varma M, Fischer JP, Riccardi R, Strauss JA, Shah S, Zhang S, Yang ZJ. J Neurosurg. 2008; 109:708–14.

Hatton J, Luer MS, Rapp RP. Pharmacotherapy. 1993; 13:17–27.

Hatton J, Rapp RP, Kudsk KA, Brown RO, Luer MS, Bukar JG, Chen SA, McClain CJ, Gesundheit N, Dempsey RJ, Young B. J Neurosurg. 1997; 86:779–86.

Hayes RL, Jenkins LW, Lyeth BG. J Neurotrauma. 1992; 9 Suppl 1:S173–87.

Holland MA, Tan AA, Smith DC, Hoane MR. J Neurotrauma. 2008; 25 1:40–52.

Juurlink BH, Paterson PG. J Spinal Cord Med. 1998; 21:309–34.

Kiymaz N, Ekin S, Yilmaz N. Surg Neurol. 2007; 68:67–70.

Levasseur JE, Alessandri B, Reinert M, Bullock R, Kontos HA. J Neurotrauma. 2000; 17:101–12.

Loan T. Nutrition. 1999; 15:809–12.

Maas AI, Stocchetti N, Bullock R. Lancet Neurol. 2008; 7:728–41.

Maegele M, Sauerland S, Bouillon B, Schafer U, Trubel H, Riess P, Neugebauer EA. Inflamm Res. 2007; 56:318–23.

Mansoor O, Beaufrere B, Boirie Y, Ralliere C, Taillandier D, Aurousseau E, Schoeffler P, Arnal M, Attaix D. Proc Natl Acad Sci USA. 1996; 93:2714–8.

Mansoor O, Cayol M, Gachon P, Boirie Y, Schoeffler P, Obled C, Beaufrère B. Am J Physiol. 1997; 273:E898–902.

Marie C, Bralet J. Cerebrovasc Brain Metab Rev. 2009; 3:29–38.

Matzilevich DA, Rall JM, Moore AN, Grill RJ, Dash PK. J Neurosci Res. 2002; 67:646–63.

McClain CJ, Twyman DL, Ott LG, Rapp RP, Tibbs PA, Norton JA, Kasarskis EJ, Dempsey RJ, Young B. J Neurosurg. 1986; 64:224–30.

McIntosh TK, Vink R, Yamakami I, Faden AI. Brain Res. 1989; 482:252–60.

Menon DK. Crit Care Med. 2009; 37:S129–35.

Moinard C, Belabed L, Gupta S, Besson V, Marchand-Verrecchia C, Chaumeil JC, Cynober L, Charrueau C. Nutrition. 2006; 22:1039–44.

Moinard C, Gupta S, Besson V, Morio B, Marchand-Leroux C, Chaumeil JC, Cynober L, Charrueau C. J Neurotrauma. 2008; 25:124–9.

Moinard C, Neveux N, Royo N, Genthon C, Marchand-Verrecchia C, Plotkine M, Cynober L. Intensive Care Med. 2005; 31:281–8.

Nordenstrom J, Carpentier YA, Askanazi J, Robin AP, Elwyn DH, Hensle TW, Kinney JM. Ann Surg. 1983; 198:725–35.

Oddo M, Schmidt JM, Carrera E, Badjatia N, Connolly ES, Presciutti M, Ostapkovich ND, Levine JM, Le Roux P, Mayer SA. Crit Care Med. 2008; 36:3233–8.

Osteen CL, Giza CC, Hovda DA. Neuroscience. 2004; 128:305–22.

Paschen W, Doutheil J. J Cereb Blood Flow Metab. 1999; 19:1–18.

Perel P, Yanagawa T, Bunn F, Roberts I, Wentz R, Pierro A. Cochrane Database Syst Rev. 2006; Issue 4. Art. No.: CD001530. DOI: 10.1002/14651858.CD001530.pub2.

Petersen SR, Jeevanandam M, Harrington T. J Trauma. 1993; 34:653–61.

Quattrocchi KB, Frank EH, Miller CH, MacDermott JPA, Hein L, Frey, Wagner FC. J Neurotrauma. 1990; 7:77–87.

Ritter AM, Robertson CS, Goodman JC, Contant CF, Grossman RG. J Neurotrauma. 1996; 13:473–85.

Robertson CS, Clifton GL, Grossman RG. Neurosurgery. 1984; 15:307–14.

Saatman KE, Contreras PC, Smith DH, Raghupathi R, McDermott KL, Fernandez SC, Sanderson KL, Voddi M, McIntosh TK. Exp Neurol. 1997; 147:418–27.

Sacks GS, Brown RO, Teague D, Dickerson RN, Tolley EA, Kudsk KA. J Parent Ent Nutr. 1995; 19:387–92.

Sakellaris G, Kotsiou M, Tamiolaki M, Kalostos G, Tsapaki E, Spanaki M, Spilioti M, Charissis G, Evangeliou A. J Trauma. 2006; 61:322–9.

Siesjo BK. J Neurosurg. 1984; 60:883–908.

Soustiel JF, Zaaroor M, Vlodavsky E, Veenman L, Weizman A, Gavish M. Exp Neurol. 2008; 214:201–8.

Stahl N, Mellergard P, Hallstrom A, Ungerstedt U, Nordstrom CH. Acta Anaesthesiol Scand. 2001; 45:977–85.

Stippler M, Fischer MR, Puccio AM, Wisniewski SR, Carson-Walter EB, Dixon CE, Walter KA. J Neurotrauma. 2007; 24:1347–54.

Suchner U, Senftleben U, Eckart T, Scholz MR, Beck K, Murr R, Enzenbach R, Peter K. Nutrition. 1996; 12:13–22.

Suh SW, Chen JW, Motamedi M, Bell B, Listiak K, Pons NF, Danscher G, Frederickson CJ. Brain Res. 2000; 852:268–73.

Sullivan PG, Thompson MB, Scheff SW. Exp Neurol. 1999; 160:226–34.

Temkin NR, Anderson GD, Winn HR, Ellenbogen RG, Britz GW, Schuster J, Lucas T, Newell DW, Mansfield PN, Machamer JE, Barber J, Dikmen SS. Lancet Neurol. 2007; 6:29–38.

Vagnozzi R, Signoretti S, Tavazzi B, Cimatti M, Amorini AM, Donzelli S, Delfini R, Lazzarino G. Neurosurgery. 2005; 57:164–71.

Verweij BH, Amelink GJ, Muizelaar JP. Prog Brain Res. 2007; 161:111–24.

Vink R, Golding EM, Headrick JP. J Neurotrauma. 1994; 11:265–74.

Wilson RF, Dente C, Tyburski JG. Neurol Res. 2001; 23:121–8.

Wu A, Ying Z, Gomez-Pinilla F. J Neurotrauma. 2007; 24:1587–95.

Young B, Ott L, Kasarskis E, Rapp R, Moles K, Dempsey RJ, Tibbs PA, Kryscio R, McClain C. J Neurotrauma. 1996; 13:25–34.

Chapter 104
Behavioral Consequences of Force-feeding

Malgorzata Starzomska and Marek Smulczyk

Motto
The Good Samaritan deserves sympathetic support, officious intermeddling must be
discouraged

(Anon. 1974).

Abbreviation

DSM-IV-TR   Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text
             Revision

104.1 Introduction

Food refusal may occur for a variety of reasons. For example, it may be used as a method of exercising control over others (either at family or society level), as a method of self-harm, or even as a way of committing suicide. It is sometimes a symptom of mental illness. Thus, management of self-starvation depends on the motivation behind it, and consequently, on specification of the extent to which incompetence influences the decision to refuse food. Forcible feeding is the most frequent behavioral intervention in the case of severely emaciated individuals but is it the only way in which they can be helped? Clearly, each case is very specific but it is important to try to analyze the unique character of food refusal and the difficulties involved in forcible feeding of emaciated individuals, at least on several examples. The author has chosen hunger strikes and anorexia nervosa to illustrate, among other things, the consequences of forcible feeding and the practical implications for therapy.

M. Starzomska (✉)
The Maria Grzegorzewska Academy of Special Education, Institute of Applied Psychology,
40 Szczesliwicka Street, 02-353 Warsaw, Poland
e-mail: eltram@life.pl

104.2 Forcible Feeding Under Existing Regulations of the Mental Health Act

Force-feeding can take the form of either oral refeeding, by which it is understood that the patient is effectively pressurized into feeding himself or herself, or tube feeding (Draper 2000). Some clinicians also apply nocturnal nasogastric refeeding (inserting a plastic tube through the nostril to the stomach to feed anorexics with a fluid diet) (Robb et al. 2002). Each forced treatment is a difficult situation for the patient, the patient's family, and the hospital staff; however, it is sometimes essential if a patient's life is to be saved (Melamed et al. 2003). Such intervention is usually undertaken within compulsory treatment. It must be underlined that any patient assessed for compulsory, and in the case of food refusal, forcible feeding, must be diagnosed not only with a mental disorder per se but also with a mental disorder with symptoms that support involuntary intervention (Brockman 1999). The key question in this case is testifying to the patient's competence (capacity), namely his or her ability to make informed decisions. Capacity (which is the equivalent of competence) (Tan et al. 2003a) is a very important issue with respect to treatment consent and refusal; it derives from the premise that the ability to decide about one's medical condition, irrespective of how imperfect or inaccurate that judgment might be, constitutes a fundamental human and legal right. Similarly, administering treatment against a patient's conscious and direct will is ethically dubious, even if not legally (Tan et al. 2003b). Nowadays, the capacity-centered approach is common in legal systems (Tan et al. 2003b). Therefore, a patient who is competent to make decisions may not be treated – and this includes artificial feeding – against his or her will (Dyer 2000).[1] It is important to remember that presence of a mental disorder does not always imply incompetence. The criteria for compulsory treatment are defined in the Review of the Mental Health Act (1999) and are shown in Table 104.1.

Table 104.1 The criteria for compulsory treatment

According to Review of the Mental Health Act 1983

"5.95. Before confirming a compulsory order the tribunal would have to be satisfied as to the following:

i. the presence of mental disorder which is of such seriousness that the patient requires care and treatment under the supervision of specialist mental health services;

and

ii. that the care and treatment proposed for, and consequent upon, the mental disorder is the least restrictive and invasive alternative available consistent with safe and effective care;

and

iii. that the proposed care and treatment is in the patient's best interests;

and, either

iv. that, in the case of a patient who lacks capacity to consent to care and treatment for mental disorder, it is necessary for the health or safety of the patient or for the protection of others from serious harm or for the protection of the patient from serious exploitation that s/he be subject to such care and treatment, and that such care and treatment cannot be implemented unless s/he is compelled under this section;

or

v. that, in the case of a patient who has capacity to consent to the proposed care and treatment for her/his mental disorder, there is a substantial risk of serious harm to the health or safety of the patient or to the safety of other persons if s/he remains untreated, and there are positive clinical measures included within the proposed care and treatment, which are likely to prevent deterioration or to secure an improvement in the patient's mental condition" (p. 70–71).

Reprinted from Review of the Mental Health Act 1983 (Report of the Expert Committee) 1999. [Online]. Available at: http://www.dh.gov.uk/assetRoot/04/06/26/14/04062614.pdf [Accessed 30 May 2009], with permission.

---

[1]With the exception of patients covered by the 1983 Mental Health Act who may be treated against their will even if they are competent, but only if the treatment is for their mental disorder (Dyer 2000).

104.3 Hunger Strikes

104.3.1 Definition of hunger strikes

The Declaration on Hunger Strikers (Declaration of Malta) (1991, http://www.wma.net/e/policy/h31.htm) defines a hunger striker as a mentally sound person who has voluntarily initiated a hunger strike and does not accept food and/or fluids over a considerable time. Oguz and Miles (2005) define a hunger strike as an action based on nourishment refusal, performed by an individual (possibly imprisoned) whose decision-making capacity is not impaired, with the aim of obtaining fulfilment of a specific demand. Most hunger strikes include the ingestion of some water and other liquids, salt, sugar, and vitamin B1 for a certain time without asserting intent to fast to death (Oguz and Miles 2005). Hunger strikes have a rich political history (Oguz and Miles 2005), starting with the suffragettes through the IRA in Britain or the Doukhobors in Canada (Lewey 1977) and ending with the famous case of Guantanamo Bay hunger strikers (e.g., Nicholl et al. 2006; Wilks 2006).

104.3.2 Causes of Hunger Strikes Among Prisoners

According to Brockman (1999), hunger strikes among prisoners may be motivated by a variety of factors. For example, sentenced young prisoners (particularly in the case of a first lengthy sentence) use self-starvation (which may be treated as a variant of self-harm) as a method of reducing tension or an attempt to precipitate change. Only a few prisoners choose to commit suicide (which may be chosen as a method of escaping punishment, a means of exercising autonomy or a method of self-killing secondary to grief or guilt) by starvation as they are prevented from killing themselves by other physical means. On the other hand, the main motivation behind hunger strikes of remanded prisoners is unfair – in their opinion – charge or refusal of application for bail. Finally, asylum seekers at an early stage of imprisonment communicate distress and their desire to change detention status through food refusal. Later, when it becomes apparent that they will be repatriated against their will, food refusal can be motivated by the desire to die rather than accept this tragic fate. Illegal immigrants most often use hunger strikes to express their outrage at having been treated as criminals when they do not perceive themselves as such. Although it is claimed from time to time that the main motivation behind hunger strikes is to draw media attention to the striker's problem (e.g., Lewey 1977, p. 416), most authors would generally agree that an unarmed individual has very few methods left to resort to if he or she wants to make a life or death decision (Oguz and Miles 2005). Thus, they think that the choice to refuse food in the case of hunger strikes in prisons can be an authentic, albeit lethal, expression of values that may end the person's life (Oguz and Miles 2005), although it cannot be excluded that prisoners sometimes seem to play with the system in undertaking their hunger strike, as Dryer suggests (2000) (Table 104.2).

104.3.3 Competence Testifying and Its Effect on Force-feeding of Hunger Strikers in Prisons

It is very important to say that the majority of cases in which prisoners refused nutrition were inspired by numerous reasons other than mental disorder (Brockman 1999) and hunger strikes are very rarely unjustified. It is therefore not surprising that society and the law now acknowledge that a competent prisoner, even with suicidal tendencies, may choose to self-starve. A prisoner's decision, regardless of

Table 104.2 Motivations behind food refusal among hunger strikers in prisons and anorexics

Motivation behind food refusal		
Hunger strikes among prisoners		Anorexics
Sentenced young prisoners	particularly in the case of a first lengthy sentence – self-starvation (which may be treated as a variant of self-harm) is used as a method of reducing tension or an attempt to precipitate change.	Distorted body image.
	self-starvation as a form of a suicide (which may be chosen as a method of escaping punishment, a means to exercise autonomy, or a method of self-killing secondary to grief or guilt), because they are prevented from killing themselves by other physical means.	An intense fear of weight gain, even when they are bordering on physical collapse.
Remanded prisoners	self-starvation as a form of protest against unfair – in their opinion – charge or refusal of their application for bail.	Efforts to exert control over their eating behavior.
Asylum seekers	At an early stage of imprisonment – food refusal as communication of distress and the desire to change detention status.	Egosyntonicity of anorexia nervosa, namely this condition is often highly valued by anorexics. This phenomenon refers to the sense, which many patients experience, of anorexia nervosa being part of themselves or of their identity.
	Later, when it becomes apparent to the asylum seeker that he will be repatriated against his will, food refusal can be motivated by the desire to die rather than accept this tragic fate. Through hunger strikes illegal immigrants most often express outrage for being treated as criminals when they do not perceive themselves as such. Although from time to time opinions are published suggesting that the main motivation behind hunger strikes is to draw media attention to their problem.	Communication of distress (usually a person is not fully aware of it) concerning adulthood, body, and especially, sexuality and the desire to manage it.
Sometimes prisoners seem to be playing with the system in undertaking their hunger strike.		

There are various motivations behind food refusal among hunger strikers in prisons and anorexics, including the desire to inflict self-harm, change one's detention status or die, escape punishment, communicate distress or play with the system (in prisoners); distorted body image, intense fear of weight gain, an effort to exert control overeating behavior, egosyntonicity, and communication of distress (in anorexics)

whether it appears to be foolish, cannot be overruled unless the individual is incompetent (Brockman 1999). When a prisoner refuses nourishment and is considered by the doctor to be capable of forming an unimpaired and rational judgment concerning the consequences of such voluntary refusal, he or she shall not be fed artificially (Kenny et al. 2004). The above attitude is further reinforced by the question of whether death by hunger strike is suicide, or simply exercising the right to self-determination (Williams 2001). Studies have shown that prisoners who go on hunger strikes have a high prevalence of depression or post-traumatic stress disorder but are not especially likely to be suicidal or incapable of making the decision to go on hunger strike (Oguz and Miles 2005, p. 170). Wynia (2007) underlines that suicide as a medical term has no place in discussing hunger strikes. Hunger strikers are not generally clinically depressed and would prefer not to die; the strikers are not suicidal, even if they are willing to die to achieve their political aims. Hernan Reyes of the International Committee of the Red Cross said that true hunger strikers do not want to die any more than soldiers charging a hill want to die (Table 104.3).

Table 104.3 Mental disability, capacity, and attitudes toward suicide among hunger strikers in prisons and anorexics

Mental disability, capacity, and attitudes toward suicide		
	In hunger strikers in prisons	In anorexics
Mental disability and capacity	Generally prisoners who go on hunger strikes are not incapable of making a decision to go on a hunger strike; food refusal by prisoners may be motivated by a variety of factors, most of which are not related to mental disorder.	According to the 1990 Mental Health Act anorexia nervosa does not meet the criteria of psychosis under the Act (so anorexics are generally competent) but this current legal conception of capacity, which is based on understanding and reasoning, does not capture the difficulty that arises from the impact of anorexia nervosa on the sense of personal identity, especially resulting in egosyntonicity.
Suicide	prisoners who go on hunger strikes have a high prevalence of depression or post-traumatic stress disorder but are not especially likely to be suicidal, suicide as a medical term, has no place in discussing hunger strikes; hunger strikers are not generally clinically depressed and would prefer not to die; they are not suicidal, even if they are willing to die to achieve their political aims.	Anorexics are genuinely terrified of the prospect of being overweight and some state openly that they would rather be dead than fat; in contrast to suicidal patients they do not explicitly discuss a desire to end their lives but their actions lead in that direction.

Generally, neither prisoners nor anorexics are incapable of making the decision to go on hunger strike but the current legal conception of capacity, which is based on understanding and reasoning, is completely inadequate for anorexia nervosa

104.3.4 Hunger Strikers' General Attitudes Toward Food Refusal

According to a blogger commenting on the situation of the Guantanamo prisoners who go on hunger strike, force-feeding not only violates US domestic and international laws but is also undisputedly perceived as cruel practice against human life and dignity (blog of rights, http://blog.aclu.org/2009/01/09/end-the-inhumane-force-feeding-of-guantanamo-prisoners/). In this vein, The World Medical Association Declaration of Malta concludes that forced feeding, unlike refusal to eat, is always accompanied by some form of physical or mental abuse and must therefore be perceived as degrading and inhuman (Wynia 2007). Most medical organizations advocate respect for a freely chosen decision to strike. Their disposition is mainly based on the concept of freedom of expression introduced by the International Covenant on Civil and Political Rights (Oguz and Miles 2005).

104.3.5 The Dilemma of the Physician Who Tries to Help a Hunger Striker in Prison

Although generally a doctor will not be neglecting his duty if he refrains from feeding a prisoner against his will, each time prisoners refuse food their doctors face a dilemma (Wynia 2007). Each case of hunger strike triggers the debate on legality and morality of force-feeding, which has continued through most of the history of prison medicine (Lewey 1977). Cases of force-feeding of prisoners (especially asylum seekers) by doctors result in great concern. When coming into contact with a prisoner on hunger strike, doctors should be aware of their professional, legal, and ethical obligations (Kenny et al. 2004). There are legal and social interests, reflecting profound ethical values, which militate against the prisoner's absolute right to die by means of hunger strike but it has been debated

whether a doctor may provide medical treatment once a hunger striker has reached the point where he is no longer capable of rational thought (Strauss 1991). Allowing the striker to die ratifies the charge that the authorities do not value the personhood of prisoners. Force-feeding to save life draws attention to the way the diminished quality of life has inspired the protest (Oguz and Miles 2005). Thus, the physicians find themselves between the rock and the hard place, where either decision is burdened with guilt (Lewey 1977). Any response by the state, including neglect, negotiation, and force-feeding, is a question of dialogue with the strikers and, consequently, is very problematic and difficult (Oguz and Miles 2005). Clearly, a physician who either respects the choice to hunger strike or force-feeds the striker is very often inevitably engaged in a political act (Oguz and Miles 2005). According to Oguz and Miles, such physicians ought to stay politically neutral and refrain from commenting in any way (positive or negative) on the striker's motifs as well as being respectful of the striker's right to exercise such a protest, by supplying him or her with essential updates on his or her condition without forcing them to terminate the protest (Oguz and Miles 2005). They should also be willing to take proactive action and provide information in advance so as to plan for loss of decision-making capacity, thus helping to delay death and reduce the risk of irreversible disabilities (Oguz and Miles 2005). Additionally, they should refrain from advocacy or criticism of the political aspirations of individuals under their care (Oguz and Miles 2005).

104.3.6 Consequences of Forcible Feeding Among Prisoners Who Undertake Hunger Strikes

Very little has been written about the consequences of forcible feeding in the case of hunger strikes in prisons. There are some reports of inquests where death was accelerated by force-feeding (due to pneumonia or syncope). Force-feeding can also lead to major infections, collapsed lungs, and other devastating health consequences, including serious digestive and pancreatic problems. Unfortunately, reports on the behavioral consequences of such forcible feeding are lacking. Evaluation of such consequences implies adopting a clear stance on values because, as was mentioned above, the strikers are not mentally disturbed, even if they are willing to die to achieve their political goals. Therefore, the physician must answer the following difficult questions: Is one individual's freedom of choice to be limited by another individual's moral obligations to benevolence? Or in this case, does freedom seem to be the highest human value? Those who value freedom of self-determination above all, even life itself, advocate noninterference. Others feel that when the choice leads to death, the human moral obligation to benevolence impels one to intervene – in a medical context, the physician must attempt to save life and preserve health (Lewey 1977). In such situations, the doctor has to apply a lesser evil to prevent a greater one. But what he shall consider to be a lesser evil is his arbitrary decision.

It is difficult to say precisely what a forcibly fed prisoner feels but there is no doubt that such intervention does not bring relief. On the one hand, forcible feeding saves life but on the other hand, as Oguz and Miles argue, for prisoners who, by and large, are deprived of means of exercising their political rights, hunger strikes convey a powerful and independent political message (Oguz and Miles 2005). Hence, forcible feeding seems to narrow their already diminished freedom.[2]

---

[2]Nowadays it is very difficult to bypass the dilemma with the so called "Cat and Mouse Act" under which hunger strikers were released from prison and then re-detained once they were fit again (Lewey 1977) because there were a lot of unintended consequences of the act. For example, the authorities experienced much more difficulty than anticipated in re-arresting the released hunger-strikers.

Table 104.4 Medical and behavioral implications of forcible feeding among hunger strikers in prisons and anorexics

Medical and behavioral implications of forcible feeding		
In hunger strikers in prisons		In anorexics
Medical	Pneumonia, syncope, major infections, collapsed lungs, serious digestive and pancreatic problems.	Pneumonia and over-hydration.
Behavioral	For prisoners, conventional means of political expression, such as voting, donating to political organizations, publishing, or national organizing are greatly diminished. They are obstructed, impracticable, or illegal. Under these circumstances, a hunger strike asserting bodily integrity is one of the few tools for strong political expression, thus forcible feeding seems to narrow already diminished freedom. Such intervention does not solve the problem of the hunger striker, for example it cannot change detention status of an asylum seeker, so not only does force-feeding not minimize his distress, it intensifies it.	Feeding alone is thought to be ineffective, and even counterproductive and antitherapeutic, and may be defined as mistreatment. Because the fundamental therapeutic aim in working with anorexia nervosa patients should be to facilitate the development of a secure, separate sense of self and minimize egosyntonicity of the condition, such behavioral treatment programs for anorexic patients are indeed paradoxical. Force-fed anorexics evidence no differences in recovery from anorexia's psychological aspects, satisfaction with treatment, or medical complication frequency compared with those who received oral kilocalories alone. In addition, such intervention clearly destroys the relationship of trust between patient and practitioner and jeopardizes the patient's prospects of long-term recovery. Force-fed patients with anorexia nervosa tended to perceive their figure and femininity more negatively than before hospitalization. Paradoxically, force-feeding may be connected with greater risk of death.

There are various negative biological and behavioral consequences of force-feeding among hunger strikers in prisons and anorexics, pneumonia being the most familiar biological consequence and failure to reduce distress being the most familiar behavioral consequence. Not only does force-feeding fail to reduce distress in prisoners, it actually exacerbates it. In anorexics, force-feeding leads to mental deterioration and may be connected with greater risk of death

Such intervention does not solve the problem of the hunger striker. For example, it cannot change the detention status of the asylum seeker and therefore force-feeding not only does not minimize his distress, it intensifies it even further (Table 104.4).

104.4 Anorexia Nervosa

104.4.1 Definition and Causes of Food Refusal in Anorexia Nervosa

It is common knowledge that anorexia nervosa is a serious psychiatric disorder characterized by distorted body image, which triggers intensive self-starvation (a person eats very small amounts of low caloric food) and – as a consequence – significantly diminished body weight. The very essence of this eating disorder is the staunch refusal to change (to gain weight) in conjunction with profound denial of illness (Harris et al. 2001). These patients often do not perceive themselves as sick (Gans and Gunn 2003). They do not want to eat and they typically manifest an intense fear of weight gain, even when they are bordering on physical collapse from malnutrition (MacDonald 2002) (Table 104.2). Clinicians working with patients suffering from anorexia nervosa must face not only the chronic but also the life-threatening (Patton 1988) nature of the illness and this is probably the most difficult aspect of their work. Although Beumont and Carney (2004) claim that patients express authentic terror at the thought of being overweight, with some of them going so far

as to claim they would rather be seen dead than fat, in contrast to suicidal patients, they do not explicitly discuss a desire to end their lives, yet their actions lead in that direction (Melamed et al. 2003, p. 622). Refusal of treatment that could look suicidal in another patient may, for the anorexic, be an affirmation of the only life she can conceive of living (e.g., Gans and Gunn 2003). Although anorexia nervosa is sometimes described as suicide in refractive or refracted (Lemma-Wright 1994; Malan 1997), the desire to assert autonomy and self-control is what eliminates the likelihood of suicide, replacing it with a process of starvation that is stretched over time (Lemma-Wright 1994). Anorexia is a paradoxical disorder in which the choice to starve is experienced existentially as the choice to be and every anorexic girl derives her fundamental meaning and satisfaction, her reason to live, from her efforts to become thin (Gans and Gunn 2003). Very often the anorexic person is unaware that her illness is a cry for help in the face of acute distress concerning adulthood, the body, and especially sexuality.

104.4.2   Egosyntonicity as the Main Feature of Anorexia Nervosa and Inadequacy of the Current Model of Capacity

Serpell et al. (2004) raise the issue of the egosyntonic nature of anorexia nervosa, which prompts people affected by the disorder to perceive it as a value (in contrast to bulimia nervosa, Serpell and Treasure 2002). Although egosyntonicity seems to be very important for the assessment of anorexic patients' capacity, its impact is still unaccounted for in the legal definition of capacity (Tan et al. 2003c). The authors (Tan et al. 2003c) suggest that personal identity should be considered a relevant factor in the assessment of competence to consent to, or refuse, treatment in anorexia nervosa, depending on how it affects an individual's sense of personal identity and her ability to make decisions. It is very important to say that the application of capacity in consideration of treatment refusal in anorexia nervosa can be problematic, especially because anorexic patients' difficulties concerning their ability to make treatment decisions, described above, are poorly captured by the concept of capacity currently in use that is based on understanding and reasoning (Tan et al. 2003a, b). The legal criteria of capacity are largely intellectual ones, based on the ability to believe and understand treatment information and to reason about it and they seem to be inadequate in the case of anorexia nervosa because anorexia affects patients' values rather than understanding and reasoning (Tan et al. 2003c). In this light, it is very controversial that, according to the 1990 Mental Health Act, anorexia nervosa does not fulfill the criteria of psychosis under the Act and therefore anorexic patients are generally competent and cannot be compulsorily hospitalized (if anorexic patients are temporarily disturbed or pose a risk to themselves, the Act allows them to be detained to facilitate emergency treatment as mentally disordered persons for a maximum of 3 days) (Lemma-Wright 1994; Griffiths et al. 1997) (Table 104.3).

104.4.3   General Attitudes Toward Forcible Feeding of Anorexic Patients

The deep existential motivation behind self-starvation in anorexia nervosa does not always seem to affect attitudes toward treatment of this condition because forcible feeding is still the main method of "helping" them in some hospitals. The strong conviction that many medical and highly dangerous complications of self-starvation may remit after re-nutrition (Corcos et al. 2003; Holtkamp et al. 2003) still lingers among some clinicians. According to MacDonald (2002), the main reason given

for rejecting the full implications of patient autonomy (for example in the case of forcible feeding) in the case of anorexia nervosa is that treatment promises both physical and psychological benefits. Many clinicians are convinced that if the treatment succeeds in inducing weight gain, the patient will be healthier physically (for example, she will have less risk of heart attack) and mentally (she will have less starvation-induced cognitive impairment). Thus the anorexic person, once admitted to hospital, very frequently may be subjected to a variety of treatment programs whose principal aim is to restore the anorexic to a normal weight (Lemma-Wright 1994). Such interventions should be deemed fundamentally improper.

104.4.4 Consequences of Forcible Feeding of Anorexic Patients

According to Draper (2000), feeding, unless administered to physically enable the patient to participate in therapy, is ineffective. Forcible feeding as a method of treating patients with anorexia nervosa may be counterproductive and antitherapeutic (Tan et al. 2003a). Thus, strict behavioral interventions (demanding, for example, that a patient eat 100% of her/his meal or be forcibly fed) may be defined as mistreatment in the case of anorexia nervosa (Treasure and Ramsay 2002), especially because of the surprising results reported by Finfgeld (2002) and Castro et al. (2004): nutritional abnormalities in adolescent anorexia nervosa persist after short-time recovery and both nonweight restored and some weight-restored individuals with anorexia nervosa experience chronic problems. Because treating patients with anorexia nervosa should be fundamentally aimed at rebuilding their stable, independent identity (Levens 1995), such behavioral treatment programs for anorexic patients are indeed paradoxical (Lemma-Wright 1994). This paradox is well exemplified by many very negative consequences of force-feeding in patients with anorexia nervosa. For example, involuntary nasogastric tube feeding (described earlier) of patients with anorexia nervosa is particularly problematic. Although according to Zuercher et al. (2003), patients who had received voluntary tube feeding gained significantly more weight per treatment week than those who received oral refeeding alone[3] and patients who had received tube feeding evidenced no differences in recovery from anorexia's psychological aspects, satisfaction with treatment, or medical complication frequency than those who received oral kilocalories alone, the effectiveness of (even voluntary) tube feeding in the treatment of anorexia nervosa is highly problematic. Such compulsory tube feeding destroys the relationship of trust between patient and practitioner and jeopardizes the patient's prospects of long-term recovery (Dresser 1984). Also literally forcing food into the mouths of sufferers decreases the chances of long-term recovery and is hardly in patients' best interest (Draper 2000, p. 121). A study conducted by Robb et al. (2002) showed that nasogastric feeding was a more effective alternative to less subtle forcible feeding as it resulted in faster and more substantial weight gain when applied over a similar period of time. A study by Mehran et al. (1999) into the perception of femininity, figure, diet, and clothing conducted before and after 3-month hospitalization also revealed a negative link between forcible feeding and patients' self-esteem: the force-fed patients evaluated both their femininity and figure in a more rejecting and unfavorable manner than before hospital admission (Figs. 104.1–104.4).

Gowers et al. (2000) find hospitalization unsupported by psychological help responsible for deterioration in patients' condition or even premature death while Draper argues that forcible feeding,

---

[3]Patients who received tube feeding for at least half of their length of stay gained 1 kg/week versus 0.77 kg/week for patients receiving oral re-feeding alone.

Fig. 104.1 Changes in perception of femininity in restricting-type anorexics (RAs) and bulimic-type anorexics (Bas) (Reprinted from Mehran et al. 1999. With permission)
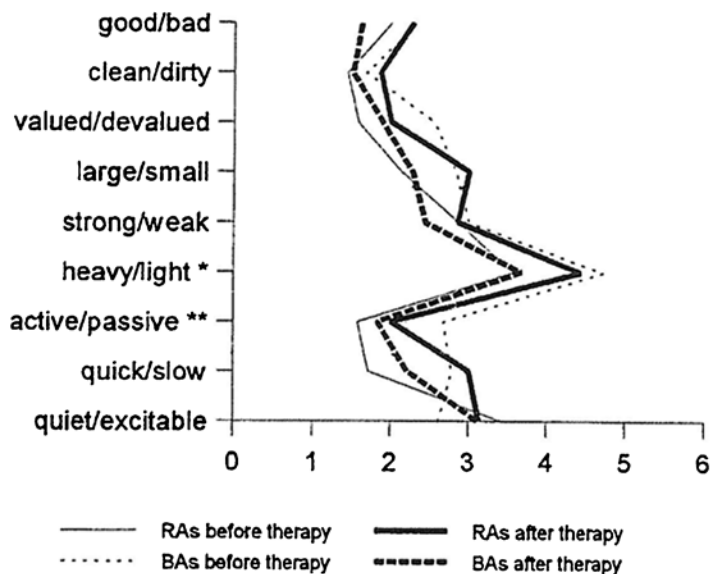
Fig. 104.2 Changes in perception of figure in restricting-type anorexics (RAs) and bulimic-type anorexics (Bas) (Reprinted from Mehran et al. 1999. With permission)
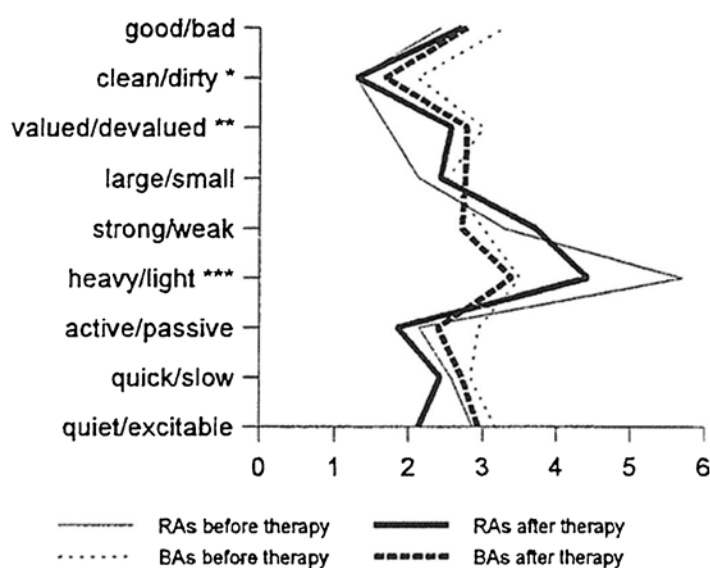
albeit life-saving, does not address the underlying condition. Coupled with physical side effects of tube feeding such as pneumonia and over-hydration as well as a possible link between hospitalization and higher mortality, the reasons for forcible feeding as a form of treating anorexia nervosa do seem controversial for anorexia nervosa patients. These words sound especially tragic in the light of intriguing considerations of Zerbe (1993) and Levens (1995) that even clinicians' words are perceived by these patients as threatening; according to Zerbe (1993), they need "homeopathic" doses of therapy. Using cybernetic terms to portray the reciprocal relationship between forcible feeding and improvement of the anorexic patient's condition, one may say that the more food is given to patients compulsorily, the worse they feel (Table 104.4).

Fig. 104.3 Changes in perception of diet in restricting-type anorexics (RAs) and bulimic-type anorexics (Bas) (Reprinted from Mehran et al. 1999. With permission)
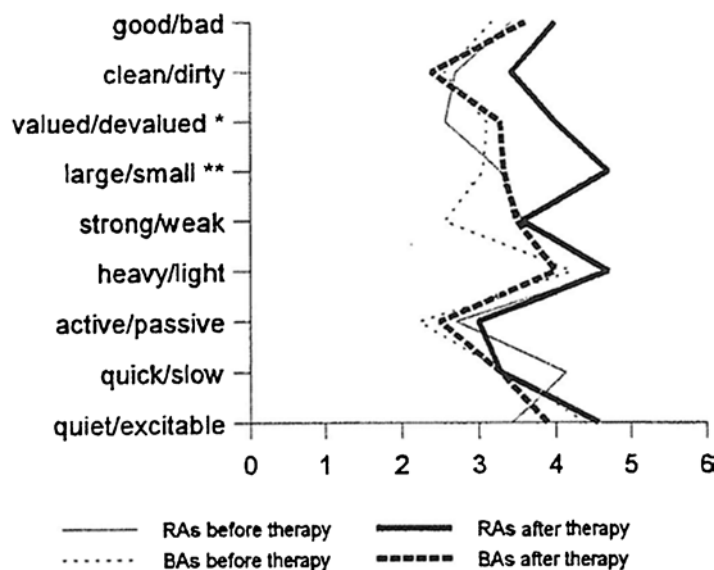
Fig. 104.4 Changes in perception of clothing in restricting-type anorexics (RAs) and bulimic-type anorexics (Bas) (Reprinted from Mehran et al. 1999. With permission)
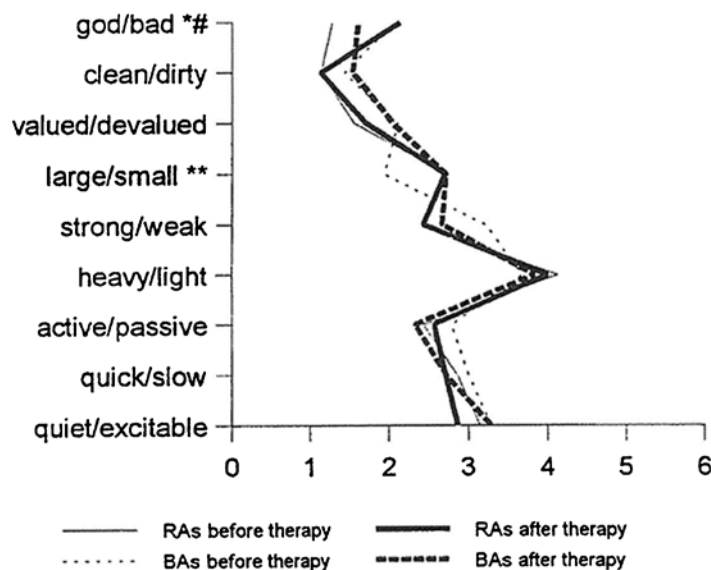
104.4.5 The Right to Die in the Case of Anorexia Nervosa?

In the context of deliberations on the chronicity of anorexia and illness-related suffering, the following question is inevitable: what is the sense of treatment and can treatment be replaced with palliative care? Draper (2000) is one researcher who has thoroughly examined the palliative care option for some anorexic patients. She maintains that abandoning treatment, however disturbing or gruesome in the case of an illness that seems easily curable, may be the only alternative for a person who refuses to be treated but cannot live without the illness either. Tan et al. (2003b) emphasize that some

patients, especially those who have been battling against anorexia for years, and some mothers, are of the opinion that if anorexia becomes chronic and does not respond to treatment, and if the sufferer exceeds a certain critical point, she should be allowed to leave. According to Manley and Leichner (2003), it is typical for a patient to experience, at one point in therapy or another, exhaustion and lack of strength to endure the struggle with the illness. As Draper (2000) says, such difficult cases are not typical, yet it should be noted that some people will never recover from anorexia or even maintain body weight stable (if low) enough to lead a normal life. Undoubtedly, when a person suffering from anorexia chooses death, this creates a serious ethical dilemma for the family and people involved in the treatment. Draper (2000) suggests that the palliative approach should be applied to patients who have been ill for a very long time (for longer than 1–8 years, i.e., the natural cycle of the illness), who have already been force-fed, are critical about making decisions concerning their own lives, are able to see the impact of anorexia on certain aspects of their lives, and whose lives are not at direct risk. According to the researcher, in such cases refusal of therapy is analogous to abandoning life-pro-longing therapy in the case of patients with disabling, chronic or acute terminal illnesses in favor of palliative treatment. When patients in full possession of their mental faculties refuse treatment, whether they are terminally ill or just choose to die, a doctor should accept the refusal (2000). An undoubtedly suggestive statement is the comparison proposed by Gans and Gunn (2003), referring to the difference between a 20-year-old woman that is secretly starving herself and a 50-year-old woman with chronic anorexia, exhausted by hospital and clinic stays and various medical appoint-ments. Gans and Gunn (2003) wonder whether there is a point when clinicians abandon hope that the patient will change her attitude and come to the conclusion that they are unable to continue in their treatment attempts that have always proved a failure? They may think this way: if no method of fully curing anorexia has been found so far, why should they hope that the next attempt is going to be suc-cessful? (Gans and Gunn 2003). Obviously, we can consider sending the patient to a better, private treatment center yet the question arises: who is going to pay for it? On the other hand, treatment of the long-term disability of anorexic patients is also expensive (Su and Birmingham 2003). Such questions seem to be highly problematic. Can we really resign from saving lives only because we feel discouraged or cannot always afford high-level therapy? Should we always do whatever is pos-sible to save somebody's life? Some researchers openly criticize the concept of palliative care of anorexic patients. Melamed et al. (2003) have no doubt that anorexia is a curable illness; frequently, therapy is only aimed at partial recovery and one must take recurrences into account, especially in chronic cases, but this is actually the reason why clinicians should focus on saving the lives of anorexic patients in the first place. The palliative care option is also considered disputable by Griffiths et al. (1997). They argue that in spite of the extreme difficulties of anorexia treatment, those who survive are deeply grateful to the doctors who have helped them. Gans and Gunn (2003) take an even more definitive stand on the issue, by saying that if an anorexic person dies, there will be no chance for recovery whatsoever.

104.4.6 Other Cases of Forcible Feeding

Forcible feeding is sometimes applied in the terminal phase of various illnesses, for example Alzheimer's disease (e.g., Sheldon 1997) or cancer (e.g., Higginson and Bruera 1996). Such patients may consistently refuse food and drink for both psychological and physical reasons. Sometimes doc-tors argue that patients who are terminally ill should be allowed to starve rather than be artificially fed. It is argued that force-feeding needlessly extends the dying phase, while starvation can offer a dignified death.

Table 104.5 Current knowledge on consequences of forcible feeding and its applications to other areas of health and disease

Current knowledge about consequences of forcible feeding	Its applications to other areas
Hunger strikes, especially among prisoners	Alzheimer's disease
Anorexia nervosa	Cancer cachexia-anorexia
	Widespread self-destructive behavior such as alcohol abuse

The behavioral implications of force-feeding in prisoners and hunger strikers may be helpful in the event of force-feeding of individuals who cannot eat for mental or bodily reasons, in the terminal phase of their disease, e.g. Alzheimer's disease or cancer cachexia-anorexia, and widespread self-destructive behavior such as alcohol abuse

Table 104.6 Key points concerning causes, problems, and consequences of forcible feeding

1. Food refusal may occur for a variety of reasons, for example it may be used as a method of exercising control over others (either at family or society level), a method of self-harm, and even committing suicide, only sometimes is it a symptom of mental illness.
2. Force-feeding always creates a difficult situation for the patient, the patient's family, as well as the hospital staff, especially physicians; however, it is sometimes essential to save a patient's life.
3. Although force-feeding, contrary to informed and voluntary refusal, is never ethically acceptable, and especially feeding accompanied by threats, coercion, force, or use of physical restraints is a form of inhuman and degrading treatment. Although previously force-fed patients, especially ones who have recovered from anorexia nervosa, are sometimes deeply grateful to the doctors who helped them, it must be underlined that using forcible feeding alone as a method of help either anorexics or self-starving prisoners may be counter-productive and may result in paradoxical effects (e.g. Brockman 1999; Draper 2000).

Food refusal may occur for a variety of reasons and it always creates a difficult situation for the patient and the social environment. In spite of the advantages of force-feeding, using it alone as a method of helping self-starving individuals may be counterproductive and may result in paradoxical effects.

104.5 Applications to Other Areas of Health and Disease

The attitude presented above may be helpful in situations described briefly in this chapter, namely in the event of force-feeding of persons, who cannot eat for mental or bodily reasons, in the terminal phase of their disease. If even in mentally and bodily healthy prisoners and generally healthy (except for the consequences of malnutrition) persons suffering from anorexia, forcible feeding may exacerbate the disease symptoms through organ damage and deepening of depression, this may also occur, but with greater intensity, in the event of patients suffering from terminal diseases. In addition, such undoubtedly self-destructive behavior as self-starvation, highlights other destructive behaviors, even those which are commonly recognized and do not qualify as mental disturbance, such as excessive alcohol consumption or nicotinism. It is worth considering whether and why only radical interventions aimed at the person's good are admissible here (Table 104.5).

104.6 Conclusion

Food refusal provokes many questions and proposed solutions. If doctors want to succeed in these difficult circumstances they should try to apply the golden mean in every situation. Both forcible feeding and such entirely different solutions as palliative care for people with anorexia or consent for a prisoner's death of malnutrition are highly inhuman; decisions in case of severe diseases such as Alzheimer's or neoplastic diseases seem to be even more difficult. In this situation, it is necessary to

clearly determine competence status in cases of anorexia whereas in prisoners, if mental disturbance is not suspected, detailed examination of mental status and exclusion of manipulation are essential in order to fulfill the requirements. Often, particularly in prisons, for example in the famous Guantanamo Bay case, force-feeding becomes one more repression or even torture technique. Of course it is not recommended to see such torture in every force-feeding event, although the prison metaphor is frequently used in existential approaches to anorexia (e.g., by Lemma-Wright 1994), but one should always carefully examine the deep-set motives underlying each case of deliberate food refusal because this is always an important message, which very rarely means a death-wish. The fact that, in spite of the extreme difficulties involved in the compulsory treatment of anorexia, survivors are very grateful to the doctors who helped them, should act as an additional incentive to undertake such efforts. This is why we should be very cautious when examining the possibility of palliative care for patients with anorexia, which in practice means permission to leave them alone. Obviously, we cannot always expect patients with anorexia, and especially prisoners, to be grateful for saving their life or to view doctors as Good Samaritans but it is always worth risking such action, knowing that we only have one life.

Summary Points

- Food refusal provokes many questions and solutions.
- Force-feeding seems to be a highly inhuman solution but is consenting to the death of another person as result of starvation not equally inhuman?
- A basic recommendation for people dealing with patients refusing food is thorough examination of their competence, which seems particularly difficult in anorexia nervosa because the capacity criteria prevailing in psychiatry are completely inadequate in case of this disease.
- You should remember that often, particularly in prisons, as for example in the famous case of Guantanamo Bay, force-feeding does not follow from the wish to help the prisoner but is yet another repression technique, sometimes a political one.
- The fact that people who refuse food are often very grateful to their doctors for saving their life (through forcible feeding among other things) should motivate us to seek the golden mean when dealing with people who refuse to eat. In this context, you should carefully examine the proposal of palliative care for people with anorexia, which practically permits us to leave them alone.

Definitions and Explanations of Key Terms

Anorexia nervosa: is a serious psychiatric disorder characterized by distorted body image, which triggers intensive self-starvation and – as a consequence – significantly diminished body weight. The very essence of this eating disorder is categorical refusal to change in conjunction with profound denial of illness.

Competence (capacity): – in psychiatry, ability to make rational decisions.

Egosyntonicity: – a phenomenon appearing in very few disorders, whose the main feature is that the afflicted person derives his or her sense of identity from the disorder.

Force-feeding: is the practice of feeding a person or an animal against their will.

Hunger strike: is a method of nonviolent resistance or pressure in which participants fast as an act of political protest, or to provoke feelings of guilt in others, usually with the objective to achieve a specific goal, such as a policy change.

References

Anon. BMJ. 1974;2:737–8.

Beumont P, Carney T. Aust N Z J Psychiatry. 2004;38:819–32.

Blog of Rights. Available at http://blog.aclu.org/2009/01/09/end-the-inhumane-force-feeding-of-guantanamo-prisoners/ Accessed 29 May 2009.

Brockman B. J Med Ethics. 1999;25:451–6.

Castro J, Deulofeu R, Gila A, Puig J, Toro J. Int Eat J Disord. 2004;35:169–78.

Corcos M, Guilbaud O, Paterniti S, Chambry J, Chaouat G, Consoli SM, Jeammet P. Psychoneuroendocrinology. 2003;28:229–49.

Draper H. Bioetics. 2000;14:120–33.

Dresser R. Wis L Rev. 1984;2:297–374.

Dyer C. BMJ. 2000;320:731.

Finfgeld DL. Arch Psychiatr Nurs. 2002;16:176–86.

Gans M, Gunn WB. Int J Law Psychiatry. 2003;26:677–95.

Gowers SG, Weetman JSA, Hossain F, Elvins R. Br J Psychiatry. 2000;176:138–41.

Griffiths RA, Beumont PJV, Russell J. Aust N Z J Psychiatry. 1997;31:525–31.

Harris, WA, Wiseman, CV, Wagner, S, Halmi, KA. In: Dewan MJ, Pies RW, editors. The difficult-to-treat psychiatric patient. Washington: American Psychiatric Publishing, Inc.; 2001. p. 243–271.

Higginson I, Bruera E (ed). Cachexia-anorexia in cancer patients. Oxford: Oxford University Press; 1996.

Holtkamp K, Hebeband J, Mika C, Grzella I, Heer M, Heussen N, Herpertz-Dahlmann B. J Psychiatr Res. 2003;37:165–9.

Kenny M, Silove D, Steel Z. Med J Aust. 2004;180:237–40.

Lemma-Wright AL. Starving to live. The paradox of anorexia nervosa. London: Central Book Publishing; 1994.

Levens M. Eating disorders and magical control of the body. Treatment through art therapy. London: Routledge; 1995.

Lewey L. Can Med Assoc J. 1977;116:416–9.

MacDonald C. Can J Psychiatry. 2002;47:267–70.

Malan D. Anorexia, murder, and suicide. What can be learned from the stories of three remarkable patients. Oxford: Butterworth Heinemann; 1997.

Manley RS, Leichner P. Crisis. 2003;24:32–6.

Mehran F, Leonard T, Samuel-Lajeunesse B. Eur Eat Disord Rev. 1999;7:111–20.

Melamed Y, Mester R, Margolin J, Kalian M. Int J Law Psychiatry. 2003;26:617–26.

Nicholl DJ, Atkinson HG, Kal J, Hopkins W, Elias E, Siddiqui A, Cranford RE, Sacks O. Lancet. 2006;367:811.

Oguz NY, Miles SH. J Med Ethics. 2005;31:169–72.

Patton GC. Psychol Med. 1988;18:947–51.

Review of the Mental Health Act 1983 (Report of the Expert Committee). 1999. Available at: http://www.dh.gov.uk/assetRoot/04/06/26/14/04062614.pdf Accessed 30 May 2009.

Robb AS, Silber TJ, Orrell-Valente JK, Valadez-Meltzer A, Ellis N, Dadson MJ, Chatoor I. Am J Psychiatry. 2002;159:1347–53.

Serpell L, Treasure J. Int J Eat Disord. 2002;32:164–70.

Serpell L, Teasdale JD, Troop NA, Treasure J. Int J Eat Disord. 2004;36:416–33.

Sheldon T. BMJ. 1997;315:327–32.

Strauss SA. ML. 1991;10:211–18.

Su JC, Birmingham CL. Eat Weight Disord. 2003;8:76–9.

Tan J, Hope T, Steward A. Int J Law Psychiatry. 2003a;26:697–707.

Tan J, Hope T, Steward A, Fitzpatrick R. Int J Law Psychiatry. 2003b;26:627–45.

Tan J, Hope T, Steward A. Int J Law Psychiatry. 2003c;26:533–48.

The Declaration on Hunger Strikers (Declaration of Malta). 1991. Available at: http://www.wma.net/e/policy/h31.htm Accessed 29 May 2009.

Treasure J, Ramsay R. Maudsley Discussion Papers. 2002;3:1–20.

Wilks M. BMJ. 2006;332:560–1.

Williams Y. MYCY. 2001;40:285–96.
Wynia MK. MGM. 2007;9:5.
Zerbe KJ. Bull Menninger Clin. 1993;57:161–77.
Zuercher JN, Cumella EJ, Woods BK, Eberly M, Carr JK. J Parenter J Enteral Nutr. 2003;27:268–76.

Chapter 105
Psychological Stress, Diary Methods, and Eating Behavior

Daryl B. O'Connor, Fiona Jones, and Mark Conner

105.1 Introduction

A growing body of research indicates that psychological stress affects health through two distinct pathways: first, via autonomic and neuroendocrine responses; second, via changes to health behaviors (e.g., Jones and Bright 2001; O'Connor et al. 2000). Changes to dietary health behaviors such as high fat intake, or low fiber or fruit/vegetable intake may be one important mechanism whereby stress indirectly contributes to both cardiovascular disease (Van Horn and Kavey 1997) and cancer risk (Wong and Lam 1999) and is the focus of this chapter. Over the last 25 years, a large volume of research has been concerned with understanding the precise nature of the relationship between stress and eating behavior. Recent findings in this area have indicated that high levels of stress can be associated with both increased and decreased overall food intake (Wardle et al. 2000), while work on between-meal snacking has found stress to be associated with an increase in snacking in adults and adolescents (Conner et al. 1999; O'Connor and O'Connor 2004). This chapter provides an overview of research findings addressing the impact of stress on eating behavior in non-eating disordered human populations. Interested readers are also directed toward other reviews of this area by Greeno and Wing (1994), Adam and Epel (2007) and Nieuwenhuizen and Rutters (2008). Before reviewing the relevant literature, this chapter first introduces the conceptualization of stress as daily hassles and then focuses on the use of diary methods as an approach for exploring the effects of stress assessed in this way on eating behavior.

105.2 Conceptualization of Stress and Daily Hassles

Over the last 30 years, there have been three different approaches to the study of stress: the stimulus-based or engineering approach; the response-based or medicophysiological approach; and the psychological "interactional-appraisal" approach. The engineering approach views stress as a demand on an individual from their environment, which produces a strain reaction: the greater the strain the larger the reaction. This approach assumes that undemanding situations are not stressful. However, monotonous undemanding work environments very often are stressful. This engineering analogy is also

D.B. O'Connor (✉)
Institute of Psychological Sciences, University of Leeds, LS2 9JT, UK
e-mail: d.b.o'connor@leeds.ac.uk

problematic because it makes the assumption that individuals function both unconsciously and automatically, no consideration is given to the mediating psychological processes (e.g., cognitive appraisal), although such processes are very important in relation to stress. The response-based approach mainly considers stress in terms of the general physiological reaction to noxious events in a person's environment such as changes in blood pressure, heart rate, and stress hormones. Again this approach fails to take account of individual psychological processes. For this reason, much recent work has adopted a *transactional* (or interactional-appraisal) approach in order to explain the stress process. Such theories have contributed to our understanding of the variation in responses to similar noxious (or stressful) stimuli by emphasizing the importance of the intervening psychological processes.

105.2.1 Transactional Theory and the Daily Hassles and Uplifts Approach

The transactional approach was developed by Lazarus and Folkman (Lazarus and Folkman 1984). They define stress as "a particular relationship between the person and the environment that is appraised by the person as taxing or exceeding his or her resources and endangering his or her well-being" (Lazarus and Folkman 1984, p. 19). However, historically stress researchers focused their attention on the impact of life events, such as divorce, moving home, and unemployment, on physiological, psychological, and behavioral outcomes. This life events approach has been heavily criticized because of the focus on major life changes, which are comparatively rare, and ignores the fact that a great deal of stress stems from recurrent day-to-day problems or chronic conditions known as *daily hassles* (Lazarus and Folkman 1984). More specifically, daily hassles are events, thoughts, or situations which, when they occur, produce negative feelings such as annoyance, irritation, worry or frustration, and/or make you aware that your goals and plans will be more difficult or impossible to achieve (see Conner et al. 1999; DeLongis et al. 1982; Jones et al. 2007).

Lazarus (1966; Lazarus and Folkman 1984) suggested a new approach to stress based on his own Transactional Theory of Stress. Central to this theory and to his definition of stress is the notion of appraisal. In other words, stress is not a property of the environment (as implied by the life events approach), nor is it a property of the individual, rather it is a transaction between the individual and the environment. The focus is, therefore, on the process of appraisal and coping. In any potentially stressful transaction or encounter, a person may appraise the situation as involving harm or threat of harm, or alternatively they may see it in a positive, optimistic light and view it as a challenge (see Table 105.1). The type of appraisal will then determine the person's coping processes, which will in turn determine subsequent appraisals.

Table 105.1 Primary and secondary appraisal (Adapted from Lazarus and Folkman 1984)

Type of appraisal	Definition
Primary appraisal	*A person considers the quality and nature of the stimulus event. Three kinds of possible stressors*:
	1. Those which harm or lead to loss
	2. Those which threaten
	3. Those which set a challenge
Secondary appraisal	*The assessment of one's resources and abilities to cope with the stressor (coping potential)*:
	1. Internal resources (e.g. strength, determination)
	2. External (e.g. social support, money)

According to Lazarus and Folkman cognitive appraisal, which is central to their Transactional Theory of Stress, has two components – primary and secondary appraisal

This approach clearly has implications for the way stress is measured. In particular, Lazarus suggests that the search for a single satisfactory measure is "doomed to failure" (see Abraham et al. 2008). He argues that stress needs to be assessed by a series of different measures, which each capture different aspects of the stress process. Relevant measures, therefore, might include environmental inputs (e.g. daily stressors as well as life events), measures of individual differences, coping, physiological and psychological responses. A critical feature of this approach is that, because stress is a process, assessments should be repeated over time. This theory led to the development of a measure of daily stressors known as the Hassles Scale (e.g., Kanner et al. 1981) and subsequently a shorter Hassles and Uplifts Scale (DeLongis et al. 1982). Research informed by the Transactional theory has been associated with a growth in the use of daily assessments to tap the stress process. This typically uses "daily diaries," which contain rating scales, such as the Hassles scale as well as other formats that use open-ended free responses.

105.3 Diary Methods and Eating Behavior

As you will discover later in this chapter, research into the impact of stress on eating behavior has been overly reliant on laboratory-based, cross-sectional methodologies that have used single indices (i.e., assessed stressful life events over the previous year or 5 years) or "snap-shot" measurements of stress (i.e., assessed perceptions of stress over the past 2 weeks). Such approaches have ignored Transactional theory and the evidence showing that fluctuations in within-person stressful daily hassles are important in understanding stress-outcome processes. An early example of this approach comes from Kanner and colleagues (1981) who suggested that indices of (life) stress provide no understanding of what actually happens in day-to-day life and it is "day-to-day events that ultimately have proximal significance for health outcomes and whose accumulative impact…. should be assessed" (p. 3). The use of open-ended daily diaries allow respondents to record day-to-day minor life events or hassles that are part of everyday life and have the advantage of not constraining respondents to a limited number of events. There are essentially three different diary method protocols as shown in Table 105.2.

Table 105.2 Key features of different types of diary methods

Type of diary method	Description
Interval-contingent	The participant completes diary at prespecified intervals (e.g., end of each day). For example, if we wanted to know whether psychological stress on one day "predicts" symptom "flare-ups" on the next day in psoriasis patients. Interval-contingent protocols are especially useful for frequent behaviors without a definitive start and end
Event-contingent	The participant completes diary each time a specific event happens. For example, if we were interested in investigating whether the act of smoking moderates daily mood. Event-contingent protocols are especially useful to estimate event prevalence
Signal-contingent	The patient completes diary in response to random "alarms" or "beeps" from a palmtop computer or similar device. For example, if we wanted to establish whether negative mood is associated with the onset of pain episodes in arthritis patients. Signal-contingent protocols are especially useful for recording data on the distribution, frequency, and duration of events

Researchers have used three different diary method protocols. Each method varies according to the number and when each observation is recorded on a daily basis

105.3.1 How Should Diary Studies Be Analyzed?

The data from diary methods are essentially hierarchical as a consequence of the sampling and experimental procedures. As such multilevel modeling procedures are used to examine such data. If we wanted to know whether daily hassles influence eating behavior and whether this relationship is moderated by personality, we would set up a multilevel model at two levels. Level-1 would be the daily variation in daily hassles and eating behavior (within-subject variation) and Level-2 would be the between-subject variation in personality (e.g., O'Connor et al. 2008; Jones et al. 2007). In multilevel modeling, the outputs at one level (regression coefficients) become the parameters that are modeled/analyzed at the next level. Multilevel modeling should be used with hierarchical data sets to avoid certain erroneous conclusions based on the *ecological fallacy* (see below) and also to produce more accurate estimates of standard errors. Multilevel modeling procedures can be used to examine data with repeated assessments and physiological data. For a detailed introduction to multilevel modeling procedures, see Kreft and De Leeuw (2006).

105.3.2 Ecological Fallacy

The ecological fallacy is based on the inappropriate assumption that relationships at one level in a hierarchy apply at another. The problem occurs where people assume that relationships that are shown based on data for a group of people are necessarily true for individuals within the group. For example, imagine the Prime Minister finds that when considering the UK as a whole (i.e., country level), increasing per capita income is associated with reduced crime rates. If she/he draws the inference, at individual level, that increases in personal income will be related to improvements in crime rates, then he may be in danger of committing the ecological fallacy, given that within the UK (hypothetically speaking), higher crime rates may always be greater in individuals with lower incomes compared to individuals with higher incomes. Within the context of psychological research, the same problem can arise if we draw within-person inferences based upon aggregated data units from across-person associations. For example, the relationship between stress levels at an organizational level and job control may be negative indicating that higher job control is associated with lower stress. However, within the organization, this inference may fail to account for the employees who will always experience greater levels of stress when they have higher control over their job compared to employees with lower control.

105.3.3 Benefits of Using Diary Methods

There are a number of benefits of using diary methods. These are best summarized in the words of Affleck and colleagues (1999) who argue that daily diary studies allow researchers "(a) to capture as closely as possible the 'real-time' occurrences or moments of change (in study variables); (b) to reduce recall bias; (c) to mitigate some forms of confounding by using participants as their own controls, and (d) to establish temporal precedence to strengthen causal inferences" (p. 747). Diary methods can also be used not just to record on-going behavior patterns but also to examine how the covariation between patterns of behavior (e.g., stress and diet) varies as a function of an intervention. Moreover, using daily diaries permit researchers to use sophisticated statistical techniques (e.g., multilevel modeling) to examine day-to-day within-person effects *together* with the impact of between-person factors such as personality or gender (see Ferguson 2005 for a detailed review).

105.4 The Impact of Different Types of Stressors on Eating Behavior

As outlined in the Introduction, stress has been found to be associated with both increased and decreased overall food intake, However, less work has explored the impact of different types of stressors and whether some serve as key moderators of eating behavior, while others have little or no effect. A number of different types of stressors have been identified in this literature and these are summarized in Table 105.3.

Previous research has found stressors of an ego-threatening nature to have distinct effects from those that elicit physical fear. Heatherton and colleagues (1991, 1992) suggest that situations involving potential negative evaluation or task failure (ego-threatening) will lead to disinhibition (overeating) in restrained eaters or current dieters whereas physically threatening situations will not. In contrast, these authors found that fear of an electric shock led to a reduction in food intake in unrestrained participants. Moreover, the impact of interpersonal stress has also been investigated (e.g. Oliver et al. 2001; Tanofsky-Kraff et al. 2000). Tanofsky-Kraff and colleagues (2000) compared the effects of interpersonal stress with ego- and physically threatening stress on eating and found that in the interpersonal stress group, individuals with high levels of restraint consumed the most food.

More recently, using laboratory methods, Lattimore and Caswell (2004) and Wallis and Hetherington (2004) have also highlighted the importance of taking into account different types of stressors together with eating style variables (e.g., restraint, emotional eating). In particular, Wallis and Hetherington (2004) showed that cognitively demanding stressors (such as the incongruent Stroop task) as well as ego threats have the capacity to increase food intake. The incongruent Stroop task was found to increase chocolate intake by 15% relative to control. Moreover, dietary restraint was associated with greater intake after the cognitively demanding stressor as well as an ego-threatening stressor compared to the control condition. In contrast, emotional eating was related to greater intake only after the ego threat, relative to control. Wallis and Hetherington argue that their findings reveal differential effects of ego-threat and cognitive demand on stress-related eating in restrained and emotional eaters. The importance of distinguishing between psychological (e.g., reaction time tasks, delivering a speech) and physical stressors (e.g., the cold pressor task) has also been demonstrated by Lattimore and Caswell (2004) when considering stress–eating relations. These authors have suggested that reaction time tasks require active coping whereas cold pressor tasks require passive coping. Within this context, active coping involves a behavioral response where an individual is able to influence the outcome of a task. Passive coping involves passive sensory intake with no opportunity to influence the outcome of a task. In their study, Lattimore and Caswell (2004) found that restrained eaters consumed more than unrestrained following the active coping stressor

Table 105.3 Main different types of stressors/hassles

Type of stressor/hassle	Definition of stressor/hassle
Ego-threatening	Stress associated with a fear of failure and/or negative evaluation (e.g., sitting an exam)
Interpersonal	Stress associated with feeling a sense of social alienation and being interpersonally ill-equipped (e.g., argument with partner)
Physically threatening	Stress associated with threat of facing physical harm (e.g., fear of an electric shock).
Work-related	Stress associated with the work environment and work-related tasks (e.g., meeting a deadline)

Previous research has identified a number of types of stressors/hassles, which impact on individuals in different ways. For example, physically threatening stressors have been found to be associated with a reduction in food intake, whereas, ego-threatening stressors have been found to be linked with an increase in food intake

compared to the passive coping stressor and to a relaxation condition. Moreover, consistent with Wallis and Hetherington (2004), these findings indicated that stressors, which are cognitively demanding, but do not have an ego-threatening or social evaluation element, still have the capacity to induce increases in food intake.

As highlighted earlier, a large proportion of the previous research into the effects of stress on eating behavior has relied upon cross-sectional, laboratory-based methodologies. One of the few exceptions is a recent open-ended diary study that found strong evidence for the moderating effects of different types of daily hassles on the stress-snacking relationship (O'Connor et al. 2008). Ego-threatening, interpersonal, and work-related hassles were found to elicit a hyperphagic response, whereas, physical hassles were found to elicit a hypophagic response. The latter findings confirm the work by Heatherton et al. (1991) and demonstrate that the differential effects of stressors observed in the laboratory are generalizable to naturalistic settings. In contrast to earlier findings, this research also identified work-related hassles, and not ego-threatening or interpersonal hassles, as the type of hassles that exerted the strongest effects on between-meal snacking (cf., Heatherton et al. 1991, 1992; Oliver et al. 2001; Tanofsky-Kraff et al. 2000). Moreover, it is important to highlight that these effects were not limited to vulnerable individuals who were inhibiting their food intake per se (e.g., restrained eaters) as they have been elsewhere (Heatherton et al. 1991; Wardle et al. 2000). Instead, these results clearly show that daily hassles can directly influence snack food intake.

105.4.1 Work Stressors

The above evidence suggests the importance of the work environment and work hassles for health behavior. However, despite the well-established importance of health behavior for psychological and physical well-being (see Abraham et al. 2008), there is relatively little research on the relationship between work stress and healthy eating compared to other health behaviors and even less using a diary approach. Much of the research that does exist has been based on the Job Strain model (Karasek and Theorell 1990) or the expanded Demand, Control, Support model (Johnson and Hall 1988), which suggests that relatively stable characteristics of work, in terms of job demands and job control (and support) predict strain outcomes. A number of studies have examined the relationships between these variables and healthy eating and/or body mass index (e.g., Hellerstedt and Jeffery 1997; Lallukka et al. 2004). Within these studies, relationships are often complex and frequently differ for men and women. For example, Hellerstedt and Jeffery (1997) found that men in high-strain jobs reported consuming more calories from high-fat foods (based on an 18-item food frequency questionnaire) than did men in low-strain jobs. In contrast, Lalluka et al. found that high-strain work was associated with eating (smoking and physical activity) for women only. Some studies have found no effects, for example, Overgaard, Gyntelberg, and Heitmann (2004) reviewed evidence in relation to obesity and found little evidence to support a link between job strain and body mass index. Occasionally, reverse effects have also been found. For example, Niedhammer et al. (1998) found that men with high control and high social support at work weighed more than those with low control and support.

Some of these conflicting findings may be explained by variations between the occupational samples used and the moderating effects of other features of work. Healthy behaviors require maintenance on a regular, often daily basis and may be disrupted (or encouraged) by a range of more proximal influences arising from both work and nonwork. The Job Strain and Demand, Control, Support approaches are designed to tap relatively objective and stable job characteristics

and, therefore, do not take into account individual daily variations in factors such as perceptions of hassles, mood, or working hours. With the exception of O'Connor et al. (2008), discussed above, few studies have investigated the impact of work-related hassles on eating behavior on a within-subject basis. However, Steptoe, Lipsey, and Wardle (1998) looked at daily hassles in a sample of teachers and nurses and found that fast food was eaten more frequently in weeks that were rated higher in perceived stress in which greater numbers of work- and home-related hassles were experienced.

Work stress has also sometimes been conceptualized in terms of length of work hours. In a review of effects of work hours on health, Van der Hulst (2003) found links between work hours and a number of health behaviors but no evidence of links between work hours and snacking. However, she only reviewed two studies that addressed this (Nakamura et al. 1998; Nakanishi et al. 1999). These studies were inconsistent with research by Wardle et al. (2000) who looked at employees working in a large department store. They found that periods of high work stress (measured in terms of long work hours) were associated with greater calorific energy, saturated fat, and sugar intake compared to periods of low stress (shorter hours). Work hours have also been examined in relation to body mass index. Six such studies were included in Van der Hulst's (2003) review. Findings were inconclusive, with only two studies reporting significant effects, one of which was in a positive direction (Emdad et al. 1998) and the other negative (Nakanishi et al. 1999).

More recently, Jones et al. (2007) looked at hours worked (as well as using measures of the psychosocial work environment such as demands and control) and found that long work hours were associated with greater consumption of high-fat and high-sugar between-meal snacks in women only, whereas higher levels of negative mood were linked to snack intake in men. These differential findings for men and women are likely to be explained by the fact that women often have greater family responsibilities, which leaves less scope for self-care on long work days. In addition, these results highlight the need for researchers to consider the fact that the impact of stress on eating behavior operates differently for men and women, an issue we return to later within the context of moderators of the stress–eating behavior relationship.

Long work hours, together with a range of other factors such as a rise in dual career families, changes in work technologies (computers and mobile phones), and a demand for 24-h services have resulted in a trend toward the erosion of work–home boundaries (Major and Germano 2006). Thus, there are increasing concerns about a lack of work–life balance and greater reports of work–family conflict. Such conflict between work and home is a well-established predictor of a range of negative outcomes, including physical and psychological symptomatology. Conflict is a bidirectional phenomenon, whereby work may interfere with home and family life or family concerns may interfere with work life. However, evidence suggests that work-to-family conflict is more prevalent than family-to-work conflict (Hammer et al. 2004). Work–home conflict is typically conceptualized in terms of time-based conflict, where the time spent in one domain reduces time available to spend in the other, and strain-based conflict, where strain experienced in one domain impinges on the other. It is highly plausible that lack of time due to work hours will impact on ability to prepare nutritious food, and strains such as tiredness and preoccupation with work worries will lead to alterations in eating patterns. It is, therefore, surprising that there is little research on these issues. However, one notable exception is a study by Allen and Armstrong (2006), which looked at work interference with family and family interference with work for a range of eating variables. They found that work interference with family was related to eating fewer healthy foods while family interference with work was linked to eating more high-fat foods. While not directly focusing on eating behavior, Grzywacz (2000) also found that work interference with family was linked to obesity; however, in this study there were no effects for family interference with work.

105.5 Moderators of Stress–Eating Behavior Relationship

A number of moderators of the stress–eating relationship have been examined (e.g. the obese, restrained eaters, women; Greeno and Wing 1994; O'Connor et al. 2008) and these are summarized in Table 105.4.

The individual differences model of stress–eating relationships (Greeno and Wing 1994) suggests that differences in learning history, attitudes toward eating, or biology produce variations in vulnerability to the effects of stress. Those exhibiting vulnerability are assumed to respond to stress by changing their eating behavior. In contrast, those with low vulnerability are assumed to not respond to stress in a way that influences eating. A number of vulnerable groups have been proposed and the research supporting such vulnerability is reviewed next. These groups include differences between: the obese and nonobese; the restrained (i.e., those attempting to control their food intake or dieters) and unrestrained; women and men; emotional and nonemotional eaters.

105.5.1 Obese Versus Nonobese

Initial interest in the effect of stress on eating in humans began as an attempt to understand obesity. It was suggested that overweight individuals were more likely to respond to stressful or emotional stimuli by eating (Stunkard 1959). Such views arose from psychosomatic views of obesity, which suggested that obese individuals did not learn to distinguish between hunger and anxiety (Kaplan and Kaplan 1957). Such individuals were assumed to respond to stress as if it were hunger (i.e., by eating) rather than anxiety. In contrast, Schachter et al. (1968) suggested that unlike normal-weight individuals, obese individuals had not learned to label various physiological cues (e.g., gastric contractions) as hunger and that these cues reduce under stress. Therefore, the prediction was that stress should produce a reduction in hunger and eating in normal-weight individuals but have no impact on the feelings of hunger and eating behavior in the obese. Despite the clear and contrasting predictions of these two views, the evidence in support of each is disappointing.

Greeno and Wing (1994) reviewed 11 studies that addressed the effect of stress on eating in obese and nonobese groups. Schachter et al. (1968) produced the first laboratory test of this effect: anticipating a painful compared to a mild shock (high versus low stress) produced a decrease in eating in

Table 105.4 Main moderators of the stress–eating relationship

Moderator	Main issue
Obese status	Do obese individuals respond differently to stress compared to nonobese individuals?
Restraint	Do individuals who restrict their food intake through self-control processes respond differently to stress compared to those who do not?
Gender	Do males respond differently to stress compared to females
Emotional eating	Do individuals who have a tendency to eat more when anxious or emotionally aroused respond differently to stress compared to nonemotional eaters?
External eating	Do individuals who are more responsive to food cues in their environment respond differently to stress compared to internal eaters?
Disinhibition	Do individuals who have a tendency to overeat respond differently to stress compared to those who do not?

A moderating variable changes the impact of one variable (independent variable) on another variable (dependent variable). The main moderators of the stress–eating relationship are listed here

normal-weight participants, but had no effect on obese participants. This finding is consistent with the Schachter et al. model outlined above. However, only one of the other ten tests of this hypothesis reviewed produced a similar decrease in consumption in normal-weight individuals. Support for the psychosomatic account has also been mixed. Of the 11 studies reviewed by Greeno and Wing (1994), three demonstrated an increase in eating for obese individuals when stressed, three studies found that some obese individuals eat more when stressed; however, five further studies failed to find a relationship between stress and eating in obese individuals. Taken together, this is only relatively modest support for the psychosomatic account of stress–eating relationships in the obese. In addition, those studies only finding partial support for the psychosomatic account suggest an alternative interpretation of these relationships. For example, Baucom and Aiken (1981) demonstrated that rather than obesity it was dieting that was the key predictor of stress-related eating in their study. For both obese and non-obese groups, stress only produced increases in eating in the dieting group. Given the fact that many obese individuals are dieting in an attempt to control their weight, the failure to control for dieting may explain the contradictory findings across studies in the impacts of stress on eating in the obese. In effect, it may be the fact that dieting is more prevalent in the obese than the nonobese, which explains why stress leads to greater eating in the obese compared to the nonobese group.

105.5.2 Restrained Versus Unrestrained

The concept of restrained eating developed from the "set point" theory of obesity (Herman and Polivy 1975). Restrained eaters are assumed to restrict their food intake through self-control processes. When these self-control processes are undermined, disinhibition of eating occurs, and excessive food intake takes place. For example, restrained eaters appear not to adjust their food intake for previous food intake (Herman and Mack 1975). Unrestrained eaters adjust for consuming a "preload" of food by eating less in a subsequent eating test; restrained eaters do not appear to perform this adjustment and eat just as much as if they had not eaten the preload. It is believed that the preload disinhibits the restraint over eating they normally show. Stress is also expected to affect restrained eaters through disrupting the control normally exerted over eating. Thus, individuals with high restraint scores should be more likely to respond to stress by eating, while those low in restraint should show no change. Heatherton et al. (1991) and Schotte et al. (1990) both compared high- and low-restrained eaters, and found that not only did restrained women eat more than unrestrained women, but restrained women who were stressed, ate more than restrained women who were not stressed. A number of other studies have also produced consistent results (see Greeno and Wing 1994; see also Adam and Epel 2007 for a useful recent review); stress produces greater increases in eating in restrained compared to unrestrained eaters. However, the majority of studies to date have only demonstrated this effect in college-aged women. Interestingly, Wardle et al. (2000) showed that work stress lead to increased eating in both restrained women and restrained men.

105.5.3 Women Versus Men

Several studies have looked at differences between female and male eating in response to stress. For example, Grunberg and Straub (1992) examined differences between women and men vulnerable to stress-induced eating. Sweet, salty, and bland foods were provided for participants while watching a video, and for half the subjects the video was unpleasant (i.e., stress inducing). Results showed that

unstressed men consumed significantly more food than any other group. However, stressed women did consume twice as much sweet food as unstressed women, suggesting the importance of food type, at least in women. Although stress generally reduced eating in men, this effect was not significant. Furthermore, some studies have failed to show gender differences. For example, Stone and Brownell (1994) examined the relationship between stress and eating for married couples, who completed daily records of stress and eating. Results showed that both men and women were likely to eat less than usual in response to stress, and the tendency to eat less with an increasing severity of stress was particularly pronounced in women. It is not clear why increased levels of stress were associated with decreased rather than increased eating in this sample. Using a similar design, O'Connor et al. (2008) reported that stress was more strongly associated with between-meal snacking in women compared to men. Interestingly stress was associated with a reduction in consumption of food at meals in this study suggesting that the nature of the eating behavior examined may be key in determining whether stress decreases, increases, or has no effect on amount eaten.

105.5.4 Emotional Versus Nonemotional Eaters

Emotional eating refers to a tendency to eat more when anxious or emotionally aroused compared to nonemotional eaters who do not show such reactivity to emotion in their eating habits. Emotional eating is found to be generally higher in women than men (Van Strien et al. 1986). Stress is assumed to lead to increased eating in emotional eaters because they fail to distinguish between anxiety and hunger (i.e., they respond to stress as if it were hunger), while not affecting those low in emotional eating. The origins in psychosomatic approaches to understanding stress–eating relationships discussed earlier in relation to understanding obesity should be clear. Psychometric measures of emotional eating have been developed (e.g., Van Strien et al. 1986). Van Strien and colleagues (1986) found that stressful life events predicted weight gain in men over a period of 18 months, but only among those who were emotional eaters. In women, stress led to weight gain irrespective of their level of emotional eating. Other studies have reported a limited or lack of impact (e.g., Conner et al. 1999) of emotional eating on stress–eating relationships. More recently O'Connor et al. (2008) reported a strong impact of emotional eating on stress–eating behavior relationships. However, given the limited number of published studies with emotional eating, its impact on stress–eating relationships remains an issue for further study.

105.5.5 Multiple Moderators

A key issue that the above review reveals is the need for integration of the effects of the different moderators of the stress–eating relationship. This is particularly important given the known interrelationship of the various moderators. For example, restrained eaters are reported to be more likely also to be emotional eaters (Weissenburger et al. 1986) and external eaters (Heatherton and Baumeister 1991). One recent large-scale study has focused on testing the above moderators simultaneously. O'Connor et al. (2008) used a daily diary study to compare eating behavior on high- and low-stress days in a sample of 422 workers over 28 consecutive days. Stress was assessed in terms of number of hassles reported while the eating behavior was number of between-meal snacks consumed. Number of snacks was significantly positively correlated with number of hassles. Multilevel modeling indicated that, consistent with previous findings, restraint, emotional eating, external eating, disinhibition,
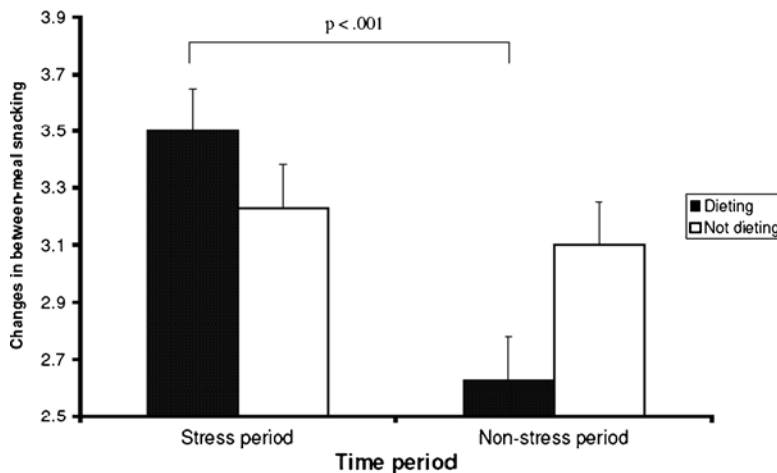
Fig. 105.1 The effects of low conscientiousness and diet status on changes in between-meal snacking. Low consci-
entiousness individuals who were currently trying to lose weight reported eating more between-meal snacks than usual
during the stressful period compared to the nonstressful period. Results are expressed as mean ± SEM, total *n* = 131
(Adapted from O'Connor and O'Connor 2004)

gender, and obesity all individually moderated the relationship between daily hassles and number of
between-meal snacks in a direction consistent with previous research. However, when considered
simultaneously only emotional eating emerged as a significant moderator of the stress–eating rela-
tionship. Moreover, an earlier study pointed toward the possibility that different moderators may
interact. For example, O'Connor and O'Connor (2004) showed that low conscientious (i.e., moderator 1)
individuals who were currently trying to lose weight (i.e., moderator 2) reported eating significantly
more between-meal snacks during a stressful period compared to a nonstressful period (see
Fig. 105.1). Taken together, these findings suggest the need for further studies to examine the simul-
taneous and interactive effects of multiple moderators of the stress–eating relationship using different
research designs. In addition, they highlight the value of further exploration of the influence of higher
order personality factors such as conscientiousness. Recent evidence suggests that conscientiousness
and its facets may influence health status directly via changes in eating behavior and indirectly
through influencing stress–eating behavior relations (see O'Connor et al. 2009).

105.6 Applications to Other Areas of Health and Disease

The research reviewed here has potential application to a number of other areas of health and disease.
For example, exploration of the impacts of stress on other health behaviors represents an important
application for this work. Given the potentially strong relationship between stress and various health
and disease outcomes we need to know more about these behavioral mediators. For example, is the
impact of stress on dietary behaviors more or less important than potential effects on exercise, smoking,
or drinking behavior (Jones et al. 2007) in relation to various health outcomes? These questions point
to the need to simultaneously consider the impacts of stress on multiple health-related behaviors. For
example, stress may simultaneously promote both health-protective and health-risking behaviors. In
addition, the methodologies developed in this area in relation to studying hassles through the use of
diary studies may have widespread application to understanding various other influences on health
and disease. This is an idea we develop further in the final section.

105.7   Conclusions and Future Directions

This review of research on the effects of stress on eating behavior indicates the considerable evidence that the impact of stress on eating behavior is an important pathway through which stress impacts on health outcomes. Stress can be associated with overall increases or decreases to the amount eaten as well as changes in the patterns of eating. The nature of the eating behavior and the stressor are crucial in determining the nature of the relationship. Considerable recent research has shown how stress is associated with *increases* in the consumption of high-fat and high-sugar foods particularly when consumed as fast food or between-meal snacks (e.g., O'Connor et al. 2008; Steptoe et al. 1998). Future research could usefully explore the impacts of stress on a broader range of eating behaviors simultaneously (e.g., meals and snacks) and use more precise measurements of food intake (e.g., 24-h recall). In relation to the stressor, ego-threatening, work, and interpersonal stressors appear to be particularly associated with increased eating (e.g., Wallis and Hetherington 2004), while physically threatening stressors are generally associated with decreased eating (e.g., O'Connor et al. 2008). Understanding of the stress–eating behavior relationship is further complicated by the presence of various important moderating effects. Here, evidence particularly suggests that stress–eating relationships are strongest among individuals high in restraint, disinhibition, external eating, or emotional eating. Only one significant study has considered these moderators simultaneously and this study identified emotional eating as the preeminent moderating variable (O'Connor et al. 2008). Future research could usefully replicate this simultaneous assessment of the effects of various moderators given their intercorrelation.

In addition to pursuing carefully designed studies in the laboratory, future research in this area should also consider using innovative multilevel, daily diary methods in the real world. Daily diary techniques can use interval-contingent (i.e., assessments completed at the end of each day), event-contingent, (i.e., assessments completed in response to an event), or signal-contingent methods (i.e., assessments completed in response to random alarms or beeps from a palmtop computer) in exploring interrelationships among important variables in real-world settings. In such designs, participants complete diaries at a fixed time point (e.g., evening), during each day triggered by stressful encounters, or in response to random signals. This methodology facilitates the use of the powerful multilevel random coefficient modeling techniques. This approach provides accurate analyses of multilevel data structures and allows the modeling of day-to-day within-person effects together with the impact of between-person factors such as potential vulnerability variables (emotional eating, restraint).

Future researchers might also usefully consider utilizing the day reconstruction method introduced recently by Kahneman and colleagues (2004). This method is a structured recall technique that enables participants to recall events, mood, and well-being indicators over the previous day. For example, Stone et al. (2006) have used the daily reconstruction method to explore the diurnal rhythms of emotions in a large-scale investigation and identified a number of specific patterns, which have not previously been observed. They argue that diary methods are frequently expensive, are associated with a heavy participant burden, and possibly interfere with daily activities. However, the daily reconstruction method does not allow us to investigate causal relations between study variables.

A final important area for development is exploration of the psychological and biological mechanisms underlying the stress–eating relationship. These mechanisms are likely to be complex to account for the complexity of findings reported. Interesting research has focused on various attentional biases that might explain some of these effects (e.g., Newman et al. 2008; Tapper et al. 2008). Advances are also being made in relation to understanding the biological mechanisms. For example, differences in cortisol reactivity appear to offer one explanation of some moderating effects on the stress–eating relationship (Fig. 105.2; Newman et al. 2007). However, further careful assessment of daily fluctuations in cortisol levels in relation to changing stress levels is required to clarify the
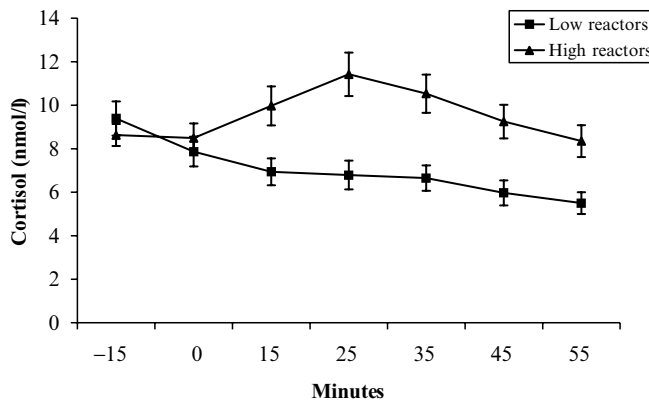
Fig. 105.2 Cortisol reactivity profiles of high and low reactors during a laboratory stress challenge. This figure shows individual differences in the cortisol response to stress that might represent a biological moderator of the stress–eating relationship. Results are expressed as mean ± SEM, *n* = 50 (Adapted from Newman et al. 2007)

importance of this pathway. Moreover, several of the studies reviewed here also point to diathesis–stress mechanisms that suggest that psychological vulnerabilities, when activated by stress, may result in negative outcomes. For example, coping styles (the behavioral and cognitive responses individuals use when they encounter stress), in particular, have been shown to have well-established moderating effects on an individual's response to a stressful encounter (cf., O'Connor and O'Connor 2004). It would, therefore, be beneficial for future research to assess the psychological factors (e.g., coping) associated with the cortisol response to stress and test whether this differs according to stressor type (e.g., ego-threatening, interpersonal, work-related).

Summary Points

- Research into the relationship between stress and eating has been dominated by laboratory studies using experimental designs and cross-sectional surveys. Such designs capture differences between individuals in the effect of stress on eating. Eating is a behavior that varies within an individual on a day-to-day basis and is affected by factors such as daily hassles, which may similarly vary within the individual. Daily diary methods are appropriate to capture these effects.
- Multilevel modeling approaches using diary methodology allow researchers to examine the impact of such daily fluctuations in stressors on eating behaviors, together with the between-subject effects of moderators such as gender or individual differences.
- Different types of stressor have different effects on eating. In particular physical threats seem to lead to a reduction in food intake whereas other types of stressors e.g. ego-threatening, interpersonal, and work-related are more likely to lead to an increase in food intake, particularly for those who are susceptible to stress-related eating.
- Daily stressors in the work environment, including long work hours have negative impact on eating, typically these lead to increases in fatty food consumption or greater consumption of fast food.
- The effect of stress on eating behavior is moderated by a range of factors, e.g. gender, obesity, and eating styles. The only study to examine a range of these moderators simultaneously found that emotional eating was the principal moderator.

Key Terms

Psychological stress: Stress is the condition that results when person/environment transactions lead the individual to perceive a discrepancy – whether real or not – between the demands of a situation and the resources of the person's biological or social systems.

Daily hassles: Hassles are events, thoughts, or situations which, when they occur, produce negative feelings such as annoyance, irritation, worry or frustration, and/or make you aware that your goals and plans will be more difficult or impossible to achieve.

Diary methods: Diaries allow respondents to record day-to-day minor life events or hassles that are part of everyday life and have the advantage of not constraining respondents to a limited number of events.

Multilevel modeling: This is a statistical technique that allows the researcher to examine day-to-day within-person effects *together* with the impact of between-person factors such as personality or gender.

Moderating variable: Moderators change the nature of the relationship between two variables, e.g., the stress–eating relationship. They may alter either the strength or direction of this relationship. For example, dietary restraint would be described as moderating the relationship between stress and between-meal snacking.

References

Abraham C, Conner M, Jones F, O'Connor DB. Health psychology: topics in applied psychology. London: Hodder Arnold; 2008.
Adam TC, Epel ES. Physiol Behav. 2007;91:449–58.
Affleck G, Zautra A, Tennen H, Armeli S. J Consult Clin Psychol. 1999;67:746–54.
Allen TD, Armstrong J. Am Behav Sci. 2006;49:1204–21.
Baucom DH, Aiken PA. J Pers Soc Psychol. 1981;41:577–85.
Conner M, Fitter M, Fletcher W. Psychol Health. 1999;14:51–63.
DeLongis A, Coyne JC, Dakof G, Folkman S, Lazarus RS. Health Psychol. 1982;1:119–36.
Emdad RK, Belkic K, Theorell T, Cizinsky S. Psychother Psychosom. 1998;67:226–40.
Ferguson E. In: Miles J, Gilbert P, editors. A handbook of research methods in clinical and health psychology. Oxford: Oxford University Press; 2005. p. 111–24.
Greeno CG, Wing RR. Psychol Bull. 1994;115:444–64.
Grunberg NE, Straub RO. Health Psychol. 1992;11:97–100.
Grzywacz JG. Work-family spillover and health during midlife: is managing conflict everything? Am J Health Promotion. 2000;14: 236–243.
Hammer TH, Saksvik PO, Nytro K, Torvatn H, Bayazit M. J Occup Health Psychol. 2004;9:83–97.
Heatherton TF, Baumeister RF. Binge eating as escape from self-awareness. Psych Bull. 1991;110: 86–108.
Hellerstedt WL, Jeffrey RW. The association of job strain and health behaviors in men and women. Int J of Epidem. 1997;26:575–583.
Heatherton TF, Herman CP, Polivy J. J Pers Soc Psychol. 1991;60:138–43.
Heatherton TF, Herman CP, Polivy J. J Pers Soc Psychol. 1992;62:801–3.
Herman CP, Mack D. J Pers. 1975;43:647–60.
Herman CP, Polivy J. J Abnormal Psychol. 1975;84:666–72.
Johnson JV, Hall EM. Am J Public Health. 1988;78:1336–42.
Jones F, Bright J. Stress: myth, theory and research. London: Prentice Hall; 2001.
Jones F, O'Connor DB, Conner M, McMillan B, Ferguson E. J Appl Psychol. 2007;92:1731–40.
Kahneman D, Krueger AB, Schkade D, Schwarz N, Stone A. Science 2004;306:1776–80.
Kanner AD, Coyne JC, Schaefer C, Lazarus RS. J Behav Med. 1981;4:1–39.
Kaplan HI, Kaplan HS. J Nerv Ment Diseases. 1957;125:181–201.
Karasek RA, Theorell R. Healthy work. New York: Basic Books; 1990.

Kreft I, De Leeuw J. Introducing multilevel modelling. London: Sage; 2006.

Lallukka T, Ek E, Sarlio-Lahteenkorva S, Roos E, Laaksonen M, Rahkonen O, Lahelma E. Prevent Med. 2004;38:48–56.

Lattimore P, Caswell N. Appetite 2004;42:167–73.

Lazarus RS. Psychological stress and the coping process. McGraw-Hill: New York; 1966.

Lazarus RS, Folkman S. Stress, appraisal and coping. New York: Springer; 1984.

Major DA, Germano LM. In: Jones F, Burke RJ, Westman M, editors. Work-life balance: a psychological perspective. New York: Psychology Press; 2006. p. 13–38.

Nakamura K, Shimai S, Kikuchi S, Takahashi H, Tanaka M, Nakano S. Occup Med. 1998;48:169–73.

Nakanishi N, Nakamura K, Ichikawa S, Suzuki Y, Tatara K. Occup Med. 1999;49:109–14.

Newman E, O'Connor DB, Conner M. Psychoneuroendocrinology 2007;32:125–32.

Newman E, O'Connor DB, Conner M. Appetite 2008;51:339–42.

Niedhammer I, Goldberg M, Leclerc A, David S, Bugel I Landre MF. J Epidemiol Comm Health. 1998;52:93–100.

Nieuwenhuizen AG, Rutters F. Physiol Behav. 2008;94:169–77.

O'Connor DB, O'Connor RC. Stress Health. 2004;20:279–91.

O'Connor DB, O'Connor RC, White BL, Bundred PE. Psychol Health Med. 2000;5:241–50.

O'Connor DB, Jones F, Conner M, McMillan B, Ferguson E. Health Psychol. 2008;27:S20–31.

O'Connor DB, Conner M, Jones F, McMillan B, Ferguson E. Ann Behav Med. 2009.

Oliver G, Wardle J, Gibson EL. Psychosom Med. 2000;62:853–65.

Oliver KG, Huon GF, Zadro L, Williams KD. Eating Behav. 2001;2:19–26.

Overgaard D, Gyntelberg F, Heitmann BL. Occup Med. 2004;54:35–41.

Schachter S, Goldman R, Gordon A. J Pers Soc Psychol. 1968;10:91–7.

Schotte DE, Cools J, McNally RJ. J Abnormal Psychol. 1990;99:317–20.

Steptoe A, Lipsey Z, Wardle J. Br J Health Psychol. 1998;3:51–63.

Stone AA, Brownell KD. Psychol Health. 1994;9:425–36.

Stone AA, Schwartz JE, Schwarz N, Schkade D, Krueger A, Kahneman D. Emotion 2006;6:139–49.

Stunkard AJ. Psychiatric Quart. 1959;33:284–92.

Stunkard AJ, Messick SM. J Psychosom Res. 1985;29:71–83.

Tanofsky-Kraff M, Wilfley DE, Spurrell E. Int J Eating Disorders. 2000;27:411–8.

Tapper K, Pothos EM, Fadardi JS, Ziori E. Appetite 2008;51:335–8.

Van der Hulst M. Scand J Work Environ Health. 2003;29:171–88.

Van Horn L, Kavey RE. Ann Behav Med. 1997;19:197–212.

Van Strien T, Frijters JE, Bergers GP, Defares PB. Int J Eating Behav. 1986;5:295–315.

Waller G, Watkins H, Shuck V, McManus F. Int J Eating Disorders. 1996;20:169–76.

Wallis DJ, Hetherington MM. Appetite 2004;43:39–46.

Wardle J, Steptoe A, Oliver G, Lipsey Z. J Psychosom Res. 2000;48:195–202.

Weissenberger J, Rush AJ, Giles DE, Stunkard AJ. Psychiatry Res. 1986;17:275–83.

Wong BC, Lam SK. GI Cancer. 1999;3:1–10.

Chapter 106
Parental Restriction and Their Children's Food Choices and Intake

Harriëtte M. Snoek

Keywords Parenting • Child • Eating behaviour • Restriction

106.1 Introduction

The environment in which children grow up largely shapes the child's food preferences, since children like and eat what is familiar to them (Fisher and Birch 2002), what is available, and what their parents eat (Ritchie et al. 2005). This has an influence on the rest of the children's lives, since dietary habits formed in childhood are likely to persist into adulthood (Klesges et al. 1991; Kelder et al. 1994; Clark et al. 2007). Food habits during childhood and the family context are therefore widely assumed to be crucial in the establishment of healthy dietary habits (Wardle 1995). These parental influences are transmitted in several ways. Firstly, weight status, food choices, food preferences, and eating behaviors "aggregate" within families (Faith et al. 2004b; Rankinen and Bouchard 2006), which suggests modeling of all these factors. Secondly, parents can influence their children through food-related parenting practices, and these food-related parenting behaviors occur within the context of parents' general parenting styles. (See Table 106.1 for definitions of general and food-related parenting practices.) Parents also have a more direct influence on their offspring by making certain foods available and accessible and reducing access to other foods (Ritchie et al. 2005). Finally, biological parents shape their child's genetic makeup. The focus of this chapter is on general and food-related parenting behaviors (especially parental control and restriction) and their relation to childrens and adolescents' food intake.

H.M. Snoek (✉)
Behavioural Science Institute, Radboud University Nijmegen,
The Netherlands
and
Agricultural Economics Research Institute, Wageningen University and Research Center,
P.O. Box 8130, 6700 EW Wageningen, The Netherlands
e-mail: harriette.snoek@wur.nl

106.2 General Parenting

General parenting style is the context in which parenting practices occur, and it is often operationalized by the dimensions control and support (Baumrind 1971). The control dimension varies from supervision and monitoring to more manipulatively suppressive control, while the support dimension refers to the affective and supportive behavior of parents (Lamborn et al. 1991; Finkenauer et al. 2005). Those two dimensions have been related to children's behaviors, including health risk behaviors and internalizing problem behaviors (Maccoby and Martin 1983).

Generally, behavioral control (active supervision of, and acquiring knowledge about, what children are doing) was found to be a protective factor for problem behavior while psychological control (harsh, suppressive, and manipulating control including behaviors such as guilt induction, love withdrawal, and excessive pressure for change) was a risk factor (Finkenauer et al. 2005). Furthermore, psychological control is suppressive and authoritarian and therefore more likely to undermine the child's autonomy and ability to self-regulate food intake. Parental support on the other hand has been associated with less problem behavior and emotional problems in children (Finkenauer et al. 2005). The support and control dimensions can also be combined into four parenting styles (see Table 106.2). An authoritative parenting style (high control, high support) is considered preferable to an authoritarian (high control, low support), permissive (high support, low control), or neglectful (low support, low control) parenting style in terms of child behavioral outcomes.

Studies on food intake, weight, and eating problems are generally in line with these findings. Lack of parental support and parental caring have been related to disordered eating and body dissatisfaction (McVey et al. 2002; Littleton and Ollendick 2003) as well as obesity (Lissau and Sorensen 1994). An authoritarian feeding style has been related to a higher fruits and vegetables consumption and (Kremers et al. 2003) and lower overweight status compared to the other parenting styles (Rhee et al. 2006). However, results are inconclusive as some studies found only weak and mostly insignifi-

Table 106.1 Definitions and explanations of key terms

General parenting	
Support	Affective and supportive behaviors and responsiveness of parents
Behavioral control	Active supervision of, and acquiring knowledge about, what children are doing
Psychological control	Harsh, suppressive, and manipulating control including behaviors such as guilt induction, love withdrawal, and excessive pressure for change
Food-related parenting	
Restriction	Parents' attempt to control their children's eating by restricting access to foods
Monitoring	Extent to which parents report watching their children's consumption of (energy-dense) foods
Pressure to eat	Prompting, pressure, or encouragement to eat more healthy foods or more food in general, particularly at mealtimes
Instrumental feeding	Using food as reward, bribe, comfort, etc.

Definition of general parenting practices and most commonly studied food-related parenting practices

Table 106.2 Parenting styles defined by the two parenting dimensions

		Support or responsiveness	
		Low (rejecting, unresponsive)	High (accepting, responsive)
Control	**Low (undemanding)**	Neglectful	Authoritarian
	High (demanding)	Permissive	Authoritative

As described in Maccoby and Martin (1983, p. 39) the dimensions of parental support and parental control can be combined into four parenting styles
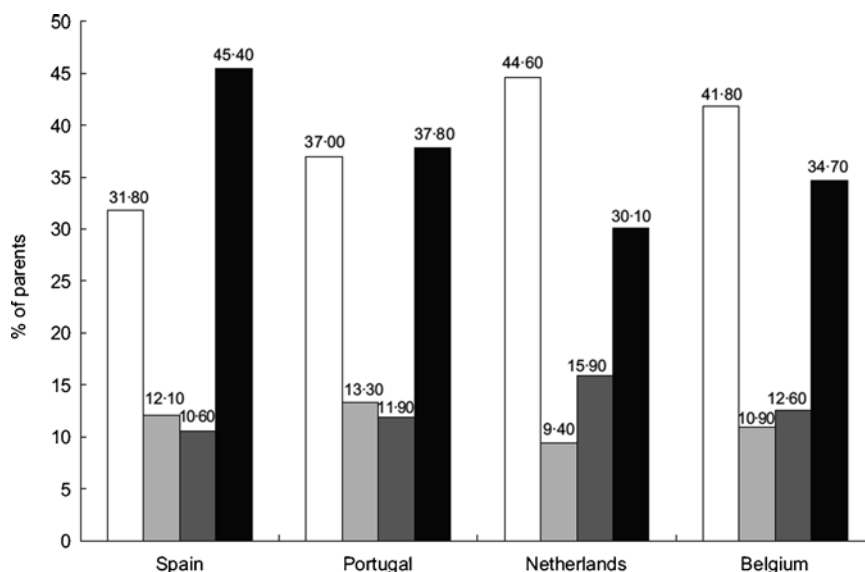
Fig. 106.1 Percentages of parents in the four categories of parenting styles (Đ, authoritative; , authoritarian; , indulgent; , neglectful) in the four countries. Data were derived from the cross-sectional study of the Pro Children project, October–December 2003. Most parents used an authoritative or neglectful parenting style although percentages differed between the four European countries (Reprinted from de Bourdeaudhuij et al. 2009, p. 261. With permission)

cant associations between general parenting style and fruit and vegetable intake. For example a study by de Bourdeaudhuij et al. (2009) measured parenting styles in four European countries. Most parents used an authoritative or neglectful parenting style (see Fig. 106.1) although percentages differed between countries. However, no differences were found in fruit and vegetable intake of children with the parenting style of their parents.

In summary, surprisingly few studies addressed the association between general parenting style and food intake and the current results are inconclusive. A number of those addressed parenting styles rather than the separate dimensions (support and control), which has the advantage that interplay between the dimensions is taken into account. However, when focusing on parental control, this further complicates conclusions on the effectiveness and desirability of a controlling parenting style. Overall, there is still some way to go before we can conclude on whether general parental control is related to a healthier food pattern.

106.3 Food-related Parenting

General feeding style and feeding practices are related. For example, a permissive parenting style has been related to lower monitoring of children's unhealthy food intake (Blissett and Haycraft 2008). Most studies, however, address either general parenting or food-related parenting. Similar terms as with general parenting styles have been used to translate food-related behaviors into feeding styles. An authoritative feeding style was defined as the balance between an authoritarian (control with little regard for the child's choices and preferences) and permissive (no active involvement of parents in type or amount of food eating) feeding style. This style has been related to a more healthy food pattern in preschool children (Patrick et al. 2005). In line with this O'Connor et al. (2009) found three clusters of parents with regard to parenting practices specific to fruit and vegetable intake. Next to the permissive (low control in general) and high controlling groups one cluster of parents scored
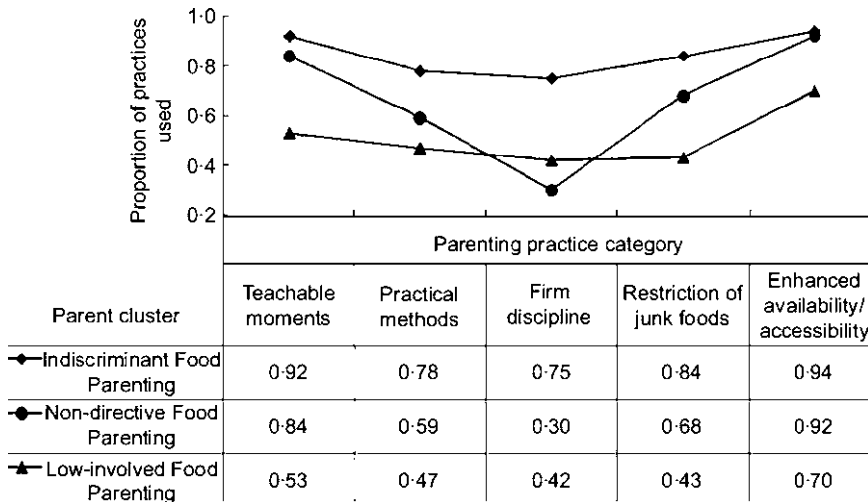
Fig. 106.2 Reported use (proportion) of each parenting practice category by K-means derived parenting practices cluster: Head Start preschool children and their parents in Houston, Texas and northern Alabama, 2004–2005. Based on the different parenting practices, three clusters were identified: permissive (low control in general), high controlling (high on control in general) and nondirective (high on most parenting practices which exception of the firm discipline). This third cluster was most strongly related to fruit and vegetable intake (Reprinted from O'Connor et al. 2009, p. 7. With permission)

high on most parenting practices which exception of the firm discipline (see Fig. 106.2). As expected this cluster was most strongly related to fruit and vegetable intake although the relation was no longer significant after controlling for parental intake.

The majority of research on food-related parenting focuses on three types of control of food intake (again sometimes also named feeding styles): Pressure to eat, restriction, and monitoring. Most of these studies further focused on preschool and primary age children (Clark et al. 2007). Restriction over food intake is the parents' attempt to control their children's eating by restricting access to foods. Pressure to eat refers to prompting, pressure, or encouragement to eat more healthy foods or more food in general, particularly at mealtimes. Finally, monitoring food intake is the extent to which parents report watching their children's consumption of (energy-dense) foods.

A series of experiments by Birch and Fisher in young children (Fisher and Birch 1999b; Birch and Fisher 2000; Fisher and Birch 2000) showed that food restrictions were associated with unintended outcomes, such as higher preference for and intake of the restricted foods and lower ability to self-regulate intake. For example, during a 5 week period of restricted access to a specific food, children ($n = 31$) consumed more of that compared to control food in a free access setting in the lab. Before the restricted access period there was no difference in intake in the lab between the restricted and control foods. Similar results of positive associations between control and snacking were found by Brown and Ogden (2004), and Johannsen, Johannsen, and Specker (2006) found that fathers' controlling behavior was associated with higher body fat percentages in girls. Others found null results or negative associations between parental control and food intake (de Boudeaudhuij 1997) or weight status (Robinson et al. 2001). See Gubbels et al. (2009) for an overview of studies on the association between parenting practices and food intake and their contradictory results. Prospective data revealed either no significant longitudinal associations between restriction, monitoring, or pressure to eat and fat mass (Spruijt-Metz et al. 2006) or showed inconsistent findings (Faith et al. 2004a; Carnell and Wardle 2007). In line with the mixed finding of the empirical studies, review studies also have not been conclusive. Clark et al. (2007) concluded that

"restriction of children's eating has most frequently and consistently been associated with weight gain" and they also stated that there is substantial evidence of a causal relationship. Wardle and Carnell (2007), on the other hand, concluded that the results of the studies they reviewed suggest that greater parental control either leads to lower adiposity in the long-term or has minimal impact on weight for the majority of the children.

In summary, there is some evidence for unintended negative effects of (firm) parental restriction on intake of (specific) foods. Also, there is some evidence that an authoritative feeding style in which parents set rules and are not permissive but also respect children's choices and preferences is the most successful style. However, evidence in this area is contradictive as in some studies it was found that restriction relates to higher intake (forbidden fruit effect), whereas others found an association with healthier eating patterns, and finally also null effects have been found. Overall more research is needed in order to be able to give well-founded advice to parents and studies should make clear distinctions between type of control used.

106.4 The Measure of Parental Control over Food Intake

For the measure of parental control there are several methodological issues to consider. Ogden, Reynolds, and Smith (2006) stated that research on parental control is confusing and used a narrow conceptualization of the ways in which parents control what and when their children eat. In addition, different forms of control may influence different areas of eating behavior. Ogden and colleagues make a distinction between overt and covert control. They argue that most of the existing scales measure overt control, which is the limitation of the child's intake of unhealthy foods "in a way that can be perceived by the child". This type of control are specific behaviors exerted while eating and during meals. In contrast, covert control "remains undetected by the child but still results in restriction" (Ogden et al. 2006, p. 102). This includes availability and accessibility of (un)healthy foods in the household in general and for the children in particular. Overt and covert control were both related to higher fruit and vegetable intake and lack of covert control was related to higher unhealthy snacks intake.

In a review, Faith et al. (2004c) concluded that, compared to measurement in which maternal feeding restrictions were explicitly assessed, measures of global parental feeding styles (including controlling efforts) did not seem to be sensitive enough to detect associations between parental behaviors and children's weight. However, questionnaires for food-related control and children's weight or food intake are subject to methodological problems. One of the most commonly used questionnaires on food-specific parental restriction of children is the Child Feeding Questionnaire (CFQ) (Birch et al. 2001). Although the CFQ showed good psychometric characteristics in some studies (Carper et al. 2000), it is still an unresolved issue how scores on the CFQ are related to parents' actual behaviors in a naturalistic setting (Orrell-Valente et al. 2007). Moreover, no clear correspondence between child and mother's reports on the CFQ scales has been found indicating discrepancies between parents' reports and children's perceptions of their parents' behavior. Carper, Fisher, and Birch (2000) found that while only 26% of the parents indicated that they pressured their daughters to eat, 61% of the daughters reported to perceive some degree of parental pressure. This raises questions about whether mothers generally give a fair and realistic report of their behavior when it comes to complex behaviors like how they handle the food intake of their children. Observational designs might be a good alternative way to study mother–child interactions on food, especially since young children cannot adequately report on perceptions of their parents' behaviors (Table 106.5).

106.5 Observations of Parental Control

Two study settings have been popular in observing parent–child interactions over food choices. First, children's involvement in food shopping has been observed and their attempts to influence their parents as well as parental reactions. For example, O'Dougherty, Story, and Stang (2006) found that children were actively engaged in food shopping. Children's requests were for sweets or snacks in half of the cases. Parents refused just over half of the requests; this was done most often by ignoring the request, by explaining why not, or by a simple verbal no. Usually, children accepted their parent's refusal at once (O'Dougherty et al. 2006).

A second often-used method for mapping parent–child interactions over food choices are observations during family meals. Moens, Braet, and Soetens (2007) for example found that during family dinners, families with an overweight child showed twice as much maladaptive control strategies and less parental support. Orrel-Valente et al. (2007) observed preschool children and their parents during meals. They found that children were very rarely restricted, rather parents more often tried to get children to eat more. This is again an important issue to consider in the comparison of observational studies and surveys as questionnaires often address both restriction of snacks and during meals and have a strong focus on restriction of food (especially unhealthy snack). Parental behaviors during meals might thus considerably differ from their rules and parenting practices regarding snack foods. Children's compliance with parental strategies was most highly associated with neutral prompts as opposed to pressuring/demanding, reasoning, offer of food or play rewards, and threats to withhold food or toys (see Table 106.3). Interestingly, parenting practices varied according to sex of both the parents and the children and by SES (Orrell-Valente et al. 2007).

In our own work (Snoek et al. in preparation a, b), mother-reported and child-reported restriction measured with the CFQ did not differ between mothers of overweight and nonoverweight children and had little main or moderating effect on the children's food choices. An observational study showed that mothers do seem to be successful in influencing their children's food choices, since children's choices in company of their mothers were healthier compared to when the child was

Table 106.3 Correlation of parental strategies with children's eating compliance and eating refusal

Type of strategy	Correlation of frequency of use and child eating ($n = 117$)	
	Eating compliance	Eating refusal
neutral prompts	0.65*	0.16
pressure/demand to eat	0.39*	0.67*
reasoning	0.32*	0.23
Offer of food rewards	0.27*	0.09
praise	0.31*	0.05
Food restraint (portion control)	−0.04	−0.06
threat to withhold food	0.23	0.14
threat to withdraw play privileges	0.09	0.67*
Offer of play rewards	0.28*	0.18*
average of all strategies per meal	0.69*	0.63*

*$p < 0.05$

Parental strategies to influence children's food intake were correlated to children's compliance and refusal. The highest compliance was found for neutral prompts while pressuring/demanding, reasoning, offer of food or play rewards, and threats to withhold food or toys was highly correlated to refusals (Reprinted from Orrell-Valente et al. 2007, p. 43. With permission)

Table 106.4 Event coding for each comment by the mothers during the role play

	Description	Examples
	Event ratings	
Neutral	Not related to the assignment.	
Monitoring	Coaching without pushing towards certain products or food groups. Child is given the freedom to choose.	"What are we going to eat tonight?", "What else do we need?"
Directive control	Mother has a clear idea about which product or food group to buy (pressure) or not to buy (restriction) and pushes child in that direction. Child is still able to make choices within certain boundaries.	"Do we eat French fries on a normal day?" (restriction), "What do we always eat with our potatoes?" (pressure)
Enforcing Control	Mother gives an order, is commanding, points at one specific product, or takes the product herself to make the child buy (pressure) or put back (restriction) something.	"Put the pizza back.", "And now some carrots."
Support	Mother agrees with something the child does or encourages child.	"Well done.", "Yes, you can take that one."

During observation of the interaction, each event, that is if the mother was speaking without being interrupted by a pause or the child, was coded as monitoring, control (directive or enforcing) and support

alone while choosing. This is in accordance with previous studies that found positive effects of maternal presence or expected presence on children's food choices (Klesges et al. 1991). Results further showed that mothers used a range of controlling and encouraging behaviors to influence their children's food purchases (Table 106.4). Observation of maternal controlling behaviors of children's food intake revealed two underlying factors, namely "monitoring control" which included support, monitoring, and directive control (pressure and restriction), and "authoritarian control" which included enforcing control (pressure and restriction). This is in line with the distinction made between types of general parental control and also supports the critique on the CFQ that it includes both monitoring and more psychological control items and does not account for differences in controlling behaviors (de Boudeaudhuij 1997; Saelens et al. 2000; Brown and Ogden 2004). Pressure to eat was not a separate factor from restriction, which is in contrast to the distinction made in the Child Feeding Questionnaire. Overall, it seems that at least in relation to children's food choices there is still some way to go in the development of a behavior-validated questionnaire on food-related parenting. In a sample larger than ours, scores on the CFQ could be linked to the observed maternal controlling behaviors and this could help to validate and/or adjust parts of the questionnaire.

Further we found that children made more unhealthy choices in dyads in which mothers were highly permissive and children dominant. Our results thus provide additional evidence that a certain degree of control is necessary, and suggest that when children are dominant, parents should also actively be involved in food choices. The way parents enforce control does not seem to be of great importance as long as they do not withdraw from the interaction and allow children to take control and make their own choices. More studies are needed to replicate our findings and look at the long-term effects.

Observation studies in conclusion seem to have a valuable contribution to the research on parental restriction and food intake. Not only because of the lack of (behavior) validated questionnaires but also because they take into account children's reactions to parental behavior and ideally also interactions between the two. Current observational studies provide some evidence for the benefits of active involvement of parents and control of children's food intake.

Table 106.5 Key facts of mapping parent–child interaction over food intake

1. Monitoring food intake, restriction of food intake, and pressure to eat are measured by the child feeding questionnaire (CFQ).
2. Parenting can be reported by parents and children separately on different versions of the same questionnaires. However, there is no strong correspondence between parent and child reports of parenting.
3. Observation studies can be a good alternative to questionnaires. Especially for young children, when parent reports are subject to social desirability, and when the available questionnaires are not validated for behavior.
4. Indifferent of the method it is important to distinguish between different types of parental control: monitoring versus restriction and directive versus enforcing control.

This table lists the key facts of mapping interactions between children and parents over food intake and the different methods that can be used.

106.6 Implications for Treatment and Prevention

The influence of maternal control might depend not only on the type of control, but also on its level. Lack of sufficient control (permissiveness) is believed to have a negative influence on children's behavior, whereas over-control is not good either. Bruch (1973) already observed that for the development of healthy eating behavior, it appears to be essential for normal development that there is a balance between stimulation coming from outside and confirmation of impulses originating in the child itself. Parents of young children are often the focus of public health interventions aimed at reducing overweight risks and/or improving diets. However, the focus of prevailing interventions is on *what* parents feed their children and not on *how* they feed them (Clark et al. 2007). There is, however, little consensus among researchers on how this should be, especially regarding control. Our results provide additional evidence that a certain degree of control is necessary.

106.7 Additional Issues to Consider

A few factors complicate the associations between food-related parenting and children's weight and eating. First, the association between parenting and child's weight and eating is likely to be reciprocal: An overweight status or increase in weight can elicit certain parental behaviors (Ventura et al. 2009). For example, higher child adiposity is been related to higher restriction (Fisher and Birch 1999a). Similarly, Faith et al. (2004a) found that (among children predisposed to obesity) elevated child weight appears to elicit restrictive feeding practices, which in turn may produce additional weight gain. Parents may adopt child-feeding behaviors in response to child weight, or perceived child weight (Clark et al. 2007).

The influence of children's weight on parental behavior is further complicated by the fact that parents do not always have an accurate perception of their child's weight status and do not always recognize their children's overweight. For example, Etelson, Brand, Patrick, and Shirali (2003) found that parents of overweight children invariably underestimated their children's weight. Only 10.5% of parents of overweight children perceived their child's weight accurately compared with 59.4% of other parents. Perception of child's weight (and of parents' own weight) can be measured with a subscale of the CFQ and several studies addressed its relation to weight status and parental feeding behaviors (Birch and Ventura 2009).

Third, maternal restriction has been linked to various maternal characteristics, such as own weight concern and restrained eating (Clark et al. 2007). Fisher and Birch (1999a) found that parents' own

restrained eating was related to higher restriction of their 3–5 years old children. Similarly, mothers' dietary restraint was related to maternal control, which in turn was related to higher 24-h recall food intake and higher weight in 5-year-old daughters (Birch and Fisher 2000). So, in addition to maternal behaviors being a reaction to children's characteristics, these behaviors can also partly be a response to their own characteristics and weight preoccupations.

106.8 Conclusion

More research is needed on the relation between parental behaviors and food intake. General control and food-related control should both be addressed, and for food-related control a clear distinction between types of control is indispensable. Given the lack of (behavior) validated questionnaires for food-related parenting practices, observational studies can add valuable information to the commonly used surveys. So far, evidence favors an authoritative feeding style in which parents are not permissive but actively control their children's food intake but, do not impose strict/harsh control, leave room for their children's own choices and preferences, and acknowledge their children's possible ability to self-regulate their energy intake.

106.9 Applications to Other Areas of Health and Disease

Like for other health-related behaviors (Van Der Vorst et al. 2007) some degree of parental control seems necessary. However, unlike for example, smoking or alcohol use everyone has to eat. Obesity only results from a long-term unhealthy food pattern and is not caused by individual foods or eating moments. So, it is not about preventing or delaying one specific behavior. A second difference with other health (risk) behaviors is that there is some evidence that children might have an innate food intake regulation. Parents thus will have to find the balance between permissiveness which probably leads to unhealthier choices and over-control which will interrupt children's ability to self-regulate their energy intake.

Summary Points

- General parental support and an authoritative parenting style were related to healthier eating patterns in some but not all studies.
- Firm and harsh control might enhance liking of a food and might undermine children's ability to self-regulate energy intake.
- Food-related restriction has been related to higher intake of unhealthy foods, healthier eating patterns, or sometimes even null effects.
- Questionnaires on food-related restriction measure different types of restriction and have not been fully validated for behavior.
- Observational studies provide tentative proof that some degree of restriction is necessary in order for children to make healthy food choices.

References

Baumrind D. Dev Psychol. 1971;4:1–103.

Birch LL, Fisher JO Am J Clin Nutr. 2000;71:1054–61.

Birch LL, Ventura AK Int J Obesity. 2009;33:S74–81.

Birch LL, Fisher JO, Grimm-Thomas K, Markey CN, Sawyer R, Johnson SL Appetite. 2001;36:201–10.

Blissett J, Haycraft E Appetite. 2008;50:477–85.

Brown R, Ogden J Health Educ Res. 2004;19:261–71.

Bruch H. In: Eating disorders. Obesity, anorexia nervosa, and the person within. New York: Basic Books Inc. Publishers; 1973. p. 44–65.

Carnell S, Wardle J Obesity. 2007;15:137–44.

Carper JL, Fisher JO, Birch LL Appetite. 2000;35:121–9.

Clark HR, Goyder E, Bissell P, Blank L, Peters J J Public Health (Oxf.). 2007;29:132–41.

de Boudeaudhuij I. J Health Psychol. 1997;2:45–56.

de Bourdeaudhuij I, Te Velde SJ, Maes L, Perez-Rodrigo C, de Almeida MD, Brug J Public Health Nutr. 2009;12:259–66.

Etelson D, Brand DA, Patrick PA, Shirali A Obes Res. 2003;11:1362–8.

Faith MS, Berkowitz RI, Stallings VA, Kerns J, Storey M, Stunkard AJ Pediatrics. 2004a;114:429–36.

Faith MS, Keller KL, Johnson SL, Pietrobelli A, Matz PE, Must S, Jorge MA, Cooperberg J, Heymsfield SB, Allison DB Am J Clin Nutr. 2004b;79:844–50.

Faith MS, Scanlon KS, Birch LL, Francis LA and Sherry B Obes Res. 2004c;12:1711–22.

Finkenauer C, Engels RCME, Baumeister RF Int J Behav Dev. 2005;29:58–69.

Fisher JO, Birch LL Appetite. 1999a;32:405–19.

Fisher JO, Birch LL Am J Clin Nutr. 1999b;69:1264–72.

Fisher JO, Birch LL J Am Diet Assoc. 2000;100:1341–6.

Fisher JO, Birch LL Am J Clin Nutr. 2002;76:226–31.

Gubbels JS, Kremers SP, Stafleu A, Dagnelie PC, Goldbohm RA, de Vries NK, Thijs C Appetite. 2009;52:423–9.

Johannsen DL, Johannsen NM, Specker BL Obesity (Silver Spring). 2006;14:431–9.

Kelder SH, Perry CL, Klepp KI, Lytle LL Am J Public Health. 1994;84:1121–6.

Klesges RC, Stein RJ, Eck LH, Isbell TR, Klesges LM Am J Clin Nutr. 1991;53:859–64.

Kremers SP, Brug J, de Vries H, Engels RC Appetite. 2003;41:43–50.

Lamborn SD, Mounts NS, Steinberg L, Dornbusch SM Child Dev. 1991;62:1049–65.

Lissau I, Sorensen TI Lancet. 1994;343:324–7.

Littleton HL, Ollendick T Clin Child Fam Psychol Rev. 2003;6:51–66.

Maccoby EE, Martin JA In: Mussen PH, Hetherington EM, editors. Handbook of child psychology. New York: Wiley; 1983. p.1–101.

McVey GL, Pepler D, Davis R, Flett GL, Abdolell M J Early Adolesc. 2002;22:75–95.

Moens E, Braet C, Soetens B J Pediatric Psychol. 2007;32:52–63.

O'Connor TM, Hughes SO, Watson KB, Baranowski T, Nicklas TA, Fisher JO, Beltran A, Baranowski JC, Qu H, Shewchuk RM. Public Health Nutr. 2009;1–11.

O'Dougherty M, Story M, Stang J J Nutr Educ Behav. 2006;38:183–8.

Ogden J, Reynolds R, Smith A Appetite. 2006;47:100–6.

Orrell-Valente JK, Hill LG, Brechwald WA, Dodge KA, Pettit GS, Bates JE Appetite. 2007;48:37–45.

Patrick H, Nicklas TA, Hughes SO, Morales M Appetite. 2005;44:243–9.

Rankinen T, Bouchard C Annu Rev Nutr. 2006;26:413–34.

Rhee KE, Lumeng JC, Appugliese DP, Kaciroti N, Bradley RH Pediatrics. 2006;117:2047–54.

Ritchie LD, Welk G, Styne D, Gerstein DE, Crawford PB J Am Diet Assoc. 2005;105:S70–9.

Robinson TN, Kiernan M, Matheson DM, Haydel KF Obes Res. 2001;9:306–12.

Saelens BE, Ernst MM, Epstein LH Int J Eat Disord. 2000;27:459–63.

Snoek HM, Sessink NY. Engels RCME (in press) J. Fam. Psychol.

Snoek HM, Janssens JMAM, Nicolasen A, de Vries E, Sessink NY. Engels RCME (in preparation b)

Spruijt-Metz D, Li C, Cohen E, Birch L, Goran M J Pediatr. 2006;148:314–20.

Van Der Vorst H, Engels RC, Deković M, Meeus W, Vermulst AA Addiction. 2007;102:1064–75.

Ventura AK, Loken E, Birch LL. Obesity (Silver Spring). 2009;17:2067–74.

Wardle J. Proc Nutr Soc. 1995;54:747–58.

Chapter 107
The False Memory Diet: False Memories Alter Food Preferences

Daniel M. Bernstein, Nicole L.M. Pernat, and Elizabeth F. Loftus

Abbreviation

FBPQ   Food and beverage preferences Questionnaire

107.1 Introduction

Consider this scenario. You are hunched over a toilet bowl (or flower pot), throwing up. You ate something that did not agree with you, and now you are suffering the consequences of it. As you are busy vomiting, you realize, or think you realize, what it was that made you sick: It was the egg salad. There is a good chance that you will avoid egg salad for a short time after the event. There is also a chance that you might altogether avoid egg salad permanently. Studies show that animals that repeatedly get sick after eating a particular food will avoid that food, and that even a single sickness experience after eating food can lead to a strong aversion to that food (Garcia and Koelling 1966; Gustavson et al. 1974; Gustavson and Nicolaus 1987). If a true food-related memory can produce these consequences, can a false memory do so too? We present evidence that false memories regarding food and alcohol can affect eating and drinking behavior.

In this chapter, we review new research, conducted over the last half decade, showing that we can plant false memories about a past experience with a particular food or alcohol. These have consequences for people; if the false memory is unpleasant, people avoid the food or drink. If the false memory is pleasant, they want the food or drink more. We discuss possible explanations for these findings. Moreover, we explore which kinds of people are more susceptible and which foods are particularly amenable to forming false food memories. We end with a discussion of applications to other areas of health and disease.

107.2 False Memory Primer

Memory is reconstructed, not a faithful replay of the past (Bartlett 1932). As a reconstruction, memory is prone to distortions, omissions, and deletions of details as well as construction of entire events that never occurred. We distinguish between two main types of false memories – those pertaining to

---

D.M. Bernstein (✉)
Department of Psychology, Kwantlen Polytechnic University,
12666 – 72nd Avenue, Surrey, BC, Canada
e-mail: daniel.berstein@kwantlen.ca

details (which we call false "detail" memories) and those pertaining to entire events (which we call *rich* false memories) (see Loftus and Bernstein 2005). False detail memories are commonplace. In fact, every memory of every event invariably contains some false detail memory. When recalling the past, we virtually never get all the details exactly right. We either subtly alter some details (we misremember that the culprit in a robbery wore a black shirt when, in fact it was grey) or grossly alter other details (we misremember that the culprit had a beard when, in fact, he was clean-shaven; for a discussion of false detail memory tasks, see Bransford and Johnson 1973; Loftus et al. 1978; Roediger and McDermott 1995). In contrast to such false detail memories for an event, we also sometimes wholly reconstruct memories for entire events that never occurred (we think we remember seeing an entire robbery when the robbery never actually occurred). Findings from studies on rich false memories demonstrate that simply imagining that an event happened in one's past makes one believe that the event actually happened (Garry et al. 1996; see also Hyman et al. 1995; Lindsay et al. 2004; Loftus and Pickrell 1995). Although less common than false detail memories, rich false memories do occur. Moreover, false detail memories and rich false memories likely share some of the same underlying processes; whatever makes us misremember details from the past also is responsible for making us misremember entire events.

Most research to date has focused on how false memories form. What has been less studied is the question of what happens after a false memory forms. False memories in the real world have real consequences for one's behavior (e.g., an adult who falsely remembers being abused by her grandfather may confront the grandfather, refuse to speak to the grandfather, or even sue the grandfather). Recent research in our laboratory has examined the behavioral consequences of false memories. In this research, we planted false memories about food and alcohol in order to provide a plausible and convenient context in which to explore the attitudinal and behavioral consequences of false memories.

107.3 False Food and Alcohol Memories

Using a combination of procedures, we and others have completed more than 20 experiments investigating false food and alcohol memories. Our studies show that people can be led to believe that they had either positive or negative experiences with food or alcohol in their past, and that these false memories affect not only their attitudes and preferences but also their behavior toward those foods and alcoholic beverages. We review this work here, starting with our basic procedure for planting memories and assessing attitudes and preferences. Next, we discuss several potential explanations of our findings. How do we know that our subjects really believe they got sick on a key food; perhaps they have guessed the true nature of our studies and are acting in accordance with how they think we want them to act? This is the age-old problem called demand characteristics. Another issue involves figuring out which subjects are most prone to developing false food memories. This refers to what is called individual differences. Finally, we discuss theoretical mechanisms involved in the formation of false food memories. For simplicity, we use the term *false food memories* to refer to both false food memories and false alcohol memories. We also use the term *false memory diet* as a shortcut to refer to the formation and consequences of false food memories. We are not proposing that this is a bona fide dieting technique, although our methodology might eventually be used for dieting purposes.

Basic procedure. Our basic procedure involves two sessions separated by 1 week, and a combination of different questionnaires designed to measure one's past experience with and preference for various foods and alcoholic beverages. We have used different combinations of these questionnaires in different studies, but here we present a comprehensive list of questionnaires to provide a broader picture of our studies to date. Briefly, in Session 1, subjects complete a series of questionnaires
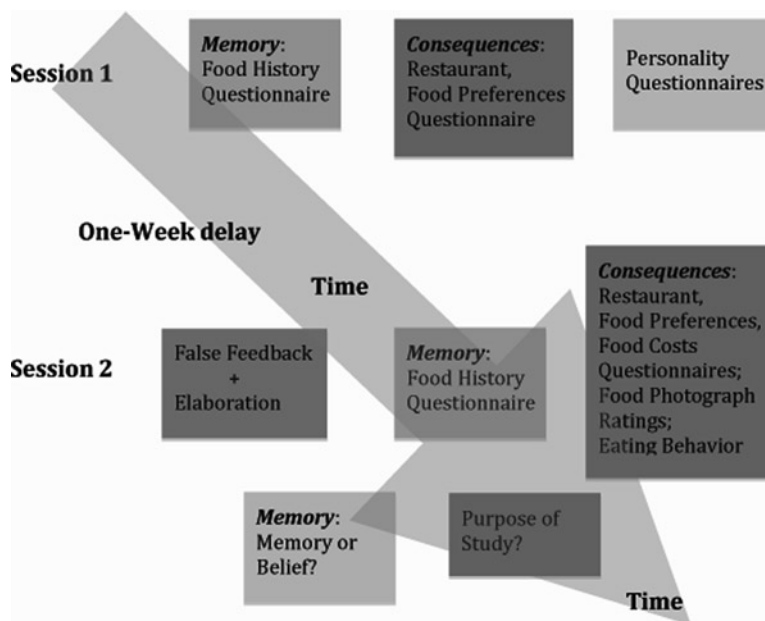
Fig. 107.1 General procedure used in our false food memory studies. Subjects complete tasks over a 2-week period, in a fixed order (read from left to right). False memory formation is indicated with the word *Memory*, and is measured using the Food History Questionnaire and the Memory or Belief? Questionnaire. *Consequences* are measured using the Restaurant, Food Preferences, and Food Costs Questionnaires, in addition to the Food Photograph Ratings and Eating Behavior measures. See text for details

aimed at measuring their childhood experiences with and current preference for various foods and beverages. In Session 2, typically conducted a week later, subjects receive false feedback about their Session 1 responses that leads them to believe that they likely experienced a variety of food- and alcohol-related events in their past. Subjects then complete some of the same measures that they completed during Session 1. Figure 107.1 depicts our procedure.

In this research, we have been interested in two intertwined issues. First, we examine the formation of false food memories. Second, we examine the consequences of these memories. To answer the first question, we see if receiving false feedback about a critical food-related childhood event (e.g., "You got sick eating egg salad") increases subjects' confidence that they experienced that event sometime in their past. To answer the second question, we see if receiving false feedback about the critical food-related event alters subjects' attitudes and behaviors. We now explain our procedure in more detail.

In Session 1, subjects complete a series of questionnaires designed to measure one's food and beverage history and preferences. Specifically, to measure food and beverage *history*, subjects complete a Food and Beverage History Questionnaire in which they rate their confidence that various food and alcohol-related events occurred sometime in their childhood. Sometimes we ask about events occurring before the age of 10 or 12 years, and sometimes (particularly in the alcohol studies) we ask about events occurring before say the age of 16 years. To measure food and beverage *preferences*, subjects complete a Food and Beverage Preferences Questionnaire (see Fig. 107.2) in which they rate how much they like each of a large number of different foods and beverages (including some alcoholic drinks) and a Restaurant Questionnaire in which subjects rate the likelihood of their ordering various foods and beverages at an imaginary restaurant (see Fig. 107.3). All rating scales used are 8-point. Whatever our critical item is for a given study (e.g., "you got sick from egg salad") that food item appears on all food and beverage history and preference measures. This allowed us to

Food & Beverage Preferences Questionnaire

Please rate each of the following food and beverage items in terms of how much you enjoy it. Put your rating in the space to the left of the item.

1 = 'definitely don't like' (for whatever reason) to 8 = 'definitely like'

___Watermelon	___Tofu	___Coke
___Lemonade	___Apple pie	___French fries
___Taffy	___Chocolate bars	___Salad
___Steak	___Pepsi	___Rum
___Vanilla Ice Cream	___Celery	___Black beans
___Deviled eggs	___Bananas	___Doughnuts
___Iced-Tea	___Rice	___Red Wine
___Zucchini	___Tequila	___Asparagus
___Pasta	___Spinach	___Almonds
___Chocolate cake	___Granola	___Cranberry Juice
___Carrots	___Onion rings	___White Wine
___Vodka	___Orange Juice	___Mango
___Potato salad	___Cheetos	___Sprite
___Cole slaw	___Omelet	___Crackers
___Tortilla chips	___Garlic	___Potato chips
___Diet Coke	___Beer	___Diet Pepsi
___Tacos	___Ginger	___Roasted eggplant
___Pizza	___7-UP	___Gin
___Broccoli	___Cheddar cheese	___Pickled herring
___Kool-Aid	___Whiskey	___Vanilla pudding
___Egg salad	___Brownies	___Root beer

1 = 'definitely don't like' (for whatever reason) to 8 = 'definitely like'

Fig. 107.2 Food and Beverage Preferences Questionnaire (FBPQ). Food and beverage preferences questionnaire used in Clifasefi et al. (submitted). This is a modification of a task used previously in several studies (e.g., Bernstein et al. 2005b)

compare scores on the critical item before and after the manipulation, in order to discover any change in food preference.

During Session 1, subjects also complete several filler questionnaires purported to measure their personality and eating habits. We have used these questionnaires for different purposes in different studies. We have used these to disguise the true nature of our studies, and make the false feedback manipulation more credible. Toward the latter purpose, we recruit subjects for a Food and Personality study, and most subjects report at the end of the studies that they thought the study was about food and personality. Occasionally the questionnaires tap demographic or other information about the subjects, which we can use for our analyses of individual differences.

One week later, subjects return to complete Session 2. At the beginning of Session 2, subjects receive false feedback regarding their responses to the Session-1 questionnaires. In particular, we tell subjects that we entered their Session-1 responses into a computer with a sophisticated program that generated an individualized profile of their childhood experiences with food. All subjects receive the same feedback about three events that we chose (specifically because these events likely occurred in anyone's childhood, e.g., you disliked spinach). Moreover, experimental subjects receive one additional and critical piece of feedback. Depending on the study, experimental subjects might read in their profile that they became ill after eating dill pickles as a child or that they loved asparagus the first time they tried it, to take but two examples from different studies.

a

Restaurant Questionnaire
Imagine that you are at a nice restaurant for a special dinner. How likely are you to order each of the items on the menu below, assuming that price is not an object?

Le Restaurant

❧

Appetizers

	definitely no			maybe			definitely yes	
Wok-seared chicken strips and lettuce wrap	1	2	3	4	5	6	7	8
Portabella mushrooms stuffed with mozzarella	1	2	3	4	5	6	7	8
Fried calamari rings with spicy sauce	1	2	3	4	5	6	7	8
Hand-breaded tiger shrimp	1	2	3	4	5	6	7	8
Seasoned potato skins with cheddar and green onions	1	2	3	4	5	6	7	8

Soup and Salad

	definitely no			maybe			definitely yes	
Homemade minestrone	1	2	3	4	5	6	7	8
French onion soup	1	2	3	4	5	6	7	8
Spicy tortilla soup	1	2	3	4	5	6	7	8
Peppered corn chowder	1	2	3	4	5	6	7	8
Caesar salad	1	2	3	4	5	6	7	8
Oriental chicken salad	1	2	3	4	5	6	7	8
Honey mustard chicken salad	1	2	3	4	5	6	7	8
Mixed baby greens vinaigrette	1	2	3	4	5	6	7	8

Fig. 107.3 Restaurant questionnaire. Restaurant questionnaire described by Laney et al. (2008a)

b   **_Main Entrees_**

	definitely no				maybe			definitely yes
Roasted salmon fillet	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Grilled fillet mignon	1	2	3	4	5	6	7	8
Chicken scaloppini with white mushroom caps	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Grilled polenta with steamed spinach and tomatoes	1	2	3	4	5	6	7	8
Linguine with wild mushrooms, eggplant and snow peas	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Pork ravioli with marinara sauce	1	2	3	4	5	6	7	8
Veal with white wine, lemon and capers	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**

Sides

	definitely no				maybe			definitely yes
Steamed summer squash	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Baked potato with butter and sour cream	1	2	3	4	5	6	7	8
Broccoli and cauliflower casserole	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Wild mushroom risotto	1	2	3	4	5	6	7	8
Sautéed asparagus spears	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
White rice	1	2	3	4	5	6	7	8

Desserts

	definitely no				maybe			definitely yes
Chocolate cake with caramel hazelnut sauce	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Peach sorbet with glazed pecans	1	2	3	4	5	6	7	8
Five layer chocolate fudge cake	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Meyer lemon cheesecake with orange sauce	1	2	3	4	5	6	7	8
Tiramisu	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Pumpkin cheesecake	1	2	3	4	5	6	7	8

Fig. 107.3 (continued)

Next, control subjects read that the computer randomly selected one event for them to consider in greater detail, e.g., that they felt happy when a classmate brought sweets to school. Experimental subjects receive the same false feedback about the sweets item, in addition to a critical item. Control subjects are asked to imagine the sweets event and experimental subjects are asked to imagine the sweets event and the critical event in great detail, as indicated in the instructions, "Think about your memory of this experience. If you don't have a specific memory, imagine what *might have* happened. Then answer the following

questions, in some detail, regarding the item listed above: (1) How old were you? (2) Where did it occur? And what were you doing at the time? (3) Who were you with? (4) How did it make you feel?"

Immediately after receiving the false feedback and elaborating on it, subjects complete some of the same questionnaires that they completed in Session 1 – specifically, the Food and Beverage History Questionnaire, the Food and Beverage Preference Questionnaire, and the Restaurant Questionnaire. Subjects also complete what we call a Memory or Belief? Questionnaire in which they report on several events from the Food and Beverage History Questionnaire, including the critical item. Subjects choose one of the following for each event: Whether they have a specific memory for the event, believe that the event occurred but lack specific memory, or are positive that the event did not occur in their past. Subjects are also instructed to provide detailed reasons for making their selections. In many of our studies, we finish by asking subjects to report what they think the study's purpose was. In all of our studies, we run subjects in groups ranging in size from 2 to 40 people. This is our basic procedure that we have followed; however, in our most recent work on this topic, we add behavioral measures either at the end of Session 2 and/or to another session occurring up to 4 months later (Geraerts et al. 2008). In these studies, we give subjects actual foods or alcohol (including the critical item) to consume, and we measure how much they consume. At the end of all studies, we fully debrief subjects.

False food memory studies done to date. Using the aforementioned procedure, we can explore both the formation and consequences of false memory. To explore false memory formation, we compare subjects' responses to the critical item on the Food and Beverage History Questionnaire before and after receiving false feedback. In all of our studies thus far, we find that experimental subjects tend to increase their ratings more than control subjects do, indicating that the false feedback affected their confidence that the critical event happened in their childhood. Next, we examine subjects' responses to the critical item on the Memory or Belief? Questionnaire. We divide our experimental subjects into two groups, Believers versus Nonbelievers. To be considered a Believer, subjects must increase their confidence in the critical event after receiving the false feedback. Moreover, they must indicate on the Memory or Belief? Questionnaire that they have a memory *or* belief for the critical event. If they fail to meet both criteria, we consider them Nonbelievers.

To explore the consequences of false memory, we can compare Believers to Nonbelievers and controls (those subjects who did not receive false feedback about the critical item) in terms of their attitudes and behaviors toward the critical item. Specifically, we measure how much subjects increase or decrease their preference ratings, or the likelihood of ordering the critical item in a restaurant, or how much of the critical item they consume. In some studies, we have included additional measures to assess the consequences of false memory. These include ratings of photographs depicting various foods and beverages, and ratings of how much subjects would pay for various foods at a local grocery store.

Now that we have described our procedures in detail, what did we find? In our first study, we used two critical items, hard-boiled egg and dill pickle (Bernstein et al. 2005a). We told half the subjects that they "got sick" after eating a hard-boiled egg, while we told the remaining subjects that they "felt ill" after eating a dill pickle. As expected, those subjects who received the hard-boiled egg feedback increased their confidence in this event, while those who received the pickle feedback increased their confidence in this event. Importantly, the egg group did not increase their confidence in the pickle item, and the pickle group did not increase their confidence in the egg item. Thus, our false feedback manipulation worked, as intended. But did false memories have any measurable consequences for subjects' food preferences? The answer is yes. Subjects who met our definition of Believer (25% of Pickle subjects and 31% of Egg subjects) indicated less willingness to eat the "offending" food as adults. These findings show that people can be led to believe that they got sick after eating a particular type of food, and that they later appear less interested in eating that food.

Next, we wished to know if we could extend these effects to fattening foods, or foods that weight-conscious people might want to avoid. We first attempted to do this with potato chips (unpublished

data). We had little trouble getting subjects to believe that they had become sick after eating chips as children, but they didn't seem inclined to avoid chips now. Perhaps, we thought, this was because people eat potato chips too often. Perhaps, we could find consequences with more novel foods (also see Martins and Pliner 2005). We set out to test this idea on two fattening foods, one that is commonly eaten (chocolate chip cookies) and one that is not as commonly eaten (strawberry ice cream) (Bernstein et al. 2005b). Confirming our hunch, we could not convince many people that they had gotten sick eating chocolate chip cookies. Moreover, the false feedback about cookies had no impact on our subjects' self-reported preferences for chocolate chip cookies.

In stark contrast, the procedure worked with strawberry ice cream, the more novel food. In this study and all subsequent studies, we used a slightly different definition of Believer than we used in our first study. We added one more constraint to our criteria before labeling someone a Believer; subjects had to provide low confidence during Session 1 on the Food and Beverage History Questionnaire. In other words, subjects had to begin the study relatively confident that they had *not* gotten sick eating strawberry ice cream as children. With this new definition, nearly 40% of our subjects became Believers and indicated that they had gotten sick eating strawberry ice cream. In addition, Believers reported less willingness to eat strawberry ice cream at a party and reported lower general preference for strawberry ice cream. These results indicate that people can be led to avoid a fattening novel food like strawberry ice cream but not a fattening common food like chocolate chip cookies. These results also indicate that stronger manipulations may be needed to make people believe that they got sick eating a familiar food and make people avoid that food.

Given that our false food feedback technique made our subjects less willing to want to eat a fattening food (a potentially healthy consequence of a false memory), we wondered whether we could use this same technique to get people to eat *more* of a healthy food (also a healthy consequence of a false memory). We chose asparagus as the critical item, because it has a distinct flavor and is relatively novel and unfamiliar.

In our first study to examine the consequences of false memory for a positive, rather than a negative food-related experience, we told some of our subjects that they loved asparagus the first time they tried it (Laney et al. 2008a). We found that approximately 50% (48% in Experiment 1 and 53% in Experiment 2) met our definition of Believer. As in our previous studies, we wished to know whether there were consequences associated with believing our false feedback. In this study, we added two new tasks to our arsenal of consequence measures. These new measures included a Food Costs Questionnaire and a Food Photograph rating task. On the Food Costs Questionnaire, subjects indicated how much they would pay for a variety of foods at the grocery store, including the critical item, "a pound of asparagus." Subjects indicated their answers by circling one of seven price options. In the Food Photograph task, subjects rated photographs depicting a variety of foods and beverages (see Fig. 107.4).

Recall that half our experimental subjects in this study came to believe that they loved asparagus the first time they tried it. In comparison to control subjects (those not exposed to false feedback), Believers indicated (a) greater preference for asparagus, (b) greater willingness to pay more for asparagus at the grocery store, and (c) that photographs of asparagus were more appetizing and less disgusting. Thus, false positive memories about a food also had consequences. Specifically, coming to believe that one loved asparagus the first time one tried it had positive and healthy consequences for one's attitudes toward asparagus. These encouraging result left us with two unanswered questions: How long do the false memories last? Do false food memories affect what people actually eat, as opposed to what they think they might want to eat?

To address these questions, we used two experimental groups, a "love" and a "hate" group who received false feedback about either loving or hating asparagus the first time they tried it, respectively. We found that our basic false food memory formation and consequence results persisted up to

Fig. 107.4 Food photographs. Photograph task used in Experiment 2 by Laney et al. (2008a). Subjects rated each food in terms of how appetizing and disgusting it was. Subjects also rated the artistic quality of each photo and whether a novice, amateur, or expert photographer took the photo. *Note*: original photographs were in color

2 weeks after subjects received the false suggestion. We also contacted subjects by email 1 week after they had completed Session 2, telling them that we would feed them during their final laboratory visit 1 week later. We asked them to rank order a list of sandwiches and vegetables (including asparagus) that they would like us to provide during their final visit. Subjects did, in fact, return to the laboratory for the final session, but we did not feed them as promised. Instead, we asked them to complete our standard self-report consequence measures during this final session. We found that Believers in the Love group (34% of Love experimental subjects) indicated via the email questionnaire that they wanted to eat asparagus upon returning to the lab (Laney et al. 2008c).

Although the subjects in these previous studies changed what foods they reported wanting to eat, we never examined what they actually ate. Two studies have since examined actual eating behavior. Each study was conducted without knowledge of the other, further lending credence to the results. In one study, we suggested to some subjects that they had gotten sick after eating egg salad as children (Geraerts et al. 2008). We then measured actual behavior at two different time points. The first occurred shortly after subjects completed our standard Session 2 measures.

Subjects were taken to another room where they received a bogus debriefing. Subjects learned that the researchers wanted to thank them for participating by providing drinks and sandwiches. The sandwiches contained five different fillings, including egg salad, tuna salad, chicken salad, cheese, and ham. While the subjects listened to the bogus debriefing, they helped themselves to the food. An experimenter recorded the type of sandwiches the subjects chose. The second way that we measured behavior was that we re-contacted subjects 4 months later and invited them to participate in what they thought was an unrelated study. Eighty-five percent of subjects returned and completed a taste test in which they tasted and rated five drinks and five sandwiches in terms of appearance, smell, flavor, and preference. After this rating exercise, subjects learned that we would be throwing away the food. We invited them to eat as much as they liked. After 15 min, the experimenter removed the food, and re-administered our Session 2 materials in a different format so as to disguise the link between this session and Session 2.

In comparison to control subjects, subjects who received and believed the false feedback about egg salad (35% of subjects) ate fewer egg salad sandwiches (a) shortly after receiving the false feedback *and* (b) 4 months later (see Fig. 107.5). Believers also gave lower ratings to the appearance and
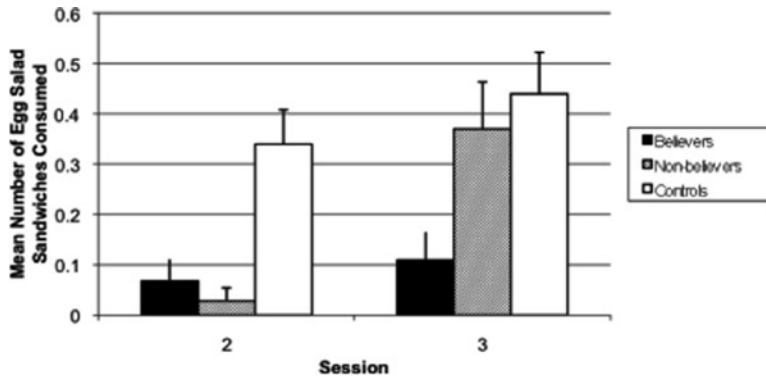
Fig. 107.5 Mean number of egg-salad sandwiches consumed by Believers, Non-Believers, and control subjects in the second and third sessions. Error bars represent standard errors of the means (Figure and caption reprinted from Geraerts et al. (2008). With permission from publisher)

flavor of egg salad than did control subjects. These results show that subjects can be led to create false food memories with real and long-lasting behavioral consequences.

Another study conducted in a different country also demonstrates the power of false suggestion in shaping actual eating behavior (Scoboria et al. 2008). Experimental subjects received both a personalized profile indicating that they very likely became ill after eating peach yogurt as children, and they received a bogus government report indicating that numerous people had become ill after eating peach yogurt that had been contaminated by *E. coli* bacteria. Experimental and control subjects then returned 1 week later for what they thought was an unrelated multi-site marketing study. During this later session, subjects completed an elaborate taste test of different crackers and yogurts in which they rated each in terms of appearance, odor, taste, and texture, in addition to how much of each food they would like to eat (food perception scores). At the end of the taste test, subjects were told that all remaining food would be discarded, so they were free to eat as much of it as they wished. After 10 min, the experimenter removed the food and weighed it to determine how much of each type of cracker and yogurt was consumed by the subjects. As expected, subjects who were exposed to the false suggestion about peach yogurt indicated lower food perception scores for peach yogurt only, in comparison to controls. More importantly, experimental subjects ate less yogurt overall (of all types presented) than did controls, even though the two groups ate equal amounts of crackers. Thus false food memories affect what people actually eat.

False alcohol memory. Because false suggestion worked so well with food, we wondered whether it also would work with alcohol. To find out, we suggested to some subjects that they had become sick after drinking rum (or vodka) in the past (Clifasefi et al., submitted). Many of these subjects came to believe the false feedback and indicated less preference for drinks containing rum (or vodka) in comparison to control subjects.

In another project involving wine, we examined real behavior by measuring actual wine consumption after subjects received false feedback concerning their past experience with white wine. We suggested to some subjects that they previously got sick after (or loved) drinking white wine. As expected, both types of false suggestion (sick, loved) increased subjects' confidence that this event occurred in their past. Moreover, false positive memories were accompanied by increased self-reported and acutal preference for white wine (Wudarzewski et al. 2009) Thus, false alcohol memories, just like false food memories, affect attitudes and behaviors.

False beliefs versus false memories. Several important questions arise from these studies. One question involves the extent to which our findings relate to memory or mere suggestion. It is possible that merely suggesting to people that they got sick on a particular food in the past is sufficient to alter preferences and eating behavior. Perhaps they don't need to develop a false memory. We have data that speak directly to this question. In nearly every experiment that we have conducted on this topic, we find that Believers show more consequences than do Nonbelievers or controls. If the suggestion itself is sufficient to elicit attitudinal and behavioral consequences, then the Nonbelievers should also show consequences because they too received the false suggestion. Thus, mere suggestion does not seem sufficient to produce the kinds of results we typically see.

In discussing our results we have used the terms "belief" and "memory." Most investigators distinguish between these constructs as follows. Beliefs pertain to ideas (which may or may not be accurate) that we have about the past in the absence of specific detail that can be recalled. For example, we know and believe that we were born, but we do not remember the event itself. Memories, in contrast to beliefs, pertain to recollected details of past experiences. For example, many of us can recall details about our first kiss. Using this distinction, we can examine the formation of false beliefs and false memories. At the end of our studies, we ask subjects whether they have a general belief in or a specific memory for the event. In our studies, the vast majority of subjects (sometimes more than 90%) report a belief rather than a memory (see Table 107.1). Thus, most subjects are forming false beliefs rather than false memories in our studies. The reason that we have not distinguished these subgroups in this chapter is because the two groups are largely indistinguishable in terms of their confidence that the critical event occurred (as measured by their responses to the Food and Beverage History Questionnaire) or the consequences that we measure. Thus, because false beliefs and false memories similarly affect attitudes and behaviors in our studies, we combine false beliefs and false memories into Believers and then compare these subjects to Nonbelievers and control subjects (but see Table 107.1 to differentiate the percentage of Believers who reportedly form a false memory and the respective context).

Table 107.1 Key features of false memory studies: proportion of believers who reported memory rather than a belief for a given critical item, across studies

Aversion vs. preference	Critical item	Believers reporting memory		Study
		Proportion	Percent (%)	
Aversion	Exp 1: Ill from strawberry ice cream	1/7	14	Bernstein et al. (2005a)
	Exp 1: Ill from chocolate chip cookies	0/4	0	Bernstein et al. (2005a)
	Exp 2: Ill from strawberry ice cream – Elaboration Group[a]	1/24	4	Bernstein et al. (2005a)
	Exp 2: Ill from strawberry ice cream – Scenario Group[a]	1/13	8	Bernstein et al. (2005b)
	Exp 2: Ill from dill pickles	4/22	18	Bernstein et al. (2005b)
	Exp 2: Ill from hard-boiled eggs	5/28	18	Laney et al. (2008a)
	Ill from egg salad	3/35	7	Geraerts et al. (2008)
	Hated asparagus	17/46	37	Laney et al. (2008c)
Preference	Loved asparagus	7/35	20	Laney et al. (2008c)
	Exp 1: Loved asparagus	10/22	45[b]	Laney et al. (2008a)
	Exp 2: Loved asparagus	11/21[b]	52	Laney et al. (2008a)
Total		**60/257**	**23**	

Exp experiment

[a]Elaboration group was asked to elaborate on and answer questions about the suggested critical event (sick from strawberry ice cream); Scenario group was asked to choose between two possible scenarios depicting the suggested critical event

[b]Believers reporting a memory differ from Believers reporting a belief on Food and Beverage History Questionnaire (False Memory subjects also rate asparagus photo as more appetizing than False Belief subjects)

One last question arises concerning whether we can know that our manipulation produced a false memory or whether it triggered a true memory of the food experience. Without knowing the actual past of each of our subjects, we cannot be sure. However, there is a clue in one study that argues against the idea that we triggered a true memory. In that study, parents of subjects were contacted and asked to verify whether the critical event (got sick eating egg salad) did or did not occur in their child's past. Notably, of those subjects who entered the study denying the event and postmanipulation developed a memory for it, none of their parents corroborated the event. Readers might wonder whether parents would be expected to recall this event even if it had happened. In fact, many subjects who appeared to have true memories of getting sick on egg salad had parents who corroborated this event (Geraerts et al. 2008).

Demand characteristics. Demand characteristics correspond to situations in which subjects try to guess the true nature of the experiment, and in turn, act according to how they think they should act to be "good" subjects (Orne 1962). If our subjects figure out the true nature of our experiments (investigation of false food memories and their consequences), then they might pretend to form false memories for the suggested event and show consequences of those false memories. Several lines of evidence argue against this possibility. First, we ask subjects at the end of our studies what they think the purpose of the study was. Very few subjects guess the true nature of our studies. When we exclude subjects who guessed the purpose of the study, our overall findings do not change (see Laney et al. 2008b). Second, in some of our studies (e.g., Bernstein et al. 2005b) our false feedback works for one item (e.g., strawberry ice cream) but not another (e.g., chocolate chip cookies). If subjects are responding to demand, one would think they would form false memories for both events. Thus, we do not think that demand characteristics are responsible for our effects.

Boundary conditions. So, false memories can be planted and they have consequences for people. For some foods, like potato chips and chocolate chip cookies (two commonly eaten, and perhaps overeaten junk foods), our procedure did not seem to work. Thus, our false food memory technique does not work with all foods. Just as our technique does not work with all foods, it doesn't work for all people. Typically fewer than half of our subjects come to form false memories (i.e. become Believers). Thus, some subjects are more prone than others to forming false memories (Hyman and Billings 1998). Although we have frequently included measures of individual differences in our studies, they generally have not been related to the likelihood of developing a false memory.

Theoretical considerations. What is the mechanism behind the false memory diet? In two unpublished studies, we ruled out the possibility that behavioral consequences were due to simple positive or negative associations with target foods. When subjects trained to merely *associate* certain critical foods (e.g., asparagus, broccoli) with positive or negative words (e.g., love, hate), self-reported preference for the critical foods did not change, unlike when false memory procedures were used.

Mazzoni, Loftus, and Kirsch (2001) proposed a three-step model to account for the formation of false memories. Elsewhere, we have expanded on aspects of this model (Bernstein et al. 2009). Here, we extend the model to include the consequences of false memories. According to the original model, (1) an event comes to be seen as plausible in the culture of the rememberer (Plausibility); (2) one obtains a personal belief that the event likely occurred to him/her (Autobiographical Belief); and (3) one interprets thoughts and images about the event as memories (Autobiographical Memory). Mazzoni and colleagues have added a step to this model in which a person views an event as personally plausible before believing that the event likely occurred to her/him (Scoboria et al. 2004).

We hypothesize that the probability that an individual comes to believe that an event is generally plausible and that it likely occurred in his/her remote past depends partially on the ease with which the event is processed. Researchers typically define ease of processing as speed, and speed of processing as fluency, because processing speed is easily measured with reaction time. However, fluency can also be the integration, coherence, or well-formedness of perceptual detail, or the perception of ease

independent of the speed of processing (Whittlesea and Leboe 2003). Fluency can be enhanced by different stimulus variables such as repetition, clarity, and presentation duration (see Alter and Oppenheimer, in press 2009). When people are unaware of the source of their fluency, they may mistake that fluency for familiarity. Put another way, when people experience fluent processing of some material, they sometimes mistakenly believe that the material is familiar to them.

We propose that fluency and familiarity precede plausibility in the formation of autobiographical beliefs and memories (see Fig. 107.6). Moreover, we argue that the consequences that we have observed in our work depend on the formation of autobiographical beliefs and memories, although it is possible that consequences like food and alcohol preferences and eating behavior also link directly to fluency, familiarity, and plausibility. For example, Scoboria et al. (2008) demonstrated such a link between plausibility and eating behavior. In their study, subjects ate less peach yogurt after reading a phony government report aimed at boosting the plausibility that they got sick eating peach yogurt as children. In fact, in that study, eating behavior was unrelated to false autobiographical beliefs and memories, thus providing further evidence for a direct link between plausibility and eating behavior.

Why should the plausibility of a food-related experience matter? The more familiar a person is with a food, like chocolate chip cookies, the more difficult it is to make that person believe that she/he got sick from eating chocolate chip cookies in the past and the more difficult it is to change her/his preference for chocolate chip cookies. From an evolutionary perspective, familiar objects tend to be more preferable, likely because familiar things are perceived as safer than unfamiliar things (see Bornstein 1989; Bronson 1968). It is less plausible that a familiar food would be unsafe and capable
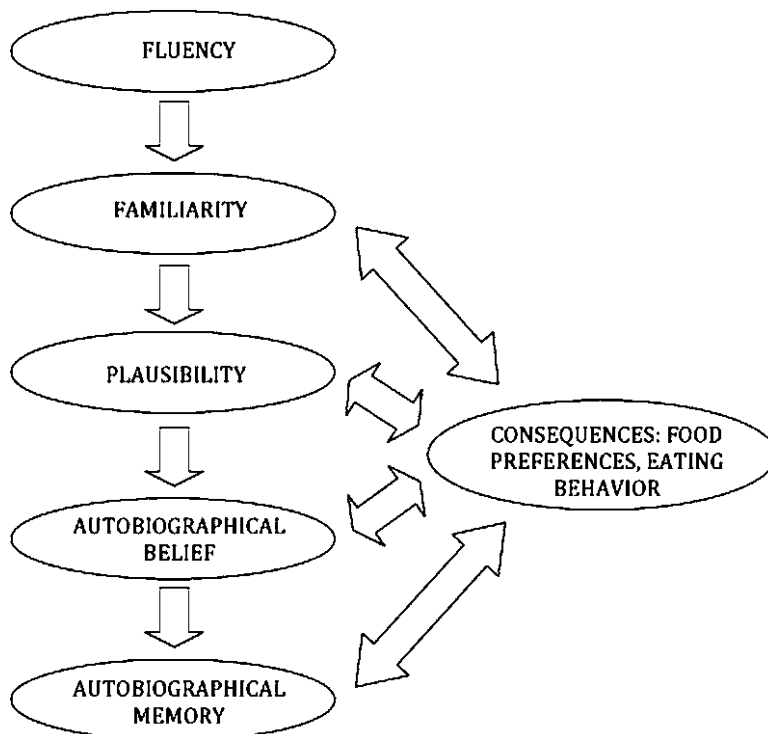
Fig. 107.6 Hypothesized steps in false memory formation and consequences. Fluency (ease of processing) produces feelings of familiarity, which increase plausibility, autobiographical belief and autobiographical memory pertaining to a food-related experience (e.g., one loved or hated asparagus in childhood). Familiarity, plausibility, autobiographical belief, and autobiographical memory affect and are affected by food preferences
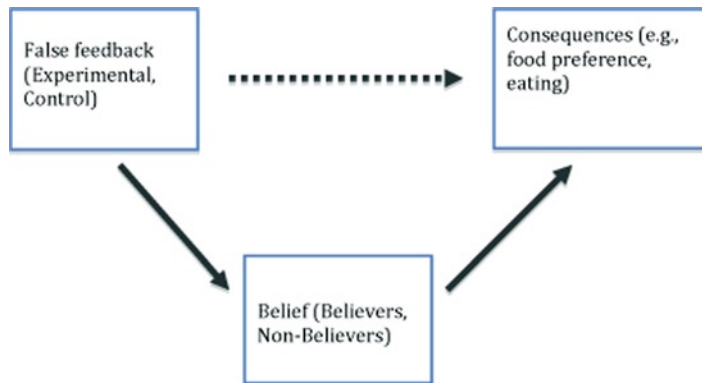
Fig. 107.7 Hypothesized model of the effect of false feedback on food preferences and eating behavior. False feedback (experimental versus control subjects in our studies) may produce consequences directly. Belief in the false feedback (Believers, Nonbelievers) partially mediates this effect. Believers and Nonbelievers are those who do and do not believe the false feedback, respectively. *Dashed arrow* denotes a weaker link than a *solid arrow*

of causing sickness. Thus, if a food is more familiar, it will be more preferred (Loewen and Pliner 1999; Mennella et al. 2001; Pliner 1982; Sullivan and Birch 1994). This explains the observation that familiarity of a food (how frequently it is eaten) enhances preference for it, apparently making it more difficult to develop false memories for having become sick from that food (Bernstein et al. 2005b). These mechanisms can help us understand food preferences, which, as we will see, is useful when it comes to therapeutic applications.

We end this section with a hypothetical model to explain the consequences of false food memories. Figure 107.7 depicts a model whereby exposure to false feedback (e.g., you got sick eating egg salad in the past) has consequences for eating behavior (e.g., you eat less egg salad now). Moreover, we propose that belief in the false feedback partially mediates this link between false feedback and consequences. Work is underway to test this model.

107.4 Applications to Other Areas of Health and Disease

In this section on applications of false memory research to eating behavior, we outline how false food memories could be utilized to influence our eating habits. We then discuss neophobia, lack of dietary variety, and obesity, followed by a therapy called covert sensitization, as well as several ethical concerns. We suggest possible applications of implementing false memories of food experiences for therapeutic means. However, we emphasize that such suggestions are cautious, in light of the scant literature on the ethics and safety of utilizing false memories for eating behavior.

There are two general ways by which false food memories could be utilized to positively influence our general eating habits. One is to increase preference for healthy foods and the other is to introduce aversion to unhealthy (junk) foods. Regarding the former, ideally people would come to believe that they enjoyed a range of food items, or at least, as in the "asparagus love" study, that they enjoyed a particular vegetable. This method would be beneficial for people who do not already consume enough vegetables and fruits in general.

In order to reduce or eliminate certain foods from the diet, aversion to those foods via false food memories could be implemented. Both preference-inducing and aversion-inducing applications of false food memories could be especially useful for people who have a tendency to avoid novel foods (neophobia) or

have health conditions requiring them to be vigilant about their diets. Obesity is one such condition, and may actually be related to neophobia. In each case, a goal is to increase healthy food intake and simultaneously decrease junk food consumption. We now consider the problems of neophobia and obesity.

Food Neophobia and Obesity. Food neophobia is the fear of trying new foods. Having evolved as omnivores with an interest in novel foods, humans historically avoided novel foods because such foods could be dangerous (Rozin 1976; Rozin and Fallon 1987). However, novel foods are rarely dangerous in our current society, reducing our need for neophobic tendencies. Furthermore, by definition, food neophobia has a constraining effect on dietary variety (Falciglia et al. 2000). This could limit the variety of nutrients consumed (Martins 2002), reducing overall health. Indeed, neophobic children tend to have poorer overall diets than non-neophobic children, consuming less vitamin E and more saturated fat (Falciglia et al. 2000). Increased dietary variety in early life increases willingness to try novel foods (Mennella et al. 2001). Thus, if a neophobic or other person who had limited childhood dietary variety formed false memories of having tried different foods as a child, they might increase their food variety in general, alongside the new penchant for eating the food for which they have the false memory.

Evolutionarily speaking, humans are presumably adapted to seek out high fat, sugary, salty foods (Galee 1996). When neophobia is coupled with the abundance of these foods, as found in North America, such foods would conceivably become the mainstay of neophobic people (Birch 1999). Indeed, as mentioned, neophobic children have higher saturated fat intake (Falciglia et al. 2000). This suggests that one answer to the burgeoning problem of obesity may lie in addressing not only the food preferences in obesity itself, but also the underlying neophobia (if present). To this end, a false memory diet (the formation and consequences of false food memories) could be used by training individuals to avoid eating fatty, sugary foods while simultaneously increasing vegetable intake.

Despite memory modification's prospects, Pezdek and Freyd (2009) object to the generalizability of Geraerts et al.'s (2008) findings, including the efficacy in treating obesity. Pezdek and Freyd assert that false memories probably will not be able to produce aversion to (a) foods that do not naturally elicit disgust already and (b) commonly eaten and enjoyed foods. Regarding obesity, they rightly remind us that no one food is responsible for obesity. Moreover, because becoming sick would be a rare occurrence for many of the culprit foods (which tend to be familiar, fatty, and sugary or salty), this event would be implausible. Thus people would be more likely to resist false memory formation for the target event (Pezdek et al. 1997). However, these objections may not be as widely applicable as Pezdek and Freyd suggest.

With regard to (a) and (b), the following foods have been used to date in published false food memory studies: Hard-boiled eggs, dill pickles, strawberry ice cream, chocolate chip cookies, asparagus, egg salad, and peach yogurt. With the exception of chocolate chip cookies, the rest of these foods produced consequences such as lowered food preference, taste ratings, and actual consumption. With the exception of hard-boiled eggs and egg salad, none of the other foods listed here is typically associated with a disgust reaction. Moreover, two of these foods are eaten regularly, including ones that do not naturally elicit disgust (i.e., peach yogurt, dill pickles), yet subjects still formed false food memories for these foods.

What we can say so far is that foods *most* amenable to the false memory diet seem to be less common foods (Bernstein et al. 2005b) – and by extension, less preferred foods, as well as foods that are naturally more disgusting. Prima facia, the potential ease of applying a false food diet to disgusting foods appears related to the plausibility of those foods inducing illness (Pezdek and Freyd 2009). Considering disgust in particular, people tend to be disgusted by meat or fat (Martins and Pliner 2006, 2005; Martins et al. 1997; Scott and Downey 2007), and bitter vegetables (Scott and Downey 2007), as well as certain textures, such as slimy substances (Martins and Pliner 2006; Scott and Downey 2007). With this in mind, we could take advantage of the disgust factor for reducing fat intake, since disgust-inducing foods – with the exception of bitter vegetables – often tend to be animal-based which are usually higher

in fat that non-animal-based foods. Regarding other fatty foods in general, the non-disgust-inducing common ones seem to be resistant to memory modification. In addition, a possible solution to modifying those tenacious memories for less common foods may be to use stronger manipulations such as photo-doctoring, whereby subjects see themselves eating the culprit food (see Wade et al. 2002). There is, however, another tentative method for the modification of nutritional behavior, called covert sensitization. Unlike the false memory diet, it does not include false belief or memory formation per se, though like the false memory diet, it is based on detailed visualization of a given script.

Covert Sensitization: A solution to alcoholism and obesity? First introduced by Cautela (1966), covert sensitization is a modification of aversion therapy, which originally used physical conditioning by way of chemical or electrical means to induce nausea and disgust associated with a particular behavior (see Davidson 1974 for review). In covert sensitization, the physical stimulus and undesirable stimulus are actually absent (hence "covert"), and are instead imagined by the patient. Sensitization occurs as the aversion intensifies across sessions (see Table 107.2). When this reaction remains consistent over time, therapy is considered successful.

Covert sensitization is supposedly rapid and has appeared useful in treating some forms of overeating, including snacking between meals, and chocolate addiction (Kraft and Kraft 2005). However, other studies have brought its efficacy into question (Little and Curran 1978). Whereas the false food memory diet that we discuss here often modulates the overall amount of food consumed, covert sensitization (assuming that it works) requires complete abstinence; this is fine if one's goal is to completely eliminate, say, cookies from one's diet. However, this is not ideal if one still would like to enjoy the occasional dessert; strawberry ice cream and vomit do not make an appealing combo. Furthermore, there may be ethical issues to consider in applying covert sensitization or false memory diets to individuals suffering from eating disorders such as anorexia or bulimia. The same could be said for false memory diets.

Ethical considerations. As asserted by Davidson (1974), whenever a therapy involves intentional change in behavior, ethics must be considered carefully. In this chapter we suggest not only solutions for eating behaviour alteration, but a possible, new way of doing so via memory modification. We know that memories are naturally fluid, subject to reconstruction, including false details. Yet when it comes to purposeful, complete fabrication of memories, one must ponder the ethics involved and whether the potential benefits outweigh the costs. A few false memories of loving asparagus or getting sick from strawberry ice cream may or may not outweigh the ethics involved in planting these memories.

Table 107.2 Procedure for covert sensitization (Amalgamated from various sources – Anant 1967; Cautela 1967; Cautela and Kearney 1986)

1. Physical relaxation and deep breathing
2. 3 steps in the imagined scene
    (a) Imagine setting
    (b) Imagine taking 1 or 2 drinks
    (c) Imagine taste changing, nausea, and vomiting
3. Incrementally introduce aversion to alcohol
    (a) 1st stage: Imagine 3 steps (above), in certain settings, and at home
    (b) 2nd stage: Imagine more scenes, different settings (Cautela 1967; Anant 1967)
    (c) 3rd stage: Imagine smell of liquor inducing nausea and vomiting
    (d) 4th stage: Imagine that the desire to drink leads to sickness
    (e) 5th session: Learn differentiation between liquor (as sickness inducing) and nonalcoholic beverages (as comfort-maintaining)
4. Session stops when therapist notices that patient's appearance becomes indicative of "disgust and nausea" (e.g., facial discoloration) (Anant 1967, p. 20)
5. Patient repeats critical procedure 10–20 times, twice per day (Cautela and Kearney 1986)
6. Patient advised to implement procedure whenever temptation arises (Cautela and Kearney 1986)

This table lists the covert sensitization procedure, using alcohol as the example target substance

Summary Points

- Thesis: False memories for a food or alcohol-related experience can affect diet and food preferences.
- Some foods are more amenable than others to false memory formation.
- Uncommonly eaten foods, even if fatty and sugary (e.g., strawberry ice cream) appear to be more amenable to false memories of sickness.
- Commonly eaten foods (e.g., cookies) seem less amenable to false memories of sickness, yet some commonly eaten foods have been shown to be amenable to false memories of sickness (e.g., yogurt, pickles).
- By definition, "Believers" tend to develop false food memories that result in attitudinal and behavioral consequences.
- By definition, "Nonbelievers," tend not to develop false food memories that show attitudinal and behavioral consequences.
- In nearly every experiment, Believers show more behavioral consequences than do Nonbelievers or control subjects.
- A minority of subjects develop false food memories.
- A "false memory diet" (i.e., false food memories and their consequences) may be applied to (a) increasing preference for healthy foods, such as asparagus and (b) creating aversion to potentially unhealthy substances like alcohol and fatty foods.
- A false memory diet could be applied to several food-related health issues such as neophobia, obesity, alcoholism.
- Covert sensitization, like false food memories, may be useful in manipulating food preferences.
- Unlike covert sensitization, false food memories can generalize to other types of similar foods.
- Future research may identify (a) a larger range of foods amenable to memory modification, (b) why some foods are more amenable than others, (c) new methods to accommodate the difficult foods, and (d) who could benefit from a false memory diet.
- Ethical considerations include (a) misuse of covert sensitization or a false memory diet by sufferers of anorexia or bulimia, (b) the sensitive nature of purposefully modifying someone's memory, and (c) the notion of intentional behavioral modification in general.

Key Terms

Believers: Subjects who incorrectly believe that a suggested event occurred to them in the past.
False belief: Incorrect belief that an event occurred, but inability to recall specific details about the event.
False food memories: Refers here to both false food memories and false alcohol memories.
False memory: Memory for a particular event that never actually occurred.
False memory diet: The formation and consequences of false food memories.
Food neophobia: Fear of trying new foods.
Food neophilia: Seeking and enjoying new foods.
Fluency: Ease of processing, which can mean speed (operationally defined as reaction time), integration, coherence, or well-formedness of perceptual detail, or the perception of ease independent of the speed of processing.
Nonbelievers: Subjects who correctly believe the false feedback to be false.
Subject: A person who participates in a research study. Participation is always voluntary, as monitored by research ethics boards.

References

Alter AL, Oppenheimer DM. *Uniting the tribes of fluency to form a metacognitive nation*. Pers Soc Psychol Rev. 2009;13:219–235.

Anant SS (1967) Can Psychologist. 8a:19–22

Bartlett FC. Remembering: a study in experimental and social psychology. Cambridge: Cambridge University Press; 1932.

Bernstein DM, Laney C, Morris EK, Loftus EF. Soc Cognition. 2005a;23:11–34.

Bernstein DM, Laney C, Morris EK, Loftus EF. P Natl Acad Sci USA. 2005b;102:13724–31.

Bernstein DM, Godfrey R, Loftus EF. In: Markman KD, Klein WMP, Suhr JA, editors. The handbook of imagination and mental simulation. New York: Psychology Press; 2009. p. 89–112.

Birch LL. Annu Rev Nutr. 1999;19:41–62.

Bransford JD, Johnson MK. In: Chase WG, editor. Visual information processing. New York: Academic; 1973. p. 383–438.

Cautela JR. Psychol Rec. Treatment of compulsive behavior by covert sensitization. 1966;16:33–41.

Cautela JR. Psychol Rep. 1967;20:459–68.

Cautela JR, Kearney AJ. The covert conditioning handbook. New York: Springer; 1986.

Clifasefi SL, Bernstein DM, Wakefield B, Loftus EF (submitted).

Davidson WS. Psychol Bull. 1974;81:S71–81.

Falciglia GA, Couch SC, Gribble LS, Pabst SM, Frank R. J Am Diet Assoc. 2000;100:1474–81.

Galee BG Jr. Neurosci Biobehav R. 1996;20:67–73.

Garcia J, Koelling RA. Psychon Sci. 1966;4:123–4.

Garry M, Manning CG, Loftus EF, Sherman SJ. Psychon B Rev. 1996;3:208–14.

Geraerts E, Bernstein DM, Merckelbach H, Linders C, Raymaekers L, Loftus EF. Psychol Sci. 2008;19:749–753.

Gustavson CR, Nicolaus LK. In: Frank H, editor. Man and wolf: advances, issues, and problems in captive wolf research. Boston: W. Junk; 1987. p.169–203.

Gustavson CR, Garcia J, Hankins WG, Rusiniak K. Science 1974;184:581–3.

Hyman IE Jr, Billings FJ. Memory 1998;6:1–20.

Hyman IE Jr, Husband TH, Billings FJ. Appl Cognitive Psych. 1995;9:181–97.

Kraft T, Kraft D. Contemp Hypn. 2005;22:202–9.

Laney C, Morris EK, Bernstein DM, Wakefield BM, Loftus EF. Exp Psychol. 2008a;55:291–300.

Laney C, Kaasa S, Morris EK, Berkowitz SR, Bernstein DM, Loftus EF. Psychol Res. 2008b;72:362–75.

Laney C, Bowman-Fowler N, Nelson KJ, Bernstein DM, Loftus EF. Acta Psychol. 2008c;129:190–7.

Lindsay DS, Hagen L, Read JD, Wade KA, Garry M. True photographs and false memories. Psychol Science 2007;15:149–154.

Little ML, Curran JP. Psychol Bull. 1978;85:513–31.

Loewen R, Pliner P. Appetite 1999;32:351–66.

Loftus E, Bernstein DM. In: Healy A, editor. Experimental cognitive psychology and its applications. Washington, DC: American Psychological Association Press; 2005. p. 101–13.

Loftus EF, Pickrell JE. Psychiat Ann. 1995;25:720–5.

Loftus EF, Miller DG, Burns HJ. J Exp Psychol-Hum L. 1978;4:19–31.

Martins Y. Pediatr Basics. 2002;98:12–20.

Martins Y, Pliner P. Appetite 2005;45:214–24.

Martins Y, Pliner P. Appetite 2006;46:75–85.

Martins Y, Pelchat ML, Pliner P. Appetite 1997;28:89–102.

Mazzoni GAL, Loftus EF, Kirsch I. J Exp Psychol-Appl.2001; 7:51–9.

Mennella JA, Coren P, Jagnow MS, Beauchamp GK. Pediatrics 2001;107: e88.

Orne MT. Am Psychol. 1962;17:776–83.

Pezdek K, Finger K, Hodge D. *Planting false childhood memories: The role of event plausibility*. Psychol Science 1997;8:437–441.

Pezdek K, Freyd JJ. Anal Soc Issues Public Policy. 2009;9:177–83.

Pliner P. Appetite 1982;3:283–90.

Roediger HL, McDermott KB. J Exp Psychol Learn. 1995;21:803–14.

Rozin P. In: Rosenblatt J, Hinde RA, Beer C, Shaw E, editors. Advances in the study of behavior, vol. 6. New York: Academic; 1976. p. 21–76.

Rozin P, Fallon AE. Psychol Rev. 1987;94:23–41.

Scoboria A, Mazzoni G, Kirsch I, Relyea M. Appl Cognit Psychol. 2004;18:791–807.

Scoboria A, Mazznoi G, Jarry J. Acta Psychol. 2008;128:304–9.

Scott CL, Downey RG. J Psychol-Interdiscip Appl. 2007;141:127–34.

Sullivan SA, Birch LL. Pediatrics 1994;93:271–7.

Wade KA, Garry M, Read JD, Lindsay DS. Psychon B Rev. 2002;9:597–603.

Whittlesea BWA, Leboe JP. J Exp Psychol Gen. 2003;129:84–106.

Wudarzewski A, Mantonakis A, Clifasefi S, Bernstein DM, Loftus EF. False past experiences can shape current preferences. Poster presented at the Society for Judgment and Decision Making, Boston, MA; 2009, November.

Chapter 108
Eating Pattern and Bariatric Surgery

Gian Franco Adami

Abbreviations

ASGB	Adjustable silicone gastric banding
VBG	Vertical banded gastroplasty
RYGBP	Roux-en Y-gastric bypass
BPD	Biliopancreatic diversion
BED	Binge eating disorder

108.1 Bariatric Surgical Interventions

Two different types of bariatric operations are currently in use – operations that restrict energy intake and operations that cause intestinal absorption limitation of the energy-rich substrate. Restriction operations are: adjustable silicone gastric banding (ASGB), vertical banded gastroplasty (VBG), and gastric bypass (RYGBP) (Favretti et al. 2007; Mason et al. 1998; MacLean and Shibata 1977). The operations aimed at limiting intestinal absorption are: biliopancreatic diversion (BPD) and its variances (Scopinaro et al. 1998; Marceau et al. 2007).

108.1.1 Operations Causing a Reduction of Food Intake

In the ASGB operation, a silicone band is strapped around the upper part of the stomach resulting in a small gastric proximal pouch, with the distal outlet, which can be adjusted to individual needs (Fig. 108.1). VBG consists in a stapled pouch with an externally banded conduit into the stomach proper (Fig. 108.2). The small size of the pouch and the small diameter of the outlet physically limit the amount of food that can be consumed during any single meal. In gastric bypass, the stomach is transected into two pouches. The proximal pouch is of very minute size and is attached to a loop of the proximal jejunum, while the distal one, which represents the near entirety of the stomach, is completely bypassed by the transit of food (Fig. 108.3). After RYGBP, food intake is reduced for

G.F. Adami (✉)

Department of Surgery, University of Genova, Largo Rosanna Benzi 8, Genova 16132, Italy
e-mail: adami@unige.it
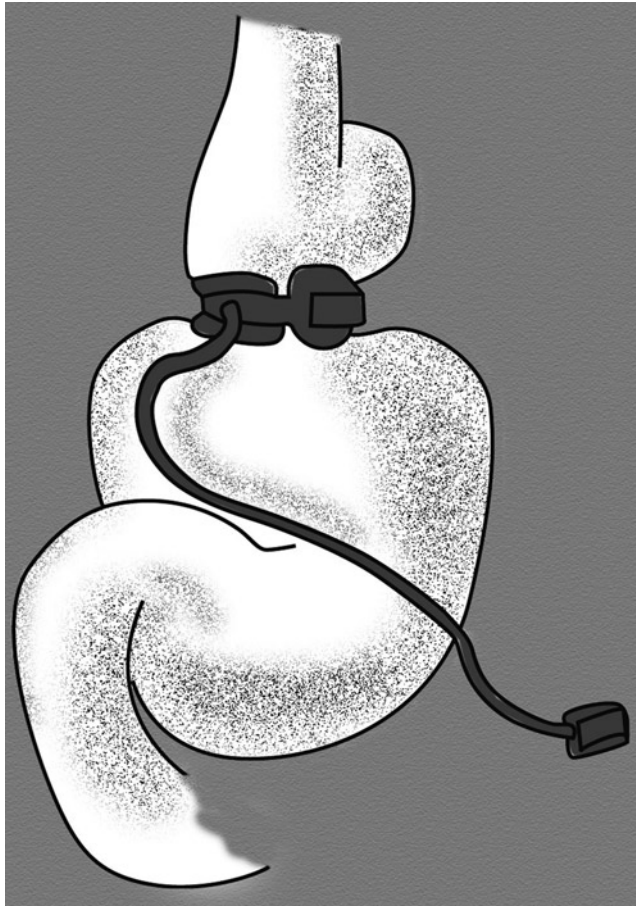
Fig. 108.1 Schematic representation of adjustable silicone gastric banding. A silicone band is strapped around the upper part of the stomach resulting in a small gastric proximal pouch, with the distal outlet which can be adjusted to individual needs. The proximal gastric pouch is rapidly filled after having introduced little amount of food, and the operated subject is compelled to stop eating, so that the overall food intake reduces

mechanical reasons due to gastric restriction as well as because of the action of specific entero-hormones, causing early satiety, which are produced by the small bowel in contact with food that is yet to be digested. Weight loss after ASGB and VBG ranges between 30% and 50% of the initial surplus weight, and long-term studies indicate the tendency toward weight regain over years (Favretti et al. 2007; Mason et al. 1998). The variances in weight loss and maintenance among different populations suggest that the weight loss/gain outcome is more dependent on individual factors than on the operation itself. RYGBP entails a weight loss of 50–60% of the initial surplus weight, with satisfactory weight maintenance, though regaining of weight throughout the years is not an unlikely finding (MacLean and Shibata 1977).

Gastric restriction procedures work by causing nausea, pain, discomfort and potentially vomiting and by forcing the individual to stop eating when the amount of food assumed exceeds the small quantity allowed by the size of the small proximal gastric pouch. After RYGBP limitation of food intake can also be accounted for by the true early satiety elicited by the action of gut hormones produced by the proximal jejunum in contact with undigested food, contributing along with gastric
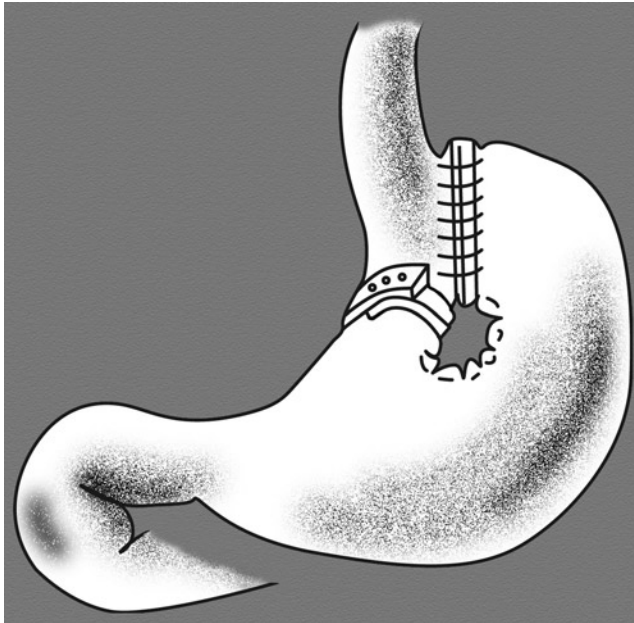
Fig. 108.2 Schematic representation of vertical banded gastroplasty. Vertical banded gastroplasty consists in a proximal stapled little pouch with an externally banded conduit into the stomach proper. The proximal gastric pouch is rapidly filled after having introduced little amount of food, and the operated subject is compelled to stop eating, so that the overall food intake reduces

restriction to the limitation of food intake. The decrease in food consumption leads to weight loss, which in turn causes the reduction of the subject's energy expenditure. When the decreased energy expenditure matches the amount of energy assumed nutritionally via the restricted stomach, the weight loss halts and body weight stabilizes at a reduced level. If habitual food intake does not change over time, body weight naturally remains stable in the long run.

Postoperation, the patient has the ability "to get around" gastric restriction and to continue to consume large amounts of food. If the frequency of eating increases, the overall amount of food ingested remains unchanged in spite of gastric restriction and early satiety, and body weight does not change or rather increases. Eating capacity increases when soft aliments are assumed, or when liquids are ingested immediately after solids. Furthermore, gastric restriction does not represent an obstacle for high-calorie beverages or heavy dressings, which may be freely ingested without the provocation of adverse effects. Though eating large amounts of food provokes marked epigastric distress and vomiting short-term, frequent overeating leads to over distension and dilatation of the gastric pouch, which completely nullifies the mechanical effects of gastric restriction.

For these reasons, weight results of the gastric restriction procedure are strictly dependent on the individual's postoperative eating habits. If eating behaviors fitting the new gastric anatomo-functional conditions created by the operation are adopted, the patient succeeds in reaching and maintaining a satisfactory body weight long term. This is no longer true when the individual assumes a behavior that overrides the effects of gastric restriction and the guidelines of the "gastroplastic diet" are not followed. Adequate changes in eating habits and behavior are therefore mandatory for obtaining satisfactory weight results; both for short and long term after gastric restriction procedures.
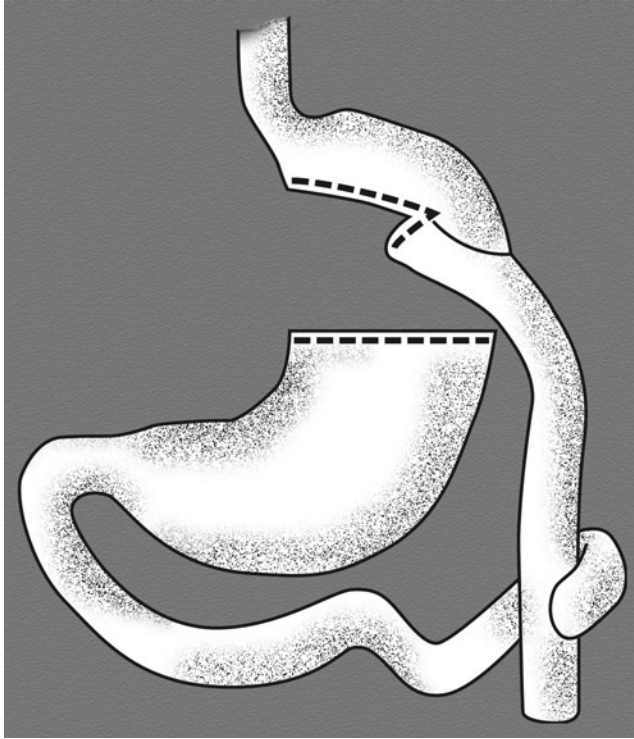
Fig. 108.3 Schematic representation of Roux-en-Y gastric bypass. In gastric bypass, the stomach is transected into two pouches. The proximal pouch is of very minute size and is attached to a loop of the proximal jejunum, while the distal one, which represents the near entirety of the stomach, is completely bypassed by the transit of food. The size of the proximal gastric pouch and the production of entero-hormones producing early satiety contribute to the limitation of food intake little

108.1.2 Operations Causing Limitation of Intestinal Absorption

Biliopancreatic diversion and its variances consist in a nearly complete separation in the intestinal tract of the combined transit of digestive juices and food, which thus produces limitation of the intestinal absorption of energy-rich substrates, while the uptake of essential nutrients (with little or no need of digestion) is nearly fully preserved (Fig. 108.4). Because of the new anatomo-functional conditions that cause the delayed meeting of food and digestive juices, subjects who have been operated on have permanent and selective maldigestion and then malabsorption of fat and starches. The rearranged gastrointestinal system presents an absorption threshold for energy-rich substrates of about 1,600 kcal/day, and the excess of calories ingested is not absorbed and is eliminated via stool (Scopinaro et al. 2000). Following the operation, body weight reduces and subsequently stabilizes when body energy expenditure matches energy intestinal absorption. When actual dietary energy intake overtakes the intestinal threshold, over-energy is eliminated and body weight does not change. Therefore, weight loss and maintenance after BPD is totally independent of individual food consumption and eating behavior, thus explaining the highly satisfactory weight loss outcome for long and very long term following intervention. The vast majority of subjects operated on lose more than 70% of their initial surplus weight, and body weight remains substantially stable at long and very long term in nearly all cases (Scopinaro et al. 1998).
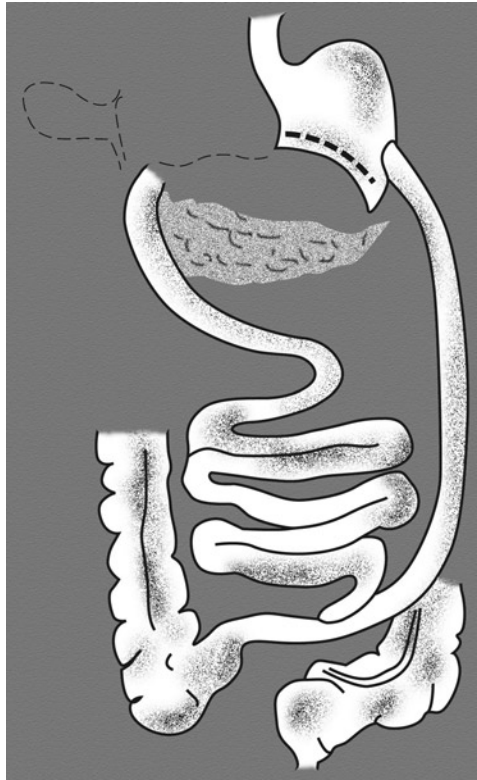
Fig. 108.4 Schematic representation of biliopancreatic diversion. Biliopancreatic diversion consists in a nearly complete separation in the intestinal tract of the combined transit of digestive juices and food, which thus produces limitation of the intestinal absorption of energy-rich substrates. Due to the permanent and selective limitation of intestinal absorption of energy-rich substrates, weight loss occurs regardless of energy intake, and body weight becomes independent from eating behavior and food consumption

108.2 Feeding Pattern Prior to Bariatric Intervention

As aforementioned, in severe cases of obesity bariatric surgery is the only therapeutic method that allows for satisfactory weight loss that is maintained in the long term. However, due to the great prevalence of severe obesity, only a small minority of severely obese patients have the opportunity to be treated via bariatric surgical intervention.

108.2.1 Characteristic of Obese Patients Requiring Bariatric Surgery

Studies carried out in recent years have shown that severely obese patients requesting bariatric surgery are metabolically more compromised and that, contrary to current opinion, they present a lower prevalenMce of binge eating, night eating, and other aberrant eating behaviors than their counterparts enrolled in conservative treatment groups (Ronchi et al. 2008; Munoz et al. 2007). A decade ago, obesity surgery was widely considered as an extreme therapy, and physicians and nutritionists were reluctant to recommend bariatric procedures for fear of complications and adverse side effects. Therefore, only few patients with very high degree of motivation caused by a drastically deranged

body image and/or seriously abnormal eating habits submitted to bariatric surgery (and in most cases against their physician's or family's advice). In recent years, the common attitude toward obesity and bariatric surgery has changed progressively and profoundly, and today severe obesity is no longer regarded as a condition arousing personal guilt and engendering social blame. It is however thought of as a severe metabolic disease, not to be stigmatized, and carrying a high risk for cardiovascular disease resulting in increased mortality. The general belief moreover has developed that with respect to severe obesity conservative therapy is without efficacy in the vast majority of the cases, with subsequently more realistic and operational attitudes toward obesity treatment and bariatric surgery. In fact, because of this, in recent years, obese patients applying for bariatric surgery are those with the highest degree of obesity and with compromised metabolic and/or cardiovascular conditions, regardless of any individual eating behavior or psychological status. The more realistic social attitudes toward severe obesity have improved the possibilities for successful treatment for a larger quantity of patients.

108.2.2 Role of Preoperative Variables in Prediction Postoperative Clinical Outcome

Though bariatric surgery is actually the only effective procedure for the treatment of severe obesity, positive results are not always obtained. In some patients weight reduction is insufficient or unsatisfactory, in others the weight loss is partially or completely gained back over the long term, and it may be that few years after intervention, body weight is higher than initially (before the procedure). In addition, those individuals who have been operated on are at risk of complications because of the surgical procedure itself, specifically the bariatric operation. Furthermore, in some cases, the operation is followed by unpleasant side effects that negatively influence the postobese subject's quality of life. In order to improve clinical results and to obtain satisfactory weight results with no complications in the greatest possible number of severely obese patients, preoperative factors were investigated, which can predict successful weight outcome and the occurrence of complications. Furthermore, a predictive factor was investigated that could provide information for the individualization of the type of operation (gastric restriction or limitation of intestinal absorption) offering the best chance of success for each individual obese patient. Unfortunately, no biological, behavioral, or psychosocial preoperative factor has unequivocally proven to be effective in predicting postoperative clinical results (Hsu et al. 1998; Bocchieri et al. 2002a; Herpertz et al. 2004; Sarwer et al. 2005). As expected, the greater the initial weight, the more substantial the weight loss: however, the initial degree of obesity is not predictive of the long-term weight results: in other words, the initial body mass index value cannot differentiate the weight-losing patients from those doomed to regain in the long term the weight lost in the first postoperative phases.

108.2.3 Cognitive Restraint and Surgically Obtained Weight Loss

As said above, some individuals who have been operated on contrast and cancel the mechanical effects of gastric restriction on food intake by consuming energy-dense food or beverages, or by eating frequently, resulting in poor weight loss and maintenance. It has therefore been suggested that snacking in between meals and a preference for sugary, high-calorie foods can be a predictive factor for poor weight loss following the gastric restrictive procedure (Sugerman et al. 1989). Accurate and

complete longitudinal investigations, however, could not find association between any preoperative eating habit or behavior and weight loss and maintenance (Hudson et al. 2002). It has been hypothesized that severely obese patients with high levels of cognitive restraint may easily succeed in achieving a permanent reduction in food intake, and then most likely achieve a positive weight loss outcome (Sarwer et al. 2005, 2008;Chevallier et al. 2007). On the other hand, to be considered are those individuals who already restrict their food intake at higher levels and may have little space for additional restriction. These individuals may be looking at poor postoperative weight results (Lindroos et al. 1996). It is therefore not surprising that correlations have not been made between weight loss and maintenance after gastric restriction operations and preoperative energy expenditure, food consumption, or cognitive restraint (Camerini et al. 2001; de Zwaan et al. 2003).

108.2.4 Disinhibition and Surgically Obtained Weight Loss

The tendency to lose control over food intake is a dietary attitude frequently observed in severely obese patients undergoing bariatric surgery. It has been suggested that high preoperative disinhibition can be a predictive factor of poor weight loss results particularly following gastric restriction operations. The disinhibition in fact may undoubtedly lead individuals to eat rapidly and frequently, and to drink highly caloric beverages, which cancel out the mechanical effects of gastric restriction on the amount of food consumed. Furthermore, the intake of a large quantity of food in one sitting could provoke dilatation of the gastric outlet, thus impairing the function of the gastric restriction mechanism itself. Finally, a high level of disinhibition could potentially reflect poor emotional conditions and an underlying eating disorder. On this perspective, obese patients with high disinhibition levels could be in a psychological state that prevents their ability to adapt themselves to the novel eating and behavioral conditions created by the operation. Some studies have suggested that high disinhibition is associated with reduced weight loss after bariatric surgery (Dymek et al. 2001; Hsu et al. 1996, 1998; Kalarchian et al. 2002). Patients with binge eating disorder (BED) who underwent RYGBP lost significantly less weight at 6 months than individuals who prior to the operation did not have this disorder (Dymek et al. 2001). Moreover, reported or current binge eating is likely associated with weight gain in patients long term after bariatric surgery (Dymek et al. 2001; Hsu et al. 1998). For these reasons, BED has been considered as a specific contraindication for gastric restrictive procedures in the treatment of severe obesity. In contrast to these reports, other longitudinal studies failed to find any relationship between weight loss and a preoperative binge eating status as assessed in clinic and via self-report, and weight outcomes in BED patients have been quite similar to those obtained in their non-binge counterparts (Powers et al. 1999; Malone and Alger-Mayer 2004; Busetto et al. 2005; Lang et al. 2002).

   Though it has been reported that patients suffering from depression after surgery tend to have less weight loss and a poorer postsurgery quality of life, in most prospective studies, specifically investigating the effects of personality traits and preoperative psychological distress has demonstrated that these variables are not a negative predictor of weight loss (Larsen et al. 2004; Herpertz et al. 2009; Norris 2007).

108.2.5 Conclusions

Taking all documentation into consideration globally, it can be noted that after bariatric surgery, dietary attitudes or behavioral or psychological factors do not exist, which can effectively predict weight loss outcome or can individualize the type of operation.

As said above, the steady weight loss obtained by bariatric operations is followed by a sharp and nontreatment-induced improvement of psychological state, emotional condition and the quality of life (Herpertz et al. 2009). Though specific studies on this topic are still unavailable, clinical experience suggests that these marked positive changes are due to subjective factors together with environmental influences. The appearance of a new physical efficiency because of the weight loss with the disappearance or improvement of complications related to the obese status undoubtedly increases individual auto-efficacy, moving postobese subjects toward true psychological well-being. Furthermore, after weight loss, somatic morphology returns within normal ranges and social stigmatization is a memory. This fact undoubtedly has a substantial positive effect on the postobese subject's psychological state and emotional condition.

In the Western World, social stigmatization deeply affects the psychological state and emotional condition of each severely obese individual in different ways. Understanding, therefore, the true personality and psychological condition of these patients regardless of their obese status might be a nearly impossible task. For each subject, psychological functioning and emotional state is deeply affected by the individual/environment relationship. The type of relationship postobese subjects have with the environment after reversion to normal somatic morphology (which is changed because of the new socially accepted somatic morphology) is completely unpredictable. Furthermore, it is impossible to know what will happen to the operated subject in the future and how the subject will cope with different situations throughout the years. The lack of any preoperative predicting factors with respect to postoperative psychological conditions is therefore not at all surprising.

108.3 Changes in Feeding Behavior After Bariatric Surgery

It is quite understandable that the effects on eating habits of a surgical procedure, which reduces the intestinal absorption of energy-rich substrates, are substantially different from those caused by an intervention aimed at restricting food intake. Patients who have undergone BPD lose weight and are able to maintain a reduced weight with a completely free diet with no limitations of food consumption. However, for those who have had gastric restriction procedures, a free diet is no longer possible. For these patients, a positive outcome in terms of weight can only be obtained with sufficient and permanent changes in eating habits and behaviors.

108.3.1 Feeding Behavior After Biliopancreatic Diversion

After BPD, in those obese patients with normal eating habits and behavior no postoperative changes were observed, while in patients with disordered eating patterns dramatic behavioral improvement was observed. The amount of food consumption remained substantially similar at the preoperative stage with a slight increase observed in only a few patients (Scopinaro et al. 1998). Furthermore, a sharp drop in the Restraint Scale and Eating Disorder Examination score was verified (Adami et al. 2001, 2002), while in postoperative subjects, long-term mean values of the Cognitive Restraint subscale score of the Three Factor Eating Questionnaire were substantially similar to those observed prior to surgical intervention (Adami et al. 1993).

These findings support two important considerations with respect to psychological construct cognitive restraint, which is frequently observed in severely obese patients. Cognitive restraint does not

necessarily correspond to a decrease in food consumption; however, in most cases represents only a psychological requirement for food intake reduction, which the subject does not or cannot put into action. In addition, postBPD findings support the hypothesis that two different types of cognitive restraint exist. Rigid and drastic restraint rapidly subsides when body weight reduces, body morphology normalizes, and the dire need to lose weight ceases. While the more flexible and reasonable cognitive restraint noted via the Three Factor Eating Questionnaire is part of the eating habits of a "normal" person regardless of his or her degree of obesity. It is therefore only minimally affected by the obese status and by weight loss.

More interestingly, after BPD patients tend to lose their tendency toward disinhibition over food intake that frequently accompanies the obese status. After surgical intervention in fact a marked decrease (leading towards normality) of the disinhibition score of the Three Factor Eating Questionnaire was observed (Adami et al. 1993). In addition, all subjects having a BED preoperatively, report completely normal eating patterns long term after intervention. (Adami et al. 1996). Moreover, although after BPD intervention, the patient can eat without gaining weight, no patients have been observed binge eating, and the preoperative normal eating pattern remains quantitatively and qualitatively unmodified by the operation (Scopinaro et al. 1998). It has been suggested therefore that BPD be considered the choice procedure for the treatment of severe obesity associated with BED. The effects of BPD on the tendency toward disinhibition with respect to food intake may have two explanations. The dissatisfaction with one's own somatic morphology leads an individual to restrain food intake cognitively with the goal of losing weight and achieving a more socially acceptable body shape. According to the counter-regulation theory, drastic and rigid cognitive restraint leads to disinhibition (Herman et al. 2005). Thanks to the limitation of intestinal absorption, subjects who have undergone BPD succeed in achieving normal or nearly normal somatic morphology with a completely free diet. It must therefore be assumed that the aforementioned patients have abandoned all concerns about weight, food, and diet, and that dieting behaviors are no longer engaged in postoperatively. This would be the reason the tendency toward disinhibition over food intake weakens or disappears. On the other hand, in recent years, the tendency toward disinhibition and binge eating has been regarded more as an index of psychological distress and emotional disturbance than as a direct effect of rigid dieting, and this psycho-behavioral construct should therefore not be simply considered as a consequence of the forced and drastic cognitive limitation on food consumption (Bryant et al. 2007; Dingemans et al. 2002). As mentioned above, in the vast majority of cases, the surgically obtained stable normalization of body weight and somatic morphology results in a marked improvement of the quality of life and psychological state (Herpertz et al. 2009; Adami et al. 2005), and this marked improvement may well correspond to a reduction of the tendency toward disinhibition regarding food and to the disappearance of binge-eating episodes. In conclusion, whatever the cause, after BPD normal eating patterns do not change. Disinhibition however reduces or disappears and abnormal or atypical eating habits and behaviors are replaced with normal eating habits and behaviors (Herpetz et al. 2009; Adami et al. 1996, 2005; Wadden et al. 2001; Sarwer et al. 2005).

On the contrary, those obese patients who reported night eating, and who had a normal disinhibition score of the Three Factor Eating Questionnaire prior to BPD, continued this behavior for a long term after surgical intervention, with body weight steady at nearly normal levels and concerns about weight, food, and diet completely forgotten (Adami et al. 1999a). Furthermore, in obese patients with night eating, a characteristic neuroendocrinal pattern was observed, with specific alteration in the melanocortin metabolism (Birketvedt et al. 1999). Metabolic and postsurgery data clearly indicates that night eating should not be merely considered as a component of the case history of BED, and suggests however that this behavior can lead to weight gain regardless of disinhibition and the loss of control over food intake.

108.3.2 Feeding Behavior After Gastric Restriction Procedures

As aforementioned, weight outcome following BPD is substantially accounted for by the limitation of intestinal absorption of energy-rich substrates and therefore completely regardless of eating pattern changes. PostBPD subjects therefore represent a very good experimental model for understanding eating behavior and its relationship with body weight and dieting. By contrast, after gastric restriction operations, weight loss is strictly dependent on new eating habits and behaviors adopted. As a result, eating behavior modifications after gastric restriction surgery take on a profoundly different meaning. In large groups of patients undergoing gastric restriction, the simple fact of having changed individual eating habits in the postoperative period represents the strongest predictor of weight outcome at 1 and 2 years postoperation (Sarwer et al. 2008; Chevallier et al. 2007). In addition, in subjects who have lost weight after RYGBP, cognitive restraint increases long term and remains at higher levels than initially observed, while a marked decrease in self-reports of hunger and disinhibition has been observed (Chevallier et al. 2007). These findings prove that after gastric restriction procedures, postoperative changes in eating habits are mandatory for a satisfactory weight loss outcome.

Following gastric restriction procedures, overall postoperative improvement in eating behavior has been documented in some studies (Sarwer et al. 2008; Silver et al. 2006; van Hout et al. 2007; Bocchieri et al. 2002b), while in other research a sharp increase in the tendency to disinhibition as well as the frequency of binge eating was observed, so that BED was regarded as a contraindication for ASGB, VBG, and RYGBP (Kalarchian et al. 2002; Saunders 2004; Lang et al. 2002; Colles and Dixon 2006). It has been suggested that following the gastric restrictive procedure, the prevalence of BED is greatly diminished solely because of the mechanical impediment preventing the consumption of an objectively large amount of food in a single sitting (Colles and Dixon 2006; Busetto et al. 1996). Because of this, the feeling of loss of control over food intake could persist. The patient would binge eat if possible, however, he or she is physically unable to do so because of the surgery. Any attempt to binge eat could result in vomiting (Powers et al. 1999), which obviously does not represent purge behavior. Both prior to and following bariatric surgery, an eating behavior that is commonly termed "grazing" has been reported, involving the consumption of smaller amounts of food over extended periods of time (Saunders 2004; Colles et al. 2008). Preoperative binge eaters may be at high risk of conversion to postoperative "grazers," and after the operation, grazing could fulfill a similar function to that of binge eating (Saunders 2004). It has been observed that in severely obese patients, grazing is common and nearly all preoperative "grazers" continue this eating pattern after the gastric restrictive procedure has taken place (Saunders 2004). After gastric restriction intervention, a noteworthy increase in grazing prevalence was observed when compared to baselines, and noted was that most subjects began grazing behavior only after the operation. This was most likely induced by the gastric restriction. Globally considered, nearly one third of those severely obese patients who submitted to gastric restriction operation make reference to grazing behavior (Colles et al. 2008). Finally, it has been observed that grazing is associated with poor postoperative psychological adjustment and with the presence of emotional distress. In this sense, grazing likely represents a marker of impaired psychological function (Saunders 2004; Colles et al. 2008). Though grazing does not predict weight results for a long term following gastric restriction, it is not surprising that postoperative grazing is associated with poor weight loss or long-term weight regain. Eating small amounts of food "permanently" renders gastric restriction useless and allows for the overall intake of a large quantity of food (Colles et al. 2008).

Contrary to postBPD, the incidence of night eating unexpectedly increases after the gastric restriction procedure. On this topic, however, longitudinal as well as cross-sectional comparisons are

Table 108.1 Key feature of eating pattern and bariatric surgery

1. Bariatric surgery, also known as weight loss surgery, refers to the various surgical procedures performed to treat obesity by modification of the gastrointestinal tract to reduce nutrient intake and/or absorption

2. Surgery should be considered as a treatment option for patients with a BMI (body weight in kg divided by stature in meters) of 40 kg/m^2 or greater who instituted but failed an adequate exercise and diet program (with or without adjunctive drug therapy) and who present with obesity-related comorbid conditions, such as hypertension, impaired glucose tolerance, diabetes mellitus, hyperlipidemia, and obstructive sleep apnea.

3. The loss of the initial excess weigh after gastric restriction procedures and after biliopancreatic diversion is 40–60% and 70%, respectively.

4. After biliopancreatic diversion a satisfactory weight loss occurs at a completely free diet, while in the other cases a good weight outcome is dependent on the individual adaptation to the gastric restriction: in these patients an eating behavior modification program could be advisable.

This table gives the accepted indication for the bariatric surgery and the weight loss results usually obtained; furthermore, the differences in eating pattern following the gastric restriction operations and those that reduce intestinal absorption are outlined

currently thwarted by inconsistent diagnostic criteria (Bocchieri et al. 2002; Colles et al. 2007). For a clear understanding of the clinical importance of night eating, agreement on behavioral features and diagnostic criteria is required. Prospective studies should explore the clinical significance of night eating and its impact on the outcome of weight loss therapies. This is of particular importance with respect to bariatric surgery, given the great prevalence of night eating observed among surgical candidates (Adami et al. 1999a).

108.4 The Role of the Behavior Assessment and Behavior Modification Treatment Prior to and Following Bariatric Surgery

As mentioned previously, no psychological or behavioral variable has found to be predictive of weight outcome or the occurrence of complications after bariatric surgery. Therefore, a behaviorally oriented preoperative evaluation would theoretically be completely useless. However, an initial psychological assessment of candidates for bariatric surgery is of a great importance to the clinical work-up of patients (Wadden and Sarwer 2006). The primary aim of the interview is to inform candidates regarding the nature of the operation they plan to have, about its potential risks and benefits, as well as the changes they must make in eating and lifestyle habits (short and long term). The likelihood of experiencing vomiting, dumping, and related complications, and how they are motivated is also discussed. Furthermore, the candidate must be well aware of the great importance of being present for regular follow-ups. For surgical intervention that determines intestinal absorption limitation, follow-up is mandatory to the prevention of calcium and vitamin deficiencies and to ensure intervention upon onset of the first symptoms of possible protein malnutrition, a serious life-threatening complication, which affects 1% of patients operated on. Subjects must acknowledge that they will need supplementation for the rest of their lives, and that intervention could cause undesirable side effects. Side effects that they must accept in exchange for stable weight loss, or with which they must learn to cope by adopting a specific behavior. Patients undergoing gastric restriction procedures must be fully aware that by necessity, feeding behavior will change after surgical intervention because of the gastric restriction in the ASGB and VBG subjects and because of early satiety in the RYGBP ones. All subjects must be informed that long-term weight outcome is substantially dependent on the changes that will come into play in eating behavior. If the patient learns to use gastric restriction and/ or early satiety to reduce food intake permanently, he or she will succeed in reaching and maintaining

a reduced weight for a long term. If on the contrary, the subject assumes behavior after the operation that nullifies the mechanical or functional effects of the operation on food transit in the upper gastro-intestinal tract, only poor weight loss results will be obtained.

Furthermore, the presence of an eating disorder together with the patient's psychosocial status must be evaluated. Those patients who are severely obese may be unwilling to accept a true psychological assessment: in these cases, it must be clearly stated that the evaluation is not the first phase of psychotherapy, but simply helps the person to decide whether bariatric surgery is the right choice. Evaluation is usually carried out with self-report questionnaires and/or structured or semistructured interviews addressing the following areas:

1. *Weight and dieting history*: The interview should be devoted to the investigation of the age of obesity onset, difficulties with food intake and body weight control throughout the subject's lifetime, as well as the maximum weight reached. As to be expected, the great majority of surgery candidates have made multiple and significant efforts at losing weight. As already mentioned, past dieting could have the opposite effect on the postoperative weight outcome. On one hand, significant weight fluctuation could lead to a global decrease in energy expenditure, preventing satisfactory postoperative weight loss even when food intake is reduced. On the other, significant past weight loss could indicate the good capability of sticking to a dietary plan, thus predicting satisfactory weight loss and maintenance. So, generally speaking, past dieting behavior cannot predict weight outcome after surgery.

2. *Expectations from surgery*: Obese patients must be informed that after gastric restriction procedures, most individuals lose nearly 30–40% of their initial weight and that this reduction requires adequate changes in eating patterns. Unrealistic expectations with respect to weight loss and other postoperative outcomes could lead to psychological distress. Instead of focusing on weight loss per se, candidates are required to measure their success by means of other improvements in health or activities linked to daily living, such as being able to play with their children or to sit comfortably in an airplane (Wadden and Sarwer 2006).

3. *Eating pattern*: Inquiries are made during the interview about the foods typically eaten and favorite foods with the goal of identifying changes required in food intake after surgery. These issues are discussed in greater detail with the program's dietician, who provides an overview of the postoperative diet, as prescribed. Eating behavior must furthermore be investigated in order to detect the presence of aberrant alimentary patterns. As noted previously, given the absence of data to warrant this practice, patients with BED and night eating are not routinely deferred from surgery. However, they are warned against the potential effects of their eating disorder on adherence to the postoperative diet, and persons of significant concern are provided a referral for cognitive behavioral therapy. Current evidence suggests that binge eating is most likely to reoccur 18–24 months after RYGBP or ASGB (Kalarchian et al. 2002; Sarwer et al. 2005; Wadden and Sarwer 2006).

4. *Psychological conditions*: Among severely obese patients, the prevalence of depression may be higher than in individuals of normal weight, and though the prevalence of depression usually decreases after surgery, subgroups of patients who remained depressed even at long-term follow-up (after surgically obtained weight loss) were observed (Mitchell et al. 2001). Clinical evaluation and Beck Depression Inventory data has revealed that more than three quarters of bariatric surgery candidates report minimal to mild symptoms of depression which are not generally of clinical concern and that disappear within the first postoperative year (Wadden et al. 2006). Only patients with potential suicidal ideation and impaired sleep, concentration, cognition (including self-critical thoughts), and social function may need psychiatric or psychological support. A small minority of surgery candidates could have severe psychiatric disorders which are independent

from the obese status, such as psychosis, bipolar disease or addiction, and as a result must be excluded from the bariatric program

5. *Family members*: The decision to turn to bariatric surgery is significant for the patient's family. The preoperative interview inquires about patient living arrangements, spousal (partner) and other intimate relationships, and whether family members and friends support his or her decision.

Theories have been made that true cognitive-behavioral intervention prior to bariatric surgery might make patients more receptive to postoperative changes in eating behavior and as a result could improve weight reduction and maintenance. This hypothesis however has not been verified due to the very poor adherence to preoperative cognitive behavioral intervention (Leahey et al. 2009).

108.4.1 Cognitive Behavioral Factors Promoting Weight Loss After Gastric Restriction Operations

As mentioned earlier, satisfactory weight results following gastric restriction surgery are substantially dependent upon adequate postoperative long-term changes in eating habits and behavior. After classic behavior modification therapy for obesity, true and permanent changes in eating patterns are very difficult to obtain. As a result, after initial weight loss, recurrence represents the rule as verified in support groups. On the contrary, after gastric restriction surgery, most of the subjects operated on achieve in maintaining a satisfactory reduced weight for a long term, thus revealing adequate postoperative eating habit changes that are steadily maintained throughout the years. Consequently, the action of powerful factors should be considered, which promote eating habit changes following the operation. Gastric restriction represents a powerful and nearly unavoidable aversive stimulus against overeating; a stimulus that is felt each time the subject eats. This fact progressively induces the individual to reduce food intake via the classical mechanism of conditioning. Following a gastric restriction procedure for a short term, for anatomical or functional reasons, the patient is unable to resume eating with patterns which are similar to habitual patterns before the operation took place. Therefore, the so-called resistance to change is completely abolished. In other words, patients engaged in a conservative weight loss program must actively avoid resuming initial eating habits starting with the first phases of treatment. Patients who have been operated on, however, are immediately compelled by gastric restriction to adopt new eating habits and behavior without the possibility of return to the preoperative state. From a cognitive-behavioral point of view, there is a third factor promoting positive long-term results during the first postoperative months. Subjects who have undergone intervention lose weight because of the liquid diet in addition to the metabolic factors resulting from surgical invention. Therefore, individuals who have been operated on begin behavior modification programs with a body weight that has been reduced, and, according to the model of operant conditioning, this represents a powerful positive reinforcement for acquiring new and appropriate eating habits and behaviors. According to the cognitive-behavioral approach, all of these factors can explain why dietary changes after gastric restriction operations take place spontaneously without any specific therapy and are more important and persistent than those observed following standard behavior modification as a form of obesity therapy. In other words, gastric restriction represents an important mechanical and/or physiological perturbation on the upper gastrointestinal tract, and as a direct result, the individual's eating habits unavoidably changes. In order to achieve satisfactory weight loss and maintenance, subjects operated on must assume new eating patterns, which entail a reduction in food intake, by means of the artificial stimuli derived from the anatomical and/or functional modifications resulting from the gastric operation.

108.4.2 Eating Behavior Modification After Gastric Restriction Operations

If the patient is able to make changes, a positive weight loss result will be achieved. If, however, the effects of the operation are contrasted negatively by rapid or frequent eating, the consumption of juices or liquid calories and by consumption of dressings or high-calorie beverages, eating behaviors will change in the opposite sense, and poor weight loss results will be unavoidable. As aforementioned, it has been demonstrated that strict postoperative dietary adherence can predict positive postoperative weight results (Chevallier et al. 2007), and that participation in support groups is far better when done following rather than prior to the bariatric operation (Leahey et al. 2009). It must therefore be hypothesized that postoperative support driving patients to assume adequate eating habits and to avoid compensatory ones could lead to an overall reduction in food intake and then might significantly improve weight loss and maintenance. It is therefore advisable that all postgastric restriction patients be enrolled in specific eating behavior modification programs. Behavioral intervention should be affected according to a methodology similar to standard eating behavior modification used in conservative obesity therapy, with bi-weekly group sessions supervised by a psychologist or a dietician with experience in the field. As in the standard approach for obesity, food logs are obtained and reviewed during sessions and appropriate feedback is given. Cognitive-behavioral techniques should be used to reduce binge-eating frequency, the tendency to loss of control while eating, and grazing. Participants should furthermore be encouraged to use cognitive restructuring techniques to replace maladaptive cognitions with more adaptive thoughts, to increase their awareness of internal sensations, including early satiety and external cues, to modify environmental cues and to improve coping skills (Sharon and Irvin 2003; Fichter et al. 1998). While the classic program is simply aimed at reducing food intake, the postgastric restriction program should be mainly devoted to inducing postoperative patients to avoid those eating behaviors apt at canceling out the effects of the gastric restriction itself. Patients must therefore be specifically trained to identify early satiety at each meal, and to do away with such behavior as eating rapidly and frequently or consuming high-calorie beverages and fluid foods. Furthermore, patients must learn to use the weight loss obtained in the first postoperative phases as a powerful positive reinforcement for making adequate changes in their eating patterns. Gastric restriction subjects should receive more training on adopting adequate feeding behaviors than on consuming a healthy diet.

108.4.3 Eating Behavior Modification After Biliopancreatic Bypass

Owing to the permanent and selective limitation of intestinal absorption of energy-rich substrates, after BPD, patients experience highly satisfactory weight loss and maintenance independent of changes in food intake (which in the majority of the cases remains substantially similar to preoperative food intake) (Scopinaro et al. 1998). Furthermore, maladaptive eating behavior spontaneously disappears with respect to the diminishing of cognitive restraint and/or the sharp improvement of psychological and emotional conditions (Adami et al. 1993, 1995, 1996). The stable achievement of normal somatic morphology represents very strong positive reinforcement of changes in eating patterns and lifestyle. The simple instructions of the surgeon or dietician are therefore usually sufficient to obtain postoperative eating behavior suitable for the prevention of deficiency complications and to eliminate or minimize unpleasant side effects of the operation. In this sense, a structured

program of behavior modification after BPD is useless in the vast majority of patients who have been operated on.

As mentioned above, after BPD satisfactory weight loss and maintenance is accompanied in the vast majority of the operated subjects by a marked improvement of psychological functioning and emotional conditions. However, in a few patients who have been operated on, psychological status does not improve or even worsens. Because preoperative parameters that can predict psychological improvement after the operation do not exist, these infrequent cases are completely unforeseeable. Stable weight reduction corresponds in the vast majority of the cases to a normalization of the body image, demonstrating that in severely obese patients body image derangement is substantially secondary to somatic morphology that is far different from the socially accepted standard (Adami 2001; Adami et al. 1996). Nevertheless, a number of postobese subjects are still dissatisfied with their bodies in spite of normal or nearly normal body weight and morphology. Because these individuals have difficulty recognizing psychological needs (Adami et al. 2001), they usually request additional weight loss. In these cases, dieting is clearly useless. As mentioned above, the new gastrointestinal apparatus that BPD subjects have entails intestinal threshold absorption of energy-rich substrates, and the energy consumed in excess is eliminated via stool (Scopinaro et al. 2000). Therefore, when dietary intake of energy-rich substrates is greater than the intestinal threshold, as is obviously the rule in healthy postoperative long term BPD subjects long term, the amount of energy actually absorbed and then disposable for the body, and above all accounting for the individual's body weight, is only determined by an intestinal factor, and completely independent of food consumption. As a consequence, the decrease of food intake is completely without effect on body weight, and this could very well create cognitive dissonance and increase psychological distress. Therefore, generally speaking, a subject after BPD long-term who asks for additional weight loss first and foremost needs careful psychological evaluation. There are a very few patients who, in the extreme, and despite having reached normal or nearly normal body weight, are so dissatisfied with their body image that they require revisional surgery to regain the weight lost and return obese.

As said above, BPD subjects have seriously modified both their gastrointestinal systems as well as somatic morphology, and necessarily require adaptation of eating habits as well as lifestyle. While in the vast majority of cases adequate modification occurs spontaneously without need of therapy, a minority of patients do not possess emotional, technical, or cultural skills to cope with these changes that deeply affect their internal and/or external world. This fact may strongly and negatively influence overall psychological conditions and quality of life. The marked weight loss experienced following BPD undoubtedly represents a "catastrophic" change for severely obese patients; a change that means radical modifications. Therefore, from a dynamic point of view, low-grade transient depression in the first postoperative phase is unsurprising. However at longer term and when the markedly positive effects of the weight loss and maintenance become evident, the prevalence of depression usually decreases sharply. Only a small minority of patients remain depressed after having reached a normal or a nearly normal weight. Those postobese subjects who remain depressed refer a quality of life which is at times worse than at the preoperative stage when they were still obese. These patients undoubtedly need psychological and/or psycho-behavioral therapy, which must be effected with standard techniques based on the therapist's experience and the patient's cultural and social characteristics. Most of these individuals have alexithymic-type personality traits that are not changed by weight loss and recovery of a socially accepted somatic morphology (Adami et al. 2001). Clinical practice has shown that bariatric surgery is experienced by patients with a great deal of emotion, and represents an occurrence of pivotal importance in their lives. Consequently, many significant events happening in the postoperative period are specifically accounted for by the operation itself. It is therefore not surprising that most patients, and specifically those with personality traits

with alexithymic characteristics, refer their symptoms and their distress to the surgeon and/or to the dietician, without requiring specific psychological, psycho-behavioral or psychiatric help. These subjects however must be referred to professionals with specific experience. In other cases, subjects operated on with severe emotional or psychological discomfort primarily seek out psychological or behavioral help. The therapist must be sure to remember that these subjects are not responsible for their obese status. Bariatric surgical intervention is the only effective therapeutic method for severe obesity. Surgically obtained weight loss is accompanied by an improvement in psychological conditions in the majority of cases and that having undergone a bariatric operation should not represent a personal source of shame. Besides the specific complications that require specific therapy and disappear within a limited period, BPD entails negative side effects that in some cases can be eliminated or improved by ad hoc behavioral modifications. Other cases of complications are the unavoidable consequence of the reduced intestinal absorption that justifies long-term weight maintenance. In some cases, the main goal of postoperative modification intervention should be to help the patient adopt behavior which can eliminate or attenuate these effects. In all cases, the principle aim of the therapy should be to encourage patients to adapt themselves to this condition, while avoiding criticism regarding the intervention or the personal decision that lead the patient to turn to bariatric surgery.

108.5 Conclusions

Severe obesity is a multifactorial chronic disease that is largely dependent on still unknown genetic and metabolic factors. Psychological and behavioral dysfunctions are essentially secondary to the obese status. Any surgical intervention, moreover, involves technological procedures directed more at the body than the individual. For those patients who have undergone any surgical procedure, the establishment of a good therapeutic relationship has undoubtedly been of only limited significance, good results being mainly dependent on the skill of the surgeon. However, bariatric surgery profoundly influences food intake as well as body weight, fundamental aspects of individual life. Therefore, to have positive clinical work as well as a satisfactory overall outcome, strict cooperation of the clinical surgeon with the psychologist or with a professional who has a history of caring for the individual as a whole is mandatory.

The psychologist or the behavior professional may initially have a substantial role in the initial assessment, when the patient's capacity to understand the risks and benefits of surgery as well as the consequences of the operation and weight loss must be evaluated. It is furthermore necessary that the presence of serious psychiatric problems, such as schizophrenia, bipolar disorder, or addiction be excluded, which could contraindicate the bariatric procedure. Finally, a careful appraisal of eating behavior is required, as well as clinical assessment of the patient's ability to adapt (including feeding pattern and lifestyle) to the new anatomo-functional and morphological changes derived from the operation and the weight loss. With multiple surgical procedures available, it is imperative that the patient be matched with the most appropriate procedure. This could be the most important task of the psychologist working with a bariatric surgery team. According to the clinical guidelines mentioned, patients with more severe cases of obesity, with deranged eating patterns, with low cultural and intellectual levels, and/or who are believed to have little capacity to change would be addressed to BPD. The younger and more highly motivated patients however can undergo gastric restriction surgery with a greater chance of successful weight loss results. Although psychological evaluation is advocated, there is currently no standard evaluation protocol or predicting factor able to exclude the choice of bariatric surgery or individualize the

type of operation most suitable. The challenge of this approach is to improve weight loss results and predict therapeutic response based on preoperative variables. Clinical findings could guide surgeons in selecting the most appropriate operation for a candidate or allow dieticians and mental health professionals to provide pre- or postoperative counseling to improve the long-term weight loss outcome and quality of life. Until such data is obtained, a patient-oriented behavioral evaluation provides candidates for bariatric surgery with an invaluable opportunity to discuss their often life-long struggle with their weight and the distress it has caused them. While after BPD psychological support is only seldom required, after gastric restriction operations postoperative routine behavior modification therapy may be advisable and could significantly improve the weight loss outcome, particularly long term. Clearly, the main goal of this support should be to encourage healthy eating patterns. Subjects must be instructed and conditioned to accept gastric restriction and to use early satiety as a means to permanently decrease food intake. In doing this, they achieve and maintain satisfactory long-term weight loss. This type of behavioral intervention has still not been schematized or formalized, and prospective results are not yet available. However, specific postoperative support theoretically represents reasonable methodology for improving the overall results of the gastric restrictive operation. From this it is clear that generic competence is not sufficient, and in-depth knowledge of bariatric surgery and related psychological problems is required of the psychologist or psychiatrist working in this field. This must obviously go hand in hand, not of least importance, with the mandatory complete abandonment of any personal blame related to obesity and obese individuals.

108.6 Applications in Other Areas of Health and Disease

In the western developed world, the prevalence of severe obesity is sharply increasing and therefore over the next few decades an even greater number of patients will undergo obesity surgery. Bariatric operations interfere with the main aspects of the subject's life such as food intake and somatic morphology. The bariatric surgery team therefore requires the direct involvement of a psychologist or a professional with experience in behavioral modification. Generic competence is not sufficient, and along with the complete lack of any personal stigmatization toward obesity, in-depth knowledge of bariatric surgery and related psychological problems is required.

Summary Points

- Two different types of bariatric operations are available, those aimed at reducing food intake (gastric restriction procedures) and those limiting intestinal absorption of energy-rich substrates (biliopancreatic diversion and its variants).
- Gastric restriction obstructs the transit of food in the upper gastrointestinal tract and food intake is then forcedly reduced. When gastric restriction leads to a decrease in habitual food intake, satisfactory weight loss results are obtained.
- After biliopancreatic diversion highly satisfactory weight loss and maintenance is achieved by the permanent limitation of the intestinal absorption of fat and starches. Weight results are therefore achieved independently from changes in food intake and behaviors.
- After any surgically obtained weight loss, as a rule sharp improvement in psychological state and eating behavior is observed, indicating that these alterations are substantially secondary to the obese status.

- For the purpose of improving weight loss results, behavioral intervention is envisaged with the aim of matching individual eating habits with gastric restriction without use of compensatory practices.
- After biliopancreatic diversion, the subjects whom have been operated on, easily and without therapy, adapt lifestyle and eating behavior to the anatomo-functional changes in the gastrointestinal tract resulting from the operation and to the new body morphology resulting from the weight loss.

Definitions of Key Terms

Full recovery from obesity: This is the steady reduction of body weight within the physiological range and the disappearance of comorbidities specifically due to the obese status.

Postobese subjects: They are formerly obese patients who steadily normalized or nearly normalized body weight.

Gastric restriction: It is a mechanical impediment of food transit due to the new anatomical condition created by gastric banding or vertical gastroplasty. The subject stops eating after having ingested only a small amount of food in order to prevent nausea, discomfort, and epigastric pain or vomiting.

Early satiety: After the gastric bypass, indigested food directly passes into the distal intestine, and this promotes the secretion of entero-hormones producing satiety. This phenomenon contributes along with gastric restriction to the reduction of overall food consumption.

Threshold for intestinal absorption: While absorption capacity of the intact intestine is not limited, the new gastrointestinal apparatus resulting from biliopancreatic diversion can absorb only a fixed amount of energy-rich substrates, and the fat and starches ingested in excess are eliminated via stool. This results in highly satisfactory weight loss and maintenance independent of food intake.

Compensatory eating behaviors after gastric restriction: They refer to behaviors engaged in consciously or unconsciously by patients who have been operated on, and which render the gastric restriction inefficient. If the subject eats rapidly or frequently, ingests fluid food, high calorie beverages or heavy dressings, drinks during meals or overeats until vomiting, food transit is unaffected and the overall food intake remains at a high level, with the obvious consequences on body weight.

Grazing: Grazing involves consumption of smaller amounts of food over extended periods. In postgastric restriction subjects, this behavior may fulfill a similar function to binge eating, likely representing a marker of impaired psychological function.

Binge eating: Episodes represented by eating large quantities of food within a limited period with the clear feeling of loss of control. After biliopancreatic diversion, binge-eating episodes disappear thanks to the renunciation of concern for diet, food, and weight, and to the sharp improvement of psychological conditions.

Body image: The body image construct defines the picture of our body we form in our mind, that is to say the way in which the body appears to us. Body image derangement is quite common in severely obese patients and as a rule, after surgically induced weigh loss sharp improvement moving toward normality of this psychological construct is observed.

Alexithymia: Alexithymia denotes an individual's difficulty to express emotions and turn emotions into symbols to facilitate interindividual communication. Alexithymic personality traits are common in eating disordered patients and in severely obese subjects.

References

Adami GF, Gandolfo P, Dapueto R, Jurich D, Scopinaro N. Eating behavior following biliopancreatic diversion for obesity: study with a three-factor eating questionnaire. Int J Eat Disord. 1993;14:81–6.

Adami GF, Gandolfo P, Meneghelli A, Scopinaro N. Binge eating in obesity: a longitudinal study following biliopancreatic diversion. Int J Eat Disord. 1996b;20:405–13.

Adami GF, Meneghelli A, Bressani A, Scopinaro N. Body image in obese patients before and after stable weight reduction following bariatric surgery. J Psychosom Res. 1999a;46:275–81.

Adami GF, Meneghelli A, Scopinaro N. Night eating and BED in obese patients. Int J Eat Disord. 1999b;25:335–8.

Adami GF. The influence of body weight on food and shape attitudes in severely obese patients. Int J Obes Relat Metab Disord. 2001;25 Suppl 1:S56–9.

Adami GF, Campostano A, Ravera G, Leggieri M, Scopinaro N. Alexithymia and body weight in obese patients. Behav Med. 2001;27:121–6.

Adami G, Campostano A, Cella F, Ferrandes G. Serum leptin level and restrained eating: study with the Eating Disorder Examination. Physiol Behav. 2002;75:189–92.

Adami GF, Ramberti G, Weiss A, Carlini F, Murelli F, Scopinaro N. Quality of life in obese subjects following biliopancreatic diversion. Behav Med. 2005;31:53–60.

Birketvedt GS, Florholmen J, Sundsfjord J, Østerund B, Dingers D, Bilker W, Stunkard AJ. Behavioral and neuroendocrine characteristics of the Night-Eating Syndrome. JAMA. 1999;282:657–63.

Bocchieri LE, Meana M, Fisher BL. Perceived psychosocial outcomes of gastric bypass surgery: a qualitative study. Obes Surg. 2002a;12:781–8.

Bocchieri LE, Meana M, Fisher BL. A review of psychosocial outcomes of surgery for morbid obesity. J Psychosom Res. 2002b;52:155–65.

Bryant EJ, King NA, Blundell JE. Disinhibition: its effects on appetite and weight regulation. Obes Rev. 2007;9:409–19.

Buchwald H, Avidor Y, Braunwald E, Jensen MD, Pories W, Fahrbach K, Schoelles K. Bariatric surgery: a systematic review and meta-analysis. JAMA. 2004;13 292:1724–37.

Busetto L, Valente P, Pisent C, Segato G, de Marchi F, Favretti F, Lise M, Enzi G. Eating pattern in the first year following adjustable silicone gastric banding (ASGB) for morbid obesity. Int J Obes Relat Metab Disord. 1996;20:539–46.

Busetto L, Segato G, De Luca M, De Marchi F, Foletto M, Vianello M, Valeri M, Favretti F, Enzi G. Weight loss and postoperative complications in morbidly obese patients with BED treated by laparoscopic adjustable gastric banding. Obes Surg. 2005;15:195–201.

Camerini G, Adami GF, Marinari GM, Campostano A, Ravera G, Scopinaro N. Failure of preoperative resting energy expenditure in predicting weight loss after gastroplasty. Obes Res. 2001;9:589–91.

Chevallier JM, Paita M, Rodde-Dunet MH, Marty M, Nogues F, Slim K, Basdevant A. Predictive factors of outcome after gastric banding: a nationwide survey on the role of center activity and patients' behavior. Ann Surg. 2007;246:1034–9.

Colles SL, Dixon JB. Night eating syndrome: impact on bariatric surgery. Obes Surg. 2006;16:811–20.

Colles SL, Dixon JB, O'Brien PE. Grazing and loss of control related to eating: two high-risk factors following bariatric surgery. Obesity (Silver Spring). 2008;16:615–22.

de Zwaan M, Mitchell JE, Howell LM, Monson N, Swan-Kremeier L, Crosby RD, Seim HC. Characteristics of morbidly obese patients before gastric bypass surgery. Compr Psychiatry. 2003;44:428–34.

Dingemans AE, Bruna MJ, van Furth EF. BED; a review. Int J Ob Relat Metab Disord. 2002;26:299–307.

Dymek MP, Le Grange D, Neven K, Alverdy J. Quality of life and psychosocial adjustment in patients after Roux-en-Y gastric bypass: a brief report. Obes Surg. 2001;11:32–9.

Favretti F, Segato G, Ashton D, Busetto L, De Luca M, Mazza M, Ceoloni A, Banzato O, Calo E, Enzi G. Laparoscopic adjustable gastric banding in 1,791 consecutive obese patients: 12-year results. Obes Surg. 2007;17:168–75.

Fichter MM, Quadflieg N, Gnutzmann A. BED: treatment outcome over a 6-year course. J Psychosom Res. 1998;44:385–405.

Garrow JS. Aetiology of obesity in man. In: Obesity and related diseases. Edinburg: Churchill Livingstone; 1988. p. 101–133.

Herman CP, Polivy L, Leone T. The psychology of overeating. In: Mela D, editor. Food, diet and obesity. Cambridge: Woodhead; 2005. p. 115–136.

Herpertz S, Kielmann R, Wolf AM, Hebebrand J, Senf W. Do psychosocial variables predict weight loss or mental health after obesity surgery? A systematic review. Obes Res. 2004;12:1554–69.

Hsu LKG, Betancourt S, Sullivan SP. Eating disturbances before and after VBG: a pilot study. Int J Eat Disord. 1996;19:3–34.

Hsu LKG, Benotti PN, Dwyer J, Roberts SB, Saltzman E, Shikora S, Rolls BJ, Rand W. Nonsurgical factors that influence the outcome of bariatric surgery: a review. Psychosom Med. 1998;60:338–46.

Hudson SM, Dixon JB, O'Brien PE. Sweet eating is not a predictor of outcome after Lap-Band placement. Can we finally bury the myth? Obes Surg. 2002;12:789–94.

Kalarchian MA, Marcus MD, Wilson GT, Labouvie EW, Brolin RE, LaMarca LB. Binge eating among gastric bypass patients at long-term follow-up. Obes Surg. 2002;12:270–5.

Leahey TM, Bond DS, Irwin SR, Crowther JH, Wing RR. When is the best time to deliver behavioral intervention to bariatric surgery patients: before or after surgery? Surg Obes Relat Dis. 2009;5:99–102.

Lang T, Hauser R, Buddeberg C, Klaghofer R. Impact of gastric banding on eating behavior and weight. Obes Surg. 2002;12:100–7.

Larsen JK, Geenen R, Maas C, de Wit P, van Antwerpen T, Brand N, van Ramshorst B. Personality as a predictor of weight loss maintenance after surgery for morbid obesity. Obes Res. 2004;12:1828–34.

Lindroos AK, Lissner L, Sjostrom L. Weight change in relation to intake of sugar and sweet foods before and after weight reducing gastric surgery. Int J Obes Relat Metab Disord. 1996;20:634–43.

MacLean LD, Shibata HR. The present status of bypass operations for obesity. Surg Annu. 1977;9:213–30.

Malone M, Alger-Mayer S. Binge status and quality of life after gastric bypass surgery: a one-year study. Obes Res. 2004;12:473–81.

Mason EE, Doherty C, Cullen JJ, Scott D, Rodriguez EM, Maher JW. Vertical gastroplasty: evolution of VBG. World J Surg. 1998;22:919–24.

Marceau P, Biron S, Hould FS, Lebel S, Marceau S, Lescelleur O, Biertho L, Simard S. Duodenal switch: long-term results. Obes Surg. 2007;17:1421–30.

Mitchell JEm Lancaster KL, Burgard MA, Howell LM, Krahn DD, Crosby RD, Wonderlich SA, Gosnell BA. Long-term follow-up patients' status after gastric bypass. Obes Surg. 2001;11:464–8.

Munoz DJ, Lal M, Chen EY, Mansour M, Fischer S, Roehrig M, Sanchez-Johnsen L, Dymek-Valenitine M, Alverdy J, le Grange D. Why patients seek bariatric surgery: a qualitative and quantitative analysis of patient motivation. Obes Surg. 2007;17:1487–91.

Norris L. Psychiatric issues in bariatric surgery. Psychiatr Clin North Am. 2007;30:717–38.

Powers PS, Perez A, Boyd F, Rosemurgy A. Eating pathology before and after bariatric surgery: a prospective study. Int J Eat Disord. 1999;25:293–300.

Ronchi A, Marinari GM, Sukkar SG, Scopinaro N, Adami GF. Behavioral characteristics of severely obese patients seeking bariatric surgery: ross-sectional study with alimentary interview. Behav Med. 2008;33:145–50.

Sarwer DB, Wadden TA, Fabricatore AF. Psychosocial and behavioral aspects of bariatric surgery. Obes Res. 2005;13:639–48.

Sarwer DB, Wadden TA, Moore RH, Baker AW, Gibbons LM, Raper SE, Williams NN. Preoperative eating behavior, postoperative dietary adherence, and weight loss after gastric bypass surgery. Surg Obes Relat Dis. 2008;4:640–6.

Saunders R. "Grazing": a high-risk behavior. Obes Surg. 2004;14:98–102.

Scopinaro N, Adami GF, Marinari GM, Gianetta E, Traverso E, Friedman D, Camerini G, Baschieri G, Simonelli A. Biliopancreatic diversion. World J Surg. 1998;22:936–46.

Scopinaro N, Marinari GM, Pretolesi F, Papadia F, Murelli F, Marini P, Adami GF. Energy and nitrogen absorption after biliopancreatic diversion. Obes Surg. 2000;10:436–41.

Sharon R, Irwin DW. A cognitive-behavioral mindfulness group therapy intervention for the treatment of binge eating in bariatric surgery patients. Cogn Behav Pract. 2003;15:364–75.

Silver HJ, Torquati A, Jensen GL, Richards WO. Weight, dietary and physical activity behaviors two years after gastric bypass. Obes Surg. 2006;16:859–64.

Sugerman HJ, Londrey GL, Kellum JM, Wolf L, Liszka T, Engle KM, Birkenhauer R, Starkey JV. Weight loss with VBG and Roux-Y gastric bypass for morbid obesity with selective versus random assignment. Am J Surg. 1989;157:93–102.

van Hout GC, Jakimowicz JJ, Fortuin FA, Pelle AJ, van Heck GL. Weight loss and eating behavior following VBG. Obes Surg. 2007;17:1226–34.

Wadden TA, Sarwer DB, Womble LG, Foster GD, McGuckin BG, Schimmel A. Psychosocial aspects of obesity and obesity surgery. Surg Clin North Am. 2001;81:1001–24.

Wadden TA, Sarwer DB. Behavioral assessment of candidates for bariatric surgery: a patient-oriented approach. Obesity (Silver Spring). 2006;14 Suppl 2:53S–62S.

Part XVIII
Pathology and Abnormal Aspects: Food Choice, Selection and Preferences

Chapter 109
Food Addiction: Analysis With an Animal Model of Sugar Bingeing

Nicole M. Avena, Miriam E. Bocarsly, and Bartley G. Hoebel

Abbreviations

ACh   Acetylcholine
BED   Binge-eating disorder
DA   Dopamine
D1   Dopamine type 1 receptor
D2   Dopamine type 2 receptor
D3   Dopamine type 3 receptor
DSM-IV   Diagnostic and Statistical Manual of the American Psychiatric Association, Fourth
           Edition
mRNA   Messenger ribonucleic acid
NAc   Nucleus accumbens

109.1 Introduction

Obesity is presently one of the greatest threats to public health in the US. It is estimated that by the year 2030, half of the population will be obese (Wang et al. 2008). Presently, in addition to the 33% of the population that is obese, about 55% are overweight (Flegal et al. 1998). Obesity and being overweight have serious physical, emotional, psychological, societal, and economic risks. Depression, substance abuse, and susceptibility to other illnesses are examples of some common comorbidities seen with obesity.

Despite the wealth of information, public warnings, and availability of diet drugs and healthly foods, people often remain overweight. Of particular note is the number of youth who are overweight. This has contributed to the rise in the incidence of Type-II diabetes among children, which has been estimated to have increased up to tenfold over the past 20 years (American Diabetes Association 2000), and it will undoubtedly result in additional health problems as these children age.

N.M. Avena (✉)
Department of Psychiatry, University of Florida,
Gainesville, FL 32608, USA
and
Department of Psychology and Program in Neuroscience, Princeton University, Princeton, NJ 08540, USA
e-mail: navena@ufl.edu

Several questions arise when considering these statistics. Why are so many individuals overweight? Why can't some people stop eating unhealthy food? Why do some people have a penchant for sugary or fat-rich foods, which are also high in calories?

109.2 What Is a Food Addiction?

The theory of food addiction posits that, for some individuals, food is like a drug of abuse. There have been several clinical accounts in which people claim to be "addicted" to certain foods, and this addiction manifests as excessive overeating, a feeling of distress when palatable food is not available, and craving of certain foods (Ifland et al. 2009). These food addictions tend to focus on highly palatable, calorically dense foods, or for some people, refined carbohydrates. Much like the relationship that emerges between a person addicted to drugs and their drug of abuse, those who feel they are addicted to certain foods can find it difficult to stop overeating, which can ultimately result in body weight gain or an eating disorder. Interestingly, a recent study has discovered that many advertisements for highly palatable snack foods targeted at children contain images of the food having drug-like properties (Page and Brewster 2009). This finding highlights the commonalities between some foods and drugs of abuse, and it reinforces the notion that the concept of food addiction permeates through our culture.

Although the term food addiction is often used colloquially, its scientific definition is now emerging, and evidence is accumulating to suggest that repeated exposure to certain foods can, indeed, produce behaviors and changes in the brain that resemble an addiction-like state. One may wonder how something as innocuous as a palatable food, which many people consume on a regular basis with no adverse effects on health or well-being, could be akin to a drug of abuse. In this chapter, we discuss instances in which a palatable food can act as an addictive substance. Although foods and drugs are vastly different in their roles in society, they rely on a common underlying brain circuitry, and thus can be quite similar in their effects on the brain, as described below.

109.3 Possible Origins of Food Addiction

The rapid rise in the overall number of adults and children who are overweight is too abrupt to suggest a genetic cause. Environmental and/or behavioral changes are more likely the source of the problem.

From an evolutionary standpoint, food is necessary for survival, and there exist innate biochemical processes that reinforce feeding behavior when one is hungry. Similarly, other "natural" behaviors, such as sexual behavior, are necessary for the survival of our species, and are thus powerful reinforcers. Some of our ancestors survived to procreate by spending their time hunting for food and then engaging in opportunistic binge eating due lack of refrigeration and the scarcity of their next meal. However, in the modern-day environment of industrialized countries food is plentiful. Those skills that were previously needed for survival may lead to detrimental behavior that affects the brain and subsequent feeding behaviors. Thus, there may exist an innate drive to overeat when food is available, and in our present environment, that may mean that people indulge on a regular basis (Stephens et al. 2004).

This drive to consume food is motivated by the release of neurochemicals that are associated with a feeling of euphoria and pleasure. As described next, palatable foods are especially strong reinforcers, sending these systems intended to motivate food consumption for survival into over-drive. It is important to note that much like the development of drug addiction, food addiction is not seen in all people and it may become most apparent in a subset of genetically susceptible individuals.

109.4 Binge Eating: A Behavioral Criterion of Food Addiction

The Diagnostic and Statistical Manual of the American Psychiatric Association (Fourth Edition, Text Revision) (DSM-IV) defines binge eating as a series of recurrent binge episodes during which one eats a larger amount of food than normal during a short period of time (usually within any 2-h period) and shows three or more of the following: (1) eating until feeling uncomfortably full, (2) eating large amounts of food when not physically hungry, (3) eating much more rapidly than nor-mal, (4) eating alone because one is embarrassed by how much s/he is eating, (5) feeling dis-gusted, depressed, or guilty after overeating, or (6) marked distress or anxiety regarding binge eating (American Psychiatric Association 2000). Meeting these criteria can lead to a diagnosis of Binge-Eating Disorder (BED), an eating disorder that affects approximately 6% of the population (Hudson et al. 2007). In addition to BED patients, there are individuals who engage in binge-eat-ing behavior that is associated with other eating disorders; e.g., bulimia nervosa. Although binge-eating behavior is traditionally associated with eating disorders, it has also been linked to obesity, and it may be a predictor of body-fat gain among children, leading to a high risk for adult obesity (Tanofsky-Kraff et al. 2006). Binge eating is also associated with increased frequency of body weight fluctuation, depression, anxiety, and substance abuse (Ramacciotti et al. 2005; Galanti et al. 2007; Grucza et al. 2007).

People usually binge on palatable, highly caloric foods, which also happen to be high in fats, sugars, or often both, and are thus normally meant to be consumed in moderation (Hadigan et al. 1989; Kales 1990; Guertin and Conger 1999). Data derived from normal-weight, binge-eating women indicate that binge episodes most often contain bread or pasta, followed in frequency by sweets, fatty foods, or salty snacks (Allison and Timmerman 2007). Individuals with a preference for bingeing on sweet foods tend to binge more frequently. Thus, there may be some property of palatable "snack" or "comfort" foods rich in sugar and/or fat that promotes binge eating.

Although the word "addiction" does not appear in the DSM-IV, substance abuse is clearly defined as an instance "when an individual persists in use of alcohol or other drugs despite problems related to use of the substance" (American Psychiatric Association 2000). A diagnosis of substance abuse is given when recurrent substance use (1) results in a failure to fulfill major obligations at work, school, or home; (2) occurs in situations in which it is physically hazardous; (3) produces related legal prob-lems; and (4) is continued despite social or interpersonal problems caused or exacerbated by the effects of the substance. Using laboratory animals, we have adapted some established procedures that are used to classify substance dependence with respect to drugs of abuse, and applied them to the study of food addiction in our model of sugar bingeing. Others have recently taken the criteria from the DSM-IV pertaining to substance abuse and applied them to describe food addiction in humans, thereby creating a food addiction scale that can be administered in a clinical setting (Gearhardt et al. 2009).

109.5 An Animal Model of Binge Eating: A Focus on Sugar Bingeing

We acknowledge that binge eating is a multifaceted behavior, with emotional and cultural components that are difficult to model in laboratory animals. Nonetheless, animal models of binge eating are integral to understanding the physiological and neurochemical basis of this behavior. Other models of binge eating are available and of great interest, as each has its own particular relationship to human behavior, such as stress-induced eating and fat bingeing (Boggiano et al. 2005; Corwin 2006; Berner et al. 2008). We chose to focus on sugar bingeing because, under normal conditions, rats and people have a pleasurable reaction to the taste of a sugar solution, sugar is ubiquitous in our society, and it has been associated with the rapid rise in the incidence of obesity.

We have developed a model in our laboratory in which food restriction and refeeding is used to precipitate daily bingeing behavior. Rats are maintained on daily 12-h food deprivation, followed by 12-h access to a 25% glucose or 10% sucrose solution (similar to the sugar concentration of a soft-drink) and rodent chow (Avena et al. 2008b). After just a few days on this schedule, the animals begin to binge on the sugar, as indicted by an increase in their intake of the sugar solution during the first hour of access. We also have data suggesting that these animals take voluntary binges throughout their 12-h access period. Animals that have unrestricted access to the sugar solution and chow consume an amount similar to that consumed by the bingeing animals, but their consumption is spread over 24 h, and these rats do not engage in bingeing episodes.

109.6 Behavioral Evidence of Sugar Addiction

In the following sections, we will describe the empirical data that suggest addiction-like brain and behavioral changes using our animal model of binge eating. The data described below have been summarized in previous reports (Avena et al. 2008b, 2009a), as well as in Table 109.1.

Table 109.1 Summary of features of food addiction

1. Bingeing is characterized by consuming a larger than normal or intended amount of food in a discrete period of time. In addition to sugar, animals will binge on pure fat, which suggests that binge eating is not exclusive to sweet taste. The combination of sweet and fat activates multiple taste receptors, postingestive signals, and neuropeptide systems. Sugar/fat combinations, in the form of cookies or sugar-fat mixtures, have been used by researchers to induce binge eating in laboratory models. Our model of sugar-bingeing produces alterations in the mesolimbic DA system and opioid systems that are consistent with the effects of substances of abuse.
2. A negative state can result when an abused substance is no longer available. In particular, opioid withdrawal has a clearly defined behavioral profile. Sugar-bingeing rats show signs of opiate-like withdrawal when sugar is removed, or when withdrawal is precipitated with an opioid antagonist. Concomitant changes in DA and ACh release in the NAc are observed, which are consistent with the findings observed during withdrawal from some drugs of abuse.
3. Craving is characterized by a profound desire to procure an abused substance. One way to examine craving after abstinence is to test for the "deprivation effect." Rats that are bingeing on sugar will lever press 23% more for it after 2 weeks of abstinence than they did prior to abstinence, while a control group with 0.5-h daily access to sugar did not show this enhanced response. These results suggest a change in the motivational impact of sugar that persists throughout a prolonged period of abstinence, leading to enhanced intake. Others have shown that responding for a cue previously associated with sugar grows with duration of abstinence, suggesting the gradual emergence of long-term changes in the neural circuitry underlying excessive motivation that results from sugar self-administration and abstinence.

This table lists key concepts and symptoms associated with food addiction, including bingeing, withdrawal, and craving that have been shown using animal models. References are included in the text below.

109.6.1 Escalation of Intake and Bingeing Behavior with Limited Daily Access to Sugar

Escalation of intake is a characteristic of drugs of abuse. Increased intake with subsequent exposures to a drug may be due, in part, to a tolerance to the drug, indicated by needing more of the substance in order to produce the same euphoric effects. Often, escalating intake is coupled with a "binge" upon access to a substance of abuse.

   As described above, our model of sugar bingeing demonstrates that rats given daily intermittent access to a sugar solution, along with rat chow, escalate their sugar intake and increase their intake during the first hour of daily access, which we define as a "binge" (Colantuoni et al. 2001). This binge-like behavior is one sign of dependence. However, what makes this model unique is that it results in multiple signs of dependence, including withdrawal, craving, cross-sensitization, and drug substitution, as described next.

109.6.2 Sugar Bingeing Results in a Withdrawal-Like State

Animals can show signs of opiate withdrawal after repeated exposure to an opiate when the substance is removed, or the opioid receptors are blocked. In rats, opiate withdrawal has clear and well-defined behavioral signs, including somatic indicators of distress, decrease in body temperature, aggression, and anxiety, as well as a motivational pattern characterized by dysphoria and depression (Martin et al. 1963; Way et al. 1969).

   We have observed similar signs of opiate-like withdrawal in rats that have been bingeing on sugar (Fig. 109.1). When administered the opioid antagonist naloxone, somatic signs of withdrawal, such
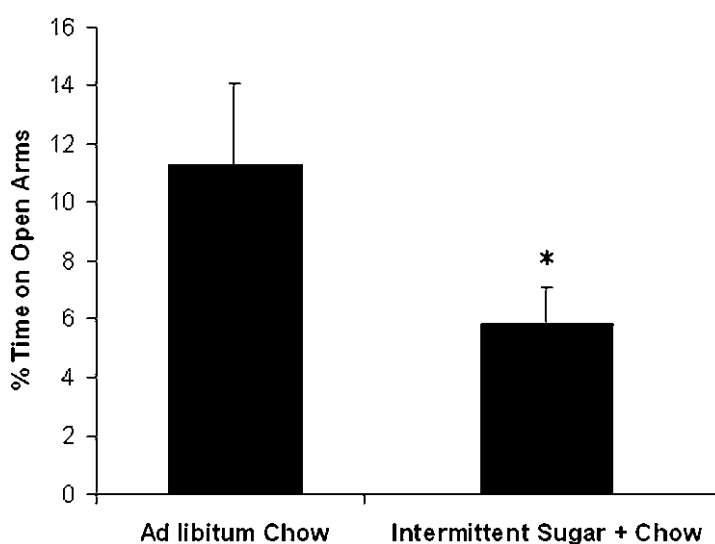
Fig. 109.1 Percent of time spent on the open arms of an elevated plus maze in sugar-binging rats versus ad libitum chow rats. Rats that had previously been bingeing on sugar spent significantly less time on the open arm of the plus maze after 36 h of fasting compared with a group previously maintained on ad libitum chow that was also fasted for 36 h. This indicates that sugar abstinence can cause anxiety ($^*p < 0.05$) (Reproduced with permission from Avena et al. 2008a)

as teeth chattering, forepaw tremor, and head shakes occur (Colantuoni et al. 2002). These animals are also anxious, as measured by reduced time spent on the exposed arm of an elevated plus maze. Signs of opiate withdrawal also emerge spontaneously without the use of an opioid antagonist, when all food is removed for 24–36 h (Colantuoni et al. 2002; Avena et al. 2008a). Therefore, our data suggest that bingeing on a sugar solution releases opioids in the brain, with resultant neural adaptations that are manifest as a dependency. Other researchers have obtained supportive findings that suggest opiate-like withdrawal using similar models of sugar bingeing. For example, signs of anxiety have been reported in rats with limited access to a high-sucrose diet (Cottone et al. 2008). The mere removal of sugar has been reported to decrease body temperature (Wideman et al. 2005). Also, signs of aggressive behavior have been found during withdrawal of a diet that includes intermittent sugar access (Galic and Persinger 2002).

109.6.3 A Dietary History of Sugar Bingeing Precipitates Increased Responding for Sugar Following Abstinence: A Possible Sign of Craving

Craving in laboratory animals can be defined as enhanced motivation to procure an abused substance (Koob and Le Moal 2005). After self-administering drugs of abuse and then being forced to abstain, when the drug again becomes available animals will take more than they did prior to abstinence (Sinclair and Senter 1968). Also, animals will often persist in unrewarded operant responding (i.e., resistance to response extinction), and over time increase their responding for cues previously associated with the drug (Ciccocioppo et al. 2001; Grimm et al. 2002; Lu et al. 2004). This increase in motivation to obtain a substance of abuse mimics the condition observed with humans, and may contribute to the likelihood of relapse.

We measured lever pressing for sugar after abstinence in rats that had been previously bingeing on sugar. Sugar-bingeing rats lever press for 23% more sugar in a test after 2 weeks of abstinence than they did before (Avena et al. 2005), while a control group with 0.5-h daily access to sugar did not show the effect. The results suggest a change in the motivational impact of sugar that persists throughout a prolonged period of abstinence, leading to enhanced intake. The results further suggest that relatively brief exposures to sugar are not sufficient to result in enhanced intake following abstinence, but rather, limited access in the form of prolonged daily binge eating is needed to produce the effect.

Additionally, as described above for drugs of abuse, the motivation to obtain sugar appears to grow with the duration of abstinence. Sucrose seeking increases during abstinence in rats that have a history of intermittent access for 10 days, and it is greater after 30 days of sugar abstinence compared with 1 week or 1 day, suggesting the gradual emergence of long-term changes in the neural circuitry underlying motivation as a result of sugar self-administration and abstinence (Grimm et al. 2005).

109.6.4 Sugar-Bingeing Rats Show Locomotor Cross-Sensitization to Psychostimulant Drugs

When animals become sensitized to some addictive drugs, it is evidenced as a lasting, growing tendency toward hyperlocomotion during abstinence in response to a low, challenge dose of a
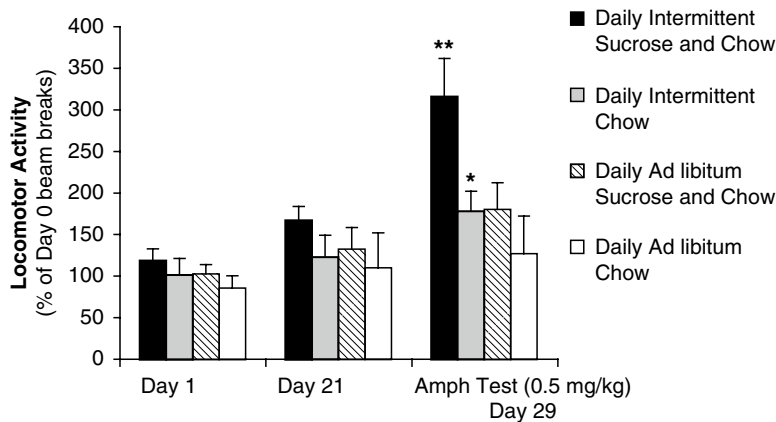
Fig. 109.2 Locomotor activity following amphetamine shown as percent of baseline photobeam breaks. Sugar-bingeing rats (Daily Intermittent Sucrose and Chow) were hyperactive 8 days following the cessation of sugar access in response to a low dose of amphetamine compared with control groups. This suggests sensitization of the dopamine system as a result of sugar bingeing ($^{**}p < 0.01$, $^{*}p < 0.05$) (Reproduced with permission from Avena and Hoebel 2003b)

psychostimulant. Additionally, cross-sensitization, whereby sensitization to one drug makes an animal susceptible to the effects of another drug, has been demonstrated (Robinson and Becker 1986; Antelman and Caggiula 1996).

We find that sugar-bingeing rats become sensitized to amphetamine. Such animals are hyperactive in response to a low, challenge dose of amphetamine that has little or no effect on naïve animals (Avena and Hoebel 2003b). This was observed after 8 days of abstinence from sugar. Rats maintained on the sugar-feeding schedule but administered saline were not hyperactive, nor were rats in control groups (e.g., allowed to binge on chow only, or with ad libitum access to sugar and chow, or ad libitum access to chow only) that were given the challenge dose of amphetamine (Fig. 109.2). Conversely, rats sensitized to amphetamine show locomotor cross-sensitization to a small meal of sugar (Avena and Hoebel 2003a). Other laboratories have reported that intermittent sucrose access cross-sensitizes with cocaine (Gosnell 2005) and facilitates sensitization to the dopamine (DA) agonist quinpirole (Foley et al. 2006). Collectively, these results support the theory that the DA system is sensitized by intermittent sugar access, as evidenced by cross-sensitization. This is important since enhanced mesolimbic dopaminergic neurotransmission plays a role in the behavioral effects of sensitization as well as cross-sensitization (Robinson and Berridge 1993).

109.6.5 Sugar Bingeing Acts as a "Gateway" to Increased Alcohol Intake During Sugar Abstinence

Sensitization to one drug can lead not only to hyperactivity, but also to subsequent increased intake of another drug or substance (Henningfield et al. 1990; Nichols et al. 1991; Volpicelli et al. 1991; Hubbell et al. 1993; Liguori et al. 1997; Ellgren et al. 2007). In the clinical literature, when one drug leads to taking another, it can be known as a "gateway effect".
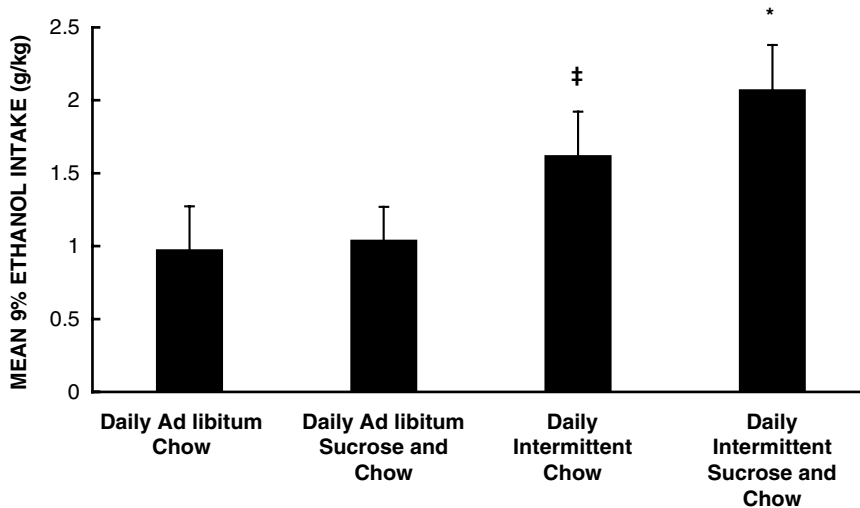
Fig. 109.3 Ethanol intake in grams per kilogram of bodyweight. Rats with a history of binge access to sugar and chow (Intermittent Sugar and Chow) consumed more 9% ethanol than rats in either the Ad libitum Sugar and Chow group or the Ad libitum Chow group ($^*p < 0.05$). In comparison with rats in the Ad libitum Chow group, rats in the Intermittent Chow group also consumed more ethanol ($^‡p < 0.05$) (Taken with permission from Avena et al. 2005)

When rats are bingeing on sugar and then forced to abstain, they subsequently show enhanced intake of 9% alcohol (Avena et al. 2004) (Fig. 109.3). This suggests that intermittent access to sugar can be a gateway to alcohol use. Others have shown that animals that prefer the sweet taste of saccharin will learn to self-administer cocaine more readily than usual (Carroll et al. 2007). Presumably underlying this behavior are neurochemical features of the brain that are inborn or learned, such as adaptations in DA and perhaps opioid functions, as described in the next section.

109.7 Neurochemistry of Food and Reward

Food is a natural reward that activates neurochemical pathways in the brain that evolved to reinforce this behavior by making it pleasurable and motivating. Non-natural reinforcers, including many drugs of abuse, exert their powerful reinforcing effects by usurping these brain pathways. Overlaps in the circuitry and brain regions regulating food and drug intake have been suggested and have inspired the model of sugar addiction that is described in this chapter. While several neurotransmitters and hormones have been studied in these brain regions, this chapter will focus on DA, the opioids, and acetylcholine (ACh) in the nucleus accumbens (NAc) shell, which so far, are the neurotransmitters that we have found to be involved with the reinforcing effects of food addiction.

109.8 Neurochemical Evidence of Sugar Addiction

The evidence described above suggests that sugar bingeing can produce behaviors that are similar to those observed in drug-dependent rats. In this section, we describe neurochemical findings that may result in, or perpetuate, these behaviors.

109.8.1 Sugar Bingeing Alters the DA System in the NAc

Drugs of abuse can alter DA receptors and DA release in the mesolimbic regions of the brain. In response to cocaine, there is an upregulation of Dopamine type 1 (D1) receptors (Unterwald et al. 1994) and increase in D1 receptor binding (Alburges et al. 1993; Unterwald et al. 2001). Conversely, Dopamine type 2 (D2) receptor density is lower in the NAc of monkeys that have a history of cocaine use (Moore et al. 1998). Drugs of abuse can also produce changes in gene expression of DA receptors, with morphine and cocaine decreasing accumbens D2 receptor messenger ribonucleic acid (mRNA) (Goeders and Kuhar 1987; Turchan et al. 1997; Georges et al. 1999), and increasing Dopamine type 3 (D3) receptor mRNA (Spangler et al. 2003). These findings with laboratory animals support clinical studies, which have revealed that D2 receptors are downregulated in cocaine addicts (Volkow et al. 1996a, b, 2006).

We have found similar changes with our animal model of sugar bingeing. Autoradiography reveals increased D1 receptor binding in the NAc and decreased D2 receptor binding in the striatum relative to chow-fed rats (Colantuoni et al. 2001). Others have reported a decrease in D2 receptor binding in the NAc of rats with intermittent access to sucrose and chow compared with rats fed restricted chow only (Bello et al. 2002). Rats with intermittent sugar and chow access also have decreased D2 receptor mRNA in the NAc, and increased D3 receptor mRNA in the NAc and caudate-putamen compared with chow-fed controls (Spangler et al. 2004).

One of the strongest neurochemical commonalities between sugar bingeing and drugs of abuse is their effect on extracellular DA. The repeated increase in extracellular DA is a hallmark of drug that are abused (Di Chiara and Imperato 1988), whereas normally during feeding the DA response fades out after repeated exposure to food as it loses its novelty (Bassareo and Di Chiara 1997). However, when rats are bingeing on sugar, the release of DA is more like that of a drug of abuse than a food. Rats that are bingeing on sugar apparently release DA every day, as measured on days 1, 2, and 21 of access (Fig. 109.4) (Rada et al. 2005). Control rats fed sugar or chow ad libitum, rats with intermittent access to just chow, or rats that taste sugar only two times, develop a blunted DA response that is typical of a food that loses its novelty. These results are supported by findings of alterations in accumbens DA turnover and DA transporters in rats maintained on an intermittent sugar-feeding schedule (Hajnal and Norgren 2002; Bello et al. 2003).

109.8.2 Sugar Bingeing Affects Endogenous Opioids

In addition to the effects on DA, opioid systems are also affected by sugar bingeing in a manner that is consistent with the effects of some drugs of abuse. Laboratory animal studies reveal that mu-opioid receptor binding is upregulated in the NAc, caudate-putamen, and cingulated cortex in response to chronic access to cocaine and morphine (Unterwald et al. 2001; Vigano et al. 2003; Bailey et al. 2005). In the striatum and the NAc, enkephalin mRNA is decreased in response to repeated injections of morphine (Uhl et al. 1988; Turchan et al. 1997; Georges et al. 1999). Similar changes have been observed by brain imaging in cocaine-dependent humans (Zubieta et al. 1996).

Sugar bingeing also produces a significant decrease in enkephalin mRNA in the NAc (Spangler et al. 2004), as does limited daily access to a sweet-fat, liquid diet (Kelley et al. 2003). Perhaps in response to decreased enkephalin production, mu-opioid receptor binding is significantly enhanced in sugar-bingeing rats, in the NAc shell, cingulate, hippocampus, and locus coeruleus, compared with chow-fed controls (Colantuoni et al. 2001) (Fig. 109.5).
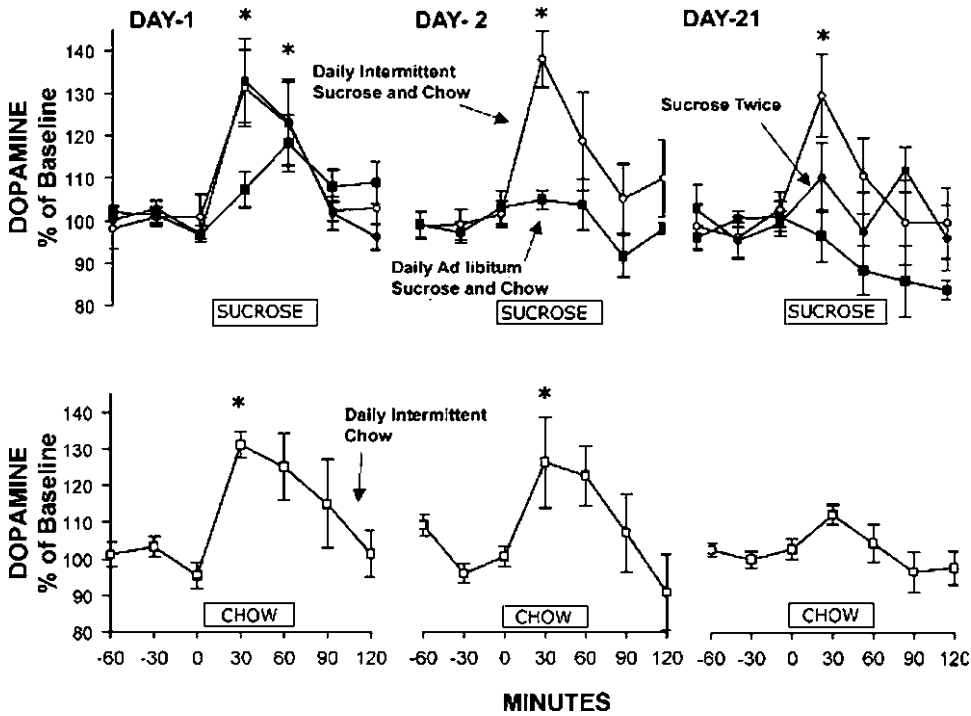
Fig. 109.4 DA release relative to baseline in sugar-bingeing rats and control rats. Sugar-bingeing rats release a surge of accumbens DA in response to drinking sucrose for an hour on day 21 of daily access. DA release, measured using in vivo microdialysis, increases for the sugar-bingeing rats (Daily Intermittent Sucrose and Chow) on days 1, 2, and 21. On the other hand, DA release was attenuated by day 21 in the control groups. The bar indicates the hour during which sucrose or chow was available during the microdialysis tests. These results suggest that repeated surges of DA may be involved in generating sugar dependency ($^*p < 0.05$) (Reproduced with permission from Rada et al. 2005)
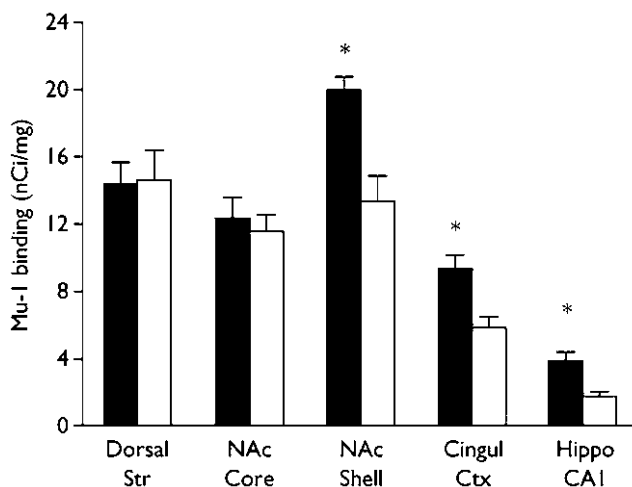
Fig. 109.5 Mu-opioid receptor binding in sugar-bingeing rats compared to controls. Animals exposed to intermittent 25% glucose and chow (*black bars*) show increases in mu-receptor binding in the NAc shell, cingulate cortex, and the CA1 pyramidal layer of the hippocampus (Hippo CA1) relative to chow-fed controls (*white bars*) ($^*p < 0.05$) (Taken with permission from Colantuoni et al. 2001)
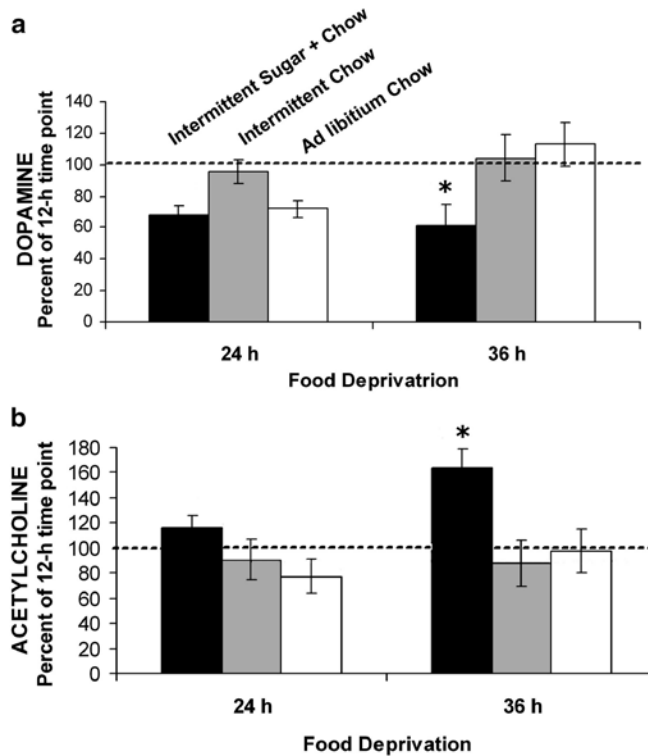
Fig. 109.6 Extracellular DA and ACh in the NAc following 24 and 36 h of fasting. (**a**) After 36 h of fasting, DA release in the intermittent sugar + chow group (*black bar*) was significantly less than both the intermittent chow (*grey bar*) and ad libitum chow (*white bar*) control groups. (**b**) Extracellular ACh was significantly increased in the intermittent sugar + chow group at the 36 h fasting point compared with both control groups. *p < 0.05 compared with both intermittent chow and ad libitum chow (Taken with permission from Avena et al. 2008a)

109.8.3 Withdrawal from Sugar Bingeing Upsets DA/ACh Balance in the Accumbens and is Opioid Mediated

Behavioral signs of drug withdrawal are usually accompanied by alterations in DA/ACh balance in the NAc; DA decreases while ACh increases. This imbalance has been shown during chemically induced withdrawal from several drugs of abuse, including morphine, nicotine, and alcohol (Rada et al. 1996, 2001, 2004).

Rats bingeing on sugar also show this neurochemical imbalance in DA/ACh during withdrawal. This result occurs both when rats are given naloxone to precipitate opiate-like withdrawal (Colantuoni et al. 2002) and after 36 h of food deprivation (Avena et al. 2008a) (Fig. 109.6).

109.9 Supporting Evidence of Food Addiction

109.9.1 Other Animal Models Show Evidence of Food Addiction

The literature suggests that, like sugar, there may be evidence of a similar addiction-like state that emerges with access to a fat-rich diet. Le Magnen (1990) noted that naloxone could precipitate withdrawal in rats on a cafeteria-style diet, which contains a variety of fat- and sugar-rich foods. Teegarden and

Bale (2007) showed that mice exposed to diets high in fat or carbohydrate for 4 weeks, and then forced to abstain, endured an aversive environment to gain access to their preferred food. They conclude that withdrawal of such a diet elevates a stress state and reduces reward, and that exposure to a high-fat diet reduces this stress and contributes to dietary relapse. We have not found signs of withdrawal or anxiety-like behaviors in rats withdrawn from a high-fat diet (Avena et al. 2009b); however, it is clear that further studies are needed to fully understand the differences between sugar and fat bingeing and their subsequent effects on behavior. Withdrawal is not necessary for drug craving, just like hunger is not necessary for food craving (Pelchat et al. 2004). Moreover, different classes of drugs (e.g., DA agonists vs. opiates) result in specific behavioral and physiological withdrawal signs. Thus, it may be that different macronutrients may also produce specific withdrawal syndromes, some of which may be more easily quantified than others. However, as of now, it appears that sugar is the only palatable substance for which bingeing, withdrawal, abstinence-induced enhanced motivation, and cross-sensitization have all been demonstrated in an animal model.

We began this chapter with a discussion relating binge eating to obesity. Indeed, the findings with animal models that have been presented suggest that binge eating sugar, and possibly even fat, may have some addiction-like properties. However, in our animal model, sucrose bingeing does not affect body weight; the rats compensate for the excess calories obtained in the sugar binge by consuming less rodent chow. But, a combination of sweet-fat does result in increased body weight (Berner et al. 2008). Thus, sweet taste may be largely responsible for producing addiction-like behaviors including a withdrawal syndrome, whereas fat may be the macronutrient that results in excess body weight. The combination of these two macronutrients constitutes a large proportion of the snacks and desserts on which people tend to over indulge, possibly contributing to the desire to overeat and, consequently, gain weight.

109.9.2 Clinical Studies Suggestive of Food Addiction

In addition to the complementary research from animal models, there is clinical support for the theory of sugar addiction. Others have speculated that obesity and eating disorders, such as bulimia and anorexia, may have properties of an "addiction" in some individuals (Gillman and Lichtigfeld 1986; Marrazzi and Luby 1986; Mercer and Holder 1997; Davis and Claridge 1998; Riva et al. 2006). The auto-addiction theory proposes that some eating disorders can be an addiction to endogenous opioids (Marrazzi and Luby 1986, 1990; Heubner 1993). In support, appetite dysfunctions in the form of binge eating and self-starvation can stimulate endogenous opioid activity (Aravich et al. 1993). Bulimic patients will binge on excessive amounts of noncaloric sweeteners (Klein et al. 2006), suggesting that they derive benefits from sweet orosensory stimulation. This finding is related to our result with sugar bingeing and purging. Using the sham feeding preparation, in which rats can binge on sugar that is then "purged" via an open gastric cannula, we have shown that the taste of sugar releases DA and hinders the release of the satiety-associated ACh in the accumbens (Avena et al. 2006). Also, the findings that sugar bingeing cross-sensitizes with amphetamine and cocaine, and fosters alcohol intake, may be related to the documented comorbidity between bulimia and substance abuse (Holderness et al. 1994). Rats will substitute a sweet taste for cocaine when the drug becomes difficult to obtain (Comer et al. 1996), and they may even prefer sweet taste to intravenous cocaine (Lenoir et al. 2007). Similarly, some drug addicts engage in binge eating early in recovery, and report using food as a substitute for drug use to satisfy drug cravings (Cowan and Devine 2008).

New studies have begun to characterize food addiction in humans. The Yale Food Addition Scale, for example, is one of the first psychometrically validated scales used to target food addiction, by identifying feeding behaviors that are paramount to dependency. This tool provides an operationalized

definition of food addiction, and brings it into the clinical realm (Gearhardt et al. 2009). Other studies have shown that self-identified refined-food addicts use food to self-medicate; they eat when they feel tired, anxious, depressed, or irritable in order to escape a negative mood state (Ifland et al. 2009).

Imaging studies in humans have supported the idea that aberrant eating behaviors, including those observed in obesity, may have similarities to drug dependence. Craving-related changes in fMRI signal have been identified in response to palatable foods, and are similar to those seen during drug craving (Pelchat et al. 2004). Similarly, PET scans reveal that obese subjects show a reduction in striatal D_2 receptor availability that is associated with the body weight of the subject (Wang et al. 2004b), and is similar in magnitude to the reductions reported in drug-addicted subjects (Wang et al. 2001). Binge eaters have also been shown to have a "gain of function" of the mu-opioid receptor gene, which correlates with higher scores on a self-report measure of hedonic eating (Davis et al. 2009). Exposure to especially palatable foods, such as cake and ice cream, activates several brain regions including the anterior insula and right orbitofrontal cortex (Wang et al. 2004a), which may underlie cognitive aspects of craving food (Rolls 2006).

109.10 Applications to Other Areas of Health and Disease

Discovering the underlying basis of food addiction will not only alter society's perception of those who are obese and overweight, but it may also impact long-standing policies and traditions regarding health and nutrition. Programs may also incorporate what is known about food addiction's neurochemical basis to help those who are at great risk for developing an addiction. Thus, knowing the underlying reasons behind food addiction will play an important role in preventing some maladaptive feeding behaviors and may even help treat those who are already afflicted.

109.11 Conclusion

This chapter presents and overview of the evidence for the concept of food addiction. The focus is on an animal model of sugar bingeing that can result in addiction-like behaviors. This model suggests that sugar bingeing shares many behavioral and neurochemical similarities with drug abuse. As such, it has implications for the further study and treatment of binge eating, with distinctions between different diets and the role of addiction in generating and perpetuating obesity.

Summary Points

- Food is a natural reinforcer that activates neural pathways that are usurped in cases of drug abuse. Studies suggest that aberrant feeding patterns, such as binging on palatable foods, can produce behaviors and changes in the brain that resemble an addiction-like state.
- Animal models of binge eating are used to study the addiction-like properties of palatable food. This chapter focuses on sugar binge eating. If given a pattern of feeding and deprivation, animals will develop binge eating behavior.
- Behavioral changes indicative of binge eating include withdrawal when the sugar is no longer available, an enhanced motivation to obtain it during abstinence, as well as cross-sensitization to other drugs or drug substitution.

- Neurochemical changes are observed in sugar-bingeing rats that are indicative of an addicted state. These include alterations in DA and opioid receptor binding and mRNA expression, repeated release of DA with repeated binges, and altered DA and ACh release during opiate-like withdrawal.
- Clinical studies have complemented the findings with laboratory animals and have given stronger validity to the concept that food addiction is a condition that exists in some individuals.

Key Terms

Addiction: A state in which the animal comes to depend on a substance for normal functioning. Addiction is characterized by tolerance to the abused substance suggested by (1) increased consumption, with sensitization of certain neurotransmitter systems (2) withdrawal signs in the case of substances that affect opioid systems; and (3) craving measured as excessive ideation or efforts focused on obtaining the substance. This cognition and behavior may become self-destructive in its intensity, and be described in terms of impulsive or compulsive acts.

Binge eating: Series of episodes during which one eats a larger amount of food than normal in a short period of time, while presenting at least three of the following: (1) eating until feeling uncomfortably full, (2) eating large amounts of food when not physically hungry, (3) eating much more rapidly than normal, (4) eating alone due to feelings of embarrassment, (5) feeling disgusted, depressed, or guilty after overeating, or (6) marked distress or anxiety after a binge.

Withdrawal: A negative physical state precipitated by the removal of an addictive substance or by blocking its action in the brain.

Craving: An intense desire for a substance, quantified in animal studies by how hard an animal is willing to work to obtain the desired substance.

Obesity: A condition of extreme overweight. In humans, a person with a body mass index (weight in kilograms divided by height in meters squared) of over 30 is considered obese. Obesity is associated with comorbid illnesses, including heart disease and diabetes. The incidence of obesity has dramatically risen over the past 20 years, and it continues to climb in the industrialized countries of the world.

References

Alburges ME, Narang N, Wamsley JK. Alterations in the dopaminergic receptor system after chronic administration of cocaine. Synapse 1993;14(4):314–23.

Allison S, Timmerman GM. Anatomy of a binge: food environment and characteristics of nonpurge binge episodes. Eat Behav. 2007;8(1):31–8.

American Diabetes Association. Type 2 diabetes in children and adolescents. American Diabetes Association. Diabetes Care. 2000;23(3):381–9.

American Psychiatric Association. Diagnostic and statistical manual of mental disorders fourth edition text revision (DSM-IV-TR). Washington, DC: American Psychiatric Association; 2000.

Antelman SM, Caggiula AR. Oscillation follows drug sensitization: implications. Crit Rev Neurobiol. 1996;10(1):101–17.

Aravich PF, Rieg TS, Lauterio TJ, Doerries LE. Beta-endorphin and dynorphin abnormalities in rats subjected to exercise and restricted feeding: relationship to anorexia nervosa? Brain Res. 1993;622(1–2):1–8.

Avena NM, Hoebel BG. Amphetamine-sensitized rats show sugar-induced hyperactivity (cross-sensitization) and sugar hyperphagia. Pharmacol Biochem Behav. 2003a;74(3):635–9.

Avena NM, Hoebel BG. A diet promoting sugar dependency causes behavioral cross-sensitization to a low dose of amphetamine. Neuroscience. 2003b;122(1):17–20.

Avena NM, Carrillo CA, Needham L, Leibowitz SF, Hoebel BG. Sugar-dependent rats show enhanced intake of unsweetened ethanol. Alcohol. 2004;34(2–3):203–9.

Avena NM, Long KA, Hoebel BG. Sugar-dependent rats show enhanced responding for sugar after abstinence: evidence of a sugar deprivation effect. Physiol Behav. 2005;84(3):359–62.

Avena NM, Rada P, Moise N, Hoebel BG. Sucrose sham feeding on a binge schedule releases accumbens dopamine repeatedly and eliminates the acetylcholine satiety response. Neurosci. 2006;139(3):813–20.

Avena NM, Bocarsly ME, Rada P, Kim A, Hoebel BG. After daily bingeing on a sucrose solution, food deprivation induces anxiety and accumbens dopamine/acetylcholine imbalance. Physiol Behav. 2008a;94(3):309–15.

Avena NM, Rada P, Hoebel BG. Evidence for sugar addiction: behavioral and neurochemical effects of intermittent, excessive sugar intake. Neurosci Biobehav Rev. 2008b;32(1):20–39.

Avena NM, Rada P, Bocarsly ME, Hoebel BG. Binge eating as a form of addiction: evidence from an animal model of sugar addiction. Binge eating: psychological factors, symptoms and treatment. In: Chambers N, editor. New York: Nova Science; 2009a. p. 95–123.

Avena NM, Rada P, Hoebel BG. Sugar and fat bingeing have notable differences in addictive-like behavior. J Nutr. 2009b;139(3):623–8.

Bailey A, Gianotti R, Ho A, Kreek MJ. Persistent upregulation of mu-opioid, but not adenosine, receptors in brains of long-term withdrawn escalating dose "binge" cocaine-treated rats. Synapse 2005;57(3):160–6.

Bassareo V, Di Chiara G. Differential influence of associative and nonassociative learning mechanisms on the responsiveness of prefrontal and accumbal dopamine transmission to food stimuli in rats fed ad libitum. J Neurosci. 1997;17(2):851–61.

Bello NT, Lucas LR, Hajnal A. Repeated sucrose access influences dopamine D2 receptor density in the striatum. Neuroreport. 2002;13(12):1575–8.

Bello NT, Sweigart KL, Lakoski JM, Norgren R, Hajnal A. Restricted feeding with scheduled sucrose access results in an upregulation of the rat dopamine transporter. Am J Physiol Regul Integr Comp Physiol. 2003;284(5):R1260–8.

Berner LA, Avena NM, Hoebel BG. Bingeing, self-restriction, and increased body weight in rats with limited access to a sweet-fat diet. Obesity (Silver Spring) 2008;16(9):1998–2002.

Boggiano MM, Chandler PC, Viana JB, Oswald KD, Maldonado CR, Wauford PK. Combined dieting and stress evoke exaggerated responses to opioids in binge-eating rats. Behav Neurosci. 2005;119(5):1207–14.

Carroll ME, Anderson MM, Morgan AD. Regulation of intravenous cocaine self-administration in rats selectively bred for high (HiS) and low (LoS) saccharin intake. Psychopharmacology (Berl). 2007;190(3):331–41.

Ciccocioppo R, Angeletti S, Weiss F. Long-lasting resistance to extinction of response reinstatement induced by ethanol-related stimuli: role of genetic ethanol preference. Alcohol Clin Exp Res. 2001;25(10):1414–9.

Colantuoni C, Schwenker J, McCarthy J, Rada P, Ladenheim B, Cadet JL, Schwartz GJ, Moran TH, Hoebel BG. Excessive sugar intake alters binding to dopamine and mu-opioid receptors in the brain. Neuroreport. 2001;12(16):3549–52.

Colantuoni C, Rada P, McCarthy J, Patten C, Avena NM, Chadeayne A, Hoebel BG. Evidence that intermittent, excessive sugar intake causes endogenous opioid dependence. Obes Res. 2002;10(6):478–88.

Comer SD, Lac ST, Wyvell CL, Carroll ME. Combined effects of buprenorphine and a nondrug alternative reinforcer on i.v. cocaine self-administration in rats maintained under FR schedules. Psychopharmacology (Berl) 1996; 125(4):355–60.

Corwin RL. Bingeing rats: a model of intermittent excessive behavior? Appetite. 2006;46(1):11–5.

Cottone P, Sabino V, Steardo L, Zorrilla EP. Opioid-dependent anticipatory negative contrast and binge-like eating in rats with limited access to highly preferred food. Neuropsychopharmacology. 2008;33(3):524–35.

Cowan J, Devine C. Food, eating, and weight concerns of men in recovery from substance addiction. Appetite. 2008;50(1):33–42.

Davis C, Claridge G. The eating disorders as addiction: a psychobiological perspective. Addict Behav. 1998;23(4):463–75.

Davis CA, Levitan RD, Reid C, Carter JC, Kaplan AS, Patte KA, King N, Curtis C, Kennedy JL. Dopamine for "wanting" and opioids for "liking": a comparison of obese adults with and without binge eating. Obesity (Silver Spring) 2009;17(6):1220–5.

Di Chiara G, Imperato A. Drugs abused by humans preferentially increase synaptic dopamine concentrations in the mesolimbic system of freely moving rats. Proc Natl Acad Sci USA. 1988;85(14):5274–8.

Ellgren M, Spano SM, Hurd YL. Adolescent cannabis exposure alters opiate intake and opioid limbic neuronal populations in adult rats. Neuropsychopharmacology 2007; 32(3):607–15. doi:10.1038/sj.npp.1301127.

Flegal KM, Carroll MD, Kuczmarski RJ, Johnson CL. Overweight and obesity in the United States: prevalence and trends, 1960–1994. Int J Obes Relat Metab Disord. 1998;22(1):39–47.

Foley KA, Fudge MA, Kavaliers M, Ossenkopp KP. Quinpirole-induced behavioral sensitization is enhanced by prior scheduled exposure to sucrose: a multi-variable examination of locomotor activity. Behav Brain Res. 2006;167(1):49–56.

Galanti K, Gluck ME, Geliebter A. Test meal intake in obese binge eaters in relation to impulsivity and compulsivity. Int J Eat Disord. 2007;40(8):727–32.

Galic MA, Persinger MA. Voluminous sucrose consumption in female rats: increased "nippiness" during periods of sucrose removal and possible oestrus periodicity. Psychol Rep. 2002;90(1):58–60.

Gearhardt AN, Corbin WR, Brownell KD. Preliminary validation of the Yale Food Addiction Scale. Appetite 2009;52(2):430–6.

Georges F, Stinus L, Bloch B, Le Moine C. Chronic morphine exposure and spontaneous withdrawal are associated with modifications of dopamine receptor and neuropeptide gene expression in the rat striatum. Eur J Neurosci. 1999;11(2):481–90.

Gillman MA, Lichtigfeld FJ. The opioids, dopamine, cholecystokinin, and eating disorders. Clin Neuropharmacol. 1986;9(1):91–7.

Goeders NE, Kuhar MJ. Chronic cocaine administration induces opposite changes in dopamine receptors in the striatum and nucleus accumbens. Alcohol Drug Res. 1987;7(4):207–16.

Gosnell BA. Sucrose intake enhances behavioral sensitization produced by cocaine. Brain Res. 2005;1031(2):194–201.

Grimm JW, Shaham Y, Hope BT. Effect of cocaine and sucrose withdrawal period on extinction behavior, cue-induced reinstatement, and protein levels of the dopamine transporter and tyrosine hydroxylase in limbic and cortical areas in rats. Behav Pharmacol. 2002;13(5–6):379–88.

Grimm JW, Fyall AM, Osincup DP. Incubation of sucrose craving: effects of reduced training and sucrose pre-loading. Physiol Behav. 2005;84(1):73–9.

Grucza RA, Przybeck TR, Cloninger CR. Prevalence and correlates of binge eating disorder in a community sample. Compr Psychiatry. 2007;48(2):124–31.

Guertin TL, Conger AJ. Mood and forbidden foods' influence on perceptions of binge eating. Addict Behav. 1999;24(2):175–93.

Hadigan CM, Kissileff HR, Walsh BT. Patterns of food selection during meals in women with bulimia. Am J Clin Nutr. 1989;50(4):759–66.

Hajnal A, Norgren R. Repeated access to sucrose augments dopamine turnover in the nucleus accumbens. Neuroreport. 2002;13(17):2213–6.

Henningfield JE, Clayton R, Pollin W. Involvement of tobacco in alcoholism and illicit drug use. Br J Addict. 1990;85(2):279–91.

Heubner H. Endorphins, eating disorders and other addictive behaviors. New York: W. W. Norton; 1993.

Holderness CC, Brooks-Gunn J, Warren MP. Co-morbidity of eating disorders and substance abuse review of the literature. Int J Eat Disord. 1994;16(1):1–34.

Hubbell CL, Mankes RF, Reid LD. A small dose of morphine leads rats to drink more alcohol and achieve higher blood alcohol concentrations. Alcohol Clin Exp Res. 1993;17(5):1040–3.

Hudson JI, Hiripi E, Pope HG Jr, Kessler RC. The prevalence and correlates of eating disorders in the national comorbidity survey replication. Biol Psychiatry. 2007;61(3):348–58.

Ifland JR, Preuss HG, Marcus MT, Rourke KM, Taylor WC, Burau K, Jacobs WS, Kadish W, Manso G. Refined food addiction: a classic substance use disorder. Med Hypotheses. 2009;72(5):518–26.

Kales EF. Macronutrient analysis of binge eating in bulimia. Physiol Behav. 1990;48(6):837–40.

Kelley AE, Will MJ, Steininger TL, Zhang M, Haber SN. Restricted daily consumption of a highly palatable food (chocolate Ensure(R)) alters striatal enkephalin gene expression. Eur J Neurosci. 2003;18(9):2592–8.

Klein DA, Boudreau GS, Devlin MJ, Walsh BT. Artificial sweetener use among individuals with eating disorders. Int J Eat Disord. 2006;39(4):341–5.

Koob GF, Le Moal M. Neurobiology of addiction. San Diego: Academic; 2005.

Le Magnen J. A role for opiates in food reward and food addiction. Taste, experience, and feeding. In: Capaldi PT, editor. Washington, DC: American Psychological Association; 1990. p. 241–52.

Lenoir M, Serre F, Cantin L, Ahmed SH. Intense sweetness surpasses cocaine reward. PLoS ONE 2007;2:e698.

Liguori A, Hughes JR, Goldberg K, Callas P. Subjective effects of oral caffeine in formerly cocaine-dependent humans. Drug Alcohol Depend. 1997;49(1):17–24.

Lu L, Grimm JW, Hope BT, Shaham Y. Incubation of cocaine craving after withdrawal: a review of preclinical data. Neuropharmacology 2004;47(Suppl 1):214–26.

Marrazzi MA, Luby ED. An auto-addiction opioid model of chronic anorexia nervosa. Int J Eat Disord. 1986; 5(2):191–208.

Marrazzi MA, Luby ED. The neurobiology of anorexia nervosa: an auto-addiction? The brain as an endocrine organ. In: Cohen M, Foa P, editors. New York: Springer; 1990.p. 46–95.

Martin WR, Wikler A, Eades CG, Pescor FT. Tolerance to and physical dependence on morphine in rats. Psychopharmacologia 1963;65:247–60.

Mercer ME, Holder MD. Food cravings, endogenous opioid peptides, and food intake: a review. Appetite 1997;29(3):325–52.

Moore RJ, Vinsant SL, Nader MA, Porrino LJ, Friedman DP. Effect of cocaine self-administration on dopamine D2 receptors in rhesus monkeys. Synapse 1998;30(1):88–96.

Nichols ML, Hubbell CL, Kalsher MJ, Reid LD. Morphine increases intake of beer among rats. Alcohol 1991;8(4):237–40.

Page RM, Brewster A. Depiction of food as having drug-like properties in televised food advertisements directed at children: portrayals as pleasure enhancing and addictive. J Pediatr Health Care. 2009;23(3):150–7.

Pelchat ML, Johnson A, Chan R, Valdez J, Ragland JD. Images of desire: food-craving activation during fMRI. Neuroimage 2004;23(4):1486–93.

Rada PV, Mark GP, Taylor KM, Hoebel BG. Morphine and naloxone, i.p. or locally, affect extracellular acetylcholine in the accumbens and prefrontal cortex. Pharmacol Biochem Behav. 1996;53(4):809–16.

Rada P, Jensen K, Hoebel BG. Effects of nicotine and mecamylamine-induced withdrawal on extracellular dopamine and acetylcholine in the rat nucleus accumbens. Psychopharmacology (Berl) 2001;157(1):105–10.

Rada P, Johnson DF, Lewis MJ, Hoebel BG. In alcohol-treated rats, naloxone decreases extracellular dopamine and increases acetylcholine in the nucleus accumbens: evidence of opioid withdrawal. Pharmacol Biochem Behav. 2004;79(4):599–605.

Rada P, Avena NM, Hoebel BG. Daily bingeing on sugar repeatedly releases dopamine in the accumbens shell. Neuroscience 2005;134(3):737–44.

Ramacciotti CE, Coli E, Paoli R, Gabriellini G, Schulte F, Castrogiovanni S, Dell';Osso L, Garfinkel PE. The relationship between binge eating disorder and non-purging bulimia nervosa. Eat Weight Disord. 2005;10(1):8–12.

Riva G, Bacchetta M, Cesa G, Conti S, Castelnuovo G, Mantovani F, Molinari E. Is severe obesity a form of addiction? Rationale, clinical approach, and controlled clinical trial. Cyberpsychol Behav. 2006;9(4):457–79.

Robinson TE, Becker JB. Enduring changes in brain and behavior produced by chronic amphetamine administration: a review and evaluation of animal models of amphetamine psychosis. Brain Res. 1986;396(2):157–98.

Robinson TE, Berridge KC. The neural basis of drug craving: an incentive-sensitization theory of addiction. Brain Res Brain Res Rev. 1993;18(3):247–91.

Rolls ET. Brain mechanisms underlying flavour and appetite. Philos Trans R Soc Lond B Biol Sci. 2006;361(1471): 1123–36.

Sinclair JD, Senter RJ. Development of an alcohol-deprivation effect in rats. Q J Stud Alcohol. 1968;29(4):863–7.

Spangler R, Goddard NL, Avena NM, Hoebel BG, Leibowitz SF. Elevated D3 dopamine receptor mRNA in dopaminergic and dopaminoceptive regions of the rat brain in response to morphine. Brain Res Mol Brain Res. 2003;111(1–2):74–83.

Spangler R, Wittkowski KM, Goddard NL, Avena NM, Hoebel BG, Leibowitz SF. Opiate-like effects of sugar on gene expression in reward areas of the rat brain. Brain Res Mol Brain Res. 2004;124(2):134–42.

Stephens DW, Kerr B, Fernandez-Juricic E. Impulsiveness without discounting: the ecological rationality hypothesis. Proc Biol Sci. 2004;271(1556):2459–65.

Tanofsky-Kraff M, Cohen ML, Yanovski SZ, Cox C, Theim KR, Keil M, Reynolds JC, Yanovski JA. A prospective study of psychological predictors of body fat gain among children at high risk for adult obesity. Pediatrics. 2006;117(4):1203–9.

Teegarden SL, Bale TL. Decreases in dietary preference produce increased emotionality and risk for dietary relapse. Biol Psychiatry. 2007;61(9):1021–9.

Turchan J, Lason W, Budziszewska B, Przewlocka B. Effects of single and repeated morphine administration on the prodynorphin, proenkephalin and dopamine D2 receptor gene expression in the mouse brain. Neuropeptides. 1997;31(1):24–8.

Uhl GR, Ryan JP, Schwartz JP. Morphine alters preproenkephalin gene expression. Brain Res. 1988;459(2):391–7.

Unterwald EM, Ho A, Rubenfeld JM, Kreek MJ. Time course of the development of behavioral sensitization and dopamine receptor up-regulation during binge cocaine administration. J Pharmacol Exp Ther. 1994;270(3):1387–96.

Unterwald EM, Kreek MJ, Cuntapay M. The frequency of cocaine administration impacts cocaine-induced receptor alterations. Brain Res. 2001;900(1):103–9.

Vigano D, Rubino T, Di Chiara G, Ascari I, Massi P, Parolaro D. Mu opioid receptor signaling in morphine sensitization. Neuroscience. 2003;117(4):921–9.

Volkow ND, Ding YS, Fowler JS, Wang GJ. Cocaine addiction: hypothesis derived from imaging studies with PET. J Addict Dis. 1996a;15(4):55–71.

Volkow ND, Wang GJ, Fowler JS, Logan J, Hitzemann R, Ding YS, Pappas N, Shea C, Piscani K. Decreases in dopamine receptors but not in dopamine transporters in alcoholics. Alcohol Clin Exp Res. 1996b;20(9):1594–8.

Volkow ND, Wang GJ, Telang F, Fowler JS, Logan J, Childress AR, Jayne M, Ma Y, Wong C. Cocaine cues and dopamine in dorsal striatum: mechanism of craving in cocaine addiction. J Neurosci. 2006;26(24):6583–8.

Volpicelli JR, Ulm RR, Hopson N. Alcohol drinking in rats during and following morphine injections. Alcohol. 1991;8(4):289–92.

Wang GJ, Volkow ND, Logan J, Pappas NR, Wong CT, Zhu W, Netusil N, Fowler JS. Brain dopamine and obesity. Lancet 2001;357(9253):354–7.

Wang GJ, Volkow ND, Telang F, Jayne M, Ma J, Rao M, Zhu W, Wong CT, Pappas NR, Geliebter A, Fowler JS. Exposure to appetitive food stimuli markedly activates the human brain. Neuroimage 2004a;21(4):1790–7.

Wang GJ, Volkow ND, Thanos PK, Fowler JS. Similarity between obesity and drug addiction as assessed by neurofunctional imaging: a concept review. J Addict Dis. 2004b;23(3):39–53.

Wang Y, Beydoun MA, Liang L, Caballero B, Kumanyika SK. Will all Americans become overweight or obese? estimating the progression and cost of the US obesity epidemic. Obesity (Silver Spring) 2008;16(10):2323–30.

Way EL, Loh HH, Shen FH. Simultaneous quantitative assessment of morphine tolerance and physical dependence. J Pharmacol Exp Ther. 1969;167(1):1–8.

Wideman CH, Nadzam GR, Murphy HM. Implications of an animal model of sugar addiction, withdrawal and relapse for human health. Nutr Neurosci. 2005;8(5–6):269–76.

Zubieta JK, Gorelick DA, Stauffer R, Ravert HT, Dannals RF, Frost JJ. Increased mu opioid receptor binding detected by PET in cocaine-dependent men is associated with cocaine craving. Nat Med. 1996;2(11):1225–9.

Chapter 110
The Lingering Impact of Negative Food Experiences: Which World War II Veterans Won't Eat Chinese Food?

Brian Wansink, Koert van Ittersum, and Carolina Werle

Abbreviation

MRE   Meal-Ready-to-Eat is a self-contained, individual field ration in lightweight packaging bought by the United States military for its service-members for use in combat or other field conditions where organized food facilities are not available

110.1 Introduction

How do long-term negative experiences shape long-term food habits? Napoleon famously said, "An army marches on its stomach," yet relatively little attention has been devoted to food in contrast to the tactics and strategies of great battles. There is abundant research demonstrating the immediate short-term influences various environmental cues have on food preferences (Wansink 2006). In contrast, very little research has invested the long-term impact of how a person's food preferences are shaped by their first experience with a food. To better understand and predict people's preferences for different types of foods, it is important to understand the origin of their preferences. This chapter investigates some of the responses American soldiers had to foods they ate during World War II and how their preferences and consumption of these foods changed after they returned to their homes.

This chapter is structured as follows. Using archived survey data collected during World War II, we will determine the most favored and least favored foods served to soldiers in combat, along with how much of them they consumed. Following this, we will review a longitudinal analysis of food consumption patterns of soldiers who were exposed to unfamiliar (Chinese) food while in combat. The combination of the two patterns of data will provide insights as to how food preferences might change under the stress of combat as well as the lingering consequences it might have on preferences and food intake (Wansink et al. 2008).

B. Wansink (✉)
Cornell University, 110 Warren Hall, Ithaca, NY 14853-7801, USA
e-mail: wansink@cornell.edu

110.2 Familiar Foods Among Combat Soldiers in World War II

Perhaps the best record of the eating habits of soldiers in World War II was included in an in-depth sociological investigation of training, living, adjusting, and recovering, which was sponsored by the US War Department's Information and Education Division. It was a system of over 150 classified stratified questionnaires covering five or six times as many issues. Parts of it were subsequently published in *The American Soldier* (Stouffer et al. 1949).

Part of the research investigated preferences for various food items that were included in either K-rations, food served in platoon-sized groups of 30, or food items that were included in C-rations, food served in individual field servings. Whereas K-rations were usually prepared in a field kitchen, C-rations were individually eaten, and were more similar to the Meals-Ready-to-Eat (MREs) eaten by today's soldiers.

In two surveys, one conducted with 402 soldiers in September 1944 (S-160-B) and another conducted with 2,549 soldiers in November–December 1944 (S-177), soldiers were asked about their preference for these items. To assess the types of foods eaten, how much they liked those foods, and how much of those foods they consumed, the raw data from the surveys was obtained from the Department of Defense and they were reanalyzed.

When meals were prepared in Army Field Kitchens, the foods were canned, but were frequently prepared and served hot. When asked if they generally received enough food to eat, 11% of the participating soldiers replied "Always," 49% replied "Usually," 39% replied "Usually not."

When asked about the most common items found in these meals, soldiers were asked to indicate which they liked best and which they liked least. For each food they were then asked to indicate whether they generally ate all of it, part of it, or none of it.

The most and least favorite foods are indicated in Table 110.1. The favorites included cheese (31%), chopped ham and eggs (27%), and beef and pork loaf (11%). The least favorite were crackers and biscuits (25%), cheese (17%), and a three-way tie with chopped ham and eggs, beef and pork loaf, and pork loaf with carrots and apple flakes (7%).

Except for three evocative foods – beef and pork loaf, pork and egg yolk, and pork loaf with carrots and apple flakes – the data in Table 110.2 also show how much these soldiers usually ate of each items.

Although chocolate bars were not in the top 3 of best liked food items, it is a food item that is most likely to be completely consumed (76%), followed by cheese (60%) and cheese and bacon (59%).

Table 110.1 The preference of combat (K) rations served from army field kitchens (in percentages)

Food	Which food items do you like best and which food items do you like least?	
	"Like the best"	"Like the least"
Cheese	31	17
Chopped ham and eggs	27	7
Beef and pork loaf	11	7
Biscuits	7	25
Chocolate bar	6	2
Fruit bar	5	3
Cheese and bacon	3	0
Pork and egg yolk	2	3
Pork loaf with carrots & apple flakes	2	7

This table shows the percentage of soldiers who indicate which food item of the list they "like the best" and which food item they "like the least." Because of non-response, not all columns sum to 100%

Table 110.2 The intake of combat (K) rations served from army field kitchens (in percentages)

| | Do you generally eat all of it, part of it, or none of it? | | |
Food	"Eat all"	"Eat part"	"Never eat"
Chocolate bar	76	12	7
Cheese	60	24	7
Cheese and bacon	59	22	7
Fruit bar	47	12	15
Biscuits	42	46	6
Chopped ham and eggs	39	12	15

This table shows for each food item the percentage of soldiers who generally consume the entire food item ("eat all"), the percentage of soldiers who only eat part of it ("eat part"), and the percentage of soldiers who never eat the food item ("never eat"). Nonresponses would bring each row total to 100%
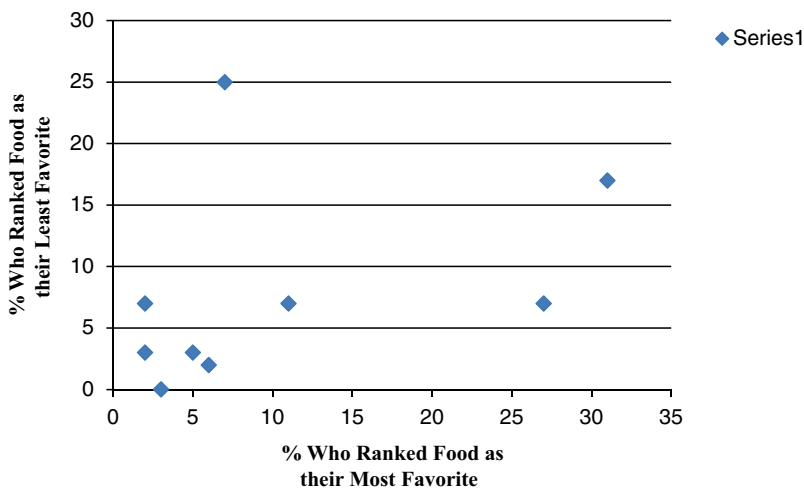
Fig. 110.1 The most favored WWII combat foods are also the least favored. This figure visualizes the relationship between the percentage of soldiers who favor food items the most and the percentage of soldiers who favor food items the least

The least liked food item, biscuits, is also the food item most likely to be only partly consumed (46%), followed by cheese (24%) and cheese and bacon (22%). Finally, there are two food items that stand out as items soldiers indicate they never eat, fruit bars (15%) and chopped ham and eggs (15%). Interestingly, enough, this latter food item is also among one of the best liked food items as well. A couple observations are notable in this data.

First, the same foods were often the most favorite and the least favorite among soldiers. While cheese, chopped ham and eggs, and beef and pork loaf were the three most favorite foods, two of them were also among the least favorite. Many of the other less valenced foods inspired neither love nor hate. Indeed the correlation between a food being the most favorite and it also being the least favorite is 0.45 ($P < 0.05$) (see Fig. 110.1). This strongly suggests there are different segments of background and taste preferences being represented in this data.

There is an expression that one man's meat is another man's poison. These data suggest that the inherent food quality of these items is acceptable to good. What causes cheese to be the most favorite of 31% of the soldiers and the least favorite of 17% probably has less to do with the cheese than with the background, taste preferences, and food associations of the soldiers.

A second observation from these data in Tables 110.1 and 110.2 is that those foods that were the most favorite were also those with relatively high nutrient density. Foods that we would think would be quite tasty – such as chocolate bars and fruit bars were among the most consumed foods in the sample (76% reported eating their entire chocolate bar). In contrast, however, these foods were not among the most favorite. While a reinvestigation of marginal notes in the data revealed no explanation, we might hypothesize that either the overriding need of protein or of the comfort of hot food would trump that of only taste.

Similar results were found with C-Rations, which are the rations soldiers carried into the field by themselves. In the individual rations – the canned C-Rations – soldiers' favorite foods were the ones highest in protein and not those that we would have otherwise assumed tasted the best. Their most favorites were meat and beans (51%), spaghetti and meat (13%), beef stew (6%), chocolate (5%), hash (5%), and ham and eggs (2%). The least favorite were hash (32%), beef stew (19%), biscuits 10%), meat (9%), beans (5%), and corned beef (2%).

In this situation, we have been discussing how a combat soldier responded to foods that were – to a great extent – foods they were familiar with before leaving for combat. In other words, their impression and preferences of these foods had already been formed, and there were associations they had that were independent of the new associations (either negative or positive) that were formed overseas in combat. What we will next examine is the long-term responses to novel or new foods that soldiers were exposed to while in combat.

The soldiers' preference for foods served in combat seems to be related to their previous habits but also to combat-related needs, which explains a preference for energy-dense foods. Energy-dense foods are more satiating providing the energy soldiers needed to accomplish their daily tasks while in the army. But the influence of the army on veteran's lives was not only on the short-term preferences for energy-dense foods; the veteran's experiences during war shaped their food preferences in the long-run. Previous research on the food preferences of children reveals that bad experiences due to the consumption of a food (such as nausea) may lead to food aversion for many years. Our research demonstrates that the context in which a food is consumed can influence adult's food preference and aversion in the long term.

110.3 The Lingering Determinants of Food Preference

Being overseas in World War II opened up the culinary world for many Americans. Indeed, Italian, French, and German food may have tasted fairly good for many returning veterans. They found jobs, started families, and the idea of spaghetti or a bratwurst was not as strange – not as "foreign-sounding" – as it was 5 years earlier (Wansink 2002). Yet compared to the taste of the meat and potato-like cuisine of the Europeans, learning to appreciate Asian cuisines, such as Chinese and Japanese food would have seemed more extreme (Scott and Downey 2007). Asian food was unlike anything most of them had ever eaten (Chin 2005). Why then, did some Pacific veterans learn to love Chinese food and others hated it – even 60 years later?

Part of this could be related to a person's food adventurousness (Stallberg-White and Pliner 1999) or to food neophobia (relative aversion to new foods). Yet another part, however, could be related to country-specific associations (Brunstrom 2005). More specifically, animosity towards foreign countries – the remnants of antipathy related to previous or ongoing military, political, or economic events – may influence different people in different ways. For instance, Klein and Ettenson (1998a, b) found animosity influenced willingness to buy Japanese products in the Chinese city of Nanjing,

where 300,000 civilians were killed by the Japanese in World War II. Similar results from World War II were found by Nijssen et al. (1999), who examined the animosity of Dutch consumers toward Germans. Such visceral experiences may also lead to biased preferences toward these relatively unfamiliar foods.

What is not clear is what causes these biases. There are numerous anecdotal accounts of Vietnam veterans returning to the US with newfound preferences for Asian foods. Yet there are also many accounts of other Vietnam veterans having a powerful aversion to any casserole or meal containing rice. This aversion might be less related to a veteran's personality (such as his adventurousness) than about his experience in the war.

Consider how Chinese food might have been perceived by American veterans of World War II. Although China was an American ally during the war, Chinese food was an unfamiliar food that many Pacific veterans may have largely associated with battles against Japan (Stouffer et al. 1949). For such veterans, the associations they have with Chinese food may have been viscerally influenced by whether their experience in the Pacific are recalled as favorable or unfavorable (Nordgren et al. 2006). For instance, those experiencing intense or frequent combat may let this unfavorable experience negatively bias their long-term perception of Chinese food, or of any Asian food they see as similar (Japanese, Thai, Korean, and so forth). For those who were more removed from the negative associations with combat, there should be less stigma. In contrast, combat experience for a European veteran should have little influence on their perception of Chinese food because there were no proximate negative associations with it.

110.3.1 Investigating Food Preferences in World War II Veterans

To examine the long-term consequences of combat experience on preferences for unfamiliar foods, the homogeneous focus of the sample was American World War II veterans (Wansink et al. 2009). A random selection of 5,000 names of veterans born before 1928 was obtained from US census data. In the year 2000, each veteran was sent a survey, a cover letter, and a business reply return envelope. The cover letter asked them to complete the survey. In return, a small donation was made to the World War II Memorial, they were sent a copy of the major findings of the project, and they were invited to a symposium – Consumer Camp™, then at the University of Illinois at Urbana-Champaign (now at Cornell University) – that discussed the results of the project.

To determine their experience in combat, respondents were first asked to indicate whether they had experienced combat while serving during World War II. Those who responded "Yes," were then asked to note the frequency (1 = infrequent; 9 = frequent) and the intensity (1 = low intensity; 9 = high intensity) of their combat experiences. Veterans were classified as having had a high level of combat experience if the average of their summated score was higher than the mean (6.1 out of 9).

Veterans were then asked to indicate their preference toward Chinese food and their preference toward Japanese food (1 = dislike very much; 9 = like very much). To be able to examine these preferences independent of their general predisposition for variety and adventure, respondents were asked to rate their general level of adventurousness immediately following the war and at the current time (1 = not adventurous; 9 = adventurous). An index for adventurousness was calculated using the average of these two measures. Last, demographic questions were asked.

While there are likely to be memory biases that can affect responses, efforts were made to minimize these biases (Bradburn et al. 2004). Based on a pre-study, questions were worded in a way where they could be answered with the least effort and greatest accuracy.

110.3.2 Is Food Preference Related to Combat Experience?

Of 2,376 surveys that were not returned and were assumed to be delivered, 493 veterans personally responded (20.7%). Among these veterans, 76% were between 76 and 80 years of age, 31% had attended at least 1 year of college, 42% were born in a town with less than 10,000 inhabitants, and 41% currently lived in a town with less than 10,000 inhabitants.

The hypotheses were tested using univariate analysis of variance. As indicated in Table 110.3, the preference for Chinese food was higher among Pacific veterans with low combat experience (little to none) than with the Pacific veterans with high combat experience (5.4 vs. 4.2; F = 8.4; p < 0.001). For European veterans, their combat experience had no impact on their preference for Chinese food (p > 0.05). As expected, previous experiences influenced food preference among Pacific veterans, but not among European veterans.

The same analysis of the liking scores for Japanese food provide further support for the view that combat experience affects long-term food preferences. As expected, Pacific veterans with high combat experience had a less favorable opinion about Japanese food than those with little or no combat experience (2.8 vs. 3.5; F = 3.0; p < 0.05). As was expected, this was not the case with European veterans. Their preferences for Japanese food were unaffected by their level of combat experience (see Table 110.3). The general preference of all veterans for Japanese food was much smaller than towards the more commonly available Chinese food (p < 0.05). Figure 110.2 summarizes the main findings.

When aggregating their responses, 31.8% of the veterans generally liked Chinese food (7–9 on the 9-point scale) and 29.2% disliked it (1–3 on the 9-point scale). Their opinions toward Japanese food were generally more negative: 58.4% of disliked it while only 12% liked it.

One's preference for Chinese food or Japanese food could also be partly explained by personality variables such as one's level of adventurousness. Veterans with a higher level of adventurousness may have a higher preference for foreign food in general. It was unclear whether this personality trait would be sufficient to overcome combat experience.

To examine this, combat experience and self-rated adventurousness were regressed upon preferences toward Chinese food and toward Japanese food. The results in Table 110.4 show that both factors are significant predictors of preference for Chinese food for Pacific Veterans. Combat experience remained an important predictor for Pacific Veteran's preference for Chinese food even when accounting for adventurousness. It is important to note, however, that combat experience and adventurousness still explains only 6.1% of the variance of Pacific veterans' preference for Chinese food 60 years after the war. Nevertheless, it is higher than the variance explained among European Veterans (Adj. R^2 = 0.004). The same analysis for Japanese food was not statistically significant for either group of veterans.

Table 110.3 How World War II combat influenced long-term preference for Asian food

	Low combat experience		High combat experience			
	Mean	SD	Mean	SD	F test value	Sig.
Preference for Chinese food						
Pacific veterans	5.4	2.5	4.2	2.2	8.4	0.004[*]
European veterans	5.1	2.5	4.7	2.8	1.1	0.286
Preference for Japanese food						
Pacific veterans	3.5	2.4	2.8	2.1	3.0	0.041[**]
European veterans	3.4	2.4	3.1	2.4	0.6	0.449

[*]p < 0.05

[**]p < 0.01, one-tailed test

This table compares the preferences for Chinese and Japanese food between Pacific and European veterans with low versus high combat experience

Food Preference
(1=dislike very much;
9 = like very much)
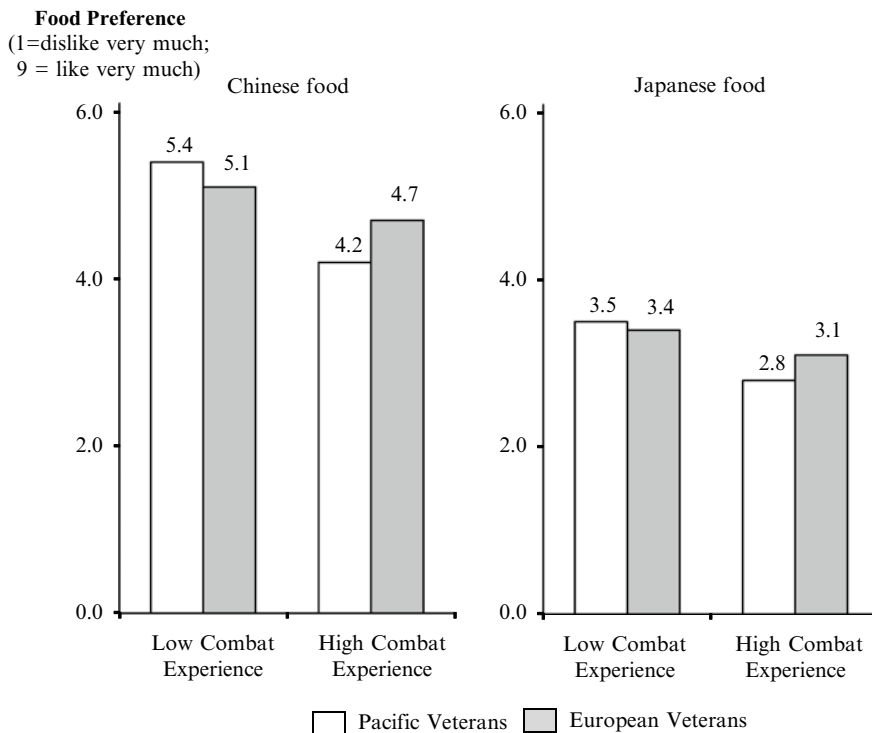
Fig. 110.2 How combat shaped preferences for Chinese and Japanese food. This figure visualizes the differences in preference for Chinese and Japanese food between Pacific and European US veterans with low versus high combat experience

Table 110.4 Combat influenced Asian food preference along with adventurousness

	Level of combat experience	Level of adventurousness		
	Standardized beta coefficients	Standardized beta coefficients	R^2	Adj. R^2
Preference for Chinese food				
Pacific veterans	–0.20[*]	0.17[**]	0.07[**]	0.06[**]
European veterans	–0.06	0.13	0.02	0.01
Preference for Japanese food				
Pacific veterans	–0.11	0.06	0.02	0.01
European veterans	–0.07	0.35[*]	0.12[**]	0.12[**]

This table compares the effects of Pacific and European veterans' levels of combat experience and adventurousness on their preference for Chinese and Japanese foods. The results are based on OLS regression analyses

[*]$p < 0.05$

[**]$p < 0.01$ one-tailed test

110.4 Applications for Food Preference Development

After accounting for demographic differences, there is an egalitarian tendency in nutrition, as in public health, to assume all people's experiences and preferences are equal. This is often not effective. For instance, it has been shown that fruit lovers have dramatic psychographic differences

compared vegetable lovers (Wansink and Lee 2004), and telling someone to "eat your fruits and vegetables" will backfire with both segments. Similarly, this paper illustrates that the most loved foods of World War II combat soldiers were also the most hated foods by others. This underscores the critical power of segmentation. Another finding shows that the most preferred foods were those that are higher in proteins, suggesting a preference for energy-dense foods among soldiers. This short-term preference for proteins could be explained by their energy needs due to the army activities. Still the army also influenced the long-term food preferences of veterans.

In the development of long-term food preferences, demographic differences are unlikely to explain anything but the most obvious. People from the South like spicy food; people from poor, rural areas like chicken. Instead, the powerful insights are more likely to be based on psychographic differences and experiences.

Of those veterans who enjoyed Chinese and Japanese food and still ate it with some frequency, there were no characteristics they had in common. Before the war, some had lived in big cities, some on farms. Some had graduated from college, others had never seen a 9th grade classroom.

What did explain their preferences was the level of combat they had experienced as soldiers. When analyzing the profiles of those Pacific veterans who liked Chinese food, we did not find Marines who had been at Iwo Jima or infantry soldiers at Guadalcanal. What we found were mechanics, clerks, engineers, and truck drivers – enlisted men who did not experience the War from the front line. Although their wartime experience was a sacrifice, they did not come home with terrible associations that tainted the taste of food even 50–60 years later. It appears the feelings we have when we first eat a food can follow us for a lifetime.

While there is abundant research demonstrating the immediate effects of environmental cues on food consumption, research investigating the potential long-term effects of contextual experiences with a food on preference remains scarce. Research generally examines the effect of specific food characteristics and for instance personality characteristics on food preferences, largely ignoring the very first experiences people had with a food. Ignoring these early experiences may be an oversight. To really understand food preference and the associated consumption behavior, a thorough and complete understanding is desirable. The importance of the first experience with an unfamiliar food on long-term preferences indicates that extra care must be taken when planning the introduction of new foods and new recipes. Changing initial food perceptions is difficult and understanding the influence of the context of the initial exposure to an unfamiliar food may give insights for improving the healthfulness of the food we eat.

Today people are more exposed to foreign foods in their daily lives; it is easy to find a Chinese or a French restaurant in almost every American city. As a consequence, preference for these foods can integrate into an individual's habits easily. Even so, the context in which a food is consumed for the first time may influence food preferences durably. This is the case when there is immigration. When someone chooses to immigrate to a country the relation established with the food of the new country may be more positive than when this immigration is imposed by political or economical reasons. Further research should look into the effects of immigration experiences and acculturation on food consumption.

Summary Points

- There is abundant research demonstrating the immediate effects of environmental cues on food preference and consumption (Wansink 2006).
- Research on the long-term effects of the context in which people first consume a food on long-term food preference is scarce.

- It is critical to understand all factors shaping food preference.
- The army influenced veteran's short-term food preferences for energy-dense foods and long-term food preferences for foreign food.
- This research demonstrates that traumatic combat experiences shape long-term food preferences, even 60 years after the very first experience with a food.

Definitions and Explanations of Key Terms and Words

Animosity towards foreign countries: The remnants of antipathy related to previous or ongoing military, political, or economic events.

C-ration: An individual canned, precooked or prepared wet ration intended to be issued to US military land forces when fresh food or packaged unprepared food prepared in mess halls or field kitchens was impractical or not available and when a survival ration was insufficient.

Food adventurousness: The self-reported frequency of trying unfamiliar foods on a scale ranging from "never" to "most of the time."

K-ration: An individual daily combat food ration which was introduced by the US Army during World War II.

Long-term food preference: An individual's enduring liking of a particular food.

Mood: A relatively long lasting, affective or emotional state.

Neophobia: The fear of new things, foods or experiences.

Ration: The food allowance for 1 day (especially for military service personnel).

Stress: A state of mental or emotional strain or suspense.

Key Facts About Food Preferences

1. There is abundant research demonstrating the immediate effects of environmental cues on food preference and consumption (Wansink 2006).
2. Research on the long-term effects of the context in which people first consume a food on long-term food preference is scarce.
3. It is critical to understand all factors shaping food preference.
4. Immediate energy needs seem to influence short-term food preferences.
5. This research demonstrates that traumatic combat experiences shape long-term food preferences, even 60 years after the very first experience with a food.

References

Bradburn N, Sudman S, Wansink B. Asking questions: the definitive guide to questionnaire design-For market research, political polls, and social and health questionnaires. San Francisco: Jossey-Bass; 2004.

Brunstrom JM. Physiol Behav. 2005;85:57–65.

Chin V. Asia Pac Arts M. 2005 July:21–7.

Klein JG Ettenson RM. J Marketing. 1998a;62:89–100.

Klein JG, Ettenson RM. J Int Cons Marketing. 1998b;4:134–45.

Nijssen EJ, Douglas SP, Bressers P. Attitudes towards the purchase of foreign products: extending the model, Working Paper, New York University. Academy of Marketing, AMA Global Marketing SIG Joint Conference; 1999.

Nordgren LF, van der Pligt J, van Harreveld F. Psychol Sci. 2006;17:635–40.

Scott CL, Downey RG. J Psychol. 2007;141:127–34.

Stallberg-White C, Pliner P. Appetite 1999;33:209–21.

Stouffer SA et al. The American soldier – combat and its aftermath. Princeton: Princeton University Press; 1949.

Wansink B. J Public Policy Mark. 2002;21:90–9.

Wansink B. Mindless eating – why we eat more than we think. New York: Bantam-Dell; 2006.

Wansink B, Lee K. J Am Diet Assoc. 2004;104:1648–50.

Wansink B, van Ittersum K, Werle C. Appetite 2009;52:750–2.

Wansink B, Payne CR, van Ittersum K. Leadership Quart. 2008;19:547–55.

Chapter 111
Changes in Food Neophobia and Food Preferences During a Weight Reduction Session: Influence of Taste Acuity on the Individual Trajectory

Marie-Odile Monneuse, Claude Marcel Hladik, Bruno Simmen, and Patrick Pasquet

Abbreviations

BMI	Body mass index
CDC	Centre for Disease Control
FFLQ	Food familiarity and liking questionnaire
FNS	Food neophobia scale
LAM scale	Labeled affective magnitude scale
LTT	Low-threshold tasters
MTT	Medium-threshold tasters
NT	Nontasters
PROP	6-n-propylthiouracil
PTC	Phenylthiocarbamide
T1, T2	Beginning and end of the WRS
VAS	Visual analog scale
WRS	Weight reduction session

111.1 Introduction

Our research on food neophobia and associated food behavior has been undertaken in the context of our studies on adaptation and adaptability of taste perception, which may shed light on relationships that were not previously observed.

Food neophobia, the reluctance to eat new foods, evolved in mammalian species in the context of environmental survival (Rozin and Vollmecke 1986). This primitive behavioral trait is genetically determined in humans as shown by twins and family studies (Cooke et al. 2007; Knaapila et al. 2007). Large variation among individuals has been observed (Potts and Wardle 1998; Pliner and Salvy 2006), of which at least two-thirds is accounted for by genetic factors. Neophobia varies from childhood to adulthood with a maximal intensity from 2 to 6 years old (cf. review by Dovey et al. 2008). Nowadays, the environment in Western societies provides a large diversity of food choices. However, the environmental context of food variety does not necessarily imply

M.-O. Monneuse (✉)

Centre National de la Recherche Scientifique, UMR CNRS/MNHN 7206: Eco-Anthropologie et Ethnobiologie, Musée National d'Histoire Naturelle Département HNS - CP135, 57 rue Cuvier, 75231 Paris Cedex 05, France
e-mail: monneuse@mnhn.fr

individual large food repertory. There is evidence that food neophobia affects diet variety, notably by reducing fruit and vegetable consumption (Galloway et al. 2003) – replaced by less healthy high-caloric foods – thus favoring the development of obesity and noncommunicable diseases (Falciglia et al. 2000). Although neophobia is largely determined by genetic factors, part of the variation of this complex behavioral characteristic should be explained by the influence of external (environmental) factors. Accordingly, investigating to what extent food neophobia is likely to vary according to these external influences can help to induce more healthy food behavior especially in subjects at risk.

Sensory factors are also important determinants of food choice (Pasquet et al. 2002). Taste perception, the result of long term coevolution between animals and plants, allowed individuals to differentiate beneficial versus toxic or antinutrient natural substances. Although reflecting partly the taste system, the relationship between taste recognition thresholds for various compounds illustrates this dichotomy (Hladik et al. 2003). The ability to perceive sugars and to prefer high caloric foods, leading to accumulation of body fat, is an adaptation to cope with environmental pressure (i.e., seasonal variation, Hladik 1988), which, as for neophobia, can be presently maladaptive. In the same vein, it has been assumed that bitter taste evolved as a defense mechanism to detect potentially harmful toxins in the environment (Wooding 2006). Bitter taste perception – especially for compounds including the N-C=S chemical group such as phenylthiocarbamide (PTC) or 6-*n*-propylthiouracil (PROP) – is genetically determined, discriminating tasters from nontasters (Blakeslee 1932). High sensitivity levels for these compounds may reduce food preferences, notably for green vegetables, and hence induce lower variety in food choices, so that the perception of bitterness might be considered a genetic marker for food preferences in humans (Drewnowski 2000; Dinehart et al. 2006). Since the food behavior of both neophobic and individuals with an increased sensitivity to detect the bitter taste show similar characteristics, it is paramount to investigate relationships between individual taste sensitivity and food neophobia.

In this chapter, we first present a review of current knowledge on the relationship between food neophobia, food preferences, and taste perception. Referring to this conceptual framework, we report the results of a recent study focusing on changes in food neophobia, food use, and food preferences in obese adolescents during a long-term weight reduction session in a residential medical center near Paris, considering their individual taste acuity. One application of this study was to adapt dieting to participants in the medical center and then to improve individual protocols designed to reduce obesity prevalence among children.

111.2 Possible Relation Between Food Neophobia, Food Preferences, and Sensory Perception

111.2.1 *Food Neophobia as a Personality Trait*

Food neophobia is an adaptive behavioral trait evolved in animal species to cope with the presence of toxic substances in several plant or animal products eventually used as food (Rozin and Vollmecke 1986). For instance, a mouse in the presence of a new type of food (potentially poisonous) will hesitate and eat just a bite, thus minimizing the risk of being poisoned. If this "trial" is followed by sickness, the new food will be totally avoided. However, in the cultural context of human societies, the adaptive value of food neophobia might be totally neglected since food choices result essentially from education.

One study (Rigal et al. 2006) has shown that when adolescents are exposed during 10 months in a residential institute out of their family food environment, their food neophobia score, measured with the declarative FNS scale, does not reduce differently from that of a control group staying in their usual environment during this period. This showed that food neophobia as a personality trait (a global response, differing from the neophobia state measured in a context of food presentation) is slowly changing throughout lifetime, when comparing childhood, adolescence, and early adult life (Skinner et al. 2002, Nicklaus et al. 2005). The variation in food neophobia can be represented by an individual trajectory into which changes could be difficult to include. In this vein, Reverdy et al. (2008) showed that at the end of a sensory education program in France, the declared food neophobia decreased significantly in the educated group compared to the control group. Nevertheless, these effects disappeared 10 months later. Thus, sensory education can influence children's food neophobia, but does so only temporarily.

111.2.2 Genetically Determined Taste Perception and Food Preferences

Taste perception has been shaped in an evolutionary context in plants and animal species allowing them to differentiate between beneficial and toxic or antinutrient natural substances (Hladik and Simmen 1996; Dong et al. 2009). In humans, the genetically determined basis of taste perception has been clearly demonstrated for some bitter substances such as thiourea, PTC, and PROP (Reed et al. 2006). The application of psychophysical and anatomical measurements to taste genetics allowed researches to identify supertasters, individuals who live in a "particularly intense taste world" (Bartoshuk 2000; Reedy et al. 1993).

The relationship between food preferences and the genetically controlled taste sensitivity was first explored by Fisher et al. (1961), who found a positive correlation between bitter sensitivity to PTC or to quinine, and the percentage of food dislikes in a list of 118 items. Later investigations were focused on the perception of the bitter compounds analogous to those present in natural foodstuffs (cruciferous vegetable containing the N-C=S chemical group). Taster preschool-aged children have also been reported to rate spinach (Turnball and Matisoo-Smith 2002) or raw broccoli (Bell and Tepper 2006) as less palatable than do nontaster children. The nontaster children (Bell and Tepper 2006) consumed more vegetables, particularly the vegetables that were bitter tasting (olives, cucumber, and broccoli) than did the taster children during a free-choice intake test. Thus PTC or PROP sensitivity could be used as a genetic marker for feeding behavior in the perspective of dietary prevention of chronic diseases (Drewnowski and Rock 1995; Drewnowski 2000; Hung et al. 2004; Tepper et al. 2008). Taking into consideration the PTC/PROP tasting status of individuals could be relevant to healthier dietary patterns, by promoting the consumption of a wider array of foods in sensitive subjects (Tepper 1998, Drewnowski and Rock 1995).

Perceived taste intensities for sweet and/or fatty compounds have also been studied in various age groups in relation to food preferences (Monneuse et al. 1991) considering the risk factors for obesity, metabolic diseases (Reed et al. 2006), and cancer (Liu 2004) related to the consumption of high calorie diets. However, the relationship between nonbitter taste perception and food behavior is still a matter of debate (Reed et al. 2006). Genes coding for sweet taste receptors have been identified (Montmayeur and Matsunami 2002), but without a clear connection with food behavior phenotypes, especially in humans (Kim et al. 2006). Authors have argued that PTC/PROP perception status must be considered prior to any investigation on taste sensitivity and hedonic responses to other taste stimuli when analyzing sensory determinants of food behavior (Pasquet et al. 2002; Yeomans et al. 2007).

111.2.3 A Case Study in Tunis

The relationships between taste sensory responses and food preferences and acceptance were studied in a sample of Tunisian subjects sharing a homogeneous cultural background (Pasquet et al. 2002). It was found that most subjects with a high sensitivity to PROP showed higher preferences for known foods (appreciated in the local cultural context) than the subjects with low taste sensitivity, but they had a reduced food repertory, thus suggesting difficulties at overcoming an inherent neophobia in most PROP-sensitive subjects.

In this study, taste recognition thresholds for sucrose, fructose, sodium chloride, quinine hydrochloride, citric acid, tannic acid, oak tannin, and PROP were determined by presenting, in a semirandomized order (blind-test), a series of graded aqueous solutions of each product. Subjects (random sample of 123 adults of both sexes, aged 19–59) also tasted and rated the pleasantness/unpleasantness of 4 supra-threshold solutions of sodium chloride and sucrose. All subjects completed a checklist of 43 food items representative of Tunisian diet rated in terms of flavor, on a Labeled Affective Magnitude (LAM) scale.

According to underlying distribution of PROP taste recognition thresholds, the subjects were separated into three categories: "nontasters" (NT), "medium-threshold tasters" (MTT), and "low-threshold tasters" (LTT) (Fig. 111.1). Results bring out the specificity of most sensitive subjects (PROP LTT), as exhibiting greater taste sensitivity for most tested substances compared to the other subjects. A relationship was found between PROP thresholds and food preferences. PROP LTT status is linked to higher food preference ratings for many currently consumed food items on the list. Mean preference rating for the presented list is also higher in LTT subjects, irrespective of sex, age, and sociocultural influences (Table 111.1).

When focusing on the list of food consumed by all subjects, there was no difference in dislikes between groups. However, when given orally solutions of sodium chloride – generally rated as aversive – the degree of dislike increases from the least sensitive (NT) group to the most sensitive group (LTT). Besides, when considering the food list including all consumed and not consumed foods, most sensitive subjects exhibited a higher percentage of unknown and not consumed food than other subjects (Fig. 111.2).
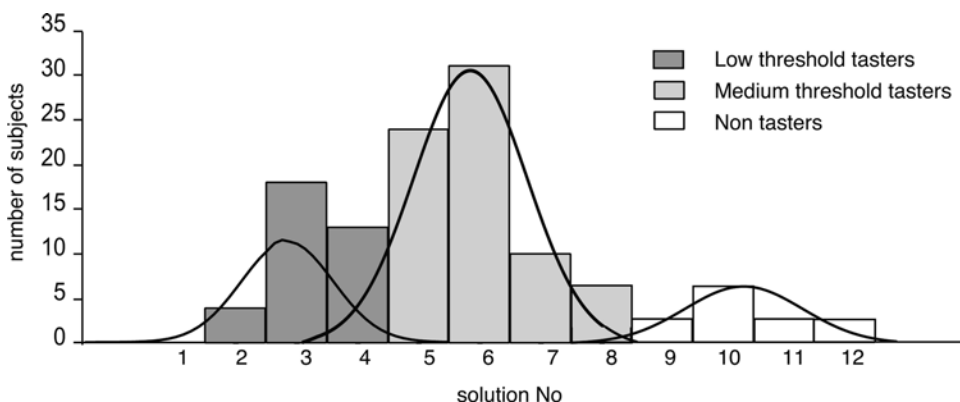
Fig. 111.1 Distribution of 123 Tunisian subjects in three groups according to PROP recognition thresholds. A range of 12 PROP solutions (1.9×10^{-6}–3.8×10^{-3} M) was used. All subjects with an actual estimated threshold above 1.68×10^{-4} M (equivalent to observed threshold at solution #8) have been classified as "nontasters" (*NT*) and subjects with a threshold below 2.1×10^{-5} M (equivalent to observed threshold at solution #5 have been classified "low threshold taster" (*LTT*)

Table 111.1 Values of the *t* test of the differences between groups of PROP tasters for preference ratings for Tunisian food items

	(LTT + MTT) Versus NT (*t*)	LTT Versus (MTT + NT) (*t*)
Barley bread	–0.60	2.17**
Chorba	–2.82**	–0.26
Aubergine	–1.28	2.95**
Oranges	0.89	2.01*
Liver	1.20	2.90**
Offal	0.29	2.01*
Eggs	0.58	3.22**
Milk	2.47*	–1.17
Lben (curdled milk)	–0.74	2.24*
Sman (rancid butter)	–1.26	2.23*
Arise	2.47*	2.02*
Chili	–1.28	2.33*
Mint	0.20	2.20*
Green tea	–2.40*	–0.92
Mean of the preference ratings	–0.25	3.17**

*$p < 0.05$;**$p < 0.001$

Low threshold tasters (LTT) tend to rate preference for foods higher than the other subjects (MTT + NT). For all other foods in the list of 43 items, no significant difference is observed
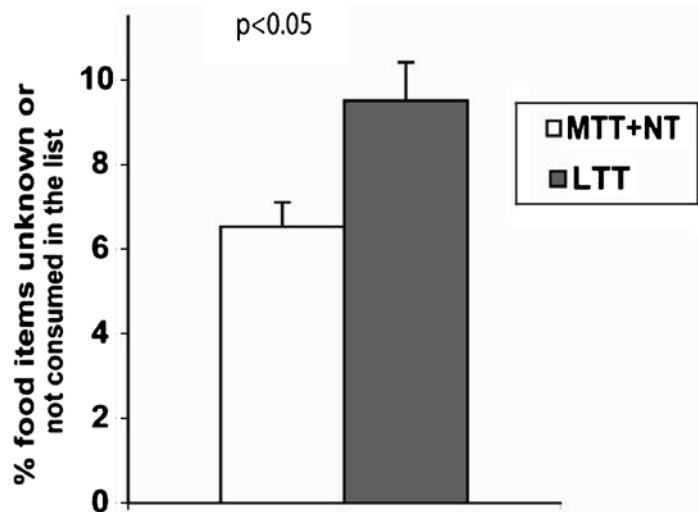
Fig. 111.2 Percentage of food items unknown or not consumed in the list by the most sensitive subjects (LTT) compared to all other subjects (MTT + NT). LTT actually consume a significantly lower number of food items ($p < 0.05$) than all other subjects

111.2.4 PROP Perception in Relation with Temperamental Traits

Few studies have investigated the relationship between PTC or PROP taste sensitivity with temperamental traits and psychometric variables. In the 1960s, Fischer moved away from the focus on genetics and began to consider the behavioral implications of genetic variation in taste. He found associations between PROP tasting and drug sensitivities (Fischer et al. 1965), personality type, food preferences, and smoking habits (Fischer et al. 1963). Mascie-Taylor et al. (1983) showed that PTC nontaster students were significantly more "placid", "relaxed", "practical" and scored higher on IQ tests than their

taster counterparts. The same relationship with IQ was observed in children in a recent paper (McAnally et al. 2007). Other studies indicated that a high PROP/PTC sensitivity generally corresponds to pickiness or to an anxious temperament, as in early infancy (Chiva 1985). Conversely Ullrich et al. (2004) did not find more subject with food adventurousness (a proxy of food neophobia) among PROP tasters than among PROP nontasters but their results suggest that, together, taste sensitivity and food-adventurousness statuses could reveal consumer likes and dislikes.

111.3   *Case Study:* Changes in Food Neophobia and Food Preferences During a Weight Reduction Session (WRS)-Relationships with Taste Acuity

According to the foregoing, it appears that investigations should be conducted to describe more directly the relationship between food neophobia and taste sensitivity.

111.3.1   *Investigating Taste Perception, Food Neophobia, Food Familiarity, and Liking in Obese Adolescents*

The relationship between taste acuity and food neophobia, and food familiarity and liking has been studied in French obese adolescents of both sexes: 28 girls and 11 boys aged 10.5–17.5 years (mean 14.7 years) in the context of a longitudinal protocol of WRS in a residential place near Paris (Monneuse et al. 2008). Mean body mass index (BMI) was 39.5 kg/m^2 (ranging from 30.9 to 51.6) at T1 and 29.7 kg/m^2 (ranging from 22.1 to 42.1) at T2. BMI for age was expressed in terms of Z-scores using the sex-specific CDC BMI for age reference curves (Centre for Disease Control and Prevention 2000). The figures are 2.47 (ranging from 2.02 to 2.99) at T1, and 1.75 (ranging from 0.48 to 2.59) at T2. The obese adolescents ate all of their meals at the clinical centre, where consumption of a wide variety of foods was encouraged with a long-term exposure to multiple food experiences (Rigal et al. 2006). Although most foods served are known by the subjects in the French cultural context, some of them may not be usually served at the family table, where a limited repertoire represents specific habits. As in most French collective systems for children, the food served during the WRS covers a very broad range.

Determination of taste recognition thresholds was carried out using a series of four pure chemicals in solution in a commercial drinking water selected for its low mineral content: sucrose, citric acid, sodium chloride, and PROP (Simmen et al. 2004). The testing procedure was the staircase-method. The four series of solutions were presented one after another, in a random order to which the subject was blind. Once the taste of two successive concentrations was recognized successfully, the subject was given the highest previously unrecognized concentration (first reversal). This up-and-down procedure was performed twice until the taste of two increasing stimuli was correctly named. The actual recognition threshold was calculated as the mean of the lowest concentrations recognized in each ascending run.

Although PROP-sensitivity could be considered a marker of global taste acuity (Pasquet et al. 2002; Hong et al. 2005), considering the moderate correlations found by Hladik et al. (2002) between taste recognition thresholds for various taste compounds, we drew also an individual global taste acuity score (GTAS). It was determined by grouping threshold data for each tested substance into

terciles and attributing, respectively, score 3, 2, and 1, for the first, the second, and the third tercile. The GTAS was then calculated as the sum of the score values. Thus, in contrast to threshold concentrations, lower GTAS scores reflect poorer taste acuity. The study sample was finally divided into three categories of subjects with increasing GTAS for testing relationships with neophobia.

Supra-threshold-perceived intensities have been measured for solutions of various concentrations provided in a random order for sodium chloride, sucrose, and PROP. The perceived intensity of each solution was marked by the subject on a nine-point scale (VAS) labeled at the extremities with "no taste" [1] and "extremely intense taste" [9], and the intensity values obtained for the concentrations of each taste were then added. According to these scores, the study sample was divided into three groups of increasing taste perceived intensity for each tested substance.

Food neophobia was measured on FNS scales, slightly modified in comparison to the one first developed by Pliner and Hobden (1992), at the beginning (T1) and at the end (T2) of the WRS. Food familiarity and likes or dislikes for different food categories were assessed. Each subject rated, at least 2 h after their last meal, a 60 items *ad hoc* food familiarity and liking questionnaire (FFLQ). The FFLQ includes seven food categories which differ by the frequency of exposure to adolescent subjects throughout the WRS. Among these categories, fruit and vegetables, calorie-reduced foods, and breakfast foods represent three categories frequently offered and for which variety is probably larger than in the participants' home. Foods rarely served were tested through two categories: animal products and relatively high energy foods. The list also included foods never served because of their very high caloric density or because of their unusual occurrence in the French adolescents' diet. We also included spices as one category because of our parallel interest in flavor responses. Different scores were calculated for each subject from the FFLQ: (a) number of unknown foods (sum of "No" responses to the familiarity question); (b) mean food liking (mean of all liking scores given for the foods that have already been tasted); and (c) food category likings (mean liking scores for each of the seven food categories). Higher scores indicate higher likings.

111.3.2 Influence of Taste Acuity on Food Neophobia and Food Liking Changes During the Weight Reduction Session (WRS)

Globally, FNS scores decreased between T1 and T2 (Monneuse et al. 2008) as previously reported in the 72-subject larger sample (Rigal et al. 2006). During this period, WRS have allowed new foods experiences as attested by the familiarity and liking results, namely a significant decrease in the number of unknown foods in the FFLQ and an increase in the scores for three food category likings (fruits and vegetables, breakfast foods, and calorie-reduced foods). Interestingly, both the decrease in food dislikes and the increase in liking for fruits and vegetables were correlated with a decrease in the BMI for age.

We found in this sample a low proportion of PROP "nontasters": six adolescents (all girls) out of 39. Obese adolescents did not differ in BMI according to PROP status. Significant correlations were observed between taste thresholds for sucrose and sodium chloride, for sucrose and PROP, for sodium chloride and citric acid, and for sodium chloride and PROP.

No significant relationships were observed at T1 between taste variables and food neophobia. However, significant relationships were observed between taste acuity data and food-related behavioral changes during the WRS. GTAS was associated positively with the change of FNS and negatively with the change in liking for fruits and vegetables: "high GTAS" category subjects (with high taste acuity) were characterized by limited reductions in FNS (T2-T1) (Fig. 111.3) and less sensitive subjects showed greater increase in the acceptability of healthy foods, especially fruits and vegetables (not shown).
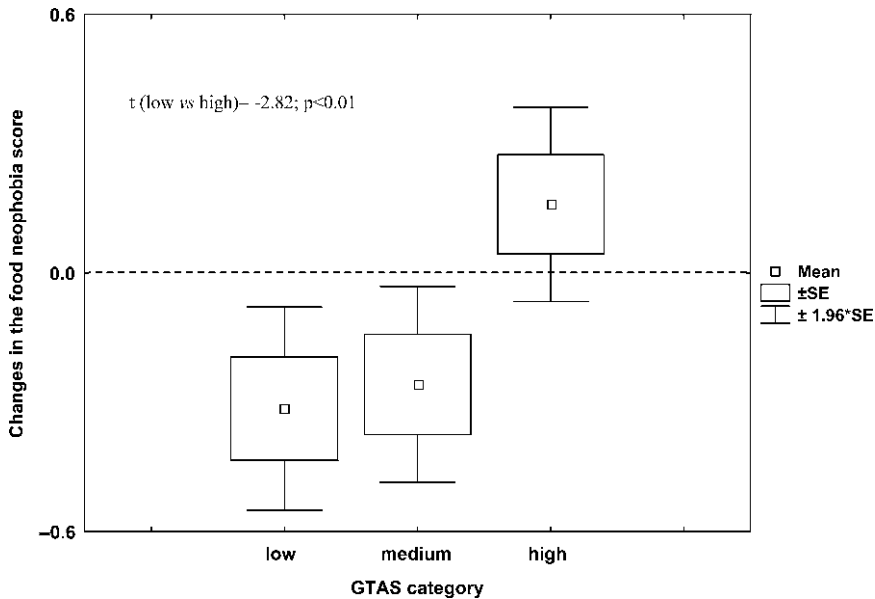
Fig. 111.3 Changes in food neophobia score of obese adolescents during a WRS according to the global taste acuity score (three categories of GTAS). The study sample is divided into three groups of subjects ($n = 11$, 14, and 14, respectively) of increasing taste acuity including, respectively, 5, 11, and 12 girls. Differences between subjects grouped according to GTAS were assessed using a Student's *t*-test. Box and whisker plot: mean and SE

As regards supra-threshold perceived intensities, PROP data gave better correlations with food-related behavioral changes than did sucrose and NaCl. PROP perceived intensity was related positively with changes in food neophobia scores (lower ratings, greater declines), and negatively with changes in liking for fruit and vegetable (lower rating, greater increase, Fig. 111.4) and for spices, consistent with the general direction of associations observed with the threshold measures.

Therefore, taste perception, especially PROP sensitivity, may reduce the likelihood and/or magnitude of food-related attitudinal changes, particularly vis-à-vis neophobia and liking for fruit and vegetable. It appears to be a predictor of the magnitude of changes in food behavior achieved during a WRS of obese adolescents.

Thus, among obese subjects participating in a WRS, those with greater taste acuity have more difficulties in overcoming food neophobia, and accepting healthy foods, notably fruit and vegetables. Conversely, subjects with low taste sensitivity can significantly improve their food behavior, increase their food repertory, and hence change their own trajectory of food neophobia.

111.3.3 Analysis of the Relation Between Taste Perception, Food Neophobia, and Food Likings

According to the results of the Tunis study, we would have expected to observe a relationship between taste (especially PROP taster status) and neophobia at the beginning of the WRS. The absence of such relationship in our study could be due to the specificity of our sample, namely subjects with metabolic disorders, that could have consequences in taste acuity levels (Pasquet et al. 2007).
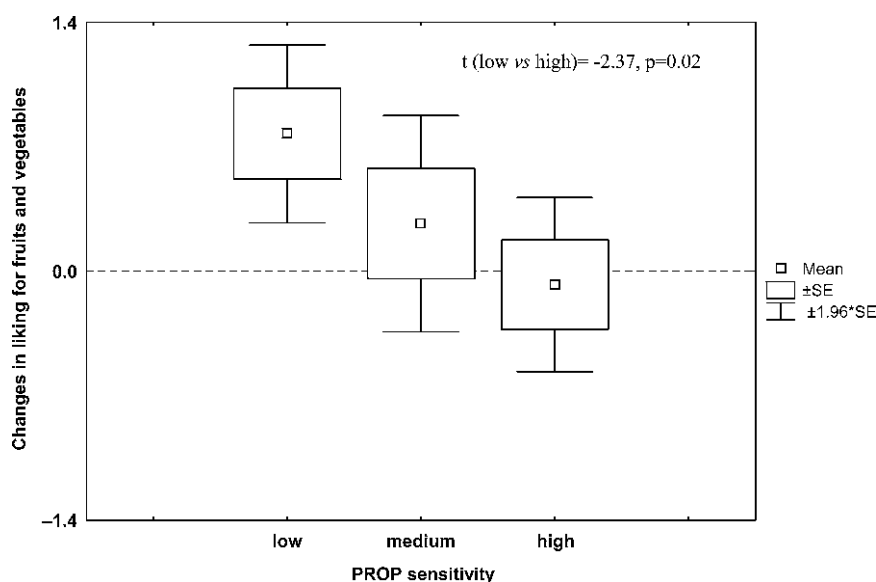
Fig. 111.4 Changes in the liking for fruit and vegetable score of obese adolescents during a WRS according to the perceived intensity of supra-threshold PROP solutions. The study sample is divided into three groups of 13 subjects of increasing PROP-perceived intensity including, respectively, 7, 10, and 11 girls. Differences between subjects grouped according to supra-threshold rating scores were assessed using a Student's *t*-test. Box and whisker plot: mean and SE
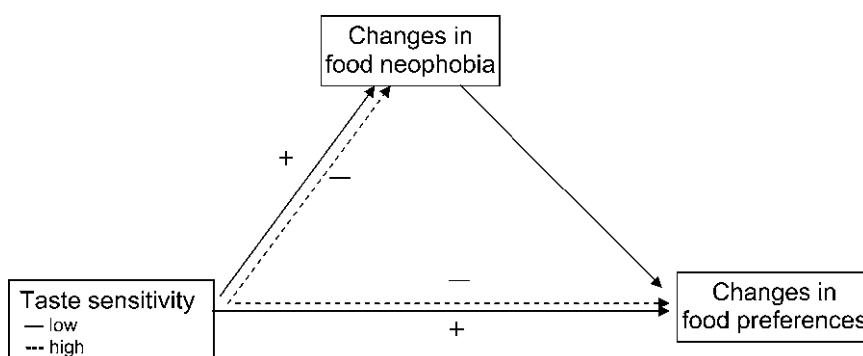
Fig. 111.5 Key features of food neophobia: hypothetical model to explain changes in food preferences, (especially for fruit and vegetables) according to taste perception differences among individuals. *Plain lines* represent the non-tasters, *dotted lines* represent the tasters

However, taste responsiveness, whether determined on the basis of taste recognition thresholds or supra-threshold intensity ratings, appears to change the attitude to food during WRS for obese adolescents. Our study is, to our knowledge, unique in showing a relationship between taste acuity and changes in attitude to food following a change in available foods, meal structure, and educational context. Greater taste acuity seems to make it more difficult to overcome food neophobia, and to accept healthy foods, notably fruit and vegetables as illustrated in a model of interaction of key features of food neophobia (Fig. 111.5).

If one considers food neophobia as a temperamental trait (at least when measured by FNS; Rigal et al. 2006), the relationship that we found between gustatory perception and changes in food neophobia highlights the relationship between psychological traits and sensory factors.

Another relationship may be suggested by the results of psychophysical studies of young and middle-aged adults (Goldstein et al. 2005; Simchen et al. 2006) showing that individuals least sensitive – either considering PROP status or global taste acuity – have higher BMIs than more sensitive individuals. Thus, lower taste acuity could favor weight gain through higher adaptability to an eating environment promoting excessive calories consumption, as in Western affluent societies. In the same way, the environmental context of our study (dieting program) and the "plasticity" of less sensitive subjects may explain the important positive changes in food-related behavior. Obese adolescents with high taste sensitivity may be less likely to benefit from WRS programs, and probably need an adapted weight reduction protocol.

Since neophobic or taste-sensitive individuals share the same tendency toward a narrow food repertory with healthy foods being under-represented, it would be necessary to investigate any possible interaction or additive effect of these parameters of food behavior. In our sample, the few adolescents that were both nontaster and non-neophobic were much more prone to liking fruit and/or vegetables at the end of WRS than did the other subjects (unpublished data). However, although this finding is consistent with current views on the relationship between sensory factors and food related attitudes, the small sample size does not allow us to draw a definitive conclusion on any interaction of both parameters. More research is necessary to propose, at the beginning of the WRS, a preventive screening of obese patients that would include the FNS questionnaire together with taste evaluation to maximize the changes of success in weight reduction and behavioral changes.

In conclusion, the results of this study suggest that taste sensitivity, especially PROP sensitivity, may reduce the likelihood and/or magnitude of food-related attitude to changes, particularly vis-à-vis neophobia and liking for fruits and vegetables. This should be taken into account in attempts to optimize the outcomes of weight reduction programs in obese adolescents.

111.3.4 Applications to Other Areas of Health and Disease

Concerning application to other areas of health and disease, in attempts to optimize the outcome of weight reduction programs in obese adolescents, taste sensitivity should be considered to adapt the program of a WRS to individual characteristics.

Indeed, in the context of our study focusing on massively obese adolescents, those who have high taste sensitivity among these obese adolescents may be less likely to benefit from the WRS, and probably need an adapted weight reduction program. To detect these individuals, quantification of fungiform papillae or taste pores and determining a global taste score as GTAS in our study would be more tedious than a rapid and simple screening test with PROP. A filter paper disk method has showed to be a reliable screening tool for assessing sensitivity to PROP (Zhao et al. 2003).

Lifestyle intervention is effective in motivated obese children to reduce excess weight and improve the cardiovascular risk factor profile. Therefore, all diseases related to obesity should be treated with lifestyle intervention in this age group whenever possible. Since genetic variations influence outcome in respect of both excess weight reduction and improvement of cardiovascular risk factor, unsuccessful children should not be blamed. Putting together genetic research and clinical intervention studies represents a new promising field to prove the impact of genetic variants on body weight and to understand the different outcomes.

Summary

- Food neophobia, the reluctance to eat new foods resulting from a long-term co-evolution of animals and plants, is genetically determined as a temperamental trait that, in humans, varies slowly throughout lifetime according to individual characteristics, but would not much vary in response to external influences.
- The genetically determined taste perception of bitter substances (such as thiourea, PTC, or PROP), as a marker of taste acuity, mediates food dislikes.
- Most subjects with a high sensitivity to PTC or PROP show higher preferences for known foods (appreciated in the local cultural context) than subjects with low taste sensitivity, but they have a reduced food repertory, thus suggesting inherent neophobia in most sensitive subjects.
- There is a relationship between sensitivity to PTC or PROP and some temperamental characteristics, a low sensitivity corresponding to relaxed or placid temperaments, whereas high sensitivity generally corresponds to pickiness and anxious temperament.
- Subjects with a low sensitivity to PROP or PTC tend to be overweight. It can be hypothesized that lower taste acuity, together with temperamental traits such as neophilia and placidity, could favor weight gain through a higher adaptability to an eating environment promoting excessive calorie consumption, as in Western affluent societies.
- Among obese subjects participating to a weight reduction session (WRS), subjects with high taste sensitivity have difficulties overcoming food neophobia.
- Among obese subjects participating in the WRS those with low taste sensitivity can significantly improve their food behavior, increasing food repertory, thus partly overcoming food neophobia.
- In the environmental context of the WRS, "plasticity" of less- sensitive subjects may explain the important positive changes of food behavior and preference for fruits and vegetables. However, additional or interactive effects of taste and neophobia statuses on food-related behavioral changes remain to be demonstrated.
- Application to other areas of health and diseases: Taste sensitivity (and perhaps neophobia) status should be determined in order to adapt weight reduction programs to individual characteristics.

Definitions

Aqueous solutions: Ranges of concentrations of solutions usually used in our studies are sucrose and fructose (10 solutions: 2.0–1,000 mM), citric acid (8 solutions: 0.20–25 mM), NaCl (12 solutions: 1.77–1,000 mM), PROP (15 solutions: 0.001–3.2 mM), quinine hydrochloride (11 solutions: 0.4–400 μM), tannic acid (12 solutions: 4–8,000 μM), oak tannin (9 solutions: 0.02–6 g/l).

BMI: Body mass index is a commonly used index of relative weight. BMI is calculated as weight divided by height squared, thus expressed in kg/m². An adult who has a BMI between 25 and 29.9 is considered overweight. An adult who has a BMI of 30 or higher is considered obese.

BMI for age and sex: It is expressed in terms of Z-scores using growth charts, such as the sex specific CDC BMI for age reference curves.

FFLQ: It is a food familiarity and liking questionnaire used to measure the food familiarity (food use) and food preference on liking scales. In our study it was composed of 60 food items, a few of them supposed to be unfamiliar for adolescents.

Food preference: It is the selection of some food items over others. Food preferences data are usually collected from answers to questionnaires with food lists adapted to age and cultural context. The food lists are presented in random order on a booklet, each item on separated sheet with a scaling system used to determine food likes and dislikes.

Food use: It is a food item that has already been tried and is known. For example, a labeled box, inserted above each preference scale, is to be filled by participants with a binary response (Yes/No) to answer the question: "Have you already tasted this food?." It is a measure of food familiarity.

Food neophobia: It is the fear of tasting a new food. It is considered a biological reflex evolved to minimize the risk of ingesting toxic foods.

FNS: Food neophobia scale is a paper and pencil measure of the trait of food neophobia (first a 10-item test). For the obese adolescents, we used a French validated translation of the declarative standard questionnaire of the FNS including 13 items.

FNS score: In our study, it was equal to the mean of ratings for 13 items/4 points (disagree a lot, disagree, agree, agree a lot, respectively from 1 to 4) scale questionnaire. According to the phrasing of the original questionnaire, seven items were reverse-scored, so that higher scores are indicative of a greater neophobia.

LAM: Labeled Affective Magnitude scale is one of the scales used to determine food preference: each sheet includes a food item presented with an 11-point labeled vertical scale.

Perceived taste intensity: It is the intensity perceived when tasting supra-threshold solutions starting from threshold to the highest concentration. It is evaluated with a scaling system.

Preference rating: It is the score of pleasantness/unpleasantness of solutions or of food items indicated on specific hedonic scales.

PROP: Genetic sensitivity to the bitter tasting 6-*n*-propylthiouracil (PROP) is considered a marker for preferences/aversions, especially foods with bitter taste.

Taste recognition threshold: It is the lowest concentration of a taste stimulus in an aqueous solution for which the subject is able to recognize the right taste. The subject is informed of various taste categories proposed before each ascending run. Taste recognition thresholds have been determined by presenting, in a semi-randomized order (blind-test), a series of graded aqueous solutions of each product.

VAS: Visual Analog Scale is one of the scales used to indicate perception intensity or liking of a taste stimulus in an aqueous solution or of a food item. For example, the 9-point scale labeled from "I don't perceive at all" (1) to "I perceive a lot" (9) or/and "I don't like at all" (1) to "I like a lot" (9).

WRS: Proposed in a residential context, it is a weight reduction session of 10 months mean duration (T1 the beginning, T2 the end) and aims at encouraging participants to consume a wide variety of foods, including fruit, vegetables, and reduced energy products. Variety is also encouraged for breakfast that should account for about 20% of daily energy intake.

References

Bartoshuk LM. Chem Senses. 2000;25:447–60.

Bell KI, Tepper BJ. Am J Clin Nutr. 2006;84:245–51.

Blakeslee AF. Proc Natl Acad Sci USA. 1932;18:120–30.

Centre for Disease Control and Prevention/National Centre for Health Statistics. CDC growth charts: The United States. Hyattsville: Department of Health and Human Services; 2000.

Chiva M. Le doux et l'amer: Sensation gustative, émotion et communication chez le jeune enfant. Paris: Presses Universitaires de France; 1985.

Cooke LJ, Haworth CMA, Wardle J. Am J Clin Nutr. 2007;86:428–33.

Dinehart ME, Hayes JE, Bartoshuk LM, Lanier SL, Duffy VB. Physiol Behav. 2006;87:304–13.

Dovey TM, Staples PA, Gibson EL, Halford CG. Appetite. 2008;50:181–93.

Dong D, Jones G, Zhang S. BMC Evol Biol. 2009;9:12.

Drewnowski A. Am J Clin Nutr. 2000;72:1424–35.

Drewnowski A, Rock CL. Am J Clin Nutr. 1995;62:506–11.

Fisher R, Griffin F, England S, Garn SM. Nature. 1961;191:1328.

Fischer R, Griffin F, Kaplan, AR. Med Exp. 1963;9:151–67.

Fischer R, Knopp W, Griffin F. Drug Res. 1965;15:1379–82.

Falciglia GA, Couch SC, Gribble LS, Pabst SM, Frank R. J Am Diet Assoc. 2000;100:1474–81.

Galloway AT, Lee Y, Birch LL. J Am Diet Assoc. 2003;103:692–8.

Goldstein GL, Daun H, Tepper BJ. Obes Res. 2005;13:1017–23.

Hladik, C. M. (1988) — Seasonal Variations in Food Supply for Wild Primates. In : I. de Garine et G. A. Harrison (Eds.), Coping with Uncertainty in Food Supply. Clarendon Press, Oxford : 1–25.

Hladik CM, Simmen B. Evol Anthropol. 1996;5:58–71.

Hladik CM, In: I. de Garine et G. A Harison (eds.) Coping with Uncertainty in food supply. 1988;1–25.

Hladik CM, Pasquet P, Simmen B. Am J Phys Anthropol. 2002;117:342–8.

Hladik CM, Pasquet P, Danilova V, Hellekant G. CR Palevol. 2003;2:281–7.

Hung HC, Joshipura KJ, Jiang R, Hu FB, Hunter D, Smith-Warner SA, Colditz GA, Rosner B, Spiegelman D, Willett WC. J Natl Cancer Inst. 2004;96:1577–84.

Hong J-H, Chung J-W, Kim Y-K, Chung S-C, Lee S-W, Kho H-S. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2005;99:711–715.

Kim U-K, Wooding S, Riaz N, Lynn B, Jorde LB, Drayna D. Chem Senses. 2006;31:599–611.

Knaapila A, Tuorila H, Silventoinen K, Keskitalo K, Kallela M, Wessman M, Peltonen L, Cherkas L F, Spector TD, Perola M. Physiol Behav. 2007;91:573–8.

Liu RH. J Nutr. 2004;134:3479S–85S.

McAnally HM, Poulton R, Hancox RJ, Prescott J, Welch D. Appetite. 2007;49:700–3.

Mascie-Taylor CGN, McManus IC, MacLarnon AM, Lanigan PM. Behav Genet. 1983;13:191–6.

Monneuse MO, Bellisle F, Louis-Sylvestre J. Physiol Behav. 1991;50:1111–7.

Monneuse MO, Rigal N, Frelut ML, Hladik CM, Marez A, Simmen B, Pasquet P. Appetite. 2008;50:302–7.

Montmayeur JP, Matsunami H. Curr Opin Neurobiol. 2002;12:366–71.

Nicklaus S, Boggio V, Chabanet C, Issanchou S. Appetite. 2005;44:289–97.

Pasquet P, Monneuse MO, Frelut ML, Simmen B, Hladik CM. Intern J Ped Obes. 2007;2:242–8.

Pasquet P, Oberti B, El Ati J, Hladik CM. Appetite. 2002;39:167–73.

Pliner P, Hobden K. Appetite. 1992;19:105–20.

Pliner P, Salvy SJ. In: Shepherd R, Raats M, editors. The psychology of food choice. Oxfordshire: CABI Publishing; 2006p. 75–92.

Potts HW, Wardle J. Appetite. 1998;30:79–92.

Reedy FE, Bartoshuk LM, Miller IJ, Duffy VB, Yanagisawa K. Chem Senses. 1993;18:619.

Reed DR, Tanaka T McDaniela AH. Physiol Behav. 2006;88:215–26.

Reverdy C, Chesnel F, Schlich P, Koster EP, Lange C. Appetite. 2008;51:156–65.

Rigal N, Frelut ML, Monneuse MO, Hladik CM, Simmen B, Pasquet P. Appetite. 2006;46:207–14.

Rozin P, Vollmecke TA. Annu Rev Nutr. 1986;6:433–56.

Simchen U, Koebnick C, Hoyer S, Issanchou S, Zunft HJF. Eur J Clin Nutr. 2006;60:698–705.

Simmen B, Pasquet P, Hladik CM. In: Macbeth H, MacClancy J, editor. Researching food habits: methods and problems. Oxford: Berghahn Books; 2004. p. 87–99.

Skinner JD, Carruth BR, Bounds W, Ziegler PJ, Reidy K. J Nutr Educ Behav. 2002;34:310–5.

Tepper BJ. Am J Hum Genet. 1998;63:1271–6.

Tepper BJ, Koelliker Y, Zhao L, Ullrich NV, Lanzara C, d'Adamo P, Ferrara A, Ulivi S, Esposito L, Gasparini P. Obesity. 2008;16:2289–95.

Turnbull B, Matisoo-Smith E. Am J Clin Nutr. 2002;76:1101–5.

Ullrich NV, Touger-Decker R, O'Sullivan-Maillet J, Tepper BJ. J Am Diet Assoc. 2004;104:543–9.

Yeomans MR, Mobini S, Chambers LC.Physiol Behav. 2007;92:831–839.

Wooding S. Genetics. 2006;172:2015–23.

Zhao L, Kirlmeyer SV, Tepper BJ. Physiol Behav. 2003;78:625–33.

Chapter 112
Dyspepsia and Appetite Regulation

Takashi Akamizu

Abbreviations

FD	Functional dyspepsia
GI	Gastrointestinal
FGDD	Functional Gastroduodenal disorders
FGID	Functional gastrointestinal disorders
NUD	Nonulcer dyspepsia
MMC	Migrating motor complex
CCK	Cholecystokinin
PYY	Peptide YY
GLP1	Glucagon-like protein 1
PP	Pancreatic polypeptide
SSRIs	Selective serotonin reuptake inhibitors
NK	Neurokinin
NMDA	*N*-methyl-d-aspartate
5-HT	Serotonin
NTS	Nucleus Tractus solitarius
AP	Area postrema
DMVN	Dorsal motor vagal nucleus
H2	Histamine 2
TCA	Tricyclic antidepressants
VR1	Vanilloid receptor-1
FDA	Food and Drug Administration

112.1 Introduction

Neural and hormonal communication between the gut and brain modulate appetite, feeding, and digestion (Bray 2000; Sanger and Lee 2008). In an integrated gut–brain–energy axis, gastrointestinal (GI) motility, gastric acid secretion, digestion, and defecation are coordinated with appetite, satiation,

T. Akamizu (✉)
Translational Research Center, Kyoto University Hospital, Kyoto University
School of Medicine, 54 Shogoin-Kawaharacho, Sakyo-ku, Kyoto 606-8507, Japan
e-mail: akamizu@kuhp.kyoto-u.ac.jp

and metabolism. Indeed, complex disorders linked with digestion including functional dyspepsia (FD), gastroesophageal reflux disease (GERD), eating disorders, gastroparesis, and irritable bowel syndrome (IBS) are associated with diverse symptoms affecting the entirety of the GI tract such as nausea, vomiting, abdominal discomfort, and early satiety. In this chapter, we illustrate the links between gastric function and appetite and their dysregulation in dyspeptic disorders. In addition, we discuss how an understanding of the relationship between the gut–brain–energy axis can be used to develop novel therapies that address the polysymptomatic nature of functional GI disorders.

112.2 Dyspeptic Disorders

Dyspepsia as defined by the Rome III criteria (Drossman 2006) requires the presence of one or more of the following symptoms: postprandial fullness, early satiety, and epigastric burning or epigastric pain (Talley et al. 2008) (Tables 112.1 and 112.2). Unexplained nausea with vomiting and heartburn were included in other categories (Table 112.3) (Drossman 2006; Tack et al. 2006; Talley et al. 2008).

Dyspepsia is associated with a variety of organic and functional disorders. Organic causes of dyspeptic symptoms include peptic ulcer, cholelithiasis, reflux disease, or malignancy. In patients initially presenting with dyspepsia, about 33–50% have an underlying organic disease (Allescher 2006). However, routine clinical evaluation and procedures do not reveal the cause of symptoms in the majority of patients with dyspepsia. If these symptoms persist for greater than 3 months with symptom onset of at least 6 months, affected patients are categorized as having FD. Functional Dyspepsia, a functional gastroduodenal disorder (FGDD) (Table 112.3) (Tack et al. 2006; Talley et al. 2008) or functional gastrointestinal disorder (FGID) (Drossman 2006), has previously been

Table 112.1 Key features of dyspepsia

1 The characteristic symptoms of dyspepsia are postprandial fullness, early satiety, and epigastric burning or epigastric pain
2. Dyspepsia is associated with a variety of organic and functional disorders
3. Dyspeptic symptoms caused by organic disorders include peptic ulcer, cholelithiasis, reflux disease, and malignant disease
4. When the routine clinical diagnostic procedures reveal no reasonable explanation for their dyspeptic symptoms, the majority of patients are categorized as having FD

This table lists the key facts of dyspepsia including the characteristic symptoms and causes

FD Functional dyspepsia

Table 112.2 Dyspeptic symptoms defined by Rome III (Adapted by permission from Elsevier Limited, Tack et al. 2006; Drossman 2006)

Symptom	Definition
Postprandial fullness	An unpleasant sensation akin to the prolonged persistence of food in the stomach
Early satiation	A feeling that the stomach is overfilled soon after starting to eat. This feeling is out of proportion to the size of the meal and results in the patient being unable to finish the meal
Epigastric pain	Pain located between the umbilicus and sternum in the midline of the torso. The pain is a subjective and unpleasant feeling but difficult to describe. Some patients may describe feelings of tissue damage or chest pain
Epigastric burning	Pain located in the epigastrium that has a burning quality but does not radiate to the chest

Table 112.3 Rome III criteria for functional gastroduodenal disorders (FGDD) (Adapted by permission from Elsevier Limited, Tack et al. 2006)

B			FGDD
	B1		Functional dyspepsia
		B1a	Postprandial distress syndrome
		B1b	Epigastric pain syndrome
	B2		Belching disorders
		B2a	Aerophagia
		B2b	Unspecified excessive belching
	B3		Nausea and vomiting disorders
		B3a	Chronic idiopathic nausea
		B3b	Functional vomiting
		B3c	Cyclic vomiting syndrome
	B4		Rumination syndrome in adults

referred to as nonulcer dyspepsia (NUD), essential dyspepsia, or idiopathic dyspepsia. Nausea, vomiting, and heartburn were previously considered in the diagnostic criteria of FD, but, because appetite is influenced by these symptoms as well as dyspepsia, we broadly consider all of these symptoms.

112.3 Physiologic Aspects of the Gut–Brain Axis

The gut and brain are highly integrated and communicate bidirectionally through neural and hormonal pathways (Jones et al. 2006). For example, psychosocial factors can influence digestive function, symptom perception, disease presentation, and outcome. Conversely, visceral pain can affect central pain perception, mood, and behavior.

112.3.1 Neural Aspects

The cephalic phase of eating prepares the gut to receive, digest, and absorb food (Sanger and Lee 2008), and this provokes significant changes in GI motor functions and the secretory response to eating. These stimuli are transmitted to the gut via the vagus nerve (Zafra et al. 2006). Thoughts of appetizing food, and the sight, smell, and taste of food, all help to initiate the cephalic phase. As the esophagus and stomach receive food, their motility changes. Completion of a meal then leads to satiation, defined as a feeling of having consumed enough or a sensation of fullness. After the stomach and upper small intestine are emptied of their contents, a fasting phase of motility is re-adopted and the migrating motor complex (MMC) returns. MMC is a cyclic pattern of motility and secretion that begins in the stomach or small intestine and terminates in the distal regions of the small intestine including the terminal ileum. Within the small intestine, the MMC exhibits three phases. Phase I is a period of near-quiescence; phase II involves short- or nonpropulsive contractions occurring with an irregular frequency; and phase III is a relatively short burst of high-amplitude propulsive contractions (Husebye 1999). The MMC is also accompanied by cyclic variations in gastric and pancreatic secretion, gallbladder emptying and splanchnic blood flow. The phase III MMC is thought to clear the stomach and intestine of undigested material, thereby preventing bacterial overgrowth in the upper gut; it may also promote sensations of hunger. Gastric, biliary, and pancreatic secretions are also affected by the MMC, and the MMC may help to prepare the gut for the consequences of eating. Finally, MMC activity is terminated upon meal ingestion.

Many upper gut functions depend on signaling by the vagus nerve. The vagus nerve extensively innervates the upper GI tract, and most of the nerve fibers are unmyelinated afferent C-fibers that function in mechanosensation (signaling muscle stretching and contraction) and chemosensation (monitoring the chemical environment of the gut lumen) (Powley et al. 2005). Most afferent nerves from the gut terminate in the nucleus tractus solitarius (NTS) in the dorsal brainstem, but several nerve fibers project to the area postrema (AP), a circumventricular organ within the brainstem. From the NTS, nerve fibers project to motor nuclei (e.g. the dorsal motor vagal nucleus (DMVN)) and higher regions of the brain including the parabrachial nucleus, hypothalamus, amygdala, and insular cortex (Andrews and Sanger 2002). The combination of projections of afferent vagal fibers in the brain and the extensive distribution of vagal terminals in the gut helps the vagus nerve fulfill its functions to regulate normal physiologic responses (e.g. the cephalic phase of eating and the subsequent response during feeding), mediate different vago-vagal reflexes (e.g. transient lower esophageal sphincter (LES) relaxation and gastric accommodation), and regulate the strength of antral propulsive contractions and other basic functions (e.g. secretion, motility, and pancreatic function). Additionally, the vagus nerve mediates pathophysiologic sensations and reflexes including nausea, early satiety, and vomiting (Powley et al. 2005; Andrews and Sanger 2002). Among the best examples of the close relationship between the vagus and the enteric nerves is gastric accommodation. This process is initiated as a vago-vagal reflex following oropharyngeal stimulation and gastric exposure to an ingested meal. Efferent vagal neurons activate inhibitory nerve pathways within the enteric nervous system (ENS) through nitric oxide signaling pathways to first promote "receptive accommodation" and then maintain this relaxation through "adaptive accommodation" (Takahashi and Owyang 1997).

112.3.2 Hormonal Aspects

A number of different hormones are secreted by the gut and adipose tissues during feeding, digestion, or fasting that can profoundly affect the GI tract (Sanger and Lee 2008). Some hormones directly affect secretory function along the GI tract (e.g. gastrin stimulates acid secretion by parietal cells), and major sites of hormone action also include the enteric and vagal neurons and the AP. The AP has a greatly reduced or absent blood–brain barrier. Consequently, the AP is one of the main sites within the central nervous system where blood-borne signals (e.g. hormones, cytokines, toxins) can directly affect the brain by initiating signaling from the AP along nerve projections to the adjacent NTS and higher regions of the brain. Additionally, some hormones can cross the blood–brain barrier including those with specific transporters such as leptin and insulin (Banks 2006). Hormones released from the gut both act on the ENS to contribute to the development of the MMC cycle and act on the CNS to promote the gradual reestablishment of appetite. Other hormones are released during fasting that are not associated with any particular phase of MMC activity. The concentrations of leptin and glucagon-like peptide 1 (GLP1) are low during fasting while those of ghrelin and orexin are high. Much research has focused on the hormones whose plasma concentrations increase during fasting, and it is hypothesized that these hormones strongly affect sensations of hunger and energy expenditure. In addition to these systemic effects, it is becoming increasingly clear that fasting-associated hormones can also strongly affect a myriad of GI functions, possibly to prepare for the reception of food. Indeed, such a role has been proposed for ghrelin, the first orexigenic hormone identified that is produced in and released from the stomach. Ghrelin has a well-established role in increasing appetite and food intake and stimulating gastric emptying and acid secretion, and it at least partly mediates these functions through a vagal nerve pathway (Date et al. 2002; Masuda et al. 2000). Table 112.4 summarizes the hormones released from the gut with known GI activity.

Table 112.4 Major hormones released from the gut with known GI activity (Adapted by permission from Nature Publishing Group, Sanger and Lee 2008)

A. Hormones released during fasting

Hormone	Release site(s) and stimuli	Functions
Ghrelin	Stomach (where the largest amounts are found) before a meal; the duodenum, small intestine, arcuate nucleus and other sites produce smaller amounts	• Increases appetite and stimulates feeding when peripherally and centrally administered • Increases the secretion of growth hormone and, to a lesser extent, the release of other hormones including prolactin, adrenocorticotropic hormone and cortisol • Stimulates gastric motility and emptying
Orexin A and B	Cells throughout the GI tract including the myenteric plexus, mucosal endocrine cells, and endocrine pancreas	• Depolarizes enteric and vagal afferent neurons and inhibits small intestinal MMC activity when locally applie • Stimulates rat gastric emptying and acid secretion
Motilin	The jejunum and duodenum during phase III of the MMC	• Initiates MMC phase III-like activity and increases gastric emptying

B. Hormones released during feeding/digestion

Hormone	Release site(s) and stimuli	Functions
Gastrin	Upper gut (antrum and duodenum) in response to food in lumen	• Stimulates gastric acid secretion by binding CCK-2 receptors on parietal cells • Also reduces lower esophageal sphincter pressure and promotes gastric emptying
CCK	Duodenum and jejunum in response to fat and protein intake	• Reduces feeding and slows gastric emptying by signaling through CCK-1 receptors on vagal mechanoreceptive nerve terminals • Reduces feeding, slows gastric emptying, and decreases nausea and vomiting by signaling through CCK-2 receptors in the AP • Stimulates gall bladder contraction and exocrine pancreas secretion
PYY	Small intestine postprandially	• Acts as an "ileal break" by reducing food intake • Slows gastric emptying, intestinal fluid and electrolyte secretion and intestinal meal transport
GLP1	Small intestine and colon after a meal containing fat or carbohydrates	• Reduces gastric emptying and small intestine transit through vagus nerve signaling • Reduces food intake in humans and stimulates insulin release
PP	The pancreas in response to food intake in a vagal cholinergic dependent manner	• Inhibits gastric emptying, acid secretion, pancreatic exocrine function, gallbladder contraction, and food intake • Alters patterns of hypothalamic gene expression suggesting a role of PP in modulating gut function and food intake over time; distinguishes the actions of PP from those of CCK
Oxyntomodulin	The pancreas in response to food ingestion, especially the presence of fatty acids in the lumen of the intestine	• Reduces food intake, gastric emptying and gastric acid secretion; may act via the GLP1 receptor
Amylin	The pancreas in response to food; co-secreted with insulin	• Decreases hunger (anorectic effects) via the AP • Slows gastric emptying (probably via the AP) • Antagonism accelerates gastric emptying of liquids in rats

GI Gastrointestinal, *MMC* Migrating motor complex, *CCK* Cholesystokinin, *AP* Area postrema, *PYY* Peptide YY, *GLP1* Glucagon-like peptide 1, *PP* Pancreatic polypeptide

112.3.3 Gut Hormone Signaling Pathways

Hormones are released during fasting that modulate vagal activity, and, via communications between the brainstem and hypothalamic areas such as the arcuate nucleus, affect brainstem activity and the sensation of hunger (Fig. 112.1a). Released hormones contribute to the development of the MMC cycle and the gradual reestablishment of appetite. Motilin, for example, may play a role in the initiation of phase III MMC activity, and increased blood concentrations of ghrelin and orexin stimulate enteric or vagal neurons to promote the sensation of hunger and prepare the stomach for the reception of food. Gut-derived signals can be transmitted to the brain via GI vagal afferents that predominantly terminate in the brainstem at the NTS. Alternatively, gut-synthesized hormones can enter the bloodstream and alter the activity of the AP, a region without an appreciable blood–brain barrier that directly communicates with the NTS. Together, these areas communicate with the DMVN, from which vagal efferents project back to the gut. Gut-released ghrelin may also directly act on the hypothalamus to increase gastric emptying and promote feeding, but this requires its transport across the blood–brain barrier.

During eating and digestion, decreases in concentrations of hormones that stimulate the appetite and promote eating are seen. In contrast, there are increased levels of hormones that contribute to satiety and regulate the rate of food transit out of the stomach and along the intestine. The arrival of food in the lumen of the gut stimulates the release of hormones from endocrine cells of the duodenum and jejunum. These hormones modulate vagal activity and affect brainstem function either directly via the vagus or, after entering the circulation, through the AP. The net result is to reduce appetite, enhance satiety/fullness, and delay gastric emptying, and this is illustrated for cholecystokinin (CCK) (Fig. 112.1b). Other hormones including peptide YY (PYY), glucagon-like protein 1 (GLP1), pancreatic polypeptide (PP), amylin, and apolipoprotein A-IV are released from distal regions of the intestine such as the pancreas and/or endocrine cells of the intestine. These hormones regulate the speed at which food exits the stomach and transits the intestine, and they also contribute to the development of satiety. A primary mechanism to achieve satiety is a reduction in gastric emptying induced by GLP1 and CCK through both vagal stimulation and modulation of AP activity following release into the circulation.

112.4 Pathological Aspects of the Gut–Brain Axis in Dyspepsia

Both organic and FGID alter the physiologic factors regulating feeding. These may affect not only gastric motility (reflux, accommodation, mixing, and emptying), but these disorders may also influence food preference, appetite, and eating behaviors (Sanger and Lee 2008).

112.4.1 Neural Aspects

A disturbance in any portion of the feeding process results in decreased food intake, and a disrupted cephalic phase of eating (e.g. taste and food aversions) may lead to an eating disorder. It is thought that declines in the senses of taste and smell may contribute to the anorexia of aging. Although the etiology of FD remains unclear, a number of factors are postulated to play a role in the development of FD symptoms (Allescher 2006) (Table 112.5). Visceral hypersensitivity is
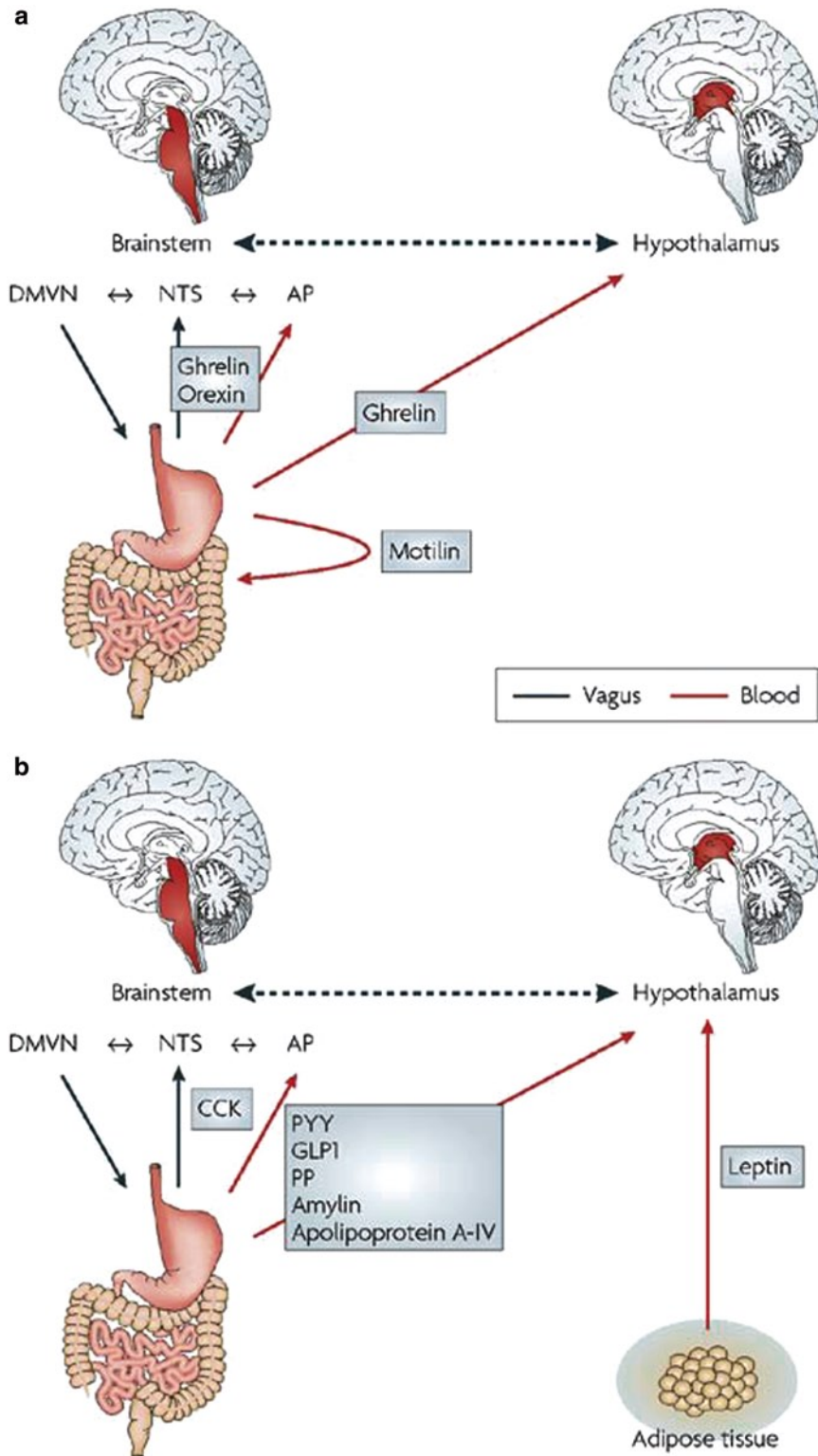
Fig. 112.1 Signal networks of gut hormones released during fasting (**a**) or during eating and digestion (**b**) (Reprinted by permission from Nature Publishing Group, Sanger and Lee 2008)

Table 112.5 Postulated mechanisms leading to the development of dyspeptic symptoms in patients with functional dyspepsia (Adapted by permission from Elsevier Limited, Allescher 2006)

- Visceral hypersensitivity
  ○ Increased perception of distention
  ○ Impaired or altered perception of acid
  ○ Visceral hypersensitivity secondary to chronic inflammation
- Motility disorders
  ○ Postprandial antral hypomotility
  ○ Reduced relaxation of the gastric fundus
  ○ Decreased or impaired gastric emptying
  ○ Changes of the gastric electric rhythm
  ○ Gastroesophageal reflux
  ○ Duodenogastric reflux
- Changes in acid secretion
  ○ Hyperacidity
- *Helicobacter pylori* infection
- Stress
- Psychological disorders and abnormalities
- Genetic predisposition

currently thought to be a key factor in causing FD through increased perception and processing of GI neural inputs (Mearin et al. 1991). In a study of experimentally induced gut distention, a majority of patients with FD developed greater discomfort than matched healthy controls. Changes in gut motility, acid secretion, and distension may all be affected by increased gut sensitivity, and this may explain many of the symptoms of FD. Patients with FD often have concomitant abnormalities in GI motility and psychiatric illness. Whether these disorders are an epiphenomenon or are related to the underlying disease remains unclear. Symptom development and exacerbation in patients with FD are often linked to stressful life events leading the patient to seek medical help at that time. Thus, patients seeking care are more likely to have active life stressors than those who do not, leading to bias in the sample population. Additionally, stress could affect intestinal function, which in connection with the observed visceral hypersensitivity, could lead to increased symptom perception.

112.4.2 Hormonal Aspects

The circulating levels of hormones related to appetite regulation are altered in dyspetic disorders. For example, plasma ghrelin levels are increased in some patients with FD, especially those with dysmotility-like FD (Suzuki et al. 2006), and elevations in the acylated form of ghrelin were significantly associated with the subjective symptom score in FD patients (Shinomiya et al. 2005). Increased ghrelin concentrations are also seen in patients with duodenal or gastric ulcers, suggesting a possible relationship with mucosal injury (Suzuki et al. 2006). Similarly, patients with dysmotility-like dyspepsia have higher serum leptin concentrations, and this was associated with the presence of gastritis and *H. pylori* infection (Lankarani et al. 2004). When considered together with our knowledge that

leptin is produced within the stomach, its ability to activate vagal nerve terminals, reduce appetite, and increase mucin secretion suggest that leptin may have a role in protecting the upper gut during states of injury (Sanger and Lee 2008).

112.5 Therapeutic Aspects of Dyspepsia

The therapies currently available for the treatment of dyspepsia, and for FD in particular, target the underlying hypothesized pathophysiology of the disease, including increased gastric acid sensitivity, delayed gastric emptying, and *H. pylori* infection. However, only a small proportion of patients experience symptom relief using these treatments (Cremonini et al. 2004). New treatment modalities targeting impaired gastric accommodation, visceral hypersensitivity, and central nervous system dysfunction are currently under development. There are several pharmacologic and nonpharmacologic approaches for the treatment of FD. Some treatments modulate established or putative physiologic disturbances, and others provide symptom relief in the absence of a well-defined pathophysiologic target (Table 112.6). Serotonergic modulators, CCK-1 antagonists, opioid agonists, *N*-methyl-d-aspartate (NMDA) receptor antagonists, neurokinin (NK) antagonists, capsaicin-like agents, ghrelin or motilin receptor agonists, and antidepressants are among the agents currently under investigation (Table 112.7).

Table 112.6 Overview of therapeutic targets and pharmacologic and nonpharmacologic treatments in functional dyspepsia (FD) (Adapted by permission from Elsevier Limited, Cremonini et al. 2004)

Targets	Agents
Acid secretion	• Proton pump inhibitors
	• H2-receptor antagonists
	• *Helicobacter pylori* eradication
Delayed emptying	• Prokinetics
Impaired accommodation	• Serotonergic agents: 5-HT1, 5-HT4 agonists
	• CCK-A antagonists
	• Opioid agonists
	• Octreotide
	• Nitrergic drugs
	• Motilin receptor agonists
	• Ghrelin receptor agonists
Visceral hypersensitivity	• Tachykinin receptor antagonists
	• Opioid receptor agonists
	• Capsaicin-like
	• NMDA receptor antagonists
	• Antidepressants (TCA and SSRIs)
Psychological factors	• Psychotherapy
	• Hypnotherapy

GI Gastrointestinal, *H2* Histamine 2, *5-HT* Serotonin, *CCK* Cholesystokinin, *NMDA* *N*-methyl-d-aspartate, *TCA* Tricyclic antidepressants, *SSRIs* Selective serotonin reuptake inhibitors

Table 112.7 Novel agents for the management of functional dyspepsia (FD). Overview of the pharmacodynamics, proposed mechanisms of action, and available clinical data (Adapted by permission from Elsevier Limited, Cremonini et al. 2004 and Nature Publishing Group, Sanger and Lee 2008)

Site of action	Agent	Pharmacodynamics	Proposed mechanisms	Clinical data	Refs
Serotonergic agents	Sumatriptan	5-HT 1 antagonist	Relaxes fundus, reduces visceral sensitivity	Failed to relieve postprandial symptoms	Boeckxstaens et al. (2002)
	Alosetron	5-HT3 antagonist	Modulates gastric accommodation, Accelerates gastric emptying, Reduces visceral sensitivity	Provided adequate relief of pain or discomfort in female patients	Talley et al. (2001a) Kuo et al. (2002)
	Tegaserod	5-HT4 partial agonist	Accelerates gastric emptying	No difference in time with symptom relief versus placebo	Cremonini et al. (2004)
CCK receptor antagonist	Dexloxiglumide	CCK-1 antagonist	Modulates gastric accommodation and duodenogastric reflexes	Reduced post-lipid infusion symptom scores during gastric distension	Feinle et al. (2001)
Opioids	Fedotozine	κ-agonist	Reduces visceral sensitivity	Reduced global dyspepsia severity and individual symptoms of pain, nausea and fullness	Read et al. (1997)
	Asimadoline	κ-agonist	Reduces visceral hypersensitivity	No patient data, reduced postprandial fullness and delayed the onset of satiety in healthy volunteers	Delgado-Aros et al. (2003)
	Alvimopan	μ-antagonist	Stimulates gastric motor function	No data in FD, relieved postoperative ileus	Taguchi et al. (2001)
NMDA modulators	Dextromethorphan	NMDA antagonist (low affinity)	Reduces visceral hypersensitivity	Reduced visceral hypersensitivity healthy volunteers	Kuiken et al. (2002)
	Ketamine Memantine	Selective NMDA antagonist	Reduces visceral sensitivity	No data in FD	
Vanilloid receptor	Capsaicin	VR1 agonist	Reduces visceral sensitivity	Reduced severity of global dyspepsia and symptoms of pain and fullness	Bortolotti et al. (2002)
Tachykininergic agents	Aprepitant	NK-1 antagonist	Provides visceral analgesia, Reduces the motor response to noxious stimuli	Approved by FDA for chemotherapy-associated nausea and vomiting	Poli-Bigelli et al. (2003) Chawla et al. (2003)
	Talnetant	NK-3 antagonist	Provides visceral analgesia	No data in FD	Giardina et al. (2003)

Target	Drug	Mechanism	Description	Notes	References
Antidepressants	Amitriptyline, Desimipramine, Mianserin, Clomipramine, Sertraline, Paroxetine	TCA and SSRIs (Blockade of serotonin transporter)	Treats comorbid psychiatric conditions, Provides visceral analgesia, Modulates gastric motor functions	Amitriptyline reduced symptoms in FD Sertraline failed to alter perception thresholds in healthy volunteers	Mertz et al. (1998)
Motilin receptor	Mitemcinal (GM-611)	Motilin receptor agonist	• Stimulates motility similar to phase III of the MMC • Increases gastric emptying of a meal over a sustained period of time	• Phase II • Reported to improve symptoms in patients with diabetic gastroparesis, compared with placebo	McCallum and Cynshi (2007)
	PF-045480434 (KOS-2187)	Motilin receptor agonist		• Preclinical • Effective as a gastric prokinetic in dogs	Peeters (2006)
	ABT-229	Motilin receptor agonist		• Trial terminated • Failed to improve symptoms in patients with FD or with type 1 diabetes mellitus • These data argue against the use of such drugs in the treatment of these disorders or alternatively, given the potential worsening of symptoms in these trials, questions the selectivity of action of this compound and the doses used; ABT-229 is, for example, reported to be effective in rats, a species in which a functional motilin receptor is not thought to exist, and, despite having a 20-h plasma half-life, ABT-229 was given twice daily	Talley et al. (2000) Talley et al. (2001b) Tack and Peeters (2001)
Ghrelin receptor	TZP-101	Ghrelin receptor agonist	• Stimulates motility and acid secretion • Increases energy intake and meal appreciation • A defensive role in the upper gut	• Phase II • Pilot study showing symptom improvement in diabetic gastroparesis after intravenous administration	Ejskjaer et al. (2009)

GI Gastrointestinal, H2 Histamine 2, 5-HT Serotonin, CCK Cholecystokinin, NMDA N-methyl-d-aspartate, TCA Tricyclic antidepressants, SSRIs Selective serotonin reuptake inhibitors, FD Functional dyspepsia, VR1 Vanilloid receptor-1, NK Neurokinin, FDA Food and Drug Administration, TCA Tricyclic antidepressants, SSRIs Selective serotonin reuptake inhibitors, MMC Migrating motor complex

Summary Points

- Dyspepsia is defined by the Rome III criteria and requires the presence of one or more of the following symptoms: postprandial fullness, early satiety, and epigastric burning or epigastric pain.
- Dyspepsia is associated with a variety of organic and functional disorders. However, a majority of patients with dyspeptic symptoms have no identifiable causes of their symptoms on routine exam and are classified as functional dyspepsia (FD).
- The gut and the brain are highly integrated and communicate in a bidirectional fashion largely through the nervous and endocrine systems.
- The vagus nerve plays an essential role in the regulation of normal physiologic responses in the gut.
- Numerous hormones are secreted by the gut and adipose tissues during feeding, digestion, or fasting that can profoundly affect gut functions. Hormones can directly affect gut secretory functions, or they may act through the enteric and vagal neurons and the area postrema (AP).
- A disturbance at any point in the feeding process results in a decline in food intake. Although the etiology of FD is still unclear, several factors and mechanisms are hypothesized to cause this disorder including visceral hypersensitivity, abnormalities in GI motility, stress, and underlying psychiatric disorders.
- Hormone concentrations in the circulation are altered in patients with dyspeptic disorders. Currently available treatments for dyspepsia, particularly FD, are based on putative underlying pathophysiologic mechanisms, including gastric acid sensitivity, slow gastric emptying, and *H. pylori* infection.
- Serotonergic modulators, CCK-1 antagonists, opioid agonists, NMDA receptor antagonists, NK antagonists, capsaicin-like agents, ghrelin or motilin receptor agonists, and antidepressants are among the agents currently under investigation for the treatment of FD.

Definitions, Key Terms and Words

Dyspepsia: A medical condition characterized by chronic or recurrent pain in the upper abdomen, upper abdominal fullness, and feeling full earlier than expected when eating.

Postprandial: After eating a meal.

Satiety: The satisfied feeling of being full after eating.

Epigastric: Of or relating to the upper central region of the abdomen.

Vagus nerve: The tenth cranial nerve, which originates in the medulla oblongata, a part of the brain stem, and wanders all the way down from the brainstem to the colon

Armamentarium: The total therapeutic assets of a physician or medical facility, including medicines and equipment.

References

Allescher HD. Phytomedicine 2006;13(Suppl 5):2–11.
Andrews PL, Sanger GJ. Curr Opin Pharmacol. 2002;2:650–6.
Banks WA. Physiol Behav. 2006;89:472–6.
Boeckxstaens GE, Hirsch DP, Kuiken SD, Heisterkamp SH, Tytgat GN. Am J Gastroenterol. 2002;97:40–8.
Bortolotti M, Coccia G, Grossi G, Miglioli M. Aliment Pharmacol Ther. 2002;16:1075–82.
Bray GA. Proc Nutr Soc. 2000;59:373–84.

Chawla SP, Grunberg SM, Gralla RJ, Hesketh PJ, Rittenberg C, Elmer ME, Schmidt C, Taylor A, Carides AD, Evans JK, Horgan KJ. Cancer 2003;97:2290–300.

Cremonini F, Delgado-Aros S, Talley NJ. Best Pract Res Clin Gastroenterol. 2004;18:717–33.

Date Y, Murakami N, Toshinai K, Matsukura S, Niijima A, Matsuo H, Kangawa K, Nakazato M. Gastroenterology 2002;123:1120–8.

Delgado-Aros S, Chial HJ, Camilleri M, Szarka LA, Weber FT, Jacob J, Ferber I, McKinzie S, Burton DD, Zinsmeister AR. Am J Physiol Gastrointest Liver Physiol. 2003;284:G558–66.

Drossman DA. Gastroenterology 2006;130:1377–90.

Ejskjaer N, Vestergaard ET, Hellstrom PM, Gormsen LC, Madsbad S, Madsen JL, Jensen TA, Pezzullo JC, Christiansen JS, Shaughnessy L, Kosutic G. Aliment Pharmacol Ther. 2009.

Feinle C, Meier O, Otto B, D'Amato M, Fried M. Gut 2001;48:347–55.

Giardina GA, Gagliardi S, Martinelli M. IDrugs 2003;6:758–72.

Husebye E. Neurogastroenterol Motil. 1999;11:141–61.

Jones MP, Dilley JB, Drossman D, Crowell MD. Neurogastroenterol Motil. 2006;18:91–103.

Kuiken SD, Lei A, Tytgat GN, Holman R, Boeckxstaens GE. Aliment Pharmacol Ther. 2002;16:1955–62.

Kuo B, Camilleri M, Burton D, Viramontes B, McKinzie S, Thomforde G, O'Connor MK, Brinkmann BH. Aliment Pharmacol Ther. 2002;16:225–33.

Lankarani KB, Moghadami M, Masoumpoor M, Geramizadeh B, Omrani GR. Dig Liver Dis. 2004;36:717–21.

Masuda Y, Tanaka T, Inomata N, Ohnuma N, Tanaka S, Itoh Z, Hosoda H, Kojima M, Kangawa K. Biochem Biophys Res Commun. 2000;276:905–8.

McCallum RW, Cynshi O. Aliment Pharmacol Ther. 2007;26:107–16.

Mearin F, Cucala M, Azpiroz F, Malagelada JR. Gastroenterology 1991;101:999–1006.

Mertz H, Fass R, Kodner A, Yan-Go F, Fullerton S, Mayer EA. Am J Gastroenterol. 1998;93:160–5.

Peeters TL. Neurogastroenterol Motil. 2006;18:1–5.

Poli-Bigelli S, Rodrigues-Pereira J, Carides AD, Julie Ma G, Eldridge K, Hipple A, Evans JK, Horgan KJ, Lawson F. Cancer 2003;97:3090–8.

Powley TL, Chi MM, Schier LA, Phillips RJ. Physiol Behav. 2005;86:698–708.

Read NW, Abitbol JL, Bardhan KD, Whorwell PJ, Fraitag B. Gut 1997;41:664–8.

Sanger GJ, Lee K. Nat Rev Drug Discov. 2008;7:241–54.

Shinomiya T, Fukunaga M, Akamizu T, Irako T, Yokode M, Kangawa K, Nakai Y. Scand J Gastroenterol. 2005;40:648–53.

Suzuki H, Nishizawa T, Hibi T. J Gastroenterol. 2006;41:513–23.

Tack J, Peeters T. Gut 2001;49:317–8.

Tack J, Talley NJ, Camilleri M, Holtmann G, Hu P, Malagelada JR, Stanghellini V. Gastroenterology 2006;130:1466–79.

Taguchi A, Sharma N, Saleem RM, Sessler DI, Carpenter RL, Seyedsadr M, Kurz A. N Engl J Med. 2001;345:935–40.

Takahashi T, Owyang C. J Physiol. 1997;504(Pt 2):479–88.

Talley NJ, Verlinden M, Snape W, Beker JA, Ducrotte P, Dettmer A, Brinkhoff H, Eaker E, Ohning G, Miner PB, Mathias JR, Fumagalli I, Staessen D, Mack RJ. Aliment Pharmacol Ther. 2000;14:1653–61.

Talley NJ, Van Zanten SV, Saez LR, Dukes G, Perschy T, Heath M, Kleoudis C, Mangel AW. Aliment Pharmacol Ther. 2001a;15:525–37.

Talley NJ, Verlinden M, Geenen DJ, Hogan RB, Riff D, McCallum RW, Mack RJ. Gut 2001b;49:395–401.

Talley NJ, Ruff K, Jiang X, Jung HK. Dig Dis. 2008;26:203–9.

Zafra MA, Molina F, Puerto A. Neurosci Biobehav Rev. 2006;30:1032–44.

Chapter 113
Overnutrition in Mothers and Appetite Regulators in Offspring

Hui Chen and Margaret J. Morris

Abbreviations

AgRP	Agouti-related protein
ARH	Arcuate nucleus
CART	Cocaine- and amphetamine-regulated transcript
G	Gestational day
HFD	High fat diet
MC3/4R	Melanocortin 3/4 receptor
MSH	Melanocyte-stimulating hormone
mTOR	Mammalian target of rapamycin
NPY	Neuropeptide Y
Ob-Rb	Long form of the leptin receptor
P	Postnatal day
POMC	Proopiomelanocortin
PVH	Paraventricular nucleus of the hypothalamus
SOCS	Suppressor of cytokine signalling
STAT	Signal transducer and activator of transcription

113.1 Introduction

The World Health Organization formally recognized the obesity epidemic in 1997; however, as obesity continues to rise exponentially, it has now reached pandemic proportions. Increasingly around the world, obesity is no longer restricted to adults. Childhood obesity is currently rising, with 20 million children under five estimated as overweight in 2005 (WHO 2006). In the USA, the number of overweight children has doubled and the number of overweight adolescents has tripled since 1980. It is increasingly accepted that obesity results from a combination of genetic and environmental factors. This chapter reviews recent experimental work in rodents and nonhuman primates that investigate the impact of maternal obesity and early postnatal overfeeding on hypothalamic appetite circuits and appetite control (Table 113.1).

M.J. Morris (✉)
Department of Pharmacology, School of Medical Sciences, University of New South Wales,
Sydney, NSW 2052, Australia
e-mail: m.morris@unsw.edu.au

Table 113.1 Key points of maternal obesity

As the obesity epidemic widens, maternal obesity is becoming a greater threat to the long-term health of offspring. Nutritional changes in utero are known to impact on subsequent disease risk, a process known as programming- Animal studies demonstrate that the hypothalamic circuits important in appetite control develop around the time of birth, and are influenced by the level of maternal obesity, as well as circulating levels of leptin, insulin and lipids. Thus the circuits are said to be 'plastic'

Offspring of obese mothers show increased adiposity and increased food intake, and often these changes persist in the long term. Alterations in hypothalamic appetite regulators are observed. Animal studies are important to provide information regarding the underlying mechanisms, as such, research is difficult to carry out in humans and the neural circuits involved in energy homeostasis are well preserved across mammalian species

Key information regarding the influence of maternal obesity on appetite control and risk of obesity

113.2 Impact of Maternal Nutrition on the Risk of Metabolic Disorders in Offspring

Overconsumption of energy-rich food and a sedentary lifestyle make significant contributions to the rising rate of childhood obesity. However, apart from the social and environmental factors that influence children's behaviour (Nielson et al. 2006), the prenatal maternal condition is also critical to offspring body composition, and can predispose the foetus to the development of obesity after birth. Increasing evidence suggests that both maternal phenotype and nutritional state during gestation, as well as nutrition during the lactation period, are important in promoting obesity in offspring. Human studies suggest that intrauterine factors may be more important than genetic factors in determining the individual changes in gene expression in response to consumption of a high-fat diet (HFD) (Tremblay and Hamet 2008). Thus intrauterine factors may have a longstanding influence.

Early research revealed an inverse relationship between low birth weight due to gestational malnutrition and the increased risks of obesity and cardiovascular disease (Fall et al. 1995; Painter et al. 2005). Barker first proposed the 'foetal origins' hypothesis in 1990, which posits that adverse environmental factors early in life cause disruption of normal growth and development, leading to a more susceptible adult phenotype prone to metabolic disorders, such as cardiovascular disease (Barker 1990).

However, under the current obesity pandemic, maternal overnutrition during gestation arguably has become a more prominent modulating force in foetal development. The observation of a 'U-shaped' relationship between birth weight and later obesity (Curhan et al. 1996) with increased risk in those who are born small and large for gestational age, means that we must now consider the potential detrimental impact of maternal overnutrition/obesity and increased birth weight on the risk of disease in childhood and in adulthood. A range of experimental approaches have been used, exploring overnutrition during different developmental windows, from maternal overnutrition prior to and/or during gestation, during lactation, and early in postnatal life.

Maternal obesity and hyperglycemia during pregnancy can lead to high birth weight, increased circulating insulin, glucose, free fatty acids and triglycerides, and glucose intolerance, as well as obesity in offspring (Armitage et al. 2005; Boney et al. 2005; Franke et al. 2005; Chen et al. 2009; Elahi et al. 2009). Offspring of obese mothers are at higher risk of becoming obese and developing insulin resistance and cardiovascular disease later in life, as evidenced in both human and animal studies (Plagemann et al. 1992; Samuelsson et al. 2007; Elahi et al. 2009).

A simple increase in body weight gain during pregnancy and lactation due to hyperphagia induced by pharmacological inhibition of melanocortin 3/4 receptors (MC3/4R) leads to the development of obesity in offspring over time (Heinsbroek and van Dijk 2009). Animal work suggests that overnutrition either starting prior to gestation, or during both gestation and lactation, exert similar effects on

Table 113.2 Parameters in P20 rat offspring of lean and obese rat dams

Offspring from	BW (g)	Fat mass (g)	TG (mM)	Glucose (mM)	Insulin (ng/ml)	AUC
Lean dams	33.1 ± 0.3	102.7 ± 6.2	0.74 ± 0.07	7.90 ± 0.29	0.22 ± 0.04	0.47 ± 0.09
Obese dams	47.4 ± 1.4*	136.5 ± 7.3	1.55 ± 0.18*	9.49 ± 0.34*	0.51 ± 0.06*	0.25 ± 0.04*

Body weight (BW), fat mass, circulating triglyceride (TG), glucose, and iusnilin, as well as area under the curve AUC of glucose tolerance test in offspring from lean or obese dams (*$P < 0.05$). Dams were fed for 6 weeks prior to mating (data based on Chen et al. 2008).
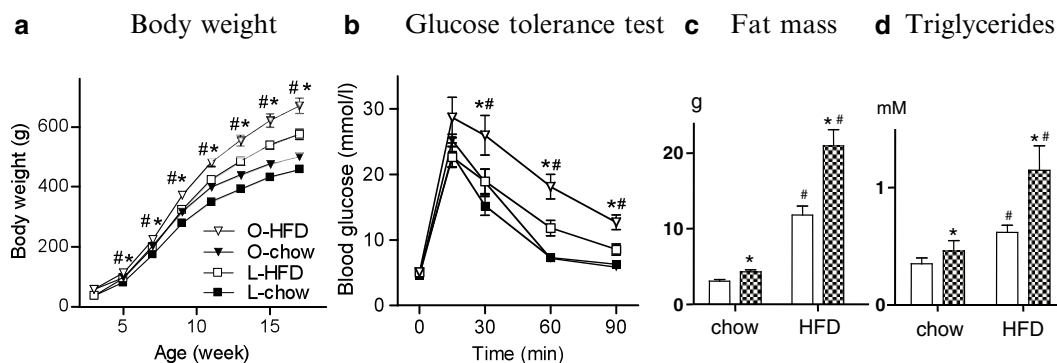
Fig. 113.1 Parameters in chow and high-fat diet (*HFD*)-fed 18 week old rats from lean and obese mothers. (**a**) Body weight trajectory, (**b**) glucose tolerance test, (**c**) white fat mass, (**d**) plasma triglyceride levels in chow and HFD-fed 18 week old rats from lean (*open bars*) and obese (*checked bars*) mothers. *, #, $P < 0.05$ maternal and post-weaning diet effects, respectively. L-chow: pups from lean mothers on chow diet; L-HFD: pups from lean mothers on high fat diet; O-chow: pups from obese mothers on chow diet; O-HFD: pups from obese mothers on high-fat diet (Modified from Chen et al. 2009)

the development of obesity and hyperinsulinemia in offspring (Howie et al. 2009). Offspring from rat dams who have established obesity induced by HFD consumption prior to gestation developed adiposity and impaired glucose and lipid metabolism as early as postnatal day (P) 20 (Table 113.2) (Bayol et al. 2007, 2008; Chen et al. 2008), and these were maintained until adulthood (Fig. 113.1) (Chen et al. 2009; White et al. 2009). Overnutrition during the suckling period can also cause an obese phenotype, even in genetically obesity-resistant rats (Gorski et al. 2006). When these obesity-resistant rats were cross-fostered by obese dams with rich milk, they went on to develop obesity when challenged by HFD after weaning (Gorski et al. 2006). Increased milk availability through litter size reduction also leads to an obese phenotype in the rat (Velkoska et al. 2005; Chen et al. 2008). Rats over-fed during the suckling period displayed persistence of overweight and hyperphagia throughout their lifespan (Bassett and Craig 1988; Plagemann et al. 1992). Furthermore, overfeeding during the suckling period showed additive effects with maternal obesity, with the combination promoting more severe adiposity and glucose intolerance at weaning (Chen et al. 2008). Thus, both maternal obesity and early postnatal overfeeding can promote an obese phenotype in offspring.

Effects of maternal overnutrition on diet preference in offspring have also been observed. Maternal consumption of a typical western 'junk food' diet, such as biscuits, chocolate, muffins, potato crisps, and sweets, in pregnancy and lactation promoted an exacerbated preference for these 'junk foods' in offspring in adulthood (Bayol et al. 2007). Maternal overnutrition has also been shown to induce greater hyperphagia and increased feeding efficiency when offspring were challenged by HFD consumption; offspring of obese dams had more severe weight gain and adiposity, as well as insulin resistance in adulthood (Chen et al. 2009; Nivoit et al. 2009).

113.3 Development of Energy Homeostasis Circuitry in the Hypothalamus

Appetite is regulated by a complex and redundant but highly reliable network. The central neural pathways involved in appetite regulation and energy metabolism are well conserved across species. The hypothalamus plays a key role in energy homeostasis. The most commonly studied circuit involves two groups of neurons concentrated in the arcuate nucleus (ARH) located in the ventral part of the hypothalamus, one expressing the appetite stimulators, neuropeptide Y (NPY) and agouti-related protein (AgRP), and the other expressing the appetite suppressors α-melanocyte stimulating hormone (αMSH) derived from proopiomelanocortin (POMC) and cocaine- and amphetamine-regulated transcript (CART), which interact with each other to match caloric intake to energy expenditure. These NPY/AgRP and POMC/CART expressing neurons project to the paraventricular nucleus (PVH) and other hypothalamic areas to exert their effects (Morton et al. 2006).

NPY is the most robust appetite stimulator, produced predominantly in the ARH. Physiologically, hypothalamic NPY concentrations are elevated before a meal to stimulate appetite, and continuous or repeated central administration of NPY leads readily to obesity. Activation of the Y1 receptor (major NPY orexigenic receptor) can increase food intake even when NPY expression is inhibited (Shintani et al. 2001). POMC derived αMSH counteracts NPY to inhibit feeding and promote negative energy balance (Morton et al. 2006). Leptin, an adipose-derived hormone, can directly access the hypothalamic ARH, to suppress NPY/AgRP and activate POMC/CART expression to inhibit feeding and increase energy expenditure via the long form of the leptin receptor (Ob-Rb). Leptin resistance is commonly observed in dietary obesity (Levin et al. 2004). The hypothalamic NPY/AgRP and POMC/CART expressing neurons are plastic, being modified by chronic overconsumption of HFD, associated with the development of metabolic disorders, such as adiposity, hyperlipidemia, hyperinsulinemia, and glucose intolerance.

In the rat, differentiation of the neuronal systems regulating energy homeostasis begins during gestation, and continues until weaning (Grove et al. 2005). In adults, the adipose hormone leptin signals fat stores; however, in rodents between P4 to 16, there is a marked increase in circulating leptin levels, which is called the '*leptin surge*' (Fig. 113.2). Leptin reaches peak levels at P9 to 10. Increased leptin is necessary to support the development and maturation of these brain neurons
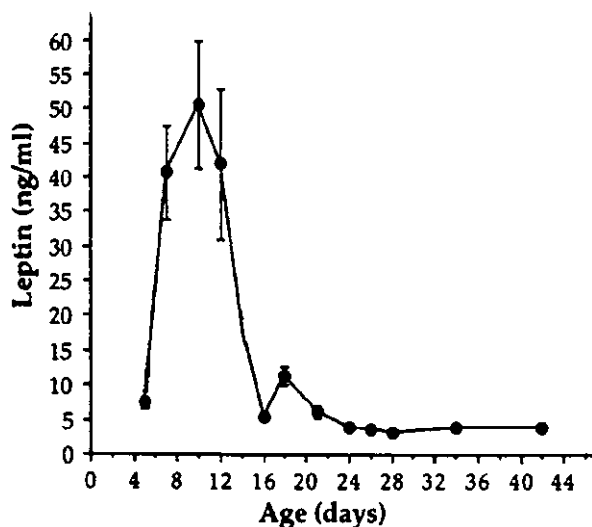
Fig. 113.2 Postnatal leptin surge in mice. Leptin surge in female C57BL/6J mice from P4 to P42 (Modified from Ahima et al. 1998. With permission)

involved in the regulation of appetite and energy metabolism (Ahima et al. 1998). The role of leptin in neural development in neonatal rodents was shown to be independent of its role in energy homeostasis, given that exogenous leptin does not reduce body weight, milk intake, or metabolic rate during the first two postnatal weeks (Ahima et al. 1998; Mistry et al. 1999; Pinto et al. 2004).

Both leptin deficiency and an abnormally high leptin surge can alter neural development, thus affecting feeding and energy metabolism, contributing to obesity (Pinto et al. 2004; Yura et al. 2005; Bouret et al. 2006; Kirk et al. 2009). The lack of *ob* gene results in leptin deficiency in *ob/ob* mice, whereas higher levels are present in mice with restricted intrauterine nutrition. Leptin deficiency in *ob/ob* mice results in a lower hypothalamic neuron density, which is thought to contribute to the obese phenotype (Bouret et al. 2004; Pinto et al. 2004). The high leptin surge due to restricted intrauterine nutrition has been shown to be linked to an increased density of hypothalamic neurons (e.g. NPY) involved in feeding and energy metabolism, leading to increased weight gain and adiposity when mice were fed a HFD after weaning (Yura et al. 2005). Thus, any abnormality in the leptin surge will likely disturb energy homeostasis.

The ontogeny of the NPY and POMC system has been most extensively studied in rodents and nonhuman primates by Grove and colleagues (Grove et al. 2003, Grove and Smith 2003). There are significant differences between rodents and the nonhuman primate. In the rat, differentiation of the neuronal systems that regulate appetite and energy expenditure begins during the last week of gestation, with development continuing until weaning (Grove et al. 2005). Therefore, in rodents, projections of ARH NPY- and POMC-expressing neurons throughout the hypothalamus do not fully mature until the second and third postnatal weeks; whereas in nonhuman primates and humans, these neural projections are fully developed at birth (Grove et al. 2003, Grove and Smith 2003). Initial studies demonstrated that NPY was not only abundantly expressed in the ARH, but transient expression of NPY was also observed in other hypothalamic regions, including the dorsomedial hypothalamic nucleus, PVH, lateral hypothalamus, and the perifornical region, where NPY is not evident in adulthood (Singer et al. 2000). NPY levels in all areas were low at P2, increased rapidly to peak at P15–16 and returned to levels observed in adulthood in the ARH, while in the other areas NPY was no longer apparent after P30 (Singer et al. 2000; Grove et al. 2003, Grove and Smith 2003). This process is more complete at birth in humans and primates. In nonhuman primates, NPY mRNA was expressed in the ARH, PVH, and dorsomedial nucleus of the hypothalamus as early as gestational day (G) 100 (Grayson et al. 2006). ARH NPY/AgRP projections to the PVH were initiated by G100, but were limited and variable. However, by G130 there was a modest increase in density and number of NPY-expressing neurons (Grayson et al. 2006). By G170, ARH NPY/AgRP fibre projections to efferent target sites were completely developed, but the density continued to increase in the postnatal period, a feature similar to the rodent (Grove and Smith 2003; Grayson et al. 2006). There were minimal αMSH fibres at G100 and G130, but they were moderate at G170.

113.4   Impact of Maternal Nutrition on Neural Development

The brain is clearly affected by the nutrition state during gestation, which may have a role in producing the long-term behavioural and physiological changes observed in offspring after weaning, including an increase in food intake, preference for fat, hyperlipidemia, and greater body weight. The use of animal models can provide a fundamental understanding of the developmental aspects of these neural circuits, while modelling maternal obesity in rodents and other species is needed to explore the programming mechanisms at play in utero and during the suckling period. As discussed above, projections from the ARH of the hypothalamus play a key role in regulating energy balance (Elmquist

et al. 2005) and changes in their development is thought to be involved the programming associated with variations in maternal nutrition.

As elucidated below, several studies have shown that exposure of pregnant rat dams to a HFD results in changes in hypothalamic neuronal development and gene expression of hypothalamic neuropeptides regulating energy balance in the offspring, even though the birth weight was not different in offspring of obese and lean mothers (Chen et al. 2008; Morris and Chen 2009). Thus, modifications to the hypothalamic circuitry may be a fundamental mechanism underlying the increased risk of obesity induced by overnutrition during critical windows of early development. Most work to date has examined gene expression or protein levels, and more work is needed to examine transmitter release and synaptic density.

113.4.1 *Impact of Maternal Obesity on Intra Uterine Neural Development*

In rats, maternal HFD-feeding from G6 increased hypothalamic proliferation of different orexigenic peptide-expressing neurons, changes that were evident at birth (Chang et al. 2008). Programming of foetal neural development due to maternal overnutrition with HFD occurred within days of overfeeding, as more active neurogenesis was evident from G11 to 15 (Chang et al. 2008). Proliferation of neuroepithelial and neuronal precursor cells of the embryonic hypothalamic third ventricle was evident in offspring of HFD-fed rat dams. Maternal HFD-feeding also increased the number of neurons expressing orexigenic peptides in offspring (Chang et al. 2008). Importantly at P15, the changes in hypothalamic peptides remained in those offspring of HFD-fed obese dams that were suckled by dams consuming control diet, suggesting prenatal exposure to HFD had persisting effects on hypothalamic peptide expression. Site-specific effects were observed, as increased expression of the orexigenic peptides, galanin, enkephalin, and dynorphin were seen in the PVH, and orexin and melanin-concentrating hormone in the perifornical lateral hypothalamus. However, the ARH expression of these genes, including AgRP, was downregulated in offspring from HFD-fed obese dams (Chang et al. 2008). Established maternal obesity that predated conception was also associated with reduced AgRP staining in the PVN of offspring as compared to offspring from control dams (Kirk et al. 2009).

Experiments using genetically obese prone rats suggested that genetic background has an important influence on the ability to form ARH projections. However, some hypothalamic neurons involved in energy homeostasis were permanently disrupted by maternal HFD consumption, particularly those involving αMSH (Bouret et al. 2008).

In term, foetus of HFD-fed obese rat mothers, plasma leptin levels were higher than those in offspring of lean dams (Gupta et al. 2009). However, at P1, without the support of foetal-placental circulation, blood leptin levels were reduced in offspring from obese rat dams, relative to those from lean dams (Morris and Chen 2009). Interestingly, the hypothalamic mRNA expression of most of the appetite regulators, NPY, AgRP, POMC, MC4R, and Ob-Rb were increased in the foetus of obese dams whereas the protein level of the downstream target of leptin, signal transducer and activator of transcription (STAT)3 was reduced (Gupta et al. 2009). However, at P1, we observed lower hypothalamic NPY, MC4R, POMC, mTOR mRNA expression in offspring from obese rat mothers (Morris and Chen 2009). Furthermore, mRNA expression of Ob-Rb, STAT3, and the inhibitor of STAT3, suppressor of cytokine signalling (SOCS)3 in the hypothalamus was also downregulated by maternal obesity (Morris and Chen 2009). The difference in mRNA expression between term foetus and newborn could be due to differences in circulating leptin levels. While different observations between laboratories may relate to strain differences, type of diet used and the extent of maternal obesity, alterations in maternal nutrition appear to permanently affect the hypothalamic processes that regulate food intake.

Several hypotheses have been advanced to explain the alterations in hypothalamic circuitry in response to maternal obesity. Chief among these are changes in circulating hormones such as leptin and insulin (Gorski et al. 2007; Chen et al. 2009). Chang et al. (2008) reported that increased neurogenesis and neurite growth in offspring of HFD-fed dams was closely associated with increased blood lipids, and these authors suggest that lipids may contribute to altered neurogenesis. We (Chen et al. 2008) and others (Srinivasan et al. 2006) have also reported increased triglycerides in offspring of obese dams. A study in nonhuman primates demonstrated that even if mothers did not develop obesity, the developing foetus is highly vulnerable to excess lipids; exposure led to increased liver triglycerides, increased markers of oxidative stress and premature gluconeogenic gene expression, promoting nonalcoholic fatty liver disease (McCurdy et al. 2009).

113.4.2 Impact of Maternal Obesity on Early Postnatal Development

At P9, leptin levels were observed to be 6 times higher in offspring from obese rat dams with greater fat mass compared with those from lean mothers (Fig. 113.3, H. Chen and M. J. Morris unpublished data). Maternal milk offers an important source of leptin and milk leptin level was shown to be higher in HFD-fed rat dams (White et al. 2009). However, the higher leptin levels in offspring from obese mothers were correlated with their fat mass (Fig. 113.3), suggesting that plasma leptin levels may be independent of milk leptin levels. Nevertheless, milk leptin has been suggested to protect the infant against several chronic diseases later in life, and particularly against obesity and related medical complications (Pico et al. 2007; Palou and Pico 2009). Oral leptin supplementation in rats during lactation was shown to improve leptin and insulin sensitivity at adulthood by increasing the hypothalamic leptin receptor, Ob-Rb, and reducing the inhibitory signal SOCS-3 (Vickers et al. 2005; Pico et al. 2007; Sanchez et al. 2008; Palou et al. 2009). Although leptin injection during the prenatal period has been shown to reverse the risk of obesity and its related metabolic disorders in rats subjected to intrauterine undernutrition (Vickers et al. 2008), to our knowledge such an approach has not yet been carried out in animals undergoing intrauterine overnutrition.

Nevertheless, leptin resistance may already exist in neonatal offspring from obese mothers as reflected by a 24% reduction of phosphorylated-STAT3 immunoreactive cell numbers upon leptin injection at P10 (Fig. 113.4) (Bouret et al. 2008), suggesting leptin signalling in hypothalamic neurons is impaired during postnatal development in offspring of obese rats. The trophic action of leptin on ARH neurons is also reduced in neonates from obese dams, reflected by reduced neurite growth after 36h in vitro incubation with leptin (Bouret et al. 2008).

By P12, ARH projections to the PVH appeared fully developed in the offspring of lean dams. In rats from obese dams, there were two to four times fewer labelled fibres compared with lean offspring at this time (Fig. 113.5). Reduced fibre densities in the PVH were still evident at P16 in offspring of

Fig. 113.3 Plasma leptin and fat mass at P9. Plasma leptin concentrations and retroperitoneal white fat mass in 9-day-old pups from lean (*open bar*) and obese (*checked bar*) mothers. (*, $P < 0.05$ maternal effect, H. Chen and M. J. Morris unpublished)
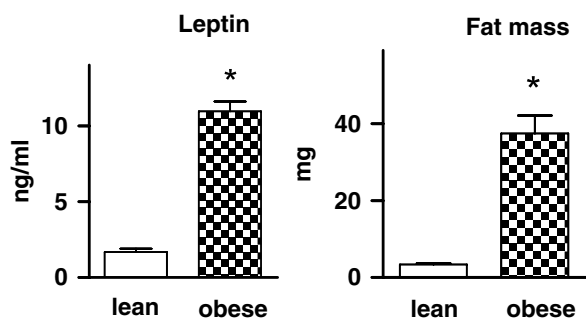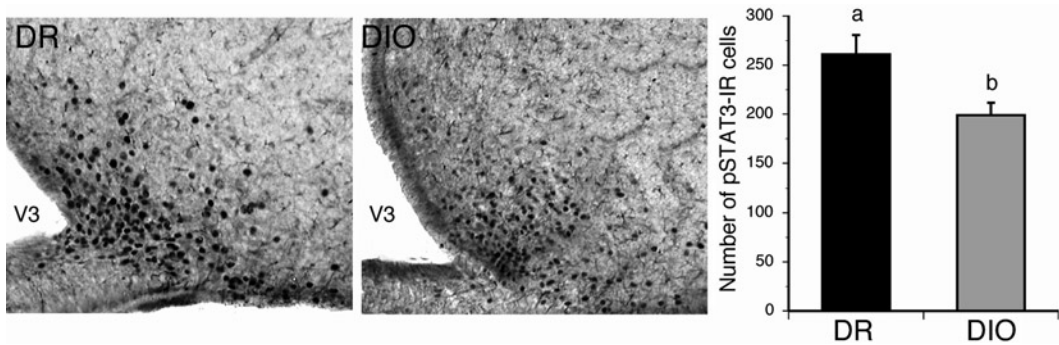
Fig. 113.4 Response of arcuate nucleus (*ARH*) neurons to leptin in lean and obese mothers. Leptin-induced phospho-STAT3 immunoreactivity in the ARH of pups from lean and obese mothers on P10. Neonates from obese mothers show a 24% reduction in the number of phospho-STAT3 cells in the ARH following leptin administration as compared to pups from lean mothers. *DIO* diet-induced obese, *DR* diet-resistant, *V3* third ventricle (Reprinted from Bouret et al. 2008. With permission)
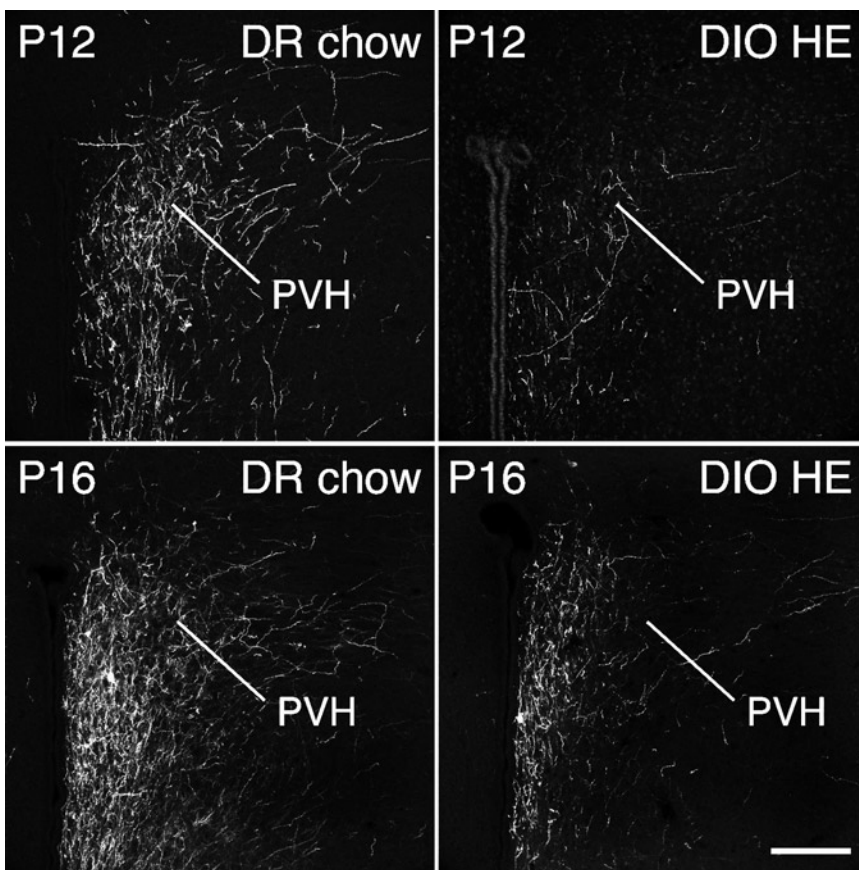
Fig. 113.5 Neural projections from the arcuate nucleus (*ARH*) to paraventricular nucleus (*PVH*) in offspring of lean or diet-induced obese dams. Dams were fed chow or high-energy (*HE*) diet throughout pregnancy and lactation. Maternal obesity permanently disrupted the projections from ARH to PVH in rat offspring at P12 (*upper panels*) and P16 (*lower panels*). *DIO* diet-induced obese, *DR* diet-resistant (Reprinted from Bouret et al. 2008. With permission)

obese versus lean dams (Bouret et al. 2008; Kirk et al. 2009) (Fig. 113.5). Thus AgRP/NPY neuron density and innervation are likely influenced in adulthood, while no effect on projections of α-MSH expressing neurons was observed (Bouret et al. 2008; Kirk et al. 2009).

Normal or increased ARH Ob-Rb expression has been observed in juvenile offspring from obese dams (Gorski et al. 2007; Chen et al. 2008); hypothalamic STAT3 mRNA expression was also observed to be upregulated by maternal obesity (Chen et al. 2008). However, both increased leptin sensitivity (Gorski et al. 2007) and leptin resistance has been reported in young offspring from obese mothers (Ferezou-Viala et al. 2007), assessed by the alteration of hypothalamic phosphorylated-STAT3 in response to leptin injection. A recent report describes resistance to the anorexigenic effects of leptin administration in offspring of obese mothers at as early as 30 days of life (Kirk et al. 2009). Also, offspring of obese dams had elevated hypothalamic MC4R, NPY Y1 and Y5 receptor mRNA expression (Gorski et al. 2007).

At P20 (normal weaning age) under a free feeding state, offspring from obese rat mothers had reduced NPY and increased POMC mRNA expression in the hypothalamus, in the face of reciprocally altered hypothalamic NPY Y1 receptor and MC4R mRNA expression (Chen et al. 2008). However, hunger is the major drive for ingestive behaviour. After overnight (14 h) fasting, in rat offspring from obese mothers, the reduced hypothalamic NPY and AgRP mRNA expression was returned to similar levels as those in rats from lean mothers (Chen and Morris 2009). The already higher NPY Y1 receptor expression in the free feeding state was further increased after overnight fasting (Chen and Morris 2009). Changes in NPY receptor may also underlie the exaggerated feeding response to NPY injection into the lateral brain ventricle in offspring from HFD-fed dams (Kozak et al. 2000). Although POMC mRNA expression was not altered by fasting, the downregulation of MC4R and its downstream mediator Sim1 was absent in rats from obese mothers. We propose that this could directly lead to increased milk consumption during the sucking period, as well as a higher daily energy intake immediately after weaning (Chen and Morris 2009). Furthermore, this could also contribute to an exacerbated preference for 'junk food' in offspring following maternal consumption of a 'junk food' diet in pregnancy and lactation (Bayol et al. 2007), although further work would be necessary to test this.

Maternal obesity has been shown to cause reductions in hypothalamic glucose sensor mammalian target of rapamycin (mTOR) and glucose transporter 4 expression in offspring at P20. As a result, after overnight fasting, hypothalamic NPY signalling in pups from obese dams was more active than that of those from lean dams (Chen and Morris 2009). This was accompanied by increased milk intake during the suckling period and energy intake immediately after weaning (Chen and Morris 2009), which could directly contribute to greater body weight, circulating triglycerides, glucose, and insulin levels in these animals both at weaning (Chen et al. 2008) and later on in adulthood (Chen et al. 2009). Therefore, we hypothesize that activation of hypothalamic mTOR may be a useful strategy to reduce the adiposity and glucose tolerance in offspring from obese mothers, especially when they consume a HFD. A summary of some of the changes induced by maternal obesity is presented in Fig. 113.6.

113.4.3 Early Postnatal Overnutrition

The early postnatal period is also a 'critical period' of development. A number of studies have demonstrated that environmental influences during the early postnatal period in humans (Fall et al. 1995) and rodents (Velkoska et al. 2005; Chen et al. 2008) can also influence body weight and energy homeostasis in adulthood.

Rodents overfed during the postnatal period induced by reducing litter size, show increased early weight gain and fat deposition, hyperleptinemia, hyperinsulinemia (Plagemann et al. 1999b), and central leptin resistance at the hypothalamic ARH (Schmidt et al. 2001). Although NPY concentration
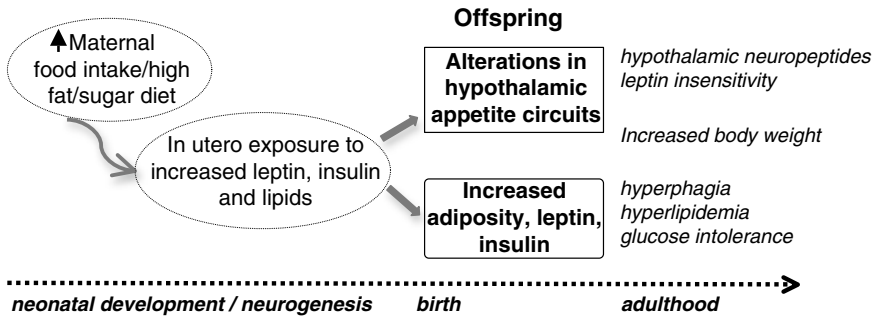
Fig. 113.6 Schematic model of effects of maternal obesity on offspring. Summary of the changes that occur in offspring of mothers exposed to overnutrition and obesity. The changes that occur in offspring are shown at right; experimental data describing these effects are presented in this chapter

was only slightly increased in the PVH in overfed rats during the suckling period, NPY neuron density was significantly increased in the ARH (Plagemann et al. 1999b). This may suggest a lack of inhibition on NPY and an acquired resistance of the hypothalamic NPY system to increased leptin levels in early postnatally overfed rats. Hypothalamic galanin is a stimulator of food intake and body weight gain. On P21, in over-fed rats, the number of galanin neurons was increased in the ARH, positively correlated to their body weight, which persisted even until adulthood (Plagemann et al. 1999a). Furthermore, male rats overfed during the suckling period exhibited a decrease in hypothalamic mRNA levels of Ob-Rb in the face of hyperleptinemia, contributing to their leptin resistance (Lopez et al. 2005). Moreover, this obese model showed an increase in the mRNA expression of CART, NPY and AgRP in the ARH (Lopez et al. 2005). These changes led to the lifelong persistence of overweight and hyperphagia in those rats overfed during the suckling period (Bassett et al. 1988; Plagemann et al. 1992; Voits et al. 1996), which may suggest a permanent disturbance of weight regulation.

The impact of maternal obesity appears to be amplified by early postnatal overfeeding, as pups from obese dams showed exaggerated adiposity and glucose intolerance at weaning if they were raised in small litters (Lucas 1998; Chen et al. 2008). This was closely linked to an alteration in hypothalamic NPY and POMC expression, as well as their functional receptors (Chen et al. 2008).

In summary, research into the long-term impact of maternal obesity on hypothalamic appetite control has grown in the last decade. Animal models can provide critical data regarding the potential mechanisms underlying the link between maternal obesity and offspring disease risk. Many questions remain, and care must be exercised when considering the clinical implications of this work. Nonetheless the appetite regulatory pathways are well conserved across species, and the models discussed here provide critical insight into hypothalamic regulation of appetite that cannot be obtained in humans. A critical distinction needs to be drawn between effects observed in response to consumption of HFD, and to established maternal obesity. Given the breadth of the obesity epidemic, attention should focus on developing strategies to ameliorate the impact of overnourishment in early life.

113.5 Applications to Other Areas of Health and Disease

Obesity represents a major public health concern and is a major risk factor for cancer, liver disease, metabolic diseases including type 2 diabetes, and cardiovascular disease. Childhood obesity is increasing in most continents. Although adult lifestyle factors undoubtedly contribute to the incidence of obesity, it is now recognized that the adaptations that occur as a result of early exposure to nutritional excess, such as

that induced by maternal obesity, may result in increased susceptibility to the development of a range of diseases. Urgent measures are required to stem the increase in childhood obesity.

Summary Points

- Earlier work showed that undernutrition in pregnancy is associated with greater risk of obesity and cardiovascular disease in offspring.
- Over the past three decades, the prevalence of obesity in both adults and children has increased around the world.
- Obesity is also increasing among women of reproductive age, and this may have consequences for the next generation.
- Obesity during pregnancy is associated with large birth weight, increased circulating insulin, glucose, free fatty acids and triglycerides in offspring.
- The impact of maternal overnutrition on the risk of metabolic disorders in offspring has been examined in both human and animal studies.
- The brain circuits that control appetite are immature at birth, and are influenced by circulating leptin, insulin and possibly lipids; leptin is critical to allow hypothalamic neuropeptide projections to form.
- Maternal obesity in the rodent has been shown to disrupt the normal postnatal surge in leptin, and to lead to changes in neuronal development and expression of transmitters important in regulating appetite.
- In rodents, leptin resistance and glucose intolerance is observed in offspring of obese mothers; whether this occurs in humans needs to be determined.
- Overfeeding in the early postnatal window also increases obesity risk in the long term, and the combination of maternal obesity and early postnatal overfeeding appears to exert additive detrimental effects.
- Further work is needed to improve our understanding of the consequences of maternal obesity and nutrient excess on the next generation. While much of the experimental work presented here was conducted in the rodent, these observations provide useful insights into avenues for future research into developing preventive measures to curb the obesity epidemic.

Definitions and Explanations of Key Terms

Anorexigenic: Inhibits feeding behaviour.

Arcuate nucleus: Key hypothalamic area that integrates peripheral signals of energy balance (e.g. adiposity signals).

Energy homeostasis: The physiological processes whereby energy intake is matched to energy expenditure.

Hypothalamus: A brain region critical in the regulation of feeding, it contains many orexigenic and anorexigenic transmitters.

Leptin: A hormone produced in the adipose tissue that acts in the hypothalamus to decrease appetite and food intake.

Maternal programming: The participation of maternal genotype or phenotype in foetal development.

Orexigenic: Inducing feeding behaviour.

References

Ahima RS, Prabakaran D, Flier JS. J Clin Invest. 1998;101:1020–7.

Armitage JA, Lakasing L, Taylor PD, Balachandran AA, Jensen RI, Dekou V, Ashton N, Nyengaard JR, Poston L. J Physiol. 2005;565:171–84.

Barker DJ. BMJ. 1990;301:1111.

Bassett DR, Craig BW. J Appl Physiol. 1988;64:1249–56.

Bayol SA, Farrington SJ, Stickland NC. Br J Nutr. 2007;98:843–51.

Bayol SA, Simbi BH, Bertrand JA, Stickland NC. J Physiol. 2008;586:3219–30.

Boney CM, Verma A, Tucker R, Vohr BR. Pediatrics. 2005;115:e290–6.

Bouret SG, Draper SJ, Simerly RB. Science. 2004;304:108–10.

Bouret SG, Simerly RB. Clin Genet. 2006;70:295–301.

Bouret SG, Gorski JN, Patterson CM, Chen S, Levin BE, Simerly RB. Cell Metab. 2008;7:179–85.

Chang GQ, Gaysinskaya V, Karatayev O, Leibowitz SF. J Neurosci. 2008;28:12107–19.

Chen H, Simar D, Lambert K, Mercier J, Morris MJ. Endocrinology. 2008;149:5348–56.

Chen H, Morris MJ. Obesity. 2009;17:1356–62.

Chen H, Simar D, Morris MJ. PLoS ONE. 2009;4:e6259. doi:6210.1371/journal.pone.0006259.

Curhan GC, Chertow GM, Willett WC, Spiegelman D, Colditz GA, Manson JE, Speizer FE, Stampfer MJ. Circulation. 1996;94:1310–5.

Elahi MM, Cagampang FR, Mukhtar D, Anthony FW, Ohri SK, Hanson MA. Br J Nutr. 2009;102:514–9.

Elmquist JK, Coppari R, Balthasar N, Ichinose M, Lowell BB. J Comp Neurol. 2005;493:63–71.

Fall CH, Osmond C, Barker DJ, Clark PM, Hales CN, Stirling Y, Meade TW. BMJ. 1995;310:428–32.

Ferezou-Viala J, Roy A-f, Serougne C, Gripois D, Parquet M, Bailleux V, Gertler A, Delplanque B, Djiane J, Riottot M, Taouis M. Am J Physiol Regul Integr Comp Physiol. 2007;293:R1056–62.

Franke K, Harder T, Aerts L, Melchior K, Fahrenkrog S, Rodekamp E, Ziska T, Van Assche FA, Dudenhausen JW, Plagemann A. Brain Res. 2005;1031:276–83.

Gorski JN, Dunn-Meynell AA, Hartman TG, Levin BE. Am J Physiol Regul Integr Comp Physiol. 2006;291:R768–78.

Gorski JN, Dunn-Meynell AA, Levin BE. Am J Physiol Regul Integr Comp Physiol. 2007;292:R1782–91.

Grayson BE, Allen SE, Billes SK, Williams SM, Smith MS, Grove KL. Neuroscience. 2006;143:975–86.

Grove KL, Allen S, Grayson BE, Smith MS. Neuroscience. 2003;116:393–406.

Grove KL, Smith MS. Physiol Behav. 2003;79:47–63.

Grove KL, Grayson BE, Glavas MM, Xiao XQ, Smith MS. Physiol Behav. 2005;86:646–60.

Gupta A, Srinivasan M, Thamadilok S, Patel MS. J Endocrinol. 2009;200:293–300.

Heinsbroek AC, van Dijk G. Int J Obes. 2009;33:104–14.

Howie GJ, Sloboda DM, Kamal T, Vickers MH. J Physiol. 2009;587:905–15.

Kirk SL, Samuelsson AM, Argenton M, Dhonye H, Kalamatianos T, Poston L, Taylor PD, Coen CW. PLoS ONE. 2009;4:e5870.

Kozak R, Burlet A, Burlet C, Beck B. Brain Res Dev Brain Res. 2000;125:75–82.

Levin BE, Dunn-Meynell AA, Banks WA. Am J Physiol Regul Integr Comp Physiol. 2004;286:R143–50.

Lopez M, Seoane LM, Tovar S, Garcia MC, Nogueiras R, Dieguez C, Senaris RM. Diabetologia. 2005;48:140–8.

Lucas A. J Nutr. 1998;128:401S–6S.

McCurdy CE, Bishop JM, Williams SM, Grayson BE, Smith MS, Friedman JE, Grove KL. J Clin Invest. 2009. doi:10.1172/JCI32661.

Mistry AM, Swick A, Romsos DR. Am J Physiol Regul Integr Comp Physiol. 1999;277:R742–7.

Morris MJ, Chen H. Int J Obes. 2009;33:115–22.

Morton GJ, Cummings DE, Baskin DG, Barsh GS, Schwartz MW. Nature. 2006;443:289–95.

Nielson MC, Gordon-Larsen P, North KE, Adair LS. Obesity. 2006;14:701–9.

Nivoit P, Morens C, Van Assche FA, Jansen E, Poston L, Remacle C, Reusens B. Diabetologia. 2009;52:1133–42.

Painter RC, Roseboom TJ, Bleker OP. Reprod Toxicol. 2005;20:345–52.

Palou A, Pico C. Appetite. 2009;52:249–52.

Pico C, Oliver P, Sanchez J, Miralles O, Caimari A, Priego T, Palou A. Int J Obes. 2007;31:1199–209.

Pinto S, Roseberry AG, Liu H, Diano S, Shanabrough M, Cai X, Friedman JM, Horvath TL. Science. 2004;304:110–5.

Plagemann A, Heidrich I, Gotz F, Rohde W, Dorner G. Exp Clin Endocrinol. 1992;99:154–8.

Plagemann A, Harder T, Rake A, Voits M, Fink H, Rohde W, Dorner G. Brain Res. 1999a;836:146–55.

Plagemann A, Harder T, Rake A, Waas T, Melchior K, Ziska T, Rohde W, Dorner G. J Neuroendocrinol. 1999b;11:541–6.

Samuelsson A-M, Matthews PA, Argenton M, Christie MR, McConnell JM, Jansen EHJM, Piersma AH, Ozanne SE, Twinn DF, Remacle C, Rowlerson A, Poston L, Taylor PD. Hypertension. 2007;51:383–92.

Sanchez J, Priego T, Palou M, Tobaruela A, Palou A, Pico C. Endocrinology. 2008;149:733–40.

Schmidt I, Fritz A, Scholch C, Schneider D, Simon E, Plagemann A. Int J Obes Relat Metab Disord. 2001;25:1168–74.

Shintani M, Ogawa Y, Ebihara K, Aizawa-Abe M, Miyanaga F, Takaya K, Hayashi T, Inoue G, Hosoda K, Kojima M, Kangawa K, Nakao K. Diabetes. 2001;50:227–32.

Singer LK, Kuper J, Brogan RS, Smith MS, Grove KL. Neuroreport. 2000;11:1075–80.

Srinivasan M, Aalinkeel R, Song F, Mitrani P, Pandya JD, Strutt B, Hill DJ, Patel MS. Am J Physiol Endocrinol Metab. 2006;290:E129–34.

Tremblay J, Hamet P. Metab Clin Exp. 2008;57:S27–31.

Velkoska E, Cole TJ, Morris MJ. Am J Physiol Endocrinol Metab. 2005;288:E1236–43.

Vickers MH, Gluckman PD, Coveny AH, Hofman PL, Cutfield WS, Gertler A, Breier BH, Harris M. Endocrinology. 2005;146:4211–6.

Vickers MH, Gluckman PD, Coveny AH, Hofman PL, Cutfield WS, Gertler A, Breier BH, Harris M. Endocrinology. 2008;149:1906–13.

Voits M, Forster S, Rodel S, Voigt JP, Plagemann A, Fink H. Naunyn Schmiedebergs Arch Pharmacol. 1996;354:374–8.

White CL, Purpera MN, Morrison CD. Am J Physiol Regul Integr Comp Physiol. 2009;296:R1464–72.

WHO. 2006. Obesity and overweight. September 2006. Available from: http://www.who.int/mediacentre/factsheets/fs311/en/index.html.

Yura S, Itoh H, Sagawa N, Yamamoto H, Masuzaki H, Nakao K, Kawamura M, Takemura M, Kakui K, Ogawa Y, Fujii S. Cell Metab. 2005;1:371–8.

Chapter 114
Sex Hormones and Appetite in Women: A Focus on Bulimia Nervosa

Sabine Naessén and Angelica Lindén Hirschberg

Abbreviations

CCK   Cholecystokinin
ER   Estrogen receptor
HPG   Hypothalamic–pituitary–gonadal axis
OC   Oral contraceptive
PCOS   Polycystic ovary syndrome
PMS   Premenstrual syndrome

114.1 Introduction

Appetite is the sensation of hunger or desire for specific food. The behavioral response to this sensation is food intake, which eventually leads to satiety. Eating behavior, however, is a complex phenomenon encompassing many factors like meal size, rate of eating, and frequency of eating episodes. Environmental and psychological inputs but also social and cultural stimuli affect eating behavior.

Many factors are involved in the regulation of appetite and food intake, both on a meal-to-meal basis and longer term. These factors may be divided into central and peripheral mechanisms (Hirschberg 2001). The hypothalamus has a key function in the central feeding system, controlling input from several neurohumoral factors and absorbed nutrients, such as glucose and free fatty acids. The peripheral feeding system involves a cascade release of gastrointestinal hormones regulating food intake in response to a meal. These peptides chemically recognize the presence of nutrients in the gastrointestinal tract and they influence gastrointestinal motility, thus signaling to the brain that the stomach is full, which leads to termination of food intake. Several gastrointestinal peptides have been suggested as putative satiety agents.

Sex hormones, i.e. estrogen, progesterone, and androgens, play an important role in the regulation of appetite and energy metabolism (Asarian and Geary 2006). In most species, food intake and

S. Naessén (✉)

Department of Obstetrics and Gynaecology, Karolinska University Hospital, SE-171 76 Stockholm, Sweden
e-mail: sabine.naessen@karolinska.se

reproductive function are closely related. The most pronounced physiological changes in appetite and body composition occur during pregnancy and lactation. Sex hormones are known to interact with gastrointestinal peptides and neurotransmitters in the central control of appetite, whereas the effects on energy expenditure seem to be mainly caused by peripheral metabolic effects in adipose tissue (Hirschberg 2001; Asarian and Geary 2006).

Eating disorders, both anorexia and bulimic behavior, are associated with sex hormone abnormalities causing menstrual disturbances and metabolic consequences. Sex hormone changes may be primary or secondary to abnormal eating. There is increasing knowledge about the role of sex hormones in disturbed eating behavior.

114.2 Sex Hormones and Eating Behavior

Eating disorders are much more common in women than in men (Andersen 1999), suggesting a possible role for sex hormone signaling in the etiology of disturbed eating. In females of many species, feeding is closely associated with hypothalamic–pituitary–gonadal (HPG) axis function. Rodents and primates eat less during estrus (time prior to and following ovulation when animals have increased sexual receptivity) (Asarian and Geary 2006). A similar decrease in eating during the ovulatory phase, when estradiol levels are high, has been demonstrated in cycling women (Fong and Kretsch 1993; Johnson et al. 1994).

Estradiol is known to inhibit feeding by reducing meal size in animal experiments (Lindén et al. 1990; Geary 2001). Several mechanisms seem to be involved including increased activity of the satiety signal cholecystokinin (CCK) released from the small intestine in response to food intake (Lindén et al. 1990; Geary 2001). In contrast, the eating-stimulatory potency of the gastric hormone ghrelin is decreased (Clegg et al. 2007). Furthermore, estradiol increases the activity of the anorectic factor corticotropin-releasing hormone in the hypothalamus, and decreases the action of the hypothalamic appetite-stimulating factor neuropeptide Y (Pelletier et al. 2007).

In the hypothalamus, both estrogen receptor (ER) a and ERb are expressed (Laflamme et al. 1998). It has been demonstrated that ERb is the receptor in the central nervous system regulating the anorectic action of estrogen in mice (Liang et al. 2002). However, ERa mechanisms also seem to be involved but the site of action is not fully elucidated (Asarian and Geary 2006). Until now only a few variants of the ERβ gene have been reported and characterized with regard to allele frequency. Polymorphisms in the ERb gene have been associated with ovulatory dysfunction (Sundarrajan et al. 2001). Recently, an association of ERb gene polymorphisms with bulimia was demonstrated (Nilsson et al. 2004). This finding points to a possible role of ERb in the etiology of bulimic disease.

In contrast to estrogen, progesterone seems to stimulate appetite. Several studies in women have demonstrated a distinct increase in food intake in the premenstrual period of the menstrual cycle, when progesterone levels are high (Dye and Blundell 1997; Cross et al. 2001; Bryant et al. 2006). It has been suggested that brain serotonin is involved in the mechanisms (Cross et al. 2001). Furthermore, intake of specific macronutrients may be affected as well. Thus, there seem to be a preference for foods containing high amounts of both fat and sugar before menstruation (Cross et al. 2001).

Testosterone is known to stimulate appetite (Asarian and Geary 2006) and to impair impulse control (Eriksson 2000). These effects of testosterone are considered to be centrally mediated but the exact mechanisms are not known (Asarian and Geary 2006). Women with high androgen levels and polycystic ovary syndrome (PCOS) have a greater craving for sweets and a tendency of binge eating (Hirschberg et al. 2004; Klein et al. 2006). It has therefore been suggested that high androgen levels may promote bulimic behavior by influencing food craving or impulse control.

114.3 Sex Hormone Disturbances in Women with Bulimia Nervosa

Bulimia nervosa is associated with menstrual dysfunction although most women with bulimia are of normal body weight. The occurrence of amenorrhea in bulimic women has been reported within the range of 7–40% (Copeland et al. 1995) and 37–64% of the patients may have irregular bleedings with long intervals (oligomenorrhea) (Cantopher et al. 1988). In comparison, the prevalence of secondary amenorrhea in the general population is between 2% and 5% (Münster et al. 1992).

Different mechanisms may interact in the etiology of menstrual dysfunction in bulimia. In anorexia nervosa, amenorrhea is explained by hypothalamic inhibition of the reproductive system due to starvation (Chan and Mantzoros 2005). Low levels of estradiol and gonadotropins, indicating hypothalamic inhibition of the HPG axis, have also been reported in bulimic women (Gendall et al. 2000). Furthermore, low levels of thyroid hormones, considered to be a consequence of the temporary starvation periods associated with the disease, have been demonstrated in bulimia nervosa (Gendall et al. 2000; Naessén et al. 2006a).

In addition, an association between bulimia and PCOS has been suggested. PCOS is the most common hormonal aberration in women of fertile age, with a prevalence of 5–10%, and is associated with menstrual disturbances due to oligo- or anovulation, clinical symptoms of hyperandrogenism, and polycystic ovaries (Fig. 114.1) (Ehrmann 2005). Furthermore, the syndrome is often associated with insulin resistance and abdominal obesity. The diagnostic criteria for PCOS are shown in Table 114.1. A genetic predisposition is required for the development of the syndrome, though there is also a link with environmental factors (Ehrmann 2005).

There are several similarities between PCOS and bulimia nervosa. Women with PCOS, like in bulimia nervosa, show disturbed appetite regulation, increased craving for carbohydrates, and impaired meal-related secretion of CCK (Hirschberg et al. 2004; Moran and Norman 2004). On the other hand, an increased frequency of PCOS symptoms has been demonstrated in bulimic women in

Fig. 114.1 Ultrasound picture of a polycystic ovary

Table 114.1 The diagnostic criteria for PCOS according to Rotterdam Consensus 2004

Diagnostic criteria for PCOS
1. Oligo-or anovulation
2. Clinical and/or biochemical signs of hyperandrogenism
3. Polycystic ovaries on ultrasound

Two out of three criteria are necessary for diagnosis

Table 114.2 Frequency of PCOS symptoms in bulimics and healthy women (Adapted from Naessén et al. 2006)

Criteria	Bulimics $n = 77$	Controls $n = 59$
1. Oligo- or anovulation (%)	31.2[***]	1.7
2. Clinical and/or biochemical hyperandrogenism (%)	27.3[*]	11.9
3. Polycystic ovaries on ultrasound (%)	7.1	6.8
PCOS diagnosis (%)	16.6[*]	1.7

[*]$p < 0.05$

[***]$p < 0.001$

comparison with healthy controls (Table 114.2). Thus, increased occurrence of polycystic ovaries, acne, hirsutism, and elevated serum levels of androgens have been reported in bulimic women (McCluskey et al. 1992; McSheery 1992; Sundblad et al. 1994; Jahanfar et al. 1995; Cotrufo et al. 2000; Monteleone et al. 2001; Morgan et al. 2002; Naessén et al. 2006b).

What is the etiological connection between bulimia and PCOS? It has been suggested that polycystic ovaries may be secondary to abnormal eating behavior (Morgan et al. 2002). Another explanation for an association between bulimia and PCOS may be that hyperandrogenism is the primary condition, which predisposes for the development of bulimic behavior and associated psychiatric comorbidity. Testosterone is appetite-stimulating (Asarian and Geary 2006) and high androgen levels in women have been associated with impaired impulse control, irritability, and depression (Eriksson 2000). These symptoms are common features in women with bulimia (Eriksson 2000). Furthermore, bulimic women are more sexually experienced and sexually experimental than control women (Abraham 1998). This may also be related to increased androgen activity since androgens have well-known stimulatory effects on female sexuality (Flöter 2009).

It could be concluded that bulimia nervosa is associated with several hormonal aberrations, which may be primary or secondary to abnormal eating. Menstrual disturbances may be caused by hypothalamic inhibition of the reproductive axis due to periods of starvation. An alternative explanation is essential hyperandrogenism like PCOS, which may promote bulimic behavior since androgens have appetite-stimulating effects and could impair impulse control.

114.4 Oral Contraceptives and Appetite

Oral contraceptives (OCs) containing the combination of a synthetic estrogen and progesterone (progestin) are used by numerous women for birth control, but OCs are also frequently used for medical treatment. Dysmenorrhea, bleeding disorders, endometriosis, hypogonadism, and PCOS are common indications for treatment with OCs. The treatment is generally well tolerated with few side effects. However, there is a small risk for thromboembolic events. Some women may experience changes in

Table 114.3 Pharmacological profile of progestins in combined oral contraceptives

	Androgenic	Antiandrogenic	Antimineralocorticoid
Levonorgestrel	+	-	-
Norethisterone	+	-	-
Norgestimate	(+)	-	-
Gestodene	(+)	-	(+)
Desogestrel	(+)	-	-
Dienogest	-	+	-
Cyproterone	-	+	-
Drospirenone	-	+	+
Progesterone	-	(+)	+

+ agonist action, (+) weak agonist action, - no effect

appetite and weight, although studies evaluating body weight all show no significant change in average weight and body composition by combined OCs (Gallo et al. 2008). The progestin component in combined OCs and particularly high-dose progestins are associated with increased appetite and weight gain (Hirschberg et al. 1996; Maltoni et al. 2001). However, despite extensive clinical experience of OC treatment, little is known about effects of different types of OCs on appetite and body weight.

Combined OCs usually contain ethinylestradiol as synthetic estrogen, whereas the type of progestin varies between different OCs. The progestins used mainly belong to two chemical families: derivates of 19-nortestosterone and derivates of 17-α-hydroxyprogesterone. Derivates of 19-nortestosterone have varying degrees of androgenic activity, whereas derivates of 17-α-hydroxyprogesterone, that are structurally related to progesterone, lack androgenic effects and may also exert antiandrogenic activity (Table 114.3). Progestins with androgenic activity in combination with ethinylestradiol seem to be associated with a lower risk of vascular thromboembolism than other combinations (Lidegaard et al. 2009; van Hylckama Vlieg et al. 2009). However, side effects like acne, increased appetite, and weight gain are more common when androgenic OCs are used. In contrast, OCs with antiandrogenic properties could be used for treatment of acne and hirsutism (Pekhlivanov et al. 2006).

Levonorgestrel and norethisterone belong to the older progestins and are derived from testosterone. They have potent antigonadotropic effects and androgenic activity by binding with high affinity to the androgen receptor (Sitruk-Ware 2006) (Table 114.3). OCs containing levonorgestrel seem to have limited influence on the coagulation system and are therefore in some countries recommended as the first choice for contraception (Lidegaard et al. 2009; van Hylckama Vlieg et al. 2009).

Later generations of progestins were developed to reduce undesirable androgenic side effects. Desogestrel is one of those but still binds to the androgen receptor and could exert weak androgenic actions (Table 114.3). Cyproterone acetate is a very potent antiandrogenic progestin and is used in combination with ethinylestradiol for treatment of acne, seborrhea, and hirsutism (van Hylckama Vlieg et al. 2009).

Drospirenone belongs to the new generation of progestins and is the first with antimineralocorticoid activity together with considerable antiandrogenic effects (Sitruk-Ware 2006) and thus differs from other synthetic progestins currently used in OCs. The antimineralocorticoid effect of drospirenone may help prevent sodium retention and a rise in blood pressure in susceptible women. Furthermore, a small reduction in body weight has been demonstrated in users of OCs containing drospirenone. Drospirenone exerts direct antiandrogenic activity due to competitive binding to the androgen receptor (Sitruk-Ware 2006). In addition, drospirenone alone or in combination with ethinylestradiol will suppress androgen production from the adrenals and ovaries. OCs containing drospirenone have been successfully used for treatment of hyperandrogenic symptoms in women with PCOS (Pekhlivanov et al. 2006).

Theoretically, OCs with antiandrogenic properties could be beneficial for bulimic patients by influencing food craving and impulse control.

114.5 Sex Hormone Treatment in Bulimia

Cognitive–behavioral therapy in combination with antidepressant medication is currently the standard treatment for bulimic women, but several cases are resistant to this therapy. Furthermore, the risk of relapse is high and about 35% (Olmsted et al. 2005). Thus, there is a need for additional treatments for bulimia and for new strategies to prevent relapse.

The associations between endocrine status and eating behavior presented above suggest that treatment with estrogenic and/or antiandrogenic activity may be effective as an additional therapy for bulimic women. In support of this hypothesis, treatment with the androgen receptor antagonist flutamide has been shown to reduce symptoms in bulimic patients (Bergman and Eriksson 1996; Sundblad et al. 2005). However, this medication has been associated with adverse liver effects (Osculati and Castiglioni 2006), which would limit the long-term use of the drug.

Recently, it was also demonstrated that treatment with an antiandrogenic OC (30 µg ethinylestradiol + 3 mg drospirenone) improved eating behavior and reduced meal-related appetite in women with bulimia nervosa (Naessén et al. 2007). The decrease in compensatory behavior and reduced hunger response was significantly related to decreased testosterone levels following treatment (Fig. 114.2). Furthermore, bulimics who responded with decreased bulimic behavior had higher pretreatment levels of testosterone and higher frequency of binge eating and of compensatory behavior than those who did not (Naessén et al. 2007). These findings are in line with previous reports on associations between high androgen levels on the one hand and increased appetite, reduced postprandial CCK secretion, deranged appetite regulation, and impaired impulse control on the other (Sundblad et al. 1994; Hirschberg et al. 2004).

Thus, treatment with an antiandrogenic OC, which is widely used and generally well tolerated with few side effects (Pekhlivanov et al. 2006), showed similar beneficial effects as treatment with an androgen receptor antagonist. The ethinylestradiol/drospirenone combination is also reported to reduce premenstrual symptoms (PMS; Brown et al. 2002). As in bulimics, increased levels of testosterone have been reported in women with PMS (Eriksson 2000). These women also suffer from increased craving for food during the premenstrual phase, where also bulimics may experience aggravation of their symptoms (Eriksson 2000).

To conclude, treatment with an antiandrogenic OC may improve meal-related appetite responses in women with bulimia nervosa and reduce bulimic symptoms. The results support the notion that androgens play a role in bulimic behavior. Hypothetically, bulimia may in some cases be a manifestation of a hormonal constitution rather than a primary psychiatric illness. Antiandrogenic OC treatment may develop into a new management of women with bulimia nervosa, particularly in those with hyperandrogenic symptoms. However, large scale placebo-controlled studies are needed to corroborate this concept.

114.6 Application to Other Areas of Health and Disease

Apart from treating bulimic behavior, menstrual disturbances and clinical signs of hyperandrogenism should be evaluated in bulimics in order to provide adequate medical care and treatment. Menstrual disturbances in women with bulimia may be caused by hypothalamic inhibition of the reproductive axis due to periods of starvation. Another mechanism may be essential hyperandrogenism like PCOS, since hirsutism, acne, and polycystic ovaries are common features in bulimic women. Androgens may promote bulimic behavior by stimulating appetite and influencing impulse control. Combined OCs with antiandrogenic properties could be beneficial for bulimic patients with hyperandrogenic symptoms.

Fig. 114.2 Levels of free testosterone, frequency of compensatory behavior, and subjective hunger response in bulimics before and during treatment with an antiandrogenic oral contraceptive. There were significant decreases of all three variables (free testosterone $p < 0.01$; compensatory behavior and subjective hunger $p < 0.05$, respectively). Horizontal lines indicate 10th, 25th, 50th, 75th, and 90th percentile (Adapted from Naessén et al. 2007)
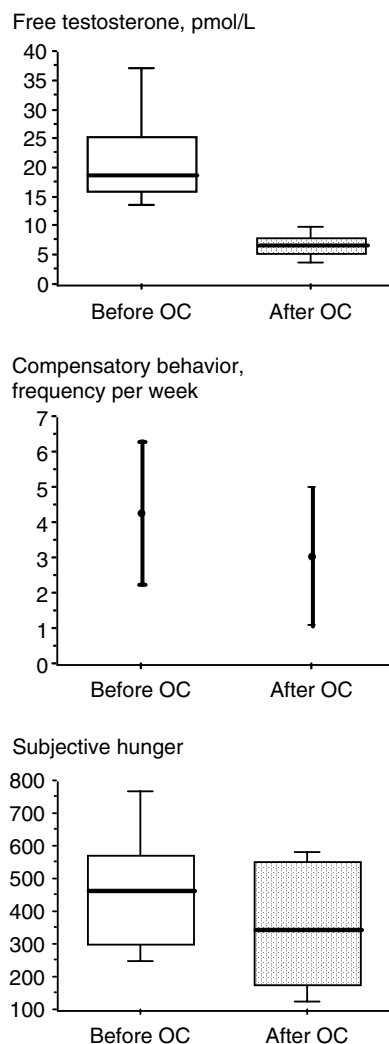
Summary Points

- Sex hormones play an important role in the regulation of appetite and energy metabolism. Estrogen is known to inhibit feeding, whereas progesterone and testosterone may stimulate appetite. Altered sex hormone activity may be involved in disturbed eating behavior.
- Bulimia nervosa is frequently associated with sex hormone disturbances, which may be secondary or primary to abnormal eating. Menstrual disorders and low estradiol levels are common although most bulimic women are of normal weight. Hypothalamic inhibition of the reproductive axis due to periodic starvation could be one underlying mechanism of menstrual disturbances in women with bulimia.
- Increased androgens, acne, hirsutism, and polycystic ovaries are also frequent among bulimics. PCOS, which has a genetic background, may therefore be an alternative cause of menstrual disturbances in bulimic women.
- Testosterone is appetite-stimulating and high androgen levels in women have been associated with impaired impulse control, irritability, and depression. It has been suggested that androgens may promote bulimic behavior.

- Antiandrogenic OC treatment seems to reduce meal-related appetite and improve bulimic behavior in relation to reduced androgen levels in women with bulimia nervosa.
- The findings support the notion that androgens play a role in bulimic behavior. Hypothetically bulimia may in some cases be a manifestation of a hormonal constitution rather than a primary psychiatric illness. Antiandrogens may develop into a new therapeutic approach in women with bulimia nervosa, particularly in those with hyperandrogenic symptoms.

Key Terms

Amenorrhea: No menstrual bleeding for 3 months or more.

Androgens: Male sex hormones.

Anovulation: Absence of ovulation due to hormonal or gonadal disorder.

Combined oral contraceptives (OCs): Medication for birth control, containing estrogen and progestin, also used for medical treatment of different disorders. The mechanism of action is suppression of ovulation and endogenous sex steroid hormone production.

Hirsutism: Increased body and facial hair growth of male type.

Hyperandrogenism: Condition of excessive production of androgens associated with increased body hair growth and acne.

Hypothalamic–pituitary–gonadal (HPG) axis: The endocrine system in women regulating ovarian function. The hypothalamus secretes gonadotropin-releasing hormone, the pituitary releases the gonadotropins luteinizing hormone and follicle-stimulating hormone, and in response the ovary secretes estradiol, progesterone, and androgens. In turn, ovarian steroid hormones modulate hypothalamic and pituitary output.

Polymorphism: The genetic variation within a population of two or more alleles of a gene, where the frequency of the rarer alleles is greater than can be explained by recurrent mutation alone.

Polycystic ovaries: Enlarged ovaries with increased number of follicles identified by gynecologic ultrasound.

Polycystic ovary syndrome (PCOS): The most common hormonal disorder in women of reproductive age, characterized by menstrual disturbances, symptoms of excess androgen, and polycystic ovaries. Insulin resistance, diabetes type 2, and abdominal obesity are associated with the syndrome. Genetic and environmental factors are important for the development of PCOS.

Progestin: Synthetic progesterone used in contraceptive pills.

Key Points

Hyperandrogenism may explain several symptoms in bulimic women. High testosterone levels in women have been associated with:

- Menstrual disturbances
- Polycystic ovaries
- Hirsutism, acne
- Increased appetite
- Impaired impulse control
- Irritability
- Depression

References

Abraham S. J Psychosom Res. 1998;44:491–502.

Andersen AE. J Gend Spec Med. 1999;2:47–54.

Asarian L, Geary N. Phil Trans R Soc B. 2006;361:1251–63.

Bergman L, Eriksson E. Acta Psychiatr Scand. 1996;94:137–9.

Brown C, Ling F, Wan J. J Reprod Med. 2002;47:14–22.

Bryant M, Truesdale KP, Dye L. Br J Nutr. 2006;96:888–94.

Cantopher T, Evans C, Lacey JH, Pearce JM. Br Med J. 1988;297:836–7.

Chan, Mantzoros CS. Lancet 2005;366:74–85.

Clegg DJ, Brown LM, Zigman JM, Kemp CJ, Strader AD, Benoit SC, Woods SC, Mangiaracina M, Geary N. Diabetes. 2007;56:1051–8.

Copeland PM, Sacks NR, Herzog DB. Psychosom Med. 1995;57:121–6.

Cotrufo P, Monteleone P, d'Istria M, Fuschino A, Serino I, Maj M. Neuropsychobiology 2000;42:58–61.

Cross GB, Marley J, Miles H, Willson K. Br J Nutr. 2001;85:475–82.

Dye L, Blundell JE. Hum Reprod. 1997;12:1142–51.

Ehrmann DA. N Engl J Med. 2005;352:1223–36.

Eriksson E. In: Steiner M, Yonkers KA, Eriksson E, editors. Mood disorders in women. London: Martin Dunitz; 2000. p. 233–46.

Flöter A. Curr Women's Health Rev. 2009;5:29–43.

Fong AK, Kretsch MJ. Am J Clin Nutr. 1993;57:43–6.

Gallo MF, Lopez LM, Grimes DA, Schulz KF, Helmerhorst FM. Cochrane Database Syst Rev. 2008 Oct 8;4:CD003987.

Geary N. Peptides 2001;22:1251–63.

Gendall KA, Bulik CM, Joyce PR, McIntosh VV, Carter FA. J Psychosom Res. 2000;49:409–15.

Hirschberg AL. In: Becker KL, editor. Principles and practice of endocrinology and metabolism. 3rd ed. Philadelphia: J. B. Lippencott; 2001. p. 1233–9.

Hirschberg AL, Byström B, Carlström K, von Schoultz B. Contraception. 1996;53:109–13.

Hirschberg AL, Naessén S, Stridsberg M, Byström B, Holte J. Gynecol Endocrinol. 2004;19:79–87.

Jahanfar S, Eden JA, Nguyent TV. Gynecol Endocrinol. 1995;9:113–7.

Johnson WG, Corrigan SA, Lemmon CR, Bergeron KB, Crusco AH. Physiol Behav. 1994;56:523–7.

Klein DA, Boudreau GS, Devlin MJ, Walsh BT. Int J Eat Disord. 2006;39:341–5.

Laflamme N, Nappi RE, Drolet G, Labrie C, Rivest S. J Neurobiol. 1998;36:357–78.

Liang YQ, Akishita M, Kim S, Ako J, Hashimoto M, Iijima, Ohike Y, Watanabe T, Sudoh N, Toba K, Yoshizumi M, Ouchi Y. Int J Obes Relat Metab Disord. 2002;26:1103–9.

Lidegaard Ø, Løkkegard E, Svendsen AL, Agger C. BMJ. 2009;339:557–60.

Lindén A, Uvnäs-Moberg K, Forsberg G, Bednar I, Södersten P. J Neuroendocrinol. 1990;2:797–801.

Maltoni M, Nanni O, Scarpi E, Rossi D, Serra P, Amadori D. Ann Oncol. 2001;12:289–300.

McCluskey SE, Lacey JH, Pearce JM. Lancet. 1992;340:723.

Monteleone P, Luisi M, Colurcio B, Casarosa E, Monteleone P, Ioime R, Genazzani AR, Maj M. Psychosom Med. 2001;63:62–8.

Moran L, Norman RJ. Best Pract Res Clin Obstet Gynaecol. 2004;18:719–36.

Morgan JF, McCluskey SE, Brunton JN, Lacey JH. Fertil Steril. 2002;77:928–31.

Münster K, Helm P, Schmidt L. Br J Obstet Gynecol. 1992;99:430–3.

Naessén S, Carlström C, Glant R, Jacobsson H, Hirschberg AL. Eur J Endocrinol. 2006a;155:245–51.

Naessén S, Garoff L, Carlström K, Glant R, Hirschberg AL. Gynecol Endocrinol. 2006b;22:388–94.

Naessén S, Carlström K, Byström B, Pierre Y, Hirschberg AL. Psychoneuroendocrinology. 2007;32:548–54.

Nilsson M, Naessén S, Dahlman I, Hirschberg AL, Gustafsson J-Å, Dahlman-Wright K. Mol Psychiatry. 2004;9:28–34.

Olmsted MP, Kaplan AS, Rockert W. Int J Eat Disord. 2005;38:1–6.

Osculati A, Castiglioni C. Lancet 2006;367:1140–1.

Pekhlivanov B, Mitkov M, Ivancheva Kh., Amaliev I. Akush Ginekol. 2006;45:25–9.

Pelletier G, Li S, Luu-The V, Labrie F. J Neuroendocrinol. 2007;19:426–31.

Sitruk-Ware R. Hum Reprod Update. 2006;12:169–78.

Sundarrajan C, Liao W, Roy AC, Ng SC. J Clin Endocrinol Metab. 2001;86:135–9.

Sundblad C, Bergman L, Eriksson E. Acta Psychiatr Scand. 1994;90:397–8.

Sundblad C, Landen M, Eriksson T, Bergman L, Eriksson E. J Clin Psychopharmacol. 2005;25:85–8.

van Hylckama Vlieg A, Helmerhorst FM, Vandenbroucke JP, Doggen CJM, Rosendaal FR. BMJ. 2009;339:b2921.

Part XX
Pathology and Abnormal Aspects: Lipids

Chapter 115
Dietary *n*-3-Polyunsaturated Fatty Acid Deprivation and Cytokine Signaling Pathways in the Brain

Sophie Laye, Virginie F. Labrousse, and Veronique De Smedt-Peyrusse

Abbreviations

15d-PGJ2	15-deoxy-delta 12,14-prostaglandin J2
AA	Arachidonic acid
ALA	Alpha linolenic acid
BBB	Blood brain barrier
CNS	Central nervous system
COX	Cyclooxygenase
cPLA2	Calcium-dependent phospholipase A2
DHA	Docosahexaenoic acid
DPA	Docosapentaenoic acid
EPA	Eicosapentaenoic acid
ERK	Extracellular signal-regulated protein kinase
GFAP	Glial fibrillary acidic protein
HEPE	Hydroxyeicosapentaenoic acid
IKK	IκB kinase
IL-1	Interleukin 1
IL-10	Interleukin 10
IL-1R	Interleukin 1 receptor
IL-1ra	Interleukin 1 receptor antagonist
IL-1RAcP	Interleukin 1 receptor accessory protein
IL-6	Interleukin 6
IL-6R	Interleukin 6 receptor
iPLA2	Calcium-independent phospholipase A2
IRAK	Interleukin-1 receptor associated kinase
IκB	Inhibitor of κB
JAK	Janus kinase

S. Laye (✉)

Psychoneuroimmunology, nutrition and genetics (Psynugen), Université Bordeaux 2, INRA,
UMR1286, CNRS, UMR5226, Bâtiment UFR Pharmacie – 2ème Tranche – 2ème Etage, Case courrier 34,
146 rue Léo Saignat, 33076 BORDEAUX, Cedex
e-mail: sophie.laye@bordeaux.inra.fr

JNK	c-Jun N-terminal kinase
LA	Linoleic acid
LOX	Lipoxygenase
LPS	Lipopolysaccharide
LT	Leukotriene
LTP	Long-term potentiation
LXA4	Lipoxin A4
LXR	Liver X receptor
MAPK	Mitogen associated protein (MAP) kinase
MHCII	Class II major histocompatibility complex
MK	MAPK-activated protein kinase
MyD88	Myeloid differentiation primary response gene (88)
NEMO	NFκB essential modulator
NFκB	Nuclear factor kappa B
NIK	NFκB inducing kinase
PAMP	Pathogen-associated molecular patterns
PC	Phosphatidylcholine
PE	Phosphatidylethanolamine
PG	Prostaglandin
PGE2	Prostaglandin E2
PGI	Prostacyclin
PPAR	Peroxisome proliferator-activated receptor
PUFA	Polyunsaturated fatty acid
RXR	Retinoid X receptor
SAMP8	Senescence-accelerated prone mouse
STAT	Signal transducers and activators of transcription
TACE	TNFα cleavage enzyme
TLR4	Toll-like receptor 4
TNFR	Tumor necrosis factor receptor
TNFα	Tumor necrosis factor alpha
TRADD	TNFR1-associated via death domain
TRAF-6	TNF receptor associated factor 6
TX	Thromboxane
Tyk	Tyrosine kinase 2

115.1 Introduction

The central nervous system (CNS) has long been considered a privileged organ from the point of view of immunity, as the blood brain barrier (BBB), thanks to its tight junctions, limits the entry of immune cells, notably lymphocytes, into the brain. Research in neuroimmunology has shown that the brain possesses its own system of defense, which, in addition to being activated by immune stimuli, is closely linked to the immune system. Inflammatory cytokines, which are important mediators of communication within the immune system, also act in the brain, in particular by activating the innate immune cells of the brain that in turn produce inflammatory cytokines. The synthesis of brain cytokines is finely regulated, allowing them to return to basal levels without leading either to a rupture of the BBB or to cerebral lesioning. On the other hand, when these factors are synthesized in large quantities or in a chronic manner by the brain, they have toxic effects on neurons, resulting in

substantial neuronal dysfunction that can lead to cell death. The fragilization of neuronal function due to cytokines is also seen during aging, where microinflammation, characterized by microglial reactivity and the chronic production of low levels of inflammatory cytokines, is seen to occur. Numerous epidemiological studies show a correlation between the expression levels of inflammatory cytokines and the incidence of functional alterations (cognitive or mood disorders) in elderly subjects. This microneuroinflammation, which increases the vulnerability of the aging brain to immune stimuli, is characterized by the increased production of brain cytokines and the risk of developing delirium and/or neurodegenerative disorders with an inflammatory component, such as Alzheimer's disease. Limiting the development of chronic neuroinflammation is a key element in the protection of the brain against neurodegenerative disorders.

In this context, diet constitutes a strategy of choice, since it is an environmental factor to which individuals are exposed throughout life. Increasing attention has been paid to ω3 and ω6 polyunsaturated fatty acids (PUFAs), micronutrients that are essential since they cannot be synthesized de novo by the organism. An increasing store of information attests to the powerful immunomodulatory effects of the PUFAs. Thus, ω3 PUFAs form the basis of lipid derivatives (neuroprotectins and resolvins) with anti-inflammatory properties, whereas ω6 PUFAs are the precursors of the proinflammatory prostacyclins, and stimulate the production and activity of inflammatory cytokines. In addition, the brain is extremely rich in PUFAs. Their accumulation takes place during the perinatal period, in proportions dependant on maternal dietary levels. Conversely, their levels diminish as the individual ages, but can be corrected by appropriate nutritional strategies. During the last few decades, the lifestyle of Western societies has evolved towards a decrease in energy expenditure mainly related to our sedentary life style, and a change in our dietary habits towards the consumption of energy-rich foods with high levels of saturated fats, ω6 PUFAs, and sugar, and poor in vitamins and micronutrients. The dramatic reduction in the dietary supply of ω3 PUFAs and the corresponding increase in ω6 PUFAs, by leading to an imbalance in the ω6/ω3 ratio, estimated at between 12 and 20 in developed countries at present (the current recommended ratio is 5), could contribute to the fragilization of the brain with respect to inflammatory cytokines, and thus to the development of neurodegenerative disorders.

115.2 The Innate Immune System of the Brain

115.2.1 Glial Cells

Microglial cells are the resident macrophages of the brain and constitute the first line of immune defense of the brain (phagocytosis, antigen presentation, and secretion of proinflammatory cytokines). Microglial cells have a ramified morphology when quiescent and an ameboid morphology when they are activated and produce cytokines. Ramified microglia cells generally do not display phagocytic activity and weakly express ligands and receptors involved in macrophage function. These ramified microglial cells, disseminated throughout the brain parenchyma, use their processes to receive signals such as inflammatory cytokines from their microenvironment, which reveal the existence of a lesion or the presence of a pathogen. In order to do this, microglial cells express several membrane receptors, including those for the inflammatory cytokines IL-1β, TNFα, and IL-6, as well as those that allow the recognition of PAMPs (pathogen-associated molecular patterns) such as the bacterial endotoxin receptors TLR4 and CD14. Microglia cells are involved in the pathophysiology of neurodegenerative disorders. Thus, during infection, there is a massive infiltration of peripheral immune cells, notably neutrophils, into the brain, along with an aggravated inflammatory response. During aging, the accumulation of damaged DNA activates parenchymatous microglia, which proliferate, become reactive

(a phenomenon called microglial "priming"), and produce inflammatory cytokines (reviewed in Dyerberg and Bang 1979). This microglial dysfunction is responsible for the exacerbation of the microglial reaction in response to an inflammatory stimulus, and for a massive recruitment of cells of the myeloid lineage, which, by infiltrating the parenchyma, reinforce the inflammation of the CNS, or neuroinflammation. These phenomena together contribute to the development of disorders with an inflammatory component linked to aging, such as Alzheimer's disease.

Astrocytes also participate in brain immunity and in the maintenance of tissue integrity in the nervous system. In fact, any pathological or injury-related inflammatory state leads to an astrocytic reaction, called reactive astrogliosis. Astrocytes proliferate, hypertrophy, and undergo an increase in new protein synthesis, including that of GFAP (glial fibrillary acidic protein). These phenotypic changes of astrocytes in response to inflammation constitute a physical and biochemical barrier that isolates the lesion site from the remaining, healthy tissue. The astrocytic response is regulated by growth factors and inflammatory cytokines that are liberated by the lesioned cells (astrocytes, neurons, etc.) as well as by microglial cells. Astrocytes, by virtue of expressing cytokine receptors, are in fact sensitive to the effects of cytokines. Numerous studies carried out in vitro and in vivo demonstrate that these cells produce inflammatory and anti-inflammatory cytokines. During aging, astrocytes become reactive and produce inflammatory cytokines. In addition, these cells partially lose their neuroprotective properties with age, thus contributing to the exacerbation of neuronal lesions participating in age-related neurodegeneration (reviewed in Pertusa et al. 2007). These phenomena together contribute to the development of neurodegenerative disorders with an inflammatory component linked to aging.

115.2.2 Inflammatory Cytokines, Their Receptors, and Their Signaling Pathways in the Brain

115.2.2.1 Inflammatory Cytokines and Their Receptors

The IL-1 family consists of two agonists, IL-1α and IL-1β, and one antagonist, IL-1ra. IL-1α and IL-1β are synthesized as inactive precursors which are cleaved by the calpains and by caspase-1 respectively to generate active peptides of 17 kDa. They bind to type I (IL-1R1) and type II (IL-1R2) receptors, of which the latter is a decoy receptor. These receptors all exist as soluble forms, which, by trapping IL-1, negatively regulate its actions. IL-1RAcP is an accessory protein that is indispensable for the intracellular signal transduction of IL-1 by IL-1R1. Association of IL-1 to its receptors enhances the receptors' affinity for the ligand. Nevertheless, when IL-1ra binds to IL-1R1, the IL-1R1/IL-1RAcP complex dissociates, explaining the absence of a biological effect of IL-1ra (reviewed in Rothwell and Luheshi 2000). Studies in rodents have revealed that IL-1 binding sites are very dense in the hippocampus and hypothalamus. IL-1R1 is expressed by neurons in the mouse hippocampus, and by cells of the choroid plexus and cerebral vasculature in the rat (Ericsson et al. 1995; Konsman et al. 2004).

TNFα is synthesized as a 26 kDa precursor that, after proteolytic cleavage by the metalloprotease TACE (TNFα converting enzyme), yields a 17 kDa peptide. The extracellular soluble form of TNFα is a homotrimer of the 17 kDa peptide. TNFα is the agonist of the type 1 (TNFR1 or p55) and type 2 (TNFR2 or p75) TNF receptors. The soluble forms of these receptors constitute decoy receptors for TNFα. Etanercept, a fusion protein that combines the p75 fraction of the soluble TNFα receptor with the Fc fragment of human immunoglobulin G1, is used in the treatment of rheumatoid arthritis, and is currently undergoing trials for use in Alzheimer's disease. TNFR1 is expressed by microglial cells

and astrocytes in culture. In rodents, TNFR1 is expressed by the circumventricular organs, the choroid plexus, and blood vessels. In the human brain, constitutive expression has been described in neurons and in blood vessels (reviewed in McCoy and Tansey 2008).

IL-6 is synthesized as a precursor, and released after proteolytic cleavage by as yet unidentified proteases. IL-6 binds to its receptor, IL-6R, which associates with a 130 kDa transmembrane glycoprotein, gp130. The IL-6/IL-6R/gp130 active complex is a hexamer composed of an IL-6 dimer, an IL-6R dimer, and a gp130 dimer. The formation of a gp130 homodimer leads to the activation of IL-6-related signaling pathways. The soluble form of IL-6R bound to IL-6 interacts with gp130 to trigger agonistic effects, whereas the soluble form of gp130 neutralizes the effects of IL-6. In rodents, IL-6R mRNA is expressed by neurons and glial cells in the hippocampus, the hypothalamus, and certain zones of the cortex. A weaker expression pattern is also detected in several circumventricular organs, where it is rapidly upregulated during inflammatory states. Neurons that express gp130 but not IL-6R are sensitive to IL-6 as a result of the soluble receptor (reviewed in Jones et al. 2005).

115.2.2.2 Signaling Pathways Associated with the Activation of the Cytokine Receptors

IL-1β and TNFα mainly activate the NFκB and MAP kinase (MAPK) signaling pathways. Activation of the NFκB pathway through the p50–p65 complex leads to the formation of NIK (NFκB inducing kinase), IKK (IκB kinase) α and β, and NEMO (NFκB essential modulator). This complex of kinases phosphorylates IκB, the inhibitor of NFκB, which is then degraded by ubiquitination. NFκB is then translocated to the nucleus and activates the transcription of target genes involved in inflammation (inflammatory cytokines, chemokines, eicosanoid pathway enzymes, endotoxin receptors, etc.). The MAPKs ERK 1/2 (extracellular signal-regulated protein kinase 1/2), p38, and JNK (c-Jun N-terminal kinase) catalyze the phosphorylation of the MKs (MAPK-activated protein kinases). While ERK 1/2 and JNK are implicated in cell proliferation and differentiation, p38 is essential for immune and inflammatory responses. The cascade of intracellular events that leads to the activation of NFκB and the MAPK pathways by IL-1 requires the recruitment of MyD88, IRAK, and TRAF-6 (Fig. 115.1). On the other hand, the activation of the same pathways by TNFα requires the adaptor protein TRADD and the death domain (DD). In this case, the activation of the NFκB pathway is initiated by the binding of the adaptor protein RIP (receptor interactive protein) to TRADD. The activation of TRAF2 (TNF receptor associated factor)-dependant MAPK or FADD (Fas associated death domain) caspases follows (reviewed in Liu 2005). IL-1β activates NFκB and MAPK signaling pathways in neurons and glial cells (Nadjar et al. 2003). In the aging brain, the activations of the JNK/p38 and caspase-3 pathways depend on IL-1β and its receptor, the synthesis of which is augmented in the hippocampus (Lynch and Lynch 2002). The overactivation of these pathways participates in the increase in neuronal death in the aging brain. Additionally, the overproduction of IL-6 by microglial cells in old mice is linked to the prolonged activation of NFκB (Ye and Johnson 2001).

The binding of IL-6 to its receptors leads to their phosphorylation by the Janus kinases (JAK1, 2 and Tyk). This leads to the recruitment of the STAT (signal transducers and activators of transcription) transcription factors, mainly STAT1 and STAT3, which are in turn phosphorylated. The phosphorylated forms of STAT form homo- or heterodimers via their SH2 domains, and subsequently migrate into the nucleus to activate the synthesis of target genes (Fig. 115.2). The constitutive expression of STAT1 and 3 proteins in the CNS has been demonstrated during postnatal development and in adulthood (reviewed in Dziennis and Alkayed 2008). In the adult brain, STAT3 is activated in astrocytes and endothelial cells in response to the administration of lipopolysaccharide (LPS) or IL-6 (Gautron et al. 2002; Harré et al. 2002). In the aging brain, IL-6 inhibits hippocampal long-term potentiation (LTP) through the intermediary of the ERK 1/2 pathways (Tancredi et al. 2000).
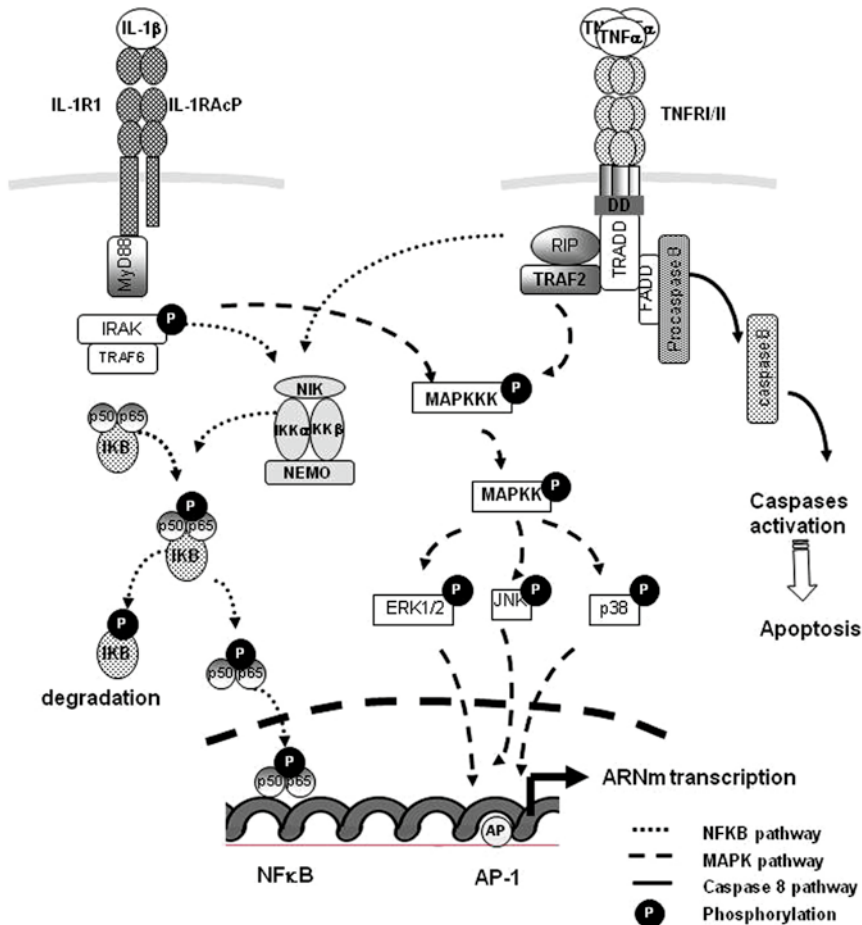
Fig. 115.1 Receptors and IL-1β and TNFα signaling pathways. *AP-1* activating protein 1, *DD* death domain, *ERK1/2* extracellular signal-regulated protein kinase ½, *FADD* fas associated death domain, *IKB* inhibitor of KB, *IKKα/β* IκB kinase α/β, *IL-1* interleukin 1, *IL-1R* interleukin 1 receptor, *IL-1RAcP* interleukin 1 receptor accessory protein, *IRAK* interleukin-1, receptor associated kinase, *JNK* cJun N-terminal kinase, *MAPK* mitogen associated protein (MAP) kinase, *MK* MAPK-activated protein kinase, *MyD88* myeloid differentiation primary response gene (88), *NEMO* NFκB essential modulator, *NFκB* nuclear factor kappa B, *RIP* receptor interactive protein, *TNFR* tumor necrosis factor receptor, *TNFα* tumor necrosis factor alpha, *TRADD* TNFR1-associated via death domain, *TRAF-2* TNF receptor associated factor 2, *TRAF-6* TNF receptor associated factor 6

115.3 Polyunsaturated Fatty Acids and Their Role in the Control of Innate Cerebral Immunity and Its Behavioral Effects

Polyunsaturated fatty acids (PUFAs) of the ω3 or ω6 families are essential nutrients, since they cannot be generated *de novo* in mammals. In plants, they exist as precursors (linoleic acid (18:2ω6, LA) and α-linolenic acid (18:3ω3, ALA)) that are metabolized by a series of elongation and desaturation steps into arachidonic acid (20:4ω6, AA) in the first case and eicosapentaenoic acid (20:5ω3, EPA) and docosahexaenoic acid (22:6ω3, DHA) in the second. These PUFAs are incorporated into cell membranes as phospholipids. The liver is the principal site of conversion of the precursors LA and
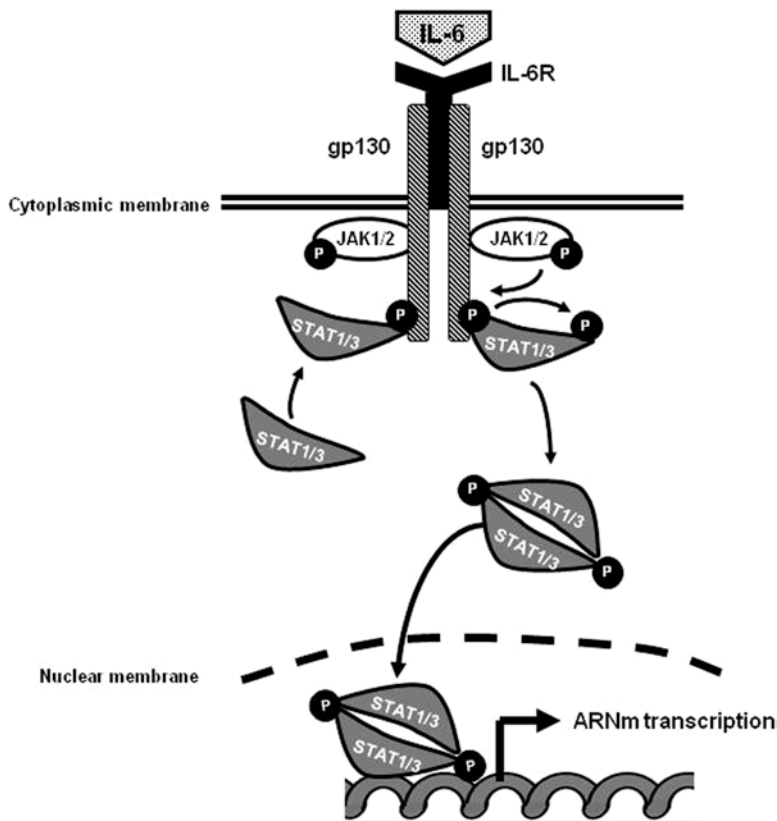
Fig. 115.2 Receptors and IL6 signaling pathways. *GP130* glycoprotein 130, *IL-6* interleukin 6, *IL-6R* interleukin 6 receptor, *JAK* Janus kinase, *STAT* signal transducers and activators of transcription

ALA into long-chain PUFAs, although other organs such as the brain also express the necessary elongases and desaturases. Since the two series of PUFAs compete for the use of the enzymes necessary for their biosynthesis, and because they have distinct physiological properties, the ω6/ω3 ratio in the diet is of particular importance. Foods previously consumed by humans were rich in ω3 PUFAs (products of hunting), while those consumed today are poor in these nutrients. Thus, since the industrial revolution, the ratio of ω6/ω3 PUFAs in the diet has increased from 1 to almost 20 in industrialized countries like the USA, leading to a significant deficiency in ω3 PUFAs (reviewed in Simopoulos 2009).

The dietary deficiency in ω3 PUFAs, by decreasing their intracerebral levels, promotes neuroinflammation and consequently the development of CNS disorders with an inflammatory component. Indeed, the low incidence of inflammatory disorders (psoriasis or asthma) as well as the total absence of multiple sclerosis in Eskimos from Greenland, whose dietary supply of ω3 PUFAs is high due to the consumption of fish, points to the importance of the interaction between ω3 PUFAs and inflammation (Dyerberg and Bang 1979). On the other hand, the effect of ω3 supplementation is subject to debate. Certain clinical studies have reported anti-inflammatory effects of ω3 PUFAs administered in the context of chronic and autoimmune inflammatory disorders, while other studies have failed to reproduce these findings. Conversely, dietary supplementation with fish oil rich in EPA and DHA

leads to an amelioration of symptoms in patients with rheumatoid arthritis, chronic inflammatory intestinal disorders, or multiple sclerosis.

In this chapter, we will discuss the effects of the deficiency of ω3 PUFAs on neuroinflammation, and its behavioral consequences.

115.3.1 Consequences of the Decrease in ω3 PUFAs on Neuroinflammation Related to the Activation of Innate Immunity

After adipose tissue, the brain and retina are the organs that contain the highest levels of fatty acids (50–60% of the dry weight of the brain consists of lipids), which are principally PUFAs (35% of the lipids of the brain). The principal PUFAs of the cell membranes of the nervous system are AA and DHA, which are mainly incorporated into the phospholipids phosphatidylethanolamine (PE) and phosphatidylcholine (PC) in neuronal membranes. Neurons do not contain the elongases or desaturases necessary for the synthesis of long-chain PUFAs from their precursors LA and ALA. Most of the DHA and AA incorporated into neuronal membranes thus need to be provided by the diet in the form of presynthesized PUFAs. Nevertheless, a portion of these PUFAs can be derived from the precursors LA and ALA, mainly in the liver. Such biosynthesis is minimal in the brain, where the activity of desaturase corresponds to a mere 6% of that measured in the liver (Bourre and Piciotti 1992). Endothelial cells convert ALA into EPA, and astrocytes produce DHA from EPA in order to supply it to neurons. Recent studies in the rat demonstrate that when 4.6% of ALA is provided by the diet (considered an adequate supply), the conversion of ALA into DHA by the liver is sufficient to meet the DHA needs of the brain. When the diet is poor in ALA, the synthesis of DHA by the brain in increased. Conversely, the expression of iPLA2 (calcium-independent phospholipase A2), which mobilizes the DHA associated with phospholipids, is inhibited in the brain, thus increasing the half-life of DHA in this organ (reviewed in Rapoport et al. 2007). In rodents, a dietary deficiency of ω3 PUFAs leads to a decrease in the brain concentration of DHA, and a corresponding increase in AA and the ω6 equivalent of DHA in terms of the number of carbon atoms – docosapentaenoic acid (DPAω6, 22:5n-6) (Table 115.1). This substitution takes place to the detriment of the specific biophysical properties of DHA, leading to various functional disturbances that can be seen both at the level of synaptic transmission and at the behavioral level.

In vitro, ω3 PUFAs efficiently inhibit the synthesis of the inflammatory cytokines IL-1β, TNFα, and IL-6 (Fig. 115.3) and their signaling pathways, in particular the NFκB and MAPK pathways. However, results obtained in vivo are more controversial. In rodents, supplementation with fish oil either decreases or increases the production of IL-1β, TNFα, and IL-6 by monocytes and macrophages

Table 115.1 Impact of DHA deficiency in diet on DPA (22:5 n-6) and DHA (22:6 n-3) levels in brain cortex phospholipids of mice

| | PUFA (%) in phosphatidylethanolamine (PE) | |
	Control	N-3 deficiency
22:5n-6 (DPA, n-6)	0.5 ± 0.0	$13.8 \pm 1.0^{***}$
22:6n-3 (DHA, n-3)	26.4 ± 0.3	$11.1 \pm 0.5^{***}$

Mice were fed with either n-3/n-6 (control) and n-6 (n-3 deficiency) diet. DHA was strongly decreased in cortex PE of mice fed the n-6 diet as compared with the n-3/n-6 diet while DPA was increased. Data are mean ± SEM values, expressed as weight percentage of total fatty acids ($n = 4$)

$^{***}p < 0.001$ n-3/n-6 versus n-6 groups (Data from Dr S. Layé group)
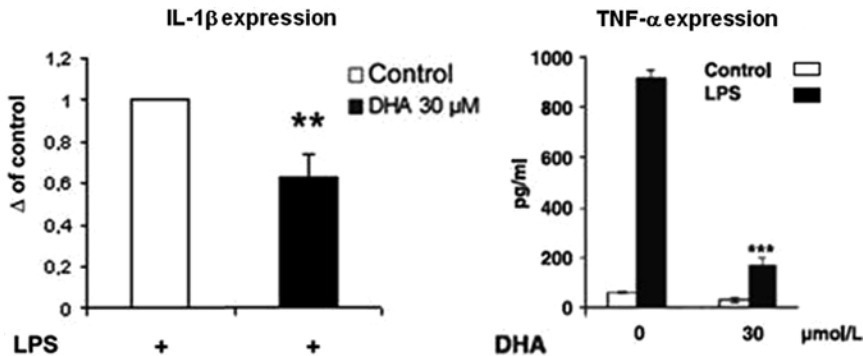
Fig. 115.3 Docosahexanenoic acid (*DHA*) inhibits lipopolysaccharide (*LPS*)-induced Interleukin-1beta (*IL-1β*) and Tumor Necrosis Factor alpha (*TNFα*) expression in BV-2 cells. BV-2 cells (microglia cell line) were treated or not with 30 μM DHA for 24 h and then stimulated with LPS (1 μg/mL) or its solvent (control) for 6 h. IL-1β expression normalized to actin (Δ of control) was measured by quantification of western blots. TNF-α levels were measured in cell supernatants by ELISA. Results are expressed as mean ± SEM, $n = 3$. **$p < 0.01$, ***$p < 0.001$ (Data from Dr S. Layé group)

ex vivo. EPA and DHA, by reducing the availability of AA, decrease the production of prostaglandin E2 (PGE2), which is anti-inflammatory at low doses and proinflammatory at high doses (reviewed in Calder 2006). In vivo, the synthesis of the inflammatory cytokines IL-1β, TNFα, and IL-6 is weaker, whereas that of anti-inflammatory cytokines is higher in rodents subjected to a diet enriched in fish oil. Similar results have been reported in healthy human volunteers. Thus circulating leukocytes stimulated ex vivo by LPS produced less IL-1β, TNFα, and IL-6 when they were derived from subjects who had consumed fish oil capsules. However, these results were not reproduced by another supplementation study with doses less than or equal to 1.7 g/day of EPA and DHA. Other studies using supplementation with higher doses of EPA and DHA also demonstrated no effect on the production of cytokines by blood leukocytes (reviewed in Calder 2006). Nevertheless, a prospective study carried out in a sample of 1,123 subjects has shown that the levels of total circulating ω3 PUFAs (ALA, EPA, and DHA) are inversely correlated to the concentrations of TNFα and IL-6, whereas the ω6/ω3 ratio is inversely correlated to the level of IL-10 (Ferrucci et al. 2006).

The symptoms of the disorder (social withdrawal, piloerection, etc.) as well as the elevation of plasma IL-6 induced by the administration of IL-1β in the rat are attenuated by a diet enriched in fish oil (Miguelez et al. 2006). Nevertheless, other studies demonstrate an increase in plasma TNFα in response to LPS in mice fed with oils rich in ω3 PUFAs (Chavali et al. 1998). In humans, dietary supplementation with fish oil capsules for 3–4 weeks attenuates the febrile response but does not affect plasma concentrations of cytokines in healthy volunteers given an intravenous injection of LPS (Michaeli et al. 2007). However, the intravenous administration of fish oil 24–48 h before LPS injection attenuates the production of plasma TNFα and aggravates the fever (Pluess et al. 2007). In addition, a diet rich in EPA attenuates the alterations in spatial memory induced by a central injection of IL-1β in rats (Song and Horrobin 2004). A dietary deficiency of ω3 PUFAs also reduces the DHA content of the brain and increases the peripheral and central production of IL-6 in response to LPS. However, this overproduction of IL-6 does not induce behavioral changes, since the STAT3 signaling pathway in the brain is only weakly activated (Fig. 115.4) due to mechanisms that remain to be elucidated (Mingam et al. 2008). The inhibitory effects of LPS on hippocampal LTP disappear in rats given a diet rich in EPA, or when hippocampal slices are treated in vitro with EPA, in which case this effect is associated with a decrease in the production of IL-1β in the hippocampus (Kavanagh et al. 2004). The protective effects of EPA on the LTP alterations induced by the amyloid β peptide

Fig. 115.4 STAT3 signaling pathway is altered in *n*-3 PUFA depleted mice. The *n*-3 PUFA deficient diet reduces the LPS-induced STAT3 activity in mice hippocampi. STAT3 activity was determined by quantification of western blot. Data are given as the mean of phosphorylated STAT3 on tyrosine 705 to STAT3 ± SEM. * $p < 0.05$ (Data from Dr S. Layé group)
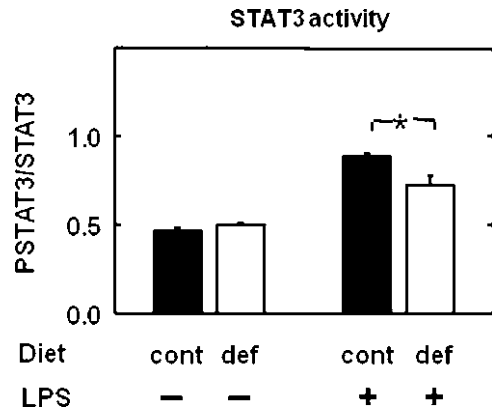
(Aβ) are associated with the inhibition of the expression of IL-1β in the hippocampus (Minogue et al. 2007). These data, taken together, suggest that dietary ω3 PUFAs limit the central effects of inflammatory cytokines under conditions of innate immune system stimulation.

115.3.2 Consequences of the Decrease in ω3 PUFAs on Age-related Neuroinflammation

During aging, the level and replacement of brain PUFAs decrease, particularly in the hippocampus, cortex, striatum, and hypothalamus. Brain levels of DHA and AA diminish in aging rats that display alterations in cognition and in LTP in the hippocampus (Favrelière et al. 2003; McGahon et al. 1999a). In transgenic SAMP8 mice, in which aging is accelerated, DHA decreases with age whereas lipid peroxidation increases (Petursdottir et al. 2007). In addition, the conversion of the precursors LA and ALA into their long-chain derivatives becomes less efficient. In fact, the activity of the desaturases responsible for the conversion of LA and ALA into their respective long-chain derivatives, and the activity of the Δ6 desaturase in particular, decreases with age in the liver and the brain. Phospholipid synthesis pathways are also altered with age, thus reducing the incorporation of PUFAs into membranes. The combination and interaction of these different alterations associated with aging contributes to a reduction in the level of DHA, i.e. a reduction in the index of membrane fluidity, in the brain of elderly people. In old animals that display a decrease in the membrane content of AA in the hippocampus, LTP is attenuated, but can be reestablished by a diet containing AA (McGahon et al. 1999b). These data serve to accentuate the importance of the dietary supply of DHA in aged subjects.

The expression of markers of microglial activation (CD68, MHCII and CD11b) increases with age in animals, as does the number of microglia in the brain of humans, attesting to the occurrence of age-related neuroinflammation (Godbout et al. 2005). Microglial cell reactivity is involved in the age-dependant increase in the production of inflammatory cytokines, as demonstrated by the inhibition of inflammatory cytokine overexpression by minocycline, an inhibitor of microglial reactivity, in aged rats (Griffin et al. 2006). In this context, the anti-inflammatory effect of long-chain ω3 PUFAs in the developing and aged brain could be due to their antioxidant activity. DHA and EPA are powerful antioxidants due to the presence of double bonds that are capable of capturing free radicals. It has been shown, notably, that DHA protects neurons in culture against the oxidative stress induced by methylmercury (Kaur et al. 2008), and that dietary supplementation with fish oil for 14 days reduces the levels of nitric oxide induced by cerebral ischemia, while promoting the activity of antioxidant enzymes such as sodium oxide dismutase and glutathione

peroxidase (Bas et al. 2007). In a cohort of elderly subjects, depressive individuals with an elevated plasma ω6/ω3 ratio present higher levels of TNFα and of IL-6 (Kiecolt-Glaser et al. 2007). Additionally, ω3 PUFA supplementation in elderly subjects reduces the levels of inflammatory cytokines produced by blood leukocytes stimulated in vitro (Meydani et al. 1991). The production of PGE2 by monocytes is inversely correlated to the EPA content of leukocytes obtained from aged subjects after the consumption of dietary complements containing different doses of EPA (Rees et al. 2006). To the extent that the level of peripheral cytokines reflects that of cytokines in the brain, these results, taken together, suggest that dietary ω3 PUFAs modulate neuroinflammation in elderly individuals. In rats, microglial activation, the production of IL-1β and alterations in hippocampal LTP with age are attenuated by EPA (Lynch et al. 2007). These data suggest that dietary ω3 PUFAs affect the inflammatory status of elderly subjects, and could thus modulate the associated cognitive deficits.

Epidemiological studies reveal the importance of ω3 PUFA levels in the development of age-linked neurodegenerative disorders. Thus, the plasma and brain levels of DHA decrease in patients with Alzheimer's disease. These results, however, remain controversial, since other studies demonstrate an increase or an absence of variation in brain DHA levels. Nonetheless, the risk of dementia is augmented in elderly subjects presenting low levels of circulating EPA. The use of a mouse model of Alzheimer's disease, the Tg2576 mouse, has demonstrated that a dietary supply of DHA leads to a reduction in the formation of amyloid plaques. However, the administration of dietary supplements containing DHA to patients with Alzheimer's disease or mild cognitive impairment has not yielded conclusive results (reviewed in Calon and Cole 2007).

115.4 Mechanisms of Action of Polyunsaturated Fatty Acids in Neuroinflammation

115.4.1 Lipid Derivatives of the PUFAs and Neuroinflammation

The hypothesis that the PUFAs regulate neuroinflammation relies on their previously described role in the control of inflammation in the periphery. In this chapter, we will review the pro- and anti-inflammatory properties of the PUFAs and their occurrence in the brain. It is well established that ω3 and ω6 PUFAs exert opposing effects on the regulation of inflammation. However, their effects are more nuanced. Thus ω6 PUFAs, AA in particular, are the precursors of the eicosanoids, which have proinflammatory effects, whereas ω3 PUFAs have weaker inflammatory effects. The PUFAs are released from membrane phospholipids principally by calcium-dependant phospholipase A2 (cPLA2), which is activated under inflammatory conditions. The released PUFAs enter two distinct metabolic pathways, the cyclooxygenase (COX) pathway leading to the formation of prostaglandins (PGs), prostacyclins (PGIs), and thromboxanes (TXs); and the lipoxygenase (LOX)/leukotriene synthase pathway leading to the formation of leukotrienes (LTs) (Fig. 115.5).

COX-1 and COX-2 are constitutively expressed in microglial cells and neurons, respectively. Under inflammatory conditions, their expression is induced in glial cells and endothelial cells of blood vessels in the brain. The eicosanoids produced by the inflammatory activity of COX-2 mainly yield PGE2, which is synthesized from AA. The actions of PGE2 in the brain lead to fever and an increase in vascular permeability, vasodilation, pain, and edema. However, a portion of the eicosanoids derived from AA metabolism is responsible for silencing the inflammatory response before it becomes detrimental to the organism. The lipoxins produced by the 15-LOX pathway, especially
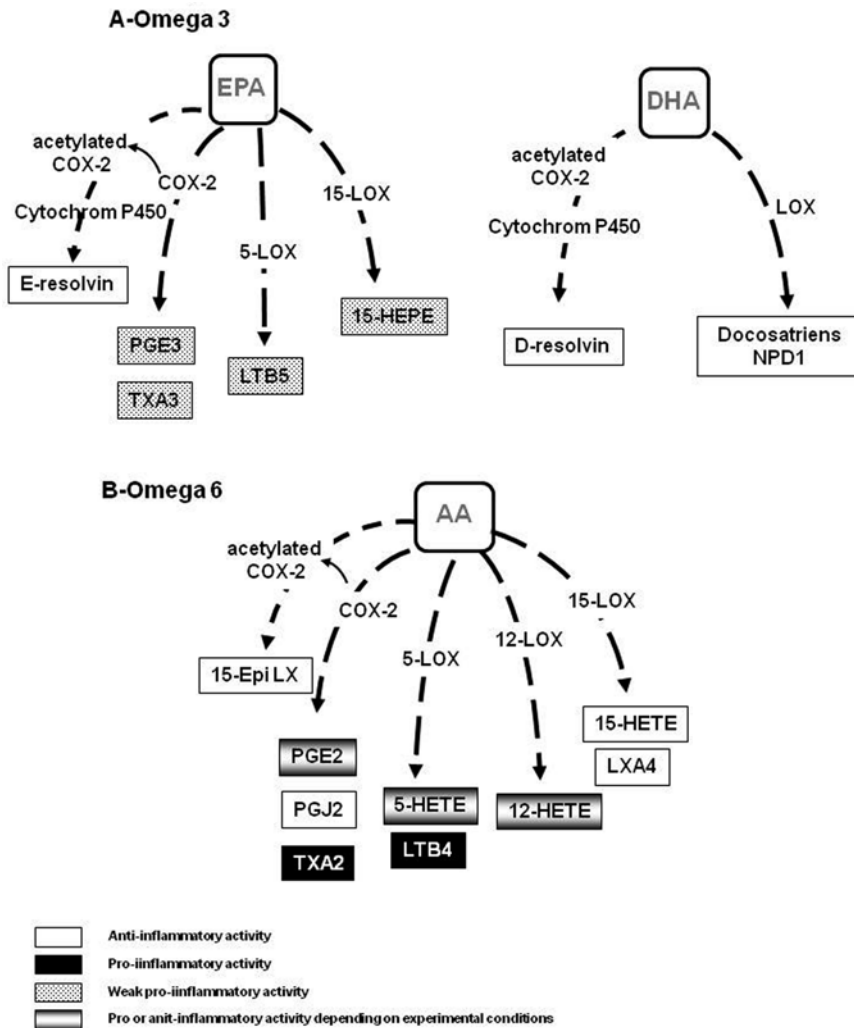
Fig. 115.5 Metabolic derivatives of PUFAs. (**a**) Metabolic derivatives of docosahexaenoic acid (*DHA*) and eicosapentaenoic acid (*EPA*). (**b**) Metabolic derivatives of arachidonic acid (*AA*). *COX* cyclooxygenase, *HEPE* hydroxyeicosapentaenoic acid, *HETE* hydroxyeicosatetraenoic acid, *LOX* lipoxygenase, *LT* leukotriene, *LXA4* lipoxin A4, *PG* prostaglandin, *PGE2* prostaglandin E2, *TX* thromboxane, *NPD1* neuroprotectin D1

LXA4, are included among these mediators and, as such, have anti-inflammatory effects (reviewed in Serhan 2008). There exist other anti-inflammatory lipoxins, the 15-epi-lipoxins, which are produced not by the 5-LOX pathway but by the acetylation of COX-2 under the influence of aspirin. Certain series 2 prostaglandins, such as PGE2 and 15-deoxy-delta 12,14-prostaglandin J2 (15d-PGJ2), also display anti-inflammatory properties, blocking the synthesis of the LTs by the inhibition of 5-LOX, and inducing 15-LOX and the formation of lipoxins (reviewed in Serhan 2008). PGE2 and 15d-PGJ2 also inhibit the synthesis of the inflammatory cytokines IL-1β and TNFα (reviewed in Calder 2009). In vivo, these lipid derivatives of AA inhibit the inflammation associated with ischemia, colitis, arthritis, and fever (review in Scher and Pillinger 2005). The ω3 PUFAs reduce the synthesis of eicosanoids by inhibiting the activity of PLA2 and, as a consequence, the production of PGE2, TXA2, and LTB4 (reviewed in Calder 2009). The global impact on inflammation thus remains

complex. However, EPA is also metabolized by the COX and LOX enzymes, generating series 3 PGs and TXs, series 5 LTs and hydroxyeicosapentaenoic acids (HEPEs) with weak inflammatory or even anti-inflammatory effects in certain cases (Fig. 115.5). These examples clearly illustrate the complexity of the effects of the lipid derivatives of the PUFAs on inflammation. The recent discovery of resolvins and protectins, lipid derivatives of the ω3 PUFAs that play a key role in the termination phase of the inflammatory response, has clarified this situation. The synthesis of these derivatives from EPA and/or DHA depends on the acetylation of COX-2 by aspirin or by the cytochrome P450 pathway. The docosanoids derived from the metabolism of DHA (Fig. 115.5) include the docosatrienes generated by LOX. D series resolvins and the docosatrienes (or neuroprotectin D1) have been described in the blood and in glial cells in humans as well as in the mouse brain. In the brain, they have an anti-inflammatory and neuroprotective effect. In fact, resolvins inhibit the leukocytic infiltration that follows ischemia. These antiapoptotic compounds are synthesized by epithelial cells of the retina under conditions of oxidative stress, and in the brain of patients with Alzheimer's disease or after a stroke (reviewed in Serhan 2008). In addition, neuroprotectin D1 decreases the release of amyloid β peptide by neurons stimulated with IL-1β (Lukiw et al. 2005). While these results suggest that the resolvins and neuroprotectin D1 are powerful anti-inflammatory agents, their involvement in the protective effects of DHA with respect to neuroinflammation remains to be proven.

115.4.2 The Role of Nuclear Receptors in the Immunomodulatory Properties of the PUFAs

The PUFAs and some of their metabolites can regulate gene expression through the intermediary of members of the superfamily of nuclear receptors. This is true particularly with respect to the peroxisome proliferator-activated receptors (PPARs), the liver X receptors (LXRs), and the retinoid X receptors (RXRs), transcription factors that are mainly involved in the regulation of lipid metabolism and inflammation. The PPARs bind to DNA after forming a heterodimer with an RXR. Several ligands of PPARα and PPARγ inhibit the transcription of the genes for IL-1β, TNFα, IL-6, and COX-2, notably by attenuating the activation of the NFκB pathway. In addition, mice lacking the gene for PPARα display a prolonged inflammatory response, pointing to an anti-inflammatory effect of this receptor. DHA is one of the natural ligands of PPARα, and EPA can bind to all members of the PPAR family. The anti-inflammatory effects of the ω3 PUFAs and their effects on the regulation of lipid metabolism could thus bring these receptors into play. PPARγ is more involved in the anti-inflammatory activity of 15d-PGJ2, one of its natural agonists (review in Scher and Pillinger 2005). Nevertheless, in vivo, not much information is available regarding the role of these receptors in the modulation of neuroinflammation by the ω3 PUFAs.

115.4.3 The Role of Lipid Rafts in the Immunomodulatory Properties of the PUFAs

The ω3 PUFAs have an impact on the physiochemical properties of the cell membrane by virtue of their incorporation into membrane phospholipids. They can thus act directly on the activity of membrane proteins, especially through the modulation of lipid rafts. Lipid rafts are membrane microdomains with a high concentration of numerous receptors and proteins involved in signal transduction, thus

constituting veritable signaling platforms. The receptors of LPS, TLR4, and CD14, as well as TNFR1, gp130, and certain proteins involved in their signaling such as STAT3, are associated with lipid rafts (Triantafilou et al. 2002; Legler et al. 2003; Sehgal et al. 2002). The rafts are enriched in cholesterol and sphingolipids and poor in PUFAs, in contrast to the more fluid surrounding membrane, thus allowing them to float freely throughout the membrane. DHA is the PUFA with the highest conformational flexibility due to its six double bonds, which behave like joints around which the molecule undergoes tortional rotations. It has been shown that DHA and EPA modify the association of proteins with the lipid rafts, as well as the lipid composition of the rafts themselves, thus inhibiting the signal transduction associated with IL-2 in human T-lymphocytes (Jurkat cells) (reviewed in Chapkin et al. 2008). In mice, the consumption of fish oil leads to an increase in the ω3 PUFA content of raft and non-raft fractions of T-lymphocyte membranes, as well as to a reduction in the sphingolipid content of the rafts, along with a suppression of the activation of the IL-2 signaling pathway. Pretreatment with DHA strongly inhibits the production of IL-1β and of TNFα by microglial cells. This decrease is associated with a suppression of the cell surface expression of the proteins CD14 and TLR4 of the LPS receptor complex in microglia, without any modification in their subcellular localization, i.e. raft for CD14 and nonraft for TLR4 (De Smedt-Peyrusse et al. 2008). It remains to be determined if this is also the case for microglial cells in vivo.

115.5 Conclusion

There is growing evidence that the expression and action of proinflammatory cytokines in the brain are responsible not only for the development and maintenance of sickness behavior during the host response to infection, but also for the occurrence of nonspecific symptoms of sickness during chronic inflammatory disorders and aging. In addition, neuroinflammation can have detrimental consequences on neuronal viability, especially when maintained over long periods of time and transiently amplified by peripheral infectious episodes. All of this points to the interest of finding new ways of controlling inflammation in the brain. Because of their abundance in the brain and their modulatory effects on inflammation and cell functions, PUFAs definitely play a role in this process. However, this role needs to be better characterized by multidisciplinary studies aimed at assessing the effects of these molecules at different levels, from the molecular level to that of the organism as a whole.

Key Terms

Innate immune system: Comprises the cells and mechanisms that defend the host from infection by other organisms, in a nonspecific manner. Innate immune systems provide immediate defense against infection.

Cytokines: Immunomodulating agents secreted by certain cells of the immune system, which carry signals locally between cells; and thus have an effect on other cells. They are a category of signaling molecules.

PUFA: Depending on their degree of saturation, fatty acids are classified as either saturated fatty acids, monounsaturated fatty acids, or polyunsaturated fatty acids (PUFA). PUFA are found in dietary fats and oils, and are known as essential fats. Like vitamins, fatty acids are essential for life; they cannot be made in the body and must be obtained via the diet.

Lipid rafts: Cholesterol and sphingolipid-enriched microdomains floating freely in the cell membrane bilayers. They serve as organizing centers for the assembly of signaling molecules, influencing membrane fluidity and membrane protein trafficking.

Key Features

1. Microglial cells and astrocytes represent cerebral innate cells. They are activated by immunogenic stimuli to produce inflammatory cytokines.
2. During aging, the reactivity of microglial cells and astrocytes increase, leading to cerebral micro inflammation and consequently higher sensitivity of the neurons towards cytokines.
3. IL-1β, IL-6, and TNF-α and their receptors are expressed in the central nervous system, especially in glial cells throughout life.
4. Binding of IL-1β and TNF-α to their receptors is associated to the activation of NFκB and MAP kinases signaling pathways.
5. Binding of IL-6 to its receptor is associated to the activation of JAK/STAT signaling pathway.
6. Omega3 (ω3) and omega 6(ω6) represent two distinct PUFA families.
7. Linoleic acid (LA) is the precursor of ω6 PUFA family including arachidonic acid (AA).
8. α-Linolenic acid (ALA) is the precursor of ω3 PUFA family including docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA).
9. Ratio of ω6 to ω3 recommended in the diet is about 1:5, while in industrialized countries, ω6/ω3 reaches 1:20, leading to a significant deficiency in ω3 PUFAs.
10. PUFAs are essential and represent 35% of the lipids of the brain.
11. The brain PUFAs, mainly DHA and AA, are provided either directly from the diet or from their precursors ALA and LA via the liver.
12. Dietary ω3 PUFAs limit the central effects of inflammatory cytokines under conditions of innate immune system stimulation.
13. Aging goes with a decrease of brain ω3 PUFAs content.
14. Deficit of brain ω3 PUFAs content is a risk factor for age-related cognitive decline and or the development of inflammatory neurodegenerative diseases.
15. Dietary ω3 PUFAs affect the inflammatory status of elderly subjects and could modulate the associated cognitive deficits.
16. ω6 PUFAs and especially AA generate lipid derivatives with inflammatory activities while ω3 PUFAs (EPA and DHA) generate lipid derivatives with anti-inflammatory properties.
17. Dietary PUFAs modulate expression, production, and activation of signaling pathways of inflammatory cytokines.
18. PUFAs regulate gene expression via the nuclear receptors PPAR and RXR.
19. PUFAs modulate the expression of cytokine receptors and their signaling pathways via lipid rafts in the membranes.

References

Bas O, Songur A, Sahin O, Mollaoglu H, Ozen OA, Yaman M, Eser O, Fidan H, Yagmurca M. Neurochem Int. 2007;50:548–54.
Bourre JM, Piciotti M. Neurosci Lett. 1992;141:65–8.
Calder PC. Am J Clin Nutr. 2006;83:1505S–19S.
Calder PC. Biochimie. 2009;91:791–5.
Calon F, Cole G. Prostaglandins Leukot Essent Fatty Acids. 2007;77:287–93.
Chapkin RS, McMurray DN, Davidson LA, Patil BS, Fan YY, Lupton JR. Br J Nutr. 2008;100:1152–7.

Chavali SR, Zhong WW, Forse RA. Prostaglandins Leukot Essent Fatty Acids. 1998;58:185–91.

De Smedt-Peyrusse V, Sargueil F, Moranis A, Harizi H, Mongrand S, Layé S. J Neurochem. 2008;105:296–307.

Dyerberg J, Bang HO. Lancet. 1979;2:433–5.

Dziennis S, Alkayed NJ. Rev Neurosci. 2008;19:341–61.

Ericsson A, Liu C, Hart RP, Sawchenko PE. J Comp Neurol. 1995;361:681–98.

Favrelière S, Perault MC, Huguet F, De Javel D, Bertrand N, Piriou A, Durand G. Neurobiol. Aging. 2003;24:233–43.

Ferrucci L, Cherubini A, Bandinelli S, Bartali B, Corsi A, Lauretani F, Martin A, Andres-Lacueva C, Senin U, Guralnik JM. J Clin Endocrinol Metab. 2006;91:439–46.

Gautron L, Lafon P, Chaigniau M, Tramu G, Layé S. Neuroscience. 2002;112:717–29.

Godbout JP, Chen J, Abraham J, Richwine AF, Berg BM, Kelley KW, Johnson RW. FASEB J. 2005;19:1329–31.

Griffin R, Nally R, Nolan Y, McCartney Y, Linden J, Lynch MA. J Neurochem. 2006;99:1263–72.

Harré EM, Roth J, Pehl U, Kueth M, Gerstberger R, Hübschle T. J Appl Physiol. 2002;92:2657–66.

Jones SA, Richards PJ, Scheller J, Rose-John S. J Interferon Cytokine Res. 2005;25:241–53.

Kaur P, Heggland I, Aschner M, Syversen T. Neurotoxicology. 2008;29:978–87.

Kavanagh T, Lonergan PE, Lynch MA. Prostaglandins Leukot Essent Fatty Acids. 2004;70:391–7.

Kiecolt-Glaser JK, Belury MA, Porter K, Beversdorf DQ, Lemeshow S, Glaser R. Psychosom Med. 2007;69:217–24.

Konsman JP, Vigues S, Mackerlova L, Bristow A, Blomqvist A. J Comp Neurol. 2004;472:113–29.

Legler DF, Micheau O, Doucey MA, Tschopp J, Bron C. Immunity. 2003;18:655–64.

Liu ZG. Cell Res. 2005;15:24–7.

Lukiw WJ, Cui JG, Marcheselli VL, Bodker M, Botkjaer A, Gotlinger K, Serhan CN, Bazan NG. J Clin Invest. 2005;115:2774–83.

Lynch AM, Loane DJ, Minogue AM, Clarke RM, Kilroy D, Nally RE, Roche OJ, O'Connell F, Lynch MA. Neurobiol Aging. 2007;28 (6):845–55.

Lynch AM, Lynch MA. Eur J Neurosci. 2002;15:1779–88.

McCoy MK, Tansey MG. J Neuroinflammation. 2008;5:45.

McGahon BM, Martin DS, Horrobin DF, Lynch MA. Neuroscience. 1999a;94:305–14.

McGahon BM, Murray CA, Horrobin DF, Lynch MA. Neurobiol Aging. 1999b;20:643–53.

Meydani SN, Endres S, Woods MM, Goldin BR, Soo C, Morill-Labrode A, Dinarello CA, Gorbach SL. J Nutrition. 1991;121:547-555.

Michaeli B, Berger MM, Revelly JP, Tappy L, Chiolero R. Clinical nutrition (Edinburgh, Scotland) 2007;26:70-77.

Miguelez M, Anisman H, Weber JM, Merali Z. J Neuroimmunol. 2006;181:19–28.

Mingam R, Moranis A, Bluthé RM, De Smedt-Peyrusse V, Kelley KW, Guesnet P, Lavialle M, Dantzer R, Layé S. Eur J Neurosci. 2008;28:1877–86.

Minogue AM, Lynch AM, Loane DJ, Herron CE, Lynch MA. J Neurochem. 2007;103:914–26.

Nadjar A, Combe C, Layé S, Tridon V, Dantzer R, Amédée T, Parnet P. J Neurochem. 2003;87:1024–36.

Pertusa M, García-Matas S, Rodríguez-Farré E, Sanfeliu C, Cristòfol R. J Neurochem. 2007;101:794–805.

Petursdottir AL, Farr SA, Morley JE, Banks WA, Skuladottir GV. Neurobiol Aging. 2007;28:1170–8.

Pluess TT, Hayoz D, Berger MM, Tappy L, Revelly JP, Michaeli B, Carpentier YA, Chioléro RL. Intensive Care Med. 2007;33:789–97.

Rapoport SI, Rao JS, Igarashi M. Prostaglandins Leukot Essent Fatty Acids. 2007;776:251–61.

Rees D, Miles EA, Banerjee T, Wells SJ, Roynette CE, Wahle KW, Calder PC. Am J Clin Nutr. 2006;83:331–42.

Rothwell NJ, Luheshi GN. Trends Neurosci. 2000;23:618–25.

Scher JU, Pillinger MH. Clin Immunol. 2005;114:100–9.

Sehgal PB, Guo GG, Shah M, Kumar V, Patel K. J Biol Chem. 2002;277:12067–74.

Serhan CN. Prostaglandins Leukot Essent Fatty Acids. 2008;79:157–63.

Simopoulos AP. World Rev Nutr Diet. 2009;99:1–16.

Song C, Horrobin D. J Lipid Res. 2004;45:1112–21.

Tancredi V, D'Antuono M, Cafè C, Giovedì S, Buè MC, D'Arcangelo G, Onofri F, Benfenati F. J Neurochem. 2000;75:634–43.

Triantafilou M, Miyake K, Golenbock DT, Triantafilou K. J Cell Sci. 2002;115:2603–11.

Ye SM, Johnson RW. J Neuroimmunol. 2001;117:87–96.

Chapter 116
Dietary Supplementation of Omega-3 Polyunsaturated Fatty Acids in Autism

Pierluigi Politi, Hellas Cena, and Enzo Emanuele

Abbreviations

AA	Arachidonic acid
ABC	Aberrant behavior checklist
ABLLS	Assessment of basic language and learning skills
ADI-R	Autism diagnostic interview-revised
ALA	Alpha-linolenic acid
ASD	Autistic spectrum disorder
ASP	Asperger syndrome
CARS	Childhood autism rating scale
DHA	Docosahexaenoic acid
DSM-IV	Diagnostic and statistical manual of mental disorders
EPA	Eicosapentaenoic acid
GLA	Gamma-linolenic acid
PDD	Pervasive developmental disorders
PUFA	Polyunsaturated fatty acids

116.1 Introduction

Autism is a behaviorally defined neurodevelopmental disorder characterized by social and communication deficits, accompanied by repetitive and stereotyped behaviors, with onset before 3 years of age (Sigman et al. 2006). Leo Kanner of the Johns Hopkins Hospital first used the term autism in its modern sense when he introduced the label early infantile autism in a 1943 report of 11 children with striking behavioral similarities (Lyons and Fitzgerald 2007). In his words, "There is from the start an extreme autistic aloneness that, whenever possible, disregards, ignores, shuts out anything that comes to the child from the outside." It is this social impairment, along with impairments in communication, and the presence of restricted patterns of behaviors and interests that characterize autism (see Table 116.1).

The diagnostic indicators of autism are core behavioral symptoms rather than definitive neuropathologic markers. Autistic symptoms, however, can occur in a variety of combinations and present with

P. Politi (✉)

Department of Health Sciences, Section of human nutrition and dietetics, University of Pavia,
Via Bassi 21, I-27100 Pavia, Italy
e-mail: pierluigi.politi@unipv.it

Table 116.1 Key features of autism

1. Autism is a complex developmental disability that causes problems with social interaction and communication.
2. Health care providers think of autism as a "spectrum" disorder, a group of disorders with similar features. One person may have mild symptoms, while another may have serious symptoms. But they both have an autism spectrum disorder.
3. People with autism may show unsuspected abilities.
4. Behavioral problems (aggressive and/or self-injurious behavior, tantrums) are frequently present.
5. Autism is generally diagnosed in the first 3 years of life.
6. Nevertheless, it is a lifelong condition.
7. Despite the clinical severity, people with autism can learn and function normally and show improvement with appropriate intervention, care, and education
8. Lifelong care is often a burden for families, but its costs can be strongly reduced with early diagnosis and intervention.

This table lists the key features of autism, including some basic epidemiology, clinical presentation, treatment and care

varying degrees of severity. The heterogeneity and clinical variability of autism has prompted the use of the term autistic spectrum disorders (ASDs) instead of autism. There are five ASDs described in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition-Text Revision of the American Psychiatric Association, i.e. (a) autistic disorder; (b) Asperger syndrome; (c) pervasive developmental disorder—not otherwise specified; (d) childhood disintegrative disorder; and (e) Rett syndrome. According to the ICD-10 categorization (code F84), there are nine different forms of ASDs comprising childhood autism, atypical autism, Rett syndrome, other childhood disintegrative disorder, overactive disorder associated with mental retardation and stereotyped movements, Asperger syndrome, other pervasive developmental disorders, and pervasive developmental disorder, unspecified. In any case, there is continued debate regarding the clinical boundaries of these disorders inasmuch as autistic-like traits and behaviors represent a continual spectrum rather than clinically defined diagnostic categories.

Although epidemiology data reported an incidence of 2–5 in 10,000 newborn babies before 1985, studies performed after the year 2000 converge upon rates of ASDs as high as 20–60 in 10,000 (Lintas and Persico 2009). This alarming rise in the prevalence of ASDs compelled researchers to explore why the number of children with ASDs seemed to be rising and sparked debate about a possible autistic "epidemic." There is uncertainty, however, regarding whether the increase in reported prevalence reflects a true increase in the incidence of ASD. In addressing the increased prevalence reports, experts frequently refer to the recent "broadening" phenotype of ASDs and the resulting inclusion of children with disorders that do not necessarily meet the criteria for true autism as a potential influence on the increased numbers (Kippes and Garrison 2006). Of note, the male: female sex ratio is 4:1, implying an involvement of X-linked genetic factors and/or imprinting mechanisms in the pathogenesis of this condition.

In general, it is believed that autism is a complex multifactorial disorder and has no single cause. Accordingly, growing evidence supports the idea that ASDs may be caused by several factors, including multigenic interactions and complex environmental contributions (Zecavati and Spence 2009). From a genetic standpoint separate genes seem to contribute to the social impairment, communicative impairment, and the rigid or repetitive behaviors, thus explaining the variation found along the spectrum of ASDs. Although most experts agree that there is a strong genetic component to autism, the more controversial discussions revolve around the possible environmental factors that may influence the phenotypic expression of ASDs. Most commonly cited environmental factors include immunizations (child and maternal immunization during pregnancy), environmental exposure (to infection, medications, or toxins), intolerance to food (primarily those containing casein and gluten), and specific perinatal events (e.g., fetal distress or anoxia, prematurity, low birth weight, uterine bleeding, or induced labor. Studies now under way are also investigating the relationship between factors such as atypical placental growth, abnormal gut tissue, inflamed tissue in the brain,

maternal/paternal age, and nutritional deficiencies. What was once considered a primary disorder of the brain is now being conceptualized as a multifactorial disorder, whereby the interaction between the genetic predisposition and environmental factors leads to a change in cerebral function.

116.2 Omega 3 Fatty Acids: A Clue for Orthomolecular Psychiatry?

In 1968, the two-time Nobel Prize winner and molecular biologist Linus Pauling published an article in *Science* entitled "Orthomolecular psychiatry" in which he described a biochemical model for investigating nutritional therapies for mental diseases (Pauling 1968). Reading (1979) defined orthomolecular psychiatric therapy as the study of the metabolic, endocrine, immunological, and toxic disturbances that are contributing to, perpetuating, exacerbating or even causing psychiatric symptomatology. In orthomolecular psychiatry, diseases are assumed to originate from multiple nonspecific causes, congenital and acquired. These causes give rise to biochemical aberrations, the accumulation of which results in symptoms and signs, from which the perception of a disease state follows. Orthomolecular psychiatry, therefore, pursues the treatment of mental disease by the provision of the optimum molecular environment for the brain, especially the optimum concentrations of substances normally present in the body. Successful treatment for psychiatric conditions according to orthomolecular psychiatry thus includes natural therapies such as nutrients and dietary changes. Modern advances in molecular biology generally support the concept of orthomolecular psychiatry as proposed 40 years ago. Accordingly, growing scientific evidence suggests that omega-3 polyunsaturated fatty acids (PUFA) may exert significant therapeutic effect as an orthomolecular psychiatry tool in a variety of different mental disorders, including schizophrenia, depression, and attention deficit hyperactivity disorder (Ross et al. 2007). This is both somewhat surprising, considering some of the fundamental differences between these conditions, but also promising, in particular in areas in which therapeutic options are limited.

   There is now good evidence indicating that PUFA accrued in rodent, primate, and human brain during active periods of perinatal cortical maturation, and that essential fatty acids play an important role in neuronal differentiation, synaptogenesis, and synaptic function (Green et al. 2006). PUFA are subdivided into the omega-3 (*n*-3) series (the first double bond is three carbons from the end (omega) carbon atom of the molecule) that are synthetically derived from linoleic acid (LA), and the omega-6 (*n*-6) series which are derived from alpha-linolenic acid (ALA), both 18 carbon atom containing fatty acids (see Table 116.2). LA and ALA are termed essential fatty acids because mammalian cells are unable to synthesize these fatty acids from simpler precursors. LA can be converted sequentially via a biosynthetic pathway into other omega-6 fatty acids, the 18 carbon gamma linolenic acid (GLA), and the 20 carbon arachidonic (AA) and dihomogammalinolenic acids (DGLA). Similarly, ALA is converted into longer chain omega-3 fatty acids such as 20 carbon eicosapentaeoic acid (EPA) and 22 carbon docosahexaenoic acid (DHA).

Table 116.2 Key features of omega-3 fatty acids

1. Omega-3 fatty acids are necessary for conception, growth, and fetal development.
2. Brain and nervous system development depends on omega-3 fatty acids.
3. Omega-3 fatty acids are found in human milk and their concentrations are higher in red blood cells of breast-fed infants than of bottle-fed infants.
4. Adequate omega-3 fatty acids are important for maintaining an adequate brain neurotransmitter function.
5. Omega-3 fatty acids have anti-inflammatory effects that may contribute to their neuroprotective properties.
6. Great progress has been made in the understanding of the role of omega-3 fatty acids in health and disease.
7. Promotion of adequate dietary recommendations on omega-3 intake is important in the prevention and management of neuropsychiatric disorders and mental wellness.

This table lists the key features of omega-3 fatty acids, with a special focus on their role in the central nervous system

Table 116.3 Omega-3 fatty acids and neuropsychiatric disorders

1. Autism
2. Attention deficit-hyperactivity disorder
3. Depression
4. Anxiety disorder
5. Bipolar disorder
6. Personality disorders
7. Schizophrenia
8. Eating disorders
9. Epilepsy
10. Alzheimer's disease
11. Sleep disorders

This table summarizes examples of clinical conditions with neuropsychiatric features for which the usefulness of omega-3 fatty acids has been suggested

Increasing evidence indicates, however, that although LA and ALA can be converted into their longer chain length metabolites, the rate of conversion in humans is very slow, resulting in an estimated 2–10% of ALA being converted to DHA or EPA. This suggests that a major source of the longer chain polyunsaturated fatty acid species such as EPA and DHA is likely to be dietary. Such a view is supported by data that supplementation with fish oils can markedly elevate the cellular levels of both these omega-3 PUFA (Gerster 1998).

Omega-3 PUFA are of particular interest from a nutritional standpoint in the field of orthomolecular psychiatry since the intake of these fatty acid is considered to be currently low in Western diets (see Table 116.3). Such a use is biologically plausible given that omega-3 fatty acids, in particular DHA, are abundant in the brain and are involved in, or modulate, the mechanism by which brain neurons communicate. Relative to brain maturation in humans, DHA accumulates in cerebral tissue at a rapid rate (14.5 mg/week) during the third trimester (gestational weeks 26–40) (McCann and Ames 2005). At term birth, DHA represents approximately 9% of total cortical fatty acid composition and increases by an additional 6% between birth and age 20 to compose 15% total cortical fatty acid composition. Of note, infants born preterm (<33 weeks of gestation) exhibit lower (−40%) cortical DHA concentrations relative to term infants (McNamara and Carlson 2006). These data indicate that the majority of DHA accumulation occurs in the human brain during the last trimester of normal gestation, and that DHA continues to accumulate throughout postnatal brain maturation. The linear increase in DHA accumulation in human frontal cortex between birth and 20 years of age corresponds with linear increases in frontal cortex white matter during this period, and additionally corresponds with the initial frontal gray matter expansion which continues until 12 years of age and then declines thereafter (Young et al. 1997). Interestingly, experimental studies in animals have shown that prenatal deficits in brain DHA accrual are associated with clear deficits in neuronal arborization, multiple indices of synaptic pathology, deficits in mesocorticolimbic dopamine neurotransmission, deficits in hippocampal serotonin and acetylcholine neurotransmission, neurocognitive deficits on hippocampus- and frontal cortex-dependent learning tasks, and elevated behavioral indices of aggression.

116.3 Evidence of Omega-3 Alterations in Autism

Previous studies linking reduced PUFA levels to autism represent the rationale for their use as a therapeutic means in this condition (see Table 116.4). Vancassel et al. (2001) were the first to compare essential fatty acid levels in the plasma of children with autism versus those with mental retardation.

Table 116.4 Studies examining the levels of omega-3 fatty acids in patients with autism compared with controls

Study	Participants	Target Analytes	Results
Meguid et al. (2008)	30 autistic children (18 males and 12 females) aged 3–11 years and 30 healthy children as control group	Linolenic acid Linoleic acid Arachidonic acid Docosahexaenoic acid	ASD children display reduced levels of linoleic acid (71%), DHA (65%) and arachidonic acid (45%) compared to apparently healthy subjects
Bu et al. (2006)	40 children with autism (20 with early onset autism and 20 with developmental regression) and age-matched, 20 typically developing controls and 20 subjects with nonautistic developmental disabilities	Fatty acids extracted from RBC	No major differences in essential fatty acids composition; however, increased levels of eicosenoic acid (20:1n9) and erucic acid (22:1n9) were found in autistic subjects with developmental regression compared with typically developing controls.
Sliwinski et al. (2006)	16 high-functioning male youngsters with autism (age 12–18) and 22 healthy volunteers	Plasma phospholipid omega-3 (3) and omega-6 (6) PUFA fractions and the 3/6 ratio	Patients with autism showed a significant increase in the fraction of C22:6–3 (docosahexaenoic acid, DHA) and an increase in the total 3/6 ratio
Hardy and Hardy (2002)	Subjects with pervasive developmental disorders	DHA/EPA in red blood cells membrane	90% of subjects with pervasive developmental disorders showed deficiencies of DHA/EPA in red blood cells membrane
Vancassel et al. (2001)	15 children with autism (4 girls, 11 boys) aged between 3 and 17 years (mean age 8 years 4 months), and 18 mentally retarded children (5 girls, 13 boys) aged between 1 and 19 years (mean age 8 years 8 months).	DHA, total PUFA	Significantly lower DHA and total PUFA concentrations in ASD children, omega-6 fatty acid levels were within the normal range

This table summarizes the studies in favor or against an altered omega-3 fatty acid status in autism

The authors reported significantly lower DHA and total PUFA concentrations in ASD children, whereas omega-6 fatty acid levels were within the normal range. In keeping with previous results, other authors (Bradstreet and Kartzinel 2001) detected omega-3 fatty acid deficiencies in nearly 100% of patients diagnosed with ASD. Another study has indicated that 90% of subjects with PDD have deficiencies of DHA/EPA in red blood cells membrane (Hardy and Hardy 2002). Reduced total omega-3 levels have been also reported in patients with regressive autism and Asperger syndrome (Bell et al. 2004). Recently, it has been suggested that ASD children display reduced levels of linoleic acid (71%), DHA (65%) and arachidonic acid (45%) compared to apparently healthy subjects (Meguid et al. 2008). Sliwinski et al. (2006) measured the levels of omega-3 and omega-6 polyunsaturated fatty acids in 16 high-functioning males with autism aged between 12 and 18 years. The authors reported a significant increase in DHA levels in autism that awaits independent replication. Although the great majority of published studies have suggested an unbalance of omega-3 levels in autism, one report (Bu et al. 2006) found no significant differences in essential fatty acids composition in 20 autistic patients compared with controls. However, different experimental designs, different number and characteristics of subjects recruited, ethnical differences, medical treatments, lack of standardization of methods for the determination of omega-3 levels and different ways in which serum or plasma samples were handled might at least partially explain the differences in the published data.

116.4 Omega-3 Fatty Acids as Treatments for Autism

The evidence that omega-3 fatty acid may be deficient in autism has prompted the idea that omega-3 supplementation might lead to an improvement in clinical symptoms and behavioral aberrations (Bent et al. 2009). Additionally, preliminary evidence mainly derived from clinical studies seems to suggest that specific nutraceutical interventions aiming to correct biochemical imbalances ASD may improve behavioral problems in this patient group (Chez et al. 2007; Dosman et al. 2007). This review considers the findings of the clinical trials and case reports that form the basis to support for the use of omega-3 PUFA as a treatment for autism. To accomplish this we utilized PubMed and PsycINFO to identify clinical trials and case reports of omega-3 fatty acids in patients with autism. The strategy employed was to search for articles which contained search terms "autism" and "omega-3, *n*-3 alpha linoleic, eicosapentaenoic, docosahexaenoic, EPA, DHA, ALA" limited by clinical trials and case reports.

A total of six studies were identified (see Table 116.5). Politi et al. (2008) conducted an open-label study in a single farm community center specifically designed for individuals with autism (Cascina Rossago, Ponte Nizza, Italy).

The trial involved 19 adults (15 males, 4 females) aged 18–40 years with severe autism (Childhood Autism Rating Scale [CARS] scores ≥40 in all subjects) during three different 6-week periods. Subjects were given 0.93 g of EPA and DHA. The frequency and severity of problematic behaviors was assessed before, during, and after treatment using the Rossago Behavioral Checklist, an ad hoc caregiver questionnaire focusing on behavioral problems.

The authors did not find any significant reduction of the severity and frequency of symptoms during the pretreatment and treatment periods. A slight improvement in behavioral alterations was evident during the post-treatment period, albeit not reaching the statistical significance threshold. However, this may due to random fluctuations in problematic behaviors due to seasonality and other factors (see Fig. 116.1). It is therefore concluded that variations in the behavioral scores found during the study could be due to caotic fluctuations in behavioral problems, and not to treatment effects. However, it should be kept in mind that this study involved a small sample size and was not carefully controlled.

Meguid et al. (2008) treated 30 autistic subjects (3–11 years) and 30 healthy controls with 130 mg of DHA, 35 mg of EPA, 10 mg of arachidonic acid. The treatment lasted for three months. Autistic behavior was evaluated with the CARS. Following the treatment schedule, 66% of patients showed an increase in plasma omega-3 concentrations as well as a significant improvement of autistic behavior.

Amminger et al. (2007) conducted a randomized, double-blind, placebo-controlled trial aiming at evaluating the efficacy of omega-3 fatty acids for the treatment of autism. The authors enrolled 13 children with autism (based on DSM-IV criteria and the ADI-R) and randomly assigned them to the daily use of 1.5 g of omega-3 fatty acids (0.84 g/day EPA, 0.7 g/day DHA) or a placebo for 6 weeks. They evaluated changes in the scores of the Aberrant Behavior Checklist (ABC) at 6 weeks. Although the authors observed a greater improvement in each subscales of the ABC (especially as regard hyperactivity and stereotypy), none of the reported changes reached the statistical significance threshold. Future studies should address the limitations of this randomized controlled trial by using a larger sample size with sufficient power to detect clinically important benefits, treating for a longer duration to examine the time course of treatment effects, including a biomarker to examine the mechanism of action of any benefits, including a broader array of outcome measures of potential areas of benefit in ASD, conducting careful assessments of side effects and safety, and assessing the adequacy of blinding.

Table 116.5 Studies examining the effects of omega-3 fatty acids supplementation in patients with autism

Study	Methods (type, length)	Participants	Interventions (daily dose)	Outcomes	Notes
Politi et al. (2008)	6-week open label, uncontrolled trial	Young adults with severe autism (n = 19)	0.93 g of DHA plus EPA. 5 mg of vitamin E	Rossago Behavioral Checklist (22-item list, each rated 0–4) No significant improvement from baseline scores	No mention about side effects
Meguid et al. (2008)	3-month uncontrolled trial	Autistic children aged 3–11 years (n = 30)	240 mg DHA plus 52 mg EPA and vitamin E 68 mg omega-6 fatty acids	CARS Significant improvement in CARS scores in 20 of 30 children	Vitamin E dose was not reported, no mention about side effects
Amminger et al. (2007)	6-week RCT	Children attending a specialized day care center for long-term treatment of autism (n = 13)	840 mg EPA plus 700 mg DHA and 7 mg vitamin E	ABC Nonsignificant advantage of omega-3 fatty acids compared with placebo for hyperactivity and stereotypy	One patient dropped out due to side effects
Patrick and Salik (2005)	3-month uncontrolled trial	Patients with autism and Asperger's syndromes (n = 22)	247 mg omega-3, plus 40 mg omega-6 and 27 IU vitamin E	ABLLS Significant increase in the 8 subscales	There was no control group, and 4 patients dropped out
Bell et al. (2004)	6-month uncontrolled trial	Two patients with Asperger syndrome and 7 with autism	860 mg EPA 300 mg DHA 2 IU vitamin E	Parents reported improvements in eye contact, social contact, irritability, aggression, hyperactivity	There was no control group and outcome measures were not standardized
Johnson and Hollander (2003)	Case report	1 male subject with autism, diagnosed at age 2.5	3 g/day (540 mg EPA/day)	Nonstandard clinician and parent reports Ease of anxiety and agitation	No mention about side effects

RCT randomized controlled trial, *ABC* aberrant behavior checklist, *CARS* childhood autism rating scale, *ABLLS* assessment of basic language and learning skills
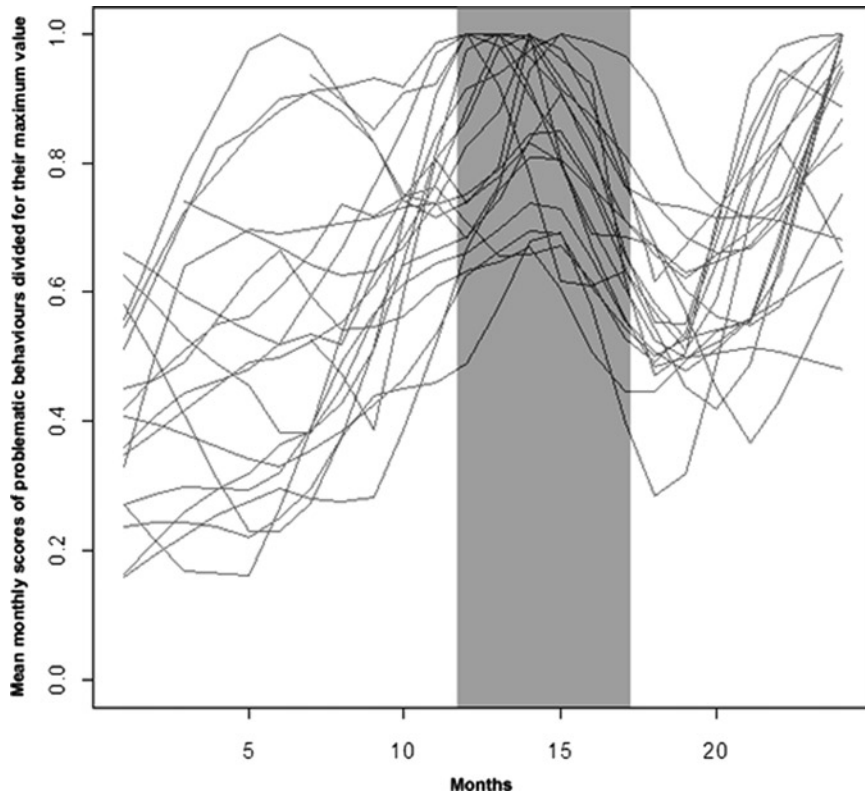
Fig. 116.1 Periodic fluctuations of problematic behaviors according to seasonality in autistic patients at Cascina Rossago. The solid gray rectangle indicates the study period in the report by Politi and coworkers (2008)

Patrick and coworkers (Patrick and Salik 2005) enrolled 22 patients with autism or Asperger syndrome in an open-label study. During the study period (90 days) all patients were administered 247 mg of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) and 40 mg of gamma-linolenic acid (GLA). The subjects were evaluated at baseline, after 45 days and after 90 days of treatment using the Assessment of Basic Language and Learning Skills (ABLLS) test. The main finding of the trial was a statistically significant increase in the score of each subscale of ABLLS.

Bell and colleagues (Bell et al. 2004) ran a short (6-month) open-label trial in which 9 children with autism or Asperger syndrome were treated with two different form of omega-3 at different concentrations. No structured assessment was conducted but parents reported a significant improvement of their children behavior and general health.

A case report from Johnson and Hollander (2003) described an 11-year-old autistic boy with severe symptoms including tantrums, aggression, and compulsive rituals. After a gradual titrage (3 g/day) over 4 weeks, he was given 540 mg of EPA daily for 8 more weeks. Following the treatment, both parents and the physician observed an improvement of his behavior and quality of life. These improvements appeared after one week and continued throughout the entire study period.

Megson (2000) reported that administration of cod liver oil – which is rich in omega-3 and vitamins A and D – provided substantial benefits for persons with autism, suggesting that omega-3 or vitamins A and D could be potential complementary treatments for this condition.

116.5 Conclusions

EPA and DHA have been shown to positively influence a number of aspects of brain function and dysfunction; however, for many of these effects their mechanism of action remains to be fully elucidated. It is very likely that EPA and DHA operate through a number of different, potentially overlapping mechanisms, involving various cellular targets. Adequate dietary availability of DHA and EPA is clearly fundamental to brain function. DHA and EPA are important throughout adulthood, as well as during the brain growth spurts that characterize prenatal and postnatal development. Based on the available evidence, however, it is not possible to firmly recommend PUFA as a treatment for autism. As this condition is a notoriously complex disease, omega-3 supplementation may not prove to be an effective treatment for all autistic patients since the use of these compounds may benefit one patient but not be as successful with another; there appears to be no panacea. However, the large majority of the trials reported here had one conclusion in common – that omega-3 fatty acids had no serious side effects. Although the clinical trials varied in quality of design and tended to be small in terms of participants, further investigation of the use of omega-3 PUFA to treat at least some mental health problems is warranted. Further work is specifically required to determine if omega-3 supplementation might specifically benefit autistic patients showing abnormalities of omega-3 fatty acids in their sera. Other important issues for future studies of PUFA in autism concern the correct use and dosage of any fish oil product. Early studies into the effects of ALA, EPA and DHA have tended not to differentiate between these omega-3 PUFA, with the results broadly attributed to the omega-3 PUFA series as a whole. However, there is evidence to suggest that certain effects may be specific and unique for the different types of PUFA. It can no longer be assumed they have a mechanistic equivalence. In this regard, a recent review into the effects of omega-3 PUFA in mental illness has indicated that EPA may be more beneficial in mood disorders than DHA (Ross et al. 2007). Further an important, but as yet largely unexplored, issue is the most appropriate dosage of omega-3 PUFA to be used. Future studies will no doubt provide a more focused approach to the type and dose of omega-3 PUFA that is most appropriate for ASD.

116.6 Applications to Other Areas of Health and Disease

Although the effects of EPA for the brain development *in utero* are unclear, the presence of EPA and DHA in colostrum and breast milk suggests that these molecules may be involved in early development of CNS. Accordingly, due to their highly fluidizing properties, DHA and EPA can be found at the highest concentrations in the most dynamic membranes of the neural cells. The evidence presented here on omega-3 in ASD may prompt further research in other childhood neuropsychiatric disorders, including Tourette's syndrome, hyperkinetic disorder, and obsessive-compulsive disorder.

Summary Points

- People with autism can show remarkable alterations in omega-3 fatty acids concentration.
- Omega-3 fatty acids are essential for normal membrane function in neural cells.
- Controversy surrounds the issue of omega-3 fatty acids potential benefit on autism.
- These supplements may help some patients, not everyone; they cannot be considered panacea.
- Further evidence-based research is required to determine whether omega-3 supplementation might specifically benefit autistic patients showing serum abnormalities of omega-3 fatty acids.

Definitions and Explanations

Autism: A developmental disability marked by impairments in social interaction and communication and the presence of unusual, restrictive, and repetitive behaviors.

Omega-3: Important nutritionally-essential family of unsaturated fatty acids.

Randomized clinical trial: A clinical trial in which participants are assigned by chance to different treatments.

Uncontrolled study: A clinical trial in which participants are not assigned by chance to different treatments.

Nutraceutical: Any food or food ingredient that is considered to have a beneficial effect on health.

References

Amminger GP, Berger GE, Schafer MR, Klier C, Friedrich MH, Feucht M. Biol Psychiatry. 2007;61:551–3.

Bell JG, MacKinlay EE, Dick JR, MacDonald DJ, Boyle RM, Glen AC. Prostaglandins Leukot Essent Fatty Acids. 2004;71:201–4.

Bent S, Bertoglio K, Hendren RL. J Autism Dev Disord. 2009. doi: 10.1007/s10803-009-0724-5.

Bradstreet J, Kartzinel J. In: Rimland B, editor. DAN! (Defeat Autism Now!) Fall 2001 Conference. San Diego: Autism Research Institute; 2001.

Bu B, Ashwood P, Harvey D, King IB, Water JVd, Jin LW. Prostaglandins Leukot Essent Fatty Acids. 2006;74:215–21.

Chez MG, Burton Q, Dowling T, Chang M, Khanna P, Kramer C. J Child Neurol. 2007;22:574–9.

Dosman CF, Brian JA, Drmic IE, Senthilselvan A, Harford MM, Smith RW, Sharieff W, Zlotkin SH, Moldofsky H, Roberts SW. Pediatr Neurol. 2007;36:152–8.

Gerster H. Int J Vitam Nutr Res. 1998;68:159–73.

Green VA, Pituch KA, Itchon J, Choi A, O'Reilly M, Sigafoos J. Res Dev Disabil. 2006;27:70–84.

Hardy PM, Hardy SM. In: Rimland B, editor. DAN! (Defeat Autism Now!) Spring 2002 Conference. San Diego: Autism Research Institute; 2002.

Johnson SM, Hollander E. J Clin Psychiatry. 2003;64:848–9.

Kippes C, Garrison CB. Mo Med. 2006;103:65–8.

Lintas C, Persico AM. J Med Genet. 2009;46:1–8.

Lyons V, Fitzgerald M. J Autism Dev Disord. 2007;37:2022–3.

McCann JC, Ames BN. Am J Clin Nutr. 2005;82:281–95.

McNamara RK, Carlson SE. Prostaglandins Leukot Essent Fatty Acids. 2006;75:329–49.

Megson MN. Med Hypotheses. 2000;54:979–83.

Meguid NA, Atta HM, Gouda AS, Khalil RO. Clin Biochem. 2008;41:1044–8.

Patrick L, Salik R. Autism Asperger's Digest. 2005;7:36–7.

Pauling L. Science. 1968;160:265–71.

Politi P, Cena H, Comelli M, Marrone G, Allegri C, Emanuele E, Ucelli di Nemi S. Arch Med Res. 2008;39:682–5.

Reading CM. Med J Aust. 1979;2:40.

Ross BM, Seguin J, Sieswerda LE. Lipids Health Dis. 2007;6:21.

Sigman M, Spence SJ, Wang AT. Annu Rev Clin Psychol. 2006;2:327–55.

Sliwinski S, Croonenberghs J, Christophe A, Deboutte D, Maes M. Neuro Endocrinol Lett. 2006;27:465–71.

Vancassel S, Durand G, Barthelemy C, Lejeune B, Martineau J, Guilloteau D, Andrès C, Chalon S. Prostaglandins Leukot Essent Fatty Acids. 2001;65:1–7.

Young C, Hikita T, Kaneko S, Shimizu Y, Hanaka S, Abe T, Shimasaki H, Ikeda R, Miyazawa Y, Nakajima A. Acta Paediatr Jpn. 1997;39:299–304.

Zecavati N, Spence SJ. Curr Neurol Neurosci Rep. 2009;9:129–36.

Chapter 117
Docosahexaenoic Acid and Cognitive Dysfunction

Michio Hashimoto, Hossain Md Shahdat, and Masanori Katakura

Abbreviations

Aβ	Amyloid β peptide
AD	Alzheimer's disease
ALA	α-linolenic acid
ATP	Adenosine triphosphate
CAT	Catalase
CNS	Central nervous system
DG	Dentate gyrus
DHA	Docosahexaenoic acid
EPA	Eicosapentaenoic acid
GPx	Glutathione peroxidase
GSH	Reduced glutathione
Hes1	Hairy and enhancer of split 1
LTP	Long-term potentiation
MCI	Mild cognitive impairment
MS	Multiple sclerosis
NMDA	N-methyl-D-aspartate
NSC	Neural stem cell
PPAR	Peroxisome proliferator-activated receptors
PUFA	Polyunsaturated fatty acid
ROS	Reactive oxygen species
RXR	Retinoid X receptor
SREBP	Sterol regulatory element-binding protein
ThT	Thioflavin T

M. Hashimoto (✉)
Department of Environmental Physiology, Shimane University Faculty of Medicine,
Izumo, Shimane 693-8501, Japan
e-mail: michio1@med.shimane-u.ac.jp

117.1 Introduction

Docosahexaenoic acid (DHA, C22:6*n*-3), a dietary essential *n*-3 polyunsaturated fatty acid (*n*-3 PUFA) in highly-enriched fish oils, is synthesized through the elongation and desaturation of eicosapentaenoic acid (EPA, C20:5*n*-3) or the elongation of α-linolenic acid (ALA, C18:3*n*-3). Neural membranes of the cerebral cortex and the retina are very rich in DHA, which accounts for approximately 30–40% of the acyl group in glycerophospholipids (Lauritzen et al. 2001). The concentration of DHA is particularly high in gray matter of the cerebral cortex and in photoreceptor cells. DHA constitutes >17% by weight of total fatty acids in the brain of adult rats. It is recycled and used continuously for the biogenesis and maintenance of neuronal membranes. Neurons lack the ability to synthesize DHA from its precursor, ALA. DHA is obtained either directly from the diet or synthesized from ALA and/or EPA in the liver, and then transported to the brain through plasma lipoprotein (Scott and Bazan 1989). The cerebral endothelium and astrocytes have the ability to synthesize DHA from dietary precursors, suggesting that after its release from these tissues, DHA is taken into neurons from an extracellular medium. Nonetheless, this may be a minor pathway in quantitative terms as compared to DHA supplied to brain tissue from plasma (Rapoport et al. 2001).

During the growth spurt of the central nervous system (CNS) for 18 months after birth, accretion of DHA takes place rapidly (Bourre et al. 1989). DHA is an absolute prerequisite for the development of the human CNS and the continuous maintenance of brain cell function, which implies the essentiality of DHA for the human mental condition (Broadhurst et al. 1998) and intellectual evolution (Helland et al. 2003). DHA not only modulates physical properties of the lipid bilayer (Hashimoto et al. 2006a), but also provides second messengers for biological signaling (Phillis et al. 2006). In addition, DHA provides neural membranes with a physical environment for the activity of integral membrane proteins such as membrane-bound enzymes. It modulates ion channels and neurotransmitter receptors (Yehuda et al. 2002) and stabilizes neuronal membranes by suppressing voltage-gated Ca^{2+} currents and Na^+ channels (Young et al. 2000). Recent studies indicate that this fatty acid is implicated in cognitive development and learning ability and increases the plasticity of nerve membranes, the process of synaptogenesis, all of which are involved in synaptic transmission and the well-being of normal brain functions. Conversely, morphological and neurochemical consequences of DHA deficiency produce a decrease in neuronal cell bodies in several regions of the rat brain, a deficit in serotonin and dopamine neurotransmission, a decrease in glucose uptake, a reduction in cytochrome oxidase activity and a decrease in G-protein coupled signaling efficiency (Horrocks and Farooqui 2004) (Fig. 117.1). These neurochemical changes in brain tissue result in reduced learning and memory, and in elevated behavioral indices of anxiety, aggression, and depression (McNamara and Carlson 2006).

Alzheimer's disease (AD), a progressive neurodegenerative disorder characterized by progressive cognitive and memory decline, is the most common neurodegenerative disease that deprives millions of people worldwide of enjoying successful aging (Cummings and Cole 2002). Currently, there is no known treatment for AD. Epidemiological studies show that consumption of selected types of fats and antioxidants such as vitamin E and C lowers the risk of AD (Morris et al. 2003). In particular, growing evidence has shown that *n*-3 fatty acids from marine-life oils containing DHA and EPA may have therapeutic potential for the prevention and treatment of AD. AD is characterized by general loss of memory as well as a paucity of PUFAs, particularly of DHA (Horrobin 1998). Dietary DHA improves spatial learning ability associated with its accumulation in the hippocampus and cerebral cortex of young (Gamoh et al. 1999) and aged rats (Gamoh et al. 2001) and mice (Lim and Suzuki 2001), although the exact mechanism of the action of DHA in cognitive functions is not known. Furthermore, dietary DHA protects against (Hashimoto et al. 2002) and ameliorates (Hashimoto et al. 2005)
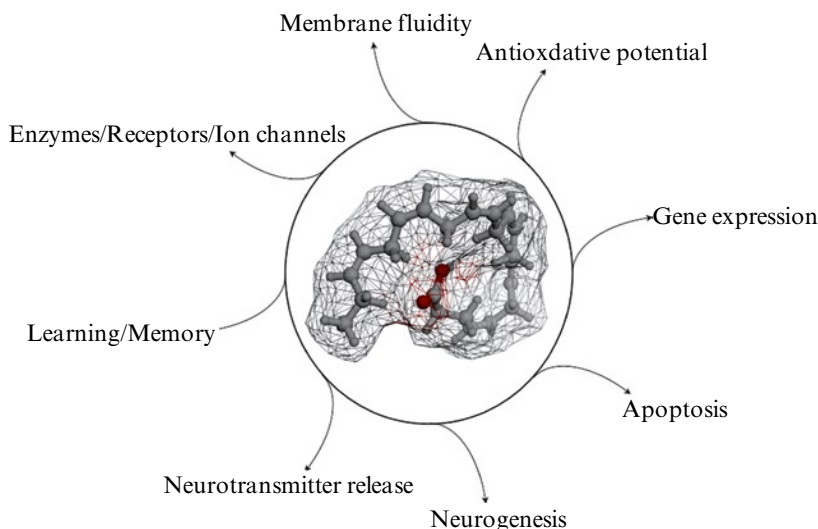
Fig. 117.1 Roles of docosahexaenoic acid in brain

memory deficits in the amyloid β (Aβ)-peptide-infused AD model rat and in the transgenic AD model mouse (Calon et al. 2004), suggesting a therapeutic effect of this fatty acid on AD. In the present review, we provide an overview of the literature regarding the role of DHA in AD and other neuronal dysfunctions involving cognitive deficits.

117.2 Characterization and Physiological Function of DHA

117.2.1 The Intrinsic Properties of DHA in Membrane-related Functions

DHA is one of the typical constituents of membrane phospholipids that are known as structural components of biomembranes. For the manifestation of signals to and from cells the signal ligands need to interact with plasma membranes and intracellular membranes. Therefore, DHA in the biomembranes is assumed to affect the functions of proteins, receptors, enzymes which get laid by DHA. In this context, membrane disorder (fluidity) is an important parameter that may affect the membrane-bound receptor and/or enzyme functions, suggesting that DHA in membranes plays both structural and functional roles. DHA increases the membrane fluidity of a variety of cells including platelet membranes (Hashimoto et al. 2006b), endothelial cells (Hashimoto et al. 1999), liver hepatocytes (Hashimoto et al. 2001), and synaptic plasma membranes (Shahdat et al. 2004). The effect of DHA on membrane fluidity and functions is controversial; however, Gordon et al. (1980) have reported that both membrane fluidity and membrane-bound enzyme activity increase in DHA-rich membranes. Many of the membrane-related functions require microaggregation, segregation, and dimerization in the bilayer environment. Thus, membrane fluidity plays a definite role in these membrane-related functions. In addition, the docking of synaptic vesicles or vesicles for exocytosis is assumed to be affected by the membrane microenvironment. The hydrophobic volume and the cross-sectional area of DHA are large. Also, DHA is believed to provide plasticity *in situ*. These inherent properties of DHA are believed to significantly affect overall bilayer physical properties and, subsequently, the functions of the proteins

laid by them. DHA remains highly concentrated in synaptic plasma membranes with an increase in the exocytosis of neurotransmitter-containing vesicles, suggesting that DHA-induced increase in membrane fluidity increases neurotransmission and related brain functions.

117.2.2 Antioxidative Effects of DHA

DHA is critical for cellular functioning and normal brain development in animals and humans (Calderon and Kim 2004; Wainwright et al. 1994). In aged animals, memory impairment occurs, in part, by reduced levels of cerebral DHA (Delion et al. 1996). Moreover, loss of brain DHA content in patients with AD is accompanied by loss of memory and learning ability (Horrobin 1998). The reduced DHA content may be due to enhanced free radical-mediated lipid peroxidation (Nourooz-Zadeh et al. 1999), decreased dietary intake, undefined impediments to the uptake and utilization of *n*-3 PUFAs, or impeded shuttling of DHA from the liver to the brain. A decrease in the level of serum DHA correlates with cognitive impairment (Suzuki et al. 1998), and epidemiological studies suggest neuroprotective consequences of diets enriched with *n*-3 PUFAs (Morris et al. 2003). DHA deficiency has been associated with the impairment of cognitive processes (Gamoh et al. 2001). Moriguchi et al. (2000) have shown longer escape latency in *n*-3 PUFA-deficient rats than in control rats, suggesting that an *n*-3 PUFA deficient diet affects the process of habituation, a simple form of learning. From these results, it is conceivable that the intake of DHA inhibits the accrual of oxidative stress and the decline in learning ability with aging.

How does DHA exert antioxidative effects while it is a highly PUFAs? The question could be considered very simple if the content of DHA in brain lipids is taken into account. The brain is very weak in antioxidative defense as compared with other organs of the body (Hossain et al. 1999). The brain consumes about one fifth of the total oxygen demand of the body to produce huge amounts of adenosine triphosphate (ATP) required for the 24-h opening and closing of neural ion channels for neurotransmission and for rapidly synthesizing synapatosomal plasma membranes of neuronal networks. Under these circumstances if DHA were an extra burden on the oxidative environment, the brain would degenerate very rapidly (Fig. 117.2). The reverse is known to be true, however, because brain functions benefit from an abundance of DHA, in other words, DHA increases, not impedes,
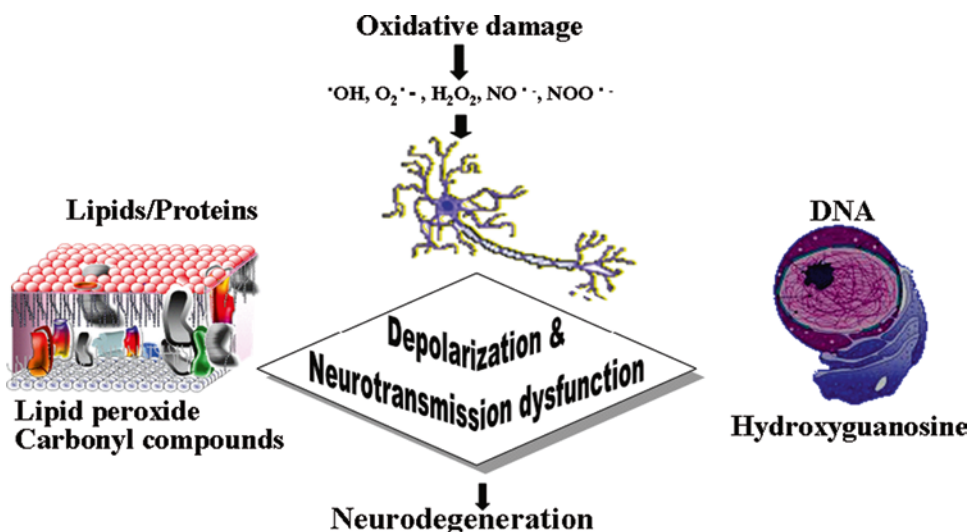
Fig. 117.2 Effects of oxidative stress on neurodegeneration

oxidative defense. Chronic administration of dietary DHA significantly decreases lipid peroxide levels by activating antioxidative enzymes including glutathione peroxidase (GPx), catalase, glutathione reductase, and antioxidant substrate-reduced glutathione (GSH) (Hossain et al. 1998, 1999). Infusion of DHA into amniotic fluid inhibits lipid peroxide levels in fetal brains (Green and Yavin 1995). In contrast, Arab et al. (2006) have reported that DHA increases the intracellular content of GSH with a concomitant increase in glutathione reductase and glutathione-S transferase (characteristics of antioxidative response) as confirmed by the increased mRNA levels of these enzymes. Bazan (2005) have reported that DHA is converted to docosahexatriene or the so-called neuroprotectin D1 which increases antioxidative defense or acts as an antioxidant. Therefore, whether DHA itself and/or DHA-derived docosanoid, or both, affect antioxidative defense remains to be clarified.

117.2.3 Modulation of Gene Expression by DHA

DHA supplementation produces overexpression, in animal brains, of many genes associated with signal transduction, synaptic plasticity, energy metabolism, and membrane trafficking (Kitajka et al. 2002). DHA is a ligand for the retinoid X receptor (RXR) that serves as a fatty acid sensor in the brain *in vivo* (Farooqui et al. 2004). In addition, DHA not only modulates gene expression, but also induces changes in the stability of the mRNA of lipogenic enzymes. DHA deficiency downregulates the expression of brain glucose transporters, resulting in a decrease of brain glucose utilization by the cerebral cortex in DHA-deficient rats (Pifferi et al. 2005). Changes in DHA-mediated gene expression are critical for adaptive responses for neural cell survival. Key transcription factors associated with these processes include peroxisome proliferator-activated receptors (PPAR) and sterol regulatory element-binding protein (SREBP) (Jump 2002). This evidence suggests that dietary DHA supplementation imparts numerous beneficial effects to the health of the human brain through the modulation of genes associated with synaptic plasticity, neuroinflammation, and energy metabolism (Horrocks and Farooqui 2004).

117.3 Cognitive Ability and DHA

DHA deficiency is associated with loss of discriminative learning ability (Neuringer et al. 1986; Yamamoto et al. 1987); thus, intake of DHA may restore lost learning ability (Gamoh et al. 1999). Long-term deficiency in ALA, a precursor of EPA and DHA, leads to decreases in the amount of DHA, in the density of synaptic vesicles, and in synaptic membrane fluidity in the brain (Calon et al. 2004). Moreover, *n*-3 PUFA deficiency causes a decline in learning ability in various tasks, such as light–dark discrimination (Yamamoto et al. 1987), shuttle avoidance (Hashimoto et al. 2002), and those posed by the radial-arm maze (Gamoh et al. 1999, 2001; Hashimoto et al. 2005) and the Morris water maze (de Wilde et al. 2002). It is thus plausible that the uptake of DHA into neural membranes, particularly in synaptic membranes, is related to the efficiency of learning ability. Based on these reports, DHA may play a principal role in memory formation, although the pertinent mechanisms are not clearly understood. Chronic administration of DHA increases DHA content in the hippocampus and the cerebral cortex and improves the performance of radial maze tasks by young and old rats (Gamoh et al. 1999, 2001), signifying the beneficial effect of DHA on learning ability. Enrichment with DHA promotes neuronal membrane synthesis and increases dendritic spine density in the hippocampus of adult gerbils (Sakamoto et al. 2007). A host of potential mechanisms of DHA action has been proposed: DHA may act by binding directly to the *N*-methyl-d-aspartate (NMDA) receptor

or by altering its lipid environment and thereby potentiating the NMDA response. It is also thought that DHA enhances the induction of long-term potentiation (LTP).

To the extent that *n*-3 PUFAs have trophic neural effects, higher consumption of these fatty acids is expected to correlate positively with the volume of gray matter in brain regions such as the amygdala, the hippocampus, and the anterior cingulated cortex. These regions are core components of a distributed corticolimbic circuitry that regulates emotional arousal in response to the regulation of affect in the service of adaptive behavioral responses. Higher consumption of long-chain omega-3 fatty acids is associated with a larger volume of gray matter in nodes of a corticolimbic circuitry supporting emotional arousal and regulation (Conklin et al. 2007). DHA promotes significant changes in neurotransmitter function, brain structure, and behavior. For example, animals fed DHA-deficient diets show reduced frontal cortex concentrations of monoamine neurotransmitters, dopamine, and serotonin (de la Presa Owens and Innis 1999). We have demonstrated that the number of Fos-positive neurons in the CA1 region of the hippocampus increase significantly in rats administered DHA for 15 weeks compared with controls, with a significant negative correlation of the number of Fos-positive neurons with reference memory errors measured by tasks in an eight-arm radial maze (Tanabe et al. 2004). The Fos protein, encoded by the immediately early gene c-fos, is known to be a transcription factor and a functional marker of neuronal activity. Thus, DHA intake could influence brain morphology through some or all of these mechanisms. Such associations may mediate previously observed effects of *n*-3 PUFAs on memory, mood and affect regulation.

117.4 Cognitive Dysfunction and DHA

117.4.1 Aging and DHA

The most notable risk factor of neurodegenerative disease in humans is old age. The onset of disease usually occurs from mid to late life, with progression depending on not only genetic but also environmental factors. DHA is retained in the brain during early development; however, generation of free radicals and reactive oxygen species (ROS) during the aging process causes a detrimental decline in DHA levels in neural membranes (Lauritzen et al. 2001). Also, a decline in the level of plasma DHA is associated with cognitive impairment with in aging (Conquer et al. 2000) and does not seem to be limited to AD patients (Yehuda et al. 2002). There are several possible reasons for this decline: a decrease in the ability of dietary fatty acids to cross the blood–brain barrier due to impaired transport function with aging, lipid peroxidation caused by accumulation of free radicals (Bjorkhem et al. 1998), a decrease in dietary intake, or impaired shuttling of DHA from the liver to the brain (Abad-Rodriguez et al. 2004). The deficiency affects mostly the cortex and hippocampus, areas which mediate learning and memory, and has been demonstrated in the Shimane Elderly Cohort Study of senior citizens older than 65 years of age, in which regression analysis reveals a positive correlation between EPA content in erythrocyte membranes and the scores of the revised Hasegawa dementia rating scale. Dietary administration of EPA increases not only EPA but also DHA in plasma and erythrocyte membrane levels in rats, leading to an increase of DHA levels in the hippocampus (Hashimoto et al. 2009). In a recent study, patients with blood DHA concentrations in the highest quartile have demonstrated a lower risk of developing dementia compared with the lowest three quartiles during a mean follow-up of 9 years (Schaefer et al. 2006). These results suggest that dietary supplementation with DHA alters the risk of cognitive impairment with aging and/or developing AD over the long term and that low concentrations of blood DHA account for a critical risk factor for cognitive dysfunction.
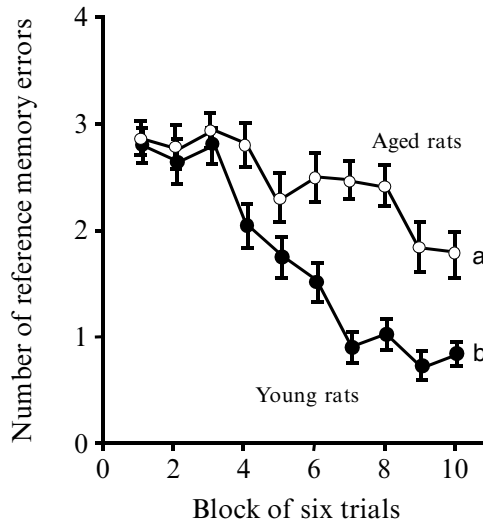
Fig. 117.3 Effect of aging on spatial-memory-related learning ability. Male Wistar rats at the age of 5 (○) and 100 (●) weeks fed a fish oil-deficient diet over two generations. The rats were subjected to the maze task using a partially (4/8) baited eight-arm radial maze. The learning ability is reflected in the number of reference memory errors, times of entry into unbaited arms. Values are means ± SEM in each block of six trials. Groups without a common letter for the main effects of groups are significantly different at $P < 0.05$. (Two-way ANOVA)

Aging is associated with not only a decrease in the content of DHA in the brain, but also loss of memory and learning ability. In aged animals, memory impairment occurs (Fig. 117.3), in part, by reduced levels of cerebral DHA (Delion et al. 1996). Reduced DHA levels and spatial cognitive learning ability with age can be restored by DHA supplementation (Gamoh et al. 2001). Glutamate receptor subunits GluR2 and NR2B in the rat forebrain, which decline with age and are related to memory function (Le Jeune et al. 1996), are up-regulated by DHA supplementation (Dyall et al. 2007). DHA administration reduces neuronal damage caused by ischemia (Okada et al. 1996). These data are consistent with our previous reports indicating that chronic administration of DHA reduces the levels of lipid peroxide by enhancing the cerebral activities of catalase and glutathione peroxidase in old rats (Hossain et al. 1998, 1999). Moreover, DHA supplementation not only restores the levels of DHA, but also increases membrane fluidity in synaptosomal plasma membranes of the rat cerebral cortex (Hashimoto et al. 2006a). Thus, the foregoing studies suggest that during aging DHA supplementation not only promotes normal membrane fluidity but also turns on the mechanism that maintains normal cognition and brain function.

117.4.2 Alzheimer's Disease and DHA

117.4.2.1 Human Studies

AD, a neurodegenerative disease that commonly affects the elderly, is characterized by loss of short-term memory and cognitive impairment. The cause of AD is unknown; however, the disease is associated with major pathological traits, such as overproduction and accumulation of Aβ produced by the proteolytic processing of amyloid precursor protein (APP) (Brunkan and Goate 2005), formation of neurofibrillary tangles caused by the aggregation of Tau protein within neurons (Mattson 2004), and

neuronal cell loss. Although treatment for AD is unknown, there is growing interest in the role of diet for its prevention and treatment. Numerous epidemiological studies have described an inverse association between AD risk and the status of *n*-3 PUFA intake. Studies among participants in the population-based prospective Rotterdam study have shown that consumption of fish, an important source of *n*-3 PUFAs, is inversely related to dementia, in particular to AD (Morris et al. 2003), in a prospective study of a human population on the progression of AD, have found that total intake of *n*-3 PUFAs is associated with reduced risk of AD, particularly the intake of DHA, but not of EPA. Moreover, cross-sectional analyses have linked low levels of plasma DHA with dementia and with AD in particular. Despite promising findings from epidemiological studies, no effect of EPA or DHA on AD has been observed in clinical studies (Freund-Levi et al. 2006; Kotani et al. 2006); nonetheless, analyses of subgroups suffering from mild AD or mild cognitive impairment (MCI) have shown benefit from DHA treatment (Freund-Levi et al. 2006; Kotani et al. 2006). The contrasting outcomes of those epidemiological and clinical studies suggest that *n*-3 PUFAs are effective only when consumed before the onset of the disease and when symptoms are mild.

117.4.2.2 Studies on AD Model Animals

Deposition of insoluble neuritic plaques and neurofibrillar tangles in the brain are the pathological hallmarks of AD, which is characterized by progressive neuronal loss with concomitant deterioration of memory and memory-related learning ability. Learning-related memory impairment is induced by the infusion of Aβ peptides into the cerebral ventricle of rats (Oka et al. 1999). AD model rats produced in our laboratory by the intraventricular infusion of A$\beta_{(1-40)}$ peptide solution have been used for the evaluation of the effects of dietary DHA administration on their learning-related ability. The results have demonstrated that the mean total number of avoidance responses, which was measured by the shuttle avoidance system, is higher in DHA preadministered AD model rats than in the AD model rats (Hashimoto et al. 2002), suggesting a protective effect of dietary DHA on the impairment of learning ability. Furthermore, DHA administration for 12 weeks reduces the increase in the number of memory errors, which was measured by the radial-arm maze, in AD model rats, suggesting an amelioration of impaired spatial cognition learning ability (Hashimoto et al. 2005). Intervention with DHA supplementation, even late in the life of the transgenic mouse model APPswe (Tg2576) of AD, has shown improvement in cognitive function as measured with the use of the Morris water maze (Calon et al. 2004). Thus, these results suggest that DHA is a possible therapeutic agent for protecting against and ameliorating learning deficiencies attributed to AD.

Dietary DHA administration inhibits *in vivo* levels of Aβ_{1-40} in AD model rats (Hashimoto et al. 2005). DHA has also been reported to lower the Aβ burden in the brains of transgenic mice (Lim et al. 2005), although the mechanisms remain unclear. Thus, it is assumed that DHA inhibits the extent of amyloid fibrillation *in situ*. DHA can inhibit *in vitro* fibrillation and help in the dissolution of pre-formed Aβ_{1-40} fibrils (Hashimoto et al. 2008). These results are thus in line with the notion that DHA is one of the essential brain nutrients that could reduce the prevalence of AD.

117.5 In vitro Amyloid Fibrillation and DHA

Amyloid plaques and neurofibrillar tangles are fibrillated Aβs. The molecular event of the α-helix to β-sheet transformation is not clearly understood, although numerous studies have been conducted on the topic. Figure 117.4 shows a schematic morphology from monomers to amyloid fibrillation: monomeric
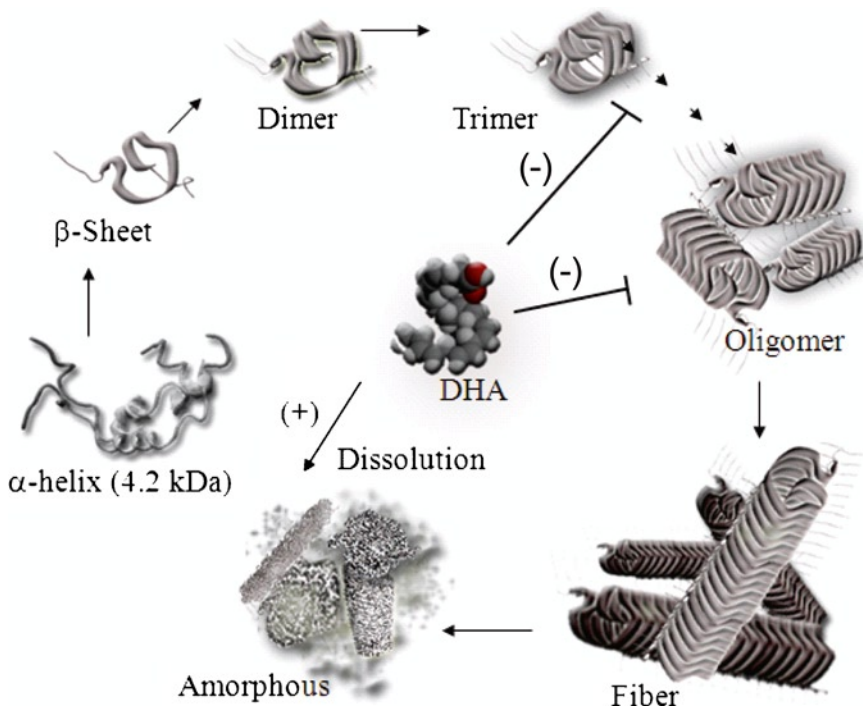
Fig. 117.4 Schematic morphologies from monomers to amyloid fibrillation. The Aβ peptides remain in-membrane with their random coiled α-helical conformation. They are then misfolded into β-sheets and run orthogonally to form oligomers (protofilaments). The oligomers elongate by the addition of more β-sheet units and then mature to amyloid fibrils

α-helical units are transformed into β-sheets that through a lag phase run orthogonally to give rise to the so-called prefibrillar seeds or oligomers, which in turn elongate through the stacking of more β-sheet units to rod-like structures, then by further extension finally mature to fibrils. The driving force for these interactions involves both hydrophobic and electrostatic interactions (Khurana et al. 2003). Chronic administration of DHA significantly decreases Aβ levels in the detergent-insoluble membrane fractions prepared from the cortex of AD model rats (Hashimoto et al. 2005). Lim et al. (2005) have also reported that DHA decreases the amyloid burden in the mouse brain. In the light of these findings, it is assumed that DHA directly affects the process of fibrillation. In our studies, DHA was directly incubated with monomeric Aβ peptide, and the degree of fibrillation was evaluated through thioflavin (ThT) fluorescence intensity. ThT binds with the β sheet and emits fluorescence. In most of the visual fields of the confocal laser and electron micrographic grids, DHA-incubated samples had a smaller number of aggregates (Fig. 117.5b) than did the controls (Fig. 117.5a) or the fibers, indicating a clear-cut inhibitory effect by DHA on the extent of fibrillation.

The electron micrographs revealed that monomeric amyloids were transformed into a β-sheet and subsequently stacked orthogonally (polymerized) to form a ribbon-like fiber (Fig. 117.6). It is specu-lated that the hydrophilic side chains shield inside the fiber core while the hydrophobic structures normally remain buried in the interior of the native conformation. During this radical transformation, the amino acids of the Aβ peptide that take part in β-sheet constructs are not known; also, how DHA inhibits β-sheet elongation remains to be clarified. Since DHA is reported to stabilize the oligomers of Aβ (Johansson et al. 2007), we investigated whether DHA-induced inhibition of fibrillation occurs at the oligomeric stage. Accordingly, gel electrophoresis of samples incubated with DHA showed
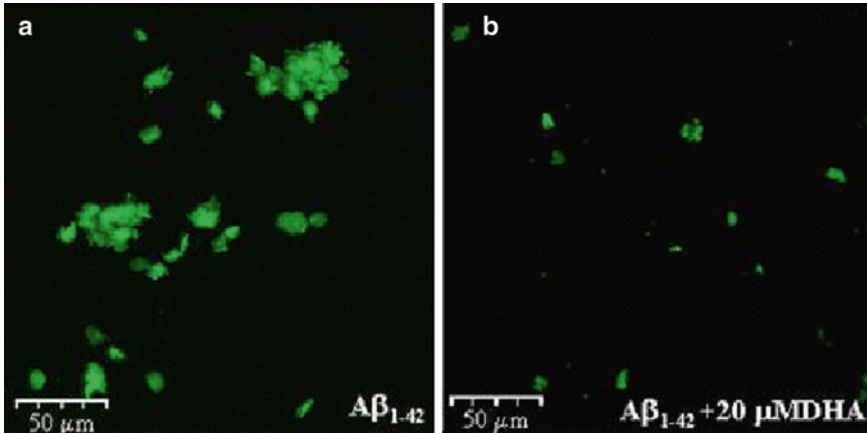
Fig. 117.5 The effect of docosahexaenoic acid on Aβ fibrillar deposits. Aβ peptide$_{1-42}$ (**a**, **b**) was incubated with (20 μM) (**a**) or without (**b**) DHA for 24 h. A two-microliter sample from each was transferred to a glass slide, mixed with and equal volume of 5 μM ThT in 50 mM Tris-glycine buffer (pH 8.5) and visualized under a laser microscope. The number of pellets was lower in the DHA-incubated samples
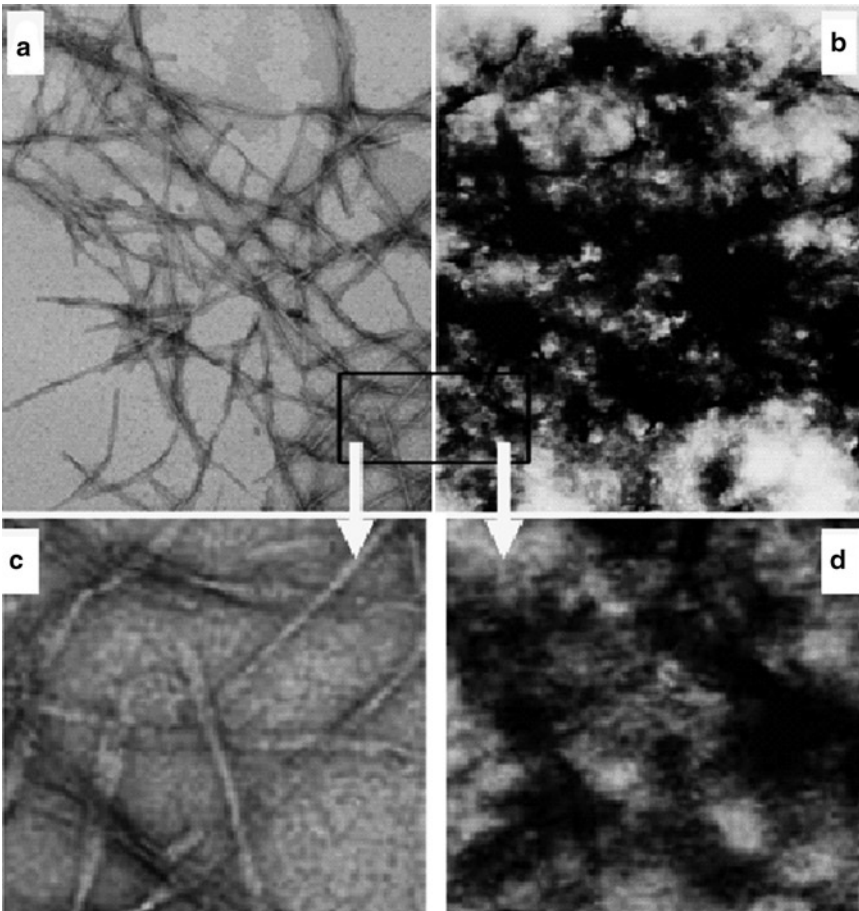
Fig. 117.6 The effect of docosahexaenoic acid (DHA) on Aβ fibril formation. Aβ peptide$_{1-40}$ was incubated with (20 μM) (**b**) or without (**a**) DHA for 24 h. Two-microliter samples were subjected to 400-mesh grid, dried for 1 min, stained with 1% uranyl acetate, and visualized under an electron microscope. (**c**) and (**d**) are the insets of (**a**) and (**b**), respectively. The amplification is 66 K
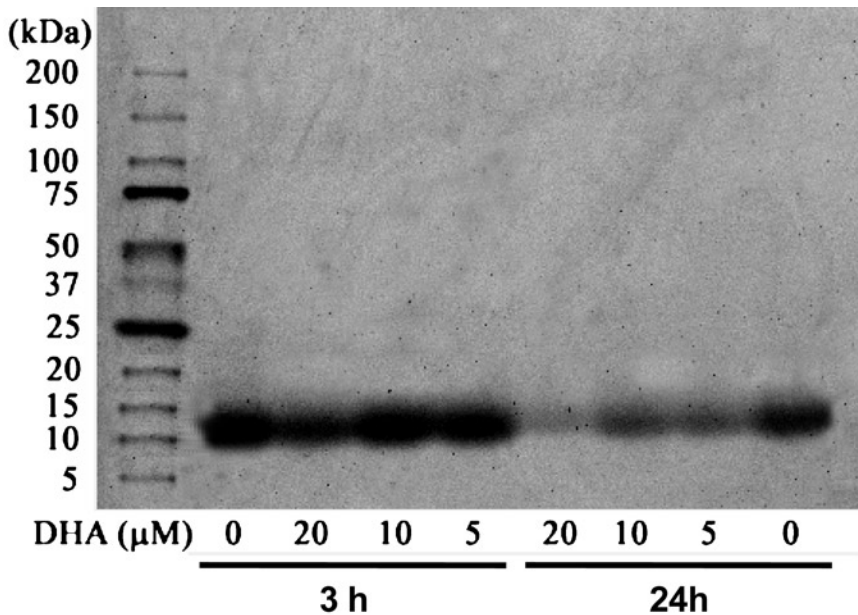
Fig. 117.7 Effect of DHA on Aβ$_{1-40}$ oligomer species by gel electrophoresis. Aβ$_{1-40}$ was incubated with or without DHA at 37°C for 3 and 24 h; the mixture was then centrifuged at 13,800× *g*, and the supernatant containing the soluble oligomer fractions was subjected directly to 4–20% Tris-Tricine gradient gel analyses. The bands were stained with Coomassie brilliant blue. The amyloid species of molecular mass ~10 to 15 kDa oligomer (equivalent to tri-tetramers) were identified in the gels. DHA dose-dependently inhibited amyloid oligomer concentrations. The effect was prominent at 24 h

significantly decreased Aβ oligomeric species ranging from 10 to 14 kDa. The inhibitory effect was both time and concentration dependent, as indicated by the gradual decrease in the density of the oligomer band with higher DHA concentrations (Fig. 117.7). No high molecular weight oligomers were observed. The mechanism through which DHA inhibits the oligomerization of Aβ remains to be explored. DHA decreased the intensity of the intrinsic tyrosine fluorescence of Aβ fibrils (data not shown), indicating a perturbing effect during the α to β transformation and the subsequent stacking of β sheets during the elongation process. Nonetheless, further studies are needed to clarify the mechanisms of DHA in the inhibition of *in vitro* fibrillation. DHA not only inhibits the formation of amyloid fibers, but also significantly induces the defibrillation of preformed fibers (Hashimoto et al. 2008). These results are thus consistent with the results of *in vivo* studies demonstrating that DHA decreases the burden of amyloid fibers by inhibiting their fibrillation.

117.6 Neurogenesis and DHA

117.6.1 In Vitro and In Vivo Neurogenesis and DHA

Recent evidence strongly suggests that newborn neurons participate in the formation of learning and memory (Schinder and Gage 2004). Newly generated neurons are functionally integrated into hippocampal circuits, can survive for several months (Song et al. 2002), facilitate synaptic plasticity,

and enhance the LTP (Schinder and Gage 2004). Moreover, a significant relation has been demonstrated between the number of newborn neurons and cognitive learning performance of tasks in the Morris water maze (Kempermann et al. 1997). Based on this evidence, it is highly probable that endogenous neurogenesis modulates learning and memory functions. DHA is crucial for inducing LTP in the CA1 region of rat hippocampus slices and for enhancing the potassium chloride-evoked release of acetylcholine in the rat hippocampus (Fujita et al. 2001). Also, dietary administration of DHA increases the levels of DHA in the hippocampus and improves learning and memory performance tasks in the eight-arm radial maze (Gamoh et al. 1999, 2001). These data suggest that DHA increases newborn neurons and imparts beneficial properties to the function of learning and memory. We therefore hypothesized that DHA modulates both the generation of new functional neurons and the functions of the already existing neurons, as well as improves the hippocampal function of learning and behavior.

The effect of DHA on neuronal differentiation of neural stem cells (NSCs) *in vitro* and *in vivo* has been assessed in our laboratory (Kawakita et al. 2006): in the presence of DHA, neural stem cells obtained from 15.5-day-old rat embryos significantly increased the number of Tuj1 (a neural marker)-positive neurons compared with the control on four or seven culture days, and the newborn neurons in the DHA group were morphologically more mature than those in the control. In *in vivo* experiments, the proliferation of neurons in the hippocampus, estimated after chronic administration of DHA for 12 weeks, revealed that the number of 5-bromo-2′-deoxyuridine(+)/NeuN(+) newborn neurons increased significantly in the granule cell layer of the dentate gyrus (DG) in adult rats (Fig. 117.8). These results demonstrate that DHA effectively promotes neurogenesis both *in vitro* and *in vivo*, and suggest that DHA has the new property of modulating hippocampal function regulated by neurogenesis, neuronal growth, dendritic arborization and synapse formation, and thereby exhibits the cognition-enhancing ability.

Since NSCs in the adult hippocampus, including those in rats and humans, generate new neurons in adulthood (Schinder and Gage 2004), we administrated dietary DHA to adult rats and examined the effect on active hippocampal neurogenesis. Dietary administration of DHA significantly increased the number of newborn neurons (Fig. 117.8c), demonstrating that DHA promotes neurogenesis not only in cultured embryonic NSCs but also in the hippocampus of adult rats, and suggesting that DHA also modulates the generation of new neurons in the adult brain.
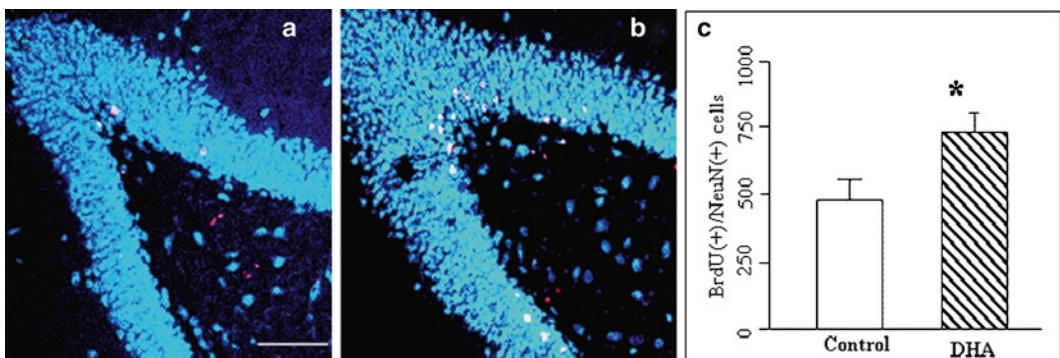
Fig. 117.8 Neuronal identity of newly divided cells in the adult dentate gyrus (DG). (**a, b**) Confocal images of DG in vehicle- (**a**) and DHA-treated (**b**) rats. BrdU (*red*), NeuN (*blue*). Scale bar = 50 µm. (**c**) Quantitative analysis of the number of newborn neurons in the entire granule cell layer of the DG in control and DHA groups. Data are shown as the means ± S.E.M. obtained from six hemispheres in three animals. $P < 0.005$
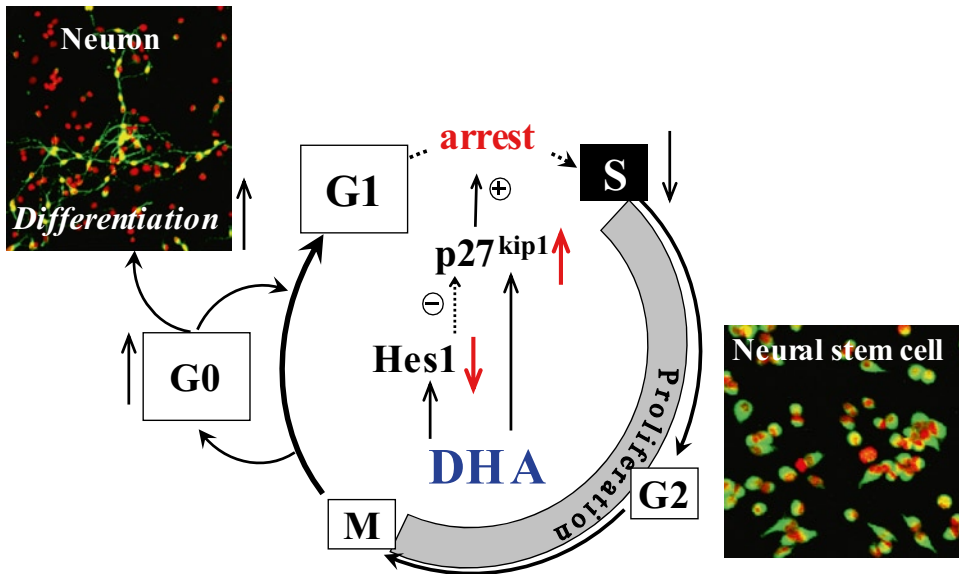
Fig. 117.9 Mechanisms of DHA-induced neuronal differentiation of neural stem cells

117.6.2 The Mechanisms of DHA-induced Neurogenesis

Activator-type bHLH transcription factors such as neurogenin, Mash1, and NeuroD enhance neuronal differentiation; on the other hand, repressor-type bHLH transcription factors such as hairy and enhancer of split 1 (Hes1) and Hes5 are essential for the maintenance and proliferation of NSCs (Kageyama et al. 2005). Crosstalk between these two types of bHLH transcription factors allows some NSCs to undergo differentiation and some to remain as NSCs. DHA decreases Hes1 mRNA and protein levels and increases NeuroD mRNA levels; furthermore, it increases MAP2, a target gene of Hes1 and NeuroD, mRNA and protein levels (Katakura et al. 2009), suggesting that it enhances neuronal differentiation of NSCs, in part, by controlling bHLH transcription factors. Hes1 directly controls cell proliferation through the transcriptional repression of CDK–cyclin complex inhibitor, $p27^{kip1}$ (Murata et al. 2005). Treatment of NSCs with DHA for 24 h significantly decreased the proportion of S-phase cells, whereas it significantly increased the proportion of G0/G1-phase cells, indicating that DHA promotes neuronal differentiation of NSCs, at least in part, through Hes1 repression and $p27^{kip1}$ induction (Fig. 117.9). At present, however, how DHA represses Hes1 gene expression is not clear. Further studies are needed to establish the mechanisms of Hes1 repression by DHA in NSCs. Using the assumed DHA characteristic of controlling cell fate might help in the restoration of injured neurons in neurodegenerative diseases including AD.

117.7 Multiple Sclerosis and DHA

An early Norwegian study has shown a lower incidence of multiple sclerosis (MS) in coastal communities with a high intake of fish, compared with inland rural communities where consumption of saturated fat is higher (Swank et al. 1952). Both mental and physical assessments tend to show improvement in MS patients ingesting fish oil with a very low-fat diet. Nonetheless, evidence regarding the progression

Table 117.1 Key features of docosahexaenoic acid

1. Docosahexaenoic acid (DHA, C22:6*n*-3) is an essential *n*-3 polyunsaturated fatty acids in the brain.
2. DHA remains highly concentrated in synaptic plasma membranes and increases neurotransmission and related brain functions.
3. DHA has strong antioxidative properties.
4. DHA supplementation imparts numerous beneficial effects to the health of the human brain through the modulation of genes associated with synaptic plasticity, neuroinflammation, and energy metabolism.
5. Chronic administration of DHA increases DHA content in the hippocampus and the cerebral cortex, and improves the memory related learning ability. Deficiency of DHA is linked to the impairment of neuronal development and cognitive learning ability related to a host of neurodegenerative diseases including AD.
6. DHA acts against amyloid fibrillation and decreases the amyloid burden in the brain.
7. DHA protects against and ameliorates the impairment of learning ability in the amyloid-infused AD model rats.

This table lists the key aspects of the DHA including its physical characteristics, the function at normal and pathological conditions

of MS is inconsistent and inconclusive, with no apparent significant association between *n*-3 PUFAs and the incidence of MS. A case-control study has demonstrated a reduced risk of MS attributed to fish consumption, but only among women (Marcheselli et al. 2003). The levels of *n*-3 and *n*-6 PUFAs in red blood cells and plasma of patients diagnosed with MS are low (Holman et al. 1989). MS is associated with an activated inflammatory response, and *n*-3 PUFAs can suppress interleukin and tumor necrosis factor-α production in MS subjects (Gallai et al. 1995). Moreover, a reduction in the amount of *n*-3 PUFA intake enhances several indices of immune response, including lymphocyte proliferation, natural-killer-cell activity, cytokine production, and delta-type hypersensitivity (Miles et al. 2004; Pischon et al. 2003). Fish oil supplementation given together with vitamins and dietary advice can improve clinical outcome in patients newly diagnosed with MS (Nordvik et al. 2000), presumably through the modulation of cytokines. Therefore, it seems reasonable to assume that treatment with *n*-3 PUFAs such as DHA may have a theoretical basis in the incidence of MS.

117.8 Applications to Other Areas of Health and Disease

Besides its beneficial role in neurodegeneration and memory loss (Table 117.1), DHA reduces the risk of depression and cardiovascular diseases such as atherosclerosis, coronary heart disease, inflammatory disease and platelet pathology. DHA supplementation promotes accretion of DHA in plasma, erythrocytes, the liver, visceral adipose tissue, spermatozoon, and brain segments (frontal cortex, hippocampus, and cerebellum) of adults as well as of fetuses and neonates; it helps in bone modeling of newborns, and both humoral and cellular immune functions are also ameliorated. Gestational diabetes, Type 2 diabetes mellitus, and insulin resistance is related to this fatty acid profile in red blood cells and skeletal muscle membranes. Moreover, DHA might help in the restoration of injured neurons in neurodegenerative Parkinson's disease, stroke, and brain ischemia. Thus, dietary intervention with DHA is suggested for the moderation of these complications.

Summary Points

- DHA remains highly concentrated in neuronal membranes.
- Deficiency of DHA is associated with generalized cognitive deficits and a host of neurodegenerative disorders, including Alzheimer's disease.

- DHA can easily pass through the blood–brain barrier. Thus supplementation with DHA would elevate brain DHA levels.
- Studies on the molecular mechanisms underlying the beneficial effects of DHA need to be carried out to reinforce the hypothetical concept that changing dietary habits or promoting dietary DHA could benefit human health, by the prevention or the slowing of cognitive impairment in mild cases of AD.
- DHA decreases the amyloid burden in the brain by inhibiting their fibrillation and deposition, suggesting that DHA is one of the essential brain nutrients that could reduce the prevalence of AD.
- DHA promotes neuronal differentiation of NSCs, at least in part, through Hes1 repression and p27^{kip1} induction.
- Further effort toward the accumulation of knowledge on the molecular mechanisms involved in this field of research is needed now in order to better clarify this concept.

Dictionary Terms

Docosahexaenoic acid: Docosahexaenoic acid (DHA; 22:6(*n*-3), all-*cis*-docosa-4,7,10,13,16,19-hexa-enoic acid) is an *n*-3 essential polyunsaturated fatty acid. Fish oils are rich in DHA. Most of the DHA originates in photosynthetic and heterotrophic microalgae, and is concentrated in organisms. Most animals make very little DHA, thus supplementation is encouraged.

Cognitive dysfunction: This is defined as unusually poor mental function associated with forgetfulness, confusion, and memory retention and attention deficit.

Alzheimer's disease: (AD) A neurodegenerative disorder, this is the most common cause of dementia, characterized clinically by progressive loss of memory and pathologically by neurofibrillar tangles and amyloid plaques in or out of neurons.

Amyloid beta: (Aβ) This is a peptide of 39–43 amino acids that appears to be the main constituent of amyloid plaques in the brains of Alzheimer's disease patients. Aβ is formed after sequential cleavage of an amyloid precursor protein, a transmembrane glycoprotein of undetermined function.

Amyloid fibrillation: The polymerization of amyloid beta sheets that are formed by vertical stacking along the long axis of fibers. Amyloid plaques and neurofibrillar tangles are the polymerized amyloid beta peptides.

Neurogenesis: This is the process by which neurons are created from neural stem cells. Adult neurogenesis is observed in predominantly two regions of the brain: the subventricular zone where the new cells migrate to the olfactory bulb, and the subgranular zone of the dentate gyrus of the hippocampus.

Neural stem cell: (NSCs) are the self-renewing, multipotent cells that generate the main phenotypes of the nervous system. NSCs differentiate into various tissues (neurons, glia, and oligodendrocytes).

Neurogenin: A transcription factor that enhances neuronal differentiation.

Multiple sclerosis: (MS) is an autoimmune disease in which the body's immune response attacks the central nervous system (brain and spine), leading to demyelination and often progresses to physical and cognitive disability. The onset of the disease usually occurs in young adults and is more common in females.

bHLH transcription factor: This factor's motif is characterized by two α-helices connected by a loop. The helix typically contains the DNA-binding regions and E-box; it binds to other proteins.

References

Abad-Rodriguez J, Ledesma MD, Craessaerts K, Perga S, Medina M, Delacourte A, Dingwall C, De Strooper B, Dotti CG. J Cell Biol. 2004; 167:953–60.

Arab K, Rossary A, Flourie F, Tourneur Y, Steghens JP. Br J Nutr. 2006; 95:18–26.

Bazan NG. Brain Pathol. 2005; 15:159–66.

Bjorkhem I, Lutjohann D, Diczfalusy U, Stahle L, Ahlborg G, Wahren J. J Lipid Res. 1998; 39:1594–600.

Bourre JM, Francois M, Youyou A, Dumont O, Piciotti M, Pascal G, Durand G. J Nutr. 1989; 119:1880–92.

Broadhurst CL, Cunnane SC, Crawford MA. Br J Nutr. 1998; 79:3–21.

Brunkan AL, Goate AM. J Neurochem. 2005; 93:769–92.

Calderon F, Kim HY. J Neurochem. 2004; 90:979–88.

Calon F, Lim GP, Yang F, Morihara T, Teter B, Ubeda O, Rostaing P, Triller A, Salem N, Jr., Ashe KH, Frautschy SA, Cole GM. Neuron. 2004; 43:633–45.

Conklin SM, Gianaros PJ, Brown SM, Yao JK, Hariri AR, Manuck SB, Muldoon MF. Neurosci Lett. 2007; 421:209–12.

Conquer JA, Tierney MC, Zecevic J, Bettger WJ, Fisher RH. Lipids. 2000; 35:1305–12.

Cummings JL, Cole G. JAMA. 2002; 287:2335–8.

de la Presa Owens S, Innis SM. J Nutr. 1999; 129:2088–93.

de Wilde MC, Farkas E, Gerrits M, Kiliaan AJ, Luiten PG. Brain Res. 2002; 947:166–73.

Delion S, Chalon S, Guilloteau D, Besnard JC, Durand G. J Neurochem. 1996; 66:1582–91.

Dyall SC, Michael GJ, Whelpton R, Scott AG, Michael-Titus AT. Neurobiol Aging. 2007; 28:424–39.

Farooqui AA, Antony P, Ong WY, Horrocks LA, Freysz L. Brain Res Brain Res Rev. 2004; 45:179–95.

Freund-Levi Y, Eriksdotter-Jonhagen M, Cederholm T, Basun H, Faxen-Irving G, Garlind A, Vedin I, Vessby B, Wahlund LO, Palmblad J. Arch Neurol. 2006; 63:1402–8.

Fujita S, Ikegaya Y, Nishikawa M, Nishiyama N, Matsuki N. Br J Pharmacol. 2001; 132:1417–22.

Gallai V, Sarchielli P, Trequattrini A, Franceschini M, Floridi A, Firenze C, Alberti A, Di Benedetto D, Stragliotto E. J Neuroimmunol. 1995; 56:143–53.

Gamoh S, Hashimoto M, Sugioka K, Shahdat Hossain M, Hata N, Misawa Y, Masumura S. Neuroscience. 1999; 93:237–41.

Gamoh S, Hashimoto M, Hossain S, Masumura S. Clin Exp Pharmacol Physiol. 2001; 28:266–70.

Gordon LM, Sauerheber RD, Esgate JA, Dipple I, Marchmont RJ, Houslay MD. J Biol Chem. 1980; 255:4519–27.

Green P, Yavin E. J Neurochem. 1995; 65:2555–60.

Hashimoto M, Hossain S, Yamasaki H, Yazawa K, Masumura S. Lipids. 1999; 34:1297–304.

Hashimoto M, Hossain MS, Shimada T, Yamasaki H, Fujii Y, Shido O. J Lipid Res. 2001; 42:1160–8.

Hashimoto M, Hossain S, Shimada T, Sugioka K, Yamasaki H, Fujii Y, Ishibashi Y, Oka J, Shido O. J Neurochem. 2002; 81:1084–91.

Hashimoto M, Tanabe Y, Fujii Y, Kikuta T, Shibata H, Shido O. J Nutr. 2005; 135:549–55.

Hashimoto M, Hossain S, Shimada T, Shido O. Clin Exp Pharmacol Physiol. 2006a;33:934–9.

Hashimoto M, Hossain S, Shido O. Mol Cell Biochem. 2006b;293:1–8.

Hashimoto M, Shahdat HM, Yamashita S, Katakura M, Tanabe Y, Fujiwara H, Gamoh S, Miyazawa T, Arai H, Shimada T, Shido O. J Neurochem. 2008; 107:1634–46.

Hashimoto M, Hossain S, Tanabe Y, Kawashima A, Harada T, Yano T, Mizuguchi K, Shido O. J Nutr Biochem. 2009; 20:965–73.

Helland IB, Smith L, Saarem K, Saugstad OD, Drevon CA. Pediatrics. 2003; 111: e39–44.

Holman RT, Johnson SB, Kokmen E. Proc Natl Acad Sci USA. 1989; 86:4720–4.

Horrobin DF. Schizophr Res. 1998; 30:193–208.

Horrocks LA, Farooqui AA. Prostaglandins Leukot Essent Fatty Acids. 2004; 70:361–72.

Hossain MS, Hashimoto M, Masumura S. Neurosci Lett. 1998; 244:157–60.

Hossain MS, Hashimoto M, Gamoh S, Masumura S. J Neurochem. 1999; 72:1133–8.

Johansson AS, Garlind A, Berglind-Dehlin F, Karlsson G, Edwards K, Gellerfors P, Ekholm-Pettersson F, Palmblad J, Lannfelt L. FEBS J. 2007; 274:990–1000.

Jump DB. J Biol Chem. 2002; 277:8755–8.

Kageyama R, Ohtsuka T, Hatakeyama J, Ohsawa R. Exp Cell Res. 2005; 306:343–8.

Katakura M, Hashimoto M, Shahdat HM, Gamoh S, Okui T, Matsuzaki K, Shido O. Neuroscience. 2009; 160:651–60.

Kawakita E, Hashimoto M, Shido O. Neuroscience. 2006; 139:991–7.

Kempermann G, Kuhn HG, Gage FH. Nature. 1997; 386:493–5.

Khurana R, Ionescu-Zanetti C, Pope M, Li J, Nielson L, Ramirez-Alvarado M, Regan L, Fink AL, Carter SA. Biophys J. 2003; 85:1135–44.

Kitajka K, Puskas LG, Zvara A, Hackler L, Jr., Barcelo-Coblijn G, Yeo YK, Farkas T. Proc Natl Acad Sci USA. 2002; 99:2619–24.

Kotani S, Sakaguchi E, Warashina S, Matsukawa N, Ishikura Y, Kiso Y, Sakakibara M, Yoshimoto T, Guo J, Yamashima T. Neurosci Res. 2006; 56:159–64.

Lauritzen L, Hansen HS, Jorgensen MH, Michaelsen KF. Prog Lipid Res. 2001; 40:1–94.

Le Jeune H, Cecyre D, Rowe W, Meaney MJ, Quirion R. Neuroscience. 1996; 74:349–63.

Lim GP, Calon F, Morihara T, Yang F, Teter B, Ubeda O, Salem N, Jr., Frautschy SA, Cole GM. J Neurosci. 2005; 25:3032–40.

Lim S, Suzuki H. J Nutr. 2001; 131:319–24.

Marcheselli VL, Hong S, Lukiw WJ, Tian XH, Gronert K, Musto A, Hardy M, Gimenez JM, Chiang N, Serhan CN, Bazan NG. J Biol Chem. 2003; 278:43807–17.

Mattson MP. Nature. 2004; 430:631–9.

McNamara RK, Carlson SE. Prostaglandins Leukot Essent Fatty Acids. 2006; 75:329–49.

Miles EA, Banerjee T, Dooper MM, M'Rabet L, Graus YM, Calder PC. Br J Nutr. 2004; 91:893–903.

Moriguchi T, Greiner RS, Salem N, Jr. J Neurochem. 2000; 75:2563–73.

Morris MC, Evans DA, Bienias JL, Tangney CC, Bennett DA, Wilson RS, Aggarwal N, Schneider J. Arch Neurol. 2003; 60:940–6.

Murata K, Hattori M, Hirai N, Shinozuka Y, Hirata H, Kageyama R, Sakai T, Minato N. Mol Cell Biol. 2005; 25:4262–71.

Neuringer M, Connor WE, Lin DS, Barstad L, Luck S. Proc Natl Acad Sci USA. 1986; 83:4021–5.

Nordvik I, Myhr KM, Nyland H, Bjerve KS. Acta Neurol Scand. 2000; 102:143–9.

Nourooz-Zadeh J, Liu EH, Yhlen B, Anggard EE, Halliwell B. J Neurochem. 1999; 72:734–40.

Oka J, Suzuki E, Goto N, Kameyama T. Neuroreport. 1999; 10:2961–4.

Okada M, Amamoto T, Tomonaga M, Kawachi A, Yazawa K, Mine K, Fujiwara M. Neuroscience. 1996; 71:17–25.

Phillis JW, Horrocks LA, Farooqui AA. Brain Res Rev. 2006; 52:201–43.

Pifferi F, Roux F, Langelier B, Alessandri JM, Vancassel S, Jouin M, Lavialle M, Guesnet P. J Nutr. 2005; 135:2241–6.

Pischon T, Hankinson SE, Hotamisligil GS, Rifai N, Willett WC, Rimm EB. Circulation. 2003;108:155–60.

Rapoport SI, Chang MC, Spector AA. J Lipid Res. 2001; 42:678–85.

Sakamoto T, Cansev M, Wurtman RJ. Brain Res. 2007; 1182:50–9.

Schaefer EJ, Bongard V, Beiser AS, Lamon-Fava S, Robins SJ, Au R, Tucker KL, Kyle DJ, Wilson PW, Wolf PA. Arch Neurol. 2006; 63:1545–50.

Schinder AF, Gage FH. Physiology (Bethesda). 2004; 19:253–61.

Scott BL, Bazan NG. Proc Natl Acad Sci USA. 1989; 86:2903–7.

Shahdat H, Hashimoto M, Shimada T, Shido O. Life Sci. 2004; 74:3009–24.

Song H, Stevens CF, Gage FH. Nature. 2002; 417:39–44.

Suzuki H, Park SJ, Tamura M, Ando S. Mech Ageing Dev. 1998; 101:119–28.

Swank RL, Lerstad O, Strom A, Backer J. N Engl J Med. 1952; 246:722–8.

Tanabe Y, Hashimoto M, Sugioka K, Maruyama M, Fujii Y, Hagiwara R, Hara T, Hossain SM, Shido O. Clin Exp Pharmacol Physiol. 2004; 31:700–3.

Wainwright PE, Huang YS, Coscina DV, Levesque S, McCutcheon D. Dev Psychobiol. 1994; 27:467–87.

Yamamoto N, Saitoh M, Moriuchi A, Nomura M, Okuyama H. J Lipid Res. 1987; 28:144–51.

Yehuda S, Rabinovitz S, Carasso RL, Mostofsky DI. Neurobiol Aging. 2002; 23:843–53.

Young C, Gean PW, Chiou LC, Shen YZ. Synapse. 2000; 37:90–4.

Part XXI
Pathology and Abnormal Aspects: Miscellaneous Topics

Chapter 118
Maternal Dietary Intake of N-Nitroso Compounds from Cured Meat and the Risk of Pediatric Brain Tumors

Michael Huncharek

Abbreviations

NOC	N-nitroso compounds
PBT	Pediatric brain tumors
SEER	Surveillance, Epidemiology and End Results
PNET	Primitive neuroectodermal tumor
CNS	Central nervous system
NOS	Not otherwise specified

118.1 Introduction

Central nervous system (CNS) tumors are the most common solid tumor of the pediatric age group in the United States with approximately 3,500 new cases diagnosed each year. Since brain neoplasms are also the second leading cause of death among children under the age of 15, they represent an important clinical and public health problem. Unfortunately, little is currently understood about their etiology. Although prior work suggests a role for certain genetic disorders in the development of pediatric brain tumors (PBT), e.g. neurofibromatosis type 1, ataxia telangiectasia, Li-Fraumeni syndrome, as well as cranial irradiation, such cases account for a small minority of all patients with this disease (Bunin 2000). The etiology of the vast majority of these tumors remains obscure.

Over the last 2 decades, the role of diet in cancer causation in general, and PBT in particular, has been a topic of increasing interest. Dietary N-nitroso compounds (NOCs) are suspected of playing a role in the development of childhood CNS tumors based on evidence of carcinogenicity in animal studies (Magee 1989). Of particular interest is the finding that the carcinogenic effects of these compounds may be age-dependent with the fetus being particularly susceptible. Various foods are sources of both preformed NOCs and NOC precursors that may form NOCs in vivo via the acidic environment of the stomach. Nitrosamides may be formed endogenously, along with other NOCs, from precursors such as nitrite derived from cured meats or other foods cured with sodium nitrite. All of the above contribute to the hypothesis that these compounds may play a role in the development of PBT.

M. Huncharek (✉)

Meta-Analysis Research Group, 10 Sasanqua Circle, Columbia, SC 29209, USA

e-mail: Info@metaresearchgroup.org; metaresearch@hotmail.com

An important feature of studying the potential etiological role of diet in human cancer is that it represents a potentially modifiable behavior. Determining whether maternal cured meat consumption impacts on disease development among this patient group may, therefore, represent an important disease prevention strategy. This article will examine the existing scientific evidence related to the hypothesis that maternal dietary intake of NOCs from cured meat during pregnancy influences PBT risk.

118.2 Epidemiology of Childhood Brain Tumors

Brain tumors are the most common solid tumor of childhood with an incidence of roughly 24–27 cases per million in the United States and Western Europe (Little 1999). They account for 20% of childhood neoplasms exceeded in frequency only by the leukemias. PBTs also represent the leading cause of cancer-related death in children with an overall mortality rate of 2.7 per 100,000 in the United States among children less than 15 years of age (Bleyer 1999). Currently PBTs account for approximately one-third of cancer-related deaths in this age group. Regarding specific age categories, PBTs are most common among children ages 2–5 and 5–10 years old, with 30% of such neoplasms occurring in each of these age ranges (Gilles et al. 1995).

The past several decades have witnessed an increased incidence of PBTs. For instance, based on data from the Surveillance, Epidemiology and End Results (SEER) program, the incidence of PBTs in 1973 was 2.4 cases per 100,000 children aged <15 years versus 3.5 cases per 100,000 in 1994 (Boyle et al. 1985) with a number of studies corroborating this increase (e.g. Bunin et al. 1996). Interestingly, the noted increase appears not to be linear over time but rather to have accelerated after 1985 (Smith et al. 1998). Although some investigators suggests that the wider availability of magnetic resonance imaging (MRI) post-1985, could account for the increased incidence secondary to improved diagnostic techniques, the fact that the higher incidence rates have persisted brings this theory into question.

Anatomically and histologically, PBTs represent a heterogeneous group of tumors with roughly 50% occurring supratentorially and 50% being infratentorial in origin. As seen in Table 118.1, astrocytomas represent the most common histology of the supratentorial tumors (roughly 25%), versus medulloblastoma among those arising infratentorially. Interestingly, about 20% of PBTs occur in infants and children less than 3 years of age. Compared with older children, intracranial neoplasms in the 0–3 year age group are more likely to be malignant, both histologically and in terms of malignant behavior, and are more commonly supratentorial in location (Cohen et al. 1993).

Table 118.1 Relative frequency of histological types of PBTs

Tumor histology	Relative frequency (%)
Supratentorial	
Astrocytoma	23
Craniopharyngioma	6
Embryonal tumors	6
Pineal region tumors	4
Ependymoma	4
Infratentorial	
Medulloblastoma	20
Astrocytoma	15
Brain stem glioma	10
Ependymoma	6

Overview of types of pediatric brain tumors categorized by histology

Astrocytoma is the most common CNS tumor in children constituting approximately half of all PBTs and about 9% of all neoplasms in the pediatric age group (Young et al. 1986). The second most common PBT is the cerebellar medulloblastoma, accounting for approximately 20% of PBTs. A histologically related tumor, primitive neuroectodermal tumor (PNET) occurs suprtentorially with medulloblastoma making up 80% of medulloblastoma/PNET combined. PNET is essentially an undifferentiated embryonal neoplasm distinct from the classic embryonal tumors. Medulloblastoma/PNET is characterized by a young age at onset, i.e. half of all cases are diagnosed prior to age 6, with approximately 30% occurring in children younger than 3 years of age.

Malignant gliomas are less common in children than adults and represent approximately 7–10% of PBTs. Histologically, 50–60% are anaplastic astrocytomas, 30–40% are the highly malignant glioblastoma multiforme with another 10–20% characterized as anaplastic oligodendrogliomas and malignant mixed gliomas (Dropcho et al. 1987). Most occur in the cerebral hemispheres with up to 25–35% diagnosed in children younger than 5 years. Brainstem gliomas are a devastating clinical entity and arise in the midbrain, pons or medulla in children between 3 and 9 years old. The majority are diffuse pontine tumors presenting as diffuse, expansile lesions. Although histological confirmation is often unavailable given their anatomic location, autopsy data shows that most of these lesions are malignant. Diffusely infiltrating pontine gliomas are highly aggressive with median survivals of 10–12 months. Focal pontine lesions, tumors with predominant cystic components and diffuse tumors arising outside the pons show markedly superior survivals with the dorsally exophytic or focal pontine lesions having 5-year survival rates of 90% or more.

As outlined above, PBTs represent a pathologically and clinically diverse group of neoplasms. It must be appreciated that this complicates epidemiological analyses of potential risk factors for this disease entity. Given the rarity of PBTs, many observational studies do not stratify analyses by histological subtype. Since evidence exists that pathological subtypes have distinct genetic and clinical characteristics, it is likely that risk factors may vary substantially across tumor histologies. Failure to consider histological subtype of PBTs in epidemiological studies may obscure potential underlying cause-effect relationships.

118.3 N-Nitroso Compounds as Human Carcinogens

Substantial evidence exists linking environmental factors and cancer risk in humans with Doll and Peto suggesting that as much as 60% of the human cancer burden may be attributable to the effects of diet (Doll and Peto 1981). Epidemiological evidence provides support for the central role played by dietary factors in cancer etiology. For instance, international incidence rates for colorectal cancer vary substantially with migrant studies documenting increasing incidence rates among groups moving from low-incidence to high-incidence areas (Boyle et al.1985). Similarly, prostate cancer incidence shows wide variation across populations with relatively high rates experienced among men in the United States and Western Europe and much lower incidence rates in Japan. As with colorectal cancer, migrant studies document that Japanese immigrant to the United States experience a substantial increase in risk versus their native counterparts (Haenzel and Kurihara 1968).

The NOCs constitute a large group of chemicals present in the environment and the human food supply. Concern over their possible risk to human health derives from initial observations of liver toxicity in sheep fed fish meal treated with sodium nitrite (Koppang 1964). Previously, Magee and Barnes reported on the carcinogenicity of nitrosodimethylamine (NMDA) which spawned substantial interest in this group of chemical carcinogens (Magee and Barnes 1956). Further evidence of concern regarding NOC developed from the work of Sander, demonstrating the formation of

carcinogenic nitrosamines from amine precursors and nitrite under conditions resembling those present in the mammalian stomach (Sander 1967). Since that time, animal studies with various NOCs unequivocally demonstrate multi-organ carcinogenicity in at least 40 different animal species, including higher primates (Bogovski and Bogovski 1981). Animal data also suggested that, unlike other carcinogens, there was probably no "non-susceptible" species (e.g. humans) (Lijinsky1999). Wide variation in susceptible target organ is seen among the animal experiments and appears dependent on the chemical structure of the carcinogen. Interestingly, dose, frequency of exposure, and route of administration appear to influence/change the observed target organ (Lijinsky and Kovatch 1989). Overall, data exist documenting the carcinogenicity of over 300 NOCs in one or more animal species.

118.3.1 SubGroups of NOCs

Based on chemical structure, NOCs can be divided into two distinct groups, i.e. N-nitrosamines and N-nitrosamides. Both are formed by the chemical reaction of a nitrite compound with amines or amides. N-nitrosamines have been the subject of substantial scientific investigation and are known to induce tumors of the liver, lung, esophagus, bladder, and pancreas, among others, in numerous animal species (Hecht 1997). The toxic effects of N-nitrosamines appear species-specific and independent of route of administration ; they require metabolic activation by cytochrome P450's to act as carcinogens (Hecht 1997). Interestingly, although capable of inducing a variety of neoplasms, N-nitrosamines do not appear associated with tumors of the brain or spinal cord.

N-nitrosamides are direct alkylating compounds and are carcinogenic in various animal models and mostly induce tumors of the CNS. Ivankovic et al. studied the effects of these compounds on prenatal rats, administering ethylurea together with a nitrite during pregnancy, resulting in CNS tumors in the offspring (Ivankovic 1979). These experiments showed that ethylnitrosourea forms in vivo in animals and results in CNS malignancies.

N-nitrosamides can also be formed endogenously in the stomach as shown by Sen et al., among others (Sen et al. 2001). This is supported also by animal experimentation, for instance, via the work of Mirvish et al. showing N-nitrosalkylurea formation in rats by adding nitrite and the N-nitroso-precursor methyl- and dimethylurea to food and drinking water (Mirvish and Chu 1973). The majority of the experimental animals developed CNS tumors, suggesting that N-nitrosamides formed in the stomach can cross the blood–brain–barrier to reach their target organ. This latter finding has obvious implications with regard to potential CNS cancer risk associated with these compounds in humans.

118.4 NOCs in Foods

A variety of food items may contain preformed NOCs secondary to food processing, such as nitrite-cured and smoked meat, fish, cheese, and beer (Dietrich et al. 2005). During the curing process of meats, nitrosation of amines/amides can occur. For instance, salt containing sodium nitrite used in the curing process can nitrosate amines or amides and result in the formation of NOCs. Smoking or drying of meat that involves exposure to higher concentrations of nitrogen than in ambient air can also act as a potential nitrosating agent (Dietrich et al. 2005). Nitrites present in foods can form N-nitrosamides in the presence of nitrosable precursors such as amides and amide-like compounds, including ureas and gaunidines, e.g. meat derived creatine and creatinine (Shepard et al. 1987). Vegetables are the main

dietary source of nitrates, which are converted to nitrite in saliva. In fact, vegetables contribute approximately 75% of the total daily intake of nitrate. High levels are found in lettuce, spinach, celery and turnip greens among others. N-nitrosamides are unstable compounds and pre-formed N-nitrosamides are unlikely to be present in large quantities in foods, in contrast to the N-nitrosamines.

It is interesting to note that with the identification of the carcinogenicity of NOCs, subsequent efforts were directed at decreasing the amounts of nitrite used for curing meats. Since the early 1970s, the amount of nitrite added to meat has been substantially reduced with vitamin C added as a nitrosation inhibitor (Dietrich et al. 2005). Surveys of sodium nitrite levels in cured meat products between 1970 and 1990 documented decreased levels in all products investigated with the exception of hot dogs. The reduction in nitrite and elimination of nitrate has taken place by both voluntary efforts by manufacturers as well as via government regulation in some countries. These controls have led to the reduction of the nitrosamine content of many cured meats and reduced exposure to nitrite which is involved in the endogenous formation of NOCs. Nonetheless, the impact of these compounds on human health secondary to presence in the food supply is complex for many reasons. Nitrate, nitrite and NOC concentrations in food products can vary widely for the same food item from different sources. Epidemiological studies are complicated by accurate recall of food intake and the use of proxy measures of exposure. In addition, the endogenous formation of NOC and its precursors may represent an even more important source of exposure than exogenous intake. All of these factors, and others, contribute to uncertainty in accurately evaluating the risk posed to human health.

118.5 NOCs and Brain Tumor Risk in Children: Epidemiological Data

As outlined above, experimental studies show that certain NOCs, particularly nitrosamides (in particular, nitrosureas) can induce brain tumors in the offspring of pregnant rodents and monkeys, illustrating that these compounds represent transplacental carcinogens. Experimental evidence also suggests that methylureas can be produced from meats secondary to reactions with creatinine in the presence of nitrite in an acidic environment. This latter finding provides a biologically plausible mechanism for the endogenous formation of these compounds in the acidic milieu of the stomach. These laboratory findings prompted the first report of epidemiological evidence that consumption of cured meats by pregnant mothers could increase the risk of brain tumors in their offspring (Preston-Martin et al. 1982).

Preston-Martin et al. conducted a case-control study in Los Angeles County, enrolling 209 young brain tumor patients (less than 25 years of age) and 209 controls. Patients were identified via the Los Angeles County Cancer Surveillance Program. Dietary intake data were obtained via a questionnaire administered by a single interviewer. Dietary information pertained to food items ingested during pregnancy.

The distribution of tumor histologies of included patients is given in Table 118.2.

As seen in Table 118.3, information on dietary intake of multiple varieties of cured meats was obtained, including fried bacon, ham, sausage, hot dogs, and salami among others. Using the highest reported intake of each item as the exposure of interest showed statistically significant effects for dietary intake of ham and "all cured meats combined". Lunch meats and fried bacon showed no effect while the other included dietary items were borderline, non-statistically significant. The authors hypothesized that brain tumors in study subjects were related to in utero exposure to NOCs and their precursors.

Some of the limitations of this report include the fact that the study population was not truly "pediatric" in that subjects up to age 25 were included in the analysis. Also, it was not possible to adjust for

Table 118.2 Distribution of tumor types (Preston-Martin et al. 1982)

Tumor histology	# patients
Astrocytoma	93
Medulloblastoma	31
Glioblastoma	19
Ependymoma	12
Glioma NOS	17
Meningiomas	13
Neuromas	9
Gangliogliomas	3

Types of pediatric brain tumors included in case–control study published by Preston-Martin in 1982

NOS not otherwise specified, # number, 11 additional tumors were of other or unknown histology

Table 118.3 Odds ratios for specific dietary factors during pregnancy and brain tumor risk

Food item	Odds ratio for highest intake level	One sided p-value
Fried bacon	1.1	0.39
Ham	1.9	0.008
Sausage	1.4	0.07
Hot dogs	1.7	0.06
salami	1.3	0.09
Other lunch meats	1.1	0.38
All cured meats combined	2.3	0.008

This table shows the risk of developing pediatric brain tumors associated with the dietary intake of specific cured meat by study subjects' mothers during pregnancy

the intake of vitamins such as vitamin C and E which block nitrosation reactions and could modify effects seen in observational studies. The report also included a wide variety of tumor histologies which may confound epidemiological analyses if the biology and etiology of tumor types differ.

In a 1989 epidemiological study, Howe et al. reported on cured meat intake and brain tumor risk among patients aged 19 years or younger treated at two Canadian Hospitals (Howe 1989). No other maternal dietary factors were examined. As in the above noted study by Preston-Martin et al., the Howe et al. case-control analysis included a very wide range of tumor histologies with approximately 60% of cases having either an astrocytoma (not otherwise specified) or medulloblastoma. Cured meat consumption by pregnant mothers stratified as less than or greater than once per week showed an odds ratio of 1.13 (0.551–2.31), a non-statistically significant result. Important caveats are that the wide variety of tumor histologies included and an imprecise measure of exposure which could both contribute to attenuation of an overall effect for cured meat on the outcome of interest.

118.5.1 Relevant Data from the 1990s

Kuijten et al. published a case-control study examining a number of gestational factors and the risk of childhood astrocytoma, the most common pediatric brain tumor (Kuijten et al. 1990). The report included data on 163 cases, aged under 15 years, derived from hospital-based registries in Pennsylvania, Delaware, and New Jersey, along with population-based controls. Relevant exposure data were obtained via telephone interview. The only dietary factors explored were consumption of

alcohol and cured meats. The latter showed an odds ratio of 1.9 (0.9–4.2) although this association was seen only among women with more than a high school education.

The relationship between maternal diet and risk of primitive neuroectodermal brain tumors (PNET) was studied by Bunin et al. and reported in the New England Journal of Medicine in 1993 (Bunin et al. 1993). Again, using a case-control design, data on 166 patients diagnosed prior to age 6 were obtained from the Children's Cancer Group. Population-based controls were selected by random-digit dialing and were matched by area code and the next five digits of the telephone number, date of birth, and race. Dietary data were obtained via interview with the mother by trained interviewers.

Odds ratios related to the risk of PNET secondary to maternal intake of a number of cured meats were calculated (Table 118.4). Only bacon intake showed a significantly increased risk of disease with a 71% greater risk associated with maternal intake of this food item. None of the other cured meats studies were found to increase brain tumor risk.

Interestingly, green salad, sweet potatoes, oranges and grapefruit showed protective effects of a greater than 50% reduction in risk. Overall, the authors felt the resultant data provided little support for the hypothesis that NOCs are potential risk factors for PNET in young children.

Paris was the setting for a French case-control study of 109 pediatric brain tumor patients collected from 13 hospitals in the city over a 2-year period (1985–1987) (Cordier et al. 1994). Almost half of the patients carried a diagnosis of astrocytoma (45%) with 17% diagnosed with medulloblastoma. Ependymoma (14%), neuroblastoma (2%), other gliomas (8%), and tumors classified as "other" composed 15% of the patients group. Patients were aged 0–15 years, and 73% of the group had biopsy-confirmed tumors. One hundred and thirty population controls, frequency matched by year of birth, were included in the study. Risk factor data were obtained via interview by a single interviewer.

A variety of data on maternal intake of cured meats during pregnancy were collected with exposures classified as "all cured meats", "ham", and "cured meats other than ham", with the latter including bacon, sausage, and salami, among others. Adjusting outcomes for child's age and sex, maternal age, and number of years of schooling of the mother, no increased risk of PBT was seen with maternal ingestion of any of the above noted food items, with odds ratios ranging from 0.7 to 0.9 with non-statistically significant 95% confidence intervals. Several foods were shown to be protective, including carrots, leeks, green peppers and fresh or frozen fish.

An addition epidemiological study from 1994 originated from Australia (McCredie et al. 1994). As with the studies previously reviewed, the sample size for the McCredie report was small, i.e. 82 cases and 164 population-based controls. Study subjects ranged in age from 0–14 years and were diagnosed during the period of 1985–1989. Cases were identified using the New South Wales Cancer Registry. Although the authors state that 72% of subjects were diagnosed with malignant gliomas, tumor histology was not otherwise characterized. The vast majority of tumors, i.e. 96%, were histologically verified. Dietary information of maternal diet during pregnancy was obtained via a structured questionnaire and personal interview. The exposure category of interest, i.e. "cured meats" included, ham, bacon, hot dogs, salami, devon, corned beef, spam and sausage.

Table 118.4 Odds ratios and 95% confidence intervals of cured meat intake and PNET risk (Bunin et al. 1993)

Cured meat type	Odds ratio	95% confidence interval
Bacon	1.71	(1.02–2.89)
Sausage	1.44	(0.81–2.56)
Hot dogs	1.00	(0.59–1.70)
Ham	0.77	(0.41–1.14)
Lunch meat	0.92	(0.55–1.53)

This table shows the risk of development of pediatric brain tumors associated with maternal intake during pregnancy of specific cured meat types

Comparing the highest quartile of intake with the lowest, and adjusting for age, sex, mother's education and mother's body mass index, yielded an odds ratio of 2.5(1.2–5.7) indicating a more than doubling of the risk of PBT associated with antenatal maternal intake of cured meats. As opposed to a number of the prior studies noted previously, McCredie et al. found no protective effect associated with intake of fruits or vegetables. Although, as the authors point out, the study results are based on a small sample size, they conclude that the analysis provides limited support for a PBT risk secondary to maternal intake of cured meats.

Bunin et al., in a study performed simultaneously with their previously referenced article on PNET, examined the role of maternal diet and the risk of astrocytoma in children under the age of 6 years (Bunin et al. 1994). The tumor types included in this analysis were astrocytoma, anaplastic astrocytoma, glioblastoma multiforme, mixed glioma with astrocytic elements, or glioma not otherwise specified (NOS). Spinal cord and optic nerve malignancies were specifically excluded. Eighty-nine percent of the 155 tumors included in the analysis were biopsy-proven with 60% confirmed as astrocytoma, and 19% as glioblastoma or anaplastic astrocytoma. Of the 27 gliomas NOS, 25 occurred in the brain stem. Controls were selected via a previously published random digit dialing procedure with controls pair-matched to cases on telephone area code and next five digits of the telephone number, date of birth of the subject and race. Relevant data were collected by trained interviewers via telephone. The types of cured meat considered in the analysis were bacon, sausage, hot dogs, ham and lunch meat.

The statistical analysis reported on "cured meats" only as a single variable and showed no effect on PBT risk, i.e. OR = 1.7 (0.8–3.4) comparing the highest to lowest quartile. If subjects were stratified by family income, a significant effect for bacon was seen, i.e. OR = 2.5(1.2–5.3) for those with a family income less than $25,000 versus income greater than $25,000 (i.e. OR = 0.7 [0.3–1.3]). Income stratification showed no effect on PBT risk in either the lower or higher income category for "cured meat" intake. Weekly consumption of hot dogs was associated with an almost doubling of PBT risk although the 95% confidence interval for this exposure included the null value. Overall, the study results do not provide support for the hypothesis that cured meats increase the risk of childhood astrocytomas.

Sarasua and Savitz (1994) examined cured and broiled meats in relation to childhood cancer, including 45 with brain tumors. It appears that all tumor types were included in the analysis without restriction to malignant versus benign tumors or by histology (Sarasua and Savitz 1994). Subjects were children aged 0–14 years diagnosed with any form of cancer between January of 1976 and December 31st, 1983 while residents of the 1970 Denver, Colorada standard metropolitan statistical area. Controls were chosen by random digit dialing and matched to cases on age, gender, and telephone exchange area.

The meat groups studied included ham, bacon, sausage, hot dogs, and lunch meats. Exposure categories were stratified, in general, into two groups, i.e. intake of less than one time per week and 1+ times per week. A number of variables in the analysis were considered as potential confounders, including child's age, maternal smoking, maternal vitamin use, per capita income, father's education, and year of diagnosis. Information on diet was obtained during an in-home interview with a parent, in most cases, the patient's mother.

Table 118.5 provides an overview of the relevant study results. Of the cured meats examined, only ingestion of hot dogs appeared associated with an increased risk of PBT, i.e. OR = 2.3 (1.0–5.4), although the 95% confidence interval included the null value. Lunch meats and the exposure classified as "ham, bacon and sausage" both showed no positive effect. Surprisingly, the data on lunch meats showed a small protective effect. Table 118.6 shows the effect of stratification of the data based on whether the study subjects took vitamins. Clearly, vitamin intake resulted in profound changes in the resultant odds ratios with substantial attenuation of effect secondary to vitamin intake. These finding suggest and important role for these nutrients in modifying PBT risk secondary to cured meats and highlights the need to take vitamin intake into account in any observational study of the cured meat/PBT association.

Table 118.5 Association between maternal cured meat consumption and PBTs (Sarasua and Savitz 1994)

Exposure	Odds ratio	95% confidence interval
Ham, bacon, sasauge 1+/week	1.0	(0.5–2.1)
Hot dogs >0/week	2.3	(1.0–5.4)
Lunch meats 1+/week	0.4	(0.2–0.8)

The table shows the strength of the association between maternal intake of specific cured meats and the risk of pediatric brain tumors in the case-control study by Sarasua et al

Table 118.6 Effects of vitamin intake on the association of cured meats and PBTs (Sarasua and Savitz 1994)

Exposure	Odds ratio	95% confidence interval
Without vitamin intake		
Ham,bacon,sasauge 1+/week	4.8	(1.5–13.7)
Hot dogs >0/week	6.8	(2.5–18.5)
Lunch meats 1+/week	3.2	(1.0–9.8)
With vitamin intake		
Ham, bacon, sausage 1+/week	1.3	(0.6–3.0)
Hot dogs >0/week	1.8	(0.8–3.9)
Lunch meats 1+/week	1.0	(0.5–2.1)

The data in this table compliment those shown in Table 118.5. The data in Table 118.6 show the effects of maternal dietary intake of vitamins on pediatric brain tumor risk associated with intake of specific cured meats

In 2007, Pagoda et al. published an update of their prior study from 1996 examining maternal cured meat consumption and PBT risk. The updated report attempted to use "more valid" measures of exposure using a database of published nitrite levels of various food items. They then determined predicted nitrite levels of various cured meat types and used these values to assign nitrite exposure levels to their study subjects.

The study subjects were obtained via the West Coast Childhood Brain Tumor Study and included 540 cases and 801 population-based controls aged 0–19 years from 19 counties in three West Coast regions. Frequency of consumption and portion size for cured meat items were obtained from the mothers of cases and converted to average daily grams of consumption. "Cured meats" included bacon, sausage, hot dogs, ham and "other cured meats". Tumor types included were "astroglial tumors", "medulloblastoma/ PNET" and "other", with astroglial tumors making up 57% of the study population.

Nitrite levels were found to have decreased in all of the cured meat items considered with the exception of hot dogs. PBT risk among pregnant women ingesting the highest level of dietary nitrite, i.e. >3.0 mg/day, showed a tripling of PBT risk among their offspring with an odds ratio of 3.0 (1.2–7.9). This nitrite intake is roughly equivalent to eating three hot dogs per day throughout pregnancy. Lower intakes were also associated with somewhat lower cancer risk. The authors concluded

that "A substantial risk of pediatric brain tumors appears to be associated with relatively high levels of maternal cured meat consumption during pregnancy".

118.5.2 Recent Data

Several additional recent epidemiological studies address the question of maternal cured meat intake and PBT risk. These include an analysis by Lubin et al. (2000). In this case-control study all cases of brain tumor among subjects less than 18 years old diagnosed between 1984 and 1993 in Israel constituted the study group. A total of 300 cases were matched two-to-one with control subjects obtained via the Population Registry and matched by sex, country and year of birth. Approximately 47% of patients suffered from "astroglial" tumors with medulloblastoma accounting for an additional 25.3% (Lubin et al. 2000). As seen in a number of previously viewed studies, dietary data were collected via personal interview with the study subject's mother using a semi-quantitative food questionnaire. Monthly and weekly reported food consumption was converted into average daily amounts.

The only relevant "cured meat" related food category analyzed by the authors was "preserved meat and sausages". Comparing the highest tertile of intake with lowest yielded an odds ratio of 1.13 (0.8–1.6), which does not support a role for this food item in PBT risk. Interestingly, neither vitamin C nor E intake during pregnancy showed any protective effect.

In a 2005 study, Bunin et al. readdress the issue of maternal diet and the risk of medulloblastoma/ PNET among children aged less than 6 years (Bunin et al. 2005). The study used methods similar to their previous paper on this topic (Bunin et al. 1993) as well as the same database as the source of patients. "Cured meat" consisted of separate categories for ham, lunch meat, hot dogs and lunch sausage. The authors also presented data for an exposure category termed "cured meat and fish". None of the cured meat categories showed any effect of intake during pregnancy and PBT risk with ORs ranging from 0.8 to 1.1 comparing highest to lowest weekly intake. All associations showed non-statistically significant 95% confidence intervals. A 2006 study by the same group of authors did not present any new data on the cured meat/PBT relationship (Bunin et al. 2005).

118.6 Meta-Analysis of Observational Data

As detailed above, the biological plausibility of an association between NOCs and PBT's and the initial epidemiological evidence provided by Preston-Martin et al. (1982) prompted additional exploration of this topic by others. A major limitation of the existing literature is the relatively small number of patients enrolled in any individual study. This is understandable given the rarity of PBTs. Nonetheless, small sample size limits the statistical power to detect an effect, if, in fact, one exists. Meta-analysis provides an avenue for a more critical appraisal of a body of knowledge plagued by such shortcoming by allowing the pooling of data and thereby increasing sample size. Such methods also allow examination of the study design issues that may influence study outcome and interpretation. The strength of meta-analysis is its dependence on a prospectively defined protocol, explicit study inclusion criteria, comprehensive literature search, and use of accepted statistical methodologies to evaluate the validity of the observed outcome based on various assumptions in study design and statistical analyses.

In 2004, Huncharek et al. published a meta-analysis examining the cured meat/PBT association. Using methods described by Greenland, the author conducted a Medical Literature Analysis and Retrieval System (MEDLARS) literature search covering the years 1966–2001. This electronic

search was supplemented by searches of the CancerLit and Excerpta Medica databases as well as the CD-ROM version of "Current Contents". Electronic searches were supplemented by manual literature searches of study bibliographies, review articles, textbooks, etc.

The literature search yielded seven observational studies available for statistical pooling (i.e. Bunin et al. 1993, 1994; Cordier et al. 1994; Kuijten et al. 1990; McCredie et al. 1994; Preston-Marin 1996; Sarasua and Savitz 1994). A total of 1,226 cases and 1,768 controls were enrolled in the seven reports. Only McCredie et al. (1994) and Prestin-Martin et al. (1996) showed statistically significant increased risk with maternal cured meat intake during pregnancy. The summary relative risk derived by pooling individual study odds ratios and 95% confidence intervals was 1.68 (1.30–2.17), consistent with a 68% increase risk of PBT among children of mothers ingesting "high" levels of dietary cured meats during pregnancy compared with "low" intake as defined in the individual reports.

Four of the studies included in the meta-analysis stratified cured meat by type, e.g. bacon, hot dogs etc. (Bunin et al. 1993; Cordier et al. 1994; Preston-Martin 1996; Sarasua and Savitz 1994). Pooling data using hot dogs as the exposure of interest showed a summary relative risk of 1.33 (1.08–1.66) while "high" versus "low" intake of sausage yielded a result consistent with a 44% increased risk of PBT associated with this intake, i.e. summary relative risk of 1.44 (1.01–2.06). Maternal consumption of ham during pregnancy was not associated with an increased risk of PBT with a summary relative risk of 0.96 (0.75–1.23).

Although the data from this meta-analysis are intriguing with a total sample size greater than 1,000 subjects, numerous limitations characterize the available database. The number of published studies examining the PBT/dietary cured meat relationship is small. In addition, inadequate information exists for a detailed appraisal of a dose-response relationship. Demonstration of a dose-response between exposure and outcome is an important criterion for drawing causal inferences. Almost all of the existing studies stratified cured meat intake categorically, e.g. by tertile or quartile, without quantitatively defining the stratified intakes. It is therefore impossible to directly compare intake categories without such information and precludes a rigorous meta-analytic evaluation of dose response, such as that described by Berlin et al. (1993). A dichotomous classification of "high" versus "low" is not fully informative and may provide a spurious result depending on the absolute nutrient intake across studies. Further work needs to incorporate such information. In addition, the small numbers of studies available for statistical pooling does not allow for an analysis of the effects of maternal intake of cured meat and PBT of specific histologies. The striking differences seen among brain tumor types in terms of natural history and biological behavior/genetic characteristics may, at least partly, reflect distinct etiologies. Lack of stratification based on tumor type could confound pooled analyses.

118.7 Conclusions

Malignant brain tumors remain an important cause of morbidity and mortality among the pediatric age group. Other than rare genetic syndromes associated with increased PBT risk, the etiology of this group of devastating tumors is largely unknown. In this context, numerous epidemiological studies have implicated environmental exposures in brain tumor development These include maternal/paternal smoking during pregnancy (Gold 1994), insecticides (Gold et al. 1979) and dietary factors (Preston-Martin et al. 1982).

Prior work suggests that various NOCs are neural carcinogens in a variety of animal models. This finding is of epidemiological interest since both preformed NOCs and precursors occur in the human diet from various sources. Animal feeding studies suggest that in vivo nitrosation may be an important source of carcinogenic compounds from NOC precursors. Tannenbaum and Mergens demonstrated that feeding pregnant rate nitrites along with amines or amides resulted in offspring at high

risk for brain tumors (Tannenbaum and Mergens 1980). Interestingly, this effect was attenuated by the administration of vitamins E and C.

As discussed above, Preston-Martin et al. published data in 1983 suggesting that maternal cured meat consumption during pregnancy increases brain tumor risk in offspring (Preston-Martin 1983). This question was examined in the context of the "NOC hypothesis" with the authors pointing out that cured meat contains nitrosamines and that high levels may also be released in cooking fumes. The biological plausibility of the association between NOCs and pediatric CNS tumors and the initial epidemiological evidence provided by Preston-Martin et al. prompted addition studies by others. Nonetheless, numerous limitations of the existing scientific database preclude definitive conclusions regarding the validity of this suspected association. As discussed throughout this review, these limitations include, among others; (1) the small size of the available epidemiological database, (2) lack of stratification of available data by tumor histology, (3) lack of data on the effects of adjustment for vitamin intake, (4) use of crude, non-quantitative exposure classifications in most observational studies, (5) inability to quantify possible endogenous formation of NOCs in human epidemiological analyses and (6) lack of a clear dose-response between exposure and outcome of interest. Cleary, overcoming many of the above study design limitations would contribute to a clearer understanding of the true association between maternal intake of NOCs and PBT risk. At present, the validity of the "NOC hypothesis" remains uncertain.

118.8 Applications to Other Areas of Health and Disease

Work related to understanding the biology of NOCs, their ability to induce cancer in animals and humans and elucidating the epidemiological characteristics of these cancers is an important area of research. Prior work, as outlined above, suggests that diet is a major determinant of cancer in human populations. Sufficient epidemiological evidence exists highlighting the role of dietary factors in the development of cancer in humans with migrant studies providing important substantiating evidence. Nonetheless, the proposed association between maternal NOC intake during pregnancy and PBT remains uncertain. The problems that limit interpretation of the existing database regarding this association are similar to those encountered in other diet/disease contexts. Therefore, the NOC/PBT relationship serves as an important paradigm for nutritional cancer epidemiology in general.

Additional research with regard to NOC/PBT may include more detailed characterization of the correlation, or lack thereof, between intake of total cured meats and specific meat types and rates of childhood brain tumors, as well as other cancers, across multiple populations. Due to problems with case-control studies in terms of recall or selection bias, cohort studies may be particularly relevant. Although childhood brain tumors are rare, additional work using adult cohorts could provide important relevant information, since extrapolations from adults to children would support a potential causal association. Clearly, methodological refinements could lead to improved insight into this suggested cause/effect relationship.

Additional work aimed at further elucidation of the biological plausibility of the association would also contribute to more clearly establishing a causal connection. Determining more precise estimates of human intake, including endogenous production of NOCs, could bolster the human observational data. Developments in the area of biomarkers may represent a potential avenue for improved "molecular epidemiology" in this field.

Clearly, an important aspect of establishing a possible causal connection between NOCs and PBT risk is the potential for development of cancer prevention strategies based upon this information. Dietary factors are potentially modifiable and therefore represent a method for direct intervention in a causal pathway leading to a devastating disease in humans. Community-based initiatives or other

public health intervention programs could represent an important research field to develop from the more fundamental laboratory and epidemiological work currently being done in this area.

118.9 Methodological Consideration

An important caveat regarding the human epidemiological data reviewed above centers on the possible confounding of a NOC/PBT relationship by other dietary factors, specifically, intake of fruits and vegetables. Prior work shows that, in general, there is an inverse relationship between dietary intake of cured meats and ingestion of fruit and vegetable. Some of the available observational studies show that PBT risk was lower among those subjects with "high" fruit/vegetable consumption.

This raises the possibility that the observed association between NOC intake and PBT could be due to a protective effect of fruits and vegetables with the cured meat association due to meat's negative correlation with fruits and vegetables. Other epidemiological studies show a protective effect between increasing fruit/vegetable intake and decreased risk of a number of human cancers and such a relationship may also exists with regard to PBTs. This issue has received inadequate consideration in the relevant literature and represents an important avenue for further research.

Summary Points

- CNS tumors are the most common solid tumor of the pediatric age group in the United States with approximately 3,500 new cases diagnosed each year.
- Since brain neoplasms are also the second leading cause of death among children under the age of 15, they represent an important clinical and public health problem.
- Dietary NOCs are suspected of playing a role in the development of childhood CNS tumors based on evidence of carcinogenicity in animal studies.
- Astrocytoma is the most common CNS tumor in children constituting approximately half of all PBTs and about 9% of all neoplasms in the pediatric age group.
- Malignant gliomas are less common in children than adults and represent approximately 7–10% of PBTs. Histologically, 50–60% are anaplastic astrocytomas, 30–40% are the highly malignant glioblastoma multiforme with another 10–20% characterized as anaplastic oligodendrogliomas and malignant mixed gliomas.
- The NOCs constitute a large group of chemicals present in the environment and the human food supply. Concern over their possible risk to human health derives from initial observations of liver toxicity in sheep fed fish meal treated with sodium nitrite.
- Evidence of concern regarding NOC developed from the work of Sander demonstrating the formation of carcinogenic nitrosamines from amine precursors and nitrite under conditions resembling those present in the mammalian stomach (Sander 1967).
- The toxic effects of N-nitrosamines appear species specific and independent of route of administration and require metabolic activation by cytochrome P450's to act as carcinogens.
- N-nitrosamides are direct alkylating compounds and are carcinogenic in various animal models and mostly induce tumors of the CNS.
- In 2004, Huncharek et al. published a meta-analysis examining the cured meat/PBT association. Pooling data using hot dogs as the exposure of interest showed a summary relative risk of 1.33 (1.08–1.66) while "high" versus "low" intake of sausage yielded a result consistent with a 44% increased risk of PBT associated with this intake, i.e. summary relative risk of 1.44 (1.01–2.06).
- At present, the validity of the "NOC hypothesis" remains uncertain.

Definitions and Explanations

PBT: Pediatric brain tumor.

NOC: N-nitroso compound. This group of chemicals represents a large group of carcinogens that occur in the environment and can be formed in the body by nitrosation of secondary or tertiary amines. Total human exposure includes both exogenous and endogenous components.

Meta-analysis: A group of statistical procedures for pooling data from multiple clinical trials or observational studies to obtain a summary measure of effect.

Summary relative risk: A summary outcome measure used in meta-analyses designed to pool data from observations studies using individual study outcomes (either odds ratios or relative risks) and 95% confidence intervals.

Pons: Is a structure located on the brain stem. It is cranial to the medulla oblongata, caudal to the midbrain, and ventral to the cerebellum. In humans and other bipeds this means it is above the medulla, below the midbrain, and anterior to the cerebellum.

Key features of N-nitroso compounds

Characteristic	N-nitrosamines	N-nitrosamides
Formation	Reaction of a nitrite compound with amines or amides	Same as N-nitrosamines
Formation inhibitor	Redox compounds	Redox compounds
carcinogenicity	-Require activation via cytochrome P450	Do not require activation via cytochrome P450
	Induce tumors at multiple sites including, liver, lung, esophagus, bladder, pancreas, kidney, trachea, nasal cavity	Induce tumors of central nervous system, lymphatic system, stomach, gastrointestinal system, bone
neuro-carcinogen in animals?	No	Yes

This table compares and contrasts some key features of nitrosamides and nitrosamines

References

Berlin JA, Longnecker MP, Greenland S. Epidemiology. 1993;4:218–28.

Bleyer WA. Childs Nerv Syst. 1999;15:758–63.

Bogovski P, Bogovski S. Int J Cancer. 1981;27:471–4.

Boyle P, Zaridze DG, Smans M. Int J Cancer. 1985;36:9–18.

Bunin G. Pediatr Neurosurg. 2000;32:321–6.

Bunin GR, Kuijten RR, Buckley JD, Rorke LB, Meadows AT. N Engl J Med. 1993;329:536–41.

Bunin GR, Kuijten RR, Boesel CP, Buckley JD, Meadows AT. Cancer Causes Control. 1994;5:177–87.

Bunin GR, Feuer EJ, Witman PA, Meadowns AT. Peadiatr Preinat Epidemiol. 1996;10:319–338.

Bunin GR, Kushi LH, Gallagher PR, Rorke-Adams LB, McBride ML, Cnaan A. Cancer Causes Control. 2005;16:877–91.

Bunin GR, Gallagher PR, Rorke-Adams LB, Robison LL, Cnaan A. Cancer Epidemiol Biomarkers Prev. 2006;15;1660–7.

Cohen B, Packer RJ, Siegel KR,et al. Pediatr Neurosurg. 1993;19:171–9.

Cordier S, Iglesias MJ, LeGoaster C, Guyot MM, Madereau L, Hemon D. Int J Cancer. 1994;59:776–82.

Dietrich M, Block G, Pogoda JM, Buffler P, Hecht S, Preston-Martin S. Cancer Causes Control 2005;16:619–35.

Doll R, Peto R. J Natl Cancer Instit. 1981;66:1191–308.

Dropcho EJ, Wisoff JH, Walker RW,et al. Ann Neurol. 1987;22:355–64.

Gilles FH, Sobel EL, Tavare CJ,et al. Age-related changes in diagnoses, histological features, and survival in children with brain tumors: 1930–1979. Neurosurgery 1995;37:1056–68.

Gold EB, Gordis L, Tonascia J, Sklo M. Am J Epidemiol. 1979;109:309–19.

Gold EB, Leviton A, Lopez R, Gilles FH, Hedley-White T, Kolonel LN, Lyon JL, Swanson GM, Weiss NS, West D, Aschenbrenner C, Austin D. Cancer Res. 1989;49:4349–52.

Gold EB, Leviton A, Lopez R et al. Cancer. 1994;73(4):1302–11.

Greenland S. Epidemiol Rev. 1986;9:1–30.

Haenzel W, Kurihara M. States J Natl Cancer Instit. 1968;40:43–68.

Hecht S. Proc Soc Exp Biol Med. 1997;216:181–91.

Howe Gr, Burch JD, Chiarelli AM, Risch HA, Choi BC. Cancer Res. 1989;49:4349–52.

Huncharek M, Kupelnick B. Neuroepidemiology. 2004;23:78–84.

Ivankovick S. Natl Cancer Inst Mongraph. 1979;51:103–15.

Lijinsky W. Mutation Res. 1999;443:129–38.

Lijinsky W, Kovatch RM. Biomed Env Sci. 1989;2:154–9.

Lubin F, Farbstein H, Chetrit A, Farbstein M, Freedman L, Alfandary E, Modan B. Int J Cancer. 2000;86:149–3.

Koppang N. Nord Vet Med. 1964;16:305–22.

Kuijten RR, Bunin GR, Nass CC, Meadows AT. Cancer Res. 1990;50:2608–12.

Little J. Int Agency Cancer Res. 1999;149.

Magee PN. Cancer Surv. 1989;8(2):207–39.

Magee PN, Barnes JM. Br J Cancer. 1956;10:114–22.

McCredie M, Maisonneuve P, Boyle P. Int J Cancer. 1994;56:6–10.

Mirvish SS, Chu C. J Natl Cancer Inst. 1973;50:745–50.

Preston-Martin S, Yu MC, Benton B, Henderson BE. Cancer Res. 1982;42:5240–5.

Preston-Martin S, Yu MC, Henderson BE, Roberts C. JNCI 1983;70(5):863–6.

Preston-Martin S, Pagoda JM, Mueller BA, Holly EA, Lijinsky W, Davis RL. Cancer Epidemiol Biomarkers Prev. 1996;5(8):599–05.

Sander J. Arch fur Hygen. 1967;151:22–8.

Sarasua S, Savitz DA. Cancer Causes Control. 1994;5:141148.

Sen NP, Seaman SW, Baddoo PA, Burgess C, Weber D. J Agric Food Chem. 2001;49:2096–103.

Shepard SE, Schlatter C, Lutz WK. Food Chem Toxicol. 1987;25:91–108.

Smith MA, Freidline B, Ries LAG, Simon R. J Natl Cancer Inst. 1998;90:1269–77.

Tannenbaum SR, Mergens W. Ann NY Acad Sci. 1980;355:267–77.

Young JL, Ries LG, Silverberg E, Horm JW, Miller RW. Cancer. 1986;58:598–602.

Chapter 119
Behavioral Aspects of Nonalcoholic Fatty Liver Disease: Diet, Causes, and Treatment

Giulio Marchesini, Chiara Nuccitelli, Elena Centis, Silvia Di Domizio, Alessandro Suppini, Rebecca Marzocchi, and Riccardo Dalle Grave

Abbreviations

ALT	Alanine aminotransferase
BMI	Body mass index
HDL	High density lipoprotein
HOMA	Homeostasis model assessment
CBT	Cognitive-behavioral treatment
NAFLD	Nonalcoholic fatty liver disease
NAS	NAFLD activity score
NASH	Nonalcoholic steatohepatitis

119.1 Introduction

Nonalcoholic fatty liver disease (NAFLD) is a clinical/biochemical condition characterized by fatty liver with/without necroinflammation and fibrosis, and is considered the hepatic expression of the metabolic syndrome (Marchesini et al. 2003). The disease has long been considered a benign condition, but there is now evidence that fatty liver may progress to nonalcoholic steatohepatitis (NASH), to fibrosis, cirrhosis, and ultimately to terminal liver failure or hepatocellular carcinoma (Caldwell and Crespo 2004). The hepatic involvement has obesity and diabetes as pivotal expressions and insulin resistance as the underlying metabolic defect (Sanyal 2002), also in normal-weight subjects without diabetes (Bugianesi et al. 2005). Low insulin sensitivity, either genetically determined or obesity associated (acquired), favors the accumulation of free fatty acids and triglycerides within the liver cells, resulting in hepatocellular damage, which may be self-maintaining and progressive (Table 119.1).

From an epidemiological point of view, the increasing prevalence of NAFLD parallels the worldwide epidemics of diabetes and obesity in Western countries. Despite increased awareness of the multiple diseases associated with being overweight and obese, the prevalence of obesity and metabolic syndrome has increased dramatically in recent years, and NAFLD incidence in adults and children is rapidly rising as well (Charlton 2004; Fraser et al. 2007).

G. Marchesini (✉)
Unit of Metabolic Diseases & Clinical Dietetics, "Alma Mater Studiorum" University,
University of Bologna, Policlinico S. Orsola, Via Massarenti 9, I-40138, Bologna, Italy
e-mail: giulio.marchesini@unibo.it

Table 119.1 Key facts of nonalcoholic fatty liver disease (NAFLD)

1. Nonalcoholic fatty liver disease (NAFLD) encompasses a spectrum of liver involvement in subjects without significant alcohol intake (<20 g/day), characterized by accumulation of triglycerides in the hepatocytes (steatosis). NAFLD is largely caused by unhealthy lifestyles (excess calorie intake, low physical activity), favoring obesity and diabetes mediated by insulin resistance
2. Steatosis (>5% of hepatocytes) is present in 30% or more of the adult population in Western countries. Steatosis may be accompanied by necroinflammation and fibrosis, leading to disease progression
3. Subjects with NAFLD are at risk of developing advanced liver disease (cirrhosis, terminal liver failure, hepatocellular carcinoma) of metabolic origin. Reduced calorie intake and increased physical activity are the key issues in disease prevention and in treatment strategies

This table lists the key facts of NAFLD, including the diagnosis of disease, the factors associated with disease progression, the possible outcome of disease and prevention and treatment strategies

The various features of the metabolic syndrome appear in chronological order in NAFLD patients (Suzuki et al. 2005a). Weight gain and low High density lipoprotein (HDL) cholesterol generally precede raised liver enzymes and the other insulin resistance-related features. Raised aminotransferase levels (namely alanine aminotransferase – ALT), hypertriglyceridemia, and hypertension appear nearly simultaneously, and precede glucose intolerance. However, NAFLD may also exist in the presence of normal ALT, and the use of raised liver enzymes as a surrogate marker of NAFLD leads to underestimation of the prevalence of the disease to an extent variable according to gender and age.

As the disease stems from excess calorie intake and lack of physical activity, the correction of unhealthy lifestyles forms the background approach to any prevention and treatment strategy (Bellentani et al. 2008), even when pharmacological agents (mainly insulin-sensitizing agents) are tested. As it is the case of obesity, drug therapy remains a second line treatment, to be added to behavior therapy if and when lifestyle modifications are not achieved or have not produced the expected liver improvement in patients at risk of progressive disease.

119.2 Overweight/Obesity and Weight Loss

NAFLD patients are typically overweight or obese and insulin resistant, and compared to individuals without hepatic steatosis, they show a significantly higher energy intake.

Weight loss may rapidly reverse fatty liver, even in subjects with diabetes, by decreasing the overflow of fatty acids responsible for hepatic and peripheral insulin resistance and the levels of proinflammatory and profibrotic adipokines (Petersen et al. 2005). Even a 2-week calorie restriction, independently of exercise (Tamura et al. 2005), causes a 27% reduction in intrahepatic fat content despite a minimal change in total body fat in type 2 diabetic patients. The change in hepatic triglyceride content is also associated with significant changes in hepatic glucose production and whole-body insulin sensitivity (Petersen et al. 2005).

A weight loss of at least 10% of initial body weight in obese patients undergoing dietary treatment is frequently associated with reversal of abnormal liver function tests. More recently, even a moderate weight loss (approximately 6%) improved insulin resistance and reduced the intrahepatic fat content (Sato et al. 2007). In 15 biopsy-proven NASH patients, a 1-year intense nutritional counseling and a moderately restricted diet producing a mean weight loss of 2.9 kg (3% of body weight) led to a histological improvement in 60% of cases, who had experienced an average weight loss of only 7% (Huang et al. 2005). Even a 4–4.5% Body mass index (BMI) loss may be sufficient to achieve a 50% reduction in ALT levels (Sreenivasa Baba et al. 2006). Similarly, in 48 patients undergoing dietary restrictions resulting in a moderate weight loss (mean 3.7 kg at 24-month followup) liver

Table 119.2 Potential components of fast-food diet accounting for hepatotoxicity

- High-fructose corn syrup
  - Makes food more palatable
  - Reduces central satiety (lower effect on ghrelin)
- High glycemic index
- Higher consumption of saturated and *trans*-fats
- Caramel coloring rich in advanced glycated end-products
- Increased consumption of red meat
- High calorie intake

The detrimental effects of fast-food diet have been largely reproduced in experimental animals fed high-fructose corn syrup and *trans*-fatty acids (Tetri et al. 2008)

function tests improved in 96% of cases and 50% had a complete reversal of previously elevated ALT (Knobler et al. 1999). A few studies have also tested the effects of moderately energy-restricted diets, supplemented with vitamins or polyunsaturated fatty acids, without any significant deterioration in inflammation and fibrosis (Okita et al. 2001). More rapid weight loss (1.6 kg/week achieved by very low calorie diets) may be harmful, and should not be suggested (Andersen et al. 1991), even if very recent studies did not confirm the deleterious effects of massive weight loss induced by bariatric surgery on the liver.

Beside total energy intake, there is evidence that also dietary fat composition may have an independent effect on insulin sensitivity. Musso et al. showed that the nutritional habits of NASH patients are characterized by a different quality of fat and vitamins compared with controls, independently of calorie intake (Musso et al. 2003). Other studies reported significant differences in total fat and saturated fat and low fiber contents (Cortez-Pinto et al. 2006) or increased amounts of refined carbohydrates (Solga et al. 2004), which may easily activate lipogenesis. This could partly explain why even lean and nondiabetic subjects may develop NAFLD (Kim et al. 2004).

In general, the detrimental effect of fast-food (or cafeteria) diets on liver enzymes is well documented in several studies in experimental animals, as well as in humans, through mechanisms which may add to each other to a variable extent (Table 119.2) (Marchesini et al. 2008). For the majority of them, the final effect is excess calorie intake, leading to obesity, but specific negative effects of individual components of fast-food diet on the liver and on insulin sensitivity may also be suggested.

In a pilot experiment carried out in 18 young healthy subjects who doubled their caloric intake by means of a fast food-based diet for 4 weeks and limited physical activity, body weight increased dramatically (+6.4 kg, 10% weight gain), and serum ALT increased on average from 22 U/L to 68 (+220%, much more in males), accompanied by a remarkable accumulation of triglycerides in the liver, measured by magnetic resonance spectroscopy (+155%) (Kechagias et al. 2008). These results are supported by data in experimental animals, where combining risk factors for the metabolic syndrome, by feeding mice trans-fats and high fructose corn syrup, induced histological changes resembling NASH and produced a metabolic profile similar to that observed in NASH patients (Tetri et al. 2008).

119.3 Sedentary Lifestyle and Physical Activity

Beside calorie restriction and gradual weight reduction, physical activity represents a pivotal factor of healthy lifestyle with a protective and therapeutic role in NAFLD (Zelber-Sagi et al. 2008). Moderate-intensity aerobic exercise has beneficial effect on adiponectin, insulin resistance, resistin, and nutritional factors, and alters substrate use in skeletal muscle (Perseghin et al. 1996). A variety

of adipocytokines have been implicated in the development of hepatic steatosis, as well as in disease progression to inflammation and fibrosis (Marra et al. 2008), and they all are sensitive to physical exercise. Also in the absence of weight loss, physical activity enhances insulin sensitivity and glucose homeostasis through an insulin receptor upregulation in muscle tissue and increased delivery of glucose and insulin to the muscles. Exercise also reduces the accumulation of hepatic triglycerides by stimulating lipid oxidation and inhibiting lipid synthesis in liver, and higher levels of physical activity were associated with lower intrahepatic fat content in individuals with or without fatty liver (Perseghin et al. 2007). Liver enzyme levels were independently associated with physical activity in a large sample of British women (Lawlor et al. 2005) and an inverse association was demonstrated between physical fitness and the prevalence of NAFLD (Church et al. 2006).

As exercise is helpful in redistributing fat stores and reducing visceral obesity, in increasing HDL cholesterol levels and reducing the risk of type 2 diabetes mellitus, the beneficial effect of exercise on NAFLD might also be mediated by changes in risk factors for steatosis.

Epidemiological trials reported an inverse association between the metabolic syndrome and the participation in intense physical activity, high muscle strength and high cardio-respiratory fitness (measured by peak oxygen uptake by the working muscles) (Farrell et al. 2004; Jurca et al. 2004; Lakka et al. 2003). In keeping with these data, Krassnoff et al. reported suboptimal health-related fitness (cardio-respiratory fitness, body composition, muscle strength) and physical activity in patients with NAFLD, in relation to the different histological severity (Krasnoff et al. 2008). In particular, low cardio-respiratory fitness was associated with increasing disease severity, graded according to NAFLD activity score (NAS) criteria (Kleiner et al. 2005). More recently, only resistance (vs. aerobic) physical activity was associated with a lower prevalence of NAFLD, lower concentrations of leptin and lower rates of abdominal obesity (Zelber-Sagi et al. 2008).

Any attempt to stimulate physical activity in NAFLD is limited by the demonstration that fatigue is a significant problem in NAFLD, associated with impairment in physical function (Newton et al. 2008). Although fatigue appears to be unrelated to either severity of underlying liver disease or insulin resistance, it may increase sedentary habits, creating a vicious circle where adherence to exercise programs may be limited (Fig. 119.1).
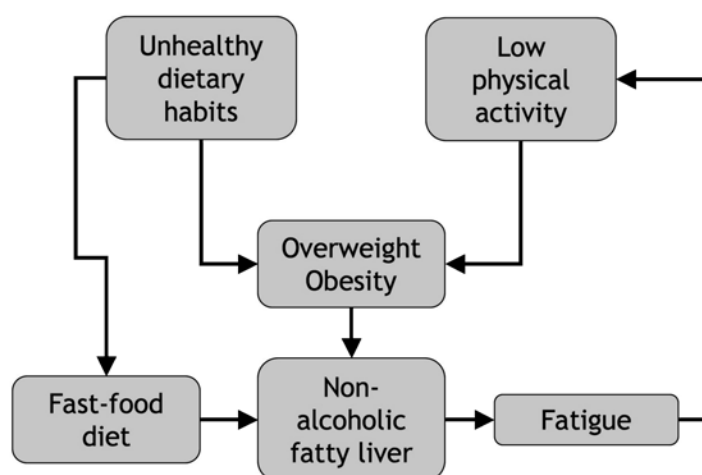
Fig. 119.1 Vicious circle linking diet/nutrition and physical activity to nonalcoholic fatty liver via fast-food diet and fatigue. Dietary habits and physical activity contribute to overweight and obesity. Excessive dietary intake is frequently associated with fast-food diet, which adds to overweight/obesity in the pathogenesis of nonalcoholic fatty liver disease. Hepatic steatosis is characterized by fatigue, which may contribute to low physical activity creating a vicious circle

Very few studies have been carried out on the therapeutic effectiveness of physical activity, usually in combination with diet and weight reduction (Hickman et al. 2004; Ueno et al. 1997). In the Ueno study (1997), the amount of physical activity was so strenuous (walking from 3,000 to 10,000 steps at 500-step increase every 3rd day, then jogging, 20 min twice a day) that it can hardly be proposed outside controlled clinical studies. More recently, Sreenivasa Baba (Sreenivasa Baba et al. 2006) demonstrated a significant reduction in ALT levels in patients with NASH who adhered to a moderate intensity aerobic exercise (45 min/day, for at least 5 days/week), regardless of weight loss. However, resistance training can also improve insulin sensitivity, metabolic profile, and decrease visceral fat, regardless of weight loss (Ibanez et al. 2005; Tsuzuku et al. 2007).

Exercise intervention is usually represented by regular aerobic exercise, such as brisk walking, jogging, stationary and outside biking, and stepping, and plays a fundamental role in preventing lean body mass wasting during weight loss. Resistance training may result in even larger favorable effects in lean body mass. Given the extensive evidence of the benefits of aerobic exercise training on the modulation of cardiovascular risk factors, the 2007 update of the American Heart association concludes that resistance training should be viewed as a complement to, rather than a replacement for, aerobic exercise (Williams et al. 2007).

Considering that both nutritional therapy and physical intervention are effective in NAFLD, their combination is more effective than physical activity alone, at least in the short-term (10 weeks) (Chen et al. 2008). However, in NAFLD patients without overweight/obesity, physical activity may represent the single first line approach to improve insulin resistance.

119.4 Behavior Therapy

Given the general consensus on the synergistic action between calorie restriction and exercise on NAFLD, behavior therapy addressing both changes is the mainstay of treatment, but achieving and maintaining long-term lifestyle modification is not free from difficulties.

Prescriptive diets have a limited long-term efficacy on weight loss; the prescriptive approach does not help patients change nutritional habits in their daily life by cognitive restraint, but merely imposes restrictions. After the prescriptive period, most patients resume their old habits and regain weight. Making patients increase their physical activity is even more difficult. Sedentary people do not easily understand the importance of physical exercise for psychological and physical health and how much exercise is needed to improve cardiovascular and metabolic diseases. Besides, barriers to physical exercise are extremely strong, mainly on the side of logistics (time constraints, job and family duties, etc.). Patients with higher BMI and older age are less compliant to exercise, and they might have poor motivation to make lifestyle modifications (Sreenivasa Baba et al. 2006). Only a few obese patients are able to adopt and sustain modifications of their habits, and to implement lifestyle changes is both complex and costly. In particular, most patients attending obesity and diabetes clinics are well aware of the need to reduce calorie intake, but do not perceive increased physical activity as a mandatory target of treatment. In a recent study integrating the activity of general practitioner and specialist centers in the care of subjects with the metabolic syndrome, we showed that most patients belonged to the very early stages of change (i.e., the willingness and ability to modify specific lifestyle habits) when asked their willingness to be engaged in physical exercise, whereas most of them considered a restricted diet a necessary component of weight loss (Fig. 119.2) (Melchionda et al. 2006). Nearly half of our male population and 80% of females reported a completely sedentary lifestyle, and 29% of cases had raised ALT levels.

Only behavioral treatment can give patients the practical instruments to achieve their eating and exercise goals, incorporate them into lifestyle, and maintain the results for a long period, possibly
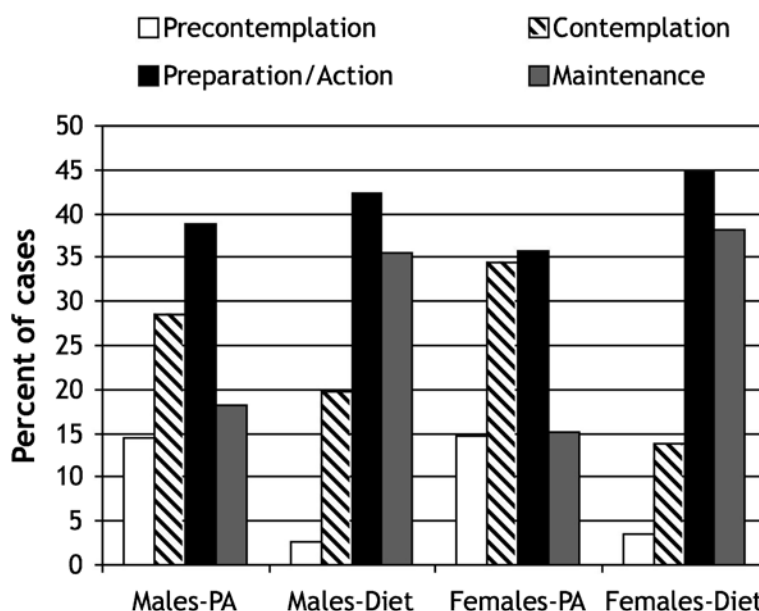
Fig. 119.2 Stage of change in 503 patients with the metabolic syndrome enrolled in a study involving general practitioners and a specialist unit (Melchionda et al. 2006). Note the much higher prevalence of subjects in the precontemplation and contemplation stage for engaging in physical activity (PA – from 40% to 50%, both in males and females) than for engaging in dietary restraint (Diet – 25% or less)

Table 119.3 Principles of behavior therapy in the NAFLD area

- Communicate with empathy
- Discuss the long-term risks associated with NAFLD
- Discuss pros and cons of proposed changes to lifestyle
- Explore reasons for perpetual poor dietary choices and limited exercise
- Explain treatment and its benefits
- Encourage self-efficacy
- Design individualized programs of healthy eating and stimulate physical activity, according to individual preferences

Note that the principles are perfectly similar to those used in obesity. A liver biopsy is needed for a precise diagnosis of grade and stage, and may help stimulate adherence to the behavior program

indefinitely. During the behavior program patients are given a set of principles and techniques for modifying their diet and exercise, such as keeping a record of their daily food intake and physical activity, counting food calories and duration of exercise or steps with pedometers, and exercising during routine daily life without disrupting their habits.

Behavioral change strategies are designed to develop and maintain desirable lifestyles and/or to reduce undesirable habits; in the area of weight loss this means to develop "food intake control" and "regular physical activity", and to decrease "uncontrolled food intake" and "sedentary habits", as well as to acquire relapse-prevention strategies that may guarantee long-term durability of change (Table 119.3).

The behavioral approach to weight loss has been shown to produce an average 0.5–1 kg weekly weight loss, or an approximate 8–10% total weight loss, with drop-out rates less than 20%. In the last 30 years, the average weight loss which may be achieved by the behavioral approach has doubled, but treatment length has tripled (Wadden et al. 2007), carrying out a progressively larger risk of dropout in the "real world" of obesity clinics.

Table 119.4 Suggested amount of calorie restriction and physical activity in the treatment of nonalcoholic fatty liver

Calorie restriction

- Daily intake of 25 kcal/kg ideal body weight
- Daily calorie defect of 500 kcal of pre-treatment calorie intake
- Daily calorie defect equal to 20% of pre-treatment calorie intake

Physical activity

- Brisk walking – 30 min/day or 10.000 steps (5–7 sessions/week)
- Bike or stationary bike – 30 min (5–7 sessions/week)
- Swimming – 1 h (3–4 sessions/week)
- Other aerobic exercise – 1 h (3–4 sessions/week)

Nontrained patients should progressively increase their physical activity from 15 min during the first week to 20 min during the second week and then to 30 min from the third week

Behavior therapy is usually delivered in groups of 10–20 participants, with weekly sessions for a period of 3–12 months. The approach is based on several strategies aimed at enhancing patients' compliance to lifestyle modification (Vuppalanchi and Chalasani 2009). Clinical practice also suggests the importance of making patients aware of their disease, i.e., of giving patients appropriate information about the causes, the risk factors, the mechanism(s) of progression, the prognosis, and the appropriate therapy of liver disease, as well as of giving them appropriate targets (Table 119.4).

Only a few studies have explored the effect of behavioral approach in NAFLD patients. A recent review (Bellentani et al. 2008) pointed out that, among the ten studies in which behavioral approach had been used to promote lifestyle change in NAFLD, only two were controlled (Kugelmas et al. 2003; Zelber-Sagi et al. 2008). In the first study, lifestyle modifications were compared with life style modification plus vitamin E administration, and in both arms the only beneficial effect was attributable to behavioral intervention, without any additional effect of vitamin E supplementation. The second study considered the effects of a lifestyle approach with or without orlistat therapy. In this case, the lifestyle approach was beneficial, but orlistat treatment showed the expected additive effect in favoring weight loss.

Although the methodology of lifestyle intervention is different from adults, several data suggest that behavioral therapy is also effective in children with NASH. In a randomized controlled trial, a lifestyle intervention consisting of a diet, tailored to individual requirements, and increased physical activity significantly improved liver histology and laboratory abnormalities, without any additional effects of vitamin E plus ascorbic acid (Nobili et al. 2008). In a very recent study, a multidisciplinary lifestyle intervention (physical activity, nutrition education and behavior therapy) was effective in improving ALT and reducing the prevalence of NAFLD in obese children with a diagnosis of fatty liver at ultrasounds (Reinehr et al. 2009).

We recently reanalyzed the approach based on lifestyle changes in our first 120 NAFLD cases treated either by a standard nutritional counseling and prescriptive diet or a more intense behavior therapy. The study was part of a protocol used in our Unit in the treatment of metabolic diseases (namely obesity and diabetes) and consisted of 12 weekly group sessions, chaired by physicians, dieticians, psychologists, and exercise experts for 3 months (Forlani et al. 2009). Fifty-three cases accepted the intensive treatment (cognitive-behavior treatment – CBT group). Compared with subjects entering the prescriptive diet protocol (diet group), the CBT group was characterized by higher BMI ($36.2 \pm$ SD 4.9 kg/m^2 vs. 30.9 ± 4.9; $P < 0.001$), higher insulin (21.7 ± 9.4 μU/mL vs. 16.9 ± 9.2; $P = 0.011$), without differences in fasting glucose (109 ± 24 mg/dL vs. 106 ± 27; $P = 0.665$) and in ALT (moderately lower in CBT; 61 ± 28 mU/mL vs. 74 ± 43; $P = 0.055$). After adjustment for sex, age, the parameters of the metabolic syndrome, and the pre-treatment levels of ALT, the probability to normalize ALT during a 2-year followup was higher in the CBT group (odds ratio, 3.34; 95% confidence interval, $1.19 – 9.35$; $P = 0.022$). Also the time course of ALT was different, and was

Fig. 119.3 Time-course
of body mass index
(BMI – *upper panel*) and
alanine aminotransferase
(ALT – *lower panel*) in
NAFLD patients treated by
prescriptive diet (Diet) or
cognitive-behavior treatment
(CBT). Data are presented as
mean ± SD. Note that the
time x treatment, repeated
measures ANOVA shows a
statistically significant
advantage of CBT on Diet in
both BMI ($P < 0.001$) and
ALT levels ($P = 0.043$)
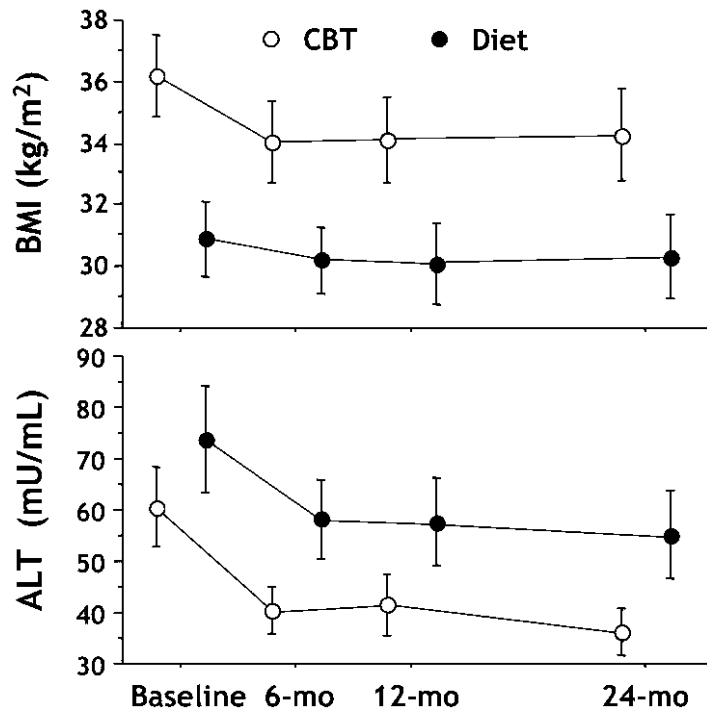
characterized by a more rapid reduction of enzyme levels in response to behavior therapy ($P = 0.043$), whereas the changes in insulin resistance (measured by the homeostasis model assessment – HOMA technique), although larger in CBT, did not reach statistical significance (Fig. 119.3).

On a population base, the effects of behavior therapy aimed at improving life-style modifications were tested in a Japanese cohort of NAFLD subjects (Suzuki et al. 2005b). Subjects with raised liver enzymes received detailed health care instructions through customized brochures on diet (total calorie and fat restriction and simplified calorie calculations), exercise (increase daily activity and fitness exercise for 20–30 min/day, at least three times per week), and giving up alcohol if necessary. Lifestyle modifications were assessed by questionnaires and by physicians' interviews during annual followup visits. After 1 year, 5% or greater weight reduction was associated with ALT improvement and a 3.6-fold increased odds of ALT normalization. Furthermore, maintaining weight loss (<5% weight regain) was associated with a 4.6-fold increased odds of maintaining normal ALT in a 2-year followup.

When health instructions are administered in a tailored and specific way, the efficacy of behavioral treatment can also be operator-independent and not related to the frequency of followup visits.

119.5 Conclusions

Given that NAFLD is increasing worldwide and that the efficacy of dieting and increased physical exercise strengthen each other, behavioral approach should be encouraged for preventing and treating fatty liver, both in adults and in children. Prevention should start from young age with programs addressed to increase population awareness about metabolic diseases. Changing lifestyle habits is easier if prevention programs start from early childhood, when unhealthy habits are not definitely established.

In a previous paper we brought to the attention of the scientific community a superficial attitude in the definition of programs aimed at lifestyle modifications (Marchesini et al. 2005). In general, the programs referred to as "nutritional counseling" are not structured according to the principles of behavioral treatment, and the interventions are frequently limited to diet prescription. In this area, adequate long-term trials having histology as outcome measure are urgently needed to show the potential effectiveness of structured behavior programs to avoid progression to NASH, liver cirrhosis and eventually hepatocellular carcinoma.

The role of physicians and other health professionals in lifestyle modifications needs to be re-evaluated and a "team approach" should be tested. Unfortunately, competence in behavior therapy is rarely present in Liver Units, and time constraints limit the possibility of undertaking lifestyle programs (Bellentani et al. 2008). Hepatologists treating NAFLD patients, as well as general practitioners providing baseline care, should either receive adequate training in behavioral therapy or limit their intervention to engaging patients and referring them to trained lifestyle therapists who operate in the area of metabolic diseases (dietitians, psychologists, physical activity supervisors, case managers). They should be given full responsibility for their intervention, working closely with the liver specialists who should periodically monitor the clinical course of liver disease and the associated pharmacological treatment.

This strategy might be successful, but other strategies need to be adopted at the population level for prevention. Only a synergistic approach involving all the nodes of a treatment network and a global societal response might be effective in reducing the burden of advanced liver disease and premature death due to NAFLD/NASH.

119.6 Applications to Other Areas of Health and Disease

The dissemination of the knowledge about the relationship between behavior and NAFLD also extends to all the other diseases that are part of the metabolic syndrome, as well as to other conditions significantly associated with insulin resistance, in particular:

- Atherosclerosis
- Diabetes
- Dyslipidemia
- Hypertension
- Overweight/Obesity
- Renal failure
- Polycystic ovary syndrome

Summary Points

- The association of unhealthy lifestyles (high calorie intake, low physical activity) with insulin resistance and the presence of liver fat (NAFLD) is well established.
- Reduced calorie intake and physical exercise exert a synergistic effect on insulin sensitivity and favor the removal of triglycerides and free fatty acids from the hepatocytes.
- The adherence to lifestyle changes and the maintenance of long-term weight loss can only be achieved by a behavioral approach.
- Very few studies have so far tested the effectiveness of lifestyle approach in the prevention of fatty liver progression to advanced fibrosis and cirrhosis, assessed by liver histology.

- Due to time constraints in busy liver units, hepatologists might limit their activity to engaging patients and refer them to teams operating in the area of diabetes and obesity, including dietitians, psychologists, and exercise experts.
- Prevention programs should address the problem of nonalcoholic fatty liver in childhood.

Definitions and Explanations

Aerobic and resistance exercise: Aerobic exercise is any exercise that involves or improves oxygen consumption. Examples of aerobic exercise are brisk walking, bike and stationary bike, running, and jogging. Aerobic exercise and fitness are frequently compared with anaerobic exercise, of which strength training and weight training are the most salient examples. The two types of exercise differ in the duration and intensity of muscular contractions involved.

Insulin resistance: A condition where lower-than-normal insulin effects are produced by normal insulin concentrations or where higher-than-normal insulin concentrations are needed to produce normal insulin effects.

Lifestyle: Lifestyle is the behavior characteristic of each person, i.e., the way he/she lives. The behaviors and practices within lifestyles are a mixture of habits, conventional ways of doing things, and reasoned actions.

Nonalcoholic fatty liver: A liver disease of metabolic origin developing in individuals with negligible alcohol intake (<20 g/day), linked to insulin resistance, histologically similar to the liver disease occurring in persons who consume alcohol in amounts at risk of alcoholic liver disease.

Physical fitness: The capacity to perform physical exercise, measured by the maximal amount of oxygen consumption.

Prescriptive diet: A rigid scheme of daily diet, with reference to amounts (in grams) or portions. The use of substitutions is allowed only within the same group of nutrients.

References

Andersen T, Gluud C, Franzmann MB, Christoffersen P (1991) Hepatic effects of dietary weight loss in morbidly obese subjects. J Hepatol. 12: 224–229.

Bellentani S, Dalle Grave R, Suppini A, Marchesini G (2008) Behavior therapy in nonalcoholic fatty liver disease: The need for a multidisciplinary approach Hepatology. 47: 746–754.

Bugianesi E, Gastaldelli A, Vanni E, Gambino R, Cassader M, Baldi S, Ponti V, Pagano G, Ferranninni E, Rizzetto M (2005) Insulin resistance in non-diabetic patients with non-alcoholic fatty liver disease: sites and mechanisms. Diabetologia. 48: 634–642.

Caldwell SH, Crespo DM (2004) The spectrum expanded: cryptogenic cirrhosis and the natural history of non-alcoholic fatty liver disease. J Hepatol. 40: 578–584.

Charlton M (2004) Nonalcoholic fatty liver disease: a review of current understanding and future impact. Clin Gastroenterol Hepatol. 2: 1048–1058.

Chen SM, Liu CY, Li SR, Huang HT, Tsai CY, Jou HJ (2008) Effects of therapeutic lifestyle program on ultrasound-diagnosed nonalcoholic fatty liver disease. J Chin Med Assoc. 71: 551–558.

Church TS, Kuk JL, Ross R, Priest EL, Biltoft E, Blair SN (2006) Association of cardiorespiratory fitness, body mass index, and waist circumference to nonalcoholic fatty liver disease. Gastroenterology. 130: 2023–2030.

Cortez-Pinto H, Jesus L, Barros H, Lopes C, Moura MC, Camilo ME (2006) How different is the dietary pattern in non-alcoholic steatohepatitis patients? Clin Nutr. 25: 816–823.

Farrell SW, Cheng YJ, Blair SN (2004) Prevalence of the metabolic syndrome across cardiorespiratory fitness levels in women. Obes Res. 12: 824–830.

Forlani G, Lorusso C, Moscatiello S, Ridolfi V, Melchionda N, Di Domizio S, Marchesini G (2009) Are behavioural approaches feasible and effective in the treatment of type 2 diabetes? A propensity score analysis vs. prescriptive diet. Nutr Metab Cardiovasc Dis. 19: 313–320.

Fraser A, Longnecker MP, Lawlor DA (2007) Prevalence of elevated alanine aminotransferase among US adolescents and associated factors: NHANES 1999-2004. Gastroenterology. 133: 1814–1820.

Hickman IE, Jonsson JR, Prins JB, Ash S, Purdie DM, Clouston AD, Powell EE (2004) Modest weight loss and physical activity in overweight patients with chronic liver disease results in sustained improvements in alanine aminotransferase, fasting insulin, and quality of life. Gut. 53: 413–419.

Huang MA, Greenson JK, Chao C, Anderson L, Peterman D, Jacobson J, Emick D, Lok AS, Conjeevaram HS (2005) One-year intense nutritional counseling results in histological improvement in patients with non-alcoholic steatohepatitis: a pilot study. Am J Gastroenterol. 100: 1072–1081.

Ibanez J, Izquierdo M, Arguelles I, Forga L, Larrion JL, Garcia-Unciti M, Idoate F, Gorostiaga EM (2005) Twice-weekly progressive resistance training decreases abdominal fat and improves insulin sensitivity in older men with type 2 diabetes. Diabetes Care. 28: 662–667.

Jurca R, Lamonte MJ, Church TS, Earnest CP, Fitzgerald SJ, Barlow CE, Jordan AN, Kampert JB, Blair SN (2004) Associations of muscle strength and fitness with metabolic syndrome in men. Med Sci Sports Exerc. 36: 1301–1307.

Kechagias S, Ernersson A, Dahlqvist O, Lundberg P, Lindstrom T, Nystrom FH (2008) Fast-food-based hyper-alimentation can induce rapid and profound elevation of serum alanine aminotransferase in healthy subjects. Gut. 57: 649–654.

Kim HJ, Lee KE, Kim DJ, Kim SK, Ahn CW, Lim SK, Kim KR, Lee HC, Huh KB, Cha BS (2004) Metabolic significance of nonalcoholic fatty liver disease in nonobese, nondiabetic adults. Arch Intern Med. 164: 2169–2175.

Kleiner DE, Brunt EM, Van Natta M, Behling C, Contos MJ, Cummings OW, Ferrell LD, Liu YC, Torbenson MS, Unalp-Arida A, Yeh M, McCullough AJ, Sanyal AJ (2005) Design and validation of a histological scoring system for nonalcoholic fatty liver disease. Hepatology. 41: 1313–1321.

Knobler H, Schattner A, Zhornicki T, Malnick SD, Keter D, Sokolovskaya N, Lurie Y, Bass DD (1999) Fatty liver--an additional and treatable feature of the insulin resistance syndrome. Q J Med. 92: 73–79.

Krasnoff JB, Painter PL, Wallace JP, Bass NM, Merriman RB (2008) Health-related fitness and physical activity in patients with nonalcoholic fatty liver disease. Hepatology. 47: 1158–1166.

Kugelmas M, Hill DB, Vivian B, Marsano L, McClain CJ (2003) Cytokines and NASH: a pilot study of the effects of lifestyle modification and vitamin E. Hepatology. 38: 413–419.

Lakka TA, Laaksonen DE, Lakka HM, Mannikko N, Niskanen LK, Rauramaa R, Salonen JT (2003) Sedentary lifestyle, poor cardiorespiratory fitness, and the metabolic syndrome. Med Sci Sports Exerc. 35: 1279–1286.

Lawlor DA, Sattar N, Smith GD, Ebrahim S (2005) The associations of physical activity and adiposity with alanine aminotransferase and gamma-glutamyltransferase. Am J Epidemiol. 161: 1081–1088.

Marchesini G, Bugianesi E, Forlani G, Cerrelli F, Lenzi M, Manini R, Natale S, Vanni E, Villanova N, Melchionda N, Rizzetto M (2003) Nonalcoholic fatty liver, steatohepatitis, and the metabolic syndrome. Hepatology 37: 917–923.

Marchesini G, Suppini A, Forlani G (2005) NAFLD treatment: cognitive-behavioral therapy has entered the arena. J Hepatol. 43: 926–928.

Marchesini G, Ridolfi V, Nepoti V (2008) Hepatotoxicity of fast food? Gut. 57: 568–570.

Marra F, Gastaldelli A, Svegliati Baroni G, Tell G, Tiribelli C (2008) Molecular basis and mechanisms of progression of non-alcoholic steatohepatitis. Trends Mol Med. 14: 72–81.

Melchionda N, Forlani G, La Rovere L, Argnani P, Trevisani F, Zocchi D, Savorani G, Covezzoli A, De Rosa M, Marchesini G (2006) Disease management of the metabolic syndrome in a community: study design and process analysis on baseline data. Metab Syndr Relat Disord. 4: 7–16.

Musso G, Gambino R, De Michieli F, Cassader M, Rizzetto M, Durazzo M, Faga E, Silli B, Pagano G (2003) Dietary habits and their relations to insulin resistance and postprandial lipemia in nonalcoholic steatohepatitis. Hepatology. 37: 909–916.

Newton JL, Jones DE, Henderson E, Kane L, Wilton K, Burt AD, Day CP (2008) Fatigue in non-alcoholic fatty liver disease (NAFLD) is significant and associates with inactivity and excessive daytime sleepiness but not with liver disease severity or insulin resistance. Gut. 57: 807–813.

Nobili V, Manco M, Devito R, Di Ciommo V, Comparcola D, Sartorelli MR, Piemonte F, Marcellini M, Angulo P (2008) Lifestyle intervention and antioxidant therapy in children with nonalcoholic fatty liver disease: a randomized, controlled trial. Hepatology. 48: 119–128.

Okita M, Hayashi M, Sasagawa T, Takagi K, Suzuki K, Kinoyama S, Ito T, Yamada G (2001) Effect of a moderately energy-restricted diet on obese patients with fatty liver. Nutrition. 17: 542–547.

Perseghin G, Price TB, Petersen KF, Roden M, Cline GW, Gerow K, Rothman DL, Shulman GI (1996) Increased glucose transport-phosphorylation and muscle glycogen synthesis after exercise training in insulin-resistant subjects. N Engl J Med. 335: 1357–1362.

Perseghin G, Lattuada G, De Cobelli F, Ragogna F, Ntali G, Esposito A, Belloni E, Canu T, Terruzzi I, Scifo P, Del Maschio A, Luzi L (2007) Habitual physical activity is associated with intrahepatic fat content in humans. Diabetes Care. 30: 683–688.

Petersen KF, Dufour S, Befroy D, Lehrke M, Hendler RE, Shulman GI (2005) Reversal of nonalcoholic hepatic steatosis, hepatic insulin resistance, and hyperglycemia by moderate weight reduction in patients with type 2 diabetes. Diabetes. 54: 603–608.

Reinehr T, Schmidt C, Andler W, Toschke AM (2009) Lifestyle intervention in obese children with non-alcoholic fatty liver disease: two years follow-up study Arch Dis Child.

Sanyal AJ (2002) AGA technical review on nonalcoholic fatty liver disease. Gastroenterology. 123: 1705–1725.

Sato F, Tamura Y, Watada H, Kumashiro N, Igarashi Y, Uchino H, Maehara T, Kyogoku S, Sunayama S, Sato H, Hirose T, Tanaka Y, Kawamori R (2007) Effects of diet-induced moderate weight reduction on intrahepatic and intramyocellular triglycerides and glucose metabolism in obese subjects. J Clin Endocrinol Metab. 92: 3326–3329.

Solga S, Alkhuraishe AR, Clark JM, Torbenson M, Greenwald A, Diehl AM, Magnuson T (2004) Dietary composition and nonalcoholic fatty liver disease. Dig Dis Sci. 49: 1578–1583.

Sreenivasa Baba C, Alexander G, Kalyani B, Pandey R, Rastogi S, Pandey A, Choudhuri G (2006) Effect of exercise and dietary modification on serum aminotransferase levels in patients with nonalcoholic steatohepatitis. J Gastroenterol Hepatol. 21: 191–198.

Suzuki A, Angulo P, Lymp J, St Sauver J, Muto A, Okada T, Lindor K (2005a) Chronological development of elevated aminotransferases in a nonalcoholic population. Hepatology. 41: 64–71.

Suzuki A, Lindor K, St Sauver J, Lymp J, Mendes F, Muto A, Okada T, Angulo P (2005b) Effect of changes on body weight and lifestyle in nonalcoholic fatty liver disease. J Hepatol. 43: 1060–1066.

Tamura Y, Tanaka Y, Sato F, Choi JB, Watada H, Niwa M, Kinoshita J, Ooka A, Kumashiro N, Igarashi Y, Kyogoku S, Maehara T, Kawasumi M, Hirose T, Kawamori R (2005) Effects of diet and exercise on muscle and liver intracellular lipid contents and insulin sensitivity in type 2 diabetic patients. J Clin Endocrinol Metab. 90: 3191–3196.

Tetri LH, Basaranoglu M, Brunt EM, Yerian LM, Neuschwander-Tetri BA (2008) Severe NAFLD with hepatic necroinflammatory changes in mice fed trans-fats and a high fructose corn syrup equivalent. Am J Physiol Gastrointest Liver Physiol. 295: G987–G995.

Tsuzuku S, Kajioka T, Endo H, Abbott RD, Curb JD, Yano K (2007) Favorable effects of non-instrumental resistance training on fat distribution and metabolic profiles in healthy elderly people. Eur J Appl Physiol. 99: 549–555.

Ueno T, Sugawara H, Sujaku K, Hashimoto O, Tsuji R, Tamaki S, Torimura T, Inuzuka S, Sata M, Tanikawa K (1997) Therapeutic effects of restricted diet and exercise in obese patients with fatty liver. J Hepatol. 27: 103–107.

Vuppalanchi R, Chalasani N (2009) Nonalcoholic fatty liver disease and nonalcoholic steatohepatitis: Selected practical issues in their evaluation and management. Hepatology. 49: 306–317.

Wadden TA, Butryn ML, Wilson C (2007) Lifestyle modification for the management of obesity. Gastroenterology. 132: 2226–2238.

Williams MA, Haskell WL, Ades PA, Amsterdam EA, Bittner V, Franklin BA, Gulanick M, Laing ST, Stewart KJ (2007) Resistance exercise in individuals with and without cardiovascular disease: 2007 update: a scientific statement from the American Heart Association Council on Clinical Cardiology and Council on Nutrition, Physical Activity, and Metabolism. Circulation. 116: 572–584.

Zelber-Sagi S, Nitzan-Kaluski D, Goldsmith R, Webb M, Zvibel I, Goldiner I, Blendis L, Halpern Z, Oren R (2008) Role of leisure-time physical activity in nonalcoholic fatty liver disease: a population-based study. Hepatology. 48: 1791–1798.

Chapter 120
Interactions Between Diet, Immune System and Brain Function in the Symptom Profile of Chronic Fatigue Syndrome

Yvonne Christley, Tim Duffy, and Colin R. Martin

Abbreviations

CFS	Chronic fatigue syndrome
EFA	Essential fatty acid
CDC	Centre for Disease Control and Prevention
5-HT	5-hydroxytryptamine
EPA	Eicosapentaenoic acid
LA	Linoleic acid
Th1	T helper cell type 1
Th 2	T helper cell type 2
T cell	Lymphocyte
NK	Natural killer
RBC	Red blood cell
AA	Arachidonic acid
SFA	Saturated fatty acid

120.1 Introduction

Chronic fatigue syndrome (CFS) has been identified as being a severe, systemic, acquired illness which is accompanied by debilitating fatigue. Little or no improvement in fatigue follows periods of rest. It is recognised that CFS may be aggravated by physical or mental activity that lasts more than 6 months. As well as incapacitating fatigue, CFS is also characterised by a wide range of other symptoms (see Fig. 120.1) including cognitive dysfunction, sleep disturbance, myalgia, arthralgia, headache, gastrointestinal upset, sore throat, painful lymph nodes and mood disturbance (Jason et al. 1997).

C.R. Martin (✉)
School of Health, Nursing and Midwifery, University of the West of Scotland,
Ayr Campus, Beech Grove, Ayr, KA8 0SR, UK
e-mail: colin.martin@uws.ac.uk
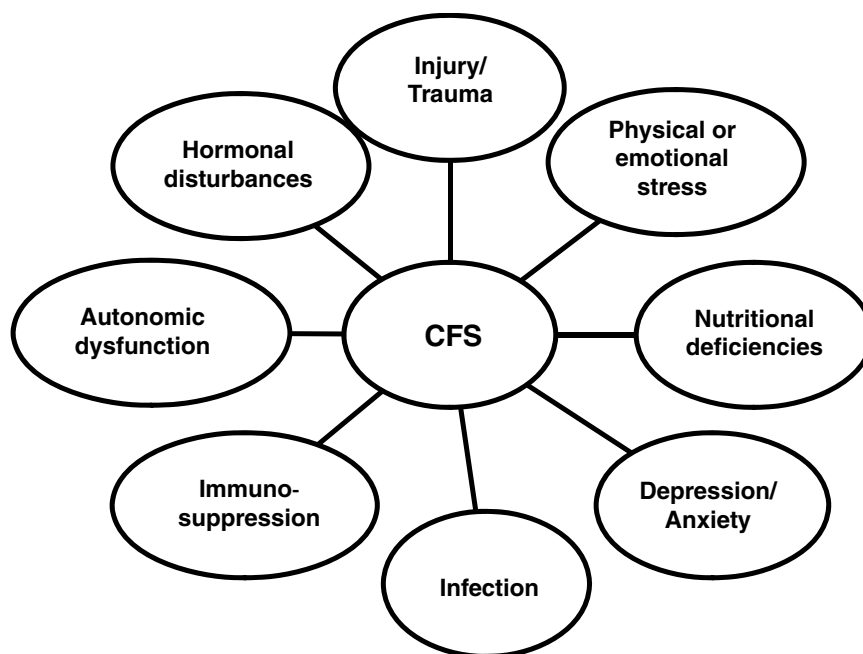
Fig. 120.1 The most frequently suggested causes of chronic fatigue syndrome are summarised below. The diagram provides a summary of the most frequently suggested and investigated causes of chronic fatigue syndrome. However, despite more than two decades of intensive research the precise cause of chronic fatigue syndrome remains unknown

Until now, researchers have been unable to identify a specific cause of CFS. Consequently, no agreed diagnostic test for CFS exists. The impact of these limitations is that diagnosis of CFS is currently one of exclusion often made on the basis of subjective clinical interpretation and of patient self report.

Despite tremendous investment of time and energy, the study of CFS has been weighed down by the absence of clear standardised diagnostic criteria and definitions. In an effort to address these problems, the Centre for Disease Control and Prevention (CDC) introduced a case definition in 1988, and subsequently revised it in 1994 (Fukuda et al. 1994) (see Table 120.1). Within the revised definition, complications were removed concerning the inadvertent inclusion by the definition of patients whose fatigue had a psychiatric basis, the inclusion of which had negative effects on the analysis of epidemiological and treatment effectiveness research in CFS (Buchwald et al. 1996).

In the absence of effective treatment strategies to alleviate the debilitating symptoms of CFS, many patients are forced to explore alternative differing therapy options. The popular dietary and nutritional literature demonstrates an abundance of alleged miracle cures. Grant et al. (1996) in an analysis of the dietary and nutritional supplement habits amongst CFS patients found that many CFS sufferers advocate the use of dietary supplements, (especially vitamins and minerals), as a method of alleviating the symptoms of their illness.

Nutritional deficiencies in CFS have been afforded considerable attention in the scientific literature, with numerous studies exploring potential links between nutritional deficits as a means of unraveling the underlying pathophysiology of CFS. Indeed some investigations have established reduced levels of magnesium (Cox et al. 1991), B vitamins (Heap et al. 1999), essential fatty acid levels (Horrobin 2002), l-carnitine (Plioplys and Plioplys 1995) and tryptophan in some CFS patients. However, these findings have been widely disputed and challenged due to methodological limitations and inconsistent results.

Much less contentious is the association between CFS and oxidative stress. A significant body of evidence has emerged from the CFS literature to support the view that oxidative stress is a core feature

Table 120.1 Centre for Disease Control and Prevention revised definitional criteria for the diagnosis of chronic fatigue syndrome

1. Clinically assessed unexplained, persistent or relapsing chronic fatigue that is of new or definitive onset. The fatigue must not be the result of ongoing exertion or relieved by rest and should results in significant reductions in occupational, educational, social or personal activities.
2. The simultaneous occurrence of *four* or *more* of the following symptoms is also required and must be present for 6 or more consecutive months of infirmity and should not have predated the fatigue.
• Short-term memory impairment or concentration
• Sore throat
• Tender cervical or auxiliary lymph nodes
• Muscle pain
• Headaches of a new type, pattern or severity
• Unrefreshing sleep
• Post-exertional malaise lasting more than 24 h
• Diffuse joint pain without swelling or tenderness

This table summarises the key symptoms and duration required to meet the Centre for Disease Control and Prevention's revised definitional criteria for the diagnosis of Chronic Fatigue Syndrome. This definition is the most commonly used definitional criteria for determining the presence or absence of chronic fatigue syndrome
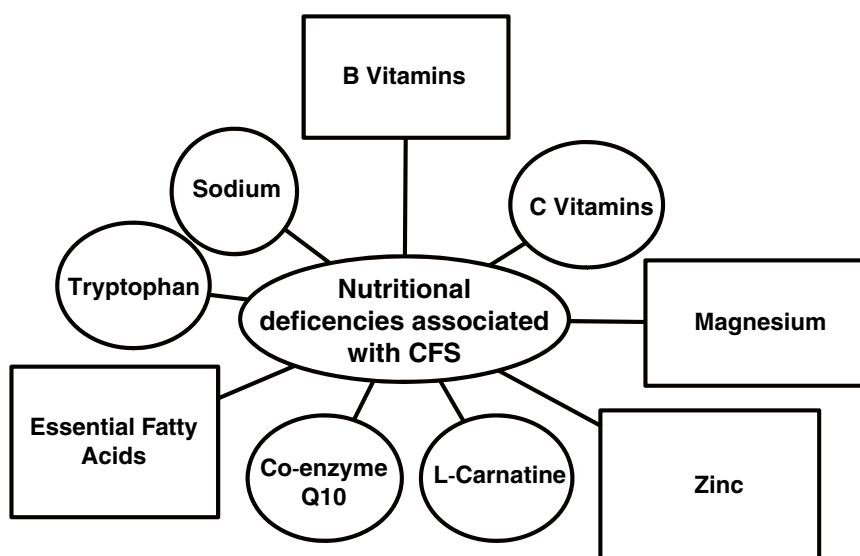
Fig. 120.2 Nutritional deficiencies associated with chronic fatigue syndrome (*CFS*). The figure illustrates the nutritional deficiency thought to be associated with the symptom profile of CFS. The research literature has found some evidence of B vitamin, essential fatty acid, magnesium and zinc deficiencies in CFS. Less consistent associations have also been made between sodium, tryptophan, C vitamins, L-carantine and coenzyme Q 10 deficiencies in CFS. *CFS* chronic fatigue syndrome

of this illness and manifests as profound fatigue due to cellular damage (Lane et al. 1998). This suggest that antioxidant supplementation in CFS might merit closer examination. As such considerable effort has been invested in exploring the impact of dietary supplements on the symptom profile of CFS. Figure 120.2 illustrates the nutritional deficiencies thought to play a causative role in CFS.

These studies however have been seriously hampered in their ability to produce reliable and valid transferable findings. The reason for this is that the vast majorities of studies have examined nutritional status in CFS by investigating individual vitamin or minerals and as such have produced very wide-ranging and inconsistent results. Because of the nature of these difficulties the actual usefulness

of nutrition supplements in CFS remains indefinite. In an effort to address these problems, Brouwers et al. (2002) investigated the therapeutic impacts of multivitamins in CFS; however, they found no evidence to support the use of a multivitamins in the treatment of CFS. Despite these inconsistencies, considerable body evidence has emerged in the literature that illustrates potential associations between deficiencies of essential fatty acids (EFA), B vitamins, magnesium and oxidative stress in CFS. In light of this evidence, this chapter will analyze and discuss EFA, B vitamin, magnesium deficiency and oxidative stress in CFS.

120.2 Essential Fatty Acids, Immunity and CFS

EFA have a number of important biological functions (see Fig. 120.3) and contribute to health and well-being throughout the lifespan. EFAs cannot be manufactured by the body and are obtained through the diet. EFAs and, in particular, omega 3 have been associated with the development of a number of diseases especially depression (Horrobin 2002). There exists substantial biochemical evidence to indicate that omega 3 EFAs have considerable impact on the neural structure and function of the brain and central nervous system.

Omega 3 EFAs have been found in elevated concentrations in both the brain and central nervous system and play an important role in neurotransmitter synthesis, degradation, release, reuptake and binding (Delion et al. 1996). Furthermore, low concentrations of omega 3 have been linked to reduced levels of the neurotransmitter dopamine, greater serotonin activity and amplified concentrations of 5-HT (5-hydroxytryptamine) receptors in the frontal cortex (Delion et al. 1996). Hibbeln (1998) further shows a strong negative association between poor oily fish consumption (known to be rich in omega 3) and depression in a study across 13 countries. A Finnish corroborated these findings, identifying an increased occurrence of depressive symptoms in persons who rarely ate oily fish compared to those who ate fish regularly (Tanskanen et al. 2001).
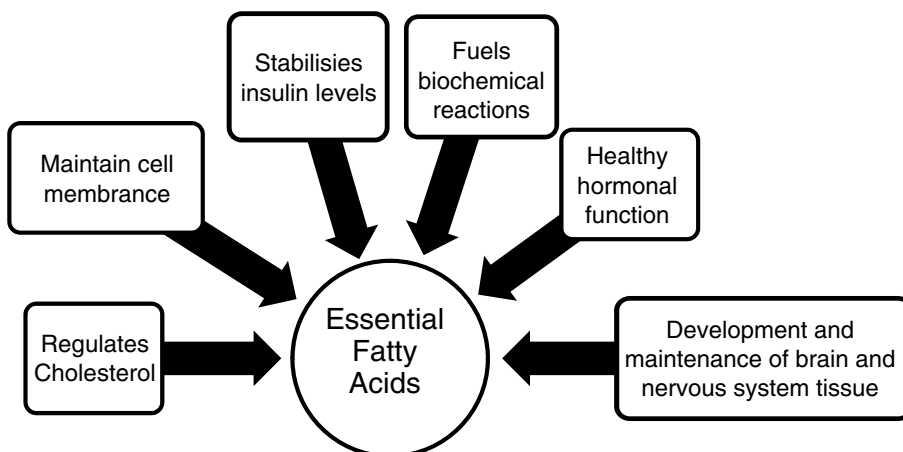
Fig. 120.3 Most important functions of Essential Fatty Acids. The six most important functions of essential fatty acids is to regulate cholesterol, maintain cell membranes, stabilise insulin levels, fuel biochemical reactions, maintain healthy hormonal function and the develop and maintain brain and nervous tissue

120.3 The Relationship Between Omega 3 Essential Fatty Acids and Depression

More clinically orientated studies have identified a relationship between omega 3 EFA consumption and depressive symptoms in patients with major depression. Low levels of omega 3 have been found in patients with major depression than in normal controls (Peat et al. 1998). In addition, Maes et al. (1999) found that depression severity is directly related to a subtle balance between plasma and erythrocyte phospholipid levels of omega 3 and omega 6.

As depression is closely associated with the symptom profile of CFS a number of studies have investigated the potential connections between the symptoms of CFS and EFA. Behan et al. (1990) in a double-blind, placebo-controlled trial found that EFAs had a therapeutic effect in patients with post viral fatigue syndrome (referred to in contemporary terms as CFS). This important study found that the CFS patients had reduced levels of EFAs and raised levels of saturated fatty acids (SFA) compared to normal controls. Eighty five percent of the CFS patients reported significant improvements in symptoms of fatigue, myalgia, dizziness, concentration and depression following a 3 month trial of high dose omega 3 and omega 6. Warren et al. (1999) attempted to replicate the Behan et al. (1990) study. However, they were unable to demonstrate any therapeutic effects of Efamol Marine (a supplement containing omega 3 and 6) in CFS patients.

Maes et al. (2006a) have argued that these seemingly paradoxical findings may be attributed to the elevated amount of omega 6 found in Efamol Marine. They contend that there is a very precise balance between decreases in eicosapentaenoic acid (EPA) (an omega 3 fatty acid) and decreases in arachidonic acid (AA) (an omega 6 fatty acid) and increases in linoleic acid (LA) an omega 6 fatty acid in CFS. In light of this they argue that EFA supplementation in CFS might be best addressed by the use of omega 3 EFAs only.

120.4 Essential Fatty Acids Zinc and the Symptoms of CFS

Puri (2004) adds further support to the use of omega 3 only, finding an improvement in CFS patient symptoms after 8–12 weeks of a high dose of omega 3. In addition to this, Maes et al. (1999) have described the important synergy between the proportions of omega 3, omega 6 and serum zinc in CFS patients. Interestingly, these findings are consistent with similar studies in major depression, which demonstrate a link between omega 3, omega 6 and zinc. Reductions in serum zinc are key features of the inflammatory process in both depression and CFS (Maes et al. 1999).

Furthermore, the symptoms associated with zinc deficiency overlap with those of CFS, especially fatigue, depression and cognitive difficulties. Low serum zinc can result in the increased creation of pro-inflammatory cytokines and may cause damage to cell-mediated and humoral immunity, thus potentially contributing to the immunological symptoms in both CFS and major depression (Bremner and Beattie 1995).

Adequate levels of EFA and zinc are of supreme importance in CFS (Puri 2004) and are central to attempts at articulating its pathophysiology (see Fig. 120.4). A number of studies have investigated immune dysfunction and its relationship to EFAs in CFS. To date immune dysfunction is thought to relate to the suppression of natural killer cells and Th1 (T helper cell type 1) cell activity, alongside elevated Th2 (T helper cell type 2) and cytotoxic T cell (lymphocyte) activity in CFS patients (Skowera et al. 2004). Immune dysfunction as described is thought to be associated with the presence of well-established and long-standing viral infections (Puri 2004).
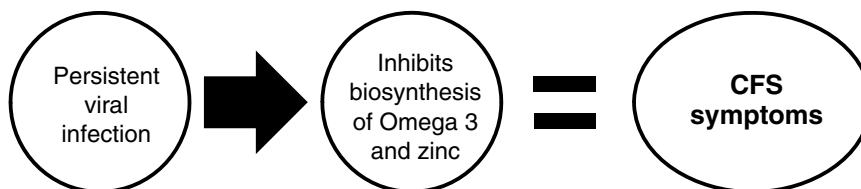
Fig. 120.4 Potential mechanism by which essential fatty acids might be associated with the symptoms of CFS. A persistent viral infection might be acting to inhibit the biosynthesis of Omega 3 and zinc (both of which have powerful antiviral properties) thus producing some of the symptoms of CFS

Here again, EFAs figure prominently in CFS. Viral infections and particularly enduring ones are thought to decrease the host's ability to utilize EFAs. The virus inhibits the use of EFA in order to nullify its potent antiviral properties (Horrobin 1999). Consequently, the virus in inhibiting the utility of EFAs causes a reduction EFA substrate. This not only disrupts the effectiveness of interferons in the administration of their antiviral role, but also considerably restrains their activity. Liu et al. (2003) in an investigation of the levels of fatty acids in CFS found that CFS patients showed signs of significantly reduced EFA compared to normal controls. The study made links between CFS and oxidative stress, produced by excessive oxidation thus resulting in the depletion of EFA in CFS patients.

In a similar study, Gray and Martinovic (1994) established that the amounts of EFA in CFS patients were comparable to the amounts detected in people who had experienced excessive and prolonged levels of stress. Such extreme deviations from normal EFA metabolism could explain some of the diverse immune, endocrine, sympathetic and nervous system symptoms that have come to typify CFS (Gray and Martinovic 1994).

120.4.1 B Vitamins

The B vitamins, especially B6, B12 and folic acid, are commonly used by CFS patients to alleviate symptoms. A tentative association between the symptoms of CFS and B vitamin deficiencies has been established in a number of studies (see Fig. 120.5). Serious questions remain, however, as to the accuracy and comparability of these results, particularly in relation to how B vitamin deficiencies should be detected and measured.

Heap et al. (1999) evaluated the B group vitamins in CFS and found consistent pyridoxine, riboflavin and thiamine deficiencies in CFS patients compared to controls. The most significant of the deficiencies being pyridoxine. This is interesting as low pyridoxine in the central nervous system can manifest as depression. Heap et al. (1999) also concluded that these deficiencies were probably not a result of poor dietary intake of B vitamins or poor absorption, but came about as a result of subnormal vitamin activity at a cellular level.

Furthermore, Jacobson et al. (1993) in a study of serum folate in CFS found that 50% of the CFS patients sampled had serious folic acid deficiencies, with a further 13% being borderline. Fatigue and depression are common symptoms in CFS and are also closely related to folate deficiency. In fact, folate deficiency is known to depress the immune system, and as CFS presents with evidence of immune activation, the contribution of a borderline folate deficiency might contribute to a better understanding of the immunological picture in CFS. The effectiveness of folate supplementation in CFS has been investigated. For example, Kaslow et al. (1989) found therapeutic benefits from the daily, intra-muscular injections of 800 mcgs of folate in CFS patients. This study was, however, severely limited in that the dose was quite small as was the time frame for measuring treatment effect.

Fig. 120.5 Association
between CFS symptoms and
Vitamin B deficiencies. The
figure illustrates the tentative
associations that have been
made between the symptom
profile of CFS and the
symptoms of vitamin B
deficiencies
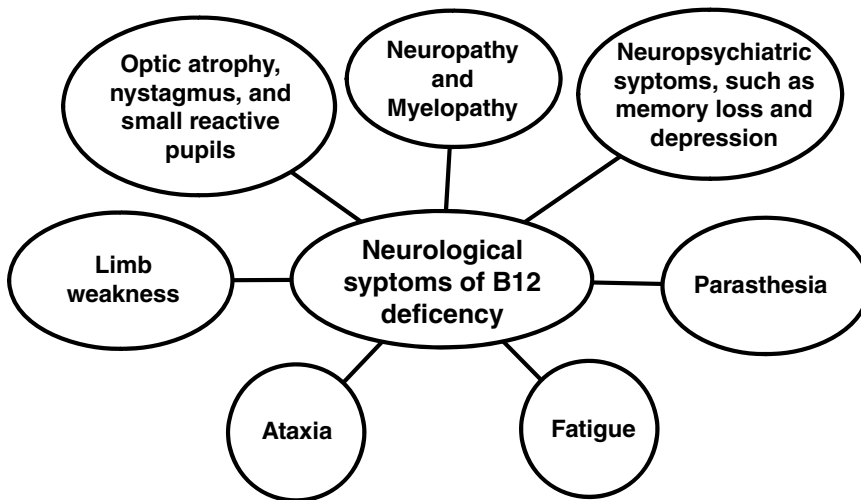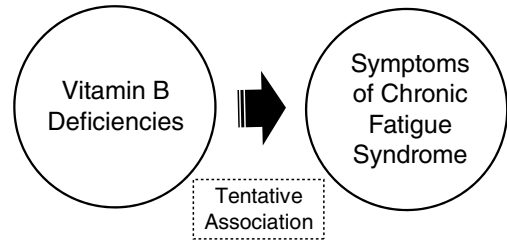
Fig. 120.6 The neurological symptoms associated with vitamin B12 deficiency. The figure illustrates the numerous neurological symptoms that are produced in consequence to Vitamin B12 deficiency

Vitamin B12 deficiency also presents with a myriad of neurological manifestations similar to CFS. Pall (2001) has investigated the biochemical abnormalities in CFS and the mechanisms by which B12 might alleviate them. Links have been found between elevated levels of nitric oxide and its oxidant by-products peroxynitrite and CFS. These substances may be directly responsible for many of the symptoms of CFS and are released in response to oxidative stress. As B12 is a powerful scavenger of nitric oxide it has considerable potential to alleviate CFS symptoms irrespective of its pathogenesis. The effects of nitric oxide on the brain and central nervous system are well established, particularly in relation to brain function and pain sensitivity. Lindenbaum et al. (1988) investigated B12 levels in serum methylmalonic acid and homocysteine, both before and after B12 therapy in patients with neuropsychiatric symptoms. The study uncovered that subclinical B12 deficiency had caused parasthesia, ataxia, muscle weakness, hallucinations, personality and mood changes, fatigue, sore tongue and diarrhoea (see Fig. 120.6).

Furthermore, Regland et al. (1997) found high levels of homocyestine in the cerebrospinal fluid of CFS patients that was positively related to low levels of B12. As B12 deficiency causes a deficient remethylation of homocyestine, the study concluded that the low B12 was contributing to the increased homocysteine levels and consequently increased fatigue.

120.4.2 Magnesium

Like CFS, magnesium deficiency has been implicated in the development of depression, myalgia, fatigue and memory problems and has been found to have some therapeutic effect in the treatment of a number of neuropsychiatric complaints. Seelig (1998) has highlighted significant covariance between key aspects of cellular and humoral immunity in magnesium deficiency and CFS. Both CFS and magnesium deficiency cause a reduction in the numbers and activity of Natural Killer (NK) cells and as observed by Levine and Chester (1994), CFS patients do tend to have an increased sensitivity to lymphoid and immune-associated malignancies.

Many of the symptoms of CFS are profoundly similar to those found in magnesium deficiency (Seelig 1998). As such, a number of studies have examined the role of magnesium in CFS. Cox et al. (1991), in a 6-week controlled study of 32 CFS patients, compared the effect of intramuscular injections of magnesium sulphate (50%) versus placebo (water). Significant improvements were demonstrated in pain and mood in the patients who received the magnesium sulphate injections compared to controls.

Jenkins and Rayman (2005) also found reduced levels of RBC (Red Blood Cell) magnesium in CFS patients. Keoney et al. (2000) studied the effects of magnesium supplementation in CFS and found that CFS patients with moderate magnesium deficiency had reduced antioxidant capacity, which was not related to poor intake of dietary magnesium. In addition Keoney et al. (2001) investigated the antioxidant status of lipoprotein peroxidation in CFS. In this study, it was found that alongside reduced omega 6 essential fatty acid, oxidative stress and more specifically lipid peroxidation might play a role in the pathogenesis of CFS.

Additionally, Cheney (1994) asserts that has the efficacy of magnesium in the treatment of CFS might be enhanced by the addition of an antioxidant. He argues that since magnesium deficiency is associated with free radical production, (as well as having direct effects on immunologic mechanisms) the effectiveness of magnesium supplementation might be improved by the addition of an antioxidant (Seelig 1998).

120.5 Application to Other Areas of Health and Disease

Some of the nutritional deficiencies found in CFS are also applicable and relevant to other areas of disease. In particular, the symptoms of CFS overlap significantly with a number of illnesses of unknown aetiological cause, especially fibromyalgia, which shares a number of significant symptoms with CFS. Fibromyalgia is a rheumatic condition characterized by widespread musculoskeletal pain, morning stiffness, muscle fatigue, nonrestorative sleep, depressive-anxious mood, headache, irritable bowel, tiredness and weakness (Wolfe et al. 1990). Fibromyalgia is one of the most frequently diagnosed conditions in rheumatology and has a population incidence of between 0.5% and 5.8% (Gran 2003).

Despite considerable investment in understanding fibromyalgia, its aetiology and pathogenesis remain elusive. Furthermore, between 21% and 58% of fibromyalgia patients also meet the diagnostic criteria for CFS (White et al. 2000).

120.6 Chronic Fatigue Syndrome, Fibromyalgia and the Role of Oxidative Stress

A key feature of fibromyalgia is the presence of diffuse musculoskeletal pain and as such an extensive amount of research has been conducted into the aetiological role of pain in fibromyalgia. In contrast, very little research has been conducted into the nature of pain in CFS. In light of the
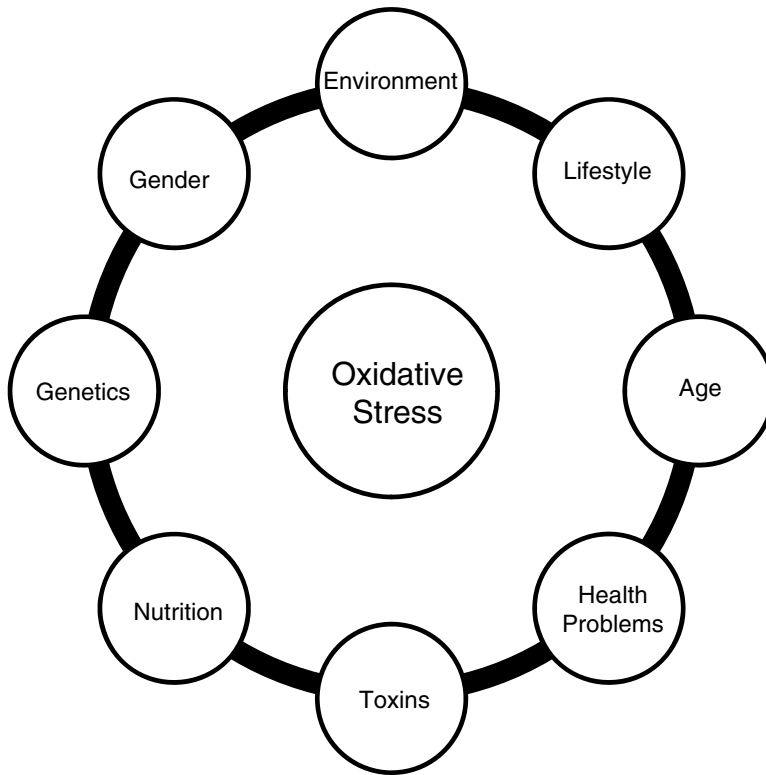
Fig. 120.7 The key factors that contribute to oxidative stress. The figure illustrates the most commonly identified factors that are thought to contribute to the development of oxidative stress. The adverse health effects of oxidative stress may occur in response to an accumulation of damage caused by multiple factors acting together

significant overlap between CFS and fibromyalgia, this is surprising as some similarities between the pain mechanism in fibromyalgia and CFS have been noted. Of particular interest the role of oxidative stress and its contribution to pain perception. Oxidative stress is known to contribute to fibromyalgia pain. A small number of studies have investigated the associations between oxidative stress and pain in CFS. Meeus and Nijs (2006) found that pain in CFS could be attributed to high levels of nitric oxide produced as a result of oxidative stress. Furthermore, significant and positive correlations between levels of oxidative stress and severity of CFS symptoms have been found and are related specifically to pain, muscular tension and fatigue (Maes et al. 2006b).

Oxidative stress leads to premature cell death and is associated with many diseases and illnesses, particularly of the central nervous system. Figure 120.7 illustrates the many factors that contribute to the development of oxidative stress. The mechanism by which this occurs is due to an increase in free radicals generated by oxidative stress, thus disrupting the delicate homeostatic balance between products of oxidation and antioxidant defences, see Fig. 120.8. These free radicals cause lipid peroxidation ultimately resulting in tissue damage (Simonian and Coyle 1996). This has a major therapeutic implication in CFS and fibromyalgia as increased lipid peroxidation, reinforces the possibility that dietary supplementation with essential fatty acids may be helpful.
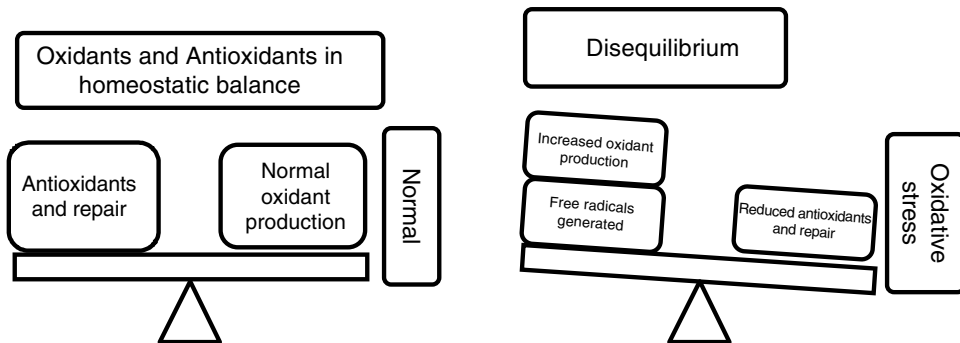
Fig. 120.8 The homeostatic balance between oxidants and antioxidants in normal individuals and individuals in a state of oxidative stress. In normal conditions, there is a homeostatic balance between the production of oxidants and antioxidants. Antioxidants play a very important role in maintaining the body's ability to repair the cellular damage caused by oxidative stress. In oxidative stress, there is disequilibrium between the production of oxidants and antioxidants. The increased levels of oxidants generate free radicals and reduce the levels of antioxidants and their consequent ability to minimise cellular damage

120.6.1 The Health Enhancing Properties of Essential Fatty Acids

An extensive body of scientific evidence already exists to illustrate the health enhancing properties of essential fatty acids in cardiovascular disease (Harris et al. 2007), diabetes mellitus (Kabir et al. 2007), Rheumatoid Arthritis (Galarraga et al.2008), Alzheimer's (Schaefer et al. 2006) and renal disease (Hogg et al. 2006) to name but a few. These studies support the need for further research into the nature of oxidative stress and nitric oxide in CFS and the associated potential that antioxidant treatments such as omega 3 and 6 fatty acids, vitamins and others might offer.

Furthermore, if oxidative stress is thought to contribute to CFS then the role of diet in the treatment of CFS may be important. Vegetarian diets that are rich in free radical scavengers have been found to have a profound effect on joint stiffness, pain and general health in fibromyalgia, these symptom improvements were attributed to increased antioxidant levels. Vegetarian diets are of considerable interest as many studies have found evidence to indicate a positive association between vegetarian diet and decreased risk for chronic illnesses such as obesity, coronary artery disease, hypertension, diabetes and some types of cancer (Fraser 2009). This is an important area for future research as very little is known about the effectiveness of different diets on the symptoms of CFS.

120.7 Conclusion

A number of nutritional and dietary deficiencies have been investigated in the study of CFS. In almost every study reviewed for this chapter, researchers have identified at the very least borderline nutritional deficiencies in essential fatty acids, B vitamins and magnesium. These important deficiencies are thought to manifest as a result of the disease process in CFS as these patients do not demonstrate evidence of poor dietary intake. Investigations into the potential role EFAs play in CFS have produced some very interesting findings. Of particular importance is the association between reduced levels of omega 3 EFAs, low zinc and oxidative stress in CFS and the consequent complex inflammatory relationship this produces.

Furthermore, B vitamins are of central importance in eliminating the toxic by-products of oxidative stress and have been found to be deficient in some CFS patients. As B vitamin deficiencies present as a myriad of neurological symptoms these deficiencies might explain some of the symptoms of CFS. In addition to this, magnesium deficiencies have also been observed in CFS and are linked with free radical production thus contributing to oxidative stress, suggesting that nutritional deficiencies of this nature might benefit from antioxidant supplementation. Thus it is evident from the literature that a better understanding of the relationship between EFA, B vitamin and magnesium deficiencies and oxidative stress in CFS is of primary importance in attempts to unravel the pathophysiology of CFS.

Summary Points

- Nutritional deficiencies in essential fatty acids (EFA), B vitamins and magnesium, have been identified in CFS. These deficiencies do not appear to be associated with reduced dietary intake and are thought to relate to oxidative stress and the illness process.
- Some CFS patients have reduced levels of essential fatty acids, in particular omega 3 and zinc which result in symptoms of depression and may account for mood related symptoms in CFS. EFA supplementation has been found in some studies to improve CFS symptoms.
- Deficiencies of B6, B12 and folic acid have been found in CFS patients. Folate deficiency is known to depress the immune system, and as CFS presents with evidence of immune activation, the contribution of a borderline folate deficiency might contribute to a better understanding of the immunological picture in CFS.
- The symptoms of CFS are associated with raised levels of nitric oxide and its oxidant by product peroxynitrite, which is released in response to oxidative stress. B12 is a powerful scavenger of nitric oxide thus providing potential mechanisms for relieving CFS symptoms regardless of the pathogenesis.
- Magnesium deficiency is associated with symptoms of depression, myalgia, fatigue and memory problems and has been found to have some therapeutic effect in the treatment of a number of neuropsychiatric complaints. Some evidence suggests magnesium supplementation in CFS improves pain and mood.
- Magnesium deficiency in CFS might be associated with reduced antioxidant capacity associated with free radical production and oxidative stress. Thus the effectiveness of magnesium supplementation might be improved by the addition of an antioxidant.

Definitions

Oxidative stress: It is a discrepancy in a cell's ability to produce oxidants (e.g. free radicals) from either intrinsic or extrinsic sources, and its ability to reduce them with endogenous scavengers. Excess oxidants injure the cell's lipids, proteins and nucleic acids, which result in cumulative damage that can initiate adverse health events or diseases.

Essential fatty acids (EFA): They are unsaturated fatty acids that are essential to health; they cannot be manufactured by the body and therefore must be obtained from the diet. There are two families of EFAs omega 3 and omega 6. It is Important to maintain a balance between omega 3 and omega 6 fatty acids in the diet as omega 3 fatty acids help reduce inflammation while most omega-6 fatty acids tend to promote inflammation. An inappropriate balance of these essential fatty acids contributes to the development of disease, where a good balance helps maintain and even improve health.

Peroxynitrite: It is a powerful oxidant formed as a result of a reaction between superoxide and nitric oxide. Peroxynitrite plays a key role in cell dysfunction and death and is associated with disease states such as diabetes and atherosclerosis.

Lipoprotein peroxidation: It is the process whereby free radicals steal electrons from the lipids in cell membranes, the result of which is cell injury and the increased development of free radicals.

Free radicals: They are a group of exceedingly reactive molecules which cause indiscriminate damage to structural proteins, enzymes, macromolecules, DNA, thus playing a significant role in tissue damage and inflammation.

Key points

Symptoms of chronic fatigue syndrome key points

- Chronic fatigue syndrome (CFS) is a debilitating and complex disorder
- It is typified by the presence of overwhelming fatigue that is not improved by rest and is present for more than 6 months
- In addition to fatigue patients also complain of numerous nonspecific symptoms, including weakness, muscle pain, impaired memory, cognitive difficulties, insomnia and post-exertional fatigue

Chronic fatigue syndrome and oxidative stress key points

- Evidence reviewed in this chapter identifies a number of nutritional deficiencies that may contribute to the wide and varied symptoms of CFS.
- Oxidative stress and its negative influence on magnesium, b vitamins and essential fatty acid metabolism may play an important role in the clinical manifestation of CFS
- Further research is required to better understand the role of Oxidative stress in chronic fatigue syndrome

Magnesium, B vitamins, essential fatty acids and chronic fatigue syndrome key points

- The aetiology and pathogenesis of chronic fatigue syndrome remains unknown
- Magnesium, b vitamins and essential fatty acids play important roles in regulating the immune, nervous and vascular as well as cellular communication functions
- Further research is required to enable a more comprehensive understanding of these mechanisms and how these might be inhibited in chronic fatigue syndrome

---

References

Afari N, Eisenberg D, Herrell R, Goldberg J, Kleyman E, Ashton S, Buchwald D. Integr Med. 2000;2:97–103.
Behan P, Behan W, Horrobin D. Acta Neurol Scand. 1990;82:209–16.
Bremner I, Beattie J. Proc Nutr Soc. 1995;54:489–99.
Brouwers F, Van Der Werf S, Bleijenberg G, Van Der Zee L, Van Der Meer J. QJM. 2002;95:677–83.
Buchwald, D, T. Pearlman T, Umali J, Schmaling K, Katon W. Am J Med. 1996;101:364–70.
Cheney P. CFIDS Chronicle. 1994;2:1–3.
Cox IM, Campbell MJ, Dowson D. Lancet. 1991;337:757–60.
Delion S, Cahlon S, Guilloteau D. J Neurochem. 1996;66:1582–91.
Fraser GE. Am J Clin Nutr. 2009;89:1607–12.
Fukuda K, Straus SE, Hickie I, Sharpe MC, Dobbins, JG, Komaroff A. Ann Intern Med. 1994;121:953–9.

Galarraga B, Ho M, Youssef H, Hill A, McMahon H, Hall C, Ogston S, Nuki G, Belch J. Rheumatology. 2008;10:1093–9.

Gran J. Best Pract Res Clin Rheumatol. 2003;17:547–61.

Grant JE, Veldee MS, Buchwald D. J Am Diet Assoc. 1996;96:383–6.

Gray JB, Martinovic AM. Med Hypotheses. 1994;43:31–42.

Harris W, Poston W, Haddock C. Atherosclerosis. 2007;193:1–10.

Heap LC, Peters TJ, Wessely S. J R Soc Med. 1999;92:183–5.

Hibbeln JR. Lancet. 1998;351:1213–4.

Hogg R, Lee J, Nardelli N, Julia B, Cattran D, Waldo B, Wyatt R, Charles J, Sibley R, Hyland K, Fitzgibbons L, Hirschman G, Donadio J, Holub B. Clin J Am Soc Nephrol. 2006;1:467–74.

Horrobin DF. In: Chiu E, Ames D, Katona C, editors. Vascular disease and affective disorders. London: Martin Dunitz; 2002. p. 332–352.

Horrobin DF. Prosta Leukotr Med. 1999;60:431–437.

Jacobson W, Saich T, Borysiewicz LK, Behan WM., Behan PO, Wreghitt TG. Neurology. 1993;43:2645–7.

Jason LA, Richman JA, Friedberg F, Wagner L, Taylor R, Jordan KM. Am Psychol. 1997;52:973–83.

Jason LA, Taylor R, Wagner L, Holden J, Ferrari JR, Plioplys AV, Plioplys S, Lipkin D, Papernik M. Am J Community Psychol. 1995;23:557–68.

Jenkins M, Rayman M. J Nutr Environ Med. 2005;15:177–89.

Kabir M, Skurnik G, Naour N, Pechtner V, Meugnier E, Rome S, Quignard-Boulangé A, Vidal H, Slama G, Clément K, Guerre-Millo M, Rizkalla S. Am J Clin Nutr. 2007;86:1670–9.

Kaslow JE, Rucker L, Onishi R. Arch Intern Med. 1989;149:2501–3.

Keenoy BM, Moorkens G, Vertommen J, Noe M, Neve J, De Leeuw I. J Am Coll Nutr. 2000;19:374–82.

Keenoy BM, Moorkens, G, Vertommen J, de Leeuw I. Life Sci. 2001;68:2037–49.

Lane RJ, Barrett MC, Woodrow D, Moss J, Fletcher R, Archard LC. J Neurol Neurosurg Psychiat. 1998;64:362–7.

Levine P, Chester A. Clin Infect Dis. 1994;18:543–8.

Lindenbaum J, Healton EB, Savage DG, Brust JC, Garrett TJ, Podell ER, Marcell PD, Stabler SP, Allen RH (1988) New Engl J Med. 318;1720–1728.

Liu Z, Wang D, Xue Q, Chen J, Li Y, Bai X, Chang L. Nutr Neurosci. 2003;6:389–92.

Maes M, Christophe A, Delanghe J, Altamura C, Neels H, Meltzer HY. Psych Res. 1999;85:275–91.

Maes M, Mihaylova I, De Ruyter M. J Affect Disord. 2006a;90:141–7.

Maes M, Mihaylova I, Leunis JC. J Affect Disord. 2006b;90:141–7.

Meeus M, Nijis J. Clin Rheumatol. 2006;18:131–42.

Peet M, Murphy B, Shay J, Horrobin D. Biol Psych. 1998;43:315–9.

Plioplys AV, Plioplys S. Neuropsychobiology. 1995;32:132–8.

Puri BK. Prostaglandins Leukot Essent Fatty Acids. 2004;70:399–401.

Pall ML. J Chronic Fatigue Syndr. 2001;8:39–44.

Regland BM, Andersson L, Abrahamsson M, Bagby J, Dyrehag LE, Gottfries CG. Scand J Rheumatol. 1997;26:301–7.

Schaefer EB, V Beiser, A, Lamon-Fava S, Robins S, Au R, Tucker K, Kyle D Wilson P, Wolf P. Arch Neurol. 2006;63:1545–50.

Seelig M. J Chronic Fatigue Syndr. 1998;4:77–108.

Simonian N, Coyle J. Annu Rev Pharmacol Toxicol. 1996;36:83–106.

Skowera A, Cleare A, Blair D, Bevis L, Wessely SC, Peakman M. Clin Exp Immunol. 2004;135:294–302.

Solomons NW. Am J Clin Nutr. 1999;70:111–2.

Tanskanen A, Hibbeln JR, Tuomilehto J. Psych Serv. 2001;52:529–31.

Warren G, McKendrick M, Peet M. Acta Neurol Scand. 1999;99:106–12.

White K, Speechley M, Harth M, Òstbye T. Scand J Rheumatol. 2000;29:44–51.

White PD. BMJ. 2004;329:928–9.

Wolfe F, Smythe H.A, Yunus M.B, Bennett R, Bombardier C, Goldenberg D. Arthritis Rheum. 1990;33:160–72.

Chapter 121
The Relationship Between Nutrition and Neurocognitive Function in Schizophrenia

Mick P. Fleming and Colin R. Martin

Abbreviations

CHD	Coronary heart disease
CLDN5	Claudin 5
DNA	Deoxyribonucleic acid
DQB1	DQ beta1
EFA	Essential fatty acids
EPA	Eicosapentaeconoic acid
IgA	Immunoglobulin A
MTHFR	Methylenetetrahydrofolate reductase
PANSS	Positive and negative syndrome scale
PUFA	Polyunsaturated fatty acids
SNP	Single nucleotide polymorphism
TGM2	Tissue transglutaminase 2

121.1 Introduction

The physical health of people who have schizophrenia is poorer compared with the general population (McCreadie 2003). The report from the House of Commons Select Committee on Health Inequalities found that those with schizophrenia are more likely to have higher rates of coronary heart disease (CHD), diabetes, stroke or respiratory disease, obesity, and on average are likely to die 10 years younger than people who do not have schizophrenia (House of Commons 2009). This confirmed findings from earlier studies which found a two- to fourfold relative risk of premature death for people with schizophrenia (Connolly and Kelly 2005). Evidence suggests that the diet of people with schizophrenia indicates poor dietary choices and poor dietary intake which is a significant contributory risk factor for the illnesses noted before (Peet 2004a).

A recognized side effect of the treatment of schizophrenia with atypical antipsychotic medication is that of increased appetite and weight gain and this contributes to the overall health profile of

C.R. Martin (✉)
School of Health, Nursing and Midwifery, University of the West of Scotland,
Ayr Campus, Beech Grove, Ayr KA8 0SR, UK
e-mail: colin.martin@uws.ac.uk

people with schizophrenia. Poor health outcomes for people with schizophrenia are also associated with sedentary lifestyles caused by sedation, lack of exercise, smoking, and other social and lifestyle factors (Peet 2004a).

Relationships have been found between diet and the maintenance of schizophrenia symptoms. Evidence dating back to 1965 has found that having a gluten intolerance also known as celiac disease is a risk factor for developing schizophrenia and that a gluten-free diet contributes to a reduction in schizophrenia symptoms (Dohan 1966, Dohan et al. 1969; Singh and Kay 1976; Potkin et al. 1981; Kalaydjian et al. 2006). Researchers have concluded that a genetic predisposition to gluten intolerance and schizophrenia is activated environmentally through diet (Eaton et al. 2004). Possible mechanisms are the influence of diet on DNA methylation which in turn encourages or discourages gene expression (Singh et al. 2003) and the blood plasma levels of certain essential fatty acids and their metabolites (Joy et al. 2003).

121.2 Schizophrenia

The conceptual framework for the syndrome of schizophrenia is characterized by severe thought disorder and disturbances to perception. A diagnosis of schizophrenia is based on the criteria within diagnostic manuals ICD10/DSMIV (Table 121.1) (WHO 1992; APA 1994). It relies on the presence of at least two symptoms which persist for a time period of at least 1–6 months. The symptoms that characterize schizophrenia are positive symptoms, those behaviors and experiences that would preferably be absent such as hallucinations in any of the five modalities (auditory, visual, olfactory, touch, taste), delusions, disorders of stream and content of thought and negative symptoms or deficits/absence of behaviors, and experiences that are desirable such as motivation, energy, volition, affective flattening, and a normal range of emotions. There are a number of long-term debilitating and distressing effects on personality. These result in negative psychological and social effects which can lead to severe impairments in physical, social, emotional, and general life functioning (Martin and Fleming 2009). The average annual incidence of schizophrenia is 15 per 100,000 persons, the average figures for prevalence are approximately 4.5 per 1,000 persons and the risk of developing the illness over a person's lifetime is 0.7% (Tandon et al. 2008).

Table 121.1 Key features of schizophrenia diagnosis

1. The conceptual framework for the syndrome of schizophrenia is characterized by severe thought disorder and disturbances to perception.
2. A diagnosis of schizophrenia is based on the criteria within diagnostic manuals ICD10/DSMIV (WHO 1992; APA 1994).
3. It relies on the presence of at least two symptoms which persist for a time period of at least 1–6 months.
4. Positive symptoms are those behaviors and experiences that would preferably be absent such as hallucinations in any of the five modalities (auditory, visual, olfactory, touch, taste), delusions, disorders of stream, and content of thought. Negative symptoms or deficits/absence of behaviors and experiences that are desirable such as motivation, energy, volition, affective flattening, and a normal range of emotions.
5. The long-term debilitating and distressing effects on personality. These result in negative psychological and social effects which can lead to severe impairments in physical, social, emotional, and general life functioning (Martin and Fleming 2009).
6. The average annual incidence of schizophrenia is 15 per 100,000 persons; the average figures for prevalence are approximately 4.5 per 1,000 persons and the risk of developing the illness over a person's lifetime is 0.7% (Tandon et al. 2008).

This table lists the key facts of schizophrenia and its diagnosis including the differences between the positive and negative symptoms of schizophrenia and figures confirming the levels of the disorder in the general population

121.2.1 Schizophrenia and Physical Health Outcomes

A literature search strategy using MEDline, PsycInfo, and CINAHL was completed; the search was conducted using the following search terms:

1. "diet" AND "schizophrenia"
   The search strategy was expanded to include:
2. search terms as keywords featured in the title, abstract, full text, or caption text;
3. an additional search term of "psychosis" was also used.

Ten sources were identified from the literature search. All these sources were relevant and so abstracts of these ten papers were collected and reviewed.

A further four relevant papers relating to diet, gluten intolerance, and schizophrenia and three relevant papers relating to diet, genetics, and schizophrenia were found by cross-referencing sources from the ten sources identified in the initial electronic search. In all 17 papers were reviewed.

Comparatively people with schizophrenia have poorer physical health than the general population. Studies have found consistent trends which show higher rates of cardiovascular disease, type 2 diabetes, and respiratory disease in people with schizophrenia (Fig. 121.1) (Brown et al. 2000; Mortensen and Juel 1993; Schizophrenia and Diabetes Expert Group 2004). Where people with schizophrenia had received a diagnosis of CHD 31% had received the diagnosis prior to age 55, compared with 18% of other people with CHD; 22% of those people with schizophrenia died within 5 years of receiving the heart disease diagnosis, compared with 8% of other people with heart disease (Fig. 121.2) (Nocon and Sayce 2008). The age of dying is also lower, people with schizophrenia are twice as likely to die early (Mortensen and Juel 1993) and this could be as many as 10 years earlier (House of Commons 2009). Physical inactivity as a result of sedative treatment or as a consequence of the deficits caused by negative symptoms contributes to these physical health outcomes. Obesity and smoking also contribute and people with schizophrenia are over-represented in both these categories.
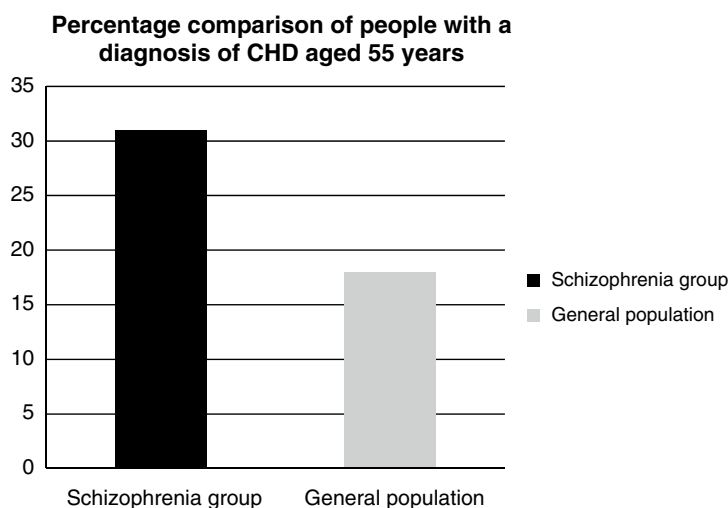
Fig. 121.1 Comparison of the numbers of people with a diagnosis of CHD aged 55 years in England and Wales (Nocon and Sayce 2008) This figure compares two groups of people, those with schizophrenia and those in the general population who have received a diagnosis of CHD by the time they have reached 55 years of age in England and Wales; the figures are in percentages
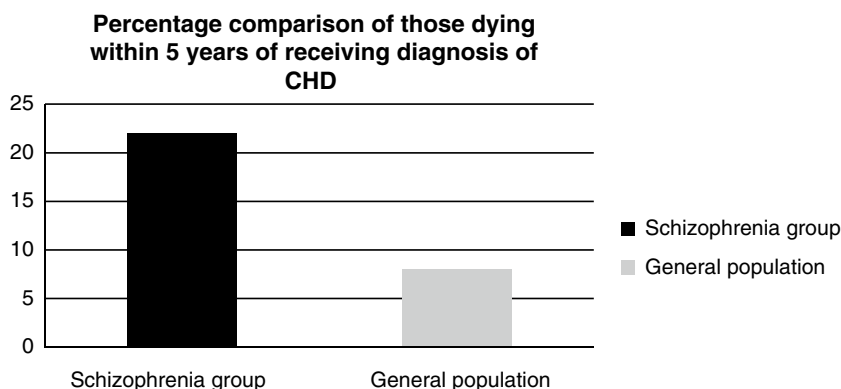
Fig. 121.2 Comparison of those people dying within 5 years of receiving diagnosis of CHD in England and Wales (Nocon and Sayce 2008) This figure compares two groups of people, those with schizophrenia and those in the general population who have died within 5 years of receiving a diagnosis of CHD in England and Wales; the figures are in percentages

McCreadie et al. (1998) found that in their sample of community dwelling people with schizophrenia that most were overweight or obese. In a sample of 226 people on long-term depot antipsychotic medication were four times more likely to be clinically obese than those in the general population (Silverstone et al. 1988). In a later report 86% of females and 70% of males using the body mass index in the sample of 102 were found to be obese or overweight (McCreadie 2003). Other studies suggest that 33% of people with schizophrenia are obese compared with 21% in the remaining population (Nocon and Sayce 2008). Obesity does increase the risks of morbidity from CHD, type 2 diabetes, hypertension, and respiratory problems (Connolly and Kelly 2005). People with schizophrenia are also more likely to smoke compared with the general population (Martin et al. 2008). Between 61% and 80% of people with schizophrenia or serious mental illness are smokers compared with 33% of the remaining population (Nocon and Sayce 2008; Rethink 2009). Diabetes has been associated with schizophrenia itself as well being a consequence of treatment either as side effect of antipsychotic medication or as an artifact of obesity caused by increased appetite and weight gain. Peet (2004a) notes that insulin resistance has been found in people with schizophrenia prior to discovery of antipsychotic medication and in drug naïve people (Fig. 121.3).

121.2.2 The Contribution of Diet to Health Outcomes

Diet plays a large part in contributing to these poor health outcomes for people with schizophrenia. McCreadie (2003) compared the dietary habits of community-dwelling people with schizophrenia to the general population, using the Scottish Health Survey. He found that the consumption of fresh fruit, vegetables, skimmed or semi-skimmed milk, potatoes, pasta or rice, and pulses by males reached less acceptable levels than by males in the general population. However, males with schizophrenia consumed breakfast cereal more frequently than their counterparts. Females with schizophrenia consumed less acceptable levels of skimmed or semi-skimmed milk, potatoes, pasta, or rice than females in the general population. The Scottish dietary targets for the period of the study was for 400 g of fruit per day or 35 portions per week. The mean number for the schizophrenia group was 16 portions of fruits and vegetables per week. These comparisons were made with people within the
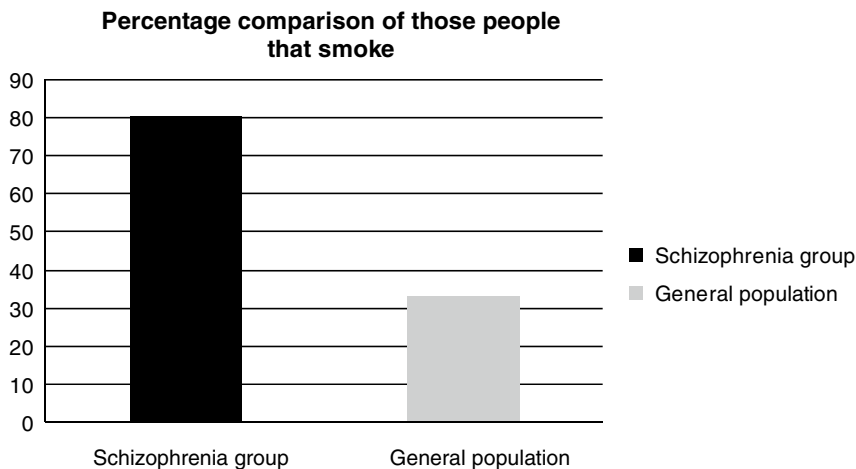
Fig. 121.3 Comparison of those people who smoke in England and Wales (Nocon and Sayce 2008). This figure compares two groups of people, those with schizophrenia and those in the general population who smoke in England and Wales; figures are in percentages

general population that were unemployed and on state benefits and in social class V. In his review of dietary studies, Peet (2004a) found that people with schizophrenia consumed less dietary fiber and antioxidant vitamins, than control groups and consumed more saturated fats and sugars. The McCreadie study involved participants who were making choices about their diet and they chose less healthy food options. Where antipsychotic medication increases appetite and where people make choices of less healthy options then they are likely to choose less healthy foods in greater amount when they have an increased appetite.

Diet is partly determined by social and political factors such as social class; however, lifestyle and dietary habits can be modified and so the effects of poor diet can be preventable. This has been borne out by studies reporting the results of diet and physical activity programs with people who have schizophrenia. Twenty-eight people with schizophrenia, rated as obese as measured by scoring 27 or above on the body mass index, were placed on a calorie-controlled diet (1,300–1,500 calories for women and 1,600–1,800 calories for men) and a 6-month regime of physical activity (60 min level walking and walking on stairs three times per week). Results showed a significant decrease in body weight, body mass index (5.4%), and waist circumference (3.3 cm; Wu et al. 2007). These results do show that dietary habits can be modified; however, all the people in the trial were in-patients and very little detail is given about the methods used to maintain compliance to the program and the amount of independent dietary choice that was given to those in the trial. As the majority of people with schizophrenia live in the community it is important to know how to support and maintain these dietary changes outside of the hospital and its influence. Weight loss of 6.19 kg compared with 1.6 kg weight gain in the control group was found after a 3-month structured diet program in 32 people with schizophrenia who were out-patients (Nese 2008). Group delivered educational interventions can reduce weight gain in comparison with a control group but the weight loss is less than for other more structured interventions (Littrell et al. 2003). McCreadie et al. (2005) randomly allocated 102 people with schizophrenia to groups which received free fruits and vegetables for 6 months and instruction in meal planning and food preparation, free fruits and vegetables or as normal diet. Those in the group receiving free fruits, vegetables, and instructions were consuming significantly more fruits and vegetables than those on the diet as usual. This change was not sustained after the intervention was withdrawn (Fig. 121.4) (McCreadie et al. 2005).

Percentage comparison of those people who are obese
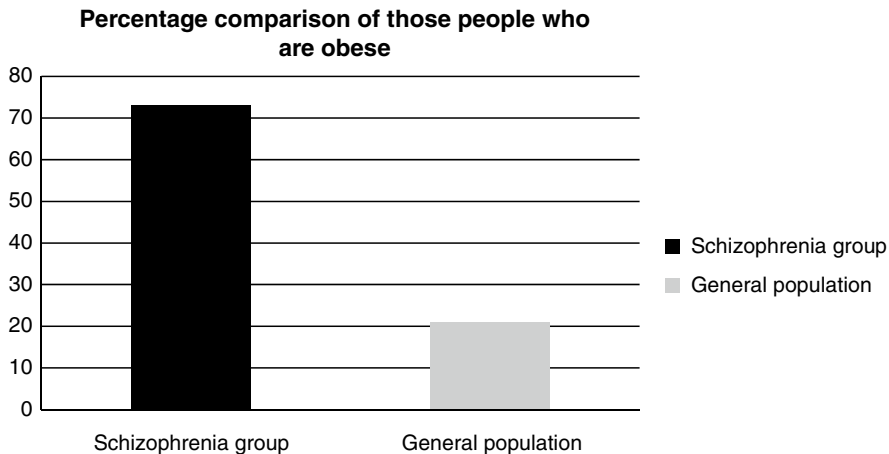
Fig. 121.4 Comparison of those people who are obese in England, Scotland, and Wales as measured by the body mass index (McCreadie 2003; Nocon and Sayce 2008). This figure compares two groups of people, those with schizophrenia and those in the general population who are considered to be obese as measured by the body mass index in England, Scotland, and Wales; figures are in percentages

121.2.3 Nutrition, Diet, and the Outcomes for Schizophrenia

121.2.3.1 Celiac Disease/Gluten Intolerance and Schizophrenia

Autoimmune diseases have been linked to schizophrenia. A history of autoimmune disease was found to be associated with a 45% increase in the risk for schizophrenia in subjects and their parents when compared with people who did not have schizophrenia (Eaton et al. 2006). In this study using subjects where the autoimmune disease had occurred prior to the onset of schizophrenia five autoimmune disorders were more prevalent than others. Celiac disease or gluten intolerance was one the diseases identified in the study (Table 121.2). An association between celiac disease and schizophrenia had already been investigated prior to 2006. Celiac disease is one that causes inflammation and damage to the villi in the small intestine. Gluten is a protein found in wheat, barley, rye, and oats. It is made up of two other proteins gliadin and glutenin. When gluten is ingested the body's immune system activates antibodies that attack the villi. These are finger-like structures and when damaged by the antibodies are unable to absorb water, vitamins, and other essential nutrients. As well as intestinal signs such as diarrhea and irritable bowel a number of neurological signs such as cerebral ataxia, peripheral neuropathy, dermatitis herpetiformis, and myopathy have commonly been linked to celiac disease (Reichelt et al. 1990). It has been noted that celiac disease can be asymptomatic which may mean that the disease may go undiagnosed in the general population and may be as high as 16% in people with undiagnosed neurological problems (Bradford et al. 2008). Testing for the presence of IgA antiendomysial and anti-tissue transglutaminase antibodies is considered to be a specific and sensitive test for the disease (Volta et al. 1991). Earlier anthropological studies had found a correlation between the scarcity and lower consumption of wheat grains during World War II and a reduction in the admissions for schizophrenia. Conversely in countries where there was an increase in wheat consumption admissions for schizophrenia increased. This relationship was further confirmed when countries that had initially had lower wheat consumption increased their wheat consumption there was an equivalent increase in the prevalence of schizophrenia (Reichelt et al. 1990). In an epidemiological study of 7,997 Danish people with a first admission for schizophrenia

Table 121.2   Key features of celiac disease

1. Celiac disease is caused by an intolerance or sensitivity to gluten.
2. Gluten is a protein found in wheat, barley, rye, and oats. It is made up of two other proteins gliadin and glutenin.
3. Villi are finger-like structures that emanate from the wall of the intestine; their function is to slow down the passage of food through the intestine so that the villi can absorb the nutrients from the food.
4. When gluten is ingested the body's immune system activates antibodies that attack the villi.
5. When damaged by the antibodies the villi are unable to absorb water, vitamins, and other essential nutrients.
6. As well as intestinal signs such as diarrhea and irritable bowel a number of neurological signs such as cerebral ataxia, peripheral neuropathy, dermatitis herpetiformis, and myopathy have commonly been linked to celiac disease (Reichelt et al. 1990).
   Celiac disease affects between 0.3% and 1% of the European population. The prevalence of celiac disease is 1:200 in the European population and 1:100 in the USA (Kalaydjian et al. 2006). Exact figures are difficult to calculate because there may be many undiagnosed cases due to the different ranges of presenting symptoms and that people do not always experience obvious symptoms.

This table defines celiac disease, the mechanisms of the intestinal structures called villi, and the effects of gluten intolerance on those structures. The table further provides a list of the main signs of celiac disease and an approximation of the prevalence

with a known maternal identity four people, five mothers, and three fathers were receiving treatments for celiac disease (1.5 per 1,000). Each subject in the study was matched by gender and year of birth with 25 controls. The authors calculated that the relative risk for schizophrenia from celiac disease was 3.2 ($P < 0.0001$; Eaton et al. 2004). Although the risk appears high because of the rarity of both disorders this risk can only account for a small number of cases of either disorder. Critics point out that the inclusion of the data from parents in the study is potentially misleading and if this data was excluded form the study then the prevalence of celiac disease in people with new onset schizophrenia would have been 0.5 per 100 which is the same as the control group (Campbell and Foley 2004). Previous studies had also found comorbid celiac disease and schizophrenia (Dohan 1983). The prevalence of known celiac disease is rare; it is 0.3–1% or lower and figures for the prevalence of schizophrenia in the general population is 4.5 per 1,000 or 0.45–1% (Kalaydjian et al. 2006; Tandon et al. 2008). This would make the finding of comorbidity unusual and significant. In their literature review, Kalaydjian et al. (2006) found that the proportion of people with celiac disease who also received a diagnosis of schizophrenia ranged between 1% and 4.2% in the studies reviewed. Gliadin antibodies have been found to be more prevalent in people with schizophrenia than in control groups (Kinnell et al. 1982). It has been stated that 30% of schizophrenia sufferers have high levels of antibodies against wheat gluten in their body (Dr. Jun Wei, BBC Website April 21, 2009). Toxic responses to gluten have been found where cats and rats have been given wheat gliadin and gluten. Responses have included changes in behavior and central nervous system monoamines and decreases in dopamine beta hydroxylase activity (Reichelt et al. 1990). Dopamine is a neurotransmitter that has been implicated in the causation of schizophrenia. This hypothesis is based on the premise that the symptoms of schizophrenia are due to overactive dopamine signal transduction (Seeman and Kapur 2000). Two key observations support this hypothesis: first antipsychotic medication particularly the phenothiazines have an antagonistic effect and have the action of promoting binding and hence blocking dopamine receptors. This results in the reduction of activity in dopaminergic tracts and alleviates the symptoms of schizophrenia (Van Rossum 1967). It has been found that phenothiazines have a specific affinity for the dopamine receptor D2. Secondly, observations show that amphetamine administration induces behaviors and symptoms similar to those of schizophrenia. Dopamine theories of schizophrenia postulate that as the use of amphetamines influence the levels of the neurotransmitter dopamine in the brain then schizophrenia is also caused by increased dopamine or the overactivity of dopamine receptors.

121.2.4 Clinical Evidence

Evidence suggests that a gluten- and casein-free diet can significantly influence the course of relapse and recovery of schizophrenia symptoms (Table 121.3). Studies have experimented by removing and then blindly reintroducing gluten and casein to the diet of people with schizophrenia who were hospitalized. Those on gluten-free diets for 10 days were discharged twice as quickly as those on the higher gluten diet (77 days vs 139 days; Dohan 1966). In a later study 47 men with schizophrenia were randomly assigned to a gluten-/casein-free diet on admission to a locked ward and compared with 55 men who were given a high cereal diet. Sixty-two percent of men on the gluten-/casein-free diet were released to an open ward quicker than those on a high cereal diet. In a replicated study that provided the same results gluten was blindly reintroduced and the observed benefits were reversed (Dohan et al. 1969). A similar study design found that the reintroduction of gluten and casein after a period of gluten- and casein-free diet showed an interruption of therapeutic improvement as measured by psychopathology, affect, and participation ratings in people with schizophrenia and continued improvement was shown when the gluten and casein were removed from their diet (Singh and Kay 1976). These findings were unrelated to changes in antipsychotic treatment. Two later studies using the same study design did not find the same pattern of results. Eight people with chronic schizophrenia were placed on a gluten-, cereal-, and milk-free diet, when gluten was reintroduced to their diet there was no consequent deterioration in schizophrenia symptoms as measured by the Brief Psychiatric Rating Scale. There was also no evidence of an inflammatory response (Potkin et al. 1981). No differences were found in a group of four people with schizophrenia after a 36-week period of gluten-free diet (Osborne et al. 1982). Studies with small numbers are likely to miss the small subset of people who have both celiac disease and schizophrenia (Kalaydjian et al. 2006).

Table 121.3 Details of the trials and results of gluten-/casein-free diets with people who have schizophrenia

Study	Study Design	Sample	Intervention	Outcome
Dohan (1966)	Blind comparison.		Gluten-free diet for 10 days.	Average length of stay: 77 days, gluten-free diet, 139 days, gluten-containing diet.
Dohan et al. (1969)	Blind randomized trial.	102	47 gluten-/casein-free diet, 55 high cereal diet.	62% on gluten-/casein-free diet versus 36% discharged to nonlocked wards after 7 days,
Singh and Kay (1976)	Blind control trial.	14	Gluten-/casein-free diet for 6 weeks followed by reintroduction of gluten/casein.	Improvement in psychopathology and social avoidance and exacerbation of psychopathology/ interruption of therapeutic progress during reintroduction of gluten/casein.
Potkin et al. (1981)	Double blind trial.	8	Gluten-/cereal grains-/ milk-free diet, gluten challenge reintroduction of 30 g of gluten for 5 weeks versus placebo for 8 weeks.	Serum alpha-1 acid glycoprotein measures no evidence of inflammatory response to gluten challenge and no deterioration in clinical status.
Vlissides et al. (1986)	Double-blind control trial.	24	Gluten-free diet vs gluten-containing diet for 14 weeks.	Improvements in behavioral dimensions as measured by psychotic in-patient profile; two relapsed during gluten challenge.

This table provides summary details of the authors, study design, numbers of participants, types of dietary intervention, and results of the studies of gluten-/casein-free diet trials with people who have schizophrenia

Beneficial changes were found in a group of 24 hospitalized people with schizophrenia/psychotic disorders as rated by the Psychotic in Patient Profile when they were given a gluten-free diet. However, there was no deterioration when gluten was reintroduced into their diet (Vlissides et al. 1986).

121.2.5 Explanatory Theories

A number of theories have been hypothesized to explain the relationship between gluten intolerance and schizophrenia. Although there is no definite evidence to point to a causal relationship between the two phenomena gluten-induced inflammatory processes may provide clues as to the development of schizophrenia. Initially, explanations were that the psychoactive ingredients in casein and gluten may be pathogenic for people who are genetically vulnerable to having schizophrenia (Dohan et al. 1969). Investigations of the common immunological responses between people with schizophrenia and those with celiac disease have found a decrease of IgA titers in people with schizophrenia and a similar deficiency in 2–3% of people with celiac disease. Raised levels of immunomodulating agents have been found in both groups and have been associated with duration of schizophrenia symptoms (Kalaydjian et al. 2006).

One category of immunomodulating agent cytokines are made up of peptides; an excess of urinary peptides were found in people with schizophrenia (Reichelt et al. 1990). This finding could be evidence of an immunomodulating process that influences the course of schizophrenia. The peptides themselves could influence brain functioning. The peptides found in the Reichelt et al. (1990) study were opioid peptides formed during digestion of the gluten and which if taken up across the blood–brain barrier can have active effects on brain functioning and neurotransmitter levels (Kalaydjian et al. 2006).

Genetic/environmental interactions have tended to dominate explanations. Explanation points to a shared genetic vulnerability to both celiac disease and schizophrenia in a small number of people and that gluten is the environmental trigger. Studies have sought to investigate the proximity of genes that have been implicated in the development of both celiac disease and schizophrenia. Tandon et al. (2008) identify three types of study design used in schizophrenia genetic research:

1. Linkage studies are used to identify specific genetic markers and chromosomes where deviant genes are situated on the human genome. These studies observe variations and abnormalities within chromosomes. Chromosome 11q23–25 and 2q11–13 have been linked to celiac disease which overlaps with chromosome 11q22.3–24.1 which has been linked to schizophrenia. The CLDN5 gene in chromosome 22 and the DQBI gene 6p21.3 are linked to the vulnerability of both celiac disease and schizophrenia (Ye et al. 2005).
2. Association studies seek to identify which gene variations modify the risk for schizophrenia. They provide evidence about the genetic markers for schizophrenia. The most common design of studies is to compare clinical (schizophrenia) and nonclinical (no schizophrenia) gene variant samples to identify those specific gene variants and the frequency of those variations that could provide a vulnerability to schizophrenia. The genetic marker for celiac disease 6p23–P22.3 is situated adjacent to the disbindin locus which has been linked to schizophrenia. Tissue transglutaminase 2 (TGM2) is involved in the production of gliadin antibodies. Single nucleotide polymorphisms (SNPs) are variants within genes that are expressed during the process of new cell development. In a sample of 131 family trios each with an offspring who has schizophrenia eight SNPs present in the TGM2 gene were found to be excessively transmitted to effected offsprings and could be implicated in the development of schizophrenia (Bradford et al. 2008). Methylation

is the reversible biochemical modification of DNA. Faulty DNA methylation may affect the expression of genes by silencing a gene which can affect the stability of chromosomes which then contributes to the development of complex multifactorial conditions such as schizophrenia. Diet is a source of methyl and can contribute to DNA methylation (Singh et al. 2003). Folic acid and other vitamins contribute significantly as a source of methyl. There are three important issues: first, the generic malabsorption as an effect of celiac disease will mean a deficiency of folic acid and an influence on DNA hypomethylation. Secondly, polymorphisms C677 > T and C1298A in the methylenetetrahydrofolate reductase (MTHFR) gene has been linked to problems with the production of DNA methylation. Thirdly, polymorphisms in the MTHFR gene have also been implicated in the development of schizophrenia. Two polymorphisms of the MTHFR gene, 677C > T and A 1298C was found in 44 people with schizophrenia compared with 35 controls; 66.7% of the schizophrenia group compared with 34.3% in the control group had the T allele of the 677C > T polymorphism. Measurement of the positive, negative, and general symptoms of schizophrenia showed a greater intensity of symptoms in those people with the 677C > T allele (Mavros et al. 2008).

121.2.6 Diet, Neurotrophins, Polyunsaturated Fatty Acids and Schizophrenia

Brain-derived neurotrophins are proteins within the central nervous system that provide nutrients for neurons and support for changes in the connection between neurons (synaptic plasticity). Deficient levels of brain-derived neurotrophins have been associated with more severe schizophrenic illness (Tan et al. 2005). A hypocalorific diet was found to increase the levels of serum brain-derived neutrophins (Guimaraes et al. 2008). A low tryptophan diet was associated on improved performance on the Stroop Color and Word Test indicating no abnormalities in frontal lobe functioning and improvements in psychotic symptomatology in a group of 11 people with schizophrenia (Rosse et al. 1992).

Data published by the Agriculture Organization of the United Nations an ecological study found a correlation between a higher national dietary intake of refined sugar, saturated fat, and dairy products and a worse 2-year outcome for schizophrenia (Peet 2004b). High sugar and high fat diet leads to reduced brain expression of brain-derived neurotrophic factor which is important for the outgrowth of dendrites (Peet 2004b). Polyunsaturated fatty acids (PUFA) make up 15–30% of the dry weight of the brain. Reduced levels of the two main types of PUFAs n6 and n3 have been found in the cell membrane of people with schizophrenia (Peet 2002). Neuronal membrane structure and metabolism is dependent on blood plasma levels of certain fatty acids (Joy et al. 2003). Inefficient fatty acid metabolism may increase the risk for schizophrenia and functional deficiencies of omega-3 fatty acids that are essential to brain development and may contribute to abnormalities of behavior, learning, and mood (Richardson 2003). Early trials of supplements enriched with PUFAs such as eicosapentaenoic acid (EPA) given in addition to antipsychotic medication showed positive results in terms of a reduction in both positive and negative schizophrenia symptoms (Peet 2002) (Table 121.4). Omega-3 fatty acids were found to correct positive and negative schizophrenia symptoms, cerebral atrophy, and an abnormal ratio of fatty acids in the cell membranes of a drug naive person with schizophrenia (Puri et al. 2000). A systematic review of the antipsychotic effects of omega-3 EPA analyzed the resul ts from five studies (*n* = 313) and found mixed results (Joy et al. 2003). Omega-3 EPA may have some antipsychotic properties when compared with placebo even if not given as supplement to antipsychotic medication. Where people were already taking antipsychotic medication they were found to have greater improvement in mental health compared to those receiving placebo supplement. Although there was less than 25% improvement in scores on PANSS

Table 121.4 Details of the trials of PUFAs for people with schizophrenia

Study	Study design	Sample	Intervention	Outcome
Holman and Bell (1983)	Double-blind crossover trial	13	Evening primrose oil with supplements.	No beneficial effects found but there is a possibility that evening primrose oil potentiates the epileptogenic properties of antipsychotics.
Wolkin et al. (1986)	Double-blind therapeutic trial	16	Prostaglandin precursor essential fatty acids	No beneficial effects on tardive dyskinesia
Fenton et al. (2001)	Blind placebo randomized control trial	87	3 g of ethyl eicosapentaenoate or placebo was given for 16 weeks as supplements to antipsychotic medications.	No difference was found between groups in terms of positive or negative symptoms, mood, cognition, or global impression ratings.
Peet and Horrobin (2002)	Blind placebo multicenter trial	115	Placebo or 1, 2, or 4 g of ethyl eicosapentaenoate was given for 12 weeks addition to typical and atypical antipsychotic medications.	In those given 2 g/day improvements were found in the PANSS and its subscales. There was a large placebo effect in those on typical and new atypical antipsychotic medications. There was a significant effect of ethyl eicosapentaenoate on all rating scales.

This table provides summary details of the authors, study design, numbers of participants, type and dosage of PUFAs used in the trial, and results of the studies of PUFA trials with people who have schizophrenia

the mental state of both medicated and unmedicated people was better if they received omega-3 EPA supplements (Joy et al. 2003). The authors recommended that large well-designed trials are required and needed.

121.3 Conclusions

There are physical health risks associated with having schizophrenia. These risks are associated with lifestyle, treatment effects, and smoking and result in obesity and premature death. Despite the political will to improve the health for this vulnerable client group clinicians need to develop healthy lifestyle initiatives. The service user group "RETHINK" has considered the factors that may have contributed to this situation and recommend antistigma training for GPs and the staff that work in their practices. They also recommend easier access and availability of smoking cessation courses in areas where people with mental health problems can attend. Health services have a responsibility to provide support with education regarding healthy eating choices, healthy options, food preparation, healthy lifestyle choices, activity and freely available fresh fruit and vegetables. Interventions should be designed for long-term delivery for people both in hospital and those living in the community.

Evidence suggests that there are a small number of people with celiac disease and also have a shared vulnerability to schizophrenia. This relationship has been confirmed in both anthropological and small clinical studies. The clinical studies have used only small numbers in their sample. Bearing in mind the small number of people with this shared vulnerability, studies require larger samples to determine the true effect of gluten-/casein-free diets on schizophrenia symptoms. Gene/environment interactions have been hypothesized as the mechanism for this shared vulnerability. However, genetic studies have failed to consistently identify a specific gene that is responsible for the shared vulnerability.

Studies have lacked precision and there is limited evidence of genetic variations being linked to specific symptoms. There appears to be a lack of consistency across the findings of the studies which inhibit the research community from drawing firm conclusions about the specific range of genes implicated in the development of schizophrenia, celiac disease, and the range of effects each of these genes have on the development of specific symptoms of schizophrenia. It is impossible to say which genetic variations lead to the development of auditory hallucinations or paranoid ideas.

Emerging ecological and clinical evidence suggest there is a link between high intake of saturated fats, refined sugar, and poorer outcomes for people with schizophrenia. Supplements of polyunsaturated fatty acids have also been linked to improvements in schizophrenia symptoms. The results from these clinical studies are promising but results from larger randomized controlled trials are needed.

121.4 Application to Other Areas of Health and Disease

There are implications for people with other serious mental health problems. Treatment for the manic phase of bi-polar disorder includes treatment with typical and atypical antipsychotic medications. The side effect of this treatment is weight gain and the tranquilizing effect may lead to a more sedentary lifestyle. Although the treatment with antipsychotic medication may be of shorter duration it may contribute to poorer physical health outcomes for people with this disorder. Health providers need to be aware of the types of physical health interventions being recommended by RETHINK.

There is some evidence to suggest that a small percentage of people have a shared vulnerability to both schizophrenia and immunological responses such as celiac disease. This knowledge has implications for health researchers. Shared vulnerability gives clues as to the etiology of schizophrenia. Already research has focused on the immunological pathway to elicit further clues. Shared genetic pathways should continue to be explored in order to develop replication, consistency, and more precision in findings.

One suggestion has been that untreated celiac disease in young people may lead to schizophrenia. Whilst there is limited evidence to support this hypothesis health practitioners need to be aware of the signs of celiac disease for early identification and treatment of the disease to avoid any future complications and potential links to mental health conditions.

PUFAs have been associated with improvements in not only schizophrenia symptoms but in depression. Health researchers need to explore the mechanisms by which these improvements are derived. Trials of PUFA's with other mental health conditions are required to increase our understanding of their wider effect. It would be of particular interest in those conditions that have a recognised pattern of neuronal deterioration such as dementia.

Summary Points

- People with schizophrenia are likely to die 10 years younger than other people because of their physical health.
- People with schizophrenia are more likely than other people to major health problems such as cardiac disease, stroke, hypertension, and diabetes.
- These higher risks have been calculated at two to four times higher for the rate of cardiovascular diseases and respiratory diseases and five times the rate for diabetes.
- Diet, lifestyle, psychiatric treatment, and diagnostic overshadowing contribute significantly to these risks.

- Both celiac disease (gluten intolerance) and schizophrenia affect 0.3–1% of the population. Anthropological studies have found a relationship between wheat consumption and hospitalization for schizophrenia.
- Biological studies have found gluten and gliadin antibodies to be more prevalent in people with schizophrenia than their relatives. Where people have been found to have both conditions a gluten-free/reduced diet has been found to provide beneficial outcomes in terms of a reduction in the positive symptoms of schizophrenia and reduced risks of hospitalization.
- Diet has been proposed as one of the environmental factors that influence the production of neutrophins or contribute to the expression or not of genes that have been implicated in the etiology of schizophrenia.
- Poorer outcomes in schizophrenia have been associated with a high ratio of saturated fatty acids to polyunsaturated fatty acids in the national diet and the consumption of refined sugar and dairy products. Reviews of trials of polyunsaturated fatty acid supplements for people with schizophrenia shows positive changes to schizophrenia symptom outcome when given along with or without antipsychotic medication.

Definition of Key Terms

Anthropological studies: Studies exploring the factors that contribute to the development of humankind, society, and civilization.

Antispsychotic medication: A term used to describe several categories of drugs that act on the functioning of the central nervous system in order to control behavior, emotion, and the distressing symptoms of schizophrenia and other psychoses. Their main effect is that of tranquilization and they have a wide range of troublesome movement, hormonal, and psychic side effects.

Gliadin: It is a protein combined with a carbohydrate, known as a glycoprotein and along with glutenin form gluten.

Gluten: A protein formed from the proteins gliadin and glutenin and is a constituent of wheat flour, barley, rye, and oats.

Lifestyle: Patterns of social relationships, culture, and consumption of material goods.

Polyunsaturated fatty acids: A group of unsaturated fatty acids where the carbon chain has two or more double or triple valence bonds per molecule. These include omega 3 and omega 6 and occur as linolenic acid and arachidonic acid. These acids are found in vegetable, fish, and seed oils.

Saturated fatty acids: A group of fatty acids that do not have the double or triple valence bond. Derived from animal fats or by the hydrogenation of unsaturated fatty acids.

Schizophrenia: A psychiatric syndrome characterized by severe thought disorder, disorders of perception, speech, and emotions, and behavioral and movement disturbances.

References

APA. Diagnostic Criteria from the DSM-IV. Washington, DC: American Psychiatric Association; 1994.

Bradford M, Law MH, Stewart AD, Shaw, DJ, Megson IL, Wei J. Am J Med Genet. 2008;150B:335–40.

Brown S, Barraclough B, Inskip H. Br J Psychiat. 2000;177:212–7.

Campbell EG, Foley S. Br Med. 2004;328:1017.

Connolly M, Kelly C. Adv Psychiat Treat. 2005;11:125–32.

Dohan F. Acta Psychiat Scand. 1966;42:125–52.

Dohan FC, Grasberger J, Lowell FM, Johnston HT, Arbegast AW. Br J Psychiat. 1969;115:595–6.

Dohan FC. Biol Psychiat. 1983;18:561–4.

Eaton WE, Mortensen PB, Agerbo E, Byrne M, Mors O, Ewald H. Br Med. 2004;328:438–9.

Eaton WW, Byrne M, Ewald H, Mors O, Chen CY, Agerbo E, Mortensen PB. Am J Psychiat. 2006;163 3:521–8.

Fenton W, Dickerson F, Boronow JJ, Hibbeln JR, Knable MB. Am J Psychiat. 2001;158:2071–4.

Guimaraes LR, Jacka FN, Gama CS, Berk M, Leitao-Avzevedo CL, Belmonye de Abreu MG, Lobato, MI, Andrezza AC, Cereser KM, Kapczinski F, Belmonte-de-Abreu P. Prog Neuro-Psychoph. 2008;32:1595–8.

Holman CP, Bell AFJ. J Orthomol Med. 1983;12:302–4.

House of Commons. Health Inequalities. House of Commons Health Committee. Third Report of Session 2008–9. House of Commons, London: The Stationery Office Limited; 2009.

Joy CB, Mumby-Croft R, Joy LA. Cochrane Db Syst Rev. 2003;(2) CD001257.

Kalaydjian AE, Eaton W, Cascella N, Fasano A. Acta Psychiat Scand. 2006;113:82–90.

Kinnell HG, Kirkwood E, Lewis C. Psychol Med. 1982;12:85–9.

Littrell KH, Hilligoss NM, Kirscher CD, Petty RG, Johnson CG. J Nurs Scholarship. 2003;3rd quarter:237–41.

Martin C.R, Allan R, Fleming M, Atkinson J. J Psychiat Ment Hlt. 2008;15:722–7.

Martin CR, Fleming MP. In Preedy VR and Watson RR editors. A handbook of disease burdens and quality of life measures. Germany: Springer; 2009.

Mavros M, Chirita V, Poescu O, Ferencz B. Revista Medico-Chirurgicala a Societatii de Medici Si Naturalisti Din Iasi, 2008;112/176–82.

McCreadie R.G. Br J Psychiat. 2003;183:534–9.

McCreadie RG, Macdonald E, Blacklock C, Tilak-Singh D, Wiles D, Halliday J, Paterson J. Br Med. 1998;317:784–5.

McCreadie RG, Kelly C, Connolly M, Williams S, Baxter G, Lean M, Paterson JR. Brit J Psychiat. 2005;187:346–51.

Mortensen PB, Juel K. Br J Psychiat. 1993;163:183–9.

Nese D. Int J Psychiat Clin. 2008;12 3:238–40.

Nocon A, Sayce L. Health Policy. 2008;86:325–34.

Osborne M, Crayton JW, Javaid, J, Davis JM. Biol Psychiat. 1982;17:627–9.

Peet M. Adv Psychiat Treat. 2002;8:223–9.

Peet M, Horrobin DF. J Psychiat Res. 2002;36.

Peet M. Br J Psychiat. 2004a;184 Suppl 47:102–5.

Peet M. Br J Psychiat. 2004b;184:404–8.

Potkin SG, Weinberger D, Kleinman J, Nasrallah H, Luchins D, Bigelow L, Linnoila M, Fischer SH, Bjornsson TD, Carman J, Gillin JC, Wyatt RJ. Am J Psychiat. 1981;138:1208–11.

Puri BK, Richardson AJ, Horrobin DF, Easton T, Saeed N, Oatridge A, Hajnal JV, Bydder GM. Int J Clin Pract. 2000;54 1:57–63.

Reichelt KL, Sagedal E, Landmark J, Sangvik BT, Eggen O, Scott H. J Orthomol Med. 1990;5 4:223–36.

Rethink. Briefing – Physical health and mental health. 2009; www.rethink.org

Richardson AJ. Scand J Nut. 2003;47 2:92–8.

Rosse RB, Schwartz BL, Zlotow S, Banay-Schwartz M, Trinidad AC, Peace TD, Deutsch SI. Clin Neuropharmacol. 1992;15 2:129–41.

Schizophrenia& Diabetes Expert Group. Br J Psychiat. 2004;184 Suppl 47:112–4.

Seeman P, Kapur S. Proc Natl Acad Sci. 5 July 2000;97 14:7673–5.

Silverstone T, Smith G, Goodall E. Br J Psychiat. 1988;153:214–7.

Singh MM, Kay S. Science. 1976;191:401–2.

Singh SM, Murphy B, O'Reilly RL. Clin Genet. 2003;64:451–60.

Tan YL, Zhou DF, Cao LY, Zou YZ, Zhang XY. Neurosci Lett. 2005;382:27–32.

Tandon R, Keshavan M.S, Nasrallah HA. Schizophr Res. 2008;102:1–18.

Van Rossum JM. In: Brill H, Cole JO, Deniker P, Hippius H, Bradley PB editors. Neuro-psycho-pharmacology, Proceedings of the 5th Interenational Congress of the Collegium Internationale Neuro-Psycho-pharmacologicum, March 1966. Amsterdam: Excerpta Medica Foundation; 1967. p. 321–329.

Vlissides DN, Venulet A, Jenner FA. Br J Psychiat. 1986;148:447–52.

Volta U, Molinaro N, Fusconi M, Cassani F, Bianchi FB. Digest Dis Sci. 1991;36:752–6.

WHO. The international classification of diseases – 10 mental and behavioural disorders. Geneva: World Health Organisation; 1992.

Wolkin A, Jordan B, Peselow E, Rubinstein M, Rotrosen J. Am J Psychiat. 1986;1437:912–4.

Wu M.K, Wang CK, Bai YM, Huang CY, Lee SD. Psychiat Serv. 2007;58 4:544–50.

Ye L, Wei J, Sun Z, Xie L, Liu S, Ju G, Shi J, Yu Y, Zhang X, Xu Q. Schizophr Res. 2005;75 1:139–41.

Chapter 122
Neuronal Circuits and Neuroendocrine Responses Involved in Dehydration Induced by Water Restriction/Deprivation

Zheng-Hua Zhu, Bai-Ren Wang, James S. McTaggart, and Li-Ze Xiong

Abbreviations

ACTH	Adrenocorticotropic hormone
AngII	Angiotensin II
AP	Area postrema
AQP4	Aquaporin-4
AV3V	Anteroventral third ventricle area
AVP	Arginine vasopressin
avPVN	Anteroventral part of PVN
BNST	Bed nuclei of the stria terminalis
CeA	Central amygdaloid nucleus
CNS	Central nervous system
CRH	Corticotropin releasing hormone
CVOs	Circumventricular organs
E	Estrogen
ECF	Extracellular fluid
ER	Estrogen receptor
Fos-LIR	Fos-like immunoreactivity
GABA	γ-aminobutyric acid
GFAP	Glial fibrillary acidic protein
HNS	Hypothalamo-neurohypophyseal system
ICF	Intracellular fluid
LPB	Lateral parabrachial nucleus
LSV	Ventrolateral septum
MCNs	Magnocellular neurosecretory cells
MeA	Medial amygdaloid nucleus
MnPO	Median preoptic nucleus
NE	Norepinephrine
NIL	Neurointermediate lobe
NO	Nitric oxide

L.-Z. Xiong (✉)

Department of Anesthesiology, Xijing Hospital, Fourth Military Medical University, 15 West Changle Rd, Xi'an, 710032, P.R. China
e-mail: mzkxlz@126.com

NTS   Nucleus tractus solitarius
OT   Oxytocin
OVLT   Organum vasculosum of the lamina terminalis
PVN   Hypothalamic paraventricular nucleus
SFO   Subfornical organ
SON   Supraoptic nucleus

122.1 Introduction

Homeostasis in the face of physical or psychological stressors (such as dehydration, hemorrhage, restraint) is essential for an individual's health and survival. In these circumstances the stable state is maintained by a series of coordinated responses including neuroendocrine, immune and behavioral changes. A typical stress response consists of three parts: (1) sensory input, detected by specific receptors, (2) central processing systems, which integrate these signals, and (3) motor output, including the executive effectors. The hypothalamo–pituitary–adrenocortical (HPA) axis is involved in the reaction to a variety of stressors, but accumulating data show that additional, specialized central networks are involved in the responses to specific stressors (Van de Kar and Blair 1999; Watts 2001; Pacak and Palkovits 2001; Herman et al. 2003). Although adaptive stress responses are beneficial to health and survival, their persistent inappropriate activation may lead to disease and even mortality.

Body fluid homeostasis involves the maintenance of body fluid volume and osmolarity within an appropriate range. Dehydration by water restriction/deprivation causes changes in intracellular fluid (ICF) volume, extracellular fluid (ECF) volume, and sodium concentrations in plasma. These changes are detected by osmoreceptors and baroreceptors in the periphery and the brain, which activate or suppress behavioral and physiological responses such as water-seeking, water intake, and salt appetite. These responses counteract changes in the volume and osmolarity of fluids (a negative feedback response), maintaining homeostasis. Over the past 2 decades, several key components of the neuronal and neuroendocrine mechanisms underlying water/salt balance have been revealed, but in many cases the details are still not well understood (Johnson and Thunhorst 1997; Watts 2001; Antunes-Rodrigues et al. 2004). In this chapter we present a brief introduction to the changes in neuronal circuits, neuroendocrine, gene and glia responses, following dehydration.

122.2 Body Fluids

Body fluids consist of water containing a variety of dissolved substances, such as electrolytes and proteins, as well as cells, such as blood cells. In adults, body fluids constitute approximately 55% of female and 60% of male total body weight.

Body fluids are divided into three main compartments – ICF, interstitial fluid, and plasma – by the plasma membranes and the membrane of the vascular endothelial cells. ICF makes up two-thirds of total body fluids. ECF makes up the remaining one-third, comprising plasma and all other interstitial body fluids, such as lymph, cerebrospinal, pleural, pericardial, and peritoneal fluids. About 80% of ECF is interstitial fluid and about 20% of ECF is plasma. Na^+ is the major ion in ECF; therefore, the maintenance of its concentration is crucial for homeostasis of osmotic pressure.

The contents of the fluids are in constant motion, and exchange by filtration, reabsorption, diffusion, and osmosis between the three compartments, which maintains fluid volume at a fairly constant level and also correctly proportioned in each compartment at any given time. This dynamic equilibrium is crucial for the maintenance of an effective circulating volume, osmotic gradients, acid–base balance, normal action potentials in neurons and muscle cells, and secondary active transport.

122.3   Water Balance

Water is the main component of all body fluids and by far the largest single component of the body itself, accounting for 45–75% of total body weight. The percentage of water in a given person depends on a variety of factors, such as the amount of fat tissue, age, body size, and gender. Fat tissue contains approximately 20% water, while muscle mass contains about 65%, therefore lean people have a greater percentage of water than overweight people, since fat tissue contains much less water. The percentage is highest in infancy and decreases with age, and males have a higher percentage of body water than females since the latter have a greater percentage of subcutaneous fat.

The body can gain water (2,500 mL/day) by the ingestion of liquids (1,600 mL/day) and moist foods (700 mL/day), and also by the metabolic synthesis of water by various chemical reactions (200 mL/day). Water can be lost from the body via urine (1,500 mL/day), skin evaporation (500 mL/day), lung exhalation (300 mL/day), and elimination by the gastrointestinal tract (200 mL/day). Normally, the daily water gain is approximately equal to the water that is lost – water balance.

When water loss is greater than water gain, such as in conditions of water restriction/deprivation, there is an inevitable loss of ICF or ECF accompanied by an increase of the sodium concentration, leading to water translocation between different body fluid compartments and a decrease of cell and/or plasma volume, which in turn increases osmolarity. The ratio of intracellular to extracellular water largely reflects an osmotic equilibrium achieved by the relative concentrations of impermeable ions found in the two compartments. The concentration of extracellular sodium is the primary ionic factor determining this osmotic equilibrium. Thus, any net change in water or sodium alters not only fluid balance but also osmotic equilibrium, resulting in altered fluid distribution between the three compartments.

Therefore, it is difficult to absolutely separate water balance from sodium balance; hence when the term "fluid balance" is used, it typically means water and sodium balance. Consequently, regulation of fluid balance may be investigated experimentally by restriction or deprivation of water, but also by injection of hypertonic saline as both approaches deplete the ICF and/or ECF compartments.

Mammals counteract electrolyte and water imbalance via a variety of neural and endocrine mechanisms and signals – e.g. thirst, anti-diuretic hormone (ADH), aldosterone, atrial natriuretic peptide (ANP), and the sympathetic nervous system (the autonomic nervous system and renin–angiotensin system). ADH, also known as arginine vasopressin (AVP), is secreted by neurons in the central nervous system (CNS) and acts in the kidney to increase the permeability of the distal tubules and collecting ducts to water, which causes increased facultative reabsorption of water. Aldosterone and angiotensin II (AngII) increase Na^+ resorption by the renal tubules, leading to increased obligatory reabsorption of water. ANP decreases Na^+ resorption, leading to both decreased obligatory reabsorption and increased water loss in urine. Thirst is stimulated along with decreased saliva production, increase of the blood osmotic pressure, and decrease of blood volume and blood pressure, which

Table 122.1 Key features of water balance and dehydration

1. Water accounts for 45–75% of the total body weight
2. The ratio of water in a given person depends on such factors as the amount of fat tissue, age, body size, and gender
3. Normally, the daily water gain is approximately equal to the water lost, e.g. 2,500 mL/day in average
4. Dehydration happens when water loss is greater than water gain, which leads to an inevitable loss of intracellular or extracellular fluid and an increase of the plasma sodium concentration accompanied by thirst, anorexia, thermoregulation, even psychological behavior
5. To maintain water balance during dehydration, a variety of neural and endocrine mechanisms are activated, such as antidiuretic hormone (ADH), aldosterone, atrial natriuretic peptide (ANP), and the autonomic nervous system/ renin–angiotensin system.

result in stimulations of the hypothalamic thirst center through the activation of tactile receptors in the mucosa of dry mouth and throat, hypothalamic osmoreceptors, and the renin–angiotensin system, respectively. All these changes lead to the desire to drink, restoring normal fluid volume (see reviews: Johnson and Thunhorst 1997; Antunes-Rodrigues et al. 2004) (Table 122.1).

122.4 Central Osmoreceptors and the Hypothalamo-Neurohypophyseal System

Central osmoreceptors are located in the circumventricular organs (CVOs), which are specialized brain structures named for their proximity to the ventricles of the brain. The CVOs include the subfornical organ (SFO), organum vasculosum of the lamina terminalis (OVLT), median eminence (ME), neurohypophysis, and area postrema (AP). In addition to their periventricular midline location in the brain, they share certain common features such as an extensive vasculature lacking a blood–brain barrier (BBB). Therefore these cells are in direct contact with both plasma and cerebrospinal fluid and ideally placed to sense any change in ECF composition. CVOs also comprise of a dense population of a variety of peptidergic factor receptors, such as the AngII receptor, ANP receptor, estrogen receptor (ER), and atypical ependymal cells. Of the CVOs listed, only three (SFO, OVLT, and AP) contain neuronal cell bodies with efferent fibers extending to other brain regions and are referred to as the "sensory CVOs." Because their neurons are directly exposed to the chemical environment of the circulation, the sensory CVOs are thought to be responsible for sensing various kinds of circulating information, including the Na^+ concentration and osmotic pressure of the body fluids (Fig. 122.1a; see reviews: McKinley et al. 1994; Bourque and Oliet 1997; Zhang and Bourque 2003).

In addition to CVOs, an increase in plasma osmolarity is also detected by intrinsic osmoreceptors of magnocellular neurosecretory neurons (MCNs) in the hypothalamo-neurohypophyseal system (HNS; Bourque and Oliet 1997; Zhang and Bourque 2003). HNS is an important integrative system that mediates neuroendocrine responses. It consists of many MCNs located in the hypothalamic paraventricular nucleus (PVN) and supraoptic nucleus (SON). These neurons synthesize the neurohormones AVP and oxytocin (OT), and release them into the blood circulation via axonal projections from the SON and PVN to the posterior pituitary to modulate the balance of body fluids and osmolarity after dehydration (Fig. 122.1b; Van de Kar and Blair 1999; Pacak and Palkovits 2001; Herman et al. 2003; Antunes-Rodrigues et al. 2004).

Regulation of ECF volume and osmolarity depends on the coordinated action of multiple mechanisms that change intake and excretion of water and sodium. The involvement of central osmoreceptors and HNS in body fluid balance has been revealed over the previous 2 decades; however, many details still need to be investigated further.
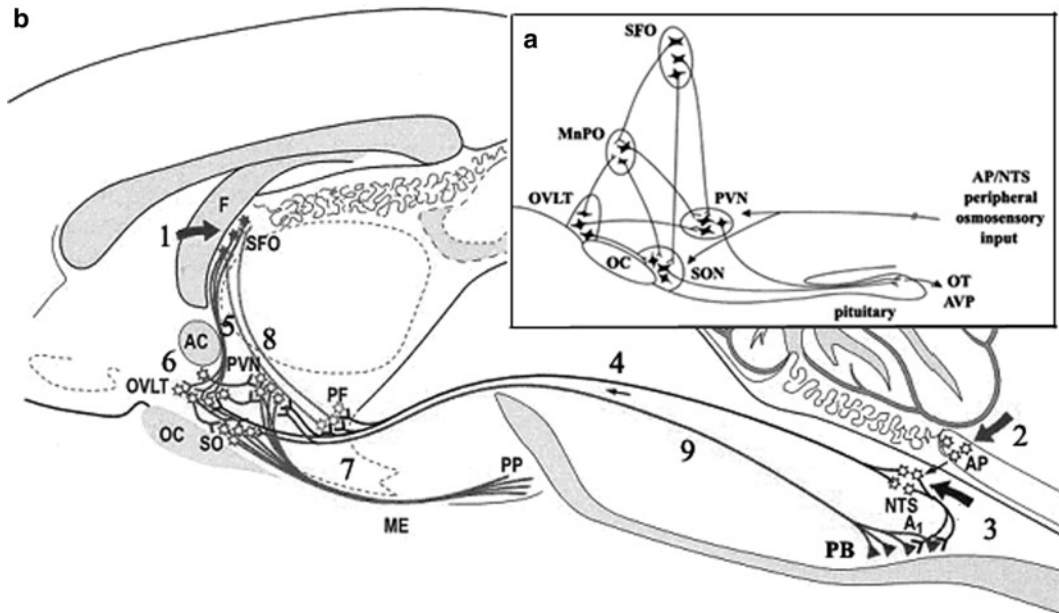
Fig. 122.1 Brain nuclei and circuits involved in dehydration. (**a**) The central osmoreceptor complex and HNS. Cell bodies of magnocellular neurons in the SON and PVN project their axon to the posterior lobe of the pituitary where they release OT and AVP into the general blood circulation. They receive afferent inputs from central osmosensitive neurons located in the OVLT, SFO, MnPO, and AP. OVLT and SFO neurons also project to the MnPO. Indirect sensory input from peripheral osmoreceptors, coming via relays in the NTS, is also represented (Reprinted from Hussy et al. (2000). With permission) (**b**) Hypothalamic neuropeptidergic circuit that regulates body fluid and mineralocorticoid homeostasis. (1) Humoral inputs to the SFO; (2) humoral inputs through the AP; (3) viscerosensory neuronal inputs to the NTS; (4) ascending projections from the NTS to the perifornical and the paraventricular nuclei, as well as to AV3V; (5) AngII-containing neurons in the SFO with their projections to the medial preoptic area; (6) ANP-containing neurons in the OVLT and the medial preoptic area with supraoptic and paraventricular projections; (7) supraoptic and paraventricular vasopressinergic projections to the PP; (8) AngII-containing projections from the PF to the SFO; (9) ascending noradrenergic fibers from the ventrolateral medulla and PB to preoptic and magnocellular hypothalamic nuclei. *AC* Anterior commissure, *AP* area postrema, *AV3V* anteroventral third ventricle area, *F* fornix, *HNS* hypothalamo-neurohypophyseal system, *ME* median eminence, *MnPO* median preoptic nucleus, *NTS* nucleus of the solitary tract, *OC* optic chasm, *OVLT* organum vasculosum of the laminae terminalis, *PB* parabrachial nucleus, *PF* perifornical nucleus, *PP* posterior pituitary lobe, *PVN* hypothalamic paraventricular nucleus, *SFO* subfornical organ, *SON* supraoptic nucleus (Reprinted from Pacak and Palkovits (2001). With permission)

122.5 Responses in CNS to Dehydration

122.5.1 Brain Regions and Neuronal Circuits Involved in Dehydration

Many different techniques, such as electrolytic lesion, electrical and chemical stimulation, as well as immunohistochemistry, have been used to identify the brain areas, neural circuits, and neurotransmitters that regulate intake and excretion of water and sodium.

Recent studies have demonstrated that immediate early genes, such as *c-fos*, are expressed transiently in the CNS in response to neuronal activation, and these expression patterns correlate with findings from other methods, such as electrophysiological studies. Therefore, immunohistochemical staining of the Fos protein has been used extensively as a marker for cellular activation in the neuroendocrine system to reveal the neural circuits of body fluid homeostasis (Mckinley et al. 1994; Rawland 1998).

To map the brain areas that respond to dehydration, *c*-Fos protein expression (Fos-like immunoreactivity, Fos-LIR) was examined following chronic water restriction in Wistar rats (Zhu et al. 2006). After 1 week to allow for environmental adaptation and another week for water intake training (twice per day at fixed time points), animals were subjected to either normal drinking (drinking as in the training period, TW group), restricted drinking (once per day and nothing at the other drinking time, WR group), or restricted drinking plus empty water bottle stimulus (drinking once per day and an empty water bottle at other drinking time, EB group) for 3, 7, and 14 days, respectively. Physical responses to the dehydration included weight loss, increases of hematocrit (HCT), serum Na^+ concentration and corticosterone levels; behavioral responses included increased attacking and exploratory behavior. In the EB and WR groups these changes were associated with a significant increase of Fos-LIR expression in SFO, median preoptic nucleus (MnPO), AP, PVN, and SON. However, the time course of Fos expression in these two groups was different. In the EB group, the increase of Fos-positive cell number occurred earlier, often starting on day 3, and peaking on day 7. In the WR group, Fos expression in these nuclei increased more slowly, often starting on day 7, and peaking on day 14 (Figs. 122.2, 122.3, and 122.4). These results indicate that the response pattern in the brain differs depending on the duration and intensity of dehydration.

Ueta et al. studied the effects of 24 and 48 h water deprivation on the expression of *c*-Fos protein in the brain of inbred polydipsic mice, which exhibit extreme polydipsia without a lack of AVP, and compared the results with nonpolydipsic mice. In both groups of mice, water deprivation induced a significant increase in Fos-LIR in the PVN, SON, MnPO, OVLT, and SFO, while a far greater increase was seen in the MnPO, SFO, and AP in the polydipsic mice compared with the nonpolydipsic control mice, indicating that neurons in the CVOs are strongly activated by water deprivation in mice, especially polydipsic mice (Ueta et al. 1995).

Chae et al. examined Fos-LIR in the SON and PVN induced by 6–18 h water deprivation in the day and night cycle with an outbred laboratory population of white-footed mice, *Peromyscus leucopus*. In this study, 6 h of water deprivation produced a near-maximal increase in the number of cells positive for Fos-LIR in the SON and PVN during the dark period, when mice are active, whereas it only slightly affected the Fos-LIR during the light period, when mice are inactive and do not drink. During the day, as much as 12 h of water deprivation was required to increase the Fos-LIR to levels
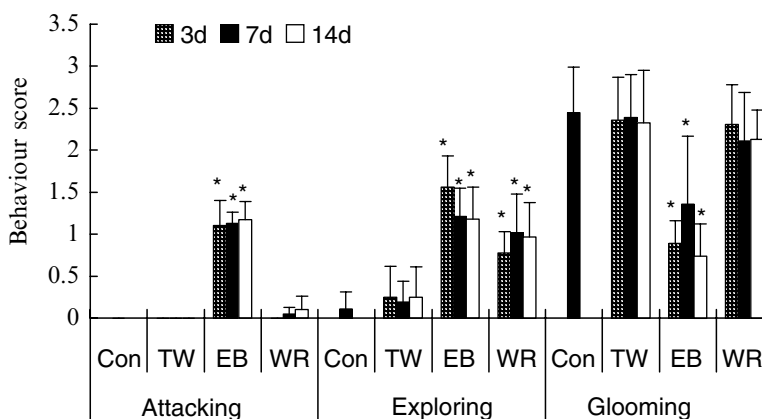
Fig. 122.2 Behavioral responses after water restriction in experimental rats. Grooming is the main behavioral response in the normal drinking animals (Control, Con) as well as drinking twice-per-day animals (TW group). Actions of attacking and exploring are significantly increased in empty bottle stimulus rats (EB group), but only exploring in water restriction rats (WR group). Results are expressed as mean ± SEM, *n* = 6, *$P < 0.01$ vs. Con group (Reprinted from Zhu et al. (2006). With permission)
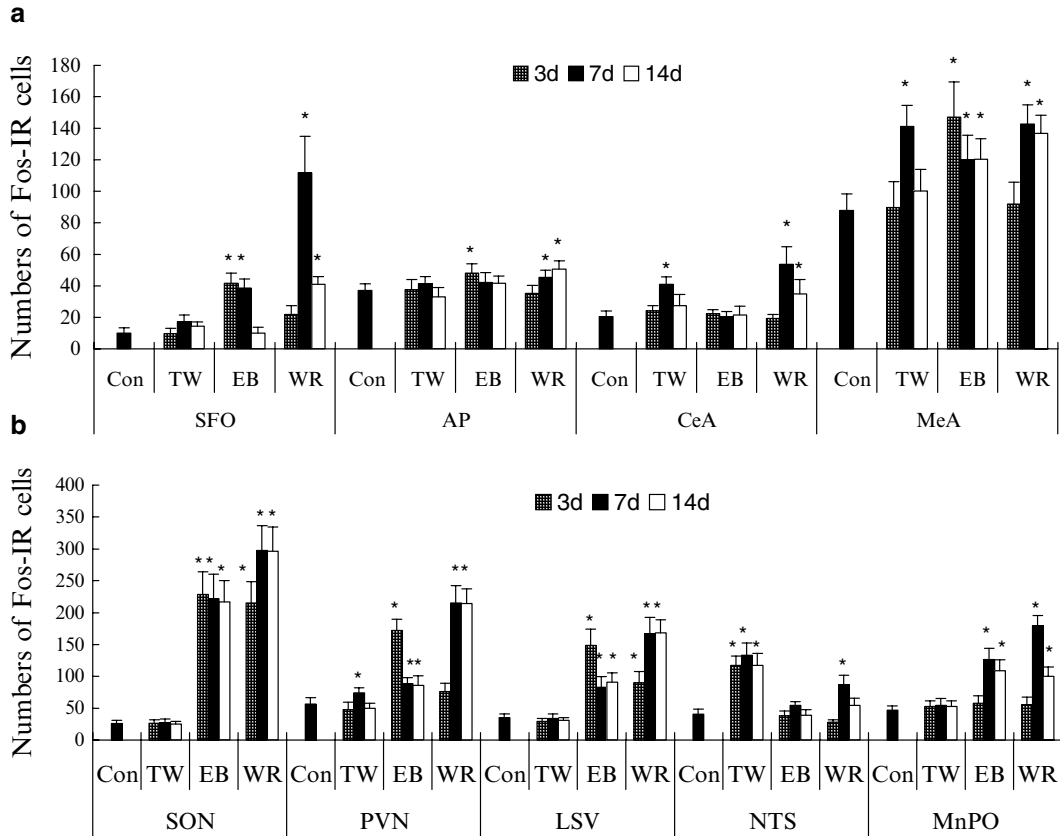
Fig. 122.3 Fos expression in rat brain at different time points following dehydration. The numbers of Fos-immunoreactive cells are increased in various areas/nuclei of the rat brain, such as SFO, MnPO, AP, PVN, SON, MeA, and LSV, after receiving water restriction stimulus (drinking twice-per-day, TW group; empty bottle stimulus, EB group; water restriction, WR group; normal drinking, Con group). Results are expressed as mean ± SEM, $n = 6$, $*P < 0.05$, $**P < 0.01$ vs. Con group. *AP* area postrema, *CeA* central amygdaloid nucleus, *LSV* ventrolateral septum, *MeA* medial amygdaloid nucleus, *MnPO* median preoptic nucleus, *NTS* nucleus of solitary tract, *PVN* hypothalamic paraventricular nucleus, *SFO* subfornical organ, *SON* supraoptic nucleus (Reprinted from Zhu et al. (2006). With permission)

comparable with those achieved at night. The circadian dependence of the changes in *c*-Fos expression in PVN and SON in response to water deprivation correlates with the circadian changes in behavioral and physical characteristics such as plasma osmolarity, weight loss, and water intake, demonstrating the activation of PVN and SON during dehydration (Chae et al. 1998).

Morien et al. examined the pattern of Fos-LIR in CVOs following 0–48 h water deprivation in rats under normal light–dark conditions (nLD) and reverse light–dark conditions (rLD). The number of Fos-positive cells increased with the duration of water deprivation in the SON, PVN, OVLT, MnPO, and SFO in both the nLD and rLD conditions. Furthermore, compared with the nLD groups, the rLD groups had significantly more Fos-LIR in SON and PVN after 5 or 24 h water deprivation, in the MnPO after 5 h, and in the SFO after 24 h water deprivation (Morien et al. 1999). Therefore, this study also demonstrates the activation of both the CVOs and HNS by water deprivation.

All these studies indicate that the activation of CVOs and HNS play an important role in the regulation of water balance during dehydration. The same phenomenon was also reported in many other investigations (see review: Rawland 1998). Moreover, certain other nuclei, such as ventrolateral
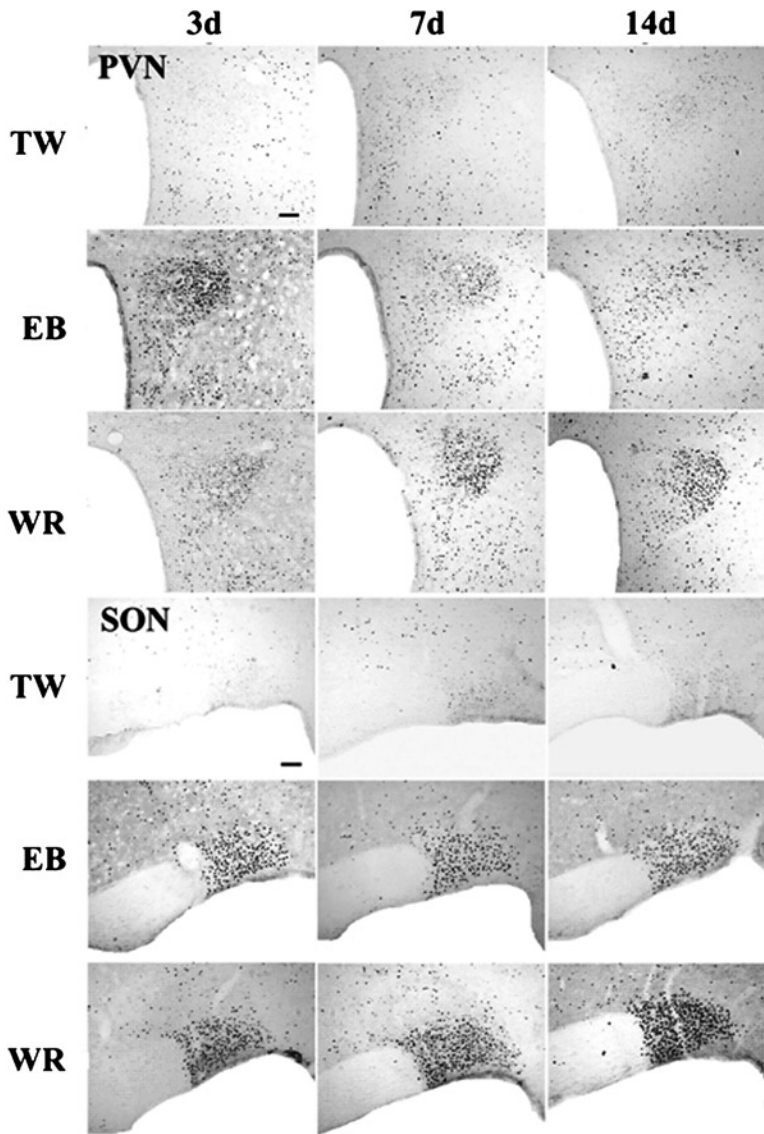
Fig. 122.4 Microphotographs showing the Fos expressions in PVN and SON after dehydration. c-Fos expression increased in a different pattern in PVN and SON depending on the duration and intensity of dehydration following 3, 7, and 14 days dehydration by drinking twice-per-day (TW), empty bottle stimulus (EB) and water restriction (WR), respectively. *PVN* hypothalamic paraventricular nucleus, *SON* supraoptic nucleus. Bar = 100 μm (Reprinted from Zhu et al. (2006). With permission)

septum (LSV), the medial part of the amygdaloid nucleus (MeA), the central part of the amygdaloid nucleus (CeA), NTS, the bed nuclei of the stria terminalis (BNST), and the lateral parabrachial nucleus (LPB), were also shown to be involved in dehydration (see review: Johnson and Thunhorst 1997; Rawland 1998; Pacak and Palkovits 2001). These data are consistent with our investigations, as Fos expression in the MeA, CeA, and LSV was also significantly increased in both the EB and WR groups, although the time course was slightly different between the two groups.

These immunohistochemical experiments suggest that numerous neuronal nuclei and circuits are activated during dehydration, and constitute a body fluid-related neural network (Honda et al. 1990;
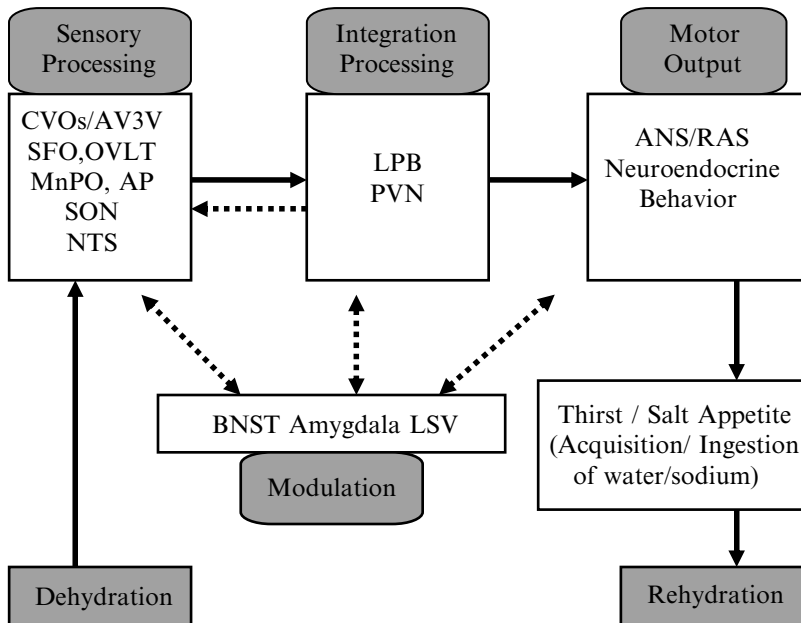
Fig. 122.5 A schematic representation of central circuits modulating dehydration. There are three parts in the response process. (1) Sensing. The CVOs, including SFO, MnPO, OVLT, and AP (i.e., the sensory complex containing abundant osmoreceptors) are activated to sense changes in body fluid volume and osmolarity. All signals from these nuclei are directly or indirectly sent to SON and PVN. The NTS might act as a relay of peripheral signals. (2) Integration. The PVN and LPB integrate the information from the HNS and send output signals to change motor behavior. (3) Motor part. Neurons in SON and PVN, which receive signals from CVOs and intrinsic osmoreceptors, secrete OT and AVP into the general circulation to provoke drinking behavior through modulation on the ANS/RAS activity, neuroendocrine response, and behavior. Some other forebrain structures (such as BNST, LSV, amygdala) are considered to play important roles in the modulation of all these responses. *ANS* autonomic nervous system, *AP* area postrema, *AV3V* anteroventral third ventricle area, *BNST* bed nuclei of the stria terminalis, *LPB* lateral parabrachial nucleus, *LSV* ventrolateral septum, *MnPO* median preoptic nucleus, *NTS* nucleus of solitary tract, *PVN* hypothalamic paraventricular nucleus, *RAS* renin–angiotensin system, *SFO* subfornical organ, *SON* supraoptic nucleus, *OVLT* organum vasculosum of the lamina terminalis

Hussy et al. 2000; Watts 2001), as described in Fig. 122.5. Further studies are needed to elucidate the connectivity of these nuclei and how these connections are employed to regulate the response to dehydration.

122.5.2   Neuropeptides and Neurotransmitters in the CNS Involved in Dehydration

There is substantial data suggesting that the HNS mediates the neuroendocrine responses to dehydration. Axons of magnocellular neurosecretory cells (MCNs) projecting from the SON and PVN MCNs to the posterior pituitary release AVP and OT. The release of AVP and OT is determined largely by the rate and pattern of MCN firing, which is modulated by osmolarity. However, it is becoming apparent that the MCNs also receive signals from a wealth of afferents containing many classic neurotransmitters and other neuropeptides co-localize with AVP and OT in MCNs. These data suggest that the secretion of AVP and OT is modulated by a complicated neuropeptide/neurotransmitter response system.

122.5.2.1 AVP and OT

AVP and OT are involved in a wide spectrum of physiological functions, including the regulation of fluid homeostasis, cardiovascular regulation, emotion, social recognition, and reproduction, but are mainly known as the principle neuropeptides for the regulation of body fluid. AVP and OT are synthesized and stored in the cell bodies of SON and PVN MCNs. When a rise in plasma osmolarity is detected by intrinsic MCN osmoreceptors, or specialized osmoreceptive neurons in the CVOs that project to the MCNs, AVP and OT are released by the activated MCNs into the circulation from terminals in the posterior pituitary gland. They then travel through the blood stream to specific receptor targets in the CNS or peripheral tissue to modulate the autonomic system, renin–angiotensin system, and the kidney, leading to increased permeability of the collecting ducts and reducing the renal excretion of water, thereby promoting water conservation, anti-diuresis, and natriuresis.

Dehydration due to water deprivation or salt loading causes axonal transport and release of AVP and OT into the blood, which decreases the content of AVP and OT in the MCNs. This, of course, causes a significant increase in plasma AVP and OT concentrations, as well as increased electrical activity of vasopressinergic and oxytocinergic neurons of magnocellular hypothalamic nuclei (also seen as increased Fos protein expression in these neurons). AVP and OT mRNA levels in the MCNs are also increased. The magnitude of these changes is correlated with the duration of the dehydration and is also dependent on the time of day the dehydration started, paralleling to the rise of the blood plasma osmolality as well as the decrease of blood volume during dehydration. All these changes almost recover to the normal level after rehydration (Xiong and Hatton 1996; Johnson and Thunhorst 1997; Rawland 1998; Pacak and Palkovits 2001; Arnhold et al. 2007).

122.5.2.2 Classic "Local" Neurotransmitters Interacted with MCNs

MCNs receive a wealth of afferents including glutamatergic, GABAergic, catercholaminergic, cholinergic, serotonergic, and histaminergic axon terminals with the corresponding receptors located in the postsynapse and/or presynapse from the CVOs as well as other forebrain, midbrain, and hindbrain structures. Administration of agonists and antagonists of the receptors for these various neurotransmitters induces different neurohypophyseal hormone responses to dehydration. Therefore, these classic neurotransmitters are likely to be involved in the regulation of AVP and OT release (Johnson and Thunhorst 1997; Van de Kar and Blair 1999). For example, Di et al. showed that dehydration leads to an increase in glutamate and GABA release in the supraoptic MCNs, and there was a marked enhancement of norepinephrine (NE)-facilitated glutamate release and NE-inhibited GABA release (Di and Tasker 2004).

Recent studies have shown that nitric oxide (NO) in the brain may also play an important role in fluid balance by modulating AVP and OT secretion from the HNS. For example, NO synthase levels increase throughout the entire HNS during acute and chronic osmotic stimulation or water deprivation as shown by immunohistochemistry, in situ hybridization, and microdialysis studies. The drinking induced by water deprivation and AngII is inhibited by intracerebroventricular (i.c.v) injection of l-arginine (see review: Kadekaro 2004). The NO signaling cascade may regulate the release of AVP and OT by enhancing the expression of Ca^{2+}-activated K^+ channels (BK channels), which are colocalized in the supraoptic nuclei and neural lobe of rats (Kadekaro et al. 2006), or in part by facilitating the local release of glutamate/aspartate following water deprivation or osmotic challenge (Gillard et al. 2007).

122.5.2.3 Peptides Co-localized with AVP or OT in MCNs

Double-immunohistochemical staining techniques have shown that many neuropeptides colocalize with AVP and/or OT in MCNs. Some of these substances are involved in osmotic function such as AngII, corticotropin-releasing hormone (CRH), apelin (APL), galanin (GAL), and neuropeptide Y (NPY).

AngII: AngII-containing fibers and angiotensin receptor I are located in CVOs. AngII-containing cell bodies are found in several brain areas, including the SON and magnocellular parts of the PVN, where AngII is colocalized with AVP. Studies of lesions on anteroventral third ventricle area (AV3V) and i.c.v. injection of AngII indicate that AngII plays a critical role in dehydration-induced thirst, water intake, and salt appetite. This occurs through effects on the angiotensin receptor I (AT-I) or interaction with other hormones such as ANP and NO in regulating the release of AVP and OT (Johnson and Thunhorst 1997; Antunes-Rodrigues et al. 2004; Bundzikova et al. 2008).

CRH: CRH is expressed in several regions of the adult rat brain, but most prominently in PVN parvocellular neurons. CRH is known to mediate endocrine, autonomic, behavioral, and immune responses to stress. During osmotic stimulation, an increase of CRH-immunoreactivity was observed in oxytocinergic magnocellular neurons in the PVN and SON, and expression of CRH receptor-1 mRNA, which was undetectable in the SON and PVN in control rats, was also significantly increased, indicating direct regulation of AVP and OT neurons (Arima and Aguilera 2000). A study by Lauand et al. (2007) showed that a significant increase in plasma ANP, OT, AVP, and corticosterone levels was observed after i.c.v. microinjections of hypertonic NaCl, AngII, or carbachol. Pretreatment with dexamethasone decreased the plasma corticosterone and OT levels, with no changes in AVP secretion. Furthermore, significant increase in Fos-immunoreactive neurons was observed in MnPO, PVN, and SON after i.c.v. stimulation. These results indicate that central osmotic, cholinergic, and angiotensinergic stimuli activate MnPO, PVN, and SON, with subsequent OT, AVP, and ANP release. The responses are also modulated by glucocorticoids, the endpoint effector of the HPA axis, implying that CRH can also indirectly regulate the secretion of AVP and OT.

Apelin: APL, a neuropeptide recently identified as the endogenous ligand for the G-protein-coupled receptor APJ, is widely expressed in the CNS, especially highly concentrated and colocalized with both AVP and OT in the MCNs of the SON and PVN. APL is involved in several physiological processes, including the regulation of the cardiovascular system and immune response. Recently, it was shown that APL influences water regulation through AVP modulation. A study by Reaux et al. found that i.c.v. administration of APL significantly reduced water intake in the initial 30 min after re-exposure to drinking water, and lowered circulating levels of AVP in mice deprived of water (Reaux et al. 2001). Reaux-Le Goazigo et al. found that APL-immunoreactive neurons in the SON and PVN also contained AVP, but the two peptides were segregated to distinct subcellular compartments. Both the number and labeling intensity of magnocellular APL-immunoreactive cells increased significantly after 24 or 48 h dehydration, whereas the number and labeling density of AVP-immunoreactive neurons were significantly decreased. The dehydration-induced increase in APL immunoreactivity was markedly diminished by central injection of a selective AVP-1 receptor antagonist, providing additional evidence that the neuropeptide APL is involved in body fluid homeostasis regulation via cross-regulation of AVP release (Reaux-Le Goazigo et al. 2004). Another study also showed that AVP and APL are conversely regulated in the facilitation of systemic AVP release and the suppression of diuresis (Llorens-Cortes and Moos 2008).

Galanin: GAL, a 29/30-amino acid peptide originally isolated from the porcine intestine, is widely distributed in the rat CNS. It is involved in numerous physiological actions, including wake–sleep regulation, reproduction, nociception, cognition, as well as energetic and osmotic homeostasis. In the hypothalamus, GAL is particularly present in the preoptic area, PVN and SON, and the arcuate nucleus/median eminence. GAL mRNA and GAL immunoreactivity have been observed in the

MCNs of the SON and PVN, and are mainly colocalized with AVP, but also to a lesser extent with OT. During dehydration or salt loading, GAL mRNA levels increase in MCNs, while GAL protein immunoreactivity markedly decreases in PVN, SON, and posterior pituitary, with increase of expression of GAL-R1 receptors. In normally hydrated rats, i.c.v. injections of GAL did not affect the hypothalamic and neurohypophysial OT content, but distinctly increased the plasma OT concentration. GAL diminished the hypothalamic AVP content, but had no effect on neurohypophyseal AVP storage. In contrast, GAL administered i.c.v. to rats deprived of water, significantly inhibited AVP and OT release from the HNS, leading to a significant decrease of plasma AVP and OT levels. These results suggest that the modulatory effect of GAL on AVP and OT release is dependent upon the hydration of the animal. GAL acts as an inhibitory neuromodulator of AVP and OT secretion under conditions of dehydration, but stimulates this process in the state of equilibrated water metabolism (Ciosek and Cisowska 2003; Kozoriz et al. 2006; Lang et al. 2007).

Neuropeptide Y: NPY co-exists with AVP or OT in the magnocellular neurons of the PVN and SON. It influences cardiovascular function, feeding, anxiety, depression, epilepsy, neuroprotection, neurogenesis, and the regulation of water homeostasis. Under basal condition, the expression of NPY immunoreactivity is primarily within fibers of the PVN and SON, but a few NPY-immunoreactive cells have also been observed in the MCNs. Subjecting animals to osmotic stressors, either water deprivation or replacing the drinking water with hypertonic saline, significantly increases NPY and Y1R mRNA and protein expression in the PVN and SON. This indicates that the overall effect of increased NPY, with regard to water balance, is similar to that of AVP and OT (Larsen et al. 1993; Urban et al. 2006).

122.5.2.4 Other Substances Involved in Dehydration

Estrogens: Previous reports suggested that the estrogens (Es) influence body fluid balance, but the precise mechanism and site of their action, which allow them to carry out this role, were only recently revealed. The demonstration of ER in neural tissues that bear no direct relation to reproduction led to the hypothesis that the expression of ER in brain nuclei is critical for the maintenance of fluid osmolarity. In the rat brain, ERβ is prominently expressed in the AVP-expressing MCNs of the hypothalamus, whereas ERα is densely expressed in neurons of the sensory circumventricular organ in the basal forebrain. During resting conditions, ERβ is densely expressed on VP-expressing MNCs. During hyperosmolarity challenge, the expression of ERβ is significantly reduced both at the mRNA and protein levels – an effect that reverses when these neurons return to their osmotic set-point. In contrast, increased expression of the ERβ transcript was observed following experimental hyponatremia, a condition in which VP release is strongly inhibited. Thus, in the MCNs, ERβ expression varies inversely with VP release, and consequently, to changes in plasma osmotic pressure. In addition to the proposed roles of ERα in mediating fluid intake through the CVOs, it is also likely to regulate the activity of the magnocellular neurons through a regulation of the output signal sent to MCNs from the forebrain osmoreceptive in the basal lamina terminalis region so as to influence magnocellular neuron ERβ expression (see the review: Sladek and Somponpun 2008).

Orexin: Rodents display increased locomotor exploration when dehydrated as shown in Fig. 122.2, a behavior that improves the likelihood of locating new sources of water while simultaneously placing additional demand on the already compromised water levels. However, the mechanisms underlying this increased exploration are unclear. Recently, Tsunematsu et al. (2008) shed new light on the matter. They found the AVP-induced activation of orexin-expressing neurons might be involved in this response. In this study, AVP and OT directly induced depolarization and an inward current in orexin neurons. AVP-induced activation of orexin neurons was inhibited by a V1a receptor (V1aR) selective antagonist, but was not observed in V1aR knock-out mice. Furthermore, i.c.v.

administration of AVP or water deprivation increased locomotor activity in wild-type mice, but not in transgenic mice lacking orexin neurons and V1aR knock-out mice were less active than wild-type controls. These results suggest that the activation of orexin neurons by AVP has an important role in the regulation of spontaneous locomotor activity in mice, which increases the likelihood of locating water when dehydrated.

Obestatin: Recently, Samson et al. showed that dehydration-induced AVP secretion was inhibited by obestatin in a dose-dependent manner without affecting the plasma OT levels. Central administration of antiobestatin antibodies resulted in an exaggerated basal AVP release and an increased AVP response to overnight water deprivation. Antiserum treatment also resulted in significantly increased *ad libitum* water drinking, as well as drinking in response to dehydration. These data indicate that obestatin may be an important contributor to the maintenance of fluid and electrolyte homeostasis by the regulation of drinking and AVP release (Samson et al. 2007, 2008).

Other proteins: Gouraud et al. used two-dimensional fluorescence difference gel electrophoresis to investigate the dehydration-induced changes of proteomes in SON and pituitary neurointermediate lobe (NIL). Seventy proteins were altered by dehydration including 45 in NIL and 25 in SON. Using matrix-assisted laser desorption/ionization mass spectrometry, some of these proteins was identified. Six proteins in NIL were identified (two upregulated, four downregulated) and nine proteins in the SON (four upregulated, five downregulated). The important of five of these proteins – heat shock protein 1alpha (Hsp1alpha), neuronal axonal membrane protein 22 (NAP22), 58 kDa glucose-regulated protein (GRP58), calretinin, and proprotein convertase subtilisin/kexin type 1 inhibitor (ProSAAS) – has been confirmed using other methods such as semiquantitative western blotting, two-dimensional western blotting, enzyme-linked immunoassay, and immunohistochemistry. Thus, these proteins may also play roles in both regulating and effecting HNS remodeling during dehydration (Gouraud et al. 2007).

Taken together, these studies indicate that the HNS undergoes a dramatic, function-related plasticity during dehydration. In addition to the direct activation by water and/or salt imbalance, the release of AVP and OT are also modulated by many other factors, such as glutamatergic, GABAergic, noradrenergic synapses and AngII, CRH, APL, GAL, NO, obestatin, orexin, and E.

122.5.3 Glial Cells in CVOs and the HNS in Response to Dehydration

122.5.3.1 New Insights into the Function of Glia in the CNS

The brain is composed of two major cell types, neurons and glia. Glial cells are divided into two major classes: microglia, which regulate the inflammatory response of neural tissue to injury or infection, and macroglia, which are composed of ependymal cells, oligodendrocytes, Schwann cells, and astrocytes. Astrocyte, the most numerous glial cell type accounting for one-third of the brain mass, has irregularly shaped cell bodies and is characterized by the expression of glial fibrillary acidic protein (GFAP) and an abundance of leaflet-like processes that maintain contact with blood vessels, neurons, and other glial cell types. Astrocytic processes rarely extend beyond a 50-μm radius, indicating that they exert largely local control. However, the propagation of Ca^{2+} waves through networks of astrocytes may affect the activity of distant neurons integrated into different neuronal circuits (Garcia-Segura and McCarthy 2004).

Though glial cells significantly outnumber neurons, they have been considered to be supportive – the "glue" that provides structural support to neurons – rather than functional. However, recent studies have revealed an important role for glia in homeostatic and neuronal modulatory functions,

including maintenance of the BBB, regulation of water and ion homeostasis and amino acid neurotransmitter metabolism, as well as energy and nutrient supply to neurons.

There is only limited evidence that glial cells contain vesicles and release transmitters in a similar way to neurons. However, it has become clear that these cells are functional components of the CNS, as they express receptors for most neuroactive compounds, including neurotransmitters and hormones, and show excitability based on intracellular Ca^{2+} alterations. Glial cells integrate signals from neurons and other glial cells, including hormonal inputs.

122.5.3.2 Role of Glia in Neuroendocrine Function

Glial cells express many of the same hormone receptors as found on neurons, such as the receptors for melatonin, thyroid, and steroid hormones, AVP, OT, leptin, CRH, and insulin. Hormones are also a critical component of neuronal/glial cross talk, leading to neuromodulatory and neurotrophic actions under physiological and pathological conditions (Newman and Volterra 2004). For a recent review of the participation of glial cells in the regulation of hormonal secretion by hypothalamic neurons, see Garcia-Segura and McCarthy (2004).

122.5.3.3 Role of Glia in the Regulation of Water and Salt Imbalance Induced by Dehydration

Astrocytes are highly complex cells that respond to a variety of external stimuli. The housekeeping role of astrocytes requires that they both sense and respond to many signals, including changes in energy supply, neuronal activity, extracellular ion concentrations, and osmolarity. Maintenance of a stable internal osmotic environment is essential for normal cerebral activity. Recently, an abundance of data has shown that astrocytes play an important role in maintaining tight control of water and ionic homeostasis via sodium-level-sensitive sodium channels (Nax), aquaporin-4 (AQP4) water channels, and taurine in CVOs and/or HNS and pituitary (Hussy et al. 2000; Simard et al. 2004).

Glial Morphological Change in the HNS and Pituitary During Dehydration

Dehydration induces profound alterations in HNS activity, a process known as function-related plasticity. Such plasticity may occur through glial-mediated alteration of neuropeptides/neuromodulators, as discussed before, but also by morphological change in the HNS and pituitary. These morphological changes may be grouped into three distinct varieties (Theodosis et al. 1998; Miyata et al. 2001; Virard et al. 2008).

The first is reversible "glial retraction" in the MCNs, which is thought to be mediated by reorganization of the astrocytic cytoskeleton, astrocytic reorientation, and astrocytes reentering the cell cycle. Under normal conditions, MCN somata are separated from their neighbors by fine astrocytic processes and/or neuropil. Following dehydration, the astrocytic covering of the MCN somata and dendrites is significantly reduced and becomes thin, such that the neuronal surfaces are extensively juxtaposed.

The second is pituicyte stellation. In the posterior pituitary, neurohypophyseal astrocytes (pituicytes) proliferate in response to local factors present during neurosecretory activity. Pituicytes also exhibit dynamic and reversible interactions with axon terminals and blood vessels, suggesting a role in the control of hormone release. In euhydrated conditions, when demand for hormone is low, pituicytes

engulf secretory endings and are interposed between the terminals and the basal lamina. In order to enter the fenestrated capillaries, hormone molecules must pass through the basal lamina into the perivascular space. Pituicyte interposition is thus a barrier to hormone entry into the circulation. During dehydration, pituicyte processes retract, enhancing neurovascular contacts by rearrangement of terminal-astrocyte and terminal-vessel contacts, rather than enlargement or sprouting of magnocellular terminals themselves, allowing increased occupation of the pericapillary basal lamina by nerve terminals and direct access to the perivascular space.

The third is reduction of the GFAP levels. Glial morphology is determined by cytoskeletal elements such as microfilaments, intermediate filaments, and microtubules. GFAP is the major constituent of the astrocytic cytoskeleton and is widely used as functional marker of glial cells. A significant reduction in GFAP-like immunoreactivity is observed in the SON as a result of dehydration, reflecting a possible role in the mediation of changes in cell shape (Hawrylak et al. 1998).

Glia and Nax in CVOs

Sodium is the major ionic component of ECF, and sodium homeostasis is inseparably linked with body fluid control. Thus, the dynamic regulation of Na^+ and water intake is essential to life. When an animal is dehydrated, the Na^+ concentration in body fluids increases, and therefore the plasma osmolarity increases by 5–10%. Although the CVOs are thought to be responsible for body-fluid homeostasis through the osmoreceptors, AngII/AngII receptors or ANP/ANP receptors, the system for sensing Na^+ levels within the brain, remains to be elucidated. Recently, studies have identified a putative Na^+ sensor – the Nax channel – located on glial cells in the CVOs within the brain and distinct from the osmosensor. These channels are able to detect an increase of Na^+ in body fluids and are involved in regulation of water/salt balance.

The Nax channel, formerly called NaG/SCL11 (in rats), Nav2.3 (in mice), and Nav2.1 (in humans), has been classified as a subfamily of voltage-gated sodium channels (Fig. 122.6a). The gene encoding Nax is designated as SCN7A. The primary structure of Nax, however, markedly differs from that of other voltage-gated sodium channel family members even in the key regions for voltage-sensing and inactivation. Noda and his colleagues have elucidated the role of these Nax channels in body fluid balance by generating a transgenic mouse with the *lacZ* reporter gene inserted in the reading frame of the Nax gene, resulting in a null phenotype (*Nax*$^{-/-}$).

lacZ expression in the brains of *Nax*$^{+/-}$ and *Nax*$^{-/-}$ mice was found in specific loci in the CNS, including the CVOs (SFO, OVLT, ME, and NHP) and several other minor nuclei (Fig. 122.6b). In *c*-Fos immunohistochemistry experiments, Fos-LIR-positive cells were not detected in any region of the CVOs of these mice when water was available; however, at 12, 24, and 48 h after water deprivation, there was significant Fos-LIR in the CVOs in both mice. The increase of FOS-LIR was particularly notable in the SFO and OVLT, where approximately twice as many Fos-positive nuclei were observed in *Nax*$^{-/-}$ mice as compared with *Nax*$^{+/+}$ mice. These results suggest that *Nax*$^{-/-}$ mice show increased neural activity in the SFO and OVLT after water deprivation compared with wild-type (*Nax*$^{+/+}$) controls (Watanabe et al. 2000).

Double-immunostaining and immuno-electron microscopic analyses have revealed that Nax are exclusively localized to perineuronal lamellate processes extending from ependymal cells and astrocytes in SFO and OVLT, and no significant immunopositive signals are detected in neuronal cell bodies and their processes, including synapses. Furthermore, in SFO cells from *Nax*$^{+/+}$ mice, all the sodium-sensitive cells are Nax immunopositive, whereas no sodium-sensitive cells were observed in SFO cells derived from *Nax*$^{-/-}$ mice, indicating that sodium-sensing cells in the SFO are almost exclusively glial cells. Further studies with *GAD-GFP* knock-in mice suggest that glial lamellate processes
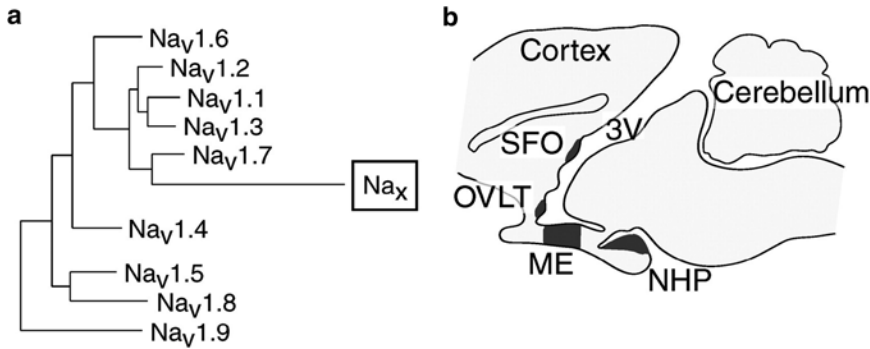
Fig. 122.6 Specialized sodium channel Nax for sodium-level sensing (**a**) phylogenetic tree of mammalian voltage-gated sodium channel subunits; (**b**) expression loci of Nax in the adult CNS. The Nax-positive circumventricular organs (CVOs) in the mid-sagittal section are schematically represented. Of note is that the AP was negative for *lacZ* expression. *AP* area postrema, *SFO* subfornical organ, *OVLT* organum vasculosum laminae terminalis, *ME* median eminence, *NHP* neurohypophysis (Reprinted from Noda (2007). With permission)

expressing Nax channels contact various neurochemical circuitries in the SFO and OVLT, encompassing GABAergic interneurons in the SFO (Watanabe et al. 2006).

Infusion of a hypertonic Na$^+$ solution into the cerebral ventricle caused increased water intake and aversion to saline in wild-type animals, but not in *Nax$^{-/-}$* mice. Importantly, the aversion to salt was not induced by the infusion of a hyperosmotic mannitol solution with a physiological Na$^+$ concentration in the *Nax$^{-/-}$* or *Nax$^{+/+}$* mice. When Nax cDNA was introduced into the brain of the knock-out mice with an adenoviral expression vector, only animals that received a transduction of the Nax gene into the SFO among the CVOs recovered salt-avoiding behavior under dehydrated conditions. These results clearly show that the SFO is the center of the control of salt-intake behavior in the brain, where the Na$^+$-level-sensitive Nax channel is involved in sensing the physiological increase in the Na$^+$ level of body fluids (Watanabe et al. 2000; Hiyama et al. 2002, 2004; Noda and Hiyama 2005; Noda 2007).

The studies discussed before indicate that glia bearing the Nax channel in CVOs, especially SFO, play an important role in the regulation of water/salt balance.

Taurine in HNS (see reviews: Hussy et al. 2000; Albrecht and Schousboe 2005)

Taurine is an abundant sulfur-containing β-amino acid and the second most abundant amino acid in the brain (after glutamate). It is widely distributed in the brain, and is especially concentrated inside cells where the concentration can reach tens of millimoles. The highest levels of taurine are found in cerebral cortex, hippocampus, caudate putamen, cerebellum, and certain hypothalamic structures, including the SON. The cellular localization of taurine is quite heterogeneous. It is found predominantly in cerebellar Purkinje neurons, and in neurons of the cerebral cortex, putamen, and hippocampus, but a prominent localization in glia in the thalamus, hypothalamus, and brain stem nuclei.

Taurine is released by hypoosmotically induced swelling of both neurons and glial cells – in culture, brain slices and in vivo – and it has been proposed as a major factor of volume regulation of brain cells. The taurine release induced by hypoosmotic stimulation is strictly dependent upon cell swelling, and not upon changes in ionic concentration (such as Ca^{2+} and Na$^+$), and is inhibited by Cl$^-$ channel blockers. Taurine release is proportional to the magnitude of the hypotonic stimulation, changes in osmolarity as little as 2.5% significantly enhance the release. Therefore, taurine is an

amino acid involved in cell volume regulation and is one of the major inorganic osmolytes used by cells to compensate for changes in extracellular osmolarity.

In the HNS, taurine is found prominently in glial cell bodies in the ventral glial lamina, as well as in the glial processes that surround the MCNs. In the posterior pituitary, which contains the axon terminals of SON and PVN MCNs, taurine is found essentially in the pituicytes – the specialized glial cells in the neurohypophysis that engulf the axonal processes and terminals. This highly specialized localization of taurine in the hypothalamo-neurohypophysial system raises the question of the specific role of this organic compound in neuroendocrine function. Because the movements of taurine in and out of the cells depend so closely on the osmotic pressure of the ECF, conceivably it could be implicated in the osmoregulation of the activity of SON neurons, thus participating in the regulation of whole body water balance.

In the SON, taurine is highly concentrated in astrocytes and released in an osmodependent manner through volume-sensitive anion channels. As taurine is an agonist of neuronal glycine receptors, it is likely to contribute to the inhibition of neuronal activity induced by hypotonic stimuli. This inhibitory influence would complement the intrinsic osmosensitivity of SON neurons, mediated by excitatory mechanoreceptors activated under hypertonic conditions; under isoosmotic conditions, the excitability of SON neurons would be partly determined by integration of the basal activity of two opposite systems: on one hand excitatory neuronal mechanoreceptors are responsible for a depolarizing cationic conductance, and on the other hand, neuronal glycine receptors are activated by taurine released from glial cells, inducing a sustained hyperpolarizing anionic current. Hyperosmotic stimuli reinforce mechanoreceptor activity and inhibit taurine release; hypoosmotic stimuli shut the mechanoreceptor channels and greatly enhance the release of taurine, resulting in activation of glycine receptors. These two complementary processes make this structure much more sensitive to the prevailing osmolarity, which is especially important to detect small alterations of salt concentration in the ECF.

The inhibitory influence of glial taurine on neuroendocrine SON neurons may not be limited to the neuronal soma and dendrites, as a similar mechanism may also be present in the neurohypophysis, where the axons of MCNs end. Indeed, preliminary results indicate the presence of glycine receptors on nerve terminals in the neurohypophysis. This could indicate additional osmotic control of AVP and OT release at the level of MCN terminals. This mechanism may also contribute to osmodetection in other hypothalamic osmosensitive structures, such as OVLT, SFO, and MnPO, because neurons in these regions also express cationic stretch-inactivated mechanoreceptor channels and are activated by glycine and/or taurine through strychnine-sensitive glycine receptors.

These recent results imply that the role of taurine is not limited to regulation of cell volume, but that is also important for whole-body fluid balance, which is achieved by its modulation of neuronal activity. The influence of glial on neurosecretion in response to changes in plasma osmolarity may complement the effects of central and peripheral osmoreceptors, resulting in osmoregulation.

Aquaporin-4 in the CVOs and HNS

AQP4 is a water-selective transporter originally cloned from lung tissue that is also expressed strongly in the brain. In situ hybridization and immunoperoxidase staining studies in adult rat brain revealed AQP4 expression in cells lining the ventricular system, the pial surface, SON, PVN, SFO, AP, median eminence, hippocampus, spinal cord, and cerebellum. Furthermore, in all these locations, the distribution of AQP4 is non-neuronal, being restricted to astrocytes or ependymal cells. Postembedding immunogold labeling for AQP4 in glial cells reveals a heterogeneous, subcellular localization, with the protein being particularly abundant in membranes of perivascular processes, suggesting a polarized expression. However, a nonpolarized distribution of AQP4 was shown in

astrocytes of the CVOs and HNS, where AQP4 is present in the plasma membranes facing both capillaries and magnocellular neurons.

Recently, analysis of transgenic mice lacking AQP4 has provided compelling evidence for the involvement of AQP4 in cerebral water balance, astrocyte migration, and neural signal transduction. In particular, AQP4-null mice have reduced brain swelling and improved neurological outcome in models of cytotoxic cerebral edema, including water intoxication, focal cerebral ischemia, and bacterial meningitis. However, in models of vasogenic (fluid leak) edema, including cortical freeze-injury, brain tumor, brain abscess, and hydrocephalus these mice experienced worse brain swelling and clinical outcome. Most importantly, the specificity and intensity of AQP4 staining within the CVOs and HNS strongly suggest that water channels allow variations of plasma osmotic pressure to be transferred from blood to osmosensitive neurons, though it is unclear whether AQP4-bearing glial lamellae act as transducers in the osmosensory response across the plasma membrane (Nielsen et al. 1997; Wells 1998; Tait et al. 2008).

In summary, glial cells regulate neuroendocrine and hormonal signaling in the HNS, contributing to the regulation of body fluid balance. the precise mechanisms that allow them to carry out this role are still poorly understood, but the striking morphological alteration observed in the SON and PVN glia, as well as pituicytes, during dehydration suggest that Nax, taurine, AQP4 all have an important role in the regulation of body fluid homeostasis (Fig. 122.7). There may, of course, be other unidentified factors.
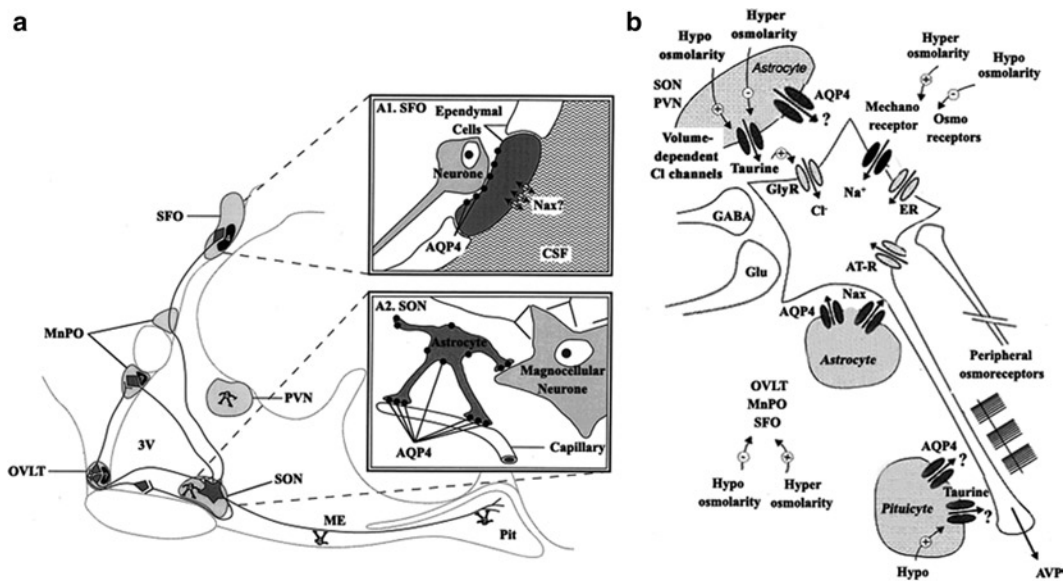
Fig. 122.7 Interaction between glia and neuron in circumventricular organs (CVOs) and hypothalamo-neurohypophyseal system (HNS) following dehydration. OT and AVP from HNS are released after receiving signals from osmoreceptor or mechanoreceptor in CVOs and HNS. This process is also modulated by other neuropeptides through receptors such as ER and AT-R. Astrocytes may also play an important role in the regulation of body fluid balance through Nax, AQP4, and taurine-related mechanisms. (**a**) Schematic representation of the interaction between AQP4-positive cells and the neuronal elements of the "osmoreceptor complex." Inset A1 shows the location of AQP4 in the basolateral membrane of a subpopulation of ependymal cells in the SFO. Inset A2 shows the expression of AQP4 in astrocyte membranes in the SON (Reprinted from Wells (1998). With permission) (**b**) A model showing the interaction of glia and neurons in CVOs and HNS through Nax channel, AQP-4 channel and secretion of taurine during dehydration. *SFO* subfornical organ, *MnPO* median preoptic nucleus, *OVLT* organum vasculosum of the lamina terminalis, *PVN* paraventricular nucleus (magnocellular), *SON* supraoptic nucleus, *ME* median eminence, *Pit* pituitary, *3V* third ventricle, *CSF* cerebrospinal fluid (Reprinted from Hussy et al. (2000). With permission)

122.5.4 Gene/Transcriptor Changes Involved in the Modulation of the HNS During Dehydration

HNS, as an important integrative system, plays an important role in mediating neuroendocrine responses to dehydration through the axonal projections from SON and PVN MCNs to the posterior pituitary. These responses are accompanied by function-related plasticity and remodeling of the HNS, including a wealth of activity-dependent changes in cell morphology, electrical properties, biosynthetic, and secretory activity which ultimately facilitates hormone production and delivery and, hence, the survival of the organism. This plasticity appears to be governed by a complex and dynamic interplay between the intrinsic properties of the MCNs, interactions between MCN neurons, interactions with glia, and the influence of extrinsic synaptic inputs. Although the molecular mechanisms of these processes are not well understood, the levels of many genes/transcriptors change during dehydration.

da Silveira et al. examined the time-course of changes in c-Fos, AVP, and OT mRNA in rat PVN and SON following acute and chronic water deprivation (6, 24, 48, and 72 h, nondehydrated as control). Besides the hematocrit, osmolarity, plasma sodium, and weight loss were increased after water deprivation, as expected, a significant increase in both AVP and OT mRNA expression was observed 6 h after dehydration, reaching a peak at 24 h and returning to basal levels at 72 h in the SON; in contrast, in the PVN, AVP and OT mRNA upregulation occurred 24 h after dehydration, but levels had decreased 72 h after dehydration (though were still higher than control animals). Additionally, c-Fos mRNA expression in both the PVN and SON was increased 6 h after water deprivation, though it progressively decreased at 24, 48, and 72 h after dehydration (da Silveira et al. 2007). These results suggest that dehydration increases not only the release of OT and AVP from MCNs, but also increases OT- and AVP-mRNA expression.

A recent microarray study identified genes and transcripts that were upregulated or downregulated in the SON, PVN, and the NIL of the pituitary gland after water deprivation. In one experiment, 459 differentially expressed transcripts were identified and many of them were novel expressed sequence tags (ESTs). In situ hybridization (ISH) revealed that four transcripts (three of which are novel: d255, d873, d1011) were significantly upregulated or downregulated in the SON after dehydration. In another experiment, downregulation of 10 and upregulation of 28 transcription factor transcripts was observed. Five of the upregulated mRNAs, namely gonadotropin inducible ovarian transcription factor 1 (Giot1), Giot2, cAMP-responsive element-binding protein 3-like 1, CCAAT/enhancer-binding protein, and activating transcription factor 4 were also probed by in situ hybridization, which revealed a significant increase in their expression in SON and PVN MCNs after 3 days of water deprivation and, in some cases, upregulation in parvocellular PVN neurons as well (Sharman et al. 2004; Ghorbel et al. 2006; Hindmarch et al. 2006).

Some of the genes/transcripts identified in these studies (Table 122.2) may be novel effectors or regulators of HNS neuronal plasticity and physiological remodeling during dehydration, although the exact roles of these novel genes within this network remain to be determined.

In summary, a complicated network in CNS is activated to keep the balance of body fluids during dehydration as described in Table 122.3, providing a normal external and internal condition for body cells to maintain survival.

122.6 Applications

Body fluid imbalances are among the most commonly encountered problems in clinical medicine. This is in large part because many different disease states can disrupt the finely balanced mechanisms that control intake and output of water and solutes. Because body water is the primary determinant of

Table 122.2 Novel genes involved in dehydration (Reprinted from Ghorbel et al. (2006). With permission)

Clone ID	Fold change	Name
d230	3.696	NOVEL-CA865433. Mm Chromosome 3
d255	3.401	NOVEL-CA865428. Mm Chromosome 2
d1011	2.808	NOVEL-CA865430. Mm Chromosome 6
d69	2.705	NOVEL-CA865429. Mm Chromosome 19
d899	2.691	NOVEL-CA865431. Mm Chromosome 14
d873	2.544	NOVEL-CA865432. Mm Chromosome X
c307	0.315	NOVEL-CA865422, BM929104. Rn Chromosome 3
c547	0.278	NOVEL-CA865421
c376	0.273	NOVEL-BM929107. Mm Chromosome 10
c357	0.254	NOVEL-CA865418
c324	0.246	NOVEL-BM929105. Mm Chromosome 3
c493	0.241	NOVEL-CA865420
c325	0.184	NOVEL-CA865419, BM929106. Mm Chromosome 3
c195	0.128	NOVEL-CA865415

Some novel genes identified in HNS during dehydration are listed, although their role in dehydration is yet unknown. Other upregulated or downregulated known genes occurred during dehydration are unlisted

Table 122.3 Brain response to dehydration

Nuclei/regions/circuits

CVOs: SFO, OVLT, MnPO, AP, sensing changes of osmolarity through osmolarity receptors

NTS: Relaying peripheral signals to thirst center

HNS: Modulating neuroendocrine or behavior response through releasing AVP and OT

LPB, BNST, LSV, and amygdala: Modulating the afferent or efferent signals to or from HNS

Neuroendocrine

AVP and OT are released into circulation to regulate water balance directly, many other neuropeptide/neurotransmitters including glutamate, GABA, NE, NO, angiotension II, CRF, apelin, galanin, orexin, Es, and obestatin, act as modulators in this process

Glia

Glia involved in dehydration through interaction with neurons by Nax channel, APQ4 channel and secretion of taurine in CVOs and HNS

Genes

During dehydration, some novel genes are identified as listed in Table 122.2; other known genes are upregulated or downregulated, indicating alteration and modulation in gene level are involved in dehydration

Brain responses to dehydration are summarized in this table, including involved central nuclei, neuroendocrine responses, gene, and glia

the osmolarity of ECF, disorders of body water homeostasis can be divided into hypoosmolar disorders, in which there is an excess of body water relative to body solute, and hyperosmolar disorders, in which there is a deficiency of body water relative to body solute. Hyperosmolarity is encountered in the clinic due to hemorrhage, hypotension, and diabetes insipidus but may also be encountered due to other "natural" circumstances, such as excessive heat (e.g., in desert environments) or a lack of access to water due to trappage (e.g., after a natural disaster). Serious dehydration without intervention is deleterious to individual health and can threaten survival. Dehydration induced by water restriction/deprivation, or injection of hypertonic sodium solution, has been widely used to explore the mechanisms that regulate water/salt balance in laboratory animals. If better, novel therapies are to be developed (and the correct existing therapies to be employed), it is crucial to better understand the neural circuitry and endocrine responses that regulate water/salt imbalance.

Summary Points

1. Water restriction induces loss of ICF and ECF, leading to imbalance of water and salt, which increases thirst and salt appetite. Behavioral changes accompany these motivational changes, such as water seeking and intake and ingestion of salt content food/fluid increases. Together, these responses work to recover fluid balance.
2. The main response nuclei and neurocircuits activated by dehydration are present in the CVOs and nucleus tractus solitarius (NTS; the sensors), SON and PVN (the effectors), and PVN and LPB (the information integrators).
3. Oxytocin and AVP from neurons in the SON and PVN are released into the general circulation to regulate water retention and natriuresis through peripheral mechanisms. This process is modulated by many other neuropeptide/neurotransmitters such as glutamate, GABA, NE, NO, angiotension II, CRH, apelin, galanin, orexin, Es, and obestatin.
4. In addition to some known genes including OT and AVP mRNA upregulated or downregulated, other novel genes and transcripts are identified during water deprivation. These may be involved in the functional plasticity and remolding of the neural circuits responsible for body fluid homeostasis.
5. Glia may play an important role in water and salt balance via modulation of Nax channels, AQP4 water channels, and secretion of taurine in CVOs and/or HNS.

Definition of Key Terms

CVOs: Are specialized brain structures proximal to the ventricles of the brain including SFO, OVLT, ME, NHP, and AP. They are thought to be the organs that sense various kinds of circulating information including Na^+ concentrations and osmotic pressure in the body fluid.

HNS: Is known as the integrative structure playing an important role in mediating neuroendocrine responses during stress challenge.

Osmoreceptor complex: Consists of both neurons and glias in CVOs and HNS sensitive to osmolality.

HNS remodeling: Refers to a series of changes including morphological, electrical, protein expression, and transcriptional alterations in neurons or glial cells in HNS during stress challenge.

Nax channel: Classified as a subfamily of voltage-gated sodium channels, is expressed in perineuronal processes of astrocytes and ependymal cells which envelope particular neural populations in the CVOs. They are considered to be sodium-level sensor involved in water/salt intake regulation in the brain.

Taurine: Is the second most abundant amino acid in the brain. It is widely distributed in the CNS and is most concentrated in glia. It has multiple functions in the brain, e.g., as a trophic factor, an osmolyte, a neuromodulator, and an inhibitory neurotransmitter.

AQP4: Originally cloned from lung tissue, is one of the aquaporin water channel family. It is expressed strongly in astrocytes throughout the CNS, particularly in the ventricular system, hypothalamus, and cerebellum. It plays an important role in the normal and pathological brain, including regulation of cerebral water balance, astrocyte migration, and neural signal transduction.

References

Albrecht J, Schousboe A. Neurochem Res. 2005;30:1615–21.

Antunes-Rodrigues J, de Castro M, Elias LL, Valenca MM, McCann SM. Physiol Rev. 2004;84:169–208.

Arima H, Aguilera G. J Neuroendocrinol.2000;12:833–42.

Arnhold MM, Wotus C, Engeland WC. Exp Neurol. 2007;206:126–36.

Bourque CW, Oliet SH. Annu Rev Physiol. 1997;59:601–19.

Bundzikova J, Pirnik Z, Zelena D, Mikkelsen JD, Kiss A. Cell Mol Neurobiol. 2008;28:1033–47.

Chae HE, Heideman PD. Brain Res. 1998;791:1–10.

Ciosek J, Cisowska A. J Physiol Pharmacol. 2003;54:625–41.

da Silveira LT, Junta CM, Monesi N, de Oliveira-Pelegrin GR, Passos GA, Rocha MJ. Cell Mol Neurobiol. 2007;27:575–84.

Di S, Tasker JG. Endocrinology 2004;145:5141–9.

Garcia-Segura LM, McCarthy MM. Endocrinology 2004;145:1082–6.

Ghorbel MT, Sharman G, Hindmarch C, Becker KG, Barrett T, Murphy D. Physiol Genomics. 2006;24:163–72.

Gillard ER, Coburn CG, de Leon A, Snissarenko EP, Bauce LG, Pittman QJ, Hou B, Currás-Collazo MC. Endocrinology 2007;148:479–89.

Goldin AL, Barchi RL, Caldwell JH, Hofmann F, Howe JR, Hunter JC, Kallen RG, Mandel G, Meisler MH, Netter YB, Noda M, Tamkun MM, Waxman SG, Wood JN, Catterall WA. Neuron 2000;28:365–8.

Gouraud SS, Heesom K, Yao ST, Qiu J, Paton JF, Murphy D. Endocrinology 2007;148:3041–52.

Hawrylak N, Fleming JC, Salm AK. Glia 1998;22:260–71.

Herman JP, Figueiredo H, Mueller NK, Ulrich-Lai Y, Ostrander MM, Choi DC, Cullinan WE. Front Neuroendocrin 2003;24:151–80.

Hindmarch C, Yao S, Beighton G, Paton J, Murphy D. Proc Natl Acad Sci U S A. 2006;103:1609–14.

Hindmarch C, Fry M, Yao ST, Smith PM, Murphy D, Ferguson AV. Am J Physiol Regul Integr Comp Physiol. 2008;295:R1914–20.

Hiyama TY, Watanabe E, Ono K, Inenaga K, Tamkun MM, Yoshida S, Noda M. Nat Neurosci. 2002;5:511–2.

Hiyama TY, Watanabe E, Okado H, Noda M. J Neurosci. 2004;24:9276–81.

Honda K, Negoro H, Dyball RE, Higuchi T, Takano S. J Physiol. 1990;431:225–41.

Hussy N, Deleuze C, Desarménien MG, Moos FC. Prog Neurobiol. 2000;62:113–34.

Johnson AK, Thunhorst RL. Front Neuroendocrin. 1997;18:292–353.

Kadekaro M. Braz J Med Biol Res. 2004;37:441–50.

Kadekaro M, Su G, Chu R, Lei Y, Li J, Fang L. Neurosci Lett. 2006;404:50–5.

Kozoriz MG, Kuzmiski JB, Hirasawa M, Pittman QJ. J Neurophysiol. 2006;96:154–64.

Lang R, Gundlach AL, Kofler B. Pharmacol Ther. 2007;115:177–207.

Larsen PJ, Mikkelsen JD, Jessop DS, Lightman SL, Chowdrey HS. J Neurosci. 1993;13:1138–47.

Lauand F, Ruginsk SG, Rodrigues HLP, Reis WL, De Castro M, Elias LLK, Antunes-Rodrigues J. Neuroscience 2007;147:247–57.

Llorens-Cortes C, Moos F. Prog Brain Res. 2008;170:559–70.

McKinley MJ, Hards DK, Oldfield BJ. Brain Res. 1994;653:305–14.

Miyata S, Takamatsu H, Maekawa S, Matsumoto N, Watanabe K, Kiyohara T, Hatton GI. J Comp Neurol. 2001;434:413–27.

Morien A, Garrard L, Rowland NE. Brain Res. 1999;816:1–7.

Murugaiyan P, Salm AK. Glia 1995;15:65–76.

Newman EA, Volterra A. Glia 2004;47:207–8.

Nielsen S, Nagelhus EA, Amirty-Moghaddam M, Bourque C, Agre P, Ottersen OP. J Neurosci. 1997;17:171–80.

Noda M. Exp Physiol. 2007;92:513–22.

Noda M, Hiyama TY. Chem Senses. 2005;30:i44–5.

Pacak K, Palkovits M. Endocr Rev. 2001;22:502–48.

Rawland NE. Neurosci Biobehav Rev. 1998;23:49–63.

Reaux A, De Mota N, Skultetyova I, Lenkei Z, El Messari S, Gallatz K, Corvol P, Palkovits M, Llorens-Corte's C. J Neurochem. 2001;77:1085–96.

Reaux-Le Goazigo A, Morinville A, Burlet A, Llorens-Corte's C, Beaudet A. Endocrinology. 2004;145:4392–400.

Samson WK, White MM, Price CP, Ferguson AV. Am J Physiol. 2007;292:R637–43.

Samson WK, Yosten GL, Chang JK, Ferguson AV, White MM. J Endocrinol. 2008;196:559–64.

Sharman G, Ghorbel M, Leroux M, Beaucourt S, Wong LF, Murphy D. Prog Biophys Mol Biol. 2004;84:151–82.

Simard M, Nedergaard M. Neuroscience 2004;129:877–96.

Sladek CD, Somponpun SJ. Front Neuroendocrin. 2008;29:114–27.

Tait MJ, Saadoun S, Bell BA, Papadopoulos MC. Trends Neurosci. 2008;31:37–43.

Theodosis DT, El Majdoubi M, Pierre K, Poulain DA. Cell Mol Neurobiol. 1998;18:285–98.

Tsunematsu T, Fu LY, Yamanaka A, Ichiki K, Tanoue A, Sakurai T, van den Pol AN. J Neurosci. 2008;28:228–38.

Ueta Y, Yamashita H, Kawata M, Koizumi K. Brain Res. 1995;677:221–8.

Urban JH, Leitermann RJ, DeJoseph MR, Somponpun SJ, Wolak ML, Sladek CD. Endocrinology 2006;147: 4122–31.

Van de Kar LD, Blair ML. Front Neuroendocrin. 1999;20:1–48.

Virard I, Gubkina O, Alfonsi F, Durbec P. Neuroscience 2008;151:82–91.

Watanabe E, Fujikawa A, Matsunaga H, Yasoshima Y, Sako N, Yamamoto T, Saegusa C, Noda M. J Neurosci. 2000;20:7743–51.

Watanabe E, Hiyama TY, Shimizu H, Kodama R, Hayashi N, Miyata S, Yanagawa Y, Obata K, Noda M. Am J Physiol Regul Integr Comp Physiol. 2006;290:R568–76.

Watts AG. Annu Rev Neurosci. 2001;24:357–84.

Wells T. Mol Cell Endocrinol. 1998;136:103–7.

Xiong JJ, Hatton GI. Brain Res. 1996;719:143–53.

Zhang Z, Bourque CW. Nat Neurosci. 2003;6:1021–2.

Zhu ZH, Wang BR, Tan QR, Duan XL, Kuang F, Xu Z, Ju G. Neurosci Bull. 2006;22:144–50.

Chapter 123
Feminine Norms and Disordered Eating

Melinda A. Green, David Kugler, Ashley Stillman, Christopher Davids,
Katherine Read, Kelly Siglin, and Amanda Jepson

Abbreviations

CFNI   Conformity to feminine norms inventory
ED   Eating disorder
MMPI   Minnesota multiphasic personality inventory
PAQ   Personal attribute questionnaire
BSRI   Bem sex-role inventory
GRAS   Groninger androgyny scale
DEBQ   Dutch eating behavior questionnaire
FIDS   Feminist identity development scale
EDI   Eating disorder inventory
PDQ   Personal description questionnaire
EDE-Q   Eating disorder examination-questionnaire
EAT   Eating attitudes test

123.1 Introduction

The etiology of eating disorders (EDs) is characterized by a complex interplay of psychological, biological, and sociocultural factors. Significantly higher prevalence rates of ED diagnoses among women have led researchers to consider the relationship between sociocultural feminine norms and disordered eating behaviors. Hyperfemininity is a gender-related construct frequently linked to heightened ED risk (see Paxton and Sculthorpe 1991). Hyperfemininity is a psychological state characterized by an extreme endorsement of traditional sociocultural feminine norms (Boskind-Lodahl 1976). The purpose of this chapter is to explore the relationship between hyperfemininity and ED symptomatology.

M.A. Green (✉)
Department of Psychology, Cornell College, 106E Law Hall,
600 First Street West, Mt. Vernon, IA 52314
e-mail: mgreen@cornellcollege.edu

123.2 Femininity Theory of EDs

The *femininity theory of EDs* suggests disordered eating results from an oversubscription to traditional feminine gender norms. Traditional feminine norms include fragility, passivity, submissiveness, dependence, approval seeking, and an intense focus on appearance characterized by the relentless pursuit of extreme thinness (Boskind-Lodahl 1976). Femininity theory conceptualizes EDs as maladaptive attempts to achieve social approval and acceptance via conformity to feminine norms. The theory proposes hyperfeminine women are at an increased risk for EDs because they are overly reliant upon sociocultural feminine norms in self-definition and personal evaluations of self-worth. As a result, hyperfeminine women overemphasize appearance, weight, shape, passivity, and dependence in personal judgments of self-worth in the same way the surrounding culture overemphasizes these characteristics in appraisals of feminine worth. According to femininity theory, the tendency to internalize such cultural values places hyperfeminine women at-risk for EDs. Figure 123.1 outlines the main tenets of femininity theory.

A significant body of research supports femininity theory. Table 123.1 provides an overview of the methodologies and findings of the relevant research. Hatsukami and colleagues (1982) surveyed masculine and feminine characteristics via the Masculinity-Femininity Scale (Scale 5) of the Minnesota Multiphasic Personality Inventory (MMPI: Hathaway and McKinley 1942) among 52 bulimic females and 120 female polysubstance abusers. Results indicate bulimic participants were significantly more likely to endorse feminine characteristics. Similarly, Norman and Herzog (1983) report restricting anorexics, normal-weight bulimics, and bulimic anorexics display hyperfeminine MMPI profiles. Williamson and colleagues (1985) indicate bulimic participants endorse the highest amount of feminine behavior on the MF Scale, obese participants an intermediate amount, and normal

Boskind-Lodahl's (1976) Femininity Theory of Eating Disorders
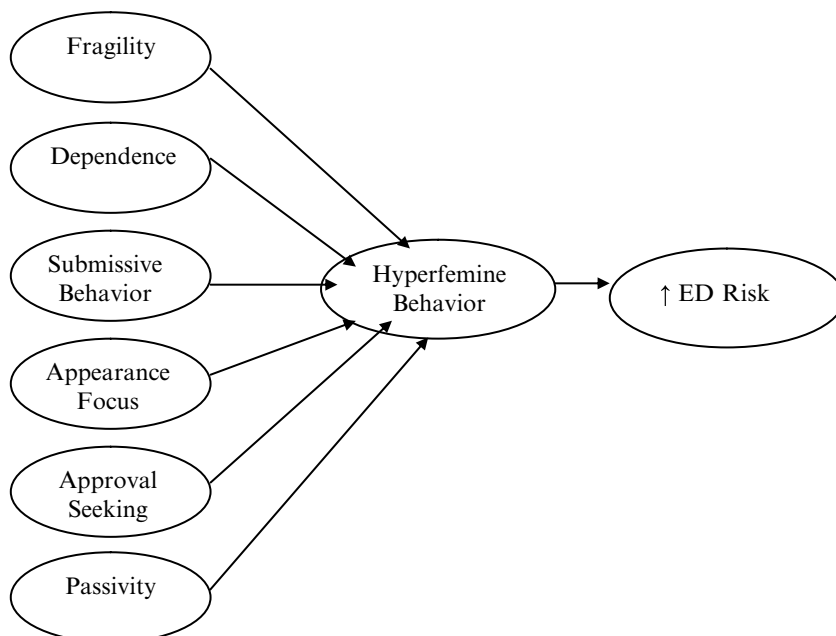
Fig. 123.1 Boskind-Lodahl's (1976) Femininity Theory of Eating Disorders

Table 123.1 Femininity and eating disorders: summary of research results

Study	Population	Measures	Results
Hatsukami et al. (1982)	51 bulimic women 120 polysubstance Abusing women	MMPI masculinity–femininity subscale	Bulimics higher femininity
Norman and Herzog (1983)	39 outpatient ED Females	MMPI Masculinity-Femininity subscale	ED patients high femininity
Williamson et al. (1985)	45 college women 15 obese 15 bulimic 15 control	MMPI masculinity-femininity subscale	Bulimics highest femininity
Squires and Kagan (1985)	162 college women	Femininity: Personal attributes questionnaire ED symptoms: DIET scale	Restrained eaters increased femininity
Heilbrun and Mulqueen (1987)	174 college women Androgynous Feminine Masculine	Femininity: sex role questionnaire ED symptoms: Eating disorder inventory	Feminine group increased ED symptoms
Pettinate (1987)	37 inpatient ED Females 12 inpatient depressed females 34 high school and college women	Femininity: Bem sex role inventory	Higher femininity scores in ED inpatients
Van Strien (1988)	540 women	Femininity: Groginger Androgyny scale ED symptoms: Dutch eating behavior scale	Higher femininity scores linked to overeating
Brown et al. (1990)	340 college women	Femininity: Attitudes toward women scale ED symptoms: BULIT Bulimia test	Higher femininity predicts ED behaviors

ED eating disorders, *MMPI* Minnesota multiphasic personality inventory

controls the lowest amount. Orleans and Barnett (1984) report a significant positive correlation between feminine behaviors as assessed by the Masculinity-Femininity Scale and ED symptomatology.

The relationship between hyperfemininity and heightened ED symptoms has been established via other instruments as well. Squires and Kagan (1985) found restrictive dieters, as indicated by the DIET scale (Kagan and Squires 1984), endorse high levels of feminine traits on the Personal Attributes Questionnaire (PAQ; Spence et al. 1974). Heilbrun and Mulqueen (1987) assessed anorexic and bulimic symptomatology according to the Eating Disorder Inventory (EDI; Garner et al. 1983) among androgynous, feminine, and masculine women. Findings indicate the highest level of ED symptomatology among feminine women. Similarly, Pettinati and colleagues (1987) found ED patients scored significantly higher on the femininity scale of the Bem Sex-Role Inventory (BSRI; Bem 1974) compared with depressed patients or normal high school and college student controls. Van Strien and Bergers (1988) also report a direct correlation between femininity as assessed by the Groninger Androgyny Scale (GRAS; De Graaf 1984) and emotional and external eating as measured by the Dutch Eating Behavior Questionnaire (DEBQ; Van Strien et al. 1986).

More recent findings indicate additional support for an association between femininity and EDs. Synder and Hasbrouck (1996) report women who demonstrate high conformity to traditional feminine norms, as indicated by high scores on Stage 1 of the Feminist Identity Development Scale

(FIDS; Bargad and Hyde 1991), are more likely to endorse body dissatisfaction and drive for thinness on the EDI (Garner et al. 1983). Similarly, meta-analytic results of 22 studies indicate a small, statistically significant relationship between hyperfeminine characteristics and ED symptomatology (Murnen and Smolak 1997). The small effect size indicates that many other biological, psychological, and sociocultural contributors are important factors in the onset and maintenance of disordered eating, but hyperfemininity does play a role.

123.3 Hyperfeminine Subtypes

Despite a robust research literature linking hyperfemininity to heightened ED symptomatology, it is unlikely all aspects of femininity are equally predictive of ED risk status. Therefore, it is important to investigate the relationship between hyperfeminine subtypes and ED symptoms. Endorsement of some feminine norms may predict heightened ED status, while other norms may show a minimal or inverse relationship to ED symptomatology. This possibility is highlighted by discrepant research findings which either (1) fail to indicate a relationship between hyperfemininity and increased ED symptomatology (e.g., Srikameswaran et al. 1984; Timko et al. 1987; Brown et al. 1990) or (2) indicate an inverse relationship (Lewis and Johnson 1985). An examination of the relationship between ED behaviors and feminine subtypes is needed in order to more fully understand how this relationship may vary as a function of norm subtype. This association has been investigated in many studies.

Paxton and Schulthorpe (1991) used the Personal Description Questionnaire (PDQ; Antill et al. 1981) to divide gender-related norms into subtypes to investigate the relationship between feminine subtypes and ED symptoms. The PDQ contains four 10-item subscales indicative of positive feminine, negative feminine, positive masculine, and negative masculine characteristics. The authors used Pearson product-moment correlation coefficients to examine the relationship between gender subtypes, as assessed by the PDQ, and ED symptomatology as assessed by the Eating Attitudes Test (EAT; Garner and Garfinkel 1979) and the Drive for Thinness, Body Dissatisfied, and Bulimia subscales of the EDI (Garner et al. 1983).

Results indicate small, statistically significant positive correlations between feminine negative characteristics and the EAT, Drive for Thinness, and Bulimia subscales (Paxton and Schulthorpe 1991). Negative feminine characteristics, as defined by the PDQ, include a predisposition to be approval seeking, worrying, nervous, timid, dependent, shy, weak, bashful, anxious, and self-critical. More recent studies have made additional efforts to identify which particular feminine norms predispose to heightened ED risk.

Mahalik and colleagues (2005) developed the Conformity to Feminine Norms Inventory (CFNI; Mahalik et al. 2005) to provide a multidimensional assessment of femininity and subsequently used the inventory to examine the relationship between conformity to feminine norms and EDs. The CFNI is an 84-item self-report instrument designed to assess attitudes, thoughts, and behaviors which reflect conformity to, and nonconformity to, eight traditional feminine norms. Norms assessed by the CFNI include niceness in relationships, involvement with children, thinness, sexual fidelity, modesty, involvement in romantic relationships, domestic behaviors, and investment in appearance. Participants respond to questions on a four-point Likert scale ranging from "strongly disagree" to "strongly agree." Higher scores indicate higher conformity to the gender norm assessed by the relevant subscale (Mahalik et al. 2005).

Mahalik and colleagues (2005) evaluated the relationship between feminine characteristics as assessed by the CFNI and ED symptoms as assessed by the EDI-2 (Garner 1991). A series of 72 Pearson product-moment correlation coefficients were calculated to evaluate relationships between

the seven EDI-2 subscales, the EDI total score, the eight CFNI subscales, and the CFNI total score. Results indicate statistically significant positive correlations between several EDI-2 subscales and the Thinness, Modesty, Romantic Relationship, and Invest in Appearance subscales of the CFNI (see Mahalik et al. 2005 for a comprehensive overview). Results further indicate statistically significant inverse relationships between the Ineffectiveness and Interpersonal Distrust subscales of the EDI-2 and the Nice in Relationships and Care for Children subscales of the CFNI. Results imply that thinness, modesty, appearance focus, and investment in romantic relationships are feminine norms which serve as sociocultural risk factors for EDs, while niceness in interpersonal relationships and caring for children are protective factors.

Mahalik and colleagues (2005) advanced understanding of the subtypes of feminine traits associated with ED risks. However, the calculation of 72 correlation coefficients as the sole analysis strategy is problematic for several reasons. First, there is an increased likelihood of Type I error because multiple analyses were conducted without a Bonferroni adjustment. Second, the analysis strategy did not account for overlapping variance between CFNI subscales. Green and colleagues (2008) attempted replication with a statistical analysis plan which controlled for overlapping variance and inflated Type I error. Table 123.2 provides an overview of statistically significant findings from both studies.

Table 123.2 Relationship between CFNI Feminine norm subtypes and ED behaviors

Study	Population	Norm subtype	Results
Mahalik et al. (2005)	328 women	Nice in relationships	Inverse relationship
			EDI ineffectiveness
			EDI inter distrust
		Thinness	Direct relationship
			EDI total
			All EDI subscales
		Modesty	Direct relationship
			EDI total
			EDI ineffectiveness
			EDI inter distrust
			EDI inter awareness
		Care for children	Inverse relationship
			EDI total
			EDI ineffectiveness
			EDI inter distrust
		Be in romantic relationship	Direct relationship
			EDI total
			EDI ineffectiveness
			EDI inter awareness
			EDI body diss.
			EDI bulimia
			EDI drive thinness
		Invest in appearance	Direct relationship
			EDI total
			EDI inter awareness
			EDI body diss.
			EDI bulimia
			*EDI Drive Thinness
Green et al. (2008)	86 college women	Thinness	Direct relationship
			EDE-Q global

EDI eating disorders inventory, *EDI inter distrust* EDI interpersonal distrust subscale, *EDI inter awareness* EDI interpersonal distrust subscale, *EDI body diss.* EDI body dissatisfaction subscale, *EDE-Q global* eating disorder examination-questionnaire global scale, *CFNI* conformity to feminine norms inventory

Green and colleagues (2008) assessed feminine characteristics via the CFNI and ED symptomatology via the Eating Disorder Examination-Questionnaire (EDE-Q; Fairburn and Beglin 1994). A multiple regression analysis was performed to evaluate the eight CFNI subscales as predictors of EDE-Q global scores. Partial regression coefficients indicate the Thinness CFNI subscale was the only statistically significant predictor of ED symptoms. Results suggest conformity to a feminine norm which equates thinness with ideal feminine appearance represents a significant risk factor for body dissatisfaction and disordered eating behaviors. To more fully understand this risk factor, it is important to gain insight into the impact of the thin-ideal. It is critical to examine how this sociocultural norm for feminine appearance exerts its impact on the eating behavior and body satisfaction of girls and women.

123.4 Impact of the Thin-Ideal

Western cultures pervasively promote and habitually reinforce thinness in girls and women (Garner et al. 1980; Morris et al. 1989; Wiseman et al. 1992). This sociocultural predilection is readily apparent across multiple contexts (Rodin et al. 1984). The feminine thin-ideal is especially prevalent in Western media (Silverstein et al. 1986). Media messages consistently equate thinness with feminine beauty, social value, and success across multiple domains including interpersonal, educational, health, and vocational (Rodin et al. 1984). The impact of such messages is significant.

Media messages exert a powerful impact upon human attitudes, thoughts, and behaviors. Media exposure is pervasive and media messages are highly accessible. Feminine appearance ideals portrayed by the mass media are inherently restrictive. The overwhelming majority of images depict thin objectified women (Fredrickson and Roberts 1997). Objectified media images devalue internal characteristics of female icons and emphasize external characteristics, such as body shape and appearance, as a source of sexual pleasure. The media inundation of thin objectified images of women creates a culture where feminine worth is largely defined by narrow standards for external appearance. Subsequently, the internal characteristics of girls and women are devalued across multiple sociocultural contexts (American Psychological Association, Task Force on the Sexualization of Girls 2007).

Saturation of thin objectified media images leads to an overly restrictive feminine appearance norm within the broader culture. The thin objectified feminine appearance norm leads to preoccupation with physical appearance and widespread body dissatisfaction among large groups of girls and women who exist in this toxic cultural milieu (Rodin et al. 1984; Fredrickson and Roberts 1997). Research indicates this sociocultural factor exacts a robust influence on the development of disturbed body image which serves as a strong predictor of subsequent eating disturbance (Hienberg and Thompson 1995). Numerous empirical studies provide evidence of the many negative psychological outcomes following exposure to the media thin-ideal.

Becker (2004) investigated reactions to the introduction of Western media among 30 Fijian girls 3 years following the introduction of television into the culture. Narrative data from semi-structured interviews shows increased body dissatisfaction and bulimic symptomatology following media exposure. Cited motives for engaging in bulimic behaviors include a desire to emulate thin female media characters. According to participants' interview responses, bulimic symptoms reflected a desire to attain social worth via appearance-based competition with success defined as achievement of the media-portrayed thin-ideal. This shift was especially notable within the Fijian culture, where a robust female body was widely celebrated prior to the introduction of Westernized television.

Additional research further highlights the detrimental psychological impact of the media feminine thin-ideal. Stice and Shaw (1994) explored exposure to media images of ultra-thin models, average-sized models, or control images among 157 female undergraduates. Results indicate women exposed to thin-ideal images showed increased depression, stress, shame, insecurity, guilt, and body

dissatisfaction. Further analyses showed thin-ideal endorsement, negative affect, and body dissatisfaction predicted bulimic symptoms following exposure. Similarly, Ogden and Mundray (1996) investigated psychological reactions following acute exposure to thin versus overweight media images among 20 men and 20 women. Results indicate enhanced body satisfaction following exposure to overweight pictures and decreased body satisfaction following exposure to thin pictures. This effect was more pronounced for women.

Hawkins and colleagues (2004) exposed 145 college women to thin-ideal or control images. Results indicate heightened negative mood, body dissatisfaction, and ED symptoms and decreased self-esteem following exposure to thin-ideal versus neutral images. Hausenblas and colleagues (2002) investigated responses to the media thin-ideal among 35 male and 30 female undergraduate students. Participants were exposed to the slides of media thin-ideal images and slides of themselves. Results show women report significantly less pleasure while viewing self-slides compared with their male counterparts. Tiggemann and Slater (2003) report increased body dissatisfaction in a sample of 84 women following exposure to a thin-ideal music video versus a neutral music video. Meta-analytic findings from 25 studies confirm exposure to the media thin-ideal is associated with increased body dissatisfaction (Groesz et al. 2002).

123.5 Differential Impact of the Thin-Ideal: Psychological Risk Factors

It is decisively clear from the thus mentioned research findings that many girls and women experience untoward psychological consequences as a direct result of exposure to the objectified media thin-ideal. However, many exposed women never develop a diagnosable ED or significant eating disturbance as a result of exposure. Therefore, risk and protective factors must play a role in differential reactions to exposure. One identified protective factor is an enhanced ability to be critical of sociocultural feminine norms which equate thinness, feminine beauty, and feminine worth (Murray et al. 1996; Green et al. 2008). Research indicates several additional psychological and sociocultural risk factors moderate the relationship between thin-ideal exposure and ED symptoms. The relevant literature on moderating factors is outlined next.

Heinberg and Thompson (1995) confirm women high in sociocultural awareness/internalization of sociocultural norms are more likely to experience depression following thin-ideal exposure. Additional findings indicate women high in initial body dissatisfaction are more likely to experience distress following exposure (Heinberg and Thompson 1995; Posavac et al. 1998). Dieters, restrained eaters, and persons high in social comparison are also more likely to react negatively to thin-ideal media exposure (Mills et al. 2002; Tiggemann and Slater 2003).

These psychological risk factors provide some insight as to why certain women and girls are more susceptible to develop ED symptoms and body dissatisfaction in response to sociocultural norms for feminine appearance. Additional research indicates that another impactful gender-related risk factor for eating disturbance includes perceived deficits in desirable masculine qualities.

123.6 The Desire for Masculine Qualities and Gender Discrepancy Theory

The gender discrepancy theory of EDs specifies women and girls are trapped by competing gender-related sociocultural messages which simultaneously encourage hyperfemininity in some domains while rewarding masculinity and devaluing femininity in others (Dunn and Ondercin 1981; Steiner-Adair 1986). The theory specifies females at-risk for eating disturbance internalize conflicted sociocultural messages.

As a result, these at-risk women try to reassert femininity via the painstaking creation of an external appearance which conforms to the thin-ideal while simultaneously striving to conform to traditional masculine attitudes and behaviors in nonappearance domains.

Gender discrepancy theorists postulate normative feminine qualities, such as cooperativeness, nurturance, relationship building, caregiving, and postpubescent weight gain, are devalued by the broader culture. Since women and girls high in ED symptomatology are more likely to display these devalued hyperfeminine traits, they are more likely to feel ostracized due to gender. Therefore, as the broader culture devalues traditional feminine characteristics, at-risk women may be likely to internalize this devaluation and instead prioritize socially rewarded external feminine traits, such as the thin-ideal. They may simultaneously embrace socially rewarded internal masculine traits, such as achievement orientation, autonomy, self-assurance, and competitiveness.

The desire to attain these socially rewarded goals is problematic because many of the goals are incompatible with hyperfeminine characteristics. According to gender discrepancy theory, this incompatible state leads at-risk girls and women to question self-identity and strive to achieve social status via conformity to highly rewarded goals (i.e., the thin-ideal, competitive behavior, autonomy) even if those goals deviate from their own natural inclinations. Steiner-Adair (1986) refers to this state as the "Super Woman" ideal of femininity. This ideal is characterized by a socially dictated, relentless desire for independence, thinness, beauty, perfection across multiple life domains including autonomous career achievement, and a devaluation of caregiving, nurturing, and interpersonal support. Women adhering to this ideal are likely to see other women as competitors and strive to defeat the competition across multiple venues, including the appearance and thinness domains. This tendency undermines cooperativeness and harmonious personal relationships and contributes directly to ED symptoms via a thinness focus. Figure 123.2 outlines the main tenets of gender discrepancy theory.

Much empirical support exists for discrepancy theory. Dunn and Ondercin (1981) indicate compulsive eaters desire higher levels of masculine traits compared with asymptomatic controls. Steiner-Adair (1986) reports significantly higher levels of ED symptoms among female adolescents endorsing the cultural "Super Woman" ideal compared with asymptomatic counterparts. Asymptomatic counterparts were significantly more likely to minimize the importance of competition and beauty and instead prioritize the maintenance of interpersonal relationships. Similarly, Hubert Lacey and colleagues (1986) demonstrate a relationship between bulimic symptomatology and autonomous achievement orientation, disconnected interpersonal relationships, and concerns regarding femininity.
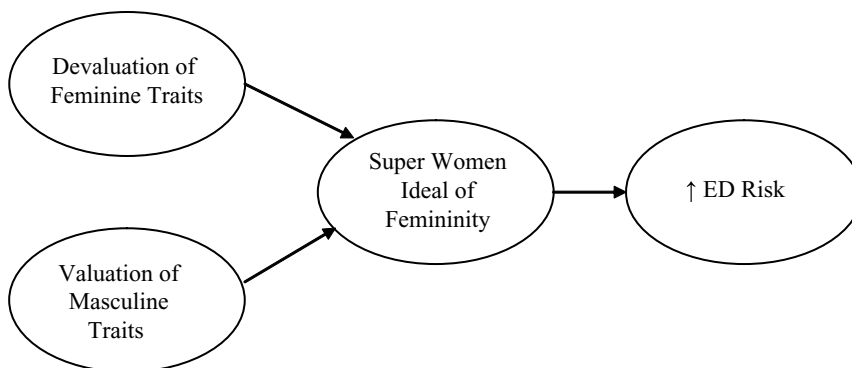
Fig. 123.2 Gender discrepancy theory of eating disorders (Dunn and Ondercin 1981; Steiner-Adair 1986)

According to gender discrepancy theory, ED risk is centered upon gender discrepancy and the desire to achieve a different balance of masculine and feminine traits rather than an association between ED risk and actual levels of masculine and feminine traits. Therefore, gender discrepancy theorists encourage the assessment of actual versus desired traits when examining the relationship between ED symptoms and gender-related traits. Empirical evidence reinforces this notion. For example, possessing actual levels of higher traditional masculine traits is correlated with decreased ED symptomatology across multiple studies (see Murnen and Smolak 1997) while a discrepancy between actual and desired masculine traits is associated with increased ED risk. In order to more fully understand why certain women devalue personal feminine characteristics, strive for masculine characteristics, compete with other women, and develop ED symptoms, it is important to understand the many sociocultural rewards and punishments contingent upon weight. Research indicates sociocultural forces confer significant weight-related rewards and punishers for women and girls.

123.7 Reinforcement for Thin-Ideal Conformity as a Function of Gender

Rodin, Silberstein, and Striegel-Moore (1984) state thinness in girls and women is equated with social worth across multiple contexts. Empirical evidence from a variety of domains supports this notion. Findings from the vocational realm indicate obese women are more likely to face unwanted career-related outcomes compared with either obese men or normal weight female counterparts. Averett and Korenman (1995) report obese women experience lower income compared with normal weight women. This effect was weak and inconsistent for obese men. Several additional studies also find obese women are more likely to experience employment discrimination compared with normal weight counterparts or obese men (Bellizzi et al. 1989; Pingitore et al. 1994).

Maranto and Fraedrich Stenoien (2000) indicate the wage penalty for obese women far exceeds that of obese men and occurs at a significantly lower level of obesity. Findings suggest mildly obese women (defined as 20% above normal weight) endure wage decrements which exceed those of morbidly obese African American men (defined as 100% above normal weight). Findings further indicate men as a group are protected from wage penalties until their level of obesity exceeds normal weight standards by at least 100 lb. Taken together, results suggest the punitive economic consequences of weight gain are markedly greater for women and occur at significantly lower levels of obesity. Adverse vocational effects for obesity as a function of gender are reviewed in Table 123.3.

Rewards for conformity to the feminine sociocultural thin-ideal are also readily apparent across several interpersonal domains. Cann (2001) reports judgments of high social competence are significantly more likely to be based on lower weights for women compared with higher weights for men. Regan (1996) investigated perceptions of obese and normal weight male and female targets among 96 college undergraduates. Results indicate obese women were viewed to be significantly less competent, sexually attractive, warm, and responsive compared with obese men. Obese women were also viewed to be significantly less attractive, warm, responsive, and skilled compared with average weight peers. Finally, obese women were considered to have significantly lower sexual desire compared with normal weight female counterparts. Perhaps such gender-related sociocultural stereotypes partially explain why obese women are significantly more likely to experience stigma in dating practices and sexual relationships compared with obese men (Chen and Brown 2005).

Table 123.3 Adverse vocational effects of obesity and overweight as a function of gender

Study	Population	Construct	Results
Averett and Korenman (1995)	5,090 women 4,951 men	Family income	Obese women: lower family income than normal weight women; minimal effect for men
Maranto and Fraedrich Stenoien (2000)	3,208 women 3,393 men	Weight-based wage penalties	Women experience weight-based wage penalties at much lower levels of obesity than men
Sargent and Blanchflower (1994)	12,537	Hourly earnings	Women: inverse relationship between weight and earnings Men: no relationship
Sarlio-Lahteenkorva and Lahelma (1999)	6,016	Unemployment Individual income Household disposable income	Overweight women: higher unemployment, lower income, lower disposable income; no effect for overweight men
Sarlio-Lahteenkorva et al. (2004)	2,068 women 2,314 men	Individual income	Obese women: significantly lower income in higher education positions or white-collar positions; no

Additional research from the dating realm indicates men are significantly less likely to choose overweight female romantic partners than women are to choose overweight male romantic partners (Stake and Lauer 1987; Sobal et al. 1995). Other research from the interpersonal realm suggests weight-related teasing by peers and family members occurs more often to overweight girls compared with overweight boys (Neumark-Sztainer et al. 2002). A recent research review of 17 studies indicates overweight girls undergo a significantly higher level of social stigmatization compared with overweight boys. Overweight girls are significantly more likely to experience physical, relational, and verbal bullying (Tang-Peronard and Heitmann 2008).

123.8 Implications for Prevention and Treatment

It is obviously apparent from the aforegiven findings that violation of the sociocultural feminine thin-ideal carries ample negative consequences for women and girls. It is also blatantly clear that extreme adherence to this ideal is a significant risk factor for eating disturbance. Therefore, women and girls experience a double-bind with regard to this norm where both adherence and dismissal can contribute to unwanted negative consequences. Women and girls less likely to experience ED symptoms in this maladaptive cultural context are those who demonstrate high awareness and skepticism of the sociocultural dictates for ideal feminine beauty. Therefore, media literacy programs should be incorporated into ED prevention and treatment programs in order to encourage healthy skepticism of the thin, objectified media thin-ideal. Such programs should effectively highlight the negative impact of this ideal on the psyches of girls and women. Researchers should critically evaluate the short- and long-term impact of media literacy interventions in treatment and prevention efforts via prospective research designs.

The intervention recommended thus is designed to reduce ED risk at the level of the individual. However, a more cost-effective and efficient long-term strategy would be to reduce the overall prevalence of sociocultural messages which narrowly define traditional feminine beauty in terms of

Table 123.4 Interventions to reduce adherence to sociocultural feminine norms linked to ED risk

Develop media literacy programs to encourage healthy skepticism of the feminine thin-ideal at the level of the individual.

Outline the negative impact of the media thin-ideal across multiple forums, both personal and political.

Introduce a wider range of feminine body types into media depictions.

Dissuade sociocultural messages which equate feminine worth with external feminine appearance.

Promote sociocultural messages which equate feminine worth with internal feminine characteristics.

Decrease the frequency of cultural practices which denigrate women and dismiss the importance of traditional feminine qualities.

Decrease the cultural objectification of women. Using feminine appearance and sexual appeal to sell products leads to a societal preoccupation with feminine external attractiveness which promotes body dissatisfaction and obsession with thinness.

Develop ED prevention programs designed to foster appreciation of positive internal feminine characteristics and decrease appearance focus in appraisals of personal self-worth.

Cultural objectification of women: Reduce the social value of women to physical appearance with a particular emphasis on viewing the female body as an object for sexual pleasure

ED eating disorder

extreme thinness. The systematic introduction of a range of feminine body types into media depictions of successful, attractive women would present alternate role models. This reform would significantly reduce sociocultural pressures to conform to an emaciated thin-ideal which is unrealistic and unhealthy for a large percentage of girls and women.

Another important intervention strategy is to dissuade adherence to sociocultural messages which equate feminine appearance with feminine worth. Primary, secondary, and tertiary programs should focus on fostering awareness of the many noteworthy internal characteristics of female participants while simultaneously discouraging an overreliance upon external appearance in self-definition. Key aspects of this intervention are to increase self-esteem via a positive focus on stable internal qualities and to decrease the need for social comparison and social competition based on appearance-related attributes. Table 123.4 provides a summary of interventions designed to reduce adherence to the traditional feminine norms and hyperfeminine behaviors linked to ED symptoms.

123.9 Application to Other Areas of Health and Disease

Sociocultural messages which equate feminine beauty, thinness, and feminine worth foster ED symptoms in women and girls who endorse such messages. This represents an important women's public health issue because EDs are accompanied by substantive decreases in physical and mental health. Anorexia nervosa has the highest mortality rate of any psychiatric diagnosis due to the detrimental impact of self-imposed starvation on multiple organ systems (American Psychiatric Association 2000). Bulimia nervosa is also accompanied by a myriad of negative physical and mental health consequences. Changing sociocultural messages surrounding feminine appearance and the thin-ideal will inevitably impact the overall prevalence of ED symptoms, exerting positive effects on the physical and mental health of women and girls. In conclusion, the many gender-related sociocultural risk factors outlined before represent important areas for future ED interventions. A summary of key points is presented in Table 123.5.

Table 123.5 Summary of gender-related sociocultural contributors to ED symptoms among women

Gender-related construct	ED risk
Increased thin-ideal internalization	Heightened
Increased self-objectification	Heightened
Increased societal objectification	Heightened
Sociocultural devaluation of postpubescent feminine weight gain	Heightened
Overt discrimination against overweight and obese women	Heightened
Exposure to objectified media thin-ideal	Heightened
Sociocultural definitions of feminine worth centered upon appearance	Heightened
Increased social competition among women on the basis of appearance	Heightened

Thin-ideal internalization: High endorsement of the media thin-ideal in personal expectations for physical appearance; Self-objectification: Tendency to view one's body as an object for sexual pleasure; Societal objectification: Tendency to view feminine worth in terms of physical appearance – female bodies are constructed as sexual objects in this cultural context

Summary Points

- Gender-related sociocultural messages contribute to heightened ED symptoms among girls and women.
- Girls and women who endorse higher levels of traditional feminine norms are at an increased risk for disordered eating.
- Adherence to a feminine norm which equates personal self-worth with thinness most notably predicts ED risk.
- Westernized media widely markets objectified images of thin women and habitually equates thin images with success and optimal femininity beauty.
- Exposure to thin, objectified media images predicts a host of negative psychological outcomes among girls and women.
- Devaluation of traditional feminine characteristics and idealization of traditional masculine characteristics creates a discrepant gender identity in women and girls at-risk for eating disturbance. Femininity is reasserted via the pursuit of extreme thinness.
- Thinness in girls and women is rewarded in Western cultures.
- Obese and overweight women experience significant discrimination in vocational, educational, and interpersonal realms.
- ED prevention and intervention efforts should provide education about the detrimental impact of sociocultural messages which equate thinness, beauty, and feminine worth.
- Alternate models of feminine worth, beauty, and success should be widely incorporated into Westernized media content.

Summary Table

Key features of feminine norms in eating disorders

- Hyperfeminine behavior increases risk for EDs.
- Increased endorsement of the cultural feminine thin-ideal is a significant risk factor for EDs.
- Sociocultural ideals reinforce the thin-ideal feminine thin-ideal.
- Punitive discriminatory practices against overweight and obese women further promote adherence to the feminine thin-ideal.
- The societal objectification of women equates feminine worth with thinness and sexual appeal, increasing risk of body dissatisfaction and EDs.

Definitions

Hyperfemininity: A psychological state characterized by an extreme endorsement of traditional sociocultural feminine norms.

Traditional sociocultural feminine norms: Cultural expectations for feminine behavior which emphasize appearance, passivity, timidity, nurturance, cooperativeness, caregiving, a relational focus, and thinness.

Femininity theory of eating disorders: Theory states eating disorders are the result of an oversubscription to traditional feminine norms.

Feminine negative characteristics: A subtype of feminine traits which serve as risk factors for eating disturbance including a predisposition to be approval seeking, worrying, nervous, timid, dependent, shy, weak, bashful, anxious, and self-critical.

Feminine thin-ideal: Prototype of ideal feminine beauty which specifies a slender body type.

Objectified media thin-ideal: Westernized media images of optimal feminine beauty which highlight a scantily clad, slender body type viewed as an object for sexual pleasure.

Gender discrepancy theory of eating disorders: Theory states competing gender-related sociocultural messages lead women to assert femininity via thinness while simultaneously asserting masculinity in other domains.

"Super Woman" feminine ideal: Feminine identity characterized by a socially dictated, relentless desire for independence, thinness, beauty, and perfection across multiple life domains including autono career achievement, serves as a risk factor for eating disturbance.

References

American Psychiatric Association. Diagnostic and statistical manual of mental disorders, 4th edn. text revision. Washington, DC: American Psychiatric Association; 2000.

American Psychological Association. Task Force on the Sexualization of Girls Report of the APA Task Force on the Sexualization of Girls. Washington, DC: American Psychological Association; 2007.

Averett S, Korenman, S. J Hum Res. 1995;31:304–30.

Antill JK, Cunningham JD, Russell G, Thompson NL. Aust J Psychol. 1981;33:169–83.

Bargad A, Hyde JS. Psychol Women Q. 1991;15:181–201.

Becker, AE. Cult Med Psychiatry. 2004;28:533–59.

Bellizzi JA, Hite RE. J Marketing. 1989;53:36–47.

Bem SL. J Consult Clin Psych. 1974;42:155–62.

Boskind-Lodahl M. J Women Cult Soc. 1976;2:342–55.

Brown JA, Cross HJ, Nelson JM. Inter J Eat Disorder. 1990;9:571–5.

Cann A. J Soc Psychol. 2001;131:225–31.

Chen EY, Brown M. Obes Res. 2005;13:1393–7.

De Graaf A. Konstructie van een verbeterde versie van de Groninger Androgynie Schaal (GRAS). Heymans Bulletins Psychologische Instituten R. U. Groningen, 1984;HB-84-710-EX.

Dunn PK, Ondercin P. J Clin Psychol. 1981;37:43–9.

Fairburn CG, Bèglin SJ. Assessment of eating disorders: Interview or self-report questionnaire? Inter J Eat Disorder. 1994;16(4):363–70.

Groesz LM, Levine MP, Murnen SK. Inter J Eat Disorder. 2002;31:1–16.

Hausenblas HA, Janelle CM, Ellis Gardner R, Hagan AL. Sex Roles. 2002;47:569–75.

Hawkins N, Scott Richards P, Mac Granley J, Stein DM. Eat Disorder. 2004;12:35–50.

Heilbrun AB, Mulqueen CM. Sex Roles. 1987;17:187–207.

Heinberg LJ, Thompson JK. J Soc Clin Psychol. 1995;14:325–38.

Hubert Lacey J, Coker S, Birtchell SA. Inter J Eat Disorder. 1986;5:475–87.

Kagan DM, Squires RL. Adolescence. 1984;19:15–29.

Fredrickson BL, Roberts T. Psychol Women Q. 1997;21:173–206.

Garner DM. *Eating Disorder Inventory – 2 manual*. Psychological Assessment Resources, Odessa, FL; 1991.

Garner DM, Garfinkel PE. Psychol Med. 1979;9:273–9.

Garner DM, Garfinkel PE, Schwartz D, Thompson M. Psychol Rep. 1980;47:483–91.

Garner DM, Olmstead MP, Polivy J. Inter J Eat Disorder. 1983;2:15–34.

Green MA, Davids CM, Skaggs AK, Riopel CM, Hallengren JJ. Eat Disorder. 2008;16:283–93.

Hathaway SR, McKinley JC. The Minnesota Multiphasic Personality Inventory. University of Minnesota, Minneapolis, MN; 1942.

Hatsukami D, Owen P, Pyle R, Mitchell J. Addict Behav. 1982;7:435–9.

Lewis LD, Johnson C. Inter J Eat Disorder. 1985;4:247–57.

Mahalik JM, Morray EB, Coonerty-Femiano A, Ludlow LH, Slattery SM, Smiler A. Sex Roles. 2005;52:417–35.

Maranto CL, Fraedrich Stenoien A. Employee Responsibilities Rights J. 2000;12:9–24.

Mills JS, Polivy J, Herman CP, Tiggemann M. Pers Soc Psychol Bull. 2002;28:1687–99.

Morris A, Cooper T, Cooper PJ. Inter J Eat Disorder. 1989;8:593–6.

Murnen SK, Smolak L. Inter J Eat Disorder. 1997;22:231–42.

Murray SH, Touyz SW, Beumont PJV. Eat Disorder. 1996;4:33–46.

Neumark-Sztainer D, Falkner N, Story M, Perry C, Hannan PJ, Mulert S. Int J Obes. 2002;26:123–31.

Norman DK, Herzog DB. Inter J Eat Disorder. 1983;2:43–52.

Ogden J, Mundray K. Eur Eat Disord Rev. 1996;4:171–82.

Orleans CT, Barnett LR. Bulimiarexia: guidelines for behavioral assessment and treatment. In: Hawkins RC, Fremouw WJ, Clement PF editors. The Binge-Purge syndrome. New York: Springer; 1984. p. 144–182.

Paxton SJ, Schulthorpe A. Sex Roles. 1991;24:587–98.

Pettinati HM, Franks V, Wade JH, Kogan LG. Distinguishing the role of eating disorders from depression in the sex role self-perceptions of anorexic and bulimic inpatients. J Abnorm Psychol. 1987;96(3):280–2.

Pingitore R, Dugoni BL, Scott Tindale R, Spring B. J Appl Psychol. 1994;79:909–17.

Posavac HE, Posavac SS, Posavac EJ. Sex Roles. 1998;38:187–201.

Rodin J, Silberstein L, Striegel-Moore R. Women and weight: a normative discontent. In: Sonderegger SB editor. Psychology and gender Nebraska symposium on motivation. Lincoln: University of Nebraska Press 1984.

Sargent JD, Blanchflower DG. Ach Pediatr Adolesc Med. 1994;148:681–7.

Sarlio-Lahteenkorva S, Lahelma E. Int J Epidemiol. 1999;28:445–9.

Sarlio-Lahteenkorva S, Silventoinen K, Lahelma E. Am J Public Health. 2004;94:468–72.

Silverstein B, Perdue L, Peterson B, Kelly E. Sex Roles. 1986;14:519–32.

Snyder R, Hasbrouck L. Psychol Women Q. 1996;20:593–8.

Sobal J, Nicolopoulos V, Lee J. Int J Obes. 1995;19:376–81.

Spence JT, Helmreich R, Stapp J. J Supp Abstract Service Catalog Selected Doc. Psychol. 1974;4:43.

Squires RL, Kagan, DM. Inter J Eat Disorder. 1985;4:539–48.

Srikameswaran S, Leichner P, Harper D. Inter J Eat Disorder. 1984;3:39–43.

Stake J, Lauer ML. Sex Roles. 1987;17:31–47.

Steiner-Adair C. J Am Acad Psychoanal. 1986;14:95–114.

Stice E, Shaw HE. J Soc Clin Psychol. 1994;13:288–308.

Tang-Peronard JL, Heitmann BL. Obes Rev. 2008;9:522–34.

Tiggemann M, Slater A. Inter J Eat Disorder. 2003;35:48–58.

Timko C, Striegel-Moore RH, Silberstein LR, Rodin J. Inter J Eat Disorder. 1987;6:701–12.

Van Strien T, Frijters JER, Bergers GPA & Defares PB. The Dutch Eating Behaviour Questionnaire (DEBQ) for assessment of restrained, emotional, and external eating behavior. Inter J Eat Disorder. 1986;5:295–315.

Van Strien T, Bergers GPA. Inter J Eat Disorder. 1988;7:89–99.

Williamson DA, Kelley ML, Davis CT, Ruggiero L, Blouin DC. J Consult Clin Psych. 1985;53:161–263.

Wiseman CV, Gray JJ, Mosimann JE, Ahrens AH. Inter J Eat Disorder. 1992;11:85–9.

Chapter 124
The Dietary Antioxidants Alpha-Tocopherol and Alpha-Lipoic Acid and Their Synergy in Brain Disorders

Oscar Gonzalez-Perez

Abbreviations

HNE	4-Hydroxy-2-nonenal
5-HT	5-Hydroxytryptamine
ATPase	Adenosine triphosphatase
ALA	Alpha-lipoic acid
DNA	Deoxyribonucleic acid
GABA	Gamma-amino butyric acid
GPX	Glutathione peroxidase
GAP43	Growth-associated protein 43
NAD+	Nicotinamide adenine dinucleotide oxidized
NADP+	Nicotinamide adenine dinucleotide phosphate oxidized
NADHP	Nicotinamide adenine dinucleotide phosphate reduced
NADH	Nicotinamide adenine dinucleotide reduced
ROS	Reactive oxygen species
RNA	Ribonucleic acid
SOD	Superoxide dismutase
VE	Vitamin E

124.1 Introduction

The consumption of edible plants, fruits, and vegetables has shown to prevent the occurrence of a number of diseases and, under certain circumstances, to reduce the oxidative damage in humans. Vegetables, fruits, and seeds are rich sources of antioxidants, for instance lipoic acid, vitamins A, C, and E, flavonoids, polyphenols, lycopenes, proanthocyanidins, astaxanthins, and others. These compounds might protect the organism against free-radical-induced injuries and diseases. The utilization

O. Gonzalez-Perez (✉)

Laboratory of Neuroscience, School of Psychology, University of Colima, Av. Universidad 333, Colima, Col 28040, México
and
Neuroscience Department, Centro Universitario de Ciencias de la Salud, University of Guadalajara, Guadalajara, Jal 44340, México
e-mail: osglez@gmail.com; osglez@ucol.mx

of antioxidants may be potentially useful for preventing lesion enlargement, and for treating pathological conditions that have an oxidative process as a major source of neurological damage, for instance brain ischemia, diabetic neuropathy, Parkinson's disease, multiple sclerosis, Huntington's disease, amyotrophic lateral sclerosis, or Alzheimer's disease. Despite dramatic advances in our understanding of these neurological diseases, at present there is no satisfactory treatment to reduce death and disability in patients. Antioxidant agents have been investigated as therapeutic alternatives to diminish cerebral damage, with varying results. In this chapter, we will discuss the role of oxidative stress in brain injury and the effects of two important antioxidants (vitamin E (VE) and lipoic acid) on the preservation of neural integrity after oxidative damage.

124.2 Reactive Oxygen Species and Oxidative Stress

Reactive oxygen species (ROS) play an important role in neuronal signaling and physiology; however, at higher levels, they can lead to neuronal dysfunction and cell death. There are two types of ROS: oxygen free radicals and nonradical oxygen derivatives (see Table 124.1).

ROS can arise from numerous sources including redox metal ion–catalyzed reactions, mitochondrial-resident electron transport chain function, glycation end products, and enzymatic reactions. Under physiological circumstances, ROS play important roles in body homeostasis by modulating and mediating vital processes, such as, glucose metabolism, cellular respiration, cerebral perfusion, vascular permeability, inflammation, immune response, physiological aging, and others. However, high levels of free radicals participate in tissue injury and disease progression in a number of pathologies: diabetes neuropathy, cancer, cardiac and brain ischemia, Alzheimer's disease, and others (Paravicini et al. 2004; Poon et al. 2004; Heo et al. 2005; Blomgren and Hagberg 2006; Butterfield 2006; Chrissobolis and Faraci 2008; Gonzalez-Perez et al. 2008).

Oxidative stress is manifested by excessive production of free radicals that, depending on the nature of the substrate attacked, produces different reactions including lipid peroxidation, protein oxidation, or deoxyribonucleic acid/ribonucleic acid (DNA/RNA) oxidation. These pathological processes have characteristic markers used to identify the targeted cell structure, for example:

1. Protein oxidation is characterized by overproduction of protein carbonyls, 3-nitrotyrosine or protein glutathionylation.
2. Lipid peroxidation is associated with production of free and protein-bound reactive alkenals as 2-propen-1-al (acrolein) and 4-hydroxy-2-nonenal (HNE); thiobarbituric acid reactive substances; and isoprostanes and neuroprostanes derived from peroxidation of arachidonic acid and docosohexanoic acid, respectively.

Table 124.1 Reactive oxygen species

Oxygen free radicals		Nonradical oxygen derivatives	
Name	Formula	Name	Formula
Hydroxyl radical	$^{\bullet}OH$	Hydrogen peroxide	H_2O_2
Hypochlorite ion	$ClO^{\bullet}$	Singlet oxygen	$^1O_2$
Superoxide anion	$^{\bullet}O_2{}^-$	Ozone or trioxygen	O_3
Hydroperoxyl	$HO_2{}^{\bullet}$	Peroxynitrite or peroxonitrite	$ONOO-$
Alkoxyl	$RO^{\bullet}$	Hypochlorous acid	$HOCl$
Peroxyl	$ROO^{\bullet}$		

Condensed formulas and chemical names of the two types of reactive oxygen species: oxygen free radicals and nonradical oxygen derivatives

3. DNA oxidation can be identified by quantifying the levels of 8-hydroxy-2-deoxyguanosine and advanced glycation end products (reaction products of reducing sugars with amines).

Regardless of the targeted cell structure, the oxidation of proteins, lipids, or DNA leads to structural changes, biochemical dysfunction, and cell death.

124.3 Brain Injury and Oxidative Stress

The brain consumes about one-third of the inspired oxygen, has the second highest concentration of fatty acids (exceeded only by adipose tissue), and has a high abundance of redox-capable transition metal ions coupled. In addition, this organ has very little glycogen deposits and a relatively low abundance of antioxidant defense systems. These characteristics make the brain the most vulnerable organ to *lipid peroxidation*. Recently, reactive nitrogen species are considered novel sources of oxidative stress in brain, which has been associated with protein deposits in several neurodegenerative disorders. This pathological process is called *nitrosative stress* and is also considered critical in brain dysfunction. The elevated production of reactive oxygen or nitrogen species, their production in inappropriate relative amounts, or deficiencies in antioxidant defenses may result in pathological stress to neurons and cerebral tissue. In summary, if oxidative or nitrosative stress is excessive or if defense and repair responses are inadequate, neuronal injury is caused. Therefore, antioxidant therapies appear to be a feasible approach to reduce brain damage and disease progression.

124.4 Dietary Antioxidants Against Oxidative Stress

There is considerable evidence for a role of antioxidant nutrients in the maintenance of health in contributing to the decreased incidence of free radical-induced diseases. Specifically, alpha-lipoic acid (ALA) and VE have been broadly studied under experimental and clinical conditions because of their unique chemical and nutritional properties. Moreover, these antioxidants are present in the normal human diet, their side effects are infrequent and the combinations of both substances appear to have synergistic effects for reducing cellular damage in oxidation-related pathological events. Therefore, this chapter will be focused on discussing the role of ALA and VE to neutralize oxidative processes in the brain.

124.4.1 Alpha-Lipoic Acid (ALA)

ALA, also known as lipoate, was discovered in 1951 as a molecule essential for aerobic life, participates in various transfer reactions within the pryruvate dehydrogenase complex by assisting in acyl-group transfer and as a coenzyme in the Krebs cycle. ALA helps preserve the homeostasis of cellular and mitochondrial membranes by modifying the metabolism of ketoacids and modulating mitochondrial ratios of nicotinamide adenine dinucleotide reduced/nicotinamide adenine dinucleotide oxidized (NADH/NAD+) and nicotinamide adenine dinucleotide phosphate reduced/nicotinamide adenine dinucleotide phosphate oxidized (NADHP/NADP+) (Packer et al. 1995, 1997). Lipoic acid is synthesized in the body in very small amounts and is covalently bound to the E2 enzyme subunit
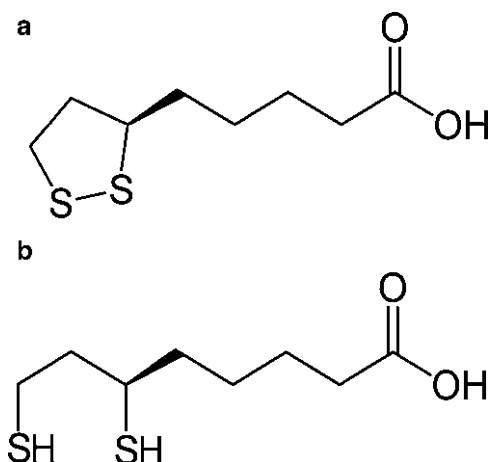
Fig. 124.1 Chemical structure of alpha-lipoic acid (ALA). Structural formulas of ALA (**a**) and dihydrolipoic acid (the reduced form of lipoate) (**b**)

of the four different alpha-keto acid dehydrogenase complexes in mitochondria. Under physiological conditions, the normal serum level of lipoate is 0.1 mg/mL, but this level can be rapidly modified by variety of foods where ALA is abundantly found, such as liver, heart, kidney, and red meat, as well as wheat germ, spinach, broccoli, potatoes, and beer yeast.

After dietary intake, lipoate is absorbed into the circulation from the intestine and within cells is reduced and exported to interstitial space as dihydrolipoate (Fig. 124.1). Due to its amphiphilic properties, the ALA neutralizes free radicals in both the fatty and watery regions of cells (Packer, et al. 1995, 1997). These antioxidant properties are mainly located in its thiol group, which reacts directly with ROS and provides strong chelating activity on transition metals. Lipoate also contributes in other antioxidant systems by enhancing the effects of superoxide dismutase (SOD) (Seaton et al. 1996), coenzyme Q10, and glutathione (Murphy et al. 1992; Roy et al. 1997), and by regenerating other antioxidants such as ascorbate (vitamin C) and alpha-tocopherol (Packer et al. 1995, 1997). Lipoic acid is thought to function as a neuroprotective agent and an anti-inflammatory compound, providing effective treatment for Alzheimer's disease, Parkinson's disease, and multiple sclerosis. Additionally, lipoic acid has been tested to treat mercury intoxication. The administration of ALA at dose of 600–1,200 mg/day is sufficient to reach therapeutic serum levels of 4–8 mg/mL at 3rd to 5th day. Taken together, this evidence indicates that ALA is an important antioxidant that may be clinically useful to control neurological conditions related to the overproduction of oxidant radicals (Packer et al. 1995).

124.4.2 Vitamin E (VE)

Alpha-tocopherol is the most abundant natural isoform of VE (Fig. 124.2) and the one with the highest bioavailability. For this reason, the term alpha-tocopherol is frequently referred as synonymous of VE. VE is abundant in wheat germ, almonds, hazelnuts, peanuts, spinaches, broccoli, kiwi, and mango, and in several oils including soybean, sunflower, corn, and safflower. In humans, the normal serum levels of VE oscillate between 11.6 and 46.4 mmol/L. The antioxidant capacity of VE is independent of enzymatic reactions and resides in transferring a phenolic H^+ to oxidant radicals derived from oxidized
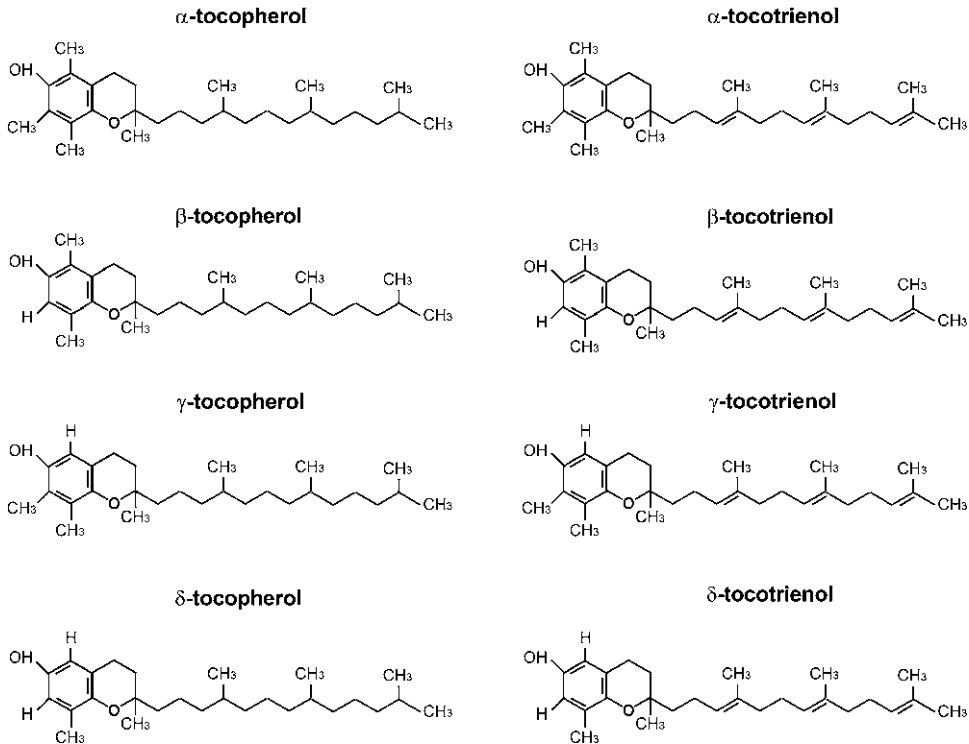
Fig. 124.2 Chemical structures of the eight isoforms of vitamin E (VE). Structural formulas of the eight isoforms of VE. The most abundant isoform in the nature is the alpha-tocopherol, which also has the highest physiological activity

polyunsaturated fatty acids. VE increases in intracellular concentrations of the antioxidant enzymes SOD and glutathione peroxidase (GPX) (Conti et al. 1993; Monget et al. 1996). In addition, VE reduces important cellular sources of oxidant radicals by diminishing malonaldehyde concentrations and mitochondrial activity (Villalobos et al. 1994). Therefore, VE is one of the first line of defense against DNA oxidative damage and lipid peroxidation of unsaturated fatty acids in the cell membrane.

124.4.3   Lipoic Acid and Vitamin E in Brain Disorders

Several studies have evaluated the therapeutic or prophylactic potential of VE or ALA in neurological diseases. Deprivation of dietary VE is associated with larger cerebral infarcts in rats (van der Worp et al. 1998). Intraperitoneal administration of alpha-tocopherol diminishes the effects of oxidative damage caused by alteration of the antioxidant defense system in rats (Naziroglu et al. 1999). VE may partially inhibit activated chaperone-mediated autophagy in status epileptic (Cao et al. 2009). Dietary supplementation of VE increases apolipoprotein E levels that, in turn, reduces amyloid-beta and age-related neurodegeneration (Chan and Shea 2009). Alpha-tocopherol improves performance on a spatial working memory task and attenuates cholinergic neuron pathology in the basal forebrain in a Down's syndrome mouse model (Lockrow et al. 2009).

Regarding the efficacy of ALA for reducing cerebral oxidative damage, several reports suggest a neuroprotective effect in models of focal and global cerebral ischemia (Cao and Phillis 1995; Muller

and Krieglstein 1995), *x*-irradiation-induced oxidative stress (Manda et al. 2007), mitochondrial aging, and peripheral neuropathy (Roy et al. 1997). ALA prevents the development of clinical signs and preserves the integrity of brain–blood barrier in acute experimental allergic encephalomyelitis, a rodent model for multiple sclerosis (Schreibelt et al. 2006) and in human patients (Yadav et al. 2005). Lipoate has important anti-inflammatory effects as shown by reducing glial reactivity and by modulating the levels of nuclear factor kappa B p65 in brain (NFkappaB) (Jesudason et al. 2008). When administered to pregnant rats, ALA decreases DNA damage and oxidative stress induced by alcohol in the developing hippocampus and cerebellum (Shirpoor et al. 2008). Dietary supplementation of ALA delays the progression of age-related cognitive decline (Arivazhagan et al. 2002; Suchy et al. 2009) and reduces ischemic cerebral damage when complicated with diabetes (Piotrowski et al. 2001). ALA is also effective in protecting neural cells against glutamate-induced cytotoxicity. This protective effect of ALA plus appears to be independent of its stereochemistry and is synergistically enhanced by selenium (Tirosh et al. 1999).

However, ALA and VE are not always effective in diminishing oxidative damage in the brain, especially when these compounds are used alone or without combination of antioxidants. For instance, alpha-tocopherol does not reduce post-traumatic cerebral edema induced by cold injury (Stoffel et al. 1997) and has limited clinical benefits in Parkinson's disease, amyotrophic lateral sclerosis, and Alzheimer's disease (Parkinson 1993; Sano et al. 1997; Gaedicke et al. 2009). Other reports indicate that ALA does not have clinical relevance to treat trigeminal trophic syndrome (Fruhauf et al. 2008) and does not have a significant neuroprotective effect in brain ischemia after intraperitoneal or intracranial administration (Wolz and Krieglstein 1996). Therefore, researchers are now interested in establishing whether beneficial effects of antioxidants become more evident when these substances are administered together. On this regard, recent evidence indicates that antioxidant combinations are more effective than the use of a single antioxidant. One of the combinations with reproducible and promising results is the combination of ALA plus VE. ALA markedly modifies in situ concentrations of VE (Packer et al. 1995, 1997). This process is mediated by ascorbate recycling, glutathione disulfide reduction, and involves ubiquinone and dehydroascorbate radicals (Fig. 124.3). The combination of VE and vitamin C has been studied, but the pro-oxidant activity of ascorbate is important and its benefits are not quite evident. In addition, ALA is also capable of reducing thioredoxin; thus the antioxidant properties of ALA are more complete than that of vitamin C (Packer et al. 1997).

124.4.4 Synergism Between Lipoate and Tocopherol

During the past 2 decades, an increasing number of reports regarding the therapeutic applications of the combination of VE plus ALA have been published (see Table 124.2). These investigations indicate that the combination of both antioxidants is effective in reducing oxidative damage in several pathological conditions, such as diabetic neuropathy, Alzheimer's disease, rheumatic arthritis, cardiac and cerebral ischemia, cataract degeneration, and in the aging process (Haramaki et al. 1993, 1995; Maitra et al. 1995; Stoyanovsky et al. 1995; Coombes et al. 2000a, b, 2001; Gonzalez-Perez and Gonzalez-Castaneda 2006). One of the first studies that revealed the synergistic effect between alpha-tocopherol and lipoate was done in microsomal fractions obtained from normal and VE-deficient animals (Scholich et al. 1989). In that study, the controls showed a prolonged lag phase before the onset of low-level chemiluminiscence in microsomes that were not found in the VE-deficient fractions. Oral supplementation of ALA–VE significantly reduces lymphocyte apoptosis in a global cerebral ischemia model. Favorable effects of an ALA–VE mixture were found in
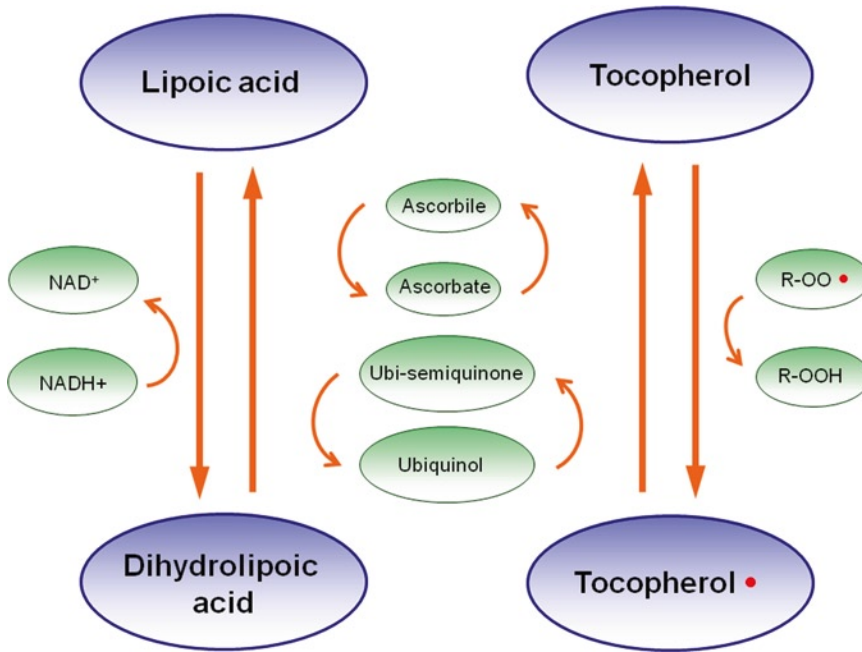
Fig. 124.3 Biochemical recycling of VE. Vitamin E is recycled via intracellular alpha-lipoic acid. In this complex mechanism, the main metabolic intermediaries are vitamin C (ascorbate) and ubiquinol. R–OO•: Oxidant radical; R–OOH: Neutralized radical

a thromboembolic stroke model; this study analyzed the efficacy of the prophylactic administration of ALA plus VE upon ischemia. ALA–VE mixtures efficiently reduced glial scar, improved the recovery after brain ischemia, and increased the tissue levels of synaptophysin and growth-associated protein 43 (GAP43), a couple of synaptic remodeling proteins (Gonzalez-Perez et al. 2002). This prophylactic treatment also reduces infarct volume and lipid peroxidation after cerebral ischemia (Garcia-Estrada et al. 2003). Additional findings indicated that the ALA–VE combination decreases the age-associated Na(+),K(+)-adenosine triphosphatase (ATPase) activity. Because of the critical importance of Na(+),K(+)-ATPase in neuronal functions, the results of this study may have important implications in controlling age-related functional deficits of the brain (Bagh et al. 2008). In a model of acute intoxication with lindane, ALA and VE were neuroprotective as shown by preservation of the neurotransmitters gamma-amino butyric acid (GABA) and serotonin (5-hydroxytryptamine, or 5-HT) in olfactory lobe, cerebrum, hippocampus–hypothalamus, cerebellum, and pons-medulla (Bist and Bhatt 2009). Interestingly, a treatment with a triple combination of VE, LA, and vitamin C protects the arachidonic acid level in the brains of diabetic and nondiabetic rats (Ozkan et al. 2005). Arachidonic acid is crucial to the optimal development of the brain and eyes and to preserve cognitive abilities.

Other findings indicate that the combination of ALA and VE increases endothelial levels of the antiapoptotic protein Bcl-2 without significant changes in the levels of the proapoptotic protein Bax (Marsh et al. 2005). In parallel, the ALA/VE mixture has been combined with other dietary antioxidants, such as vitamin C, beta-carotene, and selenium, and then evaluated under several conditions of exercise, experimental diabetes, cold, age, and cancer, and promising results have also been obtained (Bailey and Davies 2001; Sharman and Bondy 2001; Mosca et al. 2002; Schmidt et al. 2002; Mantovani et al. 2003; Ozkan, et al. 2005). Taken together, this evidence strongly suggests that the combination of ALA and VE is better than the antioxidant monotherapy.

Table 124.2 Key facts of the synergy alpha-tocopherol/alpha-lipoic acid

Findings	Antioxidant isoforms (dose)	Model (specie)	Reference
Reduction in the lipid peroxidation induced by UV-light on microsomal fractions	α-Tocopherol (62.7 mg/kg diet)/dihydrolipoic acid (50 μM)	In vitro (rat)	Scholich et al. (1989)
Less retinal degeneration induced by UV light	α-Tocopherol (50–100 μM)/dihydrolipoic acid (25–100 μM)	In vitro (rat)	Stoyanovsky et al. (1995)
Restoration of the activities of glutathione peroxidase, catalase, and ascorbate free-radical reductase in lenses that prevents cataract formation	α-Tocopherol (62.7 mg/kg diet)/lipoic acid (25 mg/kg body weight)	In vivo (rat)	Maitra et al. (1995)
Improvement of cardiac recovery, less arrhythmias incidence and lipid peroxide levels, and strong myocardiac contractility during postischemic reperfusion and posthypoxic reoxygenation of heart	α-Tocopherol (100 μM)/ dihydrolipoic acid (50 μM) (Haramaki et al. 1993, 1995)α-Tocopherol (1,000 IU VE/kg diet)/lipoic acid (1.65 g/kg diet) (Coombes et al. 2000a, b, 2001; Ko and Yiu 2001)	In vitro e in vivo (rat)	Haramaki et al. (1993, 1995); Combes et al. (2000a, b; Ko et al. (2001)
Reduction in maximal twitch tension and tetanic force production in unfatigued skeletal muscle	α-Tocopherol (1,000 IU VE/kg diet)/lipoic acid (1.65 g/kg diet)	In vivo (rat)	Coombes et al. (2001)
Attenuation of acute mountain sickness and improvement of the physiological profile of mountaineers at high altitude	α-Tocopherol (100 UI/day)/lipoic acid (150 mg/day)	In vivo (human)	Bailey and Davies (2001)
Modulation of apoptosis in CD4 and CD8 lymphocytes	α-Tocopherol (10 mg/day)/lipoic acid (100 mg/day)	In vivo (human)	Mosca et al. (2002)
Increase in remodeling proteins (GAP43 and synaptophysin) in the ischemic penumbra area and smaller brain infarction volume	α-Tocopherol (50 mg/kg body weight)/lipoic acid (20 mg/kg body weight)	In vivo (rat)	Gonzalez-Perez et al. (2002); Garcia-Estrada et al. (2003)
Reduction in serum levels of IL–6 and TNFα	α-Tocopherol (70 mg/day)/lipoic acid (200 mg/day)	In vivo (human)	Mantovani et al. (2003)
Apoptosis protection by increasing the levels of endothelial cell Bcl-2	α-Tocopherol (50 μM)/lipoic acid (1 mM)	In vitro (bovine)	Marsh et al. (2005)
Attenuation of the cyclosporine-induced decrease in erythrocyte superoxide dismutase activity and cyclosporine-induced vascular dysfunction	α-Tocopherol (1,000 IU VE/kg diet)/lipoic acid (1.6 g/kg diet)	In vivo (rat)	Lexis et al. (2006)
Less antioxidant enzyme activity of GPX and catalase under exercise training conditions	α-tocopherol (1,000 UI/kg diet)/lipoic acid (1.6 g/kg diet)	In vivo (rat)	Marsh et al. (2006)
Less accumulation of high-molecular-weight amyloid beta-proteins	α-Tocopherol (50 μM)/lipoic acid (1 mM)	In vitro (human)	Woltjer et al. (2007)
Reduction in the age-associated Na(+),K(+)-ATPase neuronal activity	α-Tocopherol (1.5 mg/100 g body weight)/lipoic acid (3 mg/100 g body weight) and N-acetylcysteine (500 mg/kg body weight)	In vivo (rat)	Bagh et al. (2008)
Neuroprotection in GABA and 5-HT levels in the brain of mice acutely intoxicated with lindane	α-Tocopherol (50 mg/kg body weight)/lipoic acid (20 mg/kg body weight)	In vivo (mouse)	Bist and Bhatt (2009)

This table summarizes the experimental and clinical evidence regarding on the synergy between ALA and VE analyzed under different oxidative processes

The mechanism by which ALA and VE have synergic effects are not well understood; as mentioned above it has been proposed that alpha-tocopherol is regenerated via lipoate (Maitra et al. 1995; Stoyanovsky et al. 1995; Ko and Yiu 2001). Yet, the VE recycling alone requires at least two metabolic intermediate steps and cannot explain the magnitude of findings described above. Therefore, it is possible that other processes are involved in this synergism. Other possible mechanisms include:

1. The increase of SOD levels, specifically the manganese SOD form (MnSOD) (Coombes et al. 2000b).
2. The increase of activity levels of GPX mediated by selenium (Scott et al. 1976; Conti et al. 1993; Haramaki et al. 1993; Coombes et al. 2000a, b).
3. The modulation of the balance between the anti- and proapoptotic proteins Bcl-2/Bax (Marsh et al. 2005).

In summary, the synergistic mechanism of ALA–VE combination is not entirely understood, but it is clear that potent antioxidant effects are achieved when both ALA and VE are administered simultaneously. Because both antioxidants are essential components in our diet and the oral supplementation is well tolerated, inexpensive, and very safe, the combination of ALA and VE can be a feasible prophylactic/therapeutic alternative for oxidative processes in the brain. Therefore, diets or commercial supplements enriched with these two specific antioxidants are a promising alternative for people suffering from neurological conditions associated with overproduction of oxygen free radicals.

124.5 Aplications to Other Areas of Health and Disease

Oxidative stress is involved in the pathogenesis of a wide spectrum of systemic conditions. Therefore, the ALA–VE combination might be useful for preventing initiation and progression of damage of many pathological conditions that have an oxidative process as the major source of injury, such as cancer, rheumatoid arthritis, chemotherapy, exercise, cataracts, heart failure, myocardial infarction, diabetic neuropathy, atherosclerosis, chronic fatigue syndrome, aging process, and others. In consequence, strategies directed at counteracting oxidative processes will certainly be important in clinical medicine. However, further experimental studies and clinical trials are needed to establish the therapeutic potential of the ALA–VE combination in humans.

Summary Points

- The central nervous system consumes about one-third of the inspired oxygen and has the second highest concentration of fatty acids. Therefore is the most vulnerable tissue to oxidative damage.
- The main mechanism of cerebral injury is called lipid peroxidation, which occurs when unsaturated fatty acids are oxidized by oxygen free radicals.
- Overproduction of oxidant radicals and/or a deficit in antioxidant defenses can give rise to a pathological condition or contribute to disease progression in the brain.
- VE and lipoic acid are dietary antioxidants that cross the brain–blood barrier and react rapidly with ROS and neutralize oxidative damage, but when they are administered as monotherapy their benefits are limited. Hence, the combination of antioxidants appears to be more effective to control oxidative brain damage.
- Besides its antioxidant capabilities, the ALA plays an important role in VE recycling. As consequence, the combination of tocopherol/lipoate has potent synergistic effects to efficiently reduce the magnitude of cerebral damage.

Definitions

Reactive oxygen species (ROS): Family of highly reactive ions or molecules that have at least one unpaired electron at their last orbital.

Oxidative stress: Biochemical process that arises when the production of free radicals is not equivalently balanced by their scavenging or conversion to non-free-radical products.

Lipid peroxidation: Mechanism of oxidative damage that occurs when a unsaturated fatty acid is oxidized by oxygen free radicals and a hydroperoxide is generated in the brain.

Antioxidant: Substances that react with ROS and inhibit initiation and propagation of oxidative damage by radical scavenging, sequestrating transition metals, and reducing peroxides by enzymatic hydrolysis of ester bonds. The efficiency of antioxidants is determined by their ability of rapidly reacting with oxidant radicals to form new radicals less reactive.

Alpha-lipoic acid ($C_8H_{14}O_2S_2$): Organic sulfur-containing fatty acid that consists of a cyclic disulfide and a carboxylic acid with a molar mass of 206.33 g/mol. It is also known as lipoate, thioctic acid, or 6,8-dithiooctanoic acid.

Vitamin E ($C_{29}H_{50}O_2$): It is the collective name for a set of eight fat-soluble vitamins (molar mass is 430.69 g/mol): α-, β-, γ-, and δ- tocopherols, and α-, β-, γ-, and δ- tocotrienols.

References

Arivazhagan P, Thilakavathy T, Ramanathan K, Kumaran S, Panneerselvam C. J Nutr Biochem. 2002;13:619–24.

Bagh MB, Maiti AK, Roy A, Chakrabarti S. Biogerontology 2008;9:421–8.

Bailey DM, Davies B. High Alt Med Biol. 2001;2:21–9.

Bist R, Bhatt DK. J Neurol Sci. 2009;276:99–102.

Blomgren K, Hagberg H. Free Radic Biol Med. 2006;40:388–97.

Butterfield DA. Antioxid Redox Signal. 2006;8:1971–3.

Cao L, Chen R, Xu J, Lin Y, Wang R, Chi Z. Neuroscience 2009.

Cao X, Phillis JW. Free Radic Res. 1995;23:365–70.

Chan A, Shea TB. J Alzheimers Dis. 2009;16:167–71.

Chrissobolis S, Faraci FM. Trends Mol Med. 2008;14:495–502.

Conti M, Couturier M, Lemonnier A, Lemonnier F. Int J Vitam Nutr Res. 1993;63:71–6.

Coombes JS, Powers SK, Demirel HA, Jessup J, Vincent HK, Hamilton KL, Naito H, Shanely RA, Sen CK, Packer L, Ji LL. Acta Physiol Scand. 2000a;169:261–9.

Coombes JS, Powers SK, Hamilton KL, Demirel HA, Shanely RA, Zergeroglu MA, Sen CK, Packer L, Ji LL. Am J Physiol Regul Integr Comp Physiol. 2000b;279:R2149–55.

Coombes JS, Powers SK, Rowell B, Hamilton KL, Dodd SL, Shanely RA, Sen CK, Packer L. J Appl Physiol. 2001;90:1424–30.

Fruhauf J, Schaider H, Massone C, Kerl H, Mullegger RR. Mayo Clin Proc. 2008;83:502–4.

Gaedicke S, Zhang X, Huebbe P, Boesch-Saadatmandi C, Lou Y, Wiswedel I, Gardemann A, Frank J, Rimbach G. Br J Nutr. 2009:1–9.

Garcia-Estrada J, Gonzalez-Perez O, Gonzalez-Castaneda RE, Martinez-Contreras A, Luquin S, de la Mora PG, Navarro-Ruiz A. Neurosci Res. 2003;47:219–24.

Gonzalez-Perez O, Gonzalez-Castaneda RE. Nutr Res. 2006;26:1–5.

Gonzalez-Perez O, Gonzalez-Castaneda RE, Huerta M, Luquin S, Gomez-Pinedo U, Sanchez-Almaraz E, Navarro-Ruiz A, Garcia-Estrada J. Neurosci Lett. 2002;321:100–4.

Gonzalez-Perez O, Moy-Lopez NA, Guzman-Muniz J. Rev Invest Clin. 2008;60:58–67.

Haramaki N, Packer L, Assadnazari H, Zimmer G. Biochem Biophys Res Commun. 1993;196:1101–7.

Haramaki N, Assadnazari H, Zimmer G, Schepkin V, Packer L. Biochem Mol Biol Int. 1995;37:591–7.

Heo JH, Han SW, Lee SK. Free Radic Biol Med. 2005;39:51–70.

Jesudason EP, Masilamoni JG, Jebaraj CE, Paul SF, and Jayakumar R. Mol Cell Biochem. 2008;313:113–23.

Ko KM, Yiu HY. Mol Cell Biochem. 2001;220:141–7.

Lexis LA, Fassett RG, Coombes JS. Alpha-tocopherol and alpha-lipoic acid enhance the erythrocyte antioxidant defence in cyclosporine A-treated rats. Basic Clin Pharmacol Toxicol. 2006;98:68–73.

Lockrow J, Prakasam A, Huang P, Bimonte-Nelson H, Sambamurti K, Granholm AC. Exp Neurol. 2009;216:278–89.

Maitra I, Serbinova E, Trischler H, Packer L. Free Radic Biol Med. 1995;18:823–9.

Manda K, Ueno M, Moritake T, Anzai K. Cell Biol Toxicol. 2007;23:129–37.

Mantovani G, Maccio A, Madeddu C, Mura L, Gramignano G, Lusso MR, Murgia V, Camboni P, Ferreli L, Mocci M, Massa E. Free Radic Res. 2003;37:213–23.

Marsh SA, Laursen PB, Pat BK, Gobe GC, Coombes JS. J Mol Cell Cardiol. 2005;38:445–51.

Marsh SA, Coombes JS. Vitamin E and alpha-lipoic acid supplementation increase bleeding tendency via an intrinsic coagulation pathway. Clin Appl Thromb Hemost. 2006;12:169–73.

Monget AL, Richard MJ, Cournot MP, Arnaud J, Galan P, Preziosi P, Herbeth B, Favier A, Hercberg S. Eur J Clin Nutr. 1996;50:443–9.

Mosca L, Marcellini S, Perluigi M, Mastroiacovo P, Moretti S, Famularo G, Peluso I, Santini G, De Simone C. Biochem Pharmacol. 2002;63:1305–14.

Muller U, Krieglstein J. J Cereb Blood Flow Metab. 1995;15:624–30.

Murphy ME, Scholich H, Sies H. Eur J Biochem. 1992;210:139–46.

Naziroglu M, Cay M, Ustundag B, Aksakal M, Yekeler H. Cell Biochem Funct. 1999;17:253–9.

Ozkan Y, Yilmaz O, Ozturk AI, Ersan Y. Cell Biol Int. 2005;29:754–60.

Packer L, Witt EH, Tritschler HJ. Free Radic Biol Med. 1995;19:227–50.

Packer L, Tritschler HJ, Wessel K. Free Radic Biol Med. 1997;22:359–78.

Paravicini TM, Drummond GR, Sobey CG. Drugs 2004;64:2143–57.

Parkinson SG. N Engl J Med. 1993;328:176–83.

Piotrowski P, Wierzbicka K, Smialek M. Folia Neuropathol. 2001;39:147–54.

Poon HF, Calabrese V, Scapagnini G, and Butterfield DA. Clin Geriatr Med. 2004;20:329–59.

Roy S, Sen CK, Tritschler HJ, Packer L. Biochem Pharmacol. 1997;53:393–9.

Sano M, Ernesto C, Thomas RG, Klauber MR, Schafer K, Grundman M, Woodbury P, Growdon J, Cotman CW, Pfeiffer E, Schneider LS, Thal LJ. N Engl J Med. 1997;336:1216–22.

Schmidt MC, Askew EW, Roberts DE, Prior RL, Ensign WY Jr, Hesslink RE Jr. Wilderness Environ Med. 2002;13:94–105.

Scholich H, Murphy ME, Sies H. Biochim Biophys Acta. 1989;1001:256–61.

Schreibelt G, Musters RJ, Reijerkerk A, de Groot LR, van der Pol SM, Hendrikx EM, Dopp ED, Dijkstra CD, Drukarch B, de Vries HE. J Immunol. 2006;177:2630–7.

Scott DL, Kelleher J, Losowsky MS. Biochem Soc Trans. 1976;4:295–6.

Seaton TA, Jenner P, Marsden CD. Biochem Pharmacol. 1996;52:1657–63.

Sharman EH, Bondy SC. Neurobiol Aging. 2001;22:629–34.

Shirpoor A, Minassian S, Salami S, Khadem-Ansari MH, Yeghiazaryan M. Cell Physiol Biochem. 2008;22:769–76.

Stoffel M, Berger S, Staub F, Eriskat J, Jacob K, Baethmann A. J Neurotrauma. 1997;14:339–48.

Stoyanovsky DA, Goldman R, Darrow RM, Organisciak DT, Kagan VE. Curr Eye Res. 1995;14:181–9.

Suchy J, Chan A, Shea TB. Nutr Res. 2009;29:70–4.

Tirosh O, Sen CK, Roy S, Kobayashi MS, Packer L. Free Radic Biol Med. 1999;26:1418–26.

van der Worp HB, Bar PR, Kappelle LJ, de Wildt DJ. Stroke 1998;29:1002–5; discussion 1005–6.

Villalobos MA, De La Cruz JP, Carrasco T, Smith-Agreda JM, Sanchez de la Cuesta F. Brain Res Bull. 1994;33:313–8.

Woltjer RL, McMahan W, Milatovic D, Kjerulf JD, Shie FS, Rung LG, Montine KS, Montine TJ. Effects of chemical chaperones on oxidative stress and detergent-insoluble species formation following conditional expression of amyloid precursor protein carboxy-terminal fragment. Neurobiol Dis. 2007;25:427–37.

Wolz P, Krieglstein J. Neuropharmacology 1996;35:369–75.

Yadav V, Marracci G, Lovera J, Woodward W, Bogardus K, Marquardt W, Shinto L, Morris C, Bourdette D. Mult Scler. 2005;11:159–65.

Chapter 125
Obsessive Eating

Naoko Narita, Mami Tazoe, and Masaaki Narita

Abbreviations

DSM-IV	Diagnostic and statistical manual of mental disorders
5-HT	5-Hydroxytryptamine, serotonin
GH	Growth hormone
IGF-1	Insulin-like growth factor-1, somatomedin-C
ACTH	Adrenocorticotropic hormone
TSH	Thyroid-stimulating hormone
TEG	Tokyo University egogram
STAI	State-trait anxiety inventory
BMI	Body mass index

125.1 Introduction

Obsessive eating is a term that is not used as a clinical diagnosis, but refers to a pathological habit of eating accompanied by neuropsychological disorders. The characteristic clinical feature that is common in obsessive eating is an obsessive and continuous ingestion of a restricted number of food items or other substances regardless of their nutritional value, which often results in nutritional and/or hormonal imbalance, and may result in serious health problems including psychological state alteration.

Eating disorders, which are subcategorized in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) as anorexia nervosa, bulimia nervosa, and eating disorder not otherwise specified, are characterized by unusual eating habits caused by an intense fear of becoming fat (American Psychiatric Association 1994). Although the precise etiology of eating disorders is unclear, abnormalities of biogenic amine neurotransmitters such as serotonin (5-hydroxytryptamine, 5-HT) and dopamine are found in some patients (Brewerton and Jimerson 1996; Kaye et al. 1999; Wolfe et al. 2000), suggesting the relevance of these factors to eating habits. Since abnormal eating habit is the essential phenotype of eating disorders (Behrman et al. 2000), the occurrence of obsessive eating habits in patients with eating disorders is not surprising (Kaye 2008).

N. Narita (✉)
Institute of Education, Bunkyo University, 3337 Minamiogishima,
Koshigaya-City, Saitama, 343-8511, Japan
e-mail: nnarita@koshigaya.bunkyo.ac.jp; naokonarita@yahoo.co.jp

The other representative disorder that may accompany obsessive eating habits is autism spectrum disorder (autism spectrum disorder). Autism spectrum disorder is a congenital neurological disorder characterized by impairment of socialization, abnormalities of communication, and limited activity and curiosity (Charman and Baird 2002; Filipek et al. 1999). The serotonergic system appears to be developmentally dysregulated in autism. Early studies showed high levels of 5-HT in the blood platelets of autistic patients (Anderson et al. 1987; Betancur et al. 2002; Cook Jr et al. 1993). More recently, PET imaging with radiolabeled L-tryptophan has demonstrated asymmetries in 5-HT synthesis in the dentatothalamocortical pathway of autistic boys (Chugani et al. 1997). 5-HT synthesis was decreased in the left frontal cortex and thalamus, but was elevated in the right dentate nucleus. Feeding problems, typically called "selective eating behavior," often coexist with the diagnosis of autism (Kodak 2008). Autism spectrum disorder patients tend to refuse food items other than the very limited number they select, which may also result in inadequate nutritional intake.

Although these disorders are clinically distinct, the obsessive–compulsive features due to their high anxiety levels, which may be caused by the 5-HT abnormalities, explain the common symptoms relating to eating. Therefore, psychobiological commonalities may exist in the preonset phase of obsessive eating. Moreover, the nutritional imbalance may modify postonset neurobiological functioning and behavior owing to the ingredients of the target food items the patients are obsessed with.

125.2 Obsessive Eating in Eating Disorders

125.2.1 Overall Etiology of Anorexia Nervosa/Bulimia Nervosa

Anorexia nervosa is characterized by self-imposed weight loss and amenorrhea. A distorted psychopathological attitude toward eating and body weight is pathognomonic of anorexia nervosa. (Behrman et al. 2000). DSM-IV (American Psychiatric Association 1994) classifies anorexia nervosa into a restricting type and binge-eating/purging type based on the presence of binge-eating/purging (rapid consumption of large amounts of food, followed by induced vomiting or misuse of laxatives). In DSM-IV, bulimia nervosa is distinguished from anorexia nervosa based on the clinical manifestations, although the psychological background including excessive concern about body shape and weight is common to both. In contrast to the emaciation generally observed in anorexia Nervosa patients, bulimia nervosa patients hardly manifest noticeable under- or overweight. The DSM-IV criteria define bulimia nervosa as follows: the binge-eating/purging episodes are observed at intervals of less than 2 h, and the patient has a minimum average of two episodes per week for at least 3 months.

Anorexia nervosa and bulimia nervosa patients share particular eating habits including binge eating, restricted food selection, and obsessive eating. Dysfunction of serotonergic or dopaminergic neuronal systems is the most likely pathophysiological process in these disorders (Bosanac et al. 2005). The serotonergic neuronal system originates from the midbrain raphe nucleus, and its projection regulates diverse physiological functions, including sleep, appetite, pain, motor function, cognition, sexual activity, and emotions such as mood and anxiety. Decreased activity of the serotonergic neuronal system is often observed in patients with eating disorders (Fumeron et al. 2001; Sorbi et al. 1998). On the other hand, the dopaminergic neuronal system has a role in cognition, locomotor activity, exploration, motivation, feeding, and sexual behavior. Activation of the dopaminergic neuronal system in restricting anorexia nervosa patients has been suspected based on their clinical manifestations and the increase of dopamine metabolites observed in their cerebrospinal fluid (Devesa et al. 1988; Kaye et al. 1999). However, no conclusive evidence is available to date.

It is conceivable that the frequent comorbidity of anorexia nervosa/bulimia nervosa with other psychiatric disorders is quite relevant to abnormalities of serotonergic/dopaminergic systems. For instance, it is fairly common to observe food- and weight-related obsessive–compulsive symptoms during the course of anorexia nervosa. Patients with anorexia nervosa often are obsessed with calculating calories, searching for low-calorie food, or performing obviously excessive amounts of exercise. All of these features can be interpreted as phenotypes of obsessive–compulsive disorder (obsessive–compulsive disorder) or obsessive–compulsive personality disorder (obsessive–compulsive personality disorder). Recent neurobiological, genetic, and psychological investigations have accumulated evidence of an overlapping spectrum between anorexia nervosa, bulimia nervosa, and Binge Eating Disorder (originally classified in the eating disorders-NOS in DSM-IV) and obsessive–compulsive disorder or obsessive–compulsive personality disorder (Lazaro et al. 2005; Serpell et al. 2002).

Prevalence rates for obsessive–compulsive disorder or obsessive–compulsive features in eating disorders are relatively high, ranging between 25% and 69% in anorexia nervosa, and 3–40% in bulimia nervosa (Lawson et al. 2007). Abnormal eating habits such as restriction and binge eating themselves can be explained by compulsive behavior to achieve affect regulation (e.g., reducing anxiety). Therefore, there is a keen debate about the pertinence of separating eating disorders and obsessive–compulsive disorder as different diagnostic categories, because they are presently assigned to separate categories in DSM-IV (Grilo 2004; Wu 2008). Moreover, mood disorders, anxiety disorders, and personality disorders are more commonly present with bulimia nervosa than anorexia nervosa, suggesting that the etiologies of anorexia nervosa and bulimia nervosa are quite similar but not identical (Carlos et al. 2009; Kaye 2008). However, it is noteworthy that such disorders, which are possibly comorbid with anorexia nervosa/bulimia nervosa, are also known to be caused at least partially by serotonergic neuronal dysregulation.

Obsessive eating in patients with bulimia nervosa/Binge Eating Disorder is more likely to involve obsession with the cycle of overeating and purging rather than with the food itself. This behavior can be understood to be similar to an addiction to drugs or other substances. Usually the patients experience regret and anguish after the binge eating episode, followed by inadequate compensatory behavior such as vomiting, laxative abuse, diuretic abuse, or overexercise, but are unable to escape from the addiction by themselves. Anxiety, depression, and low self-esteem frequently coexist in these patients, often becoming their dominant thought and subsequently increasing the likelihood of comorbidities like mood disorder and anxiety disorder (Carlos et al. 2009). In contrast to patients with bulimia nervosa/Binge Eating Disorder, those with restricting anorexia nervosa present obsessive eating habits less frequently (Emily et al. 2008). They rather develop malnutrition, hormonal imbalances, and a variety of electrocardiographic abnormalities due to reduced total calorie intake and dehydration, which are the most lethal manifestations, and thus are important in the treatment of the patients.

Recently, we encountered a remarkable and uncommon case of an adolescent with restricting anorexia nervosa who presented with obsessive and restricted banana ingestion for more than 2 years (Tazoe et al. 2007). As a result, the patient developed extreme hyperkalemia, hyperdopaminemia, pseudoaldosteronism, and dysthymia, which could not be explained by the pathology of restricting anorexia nervosa alone. Moreover, the patient had presented with obvious aggression and inner-impulse paralleling an increase in whole blood dopamine, suggesting that the brain dopamine concentration was also affected by the obsessive and restricted banana ingestion. Since bananas are known to be rich sources of both dopamine and potassium (Kanazawa and Sakakibara 2000; Kasuga and Katano 2008), the clinical condition of this patient was thought to be dramatically altered by the massive ingestion of bananas. Details of the case are presented in the following subsections.

125.2.2 Case

At the age of 15, the female patient visited a pediatric clinic for emaciation, amenorrhea, and appetite loss, which had been noted by her school teacher. The patient had been on a strict diet intentionally for the past half year, and had lost 6.2 kg of weight (decreasing from 46.9 to 40.7 kg; BMI = 15.7). She was born at term, her psychomotor development was normal, and had no past history of Attention Deficit/Hyperactivity Disorder or other behavioral problems. Her pulse rate and blood pressure were within the normal range, and the electrocardiogram and cardiac ultrasound showed no abnormality. Although no abnormality was found in the regular blood analysis data, obvious hormonal imbalances were noted as follows: GH 1.47 ng/mL ($\downarrow$), IGF-1 88 ng/mL ($\rightarrow$), ACTH 14 pg/mL ($\rightarrow$), Free T4 0.81 ng/dL ($\downarrow$), Free T3 1.65 pg/mL ($\downarrow$), TSH 1.740 μU/L ($\rightarrow$), and estradiol < 10 pg/mL ($\downarrow$). Minor elements such as Cu, Zn, vitamins B_1 and B_2, lactate, and pyruvate were all within normal ranges. She had pigmentation of the skin and was obviously hyperactive.

125.2.3 Obsessive Banana Ingestion Directly Affects the Blood Dopamine Concentration and Electrolytes

Figure 125.1 shows the course of illness observed in the patient. She was hospitalized two times over a 60-month observation period, and the lowest body weight reported was 27.0 kg (BMI = 10.3). An increase in extraordinarily obsessive behavior began to be observed during her first hospitalization period (from the 8th month of the observed period). She denied ingesting any food item other than bananas (5–20 pieces a day) and hard mineral water (up to 500 mL a day), and was obsessed by the need to engage in excessive daily exercise. Following this obsessive eating behavior, blood analysis showed a gradual increase of serum potassium and whole blood dopamine. The second hospitalization period was required when her body weight dropped as low as 27.0 kg at the 16th month of the observation period. Intravenous hyperalimentation along with cognitive–behavioral therapy was performed during each hospitalization period.

After the 24th month of the observation period, the patient's whole blood dopamine concentration jumped to 180 ng/mL. At the same time her serum potassium was as high as 6.1 mEq/L, although no abnormality was observed in electrocardiogram and blood pressure examination. Later, in the 38th month of the observed period, her dopamine concentration increased to as high as 210 ng/mL. At the 40th month of the observation period, her weight decreased again to 32 kg. Her serum potassium level was 5.7 mEq/L, aldosterone was 708.8 ng/dL, and renin was 130 pg/mL, all of which are relatively higher than the normal range in the Japanese population. Although the patient kept normal blood pressure throughout the course of the illness, the increases in renin and aldosterone suggested that she fell into a state of pseudoaldosteronism during this time period. Serum catecholamine analysis showed an extreme increase of free dopamine (0.47 ng/mL, normal range < 0.03); however, no increase in epinephrine (<0.01 ng/mL) or norepinephrine (0.39 ng/mL) was observed.

In response to treatment with cognitive–behavioral therapy, she began to ingest food items other than banana after 26 months of this restrictive eating pattern. Over the next 12 months, economic reasons prevented her from returning to the clinic; however, the most recent examination at the 56th month of the observation period showed distinct improvement in her blood values, including serum potassium of 5.6 mEq/L and whole-blood dopamine of 56 ng/mL. In addition, her weight had increased to 36 kg. She seemed at that time to have "calmed down" and her skin was obviously depigmented.

125.2.4 Obsessive Banana Ingestion May Have Modified the Psychobiological State in the Patient

The patient's psychological state had been continuously assessed by our team clinical psychologist (MT) regularly during the course of her illness, using three types of psychological tests: the tree drawing test (Koch 1952; Kosaka 2008), the Japanese version of the state-trait anxiety inventory (STAI) (Iwata et al. 1998), and the Tokyo University egogram (TEG), which evaluates ego states (Oshima et al. 1996).

The whole clinical course was classified to six stages according to the degree of emaciation, treatment, and blood analyses as follows (see also Fig. 125.1).

Stage I. Prior to the first hospitalization: She did not cooperate with the psychological therapy or with oral ingestion of nutrient drinks. She walked more than 10 km daily, and exercised her abdominal muscles intensively to build her "ideal body." One drawing (Fig. 125.2) was obtained during this stage.

Stage II. First admission: Within 6 months after the first visit, she had reduced her weight to 32.1 kg (BMI = 12.2). She underwent forced admission to the pediatric ward, where she was treated by intravenous hyperalimentation infusion, along with behavior restriction therapy. She gained 4 kg during the 30-day admission, and was discharged from the hospital afterward. Two drawings (Fig. 125.3a and b) were obtained during this period.

Stage III. Between the first and second hospitalizations: The patient was obsessed by the idea that all processed foodstuffs are contaminated by additives and pesticides. Eventually, she stopped eating
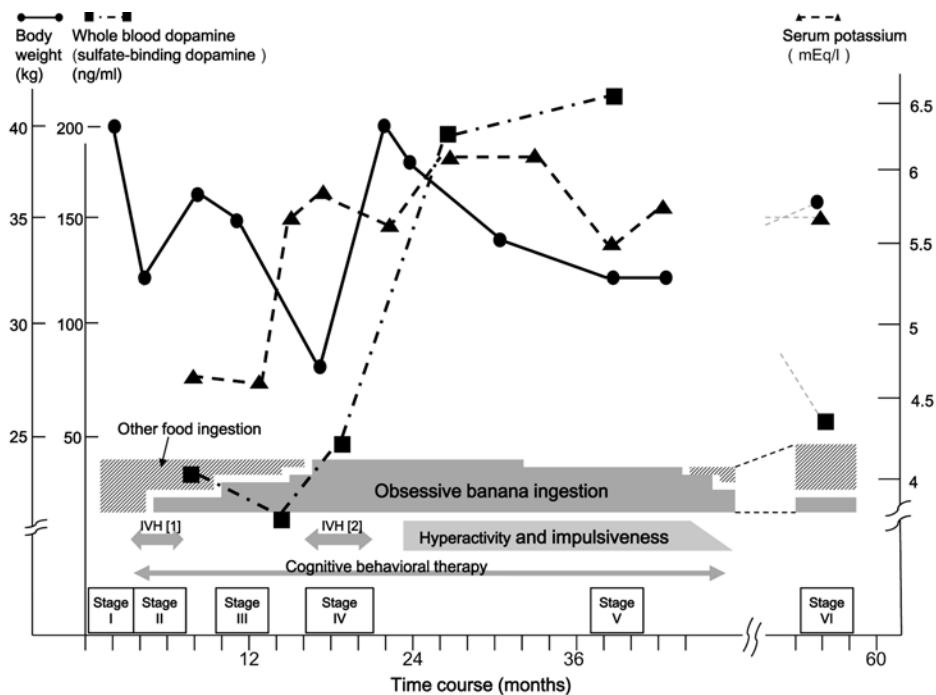
Fig. 125.1 The course of illness in the patient with obsessive banana ingestion. The illness course of the patient is schematically presented. Changes in body weight, whole blood dopamine, serum potassium, and habit of food ingestion are shown. Two intravenous hyperalimentation treatments during hospitalization (IVH [1] and IVH [2]) and continuous cognitive–behavioral therapy were performed. The stages indicated in the figure correspond to the descriptions in the text
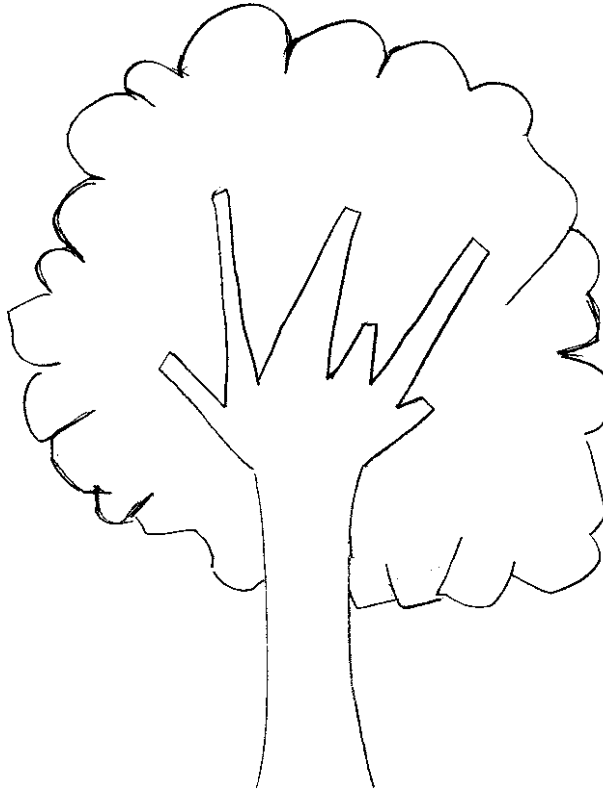
Fig. 125.2 Tree drawing test drawing of the patient at Stage I. Tree drawing test drawing of the patient at Stage I is shown. Note that the branches are cut off in the middle. This feature is consistently observed in the rest of her drawings. The rigid crown shape and the solid and strong lines are also characteristic

except for a maximum of 20 pieces of banana and 500 mL of mineral water per day. She stuck to one type of banana (an organic product from Ecuador) and one brand of hard mineral water. During this period, two drawings (Fig. 125.4a and b) were obtained from the patient.

Stage IV. Second hospitalization: Her weight dropped to 27.0 kg (BMI = 10.3) at this time, which again became an indication for intravenous hyperalimentation treatment and admission. This time she gained over 13 kg and was discharged. However, there was no change in her eating and exercise habit. Two drawings (Fig. 125.5a and b) were obtained during this period.

Stage V. Increase in blood dopamine level due to excessive consumption of bananas: Against the counsel of physicians, psychologists, and her family members, the patient continued her strict avoidance of food items other than bananas and hard mineral water. Blood analysis revealed increased levels of serum potassium, whole blood dopamine, aldosterone, renin, and angiotensin, which suggested a state of pseudoaldosteronism and hyperdopaminemia. At this stage, she also began to show obvious impulsiveness and irritability, which are not frequently observed in anorexia nervosa patients. One drawing (Fig. 125.6) was obtained during this period.

Stage VI. Remission from the obsessive banana ingestion with recovery of all of the blood values: Her impulsiveness and irritability had almost disappeared and she was eating many kinds of food, although the amount was still small. One drawing (Fig. 125.7) was obtained during this period.
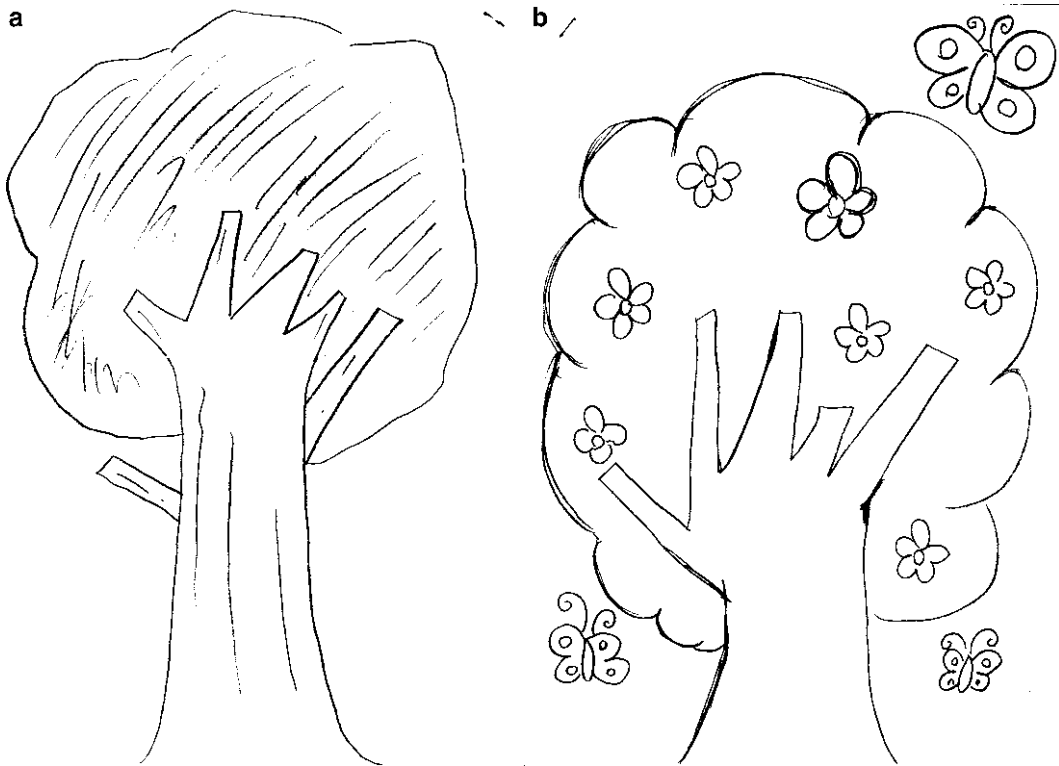
Fig. 125.3 **a** and **b** Tree drawing test drawings of the patient at Stage II. Tree drawing test drawings at Stage II, on admission (**a**) and on discharge (**b**) following the patient's first hospitalization period, are shown. Note that the defective crown size and form seen on admission have improved by discharge

125.2.4.1   The Tree Drawing Test

See Table 125.1 for key features of the tree drawing test.

Figure 125.2 shows the patient's drawing at Stage I. The form of her drawing was interpreted as defensive to stimuli from the outer world (outlining of the crown is rigidly shut) and emotionally shut off from relationships with others (the branches are all cut off in the middle), which are both considered to represent a pathologically low energy state. The lines of drawing were consistently solid and high in strength during all stages, which was thought to represent the inherent individuality of her obsessive tendency.

Figures 125.3a and b were both obtained during Stage II, the first hospitalization period. On admission (Fig. 125.3a), the crown was drawn with discontinuous lines in the tree drawing test, suggesting her susceptibility to the outer world. The branches were still the same, having the cut-off-in-the-middle shape, suggesting her emotionally shut-off state. In addition, the crown was shaded, which was thought to represent her depressive state. The size of the crown was reduced and a branch grew beneath the crown, which was considered representative of her psychological regression. On discharge after approximately a month of hospitalization, her drawing (Fig. 125.3b) still showed signs of defensiveness and emotional shutting off. However, the crown was enlarged and was no longer painted, and no branches were seen beneath the crown. These observations suggested that her
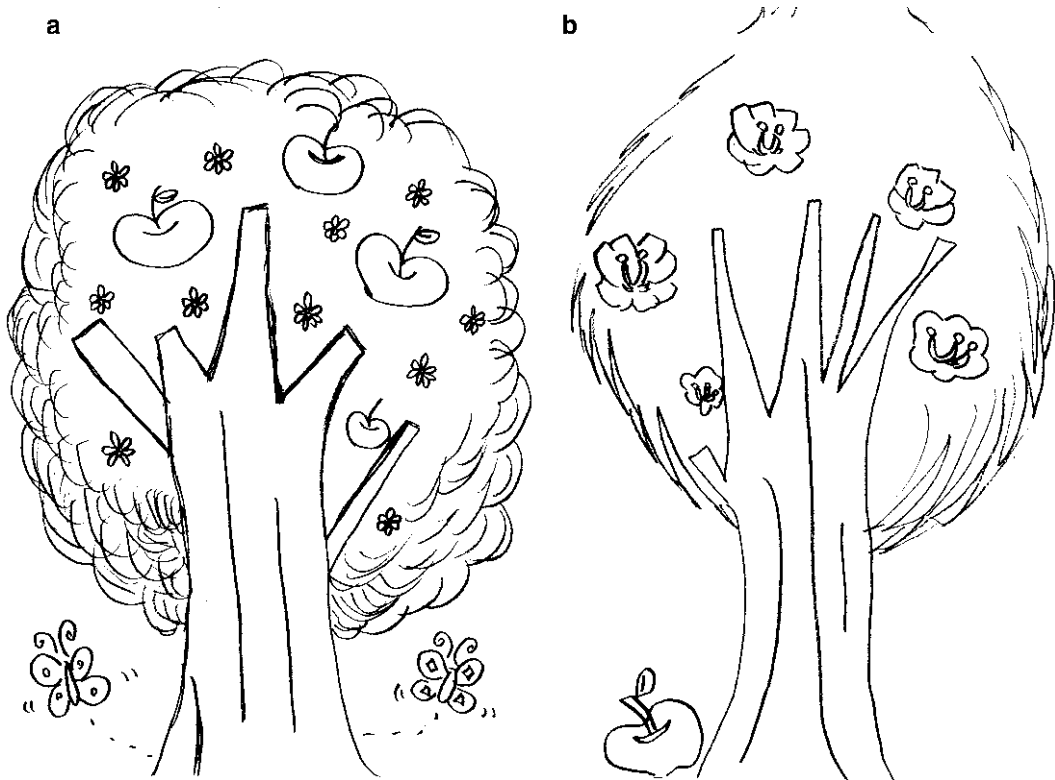
Fig. 125.4 **a** and **b** Tree drawing test drawings of the patient at Stage III. Tree drawing test drawings earlier (**a**) and later (**b**) in Stage III are shown. The patient was obsessed with banana ingestion, and her condition gradually deteriorated during this period. Note that the outline of the crown was drawn differently, and later, the crown protruded from the paper

psychological regression had ended. Instead, the drawing showed flowers and butterflies with a trunk of wide width, which was thought to represent her self-display and magnified self. The lines of the drawing are solid and very strong, similar to those of previous drawings.

During Stage III, the period when the patient's obsessive banana ingestion began and continued, tree drawing test was performed twice and an obvious change in the crown form was observed. The outline of the crown was drawn fluffy with repeated lines in the earlier drawing of Stage III (Fig. 125.4a), which was deformed into more sharp-pointed and discontinuous form in the later drawing (Fig. 125.4b). These observations were interpreted to mean that her susceptibility to outer stimuli grew and she needed to pile up the lines to be more defensive. Later on, she became irresistibly hypersensitive and more aggressive. This time, the crown protruded out from the paper, representing her acting-out state.

During Stage IV, the second period of hospitalization that occurred when her critical emaciation had progressed as a result of her obsessive banana ingestion, tree drawing test was performed twice (Fig. 125.5a and b). In Fig. 125.5a, the tree drawing test performed on admission, the patient's drawing showed a wide trunk, branches beneath the crown (regression), and a discontinuous outline of the crown. It seemed she no longer had the energy to shut the crown through repeated drawing; the single discontinuous line can easily let the outer stimuli invade into her inner-self. On discharge after the second hospitalization period, the form of the tree drawing test (Fig. 125.5b) showed slight improvement, with a wide trunk and fruits that represent self-display and magnified self.
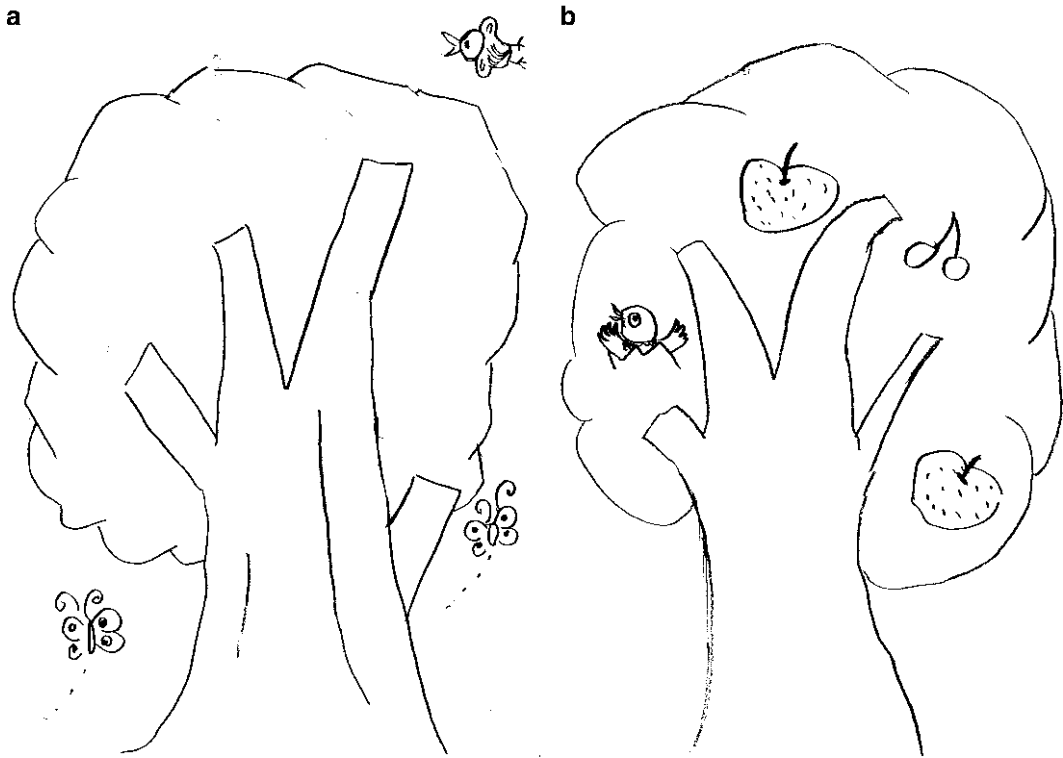
Fig. 125.5 **a** and **b** Tree drawing test drawings of the patient at Stage IV. Tree drawing test drawings at Stage IV, on admission (**a**) and on discharge (**b**) following the second hospitalization period, are shown. Note that on admission, the form of the drawing seems collapsed and the crown has a discontinuous outline, showing loss of energy

Generally speaking, to this point, her psychological energy had been decreasing in tandem with the stage progression. However, at Stage V, when her obsessive eating was at a maximum and her blood dopamine concentration was elevated as high as 180 ng/mL, her drawing showed drastic changes. Figure 125.6 shows her drawing at this stage. The form of the crown was completely changed, with lines rising one by one from the inner area of the tree, as if showing the effort of the patient's resistance to her bursting inner-impulse. For the first time, a horizon appeared in her drawing as a notched line, representing a decrease in her anxiety and an apparent stabilization (in her subjective sense, although she was not healthy). The lines were drawn smoothly with no disconnection, showing her full of energy without anxiety or depression. These changes were totally inexplicable and unexpected based on her physical state, which was characterized by body weight as low as 30 kg, indicating that she was critically ill with anorexia nervosa.

At Stage VI, the bizarre observations seen in the drawing at Stage V had completely disappeared, namely, the drawing showed the pattern that had originally been observed in the patient (Fig. 125.7). The form of the crown was smooth, with a continuous outline with no rigidness, indicating that her defensiveness and susceptibility to the outer stimuli were decreased in her current psychic state. The extremely wide trunk (especially at the bottom) and fruits/butterfly showed that her self-display and magnified self-tendency still exist, suggesting that she was not completely healthy but was seemingly back to her original psychic state as a result of stopping banana ingestion and the consequent decrease in her blood dopamine concentration.

Fig. 125.6 Tree drawing test drawing of the patient at Stage V. Tree drawing test drawing at Stage V is shown. Note the formation of the crown with lines rising one by one from the inner side of the tree, as if showing the patient's effort to resist her bursting inner-impulse
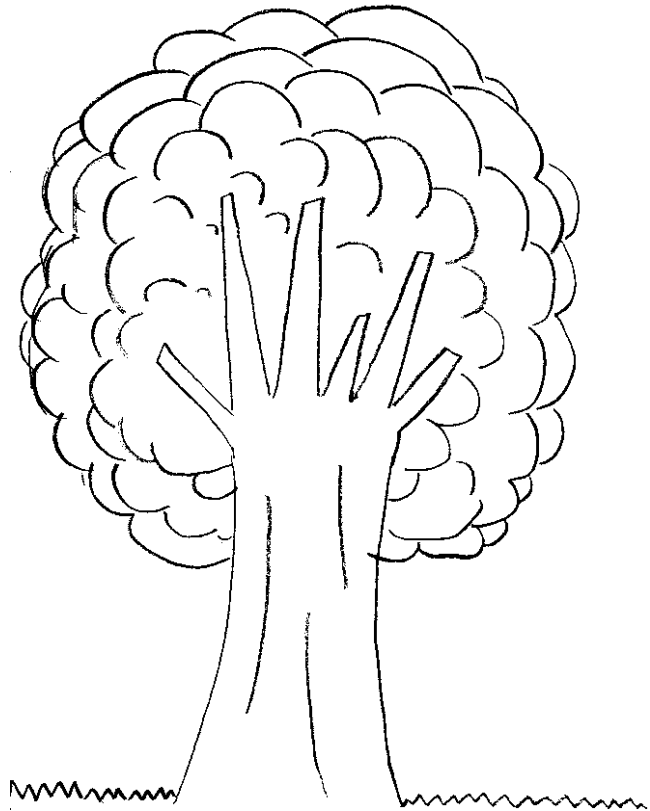
125.2.4.2 The STAI

The STAIs were performed at Stages III, IV, and V. The STAI-state anxiety score was 55, 68, and 46, and the STAI-trait anxiety score was 47, 58, and 49, respectively at each stage. At Stage V, the patient's anxiety levels, which had been rising along with her illness condition suddenly decreased, apparently showing that the patient "did not feel" anxious anymore during this period. These finding were similar to the results of the tree drawing test.

125.2.4.3 The Ego State

The patient's ego states were examined at Stage I and Stage V. At Stage I, low energy was observed in the egogram, and low CP (Critical Parent) and FC (Free Child) were observed along with high AC (Adopted Child). These results were interpreted to indicate low ego state, low self-assertion, and emotional repression with high law-abiding tendency. This observation was consistent with her tree drawing test and the diagnosis of restricting anorexia nervosa. In contrast, at Stage V, high energy was observed in the egogram. Her ego state showed a result that was the complete inverse of that in Stage I, with high-rising CP and FC, and an obvious decrease in AC. At this stage, the patient "feels" high ego energy, high self-assertion, and emotional elevation with low law-abiding tendency, and is seemingly full of vigor. Again, this observation did not contradict the results of the tree drawing test and STAI at this stage, suggesting transitory and unexpected psychological alteration had occurred at Stage V.

Fig. 125.7 Tree drawing test drawing of the patient at Stage VI. Tree drawing test drawing at Stage VI is shown. After remission of the obsessive banana ingestion, the bizarre observations seen in the Tree drawing test drawing at Stage V have completely disappeared and the drawing now resembles Figs. 125.3b and 125.5b, from the earlier post-treatment periods
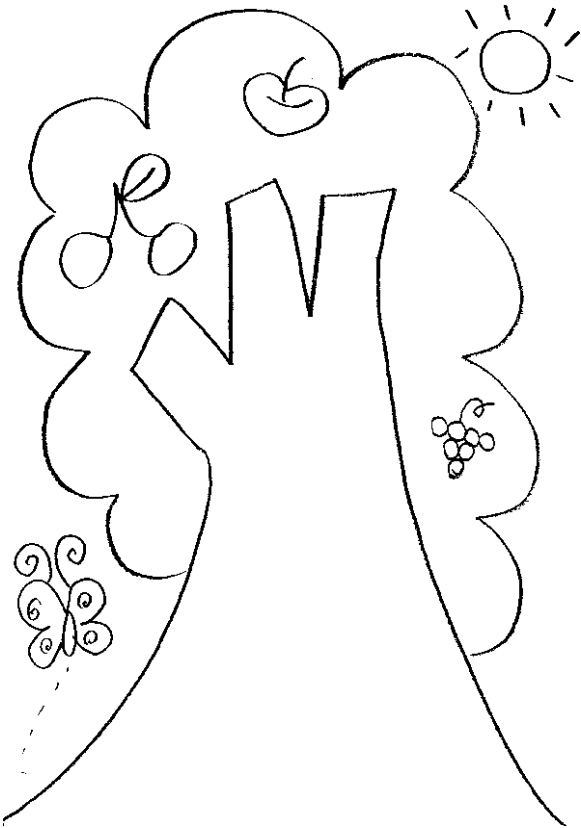
Table 125.1 Key features of the tree drawing test

1. Tree drawing test is also known as Baum test ("baum" means "tree" in German), first developed and distributed in Germany by Koch in 1950s (Koch 1952)
2. Using a size of 210 × 297 mm drawing paper, a 4B pencil, and an eraser, the subject is instructed to draw a tree which bears fruits of any kind, in any way he/she likes
3. The size and location of the tree on the sheet are considered to represent the self-cognition and relative relationship between the subject and surrounding environments
4. The shape and the size of the crown are considered to represent the subjective inner mental state, in relation with the outer world
5. The trunk and the elements drawn along with the tree (fruits, flowers, butterflies, birds, etc) are thought to represent the "self" state and desire of the subject
6. The strength, solidness, energy, continuity, and repetition of the drawing lines are examined closely to observe the subject's inherent individuality and pathological characteristics

This table lists the key features of the tree drawing test including the history, the procedure, and the tips for interpretation

125.3 The Impact of Obsessive Eating of Banana on Neurobiology and Behavior

The patient followed an unusual course of restricting anorexia nervosa, which was considered to be related to her long period of obsessive and restricted banana ingestion. The summary points of the case are shown in Fig. 125.8. Bananas are known to be a dopamine-rich food. Approximately 0.72 mg
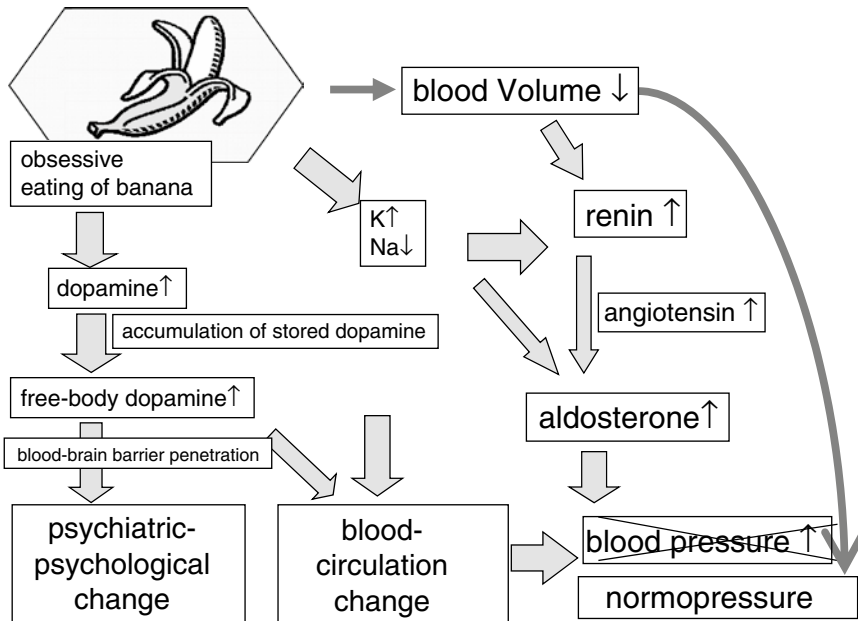
Fig. 125.8 The summarized feature of the case. The summarized feature of the case with obsessive eating of banana is shown. The increase of blood potassium and dopamine induced by unusual consumption of banana was considered to be responsible for the pseudoaldosteronism and the psychiatric-psychological change in the patient

of dopamine is contained within 100 g (approximate weight of the edible portion of one banana) of ripe banana fruit, and 100 g of unripe banana fruit contains as much as 10 mg of dopamine. Moreover, 100 g of ripe banana skin and thread contain 235 mg of dopamine and 100 g of unripe banana skin and thread contain approximately 1,940 mg of dopamine (Kanazawa and Sakakibara 2000). Dopamine is absorbed in a sulfate-conjugated form from the digestive tract, and normally the free dopamine level is not affected by the dose of ingested dopamine (Davidson et al. 1981; Dunne et al. 1983).

The patient showed some level of hyperdopaminemia from the beginning of her illness course, which is consistent with previous reports of dopaminergic neuronal hyperactivity in anorexia nervosa (Devesa et al. 1988; Kaye et al. 1999). However, the dramatic increase in her whole-blood dopamine concentration, which was observed immediately after she began excessive ingestion of bananas, cannot be explained simply based on the pathogenesis of anorexia nervosa. Rather, considering the fact that the patient preferred unripe bananas to ripe ones and often ate the skin and thread of the banana as well, her daily ingestion of dopamine must have increased significantly. That increase may eventually have led to an increase in free dopamine (0.47 ng/mL, compared with the normal range in the Japanese population of <0.03 ng/mL), without a corresponding increase in epinephrine or norepinephrine, most likely because banana contains particularly large amounts of dopamine, but relatively smaller amounts of epinephrine and norepinephrine. We suspect that in the case of this patient, sulfate-binding dopamine became oversaturated by daily ingestion of large amounts of banana, which led to the resulting increase in free dopamine.

In addition to hyperdopaminemia, the patient demonstrated hyperkalemia and pseudoaldosteronism. Bananas are also known to be rich in potassium, containing 330–400 mg of potassium in 100 g of the edible portion of the fruit (Kasuga and Katano 2008). Hyperkalemia, along with hyperdopaminemia, is considered to be the leading cause of pseudoaldosteronism. An obvious increase in

blood renin and angiotensin was observed, but her blood pressure remained normal throughout the course of her illness, probably because of her absolute hypovolemia.

In the initial tree drawing test and egogram performed prior to the onset of obsessive eating, the patient showed low energy and ego states, with defensiveness, low self-assertion, and a strong protective tendency, which were all reasonably explained by the psychopathology of anorexia nervosa and essential obsessive personality of the patient (Mizuta et al. 2002). However, in tree drawing test, egogram, and STAI performed after 2 years of obsessive ingestion of only banana, the opposite results were observed; high energy and ego states, with an extreme internal impulsiveness and low anxiety and high self-assertion. Given that this alteration in psychological state occurred with simultaneous hyperdopaminemia and disappeared along with remission of the obsessive banana ingestion, it is possible that the extreme increase in her blood dopamine level resulting from obsessive banana ingestion was responsible for saturating binding proteins and increasing free dopamine, which affected her psychological state.

Her obvious aggression and inner-impulse, in accord with the increase in whole-blood dopamine, suggest that the brain dopamine concentration was also affected by the obsessive and restricted ingestion of banana. Dopamine is well known to have poor blood–brain barrier penetration because of physiological blockade caused by its high polarity. However, a recent study revealed that blood–brain barrier penetration of dopamine could be increased in a dose- and time-dependent manner by continuous arterial infusion of dopamine (Martel et al. 1996). Thus, it seems reasonable to assume that blood–brain barrier penetration by dopamine was modified in the patient, who experienced hyper-free dopaminemia, as a result of lengthy and excessive ingestion of banana.

Nutrient imbalance resulting from deficiency of vitamins and minerals such as calcium, iron, zinc, phosphate, and magnesium may be observed in eating disorders, and this imbalance may cause skin disease, endocrinological disorder, or osteopenia (Seidenfeld et al. 2004). Zinc is an important brain nutrient, acting as a neuromodulator/neurotransmitter mainly in the cortex in relation to glutaminergic neurons (Harrison and Gibbons 1994; Takeda et al. 2000). Deficiency of zinc may be related to cognitive disorder or depression (Meunier et al. 2005). However, no clear link to eating disorders has yet been proven, and no sign of zinc deficiency was observed in the present case.

The case of our patient is noteworthy as an extreme example of how ingested food directly affects the biochemical and psychic state. The patient showed strong and irrational obsessive behavior with food and exercise compared to patients with regular anorexia nervosa. Since abnormal eating habits are common in patients with anorexia nervosa, it is necessary to identify detailed eating habits of anorexia nervosa patients to avoid the cumulative effects of a particular food on their physical and psychic state.

125.4 Applications to Other Areas of Health and Disease

As mentioned above, obsessive eating is a pathological eating habit, rather than a clinical diagnosis. Thus, any neuropsychological disorder associated with obsessive behavior caused by anxiety has the potential to provoke obsessive eating habits, regardless of its etiology. From this perspective, not only eating disorders, which are defined based on the eating habit, but obsessive–compulsive disorder, obsessive–compulsive personality disorder, autism spectrum disorder, and any other congenital chromosomal defect can show obsessive eating as one of their clinical symptoms.

Obsessive eating can accompany any type of eating disorders, especially when binge eating symptoms coexist. Recently, new concepts of night eating syndrome and sleep-related eating disorder have been proposed as atypical categories of eating disorders. They are characterized by unusual amount of food consumption during the night time, and the behavior can often be obsessive (O'Reardon et al. 2005).

Another pathological condition related to obsessive eating that should be mentioned here is pica. Pica is usually seen in infancy and early childhood and is characterized by repeated or chronic ingestion of non-nutritional substances, such as plaster, charcoal, clay, wool, ashes, paint, and earth. It is known that pica is frequently associated with neuropsychological disorders, including autism spectrum disorder, schizophrenia, and mental retardation (Herguner et al. 2008; Lockner et al. 2008; Behrman et al. 2000), and patients often fulfill the criteria of obsessive–compulsive disorder as well (Bhatia and Gupta 2007).

Interestingly, eating disorders, obsessive–compulsive disorder, autism spectrum disorder, and other psychological disorders that are potentially related to obsessive eating are comorbid among each other to some degree (Grilo 2004; Hambrook et al. 2008; Wu 2008). Moreover, pharmacological treatments, including SSRIs and topiramate, are effective to some extent in all of these disorders (Arnone 2005; Niederhofer 2008; Rosenblum and Forman 2003), suggesting that neurocognitive pathophysiology, including serotonergic and glutaminergic neuronal systems, may be involved in the etiology of these disorders, as well as in obsessive eating habit.

Summary Points

- Obsessive eating is a term not used as a clinical diagnosis, but refers to a pathological habit of eating accompanied by neuropsychological disorders.
- Obsessive eating habit can be associated with eating disorders, autism spectrum disorder, obsessive–compulsive disorder, and other neuropsychological disorders that are considered to be related to serotonergic dysfunction.
- We have reported a case of restricting anorexia nervosa in a female adolescent who was obsessed by an extremely restricted eating habit.
- As a result of eating only bananas and mineral water over more than 2 years, she exhibited biochemical and metabolic disorders as well as a psychological disorder.
- She developed hyperkalemia, hyperdopaminemia, and pseudoaldosteronism possibly as a result of an imbalance of nutritive intake. However, hypertension was not observed, most likely because of absolute hypovolemia.
- The psychological tests performed over the course of her illness showed changes in her psychic state, such as increased anxiety levels, and decreased psychological energy and ego energy.
- In her most extreme phase of hyperdopaminemia, she revealed the conflict associated with resisting her inner-impulse in her Tree drawing test drawing, which differed completely from the drawings made during other stages of the illness.
- The accumulation of free dopamine due to obsessive banana ingestion was considered to affect the patient's psychic state.

Definitions and Explanations of Key Terms or Words

Obsessive eating: A term that is not used as a clinical diagnosis, but rather refers to a pathological habit of eating accompanied by neuropsychological disorders.
Eating disorders: Unusual eating habits resulting from an intense fear of becoming fat as defined in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV).
Anorexia nervosa: A subcategory of eating disorders characterized by self-imposed weight loss and amenorrhea. A distorted psychopathological attitude toward eating and weight gain is pathognomonic of anorexia nervosa.

Bulimia nervosa: Another subcategory of eating disorders characterized by recurrent binge eating, followed by compensatory behavior such as vomiting or misuse of laxatives.

Obsessive–compulsive disorder: A subcategory of anxiety disorders in DSM-IV characterized by involuntary intrusive thoughts and compulsive behavior.

Autism spectrum disorder: A spectrum of congenital neurological disorders characterized by impairment of socialization, abnormalities of communication, and limited activity and curiosity.

Serotonin (5-hydroxytryptamine, 5-HT): A biogenic amine neurotransmitter synthesized from L-tryptophan. 5-HT modulates diverse effects of the neuronal system, including sleep, appetite, pain, motor function, cognition, sexual activity, as well as emotions such as mood and anxiety.

Dopamine: A biogenic amine neurotransmitter synthesized from l-tyrosine. Dopamine also regulates diverse functions of neuronal system, including cognition, locomotor activity, exploration, motivation, feeding, and sexual behavior.

References

American Psychiatric Association. DSM-IV. Washington, DC: American Psychiatric Association; 1994

Anderson GM, Freedman DX, Cohen DJ, Volkmar FR, Hoder EL, McPhedran P, Minderaa RB, Hansen CR, Young JG. J Child Psychol Psychiatry. 1987;28:885–900.

Arnone D. Ann Gen Psychiatry. 2005;4:5.

Behrman RE, Kliegman R, Jensen HB, editors. 16th ed. Philadelphia: Saunders; 2000.

Betancur C, Corbex M, Spielewoy C, Philippe A, Laplanche JL, Launay JM, Gillberg C, Mouren-Simeoni MC, Hamon M, Giros B, Nosten-Bertrand M, Leboyer M. Mol Psychiatry. 2002;7:67–71.

Bhatia MS, Gupta R. World J Biol Psychiatry. 2007;11:1–3.

Bosanac P, Norman T, Burrows G, Beumont P. Aust NZ J Psychiatry. 2005;39:146–53.

Brewerton TD, Jimerson DC. Psychiatry Res. 1996;62:31–42.

Carlos MG, Marney AW, Robin MM. Int J Eat Disord. 2009;42:228.

Charman T, Baird G. J Child Psychol Psychiatry. 2002;43:289–305.

Chugani DC, Muzik O, Rothermel R, Behen M, Chakraborty P, Mangner T, da Silva EA, Chugani HT. Ann Neurol. 1997;42:666–9.

Cook EH Jr, Arora RC, Anderson GM, Berry-Kravis EM, Yan SY, Yeoh HC, Sklena PJ, Charak dopamine, Leventhal BL. Life Sci. 1993;52:2005–15.

Davidson L, Vandongen R, Beilin LJ. Life Sci. 1981;29:1773–8.

Devesa J, Perez-Fernandez R, Bokser L, Gaudiero GJ, Lima L, Casanueva FF. Horm Metab Res. 1988;20:57–60.

Dunne JW, Davidson L, Vandongen R, Beilin LJ, Rogers P. Life Sci. 1983;33:1511–7.

Emily BA, Anthony P, Maria OE, Carlos MG. Can J Psychiatry. 2008;53:863.

Filipek PA, Accardo PJ, Baranek GT, Cook EH.Jr, Dawson G, Gordon B, Gravel JS, Johnson CP, Kallen RJ, Lewin GR, Levy SE, Minshew NJ, Ozonoff S, Prizant BM, Rapin I, Rogers SJ, Stone WL, Teplin S, Tuchman RF, Volkmar FR. J Autism Dev Disord. 1999;29:439–84.

Fumeron F, Betoulle D, Aubert R, Herbeth B, Siest G, Rigaud D. Mol Psychiatry. 2001;6:9–10.

Grilo CM. Behav Res Ther. 2004;42:57–65.

Hambrook D, Tchanturia K, Schmidt U, Russell T, Treasure J. Br J Clin Psychol. 2008;47:335–9.

Harrison NL, Gibbons SJ. Neuropharmacology 1994;33:935–52.

Herguner S, Ozyildirim I, Tanidir C. Prog Neuropsychopharmacol Biol Psychiatry. 2008;32:2010–11.

Iwata N, Mishima N, Shimizu T, Mizoue T, Fukuhara M, Hidano T, Spielberger CD. Ind Health. 1998;36:8–13.

Kanazawa K, Sakakibara H. J Agric Food Chem. 2000;48:844–8.

Kasuga A, Katano K. Kagawa Nutr Univ J. 2008;39:47–53.

Kaye WH. Physiol Behav. 2008;94:121–35.

Kaye WH, Frank GK, McConaha C. Neuropsychopharmacology 1999;21:503–6.

Koch C. Bern: Hans Huber; 1952.

Kodak T, Piazza C. Child Adolesc Psychiatric Clin N Am. 2008;17:887–905.

Kosaka S. Osaka: Union; 2008.

Lawson R, Waller G, Lockwood R. Eat Behav. 2007;8:305–10.

Lazaro L, Moreno E, Baos P, Castro J. Int J Eat Disord. 2005;37:275–7.

Lockner DW, Crowe TK, Skipper BJ. J Am Diet Assoc. 2008;108:1360–3.

Martel CL, Mackic JB, Adams JD Jr, McComb JG, Weiss MH, Zlokovic BV. Pharm Res. 1996;13:290–5.

Meunier N, O'Connor JM, Maiani G, Cashman KD, Secker DL, Ferry M, Roussel AM, Coudray C. Eur J Clin Nutr. 2005;59(Suppl. 2):S1–4.

Mizuta I, Inoue Y, Fukunaga T, Ishi R, Ogawa A, Takeda M. Psychiatr Clin Neurosci. 2002;56:41–53.

Niederhofer H. Med Hypotheses. 2008;70:455.

O'Reardon JP, Peshek A, Allison KC. CNS Drugs. 2005;19:997–1008.

Oshima K, Horie H, Yoshiuchi K, Shimura M, Nomura S, Wada M, Tawara R, Nakao M, Kuboki T, Suematsu H. Japan J Psychosomat Med. 1996;36:315–24.

Rosenblum J, Forman SF. Curr Opin Pediatr. 2003;15:346–7.

Seidenfeld ME, Sosin E, Rickert VI. Mt Sinai J Med. 2004;71:155–61.

Serpell L, Livingstone A, Neiderman M, Lask B. Clin Psychol Rev. 2002;22:647–69.

Sorbi S, Nacmias B, Tedde A, Ricca V, Mezzani B, Rotella CM. Lancet 1998;351:1785.

Takeda A, Takefuta S, Okada S, Oku N. Brain Res. 2000;859:352–7.

Tazoe M, Narita M, Sakuta R, Nagai T, Narita N. Brain Dev. 2007;29:369–72.

Wolfe BE, Metzger ED, Levine JM, Finkelstein DM, Cooper TB, Jimerson DC. Neuropsychopharmacology 2000;22:257–63.

Wu KD. J Anxiety Disord. 2008;22:1412–20.

Chapter 126
Eating Disorders and Suicide

Antonio Preti, Maria Valeria Camboni, and Paola Miotto

Abbreviations

AN	Anorexia nervosa
AN-BP	Anorexia nervosa, binge-eating/purging type
AN-R	Anorexia nervosa, restricting type
BD	Bipolar disorder
BED	Binge eating disorder
BMI	Body mass index
BN	Bulimia nervosa
BN-NP	Bulimia nervosa, nonpurging type
BN-P	Bulimia nervosa, purging type
CI	Confidence interval
CRF	Cortical releasing factor
CSF	Cerebrospinal fluid
DSH	Deliberate self-harm
DSM-IV-TR	*Diagnostic and Statistical Manual*, IV edition, Transitory Revision; the diagnostic manual of the American Psychiatric Association
EDNOS	Eating disorder not otherwise specified
EDs	Eating disorders
ESEMeD	European Study of the Epidemiology of Mental Disorders
5-HIAA	5-Hydroxyindolacetic acid, the major metabolite of serotonin
5-HT	5-Hydroxy-tryptophan, or serotonin
HPA	Hypothalamic pituitary adrenal axis
MDD	Major depressive disorder
NA	Noradrenalin
NCS-R	National Comorbidity Survey Replication
PD	Personality disorder
SIB	Self-injury behavior
SSRIs	Selective serotonin reuptake inhibitors
SUD	Substance use disorder

A. Preti (✉)

Department of Psychology, University of Cagliari, via is Mirrionis 1, 09123 Cagliari, Italy
and
Centro Medico Genneruxi, Via Costantinopoli 42, 09129 Cagliari, Italy
e-mail: apreti@tin.it

126.1 Introduction

Worldwide, suicide is one of the top five causes of death among 15–25 year-old people, the age group that is exposed the most to the risk of developing an eating disorder. Indeed, suicide was reported as one of the main causes of death in people with eating disorders (EDs) (Sullivan 1995), and suicidal behavior is reported as highly prevalent in patients with EDs (Franko and Keel 2006; Signorini et al. 2007).

At present, the definition of EDs is conferred to a set of behavioral disorders characterized by disordered eating and body dissatisfaction, a high level of psychological distress related to eating behavior, and high comorbidity with other mental disorders, principally anxiety, mood, and substance use disorders (SUDs).

Current classifications identify two main syndromes of EDs: anorexia nervosa (AN) and bulimia nervosa (BN), and a wide range of subclinical conditions called "eating disorders not otherwise specified" (EDNOS). Among the EDNOS, binge eating disorder (BED) recently acquired a more precise clinical and epidemiological validity and is now considered worthy of clinical and diagnostic autonomy (Hudson et al. 2007).

This chapter reviews the evidence on suicidality in EDs to provide some clues on prevention and treatment that might also be relevant for other areas of health and disease.

126.2 Eating Disorders: General Characteristics

Typically, the self-esteem of individuals with EDs is highly dependent on their body shape and weight: low self-esteem is reported as an antecedent of the development of EDs (Jacobi et al. 2004).

Severe disturbances in eating behavior are the main feature of EDs: in AN there prevails the refusal to maintain a minimally normal body weight, while BN is characterized by repeated episodes of binge eating followed by inappropriate compensatory behaviors as self-induced vomiting, misuse of laxatives, diuretics, or other medications, fasting, or excessive exercise. Episodes of binge eating and inappropriate compensatory behaviors can occur in AN too, while binge eating without compensatory techniques is the main feature of BED. Often, obesity follows as a consequence of uncompensated recurrent episodes of binge eating.

Binge is defined as eating in a discrete period of time (usually less than 2 h) an amount of food that is definitely larger than most individuals would eat under similar circumstances. It may include sweet, high calorie foods as ice cream or cake, and it comes with a sense of lack of control. People are often ashamed of their eating problems and try to conceal their symptoms, so the episodes of binge eating usually occur in secrecy. Typical triggers are dysphoric mood states, interpersonal stressors, or intense hunger following dietary restraint. Binge eating may reduce dysphoria, but generally distressing self-criticism and depressed mood follow.

The most common compensatory technique after binge eating is the induction of vomiting: it produces relief from physical discomfort and also decreases the fear of gaining weight. Individuals with EDs may also fast for a day or more or exercise excessively in an attempt to compensate for binge eating (*Diagnostic and Statistical Manual*, IV edition, Transitory Revision (DSM-IV-TR)). Individuals with diabetes mellitus and EDs may omit or reduce insulin doses in order to reduce the metabolism of the food eaten during binges, a very dangerous and life-threatening practice (Fairburn and Harrison 2003).

126.2.1 Anorexia Nervosa: Clinical Features

Diagnosis of AN is made in the presence of a refusal to maintain a minimally normal body weight (Criterion A), associated with intense fear of gaining weight or becoming fat (Criterion B), and significant disturbance in the perception of body shape or size (Criterion C). Amenorrhea (Criterion D) is usually a consequence of weight loss but sometimes it may actually precede it; in prepubertal females, the illness may delay menarche (DSM-IV-TR). The corresponding symptom in males is loss of libido.

Usually weight loss is accomplished primarily through reduction in total food intake, which may associate with purging (i.e., self-induced vomiting or the misuse of laxatives or diuretics) and increased or excessive exercise. For Criterion A to be satisfied, body weight must be consistently 15% lower than expected for the same height and age or the body mass index (BMI) must be 17.5 or lower.

When severe underweight induces depressive symptoms such as depressed mood, social withdrawal, irritability, and insomnia, the criteria for major depressive disorder (MDD) are often met. Intense obsessive-compulsive symptoms, either related or unrelated to food, can develop as well and may persist even after weight restoration (Kaye et al. 2000). Subclinical psychotic symptoms can occur during starvation, such as inflexible thinking, limited social spontaneity, and affective flattening expressed through overly restrained initiative and emotional expression.

The somatic symptoms of AN largely depend on restrictive diet (Mitchell and Crow 2006). Emaciation prevails, and there may be complaints of constipation, abdominal pain, cold intolerance, lethargy, and excess energy. There may also be significant hypotension with bradycardia, hypothermia, and dryness of skin, with some individual developing lanugo, a fine downy body hair, on their trunks. Peripheral edema may develop during weight restoration, often following the cessation of laxative and diuretic abuse. Hypertrophy of the salivary glands, particularly the parotid glands, may be present.

Severe general medical conditions may follow a semistarvation period, including impaired renal function (associated with chronic dehydration and hypokalemia), cardiovascular problems (severe hypotension, arrhythmias), dental problems, and osteoporosis (resulting from low calcium intake and absorption, reduced estrogen secretion, and increased cortisol secretion).

No laboratory abnormality is typical enough of AN to be used for diagnosis: leukopenia and mild anemia are common, as are elevated liver function tests; self-induced vomiting may lead to metabolic alkalosis (elevated serum bicarbonate), hypochloremia, and hypokalemia, and laxative abuse may cause a metabolic acidosis; low serum estrogen levels are present in females, low levels of serum testosterone in males; sinus bradycardia and arrhythmias can be observed. An increase in the ventricular-brain ratio secondary to starvation may be seen at brain imaging, and diffuse abnormalities at electroencephalography may result from significant fluid and electrolyte disturbances.

126.2.2 Bulimia Nervosa: Clinical Features

Diagnosis of BN is made in the presence of binge eating (Criterion A) and inappropriate compensatory methods to prevent weight gain (Criterion B); for diagnosis both behaviors must occur, on average, at least twice a week for 3 months (Criterion C); the self-evaluation of individuals with BN must be demonstrably influenced by body shape and weight (Criterion D).

People with BN show the same fear of gaining weight or becoming fat and the associated intense desire to lose weight and dissatisfaction with their bodies as those with AN, although they never

reach the extreme emaciation of AN, and when this does occur (BMI ≥ 17.5), the diagnosis of BN is not appropriate (DSM-IV-TR).

Mood disturbances often co-occur with BN: sometimes mood disturbance clearly precedes the onset of BN. Also, increased occurrence of anxiety and anxiety disorders does occur in association with BN. Personality disorders (PDs), particularly borderline PD, are often comorbid with BN (30–50% of cases) and substance abuse/dependence occurs in about one-third of the people suffering from BN (alcohol and stimulants more frequently) (Hudson et al. 2007; Preti et al. 2009).

No laboratory abnormality is typical of BN enough to be used for diagnosis: purging behavior can produce fluid and electrolyte abnormalities (hypokalemia, hyponatremia, and hypochloremia); the frequent induction of diarrhea through laxative abuse can cause metabolic acidosis; mildly elevated levels of serum amylase, probably reflecting an increase in the salivary isoenzyme, can be observed, and in some individuals the salivary glands, especially the parotid glands, may become notably enlarged.

Severe general medical conditions are less likely than in AN; however, rare but potentially fatal complications may occur, such as cardiac arrhythmias, esophageal tears, or gastric rupture (Mitchell and Crow 2006).

126.2.3 Subtypes of Eating Disorders

Two subtypes of AN are described: the Restricting type (AN-R), when weight loss is accomplished primarily through dieting, fasting, or excessive exercise; and the Binge-Eating/Purging type (AN-BP), when binge eating or purging (or both) occur during the current episode in addition to dieting and fasting. People affected by AN-BP are more likely than those with AN-R to have other impulse-control problems, to abuse alcohol or other drugs, to exhibit more mood instability, and to be sexually active or promiscuous.

Two subtypes of BN are described: the Purging type (BN-P), when the person regularly engages in self-induced vomiting or misuses laxatives, diuretics, or enemas during the current episode; and the Nonpurging type (BN-NP), where the only inappropriate compensatory behaviors are fasting or excessive exercise, and no self-induced vomiting or the misuse of laxatives, diuretics, or enemas occur during the current episode.

An additional diagnostic category for EDNOS concerns the EDs that do not meet the criteria of any subtype of AN or BN: most criteria are satisfied except one of those qualifying the disorder (DSM-IV-TR). BED, in particular, is characterized by recurrent episodes of binge eating (Criterion A), in the absence of regular recourse to inappropriate compensatory behaviors (Criterion E). In BED, patients manifest obvious distress concerning their eating behavior, so they eat alone because they feel embarrassed at overeating and feel intense disgust, depression, or guilt after a binge (Criterion B). Obvious and appreciable distress comes with binge eating behavior (Criterion C). To qualify for diagnosis, binge eating must occur on an average twice a week for at least 6 months (Criterion D).

126.2.4 Eating Disorders: Associated Features

Engaging in a diet is the main antecedent of EDs: indeed, obesity during childhood or adolescence may precede the development of EDs, particularly when recurrent episodes of binge eating and inappropriate compensatory behaviors do occur (Jacobi et al. 2004). Depression causes inappetence and

Table 126.1 Key facts of EDs

EDs are behavioral disorders characterized by disordered eating and body dissatisfaction, a high level of psychological distress related to eating behavior, and high comorbidity with other mental disorders, principally anxiety, mood, and substance use disorders.

Main features of EDs are:
1. A self-esteem highly dependent on body shape and weight.
2. Severe disturbances in eating behavior, from severe dieting and refusal to maintain a minimally normal body weight, to repeated episodes of binge eating followed by inappropriate compensatory behaviors as self-induced vomiting, misuse of laxatives, diuretics, or other medications, fasting, or excessive exercise.

There are two main syndromes of EDs, and a wide range of subclinical conditions called "eating disorders not otherwise specified" (EDNOS):
1. AN
2. BN
3. EDNOS (including the Binge Eating Disorder)

The etiology of EDs is complex and involves many factors: genetic predisposition, or premature birth and birth trauma might interact with chronic and acute stressful life events to precipitate the onset of an Eating Disorder.

EDs can be treated, with acceptable to good positive outcome involving up to 70% of treated patients after a 10-year follow-up in AN and a large fraction of recovered patients at short-medium term in BN, although with high risk of relapse

This table summarizes the main characteristics of EDs as they are described in current international classifications of mental disorders

AN anorexia nervosa, *BN* bulimia nervosa, *EDs* eating disorders

may precipitate an ED: low self-esteem, an oft-reported antecedent of EDs, might be a marker of depression as a predisposing factor for the onset of an ED. However, the etiology of EDs is complex and involves many factors: genetic predisposition, or premature birth and birth trauma might interact with chronic and acute stressful life events to precipitate the onset of an ED (Table 126.1).

Both AN and BN are statistically more common among family members than in the general population and their prevalence is higher in monozygotic than in dizygotic twins, but a clear genetic effect emerges only after puberty (Klump et al. 2007). Several studies found childhood physical or sexual abuse as predisposing risk factors for EDs (Jacobi et al. 2004). Childhood trauma and other stressful experiences relate to impulsivity and higher risk of suicide and self-injury behavior (SIB) in patients with EDs (Vanderlinden and Vandereycken 1997).

After the onset of the disorder, criticism from parents and conflict between them might influence its course negatively (Wade et al. 2006).

Comorbidity, i.e., the association of two or more pathologies that might also have a genetic basis, recurs in patients with EDs and in their families. Affective disorders, and in particular bipolar and unipolar depression, are two to three times higher in families whose members have been diagnosed with EDs (Strober et al. 2000); substance use and abuse disorders are more likely in those with a bulimic variant of ED and in their relatives, three to four times more than in anorexics or in controls without a family history of EDs (Krug et al. 2009; Jacobi et al. 2004).

Serotonin dysregulation was reported in low-weight AN, and is implied in many disorders co-occurring with BN. Binge eating occurs with low levels of brain serotonin (also known as 5-HT = 5-hydroxy-tryptophan); conversely, increased levels of 5-hydroxyindolacetic acid (5-HIAA), the major metabolite of serotonin, were found after recovery in both AN and BN, further corroborating the idea that abnormal low levels of serotonin are in cause in the acute phase of EDs (Kaye et al. 2000).

Multi-impulsivity is a feature of EDs, particularly those with recurring episodes of binge eating. Impulsivity is linked to reduced functioning in serotonin circuits, and it is more likely in patients with

a history of childhood trauma, sexual abuse in particular. Since impulsivity might expose to negative life events, and negative life events can cause depression, some circularity might exist between serotonin dysregulation, impulsivity, depression, childhood trauma, and the development of EDs.

126.2.5 Eating Disorders: Epidemiology

A consistent finding is the peak in ED incidence during adolescence and early adulthood; in both the US National Comorbidity Survey Replication (NCS-R) and the European Study of the Epidemiology of Mental Disorders (ESEMeD), the majority of cases had their beginning between 10 and 20 years of age (Hudson et al. 2007; Preti et al. 2009). An age-effect might involve both hormonal effects linked to puberty and psychological effects related to changes in body appearance and form, causing weight and shape concerns, as well as the impact of the new expected sexual and social role.

Comorbidity with psychosis is rarer than with mood-, anxiety-, and substance-related mental disorders. Prevalence of schizophrenia in clinical samples of patients with EDs is below 10%, as against 0.8% in community samples, but patients with EDs are more likely to report subclinical symptoms of psychosis than controls and rigidity of thought, abnormal bodily perception, and behaviors based on superstition or wrong beliefs ("magical thinking") contribute to treatment resistance (Miotto et al. 2010).

Recent studies on the prevalence of EDs in the general population showed that they are not so rare as generally thought (Fig. 126.1).

In the NCS-R, the estimated prevalence for AN, BN, and BED was 0.9%, 1.5%, and 3.5% among women, and 0.3%, 0.5%, and 2.0% among men (Hudson et al. 2007). In the ESEMeD study, applying
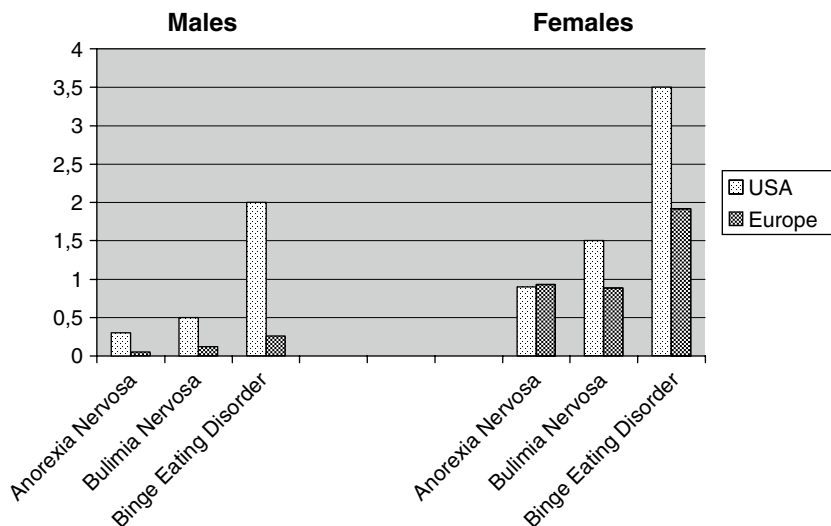
Fig. 126.1 Lifetime prevalence estimates of eating disorders. The figure summarizes the most recent lifetime prevalence estimates of Anorexia Nervosa, Bulimia Nervosa, and Binge Eating Disorder in the USA and Europe, as derived from the US National Comorbidity Survey Replication and the European Study of the Epidemiology of Mental Disorders (six participating countries: Belgium, France, Germany, Italy, the Netherlands, and Spain), within the framework of the World Mental Health Survey Initiative (2004) (Data are from Hudson et al. 2007 (USA) and Preti et al. 2009 (Europe))

the same methodology, the estimates of prevalence were 0.93%, 0.88% and 1.92% in women, and 0%, 0.12% and 0.26% in men (Preti et al. 2009). Both studies revealed some evidence of increasing prevalence in younger than in older cohorts, with most of the effect for BN and BED.

Access to care is lower than expected because of role impairment and comorbidity, especially in the mental health sector (Hudson et al. 2007; Preti et al. 2009). Nevertheless EDs can be treated, with acceptable-to-good positive outcome involving up to 70% of treated patients after a 10-year follow-up in AN (Steinhausen 2002), and a large fraction of recovered patients at short-medium term in BN, although with high risk of relapse (Berkman et al. 2007); less data are available for BED and EDNOS. The associated comorbid mental disorders are treatable too therefore the risk of suicide can be reasonably reduced in those patients who receive adequate treatment and follow-up.

126.3 Suicidal Behavior: Definition

According to a consensus operational definition, *suicide* is any "death from injury, poisoning, or suffocation where there is evidence (either explicit or implicit) that the injury was self-inflicted and that the decedent intended to kill himself/herself"; while *suicide attempt* refers to "a potentially self-injurious behavior with a nonfatal outcome, for which there is evidence (either explicit or implicit) that the person intended at some (nonzero) level to kill himself/herself. A suicide attempt may or may not result in injuries" (O'Carroll et al. 1996, pp. 246–247).

There is no agreed definition of *suicidal gestures*, often considered self-harming acts with a very low lethal potential (e.g., inflicting superficial scratches on the wrist, overdosing on vitamins). Self-harm can be defined as "any act that causes psychological or physical harm to the self without a suicide intention, and which is either intentional, accidental, committed through ignorance, apathy, or poor judgment" (McAllister 2003, p. 178); deliberate self-harm (DSH) refers to self-harming behaviors that are intentional but not aimed at killing oneself (Mangnall and Yurkovich 2008), while SIB is a kind of self-harm which leads to visible bodily injury, and is on a continuum with suicidal behavior.

Having thoughts about engaging in suicide-related behavior and/or communicating these thoughts encompass the agreed definition of *suicidal ideation*.

Suicidal behavior is thought to occur alongside a continuum, from thoughts about life being not worth living to the expression of self-harming behavior with varying degrees of severity and lethality, until suicide attempt and completion (Fig. 126.2).

Hopelessness and helplessness, two cognitive antecedents of suicide ideation and attempt, and thoughts about death or life being not worth living are starting points in the progression from suicide ideation to suicide planning, attempt, and completion (Brown et al. 2000). Early detection of these feelings, therefore, can save lives, especially of those people who attempted but failed suicide, who are particularly prone to repeat the suicide attempts until they die (Tidelman et al. 2008).

Suicide ideation is the main correlate of suicide attempt, and quite always associates with a mental disorder: people with suicide ideation have a statistically higher risk of death by suicide compared to people who did not express suicide ideation (Harris and Barraclough 1997).

There is evidence that those who express low-lethal self-harming behavior are also prone to suicidal behavior: among both adolescents and adults SIB can associate to, and precede a suicide attempt (Favaro et al. 2007; Whitlock and Knox 2007).

Finally, suicide attempt represents the primary antecedent of completed suicide (Brown et al. 2000); indeed, those who attempted suicide had a 30–40 time higher risk of death by suicide compared to the general population (Harris and Barraclough 1997).

Fig. 126.2 The continuum
of suicidality. The figure
summarizes the most
commonly agreed model of
the suicidal behavior
continuum. Competing
models emphasize the role of
genetic risk factors, or the
importance of social support,
surveillance, and availability
of lethal means as gateways
to suicide attempt and
completion

Feelings of Hopelessness/Helplessness

↓

Thoughts about death

↓

Suicide ideation

↓

Suicide planning

↓

Self-harming behavior, without a clear intent to die

↓

Suicide attempt, with a clear intent to die

↓

Failed suicide:
- Inadequate means
    Low lethality
    Insufficient concealing
- Effective rescue intervention
    Rapid rescue intervention
    High level of surveillance

⋮
↓

Death by suicide

126.3.1 The Epidemiology of Suicide

Death as result of self-inflicted injury accounts for 1.5–3% of total deaths in both sexes; in many
countries it ranks second among the major causes of death for people aged 15–34 years (Murray and
Lopez 1996).

Yearly suicide rates per 100,000 are higher among males than females, with very few exceptions
(for example, China: see He and Lester 1997); they are higher in older people than in the young and
the adults (Hawton and van Heeringen 2009). The risk of dying by suicide is higher among the sepa-
rated, the divorced, and the widowed than the married; among the unemployed; among those who
suffer from chronic, disabling and/or severely impairing mental or somatic disorders and in those
with substance abuse/dependence (Harris and Barraclough 1994, 1997; Preti and Miotto 1999).
Suicide rates show large differences by geographical region, with rates above 25 per 100,000 persons
in males and above 8 per 100,000 persons in females in Central and East Europe, to rates below

10 per 100,000 persons in males and below 3 per 100,000 persons in females in countries such as Italy, Portugal and Spain (Levi et al. 2003).

Higher suicide rates were recorded in rural areas than in urban areas: the reasons are unknown, but availability of psychiatric services and specialized medical surgery are the most likely contributing factors.

Suicide attempt rates are typically higher among females than males, and peak in young adults (18–24 years old). Unmarried or widowed people, the unemployed, those with a severe mental disorder or a PD, and those with substance abuse/dependence have an enhanced risk of attempting suicide (Bernal et al. 2007; Nock et al. 2008). In 2004 the lifetime prevalence of suicide attempt was estimated at 2.7% worldwide, varying from 0.5/0.7 to 4.7/5.0% according to the country (Nock et al. 2008).

As for suicide ideation, in 2004 prevalence estimates were 9.2% (3.0–15.9%, according to the country), while the prevalence estimates of suicide plan were 3.1% (0.7–5.6%) (Nock et al. 2008).

There are no reliable estimates of suicidal gestures in the population. Some groups have a very high occurrence of non-lethal suicidal gestures, for example people detained in prisons, with rates as high as 7.6% in men and 19.0% in women (Preti and Cascio 2006).

Nonfatal suicidal behavior is related to being female, of younger age, having fewer years of formal education, and being single/never married; age, in general, is inversely related to nonfatal suicidal behavior (Nock et al. 2008), with some differences across countries (Bernal et al. 2007). Having a major mental disorder is the most significant clinical correlate of suicide ideation, plan, and attempt, especially MDD and alcohol-related problems (Bernal et al. 2007; Nock et al. 2008).

In those with a mental disorder, earlier age-of-onset is significantly associated with a higher risk of suicidality, especially in the first year since onset of ideation. Overall, high rates of both attempted and completed suicide are associated with acute episodes of the illness, particularly in those recently discharged from hospital, or with comorbid substance abuse, past episodes of nonfatal self-harm, and living alone (Tidelman et al. 2008).

Suicide is sometimes hidden in many societies, particularly when negative stigma is attached to it, and may be underreported (Phillips and Ruth 1993). Due to this stigma, some people are hesitant in disclosing information on past episodes of nonfatal self-harming or suicidal gestures, and on suicide ideation and planning, but the vast majority is glad to have the opportunity to discuss with someone these very distressing feelings about killing themselves. The reliability of information from self-reports or interviews cannot be taken for granted; therefore, when assessing a patient with an evolving severe mental disorder, a close informant should be inquired, too. Missing information on past episodes of self-harm might have fatal consequences.

126.4 Risk Factors for Suicide

A common fallacy is to consider suicide as a rational choice made in face of adverse circumstances not amenable to change. In fact, most people experiencing very distressing stressful events never attempt suicide, nor consider taking their lives.

According to statistical data, in up to 90% of cases the people who died by suicide suffered, at that moment, from an active mental disorder (Cavanagh et al. 2003), although most people with a mental disorder do not attempt nor die by suicide. Suicidal behavior is a complex, multidimensional phenomenon, which has many "causes" as well as several biological, psychosocial, and cultural components.

The reasons why an individual wishes to die differ according to the type of suicidal behavior; nevertheless, some recurrent reasons may be reconstructed from the stories of those who survived a severe suicide attempt (Table 126.2).

Table 126.2 Motivations of suicide drawn from the case reports of survivors to severe suicide attempts (Modified from Preti and Miotto 2005)

Primary reason	Will to stop an unbearable suffering
	Will to detach oneself immediately from life circumstances
	Will to rejoin loved dead people
	Will to get revenge through the consequences of one's own death
Secondary or associated reason	Will to punish oneself
	• Out of guilt
	• Out of shame
	• Out of a sense of unworthiness
	Will to leave a strong and long-lasting impression on those who will remain alone after the death of the attempter
	Will to suppress an internal mental object, which is no longer satisfying or which is perceived as persecutory
	To force someone to help (cry for help)
Unclassified	Self-sacrifice, altruism
	Demonstrative, for political reasons
	Vexation
	To rouse compassion

The table lists the most frequent reasons for dying, reconstructed from the case histories of those who survived a severe suicide attempt: the reasons "why" an individual wishes to die differ according to the type of suicidal behavior, with different constellations of underlying "causes" corresponding to different circumstances of suicide

Suicidal events are often classified on the basis of the following elements:

- The *intent to die*, which relates to the desire to die as opposed to the desire to live, and is expressed through the degree of planning and the chances of being discovered, as resulting from the efforts to hide the attempt from discovery and intervention.
- The *lethality*, which is the degree of medical damage resulting from the attempt which largely depends on the method used for the attempt.

Women tend to use less lethal means of suicide, which implies a higher chance of survival. Women tend to behave so as to favor discovery and rescue and this is often interpreted as a "cry for help". However it is incorrect to consider a "cry for help" less dangerous, since people using this strategy also tend to repeat the attempt, and some patients could not appreciate the intrinsic lethality of the method used, or may overlook the real ability of rescue of their social network; moreover, low lethal methods can become fatal in someone whose body is otherwise harmed by somatic illnesses, as in the elderly, in people with chronic somatic disorders, or in patients with EDs.

There is some evidence that different circumstances of suicide correspond to different typologies of suicidal behavior, with different constellations of underlying "causes". The people who take their lives out of a sudden impulse might differ in their psychological dynamics from those who plan their killing in advance, and behave so as to hide their intention, also taking precautions not to be discovered, and avoid rescue.

Sometimes people make a suicidal pact with someone they trust and who chooses to share with them the same mechanics of death. There is also a subgroup of suicides that accomplishes the explicit intention of the victim to avenge himself / herself of a wrong not amenable to legal prosecution: this "suicide by revenge" or "suicide with hostile intent" encompasses a large set of highly lethal behaviors aimed at harming the others (Preti 2006).

Knowing the "reason why" of suicide is not enough to prevent it: over time, a large range of variables has been investigated as possible risk factors for suicide (Table 126.3). Some of these risk factors are amenable to treatment and their identification is therefore mandatory for prevention.

Table 126.3 Risk factors for suicide, with relative hierarchy of risk

Suicide risk factors	Risk
Clinical risk factors, often amenable to treatment	
Current axis I mental disorder	High
History of past suicide attempt	High
Current suicidal ideation	High
Co-morbid axis II personality disorder	High
Alcohol/substance abuse/dependence	High
Family history of suicide	High
Psychosocial risk factors, less likely to be treatable	
Adverse childhood experiences	Low to high
Persistent adverse life situation	Low to high
Acute stress	Low to high
Social isolation	High
Demographic risk factors, not amenable to change	
Male gender	Low to high
Adolescence or old age	Low to high
Minority status	Low to high

The table lists the most often reported risk factors for suicide: suicide mainly occurs in the course of a mental disorder, but displaying suicide behavior requires additional risk factors, because the majority of patients diagnosed with a mental disorder never attempt suicide

126.4.1 Clinical Risk Factors for Suicide

Up to 90% of those who died by suicide had an active mental disorder at the moment of the act, often undertreated or unrecognized (Cavanagh et al. 2003).

The mental disorders with the highest risk are: depression, particularly the depressive phase of bipolar disorder (BD), with higher risk in bipolar II than in bipolar I; schizophrenia; alcohol abuse and dependence, often comorbid with another axis I or II mental disorder; PDs, especially those in cluster B (borderline and antisocial PD); drug abuse and dependence; AN (Harris and Barraclough 1997).

Some chronic, disabling, or highly impairing somatic diseases too are linked with an enhanced risk of suicidal behavior: epilepsy, some types of cancer, spinal or brain lesions (head injury), AIDS and related diseases, diabetes, multiple sclerosis, disabling renal or cardiovascular diseases (Harris and Barraclough 1994). Secondary depression is considered the main reason of the higher risk of suicide in people with chronic somatic illness, while people suffering from severe mental disorders are at higher risk of developing chronic somatic illnesses, both because of maladaptive behavior associated with the psychopathology – for example the enhanced risk of alcohol and/or substance abuse – and of the long-term consequence of drug therapy.

A co-occurring SUD increases the risk of suicide in those with mental disorders. Alcohol abuse, in particular, is a risk factor for suicide independently from a comorbid mental disorder and should be treated aggressively. Tobacco smoking was reported as an additional risk factor for suicidal behavior (Hawton and van Heeringen 2009). Comorbid PDs, too, are associated with an enhanced risk of suicide in people diagnosed with a mental disorder, because they reduce attendance to care and compliance with treatment, and they increase the risk of SUDs. In the youngest cases, a history of conduct and emotional symptoms (anxiety mostly), as recorded in parent and teacher reports, is the most important predictor of attempted and completed suicide (Sourander et al. 2009).

126.4.2 Psychosocial Risk Factors for Suicide

The triad of hopelessness, pessimism, and low self-esteem represents a cognitive risk factor to be cared for, since it traps patients in an unfortunate loop: they think they are unable to change their lives and, in the meanwhile, are afraid they cannot receive nor deserve the help they feel necessary to improve. Hopelessness, per se, has emerged as a predictor of suicide attempt and completion in clinical samples (Beck et al. 1985).

In people affected by depression, the affective symptoms of irritability, inquietude, or worrisomeness until agitation, and/or a general state of mood instability are an indicator of possible bipolarity, and must be followed for with great care, since mixed/agitated depression often associates to impulsive suicidal behavior.

Guilt and shame are "moral emotions" frequently reported by patients with mental disorders: they can restrain a patient from admitting suicidal ideation, thus complicating the assessment. Their identification suggests the opportunity of inquiring with tact the presence of suicidal ideation in these patients.

Aggressiveness, conceived as the propensity to engage in assault or aggressive behavior towards things or people – associates to suicidal behavior: the reason could be the higher occurrence of aggressive behavior in people with mental disorders that are comorbid with PD and/or SUDs, as well as the higher chance of relational difficulties in aggressive people, with a worse conflict with peers and police or legal authorities, hence a higher risk of stressful events, on the one side, and less supportive relations on the other.

Persistent adverse life events, such as social and economic disadvantage, and acute stressors can both impact the risk of suicide (Haw and Hawton 2008), principally by increasing the occurrence of symptoms of depression, often mixed with demoralization (loss of positive emotions like hope or confidence, as the result of situations in which one feels powerless), or favoring the onset of a mental disorder in those constitutionally at risk. People with mental disorders, especially those with comorbid PD or SUDs, are more likely to incur in stressful events: mental disorders lead to social, economical, educational, and working difficulties, increasing the chances of losing a job and decreasing those of finding a new one; this leads to financial difficulties, which further negatively impact the life of people with mental disorders, particularly when deprived of social security protection.

People with mental disorders are also more likely to remain single, or to break affective relationships, with higher rates of separation/divorce, thus losing the support and the guidance offered by a partner. Being single entails a 25% higher risk of suicide: this can depend on singleness being a marker of severe mental disorder, but also as a consequence of reduced support, guidance, surveillance, and prompt rescue in case of suicide attempt (Qin et al. 2003).

Impulsivity, the propensity to engage in unplanned, poorly conceived, or inappropriate behaviors, often ending up in an unwanted or deleterious outcome, is a common trait to a large fraction of people with suicidal behavior (Mann 2003). Impulsivity frequently occurs in those with a PD as a feature of the disorder, particularly borderline or antisocial PD. People with SUDs, too, are prone to impulsive behavior, both as a constitutional predisposition to developing substance-related disorders, and as a result of substance abuse/dependence, consequent to the deregulation of the neurochemical circuits damaged by the abuse (Dougherty et al. 2004).

Impulsive behavior also recurs in people with BD, especially during the manic phase, and associates to the risk of developing SUDs (Tondo et al. 1999).

In adolescence, the gender-identity conflict might trigger suicidal ideation and behavior: the lack of experience makes adolescents more likely to consider a conflicting situation or a loss as irrecoverable events.

126.4.3 Availability of Lethal Means and Imitation

The availability of lethal means is a key factor in suicide, since intense, acute suicidal ideation rarely lasts more than 24 h (although it can recur and lead to planning) (Bridge 2006). In the UK, suicide rates were reduced by the detoxification of domestic gas and by the reduction of the number of analgesics in a packet, analgesics being often used for suicide by overdosing on them; other interventions, which succeeded in reducing suicide rates, were restriction laws in the prescription and sale of barbiturates, the mandatory use of catalytic converters in motor vehicles, the construction of barriers at jumping sites and the use of new, less toxic antidepressants (Mann et al. 2005). Some controversial evidence suggests that gun-control laws are having some impact, too.

Merely restricting access to lethal means could not be enough to prevent suicide, since someone who has decided to kill himself/herself can still shift to other means if the chosen method is no longer available. Surveillance must always be added to avoid suicide in those identified at higher risk.

Imitation is a controversial mechanism that can play some role in certain circumstances. Indeed, the degree of publicity given to a suicide story seems to be directly related to the number of subsequent suicides, with celebrity suicides having a particularly strong impact (Stack 2003). Media guidelines have been proposed in order to reduce the impact of suicide by imitation, particularly as far as the disclosing of the method used for suicide is concerned; currently, the impact of the Internet is under scrutiny, since people can be encouraged to attempt suicide by the provision of instructions concerning suicide methods and the active solicitation of suicide-pact partners in suicide chat rooms (Mann et al. 2005).

126.4.4 Neurobiological Risk Factors for Suicide

A family history of suicide is an important risk factor for suicidal behavior, suggesting that some genetic component is involved. Monozygotic twins have a significantly higher concordance rate for completed and attempted suicide than dizygotic twins; among the biological relatives of an adoptee who committed suicide, the rate of suicide is about several times higher than for the biological relatives of non-suicidal adopted persons (Baldessarini and Hennen 2004). However, it is still unresolved whether the familial aggregation of suicidal behavior is a reflection of genetic components, as is suggested by twin and adoption studies (Brent and Mann 2005), or whether social learning has a role, too, by means of social contagion and/or imitation (De Leo and Heller 2008). The recurrence, within a family, of some risk factors known to be associated with suicide, such as economic and financial strain, exposure to sexual and physical abuse, availability of psychoactive substances, and poor social support can contribute to the transmission of suicidal behavior in the family.

The liability to mental disorders does not seem to be the sole mechanism involved in the heritability of a propensity to suicidal behavior: for example, the parents of youth suicide victims have higher rates of suicidal behavior independently of the presence of psychopathology (Brent et al. 1996).

Abnormal serotonergic function is the most likely candidate to form the basis for the specific heritable liability to suicidal behavior. The first evidence came from studies investigating cerebrospinal fluid (CSF) levels of 5-HIAA, the major metabolite of serotonin: they were found to be lower in persons who had made serious suicide attempts than in psychiatrically matched controls (details in Mann 2003). Some studies reported up-regulation of postsynaptic serotonin 5-HT$_{1A}$ and 5-HT$_{2A}$ receptors in the prefrontal cortex of suicide victims; postsynaptic serotonin receptor up-regulation often occurs as a compensatory response to the low activity of serotonin neurons (Mann 2003).

Further postmortem brain receptor mapping studies found indicators of reduced serotonergic input to the orbital prefrontal cortex, an area involved in behavioral inhibition: this might find expression in a general propensity towards aggressive and impulsive behaviors, including suicidal behavior (Mann 2003).

Low serotonergic function may be a trait marker of the propensity to suicidal behavior: indeed, low CSF levels of 5-HIAA predict future suicide and suicide attempts in patients with mental disorders independently from the diagnosis (Mann 2003).

The noradrenergic or dopaminergic systems were less investigated. The main findings were: decreased noradrenalin (NA) levels in brainstem and increased alpha2-adrenergic receptor density, which might depend on up-regulation due to NA deficit. As for molecular genetic studies, so far the replication of findings concerning a candidate gene in association studies has been difficult, with the notable exception of the serotonin transporter gene promoter polymorphism, linked to suicidal behavior (Currier and Mann 2008).

In nonhuman primates, a low cholesterol diet results in lower serotonergic activity and higher impulsivity and aggressive behavior; in humans, clinical and epidemiological studies reported a modest but consistent link between low cholesterol levels and suicidal behavior, both in spontaneously occurring low cholesterol blood levels and when cholesterol was lowered through diet or drug treatment (Mann 2003).

Finally, suicide is associated with larger adrenal glands and less prefrontal binding of Cortical Releasing Factor (CRF): this might depend on suicide being the cause of death in people suffering from chronic, disabling and highly stressful conditions. Indeed, overactivity of the hypothalamic pituitary adrenal (HPA) axis is typically observed in patients with MDD and in victims of physical and/or sexual abuse (Mann 2003).

126.4.5 Precipitating Factors for Suicide

The continuum of suicidal behavior ranges from ideas to gestures, to risky lifestyles, suicide plans, suicide attempts, and, finally, suicide completion (Mann 2003). Suicide occurs principally in the course of a mental disorder, but displaying suicide behavior requires additional risk factors, because the majority of patients diagnosed with a mental disorder never attempt suicide (Mann 2003; Mann et al. 2005).

Most of these risk factors can act in an additive way, but some of them might interact in a synergistic fashion (Fig. 126.3); moreover, they are often not independent: for example, there is a circular relationship between aggressive or impulsive traits, suffering from depression, developing substance abuse, and cigarette smoking.

Triggering and precipitating factors are often, but not always, necessary for suicide to be committed. Common precipitants of suicidal acts include the onset or acute worsening of a mental disorder, interpersonal losses or conflicts, financial troubles, and job problems.

The suicidal crisis is a time-limited window in which the highest risk of suicide occurs: accurate assessment and intervention is mandatory in this circumstance, since most suicidal acts occur in a while. According to some studies, about 50% of those who attempt suicide make their decision within 5–10 min before acting, and up to 75% take less than 1 h to make the decision of killing themselves. In the case of alcohol or drug intoxication, the decision is made quickly, less than 30 min in about 90% of cases; on the other hand, after 24 h, about two thirds of those who intensely thought about suicide, lose the urge to kill themselves (Bridge 2006).

The most common triggers are recent negative events, particularly when caused by the person's behavior, such as a relational loss precipitated by anger outburst or recurrent conflicts, or a financial
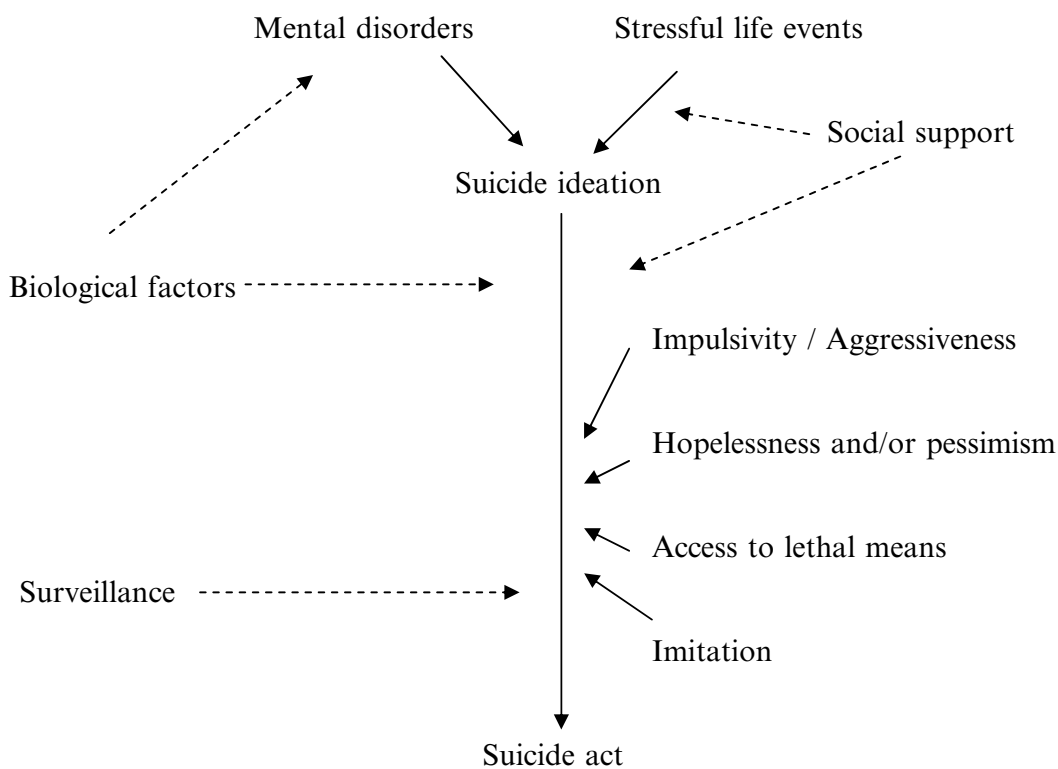
Fig. 126.3 Interacting risk factors for suicide. The figure displays a scheme of risk factors for suicide, considering antecedents, precipitating factors, and correlates of suicidal behavior

loss due to excessive or poor spending habits associated with impulsivity or excitement. The awareness of one's own responsibility in these events can confirm a negative image of oneself, further lowering self-esteem and increasing hopelessness and pessimism. Feelings of abandonment, unworthiness or repulsion, mixed with hopelessness, anger, frustration, guilt, shame, or humiliation might be a lethal admixture especially in case of low social support and/or isolation. Increasing anxiety, sleepiness, and uncontrollable anger outbursts are important predictors of impulsive suicide acts. In contrast, those who develop a detailed plan can become suddenly calm and relaxed, although mood instability is a clear indicator of risk in these people: apparently, they regain interest in life, often expecting to set or reorganize their own things; sometime, a sudden, unforeseen but long-planned highly lethal suicide attempt follows the completion of these tasks (Table 126.4).

126.5 Eating Disorders and Suicidal Behavior

EDs fit with the profile of the afore summarized risk: patients with EDs suffer from comorbid depression and PDs, mainly in the Cluster B spectrum (borderline PD) (Hudson et al. 2007; Preti et al. 2009); they are likely to behave impulsively, and anger outbursts are features of disorders presenting with binge eating, i.e. AN-BP and the two variants of BN (Miotto et al. 2008). Childhood physical or sexual abuse, two causes of intense distressful feelings and psychopathology, are known antecedents of EDs (Jacobi et al. 2004), even at subclinical level (Preti et al. 2006). Substance abuse or

Table 126.4 Key points of suicide

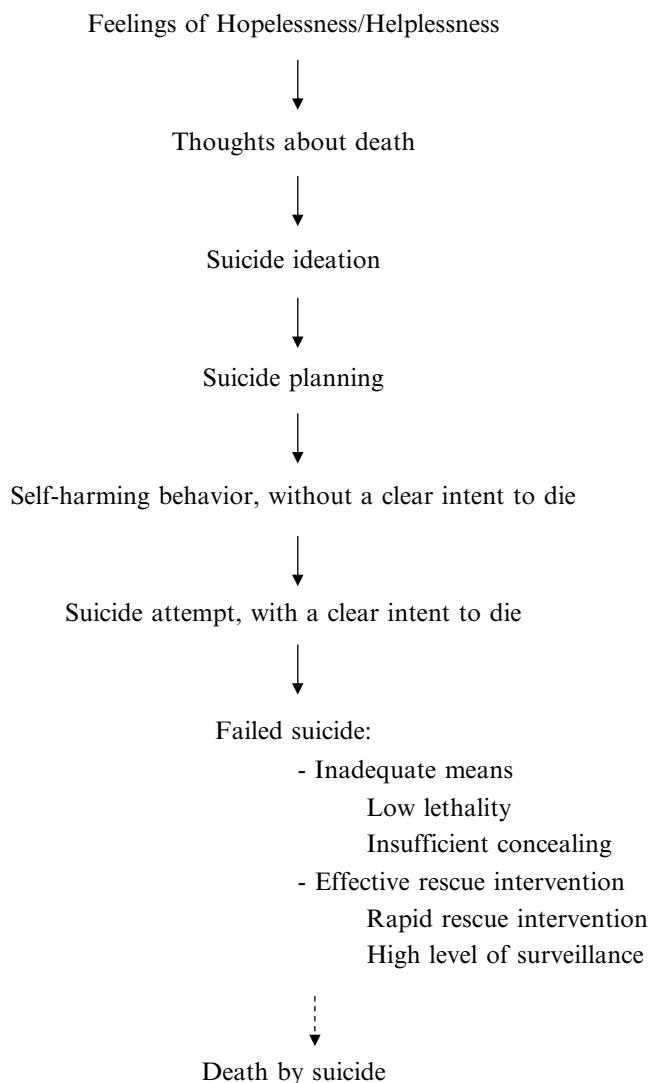| |
|---|
| Suicide is any death resulting from injury, which was self-inflicted with the intent of ultimately causing the death. |
| Suicide is thought to be at the extreme end of a continuum, from thoughts about life being not worth living, to the expression of self-harming behavior with varying degrees of severity and lethality, until suicide attempt and completion. |
| Suicide occurs principally in the course of a mental disorder, but displaying it requires additional risk factors, among others: |

 1. Low cerebrospinal fluid 5-hydroxyindolacetic acid levels
 2. Low blood cholesterol levels
 3. Alcohol and/or substance abuse
 4. Tobacco smoking
 5. Cluster B Personality Disorders
 6. Somatic illnesses
 7. A family history of suicide
 8. A childhood history of physical and sexual abuse
 9. Low self-esteem
10. Hopelessness
11. Impulsiveness
12. Aggressiveness
13. Marital isolation
14. Not living with a child under age 18

This table lists the key facts about risk factors for suicide, across the domain of clinical, psychosocial, and neurobiological dimensions

dependence recurs in the history of patients with EDs and in their close relatives, thus representing additional risk factors for suicide (Krug et al. 2009).

Most of these risk factors for suicidal behavior interact with each other: they largely share a common genetic basis, which impacts on abnormal dieting behavior of the patients, thus aggravating a preexisting dysregulation of neurochemical circuits, especially in the serotonin system, and disrupting the delicate neurohormonal equilibrium (Kaye et al. 2000). Abnormal eating, with the restriction of some types of food, can cause reduced intake of monoamine precursors, like tryptophan, and of vitamins, thus further disrupting neurobiological functioning; a balanced supply of the essential amino acids, especially from meat, is needed for the continuous replacement of serotonin and norepinephrine and for proper brain functioning (Sullivan et al. 2006). On the other hand, fruit, vegetables, and meat are consistently underconsumed by adults who have attempted suicide (Li et al. 2009), and iron deficiency, the most common cause of mild anemia in EDs, can contribute to poor impulse control in those who are genetically vulnerable.

The use of inappropriate compensatory behaviors, such as self-induced vomiting, or the misuse of laxatives and/or diuretics can induce abnormalities in fluid and electrolytes, another cause of neurochemical unbalance, which might negatively impact on impulse control and mood. EDs are also linked to an enhanced risk of stress, principally of a social nature, with a higher chance of conflict with family members, friends and acquaintances: this may induce alterations in the HPA axis, thus increasing the levels of cortisol and related hormones, with cortisol inhibiting serotonergic functions.

126.5.1 Evidence on Suicide in AN

Suicide represents the main cause of death in AN, besides medical complications of the disorder. In two large meta-analyses, suicide was the cause of death in deceased patients with AN in 27% (Sullivan 1995) and 32% (Harris and Barraclough 1997) of cases, respectively. In a meta-analysis of

11 outcome studies on AN including 2,240 patients with available follow-up between 5 and 22 years (mean: 10.7), 28 suicides were found (0.119 per 100 person-years of exposure risk), representing 22.7% of all observed deaths (Signorini et al. 2007). In another meta-analysis comparing data from nine outcome studies on AN including 1,538 patients with available follow-up between 5 and 23 years (mean: 13.6), 36 suicides were reported (0.172 per 100 person-years of exposure risk), as against 28 expected suicides (0.028 per 100 person-years of exposure risk) amongst 100,000 persons of age 14–25 without AN (Pompili et al. 2004).

Available data indicate that in patients with AN, completed suicide nearly always occurs in adult age. In a study investigating 246 women with EDs (136 with AN), four cases of suicide occurred within a 5-year follow-up, all in patients with AN (three AN-R, one AN-BP): the mean age at death was 35 years (Keel et al. 2003). In a study on 6,009 women with AN followed-up for a mean time of 13 years, the total deaths were 265, including 84 deaths by suicide (31.6% of all deaths): the mean age at death was 34 years (Papadopoulos et al. 2009).

However, a higher risk of suicide in AN compared to the appropriate control population is not universal. In a US study on data from 1986 to 1990, Coren and Hewitt (1998) found 8 suicides in 571 women who had AN as an underlying cause of death, as against 70 in 1,713 matched deceased controls. Thus, the relative risk of suicide was higher in controls (4.1%) than in patients with AN (1.4%): 2.93 (95% confidence interval (CI) = 1.38–5.85). In a long-term survival analysis of 208 patients with AN diagnosed in Rochester, Minnesota (USA) from 1935 through 1989, and monitored for up to 63 years, mortality was not higher in those patients than expected by age and sex: in this study, 2 suicides occurred in women, representing 14.2% of all deaths (Korndörfer et al. 2003).

As a matter of fact, a changing pattern in the causes of death was observed in follow-up studies from 1940–1949 to 1970–1979, with fewer deaths from medical complications of AN and more from suicide in later periods (Nielsen et al. 1998); thereafter, in more recent surveys, from the early 1980s onwards, a decrease in suicide rates was observed in a sample of patients with AN (Lindblad et al. 2006). These changes might reflect improvements in medical treatment over the last 50 years and the very recent improvement in the psychiatric treatment of AN: indeed, a better identification of cases needing treatment and the access to specialized units of care were suggested as the main factors in this effect (Lindblad et al. 2006). A recent national Swedish study based on official hospital registers reported a decrease in mortality over the last 2 decades, but still patients with AN had a significantly increased SMR for suicide: 13.6 (95% CI = 10.9–16.8), corresponding to 0.104 per 100 person-years of exposure risk (Papadopoulos et al. 2009).

For these reasons, suicide is still a matter of concern in AN, but it can be prevented essentially by increasing the identification of cases in need of care and by aggressively treating comorbidity, mainly depression, substance abuse, and impulsivity-related PDs.

126.5.2 Evidence on Suicide in BN

Overall, the risk of death in BN is much lower than in AN: a meta-analysis of 43 follow-up studies of patients with BN retrieved a not significantly enhanced SMR of 1.6 (95% CI: 0.8–2.7) (Nielsen 2003). A review of 2,194 patients with BN, drawn from 88 follow-up studies, reported two deaths by suicide representing 28.5% of all deaths (n = 7) (Keel and Mitchell 1997). Studies based on long-term follow-up studies confirmed the lack of deaths due to suicide in a sample of patients with BN (Keel et al. 1999). This is at odds with the very high occurrence of suicide attempts in patients with BN (Franko and Keel 2006).

126.5.3 Evidence on Suicide Attempts in EDs

The lifetime prevalence of a history of suicide attempts in patients with AN or BN is not statistically lower than in patients with MDD: 27%, 31% and 36%, respectively (Bulik et al. 1999). Minor differences do occur between subtypes of EDs: in 246 outpatients, 12% with AN-R (n = 51), 13.8% with AN-BP (n = 85), and 9% with BN (n = 110) reported one or more suicide attempts at assessment (Herzog et al. 1999). In an Italian study, 9% of AN (n = 166), and 18% of BN (n = 205) patients had a history of suicide attempt (Favaro and Santonastaso 1997).

Studies with follow-up show that there are differences depending on the sample and the geographical location, but patients with AN do not relevantly differ from those with BN as far as the risk of attempting suicide over time is concerned (Table 126.5).

In patients with EDs who have made one or more suicide attempts, there are a few recurring associated features: purging behavior and comorbidity with affective disorders and/or cluster B PDs (Franko et al. 2004; Milos et al. 2004). A co-occurring history of alcohol and/or substance abuse/dependence is another important correlate and a predictor of suicide attempt in patients with EDs (Franko and Keel 2006). In both AN and BN, a history of childhood abuse is an antecedent of severe suicide attempts, as well as of recurrent non-lethal self-harming behaviors (Favaro and Santonastaso 1997; Franko and Keel 2006).

Lower cholesterol levels, which may result from severe dieting, were found in patients with AN who had a history of suicide attempts and/or current suicide ideation than in patients without suicidality (Favaro et al. 2004).

126.5.4 Suicidal Gestures and Suicide Ideation in EDs

Patients with EDs often engage in SIB. In a Belgian female inpatient sample, a history of SIB was reported by 26.1% with AN-R (n = 23), 28.8% with AN-BP (n = 18), and 55.2% with BN (n = 29) (Claes et al. 2003). In an Italian sample, a history of SIB was reported by 59% with AN-R (n = 155),

Table 126.5 Follow-up studies on suicide attempt in eating disorders – sorted first by location and then year of the study

Study	Location	Diagnosis	n sample	Follow-up (years)	n attempts	Suicide attempt rate [a] (%)
Favaro and Santonastaso (1997)	Italy	AN	167	6	15	1.49
Kreipe et al. (1989)	USA	AN	49	6	2	2.04
Bulik et al. (1999)	USA	AN	70	3	19	9.04
Franko et al. (2004)	USA	AN	136	8	30	2.75
Favaro and Santonastaso (1997)	Italy	BN	210	6	38	3.01
Garfinkel et al. (1980)	Canada	BN	155	8	36	2.9
Bulik et al. (1999)	USA	BN	152	3	47	10.3
Franko et al. (2004)	USA	BN	110	8	12	1.36

The table illustrates major results from studies on suicide attempt in Eating Disorders with enough follow-up length to observe an event. To date, available data involve a scant number of countries, with no information on Eating disorder not otherwise specified and Binge Eating Disorder, despite the fact that these disorders prevail in the community and in clinical samples

AN anorexia nervosa, *BN* bulimia nervosa

[a]The suicide attempt rate is expressed as percentage per person x years of exposure to the risk of attempting suicide

68% with AN-BP (n = 81), 76% with BN-P (n = 139), and 61% with BN-NP (n = 36) (Favaro and Santonastaso 2000).

Especially in patients with BN, SIB is associated with suicide attempts, a history of sexual abuse, and depression (Favaro and Santonastaso 1999). Overall, the reported prevalence of SIB in patients with EDs is, on average, between 25.4% and 55.2% (Svirko and Hawton 2007) and it is observed in patients with EDNOS, too (Paul et al. 2002). SIB is used to reduce distress or tension and to end uncomfortable feelings; other reported functions are: to reduce anger, to self-punish, and to feel bodily instead of emotional pain (Paul et al. 2002).

In community samples, SIB is on a continuum with suicidality (Favaro et al. 2007), and those reporting SIB are more likely to report suicide ideation, plan, gesture, and attempt (Whitlock and Knox 2007).

Suicidal ideation, the most important correlate of attempted and completed suicide, is frequent in patients with EDs. In 495 Italian outpatients with EDs, 29% reported current suicidal ideation (Favaro and Santonastaso 1997). In a sample of 1,009 French inpatients, current suicidal ideation was more frequent in those with BN and with AN-BP than in AN-R (Fedorowicz et al. 2007), but in an Italian female outpatient sample (Miotto et al. 2008), patients with AN (n = 61) were more likely to report severe suicidal ideation than patients with BN (n = 51): 14.8% versus 3.9% (unpublished data). Suicide ideation was positively related to levels of bodily dissatisfaction, as measured by the Body Attitudes Test (Probst et al. 1995), in young people with subclinical symptoms of EDs (Miotto et al. 2003). Subclinical eating disturbances are predictive of suicidal ideation and attempts in female, but not male, adolescents (Crow et al. 2008).

126.6 Suicidal Behavior in EDs: A General Overview

Suicidality is undoubtedly high in patients with EDs: patients with AN experience a higher risk of death by suicide than patients with BN, despite a comparable prevalence of predictors of completed suicide, such as suicidal gestures, including SIB, and suicide attempts (Table 126.6).

Two reasons for the greater risk of dying by suicide in AN compared to BN are the higher chance of a lethal outcome of the attempt because of a compromised body condition due to medical complications secondary to starvation and unhealthy purging behavior, and the more severe suicidal ideation in

Table 126.6 Key points of risk factors for suicide in EDs

Patients with EDs present a wide range of factors related to the risk of suicide, among others:

1. Comorbid depression
2. Comorbid personality disorders
3. Comorbid substance use disorders
4. Impulsive and aggressive behavior
5. A history of physical or sexual abuse during childhood
6. Negative consequences of abnormal eating on monoamine metabolism

Evidence on suicidality in EDs

1. Patients with AN experience a higher risk of death by suicide than patients with BN, despite a comparable prevalence of predictors of completed suicide, such as suicidal gestures, including self-injuring behavior, and suicide attempts
2. In recent decades the risk of death by suicide has decreased in AN, principally because of greater detection of the cases in need of treatment and the establishment of specialized units of care.

This table lists the key facts about risk factors for suicide in EDs, detailing the main change occurred in recent decades, i.e. the substantial decrease in the risk of death by suicide in AN, as a result of better access to care

AN anorexia nervosa, *BN* bulimia nervosa, *EDs* eating disorders

patients with AN than in those with BN. One study assessed the first hypothesis, and found that in patients with AN, death after a suicide attempt is more likely to result from the use of lethal means rather than by the impact of the attempt on an already deteriorated physical state (Holm-Denoma et al. 2008). Therefore, severe current suicidal ideation might be the cause of greater lethality of the attempt in AN than in BN, but there are no detailed studies on this.

Comorbidity is another important reason for the higher lethality of suicide attempts in AN: in a sample of patients with EDs, current suicidal ideation is linked to Axis I and II comorbidity (Bulik et al. 2008; Milos et al. 2004), and both MDD and PDs with impulsive dyscontrol are associated with a higher risk of suicide. The impact of depression and/or impulsivity might be more severe in AN, owing to nutritional abnormalities secondary to starvation: indeed, low cholesterol levels have been associated with suicidal behavior in patients with AN (Favaro et al. 2004).

126.7 How to Deal with the Risk

Prevention of suicidal behavior deals with the identification of those at risk, the treatment of conditions that can be corrected, and the protection of those who have already made a suicide attempt. Unfortunately, patients with EDs are less prone to seek help from mental health care professionals (Hudson et al. 2007; Preti et al. 2009) and they are seen more often in the general medical sector or in nonmedical settings.

Increasing awareness on these disorders and reducing stigma and myths about them is mandatory to improve access to care for those in need. The multiplication of points of access can be appropriate, especially for adolescents, who are less likely to access mental health facilities for their troubles. With the establishment of specialized units of care, the risk of suicide in EDs has been considerably reduced in the areas served by them (Lindblad et al. 2006).

126.7.1 Identification of the Risk

People at risk of suicide can be identified with appropriate queries, but those who are not mental healthcare professionals can feel less comfortable in enquiring about issues related to suicidal ideation and planning. A simple question, "During the last week, have you experienced thoughts of suicide, or the idea of taking your own life?" can be enough for the purpose of assessment, but it is better to start with more general questions concerning "thoughts about death".

There is no evidence that screening young people for suicide induces suicidal thinking or behavior: on the contrary, some studies found an increased identification of cases after screening for suicide in a primary care setting (Mann et al. 2005). However, since it is inappropriate to enquire of everybody if they have thoughts about suicide, the first step in the prevention of suicidal behavior is the identification of cases with a potential risk: i.e., those who suffer from a mental disorder linked to an enhanced risk of suicide.

People with symptoms indicative of a severe mental disorder should always be asked about suicidal thoughts and past suicidal behavior: if they screen positive for suicidal ideation, then they should be asked about suicide planning (Mann et al. 2005).

Patients with EDs are largely underdiagnosed: the identification of EDs in the general medical sector occurs in a half of the cases with AN, and one in ten cases with BN (Hoek 1991). This leads to a dramatic overlooking of the risk associated with abnormal eating.

More often, people at risk of suicide are identified because they report symptoms of depression or show the distress associated with a recent stressful event.

When an ED case is detected, or symptoms of mood or other psychiatric disorders are evident, additional risk factors for suicide must be investigated. The most obvious is current suicidal ideation, which imposes a query on past suicidal gestures and attempts. Additional risk factors in people with EDs are: cluster B PDs, a history of alcohol or substance abuse, a history of impulsivity, a family history of mental disorders, particularly if severe and/or associated with suicidal events.

Whenever suicide planning is suspected, or when faced with a history of past suicide attempts, access to lethal means should be investigated and the possibility of surveillance should be ascertained, especially in teens.

126.7.2 Intervention Strategies

The treatment of mood and other psychiatric disorders is a central issue of suicide prevention. Antidepressants are effective in alleviating symptoms of depression and anxiety: Selective serotonin reuptake inhibitors (SSRIs), in particular, have been found to decrease the risk of suicide in adults and older people, although caution is still reported about their use in adolescents (Barbui et al. 2009). Patients with EDs are comorbid with BD, and often report subclinical symptoms of psychosis: however, it is difficult to use lithium in patients who self-induce vomiting or use laxatives, since these practices induce significant fluid and electrolyte disturbances, thus increasing lithium toxicity; symptoms of psychosis in EDs rarely achieve levels justifying the use of clozapine, which was found effective in protecting against suicide in schizophrenia (Mann et al. 2005).

Patients who manifest alcohol and/or substance abuse/dependence must be treated aggressively, since SUDs negatively impact on other risk factors for suicide.

Thoughts about suicide are often worse at night: treating insomnia is mandatory in patients at risk.

Some reports indicate that in selected samples of patients, psychotherapy can improve adherence to treatment, thus indirectly reducing the risk of suicide by improving compliance and regular attendance to appointments (Mann et al. 2005). Other, more direct effects are still in need of replication in well-conducted studies.

Patients who have made a suicide attempt are prone to repeat it, therefore improving follow-up care after a suicide attempt, with maintenance care including psychiatric hospitalization, if necessary, is an intuitive option for prevention. However, studies on the real effectiveness of the proposed measures have produced mixed results, with positive findings for case management and programmed long-term care, but uncertain evidence for less expensive interventions such as telephone follow-up, psychosocial follow-up, and video education plus family therapy (Mann et al. 2005).

126.7.3 Further Indications

A "chain of intervention" has been suggested to reduce the risk of suicide in the community, with guidelines concerning each step in the risk of suicide, from predisposing factors to precipitants and correlates (Table 126.7).

Each intervention could be tailored to the population of people with EDs, starting with awareness campaigns aimed at increasing knowledge of the problem and its consequences, as well as disseminating guidelines for treatment.

Table 126.7 Chain of interventions aimed at preventing suicidal behavior

Target condition or symptom	Type of intervention	Main objective
Access to care	Education and awareness program • Primary care physicians • General public • Gatekeepers, including school personnel staff	To increase knowledge of the problem and its treatment
Recognition of cases in need of treatment	Screening of individuals at high risk	To increase detection of hidden cases
Stressful life events	Screening of individuals at high risk	To increase detection of hidden cases

Mental disorders	Treatment
	• *Pharmacotherapy*
	  1. Antidepressants
	  2. Antipsychotics
	• *Psychotherapy*
	  1. Psychosocial programs for SUDs
	  2. Cognitive behavioral therapy
		To improve course of the disorder
		To increase adherence to therapy

Suicidal ideation Impulsivity	Screening of individuals at high risk
	Treatment
	• *Pharmacotherapy*
	  1. Antidepressants
	  2. Antipsychotics
	• *Psychotherapy*
	  1. Psychosocial programs for SUDs
	  2. Cognitive behavioral therapy
		To increase detection of hidden cases
		To improve course of the disorder
		To increase adherence to therapy

Hopelessness/Pessimism	Treatment • Pharmacotherapy • Psychotherapy	To reduce disinvestment To increase participation in programs of care
Access to lethal means	Restriction measures and surveillance	To decrease the chance of lethal outcome after an attempt
Suicidal act	Close follow-up care	To reduce the risk of dropping out from treatment

The table provides a list of interventions that have been suggested for preventing the risk of suicide in the general population

SUDs substance use disorders

Creating accessible networks of social support, and replacing defective ones, could be effective helpful adjuncts in adolescents and young adults. Targeting social dysfunction is critical, since many patients who are contemplating suicide could be saved by efficient social support and surveillance, which is the limiting step in the prompt rescue after an attempt.

Since stress and adverse circumstances are an oft-reported precipitant of a suicidal act, it could be appropriate to provide space for the open discussion of one's personal problems and difficulties, as well as to offer empathic supportive attention and problem-solving indications.

People hardly ever take their life when they are in company: people experiencing suicidal ideation should be encouraged to keep contacts with a friend or a family member, and they should be informed on the availability of telephone helpline services, when in need (Bridge 2006).

Even when there is not a clearly ongoing SUD, people with suicidal ideation should be advised to avoid alcohol and illicit drugs, since their use can precipitate an attempt by increasing impulsivity or by influencing the mood.

Family members should be informed of the risk, especially in teens: it is advisable to provide family support when needed.

When the risk is very high, hospitalization should be frankly discussed with the patient: the aim is to keep the patient alive, although hospitalized patients incur the highest risk of suicide after discharge, both because of the interruption of the continuity of care and because people are hospitalized when they have very severe mental disorders, most likely to end up in suicide.

Building up individual resilience and self-esteem is an essential part of recovery: patients must be encouraged to pursue their personal interests and objectives while they are recovering from their main disorder.

126.8 Application to Other Areas of Health and Disease

Findings on suicide in EDs are of great importance for other areas of health and disease: first and foremost, patients with EDs are often clients of health professionals who are not mental health experts. It is not rare that patients with evolving EDs require advice to pursue their aims of losing weight; they must be detected in order to avoid iatrogenic effects on their psychopathology. Overall, they pose a great challenge in terms of detection and correct treatment: when necessary, the patient has to be addressed to the appropriate unit of care. Continuing education on the features of these disorders is mandatory, especially in the general medical sector, in pediatrics, in gynecology, and in dentistry, as well as among staff professionals involved in counseling and social work.

Moreover, eating disturbances are frequent in the general population, particularly among women and adolescents. There is evidence that poor diet can be associated with suicidal behavior (Li et al. 2009), therefore appropriate nutritional advice can correct abnormalities that might impact on constitutional risk factors for mood and impulse dyscontrol disorders, the main clinical risk factors for suicide. Many somatic diseases, particularly cancer, lead to abnormal dieting, both as a result of the disorder and as a side effect of treatment, and this could be an additional risk factor for suicide in these diseases.

Data on suicidality in EDs are relevant for psychiatry too. EDs are frequently overlooked as a reason for suicide in adolescents and youths: the investigation on suicidal tendencies in young people might benefit from including measures of EDs to prevent the worst outcomes of minor psychological distress (Crow et al. 2008). Moreover, a past ED can be an antecedent of severe psychopathology in adulthood, mainly in the affective disorder spectrum: subclinical eating disturbances can persist despite resolution of the main symptoms, and a more detailed assessment should be undertaken to identify hidden risk factors for suicide, including nutrition-related ones.

There is a paucity of studies concerning the impact of dieting and purging on suicidal behavior: most studies are based on symptoms reported by the patients, but this could be misleading; objective measures should be necessary, also to identify deficits to be corrected. Particularly critical is the effect of stress on appetite and nutrition (Takeda et al. 2004), but again there is a lack of studies investigating the interaction of stress, nutrition, and suicidal behavior in EDs.

Moreover, there is a paucity of studies on suicidal behavior in EDNOS, including BED, despite the fact that these disorders prevail in the community and clinical samples.

Finally, there is sparse evidence regarding the effectiveness of treatment to prevent suicidal behavior in patients with EDs and on the role of stress and nutrition in suicidality: studies on these topics are advisable, due to the complex links between stress and eating disturbances on one side and suicidal behavior on the other side.

Summary Points

- The definition of eating disorders (EDs) is given to a set of behavioral disorders characterized by disordered eating and body dissatisfaction, with a high level of psychological distress related to the eating behavior and high comorbidity with other mental disorders, principally anxiety, mood, and SUDs.
- EDs might be not as rare as currently thought: in recent studies, the lifetime prevalence estimates for Anorexia Nervosa (AN), Bulimia Nervosa (BN), and Binge Eating Disorder (BED) in women were 0.9%, 1.5%, and 3.5% in the US, while they were 0.93%, 0.88% and 1.92% in Europe.
- Patients with EDs present a wide range of factors related to the risk of suicide, among others: comorbid depression, PDs, and SUDs; impulsive and aggressive behavior; a history of physical or sexual abuse during childhood; negative consequences of abnormal eating on monoamine metabolism.
- Suicidal behavior may be best understood as occurring along a continuum, ranging from ideas to gestures, to risky lifestyles, suicide plans, suicide attempts, and, finally, suicide completion.
- A large majority of people who died by suicide suffered at that moment from an active mental disorder, up to 90% of cases according to the statistics.
- Triggering and precipitating factors are often, but not always, necessary for a suicidal act to be pursued: common precipitants of suicidal acts include the onset or acute worsening of the mental disorder, interpersonal losses or conflicts, financial troubles, and job problems.
- In a community sample, those reporting self-injury behavior (SIB) are also more likely to report suicide ideation, plan, gesture, and attempt; the reported prevalence of SIB in patients with EDs is between 25.4% and 55.2%, being an important antecedent of suicide attempt.
- The lifetime prevalence of a history of suicide attempts in patients with AN or BN is not statistically lower than in patients with major depression: 27%, 31%, and 36%, respectively.
- Suicide represents the main cause of death in AN, besides medical complications of the disorder; the risk of suicide in BN is much lower than in AN, despite a comparable prevalence of predictors of completed suicide, such as suicidal gestures, including SIB, and suicide attempts.
- In recent decades the risk of death by suicide has been decreasing in AN, principally because of an increased detection of the cases in need of treatment, and the establishment of specialized units of care.
- Suicidal behavior cannot be easily predicted; however, it can be prevented, essentially by increasing the detection of cases in need of care and by aggressively treating comorbidity, mainly depression, substance abuse and impulsivity-related PDs.
- Patients with EDs are less prone to seek help from mental healthcare professionals, and they are seen more often in the general medical sector or by nonmedical professionals: increasing awareness on these disorders, and reducing stigma about them is mandatory to favor access to care of those in need.
- The multiplication of points of access to care can be appropriate, especially for adolescents, who are less likely to access mental health facilities for their troubles. With the establishment of specialized units of care, the risk of suicide in EDs has been considerably reduced.
- EDs are frequently overlooked as a reason for suicide in adolescents and youth: the investigation on suicidal tendencies in young people might benefit from including measures of EDs to prevent the worst outcomes of minor psychological distress.
- There is sparse evidence regarding the effectiveness of treatment to prevent suicidal behavior in patients with EDs, and on the role of stress and nutrition in suicidality: studies on these topics are advisable, due to the complex links between stress, eating disturbances, and suicidal behavior.

Key Terms

Body mass index or BMI: It is the ratio of weight to height, and it is calculated as weight (Kg) divided by height (m) squared.

Deliberate self-harm: Often abbreviated as DSH, the expression refers to self-harming behaviors that are intentional but not aimed at killing oneself.

Incidence rate: The total number of new cases of a disease or a disorder arising in a specific population at a point in time.

Lethality: The degree of medical damage resulting from a suicide attempt.

Prevalence rate: The total number of cases of a disease or a disorder in a specific population at a point in time.

Rate: A quantity measured with respect to another measured quantity, and in medicine the term refers to the proportion between the number of events of a given condition and the total number of people who may be exposed to it in a given area and during a given interval of time.

Standardized mortality ratio or SMR: It is the ratio of the number of deaths observed in a sample to the number of deaths expected in the population, correcting for age and sex.

Self-injury behavior: This expression refers to acts of self-harm leading to visible bodily injury, on a continuum with suicidal behavior.

Suicidal behavior: This expression refers to acts of self-harm with a fatal (suicide) or a nonfatal (attempted suicide; suicidal gestures) outcome.

Suicidality: This term refers to the occurrence of suicidal thoughts (or suicidal ideation) or suicidal behavior.

Suicidal ideation: This term refers to thoughts, ideas, or cognitions about engaging in suicide-related behavior, and/or communicating these thoughts, intentions or plans.

References

Baldessarini RJ, Hennen J. Harv Rev Psychiatry. 2004;12:1–13.

Barbui C, Esposito E, Cipriani A. CMAJ 2009;180:270–71.

Beck AT, Steer RA, Kovacs M, Garrison B. Am J Psychiatry. 1985;142:559–63.

Berkman ND, Lohr KN, Bulik CM. Int J Eat Disord. 2007;40:293–309.

Bren DA, Mann JJ. Am J Med Genet C Semin Med Genet. 2005;133C:13–24.

Brent DA, Bridge J, Johnson BA, Connolly J. Arch Gen Psychiatry. 1996;53:1145–52.

Brent, DA, Mann JJ. Am J Med Genet C Semin Med Genet. 2005;133C:13–24.

Bernal M, Haro JM, Bernert S, Brugha T, de Graaf R, Bruffaerts R, Lépine JP, de Girolamo G, Vilagut G, Gasquet I, Torres JV, Kovess V, Heider D, Neeleman J, Kessler R, Alonso J; ESEMED/MHEDEA Investigators. Risk factors for suicidality in Europe: Results from the ESEMED study. J Affect Disord. 2007;101:27–34.

Bridge S. Austr Family Physician. 2006;35:335–8.

Brown GK, Beck AT, Steer RA, Grisham JR. J Consult Clin Psychol. 2000;68:371–7.

Bulik CM, Sullivan PF, Joyce PR. Acta Psychiatr Scand. 1999;100:27–32.

Bulik CM, Thornton L, Pinheiro AP, Plotnicov K, Klump KL, Brandt H, Crawford S, Fichter MM, Halmi KA, Johnson C, Kaplan AS, Mitchell J, Nutzinger D, Strober M, Treasure J, Woodside DB, Berrettini WH, Kaye WH. Psychosom Med. 2008;70:378–83.

Cavanagh JT, Carson AJ, Sharpe M, Lawrie SM. Psychol Med. 2003;33:395–405.

Claes L, Vandereycken W, Vertommen H. Eur Eat Disorders Rev. 2003;11:379–96.

Coren S, Hewitt PL. Am J Public Health. 1998;8:1206–7.

Crow S, Eisenberg ME, Stiry M, Neumark-Sztainer D. J Consult Clin Psychol. 2008;76:887–92.

Currier D, Mann JJ. Psychiatr Clin North Am. 2008;31:247–69.

De Leo D, Heller T. Crisis 2008;29:11–9.

Dougherty DM, Mathias CW, Marsh DM, Moeller FG, Swann AC. Drug Alcohol Depend. 2004;76S:S93–105.

Fairburn CG, Harrison PJ. Lancet 2003;361:407–16.

Favaro A, Santonastaso P. Acta Psychiatr Scand. 1997;95:508–14.

Favaro A, Santonastaso P. Compr Psychiatry. 1999;40:57–60.

Favaro A, Santonastaso P. J Nerv Ment Dis. 2000;188:537–42.

Favaro A, Caregaro L, Di Pascoli L, Brambilla F, Santonastaso P. Psychosom Med. 2004;66:548–52.

Favaro A, Ferrara S, Santonastaso P. J Clin Psychiatry. 2007;68:122–31.

Fedorowicz VJ, Falissard B, Foulon C, Dardennes R, Divac SM, Guelfi JD, Rouillon F. Int J Eat Disord. 2007; 40:589–595.

Franko DL, Keel PK. Clin Psychol Rev. 2006;26:769–82.

Franko DL, Keel PK, Dorer DJ, Blais MA, Delinsky SS, Eddy KT, Charat V, Renn R, Herzog DB. Psychol Med. 2004;34:1–11.

Garfinkel PE, Moldofsky H, Garner DM. Arch Gen Psychiatry. 1980;37:1036–40.

Harris EC, Barraclough B. Medicine 1994;73:281–96.

Harris EC, Barraclough B. Br J Psychiatry. 1997;170:205–28.

Haw C, Hawton K. J Affect Disord. 2008;109:139–48.

Hawton K, van Heeringen K. Lancet 2009;373:1372–81.

He ZX, Lester D. Arch Suicide Res. 1997;3:81–9.

Herzog DB, Dorer DJ, Keel PK, Selwyn SE, Ekeblad ER, Flores AT. J Am Acad Child Adolesc Psychiatry. 1999;38:829–37.

Hoek HW. Psychol Med. 1991;21:455–60.

Holm-Denoma JM, Witte TK, Gordon KH, Herzog DB, Franko DL, Fichter M, Quadflieg N, Joiner TEJr. J Affect Disord. 2008;107:231–6.

Hudson JI, Hiripi E, Pope HG Jr, Kessler RC. Biol Psychiatry. 2007;61:348–58.

Jacobi C, Hayward C, de Zwaan M, Kraemer HC, Agras WS. Psychol Bull. 2004;130:19–65.

Kaye WH, Klump KL, Frank GKW, Strober M. Ann Rev Medicine. 2000;51:299–313.

Keel PK, Mitchell JE. Am J Psychiatry. 1997;154:313–21.

Keel PK, Mitchell JE, Miller KB, Davis TL, Crow SJ. Arch Gen Psychiatry. 1999;56:63–9.

Keel PK, Dorer DJ, Eddy KT, Franko D, Charatan DL, Herzog DB. Arch Gen Psychiatry. 2003;60:179–83.

Klump KL, Burt A, McGue M, Iacono WG. Arch Gen Psychiatry. 2007;64:1409–15.

Korndörfer SR, Lucas AR, Sunan VJ, Crowson CS, Krahn LE, Melton JM. Mayo Clin Proc. 2003;78:278–84.

Kreipe RE, Churchill BH, Strauss J. AJDC 1989;143:1322–7.

Krug I, Pinheiro AP, Bulik C, Jiménez-Murcia S, Granero R, Penelo E, Masuet C, Agüera Z, Fernández-Aranda F. Psychiatry Clin Neurosci. 2009;63:82–7.

Levi F, La Vecchia C, Lucchini F, Negri E, Saxena S, Maulik PK, Saraceno B. Acta Psychiatr Scand. 2003;108:341–9.

Li Y, Zhang J, McKeown RE. Psychiatry Res. 2009;165:111–9.

Lindblad F, Lindberg L, Hjern A. Am J Psychiatry. 2006;163:1433–5.

Mangnall J, Yurkovich E. Persp Psychiatr Care. 2008;44:175–84.

Mann JJ. Nat Rev Neurosci. 2003;4:819–28.

Mann JJ, Apter A, Bertolote J, Beautrais A, Currier D, Haas A, Hegerl U, Lonnqvist J, Malone K, Marusic A, Mehlum L, Patton G, Phillips M, Rutz W, Rihmer Z, Schmidtke A, Shaffer D, Silverman M, Takahashi Y, Varnik A, Wasserman D, Yip P, Hendin H. JAMA 2005;294:2064–74.

McAllister M. Int J Ment Health Nurs. 2003;12:177–85.

Milos G, Spindler A, Hepp U, Schnyder U. Gen Hosp Psych. 2004;26:129–35.

Miotto P, De Coppi M, Frezza M, Preti A. J Nerv Ment Dis. 2003;191:437–43.

Miotto P, Pollini B, Restaneo A, Favaretto G, Preti A. Compr Psychiatry. 2008;49:364–73.

Miotto P, Pollini B, Restaneo A, Favaretto G, Sisti D, Rocchi MBL, Preti A. Psychiatry Res. 2010;175:237–43 doi:10.1016/j.psychres.2009.03.011.

Mitchell JE, Crow S. Curr Opin Psychiatry. 2006;19:438–43.

Murray CJL, Lopez AD. The global burden of disease: a comprehensive assessment of mortality and disability from diseases, injuries, and risk factors in 1990 and projected to 2020. Cambridge, MA: Harvard School of Public Health; 1996.

Nielsen S. Arch Gen Psychiatry. 2003;60:851.

Nielsen S, Møller-Madsen S, Isager T, Jørgensen J, Pagsberg K, Theander S. J Psychosom Res. 1998;44:413–34.

Nock MK, Borges G, Bromet EJ, Alonso J, Angermeyer M, Beautrais A, Bruffaerts R, Chiu WT, de Girolamo G, Gluzman S, de Graaf R, Gureje O, Haro JM, Huang Y, Karam E, Kessler RC, Lepine JP, Levinson D, Medina–Mora ME, Ono Y, Posada–Villa J, Williams D. Br. J. Psychiatry. 2008;192:98–105.

O'Carrol P, Berman A, Maris R, Moscicki E, Tanney B, Silverman M. Suicide Life-Threat Behav. 1996;26:237–52.

Papadopoulos FC, Ekbom A, Brandt L, Ekselius L. Br J Psychiatry. 2009;194:10–7.

Paul T, Schroeter K, Dahme B, Nutzinger DO. Am J Psychiatry. 2002;159:408–11.

Phillips DP, Ruth TE. Suicide Life-Threat Behav. 1993;23:307–19.

Pompili M, Mancinelli I, Girardi P, Ruberto A, Tatarelli R. Int J Eat Disord. 2004;36:99–103.

Preti A. Crisis 2006;27:22–30.

Preti A, Cascio MT. Med Sci Law. 2006;46:127–34.

Preti A, Miotto P. J Epidemiol Community Health. 1999;53:694–701.

Preti A, Miotto P. Acta Psychiatr Scand. 2005;111:384–91.

Preti A, Incani E, Camboni MV, Petretto DR, Masala C. Compr Psychiatry. 2006;47:475–81.

Preti A, de Girolamo G, Vilagut G, Alonso J, de Graaf R, Bruffaerts R, Demyttenaere K, Pinto-Meza A, Haro JM, Morosini P, and the ESEMeD-WMH Investigators. J Psychiatr Res. 2009 (in press): doi:10.1016/j.jpsychires.2009.04.003.

Probst M, Vandereycken W, VanCoppenolle H, Vanderlinden J. Eat Disord J Treat Prev. 1995;3:133–44.

Qin P, Agerbo E, Mortensen PB. Am J Psychiatry. 2003;160:7657–72.

Signorini A, De Filippo E, Panico S, De Caprio C, Pasanisi F, Contaldo F. Eur J Clin Nutr. 2007;61:119–22.

Sourander A, Klomek AB, Niemelä S, Haavisto A, Gyllenberg D, Helenius H, Sillanmäki L, Ristkari T, Kumpulainen K, Tamminen T, Moilanen I, Piha J, Almqvist F, Gould MS. Arch Gen Psychiatry. 2009;66:398–406.

Stack S. J Epidemiol Community Health. 2003;57:238–40.

Steinhausen H. Am J Psychiatry. 2002;159:1284–93.

Strober M, Freeman R, Lampert C, Diamond J, Kaye W. Am J Psychiatry. 2000;157:393–401.

Sullivan GM, Mann JJ, Oquendo MA, Lo ES, Cooper TB, Gorman JM. Biol Psychiatry. 2006;60:500–6.

Sullivan PF. Am J Psychiatry. 1995;152:1073–4.

Svirko E, Hawton K. Suicide Life Threat Behav. 2007;37:409–421.

Takeda E, Terao J, Nakaya Y, Miyamoto K, Baba Y, Chuman H, Kaji R, Ohmori T, Rokutan K. J Med Invest. 2004;51:139–45.

Tidelman D, Långström N, Lichtenstein P, Runeson B. BMJ 2008;337:a2205.

Tondo L, Baldessarini RJ, Hennen J, Minnai GP, Salis P, Scamonatti L, Masia M, Ghiani C, Mannu P. J Clin Psychiatry. 1999;60:63–9.

Vanderlinden J, Vandereycken W. Trauma, dissociation, and impulse dyscontrol in eating disorders. New York: Brunner/Mazel; 1997.

Wade TD, Bergin JL, Martin NG, Gillespie NA, Fairburn CG. J Nerv Ment Dis. 2006;194:510–7.

Whitlock J, Knox KL. Arch Pediatr Adolesc Med. 2007;161:634–40.

Part XXII
Pregnancy

Chapter 127
Neuroendocrine Mechanisms of Change in Food Intake During Pregnancy

Alison J. Douglas

Keywords Hyperphagia • Hypothalamic resistance • Opioids • Oxytocin • Progesterone • Prolactin

Abbreviations

AgRP	Agouti-related protein
BNST	Bed nucleus of the stria terminalis
CART	Cocaine and Amphetamine-Related Transcript
CCK	Cholecystokinin
CG	Chorionic gonadotrophin
CL	Corpus luteum
CRH	Corticotrophin-releasing hormone
GABA	Gamma amino butyric acid
HPA	Hypothalamo-pituitary-adrenal
GI	Gastrointestinal
Icv	Intracerebroventricular
IGF-1	Insulin-like growth factor 1
Ip	Intraperitoneal
Iv	Intravenous
MC4R	Melanocortin receptor 4
MCH	Melanin concentrating hormone
αMSH	Alpha melanocyte stimulating hormone
mRNA	Messenger ribonucleic acid
NA	Not available
NTS	Nucleus of the solitary tract
NPY	Neuropeptide Y
POMC	Proopiomelanocortin
PVN	Paraventricular nucleus
PYY3-36	Pancreatic Peptide 3–36
SON	Supraoptic nucleus
VMN	Ventromedial nucleus of the hypothalamus

A.J. Douglas (✉)
Centre for Integrative Physiology, University of Edinburgh, Hugh Robson Building,
George Square, Edinburgh, EH8 9XD, UK
e-mail: Alison.j.douglas@ed.ac.uk

127.1 Introduction

Over the last 80 years, there appears to have been a biphasic research interest in control of food intake during pregnancy. Between the 1930s and 1960s, Edinburgh-based physiologists and biochemists Newton, Marrian, and Dewar asked questions about what controls weight gain during pregnancy (Dewar 2001). Then, after the explosion of research that identified a raft of interconnecting and integrating hypothalamic factors in the 1980s and 1990s, followed by the discovery of new gut and adipose hormones in the 1990s, as described in detail in other chapters, various laboratories worldwide, have pursued the questions in a new light. Pregnancy is a time of emerging and profound physiological and psychological change in the mother accompanied by high nutritional demand by the developing offspring, necessitating extensive maternal adaptations to provide the required sustenance. The earliest and most visible adaptation is hyperphagia. To this end, plasticity occurs body-wide throughout pregnancy, including in the synthesis and effects of brain, gut, and adipose peptides. Despite this, the initial conclusion – that progesterone, the main steroid hormone of pregnancy, plays a key role – remains valid. This chapter highlights the relationship between maternal weight and food intake, gives an overview of the changes in and roles of the key anorexic and orexigenic hypothalamic, gut and adipose peptides in driving the hyperphagia, considers how progesterone might drive increased appetite and addresses the consequences of under- and over-nutrition during pregnancy on the mother and her offspring.

127.2 Maternal Weight and Food Intake Relationship

Pregnancy precipitates a state of reversible hyperphagia, increased body weight and adiposity (Shirley 1984; Rocha et al. 2003). These changes provide for the metabolic demands of the developing young and their uterine environment, as well as other supporting maternal organs such as the heart, lungs, and kidneys. Equally importantly, preparations are made during pregnancy for birth and beyond. This includes extensive mammary gland remodeling and development in anticipation of milk production and, associated with this, huge increases in energy storage (fat deposition, positive energy balance), to provide the reserves required later in lactation (Hervey et al. 1967; Asarian and Geary 2006) which, contrary to pregnancy, is a state of negative energy balance.

The extent of increase in food intake usually depends upon the number of offspring gestating (Morgan and Winick 1981) and the species and is apparent through most of pregnancy. In women, food intake typically increases by only 10–15%, whereas in laboratory rats, it increased by as much as 60% in mid-late gestation according to some studies (overview in Douglas et al. 2007). However, the amount of food eaten does not simply mirror the body weight increase; intake per unit body weight is high in early-mid pregnancy but then declines in the last trimester pregnancy, even though the uterine contents still rapidly gain weight (fetus + placenta weight increases by more than tenfold at this time). This state of positive energy balance facilitates the deposition of energy stores into adipose tissue in anticipation of need not just in response to some signal relating to fetal size or demand. Therefore, it is important to analyze the hormonal and neuronal mechanisms underlying the dynamic regulation in food intake. Since rodent models have typically been used to investigate the adaptations underlying these overt behavior patterns, the evidence discussed below derives mostly from studies in rats and mice.

127.3 Hormonal Signals Mediating Increased Food Intake

As mentioned above, it has long been recognized that the increased secretion of progesterone correlates with and is ultimately responsible for increased food intake during pregnancy (Hervey et al. 1967; Asarian and Geary 2006). Progesterone secretion dramatically increases very early in pregnancy, firstly from the ovarian corpus luteum and then in some species the placenta takes over secretion partially or wholly. How progesterone causes increased food intake is not completely understood but several progesterone targets are likely to be involved, including the cells that are sensitive to peripheral appetite-regulating peptides (e.g., leptin and ghrelin), the hypothalamic neurons that make orexigenic and anorexigenic peptides, such as NPY/AGRP, alpha (α)MSH/CART, orexin A, and melanocortin, and other less obvious but equally important emerging factors such as oxytocin (see Chap. 20) and corticotrophin-releasing hormone (CRH). Firstly, the review will consider adaptations in these potential targets that may underlie the increased food intake in pregnancy before addressing the likely role of progesterone.

127.3.1 Peripheral Signals Regulating Food Intake in Pregnancy

Since food intake is regulated by the balance between hunger and satiety, it is useful to initially consider signaling factors from the periphery that mediate these opposite phagic states. The acute hunger signal mediated by ghrelin has not yet been well studied in pregnancy. Despite increased growth-hormone secretion in pregnancy, which might indicate increase ghrelin secretion and/or action, none of the published studies show major changes in ghrelin secretion. Therefore, ghrelin probably cannot account for the hyperphagia of pregnancy (Douglas et al. 2007; Messini et al. 2008). To date, no effect of progesterone on ghrelin has been reported, although, interestingly, ghrelin may influence progesterone secretion by directly inhibiting steroid biosynthesis (Viani et al. 2008). However, hypothalamic sensitivity to ghrelin is strongly influenced by nutritional status and hence some change in sensitivity is to be expected (Douglas et al. 2007; Fulglsang 2008).

More is understood about the gestational changes in the main satiety signal, leptin, and the consequences of its secretion. This is due to research that addressed the theory that pregnancy (a naturally reversible state of hyperphagia and adiposity) could provide a model for understanding onset and control of obesity and perhaps provide therapies. Leptin concentrations are robustly elevated throughout pregnancy, as in obesity. Therefore, since production is not suppressed, and leptin inhibits appetite, a change in leptin secretion does not account for increased food intake in pregnancy. Leptin receptor expression does not change (Rocha et al. 2003), but resistance to leptin at the hypothalamic level could explain increased appetite. Leptin resistance only develops during mid-late pregnancy (Douglas et al. 2007), so we have also argued that this cannot cause the initial increase in food intake, and primarily reflects the elevated leptin secretion of pregnancy that is a consequence of increased adiposity. Insulin is another important satiety signal from peripheral energy stores but, as for leptin, resistance develops during pregnancy, probably due to sex steroid effects via adiponectin secretion, which is also from adipose tissue (Leung et al. 2009). So, like leptin, there is no reason to believe that the emerging insulin resistance could be a cause of early hyperphagia (Douglas et al. 2007), although they could both be part of the elevated food intake patterns that are sustained in mid-late gestation. Thus, two key phases of hyperphagia in pregnancy should be recognized: initiation of increased food intake early in gestation, followed by an elevated appetite

through mid-late gestation. Most available evidence relates only to mechanisms in mid-late gestation, with sparse information on the induction of hyperphagia. Therefore, after discussion of mechanisms sustaining the elevated appetite, potential mechanisms emerging in the initial peri-implantation period will be addressed only briefly. Also, it is now recognized that pregnancy is not a good model for understanding obesity as it encompasses a much wider range of physiological changes that impact on feeding behavior, e.g., in sex steroid and novel placental hormones, and pregnancy hyperphagia arises with demand from specific reproduction-related signals that have a relatively short, defined natural lifespan.

127.3.2 Peripheral Signals Affecting Hypothalamic Appetite Control Centers

Ghrelin, leptin, and insulin all modulate neuronal activity, either directly or indirectly, depending upon multiple facets including access to the brain, receptiveness of neurons, and interaction with receptors/intracellular signaling mechanisms. As detailed in other chapters, the arcuate nucleus is considered the primary target for peripheral appetite signals, and comprises a complex network of phenotypically different but integrated neurons. These first order neurons express receptors for, and are profoundly influenced by all the above mentioned hormones. Little is known of changes in ghrelin or insulin effects in the arcuate hypothalamus in pregnancy, but leptin has been more extensively investigated. Leptin typically directly inhibits NPY orexigenic neurons and directly excites anorexigenic proopiomelanocortin (POMC)/αMSH neurons of the arcuate nucleus but, as indicated above, these first-order neurons develop leptin resistance in mid-pregnancy. Interestingly, it is not leptin alone that induces this, but the parallel increase in prolactin and placental lactogen (chorionic somatomammotrophin) secretion in pregnancy (Garcia et al. 2003; Douglas et al. 2007; Augustine et al. 2008) seems to be partly responsible. Other important peripheral factors include cholecystokinin (CCK) and PYY3-36 derived from the gastrointestinal tract. CCK acts via the gastric vagal nerve to stimulate brainstem noradrenergic, prolactin-releasing peptide, NPY, and POMC projections to the hypothalamus. It is thought they activate arcuate αMSH neurons and inhibit NPY neurons, leading to meal termination. Adaptations in CCK and PYY3-36 signaling in pregnancy are not well investigated but CCK signals are mediated in part by noradrenaline release and noradrenaline inputs to the hypothalamus are inhibited in the latter half of gestation, indicating that reduced satiety signals contribute to increased food intake at this time. Together these findings indicate a complex cascade of hormonal and neuronal adaptations that need to be considered together in relation to the sustained gestational hyperphagia (Fig. 127.1).

127.4 Adaptations in Orexigenic and Anorexigenic Neuropeptides During Pregnancy

Although there is a lack of evidence that altered peripheral hunger or satiety signals directly underlie increased appetite in pregnancy, changes in central neuronal mechanisms are emerging that enable a picture of responsible mechanisms to be constructed. These are reported for both first-order arcuate neurons as well as second-order hypothalamic neurons in the lateral hypothalamus and elsewhere.
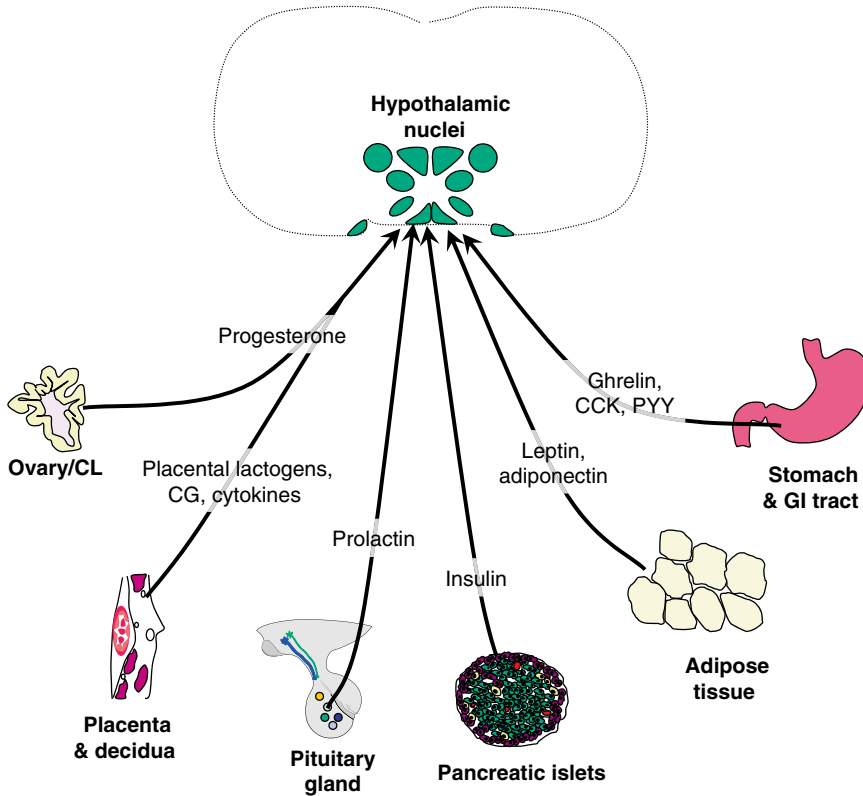
Fig. 127.1 Peripheral factors changing through pregnancy that potentially impact on the maternal hypothalamic neurons to influence hyperphagia. Peripheral factors changing through pregnancy that potentially impact the arcuate nucleus, lateral hypothalamus, paraventricular nucleus, supraoptic nucleus, ventromedial nucleus, and dorsomedial nucleus in the maternal brain cause complex interconnected adaptations that lead to increased appetite. Key hormones are indicated from each source organ/tissue that change during pregnancy and could potentially impact on the hypothalamic control of food intake. *CL* corpus luteum, *GI* gastrointestinal, *CG* chorionic gonadotrophin, *CCK* cholecystokinin, *PYY* peptide YY3-36

127.4.1 First-Order Arcuate Nucleus Neurons

127.4.1.1 Orexigenic Neuropeptides

The best described orexigenic neuropeptide is NPY, but reports vary as to whether NPY expression in the arcuate nucleus or action within the appetite centers changes during pregnancy (Widmaier et al. 1997; Ajala et al. 2001; Garcia et al. 2003; Oberto et al. 2003; Rocha et al. 2003). Even if expression is increased, it may not relate to enhanced food intake since in the pregnant rat feeding responses to central NPY administration are similar to those in virgin females (Brunton et al. 2006). On the other hand, the expression of AgRP, a more long-acting orexigenic neuropeptide, is enhanced in pregnancy (Rocha et al. 2003), indicating a possible primary change underlying the prolonged adaptation in food intake. Since AgRP is co-expressed in NPY neurons that are inhibited by leptin,

Table 127.1 Reported changes in hypothalamic appetite peptides in mid-late pregnancy

	mRNA	Protein	Activity
Orexigens			
NPY	↓↑?	↓↑#	↔
AgRP	↑	NA	NA
Opioids	↑*	↑	↔
MCH	↓	↓	NA
Orexin A	↔ ↓?	↓	↔
Anorexigens			
αMSH	↓**	NA	↓+
Oxytocin	↔	↔	↓
CRH	↓	NA	NA
CART	NA	NA	NA

↑ Increase reported

↓Decrease reported

↔No change reported

NA not available

? mixed reports of increases, lack of change and/or decreases

region-dependent: decrease in PVN and increase in VMH

+ melanocortin resistance

* POMC & Proenkephalin A in late pregnancy

** POMC in mid pregnancy

Summary of available data from the literature reporting mRNA and protein expression for appetite neuropeptides in the hypothalamus in mid-late pregnancy and any information about activity and/or effects of these neuropeptides in the context of feeding behavior or energy balance. Taken from the following references: Widmaier et al. (1997); Ajala et al. (2001); Garcia et al. (2003); Rocha et al. (2003); Oberta et al. (2003); Russell et al. (2003); Brunton et al. (2006); Sun et al. (2006); Douglas et al. (2007); Brunton et al. (2008); Augustine et al. (2008)

its increasing expression is possibly due to the emerging leptin resistance. Although neither this nor other functional aspects of AgRP in pregnancy have yet been reported, it could be that AgRP, as a first order neuropeptide, is important in maternal hyperphagia (Table 127.1).

127.4.1.2 Anorexigenic Neuropeptides

The contribution of one arcuate anorexigenic neuropeptide, CART, during pregnancy is unknown. However, expression of the αMSH precursor, POMC decreases in mid pregnancy, though it later increases again prior to birth (Russell et al. 2003), but only in a subset of POMC neurons. The synthesis and release of αMSH itself are not reported in pregnancy and may not parallel POMC expression since posttranslational processing is also sensitive to leptin. Interestingly, just as leptin and insulin resistance, melanocortin resistance also emerges (Ladyman et al. 2009), suggesting additional disruption of satiety signaling in second-order neurons. AgRP is an endogenous antagonist to αMSH, via the melanocortin 4 (MC4) receptor, so the increasing AgRP could explain melanocortin resistance and sustained hyperphagia in mid-late pregnancy. Although the identity of the likely αMSH/AgRP targets in pregnancy is unknown, they may be typical second-order neurons in the lateral hypothalamus and paraventricular nucleus (PVN), or in the supraoptic nucleus (SON), and

Table 127.2 Key features of paraventricular nucleus and supraoptic nucleus neurons in the hypothalamus

1. These groups of neurons are hypothalamic nuclei receiving innervation from multiple brain regions including the brainstem, mediating peripheral signals, the limbic system mediating emotions, and other hypothalamic nuclei that regulate multiple body functions such as reproduction, metabolism, and stress
2. The two regions are interconnected for some physiological functions, synchronization of neuron activity in the two nuclei is crucially important, e.g., birth, milk ejection

PVN

3. The PVN is an integrating nucleus, mediating converging inputs and coordinating outputs
4. The PVN encompasses subregions with distinct neuronal phenotypes – key neuropeptides include CRH, oxytocin, and vasopressin
5. CRH responds to the perception of stress from inputs from other brain regions and mediates a hormonal response that facilitates stress coping, mobilization of energy stores to enable the body to respond, and helps the return of homeostasis (i.e., to the nonstress state)
6. Oxytocin is synthesized in two populations of neurons, parvocellular and magnocellular in different subregions of the PVN. Parvocellular neurons project centrally to control physiological responses, e.g., appetite and sympathetic responses Magnocellular neurons project to the posterior pituitary and secrete hormone into the blood to control physiological functions like birth
7. Oxytocin is also released from magnocellular cell bodies into the extracellular space within the brain
8. Vasopressin is also synthesized in both parvocellular and magnocellular neurons of the PVN. Magnocellular neurons release vasopressin at the posterior pituitary into the blood to control body water balance and blood pressure. In the brain, vasopressin from parvocellular neurons helps to control daily rhythms and stress responses. It is also released from cell bodies into the extracellular space like oxytocin
9. At least part of the appetite function of arcuate nucleus peptides is via the PVN neurons

SON

10. The SON contains magnocellular neurons, ~50% are oxytocin neurons and ~50% vasopressin; they have similar functions to magnocellular neurons in the PVN
11. Despite similarities, the neurons in the PVN and SON can act differentially
12. SON neurons respond to many of the other brain appetite signals and may be important in mediating satiety/hunger effects on other behaviors

This table lists key facts of neuroendocrine neurons in the paraventricular nucleus (PVN) and supraoptic nucleus (SON); CRH- corticotrophin releasing hormone

Table 127.3 Key features of orexigenic and anorexigenic neuropeptides in increasing food intake in pregnancy

1. Although many brain factors increase food intake (are orexigens), only one called AgRP actually increases in pregnancy and might contribute to increased eating in pregnancy
2. Some brain factors that inhibit food intake (are anorexigens) are attenuated in pregnancy and so might contribute to increasing appetite
3. Oxytocin is a brain factor important for birth and lactation – it also typically inhibits food intake. Control of oxytocin adapts in pregnancy to decrease its function during gestation but increase its function at birth
4. The typical effect of oxytocin to inhibit food intake is lost in mid pregnancy
5. Brain factors stimulating oxytocin are inhibited in pregnancy – this includes other anorexigenic factors like alpha MSH – its effects in inhibiting food intake also become lost in pregnancy
6. Brain factors inhibiting oxytocin are increased in pregnancy – this includes AgRP
7. Evidence shows that increased appetite in pregnancy may be due to decreases in brain signals that usually inhibit eating

This table explains how changes in known adaptations of orexigenic and anorexigenic neuropeptides contribute to increased eating in pregnancy in rodent models

adaptations in some of these neurons have been extensively reported in the literature (Tables 127.2 and 127.3). POMC products also include βendorphin, an opioid peptide that, converse to αMSH, is orexigenic. βendorphin expression also increases in mid-late pregnancy in the arcuate nucleus, and is implicated in the adaptations of the PVN/SON neurons (Russell et al. 2003), so may be part of the network sustaining hyperphagia (Table 127.1).

127.4.2 Second-Order Hypothalamic Neurons

127.4.2.1 Lateral Hypothalamic Neurons

The orexigenic neuropeptides (melanin concentrating hormone (MCH) and orexin A) in neurons of the lateral hypothalamus are not well investigated during pregnancy. Reports indicate decreased rather than increased expression perinatally (Garcia et al. 2003; Sun et al. 2006) and, central administration of orexin A has the same effect on feeding behavior in virgin and pregnant rats (Brunton et al. 2008). So, these neuropeptides are not obvious candidates for increasing food intake. Therefore, other second-order neurons are potentially important. Indeed, pregnancy-related adaptations of PVN and SON neurons, particularly in CRH and oxytocin, are extensively reported (Russell et al. 2003; Table 127.1).

127.4.2.2 PVN and SON Neurons

The PVN and SON are extensively innervated by arcuate and lateral hypothalamus neurons, making them part of the hypothalamic appetite control network. CRH neurons in the PVN and oxytocin neurons in the PVN and SON play key roles in pregnancy and birth. CRH neurons mediate hypothalamo-pituitary-adrenal (HPA) axis responses to stress and anxiety and, to control stress coping and fetal glucocorticoid exposure, their responsiveness is strongly attenuated during mid-late gestation. Likewise, oxytocin neurons that drive birth and maternal behavior are powerfully restrained during pregnancy to preserve oxytocin stores and prepare neurons in advance for their new and unique patterns of activity then. These extensive adaptations throughout pregnancy might also contribute to maternal hyperphagia and some evidence supports this hypothesis. Although little is known about their role in feeding behaviors compared to the arcuate and lateral hypothalamic factors, these neuropeptides are anorexigenic. In early-mid pregnancy, CRH expression does not change or increases slightly, but by late pregnancy it decreases substantially (Brunton et al. 2008). This accompanies the profoundly attenuated responses to stress and is mediated in part by inhibition from opioids, which block signals from brainstem noradrenergic pathways. Interestingly, while feeding responses to administration of NPY or orexin A in late pregnancy are retained and not different from virgins, CRH and HPA axis responses to these appetite peptides in the same mothers are attenuated (Brunton et al. 2006, 2008). Also CRH responses to CCK are attenuated (Russell et al. 2003; Douglas 2005), overall indicating that CRH neurons no longer respond normally to central or peripheral hunger signals. If central CRH release and actions in the feeding circuit are similarly attenuated, it could be argued that lack of restraint by CRH would increase eating. However, direct effects of CRH on feeding behavior are generally poorly reported, let alone in pregnancy, so at present it is not easy to extrapolate to whether the inhibition of CRH neurons plays a role in the pregnancy hyperphagia.

In parallel with CRH neurons, oxytocin neurons are also inhibited in mid-late pregnancy, and their responses to a variety of stimuli, including stress and feeding signals are attenuated. Such adaptations are extensively reviewed (e.g., Russell et al. 2003; Douglas et al. 2007) in the light of oxytocin's role in parturition and lactation, and include strong inhibition by opioids (Russell et al. 2003; Brunton et al. 2006), and GABA (Brussaard et al. 2000). Oxytocin is typically anorectic; the parvocellular oxytocin neurons acting via the brainstem nucleus tractus solitarius (NTS) are involved in the regulation of gastric reflexes and, in particular, parvocellular oxytocin neurons innervate NTS neurons that are activated by CCK during feeding. In late pregnancy, oxytocin responses to CCK are attenuated (Douglas 2005; Brunton et al. 2008) and brainstem noradrenergic pathways to the
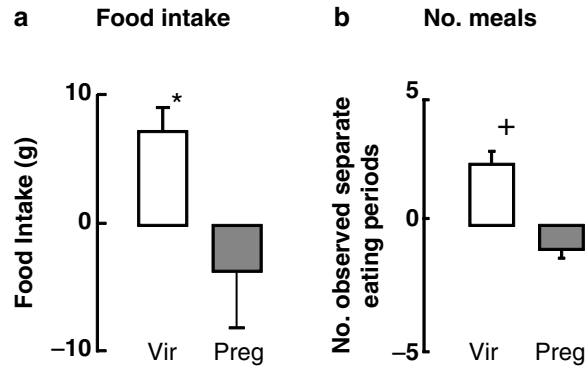
Fig. 127.2 The anorexigenic effect of central oxytocin is lost in mid-late pregnancy. Effect of central oxytocin antagonist administration on food intake and eating behaviors. Rats were fitted with an icv cannula into the lateral cerebral ventricle under halothane anesthesia. Food was removed from the cages 24 h before experiment. On the day of experiment, during the light phase, virgin and 16-day pregnant rats were injected icv with either vehicle (artificial cerebrospinal fluid; 4 μL) or oxytocin antagonist (OTA; 10mg), and then given pre-weighed food. The food remaining was weighed after 24 h (a) and eating behavior was recorded every 1 min for 2 h (b). Data are from OTA–treated rats and represent the difference from vehicle-treated rats (mean ± SEM, n = 5–14). Oxytocin antagonist increases food intake and number of meals in virgin but not in pregnant rats. (**a**) Food intake in 24 h: 2-way ANOVA $p < 0.001$, *$p < 0.05$ versus vehicle. (**b**) Number of meals in 2 h: 2 way ANOVA across group for $p < 0.01$; +$p< = 0.05$ versus vehicle (Adapted from information in Douglas et al. 2007 review)

hypothalamus are inhibited (Douglas 2005). Direct actions by NPY are also possible: SON and PVN neurons express NPY receptors, and NPY increases oxytocin neuron activity and secretion (Broberger et al. 1999; Yokosuka et al. 2001; Brunton et al. 2006; Goldstone 2006; Morin and Gehlert 2006). However, oxytocin neurons respond less to NPY in late pregnancy (Brunton et al. 2006) so, like CRH, lack of oxytocin could partly underlie maternal hyperphagia. Recently it has been shown that αMSH also stimulates oxytocin neurons and they densely express MC4 receptors (see also Chap. 20; Douglas et al. 2007) – if resistance to this anorexigen is present in oxytocin neurons it probably also contributes to hyperphagia mechanisms at this time. AgRP inhibits oxytocin neuron responses to ingestive behavior (Wirth et al. 2002), supporting the notion that increased AgRP promotes melanocortin resistance in oxytocin neurons in mid-late pregnancy. Oxytocin also plays a role in the ventromedial nucleus in controlling food intake, and the leptin resistance described above is at least partly located within this nucleus (Ladyman et al. 2009). The role of oxytocin in feeding in mid pregnancy has been investigated using a pharmacological approach (Fig. 127.2; Douglas et al. 2007), and shows that the expected increase in feeding after central oxytocin receptor antagonist administration is lost compared to virgins. This strongly indicates that anorexigenic neuropeptides, including oxytocin, play an attenuated role in the control of feeding in gestation. Other hunger signals such as leptin and prolactin are also likely components since oxytocin neurons express leptin and prolactin receptors and prolactin inhibits oxytocin neurons (Grattan and Kokay 2008); but their combined role in pregnancy is not yet investigated in terms of feeding behavior (Table 127.1).

127.4.2.3 The Potential Role of Opioids

As mentioned above, hypothalamic opioids increase appetite. Since opioid expression is increased in various brain regions and opioids strongly inhibit CRH and oxytocin in the second half of gestation, the question of whether they play a role in the maternal hyperphagia has also been asked. However,

using the general opioid antagonist, naloxone, a similar decrease in food intake in mid-pregnant and virgin rats was observed (Douglas et al. 2007). Accordingly, the strong opioid inhibition of oxytocin and CRH neurons seems not to play a role and another factor must be the key. As AgRP seems to act in parallel with opioids (Wirth et al. 2002), perhaps adaptations in AgRP/αMSH control of oxytocin neurons are responsible for appetite changes while opioid control of oxytocin neurons is responsible for control of birth-related changes. Which neuronal subpopulations these might encompass is not clear since both the parvocellular and magnocellular neurons respond to multiple and overlapping factors.

127.5 The Role of Progesterone

During pregnancy, there is a close relationship between progesterone secretion, food intake, and extra-uterine body weight. Pseudopregnancy induces the same steroid secretory patterns as pregnancy and gives rise to the same hyperphagia. Progesterone treatment induces similar changes in virgin rodents, and upon cessation of progesterone treatment, and there is a rapid rebound decrease in food intake and body weight (Hervey et al. 1967; Dewar 2001; Asarian and Geary 2006). So, how can progesterone interact with the appetite control system to effect such important adaptations? Progesterone readily crosses the blood brain barrier and can act either via its cognate receptor or by conversion to its neuroactive steroid metabolite, allopregnanolone. Clearly, hypothalamic areas that express progesterone receptors are prime candidates as causal mediators of physiological adaptations to pregnancy, and it is noteworthy that arcuate neurons expresses them in abundance. Progesterone receptor expression in the arcuate nucleus decreases mid-gestation, before increasing again toward birth (Steyn et al. 2007), possibly indicating a shift in the subpopulation phenotype susceptible to progesterone. While both NPY (Dufourny et al. 2005) and βendorphin neurons are reported to express progesterone receptors (Fox et al. 1990), their co-localization with AgRP, αMSH, or CART is uncertain from the literature. Whether progesterone has positive effects on NPY synthesis or secretion, or the co-expressed AgRP is not reported to our knowledge. Progesterone is a recognized driver of POMC expression (Hammer et al. 1994), which changes through the estrous cycle and pregnancy (Russell et al. 2003) so, potentially, the rising progesterone secretion through gestation could impact on βendorphin effects. However, if opioids are not responsible for increased food intake in mid-pregnancy (as argued above), then progesterone effects might be via αMSH or CART. As well as possible direct effects on arcuate neurons, progesterone could influence their function indirectly by altering dopamine, and therefore prolactin, secretion (Steyn et al. 2007), which mediates the leptin and melanocortin resistance described above.

Some of the second-order appetite neurons do not robustly express progesterone receptor, notably CRH and oxytocin neurons in the PVN and SON (Fox et al. 1990; Russell et al. 2003), and expression is not induced during gestation (Francis et al. 2002). Nevertheless, these neurons are strongly influenced by sex steroids; for example, oxytocin neurons are strongly inhibited by progesterone, probably via induction of inhibitory opioid tone (Russell et al. 2003). Much evidence now indicates that progesterone effects on CRH and oxytocin neurons are indirect via allopregnanolone. This neurosteroid is generated in the liver and brain during pregnancy and is a primary cause of the attenuated HPA axis responses to stress (Brunton et al. 2008, 2009). Allopregnanolone acts by binding to membrane receptors: when it binds to $GABA_A$ receptors it enhances GABA signaling, and could affect GABA input to CRH neurons from peri-PVN, NTS, or bed nucleus of the stria terminalis (BNST) neurons. Allopregnanolone also increases opioid expression in this model (Brunton et al. 2009) so may additionally act directly on arcuate or brainstem opioid neurons.

Similarly, allopregnanolone directly enhances GABA inhibition of oxytocin neurons, and contributes to their adaptations during gestation (Brussaard et al. 2000), as well as being partly responsible
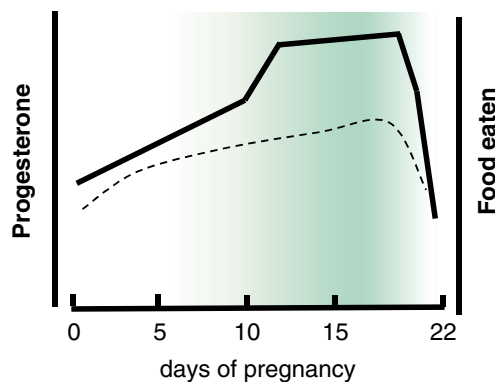
Fig. 127.3 Relationship between progesterone, food intake, and inhibition of oxytocin neurons. As progesterone (and allopregnanolone) concentration—increases so does food intake ⋯⋯ and body weight in the pregnant rat. Progesterone and allopregnanolone inhibit oxytocin neurons strongly from ~mid-gestation (*shading*), probably via GABA signalling and opioids, which then declines toward birth as progesterone secretion reduces (Interpretation and integration of information from Brussaard et al. 2000; Russell et al. 2003; Brunton et al. 2006; Douglas et al. 2007)

for the attenuation of oxytocin responses to stress perinatally (Russell and Brunton 2006). This may be important also in the context of maternal hyperphagia, so could inhibit oxytocin anorexigenic effects by controlling the activity of oxytocin neurons and the amount of oxytocin release and action at its target regions. Such an action on oxytocin neurons is more likely than on oxytocin targets, since oxytocin receptor expression is evidently not dependent on progesterone in pregnancy (Young et al. 1997; Bealer et al. 2006). Toward the end of gestation, the allopregnanolone influence on oxytocin neurons decreases in parallel with the decreasing progesterone secretion and decreasing food intake just prior to birth, and enabling the neurons to respond appropriately to the relevant birth stimuli (Russell et al. 2003). Progesterone control of oxytocin neurons is further illustrated by studies revealing that progesterone administration pre-birth maintains the inhibition of oxytocin neurons and delays delivery (Russell et al. 2003). Therefore, progesterone action via allopregnanolone is a prime candidate mechanism by which food intake increases and is maintained throughout the pregnancy period (Fig. 127.3).

Whether a neurosteroid mechanism contributes to the control of arcuate neurons in addition to direct progesterone receptor-mediated effects in pregnancy is unclear. Also direct investigation of the role of allopregnanolone in maternal hyperphagia has not been reported. There is a limited amount of information that can explain the precise role of progesterone in controlling food intake in pregnancy, but some potential mechanisms are emerging to add to the complex picture.

127.6 Initiation of Increased Food Intake in Early Pregnancy

At this stage, it is not clear what, if anything, can be specifically said about the mechanisms underlying the induction of maternal hyperphagia. All the above systems seem to adapt later, in mid-late pregnancy after food intake has already increased, including peripheral signals, increased orexigenic and decreased anorexigenic factors. Certainly progesterone and prolactin/placental lactogen secretion increase immediately, but what their early brain targets are is not known. Data from the late estrous cycle (or pseudopregnancy), when food intake also increases in parallel with increasing progesterone secretion, might be informative. Factors such as serotonin (Steffens et al. 2008), IGF-1

(Todd et al. 2007), and nitric oxide (Otukonyong et al. 2000) are all candidates as rapid responders to sex steroids. However, responses to other immediate pregnancy factors, including from the decidua and developing placenta such as cytokines and chorionic gonadotrophins, remain to be investigated.

127.7 Applications to Other Areas of Health and Disease

As mentioned above, there was initially some speculation that understanding the mechanisms behind changes in food intake during pregnancy, and particularly their reversibility after pregnancy, would give insight into mechanisms and treatment of obesity. This is not likely to transpire due to the entirely different physiological paradigms, but better understanding of the mechanisms of maternal hyperphagia may impact on other areas of health and disease. Gestational diabetes is one maternal condition that can emerge in pregnancy and have an impact on future maternal and offspring health due to over-nutrition and macrosomia. This can be a consequence of maternal overnutrition and potentially leads to the serious condition of preeclampsia later in gestation. Additionally, overnutrition in pregnancy correlates with offspring obesity later in life (Beall et al. 2004; Muhlhausler 2007; Grattan and Kokay 2008; Kirk et al. 2009). This is related to the topical issue of fetal/neonatal programming, whereby conditions experienced in the womb or early in life negatively impact on health in later life. Thus, maternal obesity provides some type of metabolic programming to the child and increases the likelihood of their obesity.

Importantly, under-nutrition during pregnancy also negatively affects offspring development and health. Under-nutrition decreases litter size and weights (Wade and Schneider 1992; Langley-Evans et al. 2005; Martin-Gronert and Ozanne 2006), and low birth weight is correlated to neurological disorders and cardiovascular disease risk later in life (El Haddad et al. 2003; Franke et al. 2005; Seckl and Meaney 2006). This may occur via developmental anomalies since, for example, a low protein diet in the early stages of gestation, peri-implantation, leads to altered microanatomy (Watkins and Fleming 2009). Furthermore, such programming increases likelihood of other adverse conditions such as decreased somatic growth, and increased risk of diabetes, cardiovascular disease, depression, and anxiety (Leonhardt et al. 2002; Lesage et al. 2004). Evidently, more research is required to further clarify the underlying mechanisms of maternal eating behavior in early pregnancy and how is it affected by conditions such as infection, stress, and obesity. Only then will there be enough knowledge to provide a valid basis for effective advice to the mother (or for women planning a pregnancy) on their optimal eating patterns to avoid a range of adverse maternal and fetal/offspring consequences.

Summary Points

- Progesterone, from the corpus luteum and subsequently the placenta, underlies the increased food intake in gestation, but there is no clear evidence about what mechanisms progesterone acts through to increase food intake.
- The brain mechanisms that mediate the induction of increased food intake in early gestation are not known.
- In mid-late pregnancy hyperphagia is maintained via a cascade of complex, interacting, peripheral and central factors controlling appetite.
- Hypothalamic leptin resistance emerges, located at least partly in the ventromedial hypothalamus but also in the arcuate nucleus.

- Arcuate orexigenic neuropeptides may increase, including NPY and AgRP.
- In second-order neurons, anorexigenic neuropeptides are inhibited, e.g., CRH and oxytocin.
- The anorexigenic responses to central oxytocin are lost in pregnancy.
- We suggest a model explaining sustained maternal hyperphagia: progesterone (and/or) prolactin (placental lactogen) induce melanocortin resistance on oxytocin neurons, via AgRP inhibition, leading to loss of oxytocin-mediated satiety signaling, which may increase meal size/number and contribute to increased food intake in mid-late gestation. (Fig. 127.4).
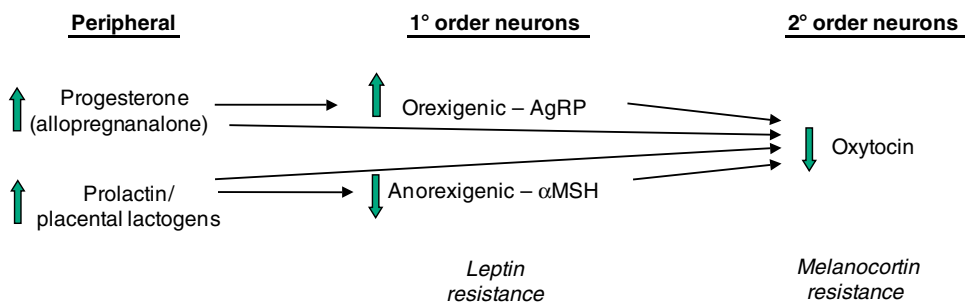
Fig. 127.4 Model for potential pathways sustaining increased food intake in mid-late gestation. Based on evidence in the literature we can suggest a model for neuroendocrine adaptations that explains sustained maternal hyperphagia. (1) Progesterone acts on NPY/AgRP neurons to increase AgRP expression and on POMC neurons to decrease αMSH expression. (2) AgRP inhibits oxytocin neurons and also antagonizes αMSH effects at MC4 receptors, which are expressed in oxytocin neurons; this may induce melanocortin resistance in oxytocin neurons. (3) Simultaneously (and possibly in synergy with progesterone), prolactin/placental lactogens induce leptin resistance and melanocortin resistance which is located in arcuate, oxytocin and/or ventromedial hypothalamus (VMH) neurons. (4) Progesterone also inhibits oxytocin neurons via allopregnanolone enhancement of GABA and opioid signalling. (5) Prolactin further inhibits oxytocin neurons directly. (6) Oxytocin neurons are robustly inhibited over mid-late gestation and anorexigenic effects of oxytocin are strongly attenuated. Thus, this integrated cascade of adaptations in neuroendocrine systems could help explain maternal hyperphagia

---

Definitions

Adipose: It is a tissue making fat, located mainly under the skin and in the abdomen – adiposity = fatness.

Anterior pituitary gland: It is a gland at the base of the brain containing multiple cell types secreting multiple hormones under the control of neuroendocrine factors from the hypothalamus.

Central: It refers to the location of neurons or targets within the central nervous system, and may signify the exogenous administration of drugs, e.g., by the intracerebroventricular route.

Decidua: It refers to the modified region of the maternal uterine endometrium that is the immediate region opposing the placenta and provides part of the barrier between mother and offspring, and also secretes local and circulating hormonal factors.

Hypothalamus: It refers to a complex brain area that regulates many important homeostatic neuroendocrine functions; different regions of the hypothalamus regulate, among many things: hunger, reproduction, stress responses, metabolism, growth, and release of hormones from many glands, especially the pituitary gland.

Hypothalamo-pituitary-adrenal axis: It is a system comprising three anatomical elements that respond to and drive responses to stress, ultimately secreting glucocorticoid hormones that aid stress coping and return of homeostasis.

Magnocellular neuron: It is a large neuroendocrine neuron of the supraoptic nuclei and para-ventricular nuclei of the hypothalamus that projects to the posterior pituitary gland.

Maternal hyperphagia: It refers to sustained increase in food intake throughout gestation.

Negative energy balance: It refers to the condition when the mother utilizes more energy than she is consuming, e.g., in lactation, due to transfer of energy store to offspring in milk.

Neuroendocrine hormones: These are hormones produced by neurons that either: (1) are secreted from the posterior pituitary into the peripheral blood circulation to directly target organs or into the hypophysial portal blood to control the secretion of anterior pituitary hormones, or (2) are released from centrally projecting axon terminals to influence neurons in other central nervous system subregions.

Neuronal network: It is a group of interconnecting and integrating neurons that communicate by physical connections via their axons or by nonphysical connections by responding as a group to an autocrine or paracrine signal, and coordinate a behavior or physiological outcome.

Neurosteroid: It refers to a steroid metabolite with distinct physiological actions that is generated within the brain from other steroids.

Parvocellular neuron: It is a centrally projecting neuron of the paraventricular nucleus.

Pharmacological experiments: It refers to the exogenous administration of drugs to test endogenous mechanisms.

Placenta: It is a fetal–maternal interface constructed from fetal membranes and/or trophoblast, which provides a barrier between mother and offspring but also is the means to provide nutrition and waste disposal as well as hormonal communication.

Positive energy balance: It is a condition when the mother consumes more energy than she is expending, e.g., in pregnancy, even though the developing embryo/fetus has high energy demands.

References

Ajala MO, Oladipo OO, Afonja AO. Niger Postgrad Med J. 2001;8:16–21.

Asarian L, Geary NP. Trans R Soc. 2006;361:1251–63.

Augustine RA, Ladyman SR, Grattan DR. J Physiol 2008;586 (2):387–97.

Bealer SL, Lipschitz DL, Ramoz G, Crowley WR. Am J Physiol. 2006;291:R53–8.

Beall MH, El Haddad M, Gayle D, Desai M, Ross MG. Clin Obstet Gynecol. 2004;47:957–66.

Broberger C, Visser TJ, Kuhar MJ, Hokfelt T. Neuroendocrinology. 1999;70:295–305.

Brunton PJ, Bales J, Russell JA. Endocrinology. 2006;147:3737–45.

Brunton PJ, McKay AJ, Ochedalski T, Piastowska A, Rebas E, Lachowicz A, Russell JA. J Neurosci. 2009;29 (20):6449–60.

Brunton PJ, Russell JA, Douglas AJ. J Neuroendocrinol. 2008;20 (6):764–76.

Brunton PJ, Sabatier N, Leng G, Russell JA. Eur J Neurosci. 2006;23:1241–7.

Brussaard AB, Wossink J, Lodder JC, Kits KS. Proc Nat Acad Sci USA. 2000;97:3625–30.

Dewar AD. The Physiology of the extra-uterine and other weight changes of pregnancy. Edinburgh: Durham Academic Press; 2001.

Douglas AJ. Stress. 2005;8 (1):5–18.

Douglas AJ, Johnstone LJ, Leng G. Physiol Behav. 2007;91 (4):352–65.

Dufourny L, Caraty A, Clarke IJ, Robinson JE, Skinner DC. Neuroendocrinology. 2005;82:21–31.

El Haddad MA, Ismail Y, Guerra C, Day L, Ross MG. Am J Obstet Gynecol. 2003;189:949–52.

Fox SR, Harlan RE, Shivers BD, Pfaff DW. Neuroendocrinology. 1990;51:276–83.

Francis K, Meddle SL, Bishop VR, Russell JA. Brain Res. 2002;927:18–26.

Franke K, Harder T, Aerts L, Melchior K, Fahrenkrog S, Rodekamp E, Ziska T, Van Assche FA, Dudenhausen JW, Plagemann A. Brain Res. 2005;1031:276–83.

Fulglsang J. Vitam Horm. 2008;77:259–84.

Garcia MC, Lopez M, Gualillo O, Seoane LM, Dieguez C, Senaris RM. FASEB J. 2003;17:1392–400.

Goldstone AP. The hypothalamus, hormones, and hunger: alterations in human obesity and illness. Hypothalamic Integration Energy Metab. 2006;153:57–73.

Grattan DR, Kokay IC. J Neuroendocrinol. 2008;20 (6):752–63.

Hammer RP, Zhou L, Cheung S. Horm Behav. 1994;28:431–7.

Hervey E, Hervey GR, Berry PM. J Endocrinol. 1967;38:R3–8.

Kirk SL, Samuelsson A-M, Argenton M, Dhonye H, Kalamatianos T, Poston L, Taylor PD, Coen C. PLoS One. 2009;4:1–13.

Ladyman SR, Tups A, Augustine RA, Swahn-Azavedo AM, Kokay IC, Grattan DR. J Neuroendocrinol. 3 Mar 2009;21:449–456.

Langley-Evans SC, Bellinger L, McMullen S. Mat Child Nutr. 2005;1:142–8.

Leonhardt M, Lesage J, Dufourny L, Dickes-Coopman A, Montel V, Dupouy JP. Neuroendocrinology. 2002;75:45–54.

Lesage J, Del Favero F, Leonhardt M, Louvart H, Maccari S, Vieau D, Darnaudery M. J Endocrinol. 2004;181:291–6.

Leung KC, Xu A, Craig ME, Martin A, Lam KS, O'Sullivan AJ. Metabolism. 2009;58:239–45.

Martin-Gronert MS, Ozanne SE. Biochem Soc Trans. 2006;34:779–82.

Messini C, Dafopoulos K, Chalvatzas N, Georgoulias P, Messinis IE. Clin Endocrinol (Oxf). 15 Dec 2008;epub.

Morgan B, Winick M. Br J Nutr. 1981;46:29–37.

Morin SM, Gehlert DR. J Mol Neurosci. 2006;29:109–14.

Muhlhausler BS. J Neuroendocrinol. 2007;19:67–72.

Oberto A, Mele P, Zammaretti F, Panzica G, Eva C. Endocrinology. 2003;144:4826–30.

Otukonyong EE, Okutani F, Takahashi S, Murata T, Morioka N, Kaba H, Higuchi T. Brain Res. 2000;887 (1):70–9.

Rocha M, Bing C, Williams G, Puerta M. Reg Peptides. 2003;114:159–65.

Russell JA, Brunton PJ. Neuroscience. 2006;138:879–89.

Russell JA, Leng G, Douglas AJ. Front Neuroendocrinol. 2003;24:27–618.

Seckl JR, Meaney MJ. Glucocorticoid "programming" and PTSD risk. Ann N Y Acad Sci. 2006;1071:351–78.

Shirley B. Lab. Animal Sci. 1984;34:169–72.

Steffens SM, da Cunha IC, Beckman D, Lopes AP, Faria MS, Marino-Neto J, Paschoalini MA. Physiol Behav. 2008;95 (3):484–91.

Steyn FJ, Anderson GM, Grattan DR. J Neuroendocrinol. 2007;19 (10):788–93.

Sun G, Tian Z, Yao Y, Li H, Higuchi T. J Mol Endocrinol. 2006;36:131–8.

Todd BJ, Fraley GS, Peck AC, Schwartz GJ, Etgen AM. Biol Reprod. 2007;77 (3):492–503.

Viani I, Vottero A, Tassi F, Cremonini G, Sartori C, Bernasconi S, Ferrari B, Ghizzoni L. J Clin Endocrinol Metab. 2008;93:1476–81.

Watkins AJ, Fleming TP. J Anat. 2009;215 (1):52–9.

Wade GN, Schneider JE. Neurosci Biobehav Rev. 1992;16:235–72.

Wirth MM, Olszewski PK, Levine AS, Giraudo SQ. Neuroreport. 2002;13:1355–1358.

Yokosuka M, Dube MG, Kalra PS, Kalra SP. Peptides. 2001;22:507–514.

Young LJ, Muns S, Wang ZX, Insel TR. J. Neuroendocrinol. 1997;9:859–865.

Chapter 128
Effect of Pregnancy and Consciousness Factors on Food-Related Behavior

J. K. Chun, S. W. Lim, and W. I. Cho

Abbreviations

5-CL	5th consciousness layer, numerical number refers to relevant consciousness layer: 6-CL, 7-CL, and 8-CL, 6th, 7th, and 8th consciousness layer, respectively
CS-Q	Cognitive sensory questionnaire
EG	Emesis gravidarum
FRL	Food-related lifestyles
MDS	Multidimensional scaling
PN	Women who had never been pregnant
PY	Women who had been pregnant
3-WBT	Three-way branch transformation

128.1 Introduction

One noticeable change in the food habits of pregnant women is loss of appetite, often referred to as morning sickness, emesis gravidarum (EG), experienced by a majority of pregnant women (Bowen 1992; Ortega 2001; Lim et al. 2008). This particular food behavior of pregnant women has been accepted as physiological phenomenon that occurs in the early stages of pregnancy and disappears as the pregnancy advances. However, the change in food habits and appetite are not merely a physiological one but also involves a significant change in the food evaluation process, which occurs in individual mind system and affects food choice motivation and food consumption.

The decision-making process underlying food choices, including perceptions about food products, has been studied for decades (Glanz et al. 1992; Shepherd and Raats 2006). Food evaluations have been conducted by panelists with respect to the sense of taste, the odor, and the kinesthetic experience of fresh and processed foods. Because the sensory judgment is subjective, the variability of the sensory data among panelists is an inherent problem.

Since Fechner (1866) noted the importance of the mind for sensory science, and Thurstone (1927) proposed a psychometric function involving psychological magnitude or perception, and his

W.I. Cho (✉)

Department of Food and Animal Biotechnology, College of Agriculture and Life Sciences,
Seoul National University, San 56-1 Sillim-dong, Gwanak-gu, Seoul 151-921, Korea
e-mail: wanilcho@gmail.com

proposal has played a major role in the theoretical development of sensory science (Ennis 1998). Although studies have focused on establishing a scale for perceptual intensity, to establish the relationship between sensory response and external stimuli, the perception mechanism is not yet fully understood (Wells 1998; Eliasmith and Thargard 2001).

Determinants of food choices have been categorized into food and nonfood factors (Rozin and Tuorila 1993, Eertmans et al. 2001). Nonfood factors include personal preferences such as dislikes and preferences, demographic variables, food-centeredness, and psychological and physiological needs and traits. The relationship between food choice and cognitive and motivational factors has been investigated by many researchers and has been related to biological, psychological, cultural, economic, and social factors (Cosper and Wakefield 1975; Bell et al. 1981; Lau et al. 1984; Michela and Contento 1986; Rappoport et al. 1992; Furst et al. 1996: Meiselman 1996).

Glassman (2000) and Kunde et al. (2003) insisted that unconscious factors play important roles in perceptions and frames of reference related to food choices. Ashby and Lee (1991), and Ennis (1998) demonstrated that human consciousness factors and nonsensory components were closely related to the process by which food is evaluated. Accordingly, food choice has been recognized as a process involving the events and experiences that occur throughout life (Furst et al. 1996). Because food choice is a particular human behavior, general behavioral theory has been applied to food-related behavior (Ajzen and Fishbein 1975) in that behavior is closely associated with lifestyle.

The lifestyle concept is rooted in models of cognition and behavior regulations that derive from psychology (Cohen 2000), and research on food-related lifestyles (FRL) has been widely conducted (Brunsø and Grunert 1995).

The FRL questionnaire is comprised of 69 items measuring 23 dimensions of lifestyle in five major domains of life, including: shopping, cooking, issues of quality, consumption situations, and purchasing motivations. This instrument was based on a hierarchical formulation of cognitive structure (Grunert and Grunert 1995). At the highest level of the hierarchy, personal values are defined as abstract and trans-situationally aggregated cognitive categories. At the lowest level, product perceptions are defined as situation-specific input into a categorization process. Scholderer et al. (2002) and Brunsø et al. (2003) have elaborated this basic theory in a dual-process framework.

128.2 A Consciousness-Oriented Approach to Food-Related Behavior

128.2.1 Vasubandhu's Consciousness-Only Structure

A similar hierarchical structure to that of Scholderer (2002) had been developed by Vasubandhu (ad 400), an Indian Buddhist scholar–monk. This structure has been popularized in non-Western contexts as a consciousness-only theory (Anacker 1984). Vasubandhu described the human mind in greater detail than did Western scholars and his classification system includes relevant causes of numerous mind states such as desire, attachment, like, dislike, and so on. He argued that humans operate within a multilayered hierarchical structure of consciousness consisting of eight layers of consciousness; three layers operate at higher levels and five sensual layers operate at lower levels. This structure is characterized by dual top-bottom consciousness streams, as schematically presented in Fig. 128.1.

People in Asian countries including India, Thailand, Vietnam, Cambodia, China, Korea, and Japan have been influenced by this conceptual framework. If appetite represents an actual desire for food, loss of appetite is based in consciousness. In this context, Chun (2002) proposed a concept
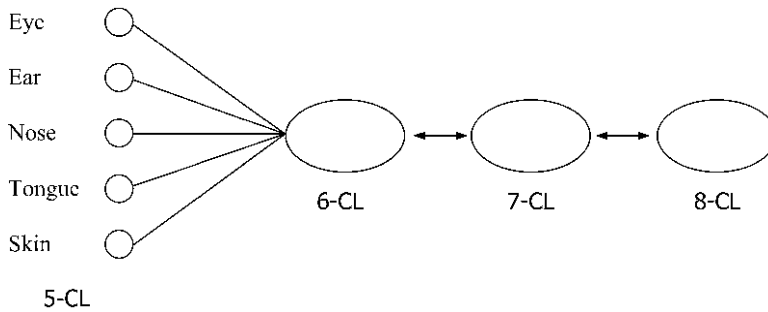
Fig. 128.1 Vasubandhu's multilayer consciousness structure (Cited in Chun 2002. With permission)

related to cognitive sensory evaluation that defined the multilayered hierarchy such that the fifth layer of consciousness (5-CL) represented the process by which the attributes of observable or sensate objects are known via the five organs of sensorial consciousness (eye, nose, tongue, ear, and skin). This framework is essentially the same as the five sensory or lower levels of the hierarchy presented in the Western conceptualization of cognitive structure (Brunsø and Grunert 1995; Cohen 2000).

The sixth consciousness layer (6-CL) is a post-sensory manager controlling the process by which meaningful information is perceived and classified; it is also comparable to the structure proposed by Rosch et al. (1976) in that it belongs to a superordinate level that organizes memories into packets that function as the basic units for categorization.

The characteristics of the multilayered structure can be understood in terms of two layers, the seventh layer of consciousness (7-CL) and the eighth layer of consciousness (8-CL), which can be considered to constitute unconsciousness in general.

The 7-CL, defined as egocentric or Manas consciousness (Anacker 1984), evaluates objects subjectively on the basis of accumulated information stored in memory. It is relevant to Karma (Anacker 1984) and represents the individual personality acting and making decisions based on personal experiences that are referenced from long-term memory (Lim et al. 2008). Personal values derive from 7-CL, which can be considered to be equivalent to the highest level in the Western conceptualization of a cognitive hierarchical structure. Egotism, including ego-image, ego-esteem, and ego-threat are developed in this layer.

The 8-CL, the ultimate level, controls the overall mental process by which homeostasis is maintained and stores abstract information, functioning as a back-up file that can be transmitted to the next generation. Thus, no thought is directly associated with this layer; rather, it represents a seed associated with the genetic code known as Karma, the habitual tendencies produced by past actions (Anacker 1984).

In short, the mind is considered to be a special type of sense, which suggests that humans have additional senses inside the mind.

128.2.2 Perception in the Consciousness

The perspective that the mind is composed of multilayered consciousness or multiple senses suggests the existence of multiple stages of perception or interperception. Chun (2002) claimed that incoming stimuli sensed by 5-CL from objects in the external world are transferred into 6-CL via passive acquisition. Thereafter, active transformations across 6-CL and 7-CL occur. As long as the egoistic 7-CL is involved, every perception process follows a three-way branch transformation (3-WBT) logic to one of three options: good, bad, or neutral, as defined by the point of view of the perceiver. After repeated

transformations, the good option will be recognized as the best when interperception among the internal mental layers or senses favor this option. Therefore, any judgment about the taste of food results from data processing or conditioning occurring across the multilayered structure, while memories of food and associated images are stored and used as the references for the next session of 3-WBT.
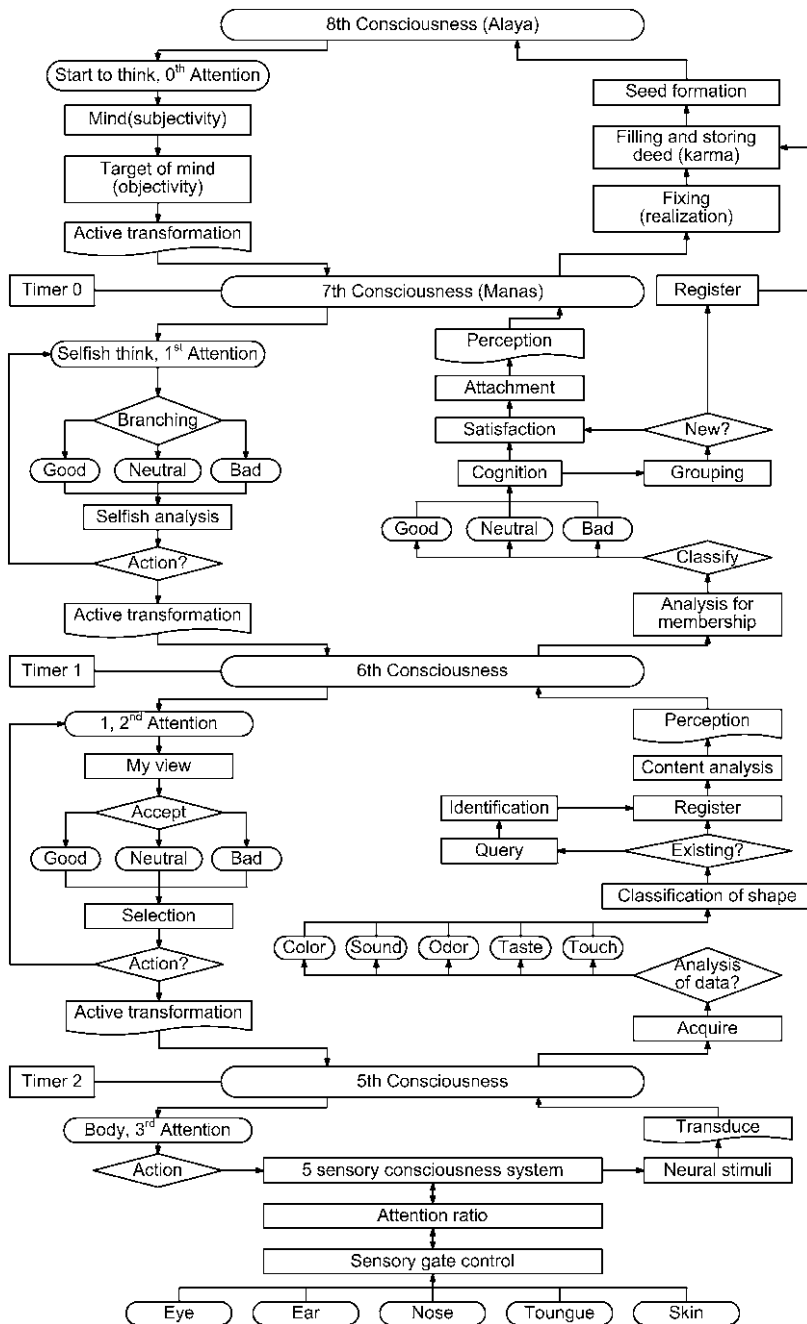
Fig. 128.2 Dual path flow according to the multilayered consciousness concept. Timer 0 through 3 refers to the time units undergoing consciousness processes in 7-CL, 6-CL, and 5-CL, respectively (Cited and revised in Chun 2002)

Key Points

Key points in the consciousness flow chart

1. Consciousness flow refers to human mental activity working across conscious and unconscious states.
2. Consciousness is considered to be a multilayered componential structure.
3. The 5th consciousness layer (5-CL) is the lowest or bottom layer, and 8-CL is considered to be the highest or top level of the mind.
4. The stimuli sensed from external objects are acquired and perceived by upper CLs and interpreted in favor of the self or 7-CL.
5. Food-related behaviors, such as food choices and rates of consumption, are determined by the ego-centric consciousness, 7-CL.

Chun (2002) schematically illustrated how the system of consciousness interfaces with the external world and generates motivation in the internal world using different time units for action (see Fig. 128.2).

Many studies have demonstrated that people automatically evaluate all stimuli (social and nonsocial objects and events) as either good or bad (Fazio et al. 1986; Bargh et al. 1996). Thus, any food-related behavior might be regarded as the outcome of the flow of consciousness through 7-CL as transformed by 3-WBT.

128.3 A Consciousness-Oriented Approach to Pregnancy

128.3.1 Two Subjects in One Food Supplier

Pregnant women experience various phenomenal changes with regard to food appetite caused by underlying psychological changes as well as changes in the environment, including such external and internal phenomena as physiological programming. Thus, anything that occurs in 5-CL and 6-CL might represent an environment for the self or 7-CL.

Key Points

Key points of the two-ego consciousness system

1. Pregnancy is a typical state of consciousness in which two selves, mother and fetus, reside in one physical food-supply system.
2. Loss of appetite might be caused by conflict between the different food habits of the two egos.
3. EG decreases or disappears as pregnancy advances due to negotiation and compromise between the two selves.
4. EG can be understood as a valuable insight into the world of consciousness, which is the origin of various food-related behaviors.

There is no doubt that pregnancy represents the beginning of the emergence of life, starting with a single cell that grows into an entire body characterized by an increasingly complex neuronal system for controlling this body. During this period, nutrients are supplied through the mother's digestion system for two purposes: to support the mother and fetus; and to support the construction of the new neural network, which progresses outside of the consciousness of the mother. In the absence of an adequate neuronal system, the fetus may share the mother's communications network.

This situation of "two subjects in one food supplier" strongly implies that a mind resides in the fertilized cell and participates in controlling the entire life course, including food consumption. Indeed, it would be difficult to assert that mother and fetus have identical minds; thus, the newcomer must have arrived with its own genetic codes, containing its history or Karma, encoded in 8-CL. That the genetic record emerging from previous generations affects the mother's food-related behaviors, including those involved in EG during pregnancy, is strongly suggested.

128.3.2 Intersubjective Communication

As long as two egoistic subjects (two 7-CLs) reside in one physical body, it is important to understand how they communicate with each other, particularly in a physical context in which only one food consumption system operates. In this framework, ultimate consciousness, 8-CL, emerges as an intersubjective capability enabling communication between the minds.

Without this assumption, we would confront questions such as: Do the two selves relate as master and slave? If so, food choice and acceptance would be decided by the mother and problems such as EG would not occur. If not, conflict deriving from the situations of the egoistic selves would ensue. Does each self have an independent consciousness? If so, how do they communicate without a terminal device to reach agreement and compromise during the early phase of neural networking? Food choice constitutes good example of how the thinking and communication of the two subjects develop.

Two contradictory facts are generally acknowledged: that the food-related behaviors of children are affected by their parents, and that the food preferences of brothers and sisters are different. These phenomena imply that genetic and familial factors contribute to attitudes toward food during pregnancy but questions about causation remain. Along these lines, pregnancy may be considered to constitute an important, particular, or boundary condition for the purpose of developing a general understanding of how the relevant components of consciousness are activated in the process of forming an ego. It might be presumed that a certain component or layer of consciousness remains latent until a critical moment arrives, and pregnancy might constitute one such critical moment.

128.4 Methodological Considerations

128.4.1 Categorization of Food and Nonfood Issues

The involvement of factors related to consciousness in food choices means that evaluations of the process by which food is selected should address conscious and unconscious issues, as previously described. In order to apply the concept of multilayered consciousness to the evaluation process, Chun (2002) classified food and nonfood issues into two categories: objective and subjective issues that pertain to the elements of consciousness as defined in Table 128.1.

Table 128.1 Food- and nonfood-related issues in the cognitive sensory evaluation of food(Cited in Chun 2002. With permission)

Issues	Component	Contents
Objective issue	Environment	Brightness, temperature, humidity, audio-factor, visual-factor
	Product property	Taste, flavor, shape, color, chewing sound, texture
Subjective issue	5-CL	Gender, age, weight, height, hunger, health (eye, ear, nose, tongue, mouth, stomach), sensitivity of sense organs, smoking, and preference associated with five senses
	6-CL	Schema, effect of schema, knowledge of product information, family education, education, concentration
	7-CL	Age of first eat, frequency of eating, cooking experience, ability of association, direction of association, preference of family, hobby, first impression, demand of unconsciousness state, ideology, feeling after eating, faith, rationality, religious teaching, frequency of dreaming, similarity of eating habit
	8-CL	Eating while pregnant, given digestibility, willingness, awareness of mind, frequency of meditation

The objective category primarily includes those attributes of food addressed by food sensory science (Meilgaard et al. 2006); the subjective category also includes certain data that can be measured with conventional sensory tests as well as lifestyle, personality, and other issues outside the domain of sensory scientists and within 7-CL and 8-CL. In order to clarify the psychological reactions that affect food choice and acceptance, it is necessary to understand how food-related stimuli are cognitively merged into the stream of consciousness.

128.4.2 Cognitive Sensory Evaluation Using the CS-Q Questionnaire

In this context, a novel methodology is necessary to account for multiple stimuli entering via the five senses, for the internal world, or layers of consciousness, as well as for a concept of time. The content and methodology of the cognitive sensory questionnaire (CS-Q) were developed by Chun (2002), and the response of the survey was presented by cognitive sensory barcodes and cognitive sensory frequencies to be described later in the Application section.

The CS-Q was designed to address all items defined in Table 128.1 (Shine and Chun 2004). It consisted of questions in the subjective category, including questions for information on subject components, about health and lifestyle, about food attitude and behavior, regarding pregnancy experience, and questions in the objective category regarding foods. It also included questions about feeling, satisfaction for each component, and overall satisfaction after consumption of food. The CS-Q test does not restrict environmental conditions because the internal environment is too complex to control; for instance, 5-CL and 6-CL can be the environments for the egocentric 7-CL.

128.4.3 Design Considerations in the CS-Q

The following are illustrative of the questions and answers are shown in brackets at the end of the questions.

- **Objective Category Referred to 5-CL**: What is the color of potato chips? (white, white-yellowish, yellow, brownish-yellow, brown); Did you have any change in appetite? Was there any change in the quantity of your meal? (not at all, slightly, quite, much, very much).
- **Subjective category, referred to 6-CL, 7-CL, and 8-CL**: How much do you know about potato chips? (nothing at all, little, fair, much, and very much) for 6-CL; How responsive are you toward a new food? (not at all, little, fair, much, and very much), What does eating potato chips cause you to imagine? (nothing at all, potato or fruit, bear, friends, event or business) for 7-CL; How often have you eaten potato chips while pregnant? (not at all, quite seldom, seldom, often, very often); Do you have any dreams particularly associated with pregnancy? (not at all, quite seldom, seldom, often, very often) for 8-CL.
- **Componential and overall satisfaction**: Do you like the color of the potato chip? (extremely dislike, dislike, slightly dislike, neutral, slightly like, extremely like).

128.4.4 Subjects and Food Items for the CS-Q

The subjects and food items included in the CS-Q should be selected in consideration of consciousness issues for two subjects groups who had experienced pregnancy and those who had not, focusing on a typical food item, potato chips on which subjects have a wide range of age with different exposure periods.

128.5 Influence of Pregnancy on Food-Related Behaviors

128.5.1 Changes in Dietary Behavior Upon Pregnancy

Lim et al. (2008) reported that in the PY group, 86% (161/188, very much 8%, much 20%, moderate 20%, low 38%) of the women experienced a change in food-related behavior such as food taste, tasting sensitivity, appetite, quantity and frequency of daily meal during pregnancy (see Fig. 128.3). About a quarter of the group showed a high degree of dietary change, and about half of the group showed a noticeable degree of dietary change. The most frequent changes were severe loss of appetite and a remarkable change in food preference, accompanied by EG.

The number of births affected the food consumption in the PY group with respect to three response categories as shown in Fig. 128.4. No remarkable changes in any category during EG, as observed in Fig. 128.4a. In contrast, after EG, the number of previous births of the PY group markedly influenced two response categories: increased food consumption and no change in food consumption, as shown in Fig. 128.4b. The percentage of respondents with increased food consumption dropped from 72% (for first-birth subject) to 38% (for third-birth subject), while the percentage with no change in food consumption increased from 25% (for first-birth subject) to 60% (for third-birth subject).

The distinct changes in food consumption in PY group after EG periods suggest that accumulated pregnancy experiences cultivate the ability to control the digestive organ, which is operated by the unconscious, or parasympathetic, nervous system. Considering the remarkable effect of EG on dietary behavior and, in particular, on food consumption during pregnancy, psychological changes accompanying the physiological changes should be considered one of the variables in the food acceptance process, such that a judgment is made as to whether a food should be accepted or rejected. Subjective memories of particular foods, as part of a woman's consciousness or psychological background, may play a role in this judgment. Thus, the experience of pregnancy may occupy an important position in

Fig. 128.3 The percentage of respondents who exhibited changes in food-related behavior during pregnancy. Data resulted from PY group (*n* = 188, mean age 43.2) (Cited in Lim et al. 2008. With permission)
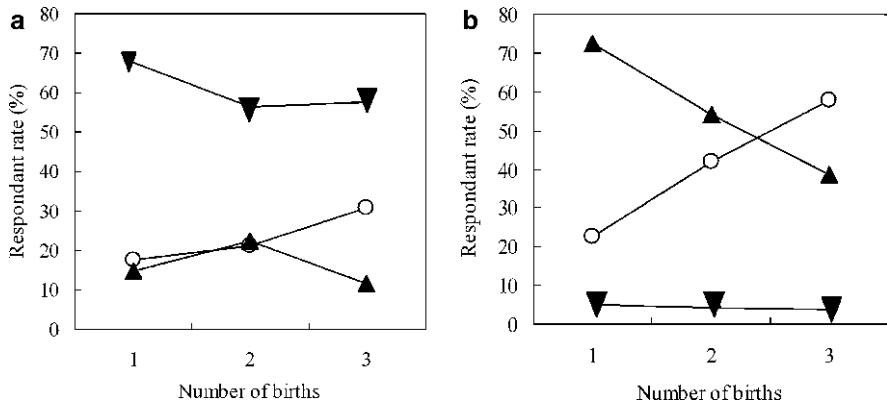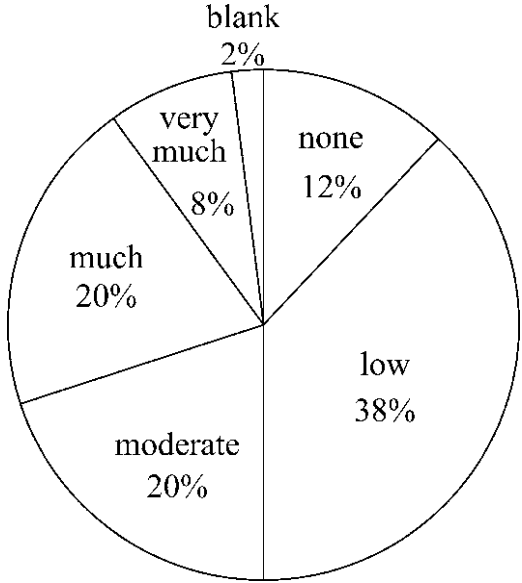
Fig. 128.4 Percentage of subject in PY group who experienced changes in dietary behavior: (**a**) During EG and (**b**) After EG. Data resulted from PY group (*n* = 188, mean age 43.2); ▲, increased food consumption; ○, no change in food consumption; ▼, decreased food consumption during and after EG according to the number of previous births (Cited in Lim et al. 2008. With permission)

a woman's reference memory, influencing dietary behaviors such as food preferences and satisfaction. This strongly suggests that the content and factors of the food evaluation process can differentiate between women who have been pregnant and those who have not. Thus, it appears that the latent consciousness layer governing the sensorial organ was activated during pregnancy.

128.5.2 Relationship Between Componential and Overall Satisfaction

The differences between PN and PY groups in dietary behavior might derive from the perceptual stage of food consumption. A comparative study on perceptions of potato chips by PN and PY groups (Lim et al. 2008) revealed that the satisfaction derived via the five sense organs and the overall

Fig. 128.5 Spider web plot of the correlations between componental satisfaction and overall satisfaction in the PN and PY groups for potato chips. Data evaluated with PN and PY groups for potato chip. ○, PN ($n = 111$, mean age 22.8); ▲, PY ($n = 188$, mean age 43.2) (Cited in Lim et al. 2008. With permission)
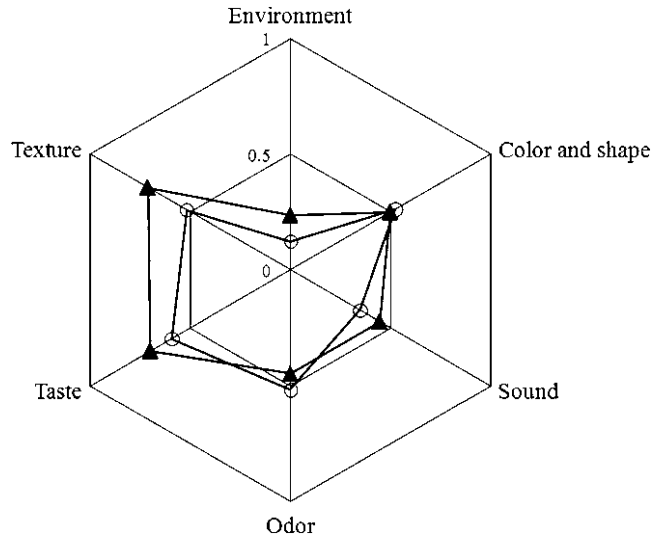
satisfaction were highly correlated, with a correlation coefficient greater than 0.4 for all components with the exception of the environmental component (0.195).

The taste (0.662) and texture (0.651) components were more closely related to overall satisfaction than were the other components, suggesting that taste and texture are critical in the process of evaluating potato chips. The spider web plot (Fig. 128.5) demonstrates clear differences in all of the components, except color and shape, between the PN and PY groups.

The asymptotic significance values were significantly higher for two components (0.939 for texture, and 0.294 for color and shape) and 0.879 for overall satisfaction, indicating similarities between the two groups of women. In contrast, the other four components (sound 0.013, odor 0.002, taste 0.018 and environment 0.057) showed significant differences between the groups but the highest similarity was observed for overall satisfaction. This suggests that food preference, defined as a subjective choice of food based on satisfaction, is not determined by satisfaction of individual relevant componental features but by satisfaction of multiple integrated components.

128.5.3 Factors Affecting Overall Food Satisfaction in the Two Groups of Women

Multidimensional scaling (MDS) analysis for all componental elements of the relevant component set is shown in Fig. 128.6.

In this map, the elements of the sensorial components did not group, in accordance with the componental classification, but instead showed scattering in all componental categories. The degree of scattering and the distance from overall satisfaction were greater in the PY group than in the PN group. The locus of overall satisfaction was in the midst of the components in the PN group but was at the outer rim in the PY group. However, the two groups showed a common consistent trend for close association or binding with the taste component. These results further confirm that a clear change in the food satisfaction process occurs during pregnancy and that taste is an important factor for either group.
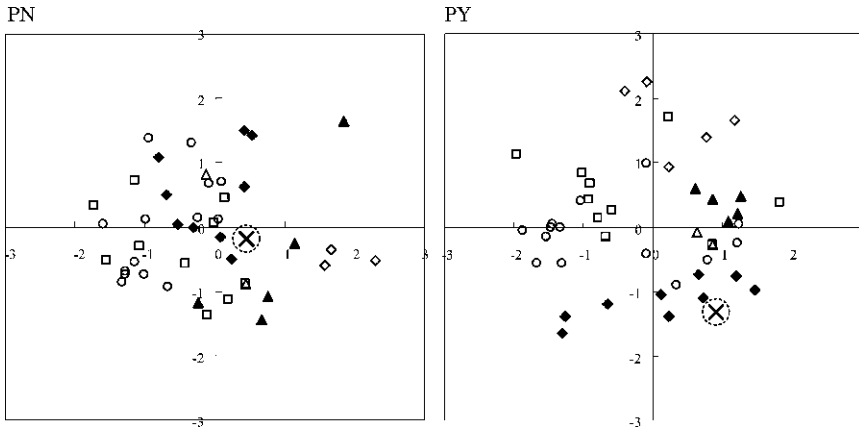
Fig. 128.6 MDS plots of stimuli score of componential elements and overall satisfaction for the PN and PY groups. Data evaluated with PN ($n = 111$, mean age 22.8) and PY ($n = 188$, mean age 43.2) groups for potato chip. ◊, environmental condition; ▲, color and shape; △, sound; □, odor; ○, taste; ♦, texture; ⊗, overall satisfaction (Cited in Lim et al. 2008. With permission)

128.5.4 Influence of Sensorial Stimulus on Overall Satisfaction

According to Chun's hierarchical consciousness framework, sensorial stimuli are acquired at bottom layer or 5-CL and perceived by the higher layer. Thus the preference and overall satisfaction are outcomes from decision made at higher level in 6-CL and 7-CL.

The positioning maps of MDS analysis shown in Fig. 128.7 indicates how influential the sensorial signal and the preference are. The sensorial stimulus, a single common symbol (▲) represents all sensorial signals (environmental condition; color and shape; sound; odor; taste; texture), and the preference is similarly indicated with a common symbol (○). In the PN group, the strength of the
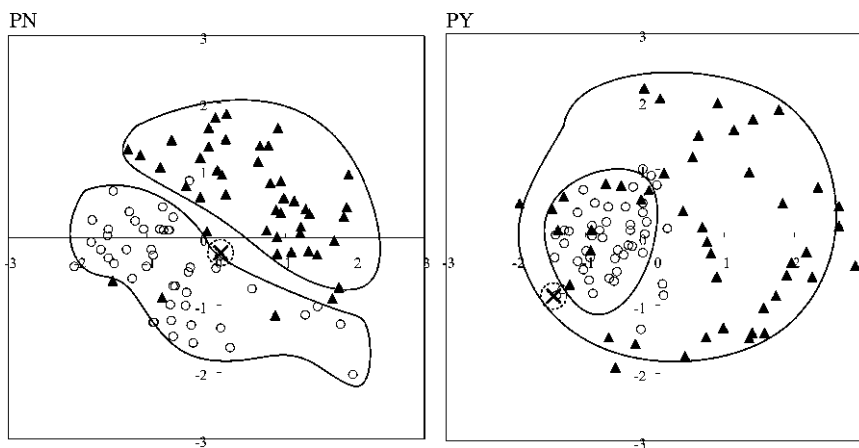
Fig. 128.7 MDS plots of strength of sensorial stimulus, preference of componential elements, and overall satisfaction. Data evaluated with PN ($n = 111$, mean age 22.8) and PY ($n = 188$, mean age 43.2) groups for potato chip. ▲, sensorial stimulus; ○, preference of componential elements; ⊗, overall satisfaction (Cited in Lim et al. 2008. With permission)

sensorial stimulus and preference of componential elements are distributed evenly around overall satisfaction (⊗). The PY group showed greater scattering than the PN group, and overall satisfaction is located at the outer edge of the plotted zone, close to the positions of preference.

Lim et al. (2008) claimed that the pregnancy experience could account for the consciousness feature of satisfaction, and that the consciousness components have as much influence on overall satisfaction as the sensorial features.

128.6 Effect Consciousness Factors on Food Consumption

128.6.1 Relationship of Consciousness Components and the Preference of Componential Elements

Figure 128.8 compares the relationship of consciousness components, represented by a common symbol (●), and preference with (○) in the MDS plot. As compared with the patterns for strength of sensorial stimulus, preference of componential elements, and overall satisfaction in Fig. 128.7, the distribution patterns of consciousness component in the positioning maps (Fig. 128.8) are very similar between the PY and PN groups with respect to both the aggregating format and the locus of overall satisfaction.

As these two results make clear, the consciousness components had as much influence on overall satisfaction as the sensorial features. Although consciousness components are not directly measurable, as are sensorial stimuli, their roles in overall satisfaction are remarkable.
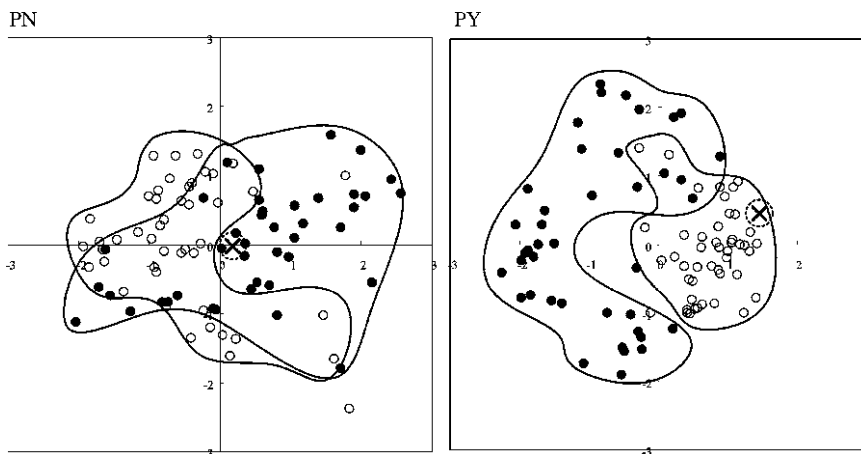
Fig. 128.8 MDS plots of consciousness component, preference of componential elements, and overall satisfaction. Data evaluated with PN (*n* = 111, mean age 22.8) and PY (*n* = 188, mean age 43.2) groups for potato chip. ●, consciousness component; ○, preference of componential elements; ⊗, overall satisfaction (Cited in Lim et al. 2008. With permission)

128.6.2 Relationship Between Consciousness and Sensorial Stimuli

Given the importance of consciousness factors, it is necessary to examine the relationship between sensorial stimuli and consciousness as related to judgments of the stimuli sensed by the sensorial organs. As above, the consciousness components were represented by common symbols shown in Fig. 128.9, the pattern of the consciousness loci (○) was similar to that seen in the consciousness vs. preference and sensorial stimulus vs. preference plots, but the aggregating format and positioning were remarkably different. Aggregation was low in both the PY and PN groups. In the PY group in particular, the aggregating phenomenon disappeared completely, suggesting that consciousness factors may be as important as sensorial factors.
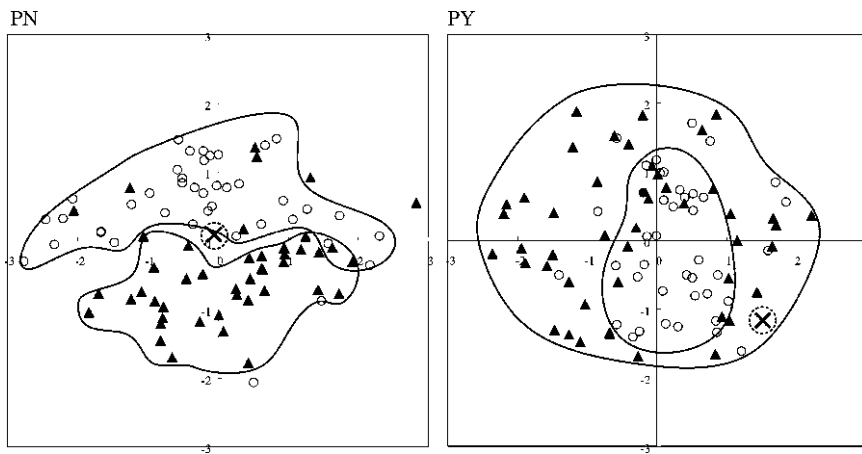
Fig. 128.9 MDS plots of consciousness for the PN and PY groups. Data evaluated with PN ($n = 111$, mean age 22.8) and PY ($n = 188$, mean age 43.2) groups for potato chip. ▲, sensorial stimulus; ○, consciousness component; ⊗, overall satisfaction (Cited in Lim et al. 2008. With permission)

128.6.3 Overall Satisfaction With Food at Various Levels of EG

When food preferences were involved in the MDS analysis, the locus of overall satisfaction emerged in the context of other subjective issues on the positioning map. This indicated that overall satisfaction was one of the states resulting from consciousness activities and that it might vary according to the consciousness of the individual. Lim and Chun (2005) reported that the locus of overall satisfaction varied according to the level of EG, as shown in Fig. 128.10. They also claimed that the number of births affected food preferences in the PY group.
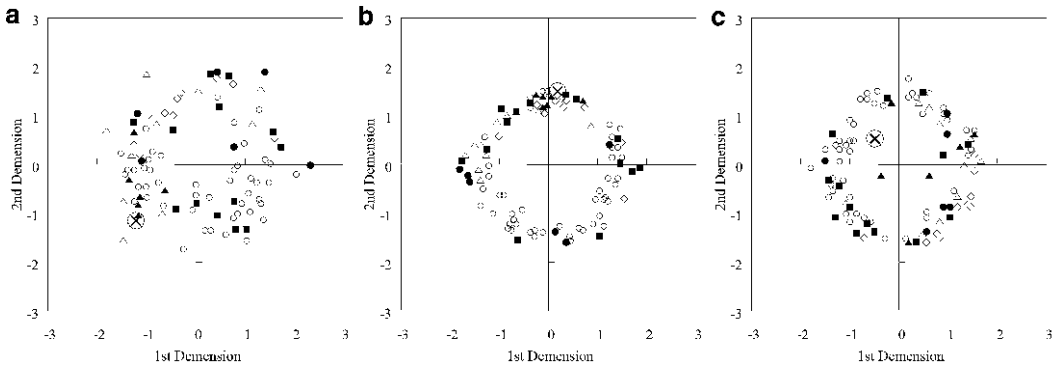
Fig. 128.10 Locus of overall satisfaction at various states of EG in the MDS plots: (**a**) No EG (**b**) Mild EG (**c**) Severe EG. Data evaluated with PN (n = 111, mean age 22.8) and PY (n = 188, mean age 43.2) groups for potato chip. ⊗, overall satisfaction; ▲, componental satisfaction; ◊, 5-CL component; ●, 6-CL component; ■, 7-CL component; Δ, 8-CL component; ○, Sensorial stimuli (Cited in Lim 2005)

128.6.4 FRL Differences Between PY and PN Groups

The MDS positioning plot differences was also found in the results obtained from the FRL questionnaire, widely accepted tool as noticed in Fig. 128.11 which depicts responses to the 23 dimensions of the questionnaire (Scholderer et al. 2004). It shows that the behaviors of those in the PY and PN groups are remarkably different in terms of their individual positioning and their responses to the 23 dimensions addressed by the questions. The responses of PN subjects are densely aggregated in a narrow zone of the sphere. In contrast, those of PY subjects are widely scattered.
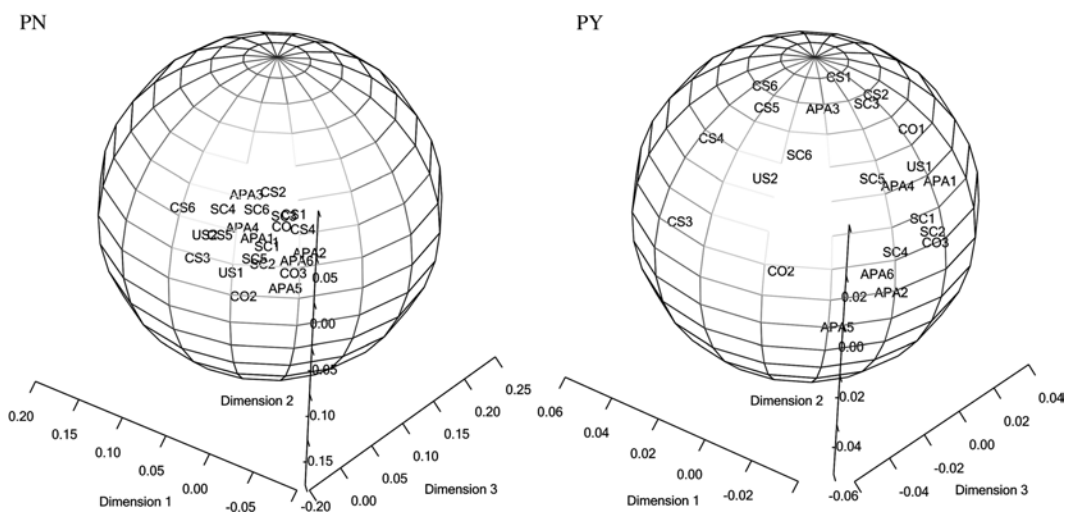
Fig. 128.11 MDS plots of the 23 dimensions of the FRL for the PN and PY groups. PN, college students, aged 20–29, n = 98; PY, housewives with at least one child, aged 30–49, n = 65 (Cited in Cho and Chun 2009. Refer to Scholderer et al. (2004) for abbreviations)

128.6.5 Differences Between PY and PN Groups With Regard to Food Acceptance and Frequency of Food Consumption

The MDS positional plots (Fig. 128.12) of food consumption and acceptance of 21 categories of Korean food, including vegetables, meats, and beverages resembled those obtained with the FRL (Fig. 128.11).

In 3D sphere MDS plots, the differences between two groups were clarified in the positional area regarding acceptance and consumption of food. The PY group showed greater scattering than the PN group. In this connection, the scattering is more remarkable in food consumption than food acceptance.
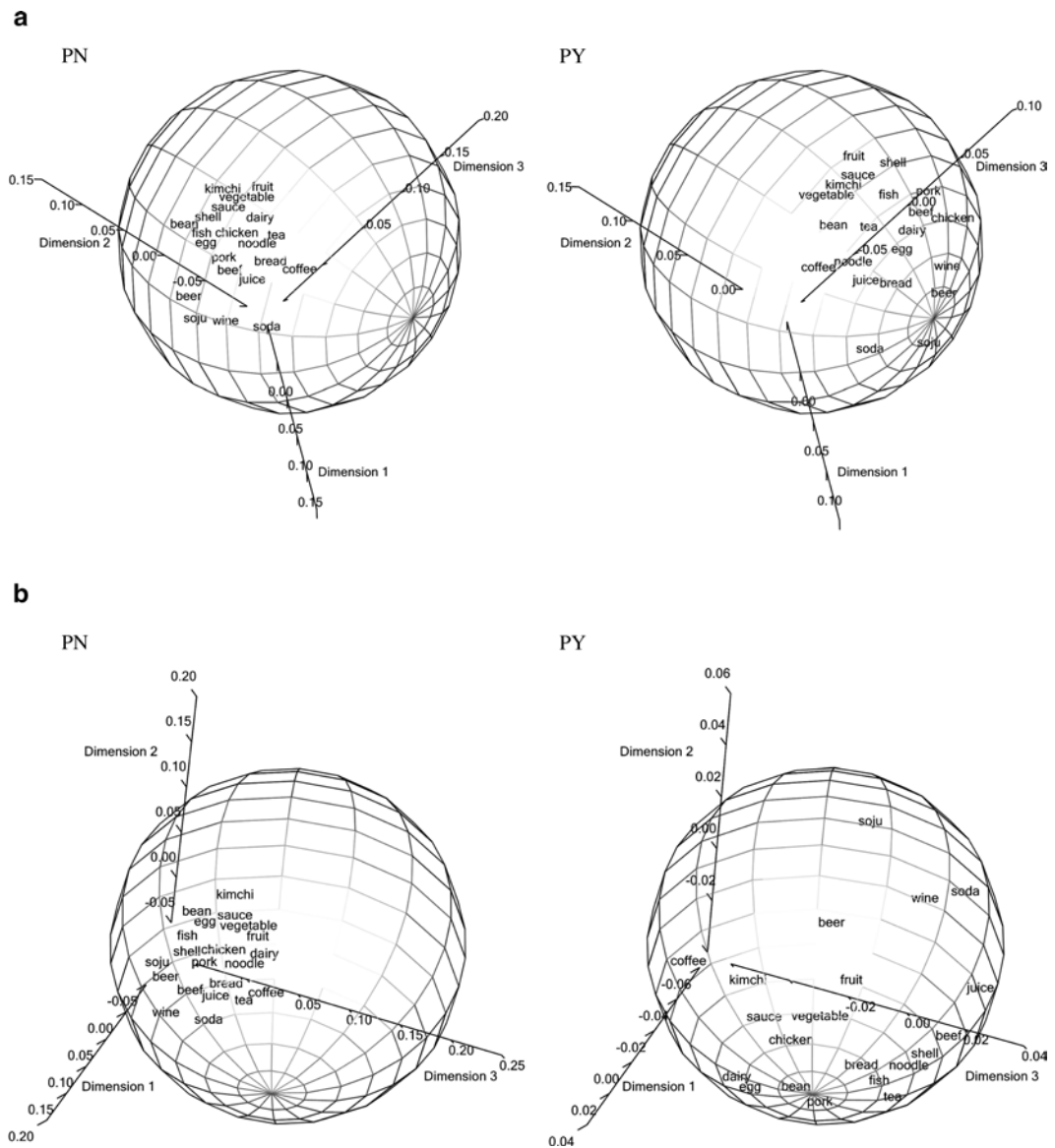
Fig. 128.12 MDS plots of food acceptance (**a**) and food consumption (**b**) among PN and PY groups (Cited in Cho and Chun 2009)

These differences between food acceptance and food consumption suggest that the experience of pregnancy shifts attitudes about food toward broader food acceptance because the motivations behind food-related decisions become more focused on the entire family

128.6.6 Comparison of FRL and Multilayered Consciousness Approaches

Using a survey based on Chun's concept of causal consciousness and the FRL instrument (Scholderer et al. 2004), which is based on actual behaviors, it could be confirmed that the experience of pregnancy affected food-related attitudes and behaviors including food preferences, choices, consumption, and satisfaction. In particular, nonfood-related psychological factors were as influential as were food-related factors. This finding needed a cross-checking of the FRL questionnaire from the perspective of Chun's layered consciousness theory. The cross-checking showed that almost all the issues covered by the FRL were related to behaviors caused by combined states of layers 5-CL, 6-CL, 7-CL, and 8-CL. Accordingly, the FRL framework using the means–ends approach to consumer behavior (Olson and Reynolds 1983) is consistent with the causal role played by consciousness of self, which includes personal values at the top level of the hierarchy.

In addition, 5-CL and 6-CL are similar to the bottom level that uses product perceptions as situation-specific input to a higher-level process. Lifestyle is considered to be an outcome of a process of conscious interperception controlled by individual egoistic personal values at 7-CL. Therefore, approaches using concepts of multiple layers will be useful for analyzing the typical food-related behaviors of pregnant women.

128.7 Applications of the Multilayer Concept

Because the concept of multilayered consciousness was developed under the assumption that anything occurring in the external world can be addressed by the internal world operating according to relative time (see Fig. 128.2), this concept can integrate all senses into one mental path. The cognitive sensory frequency curve constitutes one method for representing the outcome of this integration of our sensory system with the internal world of the mind during food consumption. Thus, this model is versatile and can be applied to areas such as sensory evaluations of food, analysis of food consumers, control of obesity, dynamic expressions of food satisfaction, and so on.

128.7.1 Construction of the Cognitive Sensory Frequency Curve

The cognitive sensory evaluation method (Chun 2002) presents all stimuli as barcodes that are integrated into a single barcode pattern. Figure 128.13a illustrates this method but converts it into multistory barcode, to avoid overlapping bars, and into frequency curves, as illustrated in Fig. 128.13b.
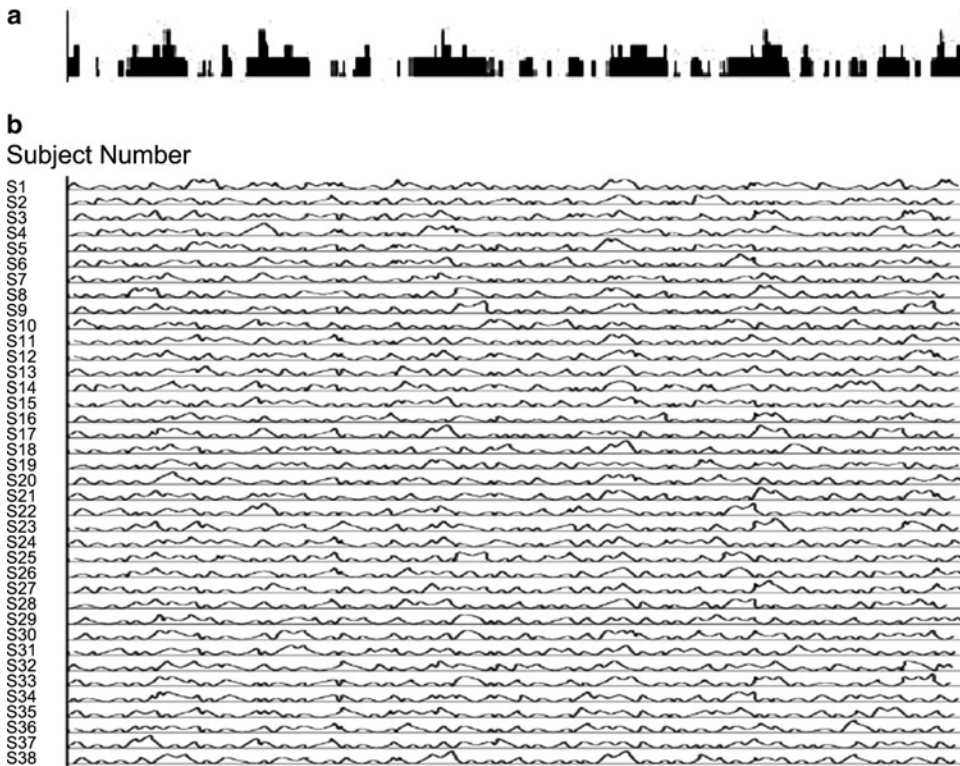
Fig. 128.13 Cognitive sensory output of 38 individual subjects: (**a**) a cognitive sensory barcode of an individual subject, and (**b**) cognitive sensory curves. Data resulted from university students ($n = 38$, mean age 22) for potato chip (Cited in Shine and Chun 2004. With permission)

The cognitive sensory frequency curve patterns (Fig. 128.13b) show that several common peaks reflect cognitive bases constructed through common cultural backgrounds, or Karma, that can be perceived across the egoistic boundaries of subjects. The conventional sensory score represents a small part of the sensory information; it lacks data about most of the real image of the food because it misses the gestalt. Yet, the scores of individual subjects can be summed to provide the basis for defining consumer groups.

128.7.2 Musical Expression of Cognitively-Expressed Food Preferences

The multilayered approach was applied to convert the cognitive expression of food preferences into a musical format, because taste is similar to the process by which an orchestra harmonizes multiple sounds. Kim et al. (2005) developed a method for musical composition and performing to dynamically express the taste of food and to replace the static expression obtained from methods relying on numerical sensory scores and linguistics. And they transformed the taste of potato chips for an individual subject into a musical format as shown in Fig. 128.14. The length of the note in the first line reflects the state of physical health of the sensorial organs in the perception of external stimuli.

The scores of lines 3 through 4 were the dynamic displays of the cognition of internal stimuli constructed in 7-CL through 8-CL where the consciousness undergoing several processes with different
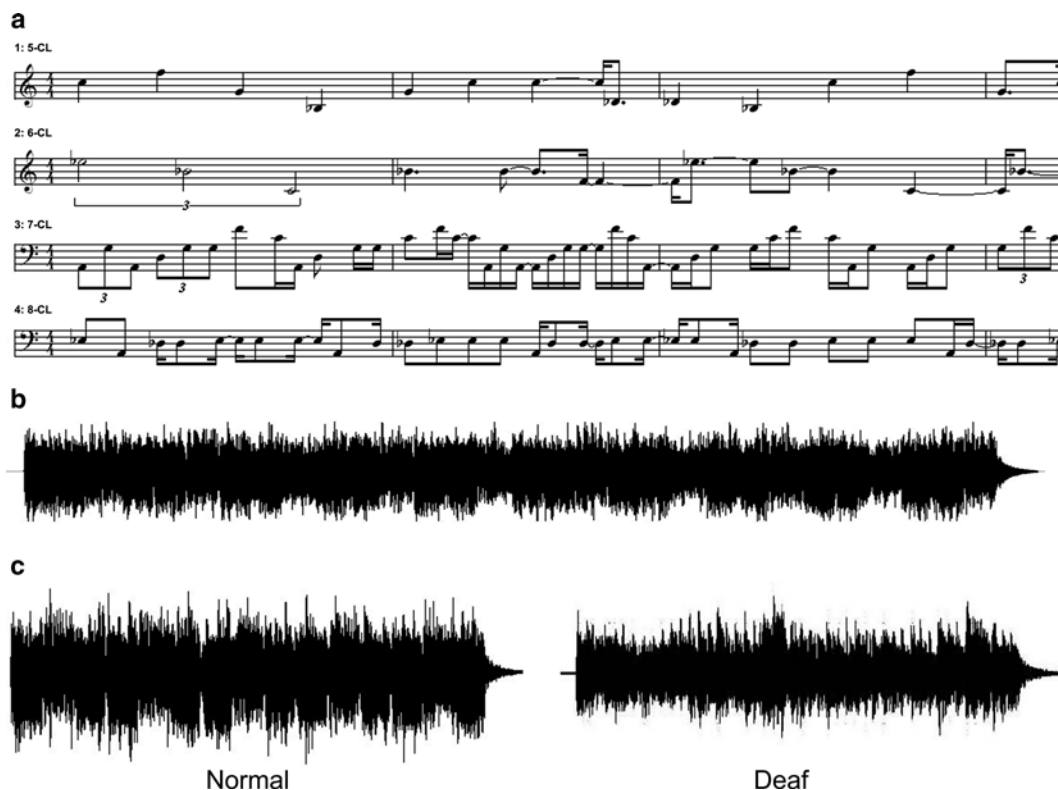
Fig. 128.14 Musical score composed on the basis of the cognitive sensory evaluation method: (**a**) Musical score note for an individual subject, (**b**) Acoustic curve obtained by performing musical score and (**c**) Acoustic curves of normal and deaf individual subjects. The musical score was composed using cognitive food sensory data gathered while eating potato chips via a computer system; Cakewalk 9.0 (for composing), Goldwave 5.0 (for recording), and Windows Media Player (for playing). (Cited in Kim et al. 2005. With permission)

time unit as described above in Fig. 128.2. Thus, the different internal processes were expressed by employing different repetition cycles in the musical score.

As the number of repetition cycles increases, the increased density of notes in the low range makes a low frequency resembling a background humming or a drum. This sound reflects a conscious background governed by the 7-CL and 8-CL.

The comparative study of the acoustical frequency curve of a handicapped subject showed a difference in the pattern (Fig. 128.14c), suggesting that the handicapped subject was also enjoying the sound of biting into a potato chip (Jin and Chun 2005; Kim et al. 2005).

128.7.3 Virtual Food Control for Obesity

The boundary model of hunger and satiation addressed the impact of physiological and cognitive factors on dietary behavior (Herman and Polivy 1975). Chun (2003) also noted that mental hunger and satiety might account for problematic obesity, in that virtual food remains in the mind, as illustrated in Fig. 128.15. As long as the satiety is followed by the satisfaction on food which resides in

Fig. 128.15 Comparison of
satiety and virtual satiety
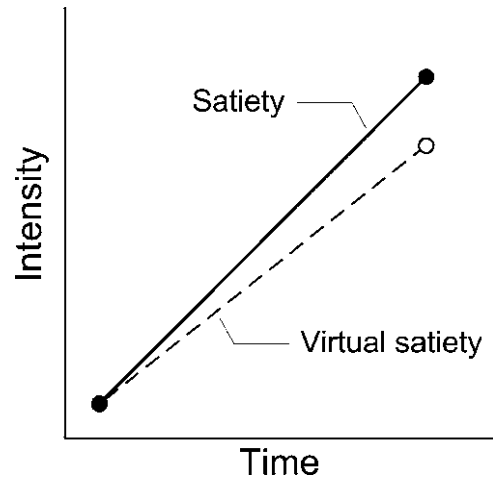
one's consciousness as virtual foods, virtual food in consciousness might serve to shift the boundary of satiety or virtual satiety.

Our interpretation of obesity in terms of virtual food indicates that a novel approach might be required, insofar as this phenomenon is closely associated with the conscious decision-making process of individuals.

128.8 The Consciousness Approach in Dietary Studies

128.8.1 Food as a Mediator for Understanding Pregnancy

The review of the comparative study involving two groups of women, PY and PN, showed two distinct findings: EG significantly affected food consumption, and the influence of EG was attenuated in a second or later pregnancy. Considering the remarkable effect of EG on dietary behavior in general, and on food consumption during pregnancy in particular, changes in consciousness should be considered as important variables operating in the process whereby food is accepted. Thus, the experience of pregnancy might occupy a principal position in the reference memory of pregnant women, influencing dietary behaviors such as food preferences and satisfaction. This strongly suggests that the content and factors contributing to the process of food evaluation can be used to differentiate between women who have and have not been pregnant. Thus, latent factors in the layer of consciousness governing sensory organs might be activated during pregnancy in favor of the fetus. This phenomenon can be illuminated by a metaphor referencing the dual operating system installed in a personal computer. At the same time that a pregnant woman wants to maintain her dietary habits, the fetus must feed itself according to the guidelines encoded in its genes and passing it to the next generation. Therefore, it might be defined as one body, two-ego system. Along these lines, 8-CL is responsible for storing the genetic code and passing it to the next generation.

The influence of EG on food consumption signals a notable change in judgments about food during and after pregnancy, and begs questions about the cause and effect of pregnancy with regard to

dietary habits. First, what is the nature of pregnancy from the perspective of consciousness? Is it the growth of a new consciousness system within an existing life, a configuration of two selves, or the establishment of a two-ego system in one physical body? Second, what does EG mean? It might represent a phase involving self-discipline or a transitional state in which the two egos refer to 7-CL to adopt a new dual system whereby compromise between the different needs for food emanating from the two selves is achieved. In this context, virtual food (Chun 2003), constructed in the background of consciousness and from memories stored in either 7-CL or 8-CL, as well as different food experiences might serve as references for the judgments underlying food consumption. Third, is it possible for the two subjects to communicate with each other in order to reach a compromise, thus avoiding critical damage to both selves using a mechanism resembling a hotline that spans dual neural networks? Because the neural networking of the fetus is not sufficiently developed to consider the operation of neural signaling, should serious consideration be given to a form of wireless communication via the consciousness channel? In this way, 8-CL, the highest level, might play a role as a communications tower in the intersubjective realm of 7-CL and 8-CL.

Therefore, the painful EG experience might be understood as a novel aspect of mutual communication between baby and mother insofar as the mother hopes for the health of her baby. It provides a valuable opportunity for insight into the real nature of two selves and the meaning of pregnancy, transforming an often physiologically painful experience into a joyful experience involving the development of competence in the process of advancing to motherhood.

128.8.2 Perception Processing and Multiple Timer Concepts

The main cause of the differences in typical food-related behaviors derives from interperception among the layers of consciousness, as described above with regard to 3-WBT. In this way, previous experiences of reacting in a selfish way due to ego-esteem and ego-threats serve as reference points. In this context, 7-CL is responsible for the selfish and egoistic aspects of the subjective decision-making process (Chun 2002, 2004; Jin and Chun 2005). Indeed, Churchland (1988), and Cohen (2000) have reported that cognitive states significantly influence the perception and observation of an object in a top-down way.

Assuming the operation of interperception and dual-flow processes in streams of consciousness, a flow chart must consider sequence and relevant time units for the internal top-level domain of consciousness as well as for the bottom-level domain that interfaces with the external world. Chun (2002) insisted that the time unit for accessing 8-CL must be reduced to nearly zero because thought necessarily travels at an unlimited speed to manage the universe of the mind. Furthermore, this account logically matches modern digital data processing with respect to compositional structure, efficacy, and economics. More specifically, consciousness has been considered as operational software for the hardware of the brain in the context of the multiple streams for data acquisition and perception, the logistics governing feedback loops, the retrieval of references, the output signals for motor neurons, and the mechanisms governing the performance of multiple tasks and record storage. Thus, the incorporation of a multiple timer concept would be helpful for approaching the world of the mind (Chun 2002).

128.8.3 Simplification of Variables Structural Equation Modeling

As described in the text, the multivariate nature of food-related behaviors was interpreted using statistical tools such as ANOVA, structural equation modeling, and MDS plotting. Factor analysis is

widely used to reduce the number of variables. Our ultimate goal of approaching consciousness did not aim to add variables but rather to reduce these into a fundamental mental framework.

Within this framework, factors such as the education and age of subjects could be neglected because education belongs to a domain of data that is classified prior to decision-making, and the concept of time is constructed in a relative manner in the internal world. Consequently, approaches focusing on consciousness might contribute to simplifying the multivariate nature of food-related behaviors.

128.9 Issues of Part and Whole

Application of Vasubandhu's theory dividing the mind into a multilayered structure of consciousness leads to arguments about the divided mind as based in irrationality (Tuske 1999) and about tastes sensed by the tongue as derived not from 5-CL but rather from a system-wide process yielding a decision. We support the latter account but the division into several subsystems aids in understanding how the system works as a whole.

In this context, the validity of the proposed path model (Cho and Chun 2009), constructed by combining subjective (nonfood memories) and objective factors (food-related memories), was investigated with respect to routes based on the hypothesis that causal routes represent a main routine of the "software" governing this path. It was hypothesized that this path was triggered by unconscious factors, but that the effective route was regulated consciously. The role of cause and effect reactions in shaping expectations and rewards entails that memories of historical experiences will serve as important references for decision-making (Wansink 2003). An egocentric unconscious process serving as the decision-maker manages the path across the limitations of time and space. This implies that future, present, and past are integrated into the path (Raftopoulos 2001) via conscious and unconscious processes (Dehaene and Naccache 2001). Because imagination enables the observation of virtual objects by the ego-self during decision-making, many researchers have investigated the notion that vision is dominant with regard to the general issues of daily life. Food products, however, are judged by taste, smell, visual appearance and sound (Kim et al. 2005). The virtual satiety may help to prolong satiety, lower hunger and desire to eat (Isaksson et al. 2008).

Summary Points

- A multilayer hierarchical structure of consciousness was applied to the food-related behaviors of pregnant women.
- Comparative studies on pregnant and nonpregnant women showed differences in their food-related behaviors, including preferences, consumption, and satisfaction with food.
- A method for cognitive sensory evaluation was described using the multilayer concept and addressing conventional sensory and unconscious factors.
- The concept of interperception was introduced using three-way-branch transformations into the path formed by the stream of consciousness.
- The method of cognitive sensory evaluation can accommodate the concept of multiple timers and can express food-related perceptions in various ways, including barcodes, frequency curves, and musical notes.

Definitions and Explanations of Key Terms

3-Way branching transformation (3-WBT): When interperception occurs among the mental layers, transformation occurs according to three options: the good, the bad, and the neutral are understood according to the perspective of the perceiver in an egoistic way. After repeated transformations or experiences with the good outcome, the latter will be recognized as the best option.

Cognitive sensory evaluation: The cognitive sensory evaluation method integrates all food and nonfood stimuli within human consciousness.

Componential satisfaction: Satisfaction based on sensory preference scores for such factors as appearance, sound, odor, flavor, texture, and environment.

Emesis gravidarum: Often referred to as morning sickness, this is a physiological phenomenon experienced by the majority of pregnant women which occurs during the early stages of pregnancy; it disappears as the pregnancy advances.

Interperception: The external stimuli sensed by sensory organs are perceived by the mind or consciousness. In multilayer theory, several perceptions occur across the layers.

Multilayered consciousness: A conception of the mind, based on the consciousness-only theory proposed by Vasubandhu, stating that the human mind is comprised of multiple functional layers or modules. The layers are hierarchically arranged and referred to as 5th consciousness, 6th consciousness, 7th consciousness, and 8th consciousness, abbreviated herein as 5-CL, 6-CL, 7-CL, and 8-CL.

Overall satisfaction: Satisfaction based on overall preference scores.

Preferences for componential elements: Preferences for each sensory attribute of food.

Sensorial stimuli: Perceived intensity of each sensory attribute of food.

Top-bottom or top-down: The terminology is used to describe the direction of the flow of consciousness because consciousness was defined as similar to a bloodstream. Therefore, top-bottom logic indicates that human behaviors are outcomes of the flow of consciousness proceeding from 8th consciousness toward 5th consciousness.

Top and bottom minds: The top mind is the ultimate or deepest mind, controlling mental activity in its entirety, and the down or bottom mind refers to the consciousness that manages the sensory organs.

Two selves concept: The pregnancy of women is considered as a typical of a stage in which two lives live together within one physical system for consuming food; thus, this is referred to as a two-ego system.

Vasubandhu: Indian monk and scholar who lived in ad 400 and insisted that everything is constructed by the mind.

References

Ajzen I, Fishbein M. Psychol Bull. 1975;82:261–77.
Anacker S. Seven works of Vasubandhu. Delhi: Motilal Banarsidass; 1984.
Ashby, FG, Lee WW. J Exp Psychol General. 1991;120:150–72.
Bargh JA, Chaiken S, Raymond P, Hymes C. J Exp Psychol. 1996;32:104–28.
Bell AC, Stewart AM, Radford AJ, Cairney PT. J Nutr Educ. 1981;13:22–6.
Bowen DJ. Appetite 1992;19:233–42.

Brunsø K, Grunert KG. Adv Consum Res. 1995;22:475–80.

Brunsø K, Scholderer J, Grunert KG. J Bus Res. 2003;57:665–70.

Cho WI, Chun JK. Presented at 2009 annual meeting of Korean Society of Food Science and Technology. Seoul, Korea; 2009.

Chun JK. Food Eng Prog. 2002;6:288–99.

Chun JK. Food Eng Prog. 2003;7:44–53.

Chun JK. In: Ottaway PB, editor. The international review of food science and technology (2004/2005 Winter Ed). London: IUFoST, Sovereign Publications; 2004. p. 72–7.

Churchland PM. Philos Sci. 1988;55:167–87.

Cohen G. Eur J Cogn Psychol. 2000;12:1–36.

Cosper BA, Wakefield LM. J Am Diet Assoc. 1975;66:152–5.

Dehaene S, Naccache L. Cognition 2001;79:1–37.

Eertmans A, Baeyens F, Van den Bergh O. Health Educ Res. 2001;16:443–56.

Eliasmith C, Thargard P. Cognitive Sci. 2001;25:245–86.

Ennis DM. Food Technol-Chicago. 1998;52:78–89.

Fazio RH, Sanbonmatsu DM, Powell MC, Kardes FR. J Pers Soc Psychol. 1986;50:229–38.

Fechner GT. Element of psychophysics: vol. 1. (Adler HE, Translator) New York: Holt, Rinehart and Winstone; 1866, Original work published 1860.

Furst T, Connors M, Bisogni CA, Sobal J, Falk LW. Appetite 1996;26:247–66.

Glanz K, Hewitt AM, Rudd J. J Nutr Educ. 1992;24:267–77.

Glassman RB. Prog Neuro-Psychoph. 2000;4:163–82.

Grunert KG, Grunert SC. Int J Res Mark. 1995;12:209–25.

Herman CP, Polivy J. J Abnorm Psychol. 1975;84:666–72.

Isaksson H, Sundberg B, Aman P, Fredriksson H, Olsson J. Food Nutr Res. 2008;52:1–7.

Jin JH, Chun JK. MS thesis, Seoul National University; 2005.

Kim SW, Lim SW, Chun JK. Food Sci Biotechnol. 2005;14:738–42.

Kunde W, Kiesel A, Hoffmann J. Cognition 2003;88:223–42.

Lau D, Krondl M, Coleman P. In: Galler JR, editor. Nutrition and behavior. New York: Plenum; 1984. p. 397–415.

Lim SW, Chun JK. PhD thesis, Seoul National University; 2005.

Lim SW, Chun JK, Cho WI. Appetite 2008;50:519–28.

Meilgaard MC, Civille GV, Carr BT. Sensory evaluation techniques. 4th ed. Boca Raton: CRC Press LLC; 2006.

Meiselman HL. In: Meiselman HL, MacFie HJH, editors. Food choice, acceptance and consumption. London: Blackie Academic; 1996. p. 239–63.

Michela J, Contento I. Health Psychol. 1986;5:209–30.

Olson JC, Reynolds TJ. In: Percy L, Woodside A, editors. Advertising and consumer psychology. Lexington: Lexington Books; 1983. p. 77–90.

Ortega RM. Public Health Nutr. 2001;4:1343–6.

Raftopoulos A. Cognitive Sci. 2001;25:423–51.

Rappoport LH, Peters GR, Huff-Corzine L Downey RG. Ecol Food Nutr. 1992;28:171–89.

Rosch E, Mervis C, Gray W, Johnson D, Boyes-Braem P. Cognitive Psychol. 1976;8:382–439.

Rozin P, Tuorila H. Food Qual Prefer. 1993;4:11–20.

Schifferstein HNJ. Acta Psychol. 2006;121:41–64.

Scholderer J, Brunsø K, Grunert KG. Adv Consum Res. 2002;29:551–7.

Scholderer J, Brunsø K, Bredahl L, Grunert KG. Appetite 2004;42:197–211.

Shepherd R, Raats M. The psychology of food choice. Cambridge, MA: CABI; 2006.

Shine SW, Chun JK. Food Eng Prog. 2004;8:242–8.

Thurstone LL. Physiol Rev. 1927;34:273–86.

Tuske J. Asian Philos. 1999;9:229–38.

Wansink B. Food Qual Prefer. 2003;14:23–6.

Wells AJ. Cognitive Sci. 1998;22:269–94.

Chapter 129
Diet in the Aetiology and Management of Postpartum Depression: Knowing the Facts

Vassiliki Costarelli

Keywords Postpartum depression • Diet • Fish oils

Abbreviations

PPD	Postpartum depression
EPDS	Edinburgh postnatal depression scale
PUFA	Polyunsaturated fatty acids
EPA	Eicosapentaenoic acid
DHA	Docosahexaenoic acid
RCT	Randomized Controlled Trial
BDI	Beck depression inventory
FFQ	Food frequency questionnaire

129.1 Introduction

Postpartum depression (PPD) is a condition that affects women who have recently delivered a baby, with most cases occurring in the first 6 months after delivery. It is a serious mental health problem characterized by a prolonged period of emotional disturbance, occurring at a time of major life change and increased responsibilities (Almond 2009).

Prevalence of postpartum depression worldwide is approximately 13–20%; however, these are probably conservative estimates because the condition is often underreported or underdiagnosed (Halbreich and Karkun 2006). It is important to note that a study conducted in the UK found that the incidence of PPD is approximately 27% in minority ethnic women (black, Asian and other) compared to 15% in white women (Onozawa et al. 2003) which indicates that women from ethnic minorities are probably a high-risk group for depression in the postpartum.

Symptoms of depression in the postpartum period may persist for any length of time after birth and range from postpartum blues to severe depression. Postpartum blues can be defined as short episodes of depressive symptoms, such as anxiety, disturbed sleeping patterns, decreased appetite

V. Costarelli (✉)
Human Ecology Laboratory, Department of Home Economics and Ecology,
Harokopio University, 70 El. Venizelou Ave, 17671 Kallithea, Athens, Greece
e-mail: costarv@hua.gr
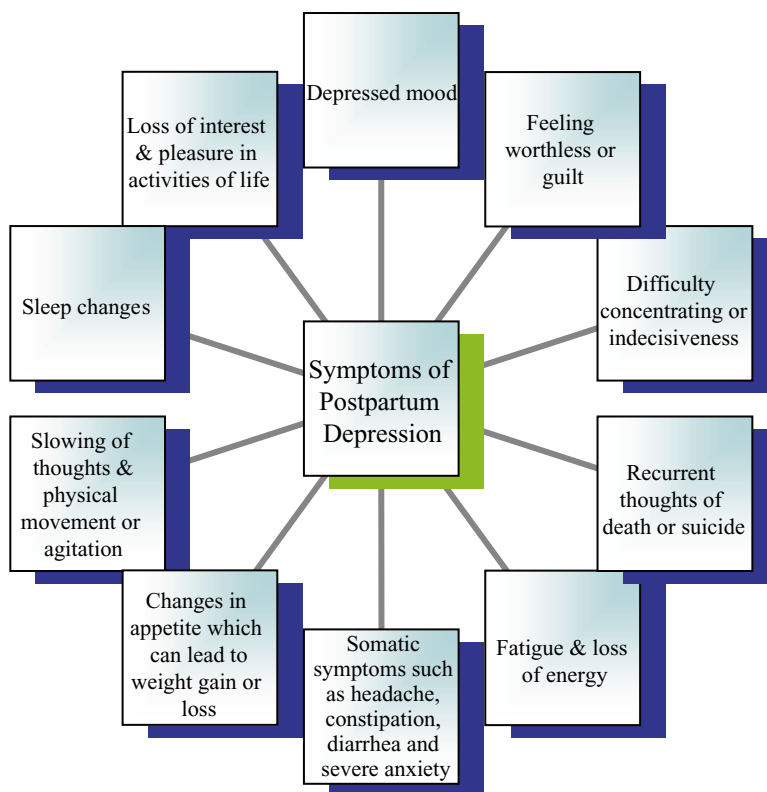
Fig. 129.1 Main symptoms of postpartum depression

and irritability, normally taking place on day 4 after delivery but may commence up to 2 weeks after delivery (Gurel and Gurel 2000). However, the symptoms of PPD which are described in detail in Fig. 129.1, are usually more severe and could include feelings of suicide, obsessive thoughts and extreme petulance (Wisner et al. 2002; Hatton et al. 2005). Postpartum psychosis, on the other hand, is the most severe form of postpartum psychiatric illness and will not be discussed in the current chapter.

The consequences of PPD can be significant for both the new mother and the child. It is important to stress that, higher rates of emotional, behavioural and cognitive problems have been reported in the children of mothers with PPD (O'Brien et al. 2004; Stewart 2007). Table 129.1 summarizes the main adverse effects reported in infants and children of mothers with PPD.

The causes of PPD remain unclear, with research suggesting a multifactorial aetiology (Verkerk et al. 2003). More specifically, evidence suggests that the key risk factors for PPD include genetic predisposition and environmental factors, together with a number of social, psychological and biological factors (Craddock and Forty 2006; Almond 2009; Leung and Kaplan 2009). The main risk factors of PPD are described in Table 129.2. The strongest predictors of postpartum depression seem to be the personal and family history of depression, antenatal depression and anxiety and most importantly the lack of social support. Two metaanalyses also found a higher risk of postpartum depression among socially disadvantaged women (O'Hara and Swain 1996; Beck 2002).

The biological risk factors linked with PPD are more difficult to determine. Biological factors that play a part to the pathophysiology of the condition include hormonal influences (Bloch et al. 2000; Murakami et al. 2008), neurotransmitter function (Dunlop and Nemeroff 2007) and nutrient deficiencies because of malnutrition or poor diet quality (Bodnar and Wisner 2005).

Table 129.1 Postulated adverse effects on children of mothers with postpartum depression (Stein et al. 2009)

Impairment in mother-infant interaction
Infants and toddlers became withdrawn, irritable and inconsolable
Higher rates of emotional and behavioural problems as children approach school age
Poorer cognitive development
Higher risk of mood and anxiety disorders in adolescence

This table lists the main negative effects on children of mothers with postpartum depression

Table 129.2 Main risk factors implicated in the aetiology of postpartum depression

Hormonal changes after childbirth
Previous experience of depression or anxiety
Family history of depression or mental illness
Stress involved in caring for a newborn and managing new life changes
Having a challenging baby who cries more than usual, is hard to comfort, or whose sleep and hunger needs are irregular and hard to predict
Having a baby with special needs (premature birth, medical complications, illness)
First-time motherhood, very young motherhood, or older motherhood
Other emotional stressors, such as the death of a loved one or family problems
Financial & employment problems
Isolation and lack of social support

Source: American Psychiatric Association (APA)

The main risk factors in the aetiology of postpartum are described in this table

Evidence suggests that inadequate intake of specific nutrients might be a substantial contributor to the development of depression in women in the postpartum period (Bodnar and Wisner 2005). Plausible associations between nutrient inadequate intake and mood have been reported for folate, vitamin B$_{12}$, calcium, iron, selenium, zinc and omega-3 fatty acids (Alpert et al. 2000; De Vriese et al. 2003). In the case of maternal and postpartum depression, the nutrient that has received the most attention has been the omega-3 essential fatty acids (Chiu et al. 2004). Finally, it is important to underline that one of the symptoms of PPD is changed appetite (increased or decreased), which would contribute to the poor dietary intake and nutritional status of women in the postpartum and hence deteriorate the management of the condition.

The purpose of the current short chapter is to present and discuss the main dietary factors implicated in the aetiology and management of PPD based on a thorough review of the scientific literature to date.

129.2 Diet and Postpartum Depression

Research on the relationship between nutrition and brain function is very large. However, while specific nutrients have been associated with depression in the general population, little is known about low nutrient levels in the aetiology and management of postpartum depression (Derbyshire and Costarelli 2008). It is well documented that pregnant women are especially susceptible to the effects of low nutrient intakes (Bodnar and Wisner 2005; Derbyshire et al. 2009) as during pregnancy and lactation, nutritional requirements are increased (Picciano 2003). In addition, there is evidence that nutrient inadequacies in pregnant women who consume a typical western diet might be

much more common than researchers and clinicians anticipated. A number of studies have reported inadequate intakes of omega-3 fatty acids, folate, B vitamins, iron and calcium in pregnant women (Giddens et al. 2000; Derbyshire et al. 2009). A British study found a significant percentage of pregnant women did not meet the estimated average requirement for folate (69%), for calcium (40%) and iron (67%) (Mouratidou et al. 2006). Similarly, a study of pregnant adolescents and adults living in the USA found mean intake for energy, iron, zinc, calcium, magnesium, folate and vitamins D and E to be below recommended standards (Giddens et al. 2000). Depletion of nutrient reserves throughout pregnancy could increase a woman's risk for maternal and postpartum depression. It is likely that the Mediterranean Dietary Pattern could be protective of PPD. More specifically, adherence to a Mediterranean Dietary Pattern ensures an adequate intake of fruits, nuts, vegetables, cereals, legumes or fish, important sources of nutrients linked to depression prevention (Sanchez-Villegas et al. 2006). A recent study investigating depression in the elderly has found that lower intake of seed oils and higher intake of olive oil prospectively predict a healthier affective state in the elderly. Most importantly, olive oil intake, in particular, predicts a lower chance of scoring in the highest part of the geriatric depression scale (Kyrozis et al. 2009). However, no studies have been found investigating the possible role of the Mediterranean style diet in PPD so far.

Finally, recent studies have also showed that insulin affects the secretion of serotonin in the brain. It is likely that PPD might be linked to the sudden fall in insulin levels occurring after delivery. A diet with a high-glycemic index, which would stimulate the secretion of insulin and thereby facilitate the transport of tryptophan, the precursor of serotonin, in the brain, would alleviate the above condition (Chen et al. 2006). However, a recent study investigating the link between glycemic load and PPD failed to substantiate a clear inverse relationship between them (Murakami et al. 2008). This hypothesis warrants further investigation given the plausibility of the above mechanism.

129.2.1 Omega-3 Fatty Acids and PPD

The nutrient that has received the most attention from nutrition researchers with respect to depression in pregnancy and the postpartum period has been the n-3 essential fatty acids. (Hibbeln 2002; Freeman et al. 2006a; Miyake et al. 2006b). Several studies, such as cohort studies, randomized controlled trials as well as ecological studies, have found mainly positive links between low n-3 levels and a higher incidence of maternal depression. Oily fish are a rich source of omega-3 fatty acids in particular eicosapentaenoic acid (EPA) and docohexaenoic acid (DHA) which are very important for brain development and function (Browne et al. 2006). It is known that omega-3 fatty acids are essential for receptor function, neurotransmitter uptake and signal transmission. More specifically, evidence indicates that adequate levels of the above fatty acids may help to regulate neurotransmitter levels, which are thought to be reduced in cases with depressive symptoms (Sapolsky 2000). In addition, it has been proposed that high concentrations of DHA located in non-myelin cell membranes of the central nervous system may help support synaptic transmissions (Holman et al. 1991).

The intake of n-3 fatty acids in the modern diet has declined with the decreased intake of sources of omega-3 fatty acids (particularly those coming from marine sources). The latest National Diet and Nutrition Survey undertaken in the United Kingdom identified that 53 g of oily fish was consumed per week, the equivalent to just 0.35 weekly servings (Henderson et al. 2002). In addition, studies suggest that there has been an increase in the amount of n-6 fatty acids in the modern diet, which can interfere with the metabolism and synthesis of DHA and EPA (Meyer et al. 2003). In addition, it has been shown that omega-3 fatty acids are transferred from the mother to fetus and baby, throughout gestation and while breastfeeding, which may result in their depletion (Browne et al. 2006).

Fish oils supplements high in omega-3 fatty acids, has been used as psychotropic medications for the treatment of major depression with conflicting results (van Strater and Bouvy 2007; Freeman et al. 2008). Other studies however, seem to support the theory that dietary and supplemental sources of omega-3 fatty acids are associated with fewer PPD symptoms (Hibbeln 2002; Freeman et al. 2006a; Miyake et al. 2006b). In addition, other studies revealed that women, with lower levels of plasma DHA in late pregnancy and the early postpartum period, may be more likely to experience postpartum depressive symptoms (Otto et al. 2003). De Vriese and colleagues also found that n-3 blood levels were considerably lower in women who developed PPD than in women who did not (De Vriese et al. 2003).

One of the largest investigations to date, the Osaka Maternal and Child Health Study carried out a prospective cohort in 865 Japanese women. Fourteen percent of Japanese women were diagnosed with PPD and omega-3 and DHA intakes were inversely associated with PND (Miyake et al. 2006b).

An analysis of ecological studies from 23 countries revealed that high DHA levels in breast milk and higher seafood consumption were positively predictive of lower rates of postpartum depression (Hibbeln 2002). A review of epidemiological evidence and intervention studies reported an association between low n-3 intake and depression (Rees et al. 2005), however, another review found inconsistent results in clinical trials with EPA and/or DHA (Freeman et al. 2006b). Similarly, Hosli and colleagues in another review, found mixed results also; clinical studies contradicted observational studies and findings from a meta-analysis were inconsistent (Hosli et al. 2007). Recent studies investigating the association between omega-3 fatty acids with both maternal depression and PPD and their results are summarized in Table 129.3.

It is important to underline that the sample size and duration of follow-up and methodologies used were problematic in some of the studies. It is also important to consider that occasionally different diagnostic criteria for depression were used in many of these studies. Although most studies utilized the Edinburgh Postnatal Depression Scale (EPDS), different cutoff points have been used, which could explain partly, the above conflicting results.

129.2.2   Other Nutrients and PPD

The research on vitamins and minerals dietary intake and postnatal depression is limited (Abou-Saleh et al. 1999; Miyake et al. 2006a). The few studies examining the effect of specific nutrients in relation to mood disorder in women in pregnancy and the postpartum period, summarized in Table 129.4, produce varying results, possibly due to the limitations on the study designs and methodologies used (e.g. examining a single nutrient, small number of subjects, different methods assessing depression).

129.2.2.1   Calcium

Calcium seems to act as an intracellular messenger and stimulates the release of neurotransmitters from the cerebral vesicles (calcium influx into a cell acts as a trigger, releasing neurotransmitters from their storage vesicles) (Llinas 1977). In a randomized controlled trial, participants were divided into two groups, one consuming 2,000 mg calcium per day, or a placebo (between 11 and 21 weeks of gestation, $n = 293$). Depression was evaluated in the puerperium using the EPDS. Results indicated that symptoms of depression were significantly reduced in subjects consuming calcium carbonate tablets ($P = 0.07$) (Harrison-Hohner et al. 2001).

In another study, 4,589 women received either 1,000 mg of calcium or placebo tablets with their morning and evening meals and a daily prenatal supplement (50 mg calcium, 30 mg iron, 400 IU

Table 129.3 Studies investigating the association between omega-3 fatty acids with both maternal depression and PPD

Author, year	Design and sample size	Main findings
Strøm et al. (2009)	Data from a large prospective cohort linked with high-quality registers, $n = 54{,}202$ women. Intake of fish and omega-3 PUFAs was assessed in midpregnancy with a food-frequency questionnaire	Weak evidence to support an association between intake of fish or omega-3 PUFAs and PPD.
Su et al. (2008)	Randomized controlled 8-week trial, $n = 36$ pregnant women, comparing omega-3 PUFAs (3.4 g/day) with placebo in pregnant women with major depressive disorder	Omega-3 PUFAs may have therapeutic benefits in depression during pregnancy
Browne et al. (2006)	Prospective cohort, $n = 80$ postnatal women, 41 diagnosed with depression and 39 controls. EPDS and BDI were used and an FFQ during pregnancy	Both postnatal ω-3 status and fish consumption in pregnancy were not associated between PPD
Freeman et al. (2006a)	Randomised controlled trial, $n = 16$ with PPD who consumed a 0.5 g/day, 1.4 g/day or 2.8 g/day ω-3 supplement daily for 8-weeks. Both the EPDS and Hamilton Rating scale were used	Omega-3 fatty acids may play a role in the treatment of PPD
Miyake et al. (2006a)	Prospective cohort, $n = 865$ women who completed a diet history questionnaire during pregnancy alongside the EPDS	No significant association found between dietary fish and fat intake with PPD
Otto et al. (2003)	Prospective cohort, $n = 112$ pregnant women. Venous blood samples were collected at week 36 of pregnancy, after delivery and 32 weeks after delivery, use of EPDS	DHA levels were significantly lower in women with depressive symptoms in comparison to women without depressive symptomatology
De Vriese et al. (2003)	Cross-sectional study, $n = 48$, 10 with PPD and 38 without. Blood samples taken after delivery analyzed for serum phospholipids and cholesteryl esters.	Fatty acids concentration was lower in women with depression in comparison to women without depression
Llorente et al. (2003)	Randomized control trial in breast feeding women. DHA (200 mg/day) $n = 44$ or placebo ($n = 45$) for a 4 month period. Plasma phospholipid fatty acids were measured and depression was assessed with a self-rating questionnaire and interview	No difference between the two groups on diagnosed or self-rated depression. The levels of DHA were significantly higher in the treatment group
Makrides et al. (2003)	Cross-sectional cohort, $n = 380$ postpartum women who completed the EPDS and iron, zinc and DHA status were measured	For every 1% elevation in plasma DHA there was a significant 59% reduction in symptoms of depression
Hibbeln (2002)	Published prevalence data for postpartum depression were included that used the EPDS ($n = 14532$ subjects in 41 studies) and measured the DHA, EPA and AA content of breast milk (studies across 23 countries)	Higher concentrations of DHA in mothers' milk and greater seafood consumption both predicted lower prevalence rates of postpartum depression
Peet et al. (1998)	Cross-sectional study, $n = 30$, 15 depressed and 15 without	Women with depression had significantly lower levels of omega-3 fatty acids and DHA

There is also good evidence that increasing the dietary omega-3 intake in late pregnancy or following delivery may reduce the risk of PPD

Table 129.4 Studies investigating the association between of selected mineral and vitamins and PPD

Author, year	Design and sample size	Nutrient	Main findings
Wojcik et al. (2006)	Observational, intervention study, $n = 66$. Women received standard vitamin, zinc and magnesium supplementation. Women completed EPDS 3 days and 30 days postpartum. Serum zinc and magnesium levels were also determined	Zinc (Zn) and Magnesium (Mg)	The severity of postpartum depression may be associated with lower serum zinc concentrations but not magnesium
Miyake et al. (2006b)	Cross-sectional ecological study, $n = 865$ Japanese women, diet history questionnaire during pregnancy alongside the EPDS	Riboflavin (B$_2$)	Riboflavin intake (3rd quartile) was inversely associated with a decreased risk of postpartum depression
Beard et al. (2005)	Prospective, randomized, controlled, intervention trial was conducted in South Africa nonanemic controls and anemic mothers, $n = 95$. Mothers of full-term normal birth weight babies were followed from 10 weeks to 9 months postpartum	Iron (Fe)	Strong relationship between maternal iron status and depression
Harrison-Hohner et al. (2001)	Randomized intervention study, $n = 247$. Women consumed either a placebo or a 2,000 mg calcium supplement daily for 6 weeks. At 6 weeks postpartum women completed the EPDS	Calcium (Ca)	Women in the calcium interventions group had significantly fewer symptoms of depression
Abou-Saleh et al. (1999)	Case-control study, 23 pregnant and 38 non pregnant controls. The EPDS was completed 7 days after birth. Plasma concentrations of tryptophan, B$_{12}$ and folate were measured	Folate and B$_{12}$	Women with depressive symptoms consumed significantly lower levels of folate compared to the controls.

The studies examining the effect of specific nutrients in relation to mood disorder in women in pregnancy and the postpartum period, summarized in this table, produce varying results

vitamin D) beginning before 22 weeks of gestation until delivery. Six weeks postpartum, the mean EPDS scores were similar between treatment groups, however at 12 weeks, a significantly larger proportion of women in the placebo group (15.3%) had EPDS scores >14 compared with the calcium treated group (5.7%) ($P = 0.014$) (Levine et al. 1997).

It is possible that calcium supplementation may serve to stabilize calcium regulation at the intracellular level in individuals with low calcium diets, which in turn would help to alleviate PPD; however, this is yet to be investigated.

129.2.2.2 Zinc

Another nutrient associated to mood is zinc, mainly through its possible influence on serotonin uptake (Levenson 2006). There is also evidence that intervention with zinc has possible antidepressant effects. In addition, studies have reported an association between low zinc status and depression (Nowak et al. 2005; Levenson 2006). A relationship between decreased serum zinc concentration and higher scores on the EPDS have been reported by Wójcik and colleagues. More specifically,

serum zinc concentrations 30 days postpartum were associated with alleviated symptoms of depression. In the same study, no statistically significant findings were reported with regard to serum magnesium concentrations and depressive symptoms (Wojcik et al. 2006).

129.2.2.3 Iron

It is documented that iron deficiency can lead to reduced memory and learning ability, impaired mood and cognition or behavioural abnormalities. As far as PPD is concerned, Beard and colleagues reported a strong relationship between maternal iron status and depression in a study that followed mothers of full-term normal-birth-weight babies from 10 weeks to 9 months postpartum (Beard et al. 2005). However, more studies are needed to confirm the above findings.

129.2.2.4 Folate and Other Vitamins

Folate is needed for the biosynthesis of the neurotransmitters: serotonin, dopamine and norepinephrine. In addition, it has been shown that the active metabolite of folate, 5-methyltetrahydrofolate, is required for remethylation of homocysteine in the production of methionine, which is involved in a number of biochemical processes involving the above neurotransmitters (Miller 2008). As a result, it is likely that a deficiency in folate would affect the production and function of these important neurotransmitters. Vitamin B_6 is also involved in neurotransmitter pathways as a cofactor in the production of serotonin from tryptophan. Low plasma levels of the B_6 derivative, pyridoxal phosphate, have been associated with symptoms of depression (Hvas et al. 2004). In addition, vitamin B_{12} plays an important role in the neurological function as a cofactor in the formation of Sadenosylmethionine, an intermediate for production of the neurotransmitters (Coppen and Bolander-Gouaille 2005).

A very small number of studies were set out to examine the effects of folate and other B vitamin consumption in relation to the development of PPD (Abou-Saleh et al. 1999; Miyake et al. 2006a). In a large recent epidemiological study conducted by Miyake et al. (2006b), 865 Japanese women were asked to complete a diet history questionnaire and the EPDS at 2–9 months postpartum. No associations were identified in this investigation between dietary intakes of vitamin B_6, B_{12} or dietary folate in relation to the onset of postnatal depression with the exception of riboflavin (mean intake 1.4 mg/day) which was inversely associated with symptoms of PPD (Miyake et al. 2006a). In another study, Abou-Saleh et a.l (1999) monitored plasma folate and vitamin B_{12} concentrations and screened women ($n = 62$) for depression using the EPDS in the puerperium. Cases with PPD had lower folate levels when compared with controls ($P < 0.01$), whereas, multiple regression analysis revealed that high vitamin B_{12} concentrations were associated with increased EPDS scores ($P < 0.01$) (Abou-Saleh et al. 1999).

Further studies are needed in this field in order to elucidate the possible role of folate and other B vitamins in the prevention and management of PPD.

129.3 Conclusions

Proper nutrition during pregnancy is vital as evidence suggests that nutrient intake can be a key factor in a woman's vulnerability to postpartum depression. It has been proposed that depletion of nutrient reserves throughout pregnancy and a lack of recovery postpartum may increase a woman's risk for

postpartum depression. Research indicates that an inadequate intake of omega 3 during pregnancy and the perinatal period may be strongly associated with the onset of PND. It is possible that omega-3 and other fatty acids may protect against the onset of PND; however, much larger investigations using prospective methodologies and larger sample sizes are now required to reinforce the findings of these investigations. Further research is also needed to evaluate the safety and recommended levels of fish oil consumption since methlymercury and additional contaminants may be present in larger oily fish.

Weaker relationships have been identified between symptoms of PND and folate, B_{12}, calcium and zinc intake. More studies are needed to investigate the role of diet and nutrition in the aetiology and management of PPD so that specific dietary recommendations can be formed.

129.4 Applications to Other Areas of Health and Disease

Midwifery and nursing: It would be useful to educate midwifes and nurses on the role of diet on the aetiology and management of PPD, so that they can better inform women in pregnancy and in the postpartum.

Social work and counseling: A higher risk of postpartum depression has been reported among socially disadvantaged women and women of ethnic minority groups; as a result, alerting social workers and counsellors on the important of nutrition on PPD would be beneficial.

Nutrigenomics: It would be interesting to investigate in the future the possible provision of tailor-made nutritional advice to women with a specific genome, predisposing them to PPD.
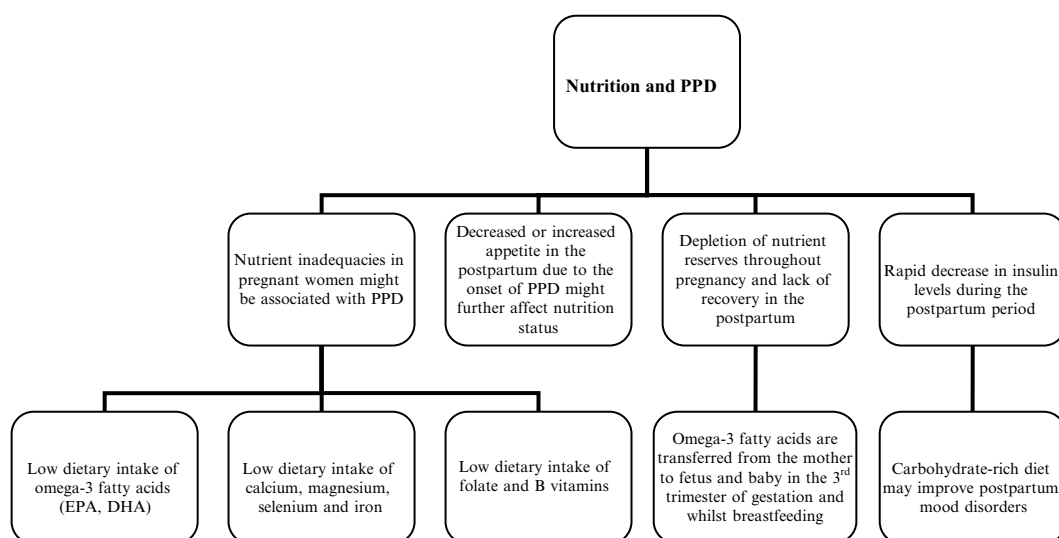
Fig. 129.2 Keys points linking nutrition with PPD. Evidence suggests that depletion of nutrient reserves throughout pregnancy can increase the risk of PPD. There is also good evidence that increasing the dietary omega-3 intake in late pregnancy or following delivery may reduce the risk of PPD. The role of the inadequate intake of folate, calcium, zinc and iron intake on the onset of PPD has also been investigated

Summary Points

- Prevalence of postpartum depression (PPD) is increasing worldwide and has potentially detrimental effects on both the mother and the offspring.
- Depletion of nutrient reserves throughout pregnancy can increase a woman's risk for PPD.
- Evidence suggests that inadequate intake of specific nutrients might be a substantial contributor to the development of depression in women in the postpartum period.
- The role of the inadequate intake of folate, calcium, zinc and iron intake on the onset of PPD has been investigated, with conflicting results.
- There is good evidence that increasing the dietary omega-3 intake in late pregnancy or following delivery may reduce the risk of PPD.

Definitions of Key Terms

Postpartum (or postnatal) depression: It is a condition that affects women who have recently had a baby, with most cases occurring in the first 6 months after delivery. It is a serious mental health problem characterized by a prolonged period of emotional disturbance.

Perinatal (or maternal) depression: This refers to major and minor episodes of depression during pregnancy.

Postpartum blues: This is defined as short lived episodes of depressive symptoms such as anxiety, disturbed sleeping patterns, decreased appetite and irritability, normally taking place on day 4 after delivery but may commence up to 2 weeks after delivery.

Postpartum psychosis: This is the most severe form of postpartum psychiatric illness. It is a rare event that occurs in approximately 1–2 per 1,000 women after childbirth. Its presentation is often dramatic, with onset of symptoms as early as the first 48–72 h after delivery.

Edinburgh postnatal depression scale: This is a 10-item questionnaire that may be used to identify women who have PPD. Usually a score of 12 or greater or an affirmative answer on question 10 (presence of suicidal thoughts) raise concern and indicate a need for more thorough evaluation.

Key facts of Postpartum Depression

- Postpartum depression (PPD), also called postnatal depression, is a form of clinical depression which can affect women after childbirth and has significant consequences for both the new mother and family.
- Prevalence of postpartum depression worldwide is approximately 13% to 20%; however, these are probably conservative estimates because the condition is often underreported or underdiagnosed.
- Main symptoms of PPD include sadness, anxiety, fatigue, insomnia, appetite changes, crying episodes, and irritability.
- The causes of PPD remain unclear, with research suggesting a multifactorial aetiology. The strongest predictors of postpartum depression seem to be the personal and family history of depression, depression and anxiety during pregnancy and most importantly the lack of social support.
- It has been suggested that postpartum depression can partly be attributed to depletion of omega-3 fatty acids from the mother's brain to support development of the brain of the fetus or breast-fed infant. Ensuring a sufficient supply of omega 3 fatty acids in the mother's diet is very important.

References

Abou-Saleh MT, Ghubash R, Karim L, Krymski M, Anderson DN. Eur Neuropsychopharmacol. 1999;9:295–300.

Almond P. Perspect Public Health. 2009;129:221–7.

Alpert JE, Mischoulon D, Nierenberg AA, Fava M. Nutrition. 2000;16:544–6.

American Psychological Association (APA) www.apa.org/pi/women/resources/reports/postpartum-dep.aspx#.

Beard JL, Hendricks MK, Perez EM, Murray-Kolb LE, Berg A, Vernon-Feagans L, Irlam J, Isaacs W, Sive A, Tomlinson M. J Nutr. 2005;135:267–72.

Beck CT. Theoretical perspectives of postpartum depression and their treatment implications. MCN Am J Matern Child Nurs. 2002;27:282–87.

Bloch M, Schmidt PJ, Danaceau M, Murphy J, Nieman L, Rubinow DR. Am J Psychiatry. 2000;157:924–30.

Bodnar LM, Wisner KL. Biol Psychiatry. 2005;58:679–85.

Browne JC, Scott KM, Silvers KM. J Affect Disord. 2006;90:131–9.

Chen TH, Lan TH, Yang CY, Juang KD. Med Hypotheses. 2006;66:820–3.

Chiu CC, Huang SY, Su KP. Am J Obstet Gynecol. 2004;190:582–3.

Coppen A, Bolander-Gouaille C. J Psychopharmacol. 2005;19:59–65.

Craddock N, Forty L. Eur J Hum Genet. 2006;14:660–8.

De Vriese SR, Christophe AB, Maes M. Life Sci. 2003;73:3181–7.

Derbyshire E, Costarelli V. Nutr. Bull. 2008;33:162–8.

Derbyshire E, Davies GJ, Costarelli V, Dettmar PW. Matern Child Nutr. 2009;5:1–9.

Dunlop BW, Nemeroff CB. Arch Gen Psychiatry. 2007;64:327–37.

Freeman MP, Davis M, Sinha P, Wisner KL, Hibbeln JR, Gelenberg AJ. J Affect Disord. 2008;110:142–8.

Freeman MP, Hibbeln JR, Wisner KL, Brumbach BH, Watchman M, Gelenberg AJ. Acta Psychiatr Scand. 2006a;113:31–5.

Freeman MP, Hibbeln JR, Wisner KL, Davis JM, Mischoulon D, Peet M, Keck PE, Marangell LB, Richardson AJ, Lake J, Stoll AL. J Clin Psychiatry. 2006b;67:1954–67.

Giddens JB, Krug SK, Tsang RC, Guo S, Miodovnik M, Prada JA. J Am Diet Assoc. 2000;100:1334–40.

Gurel S, Gurel H. Eur J Obstet Gynecol Reprod Biol. 2000;91:21–4.

Halbreich U, Karkun S. J Affect Disord. 2006;91:97–111.

Harrison-Hohner J, Coste S, Dorato V, Curet LB, McCarron D. Arch Women's Ment Health. 2001;3:141–6.

Hatton DC, Harrison-Hohner J, Coste S, Dorato V, Curet LB, McCarron DA. J Hum Lact. 2005;21:444–9.

Henderson L, Gregory J, Swann G. The National Diet and Nutrition Survey: adults aged 19–64 years. Volume 1: Types and Quantities of Foods Consumed. London: The Stationery Office; 2002.***

Hibbeln JR. J Affect Disord. 2002;69:15–29.

Holman RT, Johnson SB, Ogburn PL. Proc Natl Acad Sci USA. 1991;88:4835–9.

Hosli I, Zanetti-Daellenbach R, Holzgreve W, Lapaire O. J Perinat Med. 2007;35 Suppl 1:S19–24.

Hvas AM, Juul S, Bech P, Nexo E. Psychother Psychosom. 2004;73:340–3.

Kyrozis A, Psaltopoulou T, Stathopoulos P, Trichopoulos D, Vassilopoulos D, Trichopoulou A. J Psychiatr Res. 2009;43:763–9.

Leung BM, Kaplan BJ. J Am Diet Assoc. 2009;109:1566–75.

Levenson CW. Nutr Rev. 2006;64:39–42.

Levine RJ, Hauth JC, Curet LB, Sibai BM, Catalano PM, Morris CD, DerSimonian R, Esterlitz JR, Raymond EG, Bild DE, Clemens JD, Cutler JA. N Engl J Med. 1997;337:69–76.

Llinas RR. Neurosci Res Program Bull. 1977;15:555–687.

Llorente AM, Jensen CL, Voigt RG, Fraley JK, Berretta MC, Heird WC. Am J Obstet Gynecol. 2003;188:1348–53.

Makrides M, Crowther CA, Gibson RA, Gibson RS, Skeaff CM. Asia Pac J Clin Nutr. 2003;12:S37.

Meyer BJ, Mann NJ, Lewis JL, Milligan GC, Sinclair AJ, Howe PR. Lipids. 2003;38:391–8.

Miller AL. Altern Med Rev. 2008;13:216–26.

Miyake Y, Sasaki S, Tanaka K, Yokoyama T, Ohya Y, Fukushima W, Saito K, Ohfuji S, Kiyohara C, Hirota Y. J Affect Disord. 2006a;96:133–8.

Miyake Y, Sasaki S, Tanaka K, Yokoyama T, Ohya Y, Fukushima W, Saito K, Ohfuji S, Kiyohara C, Hirota Y. Psychol Med. 2006b;36:1727–35.

Mouratidou T, Ford F, Prountzou F, Fraser R. Br J Nutr. 2006;96:929–35.

Murakami, K, Sasaki S, Takahashi Y, Uenishi K, Watanabe T, Kohri T, Yamasaki M, Watanabe R, Baba K, Shibata K, Takahashi T, Hayabuchi H, Ohki K, Suzuki J. Nutrition. 2008;24:554–61.

Nowak G, Szewczyk B, Pilc A. Pharmacol Rep. 2005;57:713–8.

O'Brien LM, Heycock EG, Hanna M, Jones PW, Cox JL. Pediatrics. 2004;113:1242–47.

O'Hara MW, Swain AM. Intern Rev Psychiatry. 1996;8 (1):37–54.

Onozawa K, Kumar RC, Adams D, Dore C, Glover V. Arch Womens Ment Health. 2003;6 Suppl. 2:S51–5.

Otto SJ, de Groot RH, Hornstra G. Prostaglandins Leukot Essent Fatty Acids. 2003;69:237–43.

Peet M, Murphy B, Shay J, Horrobin D. Biol Psychiatry. 1998;43:315–9.

Picciano MF. J Nutr. 2003;133:1997S–2002S.

Rees AM, Austin MP, Parker G. Aust N Z J Psychiatry. 2005;39:274–80.

Sanchez-Villegas A, Henriquez P, Bes-Rastrollo M, Doreste J. Public Health Nutr. 2006;9:1104–9.

Sapolsky RM. Biol Psychiatry. 2000;48:755–65.

Stein A, Ramchandani P, Murray L. In: Rutter M, Bishop DVM, Pine DS, Scott S, Stevenson J, Taylor E, Thapar A, editors. Rutter's child and adolescent psychiatry. 5th ed., Chapter 27. London: Blackwell Publishing Ltd; 2009. p. 407–420.

Stewart RC. Matern Child Nutr. 2007;3:94–107.

Strom M, Mortensen EL, Halldorsson TI, Thorsdottir I, Olsen SF. Am J Clin Nutr. 2009;90:149–55.

Su KP, Huang SY, Chiu TH, Huang KC, Huang CL, Chang HC, Pariante CM. J Clin Psychiatry. 2008;69:644–51.

van Strater AC, Bouvy PF. Tijdschr Psychiatr. 2007;49:85–94.

Verkerk GJ, Pop VJ, Van Son MJ, Van Heck GL. J Affect Disord. 2003;77:159–66.

Wisner KL, Parry BL, Piontek CM. N Engl J Med. 2002;347:194–9.

Wojcik J, Dudek D, Schlegel-Zawadzka M, Grabowska M, Marcinek A, Florek E, Piekoszewski W, Nowak RJ, Opoka W, Nowak G, Pharmacol Rep. 2006;58:571–6.

Part XXIII
Developmental, Children and Adolescents

Chapter 130
Prenatal Diet and Stress Responsiveness

Susanne R. de Rooij

Abbreviations

ACTH	AdrenoCorticoTropic Hormone
ANS	Autonomic Nervous System
AVP	Arginine VasoPressin
CRH	Corticotropin-Releasing Hormone
Dex	Dexamethasone
FR	Food Restricted
GR	Glucocorticoid Receptor
HPA-axis	Hypothalamic–Pituitary–Adrenal axis
PVN	ParaVentricular Nucleus
TSST	Trier Social Stress Test
11β-HSD	11 Beta-Hydroxy Steroid Dehydrogenase

130.1 Introduction

The notion that early life events may affect the course of life has been part of common beliefs for a very long time. One of the first records of this thought is found four centuries BC in Plato's work. In Plato's philosophy, suffering in life is the result of the evil experience before birth. It has only been during the last few decades, however, that this notion has gained a scientific basis. Experimental and observational evidence strongly suggests that prenatal conditions play a role in determining health and behavior in later life. One of the prenatal factors, which seem to be of great importance to postnatal health and behavior, is prenatal nutrition.

S.R. de Rooij (✉)
Department of Clinical Epidemiology and Biostatistics, Room J1b 210.1,
Academic Medical Centre, University of Amsterdam, Meibergdreef 9,
1100 DD, Amsterdam, The Netherlands
e-mail: s.r.derooij@amc.uva.nl

130.2 Fetal Programming

In 1977, Anders Forsdahl found a geographical association between past infant mortality and subsequent arteriosclerotic heart disease in Norway (Forsdahl 1977). Based upon this observation, he was the first to suggest that a poor standard of living in early life was a risk factor for heart disease. Geographical studies were also the basis for the suggestion made by David Barker and Clive Osmond that coronary heart disease might be linked to impaired fetal growth (Barker and Osmond 1986). They observed that in different parts of England differences in neonatal mortality rates in the early part of the twentieth century correlated with death rates from coronary heart disease in the same generation decades later. Both mortality rates showed a similar distribution with a clear difference between the poor northern part of the country and the richer southern part. This close geographical similarity led them to the hypothesis that adverse environmental conditions in utero and during infancy increase the susceptibility to disease in later life. Detailed birth records from Hertfordshire, UK allowed them to validate this hypothesis. It appeared from thousands of records kept by midwives that a decrease in birth weight was associated with an increased risk of death from coronary heart disease. Barker went on to suggest that when faced with poor nutrition and health of the mother, the fetus has to adapt to a limited supply of nutrients, which permanently changes the body's structure, physiology, and metabolism, a process known as fetal programming or developmental plasticity. These adaptations may subsequently predispose to disease in adult life (Barker 1998) (Fig. 130.1). It has been put forward that the adaptation process is beneficial from an evolutionary point of perspective because it provides the organism with an opportunity to adapt itself to the expected environment within a single generation (Gluckman and Hanson 2004). This is in contrast to genetic adaptation, which would take much longer than a single generation to be effective. Not all responses are supposed to be adaptive though. When faced with a lack of resources, the organism may need to make trade-offs in order to simply survive. By sacrificing the development of less essential organs, more energy becomes available for essential processes.

Evidence for the "fetal origins of disease" hypothesis has mainly come from animal experimental studies and from studies investigating the consequences of low birth weight, a marker for an adverse prenatal environment. A wide range of physiological and psychological diseases have been suggested to be susceptible to fetal programming. The stress response is a logical fetal programming candidate not only because glucocorticoids (stress hormones) play an important role in fetal growth but also because altered functioning of the response to stress could be an important mechanism in the fetal origins of type 2 diabetes, hypertension, and cardiovascular disease.
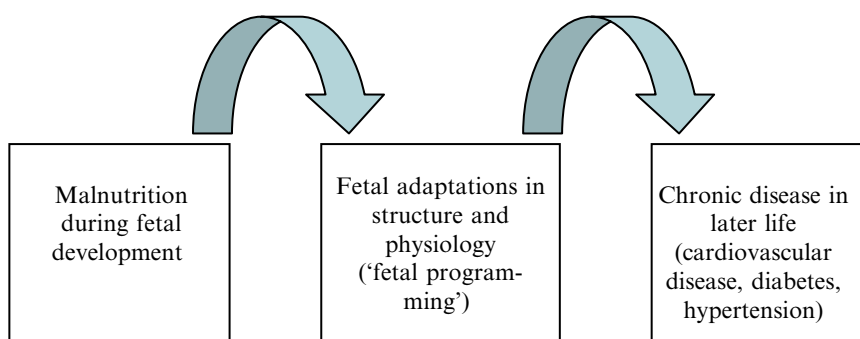
Fig. 130.1 (**a**) Fetal origins of disease hypothesis. (**b**) Schematic overview of the different steps incorporated in the fetal origins of disease hypothesis

130.3 The Stress Response

The biobehavioral response to stress has two key components: the Autonomic Nervous System (ANS) response and the Hypothalamic–Pituitary–Adrenal (HPA)-axis response (Fig. 130.2). These responses are turned on when a person is confronted with a stressful situation. The ANS reacts fast, within seconds, and the HPA-axis reacts somewhat slower, within minutes to hours. Both systems are set in motion by receiving messages from the hypothalamus, which can receive messages from several parts of the brain, including the prefrontal cortex, the amygdala, and the hippocampus. The ANS response starts in the paraventricular nucleus (PVN) from the hypothalamus, travels through sympathetic nerves originating in the brainstem, and ends in the adrenal medulla, which is stimulated to secrete epinephrine and norepinephrine into the circulation. The joined effects of this response are activation of the sympathetic part of the ANS and shutting down of the parasympathetic part of the ANS resulting in an increase in heart rate, blood pressure as well as a range of other changes in cardiovascular, gastrointestinal, renal, and endocrine function. The HPA-axis response also starts in the PVN from the hypothalamus. Here, corticotrophin-releasing hormone (CRH) is excreted, which stimulates the pituitary to secrete adrenocorticotropic hormone (ACTH), which in its turn stimulates the adrenal cortex to secrete cortisol. Cortisol has an important function in mobilizing energy during stress. It also reinforces the actions of the ANS and plays an important role in the negative feedback of the stress response eventually causing the stress response to be terminated.

130.3.1 Fetal Programming of the Stress Response

Both systems responsible for the stress response, the ANS as well as the HPA-axis have been suggested to be susceptible to fetal programming resulting in altered functioning of the stress response in later life. Exactly how this works mechanistically is largely unknown, but several hypotheses have been

Fig. 130.2 (**a**) The stress response. (**b**) Schematic overview of the physiology of the stress response PVN = ParaVentricular Nucleus; CRH = Corticotropin-Releasing Hormone; ACTH = AdrenoCorticoTropic Hormone
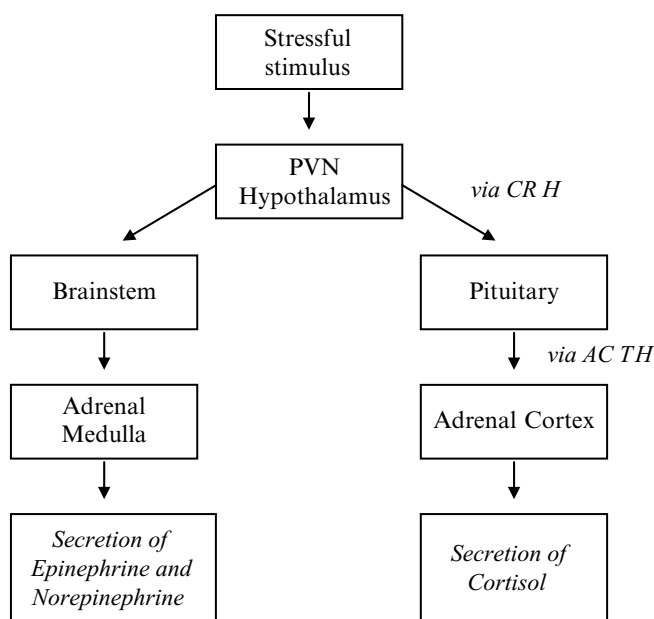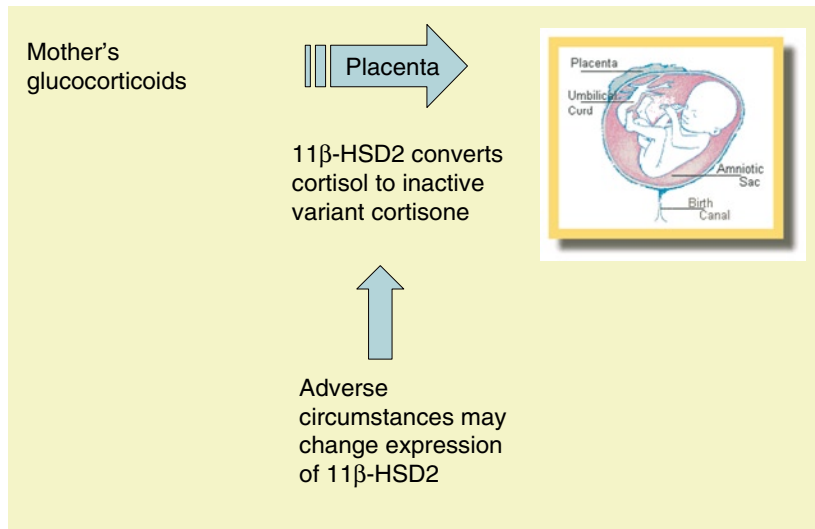
Fig. 130.3 (**a**) The fetus and cortisol. (**b**) Overview of the pathway from high levels of maternal stress hormones to fetal overexposure to stress hormones

put forward. First of all, maternal undernutrition or unbalanced nutrition could directly turn on the fetal stress response as a reaction to the shortage of nutrients supplied to the fetus. Second, the fetal stress response could also be set off indirectly by exposure to maternal glucocorticoids. Normally, maternal cortisol is converted to the inactive variant cortisone by the placental enzyme 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2). However, when maternal cortisol levels are high in response to the metabolic stress in her body, some cortisol may pass the placental barrier by changing the expression of 11β-HSD2. The cortisol that reaches the fetus could stimulate the fetal stress response or could directly affect the fetus (Fig. 130.3).

The increased cortisol and possibly also noradrenaline concentrations resulting from activation of the fetal stress response or directly passed through from the mother could have several effects on the developing fetus: they could change the set points of the stress systems, possibly by altering expression of genes important to the stress response, or directly affect the growth of organs implicated in the stress response, such as the adrenal gland.

130.3.2 Consequences of Fetal Programming of the Stress Response

If proven to be valid, the hypothesis that the fetal environment alters the stress response has important consequences for health in later life. Altered functioning of the HPA-axis and the ANS has been implicated in a range of physical as well as psychiatric diseases. Hyperactivity of the HPA-axis in the form of increased cortisol levels has been associated with increased risk of hypertension, obesity, dyslipidemia, hyperinsulinemia, hyperglycemia, and insulin resistance: all major contributors to the development of cardiovascular disease. High cortisol levels have also been found in depression patients and in patients suffering from post-traumatic stress disorder (PTSD). However, both these diseases have also been shown to be associated with very low levels of cortisol as have a number of

other abnormalities including chronic fatigue syndrome, fibromyalgia, irritable bowel syndrome, and burnout. Alterations in the ANS stress response have been linked with elevated risk for cardiovascular disease via several pathways: hypertension, ventricular arrhythmias, cardiac hypertrophy, carotid atherosclerosis, and endothelial dysfunction. Besides cardiovascular disease, ANS abnormalities have also been associated with a range of other clinical disorders including: insulin resistance, kidney disease, asthma, and depression.

130.3.3 Studying the Stress Response

The two physiological systems involved in the stress response, the HPA-axis and the ANS, can be studied in a basal condition as well as in a stressed condition. Fasting cortisol after awakening is often used as a measure of the HPA-axis in a stressful situation, because waking up highly activates the HPA-axis.

There are two ways in which the stressed HPA-axis and ANS can be measured: in response to physiological stimulation and in response to psychological stress. In physiological stress tests, the stress system is either directly activated by administering a hormone that is part of the HPA-axis or indirectly by creating a physiological stressful situation, which activates the stress response. The CRH stimulation test, the ACTH stimulation test, and the dexamethasone (dex) suppression test fit in the first category, while tests as the cold pressor test fit in the second category. In the CRH test CRH is injected, which stimulates the pituitary to produce ACTH, which subsequently stimulates the adrenals to produce cortisol. Sometimes arginine vasopressin (AVP) is simultaneously injected to maximize responses. In the ACTH test, ACTH is injected which stimulates the adrenals to produce cortisol. In the dex suppression test dex, which is a synthetic glucocorticoid, is administered. Administration leads to a lowering of cortisol levels because of the negative feedback loop that exists in the HPA-axis. In the cold pressor test, the hand of the participant is put in a container with ice water. This activates the sympathetical stress response as well as the HPA-axis.

A drawback of physiological stress tests is that they trigger the stress response at the lower levels of the stress system. Higher order brain systems that can activate the stress response, as the limbic structures and the prefrontal cortex, remain uninvolved. Psychological stress tests, though, are able to activate the stress response at the highest levels. Several different tasks are used for this ranging from mental challenges to the performing of a presentation. These tests require intense mental effort and/or stimulate several emotional responses thereby activating stress responses via the higher order brain systems. A well-established psychological stress protocol is the Trier Social Stress Test (TSST) (Kirschbaum et al. 1993). The TSST consists of a simulated job interview and a mental arithmetic task. First, the participant has to perform a speech about why he or she is a good candidate for a certain job. The speech has to be performed in front of an interview panel and is taped on camera. After the speech, the participant is asked to count down from a large prime number in increments of 13 as quickly and accurately as possible. The TSST combines two elements that have been shown to be capable of inducing quite robust physiological stress responses: uncontrollability and social evaluative threat.

The characteristics of a stress test are crucial for determining the stress response. Not only the level of activation, but also the balance between autonomic and endocrine activation depends on the sort of test. Some characteristics mainly lead to activation of the ANS while other characteristics primarily activate the HPA-axis. The choice of a test should thus be based on what the interest of the study is.

130.4.1 Evidence from Animal Experiments

Several animal models have been developed in which the consequences of dietary restriction during pregnancy have been studied. Emphasis has mostly been on effects on the HPA-axis. The majority of animal experiments aimed at studying fetal programming of the stress response have been performed in three different sorts of animals: rats, guinea pigs, and sheep. A review of the literature is given per species.

130.4.1.1 Rats

Rats have been extensively used as an animal model for studying fetal programming. An advantage of the rat model is the short gestational period of the rat, which allows studying long-term effects over a relatively short time span. A series of rat studies performed at the University of Lille (France) introduced a diet in which the daily intake of the pregnant and/or lactating rats was reduced to half the normal size. Feeding rat mothers this 50% food restricted (50% FR) diet during the last week of gestation led to an elevated level of corticosterone and a decreased level of placental 11β-HSD in the mother (Lesage et al. 2001). The newborn rat offspring had decreased body and adrenal weight and showed several alterations in the HPA-axis compared to rats born to normally fed mothers. Rat pups that were 50% FR during both the last week of gestation and during lactation showed similar changes. Additionally, when the rat pups were stressed by letting them inhale ether, they had a weaker ACTH response than control pups, providing evidence for altered HPA-axis reactivity to stress (Leonhardt et al. 2002). In young adult male rats subjected to stress by severely restraining their movement possibilities, the prenatal 50% FR diet was associated with an increased response of plasma-free corticosterone and a decreased response of adrenalin (Lesage et al. 2002). In older adult male rats subjected to stress induced by dehydration, the prenatal 50% FR diet was associated with a failure of total and free corticosterone levels to react, while basal levels of total and free corticosterone were elevated (Sebaai et al. 2004).

In summary, maternal food restriction induced intrauterine growth retardation and an overexposure of fetuses to maternal corticosterone. This led to several alterations in the development of the HPA-axis which appeared to be expressed differently with increasing age. Some alterations in the sympathoadrenal system responsiveness were also observed.

130.4.1.2 Guinea Pigs

Guinea pigs have been used in a series of experiments on fetal programming of the HPA-axis stress response. Guinea pigs are suitable animals to investigate programming, especially because they give birth to relatively mature offspring, which makes them more comparable to humans. A model in which pregnant guinea pigs were deprived of food during days 50 and 51 of gestation, which is the period of maximal fetal brain growth, showed growth restriction in the offspring (Lingas et al. 1999). Also, cortisol concentrations were increased in the mothers as well as in the offspring while expression of the glucocorticoid receptor (GR) in the fetal brain was decreased. CRH expression in the fetal brain also appeared to be decreased (Go et al. 2001). Studies on functioning of the HPA-axis in these offspring at the time when they were adults showed highly sex-specific results (Lingas and Matthews 2001). Male offspring showed lower ACTH and cortisol concentrations in a basic condition as well as in response to a number of stress challenges compared to male offspring normally fed in utero.

Female offspring, however, showed higher ACTH and cortisol concentrations basically and under stress. Interestingly, effects of prenatal nutrient restriction on the HPA-axis in guinea pigs have been shown to even pass to the next generation (Bertram et al. 2008). Offspring of guinea pigs of which the mothers received a 70% food-restricted diet during either early or late gestation had increased basal cortisol concentrations and increased cortisol response to a stress challenge. In conclusion, prenatal undernutrition has profound effects on HPA-axis functioning in the guinea pig that seem to be sex specific.

130.4.1.3 Sheep

The most extensively studied animal model on fetal programming of the stress response is the sheep model. The sheep model offers the advantage of being able to frequently sample on both sides of the placenta. Also, a lot is known on what constitutes a normal diet for sheep. In a number of experiments performed by the University College London, food intake of pregnant sheep was reduced by 15% during the first 70 days of gestation. During late gestation, the fetuses showed decreased ACTH and cortisol responses to administration of CHP+AVP (Hawkins et al. 1999). Also, CRH and GR expression in the brain were reduced (Hawkins et al. 2001). In contrast, when measured postnatally, HPA-axis response to the CHP+AVP challenge was increased (Hawkins et al. 2000). Also, heart rate was reduced and femoral artery vascular resistance in response to hypoxemia was increased. All seems to depend on the timing and degree of undernutrition though. A study that investigated the consequences of a 70% reduction in maternal nutrient intake during early gestation showed that during late gestation fetuses had increased ACTH levels (Edwards et al. 2002). Ten days of severe undernourishment of the mother during late gestation increased the HPA-axis stress response in the offspring, while 20 days did not (Bloomfield et al. 2003). A study on the effects of periconceptual undernutrition additionally revealed sex differences in functioning of the HPA-axis in the offspring. Female offspring had higher basal cortisol concentrations compared to controls, while male offspring showed no differences (Gardner et al. 2006). Increasing age also seems to matter. While a 50% FR diet during mid-gestation increased the HPA-axis response to stress in offspring at the age of 2 months, the effect had disappeared at the age of 5 and 10 months (Chadio et al. 2007). The sheep model has also been used to investigate the role of activity of the placental enzyme 11β-HSD in fetal programming of the HPA-axis. Interestingly, it was shown that 30% chronic nutrient restriction throughout gestation was associated with a decrease in placental 11β-HSD activity (McMullen et al. 2004). However, while it was expected that 11β-HSD level dictates the level of cortisol delivered to the fetus from the maternal circulation and thus fetal cortisol concentrations, the fetal cortisol concentrations were unchanged.

In summary, the sheep model provides considerable evidence that prenatal diet affects the stress response. However, data are difficult to interpret and many factors seem to be of importance in determining what the exact effects of the prenatal diet on stress responsiveness are.

130.4.2 Evidence in Humans

Due to obvious ethical restrictions to manipulate maternal diet in humans, birth weight and other anthropometric measurements performed at birth have been used as proxies for an adverse fetal environment. Clearly, there are limitations to this approach which we will come back to later.

The majority of the studies that have examined stress responsiveness in relation to birth measurements have looked at the HPA-axis and cortisol concentrations. However, recently, quite a lot of work has also been done on the ANS stress response.

At birth, fetal growth restriction was found to be associated with an increase in a number of HPA hormones in the umbilical cord blood. A first study reported elevated cortisol levels in umbilical cord blood in babies who were born small for gestational age as compared to babies who were born appropriate for gestational age (Economides et al. 1988). A second study showed that concentrations of CRH, ACTH, and cortisol concentrations in umbilical cord plasma were all higher in babies who were growth retarded (below the 10th percentile for gestational age) compared to the concentrations in normal babies (Goland et al. 1993). The first indication of a long-term association between fetal growth and HPA-axis activity was found in a cohort of 9-year-old boys and girls who were all born in Birmingham (UK) (Clark et al. 1996). In a total of 190 children, glucocorticoid metabolites were measured in a 24-h urine sample. Results showed a U-shaped association between birth weight and glucocorticoid metabolites: the highest average urinary glucocorticoid metabolite excretion was found in children who had been either light or heavy at birth. Thereafter, associations between birth weight and cortisol also began to be found in adult men and women. A series of studies performed in several cohorts reported an inverse association between birth weight and fasting cortisol concentrations. Among men and women born in Hertfordshire (UK) with a mean age of 64 years, born in Adelaide (Australia) with a mean age of 21 years, and born in Preston (UK) with a mean age of 51 years, higher fasting cortisol concentrations were found in those with lower birth weights (Phillips et al. 1998, 2000). In 2005, a meta-analysis was performed on 11 studies that investigated the association between birth weight and cortisol (van Montfoort et al. 2005). The meta-analysis revealed an inverse association between birth weight and circulating cortisol concentrations.

From the year 2000 onward, several studies have been performed in which the HPA-axis as well as the ANS has been measured in a stressed state, either provoked physiologically or psychologically. A number of studies have stimulated the HPA-axis by intravenously injecting Synacthen, which is a synthetic ACTH. One of these studies, which was performed in South Africa, observed that young men who had been born in the lowest 10th percentile of the birth-weight range had higher basal cortisol levels as well as higher cortisol responses to ACTH stimulation (Levitt et al. 2000). The other studies showed that older men and women who were born small also had increased cortisol concentrations in response to administration of Synacthen (Reynolds et al. 2001, 2005). Surprisingly, in a combined dex suppression/CRH stimulation test it was found that cortisol and ACTH levels were not higher but lower among men with low birth weight (Ward et al. 2004a). Cortisol reactivity appeared to be somewhat higher again, though, in African-American students with low birth weight who participated in a cold pressor test (McCormick 2006).

The TSST was used in a number of studies in children and adults who were small at birth and produced several sex-specific results. Boys in the age group of 7–9 years had higher cortisol responses to the psychological stress protocol when they had low birth weights, while girls of same age did not show any differences (Jones et al. 2006). On the other hand, girls who were small at birth had higher morning peak cortisol levels, whereas there was no difference in boys. Regarding the cardiovascular stress responses, in boys an association was found of lower birth weight and higher arterial pressure and vascular resistance, while in girls an association was found of lower birth weight with higher cardiac sympathetic nervous system activation (Jones et al. 2008). The authors interpreted the data as evidence for boys who were small at birth having an increased HPA-axis stress response and girls who were small at birth having an increased ANS stress response. Evidence for an enhanced autonomic response in women with low birth weight was also found in a study performed in the Adelaide

Family Heart Study cohort. Women, but not men, with low birth weights had higher blood pressure and heart rate reactivity to the psychological stress protocol than women with normal birth weights (Ward et al. 2004b). This seemed to be due to reduced baroreflex sensitivity and reduced low-frequency blood pressure variability (Jones et al. 2007).

Other studies that investigated the cortisol response to the TSST were performed in a cohort of male twins and in a Finnish cohort of men and women in their late adulthood, the Helsinki Birth Cohort. The first study confirmed the negative association between birth weight and cortisol responses to psychological stress (Wust et al. 2005). The second study found an inverse U-shaped association: increased cortisol responses to the TSST were found in men and women who were either small or large at birth (Kajantie et al. 2007).

A final interesting study was based on data from an assessment of psychological function during evaluation for military service in Sweden (Nilsson et al. 2001). It was found that stress susceptibility, as measured by a structured interview with a psychologist, decreased with increasing birth weight.

With regards to all the studies that have examined birth weight in relation to stress responsiveness it can be concluded that there are definitely associations between restricted fetal growth and HPA as well as ANS stress responsiveness. Most research seems to point at increased responsiveness of both systems in those who were small at birth, although associations are not uniform and seem to depend on gender.

As already indicated above, there are limitations to studying the effects of birth weight. Birth weight is only a surrogate marker for the prenatal environment. Other factors besides maternal nutrition contribute to birth weight. Also, the fact that organs develop during specific periods of gestation suggests that there may be a critical window for circumstances to affect the development. Looking at birth weight does not allow studying the effects of prenatal adversity during these so-called critical periods. Very few studies have looked at the direct effects of nutrition during pregnancy on stress responsiveness in later life. A first study that did look at these effects is the Dutch Famine Birth Cohort Study, which will be described in detail below. A second study that looked at these effects is the Motherwell Study (Herrick et al. 2003). The Motherwell Study included men and women who were born as term singletons in Motherwell, Scotland during 1967–1968, whose mothers were advised to eat a high-meat, low-carbohydrate diet. At the time, pregnant women attending the maternity hospital were advised to consume 1 lb (0.45 kg) of red meat per day and to restrict the intake of carbohydrate rich foods, such as potatoes or bread. Moderate consumption of fish, eggs, and cheese was encouraged together with green vegetables twice daily. The diet was intended to prevent preeclampsia, which was then thought to result from nutritional deficiency. The women's actual nutritional intake was recorded each week showing a doubling of protein intake between early and late pregnancy but a reduction in total energy intake.

At the age of 28–32 years, the sons and daughters of the Motherwell mothers were invited to the clinic to participate in glucose tolerance testing on which occasion fasting cortisol levels were also assessed. A total of 323 of them participated. The results showed that those exposed to increased meat and fish intake and lower green vegetable consumption during the second half of pregnancy had increased fasting cortisol concentrations. Cortisol concentrations increased by 5.4% per portion of maternal meat/fish consumption per day. To further understand these results, a subgroup of 70 men and women were asked to participate in TSST (Reynolds et al. 2007). Cortisol responsiveness to the TSST was again greater in those prenatally exposed to the unbalanced high-protein maternal diet. Compared with the offspring of mothers who had reported eating no more than 13 portions of meat/fish per week, the average cortisol concentrations were raised by 22% and 46% in the offspring of mothers eating 14–16 and at least 17 portions per week. Thus it appeared that an unbalanced high-protein maternal diet clearly affected stress responsiveness in adult life.

130.4.3 The Dutch Famine Birth Cohort Study

130.4.3.1 The Dutch Famine

The Dutch famine or Hungerwinter was a period of 5 months in 1944–1945, during the last winter of World War II. During this period, the urban western part of the Netherlands ran out of food as a consequence of a number of cascading events. While the southern part of the Netherlands was already liberated by the allied forces, advance of the Allies to the north of the Netherlands came to a halt when Operation Market Garden, aimed at gaining control of the bridge across the Rhine at Arnhem, failed. In order to support the Allied offensive, the Dutch government in exile called for a strike of the Dutch railways to hamper movement of the German troops. As a reprisal for the strike, the German administration banned all food transports. This embargo on food transports was partially lifted in early November 1944 by allowing transport of food across water. By then, however, it had become impossible to bring in food across water because most canals and waterways were frozen due to the extremely severe winter, which had started unusually early. Food stocks in the large cities of the western Netherlands ran out within a matter of weeks. Rations soon fell below 1,000 cal per person a day in late November 1944. At the height of the famine from December 1944 to April 1945 the official daily rations varied between 400 and 800 cal: less than a quarter of the prefamine rations (Fig. 130.4). Children younger than 1 year were relatively protected, as their official daily rations never fell below 1,000 cal. Pregnant and lactating women were entitled to an extra amount of food, but at the peak of the famine these extra supplies could not be provided anymore. The famine ended after the liberation of the Netherlands in early May 1945. The food situation improved swiftly. In June 1945, rations had risen to more than 2,000 cal a day (Burger et al. 1948). The famine had a profound effect on the general health of the population. In Amsterdam, the mortality rate in 1945 had more than doubled compared to 1939, and it is very likely that most of this increase in mortality was attributable to malnutrition (Banning 1946).
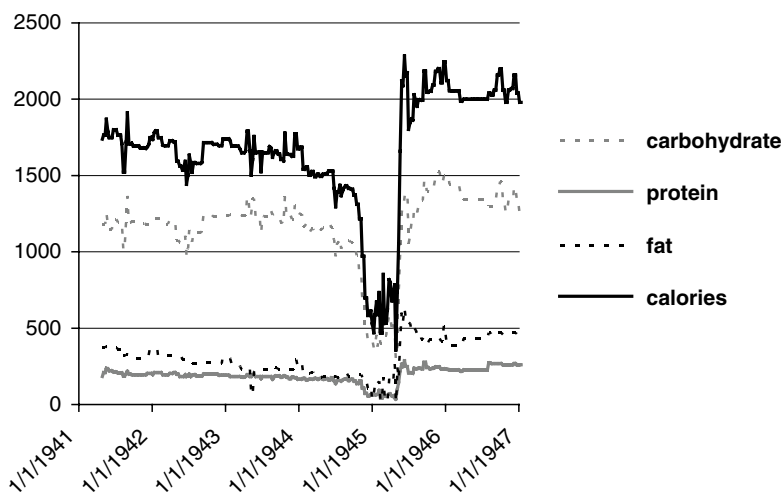
Fig. 130.4 (**a**) Rations during the Dutch famine. (**b**) Macronutrient content of rations provided to adults in Amsterdam between April 1941 and April 1947

130.4.3.2 The Dutch Famine Birth Cohort Study

The Dutch famine was a humanitarian disaster. But even during these extremely harsh circumstances, women conceived and gave birth to babies, and it is in these babies that the effects of prenatal malnutrition can be studied (Fig. 130.5). Usually, studying effects of prenatal famine in humans is difficult, because the period of undernutrition lasts longer than gestation. The Dutch famine, however, struck a population that was well fed before and after the famine. The period of undernutrition was thus restricted to 5 months, also allowing the study of gestation-specific effects of undernutrition. Furthermore, detailed information on the weekly rations of people living in Amsterdam is available. Birth records were kept on babies born in the Wilhelmina Gasthuis in Amsterdam and these men and women could be retrieved using the Dutch population registry. A total of 2,414 of them comprise the Dutch Famine Birth Cohort. People were included in the cohort when they were born as a term singleton between 1 November 1943 and 28 February 1947. The official daily food-rations for the general population of 21 years and older were used to define exposure to famine (Trienekens 1985). A person was considered to be prenatally exposed to famine if the average daily food-ration of the mother during any 13-week period of gestation contained less than 1,000 cal. Based on this definition, babies born between 7 January 1945 and 8 December 1945 had been exposed in utero. Periods of 16 weeks each were delineated to differentiate between those exposed in late gestation (born between 7 January and 28 April 1945), in mid-gestation (born between 29 April and 18 August 1945), and in early gestation (born between 19 August and 8 December 1945). People born before 7 January 1945 and conceived and born after 8 December 1945 were considered as unexposed to famine in utero and acted as control groups (Fig. 130.6).

A first round of data collection in the Dutch Famine Birth Cohort at the age of 50 years yielded remarkable results (Painter et al. 2005). Exposure to famine in early gestation appeared to be associated with an excess in dyslipidemia, altered clotting, more obesity in women, a higher prevalence of coronary heart disease, and an increased proportion of people reporting poor health. Exposure to famine in mid-gestation was associated with more obstructive airways disease and microalbuminuria. Exposure to famine during any stage of gestation was associated with impaired glucose tolerance. A second round of data collection at age 58 years showed among others that exposure to famine in mid-gestation was associated with impaired insulin secretion and exposure to famine in early gestation with an increased prevalence of breast cancer in women (Roseboom et al. 2006).

Fig. 130.5 (**a**) Dutch famine baby. (**b**) Baby born during the Dutch famine in the Wilhelmina Gasthuis in Amsterdam
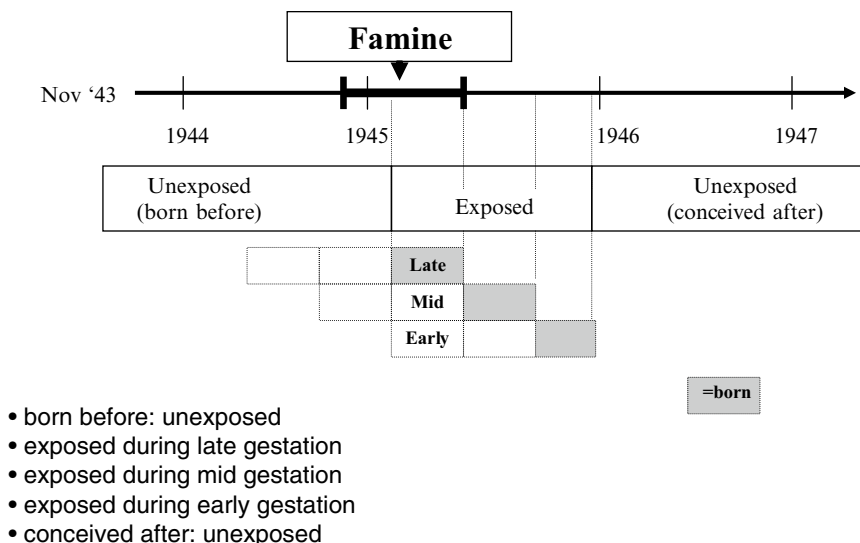
Fig. 130.6 (**a**) The Dutch Famine Birth Cohort study. (**b**) Schematic overview of exposure and nonexposure groups in the Dutch Famine Birth Cohort

130.4.3.3 Stress Response in Men and Women Prenatally Exposed to the Dutch Famine

To investigate whether exposure to undernutrition in utero alters the stress response, functioning of both HPA-axis and cardiovascular responses to stress in men and women prenatally exposed to the Dutch famine were investigated. Therefore, a combined dex suppression and ACTH stimulation test was performed to measure HPA-axis response to physiological stress and a psychological stress protocol was performed to measure HPA-axis and cardiovascular responses to psychological stress. The combined dex suppression and ACTH stimulation test was performed in a subsample of the cohort consisting of 97 men and women with a mean age of 58 years, of whom 57 had been prenatally exposed to famine (de Rooij et al. 2006a). Results of the dex suppression test showed no differences in cortisol concentrations between participants exposed and participants unexposed to famine in utero. The ACTH stimulation test also did not reveal different cortisol concentrations between the exposed and the unexposed groups.

The psychological stress protocol was also performed at age 58 years but in a much larger group of 694 cohort members (de Rooij et al. 2006b; Painter et al. 2006). The protocol consisted of three 5-min stress tasks: a Stroop test (a color-word conflict challenge), a mirror-tracing test (a star had to be traced that could only be seen in mirror image), and a speech test (a speech had to be given in front of a video camera). Cortisol concentrations were measured seven times and blood pressure and heart rate were measured continuously during the protocol. There was no effect of prenatal exposure to the Dutch famine on cortisol reactivity to the stress tests. However, men and women exposed to famine during early gestation showed larger systolic blood pressure responses to the stress protocol compared to men and women unexposed to famine in utero. Diastolic blood pressure responses were also higher, but this difference did not reach statistical significance.

Key Points of Stress Responsiveness Research in the Dutch Famine Birth Cohort

Test performed	Response measured	Number of participants	Exposure	Result
Dexamethasone-suppression test	Plasma cortisol	98	21 born before the famine 20 exposed in late gestation 20 exposed in mid-gestation 17 exposed in early gestation 20 conceived after famine	No differences found between exposed and unexposed subjects
ACTH stimulation test	"	98	"	"
Psychological stress protocol	Salivary cortisol	725	215 born before the famine 120 exposed in late gestation 100 exposed in mid-gestation 62 exposed in early gestation 197 conceived after famine	"
Psychological stress protocol	Systolic blood pressure	725	"	Subjects exposed to famine in early gestation had higher SBP stress responsiveness.
Psychological stress protocol	Diastolic blood pressure	725	"	Subjects exposed to famine in early gestation tended to higher DBP stress responsiveness
Psychological stress protocol	Heart rate	725	"	No differences found between exposed and unexposed subjects

130.4.3.4 Conclusions from the Dutch Famine Birth Cohort Study

Results from stress responsiveness studies in the Dutch Famine Birth Cohort showed that at the age of 58 years, individuals conceived in famine were more stress responsive in terms of systolic blood pressure compared with individuals who were unexposed to famine in utero. No differences were found in cortisol responsiveness to stress. It could be concluded that prenatal exposure to undernutrition programs the ANS response to stress and not so much the HPA-axis response. However, caution should be taken in interpreting the results. Cortisol responses induced by the stress protocol were not very large. They may not have been robust enough to detect any effects of prenatal famine exposure.

130.5 Conclusions

Evidence from animal studies shows that there are definitely effects of prenatal diet on functioning of the stress response in adult life. Human evidence seems to point in the same direction. Indirect evidence based on studies of the consequences of low birth weight as well as direct evidence based on the Motherwell study and the Dutch Famine Birth Cohort Study suggest a role for prenatal diet in programming the stress response. However, inconsistencies have been found. Birth-weight studies and the Motherwell study both found evidence for fetal programming of the HPA-axis, while the Dutch Famine Birth Cohort study did not. The Dutch Famine Birth Cohort study did find an association between prenatal undernutrition and the ANS response to stress, which is confirmed by a

number of birth-weight studies. Hyper- as well as hypoactivity of the stress response has been found and several factors seem to influence the direction and magnitude of the stress response as well as which parts of the response are affected. Future studies are needed to provide more clarity on the subject.

130.6 Applications to Others Areas of Health and Disease

The output of the several studies described in the present chapter is of importance to a wide range of health and disease areas because of the wide spread effects in the body of a dysfunctional stress response, as referred to in the first part of the chapter.

It also offers opportunities for public health strategies. Although most studies performed so far have mainly investigated the consequences of a restricted prenatal diet, results of the Motherwell Study suggest that an unbalanced diet in utero can equally affect the stress response in later life.

Recent research in women who were planning a pregnancy showed that only a very small proportion of these women followed the recommendations for nutrition, which include taking 400 μg or more of folic acid supplements a day, drinking four or fewer units of alcohol a week, and eating a healthy diet (Inskip et al. 2009). Remarkably, these are women who are trying to get pregnant. Of young women in general, almost one in four women in Europe were attempting to lose weight in 2001; only one-third ate fresh fruit or vegetables daily. At the other end, it is well known that the prevalence of obesity is still rising worldwide, also among pregnant women! It appears that young women are still largely unaware of the importance of a healthy diet during pregnancy. The fact that mothers can improve the health of their babies by consuming a balanced diet needs to be communicated to the greater public.

Summary Points

- Prenatal undernutrition has been shown to affect susceptibility for several diseases in later life, including type 2 diabetes and cardiovascular disease.
- Fetal programming of the stress response is one of the candidates that have been suggested to mediate the association between prenatal diet and disease in later life.
- Experiments in rats have shown that maternal food restriction induced growth retardation and overexposure of fetuses to maternal corticosterone. Several alterations in the development of the HPA-axis in the offspring have been observed, as well as some changes in responsiveness of the sympathoadrenal system.
- Studies performed in guinea pigs revealed that prenatal undernutrition had some profound effects on HPA-axis functioning in the offspring. A number of these effects seemed to depend on the gender of the guinea pig.
- Sheep have frequently been used as a model for fetal programming of the stress response. Results of these models have provided considerable evidence for a role of prenatal diet in functioning of the HPA-axis in later life. Timing and severity of undernutrition seem to be important factors.
- In human studies, birth weight has extensively been used as a marker for the fetal environment. The many studies that have been performed investigating the association between birth weight

and stress responsiveness seem to lend support to the hypothesis of fetal programming of the stress response.

- The Motherwell Study directly measured the effects of prenatal diet on stress responsiveness in later life. Fasting cortisol and cortisol responses to a psychological stress protocol were elevated in men and women whose mothers consumed a diet consisting of high meat and fish intake and low green vegetables intake.
- The Dutch Famine Birth Cohort Study examined the effects of prenatal exposure to undernutrition on stress responsiveness in later life. No effects on the HPA-axis were found, but men and women who had been exposed to famine during early gestation had increased blood pressure responses to psychological stress.
- It can be concluded that prenatal diet shapes the response to stress in later life. Exactly how this happens, to what extent and which factors are of importance remains to be clarified.
- Young women are largely unaware of the importance of a healthy diet during pregnancy. From a public health point of view, it would be wise to communicate to the greater public that a balanced diet during gestation can improve health outcomes in offspring.

Definitions and Explanations of Key Terms or Words

Autonomic Nervous System (ANS): One of the two physiological systems involved in the biobehavorial stress response. The ANS is part of the peripheral nervous system, which together with the central nervous system constitutes the nervous system. The ANS controls homeostasis in the body and can be divided in two parts: the sympathetic and the parasympathetic nervous system. The sympathetic part is mainly concerned with activation of several bodily systems and functions, while the parasympathetic part mediates calming and vegetative functions.

Biobehavorial stress response: The response set in motion by a stressful stimulus (or stimulus that is interpreted as stressful), which involves activation of the HPA-axis and the ANS resulting in the secretion of noradrenalin, adrenaline, and cortisol. For a schematic overview of the stress response, see Fig. 130.2.

Birth weight: Weight of a child at birth, which has frequently been used as a summary measure of the fetal environment. Birth weight is the end result of interplay between several factors, including gestational age, genetic factors, maternal nutrition, maternal health, and placental functioning.

Dutch famine: Period of severe undernutrition in the western urban cities of the Netherlands, which happened at the end of World War II. The famine started in November 1944 and lasted 5 months until the liberation of the northern part of the Netherlands on 5 May 1945. Daily energy intake was as low as 400–800 cal a day at the peak of the famine.

Fetal programming hypothesis: Undernutrition in utero permanently changes the body's structure, physiology and metabolism conferring a predisposition to disease in later life.

Hypothalamic–Pituitary–Adrenal (HPA)-axis: One of the two physiological systems involved in the biobehavorial stress response. The HPA-axis is part of the neuroendocrine system and consists of the interaction between the hypothalamus, the pituitary gland located below the hypothalamus, and the adrenal cortex located on top of the kidneys.

Trier Social Stress Test (TSST) (Kirschbaum et al. 1993): The TSST is a psychological stress protocol designed to provoke a stress response in the laboratory, which is subsequently being measured by means of hormone sampling or cardiovascular recording. It consists of two tasks: a public speaking task and a mental arithmetic task.

References

Banning C. Am Ac Pol Soc Sci. 1946;245:93–110.

Barker DJP. Mothers, babies and health in later life. Edinburgh: Churchill Livingstone; 1998.

Barker DJP, Osmond C. Lancet 1986;10:1077–81.

Bertram C, Khan O, Ohri S, Phillips DI, Matthews SG, Hanson MA. J Physiol. 2008;586:2217–29.

Bloomfield FH, Oliver MH, Giannoulias CD, Gluckman PD, Harding JE, Challis JR. Endocrinology 2003;144: 2933–40.

Burger GCE, Sandstead HR, Drummond JC. Malnutrition and starvation in Western Netherlands, September 1944 to July 1945. Part I and II. The Hague: General State Printing Office; 1948.

Chadio SE, Kotsampasi B, Papadomichelakis G, Deligeorgis S, Kalogiannis D, Menegatos I, Zervas G. J Endocrinol. 2007;192:495–503.

Clark PM, Hindmarsh PC, Shiell AW, Law CM, Honour JW, Barker DJ. Clin Endocrinol. (Oxf) 1996;45:721–6.

de Rooij SR, Painter RC, Phillips DI, Osmond C, Michels RP, Bossuyt PM, Bleker OP, Roseboom TJ. Eur J Endocrinol. 2006a;155:153–60.

de Rooij SR, Painter RC, Phillips DI, Osmond C, Tanck MW, Bossuyt PMM, Roseboom TJ. Psychoneuroendocrinology 2006b;31:1257–62.

Economides DL, Nicolaides KH, Linton EA, Perry LA, Chard T. Fetal Ther. 1988;3:158–64.

Edwards LJ, Bryce AE, Coulter CL, McMillen IC. Mol Cell Endocrinol. 2002;196:1–10.

Forsdahl A. Br J Prev Soc Med. 1977;31:91–5.

Gardner DS, Van Bon BW, Dandrea J, Goddard PJ, May SF, Wilson V, Stephenson T, Symonds ME. J Endocrinol. 2006;190:203–12.

Gluckman PD, Hanson MA. Science 2004;305:1733–6.

Go KS, Lingas R, Wheeler MB, Irwin DM, Matthews SG. Brain Res. 2001;896:179–82.

Goland RS, Jozak S, Warren WB, Conwell IM, Stark RI, Tropper PJ. J Clin Endocrinol Metab. 1993;77:1174–9.

Hawkins P, Steyn C, McGarrigle HH, Saito T, Ozaki T, Stratford LL, Noakes DE, Hanson MA. J Endocrinol. 1999;163:553–61.

Hawkins P, Steyn C, McGarrigle HH, Calder NA, Saito T, Stratford LL, Noakes DE, Hanson MA. Reprod Fertil Dev. 2000;12:443–56.

Hawkins P, Hanson MA, Matthews SG. J Neuroendocrinol. 2001;13:855–61.

Herrick K, Phillips DI, Haselden S, Shiell AW, Campbell-Brown M, Godfrey KM. J Clin Endocrinol Metab. 2003;88:3554–60.

Inskip HM, Crozier SR, Godfrey KM, Borland SE, Cooper C, Robinson SM. BMJ 2009;338:b481.

Jones A, Godfrey KM, Wood P, Osmond C, Goulden P, Phillips DI. J Clin Endocrinol Metab. 2006;91:1868–71.

Jones A, Beda A, Ward AM, Osmond C, Phillips DI, Moore VM, Simpson DM. Hypertension 2007;49:548–55.

Jones A, Beda A, Osmond C, Godfrey KM, Simpson DM, Phillips DI. Eur Heart J. 2008 July 22 [epub ahead of print].

Kajantie E, Feldt K, Raikkonen K, Phillips DI, Osmond C, Heinonen K, Pesonen AK, Andersson S, Barker DJ, Eriksson JG. J Clin Endocrinol Metab. 2007;92:4094–100.

Kirschbaum C, Pirke KM, Hellhammer DH. Neuropsychobiology 1993;28:76–81.

Leonhardt M, Lesage J, Dufourny L, Dickes-Coopman A, Montel V, Dupouy JP. Neuroendocrinology 2002;75:45–54.

Lesage J, Blondeau B, Grino M, Breant B, Dupouy JP. Endocrinology 2001;142:1692–702.

Lesage J, Dufourny L, Laborie C, Bernet F, Blondeau B, Avril I, Breant B, Dupouy JP. J Neuroendocrinol. 2002; 14:135–43.

Levitt NS, Lambert EV, Woods D, Hales CN, Andrew R, Seckl JR. J Clin Endocrinol Metab. 2000;85:4611–8.

Lingas R, Dean F, Matthews SG. Brain Res. 1999;846:236–42.

Lingas RI, Matthews SG. Neuroendocrinology 2001;73:302–11.

McCormick CM. Issues Compr Pediatr Nurs. 2006;29:173–87.

McMullen S, Osgerby JC, Thurston LM, Gadd TS, Wood PJ, Wathes DC, Michael AE. Reproduction 2004;127:717–25.

Nilsson PM, Nyberg P, Ostergren PO. Int J Epidemiol. 2001;30:75–80.

Painter RC, Roseboom TJ, Bleker OP. Reprod Toxicol. 2005;20:345–52.

Painter RC, de Rooij SR, Bossuyt PM, Phillips DI, Osmond C, Barker DJ, Bleker OP, Roseboom TJ. J Hypertens. 2006;24:1771–8.

Phillips DI, Barker DJ, Fall CH, Seckl JR, Whorwood CB, Wood PJ, Walker BR. J Clin Endocrinol Metab. 1998;83:757–60.

Phillips DI, Walker BR, Reynolds RM, Flanagan DE, Wood PJ, Osmond C, Barker DJ, Whorwood CB. Hypertension 2000;35:1301–6.

Reynolds RM, Walker BR, Syddall HE, Andrew R, Wood PJ, Whorwood CB, Phillips DI. J Clin Endocrinol Metab. 2001;86:245–50.
Reynolds RM, Walker BR, Syddall HE, Andrew R, Wood PJ, Phillips DI. Eur J Endocrinol. 2005;152:249–53.
Reynolds RM, Godfrey KM, Barker M, Osmond C, Phillips DI. J Clin Endocrinol Metab. 2007;92:2208–10.
Roseboom T, de Rooij S, Painter R. Early Hum Dev. 2006;82:485–91.
Sebaai N, Lesage J, Breton C, Vieau D, Deloof S. Neuroendocrinology 2004;79:163–73.
Trienekens G. Tussen ons volk en de honger. Utrecht: Matrijs; 1985.
van Montfoort N, Finken MJ, le Cessie S, Dekker FW, Wit JM. Eur J Endocrinol. 2005;153:811–7.
Ward AM, Moore VM, Steptoe A, Cockington RA, Robinson JS, Phillips DI. J Hypertens. 2004a;22:2295–301.
Ward AM, Syddall HE, Wood PJ, Chrousos GP, Phillips DI. J Clin Endocrinol Metab. 2004b;89:1227–33.
Wust S, Entringer S, Federenko IS, Schlotz W, Hellhammer DH. Psychoneuroendocrinology 2005;30:591–8.

Chapter 131
Early Nutrition and Postnatal Brain Growth in the Preterm Infant

Richard W. I. Cooke

Abbreviations

ADHD	Attention-deficit hyperactivity disorder
BPD	Bronchopulmonary dysplasia
DNA	Deoxyribonucleic acid
FIQ	Full Intelligence quotient
IQ	Intelligence quotient
M-ABC	Movement Assessment Battery for Children
MDI	Mental development index
MRI	Magnetic resonance imaging
NEC	Necrotising enterocolitis
NICHD	National Institute for Child Heath and Development
OFC	Occipitofrontal circumference
PDI	Psychomotor development index
PIQ	Performance intelligence quotient
PVL	Periventricular leucomalacia
SD	Standard deviation
SDS	Standard deviation score
VLBW	Very low birth-weight
VIQ	Verbal intelligence quotient
VMI	Visual motor integration

131.1 Introduction

Many reports and meta-analyses of reports on the cognitive development of very preterm or low birth weight infants in childhood have concluded that their Intelligence Quotients (IQ) are usually within the normal range, but approximately 0.5–1.0 SD below the mean of term infants at a similar age. Preterm infants may also show many specific developmental deficits in educational areas such as

R.W.I. Cooke (✉)
School of Reproductive and Developmental Medicine, University of Liverpool,
First Floor, University Department, Liverpool Women's Hospital,
Crown Street, Liverpool, L8 7SS, UK
e-mail: mc19@liv.ac.uk

reading, mathematics, writing, and speech, and show significant discrepancies between verbal and performance scores on IQ tests (Wolke and Meyer 1999). These deficits are seen most often in those children born preterm who are of lower weight and height and with a smaller head circumference. Most preterms with smaller heads in childhood were born with an OFC within the normal range, but have suffered postnatal growth failure. This growth failure is associated with the severity of neonatal illness, but is probably of nutritional origin. The human brain undergoes a growth spurt from about 25 weeks gestation to 18 months postnatally, and is particularly vulnerable to growth restriction at this time. Brief periods of restriction may be compensated for by catch-up growth, but longer periods may result in permanent deficits. Modern imaging techniques such as volumetric magnetic resonance imaging (MRI) have shown which parts of the brain are affected as the results of perinatal growth restriction. Improvements in nutritional management of the sick preterm infant are needed to prevent postnatal growth failure and its developmental consequences.

131.2 Developmental Outcomes in the Preterm Infant

With the improved survival of preterm infants following the introduction of neonatal intensive care several decades ago, came the increasing realization that their neurodevelopmental outcomes were often poorer than those of term infants, especially if they had suffered neonatal illness. Large controlled studies of preterm infants in later childhood have shown that at school age they experience a number of minor motor, cognitive, behavioral, and learning difficulties (Powls et al. 1995; Botting et al. 1997, 1998; Foulder-Hughes and Cooke 2003). Table 131.1 shows some of the differences in test scores between preterm infants and term controls at 7 years. These are often seen in conjunction with lower weight, height, and head circumference (Powls et al. 1996; Cooke and Foulder-Hughes 2003). These problems continue into adult life (Cooke 2004).

131.3 Tests Used to Assess Preterm Children at School Age

A wide range of tests are used to assess abilities in studies of preterm infants and for clinical purposes. Intelligence tests consist of a battery of timed subtests, roughly divided into two groups referred to as verbal and performance. The verbal tests involve understanding and memory tasks and together

Table 131.1 Comparative test results for preterm infants and term controls at 7 years (Foulder-Hughes and Cooke 2003)

Test	Preterm $n = 280$	Term controls $n = 210$	$p <$
M-ABC (<5%)	30.7%	6.7%	0.001
VMI (<85)	24.3%	8.1%	0.001
ADHD (Connors' >70)	8.9%	2.1%	0.001
VIQ (mean)	92.9	101.2	0.001
PIQ (mean)	87.8	99.6	0.001

This table shows the relative performance of 280 preterm infants and 210 term controls tested at the age of 7 years. The preterm infants perform significantly less well on all the tests, and show lower mean IQ scores

M-ABC Movement Assessment Battery for Children, *VMI* Berry test of visual motor integration, *ADHD* Connors' questionnaire for attention-deficit disorder, *VIQ* verbal intelligence quotient, *PIQ* performance intelligence quotient

give the verbal intelligence quotient (VIQ). The performance subtests involve pattern recognition and timed fine motor tasks, and as a group give the performance intelligence quotient (PIQ). All the subtest scores combined give the full intelligence quotient (FIQ). To derive the final score, the raw scores are adjusted for the subject's age and standardized to a mean of 100. Before the age of about 5–6 years, tests such as the Bayley Scales of Infant Development provide a similar sort of assessment with subtests for language or prelanguage and performance using simple tasks and puzzles. These when adjusted for age are standardized in a similar way to provide a mental and psychomotor developmental index. These are similar to VIQ and PIQ, but rather less language dependent for younger infants. To test for other aspects of development, motor skills are often tested using a test such as the M-ABC. This scores the child's performance on paper, ball, and balance skills and gives an impairment score, which is higher the less skilled the child is. A raw score of an age-standardized score can be given. The performance on the M-ABC overlaps some of the skills tested in the PIQ and PDI subtests.

131.4 Postnatal Growth Failure in the Preterm Infant

While the majority of preterm infants are born with a weight and head circumference appropriate for their gestation, it has long been recognized that early postnatal growth failure is a significant problem. Berry et al. (1997) described postnatal growth in a cohort of 109 infants with birth weights below 1,000 g. At birth, the cohort's mean weight was 94% of the mean intrauterine weight, but only 73% at 14 and 56 days. When initial clinical variables were examined, a positive correlation between energy intake over the first 56 days and protein intake over the first fortnight was seen. Duration of respiratory support and use of postnatal dexamethasone were negatively associated with postnatal growth rates. Using intensive feeding methods, they were able to improve growth from 14 to 56 days, but the infants had lost ground during the first 14 days. Clark, Thomas and Peabody (2003) also showed the extent of postnatal growth failure in a cohort of over 20,000 preterm infants from 124 US centers (Table 131.2).

Embleton et al. (2001) similarly showed the extent of growth failure in a group of 105 preterm infant of less than 34 weeks gestation. For the least mature infants (≤30 weeks), the energy deficits were 406 kcal/kg at 7 days and 813 kcal/kg at 5 weeks. Significant protein deficits were also shown and the mean weights at 5 weeks were −1.1 SD below the expected mean.

At the limits of viability, growth failure after birth becomes more marked and neurodisability more frequent. The Epicure study (Wood et al. 2000) reported on a large national cohort of infants at 23–25 weeks gestation. Half the cohort had a disability. Bayley-II scales gave mean scores of 84 on the MDI and 87 on the PDI, respectively, at 30 months. The mean OFC was 1.6 cm below the mean for the corrected age, and OFC was lower in those with disability. Even in those children without disability, 24% had an OFC more than 2 SD below the mean.

In a more recent NICHD Neonatal Research Network study, early growth was examined in a large cohort of infants with birth weights between 500 and 1,000 g (Ehrenkranz et al. 2006). The infants

Table 131.2 Percentage of infants by gestation with an OFC less than the 10th percentile for age at discharge from hospital

Gestation	23	24	25	26	27	28	29	30	31
OFC <10%	46	47	41	32	26	21	19	15	14

This table shows the marked effect of low gestational age at birth on the proportion of preterm infants having a very small head at discharge near term

OFC occipital-frontal head circumference

were divided into four quartiles based on weight gain velocity during initial hospitalization and by OFC growth velocity during the same period. The quartiles did not differ significantly by mean birth weight, gestation, intrauterine growth restriction, or sex. Weight gain in the highest quartile was 21 g/kg/day compared to 12 g/kg/day in the lowest. Although the proportion of those failing to regain their birth weight by 18 days was significantly higher in the lowest quartile, proven NEC, late onset sepsis, bronchopulmonary dysplasia (BPD), and postnatal steroid therapy were significantly more frequent in the lower quartiles, although only postnatal steroids remained significant in logistic regression analysis. Similar results were found for the four OFC velocity quartiles, with mean growth rate being 1.17 cm/week in the highest quartile and 0.67 cm/week in the lowest. At discharge 35% of the infants in the lowest quartile had an OFC less than the 10th percentile, compared to 16% in the highest. At between 18 and 22 months corrected age, survivors were assessed using the Bayley-II scales. Forty-four percent infants with an OFC in the lowest quartile had an MDI <70, compared with 22% in the highest. Similar results were shown for the PDI scores.

Other investigators have also reported the association between illness severity, postnatal head growth and subsequent neurodevelopmental outcome (Georgieff et al. 1985; Gross et al. 1983; Hack et al. 1989). While growth rates in hospital appear to be an independent risk factor for subsequent neurodisability, it remains unclear as to whether management practices or the illnesses themselves are responsible for undernutrition and growth failure.

131.5 Growth Restriction of the Developing Brain

The brain of the developing infant is highly vulnerable to the effects of growth restriction (Dobbing 1981). This is quite unlike the adult brain, which is almost immune to damage from even severe nutritional deficits. Growth restriction to the developing brain does not produce visible lesions as such, but has its effects in quantitative terms. Vulnerable periods are not the same as critical periods in brain growth, and the structures and processes affected are those developing at the time of the insult. Vulnerability is greatest at the time of the fastest growth, i.e. the time of the maximum growth spurt. Many developmental events in the brain may only have the opportunity to occur at defined times, and if they do not occur at the right time, that opportunity may be lost for ever. There is little opportunity for subsequent compensation.

Adult neuronal cell numbers are achieved early in brain development, when growth moves to glial multiplication (mainly oligodendroglial) in the first half of the growth spurt, and then myelination dominates in the second half. Myelination then continues at a slower rate for many years, with completion only in early adulthood. There are approximately eight times as many glial cells as neurons, but each neuron may have as many as 20,000 synapses. The first part of the growth spurt is concerned largely with dendritic growth and synaptic connectivity on which normal function depends.

Dobbing and Sands (1970, 1979) were able to use qualitative methods in animal and human brain to time the growth spurt. They used measurements of DNA, brain weight, and cholesterol as surrogates for neuronal tissue, brain size, and myelination. In human, the growth spurt begins at about 25 weeks gestation and continues until around 18 months post-term, with a peak velocity at term (40 weeks gestation). Only about one-sixth or less of the period of the human growth spurt is spent as a fetus, which may explain the relatively small effect of late fetal growth restriction on later development. If growth is restricted during the growth spurt for more than a short period, no catch-up is seen after the growth spurt is over, unlike the case with somatic growth where catch-up usually occurs. Undernutrition at this time does not alter the timing of cell multiplication, but only the height of the peak, producing a smaller brain. Some parts of the brain, e.g. the cerebellum, are particularly

vulnerable. In rats, it could be shown that smaller parts of the brain were associated with loss of cortical neurons and lipids (greater than that expected for brain size) and a marked reduction in synapse formation. During the human growth spurt of the brain, cellularity falls in the forebrain toward term but increases to beyond term in the cerebellum. Cell numbers continue to increase in the brain stem and cerebellum to around 2 years of age, while cholesterol (an indicator of myelination) continues to increase to 4 years and beyond.

At 10–18 weeks of fetal life, neuroblasts are forming neurons. Some loss of number of neurons may not be as important as loss of connectivity and synapse formation later. Neuronal multiplication is also not affected by maternal nutrition but only by later fetal growth restriction. Growth restriction in the neuronal multiplication stage does not allow catch-up growth, although this does tend to occur if the restriction happens later. Although the stages of brain growth are spoken of as if they occur serially, there is a great deal of overlap in their timing. Specific nutrient deficiencies have been suggested to be important, but the evidence for these is poor. An overall lack of fetal or neonatal nutrition generally is more likely to be responsible.

131.6 Magnetic Resonance Imaging Studies

Although the occipitofrontal head circumference is a good guide to brain weight in infants (Cooke et al. 1977), the availability of MRI in the last 2 decades has facilitated more detailed studies of poor brain growth in children born preterm. When overall brain size is considered, a study of 87 Very Low Birth-Weight (VLBW) children at 15–17 years showed an average reduction in coronal cross-sectional area of 7%, and of transverse section 12% (Cooke and Abernethy 1999). A similar study using volumetric analysis in 72 very preterm 15-year-old children showed broadly similar findings, with an average reduction in total brain volumes of 6%, but of 12% for the cortical gray matter volumes (Nosarti et al. 2002). Interestingly, the sex of the child appears to influence the degree of reduction in brain size. When gray and white matter volumes were estimated at 8 years in 65 very preterm children and compared with term controls, reduction in both were seen, but only statistically significant in males (Reiss et al. 2004). This may indicate that the sex of a preterm infant influences its response to perinatal adversity.

Improvements in quantitation of regional brain volumes have allowed more detailed studies to be made. Peterson et al. (2000) have published values for 25 preterm infants at 8 years compared with term controls. Reductions of 11–12% were seen in the premotor region, 14% for the sensorimotor and 7–10% for the mid-temporal region. Reductions in volume on the left and right sides of the brain were not symmetrical. Another study was able to separate gray and white matter volumes in different regions (Kesler et al. 2004). A total of 73 preterm and 33 term controls were examined at 7–11 years. MRI showed disproportionately enlarged parietal and frontal gray matter, but reduced temporal and subcortical gray matter volumes. Although statistically significant, the differences were small, ranging from 2% to 4%. The authors concluded that preterm birth may be associated with disorganized cortical development, possibly involving disrupted synaptic pruning and neural migration. Cerebral asymmetry has long been recognized, and may be seen as early as 20-week gestation. It has been associated with conditions such as autism and schizophrenia. It might be expected to be seen in preterm children with poor postnatal brain growth, but in a large study of 61 14-year-olds born at less than 30-week gestation, no significant differences were observed after controlling for confounding variables (Lancefield et al. 2006).

Although the cerebellum is important in motor coordination, often a problem in preterm children, it has been little studied with MRI until recently. In preterm children, reductions of 6–8% in volume

have been reported (Peterson et al.2000; Allin et al. 2001). A longitudinal MRI study with serial measurements of cerebellar volume of infants from 28 weeks to term showed a mean increase in cerebellar volume of 177% compared with 107% for total brain volume (Limperopoulos et al. 2005). This growth rate was seriously impaired by preterm birth even in the absence of cerebellar injury. At 15 years of age, Allin et al. (2005) showed a reduction in cerebellar volume in preterms compared with controls even after controlling for reduced overall brain volume. These reductions in lateral cerebellar volumes were associated with deficits in executive, visuospatial, and language function, while reductions in volume of the vermis were related to cognitive deficits.

The corpus callosum is responsible for most interhemispheric communication, and often shows lesions in preterms in the neonatal period and later. Most of these lesions relate to periventricular leucomalacia (PVL), and are seen as thinning, mainly of the posterior part (Stewart et al. 1999; Cooke and Abernethy 1999). Generalized reductions in cross-sectional area of different parts of the corpus callosum of 16–19% were also seen (Cooke and Abernethy 1999). A study using diffusion tensor imaging in 10-year-old preterms with attention deficit, looking at white matter integrity compared to that of term control children, showed changes that had not been compensated for by 10 years after birth (Nagy et al. 2003) (Figs. 131.1, 131.2, and 131.3).

The caudate nuclei are thought to be important in higher order motor control, learning, and memory, and many studies have shown associations between caudate volume and learning difficulties in children of school age. In preterms at 15–17 years, caudate volumes were 16–17% lower than in term controls (Abernethy et al. 2002). The reduction in volume though was of the same order as the reduction in overall brain size.

The hippocampus is important in memory and spatial navigation, and may change in size with time, increasing with use or decreasing in size with adverse experiences. A number of studies have

Fig. 131.1 A normal saggital cranial MRI scan at 15 years. The broad white c-shaped structure of the corpus callosum is easily seen

Fig. 131.2 A saggital cranial MRI of a preterm at 15 years with marked thinning of the corpus callosum. The structure of the corpus callosum can be seen to be markedly thinned at its middle and posterior part

tried to measure reductions in mean hippocampal volume in preterm children (Peterson et al. 2000; Isaacs et al. 2000, 2003; Nosarti et al. 2002; Abernethy et al. 2002). Because of its complex shape, volume measurements are difficult to make. Differences in these studies in hippocampal volumes between preterm children and controls mostly exceeded 10%.

The differences in brain size found on MRI are associated with the many neurodevelopmental deficits seen in preterm children, but caution is needed in their interpretation, as these associations may not always be causal. Major motor deficits are not uncommon in these high-risk children, and are mostly associated with PVL, although cerebral palsy may also be seen in the absence of gliosis and PVL, and simply decreased white matter volume.

Although cognitive deficits are often seen in association with cerebral palsy, they are also seen in preterms without motor deficit, and most commonly with the lowest gestation survivors. Characteristically the verbal IQ is less affected than the performance IQ. Peterson et al. (2000) showed correlations between full IQ and regional brain volumes ranging from 0.40 to 0.62 in children born very preterm. Similar significant correlations between IQ and cerebellar volumes in preterm children have been demonstrated (Allin et al. 2001). Hippocampal and caudate volumes are also seen to be reduced significantly in preterm children with low full IQ (Abernethy et al. 2002, 2004).

IQ is thought to be relatively stable over time in older children and adults, but a decline in preterm children has been described (Isaacs et al. 2004). Visible MRI abnormalities did not seem to relate to IQ, but voxel-based morphometry showed the full IQ scores to be related to areas in the parietal and temporal lobes. Decline in verbal IQ over time was associated with frontal and temporal lobe measurements, and performance IQ with the occipital and temporal lobes (including the hippocampus).

Fig. 131.3 An axial cranial
MRI of a preterm at 15 years
with ventriculomegally. The
enlargement of the cerebral
ventricles is due to cerebral
atrophy, and is strongly
associated with poorer motor
and cognitive performance in
later life
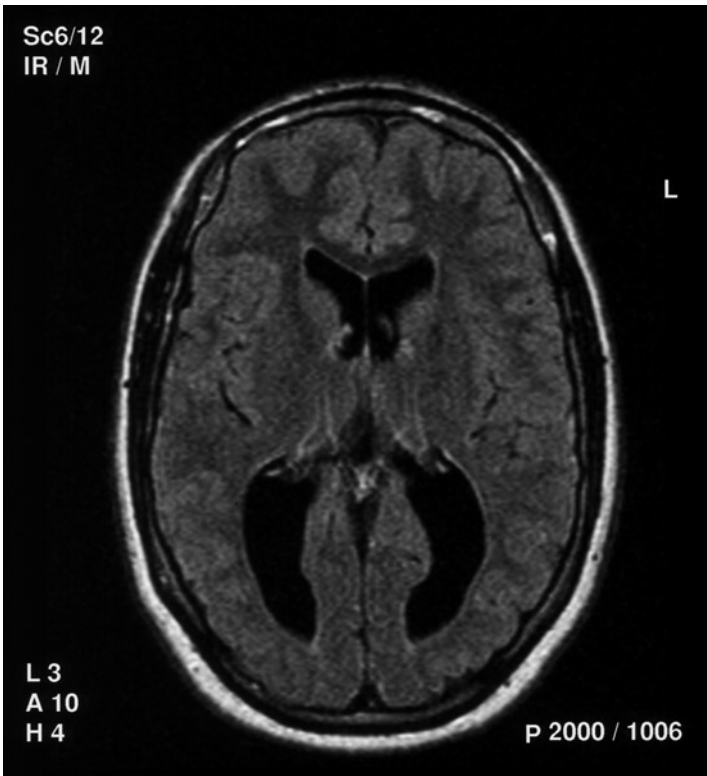
Table 131.3 Correlation between test scores and OFC at birth, OFC at 7 years and change in OFC from birth to 7 years (Foulder-Hughes and Cooke 2003)

	VMI	M-ABC	VIQ	PIQ	FIQ
OFC at birth (sds)	0.029	−0.075	0.046	−0.056	0.009
Change in OFC (sds)	0.096	−0.020	0.139	0.190[*]	0.184[*]
OFC at 7 years (sds)	0.232[**]	0.218[**]	0.252[**]	0.157[**]	0.236[**]

This table shows data on 280 preterm infants tested at 7 years, and shows that the head size at 7 is strongly correlated with all test results, but that head size at birth is not. Postnatal head growth rather than fetal head growth is a greater determinant of later high test scores

OFC occipitofrontal head circumference, *sds* standard deviation score, *VMI* Beery test of visual motor integration, *M-ABC* Movement Assessment Battery for Children, *VIQ* verbal intelligence quotient, *PIQ* performance intelligence quotient, *FIQ* full intelligence quotient

[*]$p < 0.05$, [**]$p < 0.001$

Minor motor impairments are common in preterm children and often called dyspraxia or developmental coordination disorder (Foulder-Hughes and Cooke 2003). Table 131.3 shows the correlations between impairment scores and IQ and OFC at birth, 7 years and as change in OFC between the two times. The most significant relationships are shown with current OFC. Many MRI findings have been associated with the condition, but probably not all causally. Interestingly enough cerebellar abnormalities and volumes do not seem to be associated (Allin et al. 2001). The most striking associations appear to be with reductions in the thickness of the corpus callosum. Using the Movement ABC (an impairment score), those preterm children with obvious corpus callosum thinning had an mean score of

20 compared to 7.75 for those without (Abernethy et al. 2004). Cross-sectional data confirm this association (Rademaker et al. 2004).

Preterm dyspraxia is associated with, and often complicated by other spatial and visuoperceptual problems (Foulder-Hughes and Cooke 2003). In a recent study involving preterm adolescents without visible lesions on MRI, a test was used to rate the subject's ability to judge angles, and this was compared with voxel-based morphometry of the cortical MRI. The test selected those with good and poor angular judgment. A highly significant difference was seen in the gray matter volume in the area of the right ventral extrastriate cortex, an area previously identified as associated with this skill (Isaacs et al. 2003). Rademaker et al. (2004) showed that the standardized results from the Beery Developmental Test of Visual Motor Integration (VMI) in a cohort of 7–8 year olds were associated with the cross-sectional area of the corpus callosum. The same test was used by Cooke and Foulder-Hughes (2003) when scores for preterm children were shown to be highly significantly correlated with OFC at 7 years, but not with the OFC at birth. Full IQ was similarly related.

131.7 Improving Nutrition and Effect on Outcomes

Over the years there have been very many reports of the effects of different feeding strategies on growth in the preterm newborn. Many of these have been small studies, concentrating mainly on short-term weight gain, and not considering head growth or long-term cognitive outcomes. Over 2 decades Lucas et al. (1984, 1989, 1990, 1998) have described both the early improvements in growth, and later cognitive outcome assessments in two major controlled feeding trials.

In the first of these (Lucas et al. 1984, 1989), preterm infants were randomized to be fed a special preterm formula or banked breast milk. If their own mother was providing breast milk, then the infant was randomized to be supplemented if required with preterm formula or banked breast milk. Although the formula had an energy content of 80 kcal/100 mL, the banked breast milk had an average energy content of 46 kcal/100 mL. Feeds were given at up to 180 mL/kg/day for formula and 200 mL/kg/day for banked breast milk. The intervention was continued until the infant was discharged or reached 2 kg in weight. Infants fed the special formula were the fastest to regain their birth weight, showed the fastest early growth rate (mean 18 g/kg/day), the greatest length gain (mean 1.4 mm/day), and the greatest gain in head circumference (1.6 mm/day).

The trial was extended, and a further report (Lucas et al. 1989) described the effects of type of feeding on early cognitive outcomes. The Knobloch Developmental Screening Test and a standardized neurological examination were performed at 9 months of age. No significant differences were seen in scores of infants fed formula or banked breast milk alone. In those where the formula or banked breast milk were given as a supplement to mother's own milk, a mean 4.9 point advantage for formula was seen, particularly when the formula made up more than 50% of the daily intake. One standard deviation (SD) for the score was 10 points.

Extensive use of banked breast milk for feeding preterm infants decreased as the effects of its low energy content became apparent. In a further study and follow-up study, Lucas et al. (1990, 1998) compared the effects of feeding a standard term formula and a special preterm formula to preterm infants. Infants whose mothers were supplying breast milk had term or preterm formula supplements if required. At 18 months, blind evaluation showed clear advantages to the special formula fed infants. The effects were seen mainly in motor performance, with a mean score 15 points higher, and 23 points higher in the subgroup who were small for dates. The SD for the score was 15. Significantly more infants fed the term formula had a developmental index below 85.

The participants in this trial were followed-up at 7–8 years, with a short form of the Wechsler intelligence scale for children. A major sex difference was seen in the effects of early diet on cognition. Preterm boys fed the term formula as sole diet had a mean 12-point disadvantage in verbal IQ. 47% of boys fed term formula had an IQ less than 85 compared to 13% for the preterm formula. There was also a significant excess of cases of cerebral palsy in the term formula fed infants. The latter finding suggested that suboptimal nutrition at a period of rapid brain growth may impair the ability to withstand the effects of early brain insult. It showed too that even a short period of suboptimal nutrition can have far reaching consequences, especially in males.

Wilson et al. (1997) conducted a randomized–controlled trial of early hyperalimentation in sick preterm infants with the main objective of reducing pulmonary morbidity. Both daily energy and nitrogen intake were increased in the intervention group between day 3 and 42. No differences were found in pulmonary or other neonatal morbidities, despite improvements in early growth parameters. Of interest was that the incidence of head circumference below the 3 rd percentile was 5% in the intervention group as against 16% in the standard fed controls.

In a secondary analysis of a large randomized trial of glutamine supplementation, Poindexter et al. (2006) examined the effect of early (before 5 days) or later amino acid administration in extremely low birth-weight infants. At 36 weeks postmenstrual age, there were significant differences in weight, length, and head circumference in favor of early amino acid administration. At 18 months corrected age, there were no differences in weight, length, or Bayley developmental test scores, although significantly more infants had a head circumference below the 10th or 5th percentile. Later assessments have not been reported, and the authors comment that the Bayley scales at 18 months may not reliably predict later cognitive ability.

In another study of early amino acid administration, a cohort of 117 VLBW hyperalimented infants were compared with 67 conservatively fed controls (Dinerstein et al. 2006). Significantly higher energy and nitrogen intakes were achieved during each of the first 4 weeks after birth. The intensively fed group had significantly higher weight, length, and head circumferences at term. Both groups still showed some infants with poor growth at term, and both groups had mean energy and nitrogen deficits in the first 4 weeks. No follow-up data were presented.

Although 150 mL/kg/day of a preterm formula has been said to be sufficient for normal growth in very preterm infants, in many clearly it is not. A trial comparing infants below 30-week gestation on target intakes of 150 against 200 mL/kg/day, showed higher weights and arm circumferences at 35 weeks postmenstrual age, but no differences in length or head circumference (Kuschel et al. 2000). At 1 year of age, there were no differences in any growth parameter. The study infants were not allocated to the different feeding amounts until they were already fully enterally fed, and also target feed volumes could be adjusted by the clinicians according to poor growth or intolerance. It is probable that the first 2–3 weeks after preterm birth are when postnatal growth failure becomes established.

Tan and Cooke (2008) conducted a randomized–controlled trial of hyperalimentation in 142 infants of less than 29-week gestation. The intervention group commenced parenteral nutrition with 20% more energy than standard, and 25% more protein. Eighty percent of the babies in the intervention group were still in deficit for energy and/or protein at the end of 4 weeks. In the study as a whole, 24% of those in deficit at 4 weeks had a head circumference of more than 2 sd below the mean at 36 weeks postmenstrual age, as opposed to none of those not in deficit. Surviving infants were followed-up with an MRI head at near term, and a Bayley developmental assessment at 3 and 9 months post-term (Tan et al. 2008). The total brain volume measured by MRI and the Bayley MDI and PDI at 3 months post-term were significantly correlated with energy deficit at 4 weeks. Head circumference and total brain volume were significantly correlated with MDI and PDI at 3 and 9 months. Thus, optimal nutrition in the first weeks after birth, if achievable, can be demonstrated to improve long-term cognitive ability in preterm infants.

131.8 Applications to Other Areas of Health and Disease

The area of nutrition and cognitive development in the preterm is a narrow one, but some of the principles may apply at other times in life. Although early nutritional deficits seem to have the most deleterious effects, the development of full cognitive ability occurs over many years. Nutritional deficits in later childhood may also play a role in later ability, but the deficits then may be more qualitative than quantitative. There is evidence that while older children are rarely underfed in developed countries, the quality of the food in nutritional terms may be inappropriate. The behavior as well as learning ability may be altered by quite subtle dietary manipulation.

Summary Points

- Preterm infants, particularly those born before 32 weeks of gestation, are likely to show behavioral, motor, and cognitive difficulties in later life.
- Poorer neurodevelopmental outcomes are often associated with poor postnatal growth, especially in the early weeks after birth.
- Poor postnatal growth may be due to a variety of perinatal factors and these include inadequate nutrition.
- The human brain undergoes a growth spurt in the weeks coming up to full term, which makes it more vulnerable than usual to injury from outside influences.
- MRI brain scans have been used to investigate poor brain growth in children born preterm, and have shown not only overall smaller brains but a variety of specific areas of poor growth, which in turn are associated with poor cognitive performance in childhood.
- Improving early nutrition in preterm infants has been shown to improve their brain growth.
- There is some evidence from controlled trials that intervening to improve nutrition and early brain growth improves cognitive outcomes in childhood, but these studies are quite old now and may not reflect current practice.
- There is an urgent need for further well-designed trials to investigate the value of improved early nutrition for very preterm infants.

Definitions and Explanations

Bronchopulmonary dysplasia: also known as chronic lung disease of prematurity, is a lung condition in preterm survivors, which follows mechanical ventilation for early respiratory distress. It results in these children requiring prolonged low-level oxygen supplementation, and in later wheezing. There is also often poor early growth related to increased needs and feeding difficulties.
Necrotizing enterocolitis: is a bowel disorder in preterm infants, which results in death of small areas in the intestine and frequent subsequent perforation of the gut. Its exact cause is unknown, but its importance is in that it occurs soon after preterm birth and results in major feeding difficulties and poor early growth.
Periventricular leukomalacia: is a lesion of the brain seen in very preterm infants as the result of previous brain injury. It is essentially a form of scar tissue, and is associated with later neurodevelopmental problems in most cases. It can be diagnosed in life using ultrasound or MRI scanning.

Growth spurt: is a term used to describe the period of maximum brain growth velocity in humans and animals. It occurs around term and is associated with increased vulnerability to insults such as poor nutrition.

The corpus callosum: is the largest white matter tract in the human brain and connects the right and left cerebral hemispheres. It is often affected in preterm infants by leukomalacia or generalized poor myelination in early infancy.

The caudate nuclei and the hippocampal nuclei: are often studied in children as there many functions include memory and spatial orientation, which are very important in learning. They are vulnerable to poor growth in sick preterm infants.

Dyspraxia: is a term used to describe clumsy, awkward, or inefficient motor movements in children. It is very common in children who were born preterm.

Visual motor integration: is the description of a test often used in children born preterm. It looks at their ability to copy by drawing a series of increasingly complex shapes. The score is standardized by age to a mean of 100.

Movement ABC: is a test for impairment of gross and fine motor movements in children. Eight simple tasks such as pencil and paper and ball skills are scored from 0 to 5 on the child's ability, high scores being for the poorest performance.

Key Points of Postnatal Brain Growth and Later Development in Preterms

The human brain is growing at its maximum velocity in the weeks coming up to full term, and as a result is at its most vulnerable at this time. If brain growth is restricted during this period, changes may occur, which are irreversible, and which may have lasting consequences for later cognition. There are many factors that may impair brain growth in preterm infants after birth, and these include chronic lung disease, cerebral hemorrhage and infarction, treatment with steroids, and poor nutrition. Attempts to improve nutrition in the weeks after preterm birth have resulted in better brain growth, but the evidence that this has improved later ability is still controversial.

References

Abernethy LJ, Palaniappan M, Cooke RW. Arch Dis Child. 2002;87:279–83.

Abernethy LJ, Cooke RW, Foulder-Hughes L. Pediatr Res. 2004;55:884–93.

Allin M, Matsumoto H, Santhouse AM, Nosarti C, Al-Asady MH, Stewart AL, Rifkin L, Murray RM. Brain 2001;124:60–6.

Allin M, Salaria S, Nosarti C, Wyatt J, Rifkin L, Murray RM. Neuroreport 2005;16:1821–24.

Berry MA, Abrahamowicz M, Usher RH. Pediatrics 1997;100:640–6.

Botting N, Powls A, Cooke RW, Marlow N. J Child Psychol Psychiatry. 1997;38:931–41.

Botting N, Powls A, Cooke RW, Marlow N. Dev Med Child Neurol. 1998;40:661–6.

Clark RH, Thomas P, Peabody J. Pediatrics 2003;111:986–90.

Cooke RW. Arch Dis Child. 2004;89:201–6.

Cooke RW, Abernethy LJ. Arch Dis Child Fetal Neonatal Ed. 1999;81:F116–21.

Cooke RW, Foulder-Hughes LA. Arch Dis Child. 2003;88:1–6.

Cooke RW, Lucas A, Yudkin PL, Pryse-Davies J. Early Hum Dev. 1977;1:145–9.

Dinerstein A, Nieto RM, Solana CL, Perez GP, Otheguy LE, Larguia AM. J Perinatology. 2006;26:436–42.

Dobbing J. In: Davis JA, Dobbing J, editors. Scientific foundations of paediatrics. 2nd ed. London: Heinemann; 1981. p. 744–59.

Dobbing J, Sands J. Nature 1970;226:639–40.

Dobbing J, Sands J. Early Hum Dev. 1979;3:79–83.

Embleton NE, Pang N, Cooke RJ. Pediatrics 2001;107:270–3.

Ehrenkranz RA, Dusick AM, Vohr BR, Wright LL, Wrage LA, Poole WK. Pediatrics 2006;117:1253–61.

Foulder-Hughes LA, Cooke RW. Dev Med Child Neurol. 2003;45:97–103.

Isaacs EB, Lucas A, Chong WK, Wood SJ, Johnson CL, Marshall C, Vargha-Khadem F, Gadian DG. Pediatr Res. 2000;47:713–20.

Isaacs EB, Edmonds CJ, Chong WK, Lucas A, Gadian DG. Ann Neurol. 2003a;53:768–73.

Isaacs EB, Vargha-Khadem F, Watkins KE, Lucas A, Mishkin M, Gadian DG. PNAS 2003b;1000:13060–3.

Isaacs EB, Edmonds CJ, Chong WK, Lucas A, Morley R, Gadian DG. Brain 2004;127:2595–607.

Kesler SR, Ment LR, Vohr B, Pajot SK, Schneider KC, Ebbitt TB, Duncan CC, Makuch RW, Reiss AL. Pediatr Neurol. 2004;31:318–25.

Kuschel CA, Evans N, Askie L, Bredemeyer S, Nash J, Polverino J. J Pediatr Child Health. 2000;36:581–6.

Lancefield K, Nosarti C, Rifkin L, Allin M, Sham P, Murray R. Brain Res. 2006;1093:33–40.

Limperopoulos C, Soul JS, Gauvreau K, Huppi PS, Warfield SK, Bassan H, Robertson RL, Volpe JJ, du Plessis AJ. Pediatrics 2005;115:688–95.

Lucas A, Gore SM, Cole TJ, Bamford MF, Dossetor JF, Barr I, Dicarlo L, Cork S Lucas PJ. Arch Dis Child. 1984;59:722–30.

Lucas A, Morley R, Cole TJ, Gore SM, Davis JA, Bamford MFM, Dossetor JFB. Arch Dis Child. 1989;64:1570–8.

Lucas A, Morley R, Cole TJ, Gore SM, Lucas PJ, Crowle P, Pearse R, Boon AJ, Powell R. Lancet 1990;335:1477–81.

Lucas A, Morley R, Cole TJ. BMJ 1998;317:1481–7.

Nagy Z, Westerberg H, Skare S, Andersson JL, Lilja A, Flodmark O, Fernell E, Holmberg K, Bohm B, Forssberg H, Lagercrantz H, Klingberg T. Pediatr Res. 2003;54:672–9.

Nosarti C, Al-Asady MH, Frangou S, Stewart AL, Rifkin L, Murray RM. Brain 2002;125:1616–23.

Peterson BS, Vohr B, Staib LH, Cannistraci CJ, Dolberg A, Schneider KC, Katz KH, Westerveld M, Sparrow S, Anderson AW, Duncan DC, Makuch RW, Gore JC, Ment LR. JAMA 2000;284:1939–47.

Poindexter BB, Langer JC, Dusick AM, Ehrenkranz RA. J Pediatr. 2006;148:300–5.

Powls A, Botting N, Cooke RW, Marlow N. Arch Dis Child. 1995;73:F62–6.

Powls A, Botting N, Cooke RW, Marlow N. Arch Dis Child. 1996;75:F152–7.

Rademaker KJ, Lam JN, Van Haastert IC, Uiterwaal CS, Lieftink AF, Groenendaal F, Grobbee DE, de Vries LS. Semin Perinatol. 2004;28:279–87.

Reiss AL, Kesler SR, Vohr B, Duncan CC, Katz KH, Pajot S, Schneider KC, Makuch RW, Ment LR. J Pediatr. 2004;145:242–9.

Stewart AL, Rifkin L, Amess PN, Kirkbride V, Townsend JP, Miller DH, Lewis SW, Kingsley DP, Mosley IF, Foster O, Murray RM. Lancet 1999;353:1653–7.

Tan MJ, Cooke RW. Arch Dis Child. 2008;93:F337–41.

Tan MJ, Abernethy L, Cooke RW. Arch Dis Child. 2008;93:F342–6.

Wilson DC, Cairns P, Halliday HL, Reid M, McClure G, Dodge JA. Arch Dis Child. 1997;77:F4–11.

Wolke D, Meyer R. Dev Med Child Neurol. 1999;41:94–109.

Wood NS, Marlow N, Costeloe K, Gibson AT, Wilkinson AR. N Eng J Med. 2000;343:378–84.

Chapter 132
Perinatal Undernutrition and Brain-Derived Neurotrophic Factor

Didier Vieau, Sylvain Mayeur, Marie-Amélie Lukaszewski, Fabien Delahave, Isabelle Dutriez-Casteloot, Christine Laborie, Sylvie Deloof, Jean Lesage, and Christophe Breton

Abbreviations

AD	Alzheimer Disease
AN	Anorexia Nervosa
BDNF	Brain-Derived Neurotrophic Factor
BN	Bulimia Nervosa
BrdU	Bromodeoxyuridine
CNS	Central Nervous System
DMH	Dorsomedial Hypothalamus
DOHAD	Developmental Origin of Health and Adult Diseases
E	Embryonic Day
FR50	50% Food Restriction
HD	Huntington Disease
HPA	Hypothalamo-Pituitary-Adrenal
kDa	Kilodalton
MPU	Maternal Perinatal Undernutrition
P	Postnatal Day
PC	Proprotein Convertase
PNS	Peripheral Nervous System
POMC	Proopiomelanocortin
P75^{NTR}	p75 Neurotrophin Receptor
SAS	Sympatho-Adrenal-System
TrkB	Tyrosine Kinase Receptor B
VMH	Ventromedial Hypothalamus

D. Vieau (✉)
Environment Périnatal et Croissance (EA4489), Equipe Dénutritions Maternelles Périnatales, Bâtiment SN4, 2ème étage, Université des Sciences et Technologies de Lille, 59655 Villeneuve d'Ascq, France
e-mail: didier.vieau@univ-lille1.fr

132.1 Introduction

Several data indicate that perinatal restriction of nutrients can modify morphological and functional maturation of the central nervous system (CNS). The short- and long-term consequences of this undernutrition are dependent upon specific time-windows that usually occur during the period of rapid brain growth that largely differs among species. As shown in Fig. 132.1, the major brain growth period in humans extends from the second trimester of gestation through the first 18–24 months of postnatal life. In rodents, it begins prenatally and peaks during the first 3 weeks after birth. It has been shown that in mice the first 3 weeks of postnatal life are crucial for the development of hypothalamic neuronal circuits regulating energy balance (for a review, see Bouret and Simerly 2006). Similarly, we have shown recently that a 50% decrease in maternal perinatal undernutrition (MPU) decreased the proopiomelanocortin (POMC, the precursor to α-MSH, a crucial anorexigenic neuropeptide) gene expression in the hypothalamus as well as in the nerve fiber projections from the arcuate nucleus-POMC neurons to the paraventricular nucleus in developing rats (Delahaye et al. 2008), indicating that MPU affects the development of hypothalamic neuronal circuitry. However, as specific brain regions have their own developmental "timetables," undernutrition could affect developmental events differently in the various parts of the brain before, and maybe after, the period of rapid brain growth. It is noteworthy that disturbances of the chronology of cellular and molecular events during this critical period may induce irreversible and long-lasting dysfunctions.

The pathophysiological mechanisms as well as molecules involved in the so-called "perinatal programming of adult diseases," or "developmental origin of health and adult diseases (DOHAD)" are still to be elucidated. However, there is compelling evidence showing that early undernutrition is frequently associated with altered perinatal growth and hypothalamo-pituitary-adrenal (HPA) axis
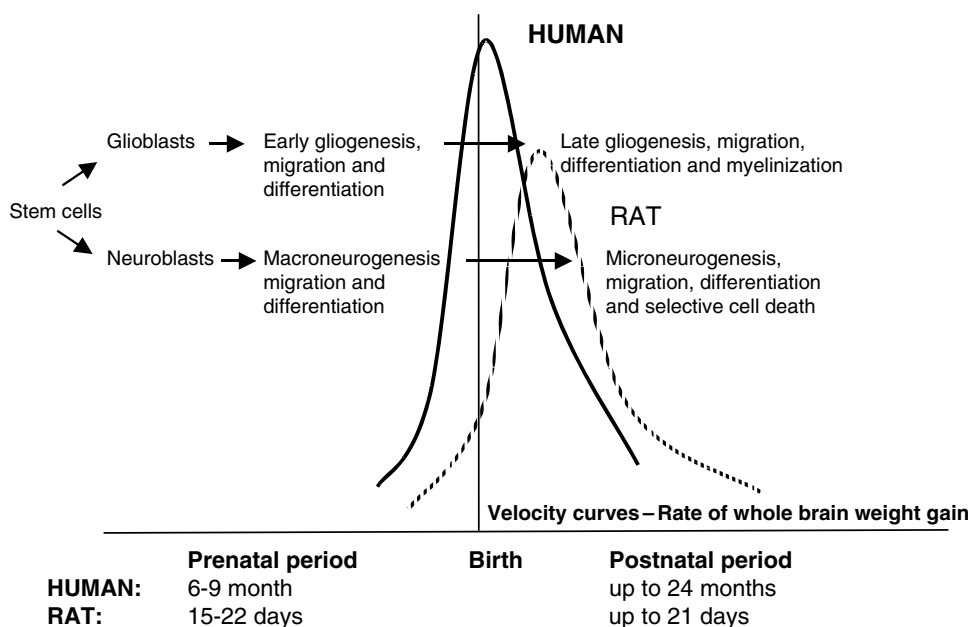
Fig. 132.1 Comparison of the periods of brain growth development in human and rat.
The velocity curves of the growth of human and rat CNS are indicated during the perinatal period. The major developmental cellular processes in man are also shown. Note the shift of events to early postnatal period in rats (Adapted from Lesage et al. 2006)

perturbations throughout a person's lifespan. Recent data have also shown that MPU alters the development of the sympatho-adrenal system (SAS) leading particularly to both morphological and functional disturbances of adrenal chromaffin cell. Together, these results suggest that MPU may program neuroendocrine stress systems whose regulation involves several CNS areas (for a review, see Lesage et al. 2006). The perinatal development and maturation of the CNS require numerous factors such as growth factors, i.e., neurotrophins. Among these latter molecules, brain-derived neurotrophic factor (BDNF) that has been originally isolated from porcine brain exhibits its highest concentration in the hippocampus and hypothalamus throughout the lifespan in rats (for review see Tapia-Arancibia et al. 2004). During early life, it influences almost all aspects of CNS development while, in adulthood, it is involved in several processes such as cellular proliferation, neuronal migration and survival, neuritogenesis, axonal and dendritic plasticity, synapse formation and efficacy, modulation of neurotransmitter, or neuropeptide synthesis and release (for review see Tapia-Arancibia et al. 2004). Interestingly, a close relationship between the nutritional status and BDNF level has been described. Conditional deletion of BDNF in the postnatal brain leads to obesity and disturbances of hypothalamic POMC gene expression (Rios et al. 2001). In addition, a selective depletion of BDNF in hypothalamic ventromedial (VMH) and dorsomedial (DMH) nuclei of adult mice leads to hyperphagia and obesity in adult mice (Unger et al. 2007). In humans, the functional loss of one copy of BDNF has been associated with severe obesity and impaired cognitive function, while a de novo mutation of tyrosine kinase receptor B (TrkB), the functional BDNF receptor, is associated with severe obesity and developmental delay (Yeo et al. 2004). Taken together, these data demonstrate that BDNF is an essential component of central mechanisms mediating development, satiety, and energetic status control. Although several studies have demonstrated that BDNF is very sensitive to diverse perinatal manipulations such as early ethanol exposure (Caldwell et al. 2008), fetal-neonatal iron deficiency (Tran et al. 2008), prenatal restraint stress (Burton et al. 2007), and opiate exposure (Schrott et al. 2008), little is known about the effects of maternal undernutrition on BDNF system in the offspring. The present chapter aims to explore the ways in which BDNF might participate in the programming of chronic adult diseases frequently observed in the offspring from undernourished mothers.

132.1.1 BDNF and Its Receptors

132.1.1.1 Biosynthesis, Structure, and Activity

Mature BDNF is a 14.5 kDa peptide that is generated by the proteolysis of a 32-kDa precursor molecule (pro-BDNF) within the regulated secretory pathway. Several lines of evidence indicate that the cleavage leading to mature BDNF is realized by enzymes belonging to the proprotein convertases (PCs) family such as furin or PC1 (Mowla et al. 2001). However, it has been shown that pro-BDNF is able to promote TrkB autophosphorylation suggesting that pro-BDNF is also biologically active (Mowla et al. 2001).

Most characterized biological effects of BDNF are mediated through the TrkB receptor (Fig. 132.2). BDNF binding to TrkB induces receptor dimerization, phosphorylation, and activation of the intracellular tyrosine kinase domain. These events initiate several complex intracellular signal transduction cascades, which subsequently induce biological responses. In addition to the full-length catalytic receptor (TrkB.FL), two truncated isoforms (TrkB.T1 and TrkB.T2) that are produced by alternative splicing of TrkB mRNA have been described in mammals (for review see Tapia-Arancibia et al. 2004) (Fig. 132.2). Although lacking the intracellular tyrosine kinase activity, the TrkB.T1 and TrkB.T2 forms are also biologically active since they trigger transduction signals that necessitate the
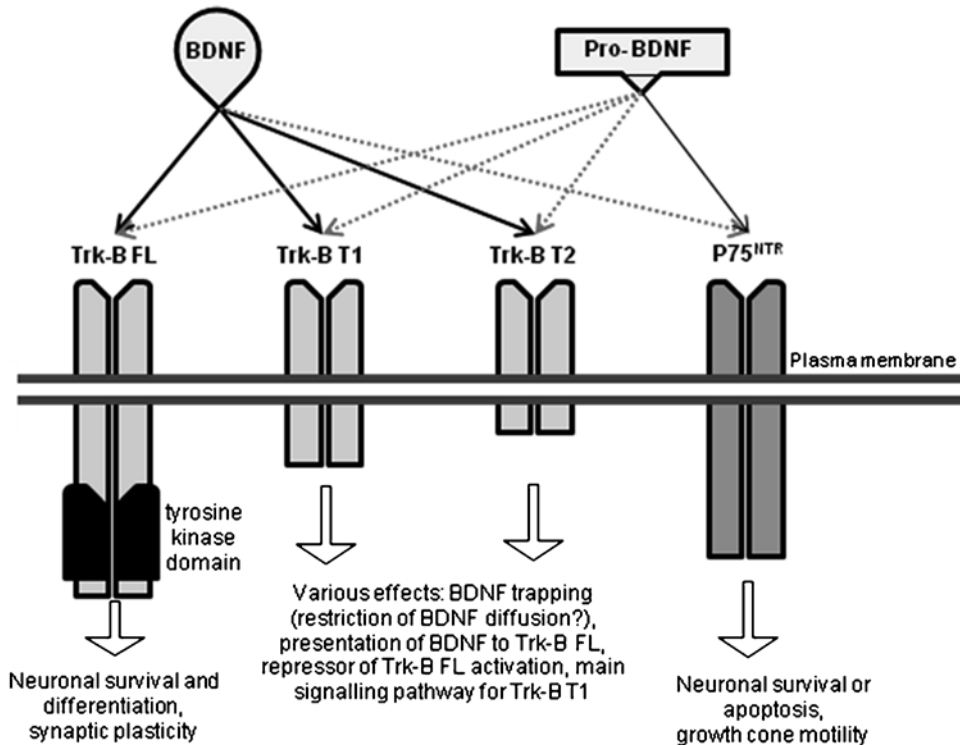
Fig. 132.2 Schematic representation of the major interactions of Pro-BDNF/BDNF with its receptors. Are illustrated the full-length (TrkB.FL), truncated (TrkB.T1 and TrkB.T2) TrkB and P75^NTR receptors in rodents. The binding capacity is indicated by solid (high) and dotted (low) lines, respectively. As indicated, Pro-BDNF is able to bind P75^NTR and TrkB receptors to a lesser extent. In contrast, BDNF binds preferentially TrkB receptors than P75^NTR. Other mature neurotrophins such as NT4 and NT3, in particular conditions, also recognize TrkB receptors. Major functions and cellular effects of receptors activation are indicated. For better clarity, interactions between P75^NTR and TrkB receptor isoforms are not indicated

presence of their short isoform-specific intracellular sequences. However, the physiological roles of TrkB.T1 and TrkB.T2 receptors remain unclear. It has been suggested that they may have at least two main functions, i.e., acting as ligand trapping molecules to regulate the local availability of neurotrophins or functioning as dominant negative receptors of neurotrophin responsiveness by heterodimerization. In addition, the p75 neurotrophin receptor (P75^NTR, Fig. 132.2) adds a new layer of complexity since it is able to bind pro-BDNF and to a lesser extent BDNF, to dimerize with TrkB isoforms and to exert specific biological activity such as cell death and functional impairment (Hennigan et al. 2007).

132.1.1.2 Tissue Distribution

In rat, BDNF mRNA is detected in numerous brain areas and in spinal cord, but also in several peripheral non-neuronal tissues such as the cardiorespiratory system, stomach, pituitary, skeletal muscle, and utero-feto-placental unit (Fig. 132.3). In human, a high gene expression has also been observed in spleen (Yamamoto et al. 1996).

The TrkB.FL and TrkB.T2 receptors display a similar tissue distribution in rat. Their mRNAs are restricted to CNS and to a limited number of peripheral organs such as adipose tissue or testis
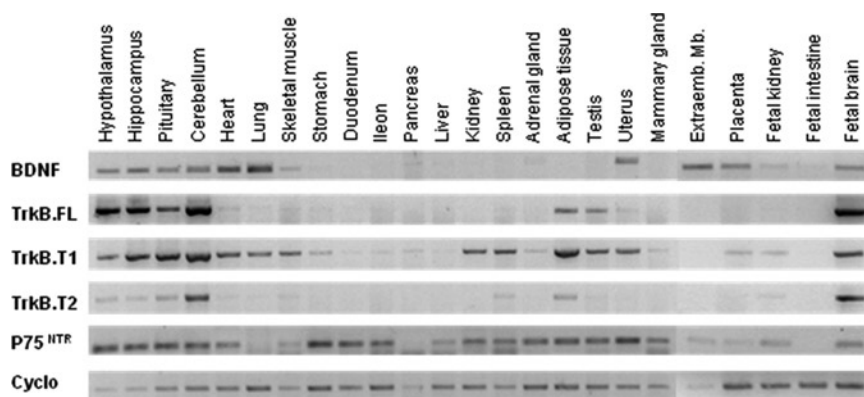
Fig. 132.3 Tissue distribution of BDNF and its receptors mRNAs in rat tissues. Tissue distribution of BDNF, full-length (TrkB.FL) and truncated (TrkB.T1 and TrkB.T2) TrkB, and P75^{NTR} receptors mRNAs determined by RT-PCR analysis in adult and feto-placental (at embryonic day 21, E21) rat tissues. Cyclophilin B (cyclo) was used as an internal control. *Extraemb. Mb*. Extraembryonic membranes. The size of the amplified products is 442 bp (BDNF), 557 bp (TrkB.FL), 563 bp (TrkB.T1), 550 bp (TrkB.T2), 106 bp (P75^{NTR}), and 456 bp (cyclo), respectively

(Fig. 132.3). In contrast, the TrkB.T1 isoform is widely distributed in both rat and human (Yamamoto et al. 1996; Fig. 132.3), with a lower synthesis in the digestive system. Although, it seems to be expressed at a lower level, the p75^{NTR} mRNA is detected in most of the tissues investigated (Fig. 132.3). These data indicate that BDNF should be implicated in many more physiological functions than initially suspected, in particular in peripheral tissues that have not all been demonstrated to be sensitive to this neurotrophin, so far.

132.1.2 Physiological Roles of BDNF

132.1.2.1 BDNF and Perinatal CNS Maturation

The so-called "neurotrophins hypothesis" states that some neuronal populations depend on exogenous neurotrophic factors for their survival, and that these factors are present in insufficient amounts to maintain all the neurons that have been initially generated during development. During early development, BDNF has been shown to influence almost all aspects of CNS maturation and neuronal functions (for review see Tapia-Arancibia et al. 2004). The ontogenesis of BDNF production has been studied in several brain areas of rat fetuses and neonates. For example, in the neocortex, it has been shown that BDNF protein progressively increased from embryonic day 21 (E21) until postnatal day (P) 14, and then progressively decreased (Das et al. 2001). Interestingly, the time-window of increased BDNF production corresponds to the period of maximal synaptogenesis that occurs between P11 and P20 in rat cortex. In the hippocampus, it has been reported that maximal BDNF immunoreactivity is observed between P7 and P21, with subtle discordances depending on the rat strain studied (Das et al. 2001; Silhol et al. 2005; Coupé et al. 2009; Fig. 132.4). We have recently published that the cellular proliferation level was dramatically increased from E21 to P15 in the hippocampal dentate gyrus indicating that BDNF may contribute to this phenomenon in this brain region (Coupé et al. 2009). In this line, it has been shown that early-weaned male mice (separated from their mothers at P14) showed decreased BDNF protein levels in the hippocampus associated with reduced cell proliferation in the dentate gyrus in adulthood (Kikusui and Mori 2009). In the

Fig. 132.4 Effect of
maternal undernutrition on
BDNF content in hippocampus
and hypothalamus of rat
neonates. Hypothalamic and
hippocampal BDNF protein
contents in developing rats
from mothers fed ad libitum
(C) or subjected to a 50%
food restriction during the
last week of gestation and
during lactation (FR50) have
been compared using ELISA.
E21 embryonic day 21, *P*
postnatal day. Statistical
analysis: *P* < 0.05; **P* <
0.01 FR50 *vs.* respective
control (Adapted from Coupé
et al. 2009)
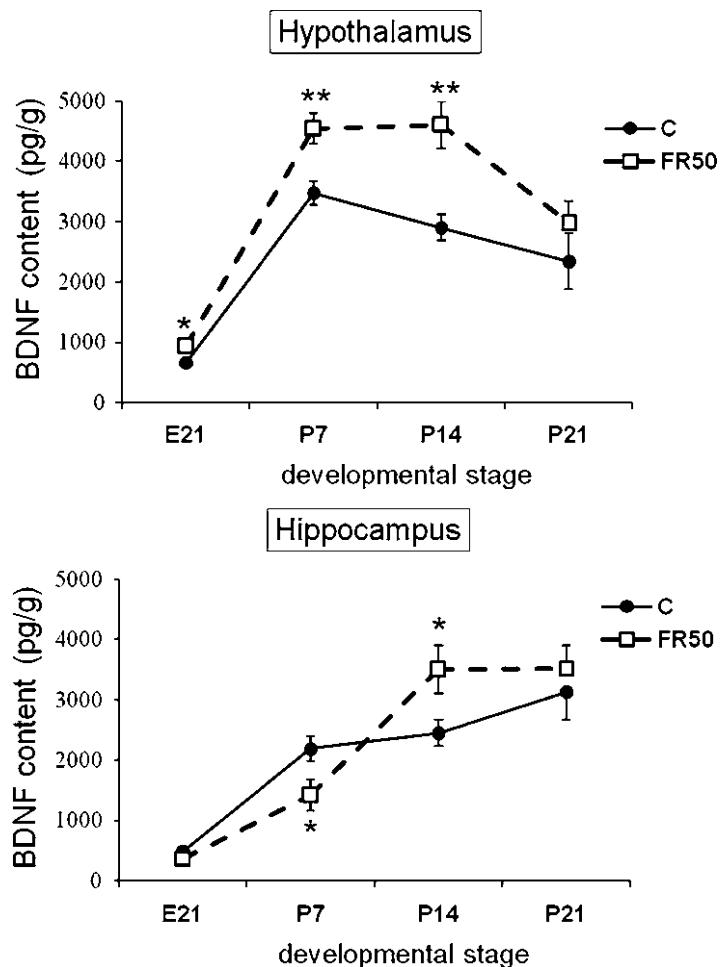
hypothalamus, it has also been demonstrated that BDNF protein levels are maximal during early lactation reaching a maximal value as soon as P7 (Silhol et al. 2005; Coupé et al. 2009; Fig. 132.4). Finally, a peak of BDNF mRNA was described in the VMH of P4 rats suggesting that this neurotrophin may contribute to the neuronal organization and functional development of this hypothalamic nucleus involved in the regulation of satiety (Sugiyama et al. 2003). Altogether, these data indicate that, in rodent, CNS BDNF protein concentration is maximal during lactation, which corresponds to the period of rapid brain growth (Fig. 132.1), to the settle of several nervous and neuroendocrine axes, and to the modification of plasma levels of hormones involved in the regulation of metabolism such as leptin, insulin, and glucocorticoids.

132.1.2.2 Role in Adult CNS

BDNF plays a major role in regulating the survival, growth, and differentiation of new neurons during early neural development, as well as maintaining neuronal populations and connections later in life in many different species. This neurotrophin and its receptor TrkB are indeed present in the adult mammalian cerebellum, cortex, hippocampus, hypothalamus (Fig. 132.3), midbrain, and spinal cord,

areas that exert numerous vital functions, in neurons as well as in glial cells. For example, BDNF infusion into the rat lateral ventricle leads to cell proliferation in the adult brain parenchyma (Pencea et al. 2001), demonstrating that BDNF is involved in the recruitment and/or generation of new cells to replace others, lost after injury or diseases.

BDNF has been proposed as a key regulator and mediator of long-term synaptic modifications related to learning and memory maintenance. The neurotrophin is involved in translating the activity signal into synaptic plasticity changes. BDNF is necessary and sufficient to induce long-lasting structural changes at the dendritic spines whose enlargement could be blocked by inhibiting protein synthesis. In addition to its classical long-lasting effects, BDNF has also been shown to exert acute effects both on synaptic transmission, possibly involved in the induction of long-term potentiation, and on membrane conductance influencing neuronal excitability and synaptic plasticity (Bouvier et al. 2006).

Data suggest a link between BDNF and respiratory control (Bouvier et al. 2006). Genetic inactivation of BDNF has been shown to induce severe respiratory disturbances and alterations in central respiration-related structures, leading to the death of mutant mice by 3 weeks of age. These animals also exhibited a significant reduction of the central respiratory frequency and an increase in the respiratory cycle variability. BDNF indeed enhances glutamatergic synaptic strength between respiratory neurons, which is in line with the fact that generation of the respiratory rhythm mainly relies on excitatory glutamatergic connections.

BDNF and its receptors are expressed in several hypothalamic and hindbrain nuclei involved in regulating energy homeostasis, in the developing and mature rat brain. In adult mice, selective deletion of BDNF in the VMH and DMH results in hyperphagic behavior and obesity (Unger et al. 2007). By contrast, infusion of BDNF into the brain of mature rats significantly reduces food intake (Lapchak and Hefti 1992). Central BDNF acts as downstream effector through which melanocortin receptor 4 (MC4R) signaling regulates energy balance. Thus, these data indicate that BDNF is a pivotal element in the regulation of energy homeostasis in the adult brain and that its secretion from the VMH and/or the DMH is required for normal appetite control.

In adult rat, BDNF has also been reported to play a role in plasticity processes related to the stress response (Rage et al. 2002), as well as in the specific guidance cue for dopaminergic neurons from the periventricular nucleus to the pars intermedia of the pituitary (Nakakura et al. 2007), suggesting that it could participate to the modulation of neuroendocrine systems.

132.1.2.3 Peripheral Functions

As indicated by the mRNA expression of pro-BDNF and its receptors outside CNS (Fig. 132.3), BDNF exerts several roles in peripheral tissues. It is involved in the activity of the peripheral nervous system (PNS) and is a key mediator of mechanisms regulating activity-dependent synaptic maturation and plasticity. Recently, BDNF has been shown to be expressed by first-order baroreceptor neurons (Martin et al. 2009). It is thus a likely mediator of both developmental and postdevelopmental modifications associated to functional characteristics of the arterial baroreceptor reflex changes throughout ontogenesis, including perinatal adjustments of the reflex gain and adult resetting during hypertension.

BDNF has been shown to be implicated in the control of peripheral respiration-related structures, since in BDNF-deficient mice the peripheral chemoafferent pathway is affected. BDNF is indeed required for survival of chemoafferent sensory neurons in petrosal and nodose ganglia that innervate the chemoreceptors in the carotid body which in turn provides chemosensory inputs on central respiratory circuits in the hindbrain (Bouvier et al. 2006).

There is growing evidence that BDNF also plays a role in gut function. BDNF, TrkB, and p75[NTR] receptors are expressed in the enteric nervous system and gut mucosa of a variety of species, including

man. For example, BDNF has been shown to be involved in the peristaltic reflex of the rat colon by increasing the release of serotonin and calcitonin gene-related peptide in response to mucosal stroking. Recent data reported that BDNF enhanced neuronal responsiveness to neurotransmitters such as serotonin and substance P suggesting that the promotion of motility by BDNF could result from its potent modulating role on enteric neuronal activity and synaptic communication (Boesmans et al. 2008).

BDNF ameliorates and normalizes glucose metabolism in obese diabetic C57BL/KsJ db/db mice (Nagakawa et al. 2000). It also enhances glucose utilization in muscle and in brown adipose tissue (Yamanaka et al. 2007a). The antidiabetic effect of BDNF, which is dependent on plasma insulin levels, modifies insulin signaling in peripheral tissues (Yamanaka et al. 2007b).

The wide expression of BDNF and/or its receptors in non-neuronal tissues (Fig. 132.3) suggests that it could exert numerous physiological functions remaining to be discovered. In this line, recent data have suggested putative roles for neurotrophins in the regulation of proliferation and survival of testicular germ cells and peritubular cells (Robinson et al. 2009).

132.1.3 BDNF and Maternal Perinatal Undernutrition

132.1.3.1 Short-Term Defects

Although it has been demonstrated that maternal stress decreased BDNF content in the olfactory bulb and hippocampus of both P1 and P5 male rat neonates (Van den Hove et al. 2006), few studies have explored the short-term consequences of maternal nutritional challenges on BDNF levels in the offspring. It has been shown that a 70% protein restriction from day eight of pregnancy until 4 weeks after birth reduced both body and brain weight as well as BDNF concentration in the hippocampus of P28 rats and was associated with impaired learning and memory ability (Wang and Xu 2007). However, this study did not provide a detailed kinetic analysis of maternal protein restriction on BDNF concentration in the offspring during the critical developmental windows corresponding to the period of maximal CNS growth velocity (Fig. 132.1). Given the critical role that BDNF plays during CNS development, we speculated that a 50% maternal food restriction (FR50) performed from E14 to P21, would modify the time course production of hippocampal and hypothalamic BDNF levels in E21, P7, P14, and P21 developing rats.

We showed that MPU modulates BDNF expression differentially in both hippocampus and hypothalamus in an age-specific manner, demonstrating that BDNF level in offspring is very sensitive to the maternal nutritional status (Coupé et al. 2009). Indeed, whereas FR50 rats displayed an augmented hypothalamic BDNF content during 2 weeks, i.e., from E21 to P14, BDNF concentration in the hippocampus, was firstly reduced at P7 and then increased at P14 (Fig. 132.4). We also observed that the hypothalamic gene expression of the truncated neuronal BDNF receptor (TrkB.T2) was augmented in FR50 rats at P14 suggesting that MPU, through both altered neuronal receptor availability and BDNF level, may compromise the neurotrophic BDNF/TrkB pathway during the perinatal life. In this study, we also analyzed the effects of MPU on the hippocampal and hypothalamic cell proliferation in the offspring, using bromodeoxyuridine (BrdU) incorporation. Interestingly, the increased concentration of BDNF observed in the FR50 hypothalamus at P7 and in the hippocampus at P14, respectively, was correlated to an augmented BrdU incorporation when compared to controls (Fig. 132.5). Together, our results reinforce the idea that BDNF plays a crucial role during the critical time-windows of rat CNS development. In addition, since MPU increases both BDNF concentration as well as cell proliferation during these stages, one could speculate that these mechanisms are part of a physiological compensatory system to maintain the CNS maturation and development even

Fig. 132.5 Effect of maternal undernutrition on cell proliferation in hippocampus and hypothalamus of rat neonates. Quantification of the amount of cell proliferation (revealed by BrdU immunoreactivity and expressed as percent of cells versus controls) in several regions of the hypothalamus (at P8) and of the hippocampus (at P15) in developing rats from mothers fed ad libitum (C) or subjected to a 50% food restriction during the last week of gestation and during lactation (FR50). *E21* embryonic day 21; *P* postnatal day; *CA* cornu ammon, *DG* dentate gyrus, *PVN* paraventricular nucleus, *VMH* ventromedial hypothalamic nucleus, *Arc* arcuate nucleus, *SE* subependymal area, *ME* median eminence. *P < 0.05; **P < 0.01; ***P < 0.001 FR50 vs. C (Adapted from Coupé et al. 2009)
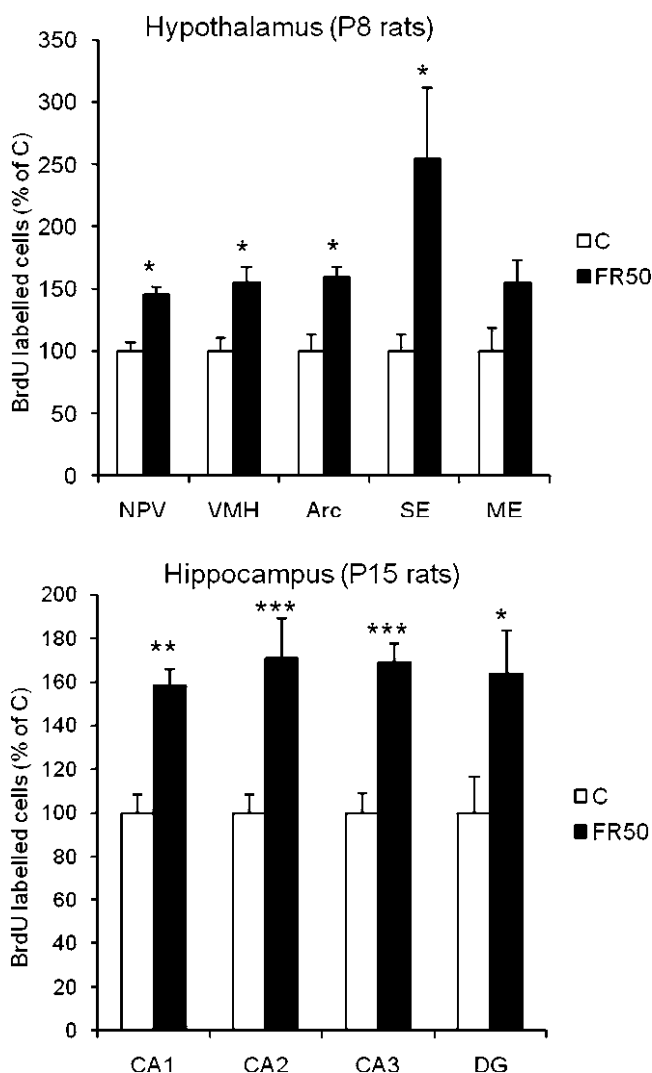
under subnutritional conditions. However, our data indicate that the time course of BDNF production and cell proliferation is modified by MPU, at a time during which an intense establishment of hypothalamic neural circuits occurs (for review see Bouret and Simerly 2006), suggesting that these perturbations may have long-lasting consequences.

132.1.3.2 Long-Term Consequences

Several studies performed both in humans and in animals have demonstrated that maternal malnutrition alters various maturational events in the brain resulting in modifications of behavior, cognition, learning, and memory that extend into the postnatal period and continue into adulthood. Surprisingly, to our knowledge, only one paper has reported the effects of a 70% maternal protein restriction throughout pregnancy on brain BDNF concentration in the adult male rat. In this recent study, it has been shown that 55- to 60-day-old animals from malnourished mothers exhibited impaired long-term

synaptic potentiation associated with a decreased expression of BDNF in the entorhinal cortex (Hernandez et al. 2008). Interestingly, perinatal undernutrition has been shown to alter several physiological functions that may be mediated by the BDNF/TrkB pathway. For example, perinatal malnutrition exposure reduces hippocampal and cognitive functions (Gomez-Pinilla and Vaynman 2005) has long-term effects on hypothalamic neural circuits regulating energy expenditure (Breton et al. 2009) and promotes the development of metabolic dysfunctions such as intolerance to glucose, altered feeding behavior, or obesity (Vickers et al. 2000; Breton et al. 2009). Accordingly, it has been reported that heterozygous BDNF$^{+/-}$ mice exhibit increased locomotor activity, hyperphagia, obesity, and disturbed insulin levels (Lyons et al. 1999; Rios et al. 2001). In this line, it has been reported recently that adult male rat from mothers that have been prenatally stressed present alterations of hippocampal BDNF levels, increased anxiety-like behavior (Zuena et al. 2008) as well as hyperphagia, glucose intolerance, and hyperglycemia when they get older (Lesage et al. 2004). Taken together, these data strongly suggest that MPU could induce long-term modifications of the BDNF/TrkB system in the offspring, which may in turn participate to the programming of chronic adult diseases frequently observed in children from undernourished mothers (for review see Barker 2006).

132.1.4 BDNF and Programming of Adult Diseases

132.1.4.1 BDNF Alterations in Adult Diseases

As already mentioned, BDNF signaling is a key factor in the regulation of energy balance, body weight, and glucose metabolism. In humans, the decreased brain levels of BDNF detected in Alzheimer's disease (AD), dementia such as schizophrenia, and depression were often associated with metabolic syndrome features such as type 2 diabetes (Krabbe et al. 2007). In addition, variation of BDNF plasma level, whose source remains to be established, as well as genetic alterations in the genes encoding BDNF or TrkB have been correlated to eating disorders. On the one hand, it has been shown that BDNF plasma concentration is significantly reduced in female patients with anorexia nervosa (AN) or bulimia nervosa (BN) and significantly increased in obese women, suggesting that its circulating level is indeed positively correlated with the subject's body mass index (Monteleone et al. 2005). On the other hand, several mutations of the BDNF and TrkB encoding genes have been described in human patients with AN or BN as well as obesity (Ribasés et al. 2003). In addition, high level of circulating BDNF has been associated with impaired glucose metabolism in obese type 2 diabetic patients whereas the serum BDNF concentration was found to significantly decrease in diabetic patients independently of obesity, thus being a potential marker of type 2 diabetes (Krabbe et al. 2007).

As previously noted, central BDNF signaling plays an important role in neuronal differentiation, growth, survival, neurotransmission modulation, and synaptic plasticity. This neurotrophin has recently emerged as one of the most important molecule for the impaired nervous system diseases exhibiting severe motor control deficiencies. Indeed, neurological diseases are highly correlated with dysregulation of BDNF signaling pathways leading to long-term gene transcription modifications. In addition, genetic studies have shown potential association of most of the neurodegenerative diseases with polymorphisms in the BDNF and/or their receptor genes (Hu et al. 2008). First, reduced mRNA expression of BDNF and increased truncated form of TrkB mRNAs and proteins were observed in the brain of AD patients. Recently, it has been shown that BDNF may prevent and reverse AD (Nagahara et al. 2009). Second, reduced BDNF production has been observed in the dopaminergic neurons of the substantia nigra that are the neuronal group most severely degenerated in the Parkinson's disease. Third, reduced BDNF and TrkB levels have been observed in the striatum of

Huntington's disease (HD) and in neural cell models of HD (Ginés et al. 2006). In addition, decreased expression of BDNF mRNAs and hippocampal volumes are observed in several rat models of depression. Although mechanisms of action are far from clear, BDNF downregulation can be prevented by treatment with antidepressants and increase in BDNF levels or TrkB signaling produces an antidepressive effect. Finally, BDNF upregulation is associated with seizure activity suggesting that it may play a role in epileptogenesis (Hu et al. 2008). Together, these data strongly suggest that BDNF could constitute a missing link between metabolic and neurodegenerative diseases that could, at least in part, both originate from perinatal alterations.

132.1.4.2 Putative Perinatal Mechanisms

Several lines of evidence indicate that embryonic and early postnatal stages are critical for the adequate development of the offspring and that deleterious exposure to several environmental factors, during these critical periods, could lead to severe physiological and metabolic alterations in adulthood. Since BDNF is very sensitive to diverse perinatal manipulations, it is suspected to be associated with increased risk for neurodevelopmental disorders that provoke learning and/or behavioral deficits. In addition, BDNF acts as an anorexigenic factor, and there is a close relationship between nutritional status and BDNF plasma concentration. It is therefore not surprising that maternal BDNF plasma levels decrease dramatically during pregnancy in order to fulfill both maternal and fetal nutrient needs (Lommatzsch et al. 2006). However, the long-term consequences of BDNF perinatal variations on the development of adult diseases remain unexplained. Interestingly, it has been reported recently that injection of recombinant BDNF protein into wild-type pregnant mice carrying E14.5 embryos leads to a dose-dependent elevation of BDNF protein levels in fetal brains (Kodomari et al. 2009). In addition, the authors also demonstrated that around E14, BDNF concentrations in the fetal brain of BDNF homozygous null mutant were comparable to the levels detected in wild-type fetuses. These findings suggest that maternal BDNF reaches the fetal brain through utero-placental barrier and thus could contribute to its development. Since, placenta and extraembryonic membranes also express the BDNF gene (Fig. 132.3) one could speculate that modifications of maternal and/or placental BDNF production might play an important role on the development of brain and other BDNF-sensitive peripheral tissues in the fetus (Fig. 132.6). In this line, prenatal environmental perturbations such as maternal undernutrition might impede BDNF plasma levels in mothers and/or in placenta, and thus could participate to the programming of adult diseases (cognitive and neurodegenerative diseases, metabolic syndrome) usually observed in offspring from prenatally stressed mothers (Fig. 132.6). We cannot exclude that perturbations of fetal BDNF production could also participate to the development of adult diseases since several fetal tissues also express the BDNF gene (Fig. 132.3).

132.2 Conclusion and Perspectives

BDNF is very sensitive to diverse environmental perturbations during critical windows of the fetal development. It participates to the development and the maturation of the CNS and exerts several metabolic functions, constituting thus a putative missing link between neurodegenerative diseases and metabolic syndrome that could result from insults during perinatal life. In addition, BDNF and its receptors mRNAs are widely expressed in adult and fetal tissues suggesting that BDNF system dysfunctions during early development might have more consequences than initially suspected. Future studies will be necessary to unravel to what extent modifications of this system, using for
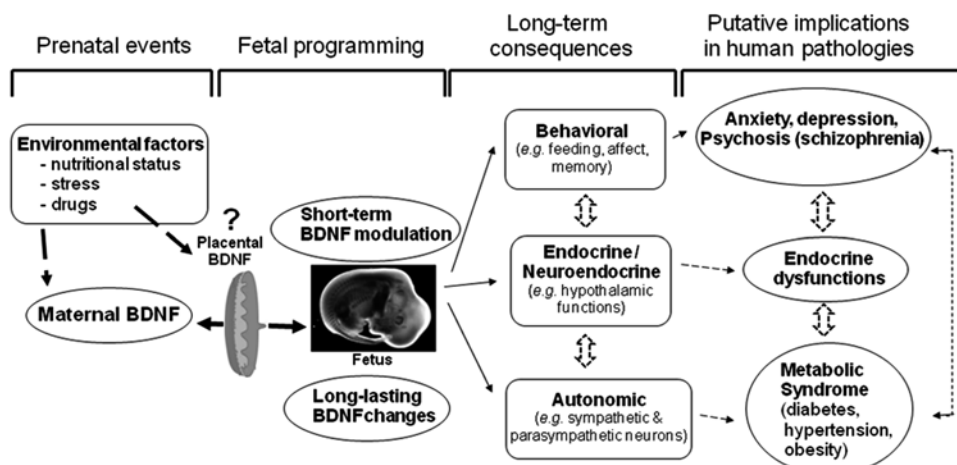
Fig. 132.6 Perinatal BDNF and programming of adult diseases. Hypothetical mechanism showing how early BDNF dysfunctions might participate in the development of chronic adult diseases. A modulation of maternal and/or placental and fetal BDNF production induced by the maternal nutritional status (or other perinatal environmental factors) could modify the development of several tissues during critical time-windows

example mutant mice, might compromise the development of several tissues and physiological functions. Finally, since it has been shown that BDNF is able to cross the utero-placental barrier, interventions such as nutritional diet or moderate exercise that have been shown to increase BDNF plasma levels (Chang et al. 2008) may constitute an alternate therapeutic option for preventing "programmed" diseases.

Summary Points

- Maternal perinatal undernutrition (MPU) sensitizes the offspring to the development of chronic adult diseases such as the metabolic syndrome (type 2 diabetes, hypertension, and obesity).
- Brain structures such as hippocampus and hypothalamus are very sensitive to environmental perturbations during the perinatal life.
- BDNF plays an important role in the functional maturation of both hippocampus and hypothalamus.
- MPU modifies the time-course production of BDNF in the brain of rat neonates.
- MPU affects the development of hypothalamic circuitry involved in the regulation of energy homeostasis in the male rat neonate.

Key Facts of BDNF

1. BDNF has been originally isolated from brain, which constitutes its principal site of production.
2. In the brain, BDNF is involved in several processes such as maturation of the CNS, cellular proliferation, neuronal migration and survival, synapse formation, axonal and dendritic plasticity.
3. BDNF also modulates the synthesis and secretion of several neurotransmitters and neuropeptides and exerts a marked anorexigenic effect.

---

4. BDNF and its receptors are also present in several peripheral tissues where they should exert diverse physiological functions.
5. BDNF concentration is very sensitive to perinatal environment.
6. BDNF levels are altered in patients suffering from brain pathologies (Alzheimer and Parkinson diseases, schizophrenia) that are frequently associated with metabolic syndrome features (obesity, hypertension, type 2 diabetes).
7. BDNF protein is able to cross the utero-placental unit.

Key Terms

Perinatal: Refers to a period of time covering both fetal (prenatal) and early postnatal life.
Programming of adult diseases: Hypothesis speculating that perinatal environmental perturbations, such as undernutrition, infection, psychological stress, gestational diabetes, or other insults, may sensitize the individual to the development of several diseases (including diabetes, obesity, hypertension, depression, and schizophrenia) in adulthood.
Hippocampus: Brain region that is a part of the limbic system, playing a major role in learning and memory processes.
Hypothalamus: Brain region that is involved in the control of almost all the neuroendocrine axes, playing a crucial role in the energy homeostasis since it contains several orexigenic and anorexigenic peptides.
Bromodeoxyuridine: Synthetic nucleoside that is an analogue of thymidine. It is a substitute to thymidine during DNA replication and thus allows the detection of proliferating cells in living tissues.

References

Barker DJ. Clin Obstet Gynecol. 2006;49:270–83.
Boesmans W, Gomes P, Janssens J, Tack J, Vanden Berghe P. Gut. 2008;57:314–22.
Bouret SG, Simerly RB. Clin Genet. 2006;70:295–301.
Bouvier J, Autran S, Fortin G, Champagnat J, Thoby-Brisson M. J Physiol. 2006;100:290–6.
Breton C, Lukaszewski MA, Risold PY, Enache M, Guillemot J, Rivière G, Delahaye F, Lesage J, Dutriez-Casteloot I, Laborie C, Vieau D. Am J Physiol Endocrinol Metab. 2009;296:E462-72.
Burton CL, Chatterjee D, Chatterjee-Chakraborty M, Lovic V, Grella SL, Steiner M, Fleming AS. Brain Res. 2007;1158:28–38.
Caldwell KK, Sheema S, Paz RD, Samudio-Ruiz SL, Laughlin MH, Spence NE, Roehlk MJ, Alcon SN, Allan AM. Pharmacol Biochem Behav. 2008;90:614–24.
Chang KL, Tong KY, Yip SP. Neurosci Lett. 2008;447:124–8.
Coupé B, Dutriez-Casteloot I, Breton C, Lefèvre F, Mairesse J, Dickes-Coopman A, Silhol M, Tapia-Aranciabia L, Lesage J, Vieau D. J Neuroendocrinol. 2009;21:40–8.
Das KP, Chao SL, White LD, Haines WT, Harry GJ, Tilson HA, Barone S. Neuroscience. 2001;103:739–61.
Delahaye F, Breton C, Risold PY, Enache M, Dutriez-Casteloot I, Laborie C, Lesage J, Vieau D. Endocrinology. 2008;149:470–5.
Ginés S, Bosch M, Marco S, Gavaldà N, Díaz-Hernández M, Lucas JJ, Canals JM, Alberch J. Eur J Neurosci. 2006;23:649–58.

Gomez-Pinilla F, Vaynman S. Exp Neurol. 2005;192:235–43.

Hennigan A, O'Callaghan RM, Kelly AM. Biochem Soc Trans. 2007;35:424–7.

Hernandez A, Burgos H, Mondaca M, Barra R, Nunez H, Perez H, Soto-Moyano R, Sierralta W, Fernandez V, Olivares A, Valladares L. Neural Plast. 2008;646–919.

Hu Y, Russek SJ. J Neurochem. 2008;105:1–17.

Kikusui T, Mori Y. J Neuroendocrinol. 2009;21:427–31.

Kodomari I, Wada E, Nakamura S, Wada K. Neurochem Int. 2009;54:95–8.

Krabbe KS, Nielsen AR, Krogh-Madsen R, Plomgaard P, Rasmussen P, Erikstrup C, Fischer CP, Lindegaard B, Petersen AM, Taudorf S, Secher NH, Pilegaard H, Bruunsgaard H, Pedersen BK. Diabetologia. 2007;50:431–8.

Lapchak PA, Hefti F (1992) Neuroreport. 3: 405–408

Lesage J, Del-Favero F, Léonhardt M, Louvart H, Maccari S, Vieau D, Darnaudéry M. J Endocrinol. 2004;181:291–6.

Lesage J, Sebaai N, Léonhardt M, Dutriez-Casteloot I, Breton C, Deloof S, Vieau D. Stress. 2006;9:183–98.

Lommatzsch M, Hornych K, Zingler C, Schuff-Werner P, Höppner J, Virchow JC. Psychoneuroendocrinology. 2006;31:388–94.

Lyons WE, Mamounas LA, Ricaurte GA, Coppola V, Reid SW, Bora SH, Wihler C, Koliatsos VE, Tessarollo L. Proc Natl Acad Sci USA. 1999;96:15239–44.

Martin JL, Jenkins VK, Hsieh HY, Balkowiek A. J Neurochem. 2009;108:450–64.

Monteleone P, Fabrazzo M, Martiadis V, Serritella C, Pannuto M, Maj M. Psychol Med. 2005;35:897–905.

Mowla JS, Farhadi HF, Pareek S, Atwal JK, Morris SJ, Seidah NG, Murphy RA. J Biol Chem. 2001;276:12660–6.

Nagahara AH, Merrill DA, Coppola G, Tsukada S, Schroeder BE, Shaked GM, Wang L, Blesch A, Kim A, Conner JM, Rockenstein E, Chao MV, Koo EH, Geschwind D, Masliah E, Chiba AA, Tuszynski MH. Nat Med. 2009;15:331–7.

Nakagawa T, Tsuchida A, Itakura Y, Nonomura T, Ono M, Hirota F, Inoue T, Nakayama C, Taiji M, Noguchi H. Diabetes. 2000;49:436–44.

Nakakura T, Suzuki M, Watanabe Y, Tanaka S. Zool Sci. 2007;24:1086–93.

Pencea V, Bingaman K, Wiegand SJ, Luskin MB. J Neurosci. 2001;21:6706–17.

Rage F, Givalois L, Marmigère F, Tapia-Arancibia L, Arancibia S. Neuroscience. 2002;112:309–18.

Ribasés M, Gratacòs M, Armengol L, de Cid R, Badía A, Jiménez L, Solano R, Vallejo J, Fernández F, Estivill X. Mol Psychiatry. 2003;8:745–51.

Rios M, Fan G, Fekete C, Kelly J, Bates B, Kuehn R, Lechan RM, Jaenisch R. Mol Endocrinol. 2001;15:1748–57.

Robinson LL, Townsend J, Anderson RA. J Clin Endocrinol Metab. 2009;88:3943–51.

Schrott LM, Franklin LM, Serrano PA. Brain Res. 2008;1198:132–40.

Silhol M, Bonnichon V, Rage F, Tapia-Arancibia L. Neuroscience. 2005;132:613–24.

Sugiyama N, Kanba S, Arita J. Brain Res Mol Brain Res. 2003;115:69–77.

Tapia-Arancibia L, Rage F, Givalois L, Arancibia S. Front Neuroendocrinol. 2004;5:77–107.

Tran PV, Carlson ES, Fretham SJ, Georgieff MK. J Nutr. 2008;138:2495–501.

Unger TJ, Calderon GA, Bradley LC, Sena-Esteves M, Rios M. J Neurosci. 2007;27:14265–74.

Van den Hove DL, Steinbusch HW, Scheepens A, Van de Berg WD, Kooiman LA, Boosten BJ, Prickaerts J, Blanco CE. Neuroscience. 2006;137:145–55.

Vickers MH, Breier BH, Cutfield WS, Hofman PL, Gluckman PD. Am J Physiol Endocrinol Metab. 2000;279:E83-7.

Wang L, Xu RJ. Asia Pac J Clin Nutr. 2007;16:467–72.

Yamamoto M, Sobue G, Yamamoto K, Terao S, Mitsuma T. Neurochem Res. 1996;21:929–38.

Yamanaka M, Tsuchida A, Nakagawa T, Nonomura T, Ono-Kishino M, Sugaru E, Noguchi H, Taiji M. Diabetes Obes Metab. 2007a;9:59–64.

Yamanaka M, Itakura Y, Tsuchida A, Nakagawa T, Noguchi H, Taiji M. Diabetes Obes Metab. 2007b;9:879–88.

Yeo GS, Connie Hung CC, Rochford J, Keogh J, Gray J, Sivaramakrishnan S, O'Rahilly S, Farooqi IS. Nat Neurosci. 2004;7:1187–9.

Zuena AR, Mairesse J, Casolini P, Cinque C, Alema GS, Morley-Fletcher S, Chiodi V, Spagnoli LG, Gradini R, Catalani A, Nicoletti F, Maccari S. PLoS ONE. 2008;3:e2170.

Chapter 133
The Developing Brain and Dietary Omega-3 Fatty Acids

Sheila M. Innis

Abbreviations

ALA   Alpha Linolenic Acid, 18:3ω-3
ARA   Arachidonic Acid, 20:4 ω-6
DHA   Docosahexaenoic Acid 22:6 ω-3
EPA   Eicosapentaenoic Acid 20:5 ω-3
EPG   Ethanolamine Phosphoglycerides Including Diacyl and Plasmalogen
FAD   Fatty Acid Desaturases
LA   Linoleic Acid, 18:2 ω-6
PC   Phosphatidylcholine
PI   Phosphatidylinositol
PS   Phosphatidylserine
TG   Triacylglycerols

133.1 Introduction

The omega (ω)-3 polyunsaturated fatty acids are a family of fatty acids which humans, as other animals are unable to synthesize due to the absence of a Δ-15 desaturase, the enzyme necessary to insert a double bond at the ω-3 position of a fatty acid carboxyl chain (Fig. 133.1). Three major forms of ω-3 fatty acids are present in usual human diets: the 18-carbon chain α-linolenic acid (ALA, 18:3ω-3), and its elongation and desaturation products eicosapentaenoic acid (EPA, 20:5ω-3) and docosahexaenoic acid (DHA, 22:6ω-3) (Fig. 133.2). In the body, the ω-3 fatty acids are found esterified in membrane glycerophospholipids where they impact membrane functions and from which they are released to participate directly or indirectly in regulation of metabolic and physiological processes. However, the ω-3 fatty acids are distributed with definitive tissue, membrane and glycerolipid specificity, and this likely underlies their contribution to normal yet diverse cell functions. DHA, but not ALA or EPA is highly enriched in mammalian brain grey matter, particularly phosphatidylserine (PS) and the ethanolamine-containing glycerophospholipids (EPG). DHA is also high in the

S.M. Innis (✉)
Department of Paediatrics, Child and Family Research Institute, University
of British Columbia, 950 West 28th Avenue, Vancouver, BC V5Z 4H4, Canada
e-mail: sinnis@interchange.ubc.ca
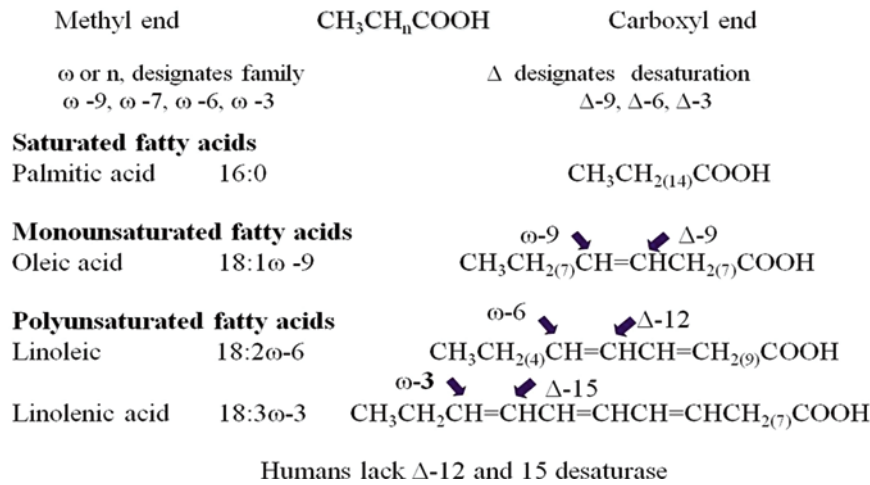
Fig. 133.1 Schematic to illustrate the major fatty acids, and use of ω and Δ nomenclature. The schematic illustrates a fatty acid carbon chain showing the methyl (CH$_3$) and carboxyl (COOH) ends and the position of the double bonds in the ω-9, ω-6 and ω-3 fatty acids. The carboxyl terminus is designated as Δ and the methyl terminus is designated ω. Humans lack a Δ-12 and Δ-15 desaturase
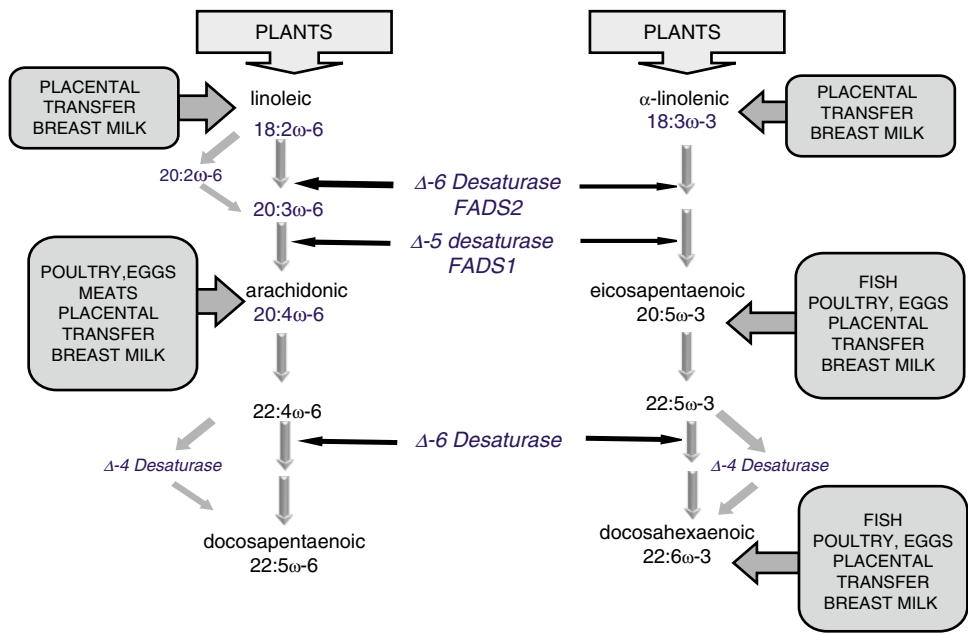
Fig. 133.2 Schematic of major steps of fatty acid desaturation and elongation and their dietary sources. The major steps of fatty acid desaturation and elongation, and the major dietary sources of ω-3 and ω-6 fatty acids at differences before and after birth, and in the diet are illustrated. Δ-6D, Δ-5D are 6 and 5 desaturases, respectively, are encoded by FADS2 and FADS1, respectively

glycerophospholipids that make up the membrane discs that comprise the highly specialized outer segments of the rods and cones in the retina. Dietary restriction of ω-3 fatty acids leads to loss of DHA and an increase in ω-6 fatty acids in the brain with effects that span from impaired neurogenesis to altered activities of proteins, ion channels, signal pathways, and gene expression, ultimately

influencing behavior and learning. During pre- and early post-natal development, DHA is provided by the mother by placental transfer and in breast milk, respectively, placing the emphasis of dietary ω-3 fatty acid adequacy on the maternal diet. With weaning, the metabolic demand for ω-3 fatty acids shifts from the mother to offspring, and thus the amounts and types of ω-3 fatty acids in diet of the child is of central importance. Pivotal questions relating dietary ω-3 fatty acids to brain development are the functional roles of and needs for ω-3 fatty acids at different stages of brain development, and whether ω-6 fatty acids modify ω-3 fatty acid requirements and function. This chapter provides a review of current knowledge on dietary ω-3 fatty acids and brain development, focusing primarily on human nutrition with information drawn from studies in other species to address mechanistic and dietary variables difficult to study in humans.

133.2 Omega-3 Fatty Acids and Lipids in the Developing Brain

The lipid composition of the mammalian brain is markedly different from other organs, notable for the unusually high levels of ether-linked glycerophospholipids and high amounts of the ω-3 DHA and the carbon chain 20 and 22 ω-6 fatty acids arachidonic acid (ARA, 20:4ω-6) and adrenic acid (22:4ω-6) (Sastry 1985; Siegel et al. 2006) (Tables 133.1 and 133.2). In contrast to plasma, liver, and other organs, brain glycerophospholipids are low in the 18-carbon chain ω-6 linoleic acid (LA, 18:2ω-6) and triacylglycerols (TG). Also unlike the liver, ethanolamine plasmalogens (1-alkenyl 2-acyl ethanolamine phosphoglyceride) are major glycerophospholipids, representing 30–50% of the EPG in grey matter and 80% or more of the myelin EPG. DHA is highest in EPG (both 1-alkenyl 2-acyl and diacyl) and PS of brain grey matter, although the same lipids in mature myelin contain low amounts of DHA; EPG but not PS is also high in ARA and 22:4ω-6, and other major classes including PC, PI and sphingomyelin are low in DHA (Svennerholm 1968; Sastry 1985; Siegel et al. 2006). EPG and PS together comprise 20–25% of brain lipid, and these glycerophospholipids are preferentially oriented on the inner leaflet of the plasma and internal membrane bilayers. DHA represents about 10% of total fatty acids in human brain grey matter, with lower amounts in white

Table 133.1 Lipid composition of adult human brain

	Grey matter (%)			White matter (%)		
	Fresh wt.	Dry wt.	Lipid	Fresh wt.	Dry wt.	Lipid
Water	81.9			71.6		
Total lipid	5.9	32.7	100	15.6	54.9	100
Cholesterol	1.3	7.2	22.0	4.3	15.1	27.5
Phospholipid, total	4.1	22.7	69.5	7.2	25.2	45.9
P'Ethanolamine	1.7	9.2	27.1	3.7	13.2	23.9
P'Choline	1.9	10.7	30.1	2.4	8.4	15.0
Sphingomyelin	0.4	2.3	6.9	1.2	4.2	7.7
P'Inositides	0.16	0.9	2.7	0.14	0.5	0.9
P'Serine	0.5	2.8	8.7	1.2	4.3	7.9
Galactocerebroside	0.3	1.8	5.4	3.1	10.9	19.8
Galactocerebroside sulfate	0.1	0.6	1.7	0.9	3.0	5.4
Ganglioside, total	0.3	1.7	–	0.05	0.18	–

This table gives the percentage of different lipids in brain grey matter and brain white matter based on fresh weight and dry weight. The major phospholipids are phosphatidylethanolamine (includes all EPG), phosphatidylcholine, sphingomyelin, phosphatidylinositol, and phosphatidylserine. The information is adapted from Siegel et al. (2006)

Table 133.2 Major ω-3 and ω-6 fatty acids in human adult cerebral grey and white matter glycerophosphoglycerides

	EPG	PS	PC	PI
Grey matter				
22:6ω-3	28.6	30.7	2.6	4.0
20:4ω-6	13.2	2.0	5.5	28.2
22:4ω-6	8.3	5.0	0.8	1.5
22:5ω-6	1.5	1.8	0.1	Trace
White matter				
22:6ω-3	3.0	0.9	0.4	1.1
20:4ω-6	7.9	1.4	2.0	17.3
22:4ω-6	13.4	2.0	0.9	2.4
22:5ω-6	0.5	0.1	0.1	Trace

This table shows the amounts of the major ω-3 and ω-6 fatty acids in the major glycerophospholipids EPG, ethanolamine phosphoglycerides; PS, phosphatidylserine; PC, phosphatidylcholine; PI, phosphatidylinositol of the adult human brain. The ethanolamine phosphoglycerides include both diacyl and plasmalogen. This shows that 22:6ω-3 (also called docosahexaenoic acid) is highest in grey matter EPG and PS, and that the same lipids differ in composition between grey and white matter. This information is adapted from Svennerholm (1968)

matter giving an average of about 7% DHA in total fatty acids of the human brain. In the rod outer segments, diacyl PE, PS, and PC are high in DHA; PE and PS are enriched on the outer monolayer, PC is enriched on the inner monolayer and plasmalogens are usually undetectable (Giusto et al. 2000). About 20% of the fatty acids in the human retina are DHA, with much higher concentrations in the rod outer segment membranes. Much remains to be discovered regarding the functional basis for the enrichment of DHA in specific brain glycerophospholipids, including the high levels of plasmalogens, and their membrane distributions.

The fatty acid composition of brain at different stages of development has been reported in animals and from analysis of human autopsy tissue. In general, these studies show a progressive increase in DHA in the brain, accompanied by an increase in ARA and 22:4ω-6 with development. The increase in DHA in the human brain is particularly robust from the beginning of the third trimester of gestation and continues to at least 4 years-of-age (Svennerholm 1968; Clandinin et al. 1981; Martinez and Mougan 1998). The increase in DHA, ARA, and 22:4ω-6 in the diacyl and plasmalogen fractions of EPG, and in PS and PC of the human forebrain from 30 week gestation to 4 years-of-age extrapolated from Martinez and Mougan (1998) is illustrated in Fig. 133.3. The increase in DHA is in part explained by brain growth; when expressed as a percent of cerebral grey matter fatty acids, DHA increases, while ARA and 22:4ω-6 decrease in EPG, and all 3 fatty acids decrease in cerebral white matter EPG with increasing age and thus maturation (Table 133.3). Autopsy analysis have been extrapolated to estimate that the human fetus accumulates about 60 mg/day DHA during the last trimester of gestation, of which 2.1–2.85 mg/day DHA is accumulated in the brain (Clandinin et al. 1981). Other analyses show accretion of DHA is linear in the human forebrain from the beginning of the third trimester of gestation continuing at a similar rate throughout at least the first one to two years after birth (Martinez 1992). However, while these data illustrate the quantitative increase in DHA in the brain during growth, changes associated with individual membranes, such as the increasing synaptic density that continues until about 5–6 years-of-age, are not reflected (Levitt 2003).

The effects of dietary ω-3 fatty acid deficiency on the composition of brain fatty acids have been extensively described in animals, with some data available from autopsy analysis of infants who had
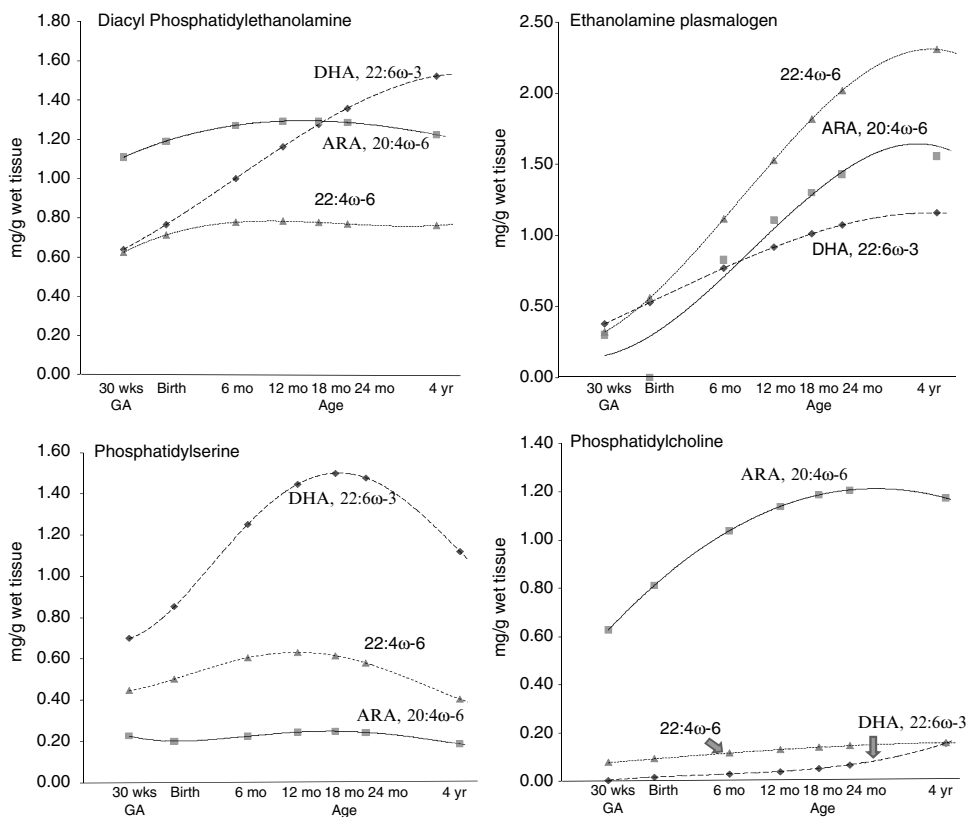
Fig. 133.3 Increase in DHA, ARA and 22:4ω-6 in the human forebrain to 4 years-of-age. Increase in DHA, ARA and 22:4ω-6 in the human forebrain from 30 weeks gestation to 4 years-of-age extrapolated from the equations of Martinez and Mougan (1998). Note that the scale of the y axis differs in the four plots

Table 133.3 Changes in docosahexaenoic acid and major long chain ω-6 fatty acids in human cerebral grey and white matter ethanolamine phosphoglycerides with increasing age

	12 week gest'n	38 week gest'n	7 months	4 years	26 years
Grey matter					
22:6ω-3	10.8	17.1	16.9	22.3	28.6
20:4ω-6	17.3	14.9	16.4	16.7	13.2
22:4ω-6	9.5	10.6	11.7	9.9	8.3
22:5ω-6	2.8	4.4	5.0	2.4	1.5
White matter					
22:6ω-3	–	17.7	8.7	5.7	3.0
20:4ω-6	–	16.2	13.4	9.5	7.9
22:4ω-6	–	13.3	19.6	18.0	13.4
22:5ω-6	–	4.8	3.5	1.4	0.5

This table shows the percentage of the major ω-3 and ω-6 fatty acids in human brain grey matter and white matter at different stages of development. The table shows that 22:6ω-3 (also called docosahexaenoic acid) increases in brain grey matter from 12 weeks of gestation throughout development to adulthood. In white matter, DHA decreases with age and 22:4ω-6 is a major polyunsaturated fatty acid. This information is adapted from Svennerholm (1968)

been breast-fed or fed formula prior to death. In animals, there is no doubt that a diet deficient in ALA leads to decreased DHA in the brain and retina and that this is accompanied by a characteristic increase in 22:4ω-6 and particularly 22:5ω-6 (Innis 1991). Clear evidence has been published to show that the in utero environment does not protect the embryonic and fetal brain during maternal dietary ω-3 fatty acid deficiency (Innis 2005, 2007). Similarly, inadequate, unbalanced, or excessive intakes of ω-3 fatty acids during the milk feeding period can also cause marked alterations in accretion of ω-3 and ω-6 fatty acids in the infant brain (Innis 2008; Novak et al. 2008). The increase in carbon chain 22ω-6 fatty acids in the brain of fetal, infant and adult animals given ω-3 fatty acid deficient diets is likely a compensatory mechanism to maintain brain membrane glycerophospholipid fatty acid homeostasis as close to normal as possible, similar to the increase in 20:3ω-9 and 22:3ω-9 in the brain that occurs when a diet lacking both ω-6 and ω-3 fatty acids is fed (Innis 1991).

In human infants, brain cortex DHA increased from birth to about 40 weeks postnatal in 15 infants who had been breast-fed, but not in 20 infants who had been fed formula before death (Makrides et al. 1994). As in animals fed a ω-3 fatty acid deficient diet, 22:4ω-6 and 22:5ω-6 were higher in the cortex of the formula-fed infants, with an inverse relationship between DHA and 22:5ω-6. Similar studies of infants in Scotland who before death had been fed formula with fat containing 16.0% LA and 1.5% ω-3 α-linolenic acid (ALA, 18:3 ω-3) or 14.5% LA and 0.4% ALA found reduced DHA and increased carbon chain 22 ω-6 fatty acids, particularly 22:5ω-6 in cerebral cortex EPG and PS, as illustrated in Fig. 133.4 (Farquharson et al. 1995). The increase in 22:5ω-6 to levels as high as 7.0% and 10.4% in cerebral cortex EPG and PS, respectively, of infants fed formula with 7% energy as LA and 0.2% as ALA mirrors the changes in the brain of animals fed milk diets with inadequate ω-3 fatty acids, or high LA/ALA ratios (Innis 1991; Novak et al. 2008; Innis 2008). These studies establish that the developing human brain is vulnerable to diet-dependent changes in DHA and ω-6 fatty acids. However, the elevation of ω-6 fatty acids, and particularly the increase in 22:5ω-6 in infants fed with formulas with no carbon chain 20 or 22 ω-6 fatty acids (Makrides et al. 1994; Farquharson et al. 1995) is not consistent with a simple conclusion that low desaturases enzyme activities limits the capacity for carbon chain 20 or 22 polyunsaturated fatty acid synthesis, unless specific to synthesis of DHA. Regardless, the changes are important since the ω-6 fatty acids do not substitute for DHA in supporting neurogenesis or neurite outgrowth, dopaminergic and
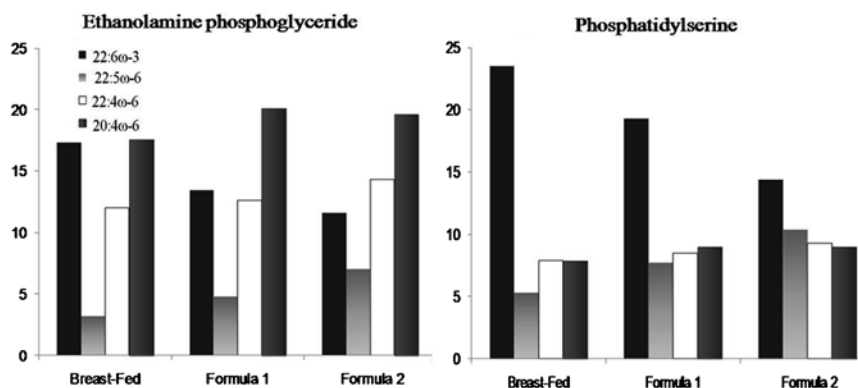
Fig. 133.4 Cerebral cortex fatty acids of breast-fed infants and infants fed formula with no DHA. Levels of fatty acids as a percentage of total fatty acids in cerebral cortex of infants who before death had been breast-fed or fed infant formula, adapted from Farquharson et al. (1995). The fat blends had for formula 1: 16.0% 18:2ω-6 (LA) and 1.5% 18:3ω-3 (ALA); formula 2: 14.5% (LA) and 0.4% (ALA), giving about 8% and 0.75% energy LA and ALA, and 7.25% and 0.2% LA and ALA in formulas 1 and 2, respectively

serotinergic neurotransmission, synthesis of neuroprotective metabolites of DHA, or learning and visual functions (Chalon 2006; Coti-Bertrand et al. 2006; Innis 2007, 2008; Dagai et al. 2009; Katakura et al. 2009; Niemoller and Bazan 2009).

133.3 Essential Fatty Acids and Their Metabolism

Humans can synthesize saturated and monounsaturated fatty acids using carbons from degradation of carbohydrates, proteins or fats, with the major products being the saturated fatty acids palmitic acid (16:0),stearic acid (18:0), and their Δ-9 desaturase products palmitoleic acid (16:1n-7) and oleic acid (18:1n-9) (Innis and Davidson 2008). Synthesis of ω-3 and ω-6 fatty acids requires insertion of a double bond at the third or sixth carbon, respectively, from the carboxyl terminus of an 18-carbon chain fatty acid in reactions that require Δ-15 and Δ-12 desaturase, respectively (Fig. 133.1). The absence of Δ-15 and Δ-12 desaturase in animals means that all animals require a dietary source of both ω-3 and ω-6 fatty acids (Innis 1991). DHA for synthesis of new membrane lipids and to replace DHA irreplaceably lost during membrane lipid turnover has two potential sources: synthesis from ALA provided in the diet or from DHA consumed in the tissues of other animals. Synthesis of DHA from EPA or chain shortening of DHA to EPA is also possible, but since foods providing EPA also provide DHA, this may be of limited relevance to normal fatty acid biochemistry. The central issue relating dietary ω-3 fatty acids to brain development and function can be summarized as to whether the desaturase enzymes for synthesis of DHA from ALA are constitutionally low or for some reason inhibited at different stages of development, thus necessitating an appropriate supply of preformed EPA and DHA. Although DHA has held centrestage because of its high concentrations in the brain and retinal membranes, ALA and EPA may also have important functions, for example, as metabolic regulators of the conversion of LA to ARA, or as a source of acetyl and malonyl CoA for brain cholesterol and fatty acid synthesis (Cunnane et al. 2006; Novak et al. 2008; Chen et al. 2009), with additional roles of EPA in modulating neuroinflammatory and eicosanoid pathways, and perhaps in synaptic plasticity and neuro-extension (Adibhatla and Hatcher 2008; Kawashima et al. 2008; Liu et al. 2008).

There is no doubt that as a species, hominins evolved consuming diets with meats, fish and plants that provided EPA, DHA, and ALA, all three ω-3 fatty acids are transported across the placenta, are present in human milk, and are taken up by the brain (Simpolous 1999; Innis 2004, 2005, 2008; Cordain et al. 2005; Eaton 2006). However, among the ω-3 fatty acids, DHA is uniquely enriched in the brain, with the far-reaching hypothesis that the changing diet during early human evolution to include rich sources of DHA and ARA in foods gathered from the land/water interface was pivotal in the evolution of the large human brain (Crawford et al. 1999). On the other hand, humans including infants can form DHA and EPA from ALA, albeit in apparently low amounts (Hussein et al. 2005; Burdge 2006; Carnielli et al. 2007), and 22:5ω-6 accumulates in high amounts in brain glycerophospholipids of infants fed formulas lacking DHA (Makrides et al. 1994; Farquharson et al. 1995). The evidence favors the physiological appropriateness of a balanced supply of ω-3 fatty acids to support brain growth and development, with the capacity for synthesis of longer chain metabolites should the exogenous supply falter.

The desaturation and elongation of ALA to EPA and DHA in humans in vivo must be considered in context from the amounts and balance of ω-3 and ω-6 fatty acids supplied in the diet, the known effects of dietary ω-3 and ω-6 fatty acids on plasma and tissue glycerolipid fatty acids and ultimately, the pathways that govern glycerophospholipid assembly and remodeling. The ω-6 fatty acids are included because the ω-6 and ω-3 fatty acids are inseparably linked, from their supply in foods, to

their metabolism and acylation into membrane glycerophospholipids and ultimately their roles in modulating development, mental and physical performance, and health. Conversion of ALA to EPA and LA via 20:3ω-6 to ARA requires sequential addition of carbon atoms (elongation) and insertion of double bonds (desaturation) by Δ-6 and Δ-5 desaturases (Fig. 133.2); these enzymes occur in animal cells, phytoplankton, and zooplankton. The most widely described pathway for synthesis of DHA from EPA in animal cells, in which a Δ-4 desaturase has not been identified, involves sequential elongation of EPA to 24:5ω-3, Δ-6 desaturation to 24:6ω-3, then a single cycle of β-oxidation in peroxisomes to yield DHA (22:6ω-3) (Innis and Davidson 2008). Synthesis of 22:5ω-6 has been proposed to follow a similar pathway although other pathways for DHA synthesis in humans as well as separate pathways for metabolism of ω-3 and ω-6 fatty acids have been proposed (Innis and Davidson 2008).

The initial Δ-6 and Δ-5 desaturation of ALA and LA is accomplished by the same enzymes, allowing competition between LA and ALA, with saturation of enzyme activity at relatively low substrate concentrations, equivalent to less than 1% dietary energy from LA or ALA (Innis 2008, 2009). Except in a few highly specialized lipids, the ω-3 and ω-6 fatty acids are esterified at the *sn*-2 position of glycerophospholipids, for which the acylation sites within the cell are finite. The ω-3 and ω-6 fatty acid supply and desaturase enzyme activities must be integrated to the needs for fatty acids for glycerophospholipid synthesis and remodeling. Co-ordinate regulation of Δ-6 and Δ-5 desaturase expression and activity is achieved through several mechanisms, including several transcription factors for which the 18-, 20-, and 22-carbon chain ω-3 and ω-6 fatty acids are promiscuous ligands and ultimately suppress expression (Jump 2008). Although most information has been gathered in the liver, inhibition of hepatic desaturases activities is relevant since secretion of lipids low in EPA and DHA or enriched in ω-6/ω-3 fatty acid alters the plasma fatty acid pool and this is a major source of long chain ω-3 fatty acids for both the developing and mature brain (Innis 2008).

In healthy humans, except during high carbohydrate feeding, de novo lipogenesis is quantitatively low and the ω-3 and ω-6 fatty acids are distributed between oxidation depending on the needs for energy and acylation in structural and storage lipids. Dietary intakes of LA, including infants fed human milk or formula, are well in excess of 1% energy, thus desaturase substrate supply is unlikely to be limiting, and excess LA must be either acylated or oxidized. Comparative studies on fatty acid oxidation indicate that LA is preferentially retained when compared to 18:1ω-9 or ALA (Innis 1991); consistent with the well-known relationship between higher intakes of LA and higher LA in plasma and blood cell and tissue lipids of adults and infants (Putnam et al. 1982; Ponder et al. 1992; Sanders et al. 1994; Makrides et al. 2000; Skeaff et al. 2006). Studies using stable isotope labeled fatty acids have uniformly found that the proportion of a dose of labeled ALA appearing in plasma EPA and DHA is low, with 1% or less appearing in DHA, with slightly higher amounts in EPA (Hussein et al. 2005; Burdge 2006; Carnielli et al. 2007). Conversion of ALA to DHA tends to be higher in pregnant women, consistent with growth, decreases in infants with increasing postnatal age, and is lower when ARA and DHA are present in the infants' feeds (Burdge 2006; Carnielli et al. 2007). Consistent with the latter studies, increasing the dietary ALA does not increase DHA in the blood lipids of infants or pregnant women, and does not increase DHA in breast milk during lactation, although a small increase in EPA is usually found (Makrides et al. 2000; Innis 2004, 2005, 2009). EPA and DHA from foods or supplements on the other hand, are readily taken up, incorporated into plasma, blood cells, and tissue glycerophospholipids, but may also decrease ARA depending on the amounts of EPA and DHA consumed (Innis 2008, 2009). These findings indicate that Δ-6 and Δ-5 desaturase activities are "low" or repressed in humans, and not limited by substrate, which is the sum of LA and ALA. Usual dietary supplies of LA are considerably in excess of needs and dietary sources of EPA and DHA are readily used to support new tissue growth and membrane lipid turnover.

Single nucleotide polymorphisms (SNP) in genes for rate-limiting enzymes are becoming increasingly recognized as important modifiers of the relationship between diet and disease risk. Common minor allele variants in fatty acid desaturase (FADS) 1 and FADS2, which encode Δ-5 and Δ-6 desaturase, respectively, are associated with increased LA and decreased ARA, as well as decreased ω-6 and ω-3 fatty acid desaturation products in plasma and blood cell lipids and human milk (Schaeffer et al. 2006; Xie and Innis 2008). New findings to show the importance of SNP in the FADS1-FADS2 gene cluster are consistent with the understanding that forward flux through the desaturase pathway is limited by desaturase activity, rather than the fatty acid substrate supply. Whether SNP in the FADS2-FADS1 gene cluster interact with the fatty acid supply to modify brain development or neurological disease is uncertain, although epidemiological data to suggest an association between SNP in FADS2 and cognitive test scores in children who had been breast-fed as infants has been reported (Caspi et al. 2007).

The highly specific ω-3 or ω-6 fatty acid distributions among different glycerophospholipids and within the same glycerophospholipid in different membranes, including those of the brain, are not readily explained by the pathways of de novo glycerophospholipid synthesis or ω-3 and ω-6 fatty acid desaturation. The major pathways for diacyl PC and EPG synthesis are considered to be the cytidine diphosphate (CDP)-choline and CDP-ethanolamine pathways using diacylglycerol as a common precursor; methylation of EPG is important in PC synthesis; base-exchange of serine for choline or ethanalomine in existing glycerophospholipids generates PS; and decarboxylation of serine in PS generates diacyl EPG (Siegel et al. 2006), all pathways involving modification of only the polar head group. Rapid turnover of *sn*-2 position fatty acids in remodeling was first proposed in 1958 to explain the difference in fatty acid patterns of PC compared to TG (Lands 1958). Since that time, several lysophospholipid acyltransferases have been identified that recognize polar head groups and fatty acyl CoAs and these enzymes function to maintain membrane asymmetry and fatty acid diversity (Hishikawa et al. 2008). Although plasmalogens arise from synthesis in peroxisomes by sequential acylaton of dihydroxyacetone phosphate remodeling of their *sn*-2 position acyl chains is similarly important to the high levels of long chain ω-3 and ω-6 fatty acids in the brain (Cook et al. 1991; Siegel et al. 2006). However, acyl transferase specificity appears to be more dependent on carbon chain length than ω-3 or ω-6 fatty acid series, and this leads to competition among ω-3 or ω-6 fatty acids for acylation (Lands 1958; Cook et al. 1991; Hishikawa et al. 2008). In vivo and in vitro, neural cells readily acylate 22:5ω-6, including 22:5ω-6 derived from the diet, and thus taken up from plasma (Innis 1991; Stark et al. 2007; Novak et al. 2008). Together, this indicates that the balance of carbon chain 22 ω-6 and DHA available to brain, but not necessary their amounts, is important to achieving neural membranes high in DHA.

133.4 Essential Fatty Acids and Their Dietary Sources

The types, amounts, and balance of ω-3 and ω-6 fatty acids in different plant and animal foods are exceedingly diverse, and this links the importance of diet to brain development and function. The 18-carbon ω-3 ALA and ω-6 LA are synthesized in plants; although most plant parts are low in fat with a LA:ALA ratio close to 1. An exception are seed oils many of which such as corn, soybean, safflower, sunflower, and some nuts (hard-shelled seeds) such as almond and peanuts are abundant in LA. Use of these oils brings of necessity an increase in LA intake and in the dietary LA/ALA balance. ALA and LA are consumed in plant foods by terrestrial animals, modified by desaturation and elongation depending on the ALA and LA quantity and balance in the diet, and passed on to animals higher in the food chain. As in the laboratory, livestock, and poultry fed grains high in LA have tissue lipids high in ω-6 fatty acids and depleted of ω-3 fatty acids, particularly when compared to their

wild counterparts (Cordain et al. 2005; Eaton 2006). EPA and DHA, on the other hand, are synthesized in abundance in aquatic phytoplankton, and these fatty acids are consumed by molluscs, crustaceans, and fish with the result that wild fish, shellfish, and molluscs are rich sources of EPA and DHA that are also low in ω-6 fatty acids. To summarize, humans consume ALA and LA in both plant and animal foods, but the amounts and proportions of ALA and LA and their metabolites EPA and DHA, and ARA, respectively, vary widely depending on the choices of vegetable fats and fats from terrestrial and aquatic food sources.

Dramatic quantitative and qualitative changes to human ω-3 and ω-6 fatty acid nutrition that began slowly with the industrial revolution, escalated in the twentieth century with the widespread introduction of LA-rich vegetable oils into the food supply (Simpolous 1999; Cordain et al. 2005; Eaton 2006). Prior to the development of technologies to extract and refine oils from seeds that are safe for human and animal consumption, and processes to convert liquid oils into solid and semisolid margarines and shortenings, the amount of LA that could be consumed by humans and animals was necessarily low (Simpolous 1999; Cordain et al. 2005; Eaton 2006). Available data show an increase in LA from about 3% dietary energy, and a dietary ω-6:ω-3 fatty acid ratio of 2:1 or lower in the early 1900s. In the modern food supply, ω-6 LA represents over 90% of all polyunsaturated fatty acids, with an average of 6.7% dietary energy from LA in the U.S. (Simpolous 1999; Innis and Jacobson 2007; Friesen and Innis 2009; Harris et al. 2009). This shift to enrich the diet with LA and decrease ω-3 fatty acids with ω-6:ω-3 fatty acid ratio of 10:1 or higher, extends to the fatty acid nutrition of the unborn child through changes in placental fatty acid transfer, to the breast-fed infant through changes in human milk fatty acids, and to the diet of young children (Innis 2004, 2005, 2009).

Numerous studies focusing on dietary fatty acids and cardiovascular disease have provided ample evidence that the amount and types of ω-3 and ω-6 fatty acids in the diet impacts plasma lipid ω-3 and ω-6 fatty acids, and this in turn influences the ω-3 and ω-6 fatty acids in blood cells, and tissue lipids. The biology relating dietary ω-6 and ω-3 fatty acids to circulating and tissue glycerophospholipid ω-3 and ω-6 fatty acids in infants and children is not different from adulthood. Particular attention has focused on DHA because DHA is high in the brain and differences in dietary intake of DHA are the most important variable explaining differences in plasma, blood cell and human milk levels of DHA in healthy humans, with DHA necessarily lower in vegans and vegetarians than in individuals consuming mixed diets that include fish or other sources of DHA (Innis 2004, 2008, 2009). However, differences in dietary intake or blood levels of DHA is only of physiological consequence if the composition of the circulating fatty acid pool interferes with the ability of the brain to take up and accumulate DHA as needed in specific membranes.

133.5 Omega-3 Fatty Acid Supply and Uptake in the Developing Brain

Important questions relating to ω-3 fatty acids to brain development and function are the amounts and balance of fatty acid substrates required to meet the needs for DHA for turnover and synthesis of new membranes, either by uptake from plasma or elaboration within the brain from ω-3 fatty acid precursors. Although the activity of Δ-6 and Δ-5 desaturase is often considered highest in the liver, Δ-6 and Δ-5 desaturase are expressed at high levels in brain (Cho et al. 1999; Leonard et al. 2000). As described, LA and ALA are present in low amounts in the brain, <2% brain fatty acids, regardless of high LA in plasma TG, glycerophospholipids and unesterified fatty acids. Highly selective uptake, or preferential disposal via selective oxidation of the 18-carbon chain ω-6 and ω-3 fatty acids and EPA must, therefore, account for the high ARA, 22:4ω-6 and DHA in the brain. Early studies using radioactive isotopes reported that brain is able to take up ALA and form DHA, although more recent studies indicate that neurons and astrocytes in vitro are unable to complete the final steps in DHA

Table 133.4 Key features of omega-3 fatty acids

1. The omega-3 docosahexaenoic acid is a major polyunsaturated fatty acid in brain grey matter.
2. The amount of docosahexaeonic acid increases in brain grey matter with brain development and maturation.
3. When omega-3 fatty acids are lacking, the brain accumulates more of the omega-6 fatty acids.
4. Docosahexaenoic acid is needed for proper development and function of brain neurons and their neurochemical functions.
5. Inadequate docosahexaeonic acid is associated with poor learning and behavior development.
6. In usual diets, docosahexaeonic acid is found only in animal lipids. The richest dietary source is fish.

This table lists the key facts of omega-3 fatty acids in brain development and function

synthesis from 22:5ω-3, or 22:5ω-6 from 22:4ω-6, although EPA and ARA are formed from their respective ALA or LA precursors (Innis 1991, 2008). Several in vivo studies have shown that brain takes up DHA from plasma, particularly albumin-bound or lysophospholipid fatty acid pools at rates which in the rat are sufficient to meet the needs for brain DHA turnover, although albumin binding and previous DHA feeding both decrease uptake (Innis 1991; Chen et al. 2008; Ouellet et al. 2009). Convincing evidence is also available to show that DHA is taken up and incorporated into brain and retina glycerphospholipids, and this occurs whether the supply of DHA is via placental transfer, in breast milk, or as DHA in diet of the young or adult animal (Innis 2008). As discussed, dietary deficiency of ω-3 fatty acids results in high levels of 22:5ω-6 in the brain. However, 22:5ω-6 is usually <1% plasma glycerolipid and red blood cell fatty acids, even in infants fed formula with no DHA, and including those with high LA (Putnam et al. 1982; Ponder et al. 1992; Makrides et al. 2000). In summary, whether the brain can synthesize DHA and the origin of the high 22:5ω-6 that accumulates in the brain in ω-3 fatty acid deficiency remains enigmatic, although it is clear that the brain can take up ALA, EPA, DHA, and 22:5ω-6 from plasma, oxidation with recycling of carbons from ALA and EPA occurs, and Δ-6 and Δ-5 desaturase are present. Dietary DHA on the other hand, is readily and effectively taken up, and prevents excess accumulation of long chain ω-6 fatty acids (Table 133.4).

133.6 Omega-3 Fatty Acid Supply in Prenatal and Postnatal Development

Before birth, the infant obtains ω-3 fatty acids necessary for brain development by placental transfer, and after birth ω-3 fatty acids are supplied in breast milk or breast milk substitutes, and later on from foods. In the human placenta, the polarized syncytiotrophoblast consisting of a microvillous membrane facing the maternal blood and basal membrane facing the fetal blood separate the maternal and fetal circulations while at the same time allowing nutrient exchange (Cunningham and Mcdermott 2009). Several membrane and intracellular binding proteins that function in the uptake and transport of ω-3 fatty acids across the placenta have been identified (Innis 2005). Both Δ-6 and Δ-5 desaturase are also present and highly expressed in the placenta, although their functional roles are unclear (Cho et al. 1999; Leonard et al. 2000). It is well-known that the proportions of DHA and ARA are higher, while LA is lower in fetal than maternal plasma glycerolipids, although on a quantitative basis the amount in mother is higher due to the higher plasma lipid concentration in the mother (Innis 2005). The relative exclusion of LA from the fetal circulating lipids is intriguing and, similar to the exclusion of LA from the brain it is of probable, although unclear biological importance. Regardless, abundant experimental evidence has shown that placental mechanisms for ω-3 fatty acid transfer do not protect the fetus during maternal dietary ω-3 fatty acid deficiency through mobilization of ω-3 fatty acids from maternal tissues (Innis 2005). In animals, a diet limiting in ω-3 fatty acids, particularly when combined with high LA in pregnancy leads decreased maternal-to-infant DHA transfer and increased 22:4ω-6 and 22:5ω-6 in the fetal brain, including neuronal growth cones (Innis 2007).

In humans, differences in maternal DHA intake explain differences in DHA in infant-cord blood at birth and increasing maternal DHA intake through diet or supplements increases placental transfer of DHA (Innis 2005, 2008).

There is also no doubt that the quality of unsaturated fatty acids in human milk is a dynamic reflection of fatty acids in the food supply, as amply illustrated by *trans* fatty acids as high as 13–18% total milk fat among breast-feeding women in the U.S. and Canada (Innis and King 1999; Mosely et al. 2005). In the mid-1900s, LA represented a mean of about 7% of milk fat and this increased to mean levels of 12–16% energy by the 1980s (Innis 2004). Human milk DHA, on the other hand, has decreased perhaps as much as 50% in some western nations to median levels below 0.35% milk fat (Innis 2004), which with the increase in LA gives a milk diet with a ω-6/ω-3 fatty acid balance of about 10:1 similar to the adult diet (Simpolous 1999; Friesen and Innis 2009). In East African coastal regions where modern vegetable oils are not consumed, LA provides 4.2% milk fat with levels of DHA of 0.73% (Kuipers et al. 2007). However, human milk levels of 22:4ω-6 and 22: 5ω-6 are exceedingly low at <0.1% milk fat and are not increased in women with diets very low in fish or DHA, or with high LA (Innis and King 1999). In contrast, rats fed a ω-3 fatty acid deficient diet have increased milk 22:4ω-6 and 22:5ω-6, with levels of 22:5ω-6 over 0.35% and exceeding DHA (Jacobson et al. 2005). This interesting species difference may serve to protect the developing breast-fed human infant from excess long chain ω-6 fatty acids that could interfere with DHA uptake into the brain. Extending to the infant, differences in dietary intake of DHA from mother's milk or formulas explain the differences in circulating lipid DHA among infants, including the low DHA in infants fed by mothers following vegan or vegetarian diets or in infants fed formula without DHA.

The period from 12 months to about 6 years-of-age is a time of remarkable transition in diet and of rapid neural development. With weaning, the infants' milk or formula intake is gradually replaced with foods that with modern weaning practices generally focus on cereals, then vegetables and fruits, all of which are low in fat and contain no EPA or DHA (Innis 2009). Weaning thus leads to a decrease in fat and ω-3 fatty acid intake. Blood levels of DHA in children 18–60 months-of-age are low, similar to those in infants fed formulas lacking DHA, and an inverse relationship has been shown between red blood cell DHA and LA over the range of 2.7–3.8% energy from LA, consistent with reduced Δ-6 and Δ-5 desaturase activity with increasing LA, or perhaps competition for acylation (Innis et al. 2004). The lower LA intake among young children than in adults is explained by lower intakes of salad oils and higher intakes of dairy products. Several recent studies have shown that in children, as in other age groups, DHA intake from foods or supplements is the most important variable influencing the circulating lipid levels of DHA (Osendarp et al. 2007; Dalton et al. 2009; Innis 2009). In summary, the ω-3 fatty acid supply during pre-natal and early postnatal development is dictated by maternal diet and in early childhood by the ω-3 fatty acid composition of the child's diet. Differences in the intake of preformed DHA translate to differences in DHA in plasma and blood cell lipid DHA across all stages of the lifespan; these will translate to have physiologically meaningful implications for brain development and function if the circulating lipid ω-3 fatty acids are too low, or if fatty acids that compete for uptake or acylation are sufficiently high as to alter the balance of DHA/22-carbon ω-6 fatty acids incorparated into important membrane lipid pools.

133.7 Functions of Omega-3 Fatty Acids in the Developing Brain

While the popular lore of fish as brain-food is well-known, its origin can be traced not to ω-3 fatty acids but to the early eighteenth century discovery of high amounts of phosphorous in brain, a notion that phosphorus is involved in thought and thus intelligence, and the discovery that fish like brain, is

high in phosphorus. It is self-evident that lack of ω-3 fatty acids for acylation into glycerophospholipids for growth of new brain membranes or to replace losses in turnover must result in either failure of membrane synthesis, or synthesis using alternate fatty acids. Human brain development begins early in gestation with neuron proliferation and continues in preset timelines into adulthood (Huttenlocher 1990; Levitt 2003; Georgieff and Innis 2005). The frontal lobes that are responsible for executive functioning develop more slowly than other structures, with spurts of development from birth to 2 years-of-age, and again at 7 and 9 years-of-age, and in adolesence. At 2 years-of-age, the frontal cortex has attained only about 55% neuronal density of the adult (Huttenlocher 1990; Thatcher 1991) which suggests that sensitivity to adverse effects of inadequate ω-3 fatty acids can extend into childhood. As for other nutrients and stressors, it is reasonable that the time in development when the brain is faced with inadequate ω-3 fatty acids will dictate the consequence of the insult, which molecular events, membrane structures and function are altered, and the potential for reversal if adequate ω-3 fatty acids are provided later on. Also reasonable, deficiencies that impact early stages of development, such as neurogenesis and neuron migration, are likely to have more long-lasting and more far reaching implications than deficiency imposed on the mature brain.

The protracted period of brain development in humans, however, adds complexity to clinical studies on ω-3 fatty acid nutrition since deficiency at any age can presumably impact function, although with different consequences. The essential roles of DHA in the brain are fulfilled both through roles in membrane glycerophospholipids, thus potentially impacting numerous and diverse cell functions in which membranes and their lipids contribute, and roles of unesterified DHA and its neuroprotective metabolites. Studies focusing on early brain development have described morphological changes in the embryonic brain with under-development of the hippocampus in a pattern suggesting impaired cell cycle exit and cell migration, with deficits also in secondary neurite outgrowth and cortical dendritic arborization (Coti-Bertrand et al. 2006; Innis 2008; Novak et al. 2008). More recent in vitro studies have confirmed that DHA is important in neural stem cell differentiation, perhaps via regulation of transcription factors and promotion of cell cycle exit, and in neurite outgrowth (Dagai et al. 2009; Katakura et al. 2009). Neural cell membrane growth requires addition of newly synthesized lipids to the growing membrane through fusion of lipid transport vesicles with the plasma membrane, involving soluble *N*-ethylmaleimide-sensitive fusion protein attachment receptor (SNARE) proteins, a process similar to the fusion preceding release of neurotransmitters from their storage vesicles (Innis 2007). Within membrane glycerophospholipids, the six double bonds of DHA gives a shortened fatty acid chain in which motion and, therefore, conformational change is severely restricted by the lack of rotation at the double bond; thus stabilizing and condensing the membrane (Martinez and Morros 1996). The small polar head group of the EPG, on the hand, gives a comparatively large hydrophobic fatty acid region which tends to bend the membrane bilayer and facilitate formation of the non-bilayer phases that are important in membrane fusion, such as occurs during fusion of transport vesicles providing lipids to growing membrane surfaces, or neurotransmitters for secretion. Hippocampal membranes from animals fed a ω-3 fatty acid deficient diet had decreased membrane DHA and increased membrane-bound SNARE protein complexes, suggesting impaired fusion, or dissociation and recycling (Innis 2007). Altered serotinergic and dopaminergic neurotransmission has also been demonstrated in ω-3 fatty acid deficiency, with complex changes at multiple levels that include the vesicular pools (Chalon 2006; Innis 2007).

Signal-induced turnover of membrane glycerophospholipids leads to generation of second messengers, such as platelet activating factor, diacylglycerol, and 2-arachidonyl glycerol, and release of unesterified ω-6 and ω-3 fatty acids which can be further metabolized to neuroprotective or neuro-inflammatory molecules, or bind to transcription factors that influence gene expression (Bazan 2006; Innis 2007). In addition to determining the DHA available for release from the membrane, DHA also appears to regulate ARA release, potentially influencing synthesis of ARA-derived eicosanoids as

well as providing DHA for synthesis of neuroprotective molecules (Bazan 2006; Niemoller and Bazan 2009). Diets rich in EPA plus DHA when compared to ALA also differ in their effects on brain gene expression, with specific effects of dietary EPA and DHA on genes controlling synaptic plasticity, cytoskeleton, and membrane association, signal transduction, ion channel formation, and energy metabolism (Innis 2007). Some recent studies also suggest that EPA may influence synaptic plasticity and the PI3-kinase/Akt pathway and, like DHA, EPA also stimulates neurite extension (Liu et al. 2008; Kawashima et al. 2009), although the physiological significance of this in the developing brain in vivo is unclear.

133.8 Dietary Omega-3 Fatty Acids and Brain Development in Infants and Children

Studies relating to ω-3 fatty acids and brain development in infants and children fall into 3 general categories, observational studies that relate outcome to maternal or child ω-3 fatty acid intake or blood levels, dietary interventions in healthy pregnant and breast-feeding women or infants, and studies with clinical populations such as prematurely born infants who may have altered needs when compared to the infant born after full-term gestation. Studies on the potential benefits of breast-feeding on neurodevelopment favor a view that the complex mix of nutrients and growth factors in human milk contribute to better development of the breast-fed infant. Among these factors, the small amounts of DHA in human milk together with the abundance of DHA in the brain has generated a large number of studies on the potential benefits of adding DHA, or DHA plus ARA to formula on infant visual, mental, and motor skill development, and reviews have been published (Heird and Lapillone 2005; Simmer et al. 2008a, 2008b; Beyerlein et al. 2009). In general, these studies show that a dietary source of DHA with ARA is important for preterm infants, with inconsistent findings of benefit for infants born after term gestation.

Preterm infants born early in the third trimester of gestation (<33 weeks-gestation) are known to be at risk of nutrient deficiencies, with low body stores and nutrient needs that exceed those that can be met by human milk, unless fortified (Georgieff and Innis 2005). Studies with preterm infants fed formulas with DHA in amounts similar to human milk (0.2–0.38% fat), with ARA included have found some benefits to growth, early measures of visual acuity, and scores on neurodevelopmental tests, particularly in smaller infants (O'Connor et al. 2001; Simmer et al. 2008a). However, estimation of the amount of DHA needed to support accretion of DHA at the same rate as that in utero indicates a need for about 60 mg/day DHA, whereas milk with 0.35% fat as DHA fed at 120 ml/day to 1 kg infant can provide only 15 mg (Georgieff and Innis 2005). This suggests most human milk, which typically contains 0.2–0.3% fat as DHA is inadequate to support the needs of small preterm infants. Preterm infants (< 33 weeks gestation) at birth fed human milk with 1% DHA and about 0.5% ARA until their estimated full-term delivery date had higher erythrocyte glycerophospholipid DHA and higher sweep visual evoked potential acuity at 4 months-of-age than infants fed milk with 0.2–0.3% fat as DHA (Smithers et al. 2008). Bayley Mental Development scores at 18 months corrected age showed girls, but not boys, and all infants of birthweight < 1,250g had better test scores when fed milk with 1% rather than 0.2–0.3% fat as DHA milk (Makrides et al. 2009). These studies show DHA needs of preterm infants are not likely to be met by milk from mothers following usual western diets low in fish or preterm formulas with 0.35% fat or less as DHA.

Studies on ω-3 fatty acid nutrition and brain development in infants born after full-term gestation are more complex. Important variables include the ω-3 fatty acid supply in gestation, the variable ω-3 fatty acids in human milk, then weaning foods, and numerous dietary, family, environmental, and genetic

factors that impact child development. While randomization distributes variables among intervention groups, it does not lessen variability and thus the need for large samples sizes. Smaller cohorts with similar socio-demographic and dietary practices, however, may limit some of these problems. Interventions to increase ω-3 fatty acid intakes in pregnant and breast-feeding women or in infants and children can only benefit individuals in the group consuming an inadequate diet, assuming no other dietary deficiency limits the ability to respond (Innis 2009). The relationship between the intake of an essential nutrient and biochemical, molecular, and physiological endpoints in which the nutrient functions is nonlinear, since no additional physiological benefit occur when nutrient intake exceed needs. Rather, a parabolic response to increasing intake of essential nutrients are more usual, with adverse or pharmalogical effects at high intakes. Finally, infants and children are not in steady-state, and this poses the need for care to avoid ceiling effects when selecting tests and the ages at which tests are given.

Visual acuity has been widely used as an endpoint in studies on the need for dietary DHA in young infants. Studies in the U.S. involving infants fed formula with about 0.35% DHA and 0.72% ARA in the fat have reported improvement in visual acuity, whether the formula with DHA was fed from birth or after initial breast-feeding, as well as benefits to visual acuity when DHA was included in weaning foods (Birch et al. 2002; Hoffman et al. 2004; Birch et al. 2005). Other studies, however, have not detected differences in visual acuity between breast-fed infants and infants fed formula with no DHA, or between infants fed formula with and without DHA (Heird and Lapillone 2005; Simmer et al. 2008b). Similarly, while some evidence of improved performance in tests of early neural development have been reported for healthy term infants provided with DHA in formula, as a supplement or in infant foods, most studies have involved small numbers of infants and studies indicating no benefit have also been published (Heird and Lapillone 2005; Simmer et al. 2008b; Beyerlein et al. 2009; Innis 2009). Variability in DHA status at birth, among groups of breast-fed infants when included for comparison, and deficiencies introduced during weaning that impact performance on developmental tests given after 6 months-of-age are all factors that may contribute to inconsistent information.

Several prospective, observational studies have linked low intakes of fish (the major diet source of EPA and DHA) in pregnant women, low blood levels of DHA in pregnancy or in infants at birth, and low breast milk DHA to lower scores on tests of mental, motor, and visual system development in infants, with the effects extending into later childhood (Hibbeln et al. 2007; Innis 2008, 2009). More direct evidence of the importance of DHA is provided by interventions to show that fish oil or other sources of DHA during gestation and lactation can, in some settings improve early infant development including early problem-solving, hand–eye coordination, visual acuity scores, and psychomotor development. Some evidence of a relationships between maternal DHA status in gestation and performance on later standardized test of development have been found in later childhood, although evidence of benefits of maternal fish oil supplementation were absent (Helland et al. 2008), and confounding by nutrients such as vitamin D are possible.

More recently, attention has turned to the low ω-3 fatty acid intakes of young children, including children in developing countries. A recent study with 7–9 year-old children in South Africa given fish flour to provide 0.335 g 18:3ω-3, 82 mg EPA and 192 mg DHA for 104 days found evidence of improved verbal learning and memory, together with an increase in the red blood cell DHA and EPA, and a decrease in ARA (Dalton et al. 2009). On the other hand, studies in India involving over 500 children 6–10 years-of-age that included supplementation with 900 mg/day ALA plus 100 mg/day DHA found no benefits on growth or cognitive test scores although a wide range of domains were tested (Muthayya et al. 2009). Similarly, 110 mg/day EPA plus DHA had no effect on cognitive performance among children 7–10 years-of-age in Australia and Indonesia (Osendarp et al. 2007). While initial findings appear discouraging, correction of long-standing ω-3 fatty acid deficiency may not be simple, particularly if combined with multiple other nutrient deficits. Optimal intakes of DHA for healthy children are also unknown, as are the dosages needed to restore depleted tissue pools.

133.9 Summary

There is no doubt that DHA is critical for the brain at all stages of the life span. Strong biological evidence is available to show DHA plays key roles in the brain that span from neurogenesis and neurite outgrowth, to dopaminergic and serotinergic neurotransmission, to generation of potent anti-inflammatory and neuroprotective metabolites; all functions for which ω-6 fatty acids cannot substitute or interfere. Consuming a diet that provides DHA unequivocally provides DHA that in gestation can be transported across the placenta, in lactation is secreted in human milk, and in the child is readily absorbed and acylated into membrane glycerophospholipids. However, there is also no doubt that dietary intakes of ω-6 and ω-3 fatty acids have become severely distorted over the last one to two centuries, with a prolific increase in LA and loss of long chain ω-3 fatty acids from the food supply, and this extends to the fatty acids transported across the placenta, secreted in human milk, and to the foods available for feeding young children. This ω-6 and ω-3 fatty acid imbalance is becoming increasingly implicated in several major chronic diseases and this chapter raises the question of whether inadequate intakes of ω-3 fatty acids coupled with excessive LA contributes to poor DHA accretion in the developing human brain.

133.10 Application to Other Areas of Health and Disease

The roles of ω-3 fatty acids in neurogenesis, serotinergic, and dopaminergic transmission, and as a precursor to neuroprotective metabolites have broad relevance to diverse areas. Altered metabolism of the long chain ω-3 fatty acids, EPA and DHA, as well as inadequate ω-3 fatty acid intakes have been implicated in several neurological disorders, including depressive and aggressive disorders, as well as behavioral problems in children (Hibbeln 2009). Several studies have reported benefit of supplementation with EPA plus DHA, or DHA alone in these problems in children (Richardson and Montgomery 2005; Vaisman et al. 2008). Docoanoids, the oxygenated metabolites of 22-carbon chain fatty acids, such as neuroprotection 1, and docosatrienes, a conjugated triene metabolite of DHA have potent anti-inflammatory effects, and these appear to be important in the response to injury, such as oxidative stress or reperfusion damage following stroke; new studies in this field may offer therapeutic tools to protect the brain and enhance recovery following inflammatory or oxidative insults (Niemoller and Bazan 2009).

Summary Points

- ω-3 fatty acids are essential dietary nutrients, the amounts, and types of ω-3 fatty acids in the diet are important to the accretion and maintenance of brain DHA.
- Loss of DHA from the brain can have an adverse effect on neurogenesis and neurite outgrowth, serotinergic, and dopaminergic neurotransmission, and protection from neuroinflammation.
- DHA provided in the diet, transferred across the placenta, or provided in breast milk or milk substitutes, or in the weaning diet is taken up and incorporated into the brain.
- Diets low in DHA and EPA and high plant-derived ω-6 fatty acids are associated with increased ω-6:ω-3 fatty acids; these dietary patterns are linked to poorer infant and child neuro-cognitive development and several psychiatric problems in adults.

- Modern food production has introduced large amounts of plant-derived ω-6 fatty acids into the diet; this has led to enrichment of ω-6 fatty acids and loss of long chain ω-3 fatty acids, and an imbalance in ω-6 and ω-3 fatty acids in the food supply.
- Differences in dietary intake of DHA explain differences in blood lipid DHA and breast milk DHA.
- The role of EPA in brain function is unclear, but EPA may be important in modulating neuro-inflammatory processes and it may have a role in some attentional and depressive disorders.
- Infants born prior to 33 weeks gestation require more DHA than is supplied by milk from mothers following typical western diets, their milk, or formula needs at least 1% fat as DHA.

Key Terms

Fatty acid: A carboxylic acid with an unbranched chain of carbon atoms. The most usual fatty acids have an even number of carbon atoms and contain no double bonds, one double bond or more than one double bond, termed saturated, monounsaturated, or polyunsaturated, respectively.

Essential fatty acid: A polyunsaturated fatty acid with two or more double bonds of either the ω-6 series or ω-3 series.

Omega-3 fatty acids: A series of polyunsaturated fatty acids in which the first double bond from the methyl end of the fatty acid is at carbon number 3. Omega-3 fatty acids are essential nutrients.

Omega-6 fatty acids: A series of polyunsaturated fatty acids in which the first double bond from the methyl end of the fatty acid is at carbon number 6. Omega-6 fatty acids are essential nutrients.

References

Adibhatla RM, Hatcher JF. Subcell Biochem. 2008;49:241–68.

Bazan NG. Trends Neurosci. 2006;29:263–71.

Beyerlein A, Hadders-Algra M, Kennedy K, Fewtrell M, Singhal A, Rosenfeld E, Lucas A, Boulostra H, Koletzko B, van Kries R. J Pediatr Gastroenterol Nutr. 2009 [Epub, ahead of print].

Birch EE, Hoffman DR, Castaneda YS, Fawcett SL, Birch DE, Uauy RD. Am J Clin Nutr. 2002;75:570–80.

Birch EE, Castaneda YS, Wheaton DH, Birch DG, Uauy RD, Hoffman DR. Am J Clin Nutr. 2005;81:891–4.

Burdge GC. Prostaglandins Leukot Essent Fatty Acids. 2006;75:161–8.

Carnielli VP, Simonato M, Verlato G, Luijendijk I, De Curtis M, Sauer PJ, Cogo PE. Am J Clin Nutr. 2007;86:1323–30.

Caspi A, Williams B, Kim-Cohen J, Craig IW, Bilne BJ, Poulton R, Schalkwyk LC, Taylor A, Werts H, Moffitt TE. Proc Natl Acad Sci USA. 2007;104:18860–5.

Chalon S. Prostaglandins Leukot Essent Fatty Acids. 2006;75:259–69.

Chen CT, Green JT, Orr SK, Bazinet RP. Prostaglandins Leukot Essent Fatty Acids. 2008;79:85–91.

Chen CT, Lui Z, Ouellet M, Calon F, Bazinet RB. Prostaglandins Leukot Essent Fatty Acids. 2009;80:157–63.

Cho HP, Nakamura MT, Clarke SD. J Biol Chem. 1999;274:471–7.

Clandinin MT, Chappell JE, Heim T, Swyer PR, Chance GW. Early Human Dev. 1981;5:355–66.

Cook HW, Thomas SE, Xu Z. Biochem Cell Biol. 1991;69:475–84.

Cordain L, Eaton SB, Sebastian A, Mann L, Lindeberg S, Watkins BA, O'Keefe JH, Brand-Miller J. Am J Clin Nutr. 2005;81:341–54.

Coti-Bertrand P, O'Kusky JR, Innis SM. J Nutr. 2006;136:1570–5.

Crawford MA, Bloom M, Broadhurst CL, Schmidt WF, Cunnane SC, Galli C, Gehbremeskel K, Linseisen F, Lloyd-Smith J, Parkington J. Lipids. 1999;34:S39–47.

Cunnane SC, Ryan MA, Lin YM, Lim SY, Salem N. Jr. Pediatr Res. 2006;59:107–10.

Cunningham P, McDermott. J Nutr. 2009;139:636–9.

Dagai L, Peri-Naor R, Birk RZ. Neurochem Res. 2009;34:66–75.

Dalton A, Wolmarans P, Witthuln R, van Stuijvenberg ME, Swanevelder SA, Smuts CM. Prostaglandins Leukot Essent Fatty Acids. 2009;80:143–9.

Eaton SB. Proc Nutr Soc. 2006;65:1–6.

Farquharson J, Jamieson EC, Abbasi KA, Patrick WJA, Logan RW, Cockburn F. Arch Dis Childhood. 1995;72:198–203.

Friesen RW, Innis SM. J Nutr. 2009 [Epub, ahead of print].

Georgieff MK, Innis SM. Pediatr Res. 2005;57:94R–103R.

Giusto NM, Pasquare SJ, Salvador GA, Castagnet PI, Roque ME, Ilincheta de Boshero MG. Prog Lipid Res. 2000;39:315–91.

Harris WS, Mozaffarian D, Rimm E, Kris-Etherton P, Rudel LL, Appel LJ, Engler MM, Engler MB, Sacks F. Circulation. 2009;119: 902–7.

Heird WC, Lapillone A. Annu Rev Nutr. 2005;25:549–71.

Helland IB, Smith L, Blomen B, Saarem K, Saugstad OD, Drevon C. Pediatrics. 2008;122:e472–9.

Hibbeln JR. World Rev Nutr Diet. 2009;99:17–30.

Hibbeln JR, Davis JM, Steer C, Emmett P, Rogers I, Williams C, Golding J. Lancet. 2007;369:587–85.

Hishikawa D, Shindou H, Kobayashi S, Nakanishi H, Taguchi R, Shimizu T. Proc Natl Acad Sci USA. 2008;105:2830–5.

Hoffman DR, Theuer RC, Castaneda YS, Wheaton DH, Bosworth RG, O'Connor AR, Morale SE, Wiedemann LE, Birch EE. J Nutr. 2004;B4:2307–13.

Hussein N, Al-Sing E, Wilkinson P, Leach C, Griffin BA, Millwood DJ. J Lipid Res. 2005;46:269–80.

Huttenlocher PR. Neuropsychologia. 1990;28:517–27.

Innis SM. Prog Lipid Res. 1991;30:39–103.

Innis SM, King DJ. Am J Clin Nutr. 1999;70:383–90.

Innis SM. Adv Exp Med Biol. 2004;554:27–43.

Innis SM, Vaghri Z, King DJ. Am J Clin Nutr. 2004;80:768–73.

Innis SM. Placenta. 2005;26:S70–5.

Innis SM. J Nutr. 2007;137:855–9.

Innis SM, Jacobson K. Nutr Rev. 2007;65:5188–9.

Innis SM, Davidson AG. Annu Rev Nutr. 2008;28:55–72.

Innis SM. Brain Res. 2008;1237:35–43.

Innis SM. J Pediatr Gastroenterol Nutr. 2009;48:S16–24.

Jacobson K, Mundra H, Innis SM. Am J Gastroenterol Liver Physiol. 2005;289:G13–G20.

Jump DB. Curr Opin Lipidol. 2008;19:242–7.

Katakura M, Hashimoto M, Shahdat HM, Gamoh S, Okui T, Matsuki K, Shio O. Neuroscience. 2009;160:651–60.

Kawashima A, Harada T, Imada K, Yano T, Mizuguchi K. Prostaglandins, Leukoto Essert Fatty Acids. 2008;79:59–65.

Kawashima A, Harada T, Kami H, Yano T, Imada K, Mizuguchi K. J Nutr Biochem. 2009;20:965–73.

Kuipers RS, Smit EN, van der Meulen J, Janneke Dijck-Brouwer DA, Rudy Boenma E, Muskiet FA. Prostaglandins Leukot Essert Fatty Acids. 2007;76:221–33.

Lands WE. J Biol Chem. 1958;231:883–8.

Leonard AE, Kelder B, Bobik EG, Chuang LT, Parker-Barnes JM, Thurmond JM, Kroeger PE, Kopchick JJ, Huang YS, Mukerji P. Biochem J. 2000;347:719–24.

Levitt P. J Pediatr. 2003;143:335–45.

Liu JW, Almaguel FG, Bu L, De Leon DD, De Leon M. J Neurochem. 2008;1006:2015–29.

Makrides M, Neumann MA, Byard RW, Simmer K, Gibson RA. Am J Clin Nutr. 1994;60:189–94.

Makrides M, Neumann MA, Jeffrey B, Lien EL, Gibson RA. Am J Clin Nutr. 2000;71:120–9.

Makrides M, Gibson RA, McPhee AJ, Collins CT, Davis PG, Doyle LW, Simmer K, Colditz PB, Morris S, Smithers LG, Willson K, Ryan P. JAMA. 2009;301:175–82.

Martinez M. J Pediatr. 1992;120:S129–38.

Martinez M, Mougan I. J Neurochem. 1998;71:2528–33.

Martinez P, Morros A. Front Biosci. 1996;1:d103–07.

Mosely EE, Wright AL, McGuire MK, McGuire MA. Am J Clin Nutr. 2005;82:1292–7.

Muthayya S, Eilander A, Transler C, Thomas T, van der Knapp HC, Srinivasan K, van Klinken BJ, Osendarp SJ, Kurpad AV. Am J Clin Nutr. 2009;89:1766–75.

Niemoller TD, Bazan NG. Prostaglandins Other Lipid Mediat. 2009 [Epub, ahead of print].

Novak E, Dyer RA, Innis SM. Brain Res. 2008;1237:136–45.

O'Connor DL, Hall R, Adamkin D, Auestad N, Castillo M, Connor WE, Connor SL, Fitzgerald K, Groh-Wargo S, Hartmann EE, Jacobs J, Janowsky J, Lucas A, Margeson D, Mena P, Neuringer M, Neisen M, Singer L, Stephen J, Szabo J, Zemon V. Pediatrics. 2001;108:359–71.

Osendarp SJ, Baghurst KI, Bryan J, Calvaresi E, Hughes D, Hussaini M, Karyadi SJ, van Klinken BJ, van der Knaap HC, Lukito W, Mikarsa W, Transler C, Wilson C. Am J Clin Nutr. 2007;86:319–33.

Ouellet M, Emond V, Chen CT, Julien C, Bourasset F, Oddos S, LaFerla F, Bazinet RP, Calon F. Neurochem Int. 2009;55:476–82.

Ponder DL, Innis SM, Benson JD, Siegman JS. Pediatr Res. 1992;32:683–8.

Putnam JC, Carlson JE, Devoe PW, Bosness LA. Am J Clin Nutr. 1982;36:106–14.

Richardson AJ, Montgomery P. Pediatrics. 2005;155:1360–6.

Sanders K, Johnson L, O'Dea K, Sinclair AJ. Lipids. 1994;29:129–38.

Sastry PS. Prog Lipid Res. 1985;24:169–76.

Schaeffer L, Gohlke H, Muller M, Heid IM, Palmer LJ, Kompauer I, Demmelmair H, Illig T, Koletzko B, Heinrich J. Human Mol Genet. 2006;15:1746–56.

Siegel GJ, Albers W, Brady ST, Price DL. Elsevier Academic Press, London. 2006.

Simmer K, Schulzke SM, Patole S. Cochrane Database Syst Rev. 2008a: CD00375.

Simmer K, Patole SK, Rao SC. Cochrane Database Syst Rev. 2008b: CD00376.

Simpolous AP. Am J Clin Nutr. 1999;70:560–95.

Skeaff CM, Hodson L, McKenzie JE. J Nutr. 2006;36:565–9.

Smithers LG, Gibson RA, McPhee A, Makrides M. Am J Clin Nutr. 2008;88:1049–56.

Stark KD, Lim S-Y, Salem N Jr. J Lipid Res. 2007;48:2471–7.

Stevens L, Zhang W, Peck L, Kuczek T, Grevstad N, Mahon A, Zentall SS, Arnold LE, Burgess JR. Lipids. 2003;38:1007–21.

Svennerholm L. J Lipid Res. 1968;9:570–4.

Thatcher RW. Dev Neuropsychol. 1991;7:397–419.

Vaisman N, Kaysar N, Zaruk-Adasha Y, et al. Am J Clin Nutr. 2008;87:1170–80.

Xie L, Innis SM. J Nutr. 2008;138:2222–8.

Chapter 134
Dietary Choline for Brain Development

Amy R. Johnson and Steven H. Zeisel

Abbreviations

ACho	Acetylcholine
PtdCho	Phosphatidylcholine
SM	Sphingomyelin
VLDL	Very-Low-Density Lipoprotein
AI	Adequate Intake
UL	Upper Tolerable Limit
SAM	S-Adenosylmethionine
PEMT	Phosphatidylethanolamine *N*-methyltransferase
CHDH	Choline Dehydrogenase
BADH	Betaine Aldehyde Dehydrogenase
PCho	Phosphocholine
BHMT	Betaine:Homocysteine Methyltransferase
MS	Methionine Synthase
CDP-Choline	Cytidine Diphosphocholine
LTP	Long-Term Potential
ED	Embryonic Day
PD	Postnatal Day
SNP	Single-Nucleotide Polymorphism
AChE	Acetylcholineesterase
ChAT	Choline Acetyltransferase
TGF-β	Transforming Growth Factor-β
DCC	Deleted in Colorectal Cancer
MAPK	Mitogen-Activated Protein Kinase
CREB	cAMP-Response Element-Binding Protein
NGF	Nerve Growth Factor
H3	Histone 3
MeCP1, 2	Methyl-CpG-Binding Protein 1, 2
MBD 1–4	Methyl-CpG-Binding Domain 1–4

S.H. Zeisel (✉)
University of North Carolina at Chapel Hill, Nutrition Research Institute, 500 Laureate Way,
Kannapolis, North Carolina 28081
e-mail: steven_zeisel@unc.edu

134.1 Introduction

In the last 20 years, a substantial body of literature has accumulated documenting the involvement of dietary choline in brain development and function. Epidemiological studies in humans (Shaw et al. 2004, 2006), as well as *in vivo* studies with rodents, indicate that the amount of choline made available to the developing fetus can have significant effects on brain formation (Fisher et al. 2001) and function, particularly in the hippocampus (Meck and Williams 1997c). In this chapter, we will discuss the effect of gestational dietary choline availability on hippocampal function, focusing primarily on memory and learning. We will also describe changes in cellular characteristics and explain how choline may be conferring these effects.

The availability to the developing fetus of extra choline enhances, while choline deficiency retards, an animal's ability to perform maze tasks designed to test memory and learning (Meck and Williams 1997a,c, 1988, 1999). Changes in the number, structure, and some functional aspects of hippocampal neurons occur as a result of both maternal dietary choline deficiency and supplementation during late pregnancy (Craciunescu et al. 2003; Li et al. 2004; Jones et al. 1999). Gestational choline availability is correlated with differences in expression and activation of proteins known to be involved in synaptic plasticity, neuronal proliferation, neuronal migration, and neuronal death (Mellott et al. 2004; Niculescu et al. 2005, 2006; Albright et al. 2005, 1999; Craciunescu et al. 2003). Although the underlying mechanisms by which choline elicits these memory phenotypes are not yet fully understood, experimental evidence suggests that choline's influence on gene expression at the level of DNA and histone methylation likely plays an important role (Davison et al. 2009; Niculescu et al. 2005, 2004) (Fig. 134.1).

Many foods normally consumed by humans contain choline (http://www.ars.usda.gov/Services/docs.htm?docid=6232), but some populations, especially those that do not regularly consume meat and eggs, are at an increased risk of developing clinical choline deficiency. Pregnant or lactating
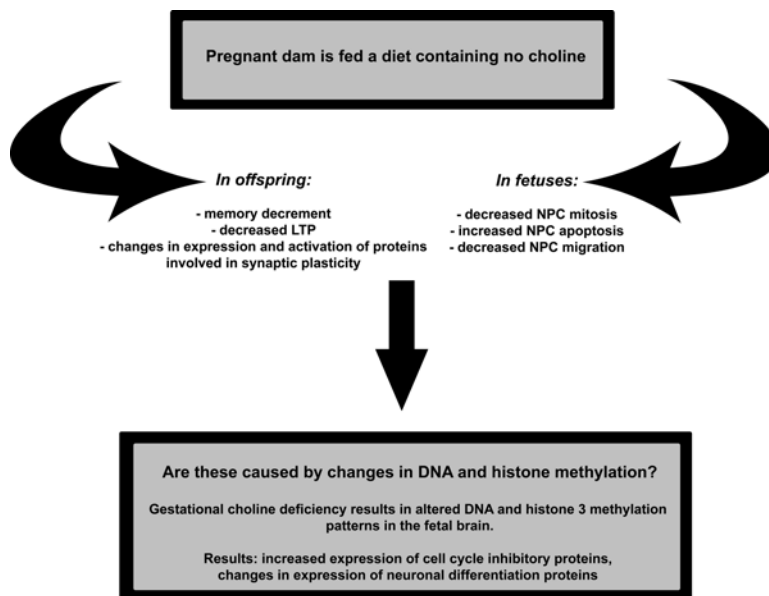
Fig. 134.1 Maternal choline deficiency during pregnancy changes brain development of both the offspring and fetus. In rodents, maternal dietary choline deficiency during pregnancy results in detrimental changes in the brain function of her offspring and development of her fetuses. Although the exact mechanism by which the changes occur is not fully understood, epigenetic gene control likely plays an important role. *LTP* long-term potential, *NPC* neural progenitor cell

women, men, postmenopausal women, and individuals harboring certain polymorphisms in genes involved in choline metabolism may have an increased requirement for dietary choline (Fischer et al. 2007). Gender and genetic profile are factors to be taken into account when determining adequate intake levels of choline, especially for women of reproductive age, as their diet directly influences the brain development of their baby.

134.2 Choline Is an Essential Nutrient

Choline is an essential nutrient for humans, and all cells require choline, or its metabolites, for maintenance of plasma membrane integrity and cellular signaling, as in the case of phopsphatidylcholine (PtdCho) and sphingomyelin (SM). Betaine, which is oxidized choline, is a major source of methyl groups in tissues and contributes to the pool of S-adenosylmethionine (SAM) available for the methylation of biological molecules including nucleic acids, proteins, and phospholipids. Also, choline may be acetylated to form acetylcholine (ACho), an important neurotransmitter and neurotrophic signaling molecule. The availability of choline can directly regulate the function of cholinergic neurons by influencing ACho concentrations within these cells (Zeisel 2006). Additionally, choline is required for the export of lipids from the liver because PtdCho is a necessary component of very-low-density lipoprotein (VLDL), hepatosteatosis, or fat accumulation in the liver, is a hallmark of dietary choline deficiency and can lead to liver damage and perhaps to carcinogenesis. Other characteristics of prolonged ingestion of a choline-deficient diet in humans include muscle cell damage, lymphocyte apoptosis, and a rise in plasma homocysteine concentrations (Zeisel 2006).

134.3 Dietary and Endogenous Sources of Choline

In 1998, the Institute of Medicine of the National Academy of Sciences (USA) set Adequate Intake (AI) levels for daily choline consumption (Institute of Medicine and National Academy of Sciences USA 1998). 550 mg/day is currently recommended for men and 425 mg/day for women (Table 134.1); it is estimated that typical daily choline intake by individuals eating normal diets is very close to, or less than, this recommendation (Shaw et al. 2004; Xu et al. 2008). Choline and choline metabolites

Table 134.1 Dietary reference intake values for choline (Information from Institute of Medicine, National Academy of Sciences USA, 1998)

Population	Age	Adequate intake (AI)	Tolerable upper limit (UL)
AI for infants	0–6 months	125 mg/day, 18 mg/kg	Not possible to establish[a]
	6–12 months	150 mg/day	
AI for children	1–3 years	200 mg/day	1,000 mg/day
	4–8 years	250 mg/day	1,000 mg/day
	9–13 years	375 mg/day	2,000 mg/day
AI for males	14–18 years	550 mg/day	3,000 mg/day
	19 years and older	550 mg/day	3,500 mg/day
AI for females	14–18 years	400 mg/day	3,000 mg/day
	19 years and older	425 mg/day	3,500 mg/day
AI for pregnancy	All ages	450 mg/day	Age-appropriate UL
AI for lactation	All ages	550 mg/day	Age-appropriate UL

AI adequate intake, *UL* upper tolerable limit

[a]Source of intake should be food and formula only

Table 134.2 Choline content in foods (Information from USDA, Nutrient Data Laboratory and Agricultural Research Service, 2008)

Food	Total choline[a] mg choline moiety/100 g food	Betaine mg/100 g food
Eggs: whole, raw	250	0.6
Chicken liver: raw	190	17
Cereal: wheat germ, toasted	180	410
Pork: cured, pan fried bacon	130	4.2
Beets: raw	6	130
Spinach: frozen, microwaved	28	130
Beef: liver, pan fried	420	6.3
Bread: whole wheat	27	38
Crackers: wheat	27	58
Bulgur wheat: cooked	6.9	83

[a]"Total choline" refers to free choline, phosphocholine, phosphatidylcholine, glycerophosphocholine and sphingomyelin content in food. Betaine is reported separately and therefore not included in this sum

can be found in significant amounts in many foods regularly consumed by humans. Additionally, some foods, such as infant formula, are fortified with choline. The United States Department of Agriculture has recently constructed a database reporting the choline content of a wide variety of foods (http://www.ars.usda.gov/Services/docs.htm?docid=6232). Foods highest in choline content per 100 g include beef and chicken liver, eggs, and wheat germ. Foods with high betaine content per 100 g include wheat bran, bulgur wheat, and spinach (Table 134.2). It is important to take betaine content into consideration since the presence of betaine will spare choline from use as a methyl-group donor, leaving more choline available for ACho or PtdCho biosynthesis.

In addition to dietary sources, choline can be synthesized de novo by the enzyme phosphatidylethanolamine *N*-methyltransferase (PEMT); this occurs primarily in the liver (Zeisel 2006). Using phosphatidylethanolamine and SAM as substrates, PEMT catalyzes the formation of PtdCho, which can be incorporated into cell membranes or hydrolyzed, generating a choline moiety. When fed a choline-deficient diet, mice with two mutated alleles of *Pemt* (*Pemt*^{-/-}) developed hepatosteatosis and severe liver damage, both of which may contribute to their premature death. Feeding these mice with excess choline prevented these outcomes and reversed the liver damage if supplementation was initiated early enough (Walkey et al. 1998). The PEMT pathway is more than a means of augmenting PtdCho formation by the cytidine diphosphocholine (CDP-choline) pathway; the PEMT pathway is a major user of methyl-groups derived from methionine (generating homocysteine). Plasma homocysteine concentrations in *Pemt*^{-/-} mice are half of those measured in wild-type mice and overexpression of *Pemt* increases homocysteine concentrations by 40% (Jacobs et al. 2005; Shields et al. 2005). The human *PEMT* gene is induced by estrogen and thus, young women have a lower dietary requirement for choline (premenopausal women are less likely to develop hepatosteatosis, liver, and muscle cell damage on a choline-deficient diet than are postmenopausal women and men (Fischer et al. 2007; Resseguie et al. 2007). However, pregnancy and lactation increases dietary choline requirements, and it is likely that most women need to eat choline during these periods (Zeisel 2006).

134.4 Genetic Polymorphisms Affect Dietary Choline Requirements

It is important to recognize that there is significant variation in dietary requirements for choline. Some individuals rapidly deplete when deprived of choline (days) while others take weeks to become depleted (Fischer et al. 2007). Some people require as much as 850 mg/day to prevent

organ dysfunction while others need less than 550 mg/day (Fischer et al. 2007). These differences are likely attributable to genetic variation among individuals. Although they would be expected to be resistant to choline deficiency, 44% of premenopausal women must eat choline, or they develop organ dysfunction in the same way that men do (Fischer et al. 2007). These differences are due, in part, to common single-nucleotide polymorphisms (SNPs) in the genes associated with choline and folate metabolism (da Costa et al. 2006; Kohlmeier et al. 2005). Eighteen percent of the Raleigh-Durham-Chapel Hill, North Carolina, USA population is homozygous (70% have 1 allele) for an SNP in the promoter region of *PEMT* (rs12325817) that makes them much more susceptible to dietary choline deficiency (odds ratio 25: risk of becoming choline deficient is increased 25x, $p = 0.002$) than are those without the SNP because endogenous production of choline molecules via PEMT is impaired (da Costa et al. 2006; Resseguie et al. 2007). 17-beta-estradiol, an estrogen analog, increases *PEMT* transcription and activity in human hepatocytes via an estrogen response element near the transcription start sites in both human and murine *PEMT* genes (Resseguie et al. 2007) and women with the common *PEMT* SNP are unresponsive to estrogen induction of the gene (manuscript in preparation). Humans with this SNP need more dietary choline as adults (da Costa et al. 2006), and we suggest that they are likely to need more choline during pregnancy to sustain normal fetal development.

134.5 Choline Metabolism

Figure 134.2 illustrates the pathways of choline metabolism. Choline can be utilized to synthesize PtdCho and SM for use in cell membranes, it can be oxidized to betaine for use as a methyl-donor and an organic osmolyte, and it can also be acetylated to form the neurotransmitter ACho.

A small portion of dietary choline is converted to ACho by the enzyme choline acetyltransferase (ChAT). This enzyme is found in high concentrations in cholinergic neurons ensuring that ACho is available for release by these cells. Since it is unlikely that choline and/or acetyl-CoA are present at levels that would saturate the ChAT enzyme, choline availability determines the rate of ACho synthesis (Blusztajn et al. 1987) and modulates the amount of this neurotransmitter released into the synapse (Cohen and Wurtman 1975; Ulus et al. 1989; Wecker 1991). Choline-containing phospholipids including PtdCho and SM, incorporated into cholinergic cell membranes, serve as a reserve of choline available for ACho synthesis in cells with a high demand for ACho (Blusztajn et al. 1986, 1987).
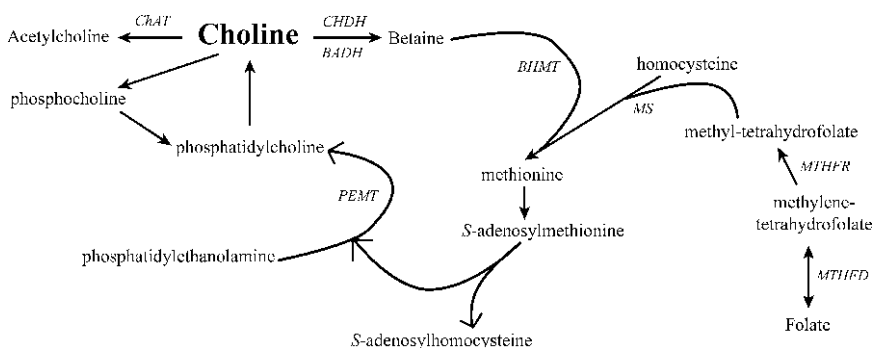
Fig. 134.2 The choline metabolic pathway. Metabolism of choline includes the interaction point between choline and folate metabolism. *ChAT* choline acetyltransferase, *CHDH* choline dehydrogenase, *BADH* betaine aldehyde dehydrogenase, *BHMT* betaine:homocysteine methyltransferase, MS methionine synthase, *MTHFR* methylene-tetrahydrofolate reductase, *MTHFD* methylene-tetrahydrofolate dehydrogenase, *PEMT* phosphatidylethanolamine N-methyltransferase
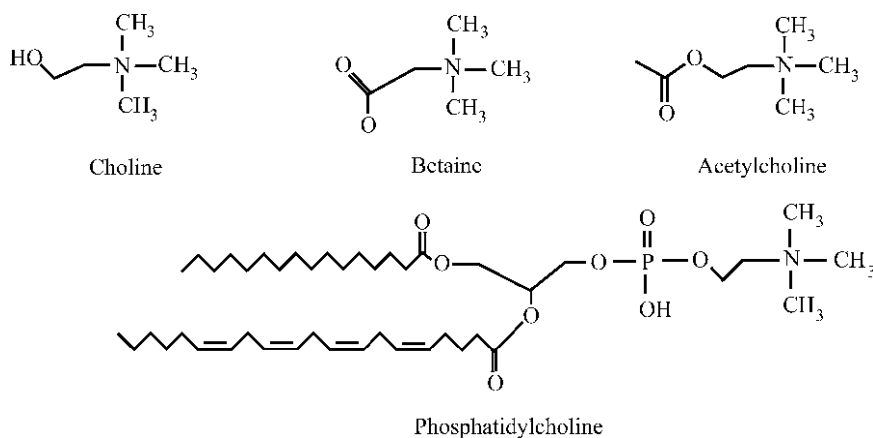
Fig. 134.3 Structures of selected choline metabolites. Choline, betaine, acetylcholine, and phosphatidylcholine play important roles in brain development and function

Two successive oxidation reactions convert choline to betaine via the formation of an aldehyde intermediate (Chern et al. 2000; Chi-Shui and Ru-Dan 1986; Haubrich and Gerber 1981). In mammals, this process involves two enzymes: choline dehydrogenase (CHDH) and betaine aldehyde dehydrogenase (BADH). This irreversible conversion takes place in the mitochondrial matrix following choline transport into these organelles. Once formed, betaine diffuses from the mitochondria into the cytosol where it can donate labile methyl-groups for SAM generation through the one-carbon metabolism pathway – the point of interaction between choline and folate metabolism. Choline oxidation occurs primarily in liver, kidney, and testis; CHDH enzyme has relatively low activity in whole mouse brain (Johnson et al. 2010).

An important role for choline is for biosynthesis of cellular membrane phospholipids, such as PtdCho (also known as lecithin) and SM. PtdCho represents more than 50% of the total phospholipid content in cell membranes. PtdCho synthesis is highly regulated and can occur through two pathways (Zeisel 2006). In the CDP-choline pathway, choline is phosphorylated, generating phosphocholine (PCho). PCho is converted to CDP-choline that is then combined with diacylglycerol, ultimately resulting in the formation of PtdCho. As discussed above, an alternative pathway synthesizes PtdCho from SAM and phosphatidylethanolamine through the enzymatic activity of PEMT. SM, another important component of membranes, is formed from PtdCho (Fig. 134.3).

134.6 Choline, Methionine, and Folate Metabolism Are Interrelated

The metabolic pathways of choline, methionine, and folate all interact at the point in which homocysteine is converted to methionine. A deficiency or excess of any one of these three nutrients will have an impact on the usage of the other two; therefore, dietary choline requirements must be considered with methionine and folate intake in mind (Zeisel 2006). Homocysteine is converted to methionine using methyl-groups from either betaine or methyl-folate. Choline is oxidized to betaine in two successive reactions as discussed above. Betaine:homocysteine methyltransferase (BHMT) methylates homocysteine using a methyl group from betaine resulting in the formation of methionine. Alternatively, methionine synthase (MS) uses folic acid and vitamin B_{12} to methylate homocysteine.

Alterations in these metabolic pathways, either by changes in dietary intake or the presence of SNPs in genes involved in these pathways, leads to compensatory changes in the usage of other methyl-group

donors (Jacobs et al. 2005; Jacques et al. 2001; Shelnutt et al. 2003; Watkins et al. 2002; Weisberg et al. 2001). Rodents treated with methotrexate, an antifolate drug, had decreased hepatic choline metabolite concentrations (Pomfret et al. 1990). On the other hand, feeding rats a choline-deficient diet resulted in significantly decreased SAM and methionine concentrations as well as increased plasma homocysteine levels (Varela-Moreiras et al. 1995). We have reported that dietary choline supplementation can revorse some of the effects of flate deficiency on fetal mouse brain development (Craciunescu et al. 2010). Humans developed elevated plasma homocysteine concentrations in response to a methionine load (da Costa et al. 2005).

134.7 Choline and Fetal Development

Pregnancy and lactation are times during which demand for choline by the fetus or neonate is very high and pregnant or lactating women could become choline depleted while meeting these needs. Pregnant rats have significantly reduced choline concentrations in their liver compared to nonmated controls and these females are also more sensitive to the effects of choline-deficient diets (Zeisel et al. 1995). Dietary choline intake is especially important for pregnant and lactating women since, as will be discussed later, choline availability influences brain development. As noted earlier, choline is also necessary for modulating maternal plasma homocysteine concentrations; high maternal plasma homocysteine during pregnancy is associated with an increased incidence of birth defects (Hobbs et al. 2005). Shaw and colleagues found that dietary choline intake among women in the United States varies enough (from less than 300 mg/day to more than 500 mg/day) to influence the risk of having a baby with a neural tube defect, with women in the lowest quartile for dietary choline intake having four times the risk of having a baby with a neural tube defect (Shaw et al. 2004). Birth defects occur in rodents when choline availability is restricted early in fetal development (Fisher et al. 2001, 2002).

Large amounts of choline are transported to the fetus across the placenta during gestation (Sweiry et al. 1986; Sweiry and Yudilevich 1985). Choline concentration in amniotic fluid is 10-fold higher than the concentration in maternal blood (S.H.Z, unpublished observation). Plasma or serum choline concentrations are 6- to 7-fold higher in the fetus than in the adult, but these levels diminish to levels measured in adult circulation within weeks following birth (Ozarda et al. 2002; Zeisel and Wurtman 1981). High circulating concentrations of choline in the fetus ensure adequate availability of choline for cell membrane biosynthesis and methylation mark maintenance in rapidly forming tissues. The choline content of human milk is also directly influenced by dietary choline intake, with lactating women eating low-choline diets producing milk with lower choline content compared to women eating a more choline-adequate diet (Zeisel et al. 1982). The choline content of human milk is very high at the beginning of lactation, but diminishes to concentrations typical of commercial bovine-derived infant formulas by 30 days postpartum (Holmes-McNary et al. 1996).

134.8 Perinatal Choline Supplementation Enhances Cognitive Function in Mice

The effect of perinatal choline supplementation (approximately three times normal choline intake) on attention, learning, and memory was first observed by testing Sprague–Dawley rats on radial arms mazes (Meck et al. 1988). In the initial experiments, rat fetuses received choline supplementation via maternal diet from embryonic day (ED) 9 through birth. At birth, pups were randomly cross-fostered to dams who had not received dietary choline supplementation. Supplementation of the pups continued

through postnatal day (PD) 30 by administration of choline by subcutaneous injection. Beginning on PD 30, and continuing throughout the remainder of their lives, all animals were fed a diet with adequate, but not excessive, amounts of choline.

Animals were tested with radial-arm maze tasks beginning between 2 and 6 months of age. By using mazes with increasing numbers of arms and subjecting the animals through several trials in rapid succession on the same day (massed trials) – thus increasing the difficulty of the task – researchers observed that the choline-supplemented pups outperformed those who were not supplemented at all degrees of testing difficulty except with the initial, easiest tests where no difference among treatments was observed (Meck et al. 1988). Perinatal choline supplementation resulted in improved performance in the working, reference and temporal memory aspects of this task, while choline deficiency impaired memory (Meck and Williams 1997a, 2003). Gestational choline availability alters memory formation strategies in rodents. Pups born to choline-supplemented dams used "chunking" strategies in memory performance testing (Meck and Williams 1997b). Chunking facilitates recall of more information because items to be remembered are grouped, or chunked, together in larger units, allowing for more efficient memory processing and retrieval. Proactive interference refers to the interference of memories from previous experiences with current memory performance. Perinatal choline supplementation significantly decreased, while choline deficiency increased, proactive interference in rats compared to normal choline controls (Meck and Williams 1999).

Adult rodents develop "senility" as they age; however, animals that received choline supplementation during the perinatal period do not show this decline in cognitive function (Meck and Williams 1997c, 2003). Conversely, accelerated age-related decline in simultaneous temporal processing was observed in animals born to choline-deficient dams. These tests were also replicated using other rat strains, as well as mice, and other tests of spatial memory, including the Morris water maze test with similar results (Brandner 2002; Schenk and Brandner 1995).

134.9 Choline Availability Alters Many Characteristics of Hippocampal Function

The hippocampus, located in the medial temporal lobe of the brain, is associated with declarative memory, new memory formation, spatial navigation, and other cognitive functions (Eichenbaum 2004). Because the radial-arm and Morris water maze studies described above indicated perinatal choline availability influences these cognitive functions, alterations in the hippocampus have been the focus of investigation. In humans, hippocampal development begins on ED 56 and continues through 4 years of age. In rodents, hippocampal development begins during late gestation, ED 11, and continues through PD 30. ED 11–17 and PD 16–30 are the two time periods in which the hippocampus is most sensitive to changes in choline availability (Meck et al, 1988).

Perinatal choline availability confers changes in morphological, electrophysical, and biochemical characteristics of the hippocampus in both fetal and adult rodent brain.

134.9.1 Gestational Choline Availability Effects in Fetal Hippocampus

Neural precursor cells are partially committed stem cells from which mature neurons are derived. These cells originate in the ventricular zone of the hippocampus and migrate to other areas of this region as they differentiate into neurons. The balance between neural precursor cell proliferation
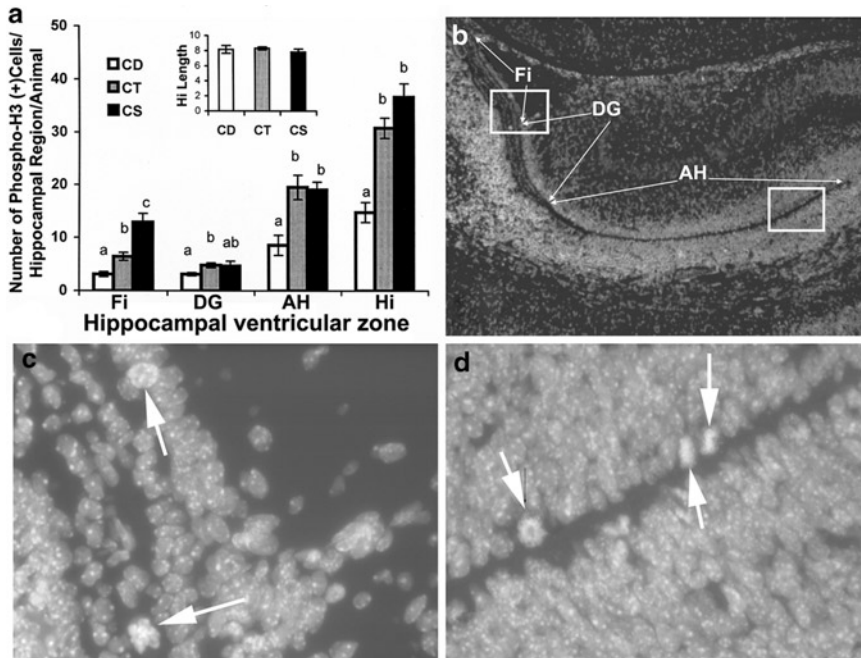
Fig. 134.4 Choline availability affects numbers of mitotic cells in fetal hippocampus. Maternal dietary choline deficiency in timed-pregnant mice fed choline-supplemented (CS), control (CT) or choline-deficient (CD) AIN-76 diet from embryonic day 12 to 17 decreases mitosis in embryonic mice on ED 17 at the ventricular surface of the ventricular zone of the hippocampus. All mice were killed on ED17 and coronal sections were prepared from the brains from the fetuses from each group for the analysis of mitosis using the mitosis-specific marker anti-phospho-histone 3. *Panel A*, In CD fetal hippocampus compared with CT, there were fewer phospho-histone three positive cells at the ventricular surface of the ventricular zone adjacent to the fimbria (Fi), dentate gyrus (DG) and Ammon's Horn (AH), and this was reflected in the calculated values for the whole hippocampal section length of the ventricular zone (Hi). Compared with the CT group, the CS group had a higher incidence of phospho-histone three labeled cells at the ventricular surface of the ventricular zone only in the fimbria. The graph insert shows the equivalence of the sections in terms of total hippocampal ventricular zone length. Values are means ± SEM of at least six pups per group from six dams. Means without a common letter, $P < 0.05$ (for each pair using Student's *t* test, for all pairs using Tukey–Kramer HSD test, and comparison with control using Dunnett's method). *Panel B* shows a representative fetal hippocampus at a magnification of 50X with the regions of interest marked. *Panels C* and *D* are 400X magnifications of the boxed regions in panel *B*, and arrows designate representative labeled cells in the hippocampal regions. *ED*, embryonic day (Reprinted from Craciunescu et al. 2003. With permission)

(mitosis) and death (apoptosis) is altered by the amount of choline a dam consumes during late pregnancy. Fetuses of dams fed a choline-deficient diet from ED 11–17 had decreased numbers of mitotic cells in their hippocampus compared to control animals (Fig. 134.4). These animals also had increased numbers of apoptotic cells in this same region (Fig. 134.5). Choline supplementation had the opposite effect, with increased cell mitosis and decreased apoptosis in this region of the brain (Craciunescu et al. 2003). Changes in rates of neural precursor cell apoptosis are a means to regulate the number of cells in neuronal subpopulations in the hippocampus, which will alter the functional characteristics of this structure.

The expression patterns of many proteins are affected by the amount of choline supplied to the fetal brain. For example, calretinin, a calcium-binding protein and a marker of GABAergic neuron differentiation, is decreased in fetuses of choline-supplemented dams (Albright et al. 2003). Choline availability alters the expression of netrin-1 and its receptor deleted in colorectal cancer
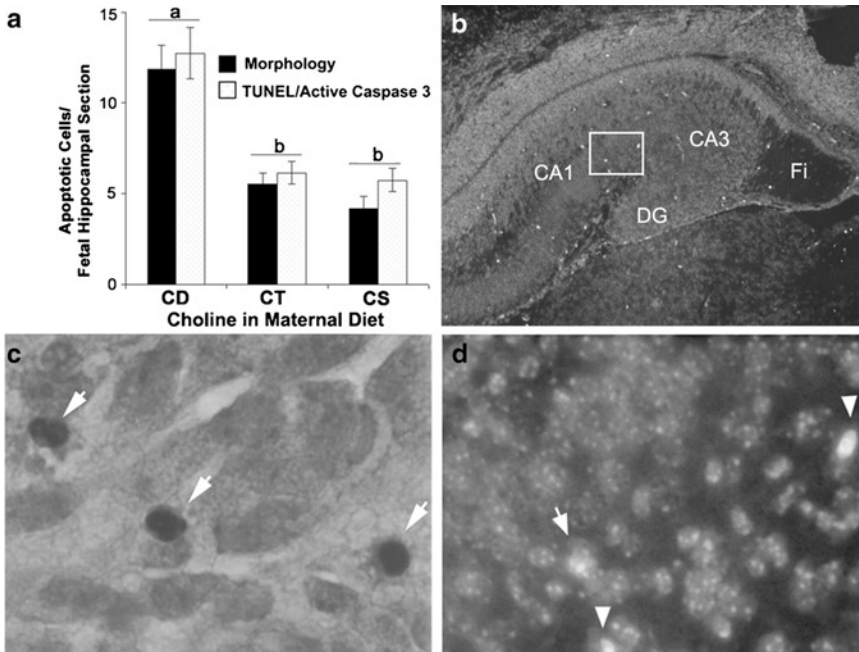
Fig. 134.5 Gestational choline availability affects rates of apoptosis in fetal hippocampus. Maternal choline deficiency in timed-pregnant mice fed choline-supplemented (CS), control (CT), or choline-deficient (CD) AIN-76A diet from ED 11 through ED 17 increases apoptosis in ED 17 hippocampus. Coronal section were prepared from the brains of ED 17 fetuses from each diet group and were analyzed for apoptosis using a combination of classical apoptotic morphology, active caspase-3 immunoreactivity and TUNEL (terminal deoxynucleotidyl transferase (TdT-mediated dUTP-digoxigenin anti-digoxigenin fluoroscein conjugate antibody nick end-labeling). Consecutive serial sections were used for TUNEL/ active caspase-3 staining. *Panel A*: The graph shows apoptotic cell counts using morphological criteria (means ± SEM, $n = 10$–12 pups/ group from at least five dams), and TUNEL-cleaved caspase-3 immunostaining (means ± SEM, $n = 6$ pups/ group from three dams). Means without common letters differ, $P < 0.05$ (for each pair using Student's t test, for all pairs using Tukey–Kramer HSD test, and comparison with control using Dunnett's method). *Panel B*: A 50X magnification image of the right hippocampal hemisphere showing TUNEL-positive cells distributed in the cortical plate (CA1, CA2, CA3), dentate gyrus (DG) and fimbria (Fi). *Panel C*, A representative image at 400X magnification is shown; the arrows point to cells showing apoptotic morphology. *Panel D*, Higher power view of the boxed area in panel B, spherical TUNEL and activated caspase-3 positive nuclei indicated by arrows. *ED* embryonic day (Reprinted from Craciunescu et al. 2003. With permission)

protein (DCC), proteins involved in migration of neuronal precursor cells from the ventricular zone to the Ammon's horn, dentate gyrus, and fimbria (Albright et al. 2005). Alterations in the expression of netrin-1 and DCC resulting from gestational choline deficiency perturbed migration of neuronal precursor cells from the neuroepithelial layer to the dentate gyrus in fetuses (Albright et al. 1999). Expression of vimentin, transforming growth factor-β (TGF-β), and cell cycle regulatory proteins p15Ink4B and p27Kip1 in the brain also were changed by choline availability during gestation (Albright et al. 1998, 2001, 2003,). These changes in brain proteins suggest increased neural and glial cell differentiation in brains of fetuses from choline-deficient mothers. As will be discussed later, epigenetic control of gene expression is one likely mechanism through which choline can elicit these protein changes by controlling transcription of the gene that encode these proteins. The relative abundance of these proteins can result in enhancement or repression of mitosis and apoptosis.

134.9.2 Gestational Choline Availability Is Associated with Hippocampal Changes in Offspring

In morphological studies, hippocampal neurons with larger soma and increased numbers of primary and secondary dendritic branches were observed in animals perinatally supplemented with choline (Li et al. 2004). Hippocampal slices from animals whose mothers were perinatally supplemented with choline were electrophysiologically more responsive, that is, were more likely to exhibit long-term potential (LTP) at a lower electrical stimulus, than were hippocampal slices from control animals. Conversely, hippocampal slices from animals whose mothers were perinatally deficient in choline were less likely to exhibit LTP at a given electrical stimulus, than were hippocampal slices from control animals (Jones et al. 1999). Because increased LTP is regarded as a biomarker for the mechanisms underlying learning, these data support the observations using radial maze testing.

Alterations in expression and activation of specific proteins in response to prenatal choline supplementation have been measured in the hippocampus, which may influence the function of neurons in this brain region. Mellot and colleagues reported increased phosphorylation of mitogen-activated protein kinase (MAPK) and cAMP-response element-binding protein (CREB) in response to stimulation of the hippocampus of rodents born to dams that were supplemented with choline during pregnancy. These animals also were able to use spatial cues effectively to complete a water maze task 3 days before unsupplemented animals (Mellott et al. 2004). Both MAPK and CREB are proteins believed to be involved in synaptic plasticity. Activity of an enzyme that hydrolyzes PtdCho, phospholipase D, as well as nerve growth factor (NGF) expression is increased in offspring of choline-supplemented animals (Holler et al. 1996; Sandstrom et al. 2002). Taken together, these studies offer compelling evidence that dietary choline intake during pregnancy can have significant and lasting effects on the development and function of the brain (Tables 134.3).

Table 134.3 Effects of perinatal choline supplementation and deficiency on brain function and biochemistry

Hippocampal characteristic	Choline supplementation[a]	Choline deficiency[a]
Memory and learning	Improved working, reference, and temporal memory	Impaired memory, especially in difficult tasks
	Enhanced simultaneous temporal processing	Decreased attention to lesser preferred signal
	Increased used of chunking memory strategy	Increased proactive interference
	Decreased age-related memory decline	Accelerated age-related decline
	Increased neuron soma size	n.s.
Morphology	Increased number of dendritic branches	n.s.
Electrophysical properties	Increased LTP	Decreased LTP
Biochemistry	Increased expression/activation of: MAPK,[b] CREB,[b] Phospholipase D, NGF, ChAT	Decreased expression/activation of: MAPK,[b] CREB[b]
	Decreased expression/activation of: Calretinin	Increased expression/activation of: Calretinin
Cellular processes	Increased neural precursor cell mitosis	Decreased neural precursor cell mitosis
	Decreased neural precursor cell apoptosis	Increased neural precursor cell apoptosis

[a]Significant changes compared to animals fed a diet containing normal amounts of choline

[b]In resposnse to hippocampal slice stimulation. n.s.: not significant

134.10 Choline May Change Hippocampal Function by Altering Epigenetic Control of Gene Transcription

The exact mechanisms through which choline influences hippocampal development, and consequent changes in learning and memory are not completely elucidated. However, changes in gene expression observed in *in vitro* and *in vivo* choline deficiency studies suggest that changes in hippocampal development and function in the developing brain may be due to alterations in epigenetic transcriptional control of these genes.

134.10.1 Gene Transcription Can Be Enhanced or Repressed by DNA and Histone Methylation

"Epigenetics" literally means "above the genes" and refers to genetic transcription control related to a "code" that does not involve altering the DNA sequence of the gene. This code is constructed of patters of methylation on both DNA and histones, the proteins around which DNA is wound. In mammals, DNA methylation occurs on cytosine resides that are directly followed by guanosine bases (CpG sites) and approximately 60–90% of these sites are methylated at any time (Holliday and Grigg 1993). Areas characterized by a higher than expected number of CpG repeats are termed CpG islands and tend to be targets for methylation (Robertson and Wolffe 2000). CpG island methylation changes can result in changes in gene expression and, ultimately, phenotype of an organism (Cooney et al. 2002; Waterland and Jirtle 2003). Although there are exceptions, hypermethylation is generally associated with gene silencing while hypomethylation tends to result in increased gene expression, perhaps because methylated cytosines bind to a family of proteins (methyl-CpG binding protein (MeCP)1 and 2 and methyl-CpG binding domain (MBD) 1–4) that block binding of transcription enhancing factors to promoter regions of these genes (Hendrich and Bird 1998; Jones and Takai 2001). Additionally, specific lysine and arginine residues on histones can be methylated resulting in alterations in heterochromatin structure which may either permit or repress transcription of genes depending on the exact methylation site (Jenuwein and Allis 2001).

134.10.2 The Role of Choline in Epigenetic Gene Control

SAM is required for methylating DNA and histones and dietary choline can directly influence the amount of SAM available for these reactions. Consumption of diets enriched with methyl-group donors (choline, betaine, methionine, folic acid) and other cofactors required by enzymes for the metabolism of these nutrients (vitamin B_{12}) can result in hypermethylation of gene-specific DNA sequences in mice correlated to phenotypic changes observed (Waterland and Jirtle 2003; Wolff et al. 1998). As discussed above, the choline metabolite betaine is an important source of methyl-groups. Choline availability during fetal development in the rodent modulates CpG island methylation, resulting in altered gene expression in the hippocampus (Niculescu et al. 2006). Choline deficiency in the pregnant mouse dam is associated with hypomethylation of genes that inhibit cell cycling in fetal neural precursor cells, resulting in increased expression of these genes and decreased cell mitosis observed in these animals (Niculescu et al. 2004, 2005). Choline deficiency in the pregnant mouse dam also alters methylation patterns on lysine residues of histone 3 (H3) in brain and these changes

Table 134.4 Key facts about choline

– Choline is an essential nutrient.

– Choline is present in many foods commonly eaten by humans and it can also be synthesized within the body.

– Mutations in choline metabolism genes commonly occur in humans and can influence the amount of dietary choline required by an individual.

– Because the metabolic pathways of choline, folate, and methionine interact with one another, increases or decreases in choline availability will alter requirements for folate and methionine.

– Pregnant and lactating women may have higher requirements for dietary choline. Adequate dietary choline intake during pregnancy is required to support normal fetal development.

– Perinatal choline supplementation enhances the function of the rodent hippocampus, while choline deficiency results in memory decrement. Gestational choline availability can influence the structure and biochemistry of the fetal hippocampus.

Described are key concepts about choline and its effect on brain development, specifically hippocampal development and function. These points will be discussed in detail through the course of this chapter

result in differences in specific gene expression, namely, genes that regulate methylation (Davison et al. 2009) and neuronal cell differentiation (Mehedint et al. 2010). The collective body of literature accumulated to date on maternal dietary choline and fetal brain development strongly suggests that the manipulation of dietary choline during pregnancy can have profound and lasting effects on function of this organ throughout life (Table 134.4).

134.11 Applications to Other Areas of Health and Disease

Using rodent models, perinatal choline supplementation has been explored as a therapeutic treatment for the amelioration of several conditions associated with altered cholinergic neuron function. Neonatal choline supplementation significantly improved the performance of rats prenatally exposed to alcohol on a T-maze, a visuaspatial discrimination task (Thomas et al. 2000). Additionally, neonatal choline supplementation of these animals resulted in attenuation of behavioral defects associated with prenatal alcohol exposure, including overactivity and other spatial learning deficits (Thomas et al. 2007). Rett syndrome is a neurodevelopmental disorder characterized by abnormalities in the brain cholinergic system caused by mutation of the *MeCP2* gene. Neonatal supplementation of mice harboring the mutated *MeCP2* gene resulted in improved motor coordination, locomotor activity and grip strength in these animals in a gender-specific pattern (Nag and Berger-Sweeney 2007). These changes may be attributable to an increase in nerve growth factor expression in the striatum in the choline – supplemented animals (Nag et al. 2008). Perinatal and postnatal dietary choline supplementation improved spatial memory and reduced brain inflammation following traumatic brain injury in rats (Guseva et al. 2008). Prenatal choline supplementation also had neuroprotective effects in a rat model of status epilepticus (Wong-Goodrich et al. 2008; Yang et al. 2000). Together, these studies offer evidence that perinatal, and even postnatal, choline supplementation can influence brain function not only in the normally developing brain, but also in the abnormally developing brain.

Summary

• Choline is an essential nutrient for humans and there is sufficient variation in dietary intake as to have an effect on fetal development.

• Choline is required by all cells for maintaining cell membrane integrity, providing a source of methyl groups for methylation reactions, and for the formation of the neurotransmitter ACho.

- The developing fetus and neonate has a high demand for choline; therefore, pregnant and lactating women have an increased need for dietary choline.
- Perinatal choline supplementation of the fetus, during the time in which the fetal hippocampus is developing, improved cognitive function in these animals; this enhancement persisted throughout life.
- Gestational choline availability changes the expression of many proteins in hippocampal cells, which affect rates of division, apoptosis, and other functions of these cells. These changes may result from alterations in DNA and histone methylation patterns.
- Choline supplementation increases, and choline deficiency decreases, neural precursor cell proliferation in fetal brain; choline supplementation decreases, and choline deficiency increases, apoptosis of these cells. Choline deficiency retards neuronal migration and increases neuronal precursor cell differentiation into neurons and glia.

Definitions

Choline: A small lipotrophic molecule generally categorized as a B vitamin; essential for the normal function of all cells; present in many foods, particularly eggs and meats.

Mitosis: In eukaryotic cells, the process whereby the nucleus is divided to produce two genetically equivalent daughter nuclei with the diploid number of chromosomes (Lodish et al. 2004).

Apoptosis: Regulated process leading to cell death mediated by a caspase cascade and marked by a series of well-defined morphological changes; also called *programmed cell death* (Lodish et al. 2004).

Epigenetics: The study of heritable modifications in DNA methylation and chromatin structure that affect gene transcription.

Neuronal precursor cell: Pluripotent stem cells from which mature neurons are derived.

References

Albright CD, Tsai AY, Mar M-H, Zeisel SH. Neurochem Res. 1998;23:751–8.

Albright CD, Tsai AY, Friedrich CB, Mar MH, Zeisel SH. Brain Res Dev Brain Res. 1999;113:13–20.

Albright CD, Mar MH, Friedrich CB, Brown EC, Zeisel SH. Dev Neurosci. 2001;23:100–6.

Albright CD, Siwek DF, Craciunescu CN, Mar MH, Kowall NW, Williams CL, Zeisel SH. Nutr Neurosci. 2003;6:129–34.

Albright CD, Mar MH, Craciunescu CN, Song J, Zeisel SH. Brain Res Dev Brain Res. 2005;159:149–54.

Blusztajn JK, Holbrook PG, Lakher M, Liscovitch M, Maire JC, Mauron C, Richardson UI, Tacconi M, Wurtman RJ. Psychopharmacol Bull. 1986;22:781–6.

Blusztajn JK, Liscovitch M, Richardson UI. Proc Natl Acad Sci U.S.A. 1987;84:5474–7.

Brandner C. Brain Res. 2002;928:85–95.

Chern MK, Gage DA, Pietruszko R. Biochem Pharmacol. 2000;60:1629–37.

Chi-Shui L, Ru-Dan W. J Prot Chem. 1986;5:193–200.

Cohen EL, Wurtman RJ. Life Sci. 1975;16:1095–102.

Cooney CA, Dave AA, Wolff GL. J Nutr. 2002;132:2393S–2400S.

Craciunescu CN, Albright CD, Mar MH, Song J, Zeisel SH. J Nutr. 2002;133:3614–8.

Craciunescu CN, Johnson AR, Zeisel SH, J Nutr. 2010;140:1162–6.

da Costa KA, Gaffney CE, Fischer LM, Zeisel SH. Am J Clin Nutr. 2005;81:440–4.

da Costa KA, Kozyreva OG, Song J, Galanko JA, Fischer LM, Zeisel SH. Faseb J. 2006;20:1336–44.

Davison JM, Mellott TJ, Kovacheva VP, Blusztajn JK. J Biol Chem. 2009;284:1982–9.

Eichenbaum H. Neuron. 2004;44:109–20.

Fischer LM, daCosta K, Kwock L, Stewart P, Lu T-S, Stabler S, Allen R, Zeisel S. Am J Clin Nutr. 2007;85:1275–85.

Fisher MC, Zeisel SH, Mar MH, Sadler TW. Teratology. 2001;64:114–22.

Fisher MC, Zeisel SH, Mar MH, Sadler TW. Faseb J. 2002;16:619–21.

Guseva MV, Hopkins DM, Scheff SW, Pauly JR. J Neurotrauma. 2008;25:975–83.

Haubrich DR, Gerber NH. Biochem Pharmacol. 1981;30:2993–3000.

Hendrich B, Bird A. Mol Cell Biol. 1998;18:6538–47.

Hobbs CA, Cleves MA, Melnyk S, Zhao W, James SJ. Am J Clin Nutr. 2005;81:147–53.

Holler T, Cermak J, Blusztajn J. FASEB J. 1996;10:1653–9.

Holliday R, Grigg GW. Mutat Res. 1993;285:61–7.

Holmes-McNary M, Cheng WL, Mar. MH, Fussell S, Zeisel SH. Am J Clin Nutr. 1996;64:572–6.

Institute of Medicine, National Academy of Sciences USA. Choline. Dietary reference intakes for folate, thiamin, riboflavin, niacin, vitamin B12, panthothenic acid, biotin, and choline. Washington, DC: National Academy Press; 1998.

Jacobs RL, Stead LM, Devlin C, Tabas I, Brosnan ME, Brosnan JT, Vance DE. J Biol Chem. 2005;280:28299–305.

Jacques PF, Bostom AG, Wilson PW, Rich S, Rosenberg IH, Selhub J. Am J Clin Nutr. 2001;73:613–21.

Johnson AR, Craciunescu CN, Guo Z, Terg Y-W, Thresher RJ, Blusztajn JK, Zeisel SH, Faseb J. 2010;24:2752–61.

Jenuwein T, Allis CD. Science. 2001;293:1074–80.

Jones JP, Meck W, Williams CL, Wilson WA, Swartzwelder HS. Brain Res Dev Brain Res. 1999;118:159–67.

Jones PA, Takai D. Science. 2001;293:1068–70.

Kohlmeier M, da Costa KA, Fischer LM, Zeisel SH. Proc Natl Acad Sci U S A. 2005;102:16025–30.

Li Q, Guo-Ross S, Lewis DV, Turner D, White AM, Wilson WA, Swartzwelder HS. J Neurophysiol. 2004;91:1545–55.

Lodish H, Berk A, Matsudaira P, Kaiser CA, Krieger M, Scott MP, Zipursky SL, Darnell J. Molecular cell biology, 5th edn. New York: W.H. Freeman; 2004.

Meck W, Williams C. Neuroreport. 1997a;8:2831–5.

Meck W, Williams C. Neuroreport. 1997b;8:3053–9.

Meck W, Williams C. Neuroreport. 1997c;8:3045–51.

Meck WH, Williams CL. Brain Res Dev Brain Res. 1999;118:51–9.

Meck WH, Williams CL. Neurosci Biobehav Rev. 2003;27:385–99.

Meck WH, Smith RA, Williams CL. Dev Psychobiol. 1988;21:339–53.

Mehedint MG, Niculescu MD, Craciunescu CN, Zeisel SH, Faseb J. 2010;24:184–95.

Mellott TJ, Williams CL, Meck WH, Blusztajn JK. Faseb J. 2004;18:545–7.

Nag N, Berger-Sweeney JE. Neurobiol Dis. 2007;26:473–80.

Nag N, Mellott TJ, Berger-Sweeney JE. Brain Res. 2008;1237:101–9.

Niculescu MD, Craciunescu CN, Zeisel SH. Brain Res Mol Brain Res. 2005;134:309–22.

Niculescu MD, Yamamuro Y, Zeisel SH. J Neurochem. 2004;89:1252–9.

Niculescu MD, Craciunescu CN, Zeisel SH. Faseb J. 2006;20:43–9.

Ozarda IY, Uncu G, Ulus IH. Arch Physiol Biochem. 2002;110:393–9.

Pomfret EA, da Costa K, Zeisel SH. J Nutr Biochem. 1990;1:533–41.

Resseguie M, Song J, Niculescu M, da Costa K, Randall T, Zeisel S. FASEB J. 2007;21:2622–32.

Robertson KD, Wolffe AP. Nat Rev Genet. 2000;1:11–9.

Sandstrom NJ, Loy R, Williams CL. Brain Res. 2002;947:9–16.

Schenk F, Brandner C. Psychobiology. 1995;23:302–13.

Shaw GM, Carmichael SL, Yang W, Selvin S, Schaffer DM. Am J Epidemiol. 2004;160:102–9.

Shaw GM, Carmichael SL, Laurent C, Rasmussen SA. Epidemiology. 2006;17:285–91.

Shelnutt KP, Kauwell GP, Chapman CM, Gregory JF, 3rd, Maneval DR, Browdy AA, Theriaque DW, Bailey LB. J Nutr. 2003;133:4107–11.

Shields DJ, Lingrell S, Agellon LB, Brosnan JT, Vance DE. J Biol Chem. 2005;280:27339–44.

Sweiry JH, Page KR, Dacke CG, Abramovich DR, Yudilevich DL. J Devel Physiol. 1986;8:435–45.

Sweiry JH, Yudilevich DL. J Physiol. 1985;366:251–66.

Thomas JD, La Fiette MH, Quinn VR, Riley EP. Neurotoxicol Teratol. 2000;22:703–11.

Thomas JD, Biane JS, O'Bryan KA, O'Neill TM, Dominguez HD. Behav Neurosci. 2007;121:120–30.

Ulus IH, Wurtman RJ, Mauron C, Blusztajn JK. Brain Res. 1989;484:217–27.

USDA, Nutrient Data Laboratory and Agricultural Research Service. United States Department of Agriculture Database for the Choline Content of Common Foods, Release 2. http://www.ars.usda.gov/Services.docs.htm?docid= 6232, 2008.

Varela-Moreiras G, Ragel C, Perez de Miguelsanz J. J Amer Coll Nutr. 1995;14:480–5.

Walkey CJ, Yu L, Agellon LB, Vance DE. J Biol Chem. 1998;273:27043–6.

Waterland RA, Jirtle RL. Mol Cell Biol. 2003;23:5293–300.

Watkins D, Ru M, Hwang HY, Kim CD, Murray A, Philip NS, Kim W, Legakis H, Wai T, Hilton JF, Ge B, Dore C, Hosack A, Wilson A, Gravel RA, Shane B, Hudson TJ, Rosenblatt DS. Am J Hum Genet. 2002;71:143–53.

Wecker L. J Neurochem. 1991;57:1119–27.

Weisberg IS, Jacques PF, Selhub J, Bostom AG, Chen Z, Curtis Ellison R, Eckfeldt JH, Rozen R. Atherosclerosis. 2001;156:409–15.

Wolff GL, Kodell RL, Moore SR, Cooney CA. Faseb J. 1998;12:949–57.

Wong-Goodrich SJ, Mellott TJ, Glenn MJ, Blusztajn JK, Williams CL. Neurobiol Dis. 2008;30:255–69.

Xu X, Gammon MD, Zeisel SH, Lee YL, Wetmur JG, Teitelbaum SL, Bradshaw PT, Neugut AI, Santella RM, Chen J. Faseb J. 2008;22:2045–52.

Yang Y, Liu Z, Cermak JM, Tandon P, Sarkisian MR, Stafstrom CE, Neill JC, Blusztajn JK, Holmes GL. J Neurosci. 2000;20:RC109.

Zeisel SH. Annu Rev Nutr. 2006;26:229–50.

Zeisel SH, Wurtman RJ. Biochem J. 1981;198:565–70.

Zeisel SH, Stanbury JB, Wurtman RJ, Brigida M, Fierro BR. New Engl J Med. 1982;306:175–6.

Zeisel SH, Mar M-H, Zhou Z-W, da Costa K-A. J Nutr. 1995;125:3049–54.

Chapter 135
Iodine and Brain Development

Pere Berbel and Gabriella Morreale de Escobar

Abbreviations

T2	3,5-Diiodo-L-thyronine or diiodothyronine
T3	3′,3,5-Triiodo-L-thyronine or triiodothyronine
T4	3′,5′,3,5-Tetraiodo-L-thyronine or thyroxine
rT3	3′,5′,3-Triiodo-L-thyronine or reverse-T3
BrdU	5-Bromo-2′-deoxyuridine
5-HTT	5-HT transporter
DAG	Diacyl glycerol
DiI	1,1′-Dioctadecyl-3,3,3′,3′-tetramethylindocarbocyanine perchlorate
DIT	Diiodotyrosine
E	Embryonic day
GABA	Gamma-aminobutyric acid
HAS	Human serum albumin
IP3	Inositol triphosphate
ICCIDD	International Council for the Control of Iodine Deficiency Disorders
D	Iodothyronine deiodinase
LID	Low-iodine diet
MMI	Methimazole
MAP	Mitogen-associated protein
MCT	Monocarboxylate transporter
MIT	Monoiodotyrosine
NHANES	National Health and Nutrition Examination Surveys
OATP	Organic anion transporting polypeptide
PLC	Phospholipase C
P	Postnatal day
PTU	Propylthiouracil
PKC	Protein kinase C
5-HT	Serotonin
TR	T3 receptor
TBG	Thyroid-binding globulin

P. Berbel (✉)
Instituto de Neurociencias, Universidad Miguel Hernández and Consejo Superior de Investigaciones Científicas, Campus de Sant Joan, Apartado de Correos 18, Sant Joan d'Alacant, 03550 Alicante, Spain
e-mail: pere.berbel@umh.es

TSH	Thyrotropin
TTR	Transthyretin
UI	Urinary iodine
WHO	World Health Organization

135.1 Thyroid Gland Function

135.1.1 Biosynthesis of Thyroid Hormones

The thyroid hormones thyroxine (3′,5′,3,5-tetraiodo-L-thyronine; T4) and triiodothyronine (3′,3,5-triiodo-L-thyronine; T3) are iodinated thyronines produced and released in the thyroid gland. Thus, reduced iodine in the form of iodide is required by the thyroid gland for thyroid hormone synthesis. Both, the iodide oxidation and binding to tyrosine residues of the thyroglobulin resulting in residues of monoiodotyrosine (MIT) and diiodotyrosine (DIT) (iodination reaction), and the subsequent MIT and DIT coupling in T3 and T4 residues bound to the thyroglobulin (coupling reaction) are catalyzed by thyroperoxidase, which is a transmembrane enzyme located in the apical membrane of thyrocytes. A typical distribution for a thyroglobulin containing 0.5% iodine (a normal amount for iodine-sufficient individuals) is five residues of MIT, five of DIT, 2.5 of T4, and 0.7 of T3 (Dunn and Dunn 2000). The substrates of the thyroperoxidase are follicular iodide and H_2O_2; the latter is synthesized and released to the follicular lumen by a dual-oxidase calcium-binding transmembrane enzyme coupled to the thyroperoxidase (Song et al. 2007). Iodide is transported to the follicular lumen by an ion channel also coupled to the dual-oxidase and thyroperoxidase complex (Fig. 135.1). Finally, synthesized thyroid hormones are released by thyrocytes due to thyrotropin (TSH)-induced pinocytosis and subsequent proteolysis of the iodinated thyroglobulin (Table 135.1).

The thyroglobulin iodination is a highly regulated process and is primarily controlled by H_2O_2 generation and iodide supply. Both, iodide release to the follicular lumen and H_2O_2 synthesis are acutely and synchronously regulated by the same intracellular signal cascades (Raspe and Dumont 1994). Thus, in thyroid hormone synthesis, the extrathyroidal pool of inorganic iodide available plays a crucial role, which is constituted by the iodide from the diet and the circulating iodide derived from the metabolism of the iodothyronines.

TSH positively regulates this process due to the presence of a TSH receptor in the basal membrane of thyrocytes. TSH receptors are coupled to Gs and Gq proteins, which respectively results in increased calcium and cAMP intracellular concentrations, activating a series of signaling cascades. These metabolic pathways trigger secretion, gene expression, H_2O_2 synthesis, and iodide transport to the follicular lumen (Song et al. 2007).

More iodine increases the ratios of DIT/MIT and T4/T3, while iodine deficiency decreases them (Dunn and Dunn 2000). In the case of mild iodine deficiency (i.e., urinary iodine in school children between 50 and 100 μg/l) to moderate iodine deficiency (i.e., urinary iodine in school children between 20 and 49 μg/l), the thyroid gland responds rapidly through autoregulatory mechanisms (independent from changes in circulating TSH) by decreasing the synthesis and secretion of T4 in favor of T3 (which is the active hormone that binds to specific nuclear receptors, see below). As a consequence, the circulating levels of T3 remain normal, or even increase slightly, and circulating TSH does not increase, as occurs in hypothyroidism (Morreale de Escobar et al. 2000, 2004).

Thyroid hormones in serum may circulate free or bound to a series of hormone-binding proteins. In normal man, approximately 0.03% of the total serum T4, and 0.3% of the total serum T3 are present
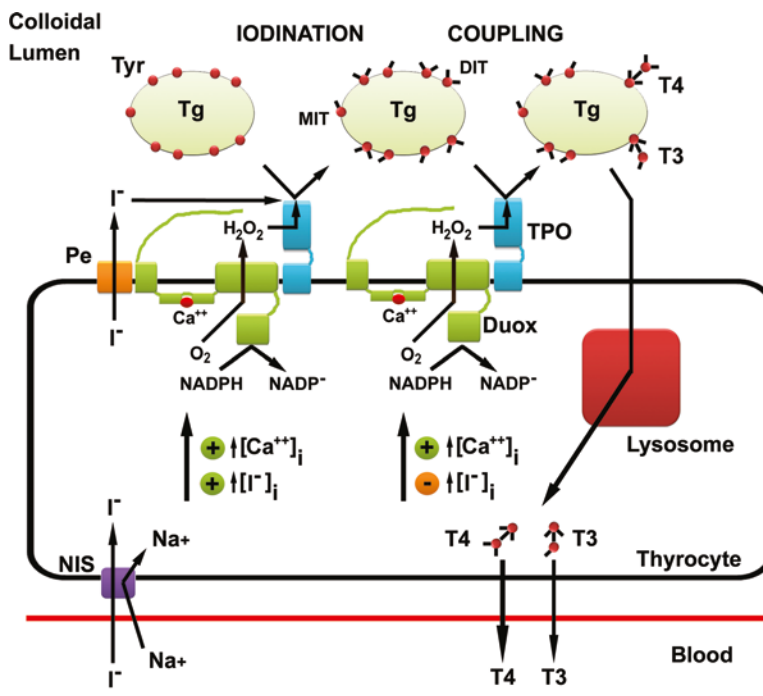
Fig. 135.1 Major metabolic pathways in thyrocytes involved in iodination and coupling reactions. Cartoon showing the major metabolic pathways in thyrocytes involved in the iodination of tyrosine (Tyr) and in the coupling of monoiodotyrosine (MIT) and diiodotyrosine (DIT) to form thyroid hormones. A sodium/iodide symporter (NIS) transports iodide into thyrocytes, transported into the colloidal lumen through an anion channel (pendrin; PE). Thyroperoxidase (TPO) oxidizes iodide in the presence of H_2O_2 and is then transferred to Tyr residues of thyroglobulin (Tg) to form MIT and DIT (iodination reaction). Again, TPO in the presence of H_2O_2 catalyzes the coupling of DIT and MIT, and of DIT and DIT to form residues of T3 and T4 coupled to Tg (coupling reaction). Thyrotropin (TSH) stimulates pinocytosis of Tg, which is subsequently hydrolyzed in the lysosomes of thyrocytes. Released T3 and T4 are then delivered to blood. H_2O_2 is produced at the apical plasma membrane by a NADPH dual-oxidase enzyme (Duox) coupled to TPO, in the presence of calcium. A high intracellular concentration of calcium favors both the iodination and coupling reactions. A high intracellular concentration of iodide favors iodination but inhibits coupling

in free or unbound form, immediately available to tissues (Refetoff et al. 1970). Under normal conditions, free hormone levels are maintained constant by appropriate stimulation or suppression of hormone secretion and disposal. The major serum thyroid hormone-binding proteins responsible for the maintenance of a large extrathyroidal pool of thyroid hormone are thyroid-binding globulin (TBG), transthyretin (TTR), and human serum albumin (HAS; Oppenheimer 1968). TBG binds 75% of serum T4, while TTR and HSA bind only 20% and 5%, respectively. One of the principal functions of T4-binding proteins in serum is to safeguard the body from the effects of abrupt fluctuations in hormonal secretion (Refetoff et al. 1970).

Thyroid hormones are transported to target tissues and in the central nervous system, the access of free thyroid hormones from the blood to neurons and glial cells is restricted by the endothelial cells of brain capillaries (the blood–brain barrier) and the epithelial cells lining the ventricular side of the choroid plexus (the blood–cerebrospinal fluid barrier). The mechanism of thyroid hormone transport through the plasma membrane of target cells is under study. Up to date, several transporters have been identified; they include amino acid transporters, organic anion transporting polypeptide (OATP), and monocarboxylate transporters (MCT; Abe et al. 2002; Friesema et al. 2005; Bernal 2005). Recent data show that brain-specific transporters of the OATP family, such as OATP1, 2, 3,

Table 135.1 Key features of iodine deficiency in thyroid function

1. The primary function of the thyroid gland is to produce adequate amounts of thyroid hormones (T3 and T4), which have genomic and nongenomic functions, regulating nuclear and mitochondrial gene expression, and intracellular metabolic pathways.
2. Thyroid hormones T3 and T4 are iodinated thyronines; therefore, an adequate iodine intake is fundamental for thyroid hormones synthesis.
3. During gestation, the maternal thyroid has to increase the synthesis of thyroid hormones since the mother is the principal source of T4 for the fetus. She is also the only source of iodine for the fetus during gestation and for the neonate during lactation (provided the infant is solely breast fed). This doubles the needs of maternal iodine intake to 250–300 μg per day.
4. Iodine deficiency is one of the most frequent causes worldwide of preventable mental retardation in children. A wide spectrum of iodine deficiency disorders has been described during gestation and the early postnatal period, including cretinism, neurocognitive delay, mental retardation, and attention-deficit hyperactivity disorders, among others.
5. Mild iodine deficiency may cause mild maternal hypothyroxinemia (i.e., circulating free T4 within the 0–10th percentile of the normal range, and normal T3 and TSH levels) that, from the beginning of gestation, causes a significant delay in the neurobehavioral development of children.
6. A daily fortification of iodine since the beginning of gestation is recommended by the WHO, so that the total iodine intake is 250 μg/day, to ensure a normal thyroid function for the mothers and their children during gestation and lactation.
7. Neurobehavioral problems of the children born to mildly hypothyroxinemic mothers are not ameliorated if the daily iodine fortification is delayed for 10–12 weeks from the beginning of gestation.

This table lists the key facts of iodine deficiency during gestation including the function of the thyroid gland, the adverse effects on the child (before and after birth) and the needs of iodine fortification during gestation, including the iodine intake recommended by the World Health Organization (WHO) and the International Council for the Control of Iodine Deficiency Disorders (ICCIDD)

and 14, the last with high affinity for T4, are mostly expressed in the endothelial cells of brain capillaries and in the choroid plexus (Gao and Meier 2001; Sugiyama et al. 2003; Ohtsuki et al. 2004; Roberts et al. 2008). MCT8 transporters are also expressed in the endothelial cells of brain capillaries and in the epithelial cells of the choroid plexus (Roberts et al. 2008; Ceballos et al. 2009), but they are more conspicuous in neuronal plasma membrane (Friesema et al. 2005) (Fig. 135.2).

135.1.2 Iodothyronine Deiodinases and Metabolism of Thyroid Hormones

Three selenoproteins catalyzing the deiodination of T4 and T3 have been identified, called type 1 (D1), type 2 (D2), and type 3 (D3) iodothyronine deiodinases. D1 is expressed mainly in the liver, the kidneys and the thyroid. D1 has high affinity for reverse-T3 (rT3; 3′,5′,3-triiodo-L-thyronine) and T4 and principally contributes to increase circulating T3 (Bianco et al. 2002; Bianco and Larsen 2005; Bianco and Kim 2006). D2 has been found in many peripheral tissues, especially in the astrocytes and tanycytes of the central nervous system (Guadaño-Ferraz et al. 1997). It is important for the local generation of T3 but does not contribute significantly to increase circulating T3. D3 is expressed in the central nervous system and mediates the degradation of T3 to diiodothyronine (3,5,diiodo-L-thyronine; T2) and T4 to rT3 (Bianco et al. 2002; Bianco and Kim 2006) (Fig. 135.3). In summary, the major role of deiodinases is to maintain adequate levels of T3 in target tissues in case of iodine sufficiency, while in iodine deficiency deiodinases maintain high levels in tissues and plasma. However, recent studies have found that the activating D2 and the inactivating D3 can locally increase or decrease thyroid hormone signaling in a tissue, independent of changes in circulating thyroid hormone concentrations in a temporal-specific fashion (Bianco and Kim 2006). These findings show that deiodinases play a much broader role than once thought, with great ramifications for the control of thyroid hormone signaling during vertebrate development and metamorphosis, as well
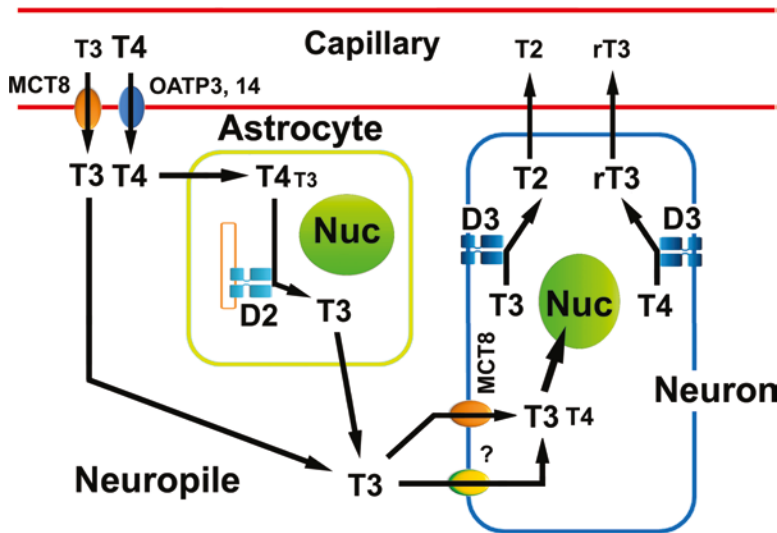
Fig. 135.2 Pathways of thyroid hormone transfer through nervous system membranes. Scheme showing major pathways of thyroid hormone transfer through nervous system membranes, some of the transporters and of the deiodination reactions involved. Organic anion transporting polypeptide (OATP; *black grey* or *blue ellipsoids*) and monocarboxylate transporter (MCT; *grey* or *red ellipsoids*) are indicated. Both, OATP14, with high-affinity for T4, and MCT8, with high affinity for T3, are expressed in the endothelial cells of brain capillaries. MCT8 is also found in neurons and mediates the transport of T3. Other not well-known transporters (?) in neurons, also involved in T3 transport, are shown (light grey or yellow ellipsoid). OATP transporters, other than OATP14, are noted. Deiodination of T3 and T4 pathways by D2 and D3 are shown. Activating D2 is mostly located in the endoplasmic reticulum (ER) of astrocytes, while inactivating D3 is located in the neuronal plasmatic membrane. *Nuc* cell nucleus, *CSF* cerebrospinal fluid
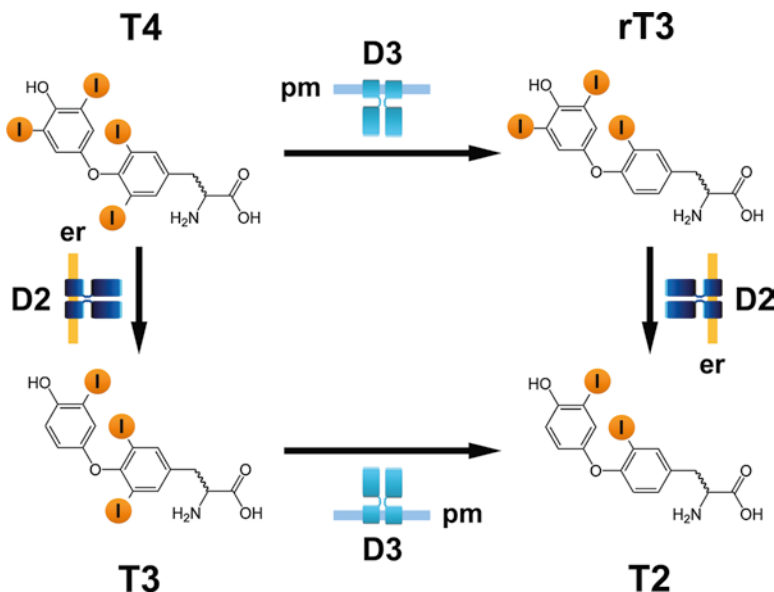
Fig. 135.3 Principal actions of the deiodinases in the central nervous system. The activating type II deiodinase (D2) catalyzes the conversion of T4 into T3. D2 also transforms rT3 into T2. Inactivating D3 transforms T4 into rT3, and T3 into T2. D3 is found in the plasmatic membrane (pm) of neurons while D2 is found in the endoplasmic reticulum (er) of astrocytes and tanycytes

as injury response, tissue repair, hypothalamic function, and energy homeostasis in adults (Gereben et al. 2008). In addition to deiodination, iodothyronines are also metabolized by conjugation of the phenolic hydroxyl group with sulfate or glucuronic acid (Visser 1996).

135.1.3 Function of Thyroid Hormones

Thyroid hormones act on mammalian development by regulating growth, maturation, and function in many organs and systems, such as brain, liver, heart, kidney, lung, skeleton, and skin. In addition, in lower vertebrates, thyroid hormones are the primary factors regulating the larvae-to-juvenile transition during metamorphosis (Power et al. 2001). In particular, the mammalian central nervous system is an important target of the thyroid hormone during all phases of the vital cycle, from fetus to adult. However, it is during the earlier stages of development that the central nervous system is more vulnerable to thyroid hormones imbalances (Berbel et al. 2007).

As already mentioned, the main active compound secreted by the thyroid gland is T3, which is also synthesized in target tissues by the deiodination of T4. T3 acts in the target cells by binding to nuclear and mitochondrial receptors and controlling of gene expression (Forrest and Vennström 2000). The T3 receptors (TR) are members of a large family of transcription factors with a ligand-binding domain that includes the receptors for endocrine or paracrine compounds such as steroids, retinoids, and vitamin D3 among others (Benoit et al. 2004). There are two TR genes, designated TRα and TRβ, located in different chromosomes, which encode a series of proteins, four of these are different T3 receptor isoforms (TRα1, TRβ1, TRβ2, and TRβ3) (Bernal 2005).

The action of thyroid hormones during the development of the central nervous system, including the generation of the active hormone, the ontogeny and distribution of receptors, and the molecular basis of thyroid hormone action in the brain has been recently reviewed (Bernal and Guadaño-Ferraz 1998; Forrest et al. 2002; Anderson et al. 2003; Bernal 2005; Santisteban and Bernal 2005; Flamant et al. 2007). T3 receptor TRα1 can be detected in the rat brain by embryonic day 12 (E12), and in the human brain by the 10th week of gestation (Bernal and Pekonen 1984; Pérez-Castillo et al. 1985; Bradley et al. 1992). In the adult rat brain, TRα1 still accounts for 70–80% of total T3 binding capacity (Ercan-Fang et al. 1996). T3 receptors are predominantly expressed in neurons but have been detected also in cultured oligodendrocytes, astrocytes, and microglia (Lima et al. 2001) and regulate the expression of many genes involved in the development and maturation of the brain (Bernal 2005; see below).

The thyroid hormone signaling, however, is more diverse and complex. Recent studies have shown broader context of extra- and intracellular regulation by thyroid hormones: control of ligand availability, changes in cell sensitivity to T3, nongenomic effects, and cross-talks with other signaling pathways (Flamant et al. 2007). An important nongenomic action of thyroid hormones in heart function and systemic vascular resistance (Davis and Davis 2002) has been observed, suggesting that thyroid hormones could promote the phosphorylation of nuclear thyroid hormone-receptors by the mitogen-associated protein (MAP) kinase, which would change their transcriptional activity (Davis et al. 2002). Thyroid hormone acting on cytoplasmic thyroid hormone-receptors could activate the phospholipase C (PLC)-inositol triphosphate (IP3) pathway to increase the intracellular concentration of calcium, released by the sarco/endoplasmic reticulum. In parallel, PLC could activate the diacyl glycerol (DAG)-protein kinase C (PKC) pathway; both PLC and PKC modulate the Na+/H+ exchanger in myoblasts L-6, modifying the intracellular pH. It is unknown whether, or not, thyroid hormones can also activate these pathways in neurons by a nongenomic pathway (D'Arezzo et al. 2004; Zinman et al. 2006a,b). Moreover, it has been observed that the activation of PKC and protein kinase A by thyroid hormones would inhibit the Na+/K+-ATPase, thus inhibiting the action of the

Na+/K+ and Na+/H+ exchangers in chicken liver cells (Incerpi et al. 2005). Recently, it has been observed in synaptosomes from the cerebral cortex of adult rats, that thyroid hormones have a rapid action (extranuclear) in different pathways involved in the regulation of the phosphorylation of proteins that influence the ATP synaptosomal uptake (Sarkar et al. 2006). All these data strongly suggest that thyroid hormones could have important nongenomic actions on nervous tissue, activating and/or influencing different metabolic pathways. Especially, an increase of the intracellular concentration of calcium and ATP might have important functional consequences in neurons, affecting many neuronal functions including neuronal migration and intraaxonal transport.

135.2   Iodine As a Crucial Micronutrient

135.2.1   Needs for Iodine At Different Ages and Physiological State of Individuals

The amount of daily iodine intake varies according to the age and physiological state of individuals (Table 135.2). Iodine intake is the principal source of circulating inorganic iodide and is therefore critical for the thyroid gland to produce adequate amounts of thyroid hormones. The concentration of inorganic iodide in the mother is particularly crucial during gestation and lactation, since during these developmental periods the mother is the only source of T4 and iodine for the fetus and of iodine for the neonate (Morreale de Escobar et al. 2004; Zoeller and Rovet 2004; Glinoer 2004, 2007).

135.2.2   Maternal and Fetal Thyroid Function During Pregnancy

The fetus depends on maternal T4 for normal development, since only very low amounts of maternal T3 reach fetal tissues. Almost all T3 found in the developing cerebral cortex is generated through local deiodination of T4, ultimately derived from the maternal circulating T4 (Calvo et al. 1990; Kester et al. 2004; Morreale de Escobar et al. 2008). To achieve this commitment, there are important changes in thyroid function of the mother during pregnancy, resulting in changes of iodine requirements. As a result of the increase of estrogens there is an increase of circulating thyroxine-binding globulin and

Table 135.2   Recommended minimum daily iodine intake

Group	Iodine requirements
Premature children	>30 μg/kg/day
Children 0–6 years[a]	90 μg/day
Children 6–10 years[a]	120 μg/day
Adults[a]	150 μg/day
Pregnant women	250–300 μg/day
Women during lactation	250–300 μg/day

This table lists the minimum daily iodine intake recommended by the World Health Organization (WHO, Andersson et al. 2007) and the International Council for the Control of Iodine Deficiency Disorders (ICCIDD; Zimmermann and Delange 2004) to different groups of population, according to the age and physiological state of individuals

human chorionic gonadotrophin. Human chorionic gonadotrophin transiently stimulates thyrocytes increasing thyroid hormone production while increased thyroxine-binding globulin contributes to an increase of the extrathyroidal pool of T4 (Glinoer 2007). Furthermore, the pool of circulating inorganic iodide is also compromised as a result of a significant increase in renal iodide clearance by 30–50%. In addition, D2 and D3 placental activity increases the peripheral metabolism of thyroid hormones, as does D3 in fetal epithelia (Bianco et al. 2002; Huang et al. 2003; Morreale de Escobar et al. 2008).

Thus, during gestation, it is essential for the mother to produce sufficient amounts of thyroid hormones for herself and her fetus. In addition to maternal thyroid hormones (fundamentally T4), the fetus also depends on the mother for its iodine supply, as does the neonatal thyroid during lactation. To achieve this, expectant mothers need to double the recommended normal daily intake of iodine for nonpregnant women by 250–300 μg/day. Furthermore, to meet neonatal requirements, iodine intake should remain increased during lactation provided the infant is solely breast fed (Kester et al. 2004; Andersson et al. 2007; Zimmermann and Delange 2004; Morreale de Escobar et al. 2008).

135.2.3 Iodine in Food

The iodine content of most foods depends on the iodine content of the soil. In general, iodine-deficient soils are in inland regions, mountainous areas, and places with frequent flooding, but they can be also found in coastal regions. Iodine concentration might be about 10 μg/kg of dry weight in plants grown in iodine-deficient soils, compared with about 1 mg/kg in plants from iodine-sufficient soils (Zimmermann et al. 2008).

Several food strategies have been proved to be efficient to increase iodine intake in iodine-deficient areas: (i) the use of iodinated salt in household, (ii) the incorporation of iodine to industrially elaborated foods (i.e., bread, milk, cheese), and (iii) to introduce dietary diversification (i.e., consuming food from iodine-sufficient areas and seafood). The use of iodinated salt in households has increased worldwide in the last ten years from less than 20–70%. Nevertheless, the highest prevalence of iodine deficiency is in Europe (52%), where the household coverage with iodized salt is the lowest (25%) (Zimmermann et al. 2008). Iodine incorporated to industrially elaborated foods, such as bread, milk, and milk derivates might also be a source of dietary iodine. However, the iodine content in food is usually unknown and in most cases not rightly indicated in the label. To avoid this, the Administration should regulate the iodine content of foods, controlling that the iodine labeled corresponds to the actual content. A recent study performed in Boston (USA) showed that the actual iodine content in seven out of eight infant formula analyzed was higher (on average 224%) than the labeled content (Pearce et al. 2004). Finally, dietary diversification incorporating foods from iodine-sufficient areas is a complementary way to prevent iodine deficiency. Eating seafood is an additional source of iodine because marine animals can concentrate the iodine from seawater; certain types of seaweed (e.g., wakame) are very rich in iodine. Dairy products might be relatively good sources of iodine provided iodine is commonly added to animal feed (Haldimann et al. 2005) (Table 135.3).

135.2.4 Iodine Fortification

With a normal diet consisting of the use of iodinated salt and eating food of marine origin 2–3 days per week, a daily iodine intake would be in the order of 250 μg per day, approximately the amount of iodine recommended during pregnancy and lactation by the World Health Organization (WHO) and

Table 135.3 Iodine content of some common foods

Food	Iodine (μg/100 g)[a]
Salt (iodized)[b]	6,000
Seaweed (dried)	70,000
Cod	115
Shrimp	40
Tuna, canned in oil	20
Milk (cow's)	69
Yogurt, low-fat	67
Mozzarella cheese	42
Red meat	5.9
Poultry	6.6
Vegetarian protein alternatives	10.9
Egg	162
Bread, baked	39
Potatoes	1.6
Pasta	7.9
Fresh fruit	1.8
Fresh vegetables	4.7

This table lists the iodine content of some common foods. The data have been extracted from Haldimann et al. (2005)

[a]The iodine content of foods can vary considerably; these values should be considered approximate (Pennington et al. 1995)

[b]The normal daily intake is about 1 g. [c] Provided iodine is commonly added to animal feed (Haldimann et al. 2005)

the International Council for the Control of Iodine Deficiency Disorders (ICCIDD) (Zimmermann and Delange 2004; Zimmermann 2007; Andersson et al. 2007) (Table 135.2). However, inadequate iodine intake actually affects a large number of pregnant women, and this situation persists even in areas where iodized salt consumption has been promoted for years and that have been classified as free of iodine deficiency (Azizi et al. 2003; Lazarus and Smyth 2008). Thus universal salt iodization, which proved to be sufficient for school children, may not be adequate for pregnant women (Andersson et al. 2007). Results published in the National Health and Nutrition Examination Surveys (NHANES) III (1988–1994) indicate that the median urinary iodine (UI) excretion for women of reproductive age is 128 μg iodine/l (6.9% of pregnant women with UI <50 μg/l). These values are well below than those found in a previous study NHANES I (1971–1974) (294 μg iodine/l), showing a decrease in iodine intake during pregnancy in USA (Hollowell and Haddow 2007).

In view of these findings, in 2007, WHO promoted iodine supplementation for pregnancy and lactation, so that the total iodine intake is 250–300 μg/day (Andersson et al. 2007). In Spain, the use of tablet containing 200 μg iodine is being promoted throughout the country and subsidized by the Spanish Public Health System.

Nevertheless, even if a pregnant woman is ingesting 250–300 μg of iodine daily (the recommended daily intake), a daily fortification with 100–200 μg iodine during a period of about 15 months (pregnancy plus lactation) does not represent danger for the fetus and neonate (Andersson et al. 2007; Zimmermann 2007; Velasco et al. 2009). The total amount of iodine intake does not block the developing thyroid gland of the fetus (see below). In contrast, the advantages of iodine supplementation are obvious: iodine supplementation from conception will ensure adequate maternal T4 during all of gestation and lactation; especially during the first half of gestation, in which the fetal brain is particularly vulnerable to iodine deficiency (Morreale de Escobar et al. 2004; Andersson et al. 2007).

135.2.5 Consequences of Iodine Excess Early in Life

Iodine supplementation, between the range recommended by WHO and ICCIDD (100–200 μg/day), given to pregnant women, even in iodine-sufficient areas, is safe for the fetus during gestation and for the neonate during lactation, because the adult maternal thyroid responds rapidly to an increase in circulating iodine by promptly activating autoregulatory mechanisms that are the opposite of those elicited by iodine deficiency. These mechanisms prevent thyroid function blockage due to an iodine excess.

These autoregulatory mechanisms do not mature until several weeks after term birth. Thus, late fetal and neonate's thyroid can be blocked for weeks if faced with an iodine overload, during a period when its brain requires T4 for its normal development. This might appear contradictory to the insistence of iodine supplementation during gestation and lactation. However, iodine supplementation during these periods is not dangerous because the amounts of iodine recommended are safe and of several orders of magnitude smaller than those that block thyroid functions in the mother, fetus, and neonate (Andersson et al. 2007; Zimmermann 2007). For example, such pathological abnormal amounts of iodine can be found in nonmedicinal compounds frequently used at home and clinically, such as iodine-containing disinfectants and contrast media (Table 135.4). In fact, the exposure of pregnant women and newborns, especially if born prematurely, to iodine-containing disinfectants and radiographic contrast media is contraindicated.

The possibly negative effects of an iodine excess during the neonatal period should not question the convenience of iodine supplementation during pregnancy, when using the amounts proposed by WHO and ICCIDD (Andersson et al. 2007; Zimmermann 2007; Glinoer 2007).

Table 135.4 Iodine concentrations in various compounds

Compound	Iodine content	Times the normal daily adult iodine intake
Iodinated salt	60 μg/g	0.25x
Amiodarone[a]	7,500 μg/tablet	50x
Disinfectants:		
Lugol's solution [b]	130,000 μg/ml	867x
Betadine (Povidone–iodine)	10,000 μg/ml	67x
10% Sodium iodide	85,000 μg/ml	567x
Radiological contrasts:		
Hexabrix (ioxaglate)	320,000 μg/ml	2,133x
Oragrafin (ipodate sodium)	308,000 μg/tablet	2,053x
Lipiodol (^{131}I-ethiodised oil)	380,000 μg/ml	2,533x
Renografin[c]	370,000 μg/ml	2,467x
Telepaque (iopanoic acid)	333,000 μg/ml	2,220x

This table lists the iodine content of various iodinated compounds of frequently used at home and clinically. The active principle is indicated within parentheses. The iodine content is expressed as times the normal daily adult iodine intake (150 μg iodine per day; see Table 135.2 for iodine requirements for other groups of the population)

[a]Amiodarone is an iodated antiarrhythmic agent that contains 37.3% iodine

[b]Standard Lugol's solution contains 5% iodine and 10% potassium iodide

[c]Renografin is a diatrizoate meglumine and diatrizoate sodium solution

135.3 Iodine Deficiency Disorders

135.3.1 Iodine Deficiency Disorders and Neurodevelopment

Iodine deficiency is one of the most frequent causes of preventable mental retardation in children worldwide. A wide spectrum of iodine deficiency disorders have been described during gestation and the early postnatal period (less than 3 years of age), ranging from abortion, stillbirths, congenital anomalies, deafness, cretinism, neurocognitive delay, and mental retardation, as well as attention-deficit hyperactivity disorders, among others (Hetzel 1994; Morreale de Escobar et al. 2007).

In children, the severity of the neurodevelopmental damage caused by iodine deficiency during gestation depends on the developmental period affected by this condition and on its severity. In 1990, it was estimated that 1,600 million people is exposed to iodine deficiency worldwide (28.9% of the world population). From these, 11 million suffered overt cretinism (the most extreme form of mental retardation due to iodine deficiency) and that 43 million people were affected by some degree of mental impairment (Glinoer and Delange 2000).

Epidemiological studies performed in The Netherlands (Pop et al. 2003; Kooistra et al. 2006), USA (Haddow et al. 1999), and Russia (Kasatkina et al. 2006) have shown neurological alterations in children from hypothyroxinemic mothers. Furthermore, a prospective study from Italy reported a positive correlation between iodine deficiency during the first half of gestation and the IQ score of their children (Vermiglio et al. 2004). In addition, 68.7% of them presented an attention-deficit hyper-activity disorder. In these studies, no signs of clinical or subclinical hypothyroidism were observed in the hypothyroxinemic mothers and their children were euthyroid at birth. In conceptual agreement with this, in a recent study performed in Spain (Berbel et al. 2009), it has been found that a mild hypo-thyroxinemia (i.e., circulating free T4 within the 0–10th percentile of the normal range) from the beginning of gestation causes a significant delay in the neurobehavioral development of children. Even more important is the finding that the deficient behavior of the children is not ameliorated if the 200 μg/day iodine supplementation is delayed for 10–12 weeks from the beginning of gestation.

135.3.2 Critical Periods in Brain Development

The central nervous system of vertebrates develops from the neural plate, which folds forming the neural tube to an extremely complex system of neurons and non-neuronal cells. During corticogenesis, different cohorts of proliferating neuroblasts located near the ventricular surface of the tel-encephalic vesicle of the neural tube successively stop dividing and become migrating neurons. During telencephalic corticogenesis in mammals, young cortical neurons migrate on radial glial processes from the ventricular zone into the cortical plate. The great majority (about 80%) of neurons migrate radially, while the rest do so tangentially (i.e., parallel to the pial surface) to their target area (O'Rourke et al. 1992). Radially migrating neurons follow an "inside-out" gradient in which the "early" cohort of cells reaching the cortical plate will be found in the adult layer VI, while the "late" neurons migrate to the superficial zone of the cortical plate and will be found in adult layers II and III. In rats, the bulk of radial migration starts by embryonic day 13 (E13), while the last cohort of cells leave the ventricular zone by E20 (Bayer and Altman 1991). Thus, in the rat, as in other mammals, including man (see below), most of neurogenesis and subsequent migration occurs when the

fetal thyroid hormones are not yet present (these begin to appear by E17.5–18). Therefore, maternal thyroid hormones are the only thyroid hormones present in the fetal cortex (Obregón et al. 1984). At the end of this process, neurons grow and differentiate to express their mature phenotype. The cortex becomes organized into functional areas and develops a mature pattern of connectivity according to the functional requirements of the system. Cortical neurons will receive and send connections from and to subcortical regions; they will establish ipsilateral intrinsic and associative connections and, contralateral homo- and heterotopic commissural connections. Most of these connections are exuberant and then specifically pruned and, eventually, connections with new targets will be alternatively established (Innocenti 1995).

During the development of the central nervous system, many genes are expressed in a spatiotemporal order (Bernal 2005). Changes in the expression of these genes may produce alterations in the organization and maturation of the central nervous system, thereby affecting its function. The expression of fundamental genes involved in this process has been shown to be regulated by thyroid hormones. The irreversibility and importance of damage will depend on when, where, and how alterations of gene expression occur (Bernal 2005). Thus, an analysis of structural and functional alterations caused by iodine deficiency during development may be of use in the search for new specific genes and add light to our understanding of neurological alterations related to iodine deficiency disorders (Berbel et al. 2007; Berbel and Bernal 2010).

In humans, neocortical development occurs between the 6th and 24th week of gestation, although the bulk of cortical cell migration occurs between the 8th and 24th week (Marín-Padilla 1978) and mostly before onset of fetal thyroid hormone secretion. The later occurs at midgestation (i.e., by the 18th week of gestation; Obregón et al. 1984). As previously indicated, neocorticogenesis begins comparatively later in the rat, at around E13, and is complete roughly at birth, with most of the process occurring between E14 and E19, again mainly before onset of fetal thyroid function (at E17.5-18). In addition, the postnatal development and maturation of the central nervous system is comparative longer in humans than in rats. However, despite these differences, similarities may be established when onset of fetal thyroid gland secretion is taken as the reference point (Fig. 135.4). For instance, the main waves of radial migration in the human neocortex occur during the first half of gestation, with peaks at 11 and 14 weeks of gestational age (Marín-Padilla 1978), roughly corresponding to waves of cell migration studied in rats which, as in humans, occurs before onset of fetal thyroid function (Fig. 135.4) (Berbel et al. 2001).

135.3.3 Experimental Models to Study Developmental Hypothyroidism and Hypothyroxinemia

Several genetic models have developed during the last decades to study different forms of developmental and postnatal hypothyroidism, such as congenital hypothyroidism (Kratzsch and Pulzer 2008). These models include mutations of the TSH receptor ($hyt^{-/-}$ mice) (Biebermann et al. 1997), agenesis or functional impairment of thyrocytes ($TTF1^{-/-}$, $TTF2^{-/-}$, $Pax8^{-/-}$ mice) (Pasca di Magliano et al. 2000), and mutations of the TR ($TRa^{-/-}$, $TRb^{-/-}$, $TRa^{-/-}b^{-/-}$ mice as well as TRα or TRβ knock-in mutations) (Flamant and Samarut 2003). However, they present some limitations; for instance, some mutant pups does not survive more than 1 month after birth (e.g., Pax8$^{-/-}$ mice), some present other types of serious alterations that might interfere with hypothyroid symptoms (e.g., poor development of respiratory system in $TTF1^{-/-}$ mutants, renal dysfunction in Pax8$^{-/-}$ mutants, etc.; Park and Chatterjee 2005), and others do not present phenotypic alterations because of an absence of gene repression ($TRa^{-/-}$ mice) (Morte et al. 2002; Flamant et al. 2007).
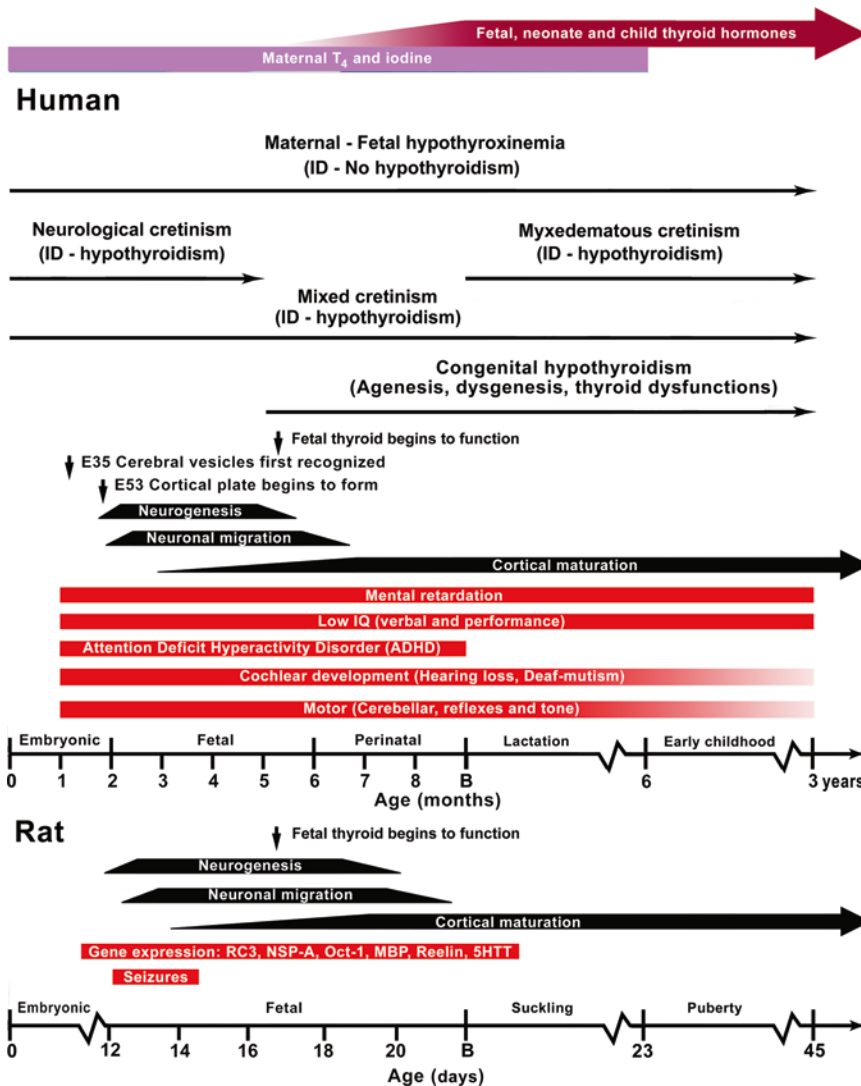
Fig. 135.4 Main neurodevelopmental events and neurological alterations associated with iodine deficiency during fetal and neonatal life. Time scales and the respective developmental periods are indicated for humans and rats in the upper and lower panels, respectively. The period in which the child's thyroid hormone is secreted is indicated by the uppermost arrow. The gradation indicates the period in which the production of fetal thyroid hormones increases to reach neonate values. The period in which both T4 and iodine are transferred from the mother to the fetus is also indicated in an adjacent bar. Thyroid hormones deficiencies and their etiologies and clinical symptoms, which are indicated in parentheses, are shown in the upper part of the human panel. *Thin black horizontal arrows* represent the critical periods related to these disorders. Some major developmental events of the cerebral cortex are also indicated both for humans and rats (*black bars*). Major neurological alterations associated with maternal/fetal T4 and iodine deficiency and critical vulnerability periods are shown by *grey bars*. In the lower (rat) panel, *grey bars* indicate genes that are regulated by thyroid hormones and behavioral alterations associated with maternal and/or fetal T4 and iodine deficiency. For cochlear and motor disorders, heavy gradation indicates the period in which the brain is more sensitive to iodine deficiency (Modified from Berbel et al. (2007). With permission)

Other models are based on the administration of antithyroid drugs, which interfere with the uptake of iodine by the thyrocytes by inhibiting the sodium/iodine symporter (e.g., potassium perchlorate and thiocyanate) and the iodination of thyroglobulin by thionamide and thiourylene drugs such as propylthiouracil (PTU) and methimazole (MMI). They may be competitive substrates for thyroid iodide peroxidase, preventing the oxidation of iodide by this enzyme (Rosenberg 1952; DeGroot and Davis 1962). In addition to the effects on the thyroid gland, PTU (and, to a much lesser extent, MMI) partially inhibits the peripheral deiodination of T4. Thus, PTU acts also directly on body tissues to inhibit the normal formation of T3 from T4 (Escobar del Rey and Morreale de Escobar 1961; Oppenheimer et al. 1972). Surgical thyroidectomy is another procedure used to induce thyroid hormone deprivation (Morreale de Escobar et al. 1987; Berbel et al. 2010; Morte et al. 2010). Antithyroid treatments result in maternal, and to a greater and lesser extent, in fetal hypothyroidism. In contrast, surgical thyroidectomy performed to pregnant dams causes maternal but not fetal hypothyroidism. When performed postnatally it results in hypothyroidism of the pups.

Models for iodine deficiency during gestation on development of the central nervous system include monkeys (Mano et al. 1987), sheep (Potter et al. 1982), and rats (Li et al. 1986). These studies have shown changes in the cerebellum with reduction in weight and cell number, and delayed maturation. The influence of maternal hypothyroxinemia on cortical development has been recently studied in rats and mice (Berbel and Bernal, 2010). In experiments for chronic and severe maternal/fetal hypothyroxinemia, pregnant rats are either fed a low-iodine diet starting before and continuing during the entire pregnancy (LID pups) (Martínez-Galán et al. 1997; Lavado-Autric et al. 2003). In experiments for mild and transient maternal hypothyroxinemia, pregnant rats and mice are treated with MMI for 3 days beginning at E12 (i.e., the onset of fetal neocorticogenesis; $3MMI_{12}$ pups) (Ausó et al. 2004; Cuevas et al. 2005).

135.4 Alterations in Cortical Development

135.4.1 Altered Migration During Corticogenesis

The radial migration during corticogenesis has been studied in the cerebral cortex of hypothyroid rats (Berbel et al. 2007) as well as in other cortical regions of the brain such as the cerebellum (Bernal 2005). In the auditory and somatosensory cortical areas, there was a decrease in the proportion of 5-bromo-2′-deoxyuridine-positive (BrdU-positive) cells in the normally expected supragranular layers and an increase of BrdU-positive cells in the infragranular layers whichever the age of BrdU injection (Fig. 135.5a,b) (Lucio et al. 1997; Berbel et al. 2001). These studies also reported a high proportion of heterotopic neurons (i.e., cells found in abnormal locations) in the subcortical white matter (Lucio et al. 1997; Berbel et al. 2001) and corpus callosum (Goodman and Gilbert 2007) (Fig. 135.6).

Fig. 135.5 (continued) since they are blurred in cresyl violet-stained adjacent sections. LID pups were born to rats that were fed a low-iodine diet during pregnancy and lactation. LID+I pups were born to dams that received LID containing KI (approximately 10 μg of iodine per day). Dams were injected intraperitoneally for 3 days with BrdU (20 mg/kg per day in physiological saline), starting at either at E14, E15, and E16 (Further details are given in Lavado-Autric et al. 2003). (**d**) Plots of BrdU-labeled cells from normal, $3dMMI_{12}+T4_{13}$, $3dMMI_{12}+T4_{15}$, and $3dMMI_{12}$ pups. The borders between layers are indicated by horizontal lines. Note the increased number of labeled cells, with respect to normal and $3dMMI_{12}+T4_{13}$, in the white matter (wm) of $3dMMI_{12}+T4_{15}$ and $3dMMI_{12}$ pups. $3dMMI_{12}$ pups were born to dams that received methimazole (MMI) from E12 to E15, $3dMMI_{12}+T4_{13}$ pups were born to $3dMMI_{12}$ dams infused daily with T4 from E14 to E16, and $3dMMI_{12}+T4_{15}$ pups were born to $3dMMI_{12}$ dams infused daily with T4 from E16 to E18 (Panels a and b – Modified from Berbel et al. (2001). With permission; Panel c – Reprinted from Lavado-Autric et al. (2003). With permission; Panel d – Reprinted from Ausó et al. (2004). With permission)
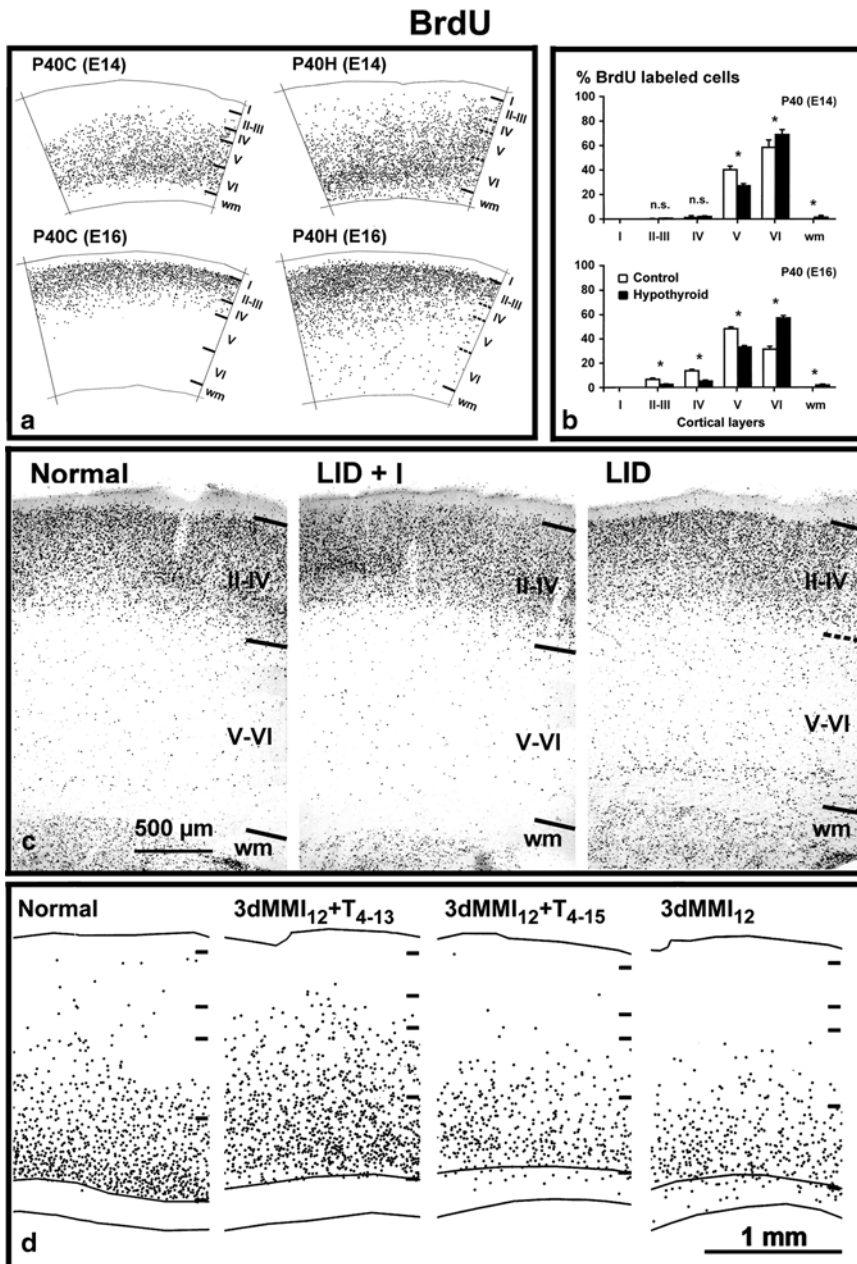
Fig. 135.5 Radial migration during corticogenesis in developmental hypothyroidism and maternal hypothyroxinemia. Developmental hypothyroidism and maternal hypothyroxinemia alter radial migration during corticogenesis. (**a**) Outlines of coronal sections of the primary somatosensory cortex from normal (P40C) and hypothyroid (P40H) pups, showing the distribution of BrdU-labeled cells at P40, following injections of BrdU at E14 and E16. Cells are more widely distributed in hypothyroid rats. Note the increased number of labeled cells, with respect to normal, in the white matter (wm) of hypothyroid rats at E14 and E16. Mediodorsal is to the right. (**b**) Histograms showing the mean percentage (±S.D.) of BrdU-labeled cells in normal pups (*white bars*) and hypothyroid pups (*black bars*), in different cortical layers. The number of labeled cells in the white matter (wm) is significantly higher in hypothyroid pups ($P < 0.05$; asterisks) (Further details are given in Berbel et al. 2001). (**c**) Photomicrographs of coronal sections of the primary somatosensory cortex showing BrdU-labeled cells in normal, LID+I and LID pups at P40. BrdU labeling after E17–19 injections shows that in the neocortex the radial distribution of BrdU-labeled cells is more widespread in LID than in normal and LID+I pups. The borders between layers are indicated by horizontal lines. Borders in the LID section are indicated by *dashed lines*
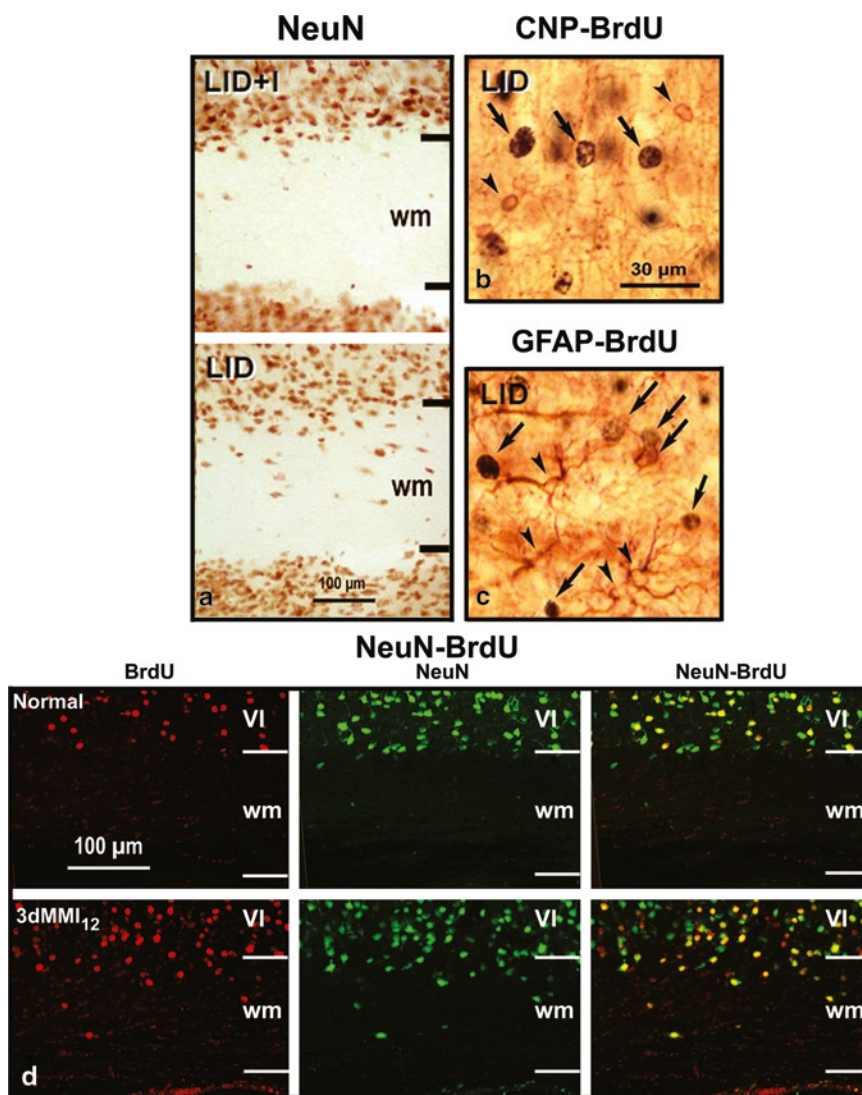
Fig. 135.6 Immunocytochemical characterization of heterotopic cells in maternal hypothyroxinemia. Immunocytochemical characterization of heterotopic cells. (**a**) Photomicrographs of NeuN-immunostained coronal sections of the primary somatosensory cortex in LID+I and LID pups at P40. The number of heterotopic NeuN-labeled neurons in subcortical white matter increases in LID as compared with LID+I pups. (**b**) and (**c**) CNP- and GFAP-positive oligodendrocytes and astrocytes, respectively, (*arrowheads*) and BrdU-labeled nuclei (*arrows*) are shown in layer V of LID pups. Note that CNP- and GFAP-positive cells are BrdU negative. The description of the experimental groups is given in Fig. 135.5. (**d**) Confocal photomicrographs showing BrdU and NeuN immunostaining in the primary somatosensory cortex of normal and 3dMMI$_{12}$ pups at P40. Single-labeling to BrdU (*left* and *red*) and to NeuN (*middle* and *green*), and double-labeling (*right* and *yellow*) are shown. Note the absence of immunoreactive cells in the subcortical white matter (wm) of the primary somatosensory cortex in normal pups. In the 3dMMI$_{12}$ pups, all cells in wm immunoreactive to BrdU (*left* and *red*) are neurons (*right* and *yellow*) (Panels a and b – Reprinted from Lavado-Autric et al. (2003). With permission; Panel d – Reprinted from Ausó et al. (2004). With permission)

These findings have also been confirmed in rat models for gestational hypothyroxinemia. In two recent studies, of chronic and transient maternal and fetal hypothyroxinemia, alterations in radial and tangential neuronal migration have been shown during neocorticogenesis, causing a blurred lamination in the neocortex and heterotopic neurons in the subcortical white matter (Lavado-Autric et al. 2003; Ausó et al. 2004; Cuevas et al. 2005) (Fig. 135.7). Similar results have been found in the cerebral
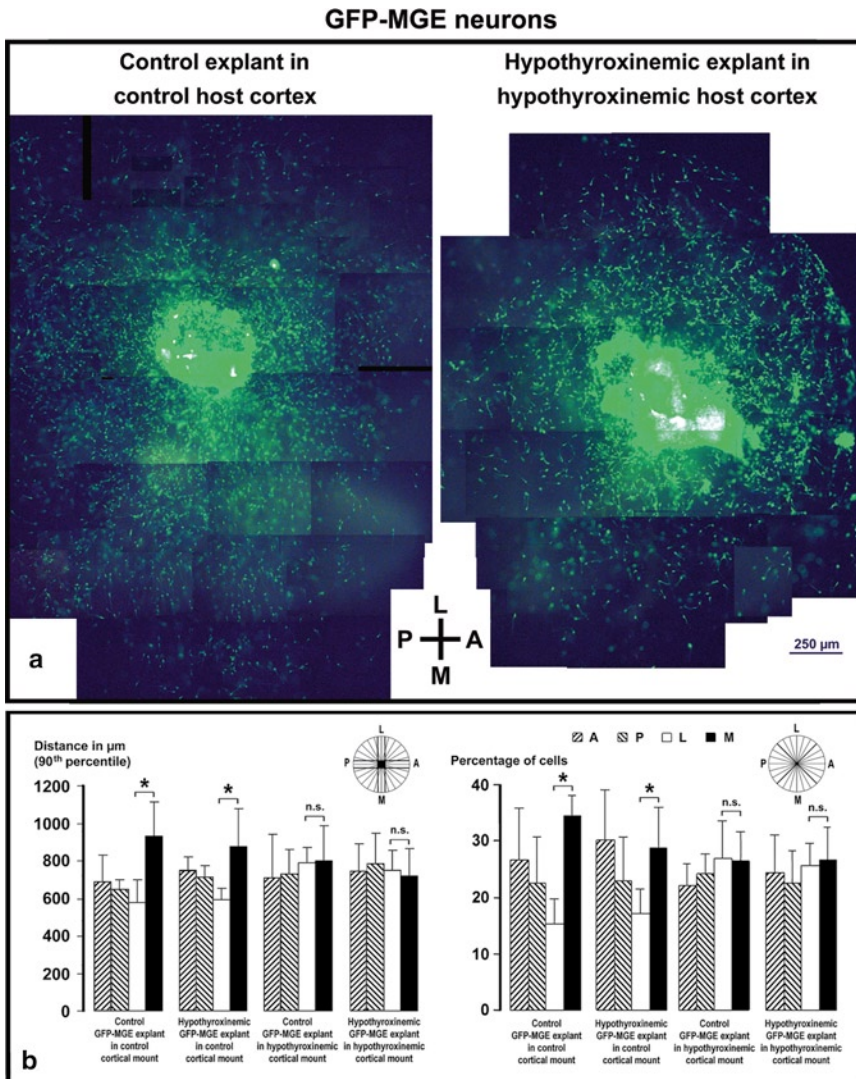
Fig. 135.7 Tangential migration during corticogenesis in maternal hypothyroxinemia. Maternal hypothyroxinemia affects tangential migration in the neocortex. (**a**) Low power fluorescent photomicrograph collage illustrating the tangential distribution of GFP-MGE control migrating neurons in wild control flat cortical mounts (*left*). The same for GFP-MGE hypothyroxinemic migrating neurons in hypothyroxinemic flat cortical mounts (*right*). Note the higher number of migrating neurons toward the medial (M) region in the control compared to the hypothyroxinemic cortical mount, where the distribution of the migrating neurons is more symmetrical. (**b**) On the *left* are histograms showing the mean (±SD) of the 90th percentile values of the distances from the outer limits of the GFP–MGE explants that are covered by migrating cells in the L, M, P, and A directions along the strips shown in the inset at the upper right corner of the graph. The distance covered by migrating cells in the M direction is higher when control and hypothyroxinemic GFP–MGE-derived cells migrate in control cortical mounts; these differences disappeared when they migrated in hypothyroxinemic ones. On the *right* are histograms showing the percentage of cells found in the L, M, P, and A sectors shown at the inset at the upper right corner of the graph. The percentages of cells are also greater in the M sector when control and hypothyroxinemic GFP–MGE-derived cells migrate in control cortical mounts than when they migrate in hypothyroxinemic ones. Statistically significant differences are indicated by asterisks; *n.s.* no statistically significant differences, *M* medial, *L* lateral, *P* posterior, *A* anterior (Reprinted from Cuevas et al. (2005). With permission)

cortex of pups born to late hypothyroidectomized rats (Berbel et al. 2010). These findings are in agreement with previous studies showing impaired maturation of radial glia in the hippocampus of pups born to chronic hypothyroxinemic rats (Martínez-Galán et al. 1997). Furthermore, these studies reported that substitution T4 treatment prevented the neurodevelopmental damage only when it was administered within one day after the induction of hypothyroxinemia. When T4 treatment began later, the alterations in neuronal migrations were not ameliorated (Ausó et al. 2004) (Fig. 135.5c,d). The presence of heterotopic neurons the subcortical white matter clearly shows an alteration of cell migration during corticogenesis, which may affect cortical function. In conclusion, these studies stress the importance of maintaining normal levels of maternal thyroid hormones during early pregnancy, especially that of circulating T4, to achieve normal neurodevelopment of the progeny.

135.4.2 Abnormal Cortical Cytoarchitecture

In adult hypothyroid rats, neocortical layering is blurred and only the lower border of layer I and the upper border of layer VI can be identified (Berbel et al. 1993). These changes are more pronounced in the somatosensory cortex where there is an absence of normal solid barrels. Instead, small dispersed patches of densely packed cells, located above the putative lower limit of layer IV can be observed (Fig. 135.8a; Berbel et al. 2001). In pups born to hypothyroxinemic pregnant rats, alterations in cortical cytoarchitecture were also found both in the neocortex and hippocampus. Cortical layering was also more blurred than in control rat (Lavado-Autric et al. 2003; Ausó et al. 2004) (Fig. 135.8b,c).

Although abnormal migration due to hypothyroidism is probably one of most important factors that can affect barrel cytoarchitecture, additional changes in the neocortical cytoarchitecture may be caused by other factors such as impaired neuronal maturation and connectivity (Ausó et al. 2001).

Developmental hypothyroidism also affected other aspects of cortical organization. By postnatal day 10 (P10), peanut agglutinin-negative areas were reduced by 11% in the hypothyroid as compared to the normal barrel cortex. In the adult, cytochrome oxidase labeling of barrels was reduced by 23% in the hypothyroid as compared to the normal barrel cortex (Berbel et al. 2001) (Fig. 135.9).

135.4.3 Abnormal Distribution and Maturation of Connections

Organization of intrinsic connections. In the auditory cortex, thyroid hormones have a selective effect on intrinsic connections as shown by immunohistochemistry for the calcium-binding proteins calretinin, calbindin, and parvalbumin, which stain different subpopulations of cortical gamma-aminobutyric acid (GABA)-ergic neurons forming inhibitory local circuits. The number, radial distribution, and morphology of immunopositive cells in hypothyroid and normal rats was similar, but the immunostaining pattern of *puncta* in hypothyroid rats is severely altered for calretinin and even more so for parvalbumin (Berbel et al. 1996). In hypothyroid rats, the number of parvalbumin positive terminals in layers II–VI is clearly less than in normal rats, with an especially pronounced reduction in *puncta* around unstained cell somata (Fig. 135.10a). Alterations in the tangential distribution of GABAergic cells might also occur, since the tangential migration of medial ganglionic eminence derived cells is altered in the hypothyroxinemic neocortex (Cuevas et al. 2005).

The decrease in immunostaining of parvalbumin terminals might result in a decreased inhibitory control of pyramids. This decreased inhibition might explain the high incidence of audiogenic seizures reported in hypothyroid rats (Van Middlesworth and Norris 1980) and in the pups of mild and transient hypothyroxinemic pregnant rats (Ausó et al. 2004) (Fig. 135.10b,c).
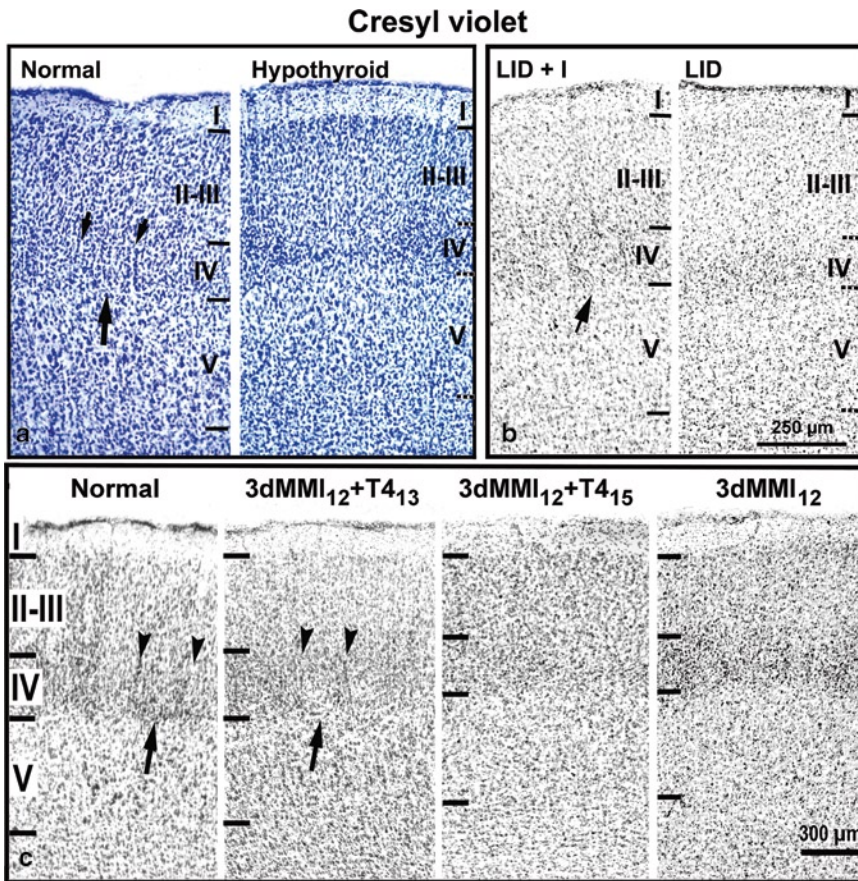
Fig. 135.8 (**a**) Cortical cytoarchitecture and laminar organization in developmental hypothyroidism and maternal hypothyroxinemia. (**a**) Cortical cytoarchitecture and laminar organization in developmental hypothyroidism and maternal hypothyroxinemia. Photomicrographs of cresyl violet-stained coronal sections showing the cytoarchitecture of the barrel cortex and layer borders in normal and hypothyroid rats. In normal rats, borders between layers are clear-cut, while in hypothyroid rats (*dashed lines*), they are blurred. Note that in layer IV of hypothyroid rats disperse patches of high cell density can be seen, instead of normal barrels (*arrow*). *Arrowheads* point the septae of a normal barrel. (**b**) Photomicrographs of cresyl violet-stained coronal sections showing the cytoarchitecture of the barrel cortex in LID+I and LID pups at P40. In the barrel cortex of LID+I pups, borders between layers are clear-cut, as expected in normal animals (*horizontal lines*), whereas in LID pups they are blurred (*horizontal dashed lines* in b and c). In layer IV of LID+I pups, barrels are normal and well defined, as indicated by an *arrow*. In contrast, barrels in layer IV of LID pups are not seen. The description of the experimental groups is given in the legend to Fig. 135.5. (**c**) Photomicrographs of cresyl violet-stained coronal sections showing the cytoarchitecture of the barrel cortex in normal, $3dMMI_{12}+T4_{13}$, $3dMMI_{12}+T4_{15}$ and $3dMMI_{12}$ pups at P40. Borders between layers (*horizontal lines*) are clear-cut in normal and $3dMMI_{12}+T4_{13}$ pups, whereas they are more blurred in $3dMMI_{12}+T4_{15}$ and $3dMMI_{12}$ animals. In layer IV of normal and $3dMMI_{12}+T4_{13}$ pups, barrels (*arrows*) are normal and well defined and demarcated by septae (*arrowheads*). In contrast, barrels in layer IV of $3dMMI_{12}+T4_{15}$ and $3dMMI_{12}$ pups are not seen (Panel b – Reprinted from Lavado-Autric et al. (2003). With permission; Panel c – reprinted from Ausó et al. (2004). With permission)

The immunocytochemical changes observed in hypothyroid rats may reflect alterations in the local circuitry, and thus, in normal cortical function.

Number and maturation of callosal axons. Transfer of information between the cerebral hemispheres is critical for higher brain function. In mammals, cortical areas of the two hemispheres are reciprocally connected by the corpus callosum, as well as the hippocampal and anterior commissures. All these connections appear in the embryo and develop postnatally (Innocenti 1995). Developmental
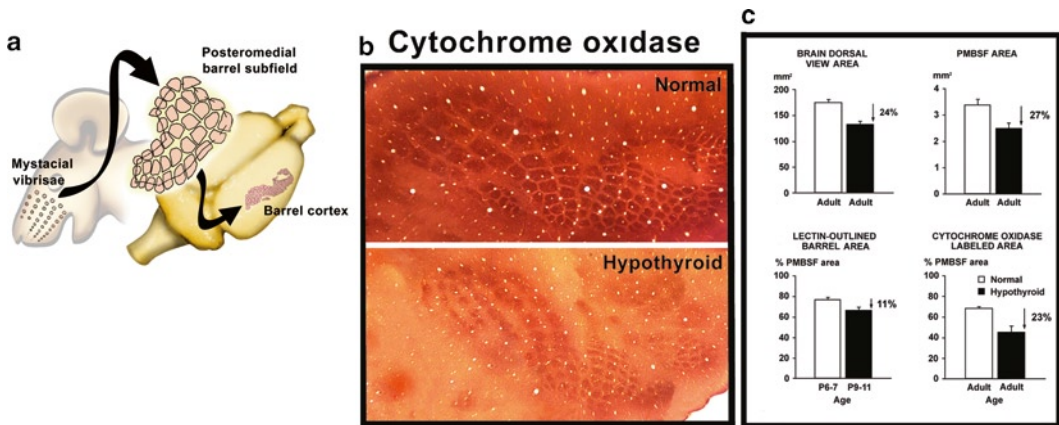
Fig. 135.9 Organization of cortical maps in developmental hypothyroidism. Reduced development of cortical maps in developmental hypothyroidism. (**a**) Figurine showing the posteromedial barrel subfield (PMBSF) of the primary somatosensory cortex in the brain of a rat. (**b**) Computer reconstruction from photomicrographs of serial tangential sections through layer IV, showing cytochrome oxidase labeling in the barrel cortex of normal and hypothyroid rats. Note the reduced tangential extension of the cytochrome oxidase labeling in hypothyroid with respect to normal rats. (**c**) Area measurements in normal and hypothyroid rats. The dorsal view brain area was, on average, 24% smaller in hypothyroid rats (*upper left*). A similar reduction (on average, 27%) was observed in the PMBSF tangential area (*upper right*). In normal rats, the total peanut agglutinin-outlined barrel tangential area at P6-7 was on average 77% of the PMBSF area; in hypothyroid rats at P9-11, it occupied only, 66% of the PMBSF, representing an 11% reduction in hypothyroid rats (*lower left*). In adult normal rats, the cytochrome oxidase-labeled tangential area was, on average, 69% of the PMBSF area; in adult hypothyroid rats, it was only, on average, 46% of the corresponding PMBSF, representing a 23% reduction with respect to normal, (*lower right*). In all cases, differences were statistically significant ($P < 0.05$) (Panels a and b – Reprinted from Berbel (2003). With permission; Panel c – Reprinted from Berbel et al. (2001). With permission)
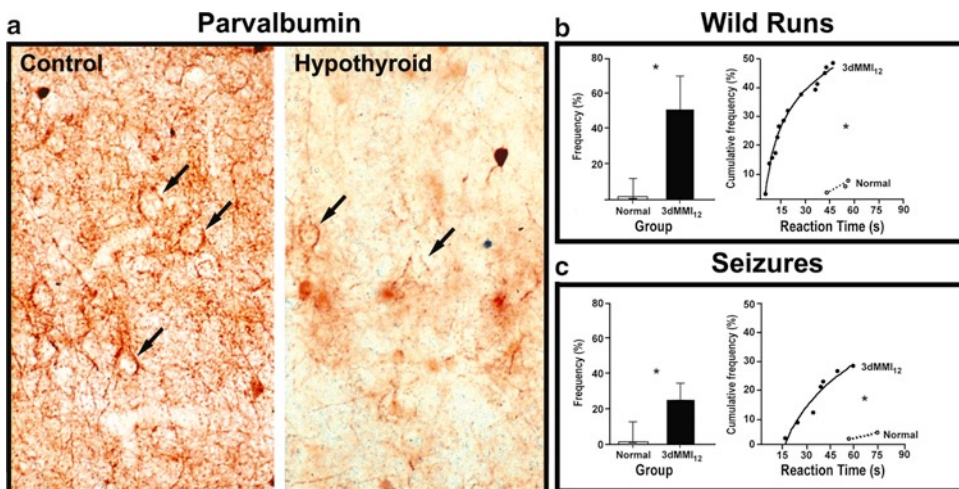
Fig. 135.10 Inhibitory local circuits and audiogenic seizures in developmental hypothyroidism. Altered inhibitory local circuits and increased audiogenic seizures in developmental hypothyroid pups. (**a**) Photomicrographs through layer V of the auditory cortex immunostained for parvalbumin in normal and hypothyroid rats. In normal rats, immunoreactive cells, processes, and perisomatic *puncta* can be seen. In hypothyroid rats, immunoreactive cells, processes, and perisomatic *puncta* can also be seen but they are less prominent than in normal rats. (**b**) and (**c**) Responses of normal and 3dMMI$_{12}$ pups to an acoustic stimulus. (**b**) Histograms on the *left* in (b) and (c) correspond to the proportion (median with 25th and 75th percentiles) of pups responding with wild runs and with wild runs followed by a seizure, respectively. Graphs on the *right* represent the cumulative frequency of pups from the same groups that respond with wild runs alone or followed by a seizure, respectively, at the intervals after onset of the stimulus that are shown in the abscissa. Asterisk indicates a statistically significant difference compared with normal (Panels b and c – Reprinted from Ausó et al. (2004). With permission)

hypothyroidism does not affect the total number of axons in the anterior commissure (Guadaño-Ferraz, et al. 1994) and corpus callosum (Gravel et al. 1990) of the adult, although the maturation of commissural axons is dramatically impaired (Gravel and Hawkes 1990; Berbel et al. 1994) (Fig. 135.11a). The proportion of myelinated axons with respect to the total number of axons was greatly reduced both in the anterior commissure and corpus callosum of hypothyroid rats. In both commissures, myelinated axons were first observed at P12 in normal and at P14 in hypothyroid rats. In the anterior commissure at P180, the number of myelinated axons was significantly lower in hypothyroid (12.7% myelinated axons) compared to normal rats (32%), representing a 66% reduction in hypothyroidism. In the corpus callosum at P180, the reduction was similar (76%); there were 2.4% myelinated axons
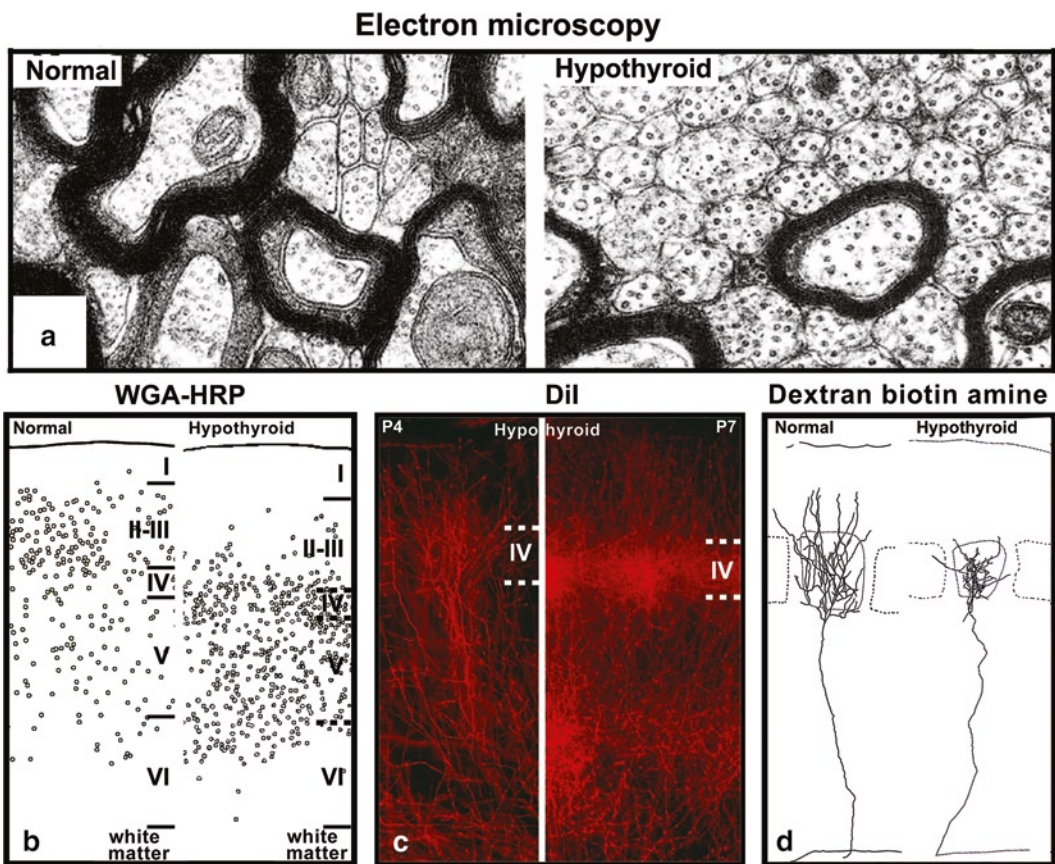
Fig. 135.11 Cortical connections in developmental hypothyroidism. Developmental hypothyroidism alters cortical connections. (**a**) Electron photomicrographs of the postlimb of the anterior commissure at P180 in normal and hypothyroid rats. Note the increased number of myelinated axons in normal as compared to hypothyroid rats. (**b**) Plots of retrograde-labeled callosal neurons in the auditory cortex of normal and hypothyroid adult rats. In normal rats, an important proportion of labeled neurons are in supragranular layers II and III. On the contrary, in hypothyroid rats, almost all labeled neurons are found between layers IV and VI. (**c**) Thalamocortical tracing in hypothyroid rats during development. Photomicrographs of coronal sections from P4 and P7 hypothyroid rats which had the lipophilic carbocyanine DiI tracer (1,1′-dioctadecyl-3,3,3′,3′-tetramethylindocarbocyanine perchlorate) implanted in the ventrobasal thalamic nucleus. At P4, similar as in normal rats, DiI-labeled thalamic afferents enter the somatosensory cortex, and form clusters in layer IV. At P7, collaterals in layer IV form more dense clusters than at P4. (**d**) Coronal views of thalamocortical terminal arbors in layer IV in the posteromedial barrel subfield of normal and hypothyroid adult rats. The barrel limit is marked with dashed lines and delineates the cytochrome oxidase positive area. Note that in hypothyroid rats terminal arbors have shorter and tortuous branches (Panel a – Reprinted from Guadaño-Ferraz et al. (1994). With permission; Panel b – Reprinted from Berbel (2003). With permission; Panels c and d – Reprinted from Ausó et al. (2001). With permission)

in hypothyroid compared to 10% in normal rats (Berbel et al. 1994). The maturation of some cytoskeletal components is delayed or does not occur in hypothyroid rats (Gravel and Hawkes 1990; Nunez et al. 1991) as is also the case for axon caliber growth (Gravel et al. 1990; Berbel et al. 1994). Development and maturation of oligodendrocytes in the forebrain commissures of hypothyroid rats may also be affected. In fact, cortical expression of myelin-associated glycoprotein, proteolipid protein, and myelin basic protein in oligodendrocytes is strongly reduced (Muñoz et al. 1991).

Distribution of callosal neurons. In hypothyroid rats, the distribution of callosally projecting neurons has been studied in the visual and somatosensory (Gravel and Hawkes 1990), and auditory cortices (Berbel et al. 1993; Lucio et al. 1997). In the auditory cortex of developing (Lucio et al. 1997) and adult (Berbel et al. 1993) hypothyroid rats, the laminar distribution of labeled neurons was abnormal. In adult normal rats, 34% of callosal neurons were in the upper tier of the cortex (roughly corresponding to layers II–III and partially IV), while in hypothyroid rats, they were mostly located in infragranular layers (Berbel et al. 1993) (Fig. 135.11b).

The finding that callosal projections originate from deeper layers in hypothyroid rats (Berbel et al. 1993; Lucio et al. 1997) is interesting since the laminar origin of cortical projections is a particularly robust and reliable trait of cortical organization, related to the birth day of cortical neurons (McConnell and Kaznowski 1991; McConnell 1992). Studies in hypothyroid rats indicate that neurons destined to a given layer can migrate abnormally and be "trapped" in a different layer, but still form projections appropriate to their birth day.

In addition to altered radial distribution, the total number of callosal neurons increased auditory (Berbel et al. 1993), visual (Gravel and Hawkes 1990) cortices and in other cortical projecting neurons such as in the occipitospinal connections (Li et al. 1995), revealing maintenance of exuberant projections in hypothyroid rats.

Organization of thalamic afferents. In the barrelfield of adult hypothyroid rats, the radial distribution of thalamic afferents, anterogradely labeled with dextran-biotin amine and DiI, was similar to normal (Ausó et al. 2001). As in normal rats, hypothyroid thalamic afferents branched profusely in layer IV, reaching layers II–III and showing collaterals in layers Vb and VI (Fig. 135.11c). However, the spread of these collaterals was reduced in hypothyroid rats, resulting in more restricted projection areas (Ausó et al. 2001). Single reconstructions of terminal arbors confirmed the results. In hypothyroid rats, the collaterals in layer IV followed more complicated trajectories than in normal rats, and the number of axonal branches that reached layer II–III was reduced (Fig. 135.11d). The total length of terminal axon arbors was 49% smaller in hypothyroid rats. This arrested growth was also reflected in a reduced number of branches and by a 58% reduction in the number of buttons per terminal. In hypothyroid rats, ramification of the thalamocortical axons would appear to be stalled postnatally, resulting in a reduced synaptogenesis as suggested by the reduced number of buttons on the thalamocortical branches (Ausó et al. 2001).

Serotonin (5-HT) immunostaining is a good transient marker for thalamic afferents in the visual, auditory, and somatosensory areas of rats during the first postnatal days. In the barrel cortex of normal rats, labeling disappeared by P11–12, while in hypothyroid rat it disappeared by P16–17 (a 5 days delay; Fig. 135.12a) (Ausó et al. 2001). In both, normal and hypothyroid rats, the heavy 5-HT labeling in the barrel cortex is located in layer IV, although a light and diffuse immunoreactivity appeared in other cortical layers.

Hypothyroidism seems to dissociate stabilization of juvenile axons from maturation, growth in caliber, and myelination processes, which were previously thought to be necessarily linked (Innocenti 1991). Speculatively, the adult hypothyroid brain may retain aspects of developmental plasticity, as observed in hypothyroid vertebrates. In amphibians, the absence of thyroid hormones prevents the onset of metamorphosis, maintaining the tadpole in a juvenile state (Kollros 1981; Schönenberger and Escher 1988). In these tadpoles, as in hypothyroid rats, normal developmental changes, including regressive events, fail to occur.

135.4.4 Altered Gene Expression in the Somatosensory Thalamus and Cortex

Until P11, the expression of 5-HT transporter (5-HTT) in the ventrobasal thalamic nucleus and cerebral cortex of hypothyroid rats was similar to normal. By P15, gene expression disappeared in normal rats, whereas it persisted in the hypothyroid condition and paralleled the protracted 5-HT immuno-labeling in the barrel cortex (Fig. 135.12b; Ausó et al. 2001).

Other genes, such as the vesicular monoamine transporter (VMAT2) and 5-HT1B receptor, are normally expressed, indicating a selective effect of hypothyroidism on the 5-HTT expression and excluding the possibility of a generalized effect of thyroid hormones on the state of thalamic neuron maturation (Ausó et al. 2001). The 5-HTT gene downregulation is most probably indirect, given that no response element to thyroid hormones is present in the 5-HTT promoter (Heils et al. 1998). Interestingly, normal rat pups display a peak in brain tissue thyroid hormone levels by P10 (Guadaño-Ferraz et al. 1994) that could contribute to the regulation of 5-HTT and other genes whose transient expression is thyroid hormone dependent.
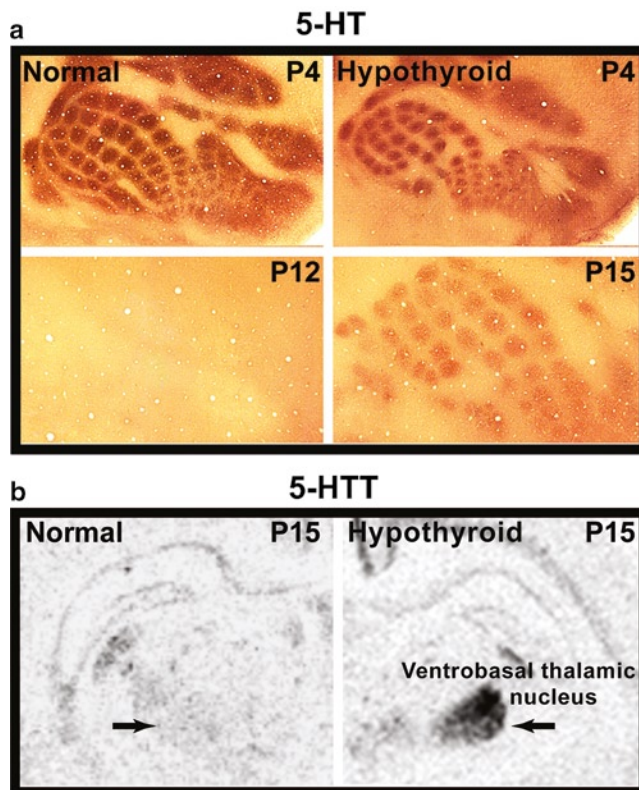
Fig. 135.12 Expression of serotonin and serotonin-transporter in developmental hypothyroidism. Altered expression of serotonin (5-HT) and serotonin-transporter (5-HTT) in developmental hypothyroidism. (**a**) Serotonin (5-HT) immunostaining in normal and hypothyroid rats during postnatal development. Photomicrographs of flattened neocortex tangential sections, containing parietal, temporal, and occipital cortices, showing 5-HT labeling in the somatosensory cortex of normal (*left*) and hypothyroid (*right*) rats at the indicated postnatal ages. At P4, heavily immunostained barrels can be seen. Decay of 5-HT labeling occurs by P11 in normal and by P16 in hypothyroid rats. Note that, in normal P12 rats, no barrels were immunostained, whereas in hypothyroid rats of the same age and at P15, they are still immunopositive. (**b**) Autoradiograms of in situ hybridization labeling using ^{35}S-labeled probes to serotonin-transporter (5-HTT). Coronal brain sections are shown at the level of the ventrobasal thalamic nucleus (VB). Both, in normal and hypothyroid rats at P8, strong 5-HTT expression is detected in the VB. At P15, a strong 5-HTT expression is still observed in the hypothyroid VB (Reprinted from Berbel (2003). With permission)

Reduced 5-HT levels in the brain during the critical period of barrel formation delay the formation and differentiation of layers II–III (Blue et al. 1991; Osterheld-Haas and Hornung 1996), and reduce the tangential extent of thalamocortical arbors within barrels (Bennett-Clarke et al. 1994). Thus, prolonged 5-HTT expression in the hypothyroid ventrobasal thalamic nucleus should decrease the concentrations of 5-HT in the extracellular space of sensory cortices, affecting their organization and differentiation.

In conclusion, we can see an asynchrony in the maturation of thalamocortical afferents and their cortical targets in hypothyroid rats. Cortical cells could be at a stage of maturation that does not allow them to respond to thalamocortical signals, resulting in an abnormal communication between thalamic axons and target cells (e.g., by a reduced synaptogenesis).

135.5 Correlates with Human Diseases

These experimental studies may help to better understand human epidemiological data, despite differences in the timing of neocorticogenesis between man and rats with respect to stages of pregnancy (Fig. 135.4). As already mentioned, the postnatal development and maturation of the central nervous system is comparatively longer in humans than in rats, but many similarities also exist (Berbel et al. 2007).

From experimental studies in rats, we can hypothesize that many events in human development might also be altered that affect cortical organization and function in the progeny of mothers who have suffered different degrees of hypothyroxinemia during gestation; a possibility that we cannot ethically confirm or disprove. These alterations may well be the underlying cause of the decreased mental development described in cretins born in areas of severe iodine deficiency. Also reported when the deficiency is mild and moderate (Vermiglio et al. 2004; Berbel et al. 2009) and the mothers are hypothyroxinemic without being clinically or subclinically hypothyroid. In fact, heterotopic cells have been described in the neocortex of therapeutically aborted human fetuses from an iodine-deficient area (Liu et al. 1984). These studies have reported heterotopic cells in the neocortex and abnormal cytoarchitecture similar to that found in rats. Although the mental impairment attributed to early maternal hypothyroxinemia is usually not as severe as that of congenitally hypothyroid children deprived of an early treatment with T4, the number of children at risk for neurodevelopmental deficits related to early maternal hypothyroxinemia is 150–200 times greater than that of newborns with congenital hypothyroidism (Morreale de Escobar et al. 2004).

135.6 Applications to Other Areas of Health and Disease

Every child has the right to receive an adequate supply of iodine to ensure his (or her) normal development and every mother has the right to receive adequate iodine nutrition during pregnancy and lactation to ensure that her unborn child experiences normal mental development. These rights were established in the resolutions of the Convention on the Rights of the Child (United Nations Assembly, New York 1989); The World Summit for Children (United Nations, New York 1990); The World Conference on Macronutrients: Elimination of "Hidden Hunger" (United Nations Children's Fund – UNICEF, WHO, Food and Agricultural Organization of the United Nations – FAO; Montreal 1991), and the World Conference on Nutrition (WHO, FAO; Rome 1992). Thus, to eradicate iodine deficiency and, consequently, to increase the quality of life of children must be one of the priority

goals of Public Health Institutions in developed countries and of the health areas concerning Primary Attention Care, Gynecology, Pediatrics, Endocrinology, Neurology, Nutrition, Psychology, and Preventive Medicine. Thyroid hormones exert both genomic and nongenomic actions during all the life cycle in many tissues, organs, and systems. In particular, they are crucial during early neurodevelopment, since key phases of the central nervous system development depend on the expression of genes that are regulated by thyroid hormones. These genes affect, among other things, proliferation, migration, and maturation of neurons and glial cells. To know how thyroid hormones regulate these phases of development may also help to understand altered regulatory mechanisms in other neurodevelopmental diseases such as schizophrenia and epilepsy with cytoarchitectonic alterations similar to those found in hypothyroidism and hypothyroxinemia. In fact, both hypothyroidism and hypothyroxinemia also increase the risk of suffering from these neurological diseases. Thyroid hormones exert a key role in the activation of peripheral glia (such a Schwann cells) playing a fundamental role in nerve regeneration and repair. The study of thyroid hormones on the regulation of the function of adipocytes is of basic importance for nutritionists and endocrinologists. In developed countries, the obesity in children is one of the principal factors affecting their quality of life and increasing the profile of cardiovascular risk factors. In addition, thyroid hormones may exert nongenomic actions in many cell types, regulating principal metabolic pathways. Thyroid hormone acting on cytoplasmic thyroid hormone-receptors could activate the PLC-IP3 and DAG-PKC pathways to increase the intracellular concentration of calcium and to modulate the Na+/H+ exchanger in myoblasts. These actions reveal a new role of thyroid hormones in cardiovascular functions. By combining basic and clinical investigation, new data will be obtained to better understand the basic phases of brain development and the genetic and physiological events underlying some of the human diseases mentioned above.

135.7 Concluding Remarks

In this chapter, we have insisted on the importance of the implementation of universal salt iodization and provision of iodine supplements during pregnancy and lactation, which can be easily implemented at a very low cost. Iodine supplementation does not exclude other ways to prevent iodine insufficiency such as the use of iodinated salt in households and in prepared foods, and the incorporation of foods from iodine-sufficient zones in the diet, such as seafood.

The present chapter does not address the controversy regarding implementation of maternal screening programs of thyroid function during the first trimester of gestation. Although Europeans from countries with National Health Systems favor such screening programs (Glinoer 1998; Morreale de Escobar et al. 2002), some North American learned Societies do not (Casey and Leveno 2006) on the questionable basis that there is not good evidence that identification and treatment improves maternal or infant outcomes.

In conclusion, we recommend the need of an iodine supplement, for all women considering conception and during pregnancy and lactation, at risk of suffering iodine deficiency, without waiting for confirmation that a pregnant woman's iodine intake is inadequate. We believe that iodine supplementation is independent from implementation of T4 screening of every pregnant woman and should be handled in the same way as folates, which are advised without prior evidence that the woman is folate deficient. We fully recommend iodine supplementation to assure that children reach the full potential of their mental capabilities according to their genetic endowment and epigenetic determinants, avoiding the tragedy of a reduced intelligence due to a preventable micronutrient deficiency such as an inadequate iodine intake.

Summary Points

- After starvation, iodine deficiency remains the most frequent cause worldwide of preventable mental retardation in children.
- Severe iodine deficiency results in a wide spectrum of disorders including cretinism.
- Mild iodine deficiency causes maternal hypothyroxinemia, which affects pregnant women even in apparently iodine-sufficient areas.
- Maternal hypothyroxinemia often goes unnoticed because T3 levels remain within the normal range, and thyrotropin is not increased.
- Recent epidemiological data have found that mild maternal hypothyroxinemia during the first month of pregnancy increases the risk of neurodevelopmental abnormalities in children.
- Experimental data in animal models have shown altered brain cortical cytoarchitecture in pups born to hypothyroxinemic dams. These alterations are prevented in hypothyroxinemic dams treated with potassium iodide.
- To prevent iodine deficiency during gestation and lactation, the WHO recommends a supplement of iodine for every expectant woman, in addition to the use of iodized salt in households and a diet comprising iodine rich foods, so that the total iodine intake is 250–300 µg iodine per day.

Definitions

Thyroid hormones: Thyroxine (T4) and triiodothyronine (T3) are endocrine hormones produced by the thyroid gland. The genomic action of thyroid hormone is mainly mediated by T3 (the active hormone). In nongenomic actions, T4 might have a prominent role activating metabolic pathways through link membrane receptors.

Iodothyronine deiodinases: Selenoproteins that catalyzes the deiodination of thyroid hormones in target cells.

Recommended iodine intake: Daily amounts of iodine intake, recommended by the World Health Organization, that are necessary to maintain an euthyroid status. The recommended iodine intake varies according to the age and physiological state of an individual. Expectant mothers need a daily intake of 250–300 µg iodine; double the recommended iodine intake for normal nonpregnant women.

Iodine deficiency: A condition in which the iodine secreted into the urine is below 100 µg per liter. Mild iodine sufficiency occurs when the urinary iodine is between 50 and 100 µg per liter, moderate if it is between 20 and 50 µg per liter, and severe iodine deficiency if is below 20 µg per liter.

Hypothyroxinemia: Low levels of circulating free T4. When T3 and TSH are within the normal range no subclinical or clinical hypothyroidism is diagnosed. Mild hypothyroxinemia during gestation may cause neurological damage to the fetus.

Hypothyroidism: Endocrine disease caused by insufficient production of thyroid hormone by the thyroid gland. Circulating T4 and T3 are below the normal range and TSH is above the normal range.

Subclinical hypothyroidism: It is caused by a deficient thyroid gland function. Circulating T4 and T3 are normal and TSH is above the normal range.

Cretinism: Brain damage caused by a severe iodine deficiency.

Telencephalic cerebral cortex: Also known as cerebral cortex, it is the outermost region of the cerebrum. It is divided into three major cortices: archicortex, paleocortex, and neocortex.

Radial migration: Migratory pathway from the germinal layers (subventricular layer) to the cortical plate that is followed by migrating neurons during the genesis of the neocortex. This is mostly followed by excitatory glutamatergic neurons.

Tangential migration: Migratory pathway from the medial ganglionic eminence to the cortex that is followed by migrating neurons during the genesis of the neocortex. This migratory pathway is mostly followed by inhibitory GABAergic neurons.

Key facts 1

- Iodine is an essential component of thyroid hormones: thyroxine (T4) and triiodothyronine (T3).
- Thyroid hormone synthesis results from the coupling of monoiodotyrosine (MIT) and diiodotyrosine (DIT) residues of colloidal thyroglobulin.
- Thyroid hormone release is due to thyrotropin (TSH)-induced thyroglobulin hydrolysis by lysosomal proteases of thyrocytes.
- Deiodination of T4 and T3 are catalyzed by type 1 (D1), type 2 (D2), and type 3 (D3) iodothyronine deiodinases.
- In the central nervous system, activating D2 catalyzes deiodination of T4 to T3. Inactivating D3 catalyzes deiodination of T4 to rT3 and that of T3 to T2.
- In the central nervous system, activating D2 is mainly found in astrocytes and tanycytes, while inactivating D3 is found in neurons.
- Thyroid hormones may exert both genomic and nongenomic actions on target cells, regulating gene expression in the nucleus and mitochondria, and metabolic signal cascades.
- Genomic action: T3 is the active hormone with high affinity for nuclear receptors.
- Nongenomic action: T4 might have a prominent role activating metabolic pathways through link membrane receptors such as integrins.

Key facts 2

- The amount of daily iodine intake varies according to the age and physiological state of an individual.
- The fetus depends on maternal T4 and iodine for normal development.
- Expectant mothers need a daily intake of 250–300 µg iodine; double the recommended iodine intake for normal nonpregnant women.
- The iodine content in foods depends on that of the soil. In general, iodine-deficient soils are in inland regions, mountainous areas, and places with frequent flooding, but they can be also found in coastal regions.
- The strategies to prevent iodine deficiency include (i) the use of iodinated salt in the household, (ii) the incorporation of iodine to industrially elaborated foods (i.e., bread, milk, cheese), and (iii) the introduction of dietary diversification (i.e, consuming food from iodine-sufficient areas and seafood).
- Mean intake of iodine does not ensure the amounts recommended by the World Health Organization (WHO) during pregnancy and lactation (250–300 µg iodine per day).
- WHO promotes daily iodine supplements during pregnancy and lactation, to reach the total daily iodine intake recommended by the WHO and ICCIDD.

Key facts 3

- The severity of the neurological damage depends both on the developmental period when the iodine deficiency is suffered and on the degree of the deficiency.
- Mild hypothyroxinemia (i.e., circulating free T4 within the 0–10th percentile of normal range and with normal T3 and TSH levels) from the beginning of gestation causes a significant delay in neurobehavioral development of children.
- Neurobehavioral outcome of children in a iodine deficient area is not ameliorated if iodine supplementation (200 μg iodine per day) is delayed 10–12 weeks from the beginning of pregnancy.
- Animal models have shown that chronic and transient maternal and fetal hypothyroxinemia causes, among others, alterations in radial and tangential neuronal migration during neocorticogenesis, resulting in a blurred lamination of the neocortex and heterotopic neurons in the subcortical white matter.
- Substitution T4 treatment prevented the neurodevelopmental damage only when it was administered one day after the induction of the hypothyroxinemia. When T4 treatment was begun later, the alterations were not ameliorated.

References

Abe T, Suzuki T, Unno M, Tokui T, Ito S. Trends Endocrinol Metab. 2002;13:215–20.

Anderson GW, Schoonover CM, Jones SA. Thyroid. 2003;13:1039–56.

Andersson M, de Benoist B, Delange F, Zupan J. Public Health Nutr. 2007;10:1606–11.

Ausó E, Cases O, Fouquet C, Camacho M, García-Velasco JV, Gaspar P, Berbel P. Eur J Neurosci. 2001;14:1968–80.

Ausó E, Lavado-Autric R, Cuevas E, Escobar del Rey F, Morreale de Escobar G, Berbel P. Endocrinology. 2004;145:4037–47.

Azizi F, Aminorroya A, Hedayati M, Rezvanian H, Amini M, Mirmiran P. Public Health Nutr. 2003;6:95–8.

Bayer SA, Altman J. Neocortical development. New York: Raven Press; 1991.

Bennett-Clarke CA, Leslie MJ, Lane RD, Rhoades RW. J Neurosci. 1994;14:7594–607.

Benoit G, Malewicz M, Perlmann T. Trends Cell Biol. 2004;14:369–76.

Berbel P. Mente Cerebro. 2003;2:10–20.

Berbel P, Guadaño-Ferraz A, Martínez M, Quiles JA, Balboa R, Innocenti GM. Eur J Neurosci. 1993;5:1465–78.

Berbel P, Guadaño-Ferraz A, Angulo A, Cerezo JR. Behav Brain Res. 1994;64:9–14.

Berbel P, Marco P, Cerezo JR, DeFelipe J. Neurosci Lett. 1996;204:65–8.

Berbel P, Ausó E, García-Velasco JV, Molina ML, Camacho M. Neuroscience. 2001;107:383–94.

Berbel P, Obregón MJ, Bernal J, Escobar del Rey F, Morreale de Escobar G. Trends Endocrinol Metab. 2007;18:338–43.

Berbel P, Mestre JL, Santamaría A, Palazón I, Franco A, Graells M, González-Torga A, de Escobar GM. Thyroid. 2009;19:511–9.

Berbel P, Navarro D, Ausó E, Varea E, Rodríguez E, Ballesta JJ, Salinas M, Flores E, Faura C, Morreale de Escobar G. Cereb Cortex. 2010;20:1462–75.

Berbel P, Bernal J. Expert Rev Endocrinol Metab. 2010;5:563–75.

Bernal J. Vitam Horm. 2005;71:95–122.

Bernal J, Guadaño-Ferraz A. Curr Opin Endocrinol Diabetes. 1998;5:296–302.

Bernal J, Pekonen F. Endocrinology. 1984;114:677–9.

Bianco AC, Kim BW. J Clin Invest. 2006;116:2571–9.

Bianco AC, Larsen PR. Thyroid. 2005;15:777–86.

Bianco AC, Salvatore D, Gereben B, Berry MJ, Larsen PR. Endocr Rev. 2002;23:38–89.

Biebermann H, Grüters A, Schöneberg T, Gudermann T. N Engl J Med. 1997;336:1390–1.

Blue ME, Erzurumlu RS, Jhaveri S. Cereb Cortex. 1991;1:380–9.

Bradley DJ, Towle HC, Young WS3. J Neurosci. 1992;12:2288–302.

Calvo R, Obregón MJ, Ruiz de Oña C, Escobar del Rey F, Morreale de Escobar G. J Clin Invest. 1990;86:889–99.

Casey BM, Leveno KJ. Obstet Gynecol. 2006;108:1283–92.

Ceballos A, Belinchon MM, Sanchez-Mendoza E, Grijota-Martinez C, Dumitrescu AM, Refetoff S, Morte B, Bernal J. Endocrinology. 2009;150:2491–6.

Cuevas E, Ausó E, Telefont M, Morreale de Escobar G, Sotelo C, Berbel P. Eur J Neurosci. 2005;22:541–51.

D'Arezzo S, Incerpi S, Davis FB, Acconcia F, Marino M, Farias RN, Davis PJ. Endocrinology. 2004;145:5694–703.

Davis PJ, Davis FB. Thyroid. 2002;12:459–66.

Davis PJ, Tillmann HC, Davis FB, Wehling M. J Endocrinol Invest. 2002;25:377–88.

DeGroot LJ, Davis AM. Endocrinology. 1962;70:492–504.

Dunn JT, Dunn AD. In: Braverman LE, Utiger R, editors. The thyroid, 8th ed. Philadelphia: Lippincott Williams & Wilkins; 2000. pp. 91–104.

Ercan-Fang S, Schwartz HL, Oppenheimer JH. Endocrinology. 1996;137:3228–33.

Escobar del Rey F, Morreale de Escobar G. Endocrinology. 1961;69:456–65.

Flamant F, Samarut J. Trends Endocrinol Metab. 2003;14:85–90.

Flamant F, Gauthier K, Samarut J. Mol Endocrinol. 2007;21:321–33.

Forrest D, Vennström B. Thyroid. 2000;10:41–52.

Forrest D, Reh TA, Rüsch A. Curr Opin Neurobiol. 2002;12:49–56.

Friesema EC, Jansen J, Milici C, Visser TJ. Vitam Horm. 2005;70:137–67.

Gao B, Meier PJ. Microsc Res Tech. 2001;52:60–4.

Gereben B, Zavacki AM, Ribich S, Kim BW, Huang SA, Simonides WS, Zeöld A, Bianco AC. Endocr Rev. 2008;29:898–938.

Glinoer D. Trends Endocrinol Metab. 1998;10:403–11.

Glinoer D. Best Pract Res Clin Endocrinol Metab. 2004;18:133–52.

Glinoer D. Public Health Nutr. 2007;10:1542–6.

Glinoer D, Delange F. Thyroid. 2000;10:871–87.

Goodman JH, Gilbert ME. Endocrinology. 2007;148:2593–7.

Gravel C, Hawkes R. J Comp Neurol. 1990;291:128–46.

Gravel C, Sasseville R, Hawkes R. J Comp Neurol. 1990;291:147–61.

Guadaño-Ferraz A, Escobar del Rey F, Morreale de Escobar G, Innocenti GM, Berbel P. Brain Res Dev Brain Res. 1994;81:293–308.

Guadaño-Ferraz A, Obregón MJ, St Germain DL, Bernal J. Proc Natl Acad Sci USA. 1997;94:10391–6.

Haddow JE, Palomaki GE, Allan WC, Williams JR, Knight GJ, Gagnon J, O'Heir CE, Mitchell ML, Hermos RJ, Waisbren SE, Faix JD, Klein RZ. N Engl J Med. 1999;341:549–55.

Haldimann M, Alt A, Blanc A, Blondeau K. J Food Comp Anal. 2005;18:461–71.

Heils A, Wichems C, Mössner R, Petri S, Glatz K, Bengel D, Murphy DL, Lesch KP. J Neurochem. 1998;70:932–9.

Hetzel BS. N Engl J Med. 1994;331:1770–1.

Hollowell JG, Haddow JE. Public Health Nutr. 2007;10:1532–9.

Huang SA, Dorfman DM, Genest DR, Salvatore D, Larsen PR. J Clin Endocrinol Metab. 2003;88:1384–8.

Incerpi S, Scapin S, D'Arezzo S, Spagnuolo S, Leoni S. Steroids. 2005;70:434–43.

Innocenti GM. Prog Sens Physiol. 1991;12:65–114.

Innocenti GM. Trends Neurosci. 1995;18:397–402.

Kasatkina EP, Samsonova LN, Ivakhnenko VN, Ibragimova GV, Ryabykh AV, Naumenko LL, Evdokimova YA. Neurosci Behav Physiol. 2006;36:619–24.

Kester MH, Martinez de Mena R, Obregón MJ, Marinkovic D, Howatson A, Visser TJ, Hume R, Morreale de Escobar G. J Clin Endocrinol Metab. 2004;89:3117–28.

Kollros JJ. In: Lawrence IG, Frieden E, editors. Metamorphosis: a problem in developmental biology, 2nd ed. London, New York: Plenum Press; 1981. pp. 445–59.

Kooistra L, Crawford S, van Baar AL, Brouwers EP, Pop VJ. Pediatrics. 2006;117:161–7.

Kratzsch J, Pulzer F. Best Pract Res Clin Endocrinol Metab. 2008;22:57–75.

Lavado-Autric R, Ausó E, García-Velasco JV, Arufe MC, Escobar del Rey F, Berbel P, Morreale de Escobar G. J Clin Invest. 2003;111:1073–82.

Lazarus JH, Smyth PPA. Lancet. 2008;372:888.

Li CP, Olavarria JF, Greger BE. Dev Brain Res. 1995;89:227–34.

Li JQ, Wang X, Yan Y, Wang K, Qin D, Xin Z, Wei J. Neuropathol Appl Neurobiol. 1986;12:261–70.

Lima FR, Gervais A, Colin C, Izembart M, Neto VM, Mallat M. J Neurosci. 2001;21:2028–38.

Liu JL, Zhuang ZJ, Tan YB, Shi ZF, Li XT, Yang XB, Wu JB, Chen BZ, Zhang JX, Qin JX, Kong D.M. Chin Med J (Engl). 1984;97:67–72.

Lucio RA, García JV, Cerezo JR, Pacheco P, Innocenti GM, Berbel P. Cereb Cortex. 1997;7:303–16.

Mano MT, Potter BJ, Belling GB, Chevadej J, Hetzel BS. J Neurolog Sci. 1987;79:287–300.

Marín-Padilla M. Anat Embryol. 1978;152:109–26.

Martínez-Galán JR, Pedraza P, Santacana M, Escobar del Ray F, Morreale de Escobar G, Ruiz-Marcos A. J Clin Invest. 1997;99:2701–9.

McConnell SK. Curr Opin Neurobiol. 1992;2:23–7.

McConnell SK, Kaznowski CE. Science. 1991;254:282–5.

Morreale de Escobar G, Obregón MJ, Escobar del Rey F. Horm Res. 1987;26:12–27.

Morreale de Escobar G, Obregón MJ, Escobar del Rey F. J Clin Endocrinol Metab. 2000;85:3975–87.

Morreale de Escobar G, Escobar del Rey F, Obregón MJ. (http://www.hotthyroidology.com/editorial_71.html); 2002.

Morreale de Escobar G, Obregón MJ, Escobar del Rey F. Best Pract Res Clin Endocrinol Metab. 2004;18:225–48.

Morreale de Escobar G, Obregón MJ, Escobar del Rey F. Public Health Nutr. 2007;10:1554–70.

Morreale de Escobar GM, Ares S, Berbel P, Obregón MJ, del Rey FE. Semin Perinatol. 2008;32:380–6.

Morte B, Manzano J, Scanlan T, Vennström B, Bernal J. Proc Natl Acad Sci USA. 2002;99:3985–9.

Morte B, Díez D, Ausó E, Belinchón MM, Gil P, Grijota-Martínez C, Navarro D, Morreale de Escobar G, Berbel P, Bernal J. Endocrinology. 2010;151:810-20.

Muñoz A, Rodríguez-Peña A, Pérez-Castillo A, Ferreiro B, Sutcliffe JG, Bernal J. Mol Endocrinol. 1991;5:273–80.

Nunez J, Couchie D, Aniello F, Bridoux AM. Neurochem Res. 1991;16:975–82.

Obregón MJ, Mallol J, Pastor R, Morreale de Escobar G, Escobar del Rey F. Endocrinology. 1984;114:305–7.

Ohtsuki S, Takizawa T, Takanaga H, Hori S, Hosoya K, Terasaki T. J Neurochem. 2004;90:743–9.

Oppenheimer JH. N Engl J Med. 1968;278:1153–62.

Oppenheimer JH, Schwartz HL, Surks MI. J Clin Invest. 1972;51:2493–7.

O'Rourke NA, Dailey ME, Smith SJ, McConnell SK. Science. 1992;258:299–302.

Osterheld-Haas MC, Hornung JP. Exp Brain Res. 1996;110:183–95.

Park SM, Chatterjee VKK. J Med Genet. 2005;42:379–89.

Pasca di Magliano M, Di Lauro R, Zannini M. Proc Natl Acad Sci USA. 2000;97:13144–9.

Pearce EN, Pino S, He X, Bazrafshan HR, Lee SL, Braverman LE. J Clin Endocrinol Metab. 2004;89:3421–4.

Pennington JAT, Schoen SA, Salmon GD, Young B, Johnson RD, Marts RW. J Food Comp Anal.1995;8:171–217.

Pérez-Castillo A, Bernal J, Ferreiro B, Pans T. Endocrinology. 1985;117:2457–61.

Pop VJ, Brouwers EP, Vader HL, Vulsma T, van Baar AL, de Vijlder JJ. Clin Endocrinol (Oxf). 2003;59:282–8.

Potter BJ, Mano MT, Belling GB, McIntosh GH, Hua C, Cragg BG, Marshall J, Wellby ML, Hetzel BS. Neuropathol Appl Neurobiol. 1982;8:303–13.

Power DM, Llewellyn L, Faustino M, Nowell MA, Björnsson BT, Einarsdottir IE, Canario AV, Sweeney GE. Comp Biochem Physiol C Toxicol Pharmacol. 2001;130:447–59.

Raspe E, Dumont JE. Endocrinology. 1994;135:986–95.

Refetoff S, Robin NI, Fang VS. Endocrinology. 1970;86:793–805.

Roberts LM, Woodford K, Zhou M, Black DS, Haggerty JE, Tate EH, Grindstaff KK, Mengesha W, Raman C, Zerangue N. Endocrinology. 2008;149:6251–61.

Rosenberg IN. Science. 1952;116:503–5.

Santisteban P, Bernal J. Rev Endocr Metab Disord. 2005;6:217–28.

Sarkar PK, Durga ND, Morris JJ, Martin JV. Neuroscience. 2006;137:125–32.

Schönenberger N, Escher G. Dev Brain Res. 1988;40:253–60.

Song Y, Driessens N, Costa M, De Deken X, Detours V, Corvilain B, Maenhaut C, Miot F, Van Sande J, Many MC, Dumont JE. J Clin Endocrinol Metab. 2007;92:3764–73.

Sugiyama D, Kusuhara H, Taniguchi H, Ishikawa S, Nozaki Y, Aburatani H, Sugiyama Y. J Biol Chem. 2003;278:43489–95.

van Middlesworth L, Norris CH. Endocrinology. 1980;106:1686–90.

Velasco I, Carreira M, Santiago P, Muela JA, García-Fuentes E, Sánchez-Muñoz B, Garriga MJ, González-Fernández MC, Rodríguez A, Caballero FF, Machado A, González-Romero S, Anarte MT, Soriguer F. J Clin Endocrinol Metab. 2009;94:3234–41.

Vermiglio F, Lo Presti VP, Moleti M, Sidoti M, Tortorella G, Scaffidi G, Castagna MG, Mattina F, Violi MA, Crisà A, Artemisia A, Trimarchi F. J Clin Endocrinol Metab. 2004;89:6054–60.

Visser TJ. Acta Med Austriaca. 1996;23:10–6.

Zimmermann M, Delange F. Eur J Clin Nutr. 2004;58:979–84.

Zimmermann MB. IDD Newsletter. 2007;23:1–2. (http://www.iccidd.org).

Zimmermann MB, Jooste PL, Pandav CS. Lancet. 2008;372:1251–62.

Zinman T, Shneyvays V, Tribulova N, Manoach M, Shainberg A. J Cell Physiol. 2006a;207:220–31.

Zinman T, Shneyvays V, Tribulova N, Manoach M, Shainberg A. J Cell Physiol. 2006b;207:220–31.

Zoeller RT, Rovet J. J Neuroendocrinol. 2004;16:809–18.

Chapter 136
Tryptophan Intake and the Influence of Serotonin on Development and Plasticity of Sensory Circuits

Claudio A. Serfaty

Abbreviations

5HT	Serotonin
5HT1B	Serotonin receptors of the 5HT1B subtype
AMPA	Glutamate receptors of the AMPA subtype
BDNF	Brain-derived neurotrophic factor
cAMP	Cyclic AMP
CREB	cAMP responsive-binding element
ECM	Extracellular matrix
GLUR1	Subunit of the AMPA receptor
GLUR2	Subunit of the AMPA receptor
IDO	Indoleamine 2,3-dioxygenase
IFN-γ	Interferon-gamma
LTD	Long-term depression of synaptic transmission
LTP	Long-term potentiation of synaptic transmission
MMP-9	Metalloproteinase 9
NMDAr	Glutamate receptors of the NMDA subtype
NR1	Subunit of the NMDA receptor
NR2A	Subunit of the NMDA receptor
NR2B	Subunit of the NMDA receptor
PKA	Protein kinase A
TNF-α	Tumor necrosis factor-alpha
tPA	Tissue plasminogen activator factor

136.1 Introduction

The intrinsic reorganization capacity of neuronal circuits, known as "neural plasticity" is one of most significant properties of brain self-organization that orchestrates brain development throughout early postnatal life. It underlies the acquisition of basic and higher brain functions, the construction of

C.A. Serfaty (✉)
Laboratory of Neural Plasticity, Fluminense Federal University, 100180, Niterói, RJ, 24001-970, Brazil
e-mail: claudio.serfaty@gmail.com; cserfaty@vm.uff.br

individuality and, ultimately, species adaptation and evolution. Neural plasticity occurs throughout life and is crucial during postnatal brain development when use-dependent synaptic modifications sculpt highly specific circuits for sensory, motor, and cognitive processing (Hensch 2005).

Serotonin (5HT) is an ancient molecule that appears during evolution in protozoans as an intracellular signaling molecule, hormone, and growth factor. Those functions precede its role as a classical neurotransmitter found in vertebrates (Turlejski 1996). Therefore, it is not surprising that in mammalian and nonmammalian species, 5HT exerts an enormous influence throughout the brain in almost every physiological process, from pain sensitivity, thermoregulation, circadian rhythm, appetite, aggression, sensorimotor activity, sexual behavior, mood, cognition, learning, and memory (Azmitia 2007).

Neuronal connections are capable of being constantly formed and eliminated in response to the physiological environment, stress, malnutrition, and all conditions that produce changes in brain structure. Accumulating research suggest that 5HT plays an important role in synaptic plasticity and brain maturation. Consequently, the disruption of serotonergic signaling may impair brain development leading to its associated disorders such as mental retardation (Serfaty et al. 2008).

Serotonin is metabolically derived from tryptophan, an essential amino acid that demands intake from its appropriate nutritional sources, mainly animal and to a lower extent, vegetable protein sources (Fernstrom 1977). Tryptophan is a limiting amino acid in corn, which is an easily accessible and inexpensive carbohydrate/energy source used by poor populations in developing countries. In fact, corn is a major carbohydrate that is broadly used by different cultures in South and Central America.

As malnutrition is one of the most important environmental factors that directly affect brain development, low tryptophan dietary content and a subsequent serotonergic dysfunction should be considered as a potential hazard for appropriate brain development.

136.2 The Development of Specific CNS Connections and the Retinotectal System as a Model for Topographically Organized Connections

During brain development, massive amounts of neurons and glial cells are generated. After migration to appropriate positions and differentiation into specific cell types, neurons start the process of dendritic and axonal outgrowth, target selection and synaptogenesis (Fig. 136.1). During this process, axons and their growth cones navigate through selective pathways guided by repulsive and attractive molecular gradients (Charron and Tessier-Lavigne 2005). On reaching the appropriate neuronal targets, the development of synapses takes place, mostly during postnatal life.

Since the pioneer studies of Roger Sperry, synaptic specification has been recognized as a major feature of brain processing, as it became clear that the sensory, motor, and cognitive abilities depend in a fundamental way, on the correct patterning of connections (Meyer 1998).

Two general strategies concur for the development of organized and specific connections found among mammalian species: an initial overproduction of neurons and synaptic contacts followed by the death of excess neurons and elimination of misplaced ineffective axons/synapses. About the time that neuronal contacts begin to emerge (starting during the last trimester in human gestation), about 50% of the immature neuronal population undergoes a process of natural neuronal death. This process is regulated by the availability of trophic factors: the so-called neurotrophins, like brain-derived neurotrophic factor (BDNF), can only be acquired by the most functional neurons/synapses. Also, during early postnatal development each axonal arbor is more expanded over the target territory than in latter stages of development and, as a result, immature neurons try to establish synaptic contacts in a more unspecific manner than mature neurons. Hence, during postnatal development neuronal

Human Brain Development
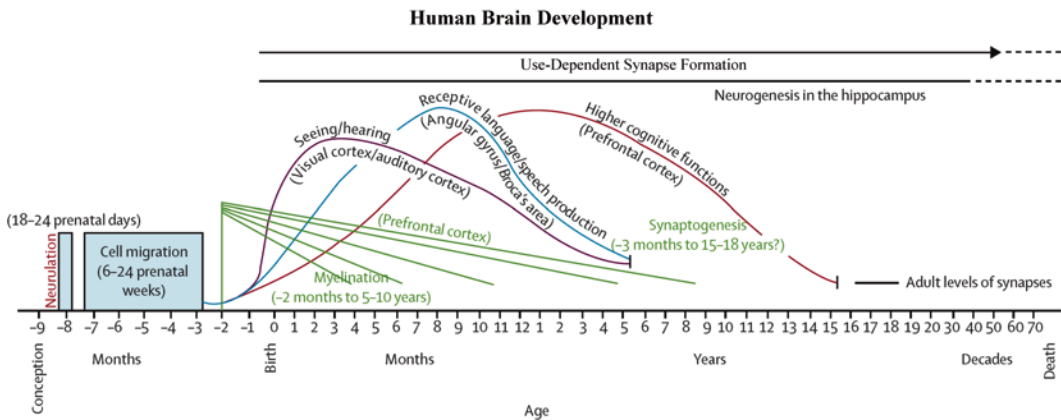
Fig. 136.1 Neurogenesis and development of the human brain. Diagram displaying the major steps of human brain development and its relation to the development of sensory, motor, and cognitive abilities (Reprinted from Grantham-McGregor et al. (2007, p. 61), with permission from Elsevier. Adapted from Thompson and Nelson (2001) and reproduced with permission of authors and American Psychological Association)

numbers decrease, transitory axons are selectively eliminated, and synapses from adjacent neurons converge at their targets into postsynaptic neighboring sites, giving rise to highly organized circuits. Those regressive events of neurogenesis are among the most important mechanisms that govern the selection of interconnecting neuronal populations in the brain.

As a model system for the study of organized brain circuits, the connections between the retina (retinal ganglion cells) and its target cells (superior colliculus or optic tectum) – the so-called retinotectal connections – have been extensively studied. It has been shown that the rodent uncrossed retinotectal pathway develops within the first three postnatal weeks, producing highly specific patterns of axonal connections at the target (Fig. 136.2). This form of developmental plasticity occurs mainly at the expense of axonal elimination and synaptic growth at appropriate territories.

The initial development of retinotectal topography is strongly influenced by repulsive/attractive molecules between retinal axons and target neurons. Retinal ganglion cells and their axons express a class of receptors to Ephrins-Eph recptors in gradients that change along the main retinal axis (dorsal to ventral/temporal to nasal). Those axons interact at the visual target with matching gradients of the corresponding Ephrin molecules located at post-synaptic membranes. The interaction of Eph receptors and Ephrins can either induce repulsion or attraction, thus providing positional molecular markers for the initial interconnection of neuronal populations, as proposed by Roger Sperry 4 decades ago. Indeed, ephrin knockout models have shown errors in connectivity of retinal axons along the target (Feldheim et al. 2000).

A later step of topographical refinement is achieved by activity-dependent mechanisms that are required to ensure the fine tuning of the correct representation of retinal axons over the superior colliculus, and thus circuitry maturation (O'Leary and McLaughlin 2005). This includes both spontaneous and evoked activity of retinal ganglion cells: even before the full differentiation of photoreceptors and eye opening, waves of correlated spontaneous activity between neighboring retinal ganglion cells seem to provide precise positional cues, thus simulating the normal activation bias and visual experience in retinal neurons (Wong et al. 1993). The resulting correlated presynaptic activity of neighbor axons induces an effective activation of postsynaptic neurons. The electrical coactivation of pre- and postsynaptic membranes triggers a process of selective synaptic stabilization while a failure of an axon to activate a postsynaptic neuron induces its selective elimination, a mechanism originally proposed by Donald Hebb in 1949. Therefore, Hebbian synapses (Butts et al. 2007) have been recognized to
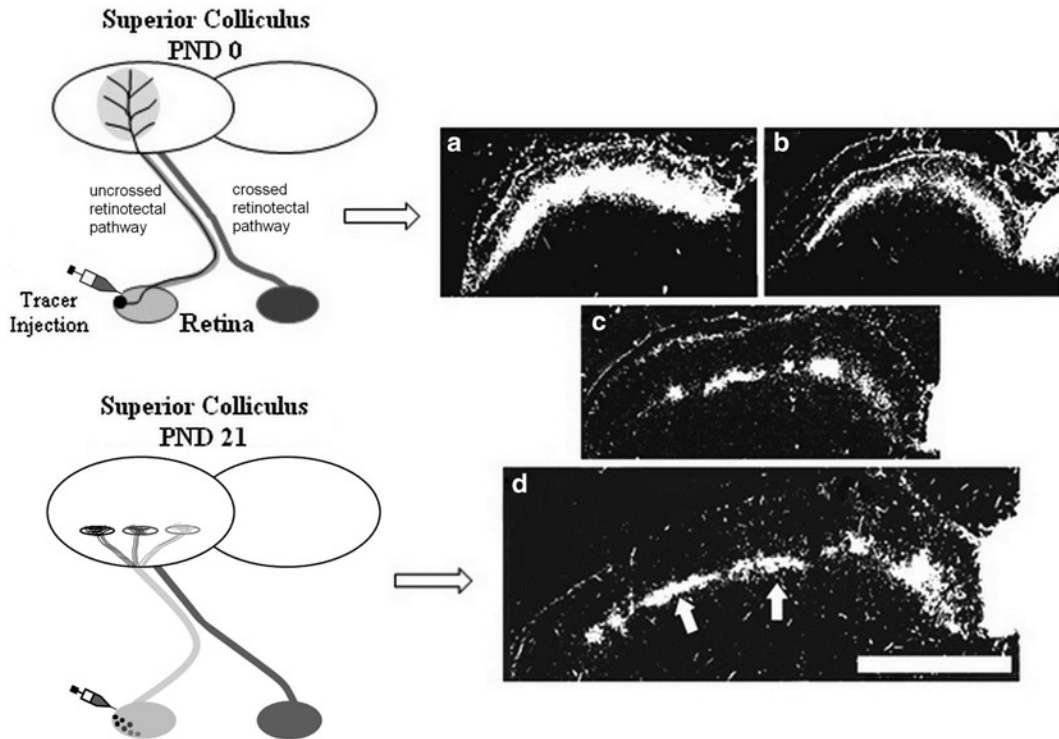
Fig. 136.2 Development of retinotectal connections. Intraocular injection of a neuroanatomical tracer reveals the pattern of axonal labeling (white labeling in dark-field photomicrographs) of retinal axons in the superior colliculus. Retinotectal axons develop from a initially widespread pattern of connections found soon after birth (diagram in *upper left*; photomicrographs **a**, **b**). By the second and third postnatal week, misplaced retinal axons have been selectively eliminated and the remaining axons concentrate at specific termination zones (diagram *lower left*; photomicrographs **c**, **d**, *arrows*). All dark-field photomicrographs represent coronal sections through the visual layers of the rat superior colliculus ipsilateral to the injected eye. Scale bar = 500 μm (Photomicrographs reprinted from Serfaty et al. (2005, p. 130), with permission from Elsevier)

activate glutamate NMDA receptors (NMDAr) that function as correlation sensors, driving downstream intracellular molecular cascades for use-dependent synaptic stabilization.

136.3 Critical Periods for Brain Development

The use-dependent development of functional, organized central connections in the mammalian brain occurs during a time window known as the critical period. A modern conception describes the critical period as the developmental stage in which environmental cues provide rapid plasticity of neuronal circuits, necessary to the acquisition of appropriate sensory, motor, and cognitive skills. The end of the critical period considerably slows plasticity in the corresponding primary sensory brain areas although does not limit plasticity in associative areas of neocortex including the hippocampus. The duration of the critical period is highly variable between mammalian species and is inversely related to the species longevity: rodents display a 3-week critical period, while humans develop protracted critical periods that extend up to 5–12 years and possibly beyond

(Berardi et al. 2000). The critical period duration may be, therefore, related to the complexity of sensory–motor–cognitive learning and thus affects directly the species' ability to adapt to their environment.

The influence of the critical period on the development of sensory brain connections was demonstrated by partial (monocular) visual deprivation studies. Experimental eyelid suture resulted in shrinkage of the respective innervation domains in the primary visual cortex – the ocular dominance columns – resulting in a severe loss of visual acuity from the deprived eye (Mower et al. 1985). In humans, neonatal strabismus can also result in similar loss of visual acuity. Eye misalignment, if not appropriately treated until the age of 5, produce a permanent loss of visual acuity also known as amblyopia. This acuity loss is produced by the loss of synapses originating from the nonaligned eye. Furthermore, cats raised under visually biased environments (e.g. exposed to visually stereotyped patterns of horizontal or vertical lines) do not develop accurate discrimination of visual stimuli (except for those horizontal or vertical stimuli), as well as the proper binocular representation of the visual field (Crair et al. 1998).

The critical period has also been demonstrated by lesion studies. In the rodent visual system, monocular enucleation or restricted retinal lesions (Serfaty et al. 2005) have been used to induce reorganization of axons originating from the intact eye. Lesion experiments revealed the whole extension of the plastic capacity during the critical period, inducing a rapid reactive growth of axons from the nonlesioned eye within the first three postnatal weeks. Surprisingly, retinal lesions after this period also have been shown to elicit a considerable amount of reorganization that takes, however, several weeks to occur, revealing a slow stage of plasticity in the mature brain (Serfaty et al. 2005). Accordingly, lesion studies have been used to reveal the plastic potential of the brain and are powerful tools for studying the forces and mechanisms that guide use-dependent modifications of neural circuits.

136.4 The Molecular Basis of Plasticity: Dendritic Spines as a Source for Synaptic Integration

Use-dependent modifications that occur at a rapid rate during the critical period occur at specific loci called dendritic spines (Fig. 136.3). Those specialized dendritic structures concentrate the biochemical machinery for use-dependent modifications in synaptic function, thus influencing the outcome of full brain development. In fact, disorders related to mental retardation are often correlated to structural and functional modifications in those structures with enormous impact on sensorimotor development as well as cognition deficits (Grossman et al. 2006).

As mentioned above, the plasticity of the developing synapses relates to the expression of glutamate NMDA receptors (NMDAr) that play a critical role as a sensor for correlated activity. During early postnatal development of the visual system, NMDAr display a composition with NR1/NR2B subunits, a configuration that allows an increased capacity for processing simultaneous inputs (extended synaptic integration), as would be expected for immature synapses. By the time of eye opening, however, NMDAr switch their subunit composition to NR1/NR2A, a configuration that requires strict temporal coactivation times, necessary for the development of highly specific connections (Lu and Constantine-Paton 2004). In accordance with a role for NMDA receptors in synaptic development and stabilization, it has been shown that the pharmacological blockade of NMDA receptors disrupts the normal connectivity pattern and, as a result, increase the sprouting of the uncrossed pathway following the partial deafferentation of the contralateral converging retinotectal projection (Colonnese and Constantine-Paton 2001).

Recent evidence also shows that the expression of glutamate AMPA receptors, and its GLUR1 and GLUR2 subunits regulate the size and shape of neuronal dendritic spines affecting the number and type of synaptic inputs, as well as the complexity retinotectal circuits (Haas et al. 2006). Activity
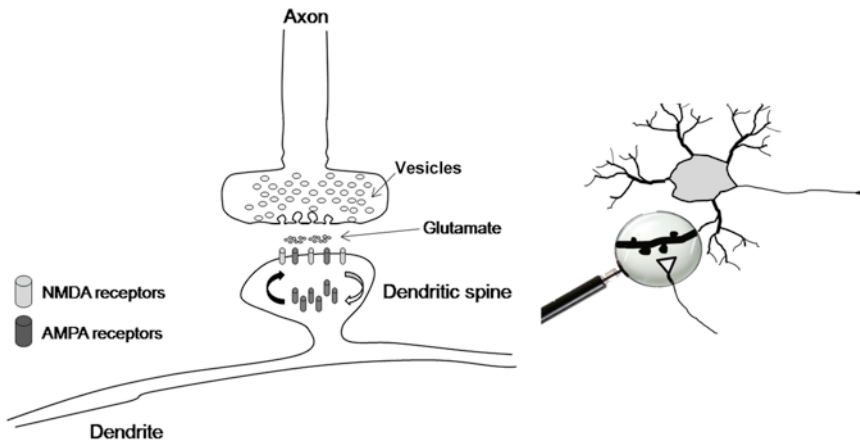
Fig. 136.3 Dendritic spines and glutamate receptors turnover. Most glutamatergic excitatory synapses occur at specialized loci along dendrites called dendritic spines. Those protruding structures are highly dynamic and change their size/shape in response to afferent stimulation. Dendritic spines concentrate glutamate receptors such as NMDA and AMPA receptors, linked to complex intracellular machinery that allows either the insertion or removal of AMPA receptors from the plasma membrane. The dynamics in AMPA receptors distribution underlies use-dependent modifications of synaptic strength

and NMDA-induced calcium influx can trigger either the membrane insertion or the internalization of AMPA receptors at synaptic membranes, resulting in long-term potentiation (LTP) or long-term depression (LTD) of synaptic activity, the physiological basis of learning and memory (Terashima et al. 2008).

In accordance with the role for NMDA receptors in synaptic plasticity, it has been shown that the development and plasticity of retinotectal projections is also influenced by other signals downstream the NMDA receptor activation. This includes local messengers such as nitric oxide and arachidonic acid, both synthesized by their calcium-dependent enzymes: nitric oxide synthase and phospholipase A2, respectively. The pharmacological blockade of those enzymes in neonatal and adult rats, respectively, disrupted the normal topographical patterning of retinal axons, suggesting their roles in the stabilization of developing and mature connections in the superior colliculus (Campello-Costa et al. 2000, 2006). Interestingly, nitric oxide and 5HT appear to have several common actions since it has been shown that 5HT depletion increases NOS activity (Tagliaferro et al. 2001).

136.5 Serotonin and Brain Plasticity

A large amount of evidence from pharmacological, biochemical, and clinical studies revealed a massive influence of 5HT for the normal CNS function and development. Serotonin acts as a growth factor during embryogenesis, since the appearance of 5HT axons throughout the brain and spinal cord occurs prior to the differentiation of most neurons. Through its receptor activity, 5HT orchestrates complex cascades of events, leading to changes in brain structure. Serotonin is involved with dendritic remodeling, dendritic spine formation, and synaptic plasticity (Sodhi and Sanders-Bush 2004). It has also been shown to affect the development and plasticity of many sensory systems including the visual (Gu and Singer 1995) and the somatosensory cortex (Lane et al. 2002).

The glutamatergic input from retinal ganglion cells to subcortical targets is greatly influenced by 5HT. Several studies described an inhibitory functional role for 5HT in the mammalian retinotectal

(Mooney et al. 1994) and retinogeniculate (Chen and Regehr 2003) synaptic transmission during development. The inhibitory action of 5HT involves presynaptic 5HT1B receptors (Mooney et al. 1994). The same modulatory role of 5HT was shown in the somatosensory cortex, where it inhibits excitatory thalamocortical transmission (Laurent et al. 2002). In the *Xenopus* retinotectal system, 5HT also inhibits retinal input to tectal neurons by means of 5HT1A and 5HT1B receptors. The activation of those receptors decreases intracellular levels of cyclic AMP (cAMP), a second messenger that influences cellular metabolism (Debski and Cline 2002). Therefore, in the sensory systems, 5HT appears to exert a modulatory function, possibly as a noise filter, which may be important for the process of axonal elimination of misplaced and to the stabilization of correctly placed synapses.

Serotonin interacts with BDNF, the astroglial growth factor S100β, and other chemical messengers (Azmitia 2007). The serotonergic system regulates its own differentiation by sequential activation of 5HT1A receptors, BDNF, and its receptor trkB, and activation of cAMP responsive-binding element (CREB) and ATF-1 transcription factors (Herdegen and Leah 1998). S100β stabilizes microtubules, the main framework of the cytoskeleton of neurons and astrocytes, and produces neurite extension (Ostendorp et al. 2007). In addition 5HT influences GABAergic, glutamatergic, and dopaminergic neurotransmitter systems (Sodhi and Sanders-Bush 2004). Furthermore, the activity of brainstem serotonergic neurons in rodents and cats has a slow and rhythmic pattern of firing, producing a constant release of 5HT that allows its action as a trophic molecule and a coordinator of brain development and plasticity rather than a neurotransmitter system involved in point-to-point rapid activity (Jacobs and Azmitia 1992).

Chronic administration of fluoxetine, a 5HT reuptake inhibitor, increases BDNF levels and thus the trophic influences on developing axons (Sodhi and Sanders-Bush 2004). On the other hand, a low-tryptophan diet has been associated with decreased 5HT and BDNF content in the mouse cortex (Lee et al. 1999).

Serotonin deprivation through the use of selective neurotoxins has been shown to impair brain plasticity (Gu and Singer 1995). On the other hand, 5HT overstimulation achieved by monoamine oxidase (MAO) knockout as well as by the use of a 5HT reuptake inhibitor has been shown to induce increased axonal outgrowth and sprouting in retinofugal (Bastos et al. 1999; Upton et al. 1999) and thalamocortical axons (Salichon et al. 2001).

136.6 Nutritional Tryptophan Restriction: Impact on Brain Development and Plasticity

Tryptophan is an essential amino acid that crosses the blood–brain barrier to enter in the CNS and the only source for 5HT synthesis (Sodhi and Sanders-Bush 2004). As a result, tryptophan restriction diets have been proposed as an efficient way to induce nonpharmacological 5HT deprivation (Fadda et al. 2000). Recent evidence from a nutritional tryptophan restriction model (Table 136.1) showed a reduction in 5HT immunoreactivity in neurons of the raphe nuclei in young rats fed through their mothers with a corn/gelatin-based diet (Fig. 136.4a–e) (González et al. 2008). Neuronal tracing studies revealed in those animals a developmental delay in the time course of axonal elimination in retinotectal connections. In the low-tryptophan diet group, axons originating from the temporal retina were still apparent at the posterior aspect of the superior colliculus by postnatal day 10. At the same developmental stage, animals fed with control diets, containing normal levels of tryptophan, presented nearly no ectopic axons at the caudal colliculus (Fig. 136.5a–f). These data suggest that a reduced serotonergic signaling would delay the time course of this major regressive event. However, this effect could not be attributed to a reduction in protein synthesis since no differences could be

Table 136.1 Corn and gelatin low-tryptophan diet

Experimental diets

	Portion (g)		Protein		Glycid		Lipid		Fiber		TRP amount	
	TRP⁺	TRP⁻	TRP⁺	TRP⁻	TRP⁺	TRP⁻	TRP⁺	TRP⁻	TRP⁺	TRP⁻	TRP⁺	TRP⁻
Corn	75.75	76.0	7.26	7.28	57.1	58.65	1.5	1.5	4.59	4.59	0.05	0.05
Soya oil	4.5	3.5	–	–	–	–	3.5	3.5	–	–	–	–
Minerals mix	3.5	3.5	–	–	–	–	–	–	–	–	–	–
Vitamin mix	1.0	1.0	–	–	–	–	–	–	–	–	–	–
Gelatin	16.0	16.0	13.66	13.66	–	–	–	–	–	–	–	–
L-tryptophan	0.25	–	–	–	–	–	–	–	–	–	0.25	–
Total	100	100	20.92	20.94	57.1	58.65	5.0	5.0	4.59	4.59	0.30	0.05
EFV (kcal)	357.08	363.45	83.68	83.76	228.4	228.4	45	45	–	–	–	–

Centesimal composition of experimental and control diets. Isocaloric, normoproteic Trp+, and Trp- diets were prepared with equivalent energetic values (EFV), and with the same constituent concentrations, except for L-tryptophan, which was complemented in Trp+ diet with 0.25 g for each 100 g. The amount of macronutrients, vitamins, and minerals was calculated according to the American Institute of Nutrition-93

Trp⁺ tryptophan-complemented, *Trp⁻* tryptophan-restricted diet

Fig. 136.4 Nutritional tryptophan restriction reduces serotonin (5HT) content in the rat brain. 5HT immunoreactivity in the rat midbrain at postnatal day 14 (PND 14). Serotonin immunoreactive cells (*arrows*) at the dorsal raphe nuclei from animals fed with control (Trp⁺) (**a**) or with tryptophan-restricted diet (Trp⁻) (**b**). Serotonin immunoreactive cells (*arrowheads*) at the ventral aspect of the raphe nuclei from animals fed with (Trp⁺) (**c**) or tryptophan-restricted diets (Trp⁻) (**d**). Notice that Trp⁺ brains presented increased immunoreactivity compared to the Trp⁻ group. Mean 5HT immunoreactive cells/section at the dorsal and ventral aspects of raphe nuclei of animals fed with Trp⁺ or Trp⁻ diets (**e**). *5HT* serotonin, *Trp⁺* tryptophan-complemented diet, *Trp⁻* tryptophan-restricted diet. Error bars represent SEM. $p < 0.05$; Scale bar = 100 μm (Reprinted from González et al. (2008, p. 443), with permission from Elsevier)
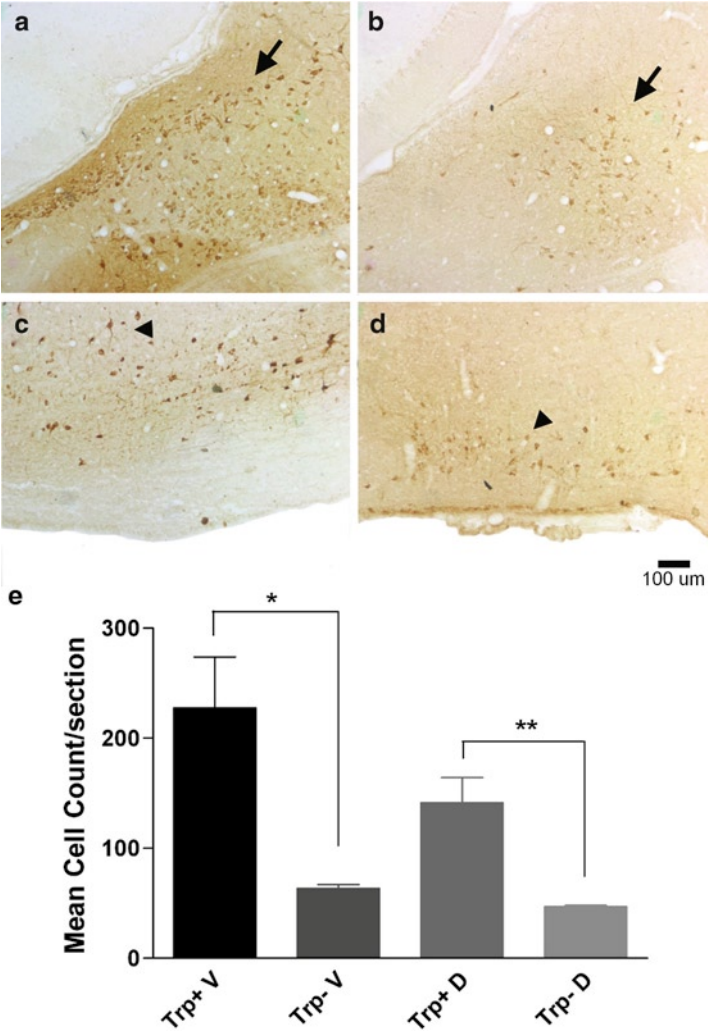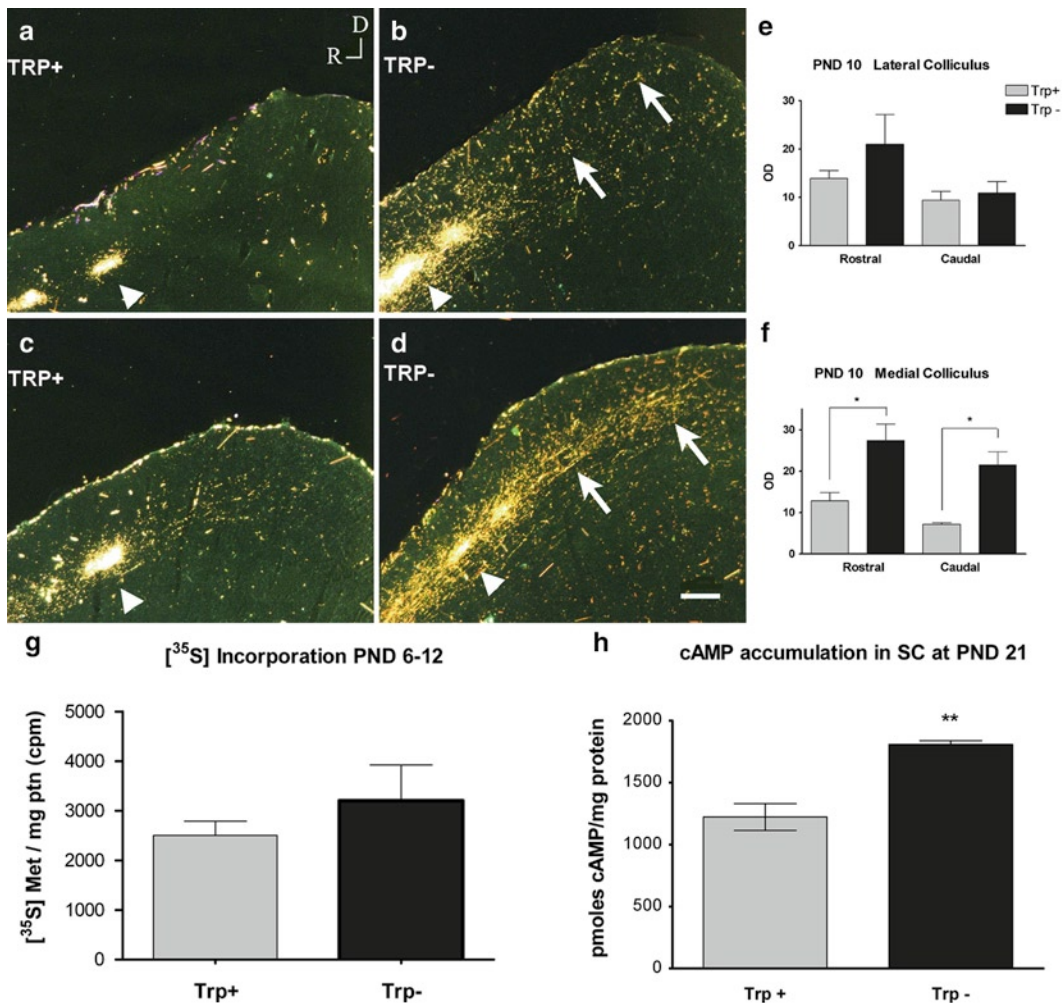
Fig. 136.5 Tryptophan restriction delays development of sensory visual connections. At postnatal day 10, rats fed with diets containing normal levels of tryptophan show axons from the temporal retina converging into clusters of terminals in the anterior aspect of the superior colliculus (**a**, **c**, *arrowheads*). Tryptophan restriction (Trp⁻) results in increased density of axons in inappropriate posterior portions of the superior (PND 10) (**b**, **d**, *arrows*). This effect was significant in the medial half of the colliculus where development lags behind the lateral half. The delay in axonal elimination and sensory development is not related to changes in protein synthesis (G). Tryptophan restriction results in increased levels in cAMP (H). *Trp⁺* tryptophan-complemented diet, *Trp⁻* Tryptophan-restricted diet. Error bars represent SEM. R/D represent Rostral and Dorsal aspects of the superior colliculus. Scale bar = 100 μm (Reprinted and adapted from González et al. (2008, pp. 444–445), with permission from Elsevier)

observed in experiments of [³⁵S] methionine incorporation between control and tryptophan-restricted groups. Those observations were, therefore, consistent with a general decrease in developmental plasticity in the sensory systems leading to delayed patterns of axonal elimination and circuit formation (González et al. 2008).

In conformity with those observations, direct evidence of limited plasticity induced by tryptophan malnutrition was obtained after lesion experiments (Penedo et al. 2009). Under normal conditions, a unilateral retinal lesion enforces a sprouting reaction of intact axon's terminal arbors into denervated territories (Serfaty et al. 2005) (Fig. 136.6). However, animals fed with a low-tryptophan diet showed

Fig. 136.6 Retinal lesion
experimental design. Diagram
representing the main aspects
of retinal lesion experiments.
Unilateral lesion to one eye
produces an intraocular
axotomy and a consequent
degeneration of ganglion cells
axons in the contralateral
retinotectal pathways (**a**). The
uncrossed retinotectal axons
(**b**) originating from the intact
eye sprout toward the surface
of the superior colliculus in
order to occupy the vacated
synaptic space left by the
degenerating contralateral
axons (**a**). Medial aspect of
the superior colliculus is
represented to the right.
Dorsal is up
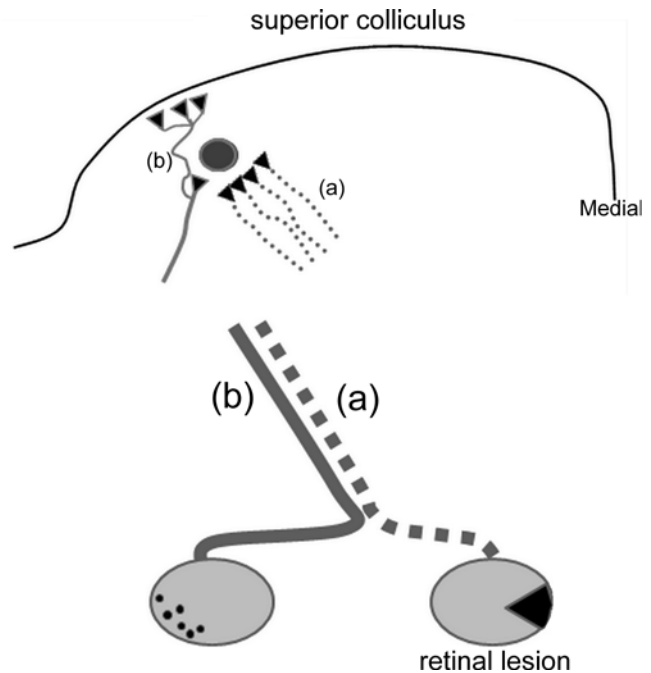
much less sprouting than obtained from control animals with similar lesions (Fig. 136.7a–c). The restoration of normal nutritional tryptophan levels during the critical period completely restored this form of plasticity (Fig. 136.8a–c). Nevertheless, the observed plasticity deficits could not be reverted by a normalization of tryptophan levels initiated after the closure of the critical period (Fig. 136.8d–f) (Penedo et al. 2009).

A corn-based, hypoproteic diet also resulted in dramatic alterations in the cerebellum development. A retardation of Bergmann glial cell maturation and a concomitant delay in granule cell migration has been reported. An increase in dendritic arbors among granule and Purkinje cells indicating a perturbation of cerebellar neuronal circuitry has also been reported (Del Angel-Meza et al. 2001). Tryptophan restriction has also been shown to reduce dendritic spines and arborizations in hippocampal and prefrontal cortical neurons (Feria-Velasco et al. 2002). Importantly, reduced 5HT immunoreactivity has also been shown to occur with a low-protein diet (Orozco-Suarez et al. 2003) suggesting that both global protein malnutrition and tryptophan restriction may have similar consequences on serotonergic hypofunction.

Nutritional tryptophan restriction has been associated with high basal levels of cAMP (González et al. 2008), which could be acting as a stabilization signal for developing synapses. An abnormally increased cAMP signaling could activate protein kinase A (PKA)-dependent CREB phosphorylation and thus, induce an overstabilization of immature synapses, thus delaying the process of natural axonal elimination. Overstabilized synapses would also decrease their ability to undergo use-dependent modifications as shown by the reduced axonal plasticity found in lesion studies (González et al. 2008; Penedo et al. 2009). Since 5HT signaling pathways involve, in sensory subcortical nuclei, 5HT1A and 5HT1B receptors, both of which reduce cAMP synthesis, high levels of cAMP found after the administration of low-tryptophan diets suggest a direct pathway between tryptophan restriction and 5HT receptors (Fig. 136.5g and h). The reduced serotonergic signaling after the administration of low-tryptophan diets could also be related to decreased AMPA receptors activation, since it has been shown that the long-term depletion of 5HT resulted in decreased expression of GLUR1 AMPA receptor subunits in cortical neurons (Shutoh et al. 2000).
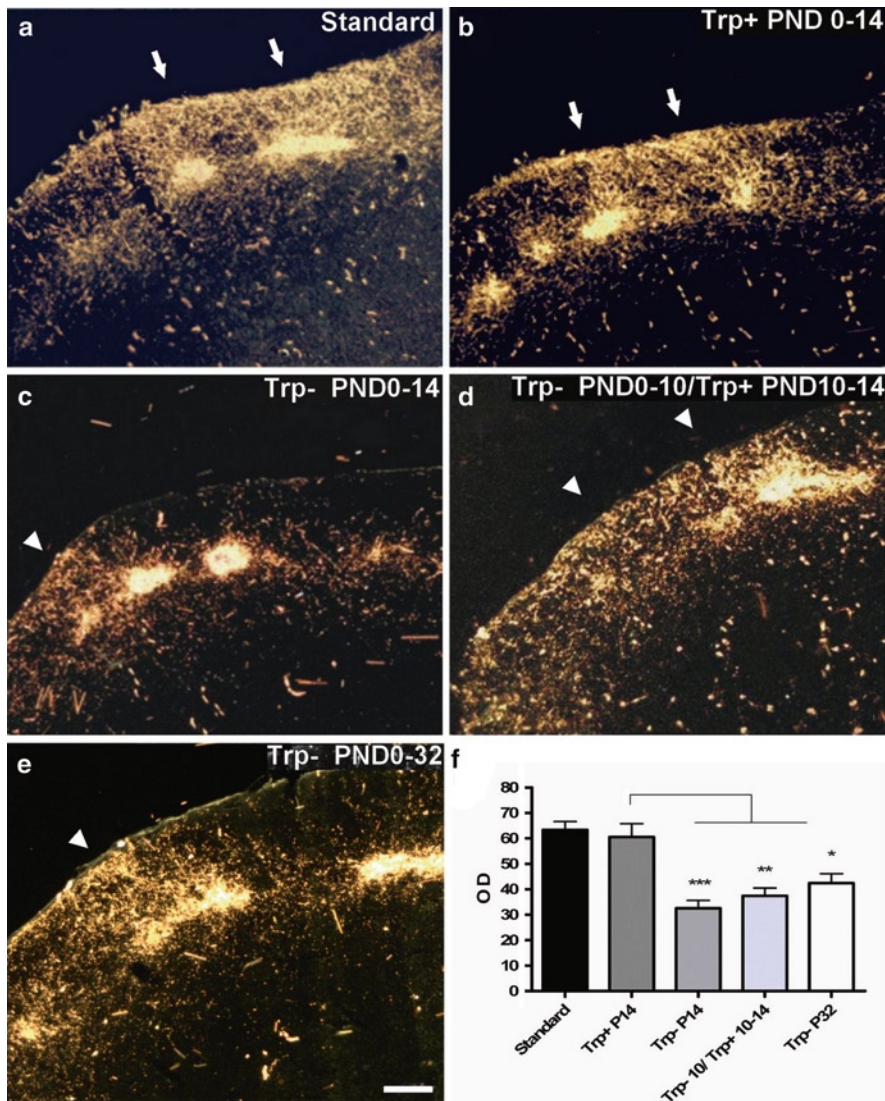
Fig. 136.7 Nutritional restriction of tryptophan reduces brain plasticity. Dark-field photomicrographs of sections through the lateral aspect of the visual layers of the superior colliculus of rats fed with Standard, Trp⁺, or Trp⁻ diets. Temporal retinal lesion was performed at postnatal day 10 (PND 10) and labeling of intact retinal axons at PND 14 (**a–d**) or PND 32 (**e**). Control groups displayed a normal sprouting of uncrossed axons to the subpial aspect of the superior colliculus (**a**, **b** *arrows*). Trp⁻ rats showed reduced axonal growth to the collicular surface (**c**, *arrowhead*). Rats that received the Trp⁻ diet until PND 10, and were subsequently given a Trp⁺ diet from PND 10 to PND 14 also failed to display normal plasticity (**d**, *arrowheads*). Animals that received a Trp⁻ diet from the day of birth until PND 32 also presented a reduced axonal growth to the collicular surface compared to the standard or Trp⁺ groups (**e**, *arrowhead*). Optical density analysis (**f**) confirmed the plasticity deficits observed in Trp⁻ fed groups ($p < 0.001^{***}$, 0.01^{**} and 0.05^{*}; $n = 4$). Error bars represent SEM. Scale bar = 100 μm. *Trp⁺* tryptophan-complemented diets, *Trp⁻* tryptophan-restricted diets. Medial, right; Lateral, left (Reprinted from Penedo et al. (2009, p. 111), with permission from Elsevier)

Therefore, the data suggest that 5HT may act in a bidirectional way: decreased 5HT signaling (as a result of tryptophan depletion) restrains whereas 5HT accumulation (as a result of antidepressant treatment) increases axonal remodeling in the sensory systems.

Taken together, experimental data on tryptophan nutritional restriction suggest that the resulting 5HT depletion profoundly influences brain development, especially the fine tuning of axonal
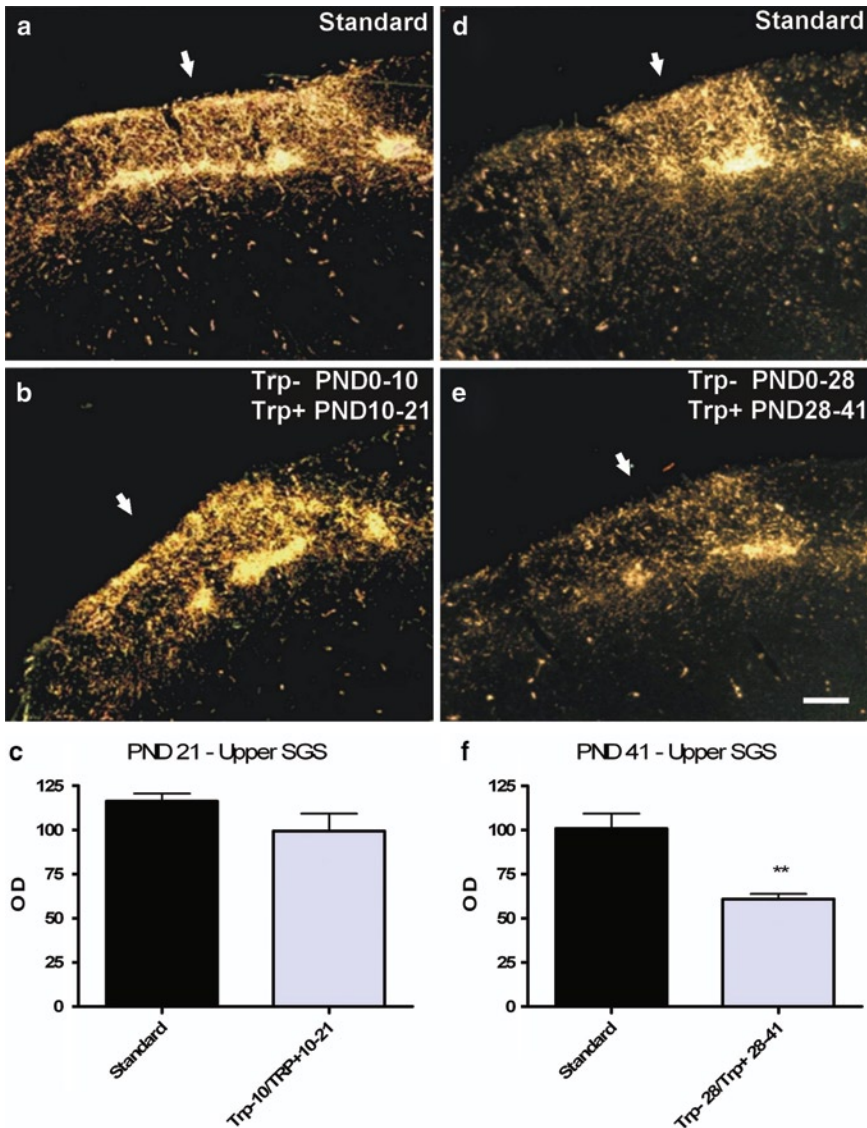
Fig. 136.8 A critical period for nutritional tryptophan complementation upon brain plasticity. Dark-field photomicrographs of coronal sections through the superior colliculus at PND 21 (**a**, **b**) or PND 41 (**d**, **e**) of standard and Trp⁻/Trp⁺ diets following a temporal lesion to the contralateral retina at PND 10. The reintroduction of tryptophan in the diet during the critical period (between PND 10–21) restored plasticity deficits (**b**) as compared to the standard rodent laboratory diet (**a**). Notice similar sprouting of retinal axons to the collicular surface (*arrows*). However, the reintroduction of normal amounts of dietary tryptophan after PND 28 (1 week after the closure of the critical period in rats) resulted in a marked reduction of lesion-induced axonal sprouting (**e**, *arrow*) as compared to control normally fed rats (**d**, *arrow*). Optical densities revealed no differences between control and early refeeding groups (**c**). Late refeeding resulted in decreased plasticity (**f**) ($p < 0.01$, $n = 4$). Error bars represent SEM. Scale bar = 100 μm. *PND* postnatal day, Trp⁺ tryptophan-complemented diets, Trp⁻ tryptophan-restricted diets. Medial, right; Lateral, left (Reprinted from Penedo et al. (2009, p. 112), with permission from Elsevier)

connections and circuitry formation. The consequences of tryptophan deprivation on plasticity may be completely reversed by appropriate complementation during the critical period. However, an extended nutritional deprivation throughout this decisive time window may result in severe loss of use-dependent plasticity with enduring consequences for the developing brain.

136.7 Tryptophan Malnutrition Alters Extracellular Matrix Proteases

A recent study brought new evidence for the involvement of extracellular matrix (ECM) proteases in cell migration and plasticity. Metalloproteinase 9 (MMP-9), a zinc-dependent matrix protease, appears to be critical on developmental and lesion-induced plasticity in the visual system. It has been shown that the expression and biological activity of MMP-9 was higher in the rodent superior colliculus during initial stages of development. Both expression and activity of MMP-9 decreased as this brain structure matures and plasticity progressively declines (Oliveira-Silva et al. 2007). The time course of MMP-9 modulation fits the critical period of visual system development within the first three postnatal weeks. Moreover the blockade of MMP-9 activity produced a distortion in retinotectal mapping, suggesting a functional role for this matrix metalloproteinase in brain development. Interestingly, recent data indicate that the nutritional tryptophan restriction reduces the activity of MMP-9 (Penedo et al. 2009).

Thus, proteolysis of ECM by MMP-9 may perform a permissive or inductive role upon axonal remodeling and synaptogenesis during development in a tryptophan dependent way. This is in keeping with previous data showing that the inhibition of MMP activity by a specific antagonist was able to modify the ability of *Xenopus* retinal ganglion cells to make connections into the optic tectum (Hehr et al. 2005). Recent reports have also shown that MMPs are related to synapse formation, remodeling, and plasticity (Nagy et al. 2006). Vaillant et al. (1999) showed that the peak of MMP 3, 9 expression and activity occurs in the rat cerebellum between PND 3 and PND 10, a period of intense synaptogenesis, where these molecules participate on the laminar organization of this structure (Vaillant et al. 1999).

During development of the visual cortex, the use-dependent modifications of dendritic spines that occur during the critical period is related to the ECM proteolytic activity by tissue plasminogen activator factor (tPA), which has been related to BDNF expression and GABAergic differentiation (Oray et al. 2004).

Therefore, the role as a presynaptic inhibitory neurotransmitter and axon growth enhancer makes tryptophan and its main metabolite, 5HT, interesting modulators of brain development. Serotonin allows the initial growth of widespread target-directed connections that is observed in early development, acts as a noise filter of excess, noncorrelated activity, that occurs when patterns of electrical activity induce use-dependent modifications of neural circuits, and has a possible link with matrix metalloproteinase activity, probably through BDNF expression, thus providing a common modulatory pathway for axonal and dendritic remodeling during developmental and lesion-induced plasticity.

136.8 Tryptophan Malnutrition and the Delay in Brain Development

Brain development consists of a series of succeeding, overlapping, and interdependent steps, which results in the buildup of sensory, motor, and cognitive skills (Fig. 136.1). It is worth noting that even small delays in developmental differentiation could be potentially harmful to this complex series of events leading to long-lasting changes in brain performance. Delaying a biological process could alter complex cascades of events such as synaptic use-dependent adjustments. This point of view is in contrast with previous ideas that considered developmental delay as a nonharmful, self-limiting event. In view of recent results, this matter should be object of further studies in order to carefully evaluate the impact of developmental delays on cognition and learning deficits.

Especially in developing countries more than 200 million children exposed to enduring malnutrition, poverty, and poor health will experience poor levels of cognition and education failing to reach their full potential (Grantham-McGregor et al. 2007). As brain development depends on the gradual

acquisition of processing abilities, a slow-down in sensory maturation would have a direct impact on motor and cognitive development. It is important to mention, however, regarding policies for nutritional care, that despite the general brain vulnerability to nutritional and other insults, recovery is always possible and should be implemented especially with an early intervention.

This would be particularly important for the prevention of neuronal deficits among poor populations, which frequently and repeatedly undergo low-protein malnutrition. More importantly, due to cultural habits, corn is often used as an alternative, low-cost carbohydrate source. As a result, tryptophan malnutrition should be seriously considered as a potential hazard for brain use-dependent development and tryptophan complementation implemented in malnourished children as a public health strategy.

136.9 Applications to Other Areas of Health and Disease: Tryptophan and the Neuroimmunomodulation of Chronic Disease

Low serum/plasma tryptophan concentration has been reported as a direct consequence of protein malnutrition. However, low levels in tryptophan concentration, particularly in the brain, have also been observed under infectious, autoimmune, and malignant disorders that involve cellular immune activation (Th1-type). Those chronic inflammatory conditions have been reported to increase the levels of cytokines such as interferon-gamma (IFN-γ) and tumor necrosis factor-alpha (TNF-α). Those cytokines, known to mediate cellular immune responses under normal acute conditions may, under chronic conditions, increase within the brain, the activity of indoleamine 2,3-dioxygenase (IDO) an enzyme that is responsible for the catabolism of tryptophan to kynurenine and as a result decrease brain 5HT levels. In fact, IFN-γ immunotherapy has been shown to elicit depressive symptoms that were alleviated by conventional antidepressant treatment. Therefore, it appears that low systemic tryptophan concentrations might be a consequence of either nutritional or chronic inflammatory conditions, leading to decreased neural plasticity and depression.

136.10 Key Features of Tryptophan, Serotonin Brain Development

The brain circuits dealing with sensory, motor, and cognitive areas are point-to-point connected in a use-dependent way during postnatal development. This is particularly true for the main sensory, motor, and cognitive circuits and also for the circuits involved in learning and memory. Tryptophan is an essential amino acid and a key nutritional factor for 5HT synthesis. As a neuromodulatory system, 5HT influences synaptic transmission throughout the brain and, thus, synapse formation during postnatal life. It is, therefore, not surprising that serotonergic disruption is closely related to psychiatric disorders such as depression, schizophrenia, and dementia as well as with mental retardation. In Down's syndrome, serotonergic neurons fail to differentiate as a result of reduced expression of 5HT receptors (mainly 5HT1A subtype) and a subsequent downregulation in S100β protein, a trophic factor for serotonergic differentiation. As a result, it has been observed that Down's syndrome patients appear to express reduced densities of dendritic spines suggesting an overall reduction in synaptic use-dependent plasticity throughout the brain. The prenatal exposure to alcohol has also been associated with decreased levels of 5HT in the brain leading to variable deficits associated with altered synapse formation.

Summary Points

- The intrinsic reorganization capacity of neuronal circuits, known as neural plasticity, is one of the most significant properties of brain self-organization that underlies the acquisition of basic and higher brain functions.
- The use-dependent development of neuronal circuits occurs during a postnatal critical period. During this time window, sensory stimulation sculpts neuronal circuits with appropriate sets of connections. The successful development of sensory connections drives most of motor and cognitive development thereafter.
- During brain development 5HT plays an important role in neuronal differentiation, axonal outgrowth, synapse formation, and brain plasticity.
- Tryptophan is an essential amino acid and the only source for 5HT synthesis. As a result, a low-tryptophan diet results in 5HT deprivation.
- Tryptophan dietary restriction during the critical period alters sensory development. It has been associated with a delay in the normal elimination of incorrect axonal connections and with a reduction in neural plasticity.
- Tryptophan malnutrition can result either form a tryptophan-restricted diet or from global protein malnutrition. As tryptophan complementation during the critical period is able to repair plasticity deficits, it should be considered as mandatory in nutritional complementation strategies.

Definitions

Critical period: A postnatal period of brain development when synapses and neuronal circuits develop in a use-dependent way. The critical period is therefore essential to acquisition of major circuits for sensory, motor, and cognitive processing

Glutamate AMPA receptors: Glutamate is the major excitatory neurotransmitter in the brain. AMPA receptors are membrane proteins, which form channels permeable to sodium ions. The activation of AMPA receptors generates ionic currents and electrical activation of postsynaptic neurons.

Glutamate NMDA receptors: A class of glutamate receptors that form ion channels permeable to calcium. The activation of NMDA receptors requires the simultaneous electrical activation of the postsynaptic membrane by other converging inputs. This feature makes NMDA receptors unique since they can signal for converging activity into neural networks.

Growth cones: The tips of growing axons and dendrites are formed by specialized structures called growth cones. Growth cones navigate through developing pathways and interact with the extracellular milieu directing axons to specific areas of the brain.

Long-term potentiation (LTP)/Long-term depression (LTD): Long-term use-dependent modifications in synaptic strength induced by periods of intense afferent stimulation or reduced afferent activity, respectively. Synaptic plasticity mediated by LTP and LTD is the basis of learning and memory as well as in synaptic development.

Monocular enucleation: Experimental manipulation in which the removal of one eye produce denervation and reactive sprouting of nonlesioned axons from the intact eye into central visual nuclei of the brain.

Natural neuronal death: Also know as naturally occurring neural death. During the late stage of neuronal development approximately 50% of neurons generated fail to establish connections with target neurons and die due to the lack of neurotrophic factors released by target cells. Natural neuronal death is believed to ensure an appropriate balance between interconnecting neuronal populations.

Neuronal tracing studies: Most of neuroanatomical data have been generated through the use of neuronal tracers, molecules that are incorporated into neuronal membranes and transported either from the cell body to the axonal tips or backward from axonal tips to cell bodies. Neuronal tracers can therefore reveal the morphology of neuronal structures and connections.

Ocular dominance columns: The visual cortex accommodates afferents that convey information from both eyes. Those thalamocortical afferents are segregated into spatially discrete alternating loci known as ocular dominance columns. The columnar organization is necessary for binocular processing of vision and is affected by the imbalance of visual stimulation that occurs in strabismus.

Optic tectum: Main target of retinal axons found in nonmammalian species. A homologue of the **superior colliculus** found in mammals.

Regressive events: During brain development some events leading to natural neuronal death and elimination of transitory axons and synapses are known as *regressive events of neurogenesis*.

Retinal ganglion cells: Main output retinal neurons that convey information from the retina to the central visual nuclei in the brain through the optic nerve.

Retinofugal projections: Axonal connections from retinal ganglion cells through the optic nerve toward subcortical visual nuclei.

Retinogeniculate: Neuronal pathway between the retina and the lateral geniculate nucleus of the thalamus.

Retinotectal: Neuronal pathway between the retina and the superior colliculus/optic tectum.

Retinotectal topography/Topographically organized connections: Neighboring neurons in the retina project their axons to matching postsynaptic neurons in the superior colliculus. A topographical matching between the retina and target nuclei ensures the correct representation of the visual field into the brain. Topographical representations are a common feature of sensory and motor systems and reflect the specificity of neuronal circuits.

Spontaneous and evoked activity: Neurons are very specialized cells that are able to generate electrical activity. This activity can be either spontaneous or evoked by afferent stimulation. Sensory neurons display spontaneous activity during early stages of development (e.g. last trimester of human gestation or early post natal life in nonprimate species) when sensory systems are not fully developed.

Thalamocortical: Neuronal pathway between the thalamus and the sensorial areas of the cortex.

Use-dependent plasticity/Use-dependent synaptic modifications: Ability of changing neuronal circuits in response to environmental changes or injury. Use-dependent plasticity modifies synaptic strength between interconnected neurons in neuronal networks.

Uncrossed retinotectal pathway: Retinal ganglion cells located at the temporal retina connect to the same side of the brain forming an uncrossed (or ipsilateral) pathway. Retinal ganglion cells located at the nasal retina connect to the opposite side of the brain forming a crossed pathway.

References

Azmitia EC. Int Rev Neurobiol. 2007;77:31–56.

Bastos EF, Marcelino JL, Amaral AR, Serfaty CA. Brain Res. 1999;824:28–35.

Berardi N, Pizzorusso T, Maffei L. Curr Opin Neurobiol. 2000;10:138–45.

Butts DA, Kanold PO, Shatz CJ. PLoS Biol. 2007;5:e61.

Campello-Costa P, Fosse AM Jr, Ribeiro JC, Paes-De-Carvalho R, Serfaty CA. J Neurobiol. 2000;44:371–81.

Campello-Costa P, Fosse-Junior AM, Oliveira-Silva P, Serfaty CA. Neuroscience 2006;139:979–89.

Charron F, Tessier-Lavigne M. Development 2005;132:2251–62.

Chen C, Regehr WG. J Neurosci. 2003;23:3130–5.

Colonnese MT, Constantine-Paton M. J Neurosci. 2001;21:1557–68.

Crair MC, Gillespie DC, Stryker MP. Science 1998;279:566–70.

Debski EA, Cline HT. Curr Opin Neurobiol. 2002;12:93–9.

Del Angel-Meza AR, Ramirez-Cortes L, Olvera-Cortes E, Perez-Vega MI, González-Burgos I. Int J Dev Neurosci. 2001;19: 447–53.

Fadda F, Cocco S, Stancampiano R. Brain Res Brain Res Protoc. 2000;5:219–22.

Feldheim DA, Kim YI, Bergemann AD, Frisen J, Barbacid M, Flanagan JG. Neuron 2000;25: 563–74.

Feria-Velasco A, del Angel AR, González-Burgos I. Prog Brain Res. 2002;136:135–43.

Fernstrom JD. Metabolism 1977;26:207–23.

González EM, Penedo LA, Oliveira-Silva P, Campello-Costa P, Guedes RC, Serfaty CA. Exp Neurol. 2008;211:441–8.

Grantham-McGregor S, Cheung YB, Cueto S, Glewwe P, Richter L, Strupp B. Lancet 2007;369:60–70.

Grossman AW, Aldridge GM, Weiler IJ, Greenough WT. J Neurosci. 2006;26:7151–5.

Gu Q, Singer W. Eur J Neurosci. 1995;7:1146–53.

Haas K, Li J, Cline HT. Proc Natl Acad Sci U S A. 2006;103:12127–31.

Hehr CL, Hocking JC, McFarlane S. Development 2005;132:3371–9.

Hensch TK. Curr Top Dev Biol. 2005;69:215–37.

Herdegen T, Leah JD. Brain Res Brain Res Rev. 1998;28:370–490.

Jacobs BL, Azmitia EC. Physiol Rev. 1992;72:165–229.

Lane RD, Rizk T, Chiaia NL, Mooney RD, Rhoades RW. Somatosens Mot Res. 2002;19:125–9.

Laurent A, Goaillard JM, Cases O, Lebrand C, Gaspar P, Ropert N. J Neurosci. 2002;22:886–900.

Lee DR, Semba R, Kondo H, Goto S, Nakano K. Biosci Biotechnol Biochem. 1999;63:337–40.

Lu W, Constantine-Paton M. Neuron 2004;43:237–49.

Meyer RL. Neuropsychologia 1998;36:957–80.

Mooney RD, Shi MY, Rhoades RW. J Neurophysiol. 1994;72:3–13.

Mower GD, Caplan CJ, Christen WG, Duffy FH. J Comp Neurol. 1985;235:448–66.

Nagy V, Bozdagi O, Matynia A, Balcerzyk M, Okulski P, Dzwonek J, Costa RM, Silva AJ, Kaczmarek L, Huntley GW. J Neurosci. 2006;26:1923–34.

O'Leary DD, McLaughlin T. Prog Brain Res. 2005;147:43–65.

Oliveira-Silva P, Jurgilas PB, Trindade P, Campello-Costa P, Perales J, Savino W, Serfaty CA. Neuroimmunomodulation 2007;14:144–9.

Oray S, Majewska A, Sur M. Neuron 2004;44:1021–30.

Orozco-Suarez S, Del Angel AR, Beas-Zarate C, Manjarrrez G, Feria-Velasco A. Int J Dev Neurosci. 2003;21:13–22.

Ostendorp T, Leclerc E, Galichet A, Koch M, Demling N, Weigle B, Heizmann CW, Kroneck PM, Fritz G. EMBO J 2007;26:3868–78.

Penedo LA, Oliveira-Silva P, González EMC, Maciel R, Jurgilas PB, Melibeu ACF, Campello-Costa P, Serfaty CA. Exp Neurol. 2009;217:108–115.

Salichon N, Gaspar P, Upton AL, Picaud S, Hanoun N, Hamon M, De Maeyer E, Murphy DL, Mossner R, Lesch KP, Hen R, Seif I. J Neurosci. 2001;21:884–96.

Serfaty CA, Campello-Costa P, Linden R. Brain Res Bull. 2005;66:128–34.

Serfaty CA, Oliveira-Silva P, Faria Melibeu AC, Campello-Costa P. Neuroimmunomodulation 2008;15:170–5.

Shutoh F, Hamada S, Shibata M, Narita M, Shiga T, Azmitia EC, Okado N. Neurosci Res. 2000;38:365–71.

Sodhi MS, Sanders-Bush E. Int Rev Neurobiol. 2004;59:111–74.

Tagliaferro P, Ramos AJ, Lopez-Costa JJ, Lopez EM, Saavedra JP, Brusco A. Brain Res Bull. 2001;54:199–205.

Terashima A, Pelkey KA, Rah JC, Suh YH, Roche KW, Collingridge GL, McBain CJ, Isaac JT. Neuron 2008;57:872–82.

Thompson RA, Nelson CA. Am Psychol. 2001;56:5–15.

Turlejski K. Acta Neurobiol Exp (Wars). 1996;56:619–36.

Upton AL, Salichon N, Lebrand C, Ravary A, Blakely R, Seif I, Gaspar P. J Neurosci. 1999;19:7007–24.

Vaillant C, Didier-Bazes M, Hutter A, Belin MF, Thomasset N. J Neurosci. 1999;19:4994–5004.

Wong RO, Meister M, Shatz CJ. Neuron 1993;11:923–38.

Chapter 137
Behavioral Aspects of Failure to Thrive in Infants and Young Children

Robert Drewett

Abbreviations

ALSPAC	Avon Longitudinal Study of Parents and Children
BMI	Body mass index
CI	Confidence interval
FTT	Failure to thrive
IQ	Intelligence quotient
SD (SDS)	Standard deviation (standard deviation score)
UK	United Kingdom
WISC	Wechsler Intelligence Scale for Children
Z	Z score

137.1 Introduction

Slow growth in infancy and early childhood is the key clinical sign of the condition traditionally called *failure to thrive* (FTT) in pediatrics. It is most widely identified by slow weight gain, though other anthropometric measures are sometimes also used, generally height or weight for height. FTT, does not, however, refer to the key clinical sign, so *weight faltering* is coming to replace it in many contexts, and this term also makes it clear that we are dealing with a sign, not a diagnosis. Whatever terminology is used, two kinds of research problem arise, concerning the causes and the consequences of the slow weight gain, and both have important behavioral aspects.

Traditional terminology also distinguishes between FTT that is attributable to an underlying medical condition and FTT that is not. The term "organic" has been used of the first, and is contrasted with "nonorganic", used of the second. There are two problems with this traditional terminology. First, there are clearly organic sources of variability in weight gain other than those attributable to underlying medical conditions, as the genetics of adiposity shows. Second, the distinction can be taken to imply an oversimple relationship between the medical condition and the child's poor weight gain, when the relationship can be quite complex. Cerebral palsy, for example, can lead to serious malnutrition by damaging a child's oral-motor skills, leading to lower food intake and poorer weight

R. Drewett (✉)
Science Laboratories, Durham University, South Road, Durham, DH1 3LE, UK
e-mail: r.f.drewett@durham.ac.uk

gain, but it is also associated with depression in the children's mothers, which may also affect their feeding of the child (Reilly and Skuse 1992). In children with gastro-intestinal reflux, a quite common condition in the first 2 years, inflammation of the esophagus is associated with significantly lower energy intake (Mathisen et al. 1999), and esophagitis might operate by making food intake aversive. The distinction made in the traditional terminology can still be important, but needs to be made with care, recognizing that there are many possible routes from a medical condition to poor weight gain.

The weight gain of infants identified as failing to thrive is improved by nutritional interventions (Whitten et al. 1969; Wright et al. 1998a) and it is reasonable to assume that its immediate cause is undernutrition. There are many possible explanations for undernutrition, but assuming that it is post-natal, they fall into four main classes:

1. Characteristics of the wider or more local family economic environment that affect the availability of food.
2. Patterns of care provided to infants and young children that affect their food intake.
3. Individual characteristics of infants that affect their food intake.
4. Individual characteristics of infants that affect their absorption of nutrients.

The first of these classes of explanations (1) is one that has been widely invoked (Spencer 2007). But clear evidence that FTT in infancy in industrialized countries is in fact related to the economic circumstances of the infant's family has never been available, and recent epidemiological work in the UK suggests that there is no clear relationship between the two (Spencer 2007). The first epidemiological study of this (Wright et al. 1994) examined weight gain over the first year in affluent, intermediate, and deprived areas of Newcastle-upon-Tyne, as identified from census data. The highest rates were found in the deprived and the affluent areas, with lower rates in the intermediate areas. A larger study (Blair et al. 2004) in which the family was classified by social and economic indicators within the family, rather than indicators based on area of residence, found that rates of FTT were not related to the social class of the family (Fig. 137.1) or to the educational attainment of the child's parents. Case-control studies also show no relationship (Drewett et al. 1999; McDougall et al. 2009). In the absence of solid evidence on its relevance, this class of explanation is not discussed further here.

Possible explanations related to patterns of care (class 2) might involve differences in mother–child interaction, and there is a substantial body of work concerning both mother–infant interaction
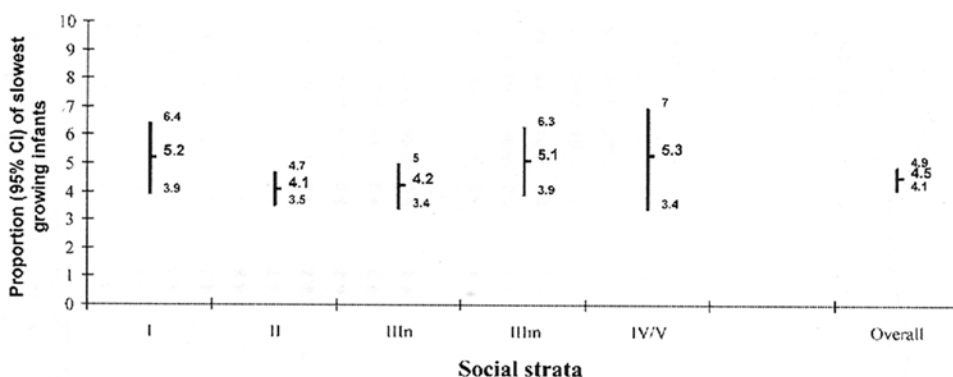
Fig. 137.1 Failure to thrive (FTT) in infants with mothers in different social classes. The bars show the proportion of infants (with 95% confidence intervals) in a UK population cohort study whose weight gain was in the lowest 5% in different social classes (UK Registrar General's occupational classification). Sample size: 11,718 (Reprinted from Blair et al. (2004). By permission of the Oxford University Press)

and attachment patterns in FTT. Possible explanations in class 3, concerning individual food intake patterns, include differences in infant appetite or feeding behavior. These topics are dealt with in some detail next.

The last of these classes of explanation (class 4), related to the absorption of nutrients by individual children, is of importance in infants whose slow weight gain is caused by an underlying medical condition. An example is cystic fibrosis, in which there is malabsorption of proteins and fats from the gut. This leads to poor weight gain, so FTT is often one of the earliest signs of the disorder (Giglio et al. 1997). There are many other examples, but in general these are best dealt with in reviews concentrating on the individual disorders concerned, so this class of explanation will not be discussed further here.

As regards the consequences of FTT, there is now a substantial body of research on early behavioral and on later intellectual development in FTT. This is also dealt with next.

137.2 Identifying Children Who Fail to Thrive

FTT in infancy has traditionally been identified using an attained weight criterion: a low weight for age relative to the distribution of the weights of children of the same age and sex in a reference population. The criterion can be expressed in centiles (for example, a weight below the third centile) or in standard deviation units or z scores (for example, a weight more than 2 SD below the average). The exact cut-off is arbitrary. Weight is used rather than length because its measurement is more precise and because weight is more sensitive to short-term changes. Weighing is also the procedure traditionally used to monitor growth in infancy in the UK.

Although FTT is intended to refer to slow weight gain after birth, a low weight for age can result from a slow weight gain either before or after birth, or from a combination of the two, so the use of an attained weight criterion preferentially selects infants with a low birthweight (Olsen et al. 2006). This means that problems associated with a slow weight gain after birth are confused with problems associated with a low birth weight (and so also, if the infants are not specifically excluded, with problems of a preterm birth). This confusion is undesirable. It is obvious that the determinants of undernutrition before and after birth are quite different and different explanations must be sought for them. Similarly, the cognitive effects associated with a low birthweight need to be distinguished from the cognitive effects associated with slow weight gain after birth, since the prevention of the first would need quite different strategies from the prevention of the second.

The confusion can be avoided by using an attained weight criterion that is conditional on birthweight (Cole 1995, 1996; Wright et al. 1994). In principle the procedure used is to compare an infant's weight at a particular age with that of other infants of the same age, sex, and birthweight. The difference between the infant's weight and the average weights of infants of the same age, sex, and birthweight then provides a measure of relative weight gain from birth: it is zero if the infant's weight gain is average, negative if it is below average, and positive if it is above average. In practice the difference is calculated as the residual from the linear regression of the later weights on birthweights (see Key Points and Fig. 137.2). If z scores are used for the weights this gives a z score that reflects weight gain from birth, but which is independent of birthweight (and uncorrelated with it). Again the exact cut-off used has been arbitrary, usually corresponding to a weight gain from birth below the fifth centile. An important research question is whether this criterion does in fact distinguish between groups with clearly different outcomes, an issue dealt with next.

Although weight gain criteria conditional on birthweight have come into use in recent research, especially in the UK, many earlier studies have identified FTT using attained weight criteria, and so
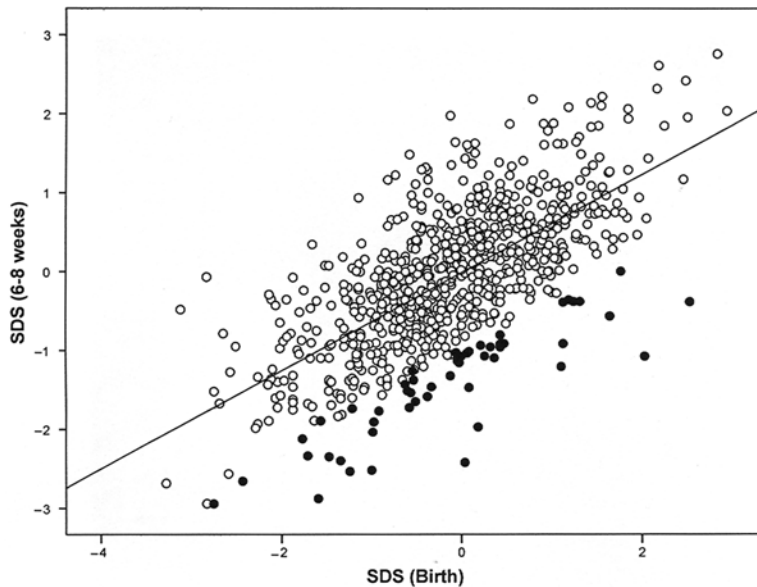
Fig. 137.2 An illustration of the use of a weight gain criterion that is conditional on birthweight. The scatterplot shows the weight of male infants in a birth cohort at the 6–8-week check plotted against their weight at birth, each in SD (*z*) scores. Reading up on a vertical line from a particular SDS at birth there is a range of 6–8-week weights. The regression line shows the average weight at 6–8 weeks. Full circles indicate those with weight gain in the lowest 5% (Details of the cohort from which the data were taken can be found in McDougall et al. 2009)

consider groups of infants who fail to thrive but whose average birthweight is also relatively low (Sherry 1999). In some studies, these have included infants born preterm. It is important then to consider whether comparisons between these infants with low attained weight and other infants have properly controlled for birthweight, for example by using controls matched on birthweight or by regression methods, if inference concerning the importance of slow weight gain after birth are to be made; and many have not.

It is also important to consider how the children concerned were identified. The most valuable studies have screened whole populations (Blair et al. 2004; Skuse et al. 1992; Wright et al. 1994), allowing inferences that are not biased by the referral process. Many studies, however, have used groups of children identified through pediatric clinics, child psychiatrists, or child protection services. There is an obvious selection bias here, since children may be referred to such clinics not simply because their weight gain is poor but also because developmental problems or more general concerns about the family have been identified (Batchelor and Kerslake 1990).

137.3 Mother–Child Interaction

Mothers provide most of the care of young infants, and a long tradition of research in this area has examined differences in mother–child interaction between the mothers of children who fail to thrive and those of control children. Studies of this kind are time-consuming. FTT is found in only a small proportion of infants and there are no useful predictors of the families in which it will occur, so most studies of mother–child interaction in FTT have been case-control studies, in which interaction was studied after the condition has been identified. While this is understandable, it does limit the

inferences that can be made from positive findings, since it cannot in general distinguish between differences that precede the weight faltering and differences that follow it, a distinction which is of obvious importance in considering causal order.

The first controlled study of mother–child interaction was carried out by Pollitt and colleagues (Pollitt et al. 1975). Cases and controls, 16 of each, averaged 3 years old at the time of the study and the weights and heights of cases were below the third centile. When compared with the mothers of the control group the mothers of the cases showed significantly less physical and verbal interaction with their children, and they were less likely to praise them and more likely to scold, slap, or show annoyance with them.

Berkowitz and Senter (1987) selected cases with height or weight below the fifth centile or dropping over two centile lines, with controls matched on age, ethnic group, birth order, and mother's age. There were no differences between the two groups in 9 of 12 maternal behaviors. The mothers of the case children made fewer positive vocalizations and fewer responses to their infant's vocalizations. However, the infants themselves produced fewer vocalizations and it is not clear whether the smaller number of responses from the mothers resulted simply from their having fewer infant vocalizations to respond to. No differences were found in mutual interactions or mutual gazing.

Hutcheson et al. (1993) compared cases and matched controls, with raters blind both to the group membership of the children and to the research hypotheses. They found no main effect group differences on any maternal infant or dyadic interactional characteristics. There was a significant group by age interaction in maternal affective tone, which was less positive with older cases, but more positive with younger cases. This might suggest that this maternal characteristic developed as a result of the infant's FTT, rather than being a cause of it.

Another study (Drotar et al. 1990) investigated interactional behavior using the scales originally developed by Ainsworth (Ainsworth et al. 1972). Observations took place in the home when infants were around 7 months of age, and involved feeding, play, and social interaction. The case infants were clinically referred, and control infants were obtained from pediatric clinics and hospitals. The case and control groups were matched for the child's age at hospitalization, for sex, race, and birth order, for maternal education and age, and for family size, income, and structure. Selection criteria for both groups included a birthweight above 1.5 kg. This is, however, sufficiently low to include infants who were born preterm or small for gestational age, and the groups were not matched on birthweight. In all the general interaction scales, and one of the three feeding scales (termination), significantly higher ratings were given to the control group mothers than to the mothers of the infants who failed to thrive, who were less sensitive, cooperative, accepting, and accessible, showed less positive affect and emotional expressiveness during interactions, and terminated feeding episodes in a more arbitrary fashion. However, as the authors noted, differences between the groups appeared to arise because of especially high scores in the control group mothers, rather than especially low scores in the FTT group mothers. Another difficulty in interpreting this study is the lack of control for birthweight.

Puckering et al. (1995) examined mother–child interaction outside the feeding situation in a group of children with persistently poor growth from birth to 4 years. This study used a case group chosen by population screening and an equal number of controls carefully pair-matched to the cases (this included matching on birthweight). Extensive observations were made during two home visits. Mothers' behavior was rated on a positive dimension (e.g., socially interacts with child, responds positively to child, complies with child's request) and a negative dimension (e.g., conflict between mother and child, negative response to child's distress, ignores child's requests). Puckering et al. used the rating scales to obtain measures of "simple" maternal behaviors, which were simple frequency scores, and "conditional" measures, which were expressed as a proportion of the total number of child behaviors in a given category. They found significant differences between the case and control groups on three of the five simple measures for the positive dimension (total amount of social

interaction, positive responses to child, follows child's lead in interaction), but on none of the conditional measures. With respect to the negative dimension, significant differences were found on only one of the six simple measures (negative response to child's request), and on none of the conditional measures. The lack of effects on the conditional measures shows that there were no significant differences between case and control dyads once the contribution of the child to the interaction had been taken into account. The differences in mothers' simple measures of positive behaviors may have been a result of the case children's lower general cognitive ability, with these children making fewer requests and comments during interaction with their mothers.

In summary, a number of the studies comparing children who failed to thrive and controls have reported significant differences between the groups in mother–child interaction (Berkowitz and Senter 1987; Drotar et al. 1990; Hutcheson et al. 1993; Pollitt 1975). But since the quality of interaction was measured after the onset of FTT, differences between the groups in this could be either a cause or a consequence of FTT. The latter possibility is made more likely by the finding that the negative maternal affective tone seen in the mothers of older children who failed to thrive was not seen in the mothers of younger children with the condition (Hutcheson et al. 1993).

One study (Vietze et al. 1980) is therefore of special interest because it used a prospective longitudinal design (and did not rely on infants being referred). A cohort of 1,400 women was interviewed prenatally. From this cohort, 498 were selected for follow-up until the infants were 18 months of age. Infants and mothers were observed during a scheduled feeding period in the hospital soon after the birth. Infants who *subsequently* failed to thrive were identified, and the infant–mother interactions with these case infants were compared with those of control infants selected randomly from the larger sample. Four types of maternal behavior (vocalize to infant, visual attention to infant, smile at infant, touch play) and three types of infant behavior (vocalize, visual attention to mother, cry) were coded. Vietze et al. found no differences between case and control mothers in any of the prenatal assessments. After the birth, the mothers of infants who went on to fail to thrive spent significantly less time visually attending to their infants than the mothers of controls, but there were no differences between the groups in the three other indices of maternal behavior. Vietze et al. also investigated dyadic behavior, involving both mother and infant. Mother of male infants who went on to fail to thrive were more likely to terminate their responses when interacting with the infant, less likely to maintain responding in the face of lack of response from the infant, and more likely to "drop out" of the interaction. These findings seem to imply that certain types of very early dyadic behavior may relate to subsequent FTT, at least in boys. However, the case infants in this study also had significantly lower birthweights, and gestational ages at birth, than the controls. Pollitt et al. (1978) investigated relations between birthweight, infant–mother interaction, and weight gain during the first month of life. Forty categories of behavior (24 maternal and 16 infant) were analysed. While only three types of maternal behavior were associated with weight gain, ten were associated with birthweight. Maternal behavior involving social interaction, such as talking or vocalizing to the infant, was not associated with weight gain, but was associated with birthweight. These results illustrate the particular importance of proper control for birthweight in future studies in this area.

One other rather general problem with this research on mother–child interaction is the large number of measures used in each analysis, and the large number of different ways that have been used to analyze the interaction. This makes is difficult to exclude Type-1 errors (false positives), and to assess the replicability of results. These problems are not shared with research on attachment, in which a single procedure, the strange situation, with a single outcome variable, has been used in most of the published studies (Chatoor et al. 1998; Crittenden 1987; Gordon and Corcoran Jameson 1979; Ward et al. 1993, 2000). Each of these studies shows a higher rate of insecure attachment in the FTT group children than in a control group, though the differences were not all statistically significant within each study, some of which were rather small.
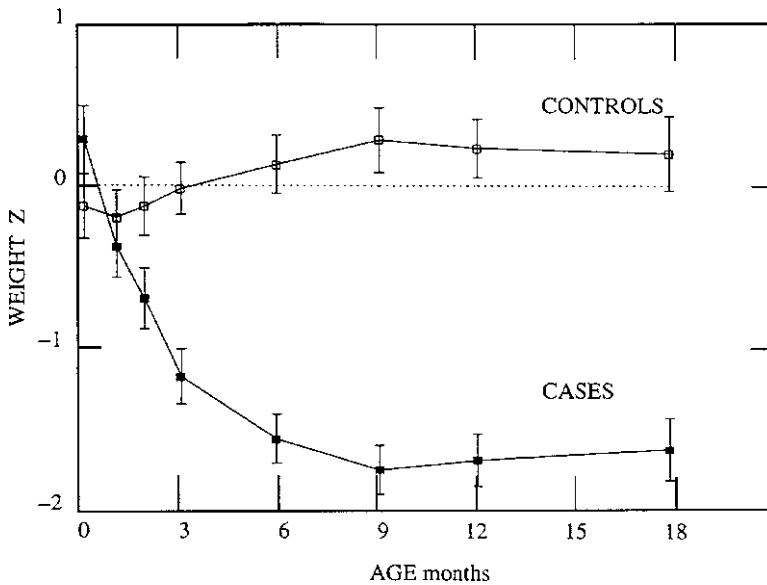
Fig. 137.3 Weight gain over the first year in a 1-year birth cohort of children identified as failing to thrive and a control group (mean *z* scores with 95% CIs). All cases whose weight gain was in the lowest 5% over the first 18 months are included and an equal number of controls (*N* = 270). Note that relative to controls the weight gain of the cases was very poor from birth (Reprinted from Drewett et al. (1999). By permission of Wiley-Blackwell)

These studies all used referred children with the associated problems of referral bias. In one case (Crittenden 1987) the children came from families receiving child protection services and they had a substantiated history of child abuse or neglect. Not surprisingly they also had very high rates of insecure attachment (94%), but this may be a consequence of the history of abuse and neglect rather than a consequence of FTT. There is, however, an interesting corroboration of this relationship between poor weight gain and insecure attachment in a study from a poor area of Chile, in which children were screened via routine data collected in well baby clinics, so that there was no obvious referral bias. Only 7% of 41 underweight children were securely attached, compared with 50% of 40 control children.

There probably is an association here, but we cannot assume from the association that insecure attachment leads to FTT. Attachment develops in the second half of the first year, while FTT, when its course has been examined (Drewett et al. 1999), often develops from birth (Fig. 137.3). It follows that insecure attachment is unlikely to be a cause of FTT. It could be a consequence of it.

137.4   Nutrition and Feeding Behavior

Except cases in which an underlying medical disorder is associated with reduced absorption of food components, any explanation of FTT has to explain why the food intake of the child is lower than is necessary to maintain a normal level of weight gain. Direct evidence for reduced food intake among children who fail to thrive is not easy to find, however, principally because of the usual difficulty of measuring nutritional intake in natural situations over extended periods. Over individual meals it can be measured accurately, and their energy intake is substantially lower than that of age-matched controls (Drewett et al. 2002; Parkinson et al. 2004). Explanation of this difference requires detailed observational studies of the child's feeding.

After the first few weeks of life, microanalysis of food intake in infants is not simple, because for most of the first year they are in the weaning period, in which infants are in a transition from feeding on milk to feeding on solid foods, and from being fed by a mother or other carer to feeding independently. The age of the infant is therefore a key variable, and any analysis must be able to deal with the various components of mealtime behavior over the weaning period. In dealing with solid food there are three possible components. First, the mother or other carer may feed the infant, for example, by putting a spoonful of food into a child's mouth. Second, the infant may feed independently, essentially in the same way as an adult does, for example by pushing a spoon into a bowl of food and then eating the food from the spoon. Third, the mother or other carer may facilitate food intake while not actually feeding the child, for example, by picking up a biscuit and handing it to the child for the child to eat. These components may vary over time, from meal to meal, and with different food types. It follows that a general coding scheme for the microanalysis of food intake over the weaning period must be able to handle all three. A coding scheme of this kind has been developed by Parkinson and Drewett (2001). Some of the coding elements are shown in Fig. 137.4; they correspond to the three possible components of weanlings' meals given earlier.

This coding method has been used to examine food intake in children who fail to thrive (Drewett et al. 2002; Parkinson et al. 2004). Energy intake was significantly lower in children who failed to thrive than in controls of the same age in both studies. In Drewett et al. (2002), there were also identifiable differences in the feeding components. The case (FTT) children fed themselves significantly less often, and although they were given or handed food equally often by their mothers, they refused it more often, suggesting that it is a lower appetite in the children that was responsible for their slower weight gain, as mothers' own reports often suggest (Wilensky et al. 1996). There were, however, no clear differences in the study of Parkinson et al. (2004). The difference may be because the cases in the earlier study were recruited via a specialist clinical service, while the cases in the later study were recruited by the screening of a whole birth cohort. Children with obvious feeding problems tend to be more readily identified as failing to thrive in clinical practice than children with the same poor weight gain who do not have obvious feeding problems (Batchelor and Kerslake 1990).

A follow-up of all infants who met the criterion for FTT in a 1-year birth cohort in a single large northern city in the UK (Newcastle-upon-Tyne) showed that these children were shorter than con-
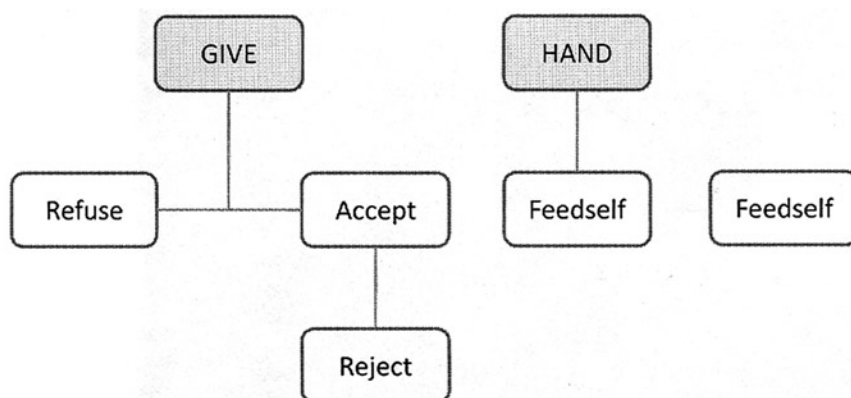
Fig. 137.4 Simplified representation of a coding scheme for the microanalysis of feeding behavior in the weaning period, based on coding scheme in Parkinson and Drewett (2001). During the weaning period infants may be fed by the mother; or they may feed themselves with some assistance from the mother; or they may feed themselves without assistance. Code sequences for each are illustrated. The two capitalized elements (GIVE, HAND) code carer behavior; the other elements (Refuse, Accept, Reject, Feedself) code the child's behavior

trols at 12 years of age, and also had a lower average body mass index (BMI) (Drewett et al. 2006). This suggests that they would be less likely to become overweight or obese. Probably as a consequence, they also showed higher levels of body satisfaction. The same study examined anxiety, depression, and self-esteem using the children and both their teachers and parents as informants, but there was no evidence of any difference in any of these measures. The children did, however, themselves report that their appetites were low compared with that of their best friend.

137.5 Intellectual Development

The most clearly documented adverse effect associated with FTT is reduced intellectual ability. This is detectable as slightly delayed development in infancy and early childhood and as a slightly lower measured intelligence in later childhood. There are currently no studies examining intellectual sequelae in adults. Figure 137.5 shows a summary of controlled studies in children (Corbett and Drewett 2004). Three of these studies used cases referred to hospitals or specialist clinics, and the mean deficit in these was about 13 IQ points. Seven used cases identified by the screening of whole populations, and the mean deficit in these was 4 IQ points.

Although this is no longer considered appropriate (Spencer 2007) historically developmental delay has often been used in clinical practice as an identifying criterion for FTT, so it is not surprising that the deficit is greater in the studies in which clinically identified cases have been used. The studies
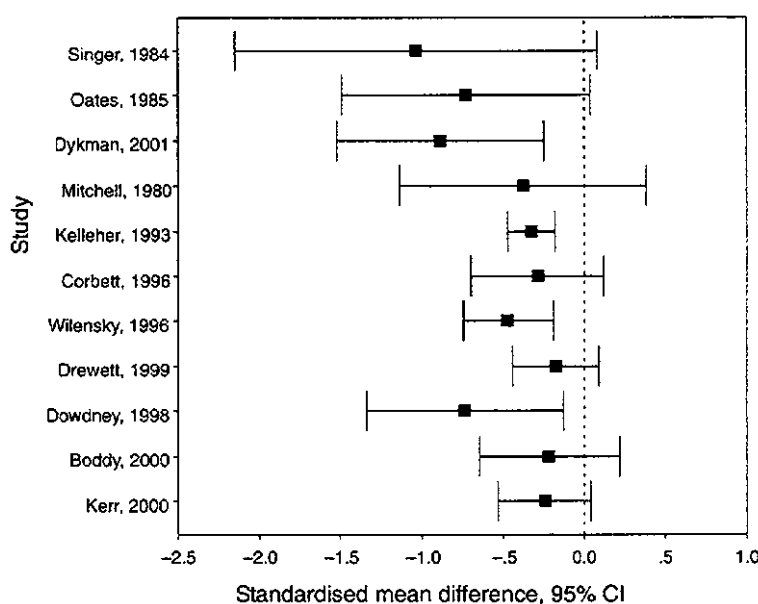
Fig. 137.5 Results of a meta-analysis of studies of intellectual sequelae of failure to thrive in infants and young children. All the studies compare an affected group and a control group, and used IQ tests, except for Wilensky et al. (1996) who used Bayley Scales. The standardized mean difference and its 95% CI are shown for each study. The top N three studies used cases identified through hospital or other specialist clinics. In the other studies recruitment was through primary care clinics by whole population screening (Reprinted from Corbett and Drewett (2004). By permission of Wiley-Blackwell)

using whole-population screening based solely on anthropometric criteria provide a more generalizable estimate of the average intellectual deficit associated with FTT, which is about 4 IQ points.

A subsequent and entirely independent estimate comes from data collected in the ALSPAC study (Emond et al. 2007). This is a large population-based birth cohort study located in Avon in southwest England. In this study the deficit (based on 258 cases and 5510 controls) was 3 IQ points, which is reasonably close to the previously published value based on the meta-analysis of earlier studies (4 IQ points). This study examined separately the relationship of IQ with slow growth over the first 6 weeks and over the remainder of the first year. Strikingly, there was a strong association with weight gain over the first 6 weeks, but no association at all with weight gain over the later part of the first year (Fig. 137.6). A similarly early sensitive period has been shown for the relationship between slow weight gain and developmental delay in infancy (Skuse et al. 1994). Equally strikingly, the relationship between weight gain in the early period and later IQ in the ALSPAC study is approximately linear over the whole range of weight gains (Fig. 137.6). At least in considering this relationship, therefore, there is in fact no threshold value which separates out a group of slowly growing children who are at risk of intellectual deficits from a larger group who are not. The traditional cut-point is entirely arbitrary.

Observational studies of this kind can never provide certainty concerning causal relationships. It is possible that some underlying medical condition leads both to lower measured intelligence and to a lower food intake, giving rise to the association between lower IQ and FTT, but to date no candidate condition has been put forward, and it is hard to think of a condition that would have this graded effect across the whole range of weight gains. It is probably more likely that we are dealing here with a graded nutritional effect restricted to a sensitive period just after birth, and that it is related to a similar graded nutritional effect just before birth. For many years it has been difficult to disentangle the intellectual sequelae of a preterm birth and those of being born small for gestational age (Drewett 2007). But there is now clearly replicated evidence that birthweight is related to later intellectual development even in infants born at term (Shenkin et al. 2004). This relationship also has no thresh-
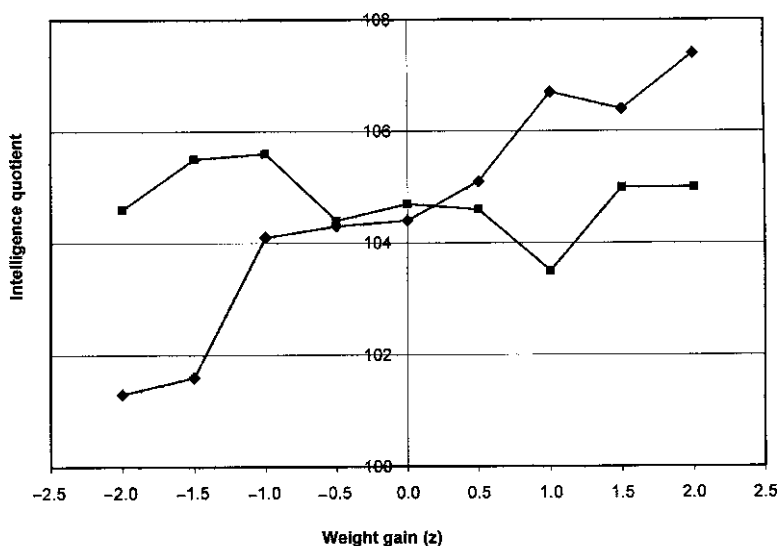
Fig. 137.6 Relationship between measured intelligence in childhood and weight gain soon after birth and later in the first year. The graph shows (*diamonds*) measured intelligence at 8 years plotted against weight gain from birth to 8 weeks (*F* = 36.09, *p* < 0.0001) and (*squares*) measured intelligence at 8 years plotted against weight gain from 8 weeks to 9 months (not significant). *N* is >7000 (Data from Emond et al. (2007), where details of control variables can also be found)

old corresponding to the traditional criterion of a low birthweight infant (a birthweight below 2,500 g). Over the whole range of birthweights measured intelligence increases with increased birthweight. The overall raw difference is about 10 IQ points. It is a plausible hypothesis, then, that later IQ is particularly sensitive to nutritional substrates just before or just after birth, and that we are dealing here with a single graded effect of nutrition on intellectual development, though its determinants are of course quite different before and after birth.

Weight monitoring of infants in primary care may serve a variety of purposes. It may, for example, identify medical conditions that would not otherwise be identified, at any rate so early in life. Whether it is effective or cost-effective for this purpose has yet to be determined. If, as the evidence suggests, it is the early weeks after birth that are important in the relationship between weight gain and intellectual development, then as regards intellectual outcomes most weight monitoring in the UK is likely to identify the condition too late for intervention to be effective. Procedures for identifying slow weight gain that are conditional on birthweight can identify it at the earliest point at which the relevant weights are generally available, the 6–8-week medical check (McDougall et al. 2009). But even this would be too late for effective intervention. The implication is that for this purpose it is not screening and treating that will be the key to progress, but primary prevention.

137.6 Application to Other Areas of Health and Disease

Conditional weight gain measurements of the kind used in recent research on FTT are based on entirely general statistical procedures (Healy 1974). They are not restricted to identifying changes from birth. Weight faltering can be identified over any period, and the methods used can be used in any context in which a measure of weight gain is needed that is independent of a starting weight. One might expect them to be of value in research concerning the predictors in infancy of later obesity, for example. The difference would be that infants with the fastest weight gain would be of special interest, rather than the infants with the slowest weight gain. They may also be of value in research concerning nutritional aspects of some medical conditions. An example is sickle cell anemia. The average IQ in children with sickle cell anemia in the UK is about 5 points lower than that of their siblings (Knight et al. 1995). Although there is evidence of direct central nervous system damage in this disorder, growth retardation in children with sickle cell disease in significant over the first 2 years and it is related to the child's IQ (Knight et al. 1995). It would be of value to know whether the sensitive periods over which poor weight gain is associated with lower IQ in FTT are also important in this condition.

In light of the evidence given here of an early sensitive period for intellectual development, the importance of the common loss of weight in the first 10 days after birth (Wright and Parkinson 2004) might also need to be reconsidered. Weight loss in the days immediately following birth in otherwise healthy infants is not usually considered of any particular importance. A recent study, however (James et al. 2007), showed that the loss or gain of weight over this period is directly related to the infant's milk intake (Fig. 137.7). So weight gain over this period depends on nutritional intake just as it does at other times, and there is no reason to ignore the nutritional importance of this period in relation to later intellectual development. Improving support for the very early stages of breastfeeding may have benefits beyond those for physical health. It needs to be born in mind, however, that different weight gain trajectories in infancy do not necessarily have consequences that are all desirable or all undesirable. Just as FTT in infancy is associated with shorter stature but also with lower adiposity and better body image in the pubertal period (Drewett et al. 2006), so faster weight gain in infancy is associated with a slightly higher IQ, but also with a greater risk of obesity (Reilly et al. 2005).
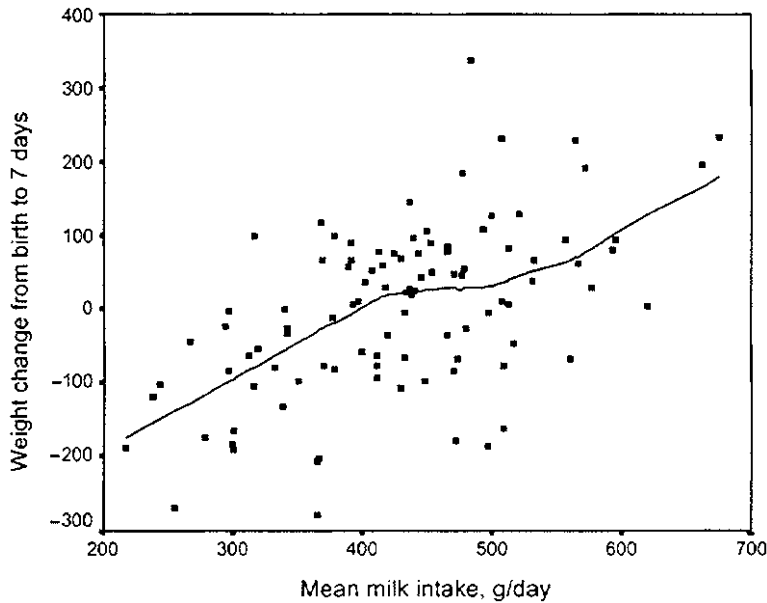
Fig. 137.7 Relationship between milk intake and weight gain immediately after birth. Weight change over the first 7 days of life plotted against mean daily milk intake. The weight change measure is the residual in grams from the regression of weight on day 7 on weight at birth. *N* is 89. The line is a locally estimated (lowess) regression line (Reprinted from James et al. (2007). By permission of Wolters Kluwer Health)

Summary Points

- FTT is a term used for infants and young children whose weight gain is unusually slow.
- As the term is intended to refer to weight gain after birth, it needs to be identified using a measure of weight gain after birth. Most suitable is a conditional weight gain measure taking into account the infants' birthweight and their sex. This avoids the confounding of prenatal and postnatal weight gain.
- The use of children clinically identified as failing to thrive in subsequent research generally overestimates the adverse sequelae of slow weight gain owing to biases in the identification and referral process. Identification by whole population screening provides more representative results.
- There is some evidence that slow weight gain in infancy is associated with different patterns of mother–child interaction, and reasonably good evidence that it is associated with insecure attachment. There is some evidence that it is associated with lower food intake, perhaps resulting from a lower appetite.
- There is good evidence that it is associated with developmental delay in infancy and a slightly reduced IQ at school age. This is, however, a graded effect. Higher IQ is associated with faster weight gain across the whole of its range.
- The effect is specific to weight gain in the first 6–8 weeks of life. Current weight monitoring practice in the UK is unlikely to detect weight faltering in time for preventative interventions to be effective as regards intellectual development.

Key Points: Weight and Weight Gain in Infancy

To understand the significance of an infant's weight it needs to be related to that of other infants of the same age and sex (the reference population). This can be achieved by expressing the infant's weight as a centile, which is typically done in clinical practice by plotting it on a growth chart. Alternatively, it can be expressed as a standard deviation (SD) or z score, which is more common in scientific work.

The reference population can be the one from which the infant is drawn, or an external reference population, such as the infants whose weights are summarized in the UK 1990 reference curves (Freeman et al. 1995).

An infant with a low weight for age relative to the reference population (e.g., with an z score below – 1.645, corresponding to the fifth centile) has gained weight more slowly since conception than most of the population, but not necessarily gained weight more slowly since birth.

The difference between an infant's z score for weight and their z score at birth is a measure of weight gain from birth, but is not easily interpreted as infants with different birthweights gain weight at different rates. The average weight at a given later age of infants of different birthweights can be established using the linear regression of later weights on birthweights:

$$Z_2 = \beta_0 + \beta_1 (Z_1) + e,$$

$$e \sim N(0, s).$$

Here Z_2 is the average weight at the later age of infants whose weight at birth is Z_1. Infants vary around the average, a variation summarized in the error term or residual (e), which has a normal distribution with a mean of zero and a standard deviation s. It is sometimes called a "thrive index" in this context (Wright et al. 1994). Because the weights are used in the form of standard scores (Z_1 and Z_2) the value b_0 will be close to 0 (so the term can generally be omitted) and b_1 will correspond to the correlation coefficient. A value of e below $-1.645s$ then indicates that the infant's weight gain was below the fifth centile.

Figure 137.2 shows the application of this procedure to male infants in an actual 1-year birth cohort to identify those whose weight gain was poor over the time from birth up to the 6–8 weeks medical check. It identified the infants with the slowest weight gain (the slowest 5%), as shown. Note that these infants were identified prospectively, using an external weight gain standard and regression line, not retrospectively, using data from the sample.

The method has been generalized so that any initial or final age can be used (Cole 1996), and a corresponding graphical method has also been developed for clinical use (Wright et al. 1998b).

Key Terms

Failure to thrive: Term used in pediatrics of infants whose growth is unusually slow. It is now generally identified using exclusively anthropometric criteria, though other criteria, especially developmental delay, have been used historically. Growth monitoring in infancy relies heavily on weighing, and slow weight gain or a low attained weight are the most generally used criteria for FTT.

Body mass index: An indirect measure of adiposity, calculated as weight (in kg) divided by height (in m) squared.

Intelligence quotient: A measure of intellectual ability from an intelligence test, such as the Wechsler Intelligence Test for Children (WISC). In populations similar to those on which the test has been standardized it has a mean of about 100 and a standard deviation of about 15.

Sensitive period: An age range over which a variable is particularly likely to affect development.

Weight faltering: A term used as an alternative to "FTT." It is essentially equivalent to "unusually slow weight gain." "Growth faltering" is a more general term and might also involve other anthropometric measurements.

References

Ainsworth MDS, Bell SM, Stayton DJ. Merrill Palmer Q. 1972;18:123–43.

Batchelor J and Kerslake A. Failure to find failure to thrive: the case for improving screening prevention and treatment in primary care. London: Whiting and Birch; 1990.

Berkowitz CD and Senter SA. J Fam Pract. 1987;25:377–81.

Blair PS, Drewett RF, Emmett PM, Ness A, Emond AM and The ALSPAC Study Team. Int J Epidemiol. 2004;33:1–9.

Chatoor I, Ganiban J, Colin V, Plummer N, Harmon R. J Amer Acad Child Adolesc Psychiatr. 1998;37:1217–24.

Cole TJ. Archs Dis Child. 1995;73:8–16.

Cole TJ. Archs Dis Child. 1996;76:47–9.

Corbett SS, Drewett RF. J Child Psychol Psychiatr. 2004;45:641–54.

Crittenden PM. Infant Ment Health J. 1987;8:51–64.

Drewett RF. The nutritional psychology of childhood. Cambridge: Cambridge University Press; 2007.

Drewett RF, Corbett SS, Wright CM. J Child Psychol Psychiatr. 1999;40:551–61.

Drewett RF, Kasese-Hara M, Wright C. Appetite 2002;40:55–60.

Drewett RF, Corbett SS, Wright CM. J Child Psychol Psychiatr. 2006;47:524–31.

Drotar D, Eckerle D, Satola J, Pallotta J, Wyatt B. Child Abuse Negl. 1990;14:41–51.

Emond A, Blair P, Emmett P, Drewett RF. Paediatrics 2007;120:e1051–8. doi:10.1542/peds.2006-2295.

Freeman JV, Cole TJ, Chinn S, Jones PRM, White EM, Preece MA. Archs Dis Child. 1995;73:17–24.

Giglio L, Cnadusso M, Orazio C, Mastella G, Faraguna D. Acta Paediatr. 1997;86:1162–5.

Gordon AH, Corcoran Jameson J. J Am Acad Child Adolesc Psychiatry. 1979;18:251–9.

Healy MJR. Ann Hum Biol. 1974;1:41–6.

Hutcheson J J, Black MM, Starr RH. J Pediatr Psychol. 1993;18:453–66.

James R, James A, Drewett R, Cheetham T. Pediatr Res. 2007;62:695–9.

Knight S, Singhal A, Thomas P, Serjeant G. Archs Dis Child. 1995;73:316–20.

Mathisen B, Worrall L, Masel J, Wall C, Shepherd RW. J Paediatr Child Health. 1999;35:163–9.

McDougall P, Drewett R, Hugin P, Wright C. Archs Dis Child. 2009;94:549–553.

Olsen E, Petersen J, Skovgaard A, Weile B, Jøgensen T, Wright C. Archs Dis Child. 2006;92:109–14.

Parkinson KN, Drewett RF. J Child Psychol Psychiatr. 2001;42:971–8.

Parkinson KN, Wright CM, Drewett RF. J Child Psychol Psychiatr. 2004;45:1030–5.

Pollitt E. Fed Proc. 1975;34:1593–7.

Pollitt E, Eichler AW, Chan CK. Am J Orthopsychiatry. 1975;45:525–37.

Pollitt E, Gilmore M, Valcarcel M. Early Hum Dev. 1978;1:325–36.

Puckering C, Pickles A, Skuse D, Heptinstall E, Dowdney L, Zur-Szpiro S. J Child Psychol Psychiatr. 1995;36:573–95.

Reilly JR, Armstrong J, Dorosty AR, Emmett PM, Ness A, Rogers I, et al. Br Med J. 2005;330:1357–63.

Reilly S, Skuse D. Devl Medi Child Neurol. 1992;34:379–88.

Shenkin S, Starr JM, Deary IJ. Psychol Bull. 2004;130:989–1013.

Sherry B. Epidemiology of inadequate growth. In: Kessler D, Dawson P, editors.) Failure to thrive and pediatric undernutrition: a transdisciplinary approach. Baltimore: Paul H Brookes; 1999. p. 19–36.

Skuse D, Wolke D, Reilly S. In: Remschmidt H, Schmidt M, editors. Developmental psychopathology. Lewiston: Hogrefe & Huber; 1992. p. 46–71.

Skuse D, Pickles A, Wolke D, Reilly S. J Child Psychol Psychiatr. 1994;35:521–45.

Spencer N. Archs Dis Child. 2007;92:95–6.

Vietze PM, Falsey S, O'Connor S, Sandler H, Sherrod K, Altemeier WA. In: Field T, editor. High risk infants and children: adult and peer interactions. New York: Academic; 1980. p. 5–23.

Ward M, Kessler D, Altman S. Infant Ment Health J. 1993;14:208–20.

Ward M, Lee S, Lipper E. Infant Ment Health J. 2000;21:428–42.

Whitten CF, Pettit MG, Fischhoff J. J Am Med Assoc. 1969;209:1675–80.

Wilensky DS, Ginsberg G, Altman M, Tulchinsky TH, Ben Yishay F, Auerbach J. Archs Dis Child. 1996;75:145–8.

Wright CM, Parkinson KN. Archs Dis Child: Fet Neonat Ed. 2004;89:F254–7.

Wright CM, Matthews JNS, Waterston A, Aynsley-Green A. Acta Paediat. 1994;83:351–6.

Wright CM, Callum J, Birks E, Jarvis S. Br Med J. 1998a;317:571–4.

Wright CM, Avery A, Epstein M, Birks E, Croft D. Arch Dis Child. 1998b;78:40–3.

Chapter 138
Video Game Play, Behavior, and Dietary Health

Mary Ballard

Abbreviations

AOA	American Obesity Association
CDC	Center for Disease Control
BMI	Body Mass Index
DDR	Dance Dance Revolution
HHS	U.S. Department of Health and Human Services
MMORPG	Massively Multiplayer Online Role-Playing Games
TAH	Trust for America's Health
TV	Television

138.1 Introduction

Video game play is a common leisure activity from childhood through mid-adulthood (Yee 2006; Nielson Company 2007). A majority of households (65%) in the U.S. currently have a video game console. It is expected that by 2012 nearly 200 million U.S. households will have one of the newest next generation game consoles and that 80% of these will be connected to the internet (GRABstats. com 2009).

Teenage males have the highest (88%) access to games in the home (Nielson Company 2007). However, although video games used to be mostly within the purview of adolescent males, their appeal has grown among women and the middle-aged (e.g., Yee 2006; Nielsen Company 2007; GRABstats.com 2009). In 2008, over a quarter (26%) of Americans over 50 years of age played video games regularly. And while males do spend significantly more time playing video games than females (e.g., Roberts and Foehr 2004), 40% of video game players are women (GRABstats.com 2009). Sports, role playing, and first person shooter games are the most popular (Ballard and Visser 2009). See Table 138.1 for *Rates of Video Game Play*, Table 138.2 for *Most Frequently Played Game Genres*, and Table 138.3 for *Key Facts about Video Game Play and MMORPG Play*.

Since video game use is becoming ubiquitous, it is important to examine the potential health effects of heavy video game play (Brown and Witherspoon 2002). Most of the research concerning

M. Ballard (✉)

Department of Psychology, Appalachian State University, Boone, NC 28608, USA
e-mail: ballardm@pm.appstate.edu; meanmary17@yahoo.com

Table 138.1 Video game play usage by age and gender

Percentage of video game play by age and gender[a]	Males	Females	Total
Ages 17 and under	17%	8%	25%
Ages 18–49	NA	NA	49%
Ages 50 and up	NA	NA	26%
Ages 18 and up inclusive	42%	33%	75%

This table includes data on video game usage for males and females both overall and from four lifespan age groups

[a]Source for statisitics: GRABstats.com 2009

Table 138.2 Most frequently played video game genres among males by age group (Source for statistics: Ballard and Visser 2009)

Game genre	Adolescent males (14–17 years)	Young adult males (18–25 years)
Sports	21.4%	40.6%
First person shooter	22.9%	22.8%
Role playing	18.6%	7.9%
Fighting	15.7%	5.0%
Racing	4.3%	5.9%
MMORPG	5.0%	2.0%
Strategy	5.8%	5.0%
Music	1.4%	3.0%
Puzzle	0%	1%
Other	4.9%	6.8%

This table includes data regarding the most frequently played video game genres among adolescent (ages 14–17) and young adult (ages 18–22) males

Table 138.3 Key facts about video game play and MMORPG play

1. Most households in the U.S. have a video game console.
2. More males than females play video games, but an increasing number of women are regularly playing video games.
3. Adolescents and young adults play video games more often than those of other developmental statuses, but game play is increasing among children and those in middle age.
4. There is a wide variety of video game genres including sports, fighting, action/war, music, racing, strategy, puzzles, and role-playing games.
5. Historically most video games have been played in a sedentary fashion, but newer game consoles allow for physically active game play.
6. Massively multiplayer online role playing games (MMORPGs), which are played in a virtual world by a large number of players at once, have recently burgeoned in popularity.
7. MMORPG players create avatars and take on roles (e.g., shaman, soldier) in a virtual community; avatars progress through a variety of levels and accumulate goods and wealth.
8. MMORPG players report that they come to depend on one another and often feel responsible for being online for many hours per week in case the services of their avatar are needed by others. Some MMORPG players spend more time playing than working.
9. Researchers have found a number of both negative (hostility, aggression) and positive (cognitive gains, improved mood) affects of both console and online video game play.

This table provides key facts about video game play and MMORPG play

video games has focused on their potential impact on aggression and hostility. There is evidence that violent video game play can result in negative affect, including hostility, and increases in aggressive cognitions and behavior (see Ballard et al. 2006 for a review). However, when played in a social context, even violent video games can be tied to positive emotions and to positive responses

toward playing partners (Ballard and Visser 2009). While previous research examining hostility and aggression has been tangentially related to health issues, there is some recent research that examines the impact of video game play on health factors more directly. Historically, much of the research examining the link between media use and physical health correlates has focused on television (TV). This is likely due to the fact that, until recently, there have been much higher rates of household access for TV than for video games (Motl et al. 2006). However, over the past few years there has been increased interest in the impact of video game play on eating, body weight, and activity levels. This research has focused on two types of gaming: traditional sedentary video game play and physically active video game play. This review will address (a) rates of obesity, overweight and physical activity in the U.S.A, (b) correlations between sedentary media use and overweight and obesity, (c) hypotheses and evidence regarding sedentary media use, obesity, and activity levels, (d) evidence regarding physically active video game play, (e) applications for health, and (f) directions for research.

138.2 Rates of Overweight and Obesity and Physical Activity

Rates of obesity have risen steadily in developed countries over the past few decades (Center for Disease Control (CDC) 2006; Trust for America's Health (TAH) 2009). In the U.S., 15.5% of children, 15.3% of adolescents, and 30.5% of adults are classified as obese (American Obesity Association (AOA) 2005). When overweight children and adults are included, these statistics increase to 45.5% for children and adolescents and 67% for adults (TAH 2009). See Table 138.4, *Key Facts about Obesity*. Many variables, including biological factors and diet, play a role in an individual's weight retention. However, recent changes in lifestyle – many Americans have increased their caloric consumption, but decreased their energy expenditure – may account for much of the recent increase in obesity (e.g., Hill et al. 2005). Lower levels of physical activity are clearly related to higher levels of body fat and higher body mass index (BMI; Stallmann-Jorgensen et al. 2007; Ballard et al. 2009). Physical activity may be declining in part because people spend more time engaged in sedentary behaviors (Nelson et al. 2007). Most American adults (53%) do not participate in regular physical activity and many (25%) are not active at all (CDC 2006). Only 22% of adults engage in the recommended amount of physical activity. Similarly, less than one-third of children engage in regular, intense physical activity (TAH 2009). Since both physical inactivity and obesity increase the risk of a host of problems across domains of functioning (e.g., health, psychological, and social problems; AOA 2005; Hill et al. 2005), these trends are of grave concern. For example, recent increases in rates of diabetes – among both children and adults – and high blood pressure are thought to be related to increases in obesity (TAH 2009).

Table 138.4 Key facts about obesity by age group (Source for statistics: TAH 2008)

	Children and adolescents	Adults
Percentage overweight	30.1	36.5
Percentage obese	15.5	30.5
Total overweight + obese	45.5	67.5

This Table provides information about the percentage of children, adolescents, and adults who are overweight and/or obese

138.3 Correlations Between Sedentary Media Use and Overweight and Obesity

A number of studies suggest that sedentary media use is a risk factor for obesity across the lifespan and across cultures (Proctor et al. 2003; Jago et al. 2005; Parsons et al. 2005; Heelan and Eisenmann 2006; Nelson et al. 2007; Stallmann-Jorgensen et al. 2007; Thomson et al. 2008).

TV Screen Time and Overweight and Obesity. Most studies have examined TV screen time and have found that time spent watching TV was significantly, positively correlated with weight, BMI, and/or percent body fat among children, adolescents, and adults in the U.S.A, France, Canada, and Great Britain (Lowry et al. 2002; Jago et al. 2005; Parsons et al. 2005; Heelan and Eisenmann 2006; Stallmann-Jorgensen et al. 2007; Nelson et al. 2007; Thomson et al. 2008)). However, using a cross-sectional design, Vandewater et al. (2004) failed to find a relationship between TV screen time and BMI among the children in their sample. But longitudinal evidence suggests that the relationship between TV screen time and BMI increases over time. For example, in a longitudinal study in Great Britain, Parsons and colleagues (2005) found that the relationship between TV viewing and BMI increased across time; there was a stronger positive relationship between TV viewing and BMI among their participants in adulthood than there had been in childhood or adolescence. Similarly, in a longitudinal study among American children who were followed from the preschool years through adolescence, Proctor and colleagues (2003) found that heavy TV viewing was a good predictor of increased body fat across time; that is, children who watched the most TV had the greatest increases in body fat across the course of the study. Several studies reported stronger correlations between TV screen time and BMI among females than among their male counterparts (Lowry et al. 2002; Oppert et al. 2005; Parsons et al. 2005). Media use may be a better predictor of weight status in females because they spend more time inside engaging in sedentary activities than do males (e.g., Hager 2006) and because males have higher activity levels in general (e.g., Mhurchu et al. 2008).

Time Spent in Video Game Play and Overweight and Obesity. Thus far, only a few studies have examined links between video game play and BMI. Both Ballard and colleagues (2009) and Vandewater and colleagues (2004) found significant positive correlations between rates of video game play and weight status. Specifically, Ballard and colleagues (2009) found that length of video game play during one sitting was significantly, positively related to BMI (see Fig. 138.1). The frequency of massively multiplayer online role-playing game play (MMORPG play; e.g., World of Warcraft) was significantly, positively correlated with BMI (Ballard et al. 2009; see Fig. 138.2). There was a stronger relationship between MMORPG play and BMI than console play and BMI. Contextual factors related to these different types of gaming might be related. For example, time spent playing a lengthy session of online computer games, which often move slowly and are controlled with one hand, can be more conducive to snacking than playing console games, which require rapid manipulation of a controller using both hands. Increased snacking is one of the factors hypothesized to mediate the link between media use and increased risk of obesity. Refer to Table 138.5 for correlations between overall game play, MMORPG play, BMI, body fat %, and exercise.

138.4 Hypotheses Regarding Media Use, Obesity, and Activity Levels

Robinson (2001) and Vandewater and colleagues (2004) posit three mechanisms to explain why sedentary media use is likely to increase the risk of overweight and obesity. The first is the "couch potato" hypothesis, which suggests that time spent engaged in media use displaces the time available
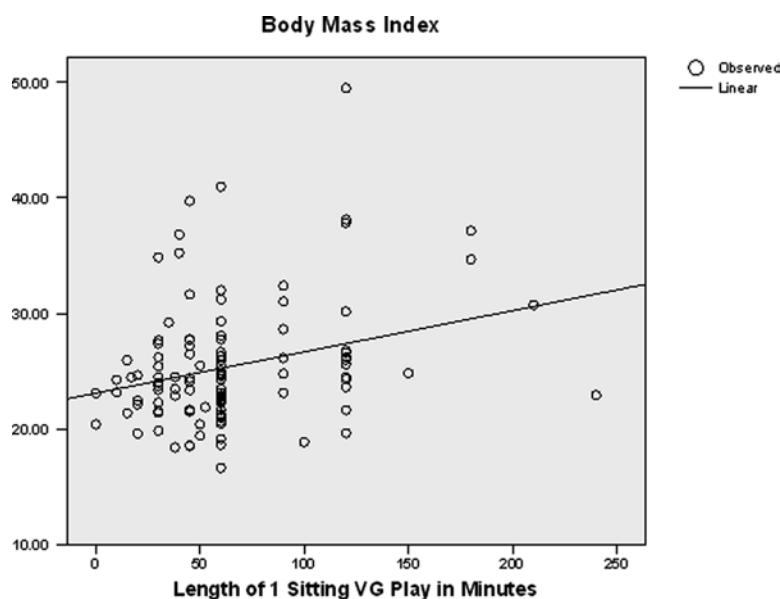
Fig. 138.1 Body mass index as a function of the length of playing video games in one sitting. The longer participants spent playing videogames in an average session, the higher their average BMI. Results are expressed in terms of how BMI is related to how long on average, in min, participants reported playing MMORPGs (Drawn from Ballard et al. 2009)
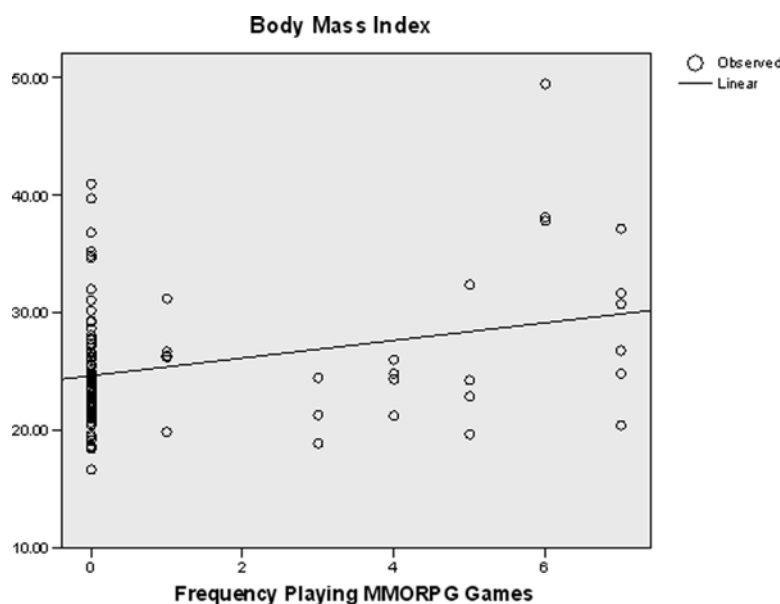
Fig. 138.2 Body mass index as a function of the frequency of playing MMORPG games. While most participant did not play MMORPGs, among MMORPG players the frequency of playing online games was related to higher BMI. Results are expressed in terms of how BMI is related to how many times in 1 week participants reported playing MMORPGs

for physical activity. Vandewater and colleagues (2004) suggest that this hypothesis could explain the link between obesity and various types of electronic media, including TV, video games, and the internet. The second hypothesis proposes that people engage in increased consumption of high calorie foods while engaged in media use, particularly while watching television. While this hypothesis

Table 138.5 Correlations between all video game play, MMORPG play, BMI, body fat, and exercise (Source for statistics: Ballard et al. 2009)

	1	2	3	4	5	6
1. Frequency of video game play	–	0.28**	0.14	0.11	0.00	−0.21*
2. Length of average game session	0.29**	–	0.27**	0.15	−0.21*	−0.06
3. BMI	0.29**	0.35***	–	0.21*	−0.19*	−0.08
4. Body fat %	0.15	0.26*	0.21*	–	−0.11	−0.08
5. Frequency of exercise	−0.12	−0.47***	−0.19*	−0.10	–	0.35***
6. Length of average exercise session	−0.04	−0.05	−0.08	−0.08	0.36***	–

This table provides correlations between the frequency and length of video game play, BMI, body fat %, and frequency and length of exercise among adolescent and young adult males. Correlations above the diagonal represent all video game play. Correlations below the diagonal represent MMORPG play

$*p < 0.05, **p < 0.01, ***p < 0.001$

may not be as salient regarding those playing video games using a hand-held controller as it is to those watching TV, it might be relevant when considering games played on a computer or via the internet (Ballard et al. 2009). The third hypothesis suggests that decreases in metabolic rate may occur as a result of reduced activity levels during media use, leading to more rapid weight gain (Klesges et al. 1993; Robinson 2001; Vandewater et al. 2004). The research examining these hypotheses is summarized next.

138.5 Sedentary Media Use and the "Couch Potato" Hypothesis

The "couch potato" hypothesis claims that media use displaces time that might be spent in other, more physically active or constructive endeavors. Media activities can be intrinsically enjoyable and rewarding. Players report that they typically play for an hour or more in one sitting (Ballard et al. 2009). Some media, particularly video games, may result in a sense of flow (i.e., pleasurable immersion in everyday activities) causing players to lose track of time (e.g., Sherry 2004). If this occurs, players may spend more time engaging in the media activity than planned and fail to complete other tasks. There is also evidence that media is used to procrastinate or avoid other responsibilities (Klassen and Kuzucu 2009). However, there is mixed evidence as to whether media use actually displaces time that might otherwise be spent in physical activity.

Ballard and colleagues (2009) examined the hypothesis that media use displaces time for physical activity among 116 male undergraduates. Of these, 26 reported frequent MMORPG play. Overall, frequency of video game play was significantly, negatively correlated with length of exercising. Length of typical video game play during one sitting was significantly negatively correlated with both frequency of exercise and days of walking. However, exploratory analyses indicated that game type seems to mediate the association between game play and exercise. The frequency of playing sports video games was significantly, positively related to the frequency of exercise and days of vigorous physical activity. Conversely, length of playing MMORPG games during one sitting was significantly, negatively related with frequency of exercise (Ballard et al. 2009). This is particularly interesting since MMORPG play was more strongly linked to high BMI than video game play in general. Sessions of online play tend to be longer than sessions of console play and may be more likely to interfere with other activities (e.g., Yee 2006). Vandewater and colleagues (2004) found that both the most active and the least active adolescents in their study played higher rates of video games than did moderately active children. Likewise, the adolescents in the lowest and the highest weight statuses played more video games than did adolescents in the mid-weight range.

In terms of other media, several studies (Lowry et al. 2002; Vandewater et al. 2004; Jago et al. 2005; Motl et al. 2006) found significant negative correlations between TV screen time and activity among adolescents. However, Ballard and colleagues (2009) found that among undergraduates an increased frequency of watching visual media (TV, DVDs, films, etc.) predicted an increased frequency of exercise, accounting for 5.6% of the variance. Other studies also failed to find a negative relationship between media use and physical activity (e.g., Van de Bulck 2000; Parsons et al. 2005; Heelan and Eisenmann 2006; Laurson et al. 2008). Similar to Ballard and colleagues (2009), Snoek and collegues (2006) found a significant positive correlation between TV screen time and physical activity for undergraduates. Finally, Van de Bulck (2000) reports that Flemish youth were just as likely to be involved in sports regardless of levels of media use.

Thus, the literature is unclear as to the impact of media use on physical activity; there may be several personality or other individual difference variables that mediate the relationship between media use and activity levels. There is evidence that heavy users of one media type also tend to use other types of media heavily (Roberts and Foehr 2004; Ballard et al. 2009). Lanningham-Foster and colleagues (2006) argue that most individuals who engage in heavy media use are likely to replace media use with other sedentary behaviors rather than with more physically demanding activities. Ballard and colleagues (2009) examined whether video game play was correlated with other media use to help test the displacement hypothesis. The frequency of video game play was not related to the use of other media (i.e., reading for enjoyment or watching TV, DVDs, etc.). However, length of video game play during one sitting was significantly, positively related to time spent reading for enjoyment and significantly, but negatively related to watching TV, DVDs, or films. Ballard and colleagues (2009) suggest that people may displace one type of media use with another and that different game genres (e.g., sports games versus MMORPGs) may displace activities differentially.

138.6 Sedentary Media Use and Increased Caloric Intake

The second hypothesis posited to explain the relationship between media use and obesity suggests that caloric intake increases during media screen time (Van den Bulck 2000; Brown and Witherspoon 2002; Snoek et al. 2006; Thomson et al. 2008). This hypothesis has been primarily examined with regard to television, but there is evidence that children eat more snacks while watching TV than when playing video games, playing on the computer, reading, or doing homework (Gorley et al. 2004; Matheson et al. 2004). A number of studies indicate that TV screen time is positively related to increased snacking, particularly in regard to energy dense snack foods (high in fat and/or sugar) and high calorie drinks (Van den Bulck 2000; Gore et al. 2003; Snoek et al. 2006; Thomson et al. 2008). Further, about one third of children's meals were eaten while watching TV (Matheson et al. 2004). Snacking while watching TV was associated with higher caloric intake and more calories from fat than snacking at other times, but there was no difference in caloric intake or calories from fat while eating meals, regardless of where meals were eaten (Gore et al. 2003). However, children were less likely to eat healthy foods, such as vegetables, while watching TV than at other times (Matheson et al. 2004). TV advertisements tend to promote high fat foods that are low in nutritional value and could contribute to this trend (Vandewater et al. 2004; Powell et al. 2007; Thomson et al. 2008). Thomson and colleagues report that snack food slogan recognition accounted for a significant amount of the variance in the relationship between TV viewing and unhealthy snacking. Children who do consume more calories from fat while watching TV have a significantly higher BMI (Matheson et al. 2004) and engage in significantly less physical activity (Snoek et al. 2006), which would moderate the relationship between snacking and BMI. In sum, while a significant portion of

children's daily caloric intake takes place in front of the TV screen, studies indicate that very little (<1%) of their caloric intake takes place while playing video games (Matheson et al. 2004; Roberts and Foehr 2004). However, the few studies that have examined video games and snacking have focused on console games, which are played using a controller in both hands, and have not examined snacking during the play of online games.

138.7 Sedentary Media Use and Decreased Metabolic Rate

The third hypothesis regarding the association between media use and obesity posits that increased screen time results in decreases in metabolic rate (e.g., Klesges et al. 1993). Only a few studies have examined this hypothesis. In one study Klesges and colleagues (1993) found that regardless of normal versus overweight weight status, girls' metabolic rate decreased significantly during TV viewing as opposed to when they were at rest. However, a second study comparing rest, reading, and TV viewing did not replicate these findings (Cooper et al. 2006).

Research on video games suggests that even sedentary game play increases physiological arousal and metabolic function (e.g., Ballard et al. 2006; Lanningham-Foster et al. 2006; Wang and Perry 2006; Mark and Janssen 2008). Lanningham-Foster and colleagues (2006) report that playing console video games while seated significantly increased energy expenditure over baseline levels. Similarly, Wang and Perry (2006) found that heart rate, systolic and diastolic blood pressure, oxygen consumption, respiratory rate, and energy expenditure all increased from baseline during seated console video game play. In a brief longitudinal study, Ballard and colleagues (2006) found similar results with regard to cardiovascular reactivity, but also found that desensitization occurred and arousal diminished with repeated instances of game play. Physically active video game play has stronger effects on arousal and metabolism (e.g., Lanningham-Foster et al. 2006).

138.8 Correlates of Physically Active Video Game Play

Physically Active Video Game Systems. The first physically active video game to attain popularity was Dance Dance Revolution (DDR). DDR, which began as an arcade game, requires players to use whole body movement to follow increasingly complex dance patterns on a weight-sensitive mat. The game can be played individually or competitively. More recently DDR has been adapted for home gaming systems. Another active gaming system that has attained some popularity is Sony's EyeToy. The EyeToy uses a USB camera mounted on the TV to integrate the player's image into the game. The player's movements control the flow of games including boxing, dancing, and biking.

The newest and most popular physically active gaming system is the Nintendo Wii. The Wii offers a variety of games (e.g., golf, tennis, and boxing) that require the participant to mimic the motions of each activity with a hand-held wireless remote and/or using a weight and balance sensitive pad (e.g., yoga; Nintendo Wii 2007). Typically the primary controller is held in the dominant hand and a secondary controller, the nunchuk, is held in the nondominant hand. Some games only require use of the primary controller and other games require both controllers. Typically the dominant hand is used more in controlling game play (e.g., baseball, tennis, bowling), but some games (e.g., boxing) require equal use of both hands.

Research on Physically Active Games. A number of recent studies have found significantly higher energy expenditure and/or physiological reactivity during the play of video games that promote

physical activity than during sedentary game play (Lanningham-Foster et al. 2006; Unnithan et al. 2006; Exner et al. 2009). Several of these studies will be described in detail.

Using a cross-sectional design, Maddison and colleagues (2007) examined energy expenditure while playing physically active video games, such as DDR and EyeToy Knockout, as compared with nonactive console games. Energy expenditure was measured via oxygen consumption (VO_2). Heart rate and activity counts were also gathered. Not only did playing the physically active games result in significantly more energy expenditure than the console games, the physically active games required as much energy expenditure as are typically reported during moderately intense physical activities such as brisk walking and jogging. A second longitudinal study found similar results (Mhurchu et al. 2008). In addition, the children who were randomly assigned to the active video game group showed decreases in overall video game play, increases in physical activity, and decreases in levels of body fat, suggesting that active game play facilitated interest in other activities.

In a similar study, Lanningham-Foster and colleagues (2006) had 8–12-year-old children play either a traditional console video game while seated or one of two physically active video games (EyeToy Nicktoons Movin' or DDR). Children's energy expenditure increased significantly above baseline levels even when they played the seated console game. However, when they played the active games energy expenditure was significantly higher than when they played the seated game. In fact, energy expenditure more than doubled when children played the active game and was equivalent to what the energy expenditure children typically demonstrate when playing actively outside. Children who were obese had, in absolute terms, significantly higher energy expenditure when playing activity-promoting games than did lean children. Lanningham-Foster and colleagues (2006) found similar results in a study with adult participants.

Graves et al. (2008) examined the relationship between energy expenditure and upper limb/total body movement during active video game play. Adolescents, aged 11–17 years, played a seated racing game on the XBOX 360 and three Wii Sports games (tennis, bowling, and boxing). Upper limb and body movement were significantly greater when the adolescents played the Wii games than when they played the sedentary racing game. As a result, adolescents' heart rate and energy expenditure were significantly higher when they played the Wii Sports games than when they played the sedentary racing game. The use of the nondominant arm was greater when playing the boxing game. Subsequently, heart rate and energy expenditure were significantly higher during the Wii boxing game than the Wii bowling or tennis games.

Using a complex design, Epstein and colleagues (2007) completed a study where children played a bicycling or dancing game. Both games could be played either actively (i.e., dancing on a pad or without the pad while watching an instructional video or pedaling and steering a stationary bicycle) or played using a controller. Conditions also varied in terms of how interactive game play could be. Children were given a choice as to how they played the games. Children preferred the interactive dance game to sedentary option. However, no difference was determined in preference for the bicycling game. Children who were not overweight were more active in playing the interactive dance game than were overweight children.

Like most video games, Wii games become more challenging as you continue to play them. Sell et al. (2008) examined the impact of gamer experience on energy expenditure. Participants in the study were 19 undergraduate males with varying levels of video game experience. The result indicated that the gamers with more experience played with a greater level of intensity and subsequently had higher levels of heart rate, oxygen consumption, respiration, and energy expenditure than the inexperienced participants.

In the only study directly comparing active video game play with other types of physical activity, Graf and colleagues (2009) compared DDR and Wii Boxing play to watching TV and walking on a treadmill among adolescents, aged 10–13. They found that physically active game play was related

to significantly higher energy expenditure than watching TV. Energy expenditure during the play of DDR and Wii Boxing was comparable to that when walking on the treadmill. They conclude that physically active video game play is a good way to promote exercise among children who play a lot of video games. Overall, the results of these studies indicate that while real exercise is preferable, virtual activities are better than sedentary activities and might create increased interest in other physical activities (Mhurchu et al. 2008; Graf et al. 2009).

138.9 Summary

In general, sedentary media use is related to lower activity levels, more snacking, and higher BMI. However, it is not clear whether sedentary media is supplanting more physically active endeavors, as Robinson (2001) and Vandewater and colleagues (2004) suggest. Rather, evidence exists (Ballard et al. 2009) that people may have a set pool of time for media use and that increases in the use of one type of media might result in decreases in the use of other forms of media. With regard to video games, different game genres might be differentially related to time use and activity levels. In the study by Ballard and colleagues (2009), the negative correlation between MMORPG play and exercise was stronger than that between game play in general and exercise. In addition, those who played more sports games also exercised more. Thus, choice of game genre may reflect individual differences in general interests, such as the player's motivation for playing video games, personality, sociability, or activity preferences that mediate the relation between game play and other activities. For example, those who enjoy physical activities, such as playing basketball, snowboarding, etc., may prefer games with similar active themes. On the other hand, individuals who play MMORPGs have been found to be less open to new experiences and more introverted (Ballard et al. 2008). Further, they often make sacrifices in other areas of their lives (e.g., social interaction, work) to devote time and energy to game play (Yee 2006). Thus, they may either be more willing to sacrifice physical activity to have more time to play games or be less inclined to be physically active in the first place. At the other end of the spectrum, physically active video games are related to high levels of energy expenditure and have promise for increasing activity levels and aiding in weight reduction. Summary points are included in Appendix A.

138.10 Applications for Health

The research reviewed suggests that there are clear implications for how video game play and other media use might affect health. Overall, the research suggests that the heavy use of sedentary media has clear negative implications for health. Increased TV screen time and sedentary video game play, particularly of MMORPGs, increases the risk of overweight and obesity. This, in turn, increases the risk of related health problems, such as diabetes, high blood pressure, heart disease, and cancer (AOA 2005; Hill et al. 2005; TAH 2009). Given this, it seems to be important to accomplish three goals. Efforts should be aimed at (1) reducing levels of sedentary media use, (2) reducing caloric intake during sedentary media use, and (3) increasing levels of physical activity. One way to accomplish these goals may be to increase levels of physically active video game play. Physically active games are engaging and serve as an alternative form of exercise. They could be used directly to increase levels of physical activity, would not be as conducive to snacking as sedentary media use, and might lead to increased physical fitness and to weight reduction. Further, since there is evidence

Table 138.6 HHS (2008) guidelines for physical activity for children and adults

	Children	Adults
Moderate physical activity	1 h seven times per week	2½ h per week minimum 5 h recommended
Vigorous physical activity	Three times per week	1¼ h per week minimum 2½ h recommended

This table lists the times per week that children should engage in moderate and vigorous physical activity. The table also lists the hours per week that adults should engage in moderate and vigorous physical activity; both minimum and recommended number of hours of activity are provided

that physically active games foster interest in other activities, their use might increase the likelihood of players engaging in more exercise and outdoor activities.

Recommendations for Physical Activity. The U.S. Department of Health and Human Services (HHS 2008) has specific recommendations for activity levels for children and adults. See Table 138.6 for these recommendations. Given that most gamers play video games several times a week, with the average session lasting over an hour (Ballard et al. 2009), physically active video game play could easily help gamers meet the requirements for moderate activity. Further, active video game play could help develop regular exercise habits among adolescents and young adults. This is important, as the health and exercise habits developed in emerging adulthood are tied to exercise habits and health status as adulthood progresses (e.g., Seidell et al. 2005).

While exercising outside or in the gym is preferable to using video games for exercise, physically active games seem to be a reasonable alternative. Furthermore, they may be more practical for those with limited time, unconventional work schedules, or during inclement weather. However, socioeconomic disparities may decrease access to new generation consoles for those in the working class. This is unfortunate, as those individuals are at higher risk for overweight, obesity, and health problems (TAH 2009).

138.11 Directions for Research

There are several fruitful avenues for future research in this area. Brief longitudinal studies could have participants maintain a log of traditional physical activity, sedentary media use, active video game play, and eating (including snacking) to examine how these factors develop and interact over time. Weight status and other health factors (e.g., blood pressure) could be monitored intermittently to study their relationship to media use, diet, and physical activity. Experimental studies could be used to examine how those assigned to an active game play regime compare with those assigned to using only sedentary media compared with regard to factors such as weight loss, controlling for other physical activity. Researchers could also examine how adding active game play might be used in conjunction with other weight loss programs.

There need to be more direct comparisons of the energy expenditure of physically active game play and the parallel traditional physical activity. Games such as tennis or dancing would be ideal to examine. Studies should also investigate how using whole body movement versus using simply wrist and controller movement for games such as Wii boxing or tennis impact cardiovascular activity and calories burned. While whole body movement is considered normative for playing those games, players can be successful playing while seated using rapid wrist motions instead of arm and body movement.

Finally, researchers should develop interventions aimed at encouraging healthier approaches to media use. Lanningham-Foster and colleagues (2006) suggest that most people will not replace media with more physically demanding activities. Therefore, it is important for health care professionals and game designers to link media and physical activity together through mediums such as interactive gaming and to educate both children and adults about healthy snacking.

Summary Points

- Rates of obesity have risen steadily in developed countries over the past few decades.
- Sedentary media use is a risk factor for obesity across the lifespan and across cultures.
- A significant portion of children's daily caloric intake takes place in front of the TV screen, but little of their caloric intake takes place while playing video games.
- Sedentary media use is related to lower activity levels, more snacking, and higher BMI.
- MORPG play is more strongly linked to high BMI than video game play in general.
- Sedentary console video game play increases physiological arousal.
- There is significantly higher energy expenditure and physiological reactivity during physically active video game play than during sedentary console game play.
- People may have a set pool of time for media use; increases in the use of one type of media might result in decreases in the use of other forms of media.
- Different video game genres might be differentially related to time use and activity levels.
- There are clear implications for how video game play and other media use might affect health.
- Interventions should be aimed at reducing levels of sedentary media use, reducing caloric intake during sedentary media use, and increasing levels of physical activity, perhaps including physically active video game play.

Key Terms

Energy expenditure: Calories burned (can be measured in multiple ways).

Energy-dense food snacks: Snacks with high fat, sugar, and/or calories.

Flow: Pleasurable immersion in everyday activities that often causes the individual to lose track of time (e.g., Sherry 2004).

Massively multiplayer online role-playing games (MMORPGs): Games played in an online virtual world by a large number of players at once. Players create avatars and take on roles (e.g., shaman, soldier). Avatars can move up through a variety of levels.

Next generation game consoles: Gaming systems now in development, such as the potential PlayStation 4 and Wii 2.

Obesity: For adults obesity is defined as a BMI > 30 and for children obesity is defined as a BMI > the 95th percentile (CDC 2006).

Overweight: For adults overweight is defined as a BMI of 25–29.9 and for children overweight is defined as a BMI of 85th–95th percentile (CDC 2006).

Physically active game play: Game play that requires gross motor movement (e.g., boxing, dancing) and/or balancing (e.g., yoga).

Sedentary media use/game play: Media use (TV, reading, traditional seated console video game play) that does not require gross motor movement.

References

American Obesity Association. Retrieved from http://www.obesity.org/; 2005.

Ballard M, Gray M, Reilly J, Noggle M. Eat Behav. 2009;10:161–7.

Ballard ME, Visser KE. Social context and video game play. Presented at The Society for Research in Child Development, Denver, Co.; 2009.

Ballard ME, Hamby RH, Panee CD, Nivens EE. Media Psychol. 2006;8:323–41.

Ballard ME, Noggle M, Reilly J, Gray M. Rates of video game play and personality characteristics. Poster presented at the Society for Research in Adolescence, Chicago, IL; 2008.

Brown JD, Witherspoon EM. J Adolescent Health. 2002;31:153–70.

Center for Disease Control. Retrieved from http://www.cdc.gov/nccdphp/dnpa/obesity/resources.htm; 2006.

Cooper TV, Klesges LM, DeBon M, Klesges RC, Shelton ML. Eat Behav. 2006;7:105–14.

Epstein LH, Beecher MD, Graf JL, Reommich JN. Ann Behav Med. 2007;33:124–31.

Exner A, Paptheodorou G, Baker C, Verdaguer S, Hluchan C, Calvert SL. Solitary versus gross motor videogame play: Energy expenditure among low-income African American adolescents. Presented at the Society for Research in Child Development, Denver, CO.; 2009.

Gorely T, Marshall SJ, Biddle SJH. Int J Beh Med. 2004;11:152–163.

Graves LEF, Ridgers ND, Stratton G. Eur J Appl Physiol. 2008;104:617–23.

GRABstats.com. Video Game Statistics/Video Game Industry Statistics. Retrieved from: http://www.grabstats.com/statcategorymain.asp?StatCatID=13#Stats on October 1, 2009.

Graf DL, Pratt LV, Hester CN, Short KR. Pediatrics. 2009;124:534–40.

Graves LEF, Ridgers ND, Stratton G. Eur J Appl Physiol. 2008;104:617–23.

Hager RL. J Adolescent Health. 2006;5:656–61.

Heelan KA, Eisenmann, JC. J Phys Act Health. 2006;3:200–9.

HHS. http://www.hhs.gov/news/press/10/20081007a.html.2008.

Hill JO, Catenacci V, Wyatt HR. Psychiat Clin N Am. 2005;28:1–23.

Jago R, Baranowski T, Baranowski JC, Thompson D, Greaves KA. Int J Obesity. 2005;29:557–64.

Klassen RM, Kuzucu E. Educ Psychol-UK. 2009;29:69–81.

Klesges RC, Shelton ML, Klesges LM. Pediatrics. 1993;91:281–6.

Lanningham-Foster L, Jenson TB, Foster RC, Redmond AB, Walker BA, Heinz D, Levine JA. Pediatrics. 2006;118:1831–5.

Lanningham-Foster L, Foster RC, McCrady SK, Jenson TB, Mitre N, Levine JA. J Pediatr. 2009;154:819–23.

Laurson K, Eisenmann JC, Moore S. Acta Paediatr. 2008;97:795–800.

Lowry R, Wechsler H, Galuska DA, Fulton JE, Kann L. J School Health. 2002;72:413–21.

Maddison R, Mhurchu CN, Jull A, Jiang Y, Prapavessis H, Rodgers A. Pediatr Exerc Sci. 2007;19:334–43.

Mark AE, Janssen I. J Pub Health. 2008;30:153–160.

Matheson DM, Killen JD, Wang Y, Varady A, Robinson TN. Am J Clin Nutr. 2004;79:1088–94.

Motl RW, McAuley E, Birnbaum AS, Lytle LA. J Adolescence. 2006;29:19–32.

Mhurchu CN, Maddison R, Jiang Y, Jull A, Prapavessis H, Rodgers A. Int J Behav Nutr Phy. 2008;5:1–5.

Nelson TF, Gortmaker SL, Subramanian SV, Cheung L, Wechsler H. Am J Health Behav. 2007;31:363–73.

Nielson Company. The state of the console: Video game console usage fourth quarter 2006. Retrieved from: http://www.nielsenmedia.com/nc/nmr_static/docs/Nielsen_Report_State_Console_03507pdf; 2007.

Nintendo Wii. In-depth regional Wii coverage. Retrieved from: http://wii.nintendo.com/software_index_en.jsp; 2007.

Oppert JM, Kettaneh A, Borys JM, Basdevant A, Ducimetiere P, Charles MA. J Public Health. 2005;14:87–93.

Parsons TJ, Power C, Manor O. Int J Obesity. 2005;29:1212–21.

Powell LM, Szczypka G, Chaloupka FJ. Am J Prev Med. 2007;33:251–6.

Proctor MH, Moore LL, Gao D, Cupples LA, Bradlee ML, Hood MY, Ellison RC. Int J Obesity. 2003;27:827–33.

Roberts DF, Foehr UG. Kids & media in America. Boston, MA: Cambridge University Press; 2004.

Robinson TN. Pediatr Clin N Am. 2001;48:1017–25.

Seidell JC, Nooyens AJ, Visscher TL. P Nutr Soc. 2005;64:1–5.

Sell K, Lillie T, Taylor J. J Am Coll Health. 2008;56:505–11.

Sherry JL. Commun Theor. 2004;14:328–47.

Snoek HM, van Strien T. Janssens JMAM, Engles RCME J Adolescent Health. 2006;39:448–51.

Stallmann-Jorgensen IS, Gutin B, Hatfield-Laube JL, Humphries MC, Johnson MH, Barbeau P. Int J Obesity. 2007;31:622–9.

Thomson M, Spence JC, Raine K, Laing L. Am J Health Promot. 2008;22:329–35.

Trust for America's Health. F as in fat 2009: How obesity policies are failing in America. Robert Wood Johnson Foundation. Retrieved October 3, 2009 from http://healthyamericans.org/reports/obesity2009/Obesity2009Report.pdf; 2009.

U.S. Department of Health & Human Services. HHS announces physical activity guidelines for Americans. Retrieved October 12, 2009 from http://www.hhs.gov/news/press/2008pres/10/20081007a.html; 2008.

Unnithan VB, Houser W, Fernhall B. Int J Sports Med. 2006;27:804–9.

Van de Bulck J. J Youth Adolescence. 2000;29:273–88.

Vandewater EA, Shim M, Caplovitz AG. J Adolescence. 2004;27:71–85.

Wang X, Perry AC. Arch Pediat Adol Med. 2006;160:411–5.

Yee N. Presence-Teleop Virt. 2006;15:309–29.

Chapter 139
Disinhibited Eating and Body Weight in Youth

Lauren B. Shomaker, Marian Tanofsky-Kraff, and Jack A. Yanovski

Abbreviations

BED	Binge eating disorder
BMI	Body mass index (kg/m^2)
BN	Bulimia nervosa
EAH	Eating in the absence of hunger
LOC Eating	Loss of control over eating

139.1 Disinhibited Eating and Body Weight in Youth

The prevalence of overweight has tripled for children (ages 6–11 years) and has more than doubled for adolescents (ages 12–19 years) over the past 3 decades (Odgen et al. 2008). Approximately 9 million youth in the United States currently meet criteria for overweight, defined as a body mass index (BMI; kg/m2) equal to or exceeding the 95th percentile for age and sex (Institutes of Medicine 2005). Such statistics are alarming because overweight youth are at heightened risk for a host of serious medical problems (Yanovski 2001), as well as psychosocial and behavioral problems (Crow et al. 2006; Csabi et al. 2000; Israel & Ivanova 2002). Given the epidemic problem of pediatric obesity, there is a critical need to illuminate the behaviors that promote overweight in children so that successful prevention and intervention strategies may be designed and implemented.

Overweight results from an energy imbalance in which energy intake exceeds energy expenditure. Frequent exposure to large portions of palatable, inexpensive, readily available, and energy-dense foods has become increasingly common over the last 30 years, and such exposure has been suggested to increase the likelihood of excess intake and, hence, excess weight gain in youth (Hill & Peters 1998). The current chapter focuses upon a number of aberrant eating patterns that may play a role in promoting a positive energy imbalance and in turn, overweight. We use the term disinhibited eating to refer to a range of eating behaviors that involve a lack of restraint over food intake,

J.A. Yanovski (✉)
Section on Growth and Obesity, Program in Developmental Endocrinology and Genetics,
Eunice Kennedy Shriver National Institute of Child Health and Human Development,
National Institutes of Health, Department of Health and Human Services, 9000 Rockvile Pike,
MSC 1103, Hatfield CRC, room IE-3330, Bethesda, Maryland 20892-1103, USA
e-mail: jy15i@nih.gov

including binge eating and loss of control (LOC) eating, emotional eating, and eating in the absence of hunger (EAH; Table 139.1). For each disinhibited eating behavior, we provide a definition, review the available evidence for its role in overweight, and discuss the correlates of or risk factors for the behavior. Subsequently, we consider the overlap and differentiation among the various disinhibited eating behaviors in youth. The next section of the chapter focuses upon the importance of careful assessment and treatment of disinhibited eating behaviors in the context of pediatric obesity intervention and prevention efforts. We also discuss potential treatment options for disinhibited eating itself. The chapter concludes with a consideration of applications for other areas of health and disease and a discussion of future research directions.

139.2 Disinhibited Eating Behaviors and Body Weight

An individual's intake at any given time is typically initiated by physiological cues for hunger and terminated by physiological cues for satiation. A number of appetitive hormones play a role in governing food intake behavior (Table 139.2). Furthermore, this process is complicated by the influence of auxiliary factors including subjective experiences such as feeling LOC over what or how much is eaten, affective states such as transient or enduring negative affect, and the availability and

Table 139.1 Key facts about disinhibited eating

1. Disinhibited eating includes a range of eating behaviors that all involve a lack of restraint over food intake
2. Examples of disinhibited eating behaviors include binge eating, loss of control (LOC) eating, emotional eating, and eating in the absence of hunger (EAH)
3. Disinhibited eating behaviors occur with considerable prevalence among youth
4. Disinhibited eating behaviors are more common among overweight (than non-overweight) children and adolescents and are associated with a heightened risk for excessive weight gain over time in children and adolescents
5. Some evidence suggests that disinhibited eating behaviors may interfere with standard-of-care weight loss treatment

Table 139.2 Appetitive hormones that play a role in governing food intake behavior

Hormone	Brief description
Ghrelin	Hormone produced in antrum of stomach that rises in response to fasting and stimulates hunger and food intake
Leptin	Fat-cell-derived hormone that signals the central nervous system when there has been change in energy stores
Cholecystokinin (CCK)	Hormone rapidly released in response to the entry of fat in the duodenum and triggers satiety, leading to meal termination
Peptide YY_{3-36} (PYY_{3-36})	Hormone secreted from the gastrointestinal tract in response to food intake and thought to exert an impact on satiety and meal termination
Insulin	Pancreatic hormone that promotes the rapid uptake and use of glucose by almost all body tissues; in the hypothalamus, increased insulin causes satiety and a reduction in food intake
Glucagon-like peptide 1 (GLP-1)	Hormone released in response to food intake from the distal intestine and induces satiety and short-acting meal termination
Amylin	Pancreatic hormone that rises rapidly with food intake and triggers satiety and short-acting meal termination
Gastric inhibitory peptide (GIP)	Gastric hormone that induces insulin secretion in response to ingestion of fat and glucose

This table provides a nonexhaustive list of hormones known to play a role in governing food intake behavior
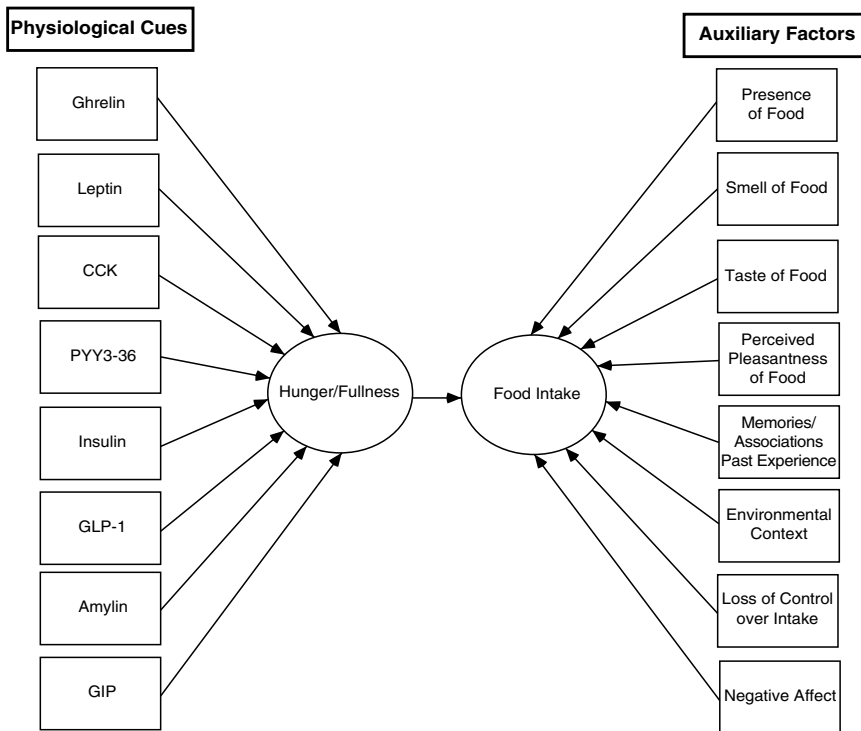
Fig. 139.1 Theoretical influences of physiological cues and auxiliary factors on food intake behavior. Physiological cues include the interplay of appetitive hormones regulating hunger and fullness, including ghrelin, leptin, cholesystokinin (CCK), peptide YY_{3-36} (PYY_{3-36}), insulin, glucagon-like peptide 1 (GLP-1), amylin, and gastric inhibitory peptide (GIP). Auxiliary factors include the presence of food, the olfactory and gustatory properties it elicits, its perceived pleasantness, past memories or associations that the food experience triggers, environment or context, subjective experiences of loss of control over eating, and transient or chronic negative affect

desirability of palatable food (Fig. 139.1). Recent evidence suggests that a propensity for food intake in response to triggers other than those physiological cues which reflect hunger and satiety may play a significant role in promoting a positive energy balance and the development of overweight in youth. To date, a relatively small literature exists on disinhibited eating and body weight in youth.

139.3   Binge Eating and LOC Eating

139.3.1   Binge Eating and Body Weight

Binge eating is defined as overeating an objectively large amount of food while experiencing a lack of control over what or how much is being eaten (American Psychiatric Association 2000). Binge eating is a core symptom of bulimia nervosa (BN) and binge eating disorder (BED) as outlined in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) (American Psychiatric Association 2000). The criteria for BN and BED are displayed in Table 139.3. Although few children and adolescents meet frequency and all symptom criteria for BN or BED, prevalence rates for binge eating in the absence of a full-syndrome eating disorder range from

Table 139.3 Diagnostic criteria for bulimia nervosa (BN) and research criteria binge eating disorder (BED)

Bulimia nervosa (BN)	Binge eating disorder (BED)
(A) Recurrent episodes of binge eating; an episode of binge eating is characterized by both of the following:	(A) Recurrent episodes of binge eating; an episode of binge eating is characterized by both of the following:
1. Eating, in a discrete period of time (e.g., ≤2-h period), an amount of food that is definitely larger than most people would eat during a similar period of time and under similar circumstances	1. Eating, in a discrete period of time (e.g., ≤2-h period), an amount of food that is definitely larger than most people would eat during a similar period of time and under similar circumstances
2. A sense of lack of control over eating during the episode	2. A sense of lack of control over eating during the episode
(B) Recurrent inappropriate compensatory behavior in order to prevent weight gain, such as self-induced vomiting; misuse of laxatives, diuretics, enemas, or other medications; fasting; or excessive exercise	(B) The binge eating episodes are associated with three or more of the following:
	1. Eating much more rapidly than normal
	2. Eating until feeling uncomfortably full
	3. Eating large amounts of food when not feeling physically hungry
	4. Eating alone because of being embarrassed by how much one is eating
	5. Feeling disgusted with oneself, depressed, or very guilty after overeating
(C) The binge eating and inappropriate compensatory behaviors both occur, on average, at least twice a week for 3 months	(C) The binge eating occurs, on average, at least 2 days a week for 6 months
(D) Self-evaluation is unduly influenced by body shape and weight	(D) Marked distress regarding binge eating is present
(E) The disturbance does not occur exclusively during episodes of anorexia nervosa	(E) The binge eating is not associated with the regular use of inappropriate compensatory behaviors (e.g., purging, fasting, excessive exercise) and does not occur exclusively during the course of anorexia nervosa or BN

The Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) (American Psychiatric Association 2000) provides criteria for a diagnosis of bulimia nervosa (BN) and recommended research criteria for a diagnosis of binge eating disorder (BED). Few children and adolescents meet full criteria for these disorders

approximately 6% to 57%, with the highest estimates among weight loss treatment-seeking (versus community) samples and higher prevalence among adolescents (versus children) (Britz et al. 2000; Tanofsky-Kraff 2008).

Binge eating typically emerges in childhood or adolescence. It has been found to occur with greater frequency (e.g., 2:1) among girls compared with boys in some samples (Ackard et al. 2003). Cross-sectional data point to a relationship between the presence of binge eating episodes and children and adolescents' body weight. For instance, among young children (6 years of age), parental reports of children's binge eating were correlated with children's overweight status (Lamerz et al. 2005). In a large survey-based study of boys and girls (9–14 years), children's self-reports of binge eating in the past month were associated with body weight (Field et al. 1999). A consistent relationship between binge eating and body weight also has been found among adolescents. In a school-based study of 7th–12th graders, overweight adolescents self-reported binge eating more frequently than their normal weight peers (Neumark-Sztainer et al. 1997). Similar findings have been reported in other adolescent community samples (Ackard et al. 2003; Field et al. 1997).

In studies of weight loss treatment-seeking overweight children and adolescents, those reporting binge eating typically have a similar BMI to those who do not endorse binge eating (Glasofer et al. 2007;

Mirch et al. 2006). However, overweight children (6–12 years) seeking weight loss treatment who self-reported at least one episode of binge eating in the 6 months prior to pretreatment assessment were found to become hungrier sooner following a preload, reported a greater subjective desire to eat, and ingested more energy during laboratory test meals (Mirch et al. 2006). Furthermore, children and adolescents with binge eating can be distinguished by greater psychological symptoms (e.g., depression and disordered eating attitudes) compared with their counterparts without binge eating (Glasofer et al. 2007; Goossens et al. 2007; Isnard et al. 2003).

Binge eating behaviors have also been shown to predict weight gain in a number of longitudinal, pediatric studies. Among adolescent girls from a community sample, binge eating as assessed by interview predicted elevated growth in weight gain (Stice et al. 1999) and obesity onset (Stice et al. 2002) over a 4-year period. In a large community cohort of youth 9–14 years of age, boys, but not girls, who reported binge eating gained significantly more weight compared with those who reported neither binge eating nor dieting (Field et al. 2003). Further, among 6–12-year-old children at heightened risk for adult obesity by virtue of their own overweight status or parental overweight, self-reported binge eating episodes predicted greater gains in body fat mass approximately 4 years later (Tanofsky-Kraff et al. 2006).

139.3.2 LOC Eating and Body Weight

Binge eating in youth, particularly pre-pubertal children, can be difficult to assess because children may be manifesting only early signs of the behavior or may have difficulty reporting their eating behaviors and accompanying emotional experiences. Similarly, what constitutes an unambiguously large amount of food in developing boys and girls of different ages and pubertal stages can be challenging to determine. For example, reported consumption of two large hamburgers, a large French fries, and a large soft drink might be considered unambiguously large for a pre-pubertal 8-year-old girl; however, the size of the same reported amount of food consumed would be much more ambiguous in a 15-year-old boy in the midst of a growth spurt.

An emerging body of data illustrate that the experience of LOC over eating, regardless of the reported amount of food consumed, may be the most salient marker of risk for overweight in youth. Loss of control over (LOC) eating is defined as a subjective experience of being unable to control or stop what or how much one is eating. The prevalence of LOC ranges from 4% to 45%, with higher estimates among overweight youth (versus nonoverweight), adolescents (versus preadolescents), and when assessed via questionnaire (versus semi-structured interview) (Tanofsky-Kraff 2008).

In a large, multisite study of binge eating behaviors in children and adolescents, youth were categorized as those who either reported at least one episode in the prior month of LOC in concert with consumption of an unambiguously large amount of food (i.e., an objective binge eating episode) or LOC when the amount was not objectively large (i.e., a subjective binge eating episode) (Tanofsky-Kraff et al. 2007a). Both groups were more likely to be heavier than youth with no episodes. In a study of children 6–13 years of age, those who reported any type of LOC eating by interview were more likely to be overweight and have greater body fat mass than children who reported overeating without LOC or no episodes of overeating (Tanofsky-Kraff et al. 2004). Youth with LOC eating also exhibit greater psychological symptoms and disordered eating cognitions and behaviors than their counterparts without LOC (Tanofsky-Kraff et al. 2004; Morgan et al. 2002).

A recent observational study of children's and adolescents' eating in the laboratory supports the possibility that LOC eating is related to behavioral patterns that might promote excessive weight gain. Among nontreatment seeking overweight and normal weight 8–17-year-olds, youth reporting

at least one episode of LOC in the past month by interview consumed a greater percentage of calories from carbohydrates, consumed a smaller percentage from protein, ate more snack and dessert-type foods, and ate less meats and dairy at laboratory test meals, compared with those without LOC (Tanofsky-Kraff et al. 2009a).

In a recent prospective investigation of 6–13-year-old children over the course of 4–5 years, those with LOC gained a significant 2.4 kg of additional weight per year than those children without LOC (Tanofsky-Kraff et al. 2009b). Further longitudinal studies of LOC eating and body weight are warranted.

139.3.3 Etiology of Binge and LOC Eating

It is well accepted that no single factor causes binge or LOC eating. Rather, these behaviors likely develop from the complex interaction of multiple biopsychosocial factors.

Socio-cultural perspectives on binge eating posit that ubiquitous cultural messages promoting the "ultra-thin" ideal of feminine beauty play a role in binge eating onset. Youth are inundated with such unrealistic ideals of beauty and a myriad of often unhealthy strategies for becoming thinner or leaner. Perceived socio-cultural pressure to be thinner or to lose weight from media and interpersonal sources such as parents and peers has been shown to predict the onset of binge eating in adolescent girls (Stice 2002). Similarly, parents' or peers' modeling of body image dissatisfaction or disordered eating behavior also predicts the onset of binge eating in adolescent girls (Stice 2002). Interpersonal theories of binge eating emphasize the role of difficulties in close, interpersonal relationships with parents, friends, and/or romantic partners in triggering and/or maintaining binge eating patterns.

In addition to these more direct effects on binge eating, perceived pressure to be thin from relationships or the media may indirectly impact binge eating in a number of ways. Affective theories posit that perceived pressure to be thin may lead to negative affect, which in turn triggers binge eating as an attempt to alleviate emotional distress. Consistent with this theoretical perspective, youth (ages 8–13 years) with LOC eating have been shown to report more maladaptive emotion regulation strategies than youth without LOC (Czaja et al. 2009). Although binge or LOC eating may temporarily alleviate negative affect, such eating patterns ultimately are not effective in coping with distress, and binge or LOC eating behaviors may be perpetuated. As another indirect effect, perceived pressure to be thin has been posited to lead to idealization of the ultra-thin ideal and body image dissatisfaction, which in turn promote dieting. Dietary restraint theory proposes that dieting, defined as a conscious attempt to restrict caloric intake in order to change body weight or shape, is a trigger for binge eating (Polivy & Herman 1985). From a cognitive-behavioral psychology perspective, dieting would likely trigger a disinhibited response over eating when dieting rules are at all violated, especially when one holds rigid rules about intake. Among children and adolescents, self-reported dieting has also been shown to be associated with both symptoms of eating disorders and weight gain (Stice et al. 1999; Field et al. 2003; Tanofsky-Kraff et al. 2006). Yet, limited work has examined the direct effects of dieting on binge or LOC eating specifically in youth.

It is possible that dietary restraint and cognitive-behavioral models might be more relevant for those susceptible to BN as compared with BED. Indeed, there is a significant percentage of overweight children who binge eat and who have never dieted (Claus et al. 2006). Interestingly, in a sample of overweight children 6–13 years of age, 25.7% reported a history of both LOC eating and dieting, among whom two-thirds reported that LOC preceded dieting (Tanofsky-Kraff et al. 2005a). These data suggest the presence of additional factors that might predispose youth to LOC or binge eating. Bolstering this possibility, family and twin studies suggest that binge eating is moderately heritable (Javaras et al. 2008; Klump et al. 2007). Recent genetic and neuroimaging investigations in

adults also provide very preliminary evidence that LOC or binge eating could be related to genetically influenced, systematic differences in neural networks relevant for processing food reward and regulation of appetite, satiety, and mood (Davis et al. 2009). Available evidence does not at present suggest that abnormalities in the peripheral humoral signals for hunger or satiety are involved in the pathogenesis of binge eating behaviors (Geliebter et al. 2004).

139.3.4 Binge Eating and LOC Eating Summary

- Binge and LOC eating are disinhibited eating behaviors reported by a substantial percentage of overweight youth.
- Binge and LOC eating are risk factors for obesity; both have been shown to predict excess weight and adiposity in youth.
- The onset and maintenance of binge and LOC eating are likely influenced by a variety of genetic, social, and psychological factors.

139.4 Emotional Eating

139.4.1 Emotional Eating and Body Weight

Emotional eating refers to consuming food in an attempt to cope with transient or enduring negative emotions. Among adults, negative affect is the most commonly cited trigger for binge eating; in children and adolescents, emotional eating is also associated with LOC or binge eating (Goossens et al. 2007; Tanofsky-Kraff et al. 2007b). However, emotional eating can occur in the absence of experiencing LOC over eating. Among nontreatment-seeking children and adolescents aged 8–18 years, over 50% reported eating in response to emotions (Tanofsky-Kraff et al. 2007b). Very limited pediatric research has examined the link between emotional eating and body weight, and the available evidence for its association with risk for obesity is mixed. One cross-sectional study found that self-reported emotional eating was associated with overweight status in 9–12-year-old children (Braet & van Strein 1997). However, other cross-sectional studies have not found a relationship between children's or adolescents' emotional eating and body weight (Tanofsky-Kraff et al. 2007b). Although a few laboratory studies have reported a main effect of negative (versus neutral) mood induction on greater observed food intake in adults, the majority of such studies report no significant main effects (Stice 2002). Adults who report excessive restraint over eating have been shown to be vulnerable to greater intake when stressed (Heatherton et al. 1991; Tanofsky-Kraff et al. 2000). However, what moderating factors may serve to make certain youth vulnerable to overeating in response to negative affect requires further investigation. To our knowledge, no studies to date have prospectively examined the impact of emotional eating on changes in body weight in youth.

139.4.2 Etiology of Emotional Eating

By definition, emotional eating is precipitated by transitory or chronic experiences of negative affect. However, there is a wide variety of possible ways to cope with negative affect, suggesting that genetic and/or psychosocial factors may predispose particular individuals to respond to negative affect by eating.

Affective theories of disinhibited eating posit that food is often sought to alleviate or provide comfort from negative affective states. Temporary alleviation of negative affect while eating may serve to negatively reinforce emotional eating episodes. Psychologically, binge eating has been suggested to temporarily reduce negative affect by serving as an "escape" from self-awareness (Heatherton & Baumeister 1991); but also, physiologically, food consumption influences the 5-HT (serotonin) system, implicated in mood (Steiger et al. 2005), such that emotional eating may temporarily enhance mood via a physiological pathway.

139.4.3 Emotional Eating Summary

- Emotional eating is a frequent component of binge or LOC eating episodes but also may occur in the absence of experiences of LOC.
- It is undetermined whether emotional eating in and of itself confers risk for excess weight gain.
- In theory, a propensity for emotional eating may promote excess intake and a positive energy balance, but much further research is needed to test this hypothesis.

139.4.4 Eating in the Absence of Hunger (EAH)

139.4.5 EAH and Body Weight

Eating in the absence of hunger refers to eating in response to the presence of palatable foods in the absence of hunger. It has been proposed that EAH is best measured by directly observing children's actual ad libitum energy intake following the consumption of a meal that induces fullness. Observations of EAH in carefully controlled laboratory settings reveal that girls 5 and 7 years of age who consumed large amounts of snack foods in the absence of hunger were 4.6 times more likely to be overweight (Fisher & Birch 2002). Similarly, in a large sample of Hispanic girls and boys 4–19 years of age, youth who displayed high levels of EAH (above the sample median) had a 50% greater likelihood of being overweight, after adjustment for age and sex (Fisher et al. 2007). Investigations of EAH in settings outside the laboratory yield similar results. After a normal classroom lunch, preschoolers' consumption of snacks was positively associated with their weight to height ratio (Cutting et al. 1999). This relationship was only observed among girls in the study (Cutting et al. 1999), whereas other studies of EAH outside the laboratory have found the relationship for boys. For example, in several studies of children between 7 and 13 years of age, snack intake as measured after a school meal or at home was positively associated with boys' BMI standard scores or overweight status, whereas the relationship did not reach significance for girls (Hill et al. 2008; Moens & Braet 2006).

Although there are limited data on the prevalence of EAH in youth, most studies find that more than two-thirds of a given sample of children or adolescents display this behavior to at least some degree (Moens & Braet 2006). Few longitudinal studies of EAH have been undertaken. In an early childhood cohort of Caucasian girls studied at ages 5, 7, and 9 years, EAH was observed to increase with age (Birch et al. 2003). At age 5, girls consumed on average 125 ± 8 kcal ($M \pm SD$) in the absence of hunger, 174 ± 9 kcal at age 7, and 225 ± 11 kcal by age 9, which constituted approximately 7%, 9%, and 11% of age- and sex-specific daily energy needs, respectively (Birch et al. 2003). In a sample of Hispanic children and adolescents 4–19 years of age (11.75 ± 0.2), each 1-year increase in age was

associated with eating an additional, approximate 40 kcal more in the absence of hunger, after accounting for sex, total energy expenditure, and overweight status (Fisher et al. 2007). Further, EAH predicted weight gain a year later after adjusting for age, sex, and puberty, but the effect was attenuated (p = 0.17) after accounting for initial BMI status (Butte et al. 2007). Additional study of the role that EAH may play in promoting excess weight gain in youth is warranted. In particular, very little work has examined EAH in adolescents. It is possible that EAH may be most likely to exert an effect on weight gain at specific developmental periods (e.g., puberty) during which youth experience rapid and substantial physical growth, and significant interindividual variations in weight gain are expected.

139.4.6 Etiology of EAH

An initial family study of EAH as assessed in the laboratory suggests that EAH is a moderately heritable, observable behavior (heritability of 0.44–0.50). This estimate is similar to that of other eating behaviors and attitudes such as self-reported dietary restraint and perceived disinhibition over eating (de Castro & Lilenfeld 2005; Provencher et al. 2005; Wade et al. 1999) and illustrates that there are both genetic and environmental factors influencing phenotypic variation in EAH.

Five-year-old boys at high risk for obesity, based on maternal prepregnancy weight and child's weight status, were found to be over twice as likely to eat large amounts in the absence of hunger than low risk boys (Faith et al. 2006). In a prospective study tracking girls from age 5 to 13 years, girls who had two overweight parents displayed higher levels of EAH at every age and showed the largest increases in EAH over time compared with girls with only one overweight parent or no overweight parent (Francis et al. 2007). Such data suggest familial influences on EAH via a combination of polygenetic risk factors and environmental factors such as social modeling of disinhibited eating behavior. Although much remains to be determined about genetic influences on EAH, a recent study found that children 4–5 years of age who had risk polymorphisms in the rs9939609 SNP of the *FTO* gene (known to be associated with obesity) ate more snack foods after a school meal (Wardle et al. 2009). These data are intriguing but require replication with larger samples and more controlled eating circumstances (e.g., serving children a standardized meal prior to the EAH paradigm).

Available data also support a role for parental feeding practices in relation to children's EAH. Among young girls (age 5), maternal restriction of daughters' intake has been shown to predict increases in EAH over 2–4 years (Fisher & Birch 2002; Birch et al. 2003). The relationship between maternal restriction and increases in EAH was strongest when either daughter or mother was overweight (Birch et al. 2003; Francis & Birch 2005). Therefore, parental feeding practices very likely interact with real concerns about a child's weight status. However, overly restrictive efforts to control children's food intake may potentially produce iatrogenic effects that lead children to eat even more in the absence of hunger.

139.4.7 EAH Summary

- EAH may represent a behavioral phenotype associated with children's risk for overweight.
- Further prospective investigations are required to determine the impact of EAH on excess weight gain.
- Preliminary data support a role for familial influences on EAH, via both genetic (e.g., *FTO*) and environmental (e.g., social modeling or feeding practices) factors.

139.5 Similarities and Differences Among Disinhibited Eating Behaviors

All forms of disinhibited eating behaviors in youth share in common a lack of reliance on physiological cues for hunger and fullness to determine initiation and/or termination of food intake. Therefore, in theory, disinhibited eating behaviors may share a common pathophysiology of impaired awareness, recognition, and/or registration of appetitive cues; alternatively (but not mutually exclusive), such behaviors might reflect a common susceptibility to reliance on external or emotional cues to determine intake.

Congruent with this perspective, the existing data point to overlaps among binge or LOC eating, emotional eating, and EAH in youth (Tanofsky-Kraff et al. 2007b; Tanofsky-Kraff et al. 2008). We propose that disinhibited eating behaviors are likely to be organized in a pyramidal fashion (Fig. 139.2), such that binge eating occurs in the smallest subset of youth, LOC eating is slightly more common, emotional eating occurs with the next greatest frequency, and EAH is the most common disinhibited eating behavior in youth. Also important to this conceptualization is that behaviors at the top of the pyramid (i.e., binge or LOC eating) commonly involve behaviors in the bottom half of the pyramid (i.e., emotional eating or EAH); however, emotional eating and EAH do not necessarily involve feelings of LOC over eating or unambiguous overconsumption. Behaviors are ordered from bottom to top in increasing likelihood of having accompanying psychological distress, such that binge eating is perceived as the most pathological. Similarly, based upon our existing knowledge, we tentatively posit that the combination of having more than one type of disinhibited eating is likely to be related to greater risk for psychological problems, and potentially excessive weight gain. For example, the combination of both experiences of LOC or binge eating and high levels of negative affect appears to be related to worse psychological correlates for youth (Goldschmidt et al. 2008).
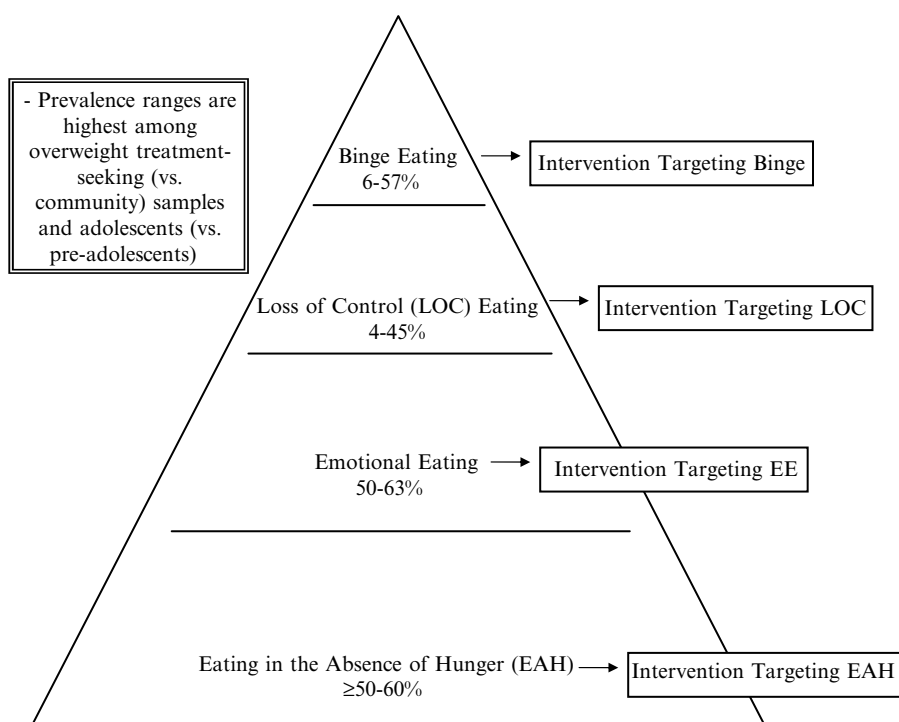
Fig. 139.2 Pyramid conceptualization of disinhibited eating behavior and targets for intervention

Yet, whether such co-morbidity is also tied to risk for excess weight gain in youth and subsequent obesity is unclear.

We do not yet have a full understanding of the age-span and time course for the onset and development of disinhibited eating behaviors. EAH has been observed in children as young as preschool, yet it has also been shown to increase with age. Binge eating primarily emerges in adolescence. However, we believe that preadolescent youth may manifest symptoms of binge eating such as LOC eating, perhaps prior to developing into full binge episodes. Both preadolescent and adolescent youth report emotional eating; however, its developmental course and implications are not well understood. Disinhibited eating behaviors also may be more common among girls versus boys (Ackard et al. 2003), although sex differences may not emerge until adolescence.

139.5.1 Similarities and Differences Summary

- Disinhibited eating behaviors share a reliance on external or emotional cues to regulate food intake rather than utilizing physiological signals of hunger and fullness to govern eating behavior.
- Binge eating may be the most pathological type of disinhibited eating behavior, especially as it relates to risk for psychological problems and excess body weight gain; the combination of experiencing multiple types of disinhibited eating behaviors may also be of significance for health outcomes.
- Disinhibited eating behaviors occur in preadolescent and adolescent youth, with the frequency and severity increasing during adolescence. We still have much to learn about the onset and developmental time course of different types of disinhibited eating behaviors.

139.6 Assessment of Disinhibited Eating

A range of assessment techniques are available for measuring disinhibited eating behaviors in youth (Tables 139.4 and 139.5). As displayed in Table 139.4, a number of self-report and parent-report questionnaires exist for measuring binge eating, LOC eating, emotional eating, and EAH. The principal

Table 139.4   Questionnaire assessment of disinhibited eating

Abbreviation	Questionnaire
BES	Binge Eating Scale (Gormally et al. 1982)
CEBQ	Children's Eating Behavior Questionnaire (Wardle et al. 2001)
DEBQ	Dutch Eating Behavior Questionnaire (van Strein et al. 1986)
DEBQ-C	Dutch Eating Behavior Questionnaire for Children (van Strein and Oosterveld 2008)
DEBQ-P	Dutch Eating Behavior Questionnaire – Parent Version (Braet and van Strein 1997)
EAH-C	Eating in the Absence of Hunger Questionnaire – Child Version (Tanofsky-Kraff et al. 2008)
EAH-P	Eating in the Absence of Hunger Questionnaire – Parent Version
EDE-Q	Eating Disorder Examination – Questionnaire (Fairburn and Beglin 1994)
EES-C	Emotional Eating Scale, Adapted for Children (Tanofsky-Kraff et al. 2007b)
QEWP-A	Questionnaire on Eating and Weight Patterns – Adolescent Version (Johnson et al. 1999)
QEWP-P	Questionnaire on Eating and Weight Patterns – Parent Version (Johnson et al. 1999)
YEDE-Q	Youth Eating Disorder Examination – Questionnaire (Goldschmidt et al. 2007)

Reliable and well-validated questionnaires exist for assessing aspects of disinhibited eating behavior in children and adolescents

Table 139.5 Overview of tools for assessment of disinhibited eating in children and adolescents

Assessment	Binge or LOC eating	Emotional eating	EAH
Questionnaire youth self-report	QEWP-A EDE-Q, YEDE-Q BES	EES-C DEBQ, DEBQ-C	EAH-C
Questionnaire parent-report	QEWP-P	DEBQ-P CEBQ	EAH-P
Semi-structured interview	EDE, ChEDE C-BEDS SCID-BN, BED modules	SPEEI	SPEEI
Observation	Let yourself go and eat as much as you want	Mood induction prior to measured food intake	Measured snack intake after serving a meal

Methods for assessing disinhibited eating in children and adolescents include youth self-report on questionnaires, parent report on questionnaires, semi-structured interviews, and observations of children's eating

EDE Eating Disorder Examination (Fairburn & Cooper), *ChEDE* Eating Disorder Examination Adapted for Children (Bryant et al. 1996), *C-BEDS* Children's Binge Eating Disorder Scale (Shapiro et al. 2007), *SCID* Structured Clinical Interview for the Diagnosis of DSM-IV Disorders, Bulimia Nervosa, and Binge Eating Disorder Modules (First et al. 1997; Spitzer et al. 1995), *SPEEI* Standard Pediatric Eating Episode Interview (Tanofsky-Kraff et al. 2007a), Questionnaire abbreviations are described in Table 139.4

advantages of questionnaire instruments are that they are low in cost and easy to administer, score, and interpret. Conversely, drawbacks of self-report measures of eating behavior include evidence that youth, especially those who are overweight, frequently underestimate food intake (Fisher et al. 2000). Parents also tend to underreport their children's intake (Baranowski et al. 1991). Further, youth and parents tend to show little agreement on disinhibited eating behaviors such as binge eating (Steinberg et al. 2004). Given these limitations, observational assessments of actual energy intake are often desirable.

Semi-structured interview methods comprise another means of assessing disinhibited eating in youth (Table 139.5). Interviews include the widely used and well-validated Eating Disorder Examination (EDE; ≥ 14 years of age) (Fairbun & Cooper 1993) and the Eating Disorder Examination Adapted for Children (ChEDE; <14 years of age) (Bryant et al. 1996). The Children's Binge Eating Disorder Scale (C-BEDS) is a brief, structured, interviewer-administered scale developed to screen for symptoms of BED in children (aged 5–13 years) (Shapiro et al. 2007). Also, the semi-structured Standard Pediatric Eating Episode Interview (SPEEI) was recently developed to assess detailed information about eating episodes among children of all ages (Tanofsky-Kraff et al. 2007a). Interview methods have the advantage of being able to probe or query youth's specific behaviors and thoughts and feelings surrounding eating episodes. Potential limitations include time constraints, interviewer training, lack of anonymity, and social desirability.

Finally, observations of disinhibited eating behavior can be conducted in a controlled setting such as the laboratory or a clinic or in children's natural environment such as at school or at home. Although observational measures are often neither feasible nor readily transferable to clinicians working with youth and families in the community, such measurements have been shown to be valid indicators of children's eating (Tanofsky-Kraff et al. 2007c). In our own lab, for example, we have assessed binge and LOC eating by asking youth to "let yourself go and eat as much as you want" from a multi-item food array (>9,000 kcal) (Mirch et al. 2006; Tanofsky-Kraff et al. 2009a) (Fig. 139.3). Emotional eating in the laboratory can be assessed by inducing a temporary mood state and subsequently observing intake (Goldschmidt et al. 2009). Finally, EAH is frequently observed by serving children a meal and asking them to eat until they are no longer hungry, and

Fig. 139.3 Multi-item food array for use in laboratory studies of disinhibited eating (>9,000 kcal). Foods include white bread, wheat bread, Kaiser rolls, ham, turkey, American cheese, chicken nuggets, peanut butter, grape jelly, tomatoes, lettuce, carrots, tortilla chips, jelly beans, M&M's, bananas, grapes, oranges, oreos, vanilla wafers, pretzels, mayonnaise, mustard, BBQ sauce, mild salsa, ranch dressing, 2% milk, lemonade, water, and apple juice

then subsequently measuring intake of highly palatable snack foods (Fisher & Birch 2002). The benefits of laboratory studies include the ability to control the exact conditions, directly observe eating behaviors, and precisely measure energy intake. There is some concern that laboratory studies may not elicit eating behaviors typical of natural environments; however, most participants in prior studies describe their behavior in the lab as typical of their ordinary eating behavior (Tanofsky-Kraff et al. 2007c).

An important consideration for assessment of disinhibited eating behavior in youth is that an ideal and thorough assessment may require measures from multiples sources (e.g., children and parents), who frequently have different, unique perspectives of a target child's eating behavior. Additionally, typically low correspondence has been found among observational assessments, youth report on questionnaire, parent report on questionnaire, and interviews assessing disinhibited eating behavior (Tanofsky-Kraff et al. 2005b). We do not yet have enough evidence to suggest that one method is superior to another, simply that the minimal shared variance highlights the importance of gathering assessment of disinhibited eating behavior via multiple methods.

139.6.1 Assessment of Disinhibited Eating Summary

- Approaches for the assessment of disinhibited eating in youth include children's and parents' reports on questionnaires, semi-structured interviews, and observations of children's eating behavior.
- There are advantages and disadvantages to each assessment technique and the methods for assessing disinhibited eating in youth tend to show limited agreement.

- Structured interviews are currently considered the "gold standard" for assessing disinhibited eating, but further empirical data are needed to validate the criteria employed.
- The most thorough assessment of disinhibited eating in youth would include reliance on as many sources (i.e., children and parents) and methods (i.e., questionnaires, interviews, observations) as possible.

139.7 Prevention and Treatment of Disinhibited Eating

Given that current treatments for obesity have met with limited long-term success, there has been an increased recognition that "one size may not fit all." In particular, interventions may need to be tailored to address subsets of overweight or at-risk for overweight individuals whose disinhibited eating problems serve to maintain or enhance their weight problems. Data from adult studies of overweight individuals with and without binge eating problems suggest that disinhibited eating may interfere with the efficacy of standard-of-care obesity treatment. In a meta-analysis of studies examining the impact of binge eating or BED on weight loss treatment outcome (Blaine & Rodman 2007), individuals with BED fared worse during treatment, with individuals having BED losing significantly less weight than non-binge eaters. In a recent study of over 5,000 adults with type II diabetes mellitus, the influence of binge eating at both baseline and post-treatment on weight loss treatment outcome was examined (Gorin et al. 2008). Participants who either never reported binge eating or reported ceasing to binge eat lost significantly more weight compared with those who persisted or commenced binge eating over the course of treatment. Studies investigating the impact of disinhibited eating behavior on weight loss treatment outcomes in youth are greatly needed.

One of the most exciting current avenues of research involves targeting disinhibited eating behavior for the treatment of obesity. The majority of available data come from randomized controlled trials of adults with BED. Cognitive-behavioral treatment (CBT) approaches, which combine cognitive therapy and behavioral strategies for modifying binge eating, diet, and exercise, have shown efficacy for reducing binge eating and weight among adults with BED (National Institute for Clinical Excellence 2004). Interpersonal psychotherapy (IPT) for adults with BED has also shown promising results (Wilfley et al. 2002). IPT targets reductions in binge eating and weight by addressing the interpersonal problems that maintain binge eating behaviors. Among adults, some pharmacological treatments also have been shown to be more efficacious than placebo in producing short-term reductions in binge eating and inducing small weight loss (Reas & Grilo 2008).

Because available treatments primarily have been shown to induce weight stabilization or modest weight loss rather than significant, sustained weight loss over time in adults with BED, very recent, novel research has turned to the targeting of disinhibited eating behaviors in youth for the prevention of adult obesity. Although designed as an intervention for binge eating, an internet-facilitated CBT program was reported to produce greater reductions in BMI and binge eating compared with a wait-list control (Jones et al. 2008). Another program that holds promise involves administering group IPT to girls at risk for adult obesity by virtue of having LOC eating and being above-average weight (Tanofsky-Kraff et al. 2007d).

Although most interventions have focused on binge or LOC eating, a small body of literature suggests that interventions targeting emotional eating or EAH might also hold promise for obesity treatment or prevention. Appetite Awareness Training (Craighead & Allen 1995) involves training individuals to regulate intake by paying attention to internal sensations for hunger and fullness rather than other eating triggers or cues (e.g., emotional). An age-appropriate adaptation piloted for youth in middle childhood showed that the intervention group had greater short-term weight and BMI reductions compared with a wait-list control (Bloom et al. 2005). It has also been shown that EAH

is modifiable with very young children. A 6-week intervention delivered in preschools produced improvements in children's observed self-regulation of intake (Johnson 2000).

139.7.1 Prevention and Treatment of Disinhibited Eating Summary

- Disinhibited eating behaviors, particularly binge eating, have been shown to interfere with standard-of-care behavioral weight loss programs among adults.
- Interventions targeting reductions in disinhibited eating behavior among overweight adults with BED have been shown to be somewhat helpful in reducing binge eating and inducing short-term weight loss or weight maintenance.
- More research is needed to investigate whether targeting the emergence of disinhibited eating behaviors in children or adolescents could serve to prevent youth from gaining too much weight as they grow.

139.8 Overall Summary and Future Research Directions

Disinhibited eating behaviors – referring to binge or LOC eating, emotional eating, and EAH – are prevalent among youth. Emerging evidence, particularly for binge and LOC eating, points to a role for their impact on excessive weight gain. There is a strong need for more longitudinal research, especially on emotional eating and EAH, to examine whether these disinhibited eating behaviors are prospective risk factors for obesity. Also important is to understand the etiology of disinhibited eating in youth. Available data suggest a role for both biological or genetic factors, as well as an impact of environmental influences. How these various factors interact to produce disinhibited eating behavioral phenotypes is a key avenue for future study.

139.9 Applications to Other Areas of Health and Disease

Knowledge of disinhibited eating behaviors' role in the etiology or maintenance of obesity has important implications for a wide range of health professionals who act to prevent and treat obesity. It will be particularly important to disentangle the impact of disinhibited eating behavior on standard-of-care weight loss interventions such that treatments can be tailored according to individual needs and what is most likely to be successful for a given youth.

Summary Points

- Disinhibited eating behaviors, referring to a range of eating behaviors that involve a lack of restraint over food intake, include binge or loss of control (LOC) eating, emotional eating, and eating in the absence of hunger (EAH).
- Disinhibited eating behaviors are prevalent among youth.
- Disinhibited eating, especially binge or LOC eating, may play a role in promoting excessive weight gain in children and adolescents.
- In theory, biological or genetic and environmental factors influence the emergence and course of disinhibited eating behaviors in youth.
- A promising new avenue of investigation focuses upon interventions targeting pediatric disinhibited eating behaviors in an effort to prevent or treat obesity.

Key Terms

Binge eating: Overeating while experiencing a lack of control over what or how much is being eaten.

Dieting: Conscious attempts to restrict caloric intake in order to change body weight or shape.

Disinhibited eating: Range of eating behaviors involving a lack of restraint over food intake.

Eating in the absence of hunger (EAH): Eating in response to the presence of palatable foods in the absence of physical hunger.

Emotional eating: Consuming food in an attempt to cope with transient or enduring negative emotions.

Loss of control (LOC) eating: Experiencing a lack of control over eating regardless of the amount of food ingested.

Overweight: BMI (kg/m^2) equal to or exceeding the Center for Disease Control's 95th percentile standard for age and sex.

References

Ackard DM, Neumark-Sztainer D, Story M, Perry C. Pediatrics. 2003;111:67–74.

American Psychiatric Association. 4th ed. Washington, DC; 2000.

Baranowski T, Sprague D, Baranowski JH , Harrison JA. J Am Diet Assoc. 1991;91:669–74.

Birch LL, Fisher JO, Davison KK. Am J Clin Nutr. 2003;78:215–20.

Blaine B, Rodman J. Eat Weight Disord. 2007;12:54–60.

Bloom T, Sharpe L, Heriot S, Zucker N, Craighead L. Children's Appetite-Awareness Training (CAAT): a cognitive-behavioural intervention in the treatment of childhood obesity. WHO Expert Meeting on Childhood Obesity, Kobe, Japan; 2005.

Braet C, van Strein T. Behav Res Ther. 1997;35:863–73.

Britz B, Siegfried W, Ziegler A, Lamertz C, Herpertz-Dahlmann BM, Remschmidt H, Wittchen HU, Hebebrand J. Int J Obes Relat Metab Disord. 2000;24:1707–14.

Bryant-Waugh RJ, Cooper PJ, Taylor CL, Lask BD. Int J Eat Disord. 1996;19:391–7.

Butte NF, Cai G, Cole SA, Wilson TA, Fisher JO, Zakeri IF, Ellis KJ, Comuzzie AG. Am J Clin Nutr. 2007;85:1478–85.

Claus L, Braet C, Decaluwe V. Int J Eat Disord. 2006;39:721–8.

Craighead LW, Allen HN. Cogn Behav Pract. 1995;2:249–70.

Crow S, Eisenberg ME, Story M, Neumark-Sztainer D. J Adolesc Health. 2006;38:569–74.

Csabi G, Tenyi T, Molnar D. Eat Weight Disord. 2000;5:43–5.

Cutting TM, Fisher JO, Grimm-Thomas K, Birch LL. Am J Clin Nutr. 1999;69:608–13.

Czaja J, Rief W, Hilbert A. Int J Eat Disord. 2009;42:356–62.

Davis CA, Levitan RD, Reid C, Carter JC, Kaplan AS, Patte KA, King N, Curtis C, Kennedy JL. Obesity. 2009; 17:1220–5.

de Castro JM, Lilenfeld LR. Nutrition. 2005;21:446–55.

Fairburn CG, Beglin SJ. Int J Eat Disord. 1994;16:363–70.

Fairburn CG, Cooper Z. The eating disorder examination, ed 12. In: Fairburn CG, Wilson GT, editors. Binge eating: nature, assessment and treatment. New York: Guilford; 1993. p. 317–60.

Faith MS, Berkowitz RI, Stallings VA, Kerns J, Storey M, Stunkard AJ. Obesity 2006;14:131–8.

Field AE, Colditz GA, Peterson KE. Ann N Y Acad Sci. 1997;817:359–60.

Field AE, Camargo CA, Jr., Taylor CB, Berkey CS, Frazier AL, Gillman MW, Colditz GA. J Am Acad Child Adolesc Psychiatry. 1999;38:754–60.

Field AE, Austin SB, Taylor CB, Malspeis S, Rosner B, Rockett HR, Gillman MW, Colditz GA. Pediatrics. 2003;112:900–6.

First M, Spitzer R, Gibbon M, Williams J. Structured Clinical Interview for DSM-IV Axis I Disorders, Research Version, Patient Edition. Biometrics Research, New York State Psychiatric Institute, New York; 1997.

Fisher JO, Birch L. Am J Clin Nutr. 2002;76:226–31.

Fisher JO, Johnson RK, Lindquist C, Birch LL, Goran MI. Obes Res. 2000;8:597–603.

Fisher JO, Cai G, Jaramillo SJ, Cole SA, Comuzzie AG, Butte NF. Obesity. 2007;15:1484–95.

Francis LA, Birch LL. Health Psychol. 2005;24:548–54.

Francis LA, Ventura AK, Marini M, Birch LL. Obesity. 2007;15:1544–53.

Geliebter A, Yahav EK, Gluck ME, Hashim SA. Physiol Behav. 2004;81:735–40.

Glasofer DR, Tanofsky-Kraff M, Eddy KT, Yanovski SZ, Theim KR, Mirch MC, Ghorbani S, Ranzenhofer LM, Haaga D, Yanovski JA. J Pediatr Psychol. 2007;32:95–105.

Goldschmidt AB, Doyle AC, Wilfley DE. Int J Eat Disord. 2007;40:460–7.

Goldschmidt AB, Tanofsky-Kraff M, Goossens L, Eddy KT, Ringham R, Yanovski SZ, Braet C, Marcus MD, Wilfley DE, Yanovski JA. Behav Res Ther. 2008;46:777–87.

Goldschmidt AB, Tanofsky-Kraff M, Wilfley DE. A laboratory-based study of mood and eating behavior in over-weight girls. Paper presented at Pediatric Academic Societies. Baltimore; 2009.

Goossens L, Braet C, Decaluwe V. Behav Res Ther. 2007;45:1–9.

Gorin AA, Niemeier HM, Hogan P, Coday M, Davis C, DiLillo VG, Gluck ME, Wadden T, West DS, Williamson DA, Yanovski SZ. Arch Gen Psychiatry. 2008;65:1447–55.

Gormally J, Sionag B, Datson S, Rardin D. Addict Behav. 1982;7:47–55.

Heatherton TF, Baumeister RF. Psychol Bull. 1991;110:86–108.

Heatherton TF, Herman CP, Polivy J. J Pers Soc Psychol. 1991;60:138–43.

Hill C, Llewellyn CH, Saxton J, Webber L, Semmler C, Carnell S, van Jaarsveld CH, Boniface D, Wardle J. Int J Obes. 2008;32:1499–505.

Hill JO, Peters JC. Science. 1998;280:1371–4.

Institutes of Medicine. Preventing childhood obesity: health in the balance. Washington, DC; 2005.

Isnard P, Michel G, Frelut ML, Vila G, Falissard B, Naja W, Navarro J, Mouren-Simeoni MC. Int J Eat Disord. 2003;34:235–43.

Israel AC, Ivanova MY. Int J Eat Disord. 2002;31:424–9.

Javaras KN, Laird NM, Reichborn-Kjennerud T, Bulik CM, Pope HG Jr, Hudson JI. Int J Eat Disord. 2008;41:174–9.

Johnson SL. Pediatrics 2000;106:1429–35.

Johnson WG, Grieve FG, Adams CD, Sandy J. Int J Eat Disord. 1999;26:301–14.

Jones M, Luce KH, Osborne MI, Taylor K, Cunning D, Doyle AC, Wilfley DE, Taylor CB. Pediatrics. 2008;121:453–62.

Klump KL, Burt SA, McGue M, Iacono WG. Arch Gen Psychiatry. 2007;64:1409–15.

Lamerz A, Kuepper-Nybelen J, Bruning N, Wehle C, Trost-Brinkhues G, Brenner H, Hebebrand J, Herpertz-Dahlmann B. J Child Psychol Psychiatry. 2005;46:385–93.

Mirch MC, McDuffie JR, Yanovski SZ, Schollnberger M, Tanofsky-Kraff M, Theim KR, Krakoff J, Yanovski JA. Am J Clin Nutr. 2006;84:732–8.

Moens E, Braet C. Behav Res Ther. 2006;45:1357–68.

Morgan C, Yanovski S, Nguyen T, McDuffie J, Sebring N, Jorge M, Keil M, Yanovski J. Int J Eat Disord. 2002;31:430–41.

Neumark-Sztainer D, Story M, French SA, Hannan PJ, Resnick MD, Blum RW. Obes Res. 1997;5:237–49.

National Institute for Clinical Excellence (NICE). Eating disorders—Core interventions in the treatment and management of anorexia nervosa, bulimia nervosa, and related eating disorders. NICE Clinical Guideline No 9, London; 2004.

Ogden CL, Carroll MD, Flegal KM. JAMA. 2008;299:2401–5.

Polivy J, Herman CP. Am psychol. 1985;40:193–201.

Provencher V, Perusse L, Bouchard L, Drapeau V, Bouchard C, Rice T, Rao DC, Tremblay A, Despres JP, Lemieux S. Obes Res. 2005;13:1624–9.

Reas DL, Grilo CM. Obesity 2008;16:2024–38.

Shapiro JR, Woolson SL, Hamer RM, Kalarchian MA, Marcus MD, Bulik CM. Int J Eat Disord. 2007;40:82–9.

Spitzer R, Williams J, Gibbon M. Structured Clinical Interview for DSM-IV Axis I Disorders, Patient Edition. Biometrics Research, New York State Psychiatric Institute, New York; 1995.

Steiger H, Gauvin L, Engelberg MJ, Ying Kin NM, Israel M, Wonderlich SA, Richardson J. Psychol Med. 2005;35:1553–62.

Steinberg E, Tanofsky-Kraff M, Cohen ML, Elberg J, Freedman RJ, Semega-Janneh M, Yanovski SZ, Yanovski JA. Int J Eat Disord. 2004;36:183–94.

Stice E. Psychol Bull. 2002;128:825–48.

Stice E, Cameron RP, Killen JD, Hayward C, Taylor CB. J Consult Clin Psychol. 1999;67:967–74.

Stice E, Presnell K, Spangler D. Health Psychol. 2002;21:131–8.

Tanofsky-Kraff M. Binge eating among children and adolescents. In: Jelalian E, Steele R, editors. Handbook of child and adolescent obesity. New York: Springer; 2008. p. 41–57.

Tanofsky-Kraff M, Wilfley DE, Spurrell E. Int J Eat Disord. 2000;27:411–8.

Tanofsky-Kraff M, Yanovski SZ, Wilfley DE, Marmarosh C, Morgan CM, Yanovski JA. J Consult Clin Psychol. 2004;72:53–61.

Tanofsky-Kraff M, Faden D, Yanovski SZ, Wilfley DE, Yanovski JA. Int J Eat Disord. 2005a;38:112–22.

Tanofsky-Kraff M, Yanovski SZ, Yanovski JA. Eat Behav. 2005b;6:95–9.

Tanofsky-Kraff M, Cohen ML, Yanovski SZ, Cox C, Theim KR, Keil M, Reynolds JC, Yanovski JA. Pediatrics. 2006;117:1203–9.

Tanofsky-Kraff M, Goossens L, Eddy KT, Ringham R, Goldschmidt AB, Yanovski SZ, Braet C, Marcus MD, Wilfley DE, Olsen C, Yanovski JA. J Consult Clin Psychol. 2007a;75:901–13.

Tanofsky-Kraff M, Theim KR, Yanovski SZ, Bassett AM, Burns NP, Ranzenhofer LM, Glasofer DR, Yanovski JA. Int J Eat Disord. 2007b;40:232–40.

Tanofsky-Kraff M, Haynos AF, Kotler LA, Yanovski SZ, Yanovski JA. Curr Nutr Food Sci. 2007c;3:55–74.

Tanofsky-Kraff M, Wilfley DE, Young JF, Mufson L, Yanovski SZ, Glasofer DR, Salaita CG. Obesity. 2007d;15:1345–55.

Tanofsky-Kraff M, Ranzenhofer LM, Yanovski SZ, Schvey NA, Faith M, Gustafson J, Yanovski JA. Appetite. 2008;51:148–55.

Tanofsky-Kraff M, McDuffie JR, Yanovski SZ, Kozlosky M, Schvey NA, Shomaker LB, Salaita C, Yanovski JA. Am J Clin Nutr. 2009a;89:738–45.

Tanofsky-Kraff M, Yanovski SZ, Schvey NA, Olsen CH, Gustafson J, Yanovski JA. Int J Eat Disord. 2009b;42:26–30.

van Strien T, Oosterveld P. Int J Eat Disord. 2008;41:72–81.

van Strein T, Frijters JER, Bergers GPA, Defares PB. Int J Eat Disord. 1986;5:295–313.

Wade T, Martin NG, Neale MC, Tiggemann M, Treloar SA, Bucholz KK, Madden PA, Heath AC. Psychol Med. 1999;29:925–34.

Wardle J, Guthrie CA, Sanderson S, Rapoport L. J Child Psychol Psychiatry. 2001;42:963–70.

Wardle J, Llewellyn C, Sanderson S, Plomin R. Int J Obes. 2009;33:42–5.

Wilfley DE, Welch RR, Stein RI, Spurrell EB, Cohen LR, Saelens BE, Dounchis JZ, Frank MA, Wiseman CV, Matt GE. Arch Gen Psychiatry. 2002;59:713–21.

Yanovski J. Rev Endocr Metab Disord. 2001;2:371–83.

Chapter 140
Gender-Based Food Stereotypes Among Young Japanese

Atsushi Kimura, Yuji Wada, and Ippeita Dan

Abbreviations

IAT   Implicit Association Test
ANOVA   Analysis of Variance
RT   Reaction Time

140.1 Introduction

In the modern era, the consumption of food is not merely a means for intake of nutrients and energy for sustaining life. Beyond the sustenance role, food selection and eating behavior play important roles in our social lives and provide tools for communication, social interaction, and identity expression (Murcott 1983). People use a variety of criteria to conceptualize their everyday food choices and eating behaviors. As a social event, food consumption is influenced by various social and cultural values, and at an individual level, one may often possess stereotypes about food and eating behavior.

The purpose of this chapter is to provide a brief overview of gender-based food stereotypes, which constitute an intriguing aspect of eating stereotypes from the cultural perspective, and to explore the feasibility of introducing indirect measures for gender stereotypes toward food. Our focus on this topic is not intended to discount the critical role played by other major stereotypes, but rather we aim to introduce a novel approach in assessing a specific aspect of food stereotypes, which could be applicable to analyzing other facets as well. To acquire a comprehensive picture of eating stereotypes, we recommend the excellent review by Vartanian et al. (2007).

140.2 Stereotype As a Mediator of Eating Behavior

In the last few decades, several studies, mostly performed in Western countries, have started to reveal the existence of various food and eating stereotypes. A stereotype is defined as a commonly held belief about the characteristics of individuals, members of social groups, or objects (Table 140.1).

Y. Wada (✉)
Sensory & Cognitive Food Science Laboratory, National Food Research Institute,
2-1-12, Kannondai, Tsukuba, Ibaraki 305-8642, Japan
e-mail: yujiwd@affrc.go.jp; yuji_wada@nifty.com

Table 140.1 Key facts of stereotypes

- A stereotype is a commonly held belief about the characteristics of all members of several groups or categories (e.g., race, ethnicity, age, or gender). This concept was introduced into social psychology in the early 1920s.
- It is generalizations about individuals, objects, or events based on limited, sometimes inaccurate, but often easily available information. Stereotypical attitudes are often formed with no or limited contact with members of the stereotyped category and by second-hand information rather than first-hand experience.
- Some cognitive factors could play important roles in both formation and use of stereotypes (Hamilton 2005). For instance, stereotype can reduce the demand of information processing. By categorizing people or objects, we bypass the need to attend to each individual that we encounter. Categorization as a foundation of stereotype also distinguishes "us" from "them." This provides individuals some psychological benefits. In comparing our own group with some other "inferior" group, we can feel pride in belonging to our group.
- Stereotypes have positive and negative impacts on the stereotyped group (Macrae et al. 1996). An especially worrying aspect of stereotypes is that they tend to dehumanize people, placing all members of a group into a homogeneous category (e.g., "Catholics," "Asian," and "scientists").
- People have stereotypical attitudes toward particular foods (e.g., high-/low-fat foods, ethnic foods, genetically modified foods). Such food-related stereotypes further influence consumers' food selections and food product evaluations. People also have stereotypical attitudes toward others based on their food intake. Such food consumption stereotypes are usually judged based on what and how much a person eats (Vartanian et al. 2007).

This table summarizes key facts of the stereotype

People have stereotypical attitudes toward particular foods and eating behaviors. For example, people tend to categorize foods as good or bad. This was first described in people with eating disorders (Garner et al. 1982): anorexia nervosa patients classify carbohydrates, sugar, and meat as "bad" foods based on mythical beliefs. Such tendencies were later generalized to include people in the general population (Rozin 1986). The bad/good food stereotypes further affect people's judgment: eaters of the "good" or "bad" foods are viewed by others in association with good or bad moral values based on what they eat (Stein and Nemeroff 1995).

Stereotypes can also be associated with foods and eating habits in specific countries or regions. For example, children who live in the U.K. exhibit rejective responses to unfamiliar French meat dishes due to stereotypes such as, "the French eat frogs" (De Moura 2007). Moreover, recent studies have begun to reveal further impacts of food stereotypes on consumers' interpretations and behaviors. Oakes (2004) demonstrated that foods containing fat, sugar, and salt lead consumers to think that the foods are deficient in vitamins and minerals. Niva (2007) reported that consumers tend to think that functional foods are healthy but unsavory. Chambers et al. (2007) found that a stereotype among U.K. consumers that local food products are more expensive than imports may prevent them from buying local products. Hoogland et al. (2007) demonstrated that an organic logo on food packages provides consumers with a positive but expensive impression, producing only small net impacts on consumers' purchase intentions. Wansink et al. (2007) revealed that a wine with a favorable (new from California) label, served complementarily with a fixed-price meal to adult diners caused a significant increase in meal intake than the same wine with an unfavorable (new from North Dakota) label. These studies have clearly demonstrated that people form stereotypical attitudes toward some food categories and the stereotypes further influence consumers' food selections and food product evaluations.

140.3 Gender-Based Food Stereotypes in Western Countries

Among the stereotypes associated with food and eating, one of the most consistently observed is a gender stereotype, in which femininity and masculinity are primarily associated with specific foods. For example, U.S. college students categorized "toasted bagel with cream cheese" and "spaghetti

with tomato sauce" as feminine foods, while "flapjacks with syrup" and "broiled sirloin" were classified as masculine foods (Mooney and Lorenz 1997). In addition, certain foods enhance or diminish the feminine or masculine impression projected by the individuals who eat them: those individuals who are described as consuming feminine foods are evaluated as more feminine and less masculine than those described as consuming masculine foods, regardless of the gender of the evaluators (Mooney and Lorenz 1997).

In Western countries, association of femininity and masculinity with specific foods is often correlated with their profiles such as health value, caloric content and fat content, and further with good/bad classifications that arise from these profiles (e.g., Barker et al. 1999; Oakes 2004, 2005a,b; Stein and Nameroff 1995). In addition to types of food, there are also gender stereotypes toward the total amount of food ingested (see Vartanian et al. 2007 for review). Specifically, ingestion volume association with female targets is well studied, and many studies have reported that the ingestion of a small amount of food is significantly bound to femininity (Basow and Kobrynowicz 1993; Chaiken and Pliner 1987). Beyond a scientific interest, investigations of gender stereotypes are of great social importance because gender stereotypes not only influence impressions of femininity or masculinity for target individuals, but also produce further impressions, including personal qualities and likeability (Mooney et al. 1994; Mooney and Lorenz 1997).

140.4 Measuring Gender-Based Food Stereotypes Among Young Japanese

As described before, most studies on gender-based food stereotypes have been conducted in Western countries. On the other hand, there have been relatively few reports on gender-based food stereotypes in Asian countries. Cross-cultural perspective is important in the area of gender stereotype because socio-cultural factors are closely associated with gender-role pressure on food selection and eating behaviors (e.g., Hsu 1989). Thus, we explored gender-based food stereotypes among young Japanese (Kimura et al. 2009). In this section, we introduce the research outline for Kimura et al. (2009).

140.4.1 Measuring Femininity and Masculinity of Foods

Two separate experiments based on Mooney & Lorenz (1997) were conducted to identify foods for the feminine and masculine food categories among young Japanese (Table 140.2). To express food at a conceptual level, the names of dishes (e.g., prepared foods) were used throughout the studies.

In study 1, fourteen Japanese undergraduate and graduate students (eight females and six males; average age = 26.5 years; SD = 5.1) were asked to name at least five foods (dishes) that they perceived as very feminine or very masculine, respectively. As a result, 48 dishes were listed as feminine foods and 41 as masculine foods (average 6.21 responses (SD = 2.41) for feminine food and average 6.64 responses (SD = 2.01) for masculine food). Then, the 28 dishes that were named by more than two participants were advanced to the second study. The dishes that were named by the largest number of respondents were *cake* (named by 10 students) among feminine dishes, and *ramen* (Chinese noodle soup; named by 10 students) among masculine dishes.

In study 2, 22 Japanese undergraduate and graduate students (10 females and 12 males; average age = 22.4 years; SD = 1.5) were asked to categorize each of 28 dishes as feminine, masculine, or neutral (neither feminine nor masculine).

Table 140.2 Key features of Japanese food culture

- The term "traditional Japanese foods" basically means traditional Japanese-style meals which were developed around the seventeenth and eighteenth centuries.
- The masculine-evaluated foods listed in Table 140. 3 were incorporated into the Japanese diet around the late nineteenth to early twentieth centuries, and thus are categorized as early-modern traditional Japanese foods.
- A typical Japanese-style meal consists of rice, soup, vegetables, and fish or meat. Kamei et al. (2002) evaluated nutritional contents of take-out lunches supplied in Japan, and revealed that traditional Japanese-style meals were relatively good regarding total energy, fat–energy ratio, and lipid-related proportions than Western-style fast foods.
- While rice is the primary staple, several kinds of noodles (including *soba*, *udon*, and *ramen* (Chinese-noodle soup) and bread are also popular for light meals in contemporary Japan.
- Recently, the diet of Japanese has been rapidly changing to a Western style. In fact, the annual per capita consumption of rice dropped by nearly 30% from 88.0 kg in 1975 to 61.0 kg in 2006.

This table summarizes key features of the contemporary Japanese food culture

Table 140.3 Feminine/masculine foods among young Japanese

	Feminine foods		Masculine foods	
	Food name	Agreement rate	Food name	Agreement rate
1	Cake	1.00	*Gyu-don* (beef rice-bowl)	1.00
2	Fruit	0.95	*Ramen* (Chinese noodle soup)	0.95
3	Pudding	0.95	*Yakiniku* (grilled/barbecued meat)	0.95
4	Ice cream parfait	0.95	*Katsu-don* (breaded pork cutlet rice-bowl)	0.95
5	Pasta	0.86	*Tonkatsu* (deep-fried, breaded pork cutlet)	0.95
6	Salad	0.86	*Sutēki* (beef steak)	0.91
7	Ice cream	0.86	*Yakisoba* (pan-fried noodles)	0.86
8	*Ichigo* (strawberry)	0.86	*Yakitori* (grilled chicken)	0.82
9	Chocolate	0.86		
10	Cookie	0.77		

This table lists the most feminine-/masculine-evaluated foods among young Japanese. All the feminine and masculine dishes listed in this table were evaluated as feminine and masculine, respectively, by more than 75% of the raters, and none of them were evaluated as the opposite classification

140.4.2 Feminine-/Masculine-Evaluated Foods Among Young Japanese

Table 140.3 shows the dishes evaluated as the most feminine/masculine among young Japanese. All the feminine and masculine dishes listed in Table 140.3 were evaluated as feminine and masculine, respectively, by more than 75% of the raters, and none of them were evaluated as the opposite classification (e.g., none of the feminine foods were evaluated as masculine, and vice versa). The dishes which were most frequently evaluated as feminine/masculine foods in study 1 (*cake* for feminine, *ramen* for masculine) were also selected in the list of the most feminine and masculine dishes, respectively, in study 2.

Feminine foods among young Japanese could be categorized into low-fat foods, sweets, and fruits (Fig. 140.1). They are also categorized as Western foods (with the exception of strawberries). Such foods are usually expressed in *katakana* (the phonetic characters used to spell loan words brought into Japanese from other (typically Western) languages). Fruits can be expressed either in their native Japanese forms or as loan words (in *katakana*) in everyday Japanese. In the present study, they were presented as loan words.

The masculine foods, with the exception of beef steak, were incorporated into the Japanese diet around the late nineteenth to early twentieth centuries, and thus are categorized as early-modern traditional Japanese dishes (Fig. 140.2). However, beef steak is considered a Western food. These

Fig. 140.1 Samples of feminine foods. Examples of feminine foods selected in study 2 (pasta and salad)

Fig. 140.2 Samples of masculine foods. Examples of masculine foods selected in study 2**:** *katsu-don* (breaded pork cutlet rice-bowl) and *gyu-don* (beef rice-bowl)

foods are commonly expressed in *kanji* characters (Chinese characters; ideograms), *hiragana* (basic syllabary characters for expressing Japanese words; phonograms), *katakana*, or a mixture of all three. Most of the masculine foods could also be categorized as high fat.

140.4.3 Measuring Stereotypes Toward Food with the Indirect Attitude Measure

Traditionally, the measurement of stereotypical attitudes, including gender-related stereotypes, has been dependent on participants' responses of explicit attitudes (Mooney et al. 1994). However, explicit attitude measured in this way is subject to the risk of reflecting a skewed attitude flawed by self-presentation or social desirability biases (Greenwald et al. 2002).

To circumvent such plausible risks, indirect attitude measures such as the affective priming paradigm (e.g., Fazio et al. 1986) and the implicit association test (IAT; Greenwald et al. 1998) have gradually come into use as alternatives to direct measures. The former is sometimes called a semantic priming paradigm when semantic primes, rather than affective primes, are used (e.g., Macrae et al. 2002). The virtue of these techniques is that they are independent of a direct verbal report of the relevant topics being studied. Rather than asking participants directly about their attitudes on a certain topic, these techniques indirectly infer their attitudes by examining their response patterns (e.g., changes in response time) toward stimuli related to the topic.

Recently, affective/semantic priming paradigms have gradually come into use in studies on attitudes and preferences toward food and eating disorders (Czyzewska and Graham 2008; Lamote et al. 2004;

Roef et al. 2005), but their application to food and eating stereotypes has yet to be explored. Indirect measurements would be of great potential use in these research domains because attitude assessments in such a socially sensitive area may be substantially influenced by factors like social appeal and social desirability (Kimura et al. 2009).

Therefore, we also explored the feasibility of introducing indirect measures for the study of gender stereotypes toward food using a semantic priming paradigm: participants were primed with a food name and immediately after the priming, they were presented with a forename, as the target stimulus, and asked to decide whether the forename given was masculine or feminine. By doing so, the semantic association between foods and genders was estimated (Kimura et al. 2009), and the conformity between indirect and self-report attitudes was also considered.

140.4.4 Applying the Semantic Priming Task to Measure Gender-Based Food Stereotypes

In study 3, 37 Japanese undergraduate and graduate students (19 females; 18 males; average age = 24.5 years; SD = 2.1) were recruited to take part in a word discrimination task experiment. The experiment involved two subsequent sessions: the semantic priming task session and the self-report session for gender-based stereotypical attitudes toward food. The semantic priming task session was conducted to measure implicit gender-based stereotypes toward food names. No explicit association between primes and targets was provided for participants, so that target response was not predictable from the primed food names. At the beginning of each trial, a fixation marker was presented for 500 ms. It was then replaced by the prime stimulus (a feminine or masculine food name), which was presented for 200 ms. After a 50 ms interstimulus interval with a blank screen, the target stimulus (a female or male Japanese forename) was presented. Participants were instructed to press the corresponding button upon judging the gender of the target forename as quickly and accurately as possible. The target stimulus remained on the monitor until a response was given or for 2,500 ms if no response was given. After an intertrial interval of 3000 ms, the next trial started (Fig. 140.3).

Fig. 140.3 The time course of stimulus presentation in the semantic priming task. In this task, participants were primed with a food name (e.g., steak) and immediately after the priming, they were presented with a forename (e.g., Ichiro), as the target stimulus, and asked to decide whether the forename given was feminine or masculine

Blank screem (3000ms)

Target: forename (until response or 2500ms)

Blank screen (50ms)

Prime: food name (200ms)

Fixation marker (500ms)
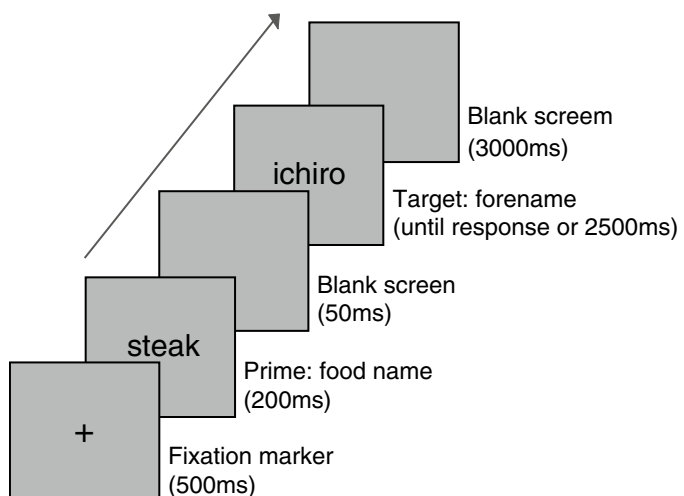
Table 140.4   Female/male Japanese forenames used in the priming task

	Female forenames		Male forenames	
	Forename	Mean femininity/ masculinity	Forename	Mean femininity/ masculinity
1	*Megumi*	1.07	*Takeshi*	6.87
2	*Reiko*	1.07	*Goro*	6.87
3	*Maiko*	1.13	*Ichiro*	6.87
4	*Michiko*	1.13	*Taro*	6.80
5	*Yoko*	1.13	*Daisuke*	6.80
6	*Yukiko*	1.13	*Ken-ichi*	6.80

This table lists the most feminine- and masculine-rated Japanese forenames and their mean femininity/masculinity scores (7-point scale: 1 = *very feminine* to 7 = *very masculine*)

The gender choice and reaction time (RT) were recorded. Participants were informed that pairs of words would be sequentially presented at the center of the PC monitor, and were instructed to concentrate only on the second word (forename).

The six foods evaluated as the most feminine and the six evaluated as the most masculine in study 2 were selected as the prime stimuli (see Table 140.3). A pilot survey was conducted to select the target stimuli. Fifteen participants (nine females and six males; average age = 24.3 years; *SD* = 2.2; range: 22–29 years) were asked to rate a list of 100 Japanese forenames (50 each of female and male) for their femininity/masculinity (7-point scale: 1 = *very feminine* to 7 = *very masculine*) and for their commonness (7-point scale: 1 = *very uncommon* to 7 = *very common*). We equalized the number of characters and the lengths of syllables of all the forenames so that they all had three or four characters and/or syllables. The six most feminine- and masculine-rated Japanese forenames, respectively, were selected as the target stimuli (see Table 140.4 for a full list of the targets). The femininity/masculinity scores of the selected female target stimuli (mean=1.11) differed significantly from those of the selected male target stimuli (mean=6.84), $t(14) = 42.15$, $p < 0.01$, but the typicality scores did not differ significantly, $t(14) = 1.01$, *n.s.* (mean for female target stimuli = 6.54; mean for male target stimuli = 6.39).

Prime and target stimuli were presented in white letters on a black background. After the semantic priming task, the self-report questionnaire for gender stereotypes was conducted to measure explicit gender-based stereotypical attitudes toward foods. Participants were asked to estimate the gender of the typical eater of each of the 12 dishes used as priming stimuli. A 5-point bipolar scale from feminine (1) to masculine (5) was used.

140.4.5 Reaction Time Analysis

The mean scores and standard error for RT in the semantic priming task are presented in Fig. 140.4 (Kimura et al. 2009). A 2 (target's gender: feminine forename vs. masculine forename) × 2 (semantic congruence: congruent vs. incongruent) × 2 (participant's gender: female vs. male) analysis of variance (ANOVA) was performed on RT. A significant main effect of semantic congruence, $F(1, 34) = 25.96$, $p < .01$, with a shorter RT for the congruent ($M = 450$ ms, $SD = 47.58$) than for the incongruent ($M = 491$ ms, $SD = 65.27$) conditions was found. There were neither significant differences in the RTs among the participant or target genders nor any interaction among factors.

Fig. 140.4 The mean RT of the semantic priming task (in ms). The RT for the semantically congruent condition (i.e., a female forename presented after a feminine food prime) was significantly shorter than that for the incongruent condition (i.e., a female forename presented after a masculine food prime). Error bars indicate standard error (male participants: $n = 17$, female participants: $n = 19$). *RT* reaction time, *MT* male target, *FT* female target
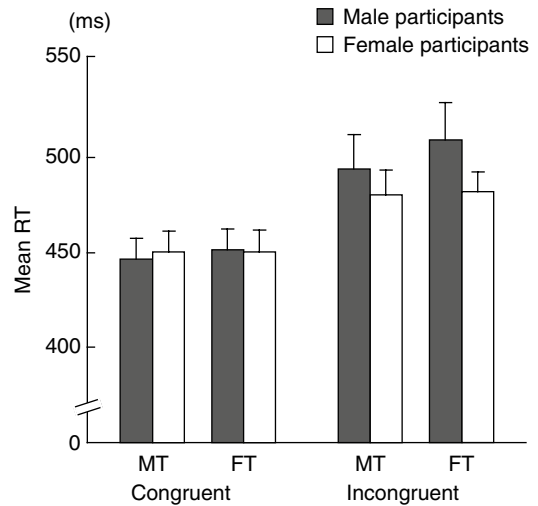
140.4.6 Error Rate Analysis

It has been demonstrated that participant response is not only faster, but also more accurate under the congruent condition than under the incongruent condition of the semantic priming test (Lamote et al. 2004). We calculated the error rate as a measure of response accuracy using the following equation: error rate = number of wrong responses/number of all responses. The mean scores and standard error for error rate in the semantic priming task are presented in Fig. 140.5. A $2 \times 2 \times 2$ (target's gender $\times$ participant's gender $\times$ semantic congruence) ANOVA was performed on the error rate of responses. The analysis of the error data exhibited a similar but more complex pattern compared with those of RT. As in the RT results, we found a significant main effect of semantic congruence, $F(1, 34) = 21.85$, $p < 0.0001$, with a higher error rate for incongruent ($M = 0.028$, $SD = 0.01$) than for congruent ($M = 0.005$, $SD = 0.03$) conditions. On the other hand, we found a significant interaction between a target's gender and the participant's gender $F(1, 34) = 4.60$, $p < 0.05$) and among all three factors ($F(1, 34) = 7.41$, $p < 0.05$). To analyze the interaction among the three factors, *post-hoc* analyses (Tukey's honestly significance difference (HSD) test) were performed. Six significant simple–simple main effects were found. The tests of simple–simple main effect showed that error rates of the incongruent condition were higher than those of the congruent condition (A) for the male participant with male target condition, (B) the male participant with female target condition, and (C) for the female participant with female target condition ($p < 0.01$ for all). Regarding the difference in target genders, the tests of simple–simple main effects detected that (D) error rate for male targets was higher than that for female targets ($p < 0.05$) in the male participant with incongruent condition. In contrast, (E) error rates for female targets was higher than that for male targets in the female participant with incongruent condition ($p < 0.01$). Regarding the difference in participant gender, the tests of simple–simple main effects indicated that (F) error rates for male participants were higher than those for female participants ($p < 0.01$) in the male target with incongruent condition.

140.4.7 Self-Report Analysis

The explicit gender-based stereotypical attitude toward each food name measured by self-report questionnaire was also analyzed to confirm whether the 12 foods selected in studies 1 and 2 were actually perceived as feminine or masculine by the participants in the experimental sessions (Kimura

Fig. 140.5 The mean error rate of the semantic priming task (in percentages). The error rate for the semantically congruent condition was significantly lower than that for the incongruent condition. The results of error rate measurements also demonstrated an interaction among the factors. Error bars indicate standard error (male participants: $n = 17$, female participants: $n = 19$). *MT* male target, *FT* female target
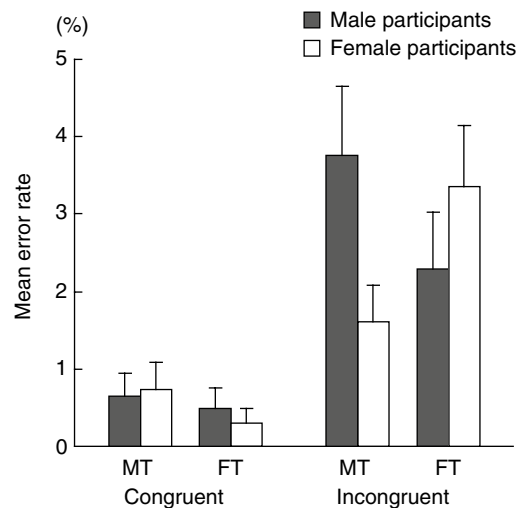
et al. 2009). A 2 (participant gender: female vs. male) × 2 (food femininity/masculinity: feminine food vs. masculine food) ANOVA was performed on the ratings of femininity/masculinity. A significant main effect of food femininity/masculinity ($F(1, 34) = 279.56$, $p < 0.01$) was found. The masculine foods ($M = 4.31$, $SD = 0.46$) were rated as more masculine than the feminine foods ($M = 1.72$, $SD = 0.52$). There were no significant differences in the masculinity/femininity ratings between participant genders or in the interaction among factors.

140.4.8 Validity of the Semantic Priming Paradigm on Measuring Gender-Based Food Stereotypes

The results of study 3 demonstrate that RT for the semantic priming task provides a good reflection of the semantic association of masculinity or femininity with specific foods. RT of the semantic priming task robustly reflected the gender-related semantic congruency between the prime stimuli (food names) and the target stimuli (forenames). Specifically, RT for the semantically congruent condition (i.e., a female forename presented after a feminine food prime and a male forename presented after a masculine food prime) was significantly shorter than that for the incongruent condition (i.e., a female forename presented after a masculine food prime and a male forename presented after a feminine food prime). This result suggests that there are tight associations between specific food names and gender among young Japanese.

Analysis of the error rate also supported the existence of a similar food-gender association pattern. Moreover, the result of error rate measurement demonstrated an interaction among the factors: target gender, participant gender, and semantic congruence. However, it is still unclear whether it is most appropriate to adopt the error rate measurements or to treat them as subsidiary to RT measurements. If we adopt the error rate measurements, the interaction may suggest the existence of complex associations between the factors tested. The error rate was higher when a participant's gender and a target's gender were opposite (c.f., D and E in the "Results" section). This leads to the postulation that, in young Japanese, the association between food and gender is stronger when the associated gender is opposite to the participant's gender than when it is the same as the participant's gender. This tendency was more explicit in male participants than in

female participants (c.f. A, B, C, and F in the "Results" section). That is, young, male Japanese tend to feel that women are supposed to eat feminine foods, while young, female Japanese are less biased. Such asymmetry in young Japanese may raise further cultural interest because the studies with Western subjects using explicit measures revealed the opposite tendency: Females have stronger gender-stereotypical thinking toward foods and tend to avoid eating masculine foods (e.g., Basow and Kobrynowicz 1993; Chaiken and Pliner 1987; Mooney et al. 1994). Although the current experiment is not sufficient to conclude whether there is a cultural difference in the way women and men hold gender stereotypes toward what women or men should eat, this would be an interesting issue to explore in the future.

140.5 Comparison of Gender-Based Food Stereotypes Between Japanese and Western Consumers

To the best of our knowledge, we have provided the first report of a three-phase cross-validation study on gender-based stereotypes toward foods among young Japanese: the most masculine or feminine foods were screened in the first phase, the candidate foods were explicitly assessed for their femininity or masculinity in the second phase, and, finally, the gender associations for the 12 foods determined to be the most feminine or masculine were validated explicitly and implicitly in the third phase. Given this, it would be worth discussing the current results from a cultural perspective.

140.5.1 Masculine Foods

Consistent with the results of the wealth of studies using Western subjects, there are gender-based stereotypes toward specific foods among young Japanese. Most of the masculine foods that were selected in study 2 include both traditional Japanese dishes and Western dishes commonly consumed in Japan (Table 140.3), including beef steak, which was also found to be masculine in a former study using Western subjects (Mooney and Lorenz 1997). These masculine foods are basically categorized as high-fat foods consisting mainly of meat or meat with rice. The association between masculinity and high-fat foods is consistent with results of a former study on dietary social stereotypes (Barker et al. 1999), and with the fact that, based on a large-scale survey of dietary records for US college students (Huang et al. 1994), young males consume more high-fat foods than do young females.

140.5.2 Feminine Foods

On the other hand, most of the feminine dishes that were selected in study 2 consisted exclusively of Western foods (Table 140.3). This was in marked contrast with the case of masculine dishes that consisted mainly of early-modern traditional Japanese foods. Since, to our knowledge, there is no study on the association between foreign/domestic foods and genders, we cannot provide any further comparative discussion on the current observation, but this would be an intriguing issue for future exploration.

    The feminine foods included low-fat foods (i.e., pasta, salad, and fruits) as in former studies on Western consumers (Barker et al. 1999; Mooney and Lorenz 1997). Although some high-fat foods

were chosen, they were all sweets, and no meat or rice dishes were selected. There is no direct study assessing the stereotypical association between femininity and sweets, but behavioral studies have consistently revealed a female craving for sweets in Western countries (Pelchat 1997; Rozin et al. 1991; Zellner et al. 1999). It seems reasonable to consider the stereotypical association between femininity and sweet foods a cross-cultural phenomenon. On the other hand, the dissociation of femininity from rice and meat seems to reflect a rather complex behavior in view of a recent food craving study on young, female Japanese: it was demonstrated that the young women had strong cravings for rice and meat, but that the cravings were not always related to their actual eating behaviors (Komatsu 2008). Komatsu postulated that the desire for thinness and the subsequent restraint in eating behavior may be the reason for such dissociation, but the current results suggest another possibility: the gender-based stereotypes that rice and meat are associated with masculinity may also induce the craving-behavior dissociation.

Kimura et al. (2009) revealed that, consistent with studies based on Western subjects, there are robust gender-based stereotypes toward foods among young Japanese that high- and low-fat foods are associated with masculinity and femininity, respectively. This study also suggests a specific tendency among young Japanese: there is a plausible complex association among masculinity, high-fat foods, and early-modern traditional Japanese foods; femininity is associated with sweets regardless of the fat content of foods, whereas there is a dissociation from rice and meat. Further research is necessary to clarify these culture-specific tendencies.

140.5.3   Application Toward Areas of Health

The recent tendency among young Japanese to avoid eating traditional Japanese foods, particularly rice, has raised growing social and political concern (Ministry of Health, Labour and Welfare Japan 2007; see also Table 140.2). It is plausible that the gender-based food stereotype among young Japanese females of associating rice with masculinity, together with forming a psychological barrier against eating masculine foods, may add to such tendencies.

These stereotype-based barriers among young Japanese females against Japanese foods might lead to loss not only for the Japanese food industry, but also for the health of individuals, given the health benefits of eating Japanese foods. For example, Kamei et al. (2002) evaluated the nutritional contents of take-out lunches supplied in Japan, and revealed that traditional Japanese-style diets were healthier in respect to total energy, fat–energy ratio, and lipid-related proportions relative to Western-style fast foods. They concluded that such Japanese-style dishes provide an advantage for preventing several kinds of lifestyle-related diseases. This further implies that an increase in the consumption of Japanese-style dishes may lead to a decreased risk of lifestyle-related diseases. Thus, the possibility of technical interventions for reducing such gender-specific biases toward Japanese foods and eating should be explored. Implicit measurements, as exemplified in the semantic priming tasks in the current study, provide effective tools in examining static and dynamic aspects of consumer stereotypes toward foods and eating.

140.6   Conclusion

There is a robust association between specific foods and masculinity or femininity among young Japanese, as has been revealed for Western subjects. As advocated by a classical study on the product personality by Wells et al. (1957), and the "you are what you eat" hypothesis of foods by Nemeroff

and Rozin (1989), stereotypes toward foods could further affect the personality of the eater, thus generating another facet of gender-based stereotype.

Research on stereotypes toward foods and eating has drawn growing interest, but is still in the development phase. To accelerate progress in this area, elaborated analysis of the social factors related to stereotypes toward foods and eating, such as culture, gender, and age is indispensable. In addition to such static analysis, dynamic intervention studies on how to reduce stereotypes are necessary.

Summary Points

- People have stereotypical attitudes toward particular foods and eating behaviors.
- Gender stereotypes occur when femininity and masculinity are consistently associated with the type of food that individuals eat. People sometimes judge the femininity and masculinity of others based on their food intake.
- There is a robust association between specific foods and masculinity or femininity among young Japanese, as has been revealed for Western subjects.
- The feminine-evaluated foods among young Japanese included low-fat foods (i.e., pasta, salad, and fruits) as with Western consumers. Although some high-fat foods were chosen, they were all sweets, and no meat or rice dishes were selected.
- The masculine-evaluated foods among young Japanese are basically categorized as high-fat foods as with Western consumers, consisting mainly of meat or meat with a carbohydrate (i.e., beef rice-bowl, Chinese noodle soup, and beef steak).
- The semantic priming task provides a good reflection of the semantic association of masculinity or femininity with specific foods. This technique provides effective tools for examining static and dynamic aspects of consumer stereotypes toward foods and eating.

Key Terms and Definitions

Consumption stereotype: Stereotypes related to food consumption and eating behavior (mostly what and how much individuals eat). In certain situations, people may exploit these stereotypes and eat in a particular way so as to project a desired impression to others (Vartanian et al. 2007).
Gender stereotype: These are culturally specific, publicly shared characteristics that are associated with one particular gender role (Holroyd et al. 2002). Several studies have shown that people use the gender stereotype as a basis for their food selection and eating behavior.
Implicit attitude: Attitudes measured by implicit attitude measures such as the affective/semantic priming test and the implicit association test (IAT). These techniques indirectly infer attitudes by examining response patterns (e.g., changes in response time) toward stimuli related to the topic.
Semantic priming task: A reaction time task that involves the successive presentation of a *prime* (usually words or pictures) and a *target* (words or pictures) that have polar balance (e.g., positive vs. negative). It is considered that the intensity of semantic association between prime and target may be reflected in response time and accuracy.
Explicit attitude: Attitudes measured by a self-report questionnaire. A self-report questionnaire has the advantage of being able to measure attitudes easily. On the other hand, these techniques may be diminished by the risk of reflecting skewed attitudes flawed by social desirability or self-presentation biases.

References

Barker ME, Tandy M, Stookey JD. Appetite. 1999;33:309–17.

Basow SA, Kobrynowicz D. Sex Roles. 1993;28:335–44.

Chaiken S, Pliner P. Pers Soc Psychol B. 1987;13:166–76.

Chambers S, Lobb A, Butler L, Harvey K, Traill WB. Appetite. 2007;49:208–13.

Czyzewska M, Graham R. Eat Behav. 2008;9:303–12.

De Moura SL. Appetite. 2007;49:716–9.

Fazio RH, Sanbonmatsu DM, Powell MC, Kardes FR. J Pers Soc Psychol. 1986;50:229–38.

Garner DM, Garfinkel PE, Bemis KM. Int J Eat Disorder. 1982;1:3–46.

Greenwald AG, McGhee DE, Schwartz JLK. J Pers Soc Psychol. 1998;74:1464–80.

Greenwald AG, Banaji MR, Rudman LA, Farnham SD, Nosek BA, Mellott DS. Psychol Rev. 2002;109:3–25.

Hamilton DL. Social cognition. New York: Psychology Press; 2005.

Holroyd EA, Bond MH, Chan HY. J Adv Nurs. 2002;37:294–303.

Hoogland CT, de Boer J, Boersema JJ. Appetite. 2007;49:47–57.

Huang Y-L, Song WO, Schemmel RA, Hoerr SM. Nutr Res. 1994;14:1143–53.

Hsu LKG. Clin Psychol Rev. 1989;9:393–407.

Kamei M, Ki M, Kawagoshi M, Kawai N. J Food Compos Anal. 2002;15:35–45.

Kimura A, Wada Y, Goto S, Tsuzuki D, Cai D, Oka T, Dan I. Appetite. 2009;52:51–4.

Komatsu S. Appetite. 2008;50:353–8.

Lamote S, Hermans D, Baeyens F, Eelen P. Appetite. 2004;42:279–86.

Macrae CN, Stangor C, Hewstone M. Stereotypes and stereotyping.New York: Guilford Press; 1996.

Macrae CN, Mitchell JP, Pendry LF. Exp Soc Psychol. 2002;38:186–93.

Ministry of Health, Labour and Welfare Japan. National Health and Nutrition Survey, Japan (in Japanese); 2007.

Mooney KM, Lorenz E. Sex Roles. 1997;36:639–53.

Mooney KM, DeTore J, Malloy KA. Sex Roles. 1994;31:433–42.

Murcott A. Aldershot, England: Grower; 1983.

Nemeroff C, Rozin P. Ethos. 1989;17:50–69.

Niva M. Appetite. 2007;48:384–93.

Oakes ME. Appetite. 2004;42:273–8.

Oakes ME. Food Qual Prefer. 2005a;16:447–54.

Oakes ME. Appetite. 2005b;44:317–24.

Pelchat ML. Appetite. 1997;28:103–13.

Roef A, Stapert D, Isabella LAS, Wolters G, Wojciechowski F, Jansen A. Eat Behav. 2005;6:151–63.

Rozin P. Sweetness, sensuality, sin, safety, and socialization: some speculations. In: Dobbing J, editor. Sweetness. New York: Springer; 1986.

Rozin P, Levine E, Stoess C. Appetite. 1991;17:199–212.

Stein RI, Nemeroff CJ. Pers Soc Psychol B. 1995;21:480–90.

Vartanian LR, Herman CP, Polivy J. Appetite. 2007;48:265–77.

Wansink B, Payne CR, North J. Physiol Behav. 2007;90:712–6.

Wells WD, Andriuli FJ, Goi FJ, Seader S. J Appl Psychol. 1957;41:317–9.

Zellner DA, Garriga-Trillo A, Rohm E, Centeno S, Parker S. Appetite. 1999;33:61–70.

Part XXIV
Starvation and Nutrient Deficiency

Chapter 141
Diet-Related Behavioral Mechanisms in Times of Economic Constraint

A.R. Kelles, M. Shroff, and A. Rinehart

Abbreviations

SES   Socioeconomic status
CVD   Cardiovascular disease
DM   Diabetes mellitus
CHD   Coronary heart disease
BMR   Basal metabolic rate
WHO   World Health Organization
DHHS   Department of Health and Human Services
USDA   Unites States Department of Agriculture
CDC   Centers for Disease Control
FSP   Food Stamp Program
WIC   Special Supplemental Nutrition Program for Women, Infants, and Children
SNAP   Supplemental Nutrition Assistance Program
FAO   Food and Agriculture Organization
HIV   Human immunodeficiency virus
AIDS   Acquired immunodeficiency syndrome
GHI   Global hunger index
IFPRI   International Food Policy Research Institute

141.1 Introduction

Obesity is a global epidemic with a rapidly increasing predominance among low-income populations. Unfortunately, low-income populations are also the least capable of dealing with the health and economic consequences directly associated with obesity and indirectly with obesity-related chronic diseases (Russell 2004; Leive and Xu 2008). Increases in chronic disease prevalence among low-income populations could ultimately lead to overall reduced quality of life as well as a substantial increase in days of work lost in the global work force (Goudge et al. 2009). Similar to the impact of obesity,

A.R. Kelles (✉)
Department of Nutrition, New York Chiropractic College, Seneca Falls, New York, USA
e-mail: akelles@nycc.edu

chronic undernutrition, still prevalent in many developing countries, leads to increased infectious disease risk and is associated with substantial days of work lost (McIntyre et al. 2006).

To curtail the global trend towards decreased health among low-income populations it is important to understand the mechanism by which economic constraint leads to adverse disease outcomes. Research has identified several possible pathways, such as the impact of economic constraint on accessibility/usage of healthcare services, physical activity, and dietary behaviors (Gordon-Larsen et al. 2006; Nelson et al. 2006; Goudge et al. 2009; Larson et al. 2009; Pollack and Armstrong 2009). A goal of this chapter is to explore specifically the mechanism by which economic constraint influences dietary behaviors among low-income populations. This information can be incorporated into the development of efficient and effective interventions and policies aimed at improving health status among the poor. Creating policy measures to support low-income populations, however, is complicated because dietary behavior responses to economic constraint differ substantially depending on the local, national, and international environmental contexts. For example, economic constraint in a developed country setting often leads to the consumption of high-energy but low-nutrient dense diets (Drewnowski and Darmon 2005). The impact of economic constraint in some developing country settings may resemble a developed country yet for others it may lead to an overall insufficient intake of both micronutrients and total calories (Hakeem 2001; Popkin 2001; Shafique et al. 2007; Vorster et al. 2007; Ntandou et al. 2009). Due to the diversity in dietary behavior response to economic constraint, we will explore this relationship in both a developed and developing country setting.

The accessibility of resources such as foodstuffs/food markets, transportation, safe environment, and healthcare is not solely influenced by the economic ability of an individual or family. In fact, the relationship between dietary choices and economic constraint differ substantially by the economic, social, and political state of an individual's or family's environment. More specifically the relationship differs for those in a developing versus a developed country setting and within countries by the level of urbanicity (Vorster 2002; Popkin 1998). There is a global nutrition phenomenon, referred to as the nutrition transition, documenting a shift from undernutrition to overnutrition as the economic wealth of a developing country increases (Popkin 1998). This transition is accompanied by an increase in food availability particularly in urban areas. The increase in food availability results in an increase in overconsumption, particularly of highly processed carbohydrates, animal fats, and a concurrent decrease in fresh fruits and vegetables (see Fig. 141.1). Compounding the emergence of this unhealthy lifestyle is a population shift from active to sedentary transportation as well as agriculture to service-oriented occupations leading to an overall sedentary population. These changes in both dietary and physical activity patterns lead to a shift in disease prevalence from infectious diseases to the emergence of obesity and related chronic diseases such as cardiovascular disease (CVD), hypertension, diabetes mellitus (DM Type 2), and many types of cancers (Ntandou et al. 2009; Misra and Khurana 2008). This phenomenon is often referred to as the epidemiologic transition (see Fig. 141.2) (Manton 1988; Mathers and Loncar 2006; Stuckler 2008). Occurring with the increased economic growth on a national level is the decrease in both fertility and mortality leading to a shift towards an aging population structure. This change is known as the demographic transition and is in part a result of increased active family planning, increased number of women in the work force, and overall improvements in sanitation and healthcare (Manton 1988; Mathers and Loncar 2006). An aging population, concurrent with the increase in obesogenic lifestyles, leads to the increase in obesity and chronic diseases versus infectious diseases found in middle- and high-income developed countries.

Within a country, both accessibility to and affordability of food resources affect the dietary behaviors of economically constrained populations. Food accessibility and affordability are in turn dependent on contextual wealth and development of a given geographic area. In a developed country, accessibility to resources, although an issue, may not be as much a limiting factor to healthy dietary

__The Nutrition Transition__

__Stage 1__	__Stage 2__	__Stage 3__	__Stage 4__	__Stage 5__
Society of hunter gatherer subsistence living	Agricultural society with high rates of undernutrition	Society experiencing industrialization with an increase availability of diverse 'rich' diets	Industrialized society with diets: high in saturated and trans fat, cholesterol, processed simple carbohydrates, and low in complex carbohydrates, and fiber	Society beginning to engage in lifestyle modifications to prevent or delay chronic disease onset

Low-income countries: developing → Increasing National GNP → **High-income countries: developed**

Fig. 141.1 Key features of the nutrition transition. This figure represents the general dietary trends observed depending on the wealth and development of a country. The trend can be used to compare the expected dietary patterns between countries but can also be used to represent the changes that occur as a country experiences increases in wealth and development and transitions from a preindustrial to a highly industrial economy

Stages of Demographic, Epidemiologic, and Nutrition Change
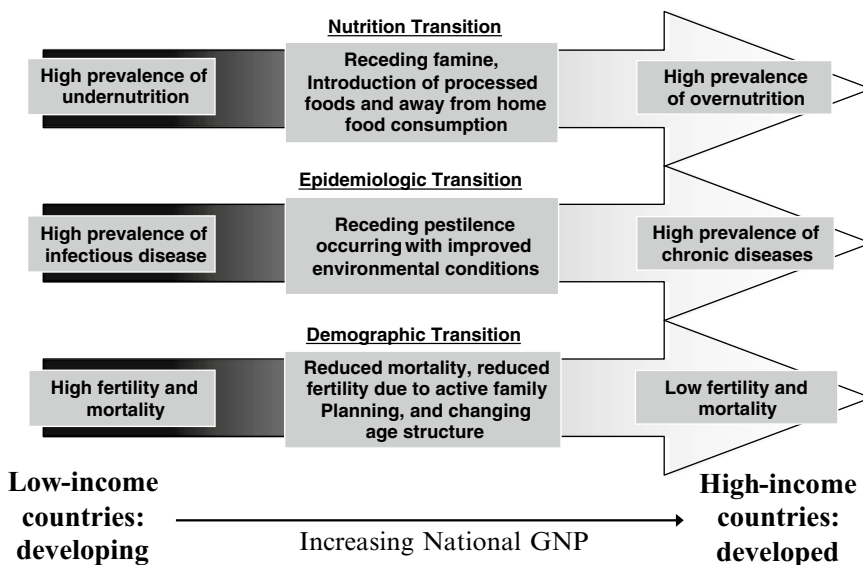
Fig. 141.2 The dietary and disease patterns as well as the population structure for countries at varying stages of wealth and development. These trends are inextricably intertwined and occur simultaneously as a country undergoes transition from a preindustrial to a highly industrialized country

behaviors as affordability among low-income groups (Darmon and Drewnowski 2008). Within a developing country context, however, there is substantial diversity in the availability of resources often, depending on the urbanicity of the environment (Dixon et al. 2007). In low- and middle-income developing countries, in a more urban environment, generally there is a greater access to resources. To create effective policies and interventions, it is therefore crucial to identify the local and national environmental context since this will determine to some extent how individuals and families will respond when faced with economic hardship. Policies and interventions in both developed and developing countries will be explored further in this chapter.

141.2 Developed Countries: Trends in Obesity and Related Diseases

In the past century, the prevalence of chronic disease has increased steadily in developed countries where people have ready access to energy-dense diets. In 1960, the estimated obesity prevalence in the US was 13.4%, but by 2000 this number had risen to 30.9% (Flegal et al. 2002). It is now estimated that roughly 2/3rds of Americans are overweight or obese (Ogden et al. 2006). As a result, researchers recently projected a decrease in the life expectancy for the twenty-first century (Olshansky et al. 2005). Similar trends exist throughout Britain and Europe (Seidell 2000). It is well documented that obesity is significantly correlated with an increased risk of many chronic diseases such as CVD, endocrine disorders, many forms of cancer, pulmonary disorders, musculoskeletal disorders, gastro-intestinal, hepatic and reproductive disorders (Brown et al. 2009). In the last decade new research has identified substantial metabolic activity in adipose tissue indicating a neuroendocrine link between obesity and chronic diseases such as CVD and diabetes (Ohman et al. 2009; Korner et al. 2009). We now know that adipose tissue releases chronic disease-related inflammatory mediators known as adipokines such as adiponectin and aromatase. For example, research indicates that Adiponectin may be the causal link between abdominal fat and atherosclerosis (Hansen et al. 2009). Aromatase, which promotes the conversion of estrogen to a carcinogenic metabolite, is now targeted using drug inhibitors as a post-menopausal breast cancer treatment (Maccio et al. 2009). Screening for overweight status can help identify high-risk individuals; however, the estimated accuracy of this tool is continually modified as our understanding of the neuroendocrine nature of adipose tissue expands. For example, a recent study in Japan found significant increases in visceral fat associated with a high risk of coronary heart disease (CHD) even among subjects with a low to normal estimated BMI (Popkin 1994). These findings have lead to a proposed lowering of the BMI cutoffs for overweight status in Asian populations (International Diabetes Institute 2000). New findings such as these also remind us that we are still in the early stages of uncovering the relationship between obesity and chronic disease.

141.2.1 Identifying Modifiable Obesogenic Behaviors

Given the strong correlation between obesity and chronic disease risk it is crucial that researchers identify modifiable behaviors leading to obesity that can be targeted by policies and interventions. Studies indicate that the rising rates of obesity are largely a result of the energy-dense diets associated with technological innovations, urbanization and improved socioeconomic status (SES) (Bleich et al. 2008). Specifically, technological advances in agriculture, food-preparation, cooking appliances, and food storage have led to significant decreases in the price of food. Greater reductions in

Table 141.1   Key features of diet quality (Kant 1996; Arvaniti and Panagiotakos 2008)

1. Diet quality, independent of diet quantity, is critical in the prevention of chronic diseases such as obesity. There are innumerable studies that have identified an association between chronic disease risk and specific dietary attributes such as the distribution of energy among the different macronutrients or the dietary adequacy of specific micronutrients

2. Diet quality is an overall balance of macronutrients with an intake of micronutrients to meet recommended levels relative to total energy intake

3. Several scoring systems exist to measure diet quality. Each system is aimed at measuring diet quality or the adherence to national dietary recommendations or guidelines constructed with the specific aim of chronic disease risk reduction (e.g. cardiovascular disease (CVD), hypertension, and cancer), including:

   (a) *Healthy Eating Index (HEI)* – was developed by the US Department of Agriculture and based on the Dietary Guidelines for America and the Food guide pyramid. The HEI has 10 component scores each with a maximum diet quality adherence score of 10, including:

    (i) Five components measure adherence to the recommended servings of each of the following major food groups: grains, vegetables, fruits, milk, and meat

    (ii) Dietary fat intake as a percent of total energy

    (iii) Saturated fat intake as a percent of total energy

    (iv) Cholesterol intake

    (v) Sodium intake

    (vi) Measure of dietary diversity

   Although the HEI provides a measure of overall dietary quality, several large scale studies found a lack of association with diet quality measured by the HEI and chronic disease risk. This lack of association may be due in part to the exclusion of food components that play a protective role such as fiber and essential fatty acids.

   (b) *Diet Quality Index (DQI)* – was specifically designed to measure diet quality as a reflection of chronic disease risk based on scientific guidelines provided by the scholars in the diet and health area. The components include:

    (i) Three components based on recommendations of dietary lipid intake (total fat, saturated fat, and cholesterol)

    (ii) Two components based on recommendations for simple and complex carbohydrate intake

    (iii) Although weighted less heavily in the total score, several components were included based on dietary protein, calcium, sodium, fluoride and supplement use

   This Index was revised (DQI-R) to include the most current US dietary guidelines and modified (DQI-I) to take into consideration diet characteristics such as: adequacy, variety, moderation, and overall balance

Several scoring systems have been created to quantify dietary quality for research and public policy purposes. This table outlines several of these indices

food prices have occurred for sweets, fats, and sugar-sweetened caloric beverages than for fresh fruits and vegetables (Drewnowski and Darmon 2005). This price disparity in turn has promoted the consumption of calorie-rich and nutrient-poor diets among low-income populations. To improve diet quality (see Table 141.1), researchers have estimated 35–40% additional food costs for low-income families (Jetter and Cassady 2005).

141.2.2 Defining the Environmental Context Associated with Obesogenic Behaviors

Various national policies and interventions exist to reduce the consumption of energy-dense foods, yet obesity continues to rise in developed countries like the United States, Canada, France, Germany, Great Britain, and several Scandinavian countries (Popkin 1994). Rising obesity trends may be due in part to a lack of consideration for the environmental context where obesity predominates.

Interventions directly targeting obesogenic behaviors often do not take into consideration underlying household factors such as SES that may influence an individual or family's ability for behavior change. In developed countries, higher rates of obesity are observed in low- versus high-income populations leading to an increased risk of many chronic diseases among the poor (Popkin 2004). This may be a direct result of the poor quality diets observed in many low-income populations. Compared to high-income families, economically constrained families are less likely to consume whole grains, lean meats, fish, low-fat dairy products, and fresh fruits and vegetables. Additionally, these low-income families tend to consume higher quantities of fatty meats, refined grains, and added fats (Darmon and Drewnowski 2008). Diets high in these energy-dense foods are associated with increased obesity risk as well as CVD and type II diabetes (Mendoza et al. 2007).

In general, as the economic status of an individual or family decreases there is an increased reliance on cheaper high-calorie diets rather than the more expensive nutrient-dense diets. Fruits and vegetables, which tend to be the most expensive foods per calorie, provide high quantities of micronutrients and fiber and thus improve the overall quality of a diet. However, fruits and vegetables are often prohibitively expensive for low income families, particularly given their relatively short shelf-life. Affordable high-calorie diets tend to consist of highly processed foods with longer shelf-lives that are high in simple sugars, saturated and trans- fats. Additionally, high-calorie foods are generally better tasting and convenient to prepare (Mendoza et al. 2007). Unfortunately, these highly processed foods are typically less satiating and therefore lead to overconsumption of total calories (Drewnowski and Darmon 2005). As a result, low-income families often meet or exceed calorie needs, but are deficient in micronutrients which come primarily from the more expensive fruits and vegetables (Andrieu et al. 2006).

141.3 Developed Countries: Why Low SES Leads to Poor Health Outcomes

There are multiple factors thought to link the effect of SES to health outcomes. Low SES groups receive less nutrition education and have poor access to healthcare services (Heck and Parker 2002; Devoe et al. 2007). Low-income families also commonly seek care for health problems later than middle or high-income families due to rapidly rising healthcare costs (Bodenheimer 2005). This leads to later diagnoses and ultimately more expensive healthcare interventions. Despite an increasing need of medical care for chronic diseases related to poor diet and sedentary lifestyles, there is a shortage of physicians interested in meeting this demand. Physicians report a lack of time, poor patient compliance, insufficient training, and lack of adequate insurance reimbursement as barriers to appropriately addressing care needs for the obese (Tsai et al. 2006). Additionally, technological innovation leading to the development of labor-saving household devices and passive forms of transportation has been estimated to contribute up to 40% of current weight gain in the United States (Lakdawalla and Philipson 2002).

141.3.1 Impact of SES on Dietary Behaviors

One of the most significant factors leading to poor health in developed countries is the impact of SES on diet behaviors. Individual and household SES is more dynamic than previously thought as families fall in and out of poverty due to unforeseen economic events and household expenses (Cornia 1994; Lokshin and Popkin 1999). Economic events can lead to periods of food insecurity characterized

by a general decrease in food availability and a concurrent reduction in diet quality due to decreased purchasing power. Generally, low-income families experience food insecurity at higher rates than middle and high-income families because they are more susceptible to falling either temporarily or permanently in to poverty during periods of economic crisis (Cornia 1994; Lokshin and Popkin 1999). Further, psychosocial problems associated with food insecurity can contribute to disease-promoting diet behavior. Specifically, individuals from poorer families experience higher levels of loneliness, boredom, and depression which can lead to behaviors such as excessive snacking, skipped meals, and sedentarianism (Darmon and Drewnowski 2008). Economic constraints can present a conflict between competing priorities such as food preferences and affordability of these foods (Dore et al. 2003) adding to the psychological stress. Wealth disparity, increased household size, unexpected family expenses, loss of food stamp benefits, and unemployment can also lead to food insecurity among families (Rose 1999). Additionally low-income families report a lack of cooking skills, lack of motivation (Dibsall et al. 2003; Henry et al. 2006) and disinterest in cooking (Henry et al. 2006) as barriers to healthy eating.

141.3.2 Who Is the Most Severely Impacted?

During periods of economic duress, the nutritional status of adults typically declines first as a result of prioritizing their children's nutritional needs over their own (Messer and Ross 2002). Despite efforts of parents to ensure adequate nutrition for their children, lower rates of breastfeeding among low-income families as compared to middle- and high-income families often results in poor childhood nutritional status. Given that dietary habits are established in childhood, children of low-income families are at particular risk of establishing lifelong poor quality dietary habits particularly during economic crises (Wang et al. 2002; Nicklas 1995). Poor dietary quality in childhood decreases overall immune function, increases the rate of dental caries, and can lead to cognitive deficiencies (Nelson 2000) and can permanently downregulate basal metabolic rate (BMR) increasing the risk of adult onset obesity.

141.4 Developed Countries: Pathways by Which Socioeconomic Status Affects Diet Quality

There are multiple proposed pathways linking the effect of SES to decreased diet quality and poor health outcomes (see Fig. 141.3). Low-income groups receive less nutrition education (Variyam et al. 1996) and have poor access to healthcare services (Devoe et al. 2007). Physical access to healthy foods is recognized as a significant factor in diet-related disease for low-income groups (Gittelsohn and Sharma 2009). Proximity to supermarkets that offer a variety of fruits, vegetables, and low-fat dairy products exist in lower concentrations in economically impoverished areas and can limit accessibility to healthy food choices for low-income families (Larson et al. 2009). Additionally, concentration of fast food restaurants is higher in low-income neighborhoods (Smoyer-Tomic et al. 2008). The low walkability and perceived safety of low-income neighborhoods limits access to facilities offering fresh produce, low-fat dairy products, and unprocessed lean meats and poultry (Maziak et al. 2008; Mujahid et al. 2008a, b). Low-income individuals from urban environments are subject to long commute times and have low vehicle ownership which dramatically decreases accessibility of large food markets (Larson et al. 2009). Further, reduced wages force many low-income individuals to work extended hours decreasing both the time available to travel to distant grocery stores and
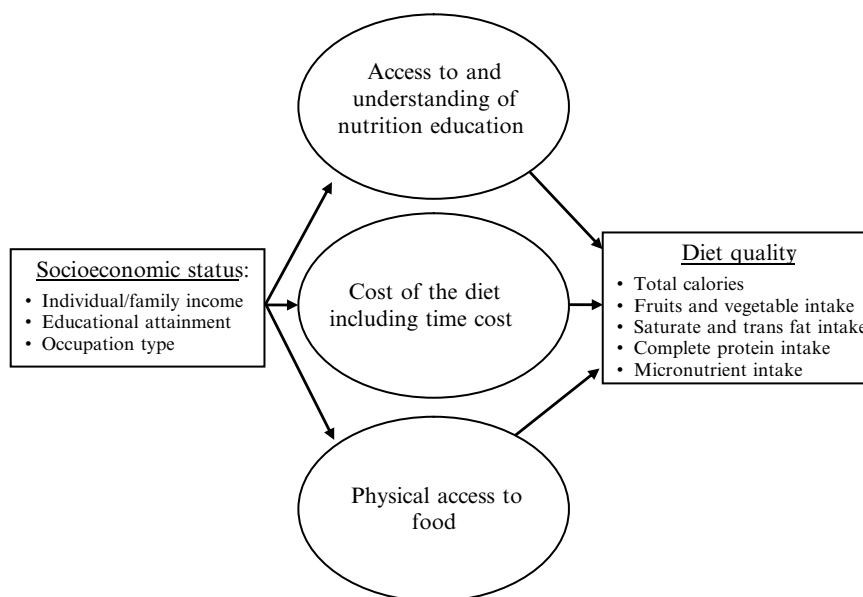
Fig. 141.3 Etiologic mechanism by which socioeconomic status (SES) impacts dietary quality. This figure illustrates the impact of SES on diet quality in developed countries. Nutrition education as well as accessibility and affordability of food are all intermediary factors linking low SES to poor diet. These factors are therefore key potential areas for interventions designed to successfully promote dietary change

prepare fresh home-prepared meals (Jabs and Devine 2006). Physical access to food stores can be complicated in districts that span large rural areas (Sharkey 2009). Quality of roads, tight district budgets, and work and commuting schedules can also complicate access for low-income families. Overall limited physical access to healthy food choices promotes the consumption of unhealthy prepackaged shelf-stable processed foods exacerbating the excess intake of total calories and insufficient micronutrient observed in low-income populations. As with food insecurity, individuals in urban versus rural areas experience more stress, which feeds psychosocial elements of disease-promoting dietary behaviors (Quine et al. 2003).

Food choices are made primarily on the basis of cost, taste, and convenience, rather than health and variety (Glanz et al. 1998). The high cost of nutrient-dense foods is likely the most significant determinant of inadequate consumption of fruits and vegetables, high quality lean meats and dairy products (Drewnowski and Specter 2004). The percentage of total family income accounting for food purchases inside and outside of the home is lowest for US families. Despite food expenditures accounting for the lowest percentage of the family budget, US families consume one of the most energy-dense diets in the world (Meade and Rosen 1996). Food costs take up a greater percentage of low- versus high-income family budgets creating an incentive for low-income families to purchase prepackaged and prepared calorie-rich foods to satisfy dietary needs. In contrast, unless consumed relatively quickly, the more expensive fresh foods such as fruits and vegetables are more likely to spoil than processed foods posing a highly inefficient use of money for overworked low-income families (Dowler 1997). Furthermore, low-income families tend to purchase highly processed fatty meats (Guenther et al. 2005) and high-fat dairy products (Prattala et al. 2003) such as hot dogs, prepackaged hamburgers, and processed cheese products due to cost and time limitations. Compared to dietary guidelines from the US Department of Health and Human Services (DHHS) and Department of Agriculture (USDA), a significant proportion of low-income families consume an excess of unhealthy fats and added sugars (DHHS and USDA 2005; Darmon and Drewnowski 2008). Overall,

low-income families in developed countries often meet or exceed calorie needs, but fall far short of dietary guidelines of 400 g of fruits and vegetables set by the World Health Organization (WHO 2010). Consequently, this insufficient intake of fruits and vegetables leads to inadequate micronutrient intakes among many low-income individuals and families (Andrieu et al. 2006). The consumption of low quality diets in response to the high cost of nutrient-dense diets has been observed in other developed countries such as the UK, France, and Denmark (Darmon et al. 2004).

141.5 Developed Countries: Public Policies and Interventions to Promote Health

A combination of environment reconfiguration, public policy initiatives, and multilevel economic strategies may be required to reduce the prevalence of obesogenic dietary and physical activity behaviors (see Table 141.2) (Sallis and Glanz 2009). Historically, policy recommendations in developed countries have focused on reducing calorie consumption (Bleich et al. 2008), increasing fruit and vegetable consumption (WHO 2010), and increasing physical activity (CDC 2009). Decreasing total calories by limiting dietary fat has had limited success. Instead of decreasing total calories, individuals commonly substitute fatty foods with high-glycemic foods that make weight loss difficult and that contributes to diet-related disease (Pawlak et al. 2002). On the other hand, limiting carbohydrates in the diet is difficult to sustain and may be associated with high intake of saturated fats (Strychar 2006). Consumption of fruits and vegetables is a major determinant of dietary energy-density due to their high water and micronutrient content. Increasing intake of fruits and vegetables along with whole-grains and fish has been consistently associated with improved health outcomes (Kant 2004). Altering the food environment to improve accessibility to health food choices and subsidizing specific fruits and vegetables may help increase diet quality for low-income populations (Powell et al. 2009). Point-of-purchase techniques (e. g. health information and detailed menu labeling where purchasing decisions are made) in addition to subsidies for fresh produce may be important components to policies that support individual food preference yet promote healthy dietary habits. Such campaigns could be utilized in worksites, universities, grocery stores, and restaurants, but few adequate research trials have been conducted to evaluate the effectiveness of such efforts (Seymore et al. 2004). As a mechanism to prevent weight gain, stimulate weight loss and maintain weight loss, a recent Center for Disease Control (CDC) and Prevention task force proposed recommendations to improve physical activity in communities (CDC 2009). Such an evidence-based campaign would combine billboards, radio, television, newspapers, mailings, self-management education, worksite programs, tenant-based rental assistance programs, center-based programs for low-income children, enhanced school-based physical education, and behavioral and social support interventions. Many of these tools have been tested and have successfully increased physical activity levels individually but they have not been evaluated as a comprehensive intervention.

141.5.1 Public Policies and Interventions Aimed at Dietary Behavior Change

Awareness of health assistance programs and services in the digital age can be problematic for low-income individuals. In rural areas, low-income individuals are much less likely to use internet resources to acquire health information (Miller 2009). Low-income groups will benefit from government-sponsored programs that equalize access and provide incentives for purchasing healthy, nutrient-dense foods.

Table 141.2 Examples of developed country government-sponsored food interventions targeting low-income individuals and families

National program	Type of intervention	Governing body	Target audience	Program goal	Potential limitation
Expanded Food, Nutrition and Food Stamp Education Program	Nutrition-related education program only	USDA Cooperative State Research, Education, and Extension Service	Low-income families with a particular focus on youth	Educate families on healthy food choices	Can fail to take into account individual preferences, behavior patterns, and high cost/accessibility of healthy food
Food Stamp Program (FSP)/Supplemental Nutrition Assistance Program (SNAP)	Direct assistance to supplement food purchasing power only	USDA Food and Nutrition Service	Employed low-income individuals and families	Reduce food insecurity among low-income families	Subject to social restraints such as complex application forms, lengthy time required for participation, cultural and language barriers, as well as social stigma
Special Supplemental Nutrition Program for Women, Infants, and Children (WIC)	Nutrition-related education and direct assistance to supplement food purchasing power	USDA Food and Nutrition Service	Low-income pregnant, breastfeeding and nonbreastfeeding postpartum women, and their infants and children of ages up to 5 years old	Reduce incidence of low birth weight and iron deficiency anemia among infants	May not reach adequate number of at risk population due to age and gender restrictions. Limited sources of fruits and vegetables covered by subsidies
Housing Assistance Program	Indirect nonfood subsidy	Department of Housing and Urban Development	State housing credit agencies provide affordable housing to 35,000 low-income households	Increase food budgets and improve overall diet quality	Limited impact on food purchasing practices towards healthier food choices

This table summarizes the existing US government programs aimed at improving dietary quality of low-income individuals and families. There are a wide range of program methods used to address poor dietary practices in developed country settings. However programs that include subsidizing targeted healthy food choices as well as providing general nutrition education may result in the most successful sustainable improvements in dietary quality in low-income populations

Programs focusing on diet education alone have been largely ineffective with respect to improving diet quality. Often, dietary advice does not take into account individual preferences and long-standing behavior patterns or the prohibitive costs of healthy food choices. Governmental programs such as the Expanded Food and Nutrition Education Program, and the Food Stamp Education Program rely exclusively on educational tools to low-income families as a means of improving food choices. Their recommendations often focus on strategies and foods with low palatability and convenience for families (Lino 2001). In place of dietary advice, studies from the UK and US have shown that providing vouchers for purchasing fruit and vegetables was a simple and effective way of increasing fruit and vegetables intakes for groups of low-income women (Burr et al. 2007; Herman et al. 2006). Unfortunately, the effectiveness of assistance programs can be limited significantly by social restraints. For example, form requirements, time required for participation, cultural and language barriers, and social stigmas can deter qualifying individuals from taking part in food assistance programs. The magnitude of the perceived assistances from the program also plays a role in sign-on rates. These barriers to utilization are difficult to quantify and measure. However, experts suggest that linking related aid/benefits into the same program may increase utilization and ultimately improve overall effectiveness (Remler and Glied 2003).

The US Food Stamp Program (FSP), now known as the Supplemental Nutrition Assistance Program (SNAP), helps low-income individuals and families purchase healthy foods and provides education on healthy eating practices and methods to incorporate physical activities into daily routines (USDA 2009). Low-income households that are enrolled in an FSP have a significantly lower incidence of food insecurity (Rose 1999). However, high dietary energy-density has also been found in diets of FSP recipients (Mendoza et al. 2006). To satisfy family dietary needs, recipients often ensure calorie-sufficiency foremost (Wilde et al. 2000) and ultimately fail to shift purchase behavior toward healthier foods (Drewnowski 2003). Additionally, food stamp recipients tend to consume more added sugars, meats, and fats and failed to improve intake of fruits, vegetables, grains, and dairy products after receiving assistance (Wilde et al. 2000). Subsidizing lean deli meats as well as specific fruits and vegetables might also improve diet quality in these low-income populations (Dore et al. 2003).

The Special Supplemental Nutrition Program for Women, Infants, and Children (WIC) program is another federally sponsored program managed at the state level that acts to provide nutritious foods, information on healthy eating, and appropriate health referrals for low-income women, infants, and children up to age 5 (FNS USDA 2009). WIC has lead to higher birth weight and lower incidence of iron deficiency anemia in infants born to participants of this program (Owen and Owen 1997). WIC provides assistance for the purchasing of milk, cheese, eggs, iron-fortified cereal, fruit juice, and adds canned tuna and fresh carrots for breastfeeding women. WIC does not provide subsidies for other fruit and vegetables. A pilot initiative which added an additional $10 weekly-voucher to the WIC program was highly utilized among program recipients and increased fruit and vegetable consumption by 0.8–1.4 servings per day depending on the purchasing environment (Herman et al. 2006) (see Table 149.1).

141.5.2 Public Policies and Interventions Created to Impact Purchasing Power

Indirect attempts, such as housing subsidies have been used to increase the percentage of family budgets available for the purchase of healthy food. However, despite improvements in housing subsidies, available income for food spending remained inadequate to promote the consumption of a nutritious diet (Kirkpatrick and Tarasuk 2007). In general, government-sponsored programs and subsidies aimed at increasing overall purchasing power have had limited impact on the improvement of diet quality

in low-income populations. An increase in economic resources tends to increase the quantity of less-expensive, energy-dense foods that are purchased rather than stimulating the purchase of healthy food choices. To be successful, future policy initiatives should be multilevel strategies to enhance accessibility to healthy food choices, provide subsidies for foods such as fresh fruits and vegetables, provide nutrition education, and promote the participation in existing government assistance program.

141.5.3 Individual/Family-Initiated Dietary Behavior Change

A recent study in Russia shows that there are some behavior modifications that are undertaken by individuals and families outside the context of government assistance to retain dietary habits during times of economic constraint. During a recent economic crisis, total energy intake of low income children remained robust, but diet composition shifted suggesting that low-income families purchased significantly less-expensive foods and prepared more meals at home. Both low and high-income families conserved diet structure by purchasing foods which provided more calories per unit cost (Dore et al. 2003). Specifically, low-income families demonstrated economic resilience by increasing consumption of less-expensive eggs and dairy products in order to provide stable sources of protein (Dore et al. 2003). This information can be used to subsidize targeted foods to ensure that families are able to purchase sufficient high quality calories.

141.6 Developing Countries: The Current Health Situation

Developing countries are characterized by low-scoring human indices such as life expectancy, per capita income, and level of literacy. Within a developing country context, the proportion of the population facing intermittent and/or chronic economic constraint far outnumbers the proportions observed in developed countries. A substantial percent of economically constrained individuals and families fall below the World Bank defined cut point for poverty, $2.00 per person per day and even the extreme poverty cut point of $1.25 in many low and middle-income countries (WB 2007). A disproportionate number of this impoverished population resides in rural areas. In contrast, many urban centers in developing countries are experiencing economic growth with a steadily growing middle-class superimposed over the urban poor. Typically, rural areas have poor transportation systems, health care infrastructure, sanitation conditions, and educational programs, which inhibit rural area growth and development. In contrast, urban centers are rapidly developing transportation infrastructure, organized healthcare systems, and educational programs including access to a diverse array of higher education institutions. Overall, economic opportunities for growth are limited in rural areas due to accessibility to resources. Similar to the dynamics observed in developed countries, populations in many developing country urban areas are limited primarily by the affordability of resources and existing services.

141.6.1 Environmental Context Underlying Obesity and Chronic Disease Trends

This widespread disparity in economic development, resource availability, and affordability of goods in developing countries also impacts dietary behaviors and ultimately health (see Fig. 141.4). Unlike developed nations, these countries are experiencing a rapid shift in health outcomes with increasing
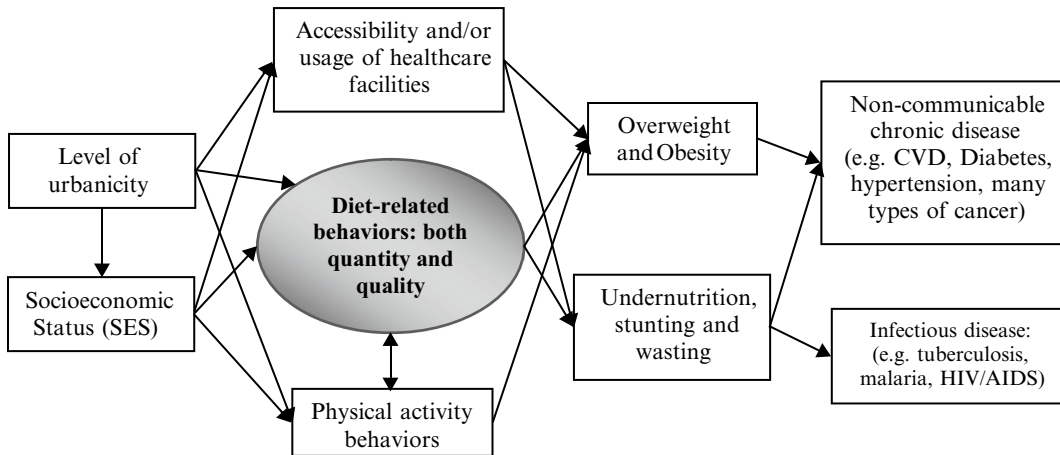
Fig. 141.4 The etiologic pathway from the socio-economic status of low-income populations leading to health status in developing countries. This figure emphasizes that, given the tremendous range of accessibility and affordability of resources (which is highly dependent on regional urbanization), there are multiple disparate pathways leading to the contrasting health outcomes of either chronic or infectious disease in developing countries. As a result blanket national policies to address malnutrition have the potential of addressing one form of malnutrition and ignoring or even exacerbating the other. Therefore, it is recommended that policy makers identify the specific etiologic framework underlying the disease status of an area and customize interventions to specific target populations

rates of obesity and chronic diseases (Popkin 2007). In economically middle-income countries of Latin America and parts of Asia, more than one third of the population is overweight (Popkin 2007). Although low-income countries in sub-Saharan Africa and south Asia are still struggling with a high prevalence of undernourished people there is a rapid rise of obesity in the urban areas (Popkin 2007). The shift from undernutrition to overnutrition is commonly referred to as the nutrition transition and the trend from infectious to chronic disease is referred to as the epidemiologic transition (Popkin 2006a). These shifts, however, occur superimposed over persistent undernutrition and infectious disease among certain low-income subpopulations. Two major factors influencing this disparity is the level of national wealth (determined by per capita income) and regional urbanization within the country both of which affect food availability as well as income potential and purchasing power. Substantial growth and development has occurred in many middle-income countries, particularly in urban centers, which has accelerated the nutrition and epidemiologic transitions towards overconsumption and increasing chronic disease prevalence. Although not as progressed, even in low-income countries where severe undernutrition persists, increases in obesity and chronic disease are occurring in response to the globalization of market systems (Gillespie and Haddad 2003). One stark difference between the urban populations in developing versus developed nations is that many adults in low and middle-income countries were chronically undernourished during the crucial developmental stages from childhood to early adulthood. Severe undernutrition during physiologic development can cause a permanent lowering of an individual's BMR. Therefore with an increased accessibility to western highly processed diets accompanying national development, these adults are even more prone to obesity than their low-income developed country counterparts.

The food accessibility and affordability in low and middle-income countries differs substantially depending on the level of urbanization of a particular region. In urban areas of developing countries food accessibility is less of a challenged than affordability. Like the developed country poor, low-income urban populations are rapidly shifting towards consumption of highly processed foods that are cheap, convenient, energy-dense, and micronutrient-poor with the exception of sodium which typically exists in excesses of recommendations (Popkin 1998, 2001). Income limitations restrict

low-income individuals and families from purchasing expensive fruits, vegetables, and high quality lean animal products. In contrast, rural populations struggle with the accessibility as well as the affordability of nutrient-rich quality foods.

141.6.2 Rising Global Food Prices Cause a Further Decline in Diet Quality

The recent global trend of rising food prices is negatively impacting access to food in developing nations at an alarming rate. Specifically, rising food prices impact both dietary convergence and dietary adaptation – terms used by researchers to explain the change in dietary pattern among population in developing countries (FAO 2004; Hawkes 2006). Dietary convergence refers to a reduction in the diet diversity found in a majority of traditional diets to a narrow range of globally accessible staple grains, meats and poultry, edible oils, salt, and sugar (FAO 2004). For example, a dramatic increase in the consumption of meat and poultry products as well as edible oils and processed high-glycemic index foods has replaced the more traditional rice and vegetable-based diet in many Asian countries (Ding and Malik 2008). A similar shift has occurred in Colombia in the last decade due to the increased production of poultry in response to a national policy which increased the import of cheap animal feed. In India, dietary convergence is characterized by increases in the consumption of quality protein sources such as eggs and milk. However, significant increases in the consumption of salty snacks, edible oils, and processed sugary foods such as baked goods and candy has also occurred in India (FAO 2004).

Dietary convergence is a function of rising food prices coupled with changes in individual or family income. Essentially, the price of a commodity influences availability and in turn consumer demand, thus creating a cyclical pattern to the availability, affordability, and consumption of specific food products. This pattern is heavily influenced by the national political environment and the government strategies towards food trade. Ultimately, products which are produced in high quantity on a global scale such as edible oils and processed sugary foods are relatively cheaper than traditional foods that are produced in much smaller quantities, thus tipping the scales towards less healthy dietary choices.

Dietary adaptation occurs in the population due to the changes in lifestyle such as increase use of transportation, eating out for convenience, and relying on cheaper foods to achieve calorie needs (FAO 2004). Adaptation is an individualized lifestyle change in response to environment changes such as: increasing food marketing and advertisements, increasing accessibility to convenient street food or fast food outlets and an increasing prevalence of supermarkets. Although dietary adaptation is less common among the severely/chronically poor in developing countries it is becoming rapidly more prevalent in intermittently poor and middle income groups. For example, recent increases in advertisements of calorie-rich low-nutrient foods in Brazil have lead to significant increases in energy-dense diets in middle-class communities. In the Philippines and other Asian countries, the change from traditional meal patterns to habits based on convenience is leading to increased consumption of processed foods high in fat, sugar, and low in micronutrients (FAO 2004; Rayner et al. 2007).

141.7 Developing Countries: Implications for Policy Makers

Given the substantial income disparity within developing countries and the complex web of environmental factors influencing dietary behavior patterns, policy makers should consider a multi-pronged strategy to address malnutrition. Low-income populations are not equipped to handle the increased

chronic disease risk associated with the emerging obesity occurring as a result of increased food accessibility and affordability (Popkin 2009). As described previously, however, the level of food accessibility and affordability is highly influenced by the level of national wealth and regional urbanization. Therefore, each developing country should customize policies and programs for the disparate economic and geographic populations facing the nutrition and epidemiological transition.

National policies created to improve the health and dietary patterns of economically-constrained groups that target only a segment of the population can often create more problems than they address (Ng et al. 2008). In particular, this is true for middle-income countries where the dual-burden of undernutrition and overnutrition occur in the same communities and in many cases in the same households. For example, in Chile, a government program designed to reduce undernutrition, exacerbated the problem of obesity for specific subgroups in urban areas of the country. In contrast, a government program in Mauritius aimed at the prevention of CVD in areas of high-risk individuals, successfully decreased obesity rates in this population (FAO 2004). As the nutrition transition continues throughout the developing world, governments must design targeted programs to address persistent undernutrition while simultaneously developing programs to address the growing prevalence of obesity and chronic diseases (see Table 141.3).

Table 141.3 Examples of developing country government-sponsored food programs and policies targeting low-income populations

Country	Type of program/policy	Target audience	Program goal	Observed outcomes
Bangladesh	Challenging the Frontiers of Poverty Reduction	Ultra poor communities in rural Bangladesh	Reduction of poverty to create a foundation for sustainable economic developments to support long term diet and health improvements	Increase intake of grains and vegetables but no reduction in mortality
Mauritius	Health Promotion program through Ministry of Health supported by health policy change	National level program to improve health status in both urban and rural environments	Reduction of cardiovascular diseases (CVD)	Increase in obesity rates due to switching of oils but reduction in cholesterol levels
Republic of Korea	Mass media campaigns to promote traditional foods and diets	Rural communities	Retain traditional diets and increase intake of vegetables and grains	Increase fresh fruit and vegetable consumption and reduce fat intake particularly animal fats
Brazil	Trade liberalization	Agrarian regions	To allow foreign investment, reduce farm tax, and lower import taxes on fertilizers and pesticides	Increase production of soybean oil to become second largest soybean exports but contribute to high consumption of soybean oil around the world

This table summarizes existing policies and programs aimed at improving health and dietary quality of low-income individuals and families in developing countries. With the given diversity of health challenges faced by urban versus many rural populations, government and nongovernmental programs will need to customize policies and interventions, e.g. programs to increase accessibility of fruits and vegetable in rural areas and a distinct program to decrease consumption of edible oils in the urban settings

141.7.1 Public Policies and Interventions Aimed at Dietary Behavior Change

An integral component of a multifaceted developing-country intervention strategy should include nutrition education programs to elucidate the negative health consequences of diets excessive in processed fats, and sugar, and deficient in micronutrient-rich fruits and vegetables. Given that traditional diets in many developing countries were inherently high in unprocessed grains, vegetable oils and fruits and vegetables, a strategy could be to preserve and reinforce the consumption of these already culturally-accepted dietary practices. For example, the Republic of Korea's Ministry of Rural Development has successfully preserved traditional dietary practices in rural communities through nutrition education on the importance of fruits and vegetables reinforced by the use of traditional Korean food recipes (Popkin et al. 2001). This has lead to decreased rates of obesity in this country in spite of the improved economic condition in the country.

The impact of economic independence on food industry dynamics and its consequent effect on the health of a population must be considered in the process of creating developing country health policy. The food industry in a country not only depends on agricultural productivity but on national and international food trade policies as well. Before making drastic changes, policy makers must carefully examine the possible consequences of modifying trade restriction and regulations in the food industry. Often it is assumed that removal of trade restrictions will automatically benefit a low-income population. For example, in Brazil, the government recently altered policies around the production of soybean oil in the country. Multiple changes were made including: opening the market to foreign investors, removing the export tax on soybean oil, restructuring the taxation for soybean farmers, and levying taxes on the imports of fertilizers and pesticides. This resulted in the reduction of prices of the edible oil not only within Brazil but also globally. This price reduction lead to significant increases in oil consumption in Brazil and is now believed to be one of the causes of increased obesity within the country. This policy also increased soybean oil consumption globally and is believed to have caused the destruction of local oilseed production in India and China, thus negatively impacting the national economies of these countries (Popkin et al. 2001; Hawkes 2006; Rayner et al. 2007).

141.7.2 Public Policies and Interventions Aimed at Overall Poverty Reduction

Given that poverty is a primary cause of poor diet quality in developing countries, programs aimed at alleviating poverty may significantly reduce malnutrition. Specifically, policy makers should consider programs to improve population quality of life by encouraging local farming, increasing accessibility to micro-finance schemes, improving the health care infrastructure, and establishing sustained educational systems (Russell 2004; Popkin 2009). Policies geared towards local community culture and practices may have an advantage over national programs with respect to improving the quality of dietary behaviors and lifestyles. Currently, in many sub-Saharan African and Asian countries, local farmers who do not produce sufficient quantities to support their communities, are becoming more dependent on foods imported via global trade. This has lead to a significant increased consumption of processed foods high in fats and sugar. To prevent this trend, governments should invest in local farming by subsidizing specific crops for poor farmers in a manner that supports local habits as well as fertilizers that will allow them to grow these crops. Often, they may not be in line with the globalization of food trade markets but it will allow the local farmer to sustain their local diets and enable a

correspondingly healthy lifestyle (Rayner et al. 2007). Micro-finance schemes, such as the programs designed by Nobel Peace prize winner Mohammed Yunus, have dramatically improved the quality of life of the ultra-poor in rural Bangladesh (Haseen 2007). This financial support has allowed rural populations to become financially viable and revive local industry of agriculture and goods. To combat poverty and malnutrition in developing countries it is also to improve the health care infrastructure promoting a healthier population free from debilitating infectious conditions such as HIV/Acquired Immunodeficiency Syndrome (AIDS), tuberculosis, and malaria. The cost of these diseases can be substantial and government and nongovernmental organizations should consider expanding the preventive services to rural populations where low-income groups predominate (Russell 2004).

Possibly the most important public policy strategy is the need for education in developing country communities – both in terms of overall education and nutritional education. The basic primary and secondary programs serve a dual purpose of building an intellectually stronger future generation as well as increasing awareness of basic nutritional needs and the hazards of inappropriately consumed foods. Institutions should have both nutritional education and hands on food-related programs as part of both the primary and secondary curriculum.

141.8 Conclusion

In recent decades rapid increases in obesity and associated chronic diseases have occurred with a disproportionately high rate of increase among low-income populations. For developed countries where affordability is a significant barrier to good nutrition, nutrient dense foods such as fruits and vegetables are prohibitively expensive for economically-constrained population. As a result low-income individuals and families rely heavily on cheap highly processed energy-dense foods. Although policies and programs exist to help alleviate food insecurity, these policies and programs have had limited success in improving the nutrient density of diets among the poor. To curb overconsumption and improve diet quality, developed country policies and interventions must address the price barrier as well as provide nutrition-based education typical of traditional interventions. In developing countries, barriers to quality nutrition include both the affordability of as well as accessibility to nutrient-rich food commodities. In urban centers where economic growth has lead to food environments similar to those found in developed countries a majority of low-income families rely on highly processed convenience foods high in fats and sugars and low in nutrients to meet energy needs. This has lead to tremendous increases in obesity and chronic disease prevalence. Low-income populations in rural developing country settings face an added barrier of food accessibility. In times of economic crisis, low-income individuals and families are more likely to experience intermittent or chronic periods of food insecurity. As a result, infectious diseases associated with chronic undernutrition are still common in rural areas of developing countries. Given the dramatic variance in dietary behavior response to economic constraint in developing countries, policies and interventions must be customized by region and take into consideration the specific barrier to quality nutrition.

Summary Points

- Obesity is a global epidemic with a rapidly increasing predominance among low-income populations. Unfortunately, low-income populations are also the least capable to deal with the health and economic consequences directly associated with obesity and indirectly with obesity-related chronic diseases.

- One of the most recognized etiologic pathways influencing obesity risk is the impact of income status on dietary behaviors and subsequent nutritional status which in turn impacts obesity risk.
- An individual or family's dietary behavior response to economic constraint is dependent on the local, national, and international environmental context.
- In developed countries, economic constraint tends to result in selective purchasing of relatively cheap processed foods high in refined carbohydrates, saturated fats, and trans fats with a concurrent decrease in expensive fruits and vegetables, lean meats, and low-fat dairy products. Consequently many low-income individuals are malnourished consuming excess calories and insufficient micronutrients.
- In many urban settings of middle-income developing countries the relationship between economic constraint and dietary behavior modification closely resembles the pattern observed in developed countries. In rural settings dietary behavior change in response to economic constraints tends to resemble patterns observed more commonly in low-income developing countries.
- In low-income developing countries, researchers have observed substantial food insecurity resulting in diets insufficient in both total calories and micronutrients among poor populations facing periods of economic constraint. This is particularly evident in rural areas where a lack of purchasing power is compounded by a lack of food availability.
- The prohibitively high cost of fruit and vegetable as well as quality meat and dairy products is at the root of insufficient intake among economically constrained populations. For this reason policies and interventions aimed at providing nutrition education as a means of improving diet quality have had negligible success.
- To be effective, policies and interventions to improve nutritional status in economically constrained populations must take in to consideration the environmental context driving the dietary behavior changes.
- In a developed country context: policies and interventions that increase economic resources for food purchasing successfully reduce incidence of food insecurity, but fail to increase consumption of nutrient-dense foods such as lean meats and fish, whole grains, and fruits and vegetables.
- Given the availability of resources, incorporating subsidies for targeted foods such as fruits and vegetables into existing or new polices and interventions may substantially increase the potential for success in developed countries.
- In developing countries there is a wide range of accessibility to and affordability of healthy food choices and is highly dependent on the urbanization of a region
- In developing countries policy makers must identify whether the cause of malnutrition is an accessibility or affordability issue to create successful sustainable interventions, e.g. if the barrier to diet quality is affordability using a food-specific subsidy might be appropriate whereas an accessibility barrier might require agricultural-based support

---

Key Terms

Nutrition transition: A phenomenon in low and middle-income countries where decreases in undernutrion concurrent with emerging overnutrition occur with increases in national gross domestic product.

Epidemiologic transition: A phase of development in a country context where a recession in the prevalence of infectious disease occurs simultaneously with an increase in the incidence of chronic noncommunicable diseases. Typically this transition is accompanied by improved national healthcare, sanitation, family participation in active family planning, and an increase in women working outside the home.

> **Demographic transition:** The transformation in a country where steady decreases in initially high birth and death rates are observed resulting in a shift towards an older population structure. This shift occurs most commonly as a country transitions from a preindustrial agrarian-focused economy to one that is highly industrialized.
>
> **Food insecurity:** A state where an individual or family lives in with intermittent or chronic hunger due to sporadic access to food and is in fear of starvation.
>
> **Poverty:** Defined by the world bank as $2.00 per person per day and for extreme poverty $1.25 per person per day.

References

Andrieu E, Darmon N, Drewnowski A. Eur J Clin Nutr. 2006;60:434–6.
Arvaniti F, Panagiotakos D. Crit Rev Food Sci Nutr. 2008;48:317–27.
Bleich S, Cutler D, Murray C, Adams A. Ann Rev Public Health. 2008;29:273–95.
Bodenheimer T. Ann Intern Med. 2005;142:847–54.
Brown WV, Fujioka K, Wilson PWF, Woodworth KA. Am J Med. 2009;122:S4–11.
Burr ML, Trembeth J, Jones KB, Geen J, Lynch LA, Roberts ZE. Public Health Nutr. 2007;10:559–65.
Centers for Disease Control and Prevention (CDC). 2009. http://www.thecommunityguide.org/pa/
Cornia GA. Am Econ Rev. 1994;84:297–302.
Darmon N, Drewnowski A. Am J Clin Nutr. 2008;87:1107–17.
Darmon N, Briend A, Drewnowski A. Public Health Nutr. 2004;7:21–7.
Devoe JE, Baez A, Angier H, Krois L, Edlund C, Carney PA. Ann Fam Med. 2007;5:511–8.
Dibsall LA, Lambert N, Bobbin RF, Frewer LJ. Public Health Nutr. 2003;6:159–68.
Ding EL, Malik VS. Global Health. 2008;4(4):8.
Dixon J, Omwega AM, Friel S, Burns C, Donati K, Carlisle R. J Urban Health.2007; 84:i118–29.
Dore AR, Adair LS, Popkin BM. J Nutr. 2003;133:3469–75.
Dowler E. Food Policy. 1997;22:405–17.
Drewnowski A. J Nutr. 2003;133:838S–40S.
Drewnowski A, Specter SE. Am J Clin Nutr. 2004;79:6–16.
Drewnowski A, Darmon N. Am J Clin Nutr. 2005;82:265S–73S.
Flegal KM, Carroll MD, Ogden CL, Johnson CL. JAMA 2002;288:1723–7.
Food and Agricultural Organization of Unites States (FAO). Globalization of food systems in developing countries: impact on food security and nutrition. 2004.
Gillespie S, Haddad L. The double burden of malnutrition in Asia. New Delhi: Sage; 2003.
Gittelsohn J, Sharma S. Am J Prev Med. 2009;36:S161–5.
Glanz K, Basil M, Maibach E, Goldberg J, Snyder D. J Am Diet Assoc. 1998;98:1118–26.
Gordon-Larsen P, Nelson MC, Page P, Popkin BM. Pediatrics 2006;117:417–24.
Goudge J, Gilson L, Russell S, Gumede T, Mills A. BMC Health Serv Res. 2009;9:75.
Guenther PM, Jensen HH, Batres-Marquez SP, Chen C-F. J Am Diet Assoc. 2005;105:1266–74.
Hakeem R. Eur J Clin Nutr. 2001;55:400–6.
Hansen T, Ahlstrom H, Soderberg S, Hulthe J, Wikstrom J, Lind L, Johansson L. Atherosclerosis 2009;205:163–7.
Haseen F. Asia Pac J Clin Nutr. 2007;16(Suppl 1):58–64.
Hawkes C. Global Health. 2006;2(4):8.
Heck KE, Parker JD. Health Serv Res. 2002;37:171–84.
Henry H, Reimer K, Smith C, Reick M. J Am Diet Assoc. 2006;106:841–9.
Herman DR, Harrison GG, Jenks E. J Am Diet Assoc. 2006;106:740–4.
International Diabetes Institute. The Asia-Pacific perspective: redefining obesity and its treatment. Australia: health communications. Australia Pty; 2000.
Jabs J, Devine CM. Appetite 2006. [Epub ahead of print]. http://www.ncbi.nlm.nih.gov/pubmed/16698116
Jetter KM, Cassidy DL. AIC issues brief. 2005. http://aic.ucdavis.edu/pub/briefs/brief29.pdf
Kant AK. J Am Diet Assoc. 1996;96:785–91.
Kant AK. J Am Diet Assoc. 2004;104:615–35.

Kirkpatrick SI, Tarasuk V. Public Health Nutr. 2007;10:1464–73.

Korner J, Woods SC, Woodsworth KA. Am J Med. 2009;122:S12–18.

Lakdawalla D, Philipson T. NER Working Paper 8946. 2002. http://www.nber.org/papers/w8946

Larson NI, Story MT, Nelson MC. Am J Prev Med. 2009;36:74–81.

Leive A, Xu K. Bull World Health Organ. 2008;86:849–56.

Lino M. Fam Econ Nutr Rev. 2001;13:50–63.

Lokshin M, Popkin BM. Econ Dev Cult Change. 1999;47:803–29.

Maccio A, Mededdu C, Mantovani G. Obes Rev. 2009. [Epub ahead of print].

Manton KG. World Health Stat Q. 1988;41:255–66.

Mathers CD, Loncar D. PLoS Med. 2006;3:e442.

Maziak W, Ward KD, Stockton MB. Obes Rev. 2008;9:35–42.

McIntyre D, Thiede M, Dahlgren G, Whitehead M. Soc Sci Med. 2006;62:858–65.

Meade M, Rosen EM. Food Rev. 1996;19:39–43.

Mendoza JA, Drewnowski A, Cheadle A, Christakis DA. J Nutr. 2006;136:1318–22.

Mendoza JA, Drewnowski A, Christakis DA. Diabetes Care. 2007;30:974–9.

Messer E, Ross EM. Nutr Clin Care. 2002;5:168–81.

Miller EA. J Health Polit Policy Law. 2009;34:261–84.

Misra A, Khurana L. J Clin Endocrinol Metab. 2008;93:S9–30.

Mujahid MS, Diez Roux AV, Shen M, Gowda D, Sánchez B, Shea S, Jacobs DR Jr, Jackson SA. Am J Epidemiol. 2008a;167:1349–57.

Mujahid MS, Diez Roux AV, Morenoff JD, Raghunathan TE, Cooper RS, Ni H, Shea S. Epidemiology 2008b;19:590–8.

Nelson M. Proc Nutr Soc. 2000;59:307–15.

Nelson MC, Gordon-Larsen P, Song Y, Popkin BM. Am J Prev Med. 2006;31:109–17.

Ng SW, Zhai F, Popkin BM. Soc Sci Med. 2008;66(2):414–26.

Nicklas TA. Am J Med Sci. 1995;310:S101–8.

Ntandou G, Delisle H, Agueh V, Fayomi B. Nutr Res. 2009;29:180–9.

Ogden CL, Carroll MD, Curtin LR, McDowell MA, Tabak CJ, Flegal KM. JAMA 2006;295:1549–55.

Ohman MK, Wright AP, Wickenheiser KJ, Luo W, Eitzman DT. Curr Vasc Pharmacol. 2009;7:169–79.

Olshansky SJ, Passaro DJ, Hershow RC, Layden J, Carnes BA, Brody J, Hayflick L, Butler RN, Allison DB, Ludwig DS. N Engl J Med. 2005;352:1138–45.

Owen AL, Owen GM. J Am Diet Assoc. 1997;97:777–82.

Pawlak DB, Ebbeling CB, Ludwig DS. Obes Rev. 2002;3:235–43.

Pollack CE, Armstrong K. Arch Intern Med. 2009;169:945–9.

Popkin BM. Nutr Rev. 1994;52:285–98.

Popkin BM. Public Health Nutr. 1998;1:5–21.

Popkin BM. J Nutr. 2001;131:871S–3S.

Popkin BM. Nutr Rev. 2004;62:S140–3.

Popkin BM. Public Health Nutr. 2006a;5(1A):205–14.

Popkin BM. Sci Am. 2007;297(3):88–95.

Popkin BM. Nutr Rev. 2009;67(Suppl 1):S79–82.

Popkin BM, Horton S, Soowan K. Food Nutr Bull. 2001;22(S4):47–51.

Powell LM, Zhao Z, Wang Y. Health Place. 2009. [Epub ahead of print].

Prattala RS, Groth MV, Oltersdorf US, Roos GM, Sekula W, Tuomainen HM. Eur J Pub Health. 2003;13:124–32.

Quine S, Bernard D, Booth M, Kang M, Usherwood T, Alperstein G, Bennett D. Rural Remote Health. 2003;3:245.

Rayner G, Hawkes C, Lang T, Bello W. Health Promot Int. 2007;21(S1):67–74.

Remler DK, Glied SA. Am J Public Health. 2003;93:67–74.

Rose D. J Nutr. 1999;129:517S–20S.

Russell S. Am J Trop Med Hyg. 2004;71:147–55.

Sallis JF, Glanz K. Milbank Q. 2009;87:123–54.

Seidell JC. Br J Nutr. 2000;83:S5–8.

Seymore JD, Yaroch AL, Serdula M, Blank HM, Khan LK. Prev Med. 2004;39:S108–36.

Shafique S, Akhter N, Stallkamp G, de Pee S, Panagides D, Bloem MW. Int J Epidemiol. 2007;36:449–57.

Sharkey JE. Am J Prev Med. 2009;36:S151–5.

Smoyer-Tomic KE, Spence JC, Raine KD, Amrhein C, Cameron N, Yasenovskiy V, Cutumisu N, Hemphill E, Healy J. Health Place. 2008;14:740–54.

Strychar I. CMAJ. 2006;174:56–63.

Stuckler D. Milbank Q. 2008;86:273–326.

Tsai AG, Asch DA, Wadden TA. J Am Diet Assoc. 2006;106:1651–5.

US Department of Agriculture (USDA). FNS Supplemental Nutrition Assistance Program (SNAP). 2009. http://www.fns.usda.gov/FSP/

US Department of Health and Human Services and US Department of Agriculture. Dietary guidelines for Americans, 2005. 6th ed. Washington, DC: US Government Printing Office; 2005.

Variyam JN, Blaylock J, Smallwood DM. Stat Med. 1996;15:23–35.

Vorster HH, Kruger A, Venter CS, Margetts BM, MacIntyre UE. Cardiovasc J Afr. 2007;18:282–9.

Vorster HH. Public Health Nutr. 2002;5:239–43.

Wang Y, Bently ME, Zhai F, Popkin BM. J Nutr. 2002;132:430–8.

Wilde PE, McNamara PE, Ranney CK. USDA/ERS FANR Report No. 9. 2000.

World Bank. Understanding poverty. 2007. http://web.worldbank.org/WBSITE/EXTERNAL/TOPICS/EXTPOVERTY/0,,contentMDK:20153855~menuPK:373757~pagePK:148956~piPK:216618~theSitePK:336992,00.html

World Health Organization (WHO). Promoting fruit and vegetable consumption around the world. 2010. http://www.who.int/dietphysicalactivity/fruit/en/index.html

Chapter 142
Food Deprivation: A Neuroscientific Perspective

Harald T. Schupp and Britta Renner

Abbreviations

AgRP	Agouti-related protein
BOLD	Blood oxygenation level dependent
EEG	Electroencephalography
ERP	Event related potential
fMRI	Functional magnetic resonance imaging
LiCL	Lithium chloride
LPP	Late positive potential
MNE	Minimum norm estimate
Nc	Nucleus
NPY	Neuropeptide Y
PET	Positron emission tomography
POMC	Proopiomelanocortin
rCBF	Regional cerebral blood flow
ROI	Region of interest

142.1 Introduction

The Russian physiologist Pavlov considered eating as the most powerful relationship an organism has to its surrounding world (Pavlov 1953). This "food connection" is heavily regulated by internal state variables such as hunger. Prolonged periods of starving are one of the most tragic experiences of humanity and even mild conditions of food deprivation clearly affect consummatory behavior as reflected in the saying "hunger is the best spice".

Everybody knows about the effects of deprivation. The effects appear intuitively so obvious that the phenomenon receives paradoxically rather too little than too much attention. Consider for instance the work of Pavlov and Skinner, in which food stimuli play a central role. The empirical finding that the contingent pairing of a tone and food establishes new behaviors is nowadays taught in high school. After training, the dog salivates to a previously neutral stimulus. Similarly, knowledge

H.T. Schupp (✉)
Department of Psychology, University of Konstanz, 78457 Konstanz, Germany
e-mail: harald.schupp@uni-konstanz.de

about the Skinner box, in which rats may learn to vigorously press a button to obtain food, is well perceived in the public. Imagine what would happen, if the animals were tested while satiated? The simple answer is they would probably not learn to press the button or to salivate. The role of deprivation in these learning principles is easily overlooked. However, Pavlov was very clear in his writing by stating that even the most avaricious dog will not learn the salivary response when satiated (Pavlov 1953). Accordingly, internal state variables have profound effects on responding to and learning about food cues.

In humans, the effects of prolonged periods of reduced food consumption were investigated in the Minnesota semi-starvation experiment, which was conducted during Second World War by Keys and colleagues (Keys et al. 1950). Food intake was greatly limited for several months resulting in pronounced loss of body weight (~25 kg). The experiment revealed massive physiological and psychological effects of semi-starvation. One notable finding is that food became the most important thing in life (Keys et al. 1950). Preoccupation with food and episodes of binge eating may be also induced by voluntary restricting food intake as in dieting and restrained eating (Polivy 1996). However, deprivation need not be sustained over long periods to affect the human feeding system. Acute food deprivation is associated with increased food consumption compared to nondeprived control groups (Spiegel et al. 1989; Drobes et al. 2001; Mauler et al. 2006) and increases the reinforce value of food in behavioral choice paradigms (Raynor and Epstein 2003).

142.2 Deprivation and the Feeding System: Conceptual Considerations

Deprivation affects almost every aspect related to food intake. Animal research over the past decade allows sketching a basic scheme of the feeding system providing a conceptual framework for the understanding of the effects of food deprivation on ingestive behaviors. As illustrated in Fig. 142.1, the organization of goal-directed ingestive behaviors rests on the integration of information about internal state (e.g., food deprivation), cues from the environment (e.g., availability of palatable food), and behavioral state (e.g., circadian rhythm). Furthermore, ingestive behavior is temporally organized in distinct appetitive and consummatory phases (cf., Timberlake 2001). To obtain food, one has first to look for potential food sources. A general search mode occurs when the subject does not know where to look for food. Exploratory behaviors bring the organism close to food and a focal search mode is engaged readying the organism for consummatory behaviors of chewing and swallowing. Ethological observations reveal reflexive-stereotypic behaviors during food consumption, while appetitive behaviors are more variable and non-stereotypic. These motivational stages differ in many respects such as temporal and spatial proximity to food consumption, engagement of distinct perception-action units, and specific cues sensitizing the engagement of stages. Recent research also suggests that the weighting of external and internal information differs among motivational stages. When food was readily available, consumption was controlled by the palatability of the food independent whether the animal underwent food restriction (~85% of normal weight) or not. Conversely, measurement of anticipatory locomotor behaviors revealed significant deprivation effects, which were independent from food palatability (Barbano and Cador 2005).

Great progress has been made to delineate mechanisms how information about internal state is represented in the brain and controls ingestive behaviors. The brain perceives an array of interosensory signals conveying information about the availability of food and nutrients generated by the gastrointestinal tract, postabsorptive sites (pancreas, liver, muscle), and stored nutrients in adipose tissue (Woods et al. 2000; Berthoud and Morrison 2008). While it is recognized that multiple brain regions are important for perceiving internal state, specific nuclei in the hypothalamus are consid-

Basic Scheme of the Feeding System
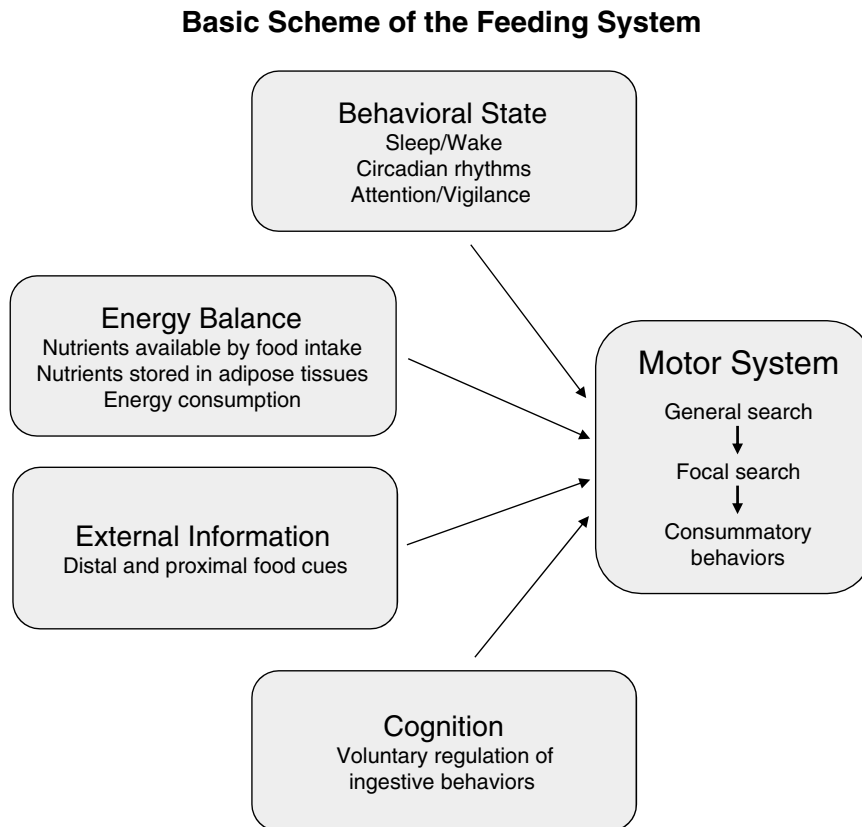
Fig. 142.1 Conceptual framework of the organization of the feeding system (Based on Swanson 2000; Timberlake 2001)

ered as key sites for the integration of metabolic-related information. The nucleus (Nc) arcuatus is assumed to integrate metabolic information via two populations of neurons (Neuropeptide Y (NPY)/ Agouti-related Protein (AgRP), Proopiomelanocortin (POMC)). These neurons are sensitive to a number of metabolic-related information (e.g., leptin, insulin, ghrelin) and exert opposite actions on feeding behavior. Efferents from these neurons to the paraventricular, lateral, and ventromedial hypothalamus provide a gateway for the translation of metabolic information to adaptive feeding responses as these neurons project widely through the entire brain (Swanson 2000; Watts and Swanson 2002; Berthoud and Morrison 2008). Based on anatomical, developmental, genetic, and functional data, Swanson introduced the concept of the behavioral control column in the rostral hypothalamus, which is considered as key motor control structure for motivated behaviors of feeding, reproduction, and defense (Swanson 2000). Consistent with its presumed role for ingestive behaviors, the paraventricular Nc affects many brain regions implicated in the selection, planning, and execution of specific somatic motor behaviors (cortical, striatal, and pallidal motor structures, brain stem motor nuclei), endocrine and autonomic responses and behavioral state regulation (see Fig. 142.2a). Overall, distinct nuclei in the rostral hypothalamus appear critical for the representation of internal state and provide mechanisms how food deprivation exerts motivational control on ingestive behaviors.

The incentive value of food is dynamically adjusted according to variations in internal state of energy balance. Even the tastiest food item is not consumed when satiated. This finding requires that

Neural Mechanisms of the Feeding System
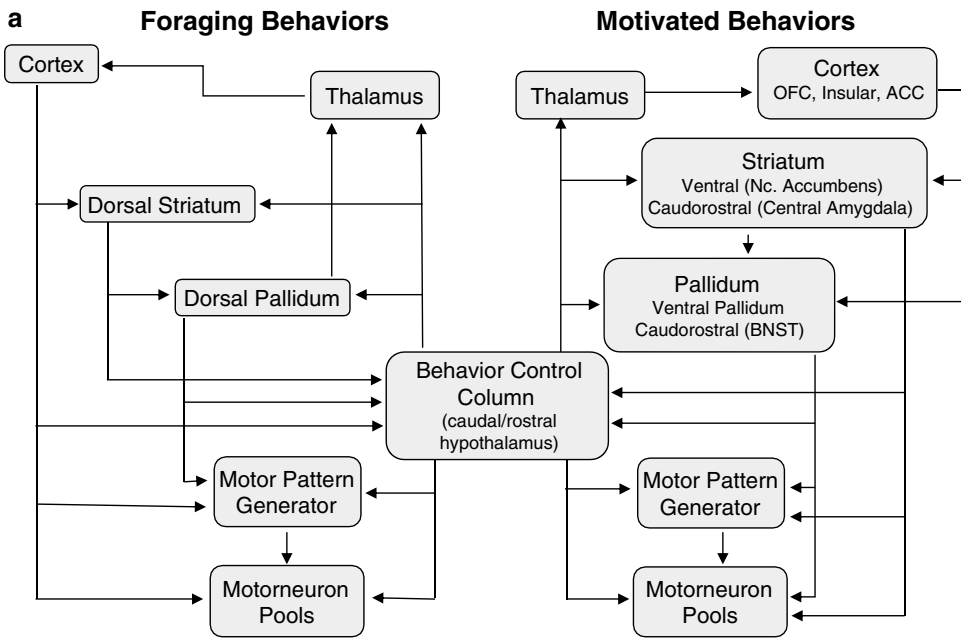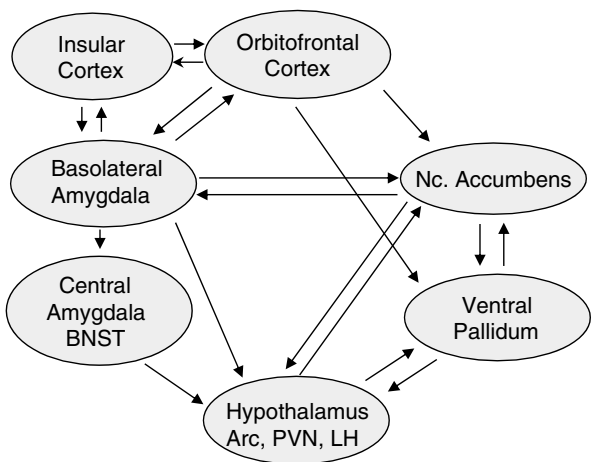
Fig. 142.2 (**a**) Illustration of the concept of the behavioral control column in the medial zone of the hypothalamus. The rostral segment is thought to regulate basic classes of motivated behaviors (ingestive, reproductive, defensive). Exploratory or foraging behaviors are assumed to involve the caudal segment (The graph is based on Swanson (2000) and Watts & Swanson (2002) and the reader is directed to these sources for details) (**b**) Schematic diagram of key structures of the motive circuitry implicated in the perception of reward and the activation of adaptive behavioral responses

reward perception is at least in some neural structures profoundly dependent on internal state of energy balance. Many neural structures sensitive to food reward have been revealed in the past decade. In the rat, a motive circuitry has been delineated responding to appetitive food stimuli including regions in the orbitofrontal cortex, insular cortex, amygdala, Nc. Accumbens, ventral pallidum,

ventral tegmental area, and dorsal thalamus (see Fig. 142.2b; Kalivas and Nakamura 1999; Holland and Gallagher 2004; Berridge and Kringelbach 2008; Smith et al. 2009). While the specific contributions of these structures to the organization of motivated behaviors remains to be determined, unique contributions among selected structures in controlling ingestive behaviors have been demonstrated. For instance, recent research has revealed "hedonic hot spots" in the Nc. accumbens and ventral pallidum of the rat brain with different functions in instrumental responding to and consumption of food and hedonic liking responses measured by facial expression (Smith et al. 2009). Furthermore, core structures of the motive circuitry are differentially implicated in the phenomenon of classically conditioned eating. In the learning phase, a cue is repeatedly presented when hungry rats are allowed to eat. During testing, presentation of this cue can stimulate eating even when the rat is satiated. A recent study suggests that this phenomenon relies on direct pathways from orbitofrontal cortex and basolateral nuclei of the amygdala but not from Nc. accumbens (Petrovich et al. 2005). Furthermore, new learning induced by devaluation of the food with LiCL (lithium chloride) is abolished when the orbitofrontal cortex but not the amygdala is lesioned before the devaluation procedure (Pickens et al. 2003). Thus, the orbitofrontal cortex seems to be critical for learning about changes in the stimulus-reinforcement contingencies. Further differentiation among the contribution of neural structures of the motive circuitry is suggested when considering the inhibition of the feeding response by fear. Specifically, inhibition of feeding by presenting a classically conditioned fear stimulus is abolished when leasoning the central (but not the basolateral) nuclei of the amygdala (Petrovich et al. 2009). Overall, an interconnected network of neural structures has been revealed which mediates reward perception and provides gateways to the engagement of feeding motivation and the organization of appropriate motor responses. In humans, a growing number of studies investigated the hypothesis that core structures of reward perception are sensitive to incentive value using functional neuroimaging (e.g., Arana et al. 2003; Killgore et al. 2003; Kringelbach et al. 2003; Beaver et al. 2006; Porubská et al. 2006; Schienle et al. 2009). Despite notable differences, the findings support the notion that incentive value modulates neural activity in core structures of reward processing.

142.3 Food Deprivation and Incentive Value

The understanding of the neural organization of reward perception provides a roadmap for the neuroscientific examination of deprivation effects in humans. Early studies investigating fasting and satiation effects on brain activity revealed that neural activity decreased among other regions in several structures of the motive circuitry including orbitofrontal cortex, insular cortex, basal ganglia, and hypothalamus in satiated as compared to hungry state (Tataranni et al. 1999; Delparigi et al. 2002, 2005). These findings imply that hunger may have profound effects on resting state activity of the motive circuitry in the absence of external stimulation.

More recent studies investigated the effects of food deprivation on food-related stimulus processing. Incentive motivation theory posits that incentive value of food items is modulated by physiological drive states (Toates 1981). According to this hypothesis, core structures of the motive circuitry are expected to show increased activity to food-related stimuli in deprived as compared to satiated state. To identify relevant studies, a literature research on public databases (PubMed, Web of Science) was conducted using a variety of key words (e.g., hunger, deprivation, eating, food). Nine studies were identified, which directly contrasted deprived and satiated state and measured brain activity in the motive circuitry to the presentation of food-related stimuli (Tables 142.1 and 142.2).

Hemodynamic measures were used in all studies with functional magnetic resonance imaging (fMRI) being more common than positron emission tomography (PET), in particular in most recent

Table 142.1 Schematic overview of fMRI- and PET-studies investigating deprivation effects on food stimulus processing

	N	Hours of deprivation (h)	Day time of session	Manipulation check	Assessment of eating	Method	Task	Stimuli
LaBar et al. (2001)	9 (8 women)	~8	5:00–8:00 pm	Self-report	Self-report	1.5 T fMRI Event-related Design	Control task	Pictures of foods and objects
Uher et al. (2006)	18 (10 women)	~24	12:30–1:30 pm	Biochemical measures	Three Factor Eating Questionnaire	1.5 T fMRI Event-related & Block-Design	Evaluative rating task	Pictures of Foods and Objects Taste of chicken broth, chocolate milk, saliva
Goldstone et al. (2009)	20 (10 women)	~16	11:00–12:00 am	Self-report	Dutch Eating Behavior Questionnaire SCOFF	3 T fMRI Block-Design	Evaluative rating task	Pictures of low- and high-caloric foods and objects
Hinton et al. (2004)	12 (0 women)	~18	12:30–1:30 pm	Biochemical measures		PET Block-Design	Evaluative rating task	Low and high incentive menus
Piech et al. (2009)	8 (3 women)	~6	6:00–7:00 pm	Self-report	History of eating disorder	1.5 T fMRI Event-related Design	Evaluative rating task	Low and high incentive menus
Morris and Dolan (2001)	10 (1 woman)	~16	4:00–5:00 pm	Biochemical measures	History of eating disorder	PET Block-Design	Picture recognition task	Pictures of foods and objects
Mohanty et al. (2008)	7	~8	?	Self-report	Restrained Eating	3 T fMRI Mixed Event-related Design	Spatial attention task	Food and object pictures
Siep et al. (2009)	12 (12 women)	~18	1:00–3:00 pm	Self-report	History of eating disorder; Restrained Eating	3 T fMRI Block-Design	Attention task: Attend taste, Attend objects, Attend bars	Pictures of low- and high caloric foods and objects
Haase et al. (2009)	18 (9 women)	~12	11:00–12:00 am	Self-report	Three Factor Eating Questionnaire	3 T fMRI Event-related Design	No task	Taste stimuli: caffeine, saccharin, sucrose, sodium chloride, guanosin 5′ monophosphate

Summary of selected methodological aspects of fMRI- and PET-studies examining food deprivation

Table 142.2 Key findings of deprivation effects

Study	Effect	Orbitofrontal cortex	Insular cortex	Amygdala	Striatum	Hypothalamus	Other regions
LaBar et al. (2001)	DEP			L			Fusiform R, Parahipp R
Uher et al. (2006)	Vision: DEP						Fusiform LR
Goldstone et al. (2009)	DEP x CAL	LR	LR	LR	LR, ventral		Hipp, ACC, DLPFC
	DEP: High vs. low CAL	LR	LR	LR	LR, ventral		
	SAT: High vs. low CAL						
Hinton et al. (2004)	DEP		L	R	LR	L	Thal L, Brainstem, ACC R
	Incentive	L		L			
	DEP x Incentive	L					
Piech et al. (2009)	Incentive	L, medial		L			Cerebellum R
	DEP x Incentive	L, lateral					
Morris and Dolan (2001)	Hunger		R, anterior	R, anterior	R, NAcc	R	
Mohanty et al. (2008)	DEP x Picture			R			Parahipp R, PCC LR, Brainstem PC R, Peristriate cortex L
Siep et al. (2009)	DEP x Picture	LR, medial; L, lateral	R		L		Fusiform, PCC
Uher et al. (2006)	Taste: DEP		L, anterior				
Haase et al. (2009)	DEP: Sucrose	R	R	R	R		DLPFC R, MPFC R, Postcen L
	DEP: Saccharin						Parahipp LR, Thal R, Hipp LR
	DEP: Caffeine				L	LR	Parahipp R, Thal R, Hipp R
	DEP: Citric acid	R	LR	LR	LR	R	Parahipp LR, Thal LR, Hipp R
							Parahipp LR, Thal L, Hipp LR

This table summarizes the main findings of deprivation effects in structures of the motive circuitry and other brain regions

DEP deprivation, *CAL* calorie, *SAT* satiated, *L* left, *R* right, *ACC* anterior cingulate cortex, *DLPFC* dorsolateral prefrontal cortex, *Fusiform* fusiform gyrus, *Hipp* hippocampus, *MPFC* medial prefrontal cortex, *NAcc* nucleus accumbens, *PC* parietal cortex, *PCC* posterior cingulate cortex, *Parahipp* parahippocampal cortex, *Postcen* postcentral gyrus, *Thal* thalamus

studies. Accordingly, before considering empirical findings, basic principles of fMRI are briefly summarized. The technique is not measuring neural activity directly but associated epiphenomena, the local vascular response. Neuronal activation is associated with an increase in blood flow (cf., Logothetis 2008). For poorly understood reasons, the delivery of oxygenated hemoglobin is larger than local oxygen consumption. Oxygenated and deoxygenated hemoglobin have different magnetic properties and changes in their relative concentration can be revealed by magnetic resonance signals. Like other brain imaging methods assessing blood flow, temporal resolution is on the order of seconds as the changes in blood flow are relatively slow. However, spatial resolution is high as the brain is divided in small cubes (e.g., $1 \times 1 \times 1$ mm). The subtraction method is used to disclose deprivation effects on food cue processing in which the Blood Oxygenation Level Dependent (BOLD) signal to food cues under deprived versus satiated state is contrasted.

Three studies examined the processing of food and control pictures in deprived and satiated state. The first of these studies observed increased BOLD activity in the amygdala when viewing food pictures in a deprived state (LaBar et al. 2001). In contrast, Uher and colleagues (2006) observed no differential activity in the motive circuitry elicited by food pictures as a function of deprivation. A recent study revealed that deprivation effects in the motive circuitry may appear specifically to high-incentive food pictures (Goldstone et al. 2009). Pronounced increases in activation of orbitofrontal and insular cortex, amygdala, and striatum were observed when contrasting high- and low incentive stimuli during deprived but not satiated state. Presenting symbolic visual representations of food items, in particular of high incentive value, is accordingly sufficient to elicit motivational responding in humans. Two further studies relied to an even greater extent on the presentation of symbolic stimuli and mental imagery. Specifically, a restaurant-like situation was realized, in which participants' brain activity was measured while they read and chose between menus items consisting of entrée, dinner, and dessert which were tailored individually to be of low and high incentive value (Hinton et al. 2004; Piech et al. 2009). A PET-study revealed that food deprivation was associated with increased BOLD activity in several structures of the motive circuitry (see Table 142.2). Furthermore, regions in the orbitofrontal cortex were particularly activated when reading high incentive menu items in a deprived state (Hinton et al. 2004). Using an event-related fMRI design, a follow-up study revealed two regions in orbitofrontal cortex, which were similarly showing an interaction of incentive value and motivational state. In addition, irrespective of food deprivation, amygdala activation was increased for menu items of high compared to low incentive value (Piech et al. 2009). Overall, food deprivation increases the incentive value of visual representations of food-related stimuli in the motive circuitry, possibly specifically for high-incentive stimuli.

Deprivation effects on the processing of taste stimuli were investigated in two studies. The study by Uher and colleagues (2006) included a taste condition in which processing of chicken broth and chocolate milk was compared to a control condition (artificial saliva). Deprivation did not alter the activity in structures of the motive circuitry when processing these complex gustatory stimuli. Studying pure taste stimuli, a recent study revealed deprivation effects in the motive circuitry (Haase et al. 2009; see Table 142.2), which, however, were most pronounced for the highly pleasant sucrose and mildly unpleasant citric acid stimuli. Overall, these studies reveal a pattern of findings similar to studies examining visual processing.

From a theoretical perspective, these studies revealed deprivation effects on food stimulus processing either in passive viewing or in active attention conditions, which were low in processing demand. Recent research suggests that task focus may have pronounced effects on food processing even when comparing passive viewing with evaluative rating tasks (Bender et al. 2009). It is therefore interesting to consider studies in which deprivation effects were investigated while participants performed explicit tasks. The first of these studies (Morris and Dolan 2001) used PET to explore whether food deprivation specifically enhances the recognition of food pictures. Blocks of either

food or non-food pictures were presented and participants' task was to indicate whether the seen pictures was included in a memory set presented immediate before the scanning took part. Furthermore, participants were initially tested in a deprived state and fed to satiety in the course of the experiment. Hunger ratings were positively correlated with BOLD activity in the insular cortex, Nc. Accumbens, and hypothalamus, irrespective whether participants viewed food or object pictures. Specificity for food picture processing was seen in the right posterior orbitofrontal cortex, which showed a positive relationship to hunger ratings. Several regions in the brain showed a relationship to memory performance, category-independent (e.g., orbitofrontal cortex) and category-dependent (e.g., left amygdala, insula), which, however, was not modulated by the motivational state. A second study examined the effects of spatial attention and food deprivation (Mohanty et al. 2008). The attention task consisted of valid, invalid, and neutrally cued responses to laterally presented target stimuli (donuts or tools) and foils (danishes and screws). In a mixed event-related paradigm, food and nonfood pictures were shown in separate blocks. Deprivation increased BOLD activity in the amygdala to blocks containing food pictures in a deprived as compared to a satiated state (see Table 142.2 for other regions). This finding was specific to food picture processing and not observed in blocks presenting tool items. A further aim of this study was to examine the relationship of anticipatory activity in neural structures of the spatial attention network and speed of responding. Deprivation specifically modulated anticipatory activity in parietal and posterior cingulate cortex during blocks of food targets. Furthermore, medial sectors of the orbitofrontal cortex were related to the performance in the attention task when hungry and lateral orbitofrontal cortex during satiety. A third study examined deprivation effects on the processing of high and low caloric food and object pictures in the context of an explicit object-based attention task (Siep et al. 2009). In separate blocks, attentional focus was directed either toward food items, towards the color of the picture, or to bars positioned at lateral sites of the pictures. A strict analysis revealed no significant three-way interaction of picture type, attention focus and deprivation. Less stringent analysis revealed that regions in the insular cortex, medial and inferior orbitofrontal cortex, and striatum showed an interaction between picture type (low calorie, high calorie food, objects) and deprivation. In these structures, low compared to high calorie stimuli seemed to elicit increased activity in the satiated state, while high compared to low calorie stimuli elicit increased activity in the deprived state. Furthermore, these effects were independent from the attention task. With regard to the effects of paying attention to food, activity in amygdala and orbitofrontal cortex was increased when food pictures where task relevant, however, the effect was similarly pronounced for low- and high calorie stimuli. Overall, deprivation effects were investigated in active task contexts by several studies adapting established paradigms from cognitive neuroscience. Albeit preliminary, evidence for modulations of incentive value by food deprivation seems ambiguous. Embedding food items in the structure of cognitive tasks may diminish their salience. The use of a passive viewing condition is recommended in order to determine the activation of structures of the motive circuitry independent from explicit task demands. Furthermore, although food stimuli are task-relevant in these studies, there are striking differences to natural situations in which goal-relevance of food stimuli serves to support adaptive behaviors.

One reading of the information depicted in Table 142.2 is that core structures of the motive circuitry are sensitive to both incentive value of food stimuli and internal state. However, there is considerable variety in experimental findings across studies. No single structure received unanimous support and positive findings showed considerable variability with regard to hemispheric lateralization. Consideration of methodological variables might be particularly informative to identify issues, which need to be addressed in future research (see Table 142.1).

The number of participants pronouncedly varied across studies raising the concern that differences in findings may simply arise because of differences in statistical power. While hours of deprivation

greatly varied across studies (6–24 h), there seems no simple relationship to the observation of deprivation effects. However, considering also the great variance with regard to time of testing, circadian rhythm might moderate the effects of food deprivation on food-related stimulus processing. Overall, a paradigmatic approach seems valuable to empirically delineate appropriate sample sizes and hours of deprivation and to reveal circadian rhythm effects.

The majority of studies presented visual stimuli. Food pictures were presented in six studies with most recent studies varying caloric content of the stimulus materials. Written descriptions of menus (starter, entrée, dessert) were used in two studies, which individually varied preference for the menus. Obviously, the quality of stimulus materials is of great importance in revealing deprivation effects. The development of freely shared stimulus materials, calibrated according to major dimensions of eating and ingestion might facilitate progress in the field, similar to the development of the International Affective Picture Series (IAPS, Lang et al. 2008) in the domain of emotion research.

In summary, insights about the neural organization of the feeding system derived from animal research can serve as theoretical foundation to investigate the neural organization of the human feeding system in general, and regarding the effects of deprivation in particular. The rather small number of studies provides promising evidence for the hypothesis that core structures of the motive circuitry, associated with reward perception and adaptive behavior organization, are sensitive to variations in internal state. However, given the importance of deprivation, the widespread practice of voluntary restricting food intake by dieting and restrained eating, a much larger database is needed to realize the potential of the neuroscientific perspective on the understanding of both basic mechanism of food intake regulation and eating-related disorders.

142.4 Overfeeding, Satiation and Incentive Value

A complementary perspective on the effects of deprivation is provided by studies investigating sensory-specific satiety and overfeeding (see Tables 142.3 and 142.4). Several studies examined the phenomenon of sensory-specific satiety, which denotes that the incentive value and rated pleasantness decreases to food, which is eaten to satiety to a greater extent than for other foods. In an fMRI-study (O'Doherty et al. 2000), processing of vanilla and banana odors was investigated in two sessions (pre- and post-meal), which were identical with the exception that the second session took part after eating bananas to satiety. The orbitofrontal cortex was related to olfactory sensory-specific satiety showing a specific decrease in BOLD signal to banana odors in the post- as compared to the pre-meal condition. These findings are consistent with single cell recording in the orbitofrontal cortex of macaques, which revealed that olfactory neurons decreased responding to food odors eaten to satiety (Critchley and Rolls 1996). A further PET- study investigated changes in brain activity related to eating chocolate. Specifically, brain activity was measured while participants were given a single piece of chocolate immediately before the scanning period, tracking the hedonic experience of chocolate from being highly pleasurable to being highly aversive (Small et al. 2001). Among other regions (see Table 142.4), medial orbitofrontal cortex, insular cortex, and striatal regions showed a decrease in activity with increasing satiety. Of particular interest, lateral orbitofrontal cortex showed opposite effects, i.e., enlarged activity when chocolate was perceived as highly aversive. Accordingly, adding further evidence for the role of orbitofrontal cortex and sensory-specific satiety, medial and lateral orbitofrontal cortex appear to be selectively responsive during states in which approach and avoidance dispositions were dominant. Effects of sensory-specific satiety were furthermore investigated in the context of associative conditioning paradigm, in which odors were paired with task-relevant visual stimuli (Gottfried et al. 2003). Devaluation affected several structures of the motive circuitry

Table 142.3 Schematic overview of fMRI- and PET-studies investigating effects of satiation, and overfeeding

Study	N	Effect	Manipulation check	Method	Task	Stimuli
O'Doherty, et al. (2000)	5	Sensory-specific satiety	Self-report	3 T fMRI Block-Design	No task	Vanilla and banana odors
Small et al. (2001)	9 (5 women)	Sensory-specific satiety	Self-report	PET Block-Design	Evaluative rating task	Pieces of chocolate
Gottfried et al. (2003)	13	Sensory-specific satiety	Self-report	1,5 T fMRI Event-related Design	Reaction time task (CS) and Implicit associative conditioning	CS: Visual images US: Odors
Holsen et al. (2005)	9 children (5 women)	Pre- vs. Post meal		3 T fMRI Block-Design	Memory task	Pictures of foods, animals and objects
Cornier et al. (2007)	25 (13 women)	2 days of overfeeding	Control of food intake	3 T fMRI Block-Design	No task	Pictures of high- and low incentive foods and objects
Cornier et al. (2009)	22, thin (10 women) 19, reduced obese (10 women)	2 days of overfeeding	Control of food intake	3 T fMRI Block-Design	No task	Pictures of high- and low incentive foods and objects

Summary of selected methodological aspects of fMRI- and PET-studies examining satiation and overfeeding

Table 142.4 Key findings of effects due to satiation and overfeeding

Study	Effect	Orbitofrontal cortex	Insular Cortex	Amygdala	Striatum	Hypothalamus	Other regions
O'Doherty et al. (2000)	Pre-> post-meal	R					
Small et al. (2001)	rCBF decreases with decreasing reward value	LR, medial	LR		LR		ITG LR, MTG LR, OTG/Cereb LR, Hipp L, Thal L
	rCBF increases with decreasing reward value	R, lateral					Precen LR, IFG L, Cing, Parahipp R, SMA R, MFG, middle FC L
Gottfried et al. (2003)	Pre-> post-meal	L, rostral R, caudal	R, anterior	L	L, ventral		ACC R
Holsen et al. (2005)	Motivational State x Picture Type	R, medial LR lateral	L	R	R		MFG L, Oper LR, Parahipp R, Cing, Fusiform L, IFG R, SFG LR, ITG R, Postcen L, Precen LR, Supra LR, Cereb/Fusiform R
Cornier et al. (2007)	EU>OF: (High Val> Low Val)					L	IVC R
Cornier et al. (2009)	Thin Subjects: EU>OF: (High Val > Obj)		X			X	
	(Thin > Reduced Obese): (EU>OF): (High Val > Obj)		LR			R	IVC R

This table summarizes effects of satiation and overfeeding on the activation of structures of the motive circuitry and other brain regions

EU eucaloric state, *OF* overfeeding, *High Val* high incentive food picture, *Low Val* low incentive food picture, *Obj* object picture, *L* left, *R* right, *ACC* anterior cingulate cortex, *Cereb* cerebellum, *Cing* cingulate cortex, *Fusiform* fusiform gyrus, *Hipp* hippocampus, *IFG* inferior frontal gyrus, *ITG* inferior temporal gyrus, *IVC* inferior visual cortex, *MFG* medial frontal gyrus, *middle FC* middle frontal cortex, *MTG* medial temporal gyrus, *OTG* occipitotemporal gyrus, *Oper* basal operculum, *Parahipp* parahippocampal gyrus, *PCG* posterior cingulate gyrus, *Postcen* postcentral gyrus, *Precen* precentral gyrus, *SFG* superior frontal gyrus, *SMA* supplementary motor area, *Supra* supramarginal gyrus, *Thal* thalamus, *rCBF* regional cerebral blood flow

(amygdala, ventral striatum, orbitofrontal cortex, insular cortex, see Table 142.4). Furthermore, regions in the amygdala and orbitofrontal cortex showed decreased BOLD signals specifically to the visual stimuli associated with the devalued odor while other brain regions (ventral striatum, insular cortex) showed both decreases and increases to visual stimuli paired with devalued and nondevalued odors, respectively. Investigating children, Holsen and colleagues (2005) presented food and object pictures in two sessions (pre- and post-meal) with participants eating a meal (500 kcal) in between the sessions. Amygdala, orbitofrontal cortex, and insular cortex showed a selective decrease to food pictures when comparing pre- and post-meal sessions. Two further studies investigated the effects of overfeeding on the processing of food (low and high incentive) and control pictures (Cornier et al. 2007; Cornier et al. 2009). Towards this end, participants were tested even after 2 days of either eucaloric or overfed (30% above eucaloric) energy intake. Overfeeding attenuated responding to high as compared to low incentive food pictures in the hypothalamus and inferior visual cortex (Cornier et al. 2007). These results were extended in a recent study investigating thin and obese participants, which reduced weight by 8% (Cornier et al. 2009). Regarding thin participants, food compared to object pictures elicited increased BOLD signals among other structures in orbitofrontal cortex, insular cortex, and ventral striatum in the eucaloric state. Overfeeding for 2 days resulted in reduced activity in these structures reaching significance in the insular cortex and hypothalamus. These effects of overfeeding were attenuated in obese participants. Overall, core structures of the reward matrix, in particular regions of the orbitofrontal cortex, showed a decrease in activity when fed to satiety.

142.5 The Motivational Regulation of Attention

The feeding system controls the organization of ingestive behaviors. Internal state and the perception of food-related cues from the immediate environment prime unique sets of perceptual-motor units that increase sensitivity to relevant stimuli at the appetitive and consummatory behavioral stage. According to this perspective, food deprivation effects operate at multiple levels, by increasing incentive value of food stimuli, and by regulating attention processes.

However, attention is not a unitary phenomenon but refers to a collection of disparate functional processes. For instance, recent research has begun to detail food deprivation effects on spatial attention mechanisms and object-based attention, which imply distinct neural mechanisms (Mohanty et al. 2008; Siep et al. 2009). Furthermore, attention is not only regulated according to explicit instructions by varying the task relevance of food stimuli, but is also passively captured by stimuli according to their motivational and emotional significance (Öhman 1986). When related to current motivational needs, stimuli may reflexively capture attentional resources to facilitate efficient responding.

Support for the obligatory nature of the motivational regulation of attention processes has been obtained in a study, in which food pictures were passively viewed, and participants performed an easy control task (detecting an occasional flicker of the images). Food deprivation enhanced the activity in higher order visual-associative regions (fusiform gyrus) when processing food pictures (LaBar et al. 2001). Conceptually similar results were observed when pictures were evaluated according to their likeability after viewing the pictures (Uher et al. 2006), but not when ratings of appealingness were made during picture viewing (Goldstone et al. 2009). Accordingly, although not explicitly designed to address the issue, there is some evidence that deprivation enhances attention processes to need-related food stimuli.

Two recent studies explicitly assessed the hypothesis that deprivation (24 h) sensitizes the processing of food cues (Stockburger et al. 2008, 2009a). Event-related brain potentials (ERPs) were measured

in these studies, which provide a voltage measurement of neural activity that can be recorded non-invasively from multiple scalp regions. More specific, ERPs are considered to reflect summed post-synaptic potentials generated in the process of neural transmission and passively conducted through the brain and skull to the skin surface where they contribute to the electroencephalogram (EEG). Since ERPs are usually hidden in the larger background EEG activity, it is necessary to use multiple stimulus presentations and stimulus-locked signal averaging to extract the ERP signal from the background EEG activity. Biophysical considerations suggest that large-amplitude ERP components reflect widespread, synchronous sources in cortical regions. Brain activity locked to the processing of a stimulus becomes apparent as positive and negative deflections in the ERP waveform. The amplitude and latency of specific ERP components provide information regarding the strength and time course of underlying neural processes. Furthermore, given appropriate spatial sampling, the topography of ERP components can be used to estimate the neural generator sites by advanced analytic tools such as L2-Minimum-Norm-Estimate (L2-MNE; Junghöfer et al. 2006).

The first study was specifically designed to determine whether motivational state modulates early visual attention processes (Stockburger et al. 2008). A rapid serial presentation technique was used in which stimuli were presented for 330 ms without any perceivable interstimulus gap. Thus, this paradigm induces perceptually demanding conditions, which are deemed as necessary to reveal attention effects. Food stimuli were interspersed in a stream of pleasant, neutral, and unpleasant control stimuli drawn from various categories of human experience, which served as control stimuli to determine the specificity of deprivation effects on food picture processing. Results showed that deprivation specifically modulated the relatively early processing of food pictures. Between 170 and 320 ms, the ERP waveform revealed enhanced posterior positive deflections for food pictures in hungry compared to satiated state (Fig. 142.3a). MNE source calculations revealed that these deprivation effects on food processing were associated with primary activations in posterior perceptual representation networks. In addition, secondary activations were suggested over anterior brain regions (Fig. 142.3b). However, spatial resolution was insufficient to determine whether this finding

Deprivation Effects on Early Cortical Food Stimulus Processing
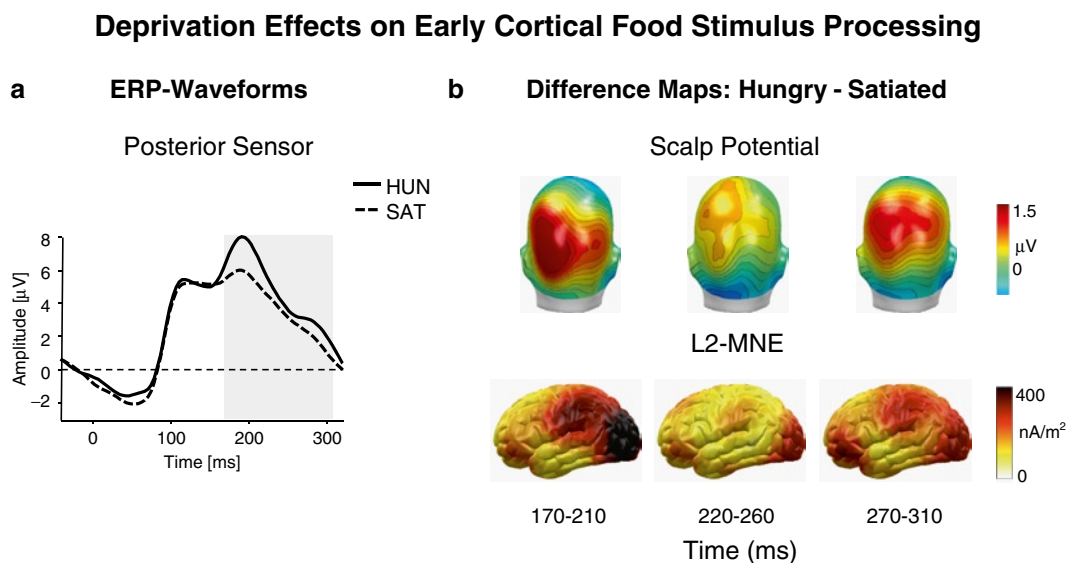
Fig. 142.3 (**a**) Representative ERP-waveforms for food pictures in the hungry (*red lines*) and satiated (*black lines*) states. (**b**) Scalp potential (*back view*) and L2-Minimum Norm estimates maps (right lateral view) show differences in processing food pictures in deprived and satiated state (Based on Stockburger et al. 2008)

relates to orbitofrontal activations, which were observed when comparing food cue processing in hungry and satiated state and food stimuli varying in their incentive value (O'Doherty et al. 2000; Morris and Dolan 2001; Arana et al. 2003). These findings suggest that perceptual stimulus processing is gated in specific ways according to motivational state. According to a functional perspective, ERP modulations in this time window have been considered to reflect a call for processing resources in later capacity-limited processing stages implicated in conscious stimulus recognition (cf. Öhman 1986; Schupp et al. 2006).

These later processing stages related to working memory and stimulus recognition were the focus of another study in which food and flower pictures were presented as rapid serial stream for 660 ms (Fig. 142.4a and b; Stockburger et al. 2009a). A consistent body of evidence revealed that emotionally relevant pictures elicit increased late positive potentials (LPP) between 350 and 700 ms post-stimulus (Schupp et al. 2006). Similarly, food deprivation specifically enhanced the LPP component to food pictures (Fig. 142.4c). The assumption that increased positive potentials to food pictures in a hungry state reflects enhanced processing is supported by L2-MNE analyses, which revealed increased dipole strength over extended posterior visual processing regions (Fig. 142.4d). Thus, consistent with its presumed relation to conscious stimulus recognition, the LPP is linked to widespread activation broadcasting stimulus information to many associative cortical regions rather than reflecting local processing (Del Cul et al. 2007). Overall, in a state of food deprivation, food pictures seem to elicit a state of heightened selective attention in a capacity-limited processing stage, which is a critical gateway for the stimulus representation in working memory and conscious stimulus recognition. Furthermore, these findings were observed while participants passively viewed the stimulus materials and the food images were not task relevant. Consequently, the motivational regulation of visual processing appears to be a spontaneous and involuntary phenomenon, important characteristics of automatic processes.

Overall, electrophysiological measures of brain activity allow delineating the regulation of attention processes at the level of distinct processing stages. Internal motivational state sensitizes responding to need-related stimuli in processing stages mandatory for stimulus recognition. This mechanism seems highly adaptive from a functional perspective. The selective responding and evaluation of need-relevant stimuli is critical for the efficient organization of food-related behaviors.

142.6 Food Deprivation and the Startle Reflex

To obtain reliable measures of brain activity related to stimulus processing, neuroimaging methods require repeated stimulus presentations. Accordingly, in the case of food deprivation, stimuli are presented while participants are denied access to food. Unfortunately, the motivational orientation elicited in these protocols is potentially ambiguous. On the one hand, viewing food-related stimuli in deprived state may prompt associated appetitive responses. Alternatively, a state of frustrative non-reward may be induced, if participants are denied the immediate consumption of food.

Studies utilizing the startle probe methodology (see Table 142.5) may help to resolve this issue (Drobes et al. 2001; Mauler et al. 2006). This research builds upon the notion that responding to emotionally and motivationally significant stimuli is organized by two basic brain circuits, one prompting appetitive responding and pleasant affects, and the other determining withdrawal and defense behaviors and unpleasant affect. The measurement of the defensive startle reflex allows inferring the engagement of basic motive systems, which is potentiated when elicited during an aversive state and inhibited during pleasant states. In their study, Drobes and colleagues (2001) presented a series of food pictures as well as emotional and neutral control pictures varying level

Deprivation Effects on Later Cortical Food Stimulus Processing
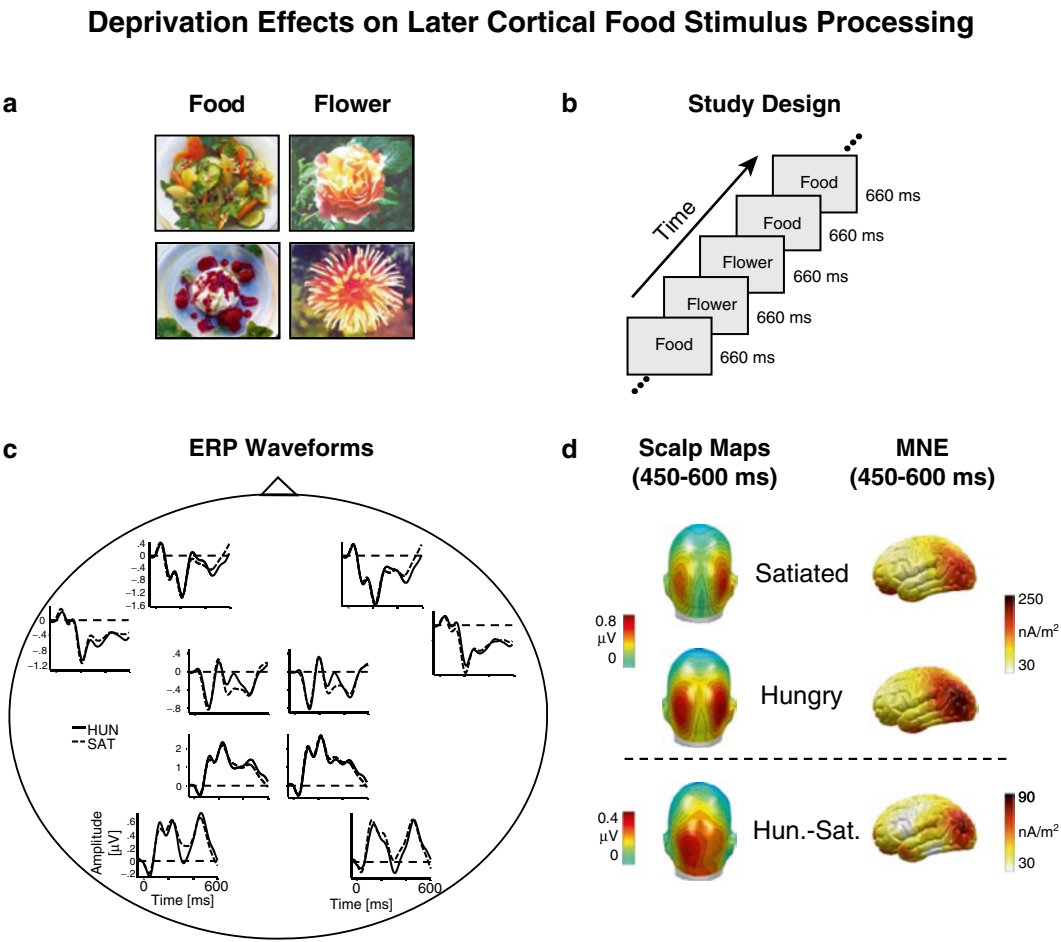
Fig. 142.4 (**a**) Representative examples of the food and flower stimuli. (**b**) Illustration of the rapid serial visual presentation paradigm. Food and flower pictures were presented for 660 ms without perceivable interstimulus gap. (**c**) Representative ERP-waveforms for food pictures in the hungry (*red lines*) and satiated (*black lines*) states. (**d**) Scalp potential (*back view*) and L2-Minimum Norm estimates maps (right lateral view) show the topography of the LPP component for food and the difference between the hungry and satiated states (Based on Stockburger et al. 2009a)

Table 142.5 Key features of the startle reflex

1. The startle reflex is a defense response that prevents organ injury and interrupts ongoing mental and behavioral activity
2. The startle reflex is a whole body response that consists of rapid flexor movements cascading throughout the body
3. The reflex is elicited by sudden, unexpected, and intense stimuli. In the laboratory, acoustic stimuli (e.g., 50 ms duration, 90–110 dB loudness, and instantaneous rise time) are often used to elicit the reflex
4. Rapid eye closure is among the most reliable components of the startle response in humans and measured by recording the electrical activity of the orbicularis oculi muscle
5. The acoustic blink reflex shows an onset latency of ~20–40 ms and usually peaks between 50 and 100 ms
6. While the startle reflex is an obligatory response, its magnitude varies as a function of emotional, motivational, and attentional processes

This table lists the key features of the startle reflex

of food deprivation across subjects (0, 6, 24 h). In a nondeprived state, food pictures revealed inhibited startle responses as compared to the other picture materials suggesting that these cues prompt an appetitive approach disposition. In contrast, startle reflexes elicited during food picture viewing were potentiated for both deprivation levels as compared to the nondeprived group. These findings were considered to reflect an aversive motivational reaction, which is attributed to a state of frustrative non reward, i.e., participants were not allowed immediate consumption (Drobes et al. 2001). However, another line of studies revealed that the active imagination of pleasant scenes triggered enhanced startle reflexes compared to neutral imagery contents (Miller et al. 2002). An alternative interpretation of the Drobes et al. (2001) and Mauler et al. (2006) findings is accordingly, that viewing food pictures elicited vivid imagination in the participants. Resolving the issue is of great theoretical importance and the startle probe methodology may serve as promising tool to disambiguate motivational orientation elicited by internal deprivation state and external food cue reactivity.

142.7 Applications to Other Areas of Health and Disease

Revealing the effects of food deprivation with regard to incentive value and attention processes provides highly relevant information for the obesity pandemic. The voluntary restriction of food intake for regulating body weight is an increasing phenomenon in many Western cultures. Such attempts in dieting and restrained eating are often accentuated towards foods considered as fattening (e.g., sweets, high-fat food). Specific food restrictions may be also due to moral and health concerns as is the case for instance in vegetarianism. It seems highly informative to determine the specificity of food restrictions on the processing of food stimuli with particular emphasis of affective attitudes and short- and long-term effects. For instance, a recent event-related brain potential study revealed the increased attention capture of meat pictures in vegetarians refraining from eating meat for several years (Stockburger et al. 2009b). Understanding food deprivation effects may be furthermore relevant in understanding eating disorders such as anorexia nervosa and bulimia.

Summary Points

- At the core of the feeding system are neural circuits that were laid down early during evolutionary history, in primitive cortex, sub-cortex, and midbrain.
- These motivational circuits are engaged by unconditioned food-related stimuli, determine general mobilization and approach behaviors of the organism, and mediate the shaping of the feeding system by learning and experience.
- Internal state variables exert a profound effect on the feeding system and neuroimaging methods appear promising to provide novel insights into the operation of food deprivation.
- Hemodynamic studies were reviewed providing some support for the notion that food deprivation increases the incentive value of food-related stimuli in core structures of the motive circuitry. There is evidence that these effects appear most robust for high-incentive stimuli.
- Furthermore, attention to need-related stimuli is regulated by motivational state. Event-related potential studies delineate motivated attention processes with high temporal resolution suggesting that deprivation effects facilitate perceptual processing in stages related to stimulus recognition and working memory representation.

- Guided by animal research about the neural organization of the feeding system, electrophysiological, hemodynamic, and reflex measures of brain activity provide a window to probe deprivation effects on food stimulus processing.
- Given the sparse number of relevant studies, a considerable research effort is needed to reveal consistent and reliable findings related to deprivation.
- Understanding these effects seems important when considering that attempts to regulate body weight and eating-related disorders often include the voluntary restriction of food intake.

Key Terms

Ingestive behavior: Ingestive behaviors are comprised by appetitive and consummatory phases which depend on the integration of information about internal state, cues from the environment, behavioral state, and cognition.

Incentive motivation: Incentives arouse motivated behaviors and form the target for goal-direct behaviors. Incentive motivation is determined by external stimuli and internal states.

Motive circuitry: Cortical, subcortical, and brainstem neural structures implicated in reward perception and activation of adaptive behaviors.

Functional magnetic resonance imaging: Neural activity is coupled with blood oxygenation level dependent (BOLD) signal changes that can be measured with MRI. Assessment of short-term changes can be used to infer functional neural activity associated with food stimulus processing in core structures of the motive circuitry.

Motivated attention: In natural environments, attention is dictated by motivational significance of salient stimuli and internal states.

Event-related brain potentials: Electrophysiological recordings of brain activity associated with food stimulus processing. Providing a high temporal resolution, event-related potential recordings allow measuring the motivational regulation of attention by food deprivation.

References

Arana FS, Parkinson JA, Hinton E, Holland AJ, Owen AM, Roberts AC. J Neurosci. 2003;23:9632–8.
Barbano MF, Cador M. Behav Neurosci. 2005;119:1244–53.
Beaver JD, Lawrence AD, van Ditzhuijzen J, Davis MH, Woods A, Calder AJ. J Neurosci. 2006;26:5160–6.
Bender G, Veldhuizen MG, Meltzer JA, Gitelman DR, Small DM. Eur J Neurosci. 2009;30:327–38.
Berridge KC, Kringelbach, ML. Psychopharmacology 2008;199:457–80.
Berthoud HR, Morrison C. Annu Rev Psychol. 2008;59:55–92.
Cornier MA, Von Kaenel SS, Bessesen DH, Tregellas JR. Am J Clin Nutr. 2007;86:965–71.
Cornier MA, Salzberg AK, Endly DC, Bessesen DH, Rojas DC, Tregellas JR. PLoS One. 2009;4:e6310.
Critchley HD, Rolls ET. J Neurophysiol. 1996;75:1673–86.
Del Cul A, Baillet S, Dehaene S. PLoS Biol. 2007;5:2408–23.
Delparigi A, Gautier JF, Chen K, Salbe AD, Ravussin E, Reiman E, Tataranni, PA. Ann N Y Acad Sci. 2002;967:389–97.
Delparigi A, Chen K, Salbe AD, Reiman EM, Tataranni PA. NeuroImage. 2005;24:436–43.
Drobes DJ, Miller EJ, Hillman CH, Bradley MM, Cuthbert BN, Lang PJ. Biol Psychol. 2001;57:153–77.

Goldstone AP, de Hernandez CG, Beaver JD, Muhammed K, Croese C, Bell G, Durighel G, Hughes E, Waldman AD, Frost G, Bell JD. Eur J Neurosci. 2009;30:1625–35.

Gottfried JA, O'Doherty J, Dolan RJ. Science 2003;301:1104–7.

Haase L, Cerf-Ducastel B, Murphy C. NeuroImage 2009;44:1008–21.

Hinton EC, Parkinson JA, Holland AJ, Arana FS, Roberts AC, Owen AM. Eur J Neurosci. 2004;20:1411–8.

Holland PC, Gallagher M. Curr Opin Neurobiol. 2004;14:148–55.

Holsen LM, Zarcone JR, Thompson TI, Brooks WM, Anderson MF, Ahluwalia JS, Nollen NL, Savage CR. NeuroImage 2005;27:669–76.

Junghöfer M, Peyk P, Flaisch T, Schupp HT. Prog Brain Res. 2006;156:123–43.

Kalivas PW, Nakamura M. Curr Opin Neurobiol. 1999;9:223–7.

Keys A, Brozek J, Henschel A, Mickelson O, Taylor HL. The biology of human starvation. 2 vols. Minneapolis: University of Minnesota Press; 1950.

Killgore WD, Young AD, Femia LA, Bogorodzki P, Rogowska J, Yurgelun-Todd DA. NeuroImage 2003;19:1381–94.

Kringelbach ML, O'Doherty J, Rolls ET, Andrews C. Cereb Cortex. 2003;13:1064–71.

Lang PJ, Bradley, MM, Cuthbert BN (2008). International affective picture system (IAPS): Affective ratings of pictures and instruction manual. Technical Report A-8. University of Florida, Gainesville, FL.

LaBar KS, Gitelman DR, Parrish TB, Kim YH, Nobre AC, Mesulam MM. Behav Neurosci. 2001;115:493–500.

Logothetis NK. Nature 2008;12:869–78.

Mauler BI, Hamm AO, Weike AI, Tuschen-Caffier B. J Abnorm Psychol. 2006;115:567–79.

Miller MW, Patrick CJ, Levenston GK. Psychophysiology 2002;39:519–29.

Mohanty A, Gitelman DR, Small DM, Mesulam MM. Cereb Cortex. 2008;18:2604–13.

Morris JS, Dolan RJ. J Neurosci. 2001;21:5304–10.

O'Doherty J, Rolls ET, Francis S, Bowtell R, McGlone F, Kobal G, Renner B, Ahne G. Neuroreport 2000;11:893–7.

Öhman A. Psychophysiology 1986;23:123–45.

Pavlov IP. Zwanzigjährige Erfahrungen mit dem objektiven Studium der höheren Nerventätigkeit (des Verhaltens) der Tiere. Berlin: Akademischer; 1953.

Petrovich GD, Holland PC, Gallagher M. J Neurosci. 2005;25:8295–302.

Petrovich GD, Ross CA, Mody P, Holland PC, Gallagher M. J Neurosci. 2009;29:15205–12.

Pickens CL, Saddoris MP, Setlow B, Gallagher M, Holland PC, Schoenbaum G. J Neurosci. 2003;23:11078–84.

Piech RM, Lewis J, Parkinson CH, Owen AM, Roberts AC, Downing PE, Parkinson JA. PLoS One. 2009;4:e6581.

Polivy J. J Am Diet Assoc. 1996;96:589–92.

Porubská K, Veit R, Preissl H, Fritsche A, Birbaumer N. NeuroImage 2006;32:1273–80.

Raynor HA, Epstein LH. Appetite 2003;40:15–24.

Schienle A, Schäfer A, Hermann A, Vaitl D. Biol Psychiatry. 2009;65:654–61.

Schupp HT, Flaisch T, Stockburger J, Junghofer M. Prog Brain Res. 2006;156:31–51.

Schupp HT, Stockburger J, Codispoti M, Junghöfer M, Weike AI, Hamm AO. J Neurosci. 2007;27:1082–9.

Siep N, Roefs A, Roebroeck A, Havermans R, Bonte ML, Jansen A. Behav Brain Res. 2009;198:149–58.

Small DM, Zatorre RJ, Dagher A, Evans AC, Jones-Gotman M. Brain 2001;124:1720–33.

Smith KS, Tindell AJ, Aldridge JW, Berridge KC. Behav Brain Res. 2009;196:155–67.

Spiegel TA, Shrager EE, Stellar E. Appetite 1989;13:45–69.

Stockburger J, Weike AI, Hamm AO, Schupp HT. Behav Neurosci. 2008;122:936–42.

Stockburger J, Schmalzle R, Flaisch T, Bublatzky F, Schupp HT. NeuroImage 2009a;47:1819–29.

Stockburger J, Renner B, Weike A, Hamm AO, Schupp HT. Appetite 2009b;52:513–6.

Swanson LW. Brain Res. 2000;886:113–64.

Tataranni PA, Gautier JF, Chen K, Uecker A, Bandy D, Salbe AD, Pratley RE, Lawson M, Reiman EM, Ravussin E. Proc Natl Acad Sci USA. 1999;96:4569–74.

Timberlake W. In: Mowrer RR, Klein SB, editors. Handbook of contemporary learning theories. Mahwah: Erlbaum; 2001. p. 155–209.

Timberlake W, Allison J. Psychol Rev. 1974;81:146–64.

Toates FM. Appetite 1981;2:35–50.

Uher R, Treasure J, Heining M, Brammer MJ, Campbell IC. Behav Brain Res. 2006;169:111–9.

Watts AG, Swanson LW. In: Gallistel CR, Pashler H, editors. Stevens' handbook of experimental psychology, volume 3, learning, motivation, and emotion. New York: Wiley; 2002. p. 563–631.

Woods SC, Schwartz MW, Baskin DG, Seeley RJ. Annu Rev Psychol. 2000;51:255–77.

Chapter 143
Symptoms of Starvation in Eating Disorder Patients

Riccardo Dalle Grave, Elettra Pasqualoni, and Giulio Marchesini

Abbreviations

DSM   Diagnostic and Statistical Manual of Mental Disorders
NOS   Not otherwise specified

143.1 Introduction

The DSM-IV classification of eating disorders includes three main diagnostic categories: anorexia nervosa, bulimia nervosa, and eating disorders not otherwise specified (NOS) (American Psychiatric Association 1994). Underweight is a key diagnostic criterion for anorexia nervosa, but could be present in a subgroup of patients with eating disorder NOS (e.g., underweight patients that meet all DSM-IV criteria for AN except amenorrhea (Dalle Grave et al. 2008b) or the overevaluation of shape and weight (Dalle Grave et al. 2008c)). Severe weight loss and dietary restriction (i.e., a persistent caloric intake lower than energy expenditure) could also be present in a subgroup of not underweight eating disorder patients with bulimia nervosa or eating disorder NOS with an history of obesity.

Keys and his colleagues in their classic two-volume, 1,385-page text *The Biology of Human Starvation* (Keys et al. 1950) gave a detailed description of the symptoms of dietary restriction and underweight, traditionally called "starvation symptoms," reported by young male volunteers. The observation that many symptoms reported by the volunteers were similar to those found in patients with anorexia nervosa improved the understanding and the treatment of eating disorders (Garner 1997). Today, it is widely accepted that many symptoms, once attributed to the psychopathology of anorexia nervosa, are the mere consequences of severe weight loss and caloric restriction.

R. Dalle Grave (✉)
Department of Eating and Weight Disorder, Villa Garda Hospital,
Via Montebaldo 89, I-37016 Garda (VR), Italy
e-mail: rdalleg@tin.it

The chapter has three main aims: (1) to review the symptoms associated with underweight and dietary restriction; (2) to describe the role of underweight and dietary restriction in the maintenance of eating disorder psychopathology; (3) to analyze the clinical implications of these symptoms in the treatment of eating disorders.

143.2 Symptoms Associated with Underweight and Dietary Restriction (Starvation Symptoms)

The Minnesota study is considered the key reference on the effect of dietary restriction and weight loss in normal weight individuals. The study was carried out at the University of Minnesota between November 19, 1944 and December 20, 1945 (Keys et al. 1950). The study was designed to evaluate the physiological and psychological effects of severe and prolonged dietary restriction and the effectiveness of nutritional rehabilitation strategies. The principal aim of the study was to guide the assistance to famine victims in Europe and Asia during and after the World War II by using the data derived by a laboratory simulation of severe famine.

More than 100 men were ready to volunteer in the study as an alternative to military service. Of this initial sample, 36 men with the best physical and psychological health and with a high motivation to participate were selected (Keys et al. 1950). The participants were all white males in the age range from 22 to 33 years. Of the 36 volunteer individuals, 25 were members of the Historic Peace Churches (Mennonites, Church of the Brethren, and Quakers).

The study was divided in three phases: a control period of 12 weeks, 24 weeks of semistarvation, and 12 weeks of rehabilitation. During the control period the mean daily caloric intake of the participants was 3,492 calories, during the period of semistarvation the calories were decreased to a mean of 1,570, and during the period of rehabilitation they were re-increased to normal levels. In the semistarvation period, participants were fed foods most likely consumed in European famine areas and lost approximately 25% of their body weight.

Complete data are available only for 32 participants because 4 participants interrupted the study during or at the end of the second phase of semistarvation. The individual reactions to semistarvation and to the weight loss were heterogeneous, but in most cases the participants experienced dramatic effects (see Table 143.1).

143.2.1 Behavioral Effects

Toward the end of the starvation phase the participants spent almost 2 h to eat a meal that they previously consumed in few minutes. Many participants read cookbooks and collected recipes. Some increased coffee and tea consumption, drank large amount of water or soups to increase their fullness, and developed specific eating rituals (e.g., eating very slowly, cutting the food in small pieces, mixing the food in a bizarre way, ingesting hot food). The use of salt, spices, and gums increased, and also nail-biting and smoking. Many of these behaviors persisted also during the 12-week weight restoration phase.

During the semistarvation period, all participants reported a significant increase hunger. However, some were able to tolerate it, while others had bulimic episodes followed by self-criticism. In the weight restoration phase, when participants had access to a large amount of foods, some lost control eating, ingesting more or less than necessary. After 5 months of rehabilitation, most of the participants normalized their eating habits, but a subgroup continued to eat large amount of foods.

Table 143.1 Starvation effects reported by the Minnesota Study (Keys et al. 1950)

Behavioral effects

- Eating rituals (eating very slowly, cutting the food in small pieces, mixing the food in a bizarre way, ingesting hot food).
- Reading cookbooks and collecting recipes
- Increasing coffee and tea consumption
- Increasing the use of salt, spices, gums, hot soup, and water
- Nail-biting
- Increased smoking
- Bulimic episodes
- Increasing exercise to avoid the reduction of the caloric content of the diet
- Self-mutilation

Psychological effects

- Impairment of concentration capacity
- Poor insight and critical judgment
- Preoccupation about thought on food and eating
- Depression
- Mood lability
- Irritation
- Hunger
- Anxiety
- Apathy
- Psychotic episodes
- Personality changes

Social effects

- Social withdrawal
- Loss of sexual appetite

Physical effects

- Abdominal pain
- Gastrointestinal discomfort
- Sleep disturbances, vertigo
- Headache
- Strength reduction
- Hypersensitivity to light and noises
- Edema
- Cold intolerance
- Paresthesia
- Reduction of basal metabolism
- Reduce of heart and respiratory frequency.

Many participants reduced their habitual level of physical activity and complained that they had less energy. However, some individuals used intense exercise to be allowed a larger amount of food or to avoid a reduction in the caloric content of the diet.

143.2.2 Psychological Effects

Most of the participants showed marked cognitive and emotional changes. They reported a decreased concentration capacity, insight, and critical judgment, while no changes in intellectual ability were observed. The impairment in concentration capacity was probably due to the presence of recurrent thoughts on food and eating that were reported by most of the participants.

Some suffered periods of depression, while others had frequent periods of mood changes. A subgroup became irritated and developed episodes of hunger explosion. Anxiety and apathy were common, and in a subgroup of participants the emotional disturbances became so severe that the authors coined the term "starvation neurosis" to describe them. The emotional changes were confirmed by the Minnesota Multiphasic Personality Inventory that showed a significant increase in depression, hysteria, and hypochondria. Two participants developed psychotic symptoms and one self-mutilated three fingers of his hand to modulate his mood. In general, the emotional changes did not disappear immediately after rehabilitation, but persisted for many weeks. However, some participants did not show any psychological deterioration during the entire study period.

143.2.3 Social Effects

Starvation had also a large effect on social functioning. Participants become inward-looking and self-focused, which led to social isolation. In general, they also reported a loss of sexual appetite, another effect that could have contributed to social withdrawal.

143.2.4 Physical Effects

The most frequent symptoms reported by participants during the dietary restriction phase were abdominal pain, difficult digestion, sleep disturbances, vertigo, headache, strength reduction, hypersensitivity to light and noises, edema, cold intolerance, sight and hearing alterations, and paraesthesias. Participants showed a marked reduction in their basal metabolism (almost a 40% decrease), as well as in heart and respiratory frequency. During the weight restoration phase their basal metabolic rate increased proportionally to the increased caloric intake and they regained their baseline body weight after a weight loss of 25% or more of initial body weight.

143.2.5 Comments by Participants to the Minnesota Starvation Experiment

In 2003–2004, 18 of the 36 participants were still alive and were interviewed by researchers of The Johns Hopkins School of Medicine, Baltimore, MD (Kalm and Semba 2005). Participants were in their 80s when interviewed and each spoke passionately when discussing why they chose to be a conscientious objector and to participate in the experiment. Although the data of the study have been reported with scientific details in *The Biology of Human Starvation* book, participants painted a more vivid picture of their daily lives during the experiment (Kalm and Semba 2005). They reported that, after an initial enthusiasm, they suffered great changes in their personalities during semistarvation. They became increasingly irritable and impatient with one another and began to suffer the physical effect of caloric restriction. They also reported an increase of introversion, less energy, dizziness, extreme tiredness, cold intolerance, muscle soreness, hair loss, reduced coordination, ringing in their ears, and poor concentration. Food became an obsession for all the participants, and several men confirmed that interest in women and dating was lost soon after study began. Despite the difficulties of starvation, they reported a strong determination to continue the study, and suggested different reasons for their dedication, including religious reasons, discipline, and will power (Kalm and Semba 2005).

For some men, the rehabilitation period was considered the most difficult part of the experiment. They reported that symptoms of dizziness, apathy, and lethargy were the first to decrease, while feelings of tiredness, loss of sex drive, and weakness were much slower to improve. They reported not being back to normal by the end of the 3-month recovery period. Many overate after they left Minnesota and became obese. They estimated that the time to achieve a full recovery ranged from 2 months to 2 years (Kalm and Semba 2005). However, none of the participants believed they experienced any negative long-term health effects as a result of the experiment (Kalm and Semba 2005).

143.3 Starvation Symptoms in Eating Disorders

The starvation study had a fundamental role in improving our understanding of eating disorders because many symptoms observed in the volunteers are similar to those reported by underweight eating disorder patients. However, to date no study has evaluated the prevalence of starvation symptoms in eating disorder individuals. Table 143.2 reports the prevalence of starvation symptoms in the

Table 143.2 Prevalence of starvation symptoms in the last 28 days reported by 50 consecutive patients with anorexia nervosa (mean BM $15.3\,\text{kg/m}^2$ – range 11.7–$17.4\,\text{kg/m}^2$)

Symptoms	Percent (%)
Preoccupation with thoughts about eating and eating	90
Irritability	82
Anxiety	78
Depression	76
Mood changes	66
Sleep disturbance	66
Social withdrawal	56
Weakness	56
Gastrointestinal discomfort	56
Cold intolerance	56
Impaired concentration	54
Apathy	50
Heightened satiety	50
Low body temperature	38
Eating very slowly	38
Reduction in sexual interest	38
Heightened sensation of fullness	36
Heightened sensation of hunger	32
Cutting the food in small pieces	30
Collecting cookbooks and recipe books	28
Increasing the consumption of coffee or tea or spice	28
Personality changes	28
Hoarding food	24
Eating hot food	24
Noise intolerance	22
Tingling	20
Edema at the legs	18
Binge eating	16
Light intolerance	16
Hearing voices in the head	4
Hallucinations	0

last 28 days reported by 50 outpatients with anorexia nervosa consecutively assessed before starting treatment at the Department of Eating and Weight Disorder, Villa Garda Hospital. Starvation symptoms were assessed with the Starvation Symptoms Check List (see Appendix). About 90% of the patients reported preoccupation with thoughts about food and eating, and 82% irritability. Other symptoms reported by at least 50% of patients were anxiety, depression, mood changes, sleep disturbances, social withdrawal, weakness, gastrointestinal discomfort, cold intolerance, impaired concentration, apathy, and heightened satiety.

143.4 Interaction of Starvation Symptoms with Eating Disorder Psychopathology

The effects of starvation symptoms in individuals with eating disorders are different from those observed in subjects without these disorders. In the absence of eating disorder psychopathology, starvation symptoms lead individuals to focus their attention primarily towards food searching, and when food becomes available, they eat without being concerned about losing their control of body shape and weight. On the contrary, the presence of the eating disorder psychopathology (i.e., the overvaluation of shape, weight, and their control) (Fairburn et al. 2003) interacts with starvation symptoms maintaining the eating disorder (see Table 143.3 for the proposed general mechanisms).

In particular, it has been suggested that some symptoms of starvation stimulate further dietary restriction by undermining the person's sense of being in control over their eating, shape, weight, or themselves in general (Fairburn et al. 1999), while other symptoms exaggerate the tendency to use control over eating as an index of self-control in general (Shafran et al. 2003). It has also been proposed that some eating disorder individuals interpret the symptoms of starvation as a positive sign of being in control and as evidence that they are working hard to achieve their goal of controlling eating, shape, and weight (Shafran et al. 2003). Support for these hypotheses is provided by two studies. The first study found that patients with eating disorders were significantly more likely to interpret four symptoms of starvation (hunger, poor concentration, heightened satiety, and reduction in rate of weight loss) as a proof of control (Shafran et al. 2003). The second study found that a significantly higher proportion of inpatient eating disorder patients interpret the symptoms of hunger, heightened satiety, and dizziness in terms of control when compared to nonclinical participants (Dalle Grave et al. 2007) (see Table 143.4 for clinical examples).

Table 143.3 Proposed mechanisms through which starvation symptoms maintain the eating disorder psychopathology (Dalle Grave et al. 2007; Shafran et al. 2003; Fairburn 2008)

1. Underweight and dietary restriction symptoms increase the need to get control over their eating, shape, weight, or themselves in general.
2. Preoccupation with food and eating keeps the eating disorder mindset permanently "in place"
3. Social withdrawal and loss of previous interests prevent the development of other domains of self-evaluation
4. The maintenance of underweight requires the adoption of a hypocaloric diet that maintains the preoccupation with food and eating
5. Indecisiveness makes it difficult for patients to decide whether to change (procrastination)
6. Heightened need for routine and predictability interferes with change
7. Heightened feeling of fullness makes it difficult to increase the amount of food.

Table 143.4 Examples of how eating disorder patients may interpret some starvation symptoms

Symptoms	Dysfunctional interpretation of eating disorder patients
Hunger	I am controlling my diet
	I have to increase my attention to avoid losing control over eating
Sense of fullness	I eat too much, I have to reduce the calories of my diet
Binge eating	I am weak, I have to increase my control over eating
Reduction in the rate of weight loss	I am losing control over my weight. I have to reduce the amount of food I eat
Mood instability	I am not in control. I have to increase my control over eating, weight, and shape
Dizziness	It is a positive sign that I am losing weight
Poor concentration	I am losing control. I have to increase my control over eating

143.5 Clinical Implications

The knowledge of starvation symptoms and how they interact with eating disorder psychopathology have important implications both for the understanding and the treatment of eating disorders.

Clinicians should be informed that many psychosocial symptoms reported by underweight eating disorder patients are the consequences of dietary restriction and underweight and not the expression of their eating disorder psychopathology. These symptoms are not related only to food and eating, but extend to the whole range of psychosocial functions. Since many symptoms reported by eating disorder patients, often suggested to be the cause of their disorder, are indeed the consequences of underweight and dietary restriction, clinicians should be aware that the weight must be completely restored before a final assessment of the psychological functions and personality of their patients is accurately performed (Garner 1998).

Patients should be educated on the starvation symptoms and on the Minnesota study (Garner 1997; Garner et al. 1997). This recommendation is based on the assumptions that patients with eating disorders often have misconceptions about the cause of their symptoms and may be less likely to continue their efforts to maintain underweight if they informed about the scientific data on the maintenance of their disorder (Garner 1998). They also should be helped to change their dysfunctional interpretation of starvation symptoms, since a subgroup of patients tend to view some of these symptoms as a positive sign of being in control (Shafran et al. 2003; Fairburn et al. 1999). Finally, they should be helped to achieve a healthy body weight since the maintenance of caloric restriction and underweight is a mechanism maintaining their eating disorder psychopathology (Fairburn 2008). Educational material on starvation symptoms for underweight eating disorders patients (Garner 1997) and manuals for clinicians describing the procedures and the strategies to address underweight and caloric restriction in eating disorder patients are available (Dalle Grave et al. 2008a; Fairburn 2008).

143.6 Applications to Other Areas of Health and Disease

The dissemination of the knowledge about symptoms associated with underweight and caloric restriction could help to improve the assessment and the treatment of the following conditions associated with underweight and low calorie intake (the list is not complete):

• AIDS
• Alcoholism
• Alzheimer's disease

- Anxiety
- Cancer
- Celiac disease
- Chronic heart disease
- Chronic lung disease
- Chronic renal disease
- Clinical depression
- Cystic fibrosis
- Dementia
- Denture difficulties
- Dysphagia
- Infections
- Inflammatory bowel disease
- Lactose intolerance
- Malabsorption
- Poverty and lack of food
- Stomach ulcer
- Stomatitis
- Systemic lupus erythematous
- Schizophrenia
- Tuberculosis
- Uncontrolled diabetes mellitus

Summary Points

- Underweight is a key diagnostic criterion for anorexia nervosa, but could be present in a subgroup of patients with eating disorder NOS (e.g., underweight patients who meet all DSM-IV criteria for anorexia nervosa except amenorrhea or the overvaluation of shape and weight).
- Severe weight loss and dietary restrictions are also present in a subgroup of nonunderweight eating disorder patients with bulimia nervosa or eating disorder NOS with previous obesity.
- Underweight and dietary restrictions are associated with several physical and psychosocial symptoms ("starvation symptoms").
- Many psychosocial symptoms observed in underweight eating disorder individuals are the consequences of underweight and dietary restriction and not the expression of their psychopathology or personality.
- The most frequent starvation symptoms reported by eating disorder patients are preoccupation with thoughts about food and eating and irritability.
- Starvation symptoms interact with eating disorder psychopathology stimulating further dietary restrictions by undermining the individuals' sense of being in control over their eating, shape, weight, or themselves in general
- Some eating disorder individuals interpret the symptoms of starvation as a positive sign of being in control and as evidence that they are working hard to achieve their goal of controlling eating, shape, and weight.
- The treatment of eating disorder patients with underweight and/or caloric restrictions should include education on starvation symptoms, strategies to change their dysfunctional interpretation of starvation symptoms, and to favor weight regain

Definitions and Explanations

Dietary restriction: Persistent caloric intake lower than energy expenditure

Eating disorders: Persistent disorder of eating behavior and/or of behaviors aimed to modify or control the shape and weight, associated with an overvaluation of shape and weight and with significant physical and psychosocial impairment not secondary to any medical or psychiatric condition known.

Overvaluation of shape and weight and their control: Judging themselves predominantly or even exclusively in term of weight, shape, and their control (it is considered the core psychopathology of eating disorders).

Starvation symptoms: Symptoms associated with dietary restriction and underweight.

Starvation neurosis: Emotional disturbances associated with dietary restriction and underweight.

Key Points

1. The presence of starvation symptoms should always be evaluated in eating disorder patients.
2. The weight must be completely restored before carrying out an accurate assessment of the psychological functions and personality of eating disorder patients
3. Eating disorder patients should be educated that the maintenance of dietary restriction and underweight is associated with severe physical and psychosocial impairment.
4. Since starvation symptoms are potent mechanisms maintaining eating disorder psychopathology, the treatment of underweight eating disorders should always address underweight and dietary restriction.

Appendix: Starvation Symptoms Check List

Riccardo Dalle Grave

Instructions: The following questions are concerned with the past 28 days only. Please read each questions with attention. Please answer all the questions circling the appropriate number on the right. Thank you

On how many of the past 28 days …	No. days	1–5 days	6–12 days	13–15 days	16–22 days	23–27 days	Every day
1. Have you spent much time thinking about eating and food?	1	2	3	4	5	6	7
2. Have you collected cookbooks and recipes?	1	2	3	4	5	6	7
3. Have you cut food into small pieces?	1	2	3	4	5	6	7
4. Have you hoarded food?	1	2	3	4	5	6	7
5. Have you eaten very slowly?	1	2	3	4	5	6	7
6. Have you eaten hot food?	1	2	3	4	5	6	7
7. Have you increased the consumption of coffee or tea or spice?	1	2	3	4	5	6	7

(continued)

Appendix (continued)

On how many of the past 28 days …	No. days	1–5 days	6–12 days	13–15 days	16–22 days	23–27 days	Every day
8. Have you eaten a large amount of food with the sensation of losing control over eating?	1	2	3	4	5	6	7
9. Have you been depressed?	1	2	3	4	5	6	7
10. Have you been anxious?	1	2	3	4	5	6	7
11. Have you been irritable?	1	2	3	4	5	6	7
12. Have you had mood changes?	1	2	3	4	5	6	7
13. Have you heard voices in your head?	1	2	3	4	5	6	7
14. Have you had hallucinations?	1	2	3	4	5	6	7
15. Have you noticed some change in your personality?	1	2	3	4	5	6	7
16. Have you been withdrawn socially?	1	2	3	4	5	6	7
17. Have you found it difficult to concentrate?	1	2	3	4	5	6	7
18. Have you been apathetic?	1	2	3	4	5	6	7
19. Have you had sleep disturbances?	1	2	3	4	5	6	7
20. Have you felt weak?	1	2	3	4	5	6	7
21. Have you had gastrointestinal discomfort?	1	2	3	4	5	6	7
22. Have you been intolerant to noise?	1	2	3	4	5	6	7
23. Have you been intolerant to light?	1	2	3	4	5	6	7
24. Have you felt your legs or other part of your body swollen?	1	2	3	4	5	6	7
25. Have you had a low body temperature?	1	2	3	4	5	6	7
26. Have you felt some tingling?	1	2	3	4	5	6	7
27. Have you felt a reduction of sexual interest?	1	2	3	4	5	6	7
28. Have you felt cold?	1	2	3	4	5	6	7
29. Have you felt an increase in hunger?	1	2	3	4	5	6	7

Appendix (continued)

On how many of the past 28 days …	No. days	1–5 days	6–12 days	13–15 days	16–22 days	23–27 days	Every day
30. Have you felt an increase in your sense of satiety?	1	2	3	4	5	6	7
31. Have you felt full after eating?	1	2	3	4	5	6	7

In females:

How many periods have you had in the last 3 months?………………

Have you been taking the "pill" ?………………

References

American Psychiatric Association. Diagnostic and statistical manual of mental disorders 4th ed. Washington, D.C: American Psychiatric Association; 1994.

Dalle Grave R, Bohn K, Hawker D, Fairburn CG. In Fairburn CG, editors. Cognitive behavior therapy and eating disorders. New York: Guilford Press 2008a: p. 231–44.

Dalle Grave R, Calugi S, Marchesini G. Behav Res Ther. 2008b;46:1290–94.

Dalle Grave R, Calugi S, Marchesini G. Int J Eat Disord. 2008c; 41:705–12.

Dalle Grave R, Di Pauli D, Sartirana M, Calugi S, Shafran R. Eat Weight Disord. 2007;12:108–13.

Fairburn CG. Cognitive Behavior Therapy and Eating Disorders. New York: Guilford Press; 2008.

Fairburn CG, Cooper Z, Shafran R. Behav Res Ther. 2003;41:509–28.

Fairburn CG, Shafran R, Cooper Z. Behav Res Ther. 1999;37:1–13.

Garner DM. In: Garner DM, Garfinkel PE, editors. Handbook of treatment for eating disorders. New York: Guilford Press; 1997. p. 145–177.

Garner DM, Vitousek K, Pike K. In: Garner DM, Garfinkel PE, editors. Handbook of treatment for eating disorders. New York: Guilford Press; 1997. p. 94–144.

Garner DM. Health Weight J. 1998;12:68–72.

Kalm LM, Semba RD. J Nutr. 2005;135:1347–52.

Keys A, Brozek J, Henschel A, Mickelsen O, Taylor HL. The biology of human starvation. Minneapolis: University of Minnesota Press; 1950.

Shafran R, Fairburn CG, Nelson L, Robinson PH. Behav Res Ther. 2003;41:887–94.

Chapter 144
Epigenetics and Nutrition: B-Vitamin Deprivation and its Impact on Brain Amyloid

Sigfrido Scarpa

Abbreviations

AD	Alzheimer Disease
C	Cytosine
CpG	Cytosine-Guanine Dinucleotides
SAM	S-Adenosylmethionine
SAH	S-Adenosylhomocysteine
HCY	Homocysteine
GSH	Glutathione
DNMT	DNA-Methyltransferase
ATP	Adenosyntriphosphate
CBS	Cystathionine-Beta-Synthase
B6	B6 Vitamin
B12	B12 Vitamin
B9	B9 Vitamin, Tetrahydrofolate
MP	Methylation Potential
APP	Amyloid-Precursor-Protein
Abeta	Beta Amyloid
PS1	Presenilin 1, Gamma-Secretase
BACE	Beta-Secretase
PD	Parkinson's Disease
ADMA	Asymmetric Dimethylarginine
NO	Nitric Oxide
DDAH	Dimethylarginine-Dimethylaminohydrolase
NOS	Nitric Oxide Synthase
PP2A	Phosphatase-2A
Tau	Tau Protein
TgCRND8	Transgenic Mice Carrying a Human Transgene with a Double Mutation Swedish/Indiana

S. Scarpa (✉)
Dip. di Chirurgia "P. Valdoni", Centro di Ricerca in Neurobiologia
"Daniel Bovet" CriN, Sapienza Università di Roma,
via Antonio Scarpa, 14, 00161 Roma, Italy
e-mail: sigfrido.scarpa@uniroma1.it

144.1 Introduction

B vitamin deficiency, namely B12, B9 (folate), and B6, is linked to hyperhomocysteinemia, to brain amyloid overproduction and to aging in one of the most devastating disease in the elderly: Alzheimer's Disease (AD).

Aging is a progressive decrease of the physiological capacity to react to stress arising from the environment, leading to increased susceptibility and vulnerability to disease. Although the activity of the brain and the individual psychology plays a major role for such phenomena through unknown mechanisms, the physiology of aging it appears must be controlled by epigenetic mechanisms that made it possible for evolution to increase our lifespan. When approaching the maximum potential lifespan humans have to face physiological modifications and diseases most likely due to alteration of those epigenetic mechanisms that enhance early survival but could be disadvantageous later in life (Egger et al. 2004; Troen 2003). One of these is evidently AD, which increases proportional to lifespan. The study of non-DNA sequence-related heredity, as epigenesis can be defined, is becoming the epicenter of modern medicine because it is beginning to clarify the relationship between genetic background, environment, aging, and disease. Although DNA sequence remains essentially the same, the epigenetic state may vary among tissues and during the lifetime; in other words, it may be responsible for phenotypic plasticity in age-related modifications. Vitamin deficiency, either due to defective nutrition or to pathology, is among the elements capable of modifying the epigenetic mechanisms in the direction of disease. The new fact is that alteration of these mechanisms is not measurable by genetic defect or pathogenic elements, but could result in the modification of gene expression regulation. Over-production of brain amyloid due to hypomethylation of at least one specific gene promoter has been shown in recent years in several publications (Fuso et al. 2007, 2009; Scarpa et al. 2003, 2006). In these papers, the authors demonstrated that B vitamin deficiency (B6, B12, and folate) may be responsible for amyloid overproduction, whether in brains of transgenic mice or in human cell culture. Widespread loss of DNA methylation was observed in colorectal cancers in 1983 and thereafter a large number of reports of either hypomethylation of oncogenes or hypermethylation of oncosuppressor genes, which may result in a variety of cancers. The most fascinating aspect of epigenesis is the possibility of reversing its changes, unlike sequence mutations in disease, which could lead to a host of new therapeutic tools.

In this review the impact of those nutritional elements – B vitamins and catabolites like homocysteine – that may influence epigenetic mechanisms by altering the metabolism of methyl donor, will be discussed.

144.2 DNA Methylation

The study of DNA methylation in aging is extremely topical because of its implication in tumorigenesis, since cancer onset increases with aging. The general decrease in total genomic methylcytosine during aging in various organisms and the apparently finite number of cell divisions, characteristic of most somatic cells, reinforces the view of overall methylcytosine loss as a cellular timing mechanism that triggers senescence. Nevertheless, it is important to underline the fact that the methylation status of the majority of examined genes seems to be intact during aging. The alterations in CpG island methylation are crucial to modulate binding of transcription factors and methyl-DNA binding proteins. Aberrant methylation of CpG islands in the promoter region may contribute to the progressive inactivation of growth-inhibitory genes during aging, resulting in the clonal selection of cells

with a growth advantage towards cancer development. Alterations in DNA methylation during aging can depend on alterations in dietary status. The great influence of nutritional components on health and lifespan is largely accepted. Among the various mechanisms by which nutritional elements could affect the progress of senescence, two pathways involve DNA methylation: the first concerns the supply of metabolites of the S-adenosylmethionine cycle (SAM, folic acid, and B vitamins), whereas the second refers to elements able to directly modify the DNA-methyltransferase (DNMT) activity (selenium, cadmium, and nickel). Clear indications of methylation alterations come from studies on aging, on various noncommunicable diseases (Prader-Willi, Angelman's, and Beckwith-Wiedemann syndromes) and on various diseases related to aging (Down's syndrome, Alzheimer's, Parkinson's, and Huntington's diseases). Changes in chromatin structure are related to epigenetic modifications that consist of DNA methylation, histone post-transcriptional modifications (methylation, acetylation, and phosphorylation) and ATP-mediated chromatin modifications. In proliferating cells, DNA is principally found as euchromatin in actively transcribed loci like the growth regulatory genes. Conversely, it has been proposed that reassembly of repressive chromatin domains (heterochromatin) may contribute to cellular senescence. The main tool of epigenetic control on gene expression seems to lie in the CpG sequence, irrespective of whether this sequence contains a methyl group bound on C (Razin and Riggs 1980). We should bear in mind that although most studies have been dedicated to DNA, methylation processes have to do also with RNA, proteins, and lipids (Chiang et al. 1996). Regulation of gene expression through DNA methylation consists of the methylation or demethylation of cytosines in CpG sequences that eventually present in the gene promoters of those genes whose regulation is controlled by methyl groups. There is a basic difference between sequences that are normally unmethylated (Bergman and Mostoslavsky 1998), like CpG islands (Cross et al. 1997), and the CpG moieties belonging to genes expressed during development that are silenced later by methylation for physiological reasons. The former may become methylated for a pathogenetic mechanism, for example in the inactivation of oncosuppressor genes in cancer, and the latter may gradually lose their methylation and therefore overexpress genes that should be downregulated.

144.3 Epigenetic Mechanisms

At the molecular level, the biochemical modifications of DNA and histone proteins are the major epigenetic mechanisms. Additional mechanisms, involving RNA interference and prion proteins contribute as well to epigenetic regulation (Levenson and Sweatt 2006), but will not be included here. Essentially, chromatin modifications comprise DNA methylation at cytosine–guanine dinucleotides and post-translational modifications of histone proteins. Post-translational histone modifications, because of their chemical properties, influence the condensation of chromatin and therefore modulate the accessibility of DNA to the transcriptional machinery. DNA methylation is functionally most relevant when present in sequences rich in CpG dinucleotides: the CpG islands. These regions with more than 500 base pairs in size and with a C+G density higher than 55% (Takai and Jones 2002) have been conserved during evolution because they are normally unmethylated. The completion of human genome sequencing revealed that about 50% of all genes contain CpG islands within their regulatory elements (Venter et al. 2001) and they are stably methylated in transcriptionally silenced genes. Epigenetic control of gene expression by cytosine methylation is made possible by the activity of DNA methyltransferases (DNMTs) (Hitchler and Domann 2007). These enzymes catalyze transmethylation of cytosines by transferring methyl groups from S-adenosylmethionine (SAM) to position 5 of the pyrimidine ring with production of 5-MeC in DNA. Cytosine methylation in mammalian genomes is mainly carried out by three DNMTs: DNMT1, DNMT3a, and DNMT3b. Maintenance
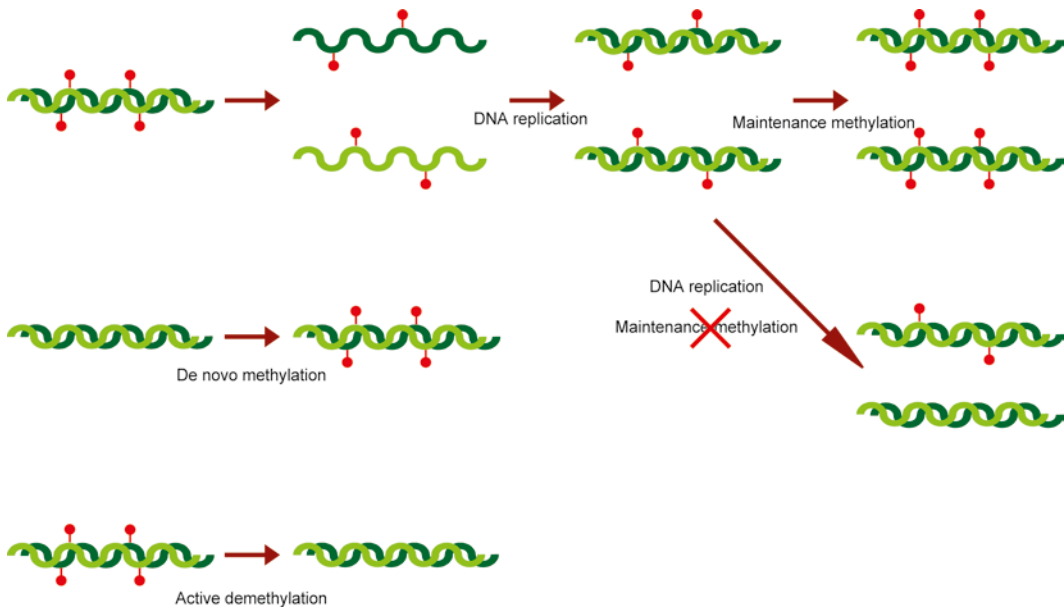
Fig. 144.1 Schematic representation of DNA methylation. DNA methylation and demethylation mechanisms: maintenance methylation, passive demethylation, de novo methylation, and active demethylation

methylation is catalyzed by DNMT1 and occurs rapidly following DNA replication. DNMT1 has the primary role of passing on epigenetic control of gene expression to daughter cells (Kautiainen and Jones 1985). De novo DNA methylation is catalyzed by DNMT3a and DNMT3b, which are primarily responsible for initiating new epigenetic events regulating gene expression. De novo methylation can occur anytime following DNA replication (Fig. 144.1). This epigenetic event can be passed on during future cell divisions. These enzymes were identified and cloned in 1998 (Okano et al. 1998, 1999; Xie et al. 1999).

144.4 DNA Demethylation

Soon after Holliday and Pugh proposed that DNA methylation could control gene expression (Holliday and Pugh 1975) it became clear that, besides the possibility of inhibiting DNA methylases (maintenance and de novo), to obtain demethylation, global demethylation known to occur during early embryogenesis has to rely on an active mechanism (Kapoor et al. 2005). The author of this chapter participated in the first study showing active demethylating activity in cell culture (Razin et al. 1986). Since then three active demethylation mechanisms have been proposed, none of which has been widely accepted (Kress et al. 2001). The first is direct replacement of the methyl moiety by a hydrogen atom. The other two both involve DNA repair processes: the second mechanism proposes the removal of methyl-C by nucleotide excision followed by replacement with an unmethylated one (Weiss et al. 1996; Weiss and Cedar 1997), the third one postulated the participation of RNA molecules and appears to have gained support by key experimental observations, although the demethylase involved has not yet been cloned. Having ascertained that DNA undergoes the establishment of an inherited methylation pattern in adult organisms (Fig. 144.2), with the formation of stably activated
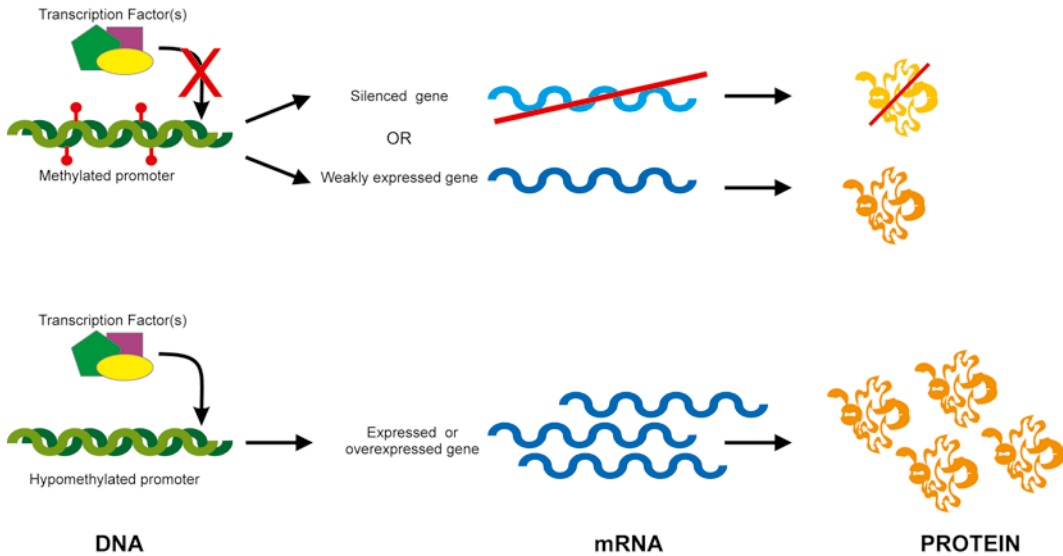
Fig. 144.2 Schematic model of methylation-dependent gene expression

genes (mostly demethylated), stably silenced genes (mostly fully methylated), and genes with specific methylation patterns able to be induced by reassessment of methyl moieties, it should be explained what mechanisms control the donation of methyl groups.

144.5 Central Role of SAM

In the last fifty years SAM has been shown to be perhaps the most frequently used substrate, after ATP, and therefore occupies a central position in human health, disease, and aging. SAM is known to be the primary methyl-donor present in eukaryotes and it is involved in methylation of target molecules as DNA, RNA, proteins, lipids, and polyamines synthesis (Fontecave et al. 2004; Lu 2000). SAM is probably second only to ATP in the variety of reactions in which it is involved; the most important ones are transmethylation, transsulfuration, and aminopropylation, which occur due to the presence of the high-energy sulfonium ion, which activates each of the attached carbons toward nucleophilic attack. SAM was discovered in 1951 by Giulio Cantoni as an important molecule in methylation reactions (Cantoni 1951, 1953; Kresge et al. 2005). It is a conjugate of methionine at the sulfur atom with adenosine, a reaction catalyzed by methionine–adenosyltransferase. SAM appears to be altered in some neurological disorders, including AD (Bottiglieri and Hyland 1994). About 95% of SAM is engaged in methylation reactions. It is then transformed in S-adenosylhomocysteine (SAH) and further hydrolyzed into homocysteine (HCY) and adenosine. The reaction is strongly reversible and HCY, if not rapidly transformed in methionine or cystathionine, forms SAH, which is a potent inhibitor of methyl-transferases. These metabolic alterations may be responsible for the generalized reduction of DNA methylations observed in aging. HCY exerts a pathogenic effect, at very high concentrations, through the alteration of oxidative metabolism, but it can even generate a pathological situation at concentrations just above normal by modifying the methylation pattern. Remethylation of homocysteine to form methionine, along with the transsulfuration pathway prevents HCY accumulation. Accumulation of homocysteine has been a great concern for human health since

hyperhomocysteinemia is present both in cardiovascular diseases and dementia. Many clinical studies have been undertaken to verify whether supplementation of human nutrition with B vitamins to lower homocysteine would be beneficial for health (Mason et al. 2008; Refsum and Smith 2008; Smith et al. 2008; Smith 2008). There seems to be a growing consensus that lowering homocysteine with vitamin supplementation does not solve the problem. Probably not enough attention has been paid to SAM production and SAH accumulation. The SAM metabolism is strictly controlled by B12 and B9 (tetrahydrofolate), except when remethylation of homocysteine to methionine occurs through betaine reaction, in its transmethylation pathway. Betaine reaction though seems to be absent in the brain. The second pathway, derived from SAM catalytic reactions to form homocysteine, is trans-sulfuration where B6 vitamin plays a fundamental role in the transformation of homocysteine to L-cystathionine to finally produce glutathione (Fig. 144.3). To mention another SAM activity, it has been shown (Lichtenthaler et al. 1999) that it functions as an allosteric activator of cystathionine beta-synthase (CBS), by increasing the enzyme activity about threefold. Low SAM concentrations generate low CBS activity, with the result that HCY is directed toward the transmethylation pathway. The result is lesser glutathione production. This alteration is exerted by poor uptake of B6 vitamin.

The most common alteration of this metabolism is the decreased uptake of vitamin B (folate, B12, and B6) with consequent HCY accumulation and SAM/SAH alteration. Diminished uptake of B12 and folate can be determined by a number of nutritional events as well as by pathological ones. *Helicobacter pylori*, which is very common in the population and very hard to eradicate, is known to
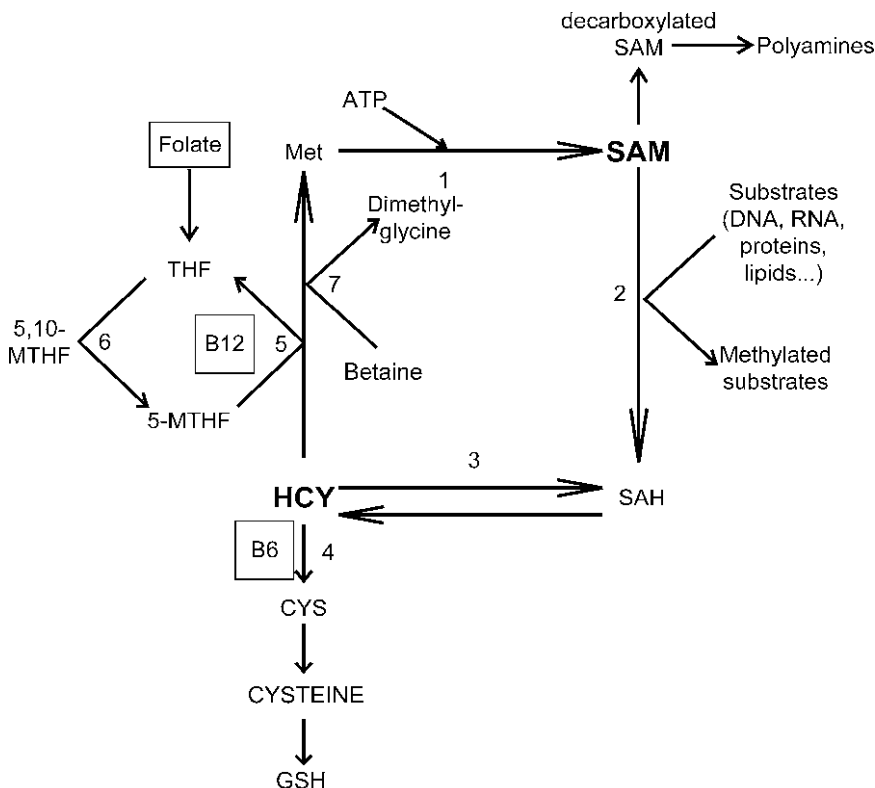
Fig. 144.3 SAM metabolism. *Met* Methionine, *SAM* S-adenosylmethionine, *SAH* S-adenosylhomocysteine, *HCY* Homocysteine, *CYS* Cystathionine, *GSH* Glutathione, *THF* Tetrahydrofolate, *MTHF* methyltetrahydrofolate, *B12* Vitamin B12, *B6* Vitamin B6, (1) Methionine adenosyltransferase (MAT); (2) Methyltransferase(s); (3) SAH hydrolase; (4) Cystathionine-β-synthase (CBS); (5) Methionine synthase; (6) Methylenetetrahydrofolate reductase (MTHFR); (7) Betaine homocysteine methyltransferase (BHMT)
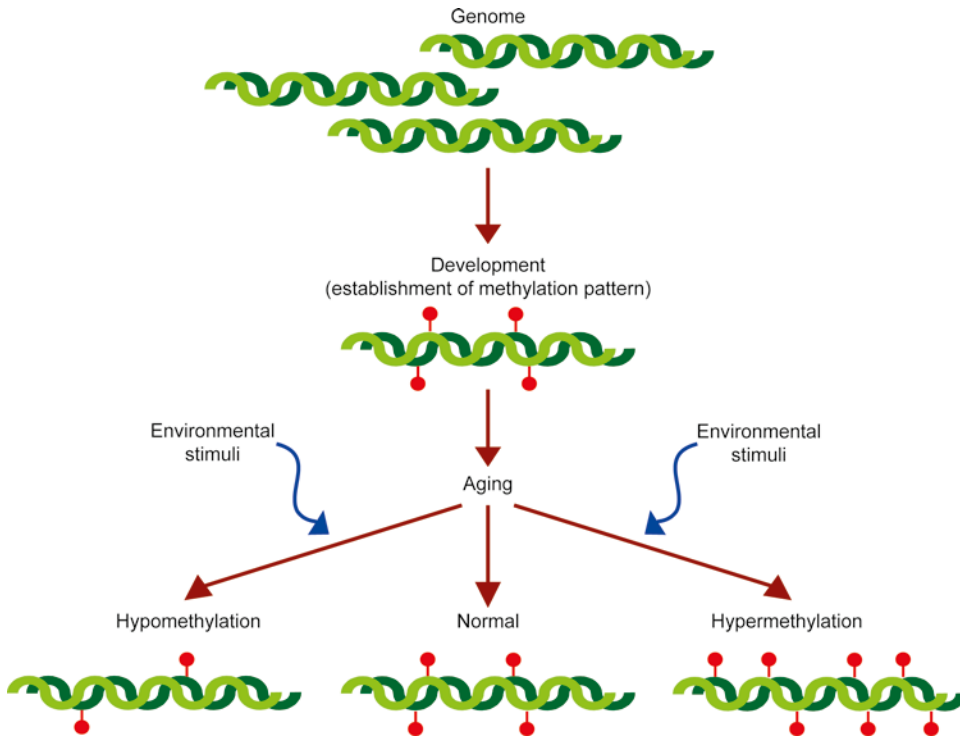
Fig. 144.4 Modifications of DNA methylation pattern with aging. DNA methylation pattern is established during embryonal development and tissue differentiation. Environmental stimuli occurring during the lifespan could generate abnormal modifications of the DNA methylation pattern in specific genes

have this effect. The result will again be the alteration of the SAM metabolism. Accumulation of amyloid protein in the brain is a clear example of this alteration. SAH increase affects SAM/SAH ratio; this is an important indicator of cellular methylation status and is usually indicated as Methylation Potential (MP) (Chiang et al. 1996; Fuso et al. 2008; Lee and Wang 1999). Although there is some disagreement about this parameter, biochemically, SAH concentration is an undiscussed indicator for appropriate methylation.

Aside of the physiological function, these epigenetic phenomena may be influenced by alterations of metabolites and of the enzymes part of the methyl-donor (SAM) metabolic cycle which may be responsible for reduced brain concentrations in elderly (Morrison et al. 1996). The consequent demethylation and overexpression of genes would not be regulated, but rather induced by reduced synthesis of the methyl-donor or by inhibition of methylases. Recent experiments on TgCRND8 mice seem to show the second hypothesis to be the most common. With the aging of an organism, the general decrease of DNA methylation can lead to overactivation of methylation-controlled genes (Fig. 144.4).

144.6 SAM and Brain Amyloid

Alzheimer's Disease (AD) is becoming one of the most common pathologies in the aging population, leading also to increased social cost and impact, because of the increase in life expectation. Besides a familial (genetic) form of the disease, which has an early onset, the higher percentage of cases is represented by the sporadic occurrence of AD with onset at an advanced age.. Whereas it is

becoming increasingly evident which is the pool of molecules involved in the pathogenesis, the causes of this form of AD are not yet well understood. Alzheimer's disease is neuropathologically characterized by the presence of amyloid plaques and neurofibrillary tangles in the brain. Amyloid plaques are extracellular deposits primarily composed of amyloid beta-peptide, which is derived from amyloid beta-precursor protein (APP) by sequential cleavages at beta-secretase and gamma-secretase sites. Neurofibrillary tangles represent intracellular bundles of self-assembled hyperphosphorylated tau protein. In recent years, hyperhomocysteinemia has began to be widely considered a risk factor in AD and this may be ascribed to alteration of the S-adenosylmethionine/homocysteine (SAM/HCY) metabolism (Seshadri et al. 2002). In fact, a frequently observed condition in AD-affected people is the increase of haematic HCY along with the decrease of B12, B6, and folate uptake (Bottiglieri 1996; Joosten 2001; Quadri et al. 2004; Selhub et al. 2000). In AD, the loss of precise control through gene methylation may alter a delicate equilibrium among the three enzymes (alpha-, beta-, and gamma-secretases) known to be involved in the production of either amyloid-beta or other nondangerous catabolites (De Strooper 2000). It is well established that alpha-secretase cleavage of APP does not produce the amyloidogenic peptides and that, on the contrary, they are produced by the activity of beta-secretases that generate an N-terminal soluble fragment and a C-terminal fragment that is sequentially cleaved by gamma-secretase to produce A-beta peptides (Tabaton and Tamagno 2007; Vassar et al. 1999; Vassar 2005). The alteration of SAM/SAH ratio is tightly related to the altered expression of two genes involved in APP metabolism, finally producing the accumulation of A-beta peptide in the senile plaque. Previous papers in cell culture showed that two of the genes responsible for amyloid-beta production (PS1 and BACE, i.e., gamma and beta secretases) are upregulated by vitamin B deficiency; exogenous SAM administration can restore the normal gene expression, thus reducing amyloid levels (Fig. 144.5) (Cavallaro et al. 2006; Fuso et al. 2005; Scarpa et al. 2003, 2006). Moreover, a study on mice carrying the transgenic beta-amyloid-protein precursor (APP) showed that vitamin B deprivation was able to induce PS1 and BACE upregulation and increased Abeta deposition (Fuso et al. 2008). Accumulation of HCY and DNA hypomethylation are metabolically related since the lack of transformation of HCY to methionine reverts the metabolism to SAH, which is a strong inhibitor of DNA methyltransferases, therefore inducing DNA hypomethylation (Chiang et al. 1996). Therefore, hypomethylation may be a mechanism through which HCY exerts its toxicity in AD and promotes amyloidogenesis.
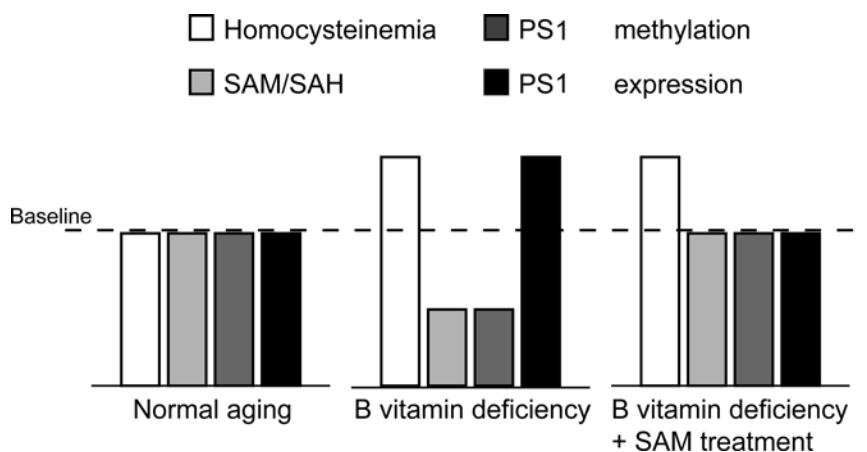
Fig. 144.5 Effect of B vitamin deficiency and SAM supplementation in TgCRND8 Alzheimer mice. Vitamin B deficiency causes hyperhomocysteinemia, decrease of SAM/SAH ratio and PS1 methylation, and upregulation of PS1 mRNA expression. SAM treatment, although it cannot completely revert high HCY can normalize the other parameters

144.7 SAM and Oxidative Stress

Increasing evidence demonstrates that oxidative stress is implicated in a number of age-related disorders among which are AD, Parkinson's disease (PD), and atherosclerosis. Hyperhomocysteinemia is a risk factor for atherosclerotic vascular disease and AD as well, and it is associated with increased oxidative stress. The central nervous system is particularly vulnerable to free radical damage owing to high brain oxygen consumption, its abundant polyunsaturated fatty acid content, and its relative paucity of anti-oxidant enzymes compared with other tissues (Guidi et al. 2006; Migliore et al. 2005; Vitvitsky et al. 2006; Zafrilla et al. 2006). Increased concentrations of HCY in the plasma of AD patients are associated with an increase of asymmetric dimethylarginine (ADMA) and a decrease in nitric oxide (NO) plasma concentrations, through inhibition of DDAH (dimethylarginine dimethylaminohydrolase, the enzyme that converts ADMA into citrulline and dimethylamine). ADMA is an endogenous inhibitor of nitric oxide synthase (NOS), and it is synthesized during the process of protein arginine methylation by SAM and subsequent hydrolysis. ADMA accumulation impairs cerebral blood flow. Brain infarcts and atherosclerosis increase the incidence and the severity of symptoms of AD patients; therefore, accumulation of ADMA may contribute to the development of AD by increasing the incidence of atherosclerosis and stroke (Selley 2003; Siroen et al. 2006; Stuhlinger et al. 2001). Moreover, the toxic effect of HCY in atherosclerosis is mainly due to the stimulation of inflammatory response through oxidative reactions, since HCY is involved in the synthesis of GSH, the major cellular antioxidant.

144.8 SAM and Tau Protein

Microtubule-associated tau protein is a phosphoprotein whose phosphorylation is regulated. The main physiological function of tau is the promotion of the assembly and stabilization of the microtubular network, which is essential for normal axonal transport of vesicles within the neuron. In humans, tau protein undergoes several post-translational modifications, such as abnormal phosphorylation, which plays a significant role in the formation of neurofibrillary pathology. Phosphorylated tau has a reduced capability of binding to microtubules and hyperphosphorylation contributes to the formation of pathological tau filaments. This leads to destabilization of the microtubular network and subsequent impairment of microtubule-associated axonal transport. The modification of tau by phosphorylation is regulated by the equilibrium between kinase and phosphatase enzymes. Previous works suggest that a decrease in Phosphatase 2A (PP2A) activity, rather than an increase in kinase activity, is crucial for the elevated levels of aberrant protein phosphorylation in AD. PP2A is abundantly expressed in the brain and its abnormal function has been demonstrated to be associated with AD. Expression of a mutant form of PP2A in mouse brain causes a marked decrease in PP2A activity and induces AD-like hyperphosphorylation of tau at specific serine/threonine residues (Kins et al. 2001). In vivo, PP2A enzymes predominantly exist as heterotrimers containing a catalytic subunit (C), a scaffolding subunit (A), and a regulatory subunit (B). The highly conserved carboxyl-terminal sequence of the C subunit can undergo post-translational modifications like methylation on the Leu-309 residue by a specific methyltransferase (PPMT). This modification critically modulates the binding of regulatory B subunits to the (AC) core enzyme, thereby affecting PP2A substrate specificity, targeting, and cellular function (Evans and Hemmings 2000; Wei et al. 2001; Yu et al. 2001). It has been observed that PPMT expression and PP2A methylation become downregulated in AD (Sontag et al. 2004). Nicola et al. 2010 showed that alteration in the SAM/HCY cycle results in decreased PP2A methylation. Reduced PP2A methylation is associated with B subunit down regulation and accumulation of phosphorylated tau (Sontag et al. 2007;

Zhang et al. 2008). Moreover, other papers showed that PP2A mRNA expression levels were increased in AD fibroblast (Zhao et al. 2003). These data suggest a double regulation both at gene and protein level.

144.9 Conclusions

Amyloid-beta has erroneously been considered toxic, but although several functions have been recently postulated, it is not yet clear which is the main one. Abeta becomes dangerous only when abundant and in oligomeric or polymeric forms. Dimers and trimers of beta-amyloid are now considered the first cause of AD onset and memory loss. These observations have quite changed the diffused idea that assigned the onset of AD to senile plaques. Recently it was demonstrated (Fuso et al. 2008) that the two genes responsible for Amyloid-beta production, beta (BACE) and gamma (PS1) secretases, are regulated by vitamin B deficiency and by SAM supplementation. Moreover, we showed that feeding either neuroblastoma cells with culture medium deficient of B12, B6, and folate, or TgCRND8 transgenic mice with food deficient in the same vitamins increased Abeta production (Fuso et al. 2005, 2008). The administration of methyl-donor has the opposite effect: it reduced significantly Abeta levels by remethylating the genes (Fuso et al. 2010). It is evident that whereas genetic factors are clearly associated with early-onset form of AD, epigenetic factors could be more easily linked to late-onset AD, since the epigenome is prone to changes during development and also aging (Bird 2007; Dolinoy 2007). The gene control mechanism here described is being studied in vivo for therapeutic applications (Table 144.1).

Table 144.1 Key epigenetic mechanisms possibly involved in Alzheimer's disease

Gene	Epigenetic modification	Treatment suggested	References
APP	APP cleavage product (AICD) recruits HAT TIP60 suggesting potential hyperacetylation.	None	Cao and Sudhof (2001)
	APP-induced death of cortical neurons causes H3 and H4 hypoacetylation.	None	Rouaux et al. (2003)
PS1	PS1 mutations prevent CBP degradation resulting in abnormal gene expression, potentially through hyperacetylation.	Substitution of PS1-mediated enzymatic activity	Marambaud et al. (2003)
	PS1 conditional knockout mice have decreased CBP level and CBP-mediated gene expression.	None	Saura et al. (2004)
	Hypomethylation of PS1 promoter increases Abeta production.	SAM administration reverses hypomethylation silencing gene and reduces Abeta production.	Fuso et al. (2009); Scarpa et al. (2003)
BACE	Vitamin B deficiency increases BACE expression and induces Abeta production.	Treatment with methyl-donor reduces BACE expression by unknown mechanism, thus reducing Abeta production	Fuso et al. (2008)

This table lists three genes implicated in Abeta production. APP is the large protein (695 amino acids) originating the 39–42 polypeptide fragment (Abeta). PS1 is presenilin 1 enzyme involved in gamma-secretase cut of APP. PS1 is also involved with Notch1 control, a factor necessary for stem cells maturation; which is the reason why knock-out of this gene cannot be applied as therapy. Beta-secretase (BACE) operates the second cut to form Abeta fragment

Although it is not clear if specific vitamins could be used as preventive therapy in the pathologies treated in this chapter, since depending on the dosage they could become responsible of the development of subclinical tumors, it will be very interesting to test clinically the use of SAM for the prevention and arrest of AD. This is only one of the cases in which gene silencing could be induced to repair or prevent pathologic outcomes due to an epigenetic disorder.

144.10   Applications to Other Areas of Health and Disease

The epigenetic mechanism outlined in this chapter will have a large number of applications. Considering the number of genes that may be controlled by methylation and the possibility to silence them by supplying the methyl-donor, it is evident that several other diseases may be studied in this respect to identify a possible target. The most delicate field seems to be cancer, since DNA methylation involvement has been shown in a large body of publications, but with contrasting results.

Summary Points

- Homocysteine accumulation is one of the key features in two major pathologies: neurodegenerative diseases and cardiovascular diseases.
- Diminished uptake of vitamins, both for nutritional or pathological reasons (helicobacter pylori), may be the main cause of AD.
- Several recent trials have shown that administration of vitamins to patients is not a sufficient remedy to control AD.
- If the hypothesis of a general loss of methyl groups in the elderly is correct, few epigenetic mechanisms are involved in these pathologies.
- The main remedy for hypomethylation of genes responsible for beta-amyloid production could be the reestablishment of correct concentrations of the main methyl-donor (SAM).
- The best indicator of altered SAM metabolism in the brain is SAH and homocysteine accumulation.
- Since the main source of SAM in humans is the liver, prevention of AD should point to liver diseases.

Key Terms

Epigenetic: DNA methylation at cytosine–guanine dinucleotides, post-translational modifications of histone proteins, RNA interference, and methylation; lipid methylation and prion proteins contribute as well to epigenetic regulation.

Transmethylation: remethylation of homocysteine to methionine where the methyl-donor is methyl-tetra-hydrofolate.

Transsulfuration: transformation of homocysteine to cystathionine; final product will be GSH, the main antioxidant agent in the body.

Gene silencing in epigenetics: the remethylation of cytosines in CpG sites or CCGG belonging to a gene promoter inactivates gene expression. It may be reversed.

Abeta: beta amyloid protein. It may be composed of 39 to 43 amino-acids. The latter is most dangerous since it aggregates more easily to form senile plaques.

Tau protein: is a phosphoprotein whose phosphorylation is regulated. The physiological function of tau is the promotion of assembly and the stabilization of a microtubular network, which is essential for normal axonal transport of vesicles within the neuron.

Vitamin B12 and folate (B9): are cofactors in the transformation of homocysteine to methionine where methyltetrahydrofolate is the methyl donor.

Vitamin B6: is cofactor of cystathionine beta-synthase transforming homocysteine in cystathionine. The end product is GSH (glutathione).

References

Bergman Y, Mostoslavsky R. Biol Chem. 1998;379:401–7.

Bird A. Nature. 2007;447:396–8.

Bottiglieri T. Nutr Rev. 1996;54:382–90.

Bottiglieri T, Hyland K. Review Acta Neurol Scand Suppl. 1994;154:19–26.

Cantoni GL. J Biol Chem. 1951;189:745–54.

Cantoni GL. J Biol Chem. 1953;204:403–16.

Cao X, Sudhof TC. Science. 2001;293:115–20.

Cavallaro RA, Fuso A, D'Anselmi F, Seminara L, Scarpa S. J Alzheimers Dis. 2006;9:415–9.

Chiang PK, Gordon RK, Tal J, Zeng GC, Doctor BP, Pardhasaradhi K, McCann PP. FASEB J. 1996;10:471–80.

Cross SH, Meehan RR, Nan X, Bird A. Nat Genet. 1997;16:256–9.

De Strooper B. Alzheimer's disease. Nature. 2000;405:627:9.

Dolinoy DC. Pharmacogenomics. 2007;8:5–10.

Egger G, Liang G, Aparicio A, Jones PA. Nature. 2004;429:457–63.

Evans DR, Hemmings BA. Mol Gen Genet. 2000;264:425–32.

Fontecave M, Atta M, Mulliez E. Trends Biochem Sci. 2004;29:243–9.

Fuso A, Seminara L, Cavallaro RA, D'Anselmi F, Scarpa S. Mol Cell Neurosci. 2005;28:195–204.

Fuso A, Cavallaro RA, Zampelli A, D'Anselmi F, Piscopo P, Confaloni A, Scarpa S. J Alzheimers Dis. 2007;11:275–90.

Fuso A, Nicolia V, Cavallaro RA, Ricceri L, D'Anselmi F, Coluccia P, Calamandrei G, Scarpa S. Mol Cell Neurosci. 2008;37:731–46.

Fuso A, Nicolia V, Pasqualato A, Fiorenza MT, Cavallaro RA, Scarpa S. Changes in Presenilin 1 gene methylation pattern in diet-induced B vitamin deficiency. Neurobiol Aging. 2010 Epub ahead of print.

Guidi I, Galimberti D, Lonati S, Novembrino C, Bamonti F, Tiriticco M, Fenoglio C, Venturelli E, Baron P, Bresolin N, Scarpini E. Neurobiol Aging. 2006;27:262–9.

Hitchler MJ, Domann FE. Free Radic Biol Med. 2007;43:1023–36.

Holliday R, Pugh JE. Science. 1975;187:226–32.

Joosten E. Clin Chem Lab Med. 2001;39:717–20.

Kapoor A, Agius F, Zhu JK. FEBS Lett. 2005;579:5889–98.

Kautiainen TL, Jones PA. Biochemistry. 1985;24:5575–81.

Kins S, Crameri A, Evans DR, Hemmings BA, Nitsch RM, Gotz J. J Biol Chem. 2001;276:38193–200.

Kresge N, Tabor H, Simoni RD, Hill RL. J Biol Chem. 2005;280:e35.

Kress C, Thomassin H, Grange T. FEBS Lett. 2001;494:135–40.

Lee ME, Wang H. Trends Cardiovasc Med. 1999;9:49–54.

Levenson JM, Sweatt JD. Cell Mol Life Sci. 2006;63:1009–16.

Lichtenthaler SF, Multhaup G, Masters CL, Beyreuther K. FEBS Lett. 1999;453:288–92.

Lu SC. Int J Biochem Cell Biol. 2000;32:391–5.

Marambaud P, Wen PH, Dutt A, Shioi J, Takashima A, Siman R, Robakis NK. Cell. 2003;114:635–45.

Mason JB, Cole BF, Baron JA, Kim YI, Smith AD. Lancet. 2008;371:1335–6.

Migliore L, Fontana I, Colognato R, Coppede F, Siciliano G, Murri L. Neurobiol Aging. 2005;26:587–95.

Morrison LD, Smith DD, Kish SJ. J Neurochem. 1996;67:1328–31.

Nicolia V, Fuso A, Cavallaro RA, Di Luzio A, Scarpa SJ. Alzheimers Dis. 2010;19:895–907.

Okano M, Xie S, Li E. Nat Genet. 1998;19:219–20.

Okano M, Bell DW, Haber DA, Li E. Cell. 1999;99:247–57.

Quadri P, Fragiacomo C, Pezzati R, Zanda E, Forloni G, Tettamanti M, Lucca U. Am J Clin Nutr. 2004;80:114–22.

Razin A, Riggs AD. DNA methylation and gene function. Science. 1980;210:604–10.

Razin A, Szyf M, Kafri T, Roll M, Giloh H, Scarpa S, Carotti D, Cantoni GL. Proc Natl Acad Sci U.S.A. 1986;83:2827–31.

Refsum H, Smith AD. Am J Clin Nutr. 2008;88:253–4.

Rouaux C, Jokic N, Mbebi C, Boutillier S, Loeffler JP, Boutillier AL. EMBO J. 2003;22:6537–49.

Saura CA, Choi SY, Beglopoulos V, Malkani S, Zhang D, Shankaranarayana Rao BS, Chattarji S, Kelleher RJ, III, Kandel ER, Duff K, Kirkwood A, Shen J. Neuron. 2004;42:23–36.

Scarpa S, Fuso A, D'Anselmi F, Cavallaro RA. FEBS Lett. 2003;541:145–8.

Scarpa S, Cavallaro RA, D'Anselmi F, Fuso A. Review J Alzheimers Dis. 2006;9:407–14.

Selhub J, Bagley LC, Miller J, Rosenberg IH. Am J Clin Nutr. 2000;71:614S–20S.

Selley ML. Neurobiol Aging. 2003;24:903–7.

Seshadri S, Beiser A, Selhub J, Jacques PF, Rosenberg IH, D'Agostino RB, Wilson PW, Wolf PA. N Engl J Med. 2002;346:476–83.

Siroen MP, Teerlink T, Nijveldt RJ, Prins HA, Richir MC, van Leeuwen PA. Annu Rev Nutr. 2006;26:203–28.

Smith AD. Food Nutr Bull. 2008;29:S143–72.

Smith AD, Kim YI, Refsum H. Am J Clin Nutr. 2008;87:517–33.

Sontag E, Hladik C, Montgomery L, Luangpirom A, Mudrak I, Ogris E, White CL, III. J Neuropathol Exp Neurol. 2004;63:1080–91.

Sontag E, Nunbhakdi-Craig V, Sontag JM, Diaz-Arrastia R, Ogris E, Dayal S, Lentz SR, Arning E, Bottiglieri T. J Neurosci. 2007;27:2751–9.

Stuhlinger MC, Tsao PS, Her JH, Kimoto M, Balint RF, Cooke JP. Circulation. 2001;104:2569–75.

Tabaton M, Tamagno E. Cell Mol Life Sci. 2007;64:2211–8.

Takai D, Jones PA. PNAS. 2002;99:3740–5.

Troen BR. Mt Sinai J Med. 2003;70:3–22.

Vassar R. Subcell Biochem. 2005;38:79–103.

Vassar R, Bennett BD, Babu-Khan S, Kahn S, Mendiaz EA, Denis P, Teplow DB, Ross S, Amarante P, Loeloff R, Luo Y, Fisher S, Fuller J, Edenson S, Lile J, Jarosinski MA, Biere AL, Curran E, Burgess T, Louis JC, Collins F, Treanor J, Rogers G, Citron M. Science. 1999;286:735–41.

Venter JC, Adams MD, Myers EW, Li PW, Mural RJ, Sutton GG, Smith HO, Yandell M, Evans CA, Holt RA, Gocayne JD, Amanatides P, Ballew RM, Huson DH, Wortman JR, Zhang Q, Kodira CD, Zheng XH, Chen L, Skupski M, Subramanian G, Thomas PD, Zhang J, Gabor Miklos GL, Nelson C, Broder S, Clark AG, Nadeau J, McKusick VA, Zinder N, Levine AJ, Roberts RJ, Simon M, Slayman C, Hunkapiller M, Bolanos R, Delcher A, Dew I, Fasulo D, Flanigan M, Florea L, Halpern A, Hannenhalli S, Kravitz S, Levy S, Mobarry C, Reinert K, Remington K, Abu-Threideh J, Beasley E, Biddick K, Bonazzi V, Brandon R, Cargill M, Chandramouliswaran I, Charlab R, Chaturvedi K, Deng Z, Di F, V, Dunn P, Eilbeck K, Evangelista C, Gabrielian AE, Gan W, Ge W, Gong F, Gu Z, Guan P, Heiman TJ, Higgins ME, Ji RR, Ke Z, Ketchum KA, Lai Z, Lei Y, Li Z, Li J, Liang Y, Lin X, Lu F, Merkulov GV, Milshina N, Moore HM, Naik AK, Narayan VA, Neelam B, Nusskern D, Rusch DB, Salzberg S, Shao W, Shue B, Sun J, Wang Z, Wang A, Wang X, Wang J, Wei M, Wides R, Xiao C, Yan C, Yao A, Ye J, Zhan M, Zhang W, Zhang H, Zhao Q, Zheng L, Zhong F, Zhong W, Zhu S, Zhao S, Gilbert D, Baumhueter S, Spier G, Carter C, Cravchik A, Woodage T, Ali F, An H, Awe A, Baldwin D, Baden H, Barnstead M, Barrow I, Beeson K, Busam D, Carver A, Center A, Cheng ML, Curry L, Danaher S, Davenport L, Desilets R, Dietz S, Dodson K, Doup L, Ferriera S, Garg N, Gluecksmann A, Hart B, Haynes J, Haynes C, Heiner C, Hladun S, Hostin D, Houck J, Howland T, Ibegwam C, Johnson J, Kalush F, Kline L, Koduru S, Love A, Mann F, May D, McCawley S, McIntosh T, McMullen I, Moy M, Moy L, Murphy B, Nelson K, Pfannkoch C, Pratts E, Puri V, Qureshi H, Reardon M, Rodriguez R, Rogers YH, Romblad D, Ruhfel B, Scott R, Sitter C, Smallwood M, Stewart E, Strong R, Suh E, Thomas R, Tint NN, Tse S, Vech C, Wang G, Wetter J, Williams S, Williams M, Windsor S, Winn-Deen E, Wolfe K, Zaveri J, Zaveri K, Abril JF, Guigo R, Campbell MJ, Sjolander KV, Karlak B, Kejariwal A, Mi H, Lazareva B, Hatton T, Narechania A, Diemer K, Muruganujan A, Guo N, Sato S, Bafna V, Istrail S, Lippert R, Schwartz R, Walenz B, Yooseph S, Allen D, Basu A, Baxendale J, Blick L, Caminha M, Carnes-Stine J, Caulk P, Chiang YH, Coyne M, Dahlke C, Mays A, Dombroski M, Donnelly M, Ely D, Esparham S, Fosler C, Gire H, Glanowski S, Glasser K, Glodek A, Gorokhov M, Graham K, Gropman B, Harris M, Heil J, Henderson S, Hoover J, Jennings D, Jordan C, Jordan J, Kasha J, Kagan L, Kraft C, Levitsky A, Lewis M, Liu X, Lopez J, Ma D, Majoros W, McDaniel J, Murphy S, Newman M, Nguyen T, Nguyen N, Nodell M. Science. 2001;291:1304–51.

Vitvitsky V, Thomas M, Ghorpade A, Gendelman HE, Banerjee R. J Biol Chem. 2006;281:35785–93.

Wei H, Ashby DG, Moreno CS, Ogris E, Yeong FM, Corbett AH, Pallas DC. J Biol Chem. 2001;276:1570–7.

Weiss A, Cedar H. Genes Cells. 1997;2:481–6.

Weiss A, Keshet I, Razin A, Cedar H. Cell. 1996;86:709–18.

Xie S, Wang Z, Okano M, Nogami M, Li Y, He WW, Okumura K, Li E. Gene. 1999;236:87–95.

Yu XX, Du X, Moreno CS, Green RE, Ogris E, Feng Q, Chou L, McQuoid MJ, Pallas DC. Mol Biol Cell. 2001;12:185–99.

Zafrilla P, Mulero J, Xandri JM, Santo E, Caravaca G, Morillas JM. Curr Med Chem. 2006;13:1075–83.

Zhang CE, Tian Q, Wei W, Peng JH, Liu GP, Zhou XW, Wang Q, Wang DW, Wang JZ. Neurobiol Aging. 2008;29:1654–65.

Zhao WQ, Feng C, Alkon DL. Neurobiol Dis. 2003;14:458–69.

Chapter 145
Reinforcement and Food Hedonics: A Look at How Energy Deprivation Impacts Food Reward

Jameason D. Cameron and Éric Doucet

145.1 Introduction

Why is it that amidst the plethora of seemingly conscious choices we make throughout our days that we often find it irresistible to reach for that next chip? After all, aren't *we* in control here? When asked such seemingly simple questions it appears as though problems such as helpless overeating – or just as germane, the command involved in dietary restriction – seems to be plainly a matter of psychological weakness and purposeful cognitive control. But, as will be discussed throughout this chapter, there is much more to feeding behavior and stable body energy reserves than self-control. In order to comprehend the physiological and psychological components involved in the uncomplicated act of eating (or not eating!) a bag of potato chips it is necessary to focus on the myriad of mechanisms that are in motion when anticipating, approaching, ingesting, and reflecting about food.

Upon closer investigation it will be argued in the following pages that a significant amount of the variation in the individual response to a similar food environment can begin to be explained not only at the gene level, but also by examining psychobiological differences in the evaluation of food *reward*. Specifically, by highlighting the potential differences in responding between lean and obese animals – spanning studies from rodents to primates (including humans) – both to the hedonic evaluation of food and to the reinforcing value of food, this chapter will attempt to describe some of the intricacies behind one the most integrated of all behaviors, feeding. Furthermore, another underlying theme will be the discussion of how energy deprivation, defined as either acute or chronic, can impact the two abovementioned components of food reward.

Beginning with the advent of agricultural practices and modernized with industrial production of food, modern-day humans are now unique to the animal kingdom in that feeding, for much of the affluent world, occurs for reasons other than sustained periods of energy deprivation. The pursuit of pleasure – or the hedonics (from the Greek word *delight*) of food – is what often guides feeding behavior. But what belies the physiology and psychobiology of what amounts to abhorrent feeding patterns still remains elusive. What is clear, however, is that when energy deprivation is prolonged there is a degree of disinhibition with respect to appetite: not only does palatable food become more salient but items that would normally not be selected can also become attractive. A plethora of research has since emerged on how homeostatic-like elements – states of nutritional need – can alter the pleasure of a sensation of food. This concept was coined as *alliesthesia* and has since received much attention.

É. Doucet (✉)
Behavioral and Metabolic Research Unit, School of Human Kinetics,
University of Ottawa, Ontario, Ottawa, Canada, K1N 6N5
e-mail: eric.doucet@uottawa.ca

Often a combination of sight, smell, touch, and previous exposure to the food stimulus, the rewarding quality of food is therefore represented by an active process of the brain that is defined by a composite reaction to the food, and as a result is not simply a physical property of the taste stimulus itself (Berridge 1996). Furthermore, the actual reward corresponds to, and is divided by, what are believed to be three separate psychological concepts ("*wanting*," "*liking*," and learning) which are underpinned by distinct neurobiological mechanisms. Each of these dissociable components describes independent qualities that define a rewarding stimulus, and each will be elaborated on in the following sections.

As a final introductory note, it must be clarified that contrary to the view that obesity is only about behavioral control (or lack thereof), that feeding behavior is not entirely a conscious process. The *Milieu Intérieur* is constantly responding to the ebb and flow of blood-borne (chemical) and mechanical (distension) signals and their sensory afferents; incentive stimuli in the external environment along with learned associations both external and internal add salience to edible objects; genotypic variations amongst several hundred genes predispose behavioral outcomes in particular environments; and the whole of the hierarchy from blood to brain necessitates access to the basal motor system to coordinate the action of hand-to-mouth. In the end this chapter is guided by the unresolved questions regarding how each level of the aforementioned hierarchy impacts the rewarding characteristics of feeding. This chapter will also serve as an analysis of the degree to which reinforcement/"wanting" and palatability/"liking" may reflect underlying nutritional needs (e.g., chronic energy deprivation) or to what extent these components of food reward can be reflected independently of need state (e.g., weight-stable and energy replete).

145.2 Reinforcement

145.2.1 Episodic Nature of Feeding: Beyond Homeostasis

Prior to beginning a discussion about the intricacies of defining and describing the rewarding attributes of a food stimulus there is a need to introduce the physiology of feeding in relatively general terms. At the behavioral level food intake is episodic (i.e., not continuous). This indicates that there must be physiologically distinct messengers that bring an animal to begin and to end a meal. In fact, nearly half a century of research has shown that there are hormonal signals released by the gastrointestinal tract – peripheral short-term feeding signals – resulting from, or prior to, a single bout of eating. These short-term signals are divided into orexigenic signals (e.g., the peptide hormone ghrelin) that convey the overall message to eat, and this in contrast with anorexigenic signals (e.g., the peptide hormones cholecystokinin and peptide YY) that convey the message of fullness (see Table 145.1). These peripheral feeding signals released from the physical act of consuming foodstuffs are first processed within the nuclei of the hindbrain (primarily, the nucleus of the solitary track, NTS). In a reciprocal manner, these stimuli are transmitted and converge to the real-time processing stations of the hypothalamus and associated cortico-limbic structures eventually leading to goal-directed motor programs that either facilitate or impede the further ingestion of food. Furthermore, there is extensive evidence that these peripheral meal-to-meal signals act directly on the arcuate nucleus of the hypothalamus by crossing the highly selective blood brain barrier, or indirectly at the arcuate through second messenger signaling. It must also be noted that there are metabolic signals such as excursions in blood glucose that can act to promote feeding. Classic work on glycemia first demonstrated in rats was extended to humans and showed that arteriovenous differences (rate of utilization) of glucose correlated with hunger and energy intake (Van Itallie et al. 1953). Although there is continued controversy on the action and mechanism of glucose's role in feeding, it appears that this metabolic signal also has downstream effects at the hypothalamus. The hypothalamus

Table 145.1 A brief list of the peripheral feeding signals implicated in the short- and long-term modulation of energy intake (Modified from Cameron and Doucet (2007). With permission)

Feeding signal	Primary site of secretion	Effect on food intake
Long term		
Insulin	Pancreatic β cells	Decreased energy intake
Leptin	Adipocytes	Decreased energy intake
Short term		
CCK	Endocrine I cells of the proximal Small Intestine	Decreased energy intake
PYY$_{3-36}$	Enteroendocrine L cells of the ileum & colon	Decreased energy intake
GLP-1	Enteroendocrine L cells of the proximal Small Intestine	Decreased energy intake
Ghrelin	Oxyntic X/A cells of the stomach	Increased energy intake

Of all the feeding signals, ghrelin is the only peptide hormone that is an orexigenic feeding signal
CCK cholecystokinin, *PYY$_{3-36}$* peptide YY, *GLP-1* glucagon-like peptide 1

acts as a primary relay station that influences three major systems: the autonomic nervous system, the endocrine system, and the nested brain areas involved in motivational systems. As previously noted, when considering feeding behavior – on a very primitive level – this response can be deconstructed and thought of as motivational states (or drives) that are based upon bodily needs. More than this, whether it is to quench one's thirst or to eat in response to severe hunger pangs, these drives often force the body into action.

Overall, there are two main points to consider regarding the short-term regulation of energy intake: meal size and frequency. What is noticed in free-feeding laboratory conditions is that meal size predicts the interval until the following eating episode. This so-called "postprandial relationship" suggests that meal size is determined via adjustments to the interval to the next meal – not dependent on mere convenience or learned time cues. Conversely, and in most cases in the Western world, meals are scheduled at specific times of the day, resulting in no significant relationship between meal size and intermeal interval (de Castro 2000). In this so-called "preprandial relationship" there is however a relationship between the intermeal interval and meal size; what can be extrapolated is that under daily circumstances, the episodic quality of feeding is lead by associative learning. However, as the period of deprivation (intermeal) increases there may be a shift to respond in a drive-induced manner. What this indicates is that there need not be a deprivation or homeostatic signal in order to initiate a drive state or to continue consummatory behavior; once an animal learns simple stimulus–response relationships, stimuli that were once meaningless become powerful cues with the potential to initiate goal-directed motor programs. Simply put, humans *learn* how and when to initiate feeding: we discover very early that the general feeling of malaise created by the rumbling of a hunger pang or light-headedness of hypoglycemia are often associated with a lack of food. And humans, like snakes and snails, learn by reinforcement.

145.2.2 Reinforcement: Psychological Theory

Although there is no single definition of reinforcement, the concept at its most basic level – in a purely behaviorist sense – can be defined by an environment–behavior relation resulting in the strengthening of an association. As an example, a foraging animal may be experiencing some form of vitamin deficiency and randomly come across a *novel* food containing the deprived vitamin. Prior to having experienced the positive postingestive consequences of that food stimulus – without the

paired experience of assuaging the metabolic requirement for the vitamin – there existed no incentive value to the object. Without previous exposure there is no goal, or direction to behavior. This definition becomes inadequate (or incomplete), however, given the evidence that the taste of sweet or salty food can be innately rewarding (Berridge 1996), and therefore considered a "primary reward/primary reinforcer." As an example, newborn babies (and chimps and rats) demonstrate stereotypical responses of "liking" of sweet foods. In the above examples, then, sweet/salty foods are innate incentive stimuli, which are analogous to unconditioned stimuli, and the initially neutral food containing the vitamin (the conditioned stimuli) becomes a predictor of reward (Berridge and Robinson 1998).

In the field of psychology some of the most used descriptors for a *reinforcer* label it as a goal and an incentive, or a stimulus that is approached or attained (Salamone and Correa 2002). Furthermore, implicit in any definition of a reinforcer is the ability for a stimulus to motivate behavior once the stimulus reward association is imprinted. The motivation to obtain the goal object (e.g., food) is not merely an immeasurable psychological concept but can be categorized (e.g., anticipatory, appetitive, etc.) and the neurotransmitters mapped. In fact, the role of midbrain dopamine projections will be argued as being one avenue for explaining the neurophychology of motivation – and specifically the incentive contribution to food reward – in the etiology of what today me be considered maladaptive behavior.

145.2.3 Food as a Reward

The concept that food can serve as a natural *reward* is not hard to grasp in the subjective sense that many foods have the quality of inducing a sense of gratified pleasure. This is most easily measured in humans because an experimenter can simply ask a subject to rate this pleasure/palatability on an analogue scale, for example. But the first neurophysiological evidence for the role of food as a *reward* emerged from brain stimulation studies during the late 1960s and throughout the 1970s. These studies demonstrated that humans would work to obtain electrical stimulation of some sites of the brain (including the lateral hypothalamus (Olds 1977; Rolls 1975), which was by definition rewarding. What is more, the rewarding quality of the brain stimulation appeared to mimic the rewarding quality of food; interestingly, it was found that animals would work harder to obtain brain stimulation when hungry (Hoebel 1969), but when an animal was fed to satiety, it was later found that the group of lateral hypothalamic neurons under observation ceased to respond to food (Rolls et al. 1986). It must be noted that evidence offered with human brain *reward* stimulation suggested that while the experience was certainly rewarding – patients could be found compulsively self-stimulating over thousands of repeated presses – there was no evidence of self-described pleasure in either case (Heath 1972; Portenoy et al. 1986). Observations such as these helped to lay the framework that disentangled the concept that rewards must be pleasurable; it is part of the *incentive salience* hypothesis (described below) that attempts to verify that under various circumstances (e.g., addiction) a *reward* need not be both pleasurable and desired at the same time.

The work on brain stimulation was extended to psychomotor stimulants and eventually it was discovered that the rewarding effects of both of these sources of unnatural reward could be blocked by dopamine antagonists. Eventually it was later confirmed that food *reward* – a natural *reward* – could be similarly attenuated (Wise et al. 1978), and thus began the explosion of studies examining how dopamine modulates feeding and food reward. The following subsections will describe some of the theoretical views of dopamine's role in feeding and reinforcement. The focus will then shift to an examination of the potential role that reinforcement (and dopamine) plays in obesity and how peripheral signals of energy deprivation (e.g., the "hunger hormone" ghrelin and the adiposity-marker hormone leptin) may modulate reinforcement through altered dopamine function.

145.2.3.1 The Dopamine Hypothesis of Feeding: From Anhedonia to Incentive Salience

The accepted hypothesis that is now entrenched in fields spanning from neuroscience to clinical psychology is what has been termed the dopamine hypothesis, or applied to food intake, the dopamine hypothesis of feeding. In brief, via dopamine signaling arising from the ventral tegmental area of the midbrain there is downstream communication with limbic and prefrontal cortex brain areas that act to focus attention on salient environmental stimuli and to promote learning associations, thereby facilitating specific behavioral output such as feeding. The thesis is that dopamine neurons form the backbone of the network of the brain's natural reinforcement system. Indeed, food consumption, in likeness with drug consumption, increases brain dopamine levels in not only in animals, but also in humans (Wang et al. 2002). A more detailed account of the effects of altered levels of dopamine in the brain is presented in Fig. 145.1. The *exact* role that dopamine plays in reward is, however, still open to debate.

Dopamine is both a hormone and neurotransmitter that occurs in a wide variety of animals, including humans. It is one of the primary neurotransmitters in the mammalian brain, where it controls cognition, emotion, locomotor activity, food intake and endocrine regulation (Missale et al. 1998). In the brain there are three major dopaminergic pathways but the most relevant to this discussion is the reward related circuit – the mesolimbic pathway – originating in the midbrain ventral tegmentum and extending to several limbic structures, including the nucleus accumbens, the amygdala, and the hippocampus (Berthoud 2007). Part of the dopamine hypothesis of food intake is based on the initial
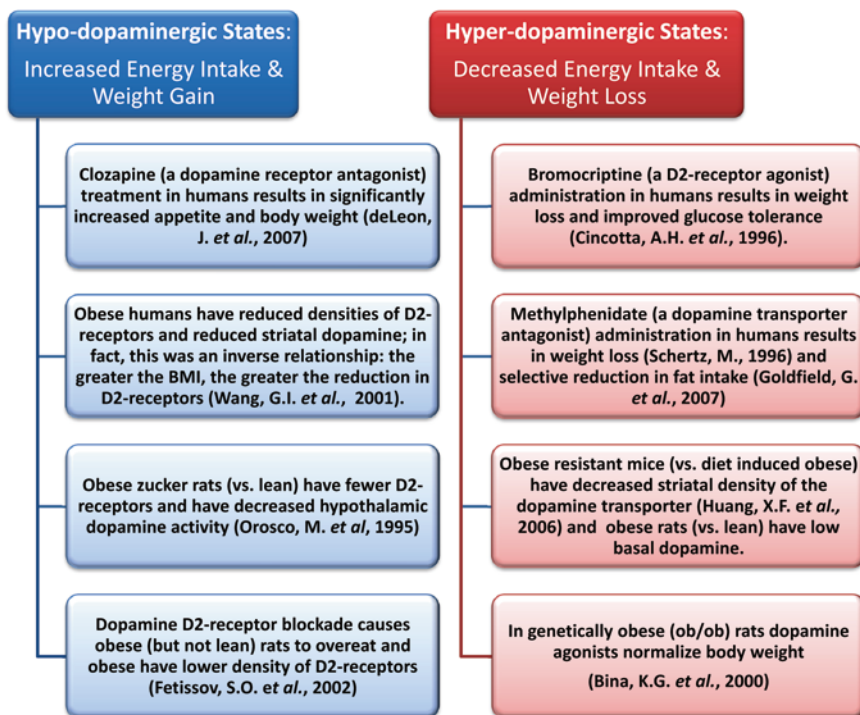
Fig. 145.1 Key points describing dopamine's role in feeding behavior. A look at how altered levels of the neurotransmitter dopamine, by pharmacological or genetic manipulation, can impact normal feeding behavior and body weight regulation in humans and in rodents. Note that a dopamine receptor antagonist *blocks* dopamine signaling by postsynaptic inhibition; oppositely, a dopamine transporter antagonist *promotes* signaling by flooding the synapse with dopamine (References are, from left side (de Leon et al. 2007; Fetissov et al. 2002; Orosco et al. 1995; Wang et al. 2001) and from the right side (Bina and Cincotta 2000; Cincotta and Meier 1996; Goldfield et al. 2007; Hauge et al. 1991))
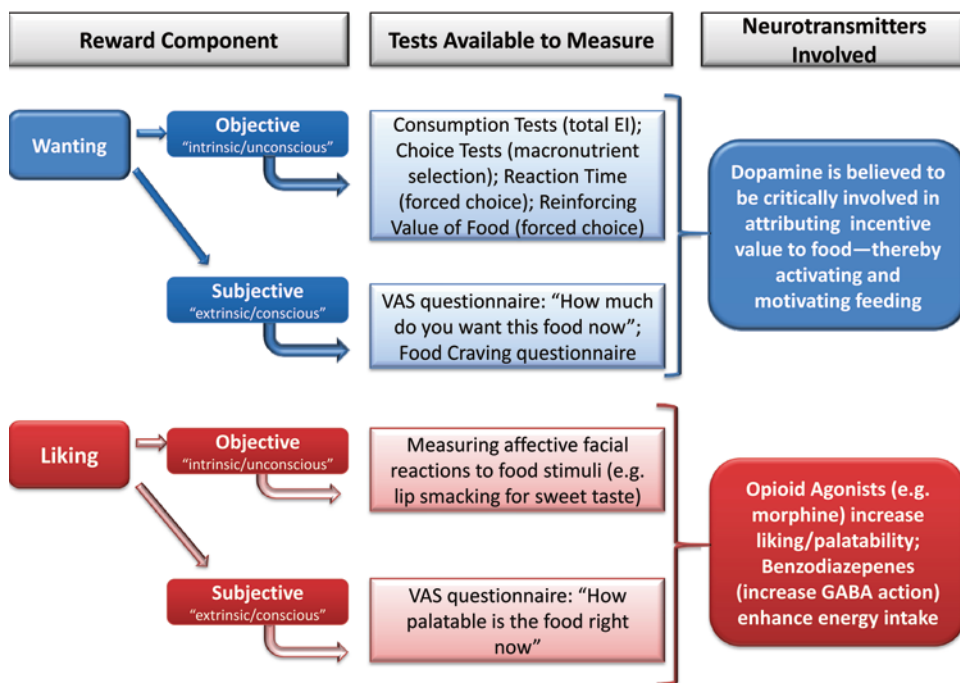
Fig. 145.2 A representation of the dissociable qualities of food reward according to the "incentive salience hypothesis" and the means by which each process can be quantitatively assessed in the laboratory. Note that EI is an abbreviation for energy intake.

work performed on animals subjected to the dopamine antagonist pimozide, which eventually led to the "Anhedonia (Greek for *without pleasure*) Hypothesis." This hypothesis stated, amongst other findings, that neuroleptics (specifically dopamine D2-receptor blockers) appeared to selectively blunt the rewarding impact of food stimuli by decreasing the pleasure of the reinforcer (Wise 1982). While other groups have arrived at many of the same conclusions – in that dopamine is required for *normal* motivation and reward – there appears to be some disagreement regarding the precise role of dopamine in reinforcement or reward. All of the intricacies of the various theories cannot be covered here; however, the view that appears most persuasive has been painstakingly developed (for review see (Berridge and Robinson 1998)) and asserts that dopamine is *not* necessary for 1) hedonic activation (i.e., normal affective reactions described as subjective/objective "liking") and, 2) for reward learning (i.e., relation between the conditioned stimulus and the unconditioned stimulus), but it *is* important for the attribution of the incentive salience of rewards. In fact, these three psychological processes are the foundation of the "incentive salience hypothesis," which offers a further description suggesting that these three processes are all dissociable qualities of reward that can be separated into components of "wanting" and "liking" (see Fig. 145.2)

145.2.3.2 "Wanting" and "Liking": Measuring Perceptual and Motivational Qualities of Food Reward

According to the "incentive salience hypothesis," there is a change at the neurological level that describes *perceptual* (e.g., cognitive) and motivational (e.g., unconscious) components that accompany the shift from a stimulus being neutral to something that is attractive and can energize and

motivate behavior (Berridge et al. 2009). The relevance for the study of feeding is that tools can be devised that measure the level of attraction to a stimulus/reinforcer and how much behavior it will support. One method that has been designed to examine *explicit* "liking"/ "wanting" and *implicit* "wanting" of food is the recent development of a forced choice computer-based procedure (Finlayson et al. 2007). This task presents photographic food stimuli of 20 different items varying along two dimensions – fat (high or low) and taste (savoury or sweet). From this computer task implicit "wanting" is measured by the speed with which one stimulus is chosen in preference to an alternative and is additionally measured by relative preference (e.g., fat vs. sweet).

In an attempt to determine whether acute energy deprivation influences food reward this forced choice paradigm was utilized at times pre- and post a standard lunch meal. The objective was to look for a state (hungry vs. satiated) dependent dissociation between "wanting" and "liking." The main findings noted that in a hungry state (3–4 h acute energy deprivation) subjects "wanted" fat (particularly high fat) and savoury food more so than fat and sweet food, but this trend was reversed and subjects "wanted" low fat sweet after the completion of an ad libitum pizza lunch. A separate study from the same group looked at the impact of meal-induced satiation on the dissociable qualities of food reward and discovered that once again implicit "wanting" for low fat sweet foods increased following a lunch meal and that "liking" for sweet foods did not decrease as much as that for fat foods (Finlayson et al. 2008). The general trend of decreased "liking" as one progresses from a hungry to satiated state is consistent with the notion of alliesthesia, a concept that will be discussed in greater detail in Sect. 145.3.

Under study designs similar to those just discussed (state-dependent), recent results from neuroimaging studies offer promising descriptions of what might be occurring in areas of the brain implicated in reward. With fMRI analysis, it was discovered that satiated normal weight women show a stronger BOLD response in the striatum and OFC – reward centers that can be viewed in Figs. 145.4 and 145.6 in Sect. 145.3 – when presented with images of low calorie foods. When hungry, however, these brain areas showed a stronger bold response to high calorie foods (Siep et al. 2009). In a separate fMRI study subjects were tested 3 h after the ingestion of a standardized meal by either infusing the "hunger hormone" ghrelin or a saline control prior to looking at food pictures (Malik et al. 2008). Ghrelin (and not saline) increased the response to food cues in the amygdala, the OFC, and the striatum. Consequently, as demonstrated by these fMRI data, the state-dependent results reported with the forced choice paradigm reported in the previous paragraph may be in part explained by a homeostatic-like influence on reward processing. To be sure, a study combining the "wanting/liking" computer task with fMRI neuroimaging and peripheral injections of ghrelin/leptin or neuropharmacological manipulation of dopamine would be of the highest impact. Unfortunately no such work has yet been performed.

145.2.3.3 The Relative-Reinforcing Value of Food & Energy Deprivation: Do Dopamine-Related Polymorphisms Impact Feeding?

In yet another definition of a reinforcing stimulus, one can describe a reinforcer as a stimulus that increases the rate of a behavior that it follows. The reinforcing value of a stimulus refers to how much behavior the stimulus will support (Epstein et al. 2007a). This can be objectively observed as the increased willingness – a quantitative measure – to work at a progressive ratio computer task to obtain a desirable food stimulus (vs. some alternative). As an example, a computer can be set up with a screen that alternates between two different choices (typically a healthy food and palatable snack food) that can be navigated with a mouse pad. It is called the relative-reinforcing value of food because the probability of earning food points varies across schedules and is contingent on performing

simple button presses on a computer joystick. The reinforcement schedule typically remains at a variable ratio (VR2) for all five trials for the healthy food, but increases progressively for the palatable snack food at VR2, VR4, VR8, VR16, and VR32 across the five trials. Thus, on average the reinforcement schedule for the healthy food is set to reinforce every second button push (VR2), and this remains the same across all trials; the reinforcement schedule for the snack food doubles across each trial, such that in the final trial (VR32) snacks were reinforced on every 32nd button press. Essentially, if subject 1 stops responding for the snack food at 16 button presses per point and subject 2 continues to respond for snack points at 32 button pushes per point, then the snack food is said to be twice as reinforcing for subject 2, as they must work twice as hard to obtain the reinforcer.

What is interesting is that comparing obese and lean individuals with this relative-reinforcing value of food paradigm, it was noted that not only did obese subjects work harder for palatable food items (vs. sedentary activities or healthy foods), but they also demonstrated an increased willingness to work for the reinforcer. In fact, this increase in the reinforcing value of food predicted ad libitum intake in the obese independently of rated pleasantness (Saelens and Epstein 1996; Temple et al. 2008). What this suggests is that the measure of motivation to work to obtain, i.e., implicit "wanting" as measured by button-presses, can in some instances be a better predictor of energy intake than explicit subjective accounts of "liking." It appears as though at the behavioral level the combination of consummatory and appetitive motivation can trump orosensory reward. Indeed a troubling finding is the observance that not only do the obese find food more reinforcing (they work more for food than for sedentary activity compared to lean) (Saelens and Epstein 1996), but obese persons also find high-fat foods more reinforcing than low-fat foods when compared to normal weight controls (Epstein et al. 1991). The reinforcing value of food, in turn, can influence how much food is eaten at an ad libitum buffet. What is more, individuals who are categorized as high in food reinforcement (i.e., spend more time at a variable ratio task working for palatable food vs. bland or nonfood items) eat more in an all-you-want-to-eat environment compared to individuals low in food reinforcement (Epstein et al. 2004a). It is unclear, however, whether these findings represent a cause or consequence of excess energy reserves.

One almost inescapable consequence of obesity is sustained periods of energy depletion or dieting. It is well known from psychological studies of reinforcement that food deprivation (and even drug deprivation) increases the reinforcing value of food. Obese and lean individuals alike pass through perturbations in body weight as a result of the prolonged interplay between energy intake, energy expenditure, and the overall involvement of gene and environment interactions. Indeed, results from an energy deprivation in lean individuals ranging in the time of ~13–20 h indicated that in this relatively short period of deprivation the reinforcing value of a palatable snack food significantly increased from the baseline measure in the fed state (Raynor and Epstein 2003). As an ecologically relevant example, if a lean person begins to regularly skip meals, then food is likely to become more reinforcing when it is finally approached. It is unknown if this phenomenon would persist with chronic periods of energy deprivation, but one could postulate that such behavior would lead to body weight gain according to the connection between the reinforcing value of food and energy intake (Raynor and Epstein 2003). Obese individuals experiencing the same feeding patterns theoretically would be even more vulnerable to weight gain, as food is already more reinforcing to begin with. What is fascinating is evidence suggests that polymorphisms of genes involved in the normal regulation of the neurotransmitter dopamine may be involved in a "high-food reinforcement" phenotype, or even related to excess energy reserves.

As a member of the catecholamine family, dopamine is synthesized from the amino acid tyrosine (produced in the liver from phenylalanine), mainly by nervous tissue and the medulla of the adrenal glands. Following the synthesis of dopamine (see Fig. 145.3) there is vesicle packaging in the nerve terminal that prepares this monoamine neurotransmitter for synaptic release. When a dopaminergic
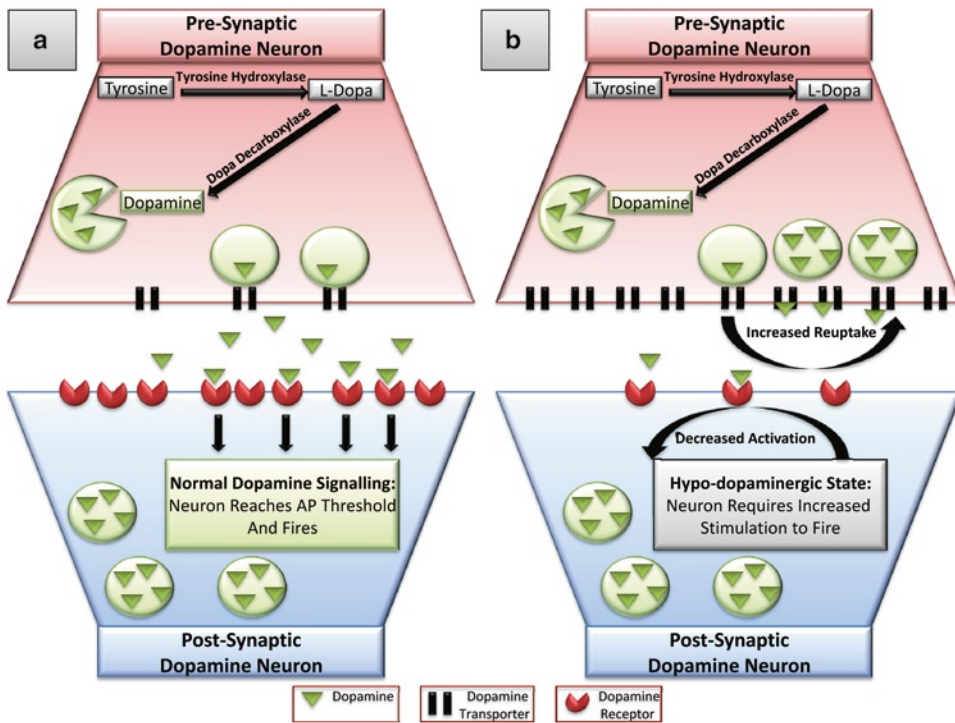
Fig. 145.3 A stylized representation of midbrain dopamine neurons representing (**a**) a typical neuron with a normal propagation of action potential (AP) and (**b**) a neuron with impeded postsynaptic signaling (a "hypodopaminergic state") due to polymorphisms of the dopamine receptor and transporter. The dopamine transporter is responsible for the reuptake of dopamine and the 10/10 allele is hypothesized to result in decreased synaptic dopamine due to *increased* transporter density (i.e., increased reuptake). Also believed to be involved in impaired dopamine signaling, the Taq1A allele of DRD2 results in *decreased* density of dopamine D2-receptors (see **b**)

neuron is sufficiently excited, dopamine is released into the synaptic cleft where it interacts with the postsynaptic receptors causing the depolarization of the postsynaptic cell and initiating a new action potential. Dopamine availability is dependent on its metabolism, release, transport, and receptor binding. Consequently, by looking at the genes involved at any one of these stages there is an opportunity to indirectly investigate brain dopamine levels – in effect looking at markers of neurotransmitter activity (Epstein et al. 2007b) – and how behavior may be resultantly impacted.

The dopamine transporter gene (SLC6A3) codes for a membrane spanning dopamine transporter protein (DAT) that mediates reuptake of dopamine from the synapse into surrounding neurons. There are multiple alleles for this DAT protein and it appears that the 10-repeat homozygous polymorphism is associated with increased dopamine transporter density and transport (Fuke et al. 2001) when compared with the 9-repeat/10- repeat allele. The hypothesis posits that due to simple mendellian genetics, people who received the same 10-repeat allele (i.e., 10/10 genotype) from both parents have lower levels of postsynaptic dopamine. This is further evidenced from in vivo PET studies in humans showing that individuals with the 9-repeat/10-repeat genotype displayed a mean 22% reduction of DAT protein availability compared with 10-repeat homozygous individuals (Heinz et al. 2000). Individuals with the 10/10 genotype can also be at increased risk to obesity. It was found that African Americans with the 10/10 genotype had an odds of having BMI values ≥ 30 kg/m^2 that were 5.2 times greater than African Americans with the 9/9 or 9/10 genotype (Epstein et al. 2002).

Another polymorphism believed to result in decreased dopamine signalling occurs due to an alteration in the ANKK1 gene, known as the Taq1A restriction fragment length polymorphism. To remain consistent with existing literature–and due to the fact that ANKK1 is believed to be in linkage disequilibrum with DRD2–Taq1A will be acknowleged as being linked to DRD2. Specifically, there are three *Taq1* A variants (A1/A1, A1/A2, and A2/A2) and compared to carriers of the *Taq1* A2 allele, in vivo imaging had shown that people with the *Taq1* A1 allele have reduced brain dopamine signaling (Pohjalainen et al. 1998). With further in vivo (PET imaging) evidence, the mechanism of action is thought to be mediated primarily with the association of the *Taq1* A1 allele with decreased DRD2 receptor density (Noble et al. 1991). What this suggests is that carriers of the *Taq1* A1 allele experience reduced dopamine signaling in the brain; indeed, it has recently been demonstrated that decreased density of DRD2 is strongly associated with human obesity, in inverse proportion to BMI (Wang et al. 2001). Linking physiology with behavior, current research has revealed that the reinforcing value of food – analogous to the "wanting" component of food reward – can not only influence energy intake, but the presence of the *Taq1* A1 allele of the dopamine receptor can interact with obesity to influence food reinforcement (Epstein et al. 2004b, 2007b). Subjects identified as high in food reinforcement who were carriers of the A1 allele consumed more food than participants high in food reinforcement without the A1 allele and participants low in food reinforcement with or without the A1 allele (Epstein et al. 2007b). Although these data are preliminary, what this suggests is that using a behavioral genetic approach to understand the interaction between genotype, obesity, and food reinforcement can be viewed as a viable research venture.

Taken together, individuals with the *Taq1* A1 or the 10/10-repeat alleles are hypothesized to be less sensitive to stimulation of dopamine-regulated reward circuits – analogous to a reward-deficiency syndrome (Noble et al. 1994) – and by enduring a hypodopaminergic state are more likely to seek reinforcers, whether it be food or drug (Blum et al. 1996). In fact, this represents one view of dopamine's involvement in food reward and it fits well with much of the literature presented thus far. Although it is a very hedonistic view of feeding behavior, it is a tenable hypothesis that overeating has emerged as a compensatory mechanism to ameliorate a deficiency in the reward circuitry (Wang et al. 2002). Others contend a somewhat opposing view that focuses on an individual's sensitivity to reward, as measured by a psychobiological questionnaire. It is argued that individuals with high levels (hyperdopaminergia) of synaptic dopamine are more sensitive and have a greater capacity for reward, thereby making them more likely to engage in pleasurable behaviors (Davis and Fox 2008). In the end, it is not clear whether the dopamine hypothesis of feeding is best explained by hypodopaminergic states as described by a reward deficiency syndrome, or by hyperdopaminergic states as described by heightened reward sensitivity, or by both.

145.2.4 Peripheral Feeding Signals Impact Brain Dopamine: Evidence That Energy Deprivation Can Impact the Motivational Component of Food Reward

A promising path has been paved with respect to adiposity signals and their possible role in mediating food reward. When leptin is administered intraventricularly in rodents, it attenuates the rewarding impact of food-restriction-sensitive stimulation (Fulton et al. 2000), where animals significantly decrease rates of brain stimulation reward. What is interesting is that this rewarding effect is potentiated by chronic food deprivation and that the ability of this deprivation to enhance brain stimulation reward is proportional to the degree of weight loss (Carr and Wolinsky 1993). In effect, with greater weight loss animals will continue pressing the lever for ever smaller amounts of stimulation, which is translated into a leftward shift in the rate–frequency curve. Further, intracerebroventricular leptin

administration causes a rightward shift in this curve, restoring the reward value to predeprivation levels (Fulton et al. 2000), but to initially respond to the deprivation, an absolute weight loss of approximately 10% was required. It may be that long-term adiposity signals like leptin actively signal reward pathways of current body reserves, thereby intrinsically making food more attractive – more rewarding – when a significant loss of body energy reserves or a similar signal (decreased leptin) is detected.

New developments into the study of leptin and ghrelin – signals of energy surfeit and deficit, respectively – have indicated that these feeding signals may play complimentary roles in the dopamine hypothesis of feeding. Mesolimbic brain circuits have recently been shown to express the long form of the leptin receptor (the main leptin receptor, OB-Rb); more than this, it has been demonstrated that OB-Rb mediated signaling modified dopamine signaling and food intake. When leptin was administered directly to the ventral tegmental area (VTA) – the central hub of dopaminergic neurons – rats decreased food intake; oppositely, when the OB-Rb was knocked out in this area, feeding was increased, especially of highly palatable chow (Hommel et al. 2006). In contrast, but consistent with its role in feeding, when ghrelin is injected into the VTA rats show a robust dose dependent feeding response (Naleid et al. 2005). Taken together, what emerges is the neurological foundation that connects dopaminergic pathways of reward with short- and long-terms feeding signals. Leptin inhibits the firing of VTA dopamine neurons and ghrelin triggers tonic dopamine release, resulting in decreased and increased feeding, respectively. Food reward appears to be impacted by homeostasis and dopamine plays an integral role in the appetitive motivation to feed. Another possible role for dopamine that cannot be discounted is that it has indirect downstream action on another neurotransmitter. Indeed, there is evidence that ghrelin can impact the opioid system in the rat (Sibilia et al. 2006). The point here is that dopamine is only one piece of the grand puzzle that describes the intricate network underlying food reward.

145.3 Food Hedonics

145.3.1 Palatability: The Multimodal Representation of Taste

Taste perception is transmitted by cranial nerves, which propagate information about the touch, temperature and pain sensation on the tongue (Kringelbach 2004). The afferent taste signal progresses from cranial nerves to the NTS, continuing to the thalamus and then to the primary taste cortex; higher order taste assimilation is believed to be accomplished by the connections of the primary taste cortex with the secondary taste cortex (i.e., the orbitofrontal cortex) (Baylis et al. 1995). With respect to the pleasantness of the taste of foods, the responsiveness of the taste neurons in the NTS and in the primary taste cortex (see Fig. 145.4) do not seem to be affected by states of deprivation and repletion (Rolls et al. 1988; Yaxley et al. 1988). What this implies is that these areas do not reflect the hedonics of feeding, but instead represent sensory qualities of food independent of motivational state. Therefore the identity and intensity of food taste is made explicit in the primary taste cortex, but it is with the rich interconnectivities of the orbitofrontal cortex (OFC) that the hedonic component of the rewarding value of food finally is coded. In short, evidence from primates indicates that the identity of a taste and its intensity are represented separately from its pleasantness (Rolls 2007).

The OFC can be subdivided into two regions: the posterior region, restricted to the limbic functions and considered part of the limbic system, and an anterior region, restricted to inhibitory control over the amygdala (Borod 2000). In order for peripheral feeding related signals to influence food pleasantness – and by convention, food reward – this must occur from the processing of the stimuli
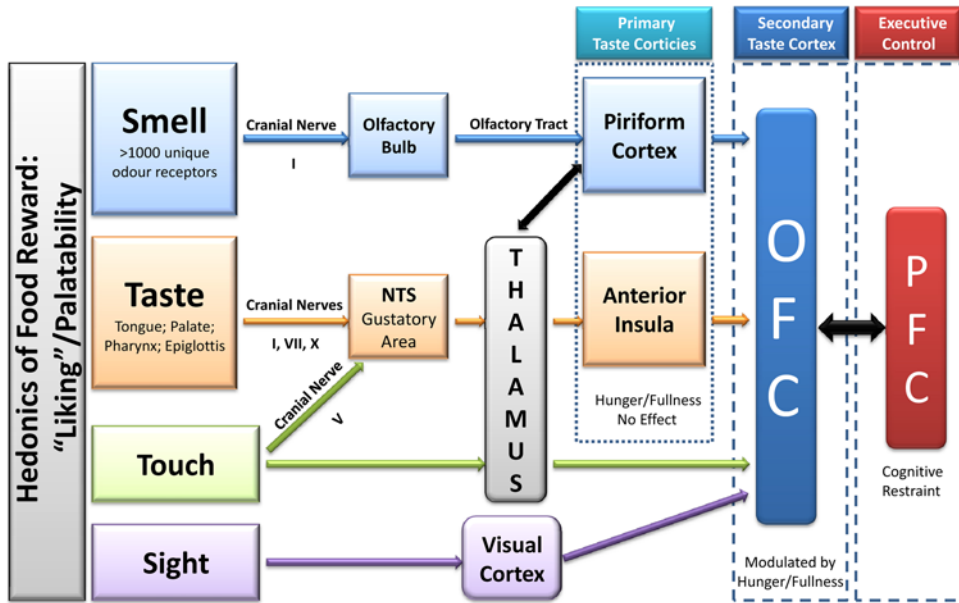
Fig. 145.4 A schematic diagram of pathways demonstrating the multimodal representation of taste and olfaction in the brain. Note that cranial nerve I is the olfactory nerve; cranial nerve VII is the facial nerve; cranial nerve X is the vagus nerve; and cranial nerve V is the trigeminal nerve (which transmits the mouthfeel of fats and oils); OFC is the orbitofrontal cortex; and PFC is the prefrontal cortex

at the level at or beyond the secondary taste cortex (Rolls et al. 1990). Efferent connections from the OFC include the amygdala, the hippocampus, the lateral hypothalamus, the striatum, and the ventral tegmental area (Kandel et al. 2000). What is interesting is that each of these brain areas is influenced by ghrelin, leptin, and dopamine. Interconnected within this network of neuromodulators and feeding-related signals lies what is believed to be a path toward describing reward signaling, or in the context of energy deprivation, *alliesthesia* (discussed below).

Pioneering work performed on primates indicated that responses from a group of OFC neurons to glucose taste decreased to zero when the monkey ate glucose to satiety; concurrently, over the course of administration of glucose the animal's behavior changed from positive to negative affective reactions (Rolls et al. 1989). Furthermore, it was demonstrated that this decrease in neural activity was specific to the ingesta, i.e., the authors discovered a piece of the neural foundation of *sensory specific satiety* (Rolls et al. 1989). What remains unclear is the role that information from the primary taste cortex and from adjacent limbic areas impacts the change in pleasantness of a food stimulus that occurs with continuous exposure over a meal or from refeeding after chronic energy deprivation.

Another area that requires clarification is to what degree the decisions regarding when, what, and with whom to eat are conscious. Indeed, much of the expression of appetite and eating is not explicit, and therefore outside of introspection. Studies from rats, to chimps, to human infants have demonstrated that "liking" of sweet foods can be implicit – and this was accomplished by measuring stereotypical facial reactions to the sweet stimuli (Steiner et al. 2001). Sweet tastes elicit a positive hedonic pattern of evaluation primarily described by tongue protrusions (licking/smacking of lips) and paw licking (Grill and Berridge 1985). Since "liking" is considered a basic evaluative reaction of the brain with objective behavioral indicators it can be implicitly measured by affective measures to the food *reward*; alternatively, the hedonic impact of "liking" can be explicitly measured in humans by describing their reaction to the food stimulus (e.g., analogue scales). A pleasant stimulus is a rewarding stimulus and for the most part feeding is a rewarding action. The "liking" component of food reward has its

biological underpinnings in at least two major neurotransmitter families defined by opioid, and endocannabinoid systems. The best studied in humans is the opioid modulation of palatability. Specifically, opioid receptor antagonists (e.g., naltrexone and naloxone) reduce the pleasantness of foods (Bertino et al. 1991; Drewnowski et al. 1992) and agonists (e.g., DAMGO and morphine) increase the pleasantness (Atkinson 1987; Levine and Atkinson 1987). This hedonic pleasure/palatability component of reward is represented in the brain mainly by pallidal circuits (Yeomans and Gray 2002) and by circuits within the shell of the nucleus accumbens (Pecina and Berridge 2005) (see *striatum* in Fig. 145.6).

145.3.2 Peripheral Feeding Signals and Taste Processing

There is limited data regarding the potential role of gut peptides (peripheral feeding signals) in taste processing. Studies on rats have indicated that PYY_{3-36}, a hormone released by L-cells of the distal colon, produced a dose-dependent conditioned taste aversion to a sweet solution (Chelikani et al. 2006; Halatchev and Cone 2005). Similarly, another peptide released by intestinal L-cells, GLP-1, also has the potential to produce a robust conditioned taste aversion to saccharine (Thiele et al. 1997). What is intriguing is that CCK, a "satiety hormone" like PYY and GLP-1, can actually produce a conditioned flavour *preference* at low doses in rats (Perez and Sclafani 1991). The authors interpreted this preference to the positive postingestive consequences of satiety. It is possible that the taste aversion with PYY and GLP-1 could be an artifact of nausea that has been reported in human subjects; nonetheless, there is evidence that these gut-peptide messengers are involved in taste-processing.

The hormone produced by the OB gene, leptin, has also been demonstrated to have a role in the hedonic evaluation of food. Specifically, leptin receptors were identified in taste cells and exogenous administration of leptin inhibited sweet taste responses in lean mice but not in db/db mice (lacking a functional leptin receptor) (Ninomiya et al. 2002). Evidence of a separate role for leptin in *olfactory processing* has also emerged from data on rats showing how nutritional status impacts olfactory perception. Specifically, intracerebroventricular leptin administration (mimicking satiety) dose dependently increases consumption of an aversive odorized drink, suggesting that leptin decreases odor sensitivity (Julliard et al. 2007). Taken together, leptin appears to play a role in *taste* and *olfactory* processing that is dependent on nutritional status. What this suggests is that when rodents are energy-replete and leptin levels are high there is a corresponding decrease in sensitivity to taste and to olfactory stimuli. Although there are limited data, human studies have also indicated that leptin is expressed and may play a functional role in the salivary glands and the oral cavity; the expression of the long form of the leptin receptor has also been discovered in the membranes of glandular cells and in the salivary ducts (Bohlender et al. 2003).

The role that *serum* leptin may play in food hedonics in humans has only been superficially investigated. In a group of six men and 20 women offered a standardized high carbohydrate breakfast, palatability was positively correlated to fasting serum leptin independently of BMI and body fat mass (Raynaud et al. 1999). One interpretation of these results is that palatability would be independent of need state, as those who had the highest leptin levels (indicating caloric surfeit) rated food as tasting most pleasant. Contrarily, these results could be demonstrative of the large variation in body composition in this study. With nearly half of the subjects being obese there could be a resistance to leptin that could not be easily detected.

In a study examining the impact of fasting leptin concentration on energy intake and macronutrient preference it was found that high fasting serum leptin was associated with lower preference for chocolate as well as lower energy intakes and specifically fat intake (Karhunen et al. 1998). These findings remained significant after adjusting leptin concentrations for body fat mass and dietary

underreporting. In a more recent study consisting of a chronic energy deprivation (8 week weight loss trial) and a repeated measure looking at food hedonics pre- and post weight loss, there was no significant relationship between serum leptin and rated pleasantness (Cameron et al. 2008). What this study did demonstrate, however, was that after the 8 weeks of caloric deprivation (−700 kcal/day) subjects rated the same foods as more pleasant to taste. Of note, both types of food presented to the subjects – vegetables and fruits vs. desserts – increased in hedonic valance. After weight loss both healthy food and "junk" food tasted better.

145.3.3 Energy Deprivation and Palatability: Evidence from Alliesthesia

A question that remains to be answered is the extent to which homeostatic components (a need-state) can impact the quality of orosensory reward, thereby enhancing food hedonics. Much of the research on this topic uses a preload paradigm that assesses the impact of a pretest snack on the subsequent ad libitum energy intake and rated palatability. The rationale behind this test supposes that if palatability is dependent on a need-state, then a preload of high energy density (vs. low) would have a greater impact on palatability of the ad libitum meal (i.e., meal becomes less pleasant following energy dense preload). There are conflicting data, but it appears that the short term manipulation of satiety does not reliably impact palatability. For example, subjects not only rated food as being less pleasant following a high energy preload (vs. low), but they consumed less total weight and calories in ad libitum feeding following the preload (Johnson and Vickers 1993) and similar findings were noted in a separate study (Booth et al. 1982).

On the other hand, several studies employing similar preload paradigms have demonstrated a lack of change in palatability with need state (Birch and Deysher 1986; Yeomans et al. 1998). Specifically, when a soup preload was covertly manipulated with maltodextrin and administered 30 min prior to ad libitum feeding, subjects did not rate the palatability lower than the trial where plain soup was consumed (Yeomans et al. 1998). However, with the added maltodextrin it was noted that subjects had lower hunger and higher fullness ratings prior to beginning ad libitum feeding. Similarly, a study of children aged 3–5 and adults 25–35 years old showed no change in pleasantness with respect to preload energy density, but both groups displayed sensory specific satiety during the lunch feeding (Birch and Deysher 1986). While the preload paradigm may be examining possible short-term signaling of need (free)-state, a far better manipulation that is unfortunately studied even less is increasing the deprivation state (e.g., chronic energy deprivation). As alluded to in much of this chapter, feeding repeatedly takes place without any measurable changes in body energy reserves, and most often according to learned cues (see Fig. 145.5). In order to truly examine how the "*internal milieu*" impacts food reward there most likely needs to be a prolonged perturbation in energy balance over days and weeks.

Some of the pioneering efforts examining energy deprivation and palatability were conducted by Michel Cabanac, the coiner of the term alliesthesia. In his seminal paper on hedonics (1971) he tested changes in gustative and olfactive perception at the subjects' normal weight, at 10% below this weight, and then again after the subject returned to normal weight. To reduce the body weight by 10% the energy intake was limited to 500–800 kcal per day until the weight was achieved, and this reduced weight was maintained for several weeks prior to the test day. In short, alliesthesia was measured by the change in subjective pleasantness ratings for multiple ingestions of sweet tasting sucrose solutions. When subjects were at their normal weight and after ingesting 200 ml of a 25% aqueous solution of glucose, these stimuli became unpleasant (negative alliesthesia). However, when subjects lost 10% of their body weight alliesthesia could no longer be demonstrated, and 50 g of glucose was insufficient to cause the negative affective ratings. Finally, the return to normal body weight restored the change in sensation from pleasant to unpleasant.
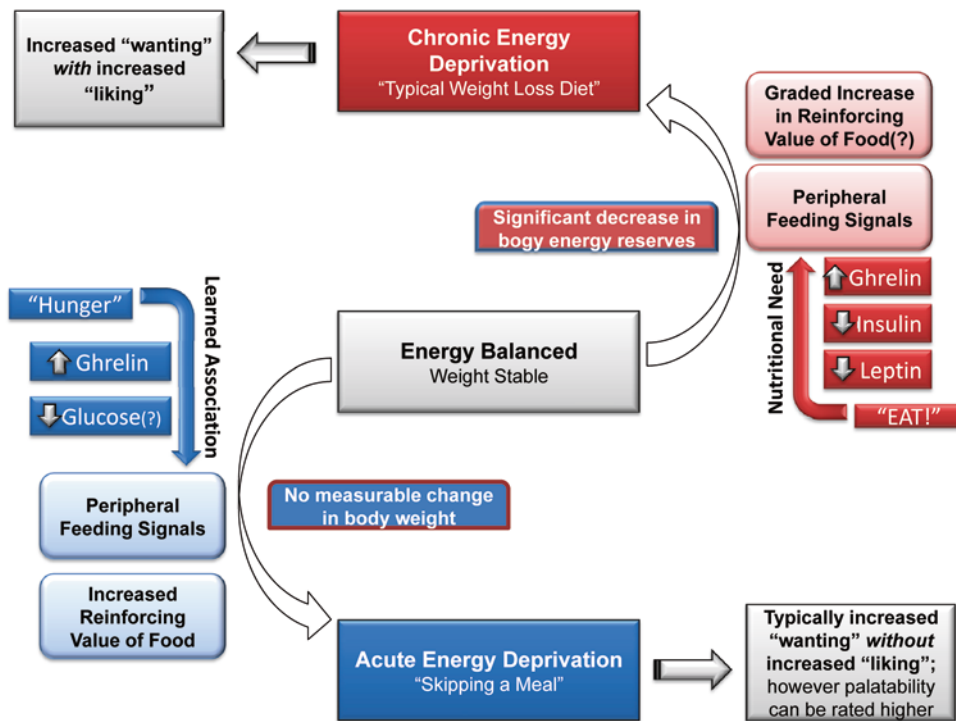
Fig. 145.5 Key Features representing the Ying and Yang of food reward as a function of energy deprivation. When there is no measurable change in body weight, it is believed that peripheral signals act as *cues* to feed, but chronic energy deprivation results in exaggerated responses from peripheral signals. It may be that significant changes in body energy reserves changes mere cues into powerful signals that motivate appetitive and consummatory feeding behavior

Corroborating these results are findings from deprivation periods of much shorter duration. By manipulating the period of energy deprivation with two separate test days, one day with a 3.5 h period of deprivation and another with an overnight fast of approximately 12–15 h, Spiegel et al. (1989) found that the deprivation period impacted palatability, consistent with alliesthesia. These results were consistent with obese and lean subjects. Germaine to this chapter are two major findings from this study: (1) the longer deprivation period resulted in increased palatability ratings and increased rate and quantity of food eaten ad libitum and (2) obese persons experienced a greater increase in palatability than lean persons, but lean individuals increased ad libitum feeding more than obese individuals.

145.4 Conclusions and Theoretical Integration

Food intake is the result of a multimodal representation of the sensory information about the food stimulus: in the brain there is a continuum consisting of the visual exteroreception of the sight of food, to the interoreception of primary and secondary taste corticies' evaluation of taste, temperature, texture, and viscosity. While energy deprivation can have an impact at several of these levels, humans also eat for reasons other than nutritional needs. For most of the developed countries meals are entrained to a schedule thereby eliminating what might be real signals of energy deprivation – this fact has raised to attention that such feeding may anticipate and prevent the development of significant

metabolic changes (Woods 1991). The study of feeding behavior, and in particular the study of subjective hedonic experience and objective measures of motivation, are central to understanding how appetite regulation can be compromised in certain individuals. Furthermore, with an integrated picture of physiological and behavioral changes that can occur as a result of caloric deprivation – particularly with regard to food palatability and reinforcement – what emerges is a better understanding of how palatable food can disrupt attempts at body weight regulation.

Epidemiological data suggests that some people are more susceptible to weight gain (Ravussin and Kozak 2004); this propensity to gain, maintain, or lose weight under similar environments has been attributed to various susceptibility levels such as metabolic, behavioral, psychological, physiologic, and genetic (Blundell et al. 2005). The fact that food intake is not merely based on nutritional or homeostatic requirements but is also very much influenced by its reinforcing properties presupposes a modulating role for dopamine in everyday feeding (Carr 2007) alongside with leptin and ghrelin (Figlewicz 2003) (see Fig. 145.6).
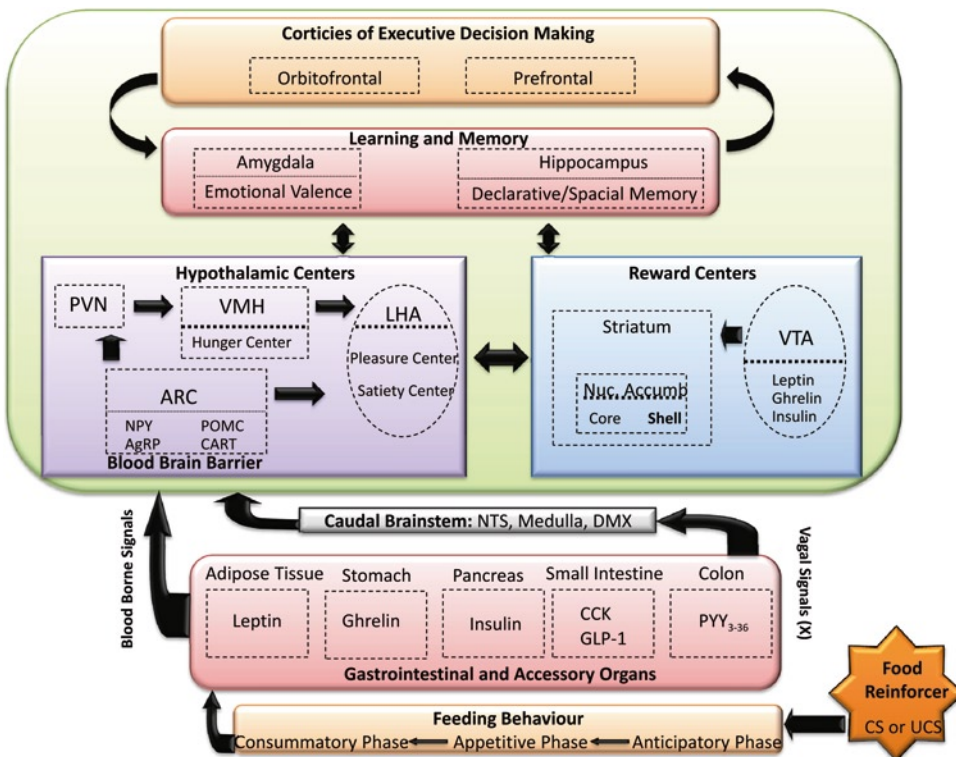
Fig. 145.6 An integrated summary of all the concepts discussed throughout this chapter: with the introduction of a food reinforcer begins the appetitive motivation to seek and finally to consume the food stimulus. When fasted for an extended period of time peripheral feeding-related signals from gastrointestinal and accessory organs are proposed to drive feeding behavior in a powerful manner via the ARC and the activation of neuropeptides that trigger hunger signals (e.g., NPY and AgRP). Conversely, when in the sated state, the nucleus accumbens and VTA may continue to promote consummatory behavior in the absence of hunger, i.e., as conditioned associations and learning interact with the reward pathways to increase implicit wanting. Equally as plausible, the palatability of food signaled by the Insular and Orbitofrontal corticies could also trigger eating in the absence of hunger. Abbreviations: *PVN* paraventricular nucleus, *LHA* lateral hypothalamic area, *ARC* arcuate nucleus, *NPY* neuropeptide Y, *AgRP* agouti-related peptide, *POMC* pro-opiomelanocortin, *CART* cocaine and amphetamine-related transcript, *Nuc. Accumb* Nucleus accumbens (Modified from Cameron and Doucet (2007). With permission)

If it can be shown with more fecundity that a biological basis exists for differences in the reward experienced in feeding, then as an example, individualized treatment and prevention programs for weight loss could differentially help those who are high in food reinforcement versus someone low in food reinforcement (Epstein et al. 2007a). Furthermore, there needs to be more data regarding the change in orosensory reward that may occur with chronic energy deprivation. One of the messages behind this chapter is that hedonic feeding results from discordance between appetitive motivation and inhibitory control. In order to help those trying to lose or maintain a specific level of body energy reserves, there needs to be a better understanding of the processes behind the rewarding qualities of food, both implicit and explicit. Behavioral strategies promoting dietary restraint – thereby shifting inhibitory control over appetitive motivation – may be what need to be promoted in a continual effort to inhibit weight gain in this modern obesogenic environment.

145.5 Applications to Other Areas of Health and Disease

Much of what has been described in this two part chapter was theoretical. Dissociating a psychological concept such as a reward into separable components of hedonic evaluation and motivation to obtain and consume does, however, have ecological validity. In particular, the tool described that measures the relative-reinforcing value of food can offer valuable information regarding the determinants of food choice. There are a lot of data showing that if access to a preferred food (such as cheesecake) is reduced, then people will choose a less preferred – although still enjoyable – alternative (such as yogurt). Applied in light of behavioral economics theory, if the price of a good that is typically purchased is increased, then as cost increases there will be a certain point where the consumer will *substitute* with something similar, though less expensive. A knee-jerk solution would be to tax foods with "empty calories" such as high fructose corn syrup, which in fact is occurring in some U.S. States. A better solution may be to promote the development of ready-to-eat healthy snacks such as the conveniently peeled and washed baby carrots, and to implement such foods across school cafeterias nationwide. At the very least, a goal should be to decrease the disparity in prices between fresh produce and the lower cost highly processed foods.

When considering the millions of people that start dieting each year, the fact that food reinforcement increases with energy deprivation has obvious concerns. The very thing that is supposed to help with weight loss (e.g., decreased energy intake) can act to increase the motivation to eat energy dense food. Although there are no definitive data to show that increased meal frequency (independent of energy intake) promotes weight loss, it may still be a good approach to prescribe such a diet in an attempt to control for overeating due to increased saliency of palatable food. To be sure, irregular meal patterns such as skipping meals can reinstate abhorrent binge-eating behavior in individuals recovering from bulimia nervosa. Nonetheless, a reduced calorie diet imposed with a greater frequency of meals may also leave individuals to choose a nonfood activity that is reinforcing (e.g., hiking) in the place of impulsively eating due to a perceived deprivation in energy and increased food reinforcement. The increased food reinforcement – and its predicting power of ad libitum feeding – experienced by the obese may also highlight the importance of limiting access to food in a strategic manner. Although there are no data about food reinforcement and success with weight loss, a valid hypothesis would be that for individuals high in food reinforcement (vs. low) a high meal frequency (e.g., six meals) diet of prepackaged meals would result in improved adherence to the diet and better appetite control vs. low meal frequency (e.g., three meals).

Regarding the forced-choice computer task that was developed in an attempt to measure *implicit* "wanting" and *explicit* "wanting" and "liking," there exists the potential to test the impact of various

forms of energy deprivation on these reward-related variables. Useful information will no doubt emerge on how relative (macronutrient) preference or reaction time – two quantitative measures of implicit "wanting" – can be impacted by not only reduced energy intake but also by increased energy expenditure. A recent study examined the impact of energy deprivation by means of exercise on food reward and ad libitum energy intake with two counterbalanced sessions, one at 50 min of high intensity exercise and then other without exercise (Finlayson et al. 2009). Although there was no significant difference in the amount of food eaten by test day for this group of lean women, it was found that after the exercise session there was a subgroup of "compensators" who ate more after exercise and also displayed a significant increase in *implicit* "wanting." After exercise there was an unconscious *implicit* desire for the "compensators" to eat high-fat sweet foods. What is interesting is that a separate study with similar exercise intensity (but longer duration) also demonstrated that lean female subjects overcompensated for the exercise session (vs. an equicaloric lower intensity exercise) when given access to an ad libitum for the remainder of the day (Pomerleau et al. 2004). In both studies there was evidence that performing intense aerobic exercise results in increased energy intake, thereby acutely promoting *positive* energy balance. It may be that some individuals are more sensitive to substrate flux and the mobilization and utilization of glucose, making them more likely to select energy dense foods following intense aerobic work. Elucidating who would potentially be "compensators" from the onset of an exercise prescription, as measured by increased implicit "wanting," could not only help with recidivism but also with weight loss success. Extending these findings to obese individuals could potentially identify those who would benefit from performing a lower intensity exercise to attain/maintain weight loss.

Summary Points

- Variation in the individual response to a similar food environment can begin to be explained not only at the gene level, but also by examining psychobiological differences in the evaluation of food reward.
- When energy deprivation is prolonged there is a degree of disinhibition with respect to appetite: not only does palatable food become more salient but items that would normally not be selected can also become attractive.
- Short-term feeding-related signals are divided into orexigenic signals (e.g., the "hunger hormone" ghrelin) that convey the overall message to eat, and this in contrast with anorexigenic signals (e.g., CCK and PYY_{3-36}) that convey the message of fullness/satiety.
- Leptin appears to play a role in taste and olfactory processing that is dependent on nutritional status: when energy-replete and leptin levels are high there is a corresponding decrease in sensitivity to taste and to olfactory stimuli.
- There need not be a deprivation or homeostatic signal in order to initiate a drive state or to continue consummatory behavior; humans *learn* how and when to initiate feeding.
- The dopamine hypothesis states that dopamine neurons form the backbone of the network of the brain's natural reinforcement system acting to focus attention on salient environmental stimuli and to promote learning associations. Leptin and ghrelin may play complimentary roles in the dopamine hypothesis of feeding.
- *Incentive salience theory* suggests that dopamine is *not* necessary for subjective/objective "liking") *nor* for reward learning, but it *is* important for the attribution of the incentive salience of rewards.
- The measure of motivation to work to obtain, i.e., implicit "wanting," can in some instances be a better predictor of energy intake than explicit subjective accounts of "liking."
- In vivo imaging suggests that individuals with the *Taq1* A1 (dopamine transporter) or the 10/10-repeat (dopamine receptor) alleles can be less sensitive to stimulation of dopamine-regulated reward circuits – analogous to a reward-deficiency syndrome – by imposing a hypodopaminergic state.

- The "liking" component of food reward has its biological underpinnings in at least two major neurotransmitter families defined by opioid and endocannabinoid systems.
- A question that remains to be answered is the extent to which homeostatic components (nutritional need-states) can impact the quality of orosensory reward, thereby enhancing food hedonics.

Definitions

Acute vs. Chronic Energy Deprivation: Acute energy deprivation will be defined as a complete fasting period of several hours (but otherwise being relatively weight stable), whereas, chronic energy deprivation will be defined as a prolonged reduction in energy intake below that would maintain body weight stability.

Alliesthesia: From the words esthesia (*meaning sensation*) and allios (*meaning changed*). It is the modification of conscious sensations by changes in internal signals, reflected by afferent actions of peripheral receptors; plainly, a pleasant or unpleasant sensation depending on the subject's internal state.

Appetite: An internal state or a specific disposition to act. Appetite as it pertains to feeding can be conceptualized as the hunger-stimulated response to a particular food and implies knowledge of the item(s) to which the actions should be directed

Incentive Salience: A motivational process that does not involve a pleasure/hedonic component, but is limited to a drive process that defines the "wanting" component of a reward. It is primarily believed to be influenced by dopaminergic neurotransmission.

Reinforcer: In a Skinnerian sense reinforcement can be viewed as behavioral measures of learning: it is the strengthening of an observed behavioral response (stimulus–response associations) or the strengthening of a learned behavioral response (stimulus–stimulus associations). A reinforcer can be a goal or a commodity.

Relative-Reinforcing Value of Food: Describes how hard an individual is willing to work for food by measuring responses at a predetermined reinforcement schedule. It is *relative-reinforcing* due to the fact that there are alternatives, albeit in a forced choice methodology.

Reward: A psychological process that is contingent on a reinforcing stimulus. Reward can be dissociated into two qualities of a food stimulus: (1) a hedonic component of "liking"/palatability and (2) a reinforcing component that is sometimes described as "wanting"/incentive motivational component.

1. "Liking": Divided into *implicit liking*, which is measured objectively by affective facial reactions to various food stimuli, and *explicit liking*, which is measured by the subjective hedonic rating of orosensory pleasure (e.g., visual analogue scales).
2. "Wanting": Divided into *intrinsic wanting*, which can be measured by choice tests, reaction time, or reinforcement, and *extrinsic wanting*, which can be defined by the intent or desire to consume a specific food and measured subjectively on a visual analogue scale.

Satiation/Satiety: Satiation refers to the processes that lead to the termination of feeding, e.g., a within-meal interval, whereas, satiety refers to the state of inhibition of feeding, e.g., a between meal interval.

Sensory-Specific Satiety: With continued exposure to the same food item there is a discernable and rather abrupt change in the overall hedonic rating, i.e., the perceived sensory qualities of the item are not absolute though the change in liking is specific to the unchanging sensory characteristics of the item itself.

References

Atkinson RL. Fed Proc. 1987;46:178–82.

Baylis LL, Rolls ET, Baylis GC. Neuroscience. 1995;64:801–12.

Berridge KC. Neurosci Biobehav Rev. 1996;20:1–25.

Berridge KC, Robinson TE. Brain Res Brain Res Rev. 1998;28:309–69.

Berridge KC, Robinson TE, Aldridge JW. Curr Opin Pharmacol. 2009;9:65–73.

Berthoud HR. Physiol Behav. 2007;91:486–98.

Bertino M, Beauchamp GK, Engelman K. Am J Physiol. 1991;261:R59–63.

Bina KG, Cincotta AH. Neuroendocrinology. 2000;71:68–78.

Birch LL, Deysher M. Appetite. 1986;7:323–31.

Blum K, Braverman ER, Wood RC, Gill J, Li C, Chen TJ, Taub M, Montgomery AR, Sheridan PJ, Cull JG. Pharmacogenetics. 1996;6:297–305.

Blundell JE, Stubbs RJ, Golding C, Croden F, Alam R, Whybrow S, Le Noury J, Lawton CL. Physiol Behav. 2005;86:614–22.

Bohlender J, Rauh M, Zenk J, Groschl M. J Endocrinol. 2003;178:217–23.

Booth DA, Mather P, Fuller J. Appetite. 1982;3:163–84.

Borod J. The neuropsychology of emotion. Oxford: Oxford University Press; 2000.

Cabanac M. Science. 1971;173:1103–7.

Cameron J, Doucet E. Appl Physiol Nutr Metab. 2007;32:177–89.

Cameron JD, Goldfield GS, Cyr MJ, Doucet E. Physiol Behav. 2008;94:474–80.

Carr KD. Physiol Behav. 2007;91:459–72.

Carr KD, Wolinsky TD. Brain Res. 1993;607:141–8.

Chelikani PK, Haver AC, Reidelberger RD. Peptides. 2006;27:3193–201.

Cincotta AH, Meier AH. Diabetes Care. 1996;19:667–70.

Davis C, Fox J. Appetite. 2008;50:43–9.

de Castro JM. Nutrition. 2000;16:800–13.

de Leon J, Diaz FJ, Josiassen RC, Cooper TB, Simpson GM. J Clin Psychopharmacol. 2007;27:22–7.

Drewnowski A, Krahn DD, Demitrack MA, Nairn K, Gosnell BA. Physiol Behav. 1992;51:371–9.

Epstein LH, Bulik CM, Perkins KA, Caggiula AR, Rodefer J. Pharmacol Biochem Behav. 1991;38:715–21.

Epstein LH, Jaroni JL, Paluch RA, Leddy JJ, Vahue HE, Hawk L, Wileyto EP, Shields PG, Lerman C. Obes Res. 2002;10:1232–40.

Epstein LH, Wright SM, Paluch RA, Leddy J, Hawk LW, Jr, Jaroni JL, Saad FG, Crystal-Mansour S, Lerman C. Physiol Behav. 2004a;81:511–7.

Epstein LH, Wright SM, Paluch RA, Leddy JJ, Hawk LW, Jr, Jaroni JL, Saad FG, Crystal-Mansour S, Shields PG, Lerman C. Am J Clin Nutr. 2004b;80:82–8.

Epstein LH, Leddy JJ, Temple JL, Faith MS. Psychol Bull. 2007a;133:884–906.

Epstein LH, Temple JL, Neaderhiser BJ, Salis RJ, Erbe RW, Leddy JJ. Behav Neurosci. 2007b;121:877–86.

Fetissov SO, Meguid MM, Sato T, Zhang LH. Am J Physiol Regul Integr Comp Physiol. 2002;283:R905–10.

Figlewicz DP. Am J Physiol Regul Integr Comp Physiol. 2003;284:R882–92.

Finlayson G, King N, Blundell JE. Neurosci Biobehav Rev. 2007;31:987–1002.

Finlayson G, King N, Blundell J. Appetite. 2008;50:120–7.

Finlayson G, Bryant E, Blundell JE, King NA. Physiol Behav. 2009;97:62–7.

Fuke S, Suo S, Takahashi N, Koike H, Sasagawa N, Ishiura S. Pharmacogenomics J. 2001;1:152–6.

Fulton S, Woodside B, Shizgal P. Science. 2000;287:125–8.

Goldfield GS, Lorello C, Doucet E. Am J Clin Nutr. 2007;86:308–15.

Grill HJ, Berridge KC. Taste reactivity as a measure of the neural control of palatability. In: Sprague JM, Epstein LH, editors. Progress in psychobiology and physiological psychology. Orlando, FL: Academic Press; 1985. pp. 1–61.

Halatchev IG, Cone RD. Cell Metab. 2005;1:159–68.

Hauge XY, Grandy DK, Eubanks JH, Evans GA, Civelli O, Litt M. Genomics. 1991;10:527–30.

Heath RG. J Nerv Ment Dis. 1972;154:3–18.

Heinz A, Goldman D, Jones DW, Palmour R, Hommer D, Gorey JG, Lee KS, Linnoila M, Weinberger DR. Neuropsychopharmacology. 2000;22:133–9.

Hoebel BG. Ann N Y Acad Sci. 1969;157:758–78.

Hommel JD, Trinko R, Sears RM, Georgescu D, Liu ZW, Gao XB, Thurmon JJ, Marinelli M, DiLeone RJ. Neuron. 2006;51:801–10.

Johnson J, Vickers Z. Appetite. 1993;21:25–39.

Julliard AK, Chaput MA, Apelbaum A, Aime P, Mahfouz M, Duchamp-Viret P. Behav Brain Res. 2007;183:123–9.

Kandel E, Schwartz JH, Jessell M, Jessell TM. Principals of neural science. Appleton and Lange; East Norwalk, Connecticut, U.S.A. 2000.

Karhunen LJ, Lappalainen RI, Haffner SM, Valve RH, Tuorila H, Miettinen H, Uusitupa MI. Int J Obes Relat Metab Disord. 1998;22:819–21.

Kringelbach ML. Neuroscience. 2004;126:807–19.

Levine AS, Atkinson RL. Fed Proc. 1987;46:159–62.

Malik S, McGlone F, Bedrossian D, Dagher A. Cell Metab. 2008;7:400–9.

Missale C, Nash SR, Robinson SW, Jaber M, Caron MG. Physiol Rev. 1998;78:189–225.

Naleid AM, Grace MK, Cummings DE, Levine AS. Peptides. 2005;26:2274–9.

Ninomiya Y, Shigemura N, Yasumatsu K, Ohta R, Sugimoto K, Nakashima K, Lindemann B. Vitam Horm. 2002;64:221–48.

Noble EP, Blum K, Ritchie T, Montgomery A, Sheridan PJ. Arch Gen Psychiatry. 1991;48:648–54.

Noble EP, Noble RE, Ritchie T, Syndulko K, Bohlman MC, Noble LA, Zhang Y, Sparkes RS, Grandy DK. Int J Eat Disord. 1994;15:205–17.

Olds J. Drives and reinforcements: Behavioral studies of hypothalamic functions. New York: Raven Press; 1977.

Orosco M, Gerozissis K, Rouch C, Meile MJ, Nicolaidis S. Obes Res. 1995;3 Suppl 5:655S–65S.

Pecina S, Berridge KC. J Neurosci. 2005;25:11777–86.

Perez C, Sclafani A. Am J Physiol. 1991;260:R179–85.

Pohjalainen T, Rinne JO, Nagren K, Lehikoinen P, Anttila K, Syvalahti EK, Hietala J. Mol Psychiatry. 1998;3:256–60.

Pomerleau M, Imbeault P, Parker T, Doucet E. Am J Clin Nutr. 2004;80:1230–6.

Portenoy RK, Jarden JO, Sidtis JJ, Lipton RB, Foley KM, Rottenberg DA. Pain. 1986;27:277–90.

Ravussin E, Kozak L. Energy homeostasis. In: Hofbauer K, Keller U, Boss O, editors. Pharmacotherapy of obesity–options and alternatives.CRC Press: Boca Raton, FL; 2004. pp. 488.

Raynaud E, Brun JF, Perez-Martin A, Sagnes C, Boularan AM, Fedou C, Mercier J. Clin Sci (Lond). 1999;96:343–8.

Raynor HA, Epstein LH. Appetite. 2003;40:15–24.

Rolls ET. The brain and reward. Pergamon Press: Oxford; 1975.

Rolls ET. Proc Nutr Soc. 2007;66:96–112.

Rolls ET, Murzi E, Yaxley S, Thorpe SJ, Simpson SJ. Brain Res. 1986;368:79–86.

Rolls ET, Scott TR, Sienkiewicz ZJ, Yaxley S. J Physiol. 1988;397:1–12.

Rolls ET, Sienkiewicz ZJ, Yaxley S. Eur J Neurosci. 1989;1:53–60.

Rolls ET, Yaxley S, Sienkiewicz ZJ. J Neurophysiol. 1990;64:1055–66.

Saelens BE, Epstein LH. Appetite. 1996;27:41–50.

Salamone JD, Correa M. Behav Brain Res. 2002;137:3–25.

Sibilia V, Lattuada N, Rapetti D, Pagani F, Vincenza D, Bulgarelli I, Locatelli V, Guidobono F, Netti C. Neuropharmacology. 2006;51:497–505.

Siep N, Roefs A, Roebroeck A, Havermans R, Bonte ML, Jansen A. Behav Brain Res. 2009;198:149–58.

Spiegel TA, Shrager EE, Stellar E. Appetite. 1989;13:45–69.

Steiner JE, Glaser D, Hawilo ME, Berridge KC. Neurosci Biobehav Rev. 2001;25:53–74.

Temple JL, Legierski CM, Giacomelli AM, Salvy SJ, Epstein LH. Am J Clin Nutr. 2008;87:1121–7.

Thiele TE, Van Dijk G, Campfield LA, Smith FJ, Burn P, Woods SC, Bernstein IL, Seeley RJ. Am J Physiol. 1997;272:R726–30.

Van Itallie TB, Beaudoin R, Mayer J. J Clin Nutr. 1953;1:208–17.

Wang GJ, Volkow ND, Fowler JS. Expert Opin Ther Targets. 2002;6:601–9.

Wang GJ, Volkow ND, Logan J, Pappas NR, Wong CT, Zhu W, Netusil N, Fowler JS. Lancet. 2001;357:354–7.

Wise RA. Behav Brain Sci. 1982;5:39–87.

Wise RA, Spindler J, deWit H, Gerberg GJ. Science. 1978;201:262–4.

Woods SC. Psychol Rev. 1991;98:488–505.

Yaxley S, Rolls ET, Sienkiewicz ZJ. Physiol Behav. 1988;42:223–9.

Yeomans MR, Gray RW. Neurosci Biobehav Rev. 2002;26:713–28.

Yeomans MR, Gray RW, Conyers TH. Physiol Behav. 1998;64:501–6.

Chapter 146
Nutritional Deficiencies and Spatial Memory Function

Sayali C. Ranade

Abbreviations

CNS	Central Nervous System
PUFA	Poly Unsaturated Fatty Acids
DHA	Docosahexanoic Acid
AA	Arachidonic Acid
EFA	Essential Fatty Acid
DNA	Deoxyribonucleic Acid
RNA	Ribonucleic Acid
CED	Chronic Energy Deficiency
BMI	Body Mass Index
PEM	Protein Energy Malnutrition
ID	Iron Deficiency
RAM	Radial Arm Maze
PD	Protein Deficiency
CA	Cornu Ammonis
IUGR	Intra Uterine Growth Retardation
BDNF	Brain Derived Neurotrophic Factor
DMT-1	Dimetallic Transporter 1
MMSE	Mini Mental State Examination
WMS-R	Wechsler Memory Scale-Revised
WAIS-R	Wechsler Adult Intelligence Scale-Revised
ERPs	Event Related Potentials
RA	Retinoic Acid

S.C. Ranade (✉)
National Brain Research Centre, National Highway-8, Near NSG Campus, Nainwal Mode, Manesar,
Haryana 122050, India
e-mail: sayali@nbrc.res.in; ranade.sayali@gmail.com

146.1 Overview

Food has classically been perceived as a means to provide energy and building material to the body. However, its role in development and maintenance of specific physiological systems has been suggested only recently. One such system which is sensitive to the effects of nutrition or lack of it is the nervous system. A healthy nervous system requires balanced intake of food. Nutrition is one of the major epigenetic factors that affects the development and functioning of the nervous system. It took long for the general acceptance of the concept that the food that you consume can have an effect on the structure and function of the brain.

The term "Nutrition" refers to the balanced intake of nutrients for proper functioning of all body systems. There could be either qualitative or quantitative deviation from this optimum food intake. The nervous system is extremely vulnerable to different types of nutritional insults. There is a wide range of defects induced by nutritional deficiencies on the nervous system. These include structural (brain size, hippocampal volume), cellular (cerebellar neurogenesis, oligodendrocyte maturation), biochemical (neurotransmitter synthesis and release), electrophysiological (excitation and inhibition levels of neurons), behavioral (antisocial/violent behavior), and cognitive (memory disturbances, learning impairment) defects. The deleterious consequences of malnutrition on the nervous system depend on various factors. The most important factors which affect the nature and severity of these defects are: type of deficiency, level of malnourishment, and timing of exposure. The interaction of these factors will decide the outcome of the nervous system's defects. There is an enormous amount of data available on the effects of nutritional deficiencies on CNS. These reports come primarily from case studies or experimentation done on children from several developing countries. In addition, animal models have also been used as they provide a great tool to study and understand the effects of malnutrition on the CNS and also the mechanisms involved therein.

146.2 Role of Different Nutrients in Normal Development and Function of the Nervous System

The role of optimum nutrition in the normal cognitive and psychological development of an individual was evidenced by studies carried out following the Dutch hunger winter of 1944–1945 and the Chinese famine of 1950. These natural experiments provide valuable information on the role of different nutritional factors in the normal psychological development of an individual. The strong evidence from these studies suggests a connecting link between neurodevelopmental disruption and increased risk of schizophrenia. Deficiency of several candidate nutrients has been implicated in the vulnerability of an offspring to different psychiatric disorders including schizophrenia. Although discussing the involvement of different nutrients in normal psychological development in detail is outside the scope of this chapter, these are perhaps initial evidences that confirm the role of optimum nutrition in the normal development of the nervous system.

The exact mechanism by which food and nutrients affect various aspects of brain development and functioning are not fully known. However, the voluminous literature available provides an insight on how specific nutrients could possibly affect various aspects of brain functioning.

The important nutrient groups that affect development and/or functioning of the nervous system are proteins, certain types of fatty acids, micronutrients like iron, zinc, certain vitamins, etc.

Several findings in humans support the hypothesis of links between n-3 polyunsaturated fatty acid (PUFA) status and psychiatric diseases. Essential fatty acids are an important component of nerve cell membranes and are also essential for neurotransmitter release (Arnold et al. 2000). The nutritionally

essential PUFAs, docosahexanoic acid (DHA), and arachidonic acid (AA) are critical for the proper development of brain structure and function during early development (Neuringer et al. 1986). EFAs provide nutrients and healthy fats necessary for the formation of myelin sheaths that cover axons, allowing faster conduction of nerve impulse.

Protein deficiency causes a variety of effects on the nervous system. In general, proteins are required by the brain for synthesis of DNA, RNA, structural proteins, growth factors, and neurotransmitters. They also play a role in synapse formation and extension of neurites, besides increasing the efficacy of neurotransmitters. Protein deficiency causes defects in the development and maturation of the nervous system, motor function, and major cognitive functions. Reduced brain size and impaired spinal cord histology are a few effects of protein deficiency on CNS.

The essential micronutrients, vitamin E, vitamin C, and selenium, affect the nervous system by virtue of their antioxidant functions. They protect the brain from oxidative insults by scavenging free radicals. Vitamin B complex is also essential for general health of the nervous system. Vitamin B12 helps in the formation of neurons, B9 is involved in synthesis of neurotransmitters, and vitamin B1 is involved in glucose metabolism of the brain.

The minerals calcium, magnesium, as well as manganese, iodine, potassium, silicon, sodium, and sulfur are all important for nervous system health. Calcium and magnesium also have an important role to play in nerve impulse conduction. There is considerable evidence that iron is important for neurological functioning and development (Lozoff 1987; Beard et al. 1993).Iron is a co-factor for several enzymes involved in neurotransmitter synthesis (Larkin and Rao 1990). It is also required for proper myelination of the spinal cord and white matter of cerebellar folds (Larkin and Rao 1990). Zinc is also an important co-factor involved in neurotransmitter synthesis. It is known to be indirectly involved in dopamine metabolism (Arnold et al. 2000)

146.3 The Factors Affecting Nature and Severity of Nervous System Defects

146.3.1 Extent of Nutritional Deficiency

The importance of the various nutrients in the development and maintenance of a healthy nervous system is well established. It can therefore be intuitively anticipated that anything less than the optimum requirement would be detrimental and induce deficits in the normal structure and function of the nervous system. The lesser the availability of the nutrient, the more severe the defects.

In a study of the effect of early long-term undernutrition on rat spatial cognition, the group with the highest level of dietary restriction showed the poorest performance on a water maze behavioral task. This effect however was significant in older rats. These findings demonstrate that the severity of the defects seen in the nervous system is directly proportional to the level of undernutrition. These findings also suggest that deficiency takes a longer time to exert its effects (Yanai et al. 2004). Rats undernourished (8% protein diet against normal 20% protein diet) during their lactational period were hyperactive to shock as adults (Vendite et al. 1985).Severe protein malnourishment causes reduction in brain size which is proportional to the degree of malnourishment. Children who are exposed to mild to moderate undernutrition are known to show varying degree of emotional instability, depending on extent of undernutrition.

However, any severity of malnourishment below a certain level exerts effects which are more general and are not limited only to the nervous system. In our own experience, female mice kept on a diet of low protein (less than 8%) had difficulty in becoming pregnant (unpublished observation).

146.3.2 Types of Nutritional Deficiency

Nutritional deficiencies are of different types. Undernutrition refers to insufficient caloric intake (chronic energy deficiency-CED, with BMI <18.5), while malnutrition implies imbalance or complete absence of one or more essential food constituents. However the term "malnutrition" is used in a more general sense, covering both under nutrition and malnutrition. The effects of malnutrition and undernutrition on nervous system development and functioning are often overlapping, but not always.

Undernutrition continues to be one of the major health hazards in developing countries and in certain sections of developed countries. Undernutrition affects several parameters of nervous system development and maintenance, including volumes of one or more brain regions (Ranade et al. 2008), their morphology, neurotransmitter metabolism, and even behavior.

Malnutritional deficiencies can be further divided into macronutrient and micronutrient deficiencies. Macronutrient deficiency is the complete absence or reduction in the amount of macronutrients in the diet.

Protein deficiency is one of the major macronutrient deficiency affecting millions of people worldwide. Protein energy malnutrition is a global problem. Nearly 20 million people worldwide suffer from various forms of PEM viz. marasmus, kwashiorkar. It is also known to induce several types of brain defects. Considerable evidence indicates that PUFAs like DHA and AA also cause some defects in visual and cognitive development (Uauy et al. 1990; Carlson et al. 1994). This can also be categorized under macronutrient deficiency.

Among the micronutrient deficiencies, iron deficiency has a significant effect on the nervous system. The brain is sensitive to dietary iron depletion and regulates iron flux homeostasis very tightly. Perinatal iron deficiency (ID) is known to produce learning and memory impairments as well as reduced psychomotor skills both in humans and animal models (Pollit 1989; Walter et al. 1989).Other micronutrient deficiencies include deficiencies of important vitamins (Vitamin A or vitamin E) and minerals (calcium, magnesium, zinc) which are essential for normal nervous system functioning.

Each of these deficiencies induces its own set of defects which could either be unique to that particular deficiency or may show common features with the defects induced by other malnutritional deficiencies.

146.3.3 Critical Period of Nutritional Deficiency

The effects of malnutrition and undernutrition are of great interest due to the widespread incidence of fetal and infantile nutritional deficiencies. There is a growing body of evidence which suggests that the effects of nutritional insult on the developing brain are long-lasting and lead to permanent deficits in learning and behavior (Van Gelder 1984; Strupp and Levitsky 1995; Galler 2001). These evidences mainly come from human studies as well as animal experimentation. The issue of timing of nutritional deficiency, therefore, is of great importance. It is generally seen that nutritional deficiencies early on in life tend to lead to permanent defects in the CNS as against nutritional inadequacies in the later part of life.

It has been observed that some nervous system defects remain irreversible even after complete restoration of optimum nutrition. This is a good indication of the presence of a "critical period" of nutritional deficiency. This "critical period" is a period during which nutritional deficiency causes maximum damage. Depending on the timing of exposure, any inadequacy during the critical period might interfere with basic developmental processes including cytogenesis, histogenesis, and functional maturation of the brain.

There is vast literature detailing the effect of perinatal malnutrition on the developing brain. "Perinatal" malnutrition refers to a large time window in terms of development. So it would be convenient to divide it further into smaller time frames in order to pinpoint specific brain defects occurring during particular developmental time points. Perinatal malnutrition can therefore be further divided into prenatal and postnatal malnutrition. Each of these can induce varying degree of defects in the developing nervous system, depending on the brain compartment involved during that particular time window. The brain compartment showing a high level of activity will be affected the most.

146.4 Spatial Memory: An Essence of Life

Yes! We all need it! We require it to go to our work place or movie theatre and get back home from there. We need it to locate objects around us and locate ourselves with respect to these objects. Grazing animals need it to locate food patches. Mice and frogs need it to save themselves from predators. What is it that is needed in all the above cases? It's spatial memory. Spatial memory is a highly specialized function of the brain that is vital for survival in all species, including humans.

Memory is the process of retention of acquired information. When this information is about the space surrounding you, it is considered as spatial memory. Literally, therefore, it means memory of the space around you. Spatial memory is an essential component of our daily life which helps us move around in our environment. It is remembrance of places visited and understanding your position with respect to your surrounding. The concept of spatial learning was first introduced by O'Keefe and Nadal. In their words "Spatial learning refers to the construction of a representation of the topographical layout of an environment, and enables goal-directed navigation on the basis of a cognitive map" (O'Keefe and Nadel 1978). In simpler words, it is the process of acquiring information related to the space around you and retaining it for future use. This process can be divided into three phases:

1. Acquisition: Wherein individuals gain information about their surroundings.
2. Retention: The acquired information is stored or retained in specialized compartments of the brain.
3. Retrieval: The stored information is retrieved or recalled for subsequent use.

Spatial memory has two components: one is "spatial" (the one related to space) while the other one is "mnemonic" (memory component). Both these components are equally important for proper spatial memory function. Impairment in any of these components significantly affects overall spatial memory function.

One of the most compelling problems in neuroscience today is to identify the mechanisms underlying memory function. The area of the brain which has been recognized to play a vital role in formation of spatial memory in particular is the hippocampus. The involvement of the hippocampus in spatial memory processes has been established in a variety of species such as birds and mammals, including humans.

The hippocampus is a cortical structure located deep in the temporal lobe. It is formed by two sheets of cortex interlocking each other and has a layered structure where rows of pyramidal cells are arranged along with these layers. The connections within the hippocampus generally follow this laminar format and are unidirectional. They form well characterized closed loops originating in the adjacent **entorhinal cortex**. The different cell layers and sections are defined by the series of connections made. The main pyramidal cell layers are the regions **CA1** and CA3 and the granule cell layer is the **dentate gyrus** (Figs. 146.1 and 146.2)
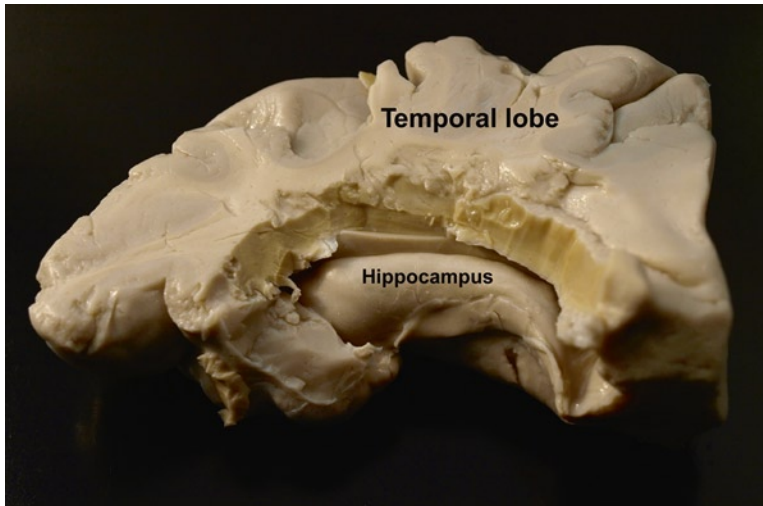
Fig. 146.1 A photograph showing human hippocampus, along with overlying temporal lobe. The hippocampus is one of the important structures involved in spatial memory function (Courtesy: Dr. Soumya Iyengar, National Brain Research Centre)
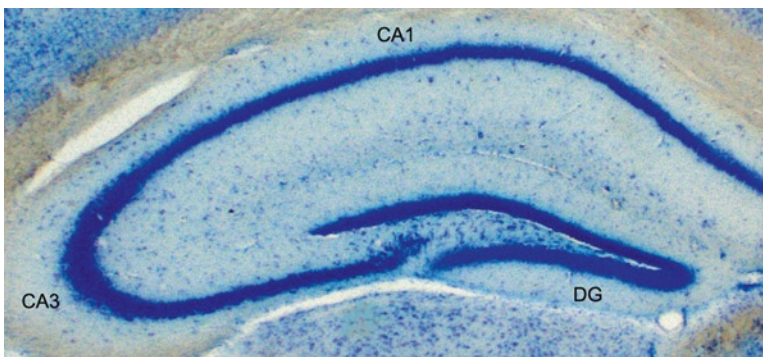
Fig. 146.2 A Nissl stained coronal section of rat hippocampus. Different subdivisions of hippocampus are seen viz. CA1, CA3 and Dentate gyrus (Courtesy: Dr. Shiv Kumar Sharma, National Brain Research Centre)

The hippocampus is a region of the brain which has both a prenatal and postnatal developmental window (Rice and Barone 2000). This course of development and the sequence of developmental processes are the same in both rodents and humans. There is a large increase in the size of the hippocampus during the first 4 postnatal weeks. The developmental processes occurring in the hippocampus during this period include neurogensis, myelination, proliferation of synapses, and dendritic remodeling (Altman and Bayer 1990). Normal progression of these processes is required for proper functioning of the hippocampus. Any deviation or disturbance in one or more of these processes can bring about defects in the normal functioning of the hippocampus, thereby affecting spatial memory function.

Although the initial knowledge about the involvement of the hippocampus in declarative memory came from patients with bilateral medial temporal lobe resection, further support and evidence indicating and confirming involvement of the hippocampus in spatial learning and memory (Witter and Amaral 1991) came from animal studies. Implication of the hippocampus in spatial memory function

Fig. 146.3 Radial arm maze. A photograph of Radial Arm Maze apparatus at the National Brain Research Centre. Radial Arm Maze is an apparatus first designed by Samuel and Olton (1976). The apparatus is used to study spatial memory in laboratory animals or human subjects. The picture shows radial arm maze used for studying spatial memory in mice. It consists of a central platform with eight arms radiating from it. At the end of each arm is food cup in which a reward (in this case a chocoflake or a small food pellet) is kept. Each arm is separated from the central platform by a Guillotine door. All the Guillotine doors are attached to common pulley. Both central platform and arms are covered with transparent plexiglass covers. Different temporal domains of spatial memory viz. reference memory, working memory can be tested by employing different experimental paradigms (Courtesy: Professor V. Ravindranath, former Director, National Brain Research Centre)

is supported by lesion, reversible inactivation, early gene expression, and electrophysiological studies (Frankland and Bontempi 2005).

There are well developed protocols available for studying, establishing, and confirming the role of the hippocampus in spatial learning. A variety of paradigms are available for investigation of spatial learning, and perhaps the most commonly used are the Morris water maze(Morris et al. 1982) and the Radial Arm Maze (Olton and Samuelson 1976) (Figs. 146.3, 146.4, and 146.5).

Another important brain area involved in spatial memory function in primates, including humans, is the prefrontal cortex. This area is also vulnerable to malnutritional insults. The effect of malnutritional insults on prefrontal cortex has been studied with respect to delay in development and maturation of cognitive function. However, its specific role in spatial memory function following malnutritional deficiencies has not been studied so far.

146.5 Malnutrition and Spatial Memory

As described previously, the effect of malnutrition on spatial memory or for that matter on any other brain function can be divided broadly into two groups:

(a) Perinatal malnutrition
(b) Malnutrition in later stages of life
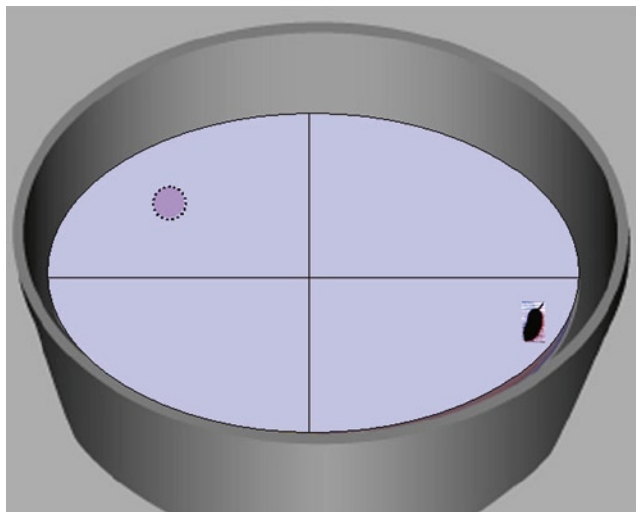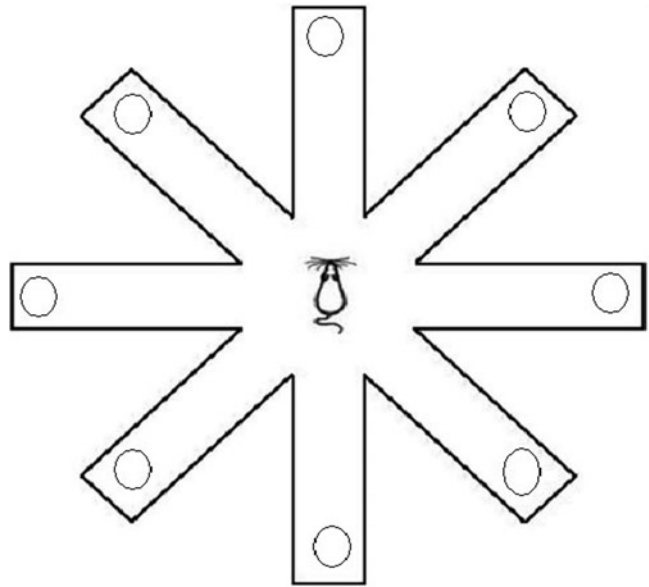
Fig. 146.5 A schematic representation of Morris Water maze designed to study spatial memory function in rodents. The Morris water navigation task is another behavioral procedure used to study spatial memory of laboratory rodents. The apparatus was devised by Professor Richard Morris. It consists of a small water pool, which contains a small escape platform submerged few millimeters below the water level. The pool is theoretically divided into four quadrants. Conspicuous visual cues are placed around the pool in plain sight of the animal. The animal is placed in the pool and it swims around the pool in search of an escape. Various parameters like total distance traveled, the time spent in each quadrant of the pool, the time taken to reach the platform are recorded. The improvement of performance on all these parameters will be measured over the period of time

There is a distinct difference between the types and severity of deficits induced by these two different time windows, and each window will result in an entirely different profile of the defects on CNS. The reasons for these differences are as follows: In the first group, where the developing brain is especially malleable, malnutrition has a more pronounced effect on brain structures and systems supporting cognitive function. These effects are more severe and long lasting. These effects are therefore more likely to

be irreversible even after subsequent rehabilitation. In the latter group, because it is the developed brain that is exposed to malnutrition the effects are less severe and can be reversed at least to a certain extent with subsequent supplementation. It is thus logical and rational to consider both these groups separately.

146.5.1 Perinatal Malnutrition/Undernutrition and Spatial Memory

Malnutrition and/or undernutrition during infancy and childhood are problems prevalent in many parts of the world. Malnutrition neither produces gross anatomical abnormalities in the nervous system nor gross mental retardation or psychopathology. The effect of malnutrition shouldn't however be underrated for this reason. The malnutritional insults rather result in permanent suboptimal development leading to long-term learning and cognitive impairments. This is an equally serious problem. It is therefore important to study these effects. Animal studies provide a reasonable means of obtaining relevant information pertaining to the effects of malnutritional insults on the developing brain. These types of spatial memory defects have been studied at various levels of organization viz. structural, functional, biochemical, physiological, behavioral, and cognitive.

The defects underlying spatial memory function are best manifested at and therefore can be best studied at a behavioral level. Behavioral testing of rodents and primates are routinely done by using either the radial arm maze or the water maze paradigm. These behavioral protocols provide valuable insights into mechanisms underlying memory process. Behavioral defects are the manifestation of spatial memory dysfunction and the underlying cause could be a structural defect. Considering the involvement of the hippocampus in spatial memory function it is reasonable to study the hippocampus with respect to structural defects if any, followed by its functional implications.

Along with other areas of the brain which undergo rapid postnatal development, the hippocampus appears to be vulnerable to early undernutrition. This provides one more reason to study the hippocampus for possible defects. In spite of early undernutrition not producing brain lesions, deficits seen in the hippocampus by early undernutrition may show some related functional disability (Lynch et al. 1975). It is therefore important to study defects other than structural defects such as lesions, if any.

The type of deficiency one is subjected to, is one of the major deciding factors of the outcome of spatial memory deficits. Different types of deficiencies may or may not have similar effects on the system under consideration, in this case spatial memory function. Ranade et al. (2008) have shown that different types of malnourishment affect different domains of spatial memory function. Although these data have been shown with only three types of nutritional deficiencies; perinatal Chronic energy deficiency (CED), Protein deficiency (PD) and Iron deficiency (ID) and studied spatial memory function only at behavioral and gross anatomical levels, it is evident from this report that the type of deficiency has a significant role to play in deciding the specificity of defects seen. It is therefore important to study each type of deficiency specifically with respect to spatial memory function. Data from such studies will help in understanding the effects of specific types of malnutrition on spatial memory function.

146.5.1.1 Undernutrition and Spatial Memory Deficits

The effects of perinatal undernutrition on spatial memory or hippocampal function are inconsistent. Some studies, using radial arm maze or Morris water maze, report significant deficits in spatial memory function. However, others claim that spatial learning is completely unaffected by early undernutrition.

Jordan et al. (1981) have shown that perinatal undernutrition in rats affected their radial arm maze performance tested on an 8- and 16-arm apparatus, when tested at 90 days of age. Significant differences were seen on many parameters. Experimental animals showed less exploratory behavior and took more time to make choices when compared with control animals. Such deficits are similar to hippocampal dysfunction defects, which severely impair the performance of animals on similar spatial tasks.

Recent studies of the effects of developmental malnutrition in rats have suggested that hippocampal formation may be especially prone to irreversible neuroanatomical and neurophysiological alterations as well.

In another study, reduced cell numbers have been reported in the dentate gyrus and in the CA fields of the hippocampus proper (Lewis et al. 1979; Jordan et al. 1982) following perinatal undernutrition. In an altogether different paradigm of postnatal undernutrition it has been shown that lengthy periods of undernutrition affect the developmental growth curve of synapse formation and also alters the neuron: synapse ratio (Ahmed et al. 1987). Yanai et al. (2004) have reported the effect of different levels of dietary restriction on spatial cognition in rats. Animals were subjected to 80%, 60%, or 40% of free feeding and tested with Morris water maze place task throughout their lives. At a younger age, no significant difference was seen among the different experimental groups. However, at 9 months and thereafter, the 40% feeding group performed poorer than the other groups. This example also confirms the long-lasting nature of early undernutrition on spatial memory function.

On the other hand, Campbell and Bedi (1989) using Morris's test showed little evidence of any differences in the spatial learning abilities of rats previously undernourished from birth up to 60 days of age compared with well-fed age-matched controls. This is despite the fact that the same group had reported significant and persistent alterations in the morphology (viz. synapses per cell) of the dentate gyrus induced by undernutrition. The possible links between morphological and behavioral defects induced by perinatal undernutrition need to be established and confirmed.

146.5.1.2 Perinatal Protein Deficiency

It is well established that protein–calorie restriction, or protein malnutrition experienced during the early postnatal period leads to significant and often permanent changes in brain anatomy physiology, biochemistry, and behavior. The damages induced by protein deficiency include the damages to the maturation of the nervous system, motor function, and major cognitive functions. These effects have been observed in protein malnourished children all over the world. Exposure to protein deficiency even for a limited period may evoke permanent impairments of several brain functions. It has also been demonstrated (Ranade et al. 2008) that early protein malnourishment affects various aspects of hippocampal structure and function.

Protein deficiency can be induced in two ways.

(a) Protein malnourishment as a result of total undernutrition. Total reduced intake of food means reduced intake of proteins which culminates in protein deficiency.
(b) Protein malnourishment because of imbalanced diet i.e. diet doesn't contain the required amount of protein although there is optimum intake of food. That means there is no quantitative reduction in food intake.

The effects of both these conditions may sometimes have similar effects but sometimes may generate an entirely different profile of defects. Unless studied strictly under defined experimental conditions these two conditions are difficult to dissociate. So for this chapter these two conditions will not be explained separately. A series of studies have shown marked and lasting changes in the structure and function of the hippocampal formation in rats subjected to prenatal protein malnutrition.

The structural changes seen in the hippocampus include volume or area changes of the total hippocampus or certain subdivisions of it. Noback and Eisenman (1981) have reported a decreased width of the dentate gyrus as a result of protein–calorie restriction on the developing brain. Paula-Barbosa et al. (1988), in a study of long-term, postweaning undernutrition, reported a decrease in the width of the dentate gyrus and decreased granule cell packing density at 6, 12, and 18 months (Diaz-Cintra et al. 1991). Perinatal protein deficiency showed the highest reduction in hippocampal volume of F1-pups. This was in comparison with control as well as other deficiencies including CED and ID. This decrement was contributed maximally by the dentate gyrus and CA1 subdivisions of the hippocampus (Ranade et al. 2008).

These gross changes in the dimensions are a result of finer changes that occur at the cellular level. These changes include reduction in total cell number or decrease in certain population of cells. It could also be due to reduction in cell size of a certain population of cells. These changes at the cellular level either in isolation or in combination can bring about changes in the volume of the hippocampus.

Diaz-Cintra et al. (1991) have shown the effect of prenatal protein deprivation on the development of granule cells in rat at different ages. They showed significant reduction in the size of granule cells, a decreased number of synaptic spines, and reduced complexity of dendritic branching in the outer two thirds of the molecular layer. The effects persisted throughout the study period of 220 days.

The functional changes in hippocampus following early protein malnourishment include a reduction in the mean threshold to produce after discharge activity within the dentate gyrus. An even greater number of stimulations is required to elicit full convulsive motor seizures in response to perforant path kindling stimuli (Bronzino et al. 1991). Prenatal protein deprivation affected certain components of long-term potentiation (Austin et al. 1986) in the dentate gyrus of adult rats.

Taken together, these results suggest the vulnerability of the hippocampus to prenatal protein insults. An important question however is whether these structural and functional defects together lead to any behavioral impairment or not. Reports suggesting the effect of protein malnourishment on behavioral parameters are inconsistent.

Barnes et al. (1966) studied learning behavior in rats that were subjected to different forms of nutritional deprivation in early life. The performance of these rats was tested on visual discrimination performance in a Y-maze at 6–9 months of age. The rats that were deprived both before and after weaning made significantly more errors in their choices than the normal controls. Rats born to females fed on 8% case in throughout pregnancy showed lower visuo-spatial memory performance. The rats were deprived either preweaning or postweaning or both. On the Y-maze task, double-deprived rats performed the worst. When these rats were tested for position reversal performance in the water maze shortly after weaning the maximum number of errors were made by the double-deprived rats. The results also showed gender biases. Valadares and Almeida (2005) tested rats fed with 16% (well-nourished) or 6% (malnourished) protein diets during the lactation phase on the Morris water-maze in procedures of spaced trials (1 trial/day), intermediate density (4, 8, 12 trials/day), and condensed trials (24 trials/day). The results showed that protein malnutrition caused deficits in spatial learning and memory in spaced but not in intermediate and condensed trials procedure. When tested again 7 and 28 days after training, malnourished animals showed significantly higher latency compared with well-nourished controls. In another study, mice which were maintained on a protein-deficient diet during both gestation and lactation were tested on the radial arm maze. The results showed a specific and significant negative effect on working memory compared to other malnourished groups (viz. CED and ID) and controls (Ranade et al. 2008). These findings are inconsistent with previous reports by Tonkiss and Galler (1990), who reported no effect on working memory of rats which were prenatally protein deprived. This working memory was tested on two different behavioral protocols of learning and memory. The differences in experimental paradigms as well as in malnutrition protocols may account for the differences in results in this case.

Taken together these results very clearly suggest vulnerability of the developing hippocampus to gestational and/or lactation protein deficiency at various organizational levels. The discrepancies seen in the effect of PD on spatial memory function at the behavioral level could arise partially from the differences in the malnutritional paradigm used and partially due to differences in the design of the spatial memory task. There is also a possibility of the existence of species-specific differences.

146.5.1.3 Iron Deficiency and Spatial Memory

Iron deficiency is the largest single-nutrient deficiency affecting millions of new born babies worldwide. The several reasons for intrauterine iron deficiency include IUGR, anemia, alcoholism, maternal diabetes mellitus, and maternal nutritional iron deficiency either prior to or during pregnancy.

Several human studies report that anemic children show lower scores on various cognitive tests. Recognition memory at birth and at follow-up seemed to be affected in children who were at risk for brain iron deficiency (ID) during the late fetal/early neonatal period of the development (Siddappa et al. 2004). Although ID is associated with long-term cognitive abnormalities (de-Regnier et al. 2000; Nelson et al. 2000) its direct role in spatial memory is supported by only a few studies. Animal models have shown irreversible behavioral abnormalities resulting from diet-induced iron deficiency during early development. B.T. Felt and B. Lozoff (1996). View Record in Scopus Cited By in Scopus (107) ID is also known to delay myelination, thus leading to behavioral deficits. Therefore, behavioral defects seen as a result of iron deficiency cannot be attributed solely to hippocampal dysfunction.

Iron deficiency is known to affect some of the developmental processes related to the hippocampus, including myelination (Lozoff 2000), proliferation, and maturation of synapses (Jorgenson et al. 2005), and dendritic remodeling. It can therefore be speculated that some functions of the hippocampus may be compromised as a result of these underlying structural changes. Spatial memory could be one of them. The link between ID and spatial memory function is indirect and speculative at this point of time. Another possibility is that iron deficiency could potentiate these effects on the hippocampus through other adverse effects like oxidative stress.

The wide range of effects of iron deficiency on the hippocampus includes decrease in hippocampal energy metabolism (deUngria et al. 2000), altered hippocampal iron concentration (Felt and Lozoff 1996), altered neurotransmission by altering glutamate and GABA concentration (Rao et al. 2003), disrupted dendritic morphogenesis in CA1 pyramidal neurons (Jorgenson et al. 2003), and maturation of synaptic function and efficacy (Jorgenson et al. 2005). In addition there is an alteration in the pattern of neurochemical profiling (Rao et al. 2003), which also suggests changes in energy status, neurotransmission, and even myelination. Fetal or neonatal iron deficiency is also known to lower BDNF function, thereby impairing neuronal differentiation in the hippocampus (Tran et al. 2008). All or some of these changes may underlie spatial memory deficits seen in ID.

There are a few studies which report direct involvement of iron deficiency in spatial memory function.In their study of the effect of different types of malnutrition on spatial memory function checked by the radial arm maze test, Ranade et al. (2008) have reported that reference memory is selectively affected in the ID model. F1-pups born to mothers who were kept on an iron-deficient diet for 6 weeks prior to conception and also during gestation and lactation were checked for their spatial memory performance at 8 weeks of age. These animals showed selective impairment of reference memory function leaving other functions like working memory intact. In a recent report by Carlson et al. (2009), the importance of iron in neuronal development and memory function has been shown in the mouse hippocampus. Double mutants of mouse DMT-1(Slc11a2) were not able to perform

Effect of Different Types of malnutrition on Different subdivisions of Hippocampus
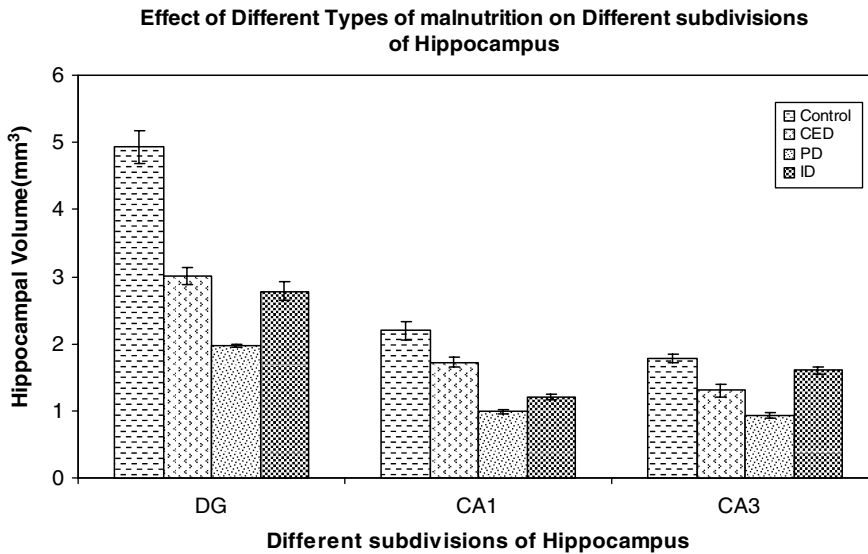
Fig. 146.6 Effect of different types perinatal malnutritional deficiencies on volumes of different hippocampal subdivisions. The *x*-axis shows different subdivisions of the hippocampus and *y*-axis shows a reduction in the volume of different hippocampal subdivisions with respect to control. This volume reduction was seen following perinatal malnutrition of different types viz. *CED* chronic energy deficiency, *PD* protein deficiency, *ID* iron deficiency. Results are expressed as mean ± SEM, *n* = 5 for each group (Reprinted from Ranade et al. 2007)

well on the difficult version of the spatial navigation task but were able to learn the easier version of it checked by the Morris water maze. No difference was found between the wild type and double mutant on learning of visual cued task.

From the above discussion it is clear that iron deficiency can cause a wide range of abnormalities in hippocampal structure and function. In addition, a strong correlation has been shown between iron deficiency and spatial memory dysfunction. However, a causal relationship between the two needs to be established. This can be achieved by suggesting a biologically plausible mechanism and studying it by using animal models. This will confirm the causal role of ID in spatial memory function (Fig. 146.6).

146.5.1.4   Other Perinatal Nutritional Deficiencies and Spatial Memory Function

Zinc deficiency occurs widely within the human population. In animal models, gestational or lactational zinc deficiency is found to produce various behavioral defects which include increased aggression (Halas et al. 1975.), increased food motivation (Halas et al. 1980), and impaired avoidance conditioning (Halas and Sandstead 1975). In their study carried out on rats Halas et al. (1985) showed the effect of perinatal zinc deficiency on learning and memory of young adult rats. Rats born to zinc-deficient mothers showed learning and memory deficits tested on the 17-arm radial arm maze. Pups which were born to zinc-deficient mothers showed significantly inferior working memory compared to the control group. No differences were seen in the reference memory of any of the experimental groups.

Choline is another important constituent which when deprived during fetal or neonatal development causes spatial memory deficits in addition to other nervous system defects. Choline is derived not only from diet but is also synthesized in the body. It influences cell proliferation and apoptosis, thereby altering brain structure and function. Choline supplementation in rats during pre- and postnatal development is known to enhance their spatial memory performance checked on the radial-arm maze (Meck et al.

1988) and water maze tasks (Schenk and Brandner 1995). Prenatally choline-supplemented and choline-deprived rats showed no difference in radial arm maze performance when the trials were spaced. Choline-deficient rats exhibited high levels of proactive interference as a function of mass trials suggesting that choline deprivation causes modification of discriminative abilities that distinguish between end of one trial and beginning of another and the capacity to remember location during a trial.

Transient vitamin D deficiency in rats is associated with subtle and discrete alterations in learning and memory. However, animals prenatally depleted of vitamin D showed impairment neither on spatial learning task in the radial arm maze nor on two-way avoidance learning in the shuttle box (Becker et al. 2005)

The initial evidence suggesting the importance of folate came from studies that established a link between increased risk of neurodevelopmental disorders and folate-deficient pregnant women (Smithells et al. 1976). Although cognitive defects following folate deficiency are well known, these defects do not pertain to spatial memory function. The mechanisms involved are also poorly understood.

Since the developing brain is an extremely transient system with its requirements very tightly regulated, any small modification or perturbation brings about a huge change in the outcome of this system at various levels. Nutritional factors which are major regulatory elements of this system have to be properly balanced in order to get the best out of it. It is therefore absolutely essential to strike the right balance of these nutrients to get the desired results of a normal functioning brain.

146.5.2 Late Age Nutritional Deficiencies and Effect on the Nervous System

In contrast to the developing brain the mature brain has long been thought to be resistant to malnutritional insults. Therefore, not much attention has been paid to the effect of nutritional deficiencies on the developed brain. But since it is evident from the literature that nutritional deficiencies not only affect development but also maintenance of the central nervous system, more efforts are being made to study the effect of nutritional deficiencies on the adult brain. A healthy diet is extremely important for the proper functioning of the developed nervous system as well. Exposure to nutritional deficiencies in adult life may not produce effects which are as severe as fetal or neonatal nutritional deficiencies. However, the adult nervous system is equally at risk to the hazardous effects of nutritional deficiencies.

A significant population of developing countries or certain socioeconomic groups of developed countries could very well serve as a model for adult malnutritional deficiency studies. However, there is a possibility that this is the same population which has also experienced fetal as well as neonatal malnutritional deficiency. So the results that one sees would be the cumulative effects of both perinatal as well as adult malnutritional insults. Population studies therefore don't offer much in terms of understanding the effects of malnutritional insults on adult brain. Once again, animal studies come as a great help. Most of our knowledge about these effects also comes from animal experimentation.

Two important deficiencies which are well studied with respect to their effects on the adult brain are protein deficiency and iron deficiency. However undernutrition is also known to have a significant effect on hippocampus-dependant cognitive function. A study carried out on 16 anorexia nervosa patients with same number of age-matched controls showed reduced hippocampal volume in anorexia nervosa patients (Connan 2006). This study did not report the link between the cause and consequence of hippocampal size and function. However, incorporation of endocrine, neuropsychological, and neuroimaging aspects in such studies would help in doing so.

In their study using a long-term low-protein diet model started in adult life, Paula-Barbosa et.al have shown that a low protein diet for an extended period of time in adult rats leads to a decrease in the numerical density of the dentate granule and CA3 pyramidal cells (Paula-Barbosa et al. 1988, 1989).The same group has further shown that the numerical density of synapses established by mossy fibers and the thorny excrescences of CA3 pyramidal cells was also decreased (Andrade et al. 1991). Paula-Barbosa further demonstrated that besides granule and CA3 pyramidal cells, the remaining neuronal populations of the hippocampal formation of the adult rat also show reduction in number as a result of long-term protein deprivation. This cell loss in the hippocampus proper, at this point of time, is a consequence of neuronal degeneration alone, as the process of cell acquisition of both CAl and CA3 pyramidal cells is accomplished before birth (Bayer1980). Therefore, the results may indicate an induction of neuronal degeneration as a result of adult protein deficiency. This study also demonstrated that rehabilitation from malnutrition does not lead to improvement in the morphological alterations induced by malnutrition. This also confirms the irreversibility of these malnutritional insults on the adult brain. Although there are no reports suggesting a direct role of adult protein deficiency in spatial memory function, the above mentioned correlation between protein deficiency and hippocampal defects can be extrapolated to establish a link between protein deficiency and hippocampus-dependant spatial memory function. The direct role of late protein deficiency in spatial memory function needs to be further investigated.

Women of reproductive age, and children, are at high risk for iron deficiency. While the effects of iron deficiency on mental function in children are well recognized, not much is known about how an iron shortage affects the adult brain. A number of investigators reported that iron deficiency anemia had a great influence on cognitive functions in infants and children. However, similar studies in adults are few and also controversial. Studies carried out on human subjects shows that reduced brain iron level or anemia in females induces attention deficits and learning and memory impairments (Murray-Kolb and Beard 2007). A study carried out by Khedr et al. on 28 young adults showed the possible influence of iron deficiency anemia and iron supplementation on cognitive function and intelligence. The patients in their study demonstrated lower scores on different cognitive tests like MMSE, WMS-R, and WAIS-R. Prolongation of ERPs and reduction in their amplitude were also seen. These performances however improved following 3 months of supplementation. There are quite a few reports suggesting the important role of iron in the normal functioning of the brain at any time in life, and several reports strongly suggest a link between ID and spatial learning and memory. However, not much data are available demonstrating the role of adult iron deficiency in spatial learning. Little evidence for this comes from the human studies, but more animal studies are needed to establish and confirm the role of adult iron deficiency, if any, in spatial learning and memory function.

The other malnutritional deficiencies known to affect the spatial memory function and hippocampus include vitamin A deficiency and folate deficiency.

Several animal studies have shown that vitamin-A plays a key role in brain development. Vitamin A deficiency exerts its effect on memory functions through retinoic acid hyposignaling (Lane and Bailey 2005; Bremner and McCaffery 2008). Long-term synaptic plasticity in hippocampal formation requires retinoids. Hypofunction of retinoid signaling is implicated in spatial memory dysfunction (Cocco et al. 2002). These types of effects can be reversed by either retinoid or vitamin-A supplementation. Long-term vitamin A deficiency is shown to decrease neurogenesis and leads to memory deficits. These effects were shown to be reversed with RA (retinoic acid) treatment which could be brought about by an upregulation of retinoid-mediated molecular events. Several reports suggest that the effects of vitamin A deficiency at the level of hippoccampal neurogenesis are reversible and that RA treatment also helps in the maintenance of the hippocampal plasticity and function.

Folic acid is another important nutrient whose deficiency has been associated with neurological diseases and mood disorders (D'Anci and Rosenberg 2004). A study which tested the effect of folate

deficiency on mice lacking uracil DNA glycosylase (*Ung_/_*) versus wild-type controls showed a clear effect on spatial learning. A hippocampus-dependant spatial learning task in the Morris water maze showed that escape latency and path length was significantly affected in folate-deficient mice. The same study also reported repression of neurogenesis in hippocampal progenitors following folate deficiency (Kronenberg et al. 2008). There is also increasing evidence of the beneficial effect of folate in protection against Alzheimer's disease and cognitive decline with age (Seshadri et al. 2002; Nurk et al. 2005).

146.5.2.1 Nutritional Deficiencies, Spatial Memory Function, and the Aging Brain

The relationship between nutrition and its brain effects become prominent during aging. The aging brain is vulnerable to various factors including malnutritional insults. A sharp decline in food intake accompanied by a slowdown in metabolism during aging contributes significantly to these effects. In addition to hampering cell function, this even weakens the cells' defenses against harmful free radicals, and also impedes the ability to grow new cells. Brain cells and neurons get affected due to free radicals generated through oxidation. All these reasons make the aging brain highly vulnerable to nutritional insults. Since these changes occur in almost all regions of the brain including the hippocampus it is possible that this in turn may contribute to memory loss.

Cognitive decline and memory loss are an inseparable part of natural aging process. So long as memory loss is not as serious as senile dementia or Alzheimer's disease, minor lapse of memory is nothing to worry about. Nutritional deficiencies contribute significantly to both general memory loss as a function of aging and more serious version of memory loss as seen in Alzheimer's disease.

As discussed, the effect of both prenatal and adult protein malnutrition or undernutrition on the brain includes a variety of dysfunctions. The hippocampus is one of the more severely affected brain compartments. Changes in the hippocampus include altered density of various important cell types, namely dentate granule or CA3 pyramidal cells. In addition there is also a reduction in dendritic spine density (Andrade et al. 1995). At the functional level, there seems to be a specific reduction of working memory checked on radial arm maze (Ranade et al. 2008). Since all these structural and functional deficits are manifested even as a function of normal aging, this decrement would be still stronger in aging brains subjected to protein malnutrition. Whether these age-dependant deficits are indirectly an effect of malnutrition by virtue of reduced food intake or not is debatable. Due to lack of experimental evidence, the effect of undernutrition or protein deficiency on the aging brain is purely speculative and needs to be studied in detail. There is growing interest in the role of nutrition in aging diseases such as dementia, in particular sporadic or late-onset Alzheimer's disease. Alzheimer's disease is the most prevalent form of dementia, characterized by significant memory loss. The nutritional deficiencies shown in Alzheimer's patients include a relative shortage of specific macro- and micronutrients. These include omega-3 fatty acids, several B-vitamins, and antioxidants such as vitamins E and C (Bourre 2004). Certain in vitro and in vivo studies also support the idea that nutritional components can compensate for specific defects of neurodegenerative disorders.

The role of iron deficiency in certain neurodegenerative disorders is also speculative at this point in time. The brain regions which accumulate iron in these disorders are the same as those compromised in early iron deficiency. The important questions that come up are: Does early life exposure to iron deficiency make one more prone to neurodegenerative disorders like Alzheimer's disease? If so, does this happen because the profile of iron-metabolizing proteins in the brain of these individuals is altered due to early iron deficiency? Also are these effects aggravated due to iron deficiency during aging? This is an idea that definitely needs to be explored in detail and supported by experimental observations.

The role of zinc deficiency is also suggested in the deterioration of learning and memory in senescence-accelerated mice. The report by Saito et al. (2000) suggests that age-dependent deficiencies of Zn in synaptic vesicles of the mossy fiber pathway induced by low expression of ZnT3 causes glutamatergic excitotoxicity in the hippocampal neurons and the deterioration of learning and memory in SAMP10 (Saito et al. 2000). An unbalanced copper metabolism and homeostasis (due to dietary deficiency) could also be linked to Alzheimer's disease.

Bourre explains the detailed role of different micronutrients on the aging brain (Bourre 2008). Vitamin B9 is known to preserve memory during aging. Vitamin B12 delays the onset of signs of dementia if administered in a precise clinical time window. Poor folate status is associated with cognitive decline and dementia in older adults.

Effects of malnutritional insults on the developing and adult brains are well known. These effects just become more pronounced on the aging brain. These effects need to be demonstrated empirically.

146.6 Applications to the Other Areas of Health and Disease

There is a strong requirement for efforts to be directed towards demonstrating the causal relationship of nutritional deficiencies and spatial memory dysfunction. A greater number of studies are needed to be carried out to demonstrate the specific involvement of a particular type of malnutritional deficiency on specific temporal domain of spatial memory function in detail. Studies which address the involvement of specific components of spatial memory function (either spatial or mnemonic) in overall compromised spatial memory dysfunction following malnutritional insults are also required to be carried out. This type of research will not only help delineate the mechanisms underlying spatial memory dysfunction but will also help us design new intervention strategies.

The information obtained from the above mentioned studies will have many added advantages and will also provide important insights into other areas of research.

A clearer and detailed understanding of the mechanisms involved in spatial memory function is valuable information that can be obtained from such studies, along with a better understanding of spatial memory function per se. The findings of these studies will help researchers link the behavior of an individual with the structural correlates of that particular behavior. This could be achieved by studying the affected brain area in detail at all levels of organization viz. structural, cellular, biochemical, and electrophysiological, and its behavioral manifestation. These studies will also offer valuable information about structural and functional development of the brain in general.

Deficiencies of certain nutrients are implicated in some neurodegenerative and psychiatric disorders. A detailed study in this context will help in finding a progression pattern of some of these disorders and may even shed some light on the detailed mechanisms involved in it. Various intervention strategies can be designed based on this knowledge. The studies will also suggest the critical period of vulnerability of the aging brain to various other insults and mechanisms involved. The mechanisms involved in brain aging can also be studied in detail by using such studies.

Thus, studying malnutritional insults with respect to spatial memory dysfunction will have several other added advantages and provide valuable information in other areas of research.

The age old saying, "You are what you eat," seems quite true even in the modern world. The advancement in techniques, expanding horizons of knowledge, availability of information put together also confirm that you are what you eat. Diet has a very strong influence not only on one's health but also on the outcome of disorders and diseases.

The nervous system is one of the systems that is highly vulnerable to nutritional insults. The effect of malnutrition on behavior and cognition are not usually life threatening but are still serious enough to demand special attention. Memory dysfunction is an issue of great concern. The types of behavioral or cognitive defects induced by malnutrition include reduced ability to learn certain tasks or inability to adapt to changes or inability to retain acquired information. Such defects do not allow an individual to make optimum use of one's own capability and to be the best that one can be in a demanding society. These types of defects deal mostly with "quality of life" issues.

The problem of fetal and neonatal malnutritional deficiencies is grimmer and also long lasting. It is almost the entire future generation which is at stake for suboptimal cognitive performance for the rest of their lives.

The increasing incidence of neurodegenerative and psychiatric disorders suggest a role of lifestyle changes due to modernization. The most obvious yet underrated factor influencing cognitive decline is the role of nutrition. Quite a few of these disorders have memory dysfunction as one of the important characteristics. Although normal decline and impairment in cognitive abilities as a function of aging is very common, increasing incidences of neurodegenerative disorders are alarming and may be blamed on unhealthy eating habits. The above discussion strongly confirms the role of nutrition as an important epigenetic factor influencing cognition and behavior.

The optimum physical, chemical, and physiological development of the brain and consequent behavior is the right of every individual irrespective of their social and/or economic background. Optimum nutrition should therefore be provided to each and every individual to ensure normal and healthy brain development. It is also imperative to employ multiple strategies at various levels to overcome the defects induced by malnutrition. Thus, a combination of economic, educational, behavioral, political, social, therapeutic, and rehabilitation strategies should be used to deal with this widespread and serious issue.

Summary Points

- Optimum nutrition is an essential factor that ensures normal structural and functional development of the brain. A change in even a single constituent of the diet can have a huge yet very specific effect on brain structure and function.
- Nutritional deficiencies affect development and maintenance of the central nervous system.
- Spatial memory function, which is a crucial function of the brain, is also compromised by nutritional deficiencies.
- Spatial memory is a memory of space around one. Spatial memory function involves processes like acquiring knowledge about the space around and retaining it for subsequent use.
- Early age nutritional deficiencies have more severe and long-lasting effects on spatial memory function as compared to late age nutritional deficiencies. The effects of fetal or neonatal nutritional deficiencies are irreversible.
- Although the adult brain is also vulnerable to nutritional insults the defects are mostly reversible at least up to a certain extent.
- Different types of nutritional deficiencies affect different domains of memory function, e.g., Protein deficiency selectively affects working memory, whereas iron deficiency affects reference memory leaving all other memory functions intact.
- Although a strong corelational link between nutritional deficiencies and spatial memory dysfunction is very well established, a causal link between the two needs to be demonstrated by suggesting a biologically plausible mechanism supported by well-designed experiments.

Definitions

Malnutrition: Reduction or complete absence of one or more food constituents in the diet.

Undernutrition: Reduction in total dietary intake or inadequate calorie intake.

Macronutrient deficiency: Reduction or complete absence of one or more macronutrients (e.g., protein or fatty acids) from the diet.

Micronutrient deficiency: Reduction or complete absence of one or more micronutrients (e.g., vitamins, minerals) from the diet.

Spatial memory: Memory of the space around an individual.

Spatial learning: The process of acquisition of information about the space around the individual.

Prenatal: Time period before birth, i.e., during pregnancy or gestation.

Postnatal: Time period just after birth, i.e., during lactation.

Perinatal: Time period covering both prenatal and postnatal periods.

Key Features of Spatial Memory Function

1. A balanced diet is important for the development and maintenance of a healthy nervous system. Imbalance in nutrition can affect various brain functions.
2. Spatial memory function refers to acquiring knowledge about the space around the individual, storing it, and retrieving it for subsequent use.
3. The hippocampus is the brain region important for spatial memory function.
4. Diet has a profound effect on spatial memory function. Any deviation from a balanced diet induces structural or functional defects either in the hippocampus or spatial memory function.
5. Human and animal studies contribute a lot to understanding the mechanisms involved in spatial memory dysfunction.
6. The effects of an imbalanced diet on the developing hippocampus are severe and long lasting.
7. The adult and aging hippocampus is also vulnerable to malnutritional insults.
8. More studies are required for a better understanding of spatial memory dysfunction. The findings of these studies will help design better interventional therapies for reversing these defects.

References

Ahmed MG, Bedi KS, Warren MA, Kamel MM J Comp Neurol. 1987;263:146–58.
Altman J, Bayer SA J Comp Neurol. 1990;301:365–81.
Andrade JP, Cadete-Leite A, Madeira MD, Paula-Barbosa MM Exp Neurol. 1991:119–24.
Andrade JP, Madeira MD, Paula-Barbosa MM J Anat. 1995;187:379–93.
Arnold AE, Pinkham SM, Votolato N J Child Adolesc Psycho Pharma. 2000;10:110–7.
Austin KB, Bronzino J, Morgane PJ Brain Res. 1986;394:267–73.
Barnes RH, Cunnold SR, Robert R, Zimmerman RR, Simmons H, Mcleod RB, Krook L J Nutri. 1966;89:399–410.
Bayer SA. J Comp Neurol. 1980;190:87–114.

Beard JL, Connor JR, Jones BC Nutr Rev. 1993;51:157–70.

Becker A, Eyles DW, McGrath JJ, Grecksch G Behav Brain Res. 2005;161:306–12.

Bourre JM. J Nutr Health Aging. 2004;8:163–74.

Bourre JM. J Nutr Health Aging. 2006;10:377–85.

Bremner JD, McCaffery P Biol Psychiatry. 2008;32:315–31.

Bronzino J, Austin-LaFrance RJ, Morgane PJ Brain Res. 1991;515:45–50.

Campbell LF, Bedi KS Physiol Behav. 1989;45:883–90.

Carlson SE, Werkman SH, Peeples JM, Wilson WM Eur J Clin Nutr. 1994;48:S27–S30.

Carlson ES, Tkac I, Magid R, O'Connor MB, Andrews NC, Schallart T, Gunshin H, Georgieff MK, Petryk A J Nutr. 2009;139:672–9.

Cocco S, Diaz G, Stancampiano R, Diana A, Carta M Neuroscience. 2002;115:475–82.

Connan, F, Murphy F, Connor S, Rich P, Murphy T, Bara-Carill N, Landau S, Krljes S, Ng V, Williams S Psychia Res. 2006;146:117–25.

D' Anci KE, Rosenberg IH Curr Opin Clin Nutr Metab Care. 2004;7:659–64.

Diaz-Cintra S, Iaz-Cintra L, Cintra A, Galvan A, Aguilar A, Kemper T, Morgane PJ J Comp Neurol. 1991;36:310–56.

de Regnier RA, Nelson CA, Thomas K, Wewerka S, Georgieff MK. J Pediatr. 2000;137:777–84.

deUngria M, Rao R, Wobken JD, Luciana M, Nelson CA, Georgieff MK Pediatr Res. 2000;48:169–76.

Felt BT, Lozoff B J Nutr. 1996;126:693–701.

Frankland PW, Bontempi B Nat Rev Neurosci. 2005;6:119–30.

Galler JR. Ambulatory Child Health. 2001;7:85–95.

Halas ES, Sandstead HH Pediatric Res. 1975;9:94–7.

Halas ES, Hanlon MJ, Sandstead HH Nature. 1975;257:221–2.

Halas ES, Burger PA, Sandstead HH Anim Learn Behav. 1980;8:152–8.

Halas ES, Hunt CD, Eberhardt MJ Physiol Behav. 1985;37:451–8.

Jordan, TC, Cane SE, Howells KF Dev Psychobiol. 1981;14:317–25.

Jordan, TC, Howells KF, McNaughton N, Heatlie PL Res Exp Med. 1982; 180:201–7.

Jorgenson LA, Wobken JD, Georgieff MK Dev Neurosci. 2003;25:412–20.

Jorgenson LA, Sun M, O'Connor M, Georgieff MK Hippocampus. 2005;15:1094–1102.

Khedr E, Hamed SA, Elbeih E, El-shereef H, Ahmad Y, Ahmed S Euro Arch Psych Clinic Neuroscience. 2008;258:489–96.

Kronenberg G, Harms C, Sobo RW, Cardozo-Pelaez F, Linhart H, Winter B, Balkaya M, Gertz K, Gay SB, Cox D, Eckart S, Ahmadi M, Juckel G, Kempermann G, Hellweg R, Sohr R, Hörtnagl H, Wilson SH, Jaenisch R, Endres M J Neuroscience. 2008;28:7219–30.

Lane MA, Bailey SJ Prog Neurobiol. 2005;75:275–93.

Larkin EC, Rao GA. In: Dobbing J., editor. Brain, behavior and iron in the infant diet. London: Springer. pp. 43–63.

Lewis PD, Patel AJ, Balazs R Brain Res. 1979;168:186–9.

Lozoff B. Pediatr Res. 2000;48:137–9.

Lozoff B, Brittenham GM, Wolf AW, McClish DK, Kuhnert PM, Jimenez E Pediatrics. 1987;79:981–95.

Lynch A, Smart JL, Dobbing J Brain Res. 1975;83:249–59.

Meck WH, Smith RA, Williams CL Dev Psychobiol. 1988;21:339–53.

Morris RG, Garrud P, Rawlins JN, O'Keefe J. Nature. 1982;297:681–3.

Murray-Kolb LE, Beard JL Am J Clin Nutr. 2007;85(3):778–87

Neuringer MWE, Connor DS, Lin LB, Luck S Proc Natl Acad Sci. 1986;83:4021–5.

Noback CR, Eisenman LM Anat Rec. 1981;201:67–73.

Nurk E, Refsum H, Tell GS, Engedal K, Vollset SE, Ueland PM, Nygaard HA, Smith AD Ann Neurol. 2005;58:847–57.

O'Keefe J, Nadel L. The hippocampus as a cognitive map. London: Oxford UP; 1978.

Olton DS, Samuelson RJ J Expert Psychol Animal Behav Processes. 1976;2:97–116.

Paula-Barbosa MM, Andrade JP, Azevedo FP, Madeira MD, Alavs MC Soc Neurosci Abs. 1988;14: 368.

Paula-Barbosa MM, Andrade JP, Castedo JL, Azevdo FP, Cames I, Volk B Expt Neurol. 1989;103:186–93.

Pollit E. Am J Clin Nutr. 1989;50:666–7.

Ranade SC, Rose AJ, Rao M, Gallego J, Gressens P, Mani S Neuroscience. 2008;152:859–66.

Rao R, Tkac I, Townsend EL, Gruetter R, Georgieff MK J Nutr. 2003;133:3215–21.

Rice D, Barone S Jr. Environ Health Perspect. 2000;108:511–33.

Saito T, Takahashi K, Nakagawa N, Hosokawa T, Kurasaki M, Yamanoshita O, Yamamoto Y, Sasaki H, Nagashima K, Fujita H Biochem Biophys Res Commun. 2000;279:505–11.

Schenk F, Brandner C Psycobiol. 1995;23:302–13.

Seshadri S, Beiser A, Selhub J, Jacques PF, Rosenberg IH, D'Agostino RB, Wilson PW, Wolf PA N Engl J Med. 2002;346:476–83.

Siddappa AM, Georgieff MK, Wewerka S, Worwa C, Nelson CA, de regnier RA. Pediatr Res. 2004;55:1034–41.

Smithells RW, Sheppard S, Schorah CJ Arch Child Dis. 1976;51:944–50.

Strupp BJ, Levitsky DA J Nutr. 1995;125:2221S–32S.

Tonkiss J, Galler JR Brain Res. 1990; 40:95–107.

Tran PV, Carlson ES, Stephanie JB, Fretham TB, Georgieff MK. J Nutr. 2008;138:1267–71.

Uauy TDG, Birch E, Birch JE, Tyson A, Hoffman DR Pediatr Res. 1990;28:485–92.

Valadares CT, Almeida SDS Nutr Neurosci. 2005;8:39–47.

Van Gelder NM. Microsc Electron Biol Cel. 1984;8:227–43.

Vendite D, Wofchuk S, Souza D J Nutr. 1985;115:1418–24.

Walter T, de Andraca I, Chadud P, Perales CG Pediatrics. 1989;84:7–17.

Witter MP, Amaral DG J Comp Neurol. 1991;307:437–59.

Yanai S, Okaichi Y, Okaichi H Neurobiol Aging. 2004;25:325–32.

Chapter 147
Arguments for a Relationship Between Malnutrition and Epilepsy

Sabrina Crepin, Bertrand Godet, Pierre-Marie Preux, and Jean-Claude Desport

Abbreviations

BMI	Body mass index
CNS	Central nervous system
CSF	Cerebral spinal fluid
GABA	Gamma amino butyric acid
NMDA	*N*-Methyl-d-aspartate
PEM	Protein-energy malnutrition
PTZ	Pentylenetetrazole
PWE	People with epilepsy

147.1 Introduction

Malnutrition is a serious public-health problem. Approximately one billion people, essentially from developing countries, are affected by malnutrition (Elia et al. 2005). In developed countries, the prevalence of malnutrition is estimated around 5% of the 15 years and older population (Charles and Basdevant 2006). The term malnutrition usually refers both to undernutrition and overnutrition. Here, we will use the term malnutrition only for undernutrition. Malnutrition can be divided into two types: protein-energy malnutrition (PEM) and micronutrient deficiencies. Malnutrition produces adverse functional effects such as loss of muscle mass or alteration of the immune system, increasing the risk of infections that have clinical and public-health consequences or more typical diseases for micronutrients deficiencies (Stratton et al. 2003).

Epilepsy is a neurological disorder that affects 50 million people throughout the world. According to the epidemiological definition from the International League against Epilepsy (ILAE), it is characterized by the occurrence of at least two unprovoked seizures spaced over 24 h (ILAE 1993). An epileptic seizure is a transient occurrence of signs and/or symptoms due to abnormal excessive and synchronous neuronal activity in the brain (Table 147.1). This activity depends on membrane potential regulated by neurotransmitters, voltage-gated ion channels, and gap junctions. Synaptic transmission

S. Crepin (✉)
Service de Toxicologie et Pharmacologie - Pharmacovigilance, Centre Hospitalier Universitaire,
F-87042 Limoges, France
e-mail: sabrina.crepin@chu-limoges.fr

Table 147.1 Key facts of epilepsy

- Epilepsy is a common chronic neurological disorder characterized by recurrent unprovoked seizures (at least two unprovoked seizures spaced over 24 h). It affects people whatever their age
- A seizure consists in the transient occurrence of signs and/or symptoms due to abnormal excessive and synchronous neuronal discharge in the brain. It can manifest as an alteration in mental state, tonic or clonic movements, convulsions, and various other psychic symptoms. Seizures can occur even in people who do not have epilepsy
- There are different types of epileptic seizures depending on the area affected by the seizures (generalized or focal), and the associated signs and the syndromes
- Epilepsy has many possible causes, including prenatal injuries, infectious diseases, head trauma, and abnormal brain development. In many cases, this cause is unknown.
- About 50 million people suffer from epilepsy all around the word, but about 80% of PWE are found in developing regions
- Drug-resistant epilepsy concerns 20–30% of PWE. This term is used when seizure control is not possible after 2 years, despite the use of at least two antiepileptic drugs from different pharmacological profiles adapted to the epileptic syndrome in a compliant patient
- PWE and their families can suffer from stigma and discrimination in many parts of the world. Stigma is a large part of the burden carried by individuals and occurs more often in developing countries

This table lists the key facts of epilepsy with regard to epidemiologic data, causes, mechanisms, and different types of seizures

is inhibited or excited according to the type of neurotransmitter, respectively gamma amino butyric acid (GABA) or glutamate. Epileptogenesis implies a local or diffuse modification of these mechanisms which are responsible for a loss of balance between GABA and glutamate. Seizure types are first organized according to whether the source of the seizure within the brain is localized (partial or focal onset seizures) or distributed (generalized seizures). The hippocampus plays a major role in partial temporal epilepsy. In these epilepsies, hippocampal modifications appear after an initial brain injury and then a latent period corresponding to epileptogenesis during which many changes occur. The limited nature of the hippocampus, the reproducibility of its reorganization during epileptogenesis made it as a preferred structure for the study of experimental models of epilepsy in animals and humans.

A relationship between nutritional status and epilepsy has been suspected for a long time. In this chapter, we will highlight the different interactions between malnutrition and epilepsy (Fig. 147.1).

Almost 1,000 years ago, Avicenna recommended that people with epilepsy (PWE) avoid excessive eating, sheep meat, fish, onion, garlic, celery, cauliflower, and carrots (Asadi-Pooya and Ghaffari 2004). Several studies examine the relationship between malnutrition and epilepsy in humans (Hackett et al. 1997; Pal 1999; Nkwetngam Ndam 2004; Bertoli et al. 2006; Crépin et al. 2007; Volpe et al. 2007). The main results are summarized in Table 147.2. The studies were carried out essentially in developing countries and the results are divergent, in part due to methodological differences. But, in case-control studies with enough power, a link between malnutrition and epilepsy is found (Hackett et al. 1997; Crépin et al. 2007; Volpe et al. 2007). Prevalence of malnutrition in epilepsy in developing areas like Africa is high: 22.1% in a recent Benin study (West Africa) regardless of age (vs. 9.2% for the population without epilepsy, $p < 0.001$) (Crépin et al. 2007). Significant differences in consumption of cereals, tubers, vegetables, fish/meat and sweets, and several sociocultural factors (food taboos, stigmatization, etc.) are reported between PWE and controls (Table 147.3) (Crépin et al. 2007). In India, only one of two studies shows a link between epilepsy and body mass index (BMI) (Hackett et al. 1997; Pal. 1999). Two other studies performed in Italy and the United States, in children with refractory epilepsy, show existence of a risk of malnutrition, but no studies have been performed in non-drug-resistant PWE from developed
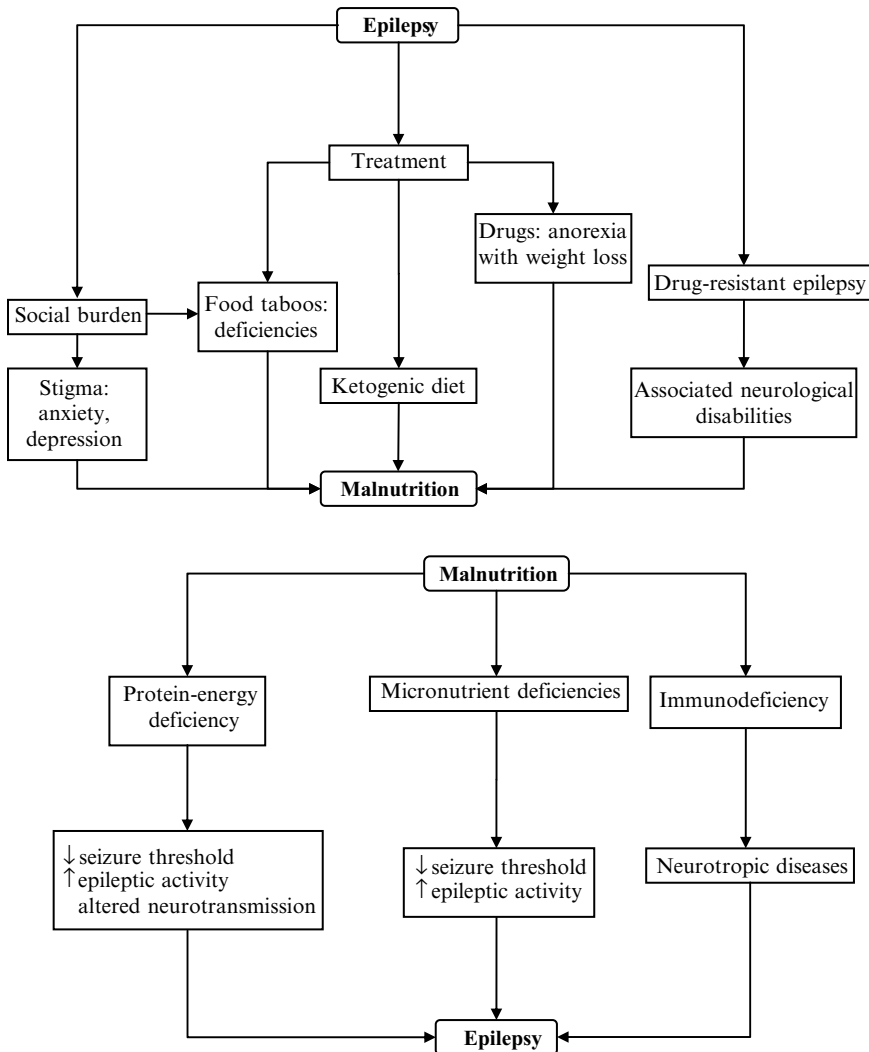
Fig. 147.1 Key facts of relationship between malnutrition and epilepsy. Links between epilepsy and malnutrition are bidirectional. Epilepsy can be responsible for the occurrence of malnutrition because of antiepileptic drugs (anorexic effect), food taboos (depending on the area in the world), and depression due to stigma. In the particular case of drug-resistance epilepsy, PWE can have other neurological disabilities (chewing problems, behavior problems or cerebral palsy, for example). Malnutrition is responsible for protein-energy malnutrition, micronutrient deficiencies, and immunodeficiency. Mechanisms implicated are decrease of seizure threshold, altered neurotransmission or increase of sensibility to infectious diseases as neurotropic diseases. In developed countries, we can speculate that malnutrition is unlikely lead to epilepsy whereas in developed countries the causal relationship is more likely. However, the relationship "epilepsy → malnutrition" is possible in any part of the world

countries. Many studies were performed in animals. The aim of these studies was to bring an assessment of the eventual role of malnutrition in seizure onset by exploring different avenues such as protein or micronutrient deficiencies, but in fact, there are two coexisting hypotheses to explain a link between malnutrition and epilepsy: on the one hand, malnutrition may contribute to the onset of epilepsy or at least seizures and on the other hand, epilepsy could be responsible for malnutrition.

Table 147.2 Studies about malnutrition and epilepsy performed in humans

Place	Study design	population	Age of subjects (years)	Results
Benin (Crépin et al. 2007)	Case-control study	131 PWE 262 controls	All ages	Risk of malnutrition higher for PWE (OR = 2.9, $p = 0.0006$)
Benin (Nkwetngam Ndam. 2004)	Case-control study	39 PWE 39 controls	All ages	No link between malnutrition and epilepsy ($p > 0.05$, lack of power)
Inde (Hackett et al. 1997)	Case-control study	26 PWE 1,146 controls	8–12	Mean BMI lower in PWE (OR = 0.74; $p = 0.023$)
Inde (Pal 1999)	Case-control study	61 PWE 59 controls	2–18	No link between BMI and epilepsy (OR = 31.3; $p > 0.05$, lack of power)
USA (Volpe et al. 2007)	Case-control study	43 PWE National Health and nutrition examination	1–9	Significant lower intakes for total energy and macro and micronutrients in children with drug-resistant epilepsy ($p < 0.05$)
Italy (Bertoli et al. 2006)	Cross-sectional study	17 PWE Standard chart	3–16	40% of children with drug-resistant epilepsy malnourished and 24% wasted ($p < 0.05$); unbalanced dietary intakes

Several studies concerning malnutrition and epilepsy are available. Most of them were performed in developing countries (4/6). Results are divergent because of methodological differences or lack of power. In case-control studies with enough power, malnutrition and epilepsy are linked

PWE people with epilepsy, *OR* odds ratio, *BMI* body mass index

Table 147.3 Factors linked with epilepsy in an African case-control study (Crépin et al. 2007)

Factors	Ajusted odds ratio (95% CI)	p
Mid arm upper circumference per unit	0.7 [0.6–0.9]	0.0020
Third party answering the questionnaire		
Yes (/no)	16.8 [3.1–90.3]	0.0010
Second occupation		
No (/yes)	7.1 [2.3–22.3]	0.0008
Cereal consumption		
≤1 time/day (/>1 time/day)	4.2 [1.8–10.0]	0.0010
Tooth decay		
Yes (/no)	2.9 [1.1–7.3]	0.0280
Food taboos		
Yes (/no)	25.0 [8.3–100.0]	<0.0001
Number of meals/day		
<3 (/≥3)	4.2 [1.6–10.9]	0.0037

In this case-control study performed in an African country, seven factors are significantly linked to epilepsy. These factors can be gathered in nutritional status factors (mid arm upper circumference, tooth decay), food consumption (cereal consumption, number of meal/day) or social factors (food taboos, second occupation, third party answering the questionnaire). Cases were people with epilepsy (PWE) and controls were people without epilepsy. In African countries, PWE don't usually answer directly to questionnaire or participate to study, a member of the family acts as a third party. It's one of the signs of stigma

CI confident interval

147.2   Effects of Malnutrition in Epilepsy

147.2.1   Protein-Energy Malnutrition

147.2.1.1   Protein Deficiency

Studies on animals show that if malnutrition is not considered a direct cause of epilepsy, it seems to favor the onset of epilepsy or seizures by various nutritional deficiencies. In rats, brain development occurs during the first 3 weeks of life. So, if this hypothesis is extrapolated to humans, it would mean that malnutrition during childhood could predispose someone to epilepsy. In humans, from the pre-natal period to third year of life is a time when the central nervous system (CNS) develops, and this is considered a sensitive period depending, in part, on protein, energy, and micronutrient availability. Malnutrition at this time adversely affects the developing brain in numerous ways, largely depending on its timing in relation to various developmental events in the brain and, to a lesser extent, on the type and severity of the deprivation. Many of the effects of prenatal malnutrition are permanent (Morgane et al. 2002). In animals, neuro-anatomical studies provide, for many years, evidences that the hippocampus and cortex are adversely affected by early malnutrition, which exerts its effects not only during the so-called brain growth spurt, but also during early organizational processes such as neurogenesis, cell migration, and differentiation in the cortex and hippocampus. Even if most of nutrients affect brain maturation, proteins seem to be the most important (Morgane et al. 2002; Georgieff 2007). In order to study the effect of malnutrition in the brain, the hippocampal neuronal model is widely used, particularly a study of the dentate gyrus, primarily because its anatomy and physiology are well-known and, secondly, because of its ideal internal geometry to study neuronal organization, reproducibility of the experiments, and its role in epilepsy. Stern et al. show that protein malnutrition during development leads to enhanced seizure susceptibility in adult rats reared on a diet containing inadequate protein levels (decreased seizure threshold and increased epileptic activity) (Stern et al. 1974). This effect is partially abrogated by restoring adequate dietary protein levels in adulthood, and seems to be specific to the type of stimulation used to induce experimental seizures (Forbes et al. 1978). Palencia et al. use a rat model of chronic malnutrition to study the possible influence of malnutrition at late stages of brain development with experimental seizures induced by pentylenetetrazole (PTZ), a $GABA_A$ receptor antagonist (Palencia et al. 1996). In this study, corn tortilla is the only solid food used. The dose of PTZ required to produce seizures is reduced in malnourished rats. This malnutrition model was used because corn and corn derivatives represent the most common food sources of undernourished people from Latin America. Histological studies of the brain show atrophic neurons especially in the hippocampus, cerebellar cortex, and cerebral cortex. In contrast with other studies, Nunes et al. find that malnourished neonatal rats (during the breast-feeding period) are not different from well-nourished rats in terms of flurothyl seizure susceptibility at postnatal day 15 or behavioral manifestations of seizures. But histological assessment shows that flurothyl-induced status epilepticus increases the expression of new cells in the dentate gyrus of malnourished immature rats compared to well-nourished rats; these results may be explained by a cumulative toxicity of malnutrition and status epilepticus (Nunes et al. 2000). However, the pathological function of these new cells has not been clearly established yet.

Protein malnutrition can affect cholinergic, GABAergic, serotoninergic, and glutaminergic transmission. Andrade and Paula-Barbosa randomly assign 2-month-old rats to three groups: (i) malnourished rats fed with an 8% low-protein diet for 12 months; (ii) recovery rats fed like the previous group for 6 months and then switched to a 17% protein standard laboratory diet for a further 6 months; and (iii) controls rats fed for 12 months with the standard laboratory diet (Andrade and

Paula-Barbosa 1996). Prolonged malnutrition lead to a substantial but reversible reduction in the cholinergic innervations of the hippocampal formation which could be explained by a lack of trophic factors, decreased synthesis, availability, and delivery of ordinarily existing neurotrophic substances or an altered ability of neurons to react to these factors. They also show irreversible loss of hippocampal cholinergic and GABAergic neurons.

We are also confronted with the problem of the mechanism leading to epilepsy from extrapolation of effects on hippocampal structures to more global alterations of the CNS explaining different types of epilepsy. Moreover, alterations of the hippocampal area play a key role in some focal epilepsy.

147.2.1.2 Neurotransmitters

Brain cells need certain amino acids and micronutrients to function normally. Several amino acids act as neurotransmitter precursors, such as tryptophan (for serotonin), and some neurotransmitters have amino acid bases, such as GABA or glutamate. Wood et al. show that malnourished rats have lower GABA concentrations in cerebral spinal fluid (CSF) than controls (Wood et al. 1979). For Steiger et al., modifications in $GABA_A$ receptors (variation of affinity or allosteric interactions between benzodiazepines and GABA receptors) are found in rats receiving a low-protein diet during gestation (Steiger et al. 2003). Schweigert et al. find that prenatal and postnatal protein-malnourished rats are more sensitive to picrotoxin ($GABA_A$ receptors antagonist) but there is no difference for quinolinic acid, which has an excitatory effect on neurons as *N*-methyl-d-aspartate (NMDA) receptor agonist. The authors also note an increase in GABA uptake in the hippocampus. In malnourished humans, GABA level is only measured in blood. The findings are contradictory. For Smith et al., this level is lower than in well-nourished humans (Smith et al. 1974) while for Agarwal et al., it is increased (Agarwal et al. 1981). When brain GABA concentration is increased by administration of antiepileptic drugs, blood and CSF GABA concentrations are also increased. But if GABA plasma concentration decreases no one knows whether CSF and brain GABA concentration is decreased as well.

Another hypothesis concerning the effects of changing cerebral concentration of GABA would be excitatory properties in connection with high intracellular concentration of chloride ($[Cl^-]_i$) due to modification of chloride transporter expression, as shown physiologically during the fetal stages and also in temporal epilepsy hippocampal pyramidal cells (Ben-Ari 2002).

We can speculate that chronic malnutrition in human induces alterations in the brain that decrease seizure threshold, facilitating epileptogenesis that occurs after cerebral injuries or disorders that are prevalent in inhabitants of developing areas.

147.2.2 Immunodeficiency

It is known that malnutrition is a major cause of immunodeficiency (Lesourd and Mazari 1997). PEM is associated with impairment of cell-mediated immunity, phagocyte function, complement system, secretory immunoglobin-A antibody concentration, and cytokine secretion. In tropical areas, poor sanitation and contaminated food or water contribute to alter immunocompetency and to increase risk of infections, especially intestinal infections, which themselves can lead to malabsorption and raise needs in order to adapt immune responses. Malnourished people are more vulnerable to infections, as for example infections known to be epilepsy risk factors, such as neurotropic viruses or cysticercosis, etc. One has to know that neurocysticercosis is the most frequent infectious cause

of epilepsy in developing countries (Preux and Druet-Cabanac 2005). Single nutrient deficiencies are also responsible for altered immune responses. This is observed even when the deficiency is mild. Zinc, copper, vitamins A, C, E, and B6 have important influences on immune responses (Lesourd and Mazari 1997).

147.2.3 Micronutrient Deficiencies

Malnutrition can be responsible for electrolyte deficiencies (calcium, magnesium, sodium, phosphorus, etc.), vitamin deficiencies (B1, B6, B12, D) or other elements (zinc or selenium). CNS homeostasis is essential for brain function. Micronutrient deficiencies can have direct or indirect effects on neuronal excitability and may facilitate epileptic activity (Table 147.4). Seizures can occur following hyponatremia, hypocalcemia, hypomagnesemia, or hypophosphatemia. There are usually tonic-clonic seizures but focal seizures are also possible (Castilla-Guerra et al. 2006). Electrolyte lab tests are recommended especially after a first seizure. Several seizure cases due to hyponatremia have been reported. A retrospective survey carried out in an American emergency department shows that hyponatremia (<126 mmol/L) is responsible for seizure occurrence in 56% of less than 2-year-old children and in 70% of children younger than 6 months old when there are no other obvious causes of seizure (Farrar et al. 1995). Seizures can be explained by a decrease in extracellular osmolality responsible for an osmotic gradient and water entry into cells. Several case-reports of seizures associated with hypocalcemia (essentially the neonatal stage, people with hypoparathyroidism or vitamin D deficiency) or hypomagnesemia are also reported (Leaver et al. 1987; Bushinsky and Monk 1998). In slices of human epileptogenic neocortex, a decrease in extracellular magnesium concentration always induces epileptiform discharges by eliminating its blocking effect on NMDA receptors (Avoli et al. 1991). Hypophosphatemia is a well known and possible cause of seizure during the refeeding

Table 147.4 Micronutrients deficiencies and seizure

Deficiencies	Hypotheses
Electrolytes	
Calcium (Bushinsky and Monk 1998)	Neuronal hyperexcitability
Sodium (Farrar et al. 1995; Castilla-Guerra et al. 2006)	Cerebral hypo-osmolality
Magnesium (Leaver et al. 1987; Avoli et al. 1991)	Neuronal excitability modulator
	Disinhibition of the complex sodium-channel- glutamate receptor NMDA-type
	Neuromodulation
Phosphorus (Sobotka 2004)	Unknown
Vitamins	
Vitamin B1 (Keyser and De Bruijn 2001)	Increase of irritative activity in predisposed people
Vitamin B6 (Kretsch et al. 1991)	Decrease of threshold seizure
Vitamin B12 (Biancheri et al. 2001)	Increase of glutamate sensitivity
Vitamine D (Johnson and Willis 2003)	Associated with consequences of calcium deficiency
Trace elements	
Zinc (Takeda 2000)	Genetic susceptibility
	Increase of cortical hyperexcitability
	Neuromodulation
Selenium (Schweizer et al. 2004)	Antioxidant effect

Micronutrient deficiency is a possible cause of seizures. Different types of micronutrients are involved (trace elements, vitamins, and electrolytes). Mechanisms implicated are various and depend on micronutrients. These data are essentially based on animal studies or human case series

syndrome (Sobotka 2004). The role of vitamin deficiencies in seizures has also been reported but mainly on case-reports (Keyser and De Bruijn 1991; Kretsch et al. 1991; Biancheri et al. 2001; Johnson and Willis 2003). For zinc and selenium, neurological effects have been studied in animal models (Takeda 2000; Schweizer et al. 2004). The hypothalamus contains high zinc levels, and is sensitive to deficiency. At a neuronal level, zinc acts as a neurotransmitter in glutaminergic and GABAergic transmission by decreasing the extracellular glutamate concentration and increasing the extracellular concentration of GABA. As selenium is an essential part of glutathione peroxidase involved in antioxidant defence, selenium deficiency can be implicated in oxidative stress (Schweizer et al. 2004). Oxidative stress seems to be implicated in occurrence of seizures. Animal models indicate that occurrence of seizures can increase the content of reactive oxygen species and superoxide generation in the brain. But also, free radicals can induce seizure activity by direct inactivation of glutamine synthase resulting in an abnormal build up of glutamate or inhibition of glutamic acid decarboxylase activity leading to a decrease of GABA. In a study performed in humans, the antioxidant status in the blood of PWE is low compared to controls (lower plasma concentration of vitamins A and C, erythrocyte glutathione reductase and high lipid peroxidation and hemolysis). This status is improved after antiepileptic treatment. Seizure activity may act directly on oxidant blood concentration and antioxidant may be useful to counteract the effect of free radicals (Sudha et al. 2001).

147.3 Effects of Epilepsy on Nutritional Status

147.3.1 Sociocultural Issues

Epilepsy is not only a clinical disorder but also a social label, especially, but not only, for PWE from developing countries. In developing countries, epilepsy is often wrongly considered a contagious disease, the transmission to bystanders being done through saliva, urine, feces, or flatus emitted during a seizure. This situation leads to a restriction on the normal life style and activities, stigma, and then social rejection (Nubukpo et al. 2003). Most African communities still view epilepsy as possession by the Devil or as a witchcraft act. As a consequence of these traditional beliefs, PWE are treated as outcasts. They can be excluded from their family, and not allowed to attend school. It can also be more difficult for them to get married. Seizure occurrence, as well as social rejection, can be responsible for anxiety, decreased food intake, and long-term malnutrition. Nubukpo et al. find that PWE are more anxious or depressed than people without epilepsy (Nubukpo et al. 2004). In developing countries, they have more food-related difficulties than controls: they frequently have fewer than three meals/day, consume cereals less often, and need family help more often (Crépin et al. 2007). Therefore, their nutritional status is worse than that of the control group.

In such countries, beliefs also dictate what PWE may eat. Indeed, food taboos can sometimes be the basis of epilepsy treatment. Nubukpo et al. report that food taboos is found in 63.9% of Benin PWE and 44.2% of Togolese PWE (Nubukpo et al. 2003). In another study performed in Benin, 64% of PWE have food taboos versus 22% for controls (Crépin et al. 2007). In France, food taboos are found in up to 19.5% of a studied population and in the United States, 6% of adults with epilepsy report food as a precipitating factor of seizure (Nubukpo et al. 2003; Asadi-Pooya and Sperling 2007). Eviction can include salty and/or spicy food, sweets, oil but also boiled meat or gummy sauces (with mucilaginous plants such as okra) depending on cultural beliefs and personal experiences (Asadi-Pooya and Sperling 2007; Crépin et al. 2007). If abstinence from certain foods is used, it is because they are considered as responsible for seizure occurrence or saliva secretion during

seizures and, in this way, can facilitate "the transmission" of the disease. For Asadi-Pooya and Ghaffari, 55.2% of parents of Iranian children with epilepsy think that there is a relationship between consumption of certain foods and seizure occurrence (Asadi-Pooya and Ghaffari 2004). In addition, this opinion is held by 58.4% of Iranian nurses and physicians (Asadi-Pooya and Hossein-Zade 2005). Almost 50% of the health care professionals and 31.2% of the family of children with epilepsy have experiences with seizure in their PWE after consumption of specific food (dairy products, sour food like vinegar, pepper, meat/fish, vegetables, or fruits) (Asadi-Pooya and Ghaffari 2004; Asadi-Pooya and Hossein-Zade 2005).

147.3.2 Specific Aspects of Drug-Resistant Epilepsy

Growth retardation is reported of children with epilepsy and this could be more prevalent in children with drug-resistant epilepsy. Several factors could explain this: frequent seizures and long post-ictal periods may lead to reduced times of alertness and may lead to decrease in total energy intake.

Two recent studies performed in developed countries suggest that drug resistance in children with epilepsy may favor malnutrition (Bertoli et al. 2006; Volpe et al. 2007). In Italy, 7 children from a cohort of 17 children with drug-resistant epilepsy are malnourished (weight < 80% compared with the reference weight for age) (Bertoli et al. 2006). Children with more severe neurological impairment have the lowest amount of fat-free mass and are hypercatabolic. In the United States, children with drug-resistant epilepsy were compared to healthy children of the same age from the National Health and Nutrition Examination Survey 2001–2002 and Dietary Reference Intakes (Volpe et al. 2007). Energy intake and macronutrients are substantially lower in the children with intractable epilepsy. About 47% of children have significantly lower intakes of total energy, protein, carbohydrate, fat, dietary fibers, certain vitamins, and trace elements compared with recommendations for sedentary healthy children. Drug-resistant epilepsy can be associated with several disabilities including metabolic diseases or cerebral palsy. However, in these two studies, all children for Bertoli et al. (2006) and 53% for Volpe et al. (2007) are at least mildly mentally retarded and, consequently, the risk of malnutrition seems to be partially linked to disabilities related to epilepsy (chewing and swallowing difficulties, anorexia, etc.).

147.3.3 Antiepileptic Treatment

Epilepsy is usually treated with drugs, but traditional treatments in developing countries and specific diets are also used. Because of cultural practices and limited access to medical care, traditional therapies are frequently used in developing countries. In Malawi, for example, treatments are often based on emetic and/or purgative preparations because Malawi people think that epilepsy originates from the stomach where insects can trigger seizures with their movements (Bernet-Bernady et al. 1997). Vomiting and diarrhea due to this type of treatment with long-term use may lead to various deficiencies and weight loss.

Numerous articles deal with the effect of antiepileptic drugs on weight: some can decrease bodyweight and others can increase it or are neutral on weight (Table 147.5). Topiramate, felbamate, zonisamide, and stiripentol induce weight loss due to loss of appetite (Biton 2003; Ben-Menachem 2007). Topiramate is one of the antiepileptics the most associated with weight loss. Weight loss depends on BMI (patients with a higher baseline BMI are more likely to lose weight), gender (females

Table 147.5 Effect of antiepileptic drugs on weight (Chiron et al. 2000; Biton 2003; Ben-Menachem 2007)

Weight gain	No effect	Weight loss
Carbamazepin	Lamotrigine	Felbamate
Oxcarbazepine	Levetiracetam	Topiramate
Gabapentine	Phenytoin	Zonisamide
Pregabalin	Tiagabine	Stiripentol
Sodium valproate	Lacosamide	
Vigabatrin		

Antiepileptic drugs are now known to have an effect on weight. This effect depends on the drug but also on risk factors linked to people with epilepsy (basal body mass index, sex…). The loss of weight is usually due to an anorexic effect of the drugs

are more likely to lose weight) and daily dose (>200 mg/J). Felbamate also significantly reduces the weight of PWE by 15–75%, with some losing up to 4% of their body weight within 6 months (Ben-Menachem 2007). Weight loss with zonisamide is reported in several clinical trials: almost 22% of PWE lose at least 2.3 kg versus 10.5% of PWE using placebo (Ben-Menachem 2007). Stiripentol is also responsible for weight loss: 7% versus 1% in placebo group (Chiron et al. 2000). Antiepileptic drugs can also be responsible for micronutrient deficiencies, such as that of vitamin D with phenytoin or phenobarbital, or taurine deficiency which seems to be responsible for the retinal toxicity of vigabatrin (Gissel et al. 2007; Jammoul et al. 2009). Even if in this chapter we only focus on under-nutrition, some antiepileptic drugs can, in contrast, be responsible for an increase of weight. The most well known weight-increasing drugs are: valproate, gabapentine, pregabalin (Biton 2003; Ben-Menachem 2007). Phenytoin, tiagabin, lamotrigine, and lacosamide are themselves considered weight-neutral antiepileptic drugs (Biton 2003; Ben-Menachem 2007).

Dietary therapies are another option in epilepsy treatment. A ketogenic diet is the most often used, but it is not the only one (a modified Atkins diet with high fat, high protein, low carbohydrate, could be used, for example). A ketogenic diet is usually proposed for the treatment of children with drug-resistant epilepsy. It is a strict high fat, adequate protein, and low carbohydrate diet (Fig. 147.2). It decreases seizure frequency in more than 50% of children on the diet. After almost one century of use, the mechanism involved in the clinical efficacy of this treatment is still not clearly understood (Fig. 147.3). The pH hypothesis is based on the idea that the ketogenic diet makes the blood (and brain) slightly acidic because of the production of ketone bodies (acetoacetate, beta-hydroxybutyrate, and acetone). The pH change would be responsible for the antiepileptic effect. In the metabolic hypothesis, a ketogenic diet makes the brain switch from a glucose-based metabolism to a ketone-based metabolism. The antiepileptic effect is due to ketone bodies being more energetic than glucose. or an increase in mitochondrial number, and a decrease in availability of fast energy (glucose) necessary for the seizure. In the amino acid theory, the neurotransmitter balance is modified with an increased production of GABA. In the ketone hypothesis, ketone bodies themselves have antiepileptic properties. A ketogenic diet is efficient in many seizure types and epilepsy syndromes, especially in children who extract and utilize ketone bodies from blood more efficiently than older PWE (Kossoff and Rho 2009). The efficacy appears quickly in the first week of diet. It allows a decrease in seizure severity or duration and increases seizure threshold. In addition to the immediate effect of ketogenic diet, it could have long-term benefits with neuroprotective or antiepileptogenic effects. However, ketone bodies also have anorexigenic properties and other adverse effects as diarrhea and vomiting and can be responsible for growth retardation or weight loss especially in the youngest (Vining et al. 2002). Like the ketogenic diet, a calorie-restricted diet seems to be effective,
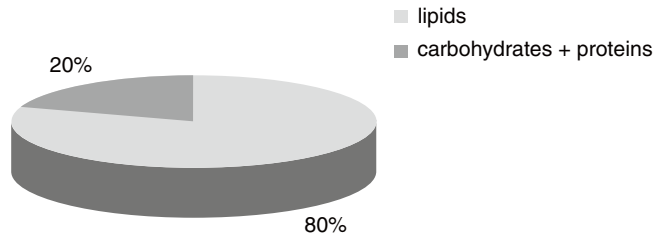
Fig. 147.2 Composition of ketogenic diet. A ketogenic diet is a high fat, adequate protein, and low carbohydrate diet. The ratio of lipid to nonlipid is usually 4:1 with a minimum of 1 mg/kg/day of proteins and a limited intake of carbohydrates (10–15 g/day). Vitamin supplementation is necessary. A nutritionally complete powdered product is available
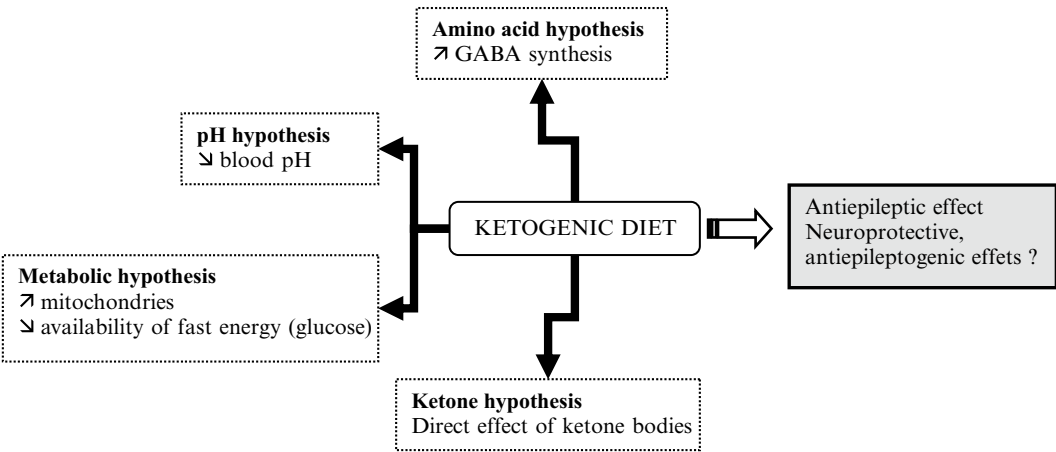
Fig. 147.3 Mechanisms of ketogenic diet. A ketogenic diet, used in drug-resistant epilepsy, is one of the possible treatments in epilepsy. It consists in a strict high fat, adequate protein, and low carbohydrates diet resulting in a production of ketone bodies (acetoacetate, beta-hydroxybutyrate, and acetone). The ketogenic diet has at least an antiepileptic effect and probably neuroprotective and antiepileptogenic effects

on rodent models, in the decrease of seizure susceptibility by reducing the brain glycolytic energy (Greene et al. 2001). It leads to a global decrease in calorie intake without modification of proportions between different food groups and so differs from acute fasting and starvation. A calorie-restricted diet seems to have an additive effect when associated with a ketogenic diet in rodents, but this possible diet therapy has not been yet formally tried on PWE.

147.4 Conclusion

Links between malnutrition and epilepsy are complex. Malnutrition, via different mechanisms, could favor seizure onset and, perhaps, epilepsy. Conversely, epilepsy has consequences on the nutritional status of PWE because of sociocultural factors, severity of epilepsy, or antiepileptic treatments. Consequently, nutritional assessment of PWE appears to be important, as well at the first examination as during the follow-up. The use of simple tools as BMI or body weight variations measurement can be adequate. A better understanding of interactions between malnutrition and epilepsy might

prevent the genesis of certain types of epilepsy, especially in developing countries, and improve control of the consequences of epilepsy on nutritional status. Indeed, nutritional interventional studies to determine the best way to limit the occurrence of epilepsy or malnutrition in PWE are lacking. In the mean time, PEM and nutrient deficiencies have to be prevented, especially during pregnancy and childhood. Antiepileptic adverse effects have also to be prevented and treated. Global programs to fight against food taboos and stigmas are necessary.

147.5 Applications to Others Areas of Health and Disease

Neurological disorders are multifactorial. In developing countries, the risk factors for these disorders are numerous and could often interact, as is the case, for example, for infectious diseases, nutrition, and epilepsy. In some African countries, acute or subacute spastic paraparesis and degenerative neuropathy are linked to cyanide intoxication of dietary origin (consumption of large amount of cassava containing cyanogens) (Osuntokun and Monekosso 1969). So the knowledge and the monitoring of nutritional status of people could help to better prevent the occurrence of disorders or to manage existing ones. Other chronic neurological disorders have nutritional consequences, as in Alzheimer's disease. Weight loss is a common problem in Alzheimer's disease and it is associated with mortality, morbidity, disease progression, and poor quality of life (Smith and Greenwood 2008). Malnutrition could also be a prognostic factor in other diseases as in amyotrophic lateral sclerosis (Desport et al. 1999). The mechanisms by which nutrition and epilepsy interact could help to understand the physiopathological mechanisms of morbidity in other diseases, leading to better comprehension and, therefore to improved global public health.

Summary Points

- Malnutrition and epilepsy are two major public health issues. About 800 million people are malnourished and 50 million people have epilepsy all around the world. Both are much more prevalent in developing countries than in developed countries. About 90% of PWE live in developing countries.
- Malnutrition and epilepsy are linked in a two-way relationship. Malnutrition can probably cause seizure and epilepsy can, in turn, lead to malnutrition.
- Malnutrition corresponds to an imbalance between dietary needs and allowance. It can be subdivided in two types: PEM and micronutrient deficiencies.
- Epilepsy is a common chronic neurological disorder characterized by recurrent unprovoked seizures (at least two unprovoked seizures spaced over 24 h).
- Protein and nutrient deficiencies are probably the two most important deficiencies implicated in the occurrence of seizure and epilepsy.
- Protein deficiency acts on epilepsy in numerous ways: decrease of seizure threshold, increase epileptic activity, affecting neurotransmission or inducing the occurrence of atrophic neurons. It can also have an indirect effect by inducing the occurrence of neurotropic infectious diseases.
- Central nervous system homeostasis is essential for brain function. Micronutrient deficiency plays a role in neuronal and epileptic activity.
- Electrolyte lab test is necessary, especially after a first seizure.
- The period between conception to first years of life is considered a sensitive period for the brain. Malnutrition during this period can be responsible for damages.

- Epilepsy occurs essentially in developing countries, where, because of sociocultural issues, it is responsible for malnutrition. Stigma and food taboos are in part responsible for it.
- Food taboos concern various types of food groups as meat/fish, mucilaginous plants, oil, sweets, and vegetables.
- Antiepileptic drugs can be responsible for malnutrition. The nutritional status of PWE on antiepileptic therapies should be monitored.
- Ketogenic diets have proved to be efficacious as treatment for epilepsy. The exact mechanisms, however, remain unknown.

Key Terms

Malnutrition: corresponds to an imbalance between dietary needs and allowance. It can be subdivided in two types: protein-energy malnutrition (PEM) and micronutrient deficiencies.

Protein-energy malnutrition: corresponds to an inadequate protein intake. It is responsible for two types of malnutrition: kwashiorkor and marasmus.

Micronutrient deficiency: concerns deficiency of one of several essential nutrients required for normal body functioning as vitamins, electrolytes, or dietary minerals.

Epilepsy: is a common chronic neurological disorder characterized by recurrent unprovoked seizures (at least two unprovoked seizures spaced over 24 h).

A seizure: consists in the transient occurrence of signs and/or symptoms due to abnormal excessive and synchronous neuronal discharge in the brain.

Drug-resistant epilepsy: corresponds to the lack of control of the disease after 2 years of treatment, despite the use of at least two antiepileptic drugs from different pharmacological profiles adapted to the epileptic syndrome in a compliant patient.

A ketogenic diet: is one of the possible treatments for epilepsy. It's used when drug-resistance is established. It consists in a very strict high lipid diet.

Stigma in epilepsy: it is a mark of shame or discredit, a stain, and an identifying mark or characteristic.

References

Agarwal KN, Bhatia BD, Batta RK, Singla PN, Shankar R. Am J Clin Nutr. 1981;34:924–7.

Andrade JP, Paula-Barbosa MM. Neurosci Lett. 1996;211:211–5.

Asadi-Pooya AA, Ghaffari A. Epilepsy Behav. 2004;5:945–8.

Asadi-Pooya AA, Hossein-Zade A. Epilepsy Behav. 2005;6:604–6.

Asadi-Pooya AA, Sperling MR. Epilepsy Behav. 2007;11:450–3.

Avoli M, Drapeau C, Louvel J, Pumain R, Olivier A, Villemure JG. Ann Neurol. 1991;30:589–96.

Ben-Ari Y. Nat Rev Neurosci. 2002;3:728–39.

Ben-Menachem E. Epilepsia 2007;48(Suppl 9):42–5.

Bernet-Bernady P, Tabo A, Druet-Cabanac M, Poumale F, Ndoma V, Lao H, Bouteille B, Dumas M, Preux PM. Med Trop (Mars). 1997;57:407–11.

Bertoli S, Cardinali S, Veggiotti P, Trentani C, Testolin G, Tagliabue A. Nutr J. 2006;5:14.

Biancheri R, Cerone R, Schiaffino MC, Caruso U, Veneselli E, Perrone MV, Rossi A, Gatti R. Neuropediatrics 2001;32:14–22.

Biton V. CNS Drugs. 2003;17:781–91.

Bushinsky DA, Monk RD. Lancet 1998;352:306–11.

Castilla-Guerra L, del Carmen Fernández-Moreno M, López-Chozas J, Fernández-Bolaños R. Epilepsia 2006;47:1990–8.

Charles M-A, Basdevant A. Obépi, enquête épidémiologique nationale sur le surpoids et l'obésité. Une enquête INSERM, TNS Healthcare SOFRES, Roche. 2006;1–54. doi: http://www.roche.fr/gear/contents/servlet/staticfilesServlet?type=data&communityId=re719001&id=static/attachedfile/re7300002/re72700003/AttachedFile_04700.pdf

Chiron C, Marchand MC, Tran A, Rey E, d'Athis P, Vincent J, Dulac O, Pons G. Lancet 2000;356:1638–42.

Crépin S, Houinato D, Nawana B, Avode GD, Preux PM, Desport JC. Epilepsia 2007;48:1926–33.

Desport JC, Preux PM, Truong TC, Vallat JM, Sautereau D, Couratier P. Neurology 1999;53:1059–63.

Elia M, Zellipour L, Stratton RJ. Clin Nutr. 2005;24:867–84.

Farrar HC, Chande VT, Fitzpatrick DF, Shema SJ. Ann Emerg Med. 1995;26:42–8.

Forbes WB, Stern WC, Tracy CA, Resnick O, Morgane PJ. Exp Neurol. 1978;62:475–81.

Georgieff MK. Am J Clin Nutr. 2007; 85: 614S–20S.

Gissel T, Poulsen CS, Vestergaard P. Expert Opin Drug Saf. 2007;6:267–78.

Greene A, Todorova M, McGowan R, Seyfried T. Epilepsia 2001;42:1371–8.

Hackett RJ, Hackett L, Bhakta P. Acta Paediatr. 1997;86:1257–60.

ILAE. Epilepsia 1993;34:592–6.

Jammoul F, Wang Q, Nabbout R, Coriat C, Duboc A, Simonutti M, Dubus E, Craft CM, Ye W, Collins SD, Dulac O, Chiron C, Sahel JA, Picaud S. Ann Neurol. 2009;65:98–107.

Johnson GH, Willis F. Med J Aust. 2003;178:467; discussion 467–8.

Keyser A, De Bruijn S. Eur Neurol. 1991;31:121–5.

Kossoff EH, Rho JM. Neurotherapeutics 2009;6:406–14.

Kretsch MJ, Sauberlich HE, Newbrun E. Am J Clin Nutr. 1991;53:1266–74.

Leaver DD, Parkinson GB, Schneider KM. Clin Exp Pharmacol Physiol. 1987;14:361–70.

Lesourd BM, Mazari L. Clin Nutr. 1997;16(Suppl 1):37–46.

Morgane PJ, Mokler DJ, Galler JR. Neurosci Biobehav Rev. 2002;26:471–83.

Nkwetngam Ndam M. Epilepsie et statut nutritionnel dans la commune de Djidja-Département du Zou au Bénin [Thèse]. Bénin, université d'Abomey-Calavi. 2004:1–74.

Nubukpo P, Preux PM, Clement JP, Houinato D, Tuillas M, Aubreton C, Radji A, Grunitzky EK, Avode G, Tapie P. Med Trop (Mars). 2003;63:143–50.

Nubukpo P, Preux PM, Houinato D, Radji A, Grunitzky EK, Avode G, Clement JP. Epilepsy Behav. 2004;5:722–7.

Nunes ML, Liptakova S, Veliskova J, Sperber EF, Moshe SL. Epilepsia 2000;41(Suppl 6):S48–52.

Osuntokun BO, Monekosso GL. Br Med J. 1969;3:178–9.

Pal DK. Neurology 1999;53:2058–63.

Palencia G, Calvillo M, Sotelo J. Epilepsia 1996;37:583–6.

Preux PM, Druet-Cabanac M. Lancet Neurol. 2005;4:21–31.

Schweizer U, Brauer AU, Kohrle J, Nitsch R, Savaskan NE. Brain Res Brain Res Rev. 2004;45:164–78.

Smith KL, Greenwood CE. J Nutr Elder. 2008;27:381–403.

Smith SR, Pozefsky T, Chhetri MK. Metabolism 1974;23:603–18.

Sobotka L. In: Sobotka L, editor. Basics in clinical nutrition. Prague: Galen; 2004. p. 288–91.

Steiger JL, Alexander MJ, Galler JR, Farb DH, Russek SJ. Neuroreport 2003;14:1731–5.

Stern WC, Forbes WB, Resnick O, Morgane PJ. Brain Res. 1974;79:375–84.

Stratton R, Green C, Elia M. Cambridge, MA: CABI; 2003. p. 824.

Sudha K, Rao AV, Rao A. Clin Chim Acta. 2001;303:19–24.

Takeda A. Brain Res Brain Res Rev. 2000;34:137–48.

Vining EP, Pyzik P, McGrogan J, Hladky H, Anand A, Kriegler S, Freeman JM. Dev Med Child Neurol. 2002;44:796–802.

Volpe SL, Schall JI, Gallagher PR, Stallings VA, Bergqvist AG. J Am Diet Assoc. 2007;107:1014–8.

Wood JH, Hare TA, Glaeser BS, Brooks BR, Ballenger JC, Post RM. Brain Research Bulletin. 1979;4:707.

Chapter 148
Cortical Spreading Depression: A Model for Studying Brain Consequences of Malnutrition

Rubem Carlos Araújo Guedes

Abbreviations

CNS	Central nervous system
CSD	Cortical spreading depression
EEG	Electroencephalogram
DC	Direct-current
GABA	Gamma-amino butyric acid
REM-sleep	Rapid-eye-movement sleep

148.1 Introduction: Malnutrition and Its Neurological Consequences

In the last decades of the twentieth century, the nutritional scenario in the world was characterized by a situation in which, due to the limited economic possibility of buying nutritionally adequate foods (which have higher costs than poor-quality foods), a large part of the human population was susceptible to the impact of inadequate feeding (Morgane et al. 1978). This situation still affects a considerable number of children, with an important influence on the morbidity and mortality indexes. In Brazil, as well in other developing countries, the poorest part of the population now experiences what has been called a rapid "nutritional transition," characterized by a simultaneous decrease of the prevalence of severe malnutrition and an increase of overnutrition (Monteiro et al. 2004). This nutritional transition has been accompanied by a diminution in the incidence of infectious and parasitic diseases and an increment of nontransmissible chronic diseases affecting homeostatic processes of the cardiovascular and renal systems, among others (Boubred et al. 2007; Ginter and Simko 2009; Popkin et al. 2001). However, the neurological impact of such conditions has not been the object of much investigation. Both the economic and social costs of that scenario are considerable, with regard to the health assistance required to be given to surviving individuals (Popkin et al. 2001). Considering the public health point of view, this situation can be characterized as a matter of great concern.

R.C.A. Guedes (✉)
Departamento de Nutrição, Universidade Federal de Pernambuco, BR-50670901, Recife, PE, Brazil
e-mail: rguedes@ufpe.br; rc.guedes@terra.com.br

The biochemical and morphological organization of the brain can be disrupted by the dietary deficiency of one or more nutrients, especially if this deficiency occurs early in life, during the so-called "brain growth spurt" period (Grantham-McGregor 1995). Nutrition-dependent alterations in brain development and organization are usually followed by deleterious repercussions on its function and these can be more or less severe, depending on the intensity and duration of the nutritional disturbances (Morgane et al. 1978). The neural analysis of sensory information and perception, as well as the efficient production and control of motor activity, are basic neural functions that can be impaired by nutritional inadequacies. Malnutrition-induced neural impairment can also affect more complex brain functions such as those involving learning, memory, consciousness, cognition, and emotion. Such disturbances can sometimes also result in permanent effects in the nervous system, with the establishment of more or less disabling diseases (Grantham-McGregor 1995). All these social- and biological-related factors illustrate the great importance of studying the effects of malnutrition on the brain. Further, experimental evidence indicates that excessive food intake too can interfere with brain development and function (Davidowa et al. 2003). The systematic investigation of this condition started to increase in the last decade. These facts have motivated a number of clinical and experimental research laboratories to study the effects of early malnutrition on the developing and adult central nervous system, resulting in a considerable amount of data. In this chapter we present experimental results on the brain electrophysiological phenomenon known as "cortical spreading depression" (CSD), and demonstrate how CSD can be used in studies comparing their features in malnourished and well-nourished rats. In addition, the CSD effects of nutritional factors are confronted with those of non-nutritional variables.

148.2 Influence of Nutrition on the Electrical Activity of the Normal Brain

The brain exerts its diverse functions basically by producing electrical signals, which constitute the so-called electrical activity of the brain. This activity can be recorded in humans and in laboratory animals by different techniques and can thus provide valuable information about brain function. For this purpose, one of the most used techniques is the electroencephalogram (EEG), which consists in recording the differences of electrical potential between one or several pairs of electrodes placed at distinct regions on the skin over the skull. As a noninvasive technique, the EEG is extensively used in human patients to help in the diagnosis of certain neurological diseases. The initial human EEG studies (in the 1940–1950s) employed trained observers, who performed a visual analysis of the EEG tracings in order to detect and define normal and pathological EEG patterns. Using this technique, Nelson and Dean (1959) have studied 46 malnourished African children and found abnormal EEG discharges in 36% of the cases, localized predominantly at the temporal region, suggesting an enhancement of the cerebral excitability as also observed in human cases of epilepsy. It must be pointed out, however, that although visual examination of the EEG can be useful for qualitative analysis, it always contains an unavoidable subjectivity. Therefore, it is very difficult to adequately analyze quantitative parameters such as frequency and amplitude of the EEG waves by visual inspection (Morgane et al. 1978). This task was later properly achieved in the 1970s by employing computation science techniques, which allowed the use of spectral analysis and fast Fourier transform algorithms to quantify EEG features (see Morgane et al. 1978). This enabled studying the ontogeny of EEG patterns both in children (Schulte and Bell 1973) and in developing laboratory animals (Gramsbergen 1976). In the malnourished rat, the main EEG disturbance was characterized by an increased power in the theta range of frequencies (Morgane et al. 1978; Cintra et al. 2002).

The hypothesis that malnourished humans would be more prone to epilepsy, as compared with well-nourished controls, is supported by some of the above EEG findings. However, studies on this

subject involving human beings are very few and are not yet enough to definitely confirm the causal relationship between malnutrition and proneness to develop epilepsy (Hackett and Iype 2001). The acceptance of this hypothesis in humans requires further extensive investigations, as are already available in laboratory animals. In rats, under conditions of early nutritional imbalance, some brain electrophysiological alterations suggest disturbances in processes related to neural excitability. This includes a lower threshold to experimentally induced seizures (Palencia et al. 1996).

The evidence indicating nutrition-related changes in neural excitability, demonstrated by electrophysiological techniques, prompted us to investigate such changes by using, as a model, the phenomenon known as CSD as a result of brain electrical activity, and this is presented in the next section.

148.3 What is "Cortical Spreading Depression" of Electrical Activity?

In 1944, a young Brazilian PhD student at Harvard University, USA, described a new electrophysiological phenomenon in the anesthetized rabbit brain. The phenomenon was denominated "spreading depression" of the cerebral cortex activity (Leão 1944). Cortical spreading depression (CSD) was then described as being a "wave-like" response, produced as a consequence of electrical, chemical, or mechanical stimulation of one point of the cortical surface. The response consisted in a reduction (depression) of the spontaneous and evoked electrical activity of the stimulated point of the cerebral cortex. From that point, CSD concentrically propagated to remote cortical regions, while the eliciting point started to recover; it is thus a propagating and reversible phenomenon, which was later shown to be accompanied by a reversible negative slow potential change (also called DC-potential change) of the EEG-depressed tissue surface (Leão 1947). This negative slow potential change reaches maximum values after 1–2 min of onset, ranging in the rat from –5 to –20 mV and being completely reverted after a few minutes (Fig. 148.1). It can be measured, with a DC-coupled amplifier, against a remote point that presents an invariant potential, as, for example, the nasal bones. An average recovery time of about 5–10 min are usually required for the depressed cortical area to completely restore the predepression EEG pattern and the baseline DC level. The CSD slow potential change has an "all-or-none" feature, which makes it very useful to calculate the CSD velocity of propagation.

Some important key features of CSD are presented in Table 148.1.

In contrast to the propagation velocity of neuronal action potential (in the order of meters per second), the velocity with which CSD propagates is considerably lower, ranging from 2 to 5 mm/min in all vertebrate species so far studied (Guedes 2005). The remarkably slow CSD propagation velocity is compatible with a humoral mechanism of propagation rather than an ion-based mechanism, as in the action potential. It is widely accepted that CSD propagation would be based on one or more chemical factors that would be released from the neural cells under CSD (Martins-Ferreira et al. 1974). These factors, once in the "extracellular milieu," would "contaminate" the neighbor cells, which would become depressed and would also release the postulated CSD factors, generating a feedback loop that would maintain the CSD propagation in an auto-regenerative mode. A complete knowledge of CSD mechanisms has not yet been achieved, despite a very extensive body of information on CSD phenomenology that has been accumulated during the 65 years elapsed from the time of the initial description of CSD.

Three relevant human diseases are currently postulated to have some relationship to CSD, in terms of sharing at least some common mechanisms: migraine (Eikermann-Haerter et al. 2009; Lehmenkühler et al. 1993), epilepsy (Fabricius et al. 2008; Gorji and Speckmann 2004; Guedes et al. 2009; Leão 1944, 1972), and brain ischemia (Dohmen et al. 2008; Pezzini et al. 2009). This deserves some comments, considering that CSD has already been demonstrated in the human brain (Dohmen et al. 2008; Fabricius et al. 2008; Gorji and Speckmann 2004).
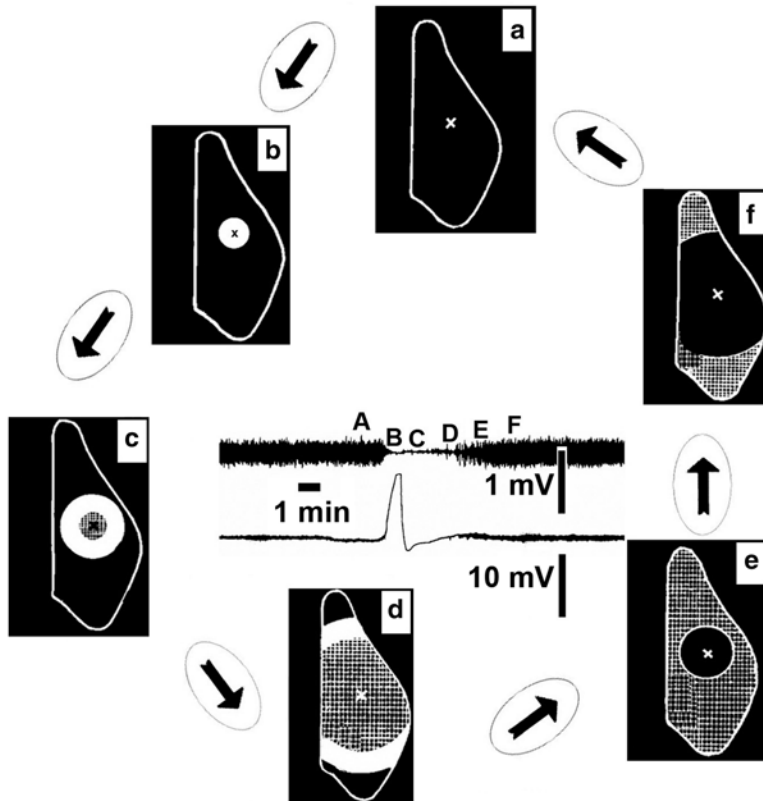
Fig. 148.1 Cycle of reversible electrophysiological events that occur during cortical spreading depression. Sequence of steps (A to F) that characterize the "cortical spreading depression cycle" in the rat cerebral cortex. In A, the normal cortical tissue is stimulated at the point marked with an "x" and one CSD episode is originated at this point. The white circle in B denotes the initially depressed area, from which CSD concentrically propagates to the entire cortex (steps C and D).The black circle in E indicates the area initially recovered after CSD. The recovery process then gradually attains remote areas (step F) and finally the entire cortex comes back to the pre-CSD condition, as in A. The square-lined area represents the post-CSD cortical *refractoriness* before full recovery. The central inset shows the electrocorticogram and the slow potential change of CSD (respectively upper and lower traces). The time-points corresponding to the conditions of the steps A to F are marked in the electrocorticogram with the respective letters]

Experimental evidence suggests that, under normal conditions, the neural tissue presents a certain degree of resistance to CSD propagation (Guedes 2005; Guedes and Do Carmo 1980). This resistance can increase or decrease as a result of experimental treatments, leading the brain to propagate CSD respectively with lower or higher velocities (Guedes 2005). In animals, the calculation of the CSD velocity of propagation along the tissue is an easy and useful way of estimating the brain's susceptibility to CSD. Therefore, animal studies under experimental conditions that either enhance or impair the brain's ability to initiate and propagate CSD may be helpful to understand both the CSD phenomenon and related diseases.

The appearance of epileptiform EEG waves during CSD at the time when spontaneous activity is depressed (Leão 1944; Guedes and Do Carmo 1980) led to the postulation of the "CSD–epilepsy link" (Leão 1944, 1972). The association between CSD and migraine has gained support from studies showing CSD-dependent brain vascular changes (Lehmenkühler et al. 1993), as well as from investigations on genetically modified animals (mouse models of familial hemiplegic migraine) showing genetic and hormonal modulation of CSD (Eikermann-Haerter et al. 2009). Data from

Table 148.1   Key features of relevant aspects of CSD

Aspect	Feature	Remarks
CNS cellular organization	Needs a minimal population of cell bodies for CSD to be generated and propagated	CSD is a "cell population", or "cooperative" phenomenon
Eliciting stimulus	Any kind of sudden energy variation (electrical, chemical, mechanical, etc.)	Eliciting stimulus does not need to be specific
Tissue condition after CSD	The depressed region recovers its electrical activity 5–10 min after depression.	It is a fully reversible phenomenon
Brain functional limits	CSD propagates equally from a sensory to a motor area and vice-versa	No evident relationship with regional functional limits
Phylogenetic aspects	Observed in all animal species so far studied, including the human species	CSD seems to be a very general phenomenon of the CNS
Velocity of propagation	In the order of a few mm/min	A paradoxically very slow propagating phenomenon (mm/min) in a tissue where action potentials propagate very fast (m/s)
Neocortical mammal structure	CSD propagates more easily in lisencephalic than in gyrencephalic brains	Cortical structural organization influences CSD propagation features.
Is CSD a physiological or a pathological phenomenon?	Some CSD features are found in certain neurological diseases	Understanding CSD mechanisms could help in understanding the mechanisms of some neurological diseases.

experimental models of brain ischemia, as well as from human ischemic patients, led also to the postulation of an important role for CSD in the physiopathology of brain ischemic disease (Dohmen et al. 2008; Pezzini et al. 2009). The following physiologic processes have been often postulated as possibly influencing CSD generation and propagation: (1) homeostasis of certain extracellular ions (Guedes and Do Carmo 1980), (2) homeostasis of free radicals produced in the nervous tissue (El-Bachá et al. 1998; Abadie-Guedes et al. 2008), and (3) neurotransmitter-dependent mechanisms (Gorelova et al. 1987; Amâncio-dos-Santos et al. 2006). These are neural processes that can be affected by nutritional and also by non-nutritional factors during brain development.

148.4 Nutritional and Non-nutritional Factors Influencing CSD Propagation

In early malnourished rats (Fig. 148.2), data from our laboratory have demonstrated a facilitation of CSD propagation, as judged by the higher CSD velocities, compared to well-nourished controls.

The maternal protein content of diet seemed to play an important role in determining the CSD effect in offspring: protein supplementation of the maternal diet abolished this effect provided the protein used in the supplementation was of high quality (casein). However, when the deficient diet was supplemented with low-quality protein (of vegetable origin), the CSD effect was not abolished (Andrade et al. 1990).

Considering that within the brain growth spurt period, the maximal intensity of various developmental processes (as, for example, neurogenesis, myelination, and gliogenesis) occurs at distinct time-points in different brain areas, we investigated if short episodes of maternal malnutrition, acting
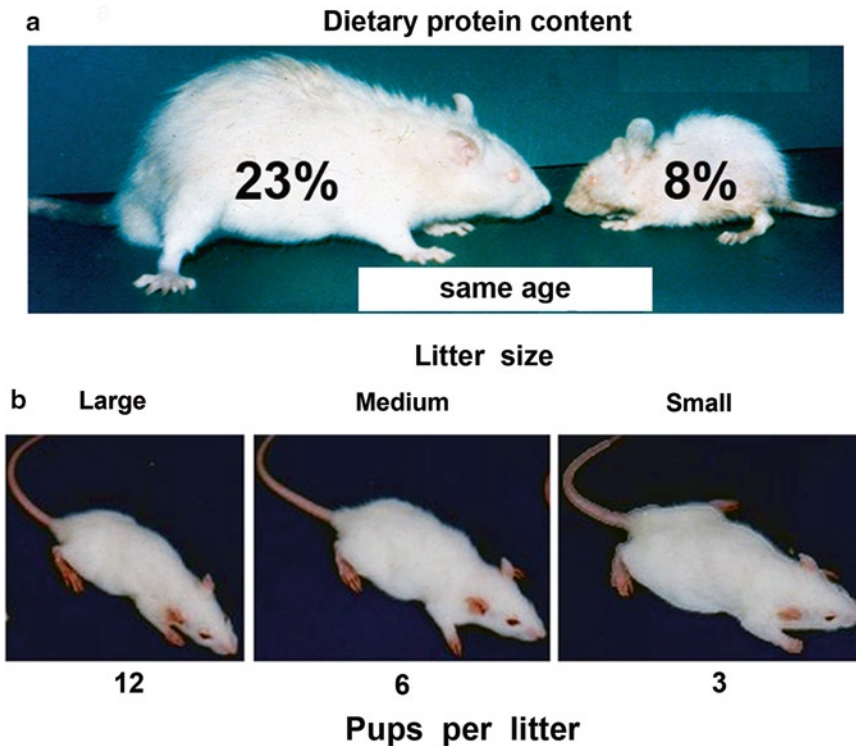
Fig. 148.2 Impact of malnutrition and "overnutrition" on body dimensions. Photographs illustrating the physical aspect of malnourished, normally nourished (control) and "overnourished" rats. In part A, (adult animals) a case of severe malnutrition is confronted with a control rat. In this case, severe malnutrition was provoked by feeding a low-protein diet (containing 8% of protein, instead of the 23% of the control diet) during the whole life. The three young animals in part B (30 days-old) were suckled in litters of different sizes, classified as large, medium, and small-size litters, containing respectively 12, 6, and 3 pups. These three lactation conditions originate pups with moderate-malnutrition (*left*), normal nutrition (*middle*), and with moderate-overnutrition (*right*), respectively. The three pictures of part B were taken under the same magnification. Note the changes in the head size, which indicates alteration in brain size]

at a certain time point within the lactation period, could affect CSD in the progeny. We demonstrated that even a 7-day period of maternal malnutrition within the lactation period was sufficient to significantly enhance CSD propagation in offspring. This effect was shown to be long-lasting, since it was still detected when the pups became adults (Rocha-de-Melo and Guedes 1997). Moreover, the effect was more conspicuous when malnutrition was induced at the late phase of lactation – the third suckling-week, as compared to the groups malnourished in the two earlier weeks (Fig. 148.3), suggesting that with regard to the nutritional effects on CSD propagation, the brain developmental events occurring in this late phase of lactation would have a greater importance.

The mechanism by which early malnutrition results in enhanced CSD incidence and propagation still deserves detailed clarification. In the rat, malnutrition has been shown to reduce brain glutamate uptake (Feoli et al. 2006) and to increase the enzyme glutamic acid decarboxylase (Diaz-Cintra et al. 2007). Both conditions might in all probability increase the brain extracellular glutamate, which would facilitate CSD propagation (Peeters et al. 2007; Tottene et al. 2009).

Three malnutrition-induced brain alterations, however, have been considered as probably involved in the CSD effects found in malnourished animals: (1) reduction in the brain myelin content, (2) impairment of glial function, and (3) increase in the cell packing density with reduction of the
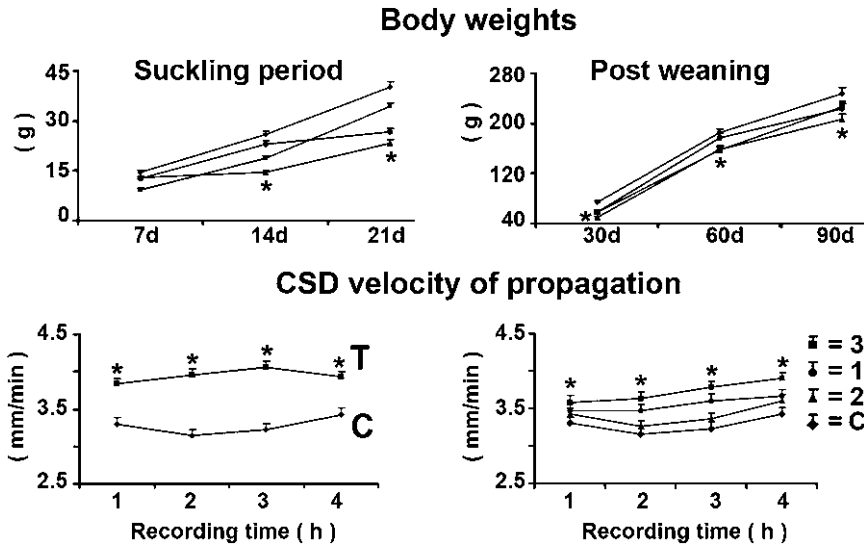
Fig. 148.3 Effect of short episodes of early malnutrition on body weight and CSD propagation. Mean ± SEM of body weights (two *upper panels*) and CSD velocities (*lower panel*) of rats suckled by dams fed a low-protein diet (with 8% protein) for a small period (7 days), during the first (*ball-symbol*; $n = 13$), second (*triangle-symbol*; $n = 17$), or third (*square-symbol*; $n = 15$) week of lactation. The control group (C; *diamond-symbol*; $n = 19$) received a standard chow-diet with 23% protein. In the lower-left panel, the T group ($n = 17$) was malnourished during the total lactation period (3 weeks). Note in the lower-right panel the greatest increase in CSD velocity in the group malnourished during the third week of lactation]

extracellular space. Brain myelin has been considered as an obstacle to the humoral propagation of CSD; thus, the less myelin in the brain, the fewer obstacles to CSD propagation (De Luca et al. 1977). Glial impairment has also been demonstrated to facilitate CSD (Largo et al. 1997). Finally, compared with the well-nourished condition, the early-malnourished brain has reduced size and mass, with smaller cells packed in a denser manner and with a reduced extracellular space volume. Since a larger extracellular space volume in the brain hinders CSD elicitation and propagation (Lehmenkühler et al. 1993; Richter et al. 2003), the higher cell packing density and the smaller extracellular space volume, found in the malnourished brain, is thought to favor CSD propagation.

In contrast to malnutrition, the influence of early overnutrition on brain development and function had been almost not investigated at that time (Davidowa et al. 2003), and only a single short report was available concerning the effects of overnutrition on CSD (De Luca et al. 1977). To address this issue, we then used a simple and interesting method to positively influence the nutritional status of the pups during the lactation period. This method consists in diminishing the litter-size (i.e., reducing the number of pups to be suckled by a single dam), and inducing in the newborns a moderate degree of overnutrition (Davidowa et al. 2003). Considering that early malnutrition had facilitated CSD (Rocha-de-Melo and Guedes 1997), we hypothesized that the brain developmental influence of the favorable lactation condition (pups reared in small litters, with only three pups) on the CSD would be to impair CSD propagation, as compared to the control-size litter (six pups). By the same logic, the prediction was made that rat-pups suckled in litters much larger than the controls (litters with 12 pups instead of 6 as in the control) would display higher CSD propagation velocities, as this suckling condition induces a moderate degree of malnutrition; this has indeed been demonstrated (Rocha-de-Melo et al. 2006), and is here illustrated in Fig. 148.4.
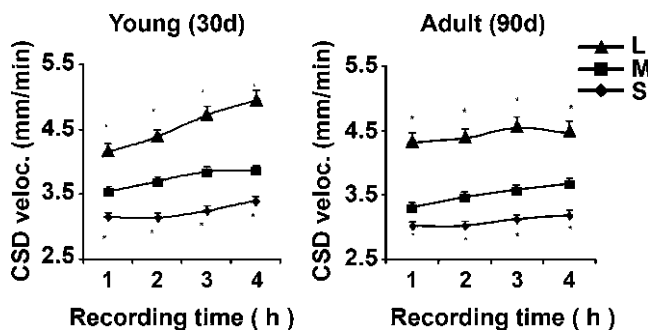
Fig. 148.4 CSD effect of suckling rat-pups in litters of different sizes. Mean ± SEM CSD velocities of propagation in the cortical surface of young (30 days old; *left panel*; $n = 54$) and adult rats (90 days old; *right panel*; $n = 48$) that have been reared, during the suckling period, in large (L; $n = 21$ and 13 rats for the 30-day and 90-day old groups, respectively), medium (M; $n = 18$ and 17 rats) and small litters (S; $n = 15$ and 18 rats). The L, M, and S litters were composed respectively by 12, 6, and 3 pups. The asterisks indicate that the extreme groups (L and S) display CSD velocities of propagation significantly different from the age-matched control (M) group

Another interesting set of results came from testing how certain molecules of metabolic importance for the brain, like glucose, or pharmacological compounds with unequivocal effectiveness in influencing brain function, like the GABAergic compound diazepam, could influence CSD propagation, and how malnutrition would interfere with this possible effect. Data indicated that hyperglycemia reduces whereas diazepam and insulin-induced hypoglycemia facilitates CSD propagation. However, those effects were not found in rats that were previously malnourished (Guedes et al. 1992; Ximenes-da-Silva and Guedes 1991). In contrast, two other drugs that have an impairing action on CSD, the selective serotonin reuptake inhibitor fluoxetine and the cholinergic agonist pilocarpine produced in the malnourished brain respectively a more intense (Vasconcelos et al. 2004) and an equal (Amâncio-dos-Santos et al. 2006) CSD effect as compared to the well-nourished brain. Taken together, these experimental data suggest that malnutrition-induced changes in the brain responsiveness to pharmacological agents may vary depending on the neurotransmitter system under investigation. Concerning CSD, it appears for instance that, in contrast to the serotoninergic system, the responsiveness of the GABAergic and cholinergic systems were respectively decreased and increased by the nutritional deficiency imposed early in life on the malnourished rats. This raises some concerns, regarding the human use of therapeutical drugs acting specifically on a certain neurotransmitter system: if the above-described experimental observations were also to reflect what happens in the human brain, then this would imply that different classes of therapeutically employed drugs (as, for example, anti-epileptics and anti-migraine drugs) could present distinct degrees of effectiveness, eventually depending on the early nutritional condition of the patients. The medical implication would be a strong recommendation for the clinical investigation of this possibility in the human being.

Besides nutritional and the pharmacological variables, other clinically important hormonal and environmental factors have also been studied in several laboratories including ours regarding their significant influence on the brain's ability to generate and propagate CSD. Some of these factors were found to enhance CSD propagation, whereas some others impaired it. Conditions such as extracellular ionic alterations (Guedes and Do Carmo 1980), deprivation of REM sleep (Guedes and Vasconcelos 2008; Vasconcelos et al. 2004), ethanol consumption (Bezerra et al. 2005; Abadie-Guedes et al. 2008), treatment with gliotoxic drugs (Largo et al. 1997), genetic "knockin" manipulation in mice (insertion of the human hemiplegic familiar migraine gene; Eikermann-Haerter et al. 2009), and toxic and autoimmune induced cortical demyelination (Merkler et al. 2009) are some of the studied situations which enhance the CSD phenomenon. A summary of the studied conditions that enhance CSD is presented in Table 148.2.

Table 148.2 Experimental studies under some clinically important conditions that enhance CSD propagation. Pertinent bibliography is also provided

Conditions That Facilitate CSD

Animal	Reference	Condition	Effect
Rabbit	Guedes and Do Carmo (1980)	Low extracellular chloride (by gastric washing with distilled water)	Increased CSD propagation and EEG epileptiform activity; appearance of a second SD in the opposite hemisphere
Rat	Rocha-de-Melo et al. (2006)	Malnutrition early in life	CSD velocities higher than in well-nourished controls
Rat	Guedes and Vasconcelos (2008)	Deprivation of REM sleep (water-tank technique)	Increased CSD velocities, as compared with nondeprived or pseudodeprived controls.
Rat	Costa-Cruz and Guedes (2001)	Hypoglycemia [by (1) insulin or (2) food restriction + insulin]	CSD velocities higher than in normoglycemic rats
Rat	Guedes et al. (1992)	Increase of the GABAergic activity by diazepam	Higher CSD velocities after diazepam as compared with predrug values
Rat	Bezerra et al. (2005)	Administration of ethanol per gavage	Ethanol facilitated CSD as compared to water-treated or naïve controls.
Rat	El-Bachá et al. (1998)	Dietary deprivation of antioxidant vitamins	Higher CSD velocities; increased CSD-eliciting action of photoactivated riboflavin
Rat	Maia et al (2009)	Early in life treatment with l-arginine, per gavage	L-Arginine facilitates CSD as compared to water-treated or naïve controls.
Rat	Farias-Santos et al. (2009)	Daily sessions of heat exposure early in life	Increase in CSD propagation as compared to controls
Rat	Largo et al. (1997)	Treatment with the gliotoxic drug fluorocitrate	Glial impairment increased CSD propagation
Rat	Fregni et al. (2005)	1 and 20 Hz cortical electrical stimulation, 2x/d, for 2 days	Increase of CSD propagation measured 1 and 15 days after electrical stimulation.
Mouse	Eikermann-Haerter et al. (2009)	Genetic ("knockin") manipulation inserting the hemiplegic familiar migraine gene	Increased SD frequency and propagation speed; enhanced corticostriatal propagation
Mouse	Merkler et al. (2009)	Hypomyelination by dietary treatment with cuprizone	Accelerated CSD propagation, reverted after switching mice to the normal diet
Rat	Tenorio et al. (2009)	Unilateral early vibrissae removal	Facilitation of CSD propagation in well-nourished and malnourished rats.

CSD impairment has also been found in animals submitted to propylthiouracil-induced hypothyroidism (Guedes and Pereira-da-Silva 1993), aging (Guedes et al. 1996), peripheral electrical (Monte-Silva et al. 2007) or environmental stimulation (Santos-Monteiro et al. 2000), antioxidants (Bezerra et al. 2005; Abadie-Guedes et al. 2008), hypermyelination, (Merkler et al. 2009), and genetical proneness to audiogenic epilepsy (Guedes et al. 2009), among other conditions (Table 148.3).

148.5 Applications to Other Areas of Health and Disease

As an "excitable tissue," one of the main physiological properties of the nervous system is that it is capable of generating electrical activity and, through this activity, to execute its normal actions, including the highly complex ones. This is the main reason for using electrophysiologically based

Table 148.3 Conditions of clinical relevance, which have been shown to impair CSD propagation. For detailed information, bibliographic reference is provided

Conditions That Antagonize CSD			
Animal	Reference	Condition	Effect
Rat	Guedes et al. (1989)	Dietary treatment with lithium	Lower CSD velocities compared with controls
Rat	Costa-Cruz and Guedes (2001); Costa-Cruz et al., (2006)	Hyperglycemia (acute and chronic)	Lower CSD velocities compared with controls
Rat	Guedes and Barreto (1992)	Anesthetics	Lower CSD velocities under anesthesia, compared to waking state in the same rat.
Rat	Guedes and Pereira-da-Silva (1993)	Early hypothyroidism (by PTU)	Reduced CSD velocities in PTU-treated rats, compared with saline-treated controls
Gerbil and Rat	Guedes et al. (1996)	Aging	Inverse correlation between age and CSD velocity that is reduced by dietary antioxidant vitamin deficiency
Rat	Santos-Monteiro et al. (2000);Monte-Silva et al (2007)	Early peripheral electrical or environmental stimulation	Reduced CSD velocities compared with nonstimulated controls
Gerbil and Rat	Guedes et al. (1987)	Treatment with the opioid antagonist naloxone	Naloxone antagonizes CSD incidence and propagation
Rat	Guedes et al. (1988)	Topical cortical application of excitatory amino acid antagonists	MK-801 antagonizes CSD propagation.
Rat	Guedes et al. (2002); Amâncio-dos-Santos et al. (2006)	Pharmacological increase of brain serotonin activity	D-Fenfluramine, citalopram, and fluoxetine antagonize CSD propagation
Rat	Guedes and Cavalheiro (1997); Guedes and Vasconcelos (2008)	Single injection of convulsing and subconvulsing dose of pilocarpine	Dose-dependent blocking of CSD propagation.
Rat	Bezerra et al. (2005); Abadie-Guedes et al. (2008)	Treatment with antioxidants, per gavage	Both shrimp carotenoids and pure astaxanthin reduce CSD propagation in ethanol-treated rats.
Mouse	Merkler et al. (2009)	Hypermyelination (transgenic mice)	Lower CSD velocities in the hypermyelinated mice, compared to the wildtype controls
Rat	Guedes et al. (2009)	Genetically prone to audiogenic epilepsy	Gender-dependent impairment of CSD

animal models such as the present one that utilizes the CSD phenomenon in order to get information on normal brain function. These models could also help us to understand how the brain's physiology is altered under nutritional and non-nutritional conditions like those discussed here. In this chapter, we have presented CSD electrophysiological data from both laboratory animals and humans, documenting the importance and usefulness of this phenomenon in studying the nervous system. In the rat, brain structural and functional maturation is programmed to occur mostly during the lactation period. The malnutrition-induced brain alterations during this period probably resulted from the decreased number and/or size of cell elements, as well as from alterations in the events that cause neuronal maturation. Processes such as cell migration, dendrite development, synapse formation, and

myelination are certainly implicated in the neurophysiological alterations found when malnutrition occurs early in life (Morgane et al. 1978). This period of intense formation of synapses can be considered equivalent to the human synaptogenic stage, which starts at the third trimester of prenatal development and continues during the first year of child life (Morgane et al. 1978). The well-grounded extrapolation of data from one species (rat) to the other (humans) is a task that, despite some attempts, still needs to be further achieved and the increasing use of the here-described models and techniques is strongly desirable, as a supporting means to clarify the relationship between diet, nutrition, and neural development and function.

In the current world scenario of nutritional transition, experienced by a considerable part of the human population, it can be concluded that the electrophysiological analysis of CSD features constitutes a valuable experimental instrument to investigate the functional brain effects of different unfavorable nutritional as well as non-nutritional conditions that are often stressing and energy-demanding for the developing brain.

Since all the factors presented above in the Tables 148.2 and 148.3 are of clinical relevance, and also considering that they are known to affect the mammalian brain development and function, it is reasonable to assume that knowing the mechanisms by which they affect CSD propagation may shed light on the role of such factors in important human diseases, such as ischemia, migraine, and epilepsy. Furthermore, the complete understanding of CSD generation and propagation mechanisms might be very helpful in developing better treatment of those human neurological diseases.

Summary Points

- The malnourished organism suffers developmental and physiological alterations consequent to insufficient food intake during a certain period of its life. Depending on the intensity and duration of malnutrition, the physiological alterations can become permanent, usually with *neurological disturbances* involving sensory-motor activity, learning, memory, consciousness, cognition and emotion.
- Some data suggest that *malnourished humans would have higher propensity to epilepsy*, as compared with well-nourished controls, but further studies are needed to definitely confirm the causal relationship between malnutrition and proneness to develop the epileptic phenomenon.
- Animal studies under conditions that either enhance or impair the brain ability to initiate and propagate "Cortical Spreading Depression" (CSD) are helpful to understand both the CSD phenomenon and the human neurological diseases related to them, such as brain ischemia, migraine, and epilepsy.
- Besides malnutrition, *excessive food intake* early in life also affects the brain's ability to produce and propagate cortical spreading depression. This raises some concerns about the *impact of obesity on brain development and function*.
- If the findings in laboratory animals reflect what happens in the human brain, then this would imply that different classes of therapeutically employed drugs (as, for example, anti-epileptics and anti-migraine drugs) could present distinct degrees of effectiveness depending on the early nutritional condition of the patients.

Definitions and Explanations of Key Terms

Nutritional transition: It is the expression used to define the current epidemiological situation of a great part of the human population, mainly in developing countries. This epidemiological situation comprises an increasing human contingent with obesity, associated to a decreasing number of malnourished persons *in the same population.*

Electroencephalogram (EEG): It is the recording of the spontaneous brain electrical activity that all living mammals present, even when they sleep. This activity can be electronically recorded in chart-paper, ink-writer machines, or digitally in computer-based devices.

Epilepsy: It is a neurological disease resulting from an exacerbated and uncontrolled activity of a certain neuronal population in the brain. The main clinical signs of a generalized epileptic seizure are loss of consciousness and exacerbated and uncontrolled muscle contractions (motor seizure).

Cortical spreading depression (CSD): It is a reversible brain phenomenon provoked by an adequate stimulation of a point of the brain tissue. Current knowledge of the phenomenon leads to the postulation of a link between CSD and human neurological diseases like epilepsy, migraine, and brain ischemia.

Fast Fourier Transform: It is a mathematical technique that employs an algorithm to decompose a sequence of values into components of different frequencies. It is used to decompose the "spectrum of EEG-waves" into its distinct component frequencies, enabling the detection of nutrition-related alterations in one or more of such frequencies.

Extracellular milieu: It is the environment outside the cells. This environment is occupied by the extracellular fluid, the composition of which includes metabolites, ions, proteins, and many other substances that might affect cellular function. These substances are provided by the foods that we daily eat.

GABAergic compound: It is a substance that favors, promotes, or facilitates action, in the neurons or glial cells, of the neurotransmitter gamma-amino butyric acid (GABA). This neurotransmitter is believed to be inhibitory in the mammalian central nervous system.

Knockin mouse: It is a genetically modified animal, in the genome of which a gene has been inserted. The animal then expresses the characteristics coded by that gene (for example, a certain disease). The opposite genetic manipulation (deletion of a gene) originates the "knockout" mouse.

References

Abadie-Guedes R, Santos SD, Cahú TB, Guedes RCA, Bezerra RS. Alcohol Clin Exp Res. 2008;32:1417–21.

Amâncio-dos-Santos A, Pinheiro PCF, Lima DSC, Ozias MG, Oliveira MB, Guimarães NX, Guedes RCA. Exp Neurol. 2006;200:275–82.

Andrade AFD, Guedes RCA, Teodósio NR. Braz J Med Biol Res. 1990;23:889–93.

Bezerra RS, Abadie-Guedes R, Melo FRM, Paiva AMA, Amâncio-dos-Santos A, Guedes RCA. Neurosci Lett. 2005;391:51–5.

Boubred F, Buffat C, Feuerstein JM, Daniel L, Tsimaratos M, Oliver C, Lelièvre-Pégorier M, Simeoni U. Am J Physiol Renal Physiol. 2007;293:F1944–9.

Cintra L, Durán P, Angel-Guevara M, Aguilar A, Castañón-Cervantes O. Nutr Neurosci. 2002;5:91–101.

Costa-Cruz RRG, Guedes RCA. Neurosci Lett. 2001;303:177–80.

Davidowa H, Li Y, Plagemann A. Eur J Neurosci. 2003;18:613–21.

De Luca B, Cioffi LA, Bures J. Activ Nerv Sup. 1977;19:130–1.

Díaz-Cintra S, González-Maciel A, Morales MA, Aguilar A, Cintra L, Prado-Alcalá RA. Exp Neurol. 2007;208:47–53.

Dohmen C, Sakowitz OW, Fabricius M, Bosche B, Reithmeier T, Ernestus RI, Brinker G, Dreier JP, Woitzik J, Strong AJ, Graf R. Ann Neurol. 2008;63:720–8.

Eikermann-Haerter K, Dileköz E, Kudo C, Savitz SI, Waeber C, Baum MJ, Ferrari MD, van den Maagdenberg AM, Moskowitz MA, Ayata C. J Clin Invest. 2009;119:99–109.

El-Bachá RS, Lima-Filho JL, Guedes RCA. Nutr Neurosci. 1998;1:205–12.

Fabricius M, Fuhr S, Willumsen L, Dreier JP, Bhatia R, Boutelle MG, Hartings JA, Bullock R, Strong AJ, Lauritzen M. Clin Neurophysiol. 2008;119:1973–84.

Farias-Santos RC, Lira MCA, Pereira DES et al. Neurosci Lett. 2009;454:218–22.

Feoli AM, Siqueira I, Almeida LM, Tramontina AC, Battu C, Wofchuk ST, Gottfried C, Perry ML, Gonçalves CA. J Nutr. 2006;136:2357–61.

Fregni, F, Monte-Silva, KK, Oliveira, MB et al. Eur J Neurosci. 2005;21:2278–84.

Ginter E, Simko V. Bratisl Med J. 2009;109:224–30.

Gorelova NA, Koroleva VI, Amemori T, Pavlík V, Bur s J. Electroencephalogr Clin Neurophysiol. 1987;66:440–7.

Gorji A, Speckmann EJ. Eur J Neurosci. 2004;19:3371–4.

Gramsbergen A. Brain Res. 1976;105:287–308.

Grantham-McGregor S. J Nutr. 1995;125:2233S–8S.

Guedes RCA, Amorim LF, Medeiros MC et al. Braz J Med Biol Res. 1989;22:923–5.

Guedes RCA, Azeredo FAM, Hicks TP et al. Exp Brain Res. 1987;69:113–8.

Guedes RCA, Andrade AFD, Cavalheiro EA et al. In: Cavalheiro EA, Lehman J, Turski L, editors. Frontiers in excit-atory amino acid research. New York: Alan R. Liss. Inc.; 1988. p.667–670.

Guedes RCA, Barreto, Braz J Med Biol Res. 1992;25:393–7.

Guedes RCA, Cavalheiro, Epil Res. 1997;27:33–40.

Guedes RCA, Amancio-dos-Santos A, Manhães-de-Castro R et al. Nutr Neurosci. 2002;5:115–23.

Guedes RCA. In: Liebermann H, Kanarek R, Prasad C, editors. Nutritional neurosciences: overview of an emerging field. New York: CRC Press, 2005. p. 39–54.

Guedes RCA, Cabral-Filho JE, Teodósio NR. In: Do Carmo RJ, editor. Spreading depression. Berlin: Springer; 1992. p. 17–26.

Guedes RCA, Amorim LF, Teodósio NR. Braz J Med Biol Res. 1996;29:1407–12.

Guedes RCA, Do Carmo RJ. Exp Brain Res. 1980;39:341–9.

Guedes RCA, Oliveira JAC, Amâncio-dos-Santos A, García-Cairasco N. Epilep Res. 2009;83:207–14.

Guedes RCA, Pereira-da-Silva MS. Braz J Med Biol Res. 1993;26:1123–8.

Guedes RCA, Vasconcelos CAC. Neurosci Lett. 2008;442:118–22.

Hackett R, Iype T. Seizure. 2001;10:554–8.

Largo C, Ibarz JM, Herreras O. J Neurophysiol. 1997;78:295–307.

Leão AAP. J Neurophysiol. 1944;7:359–90.

Leão AAP. J Neurophysiol. 1947;10:409–14.

Leão, AAP. In: Purpura DP, Penry K, Tower DB, Woodbury DM, Walter RD, editors. Experimental models of epi-lepsy. New York: Raven Press; 1972. p. 173–195.

Lehmenkühler A, Grotemeyer KH, Tegtmeier F. Migraine: basic mechanisms and treatment. Munich: Urban and Schwarzenberg; 1993.

Maia LMSS, Amancio-dos-Santos A, Duda-de-Oliveira D et al. Nutr Neurosci. 2009;12:73–80.

Martins-Ferreira H, Oliveira Castro G, Stuchiner CJ, Rodrigues PS. J Neurophysiol. 1974;37:785–91.

Merkler D, Klinker F, Jürgens T, Glaser R, Paulus W, Brinkmann BG, Sereda M, Guedes RCA, Brück W, Liebetanz D. Ann Neurol. 2009;66:355–65.

Monte-Silva KK, Assis FLN, Leal GMA, Guedes RCA. Nutr Neurosci. 2007;10:187–194.

Monteiro CA, Conde WL, Popkin BM. Am J Public Health. 2004;94:433–4.

Morgane PJ, Miller M, Kemper T, Stern W, Forbes W, Hall R, Bronzino J, Kissane J, Hawrylewicz E, Resnick O. Neurosci Biobehav Rev. 1978;2:137–230.

Nelson GK, Dean RF. Bull World Health Org. 1959;21:779–82.

Palencia G, Calvillo M, Sotelo J. Epilepsia. 1996;37:583–6.

Peeters M, Gunthorpe MJ, Strijbos PJ, Goldsmith P, Upton N, James MF. J Pharmacol Exp Ther. 2007;321:564–72.

Pezzini A, Del Zotto E, Giossi A, Volonghi I, Grassi M, Padovani A. Curr Mol Med. 2009;9:215–26.

Popkin BM, Horton S, Kim S, Mahal A, Shuigao J. Nutr Rev. 2001;59:379–90.

Richter F, Rupprecht S, Lehmenkühler A, Schaible HG. J Neurophysiol. 2003;90:2163–70.

Rocha-de-Melo AP, Guedes RCA. Braz J Med Biol Res. 1997;30:663–70.

Rocha-de-Melo AP, Cavalcanti JB, Barros AS, Guedes RCA. Nutr Neurosci. 2006;9:155–60.

Santos-Monteiro JS, Teodósio NRT, Guedes RCA. Nutr Neurosci. 2000;3 (1):29–40.

Schulte FJ, Bell EF. Neuropäd. 1973;4:30–45.

Tenorio AS, Oliveira IDVA, Guedes RCA et al. Int J Dev Neurosci. 2009;27:431–7.

Tottene A, Conti R, Fabbro A, Vecchia D, Shapovalova M, Santello M, van den Maagdenberg AM, Ferrari MD, Pietrobon D. Neuron. 2009;61:762–73.

Vasconcelos CAC, Oliveira JAF, Costa LAO, Guedes RCA. Nutr Neurosci. 2004;7:163–70.

Ximenes-da-Silva A, Guedes RCA. Braz J Med Biol Res. 1991;24:1277–81.

Chapter 149
Dietary Zinc and the Brain

Mohammad Tariqur Rahman

Abbreviations

AD	Alzheimer's disease
AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid
ATP/ADP	Adenosine tri/di phosphate
BBB	Blood brain barrier
CSF	Cerebrospinal fluid
CNS	Central nervous system
ECF	Extracellular fluid
ER	Endoplasmic reticulum
MAPK	Mitogen activated protein kinase
MT	Metallothionein
RDA	Recommended daily allowance
UIL	Upper intake level
VGCC	Voltage-gated Ca^{2+} channels
(S)VZ	(Sub)Ventricular zone
ZIP	Zn^{2+} importing proteins
[Zn]	Concentration of Zn
ZnT	Zn transporter

149.1 Introduction

The physiological importance of zinc (Zn) was first recognized in 1940 when the Zn-containing enzyme, carbonic anhydrase, was described (Keilin and Mann 1940). Eventually, Zn was recognized as an 'essential' trace element found widely distributed in all human organs and tissues and required for the structure and functions of many cellular proteins (Table 149.1). Today, the importance of Zn in human health is well documented (Frederickson et al. 2005; Maret and Sandstead 2008). In the brain, Zn plays important roles both in its development and function.

M.T. Rahman (✉)
Department of Biomedical Science, Kulliyyah of Science, International Islamic
University Malaysia (IIUM), Jalan Istana, Bandar Indera Mahkota, 25200 Kuantan, Malaysia
e-mail: tarique@iiu.edu.my; m.tariqur.rahman@gmail.com

Table 149.1 Key facts on zinc

Chemistry and physical properties

- Discovery: German chemist Andreas Sigismund Marggraf (1746) is normally given credit for discovering pure metallic Zn.
- Avaialability: the 24th most abundant element on the Earth's crust
- Empirical formula: Zn
- Position in the periodic table: 1st element in group 12
- Number of stable isotopes: five
- Atomic number: 30
- Atomic weight: 65.39 g

Uses

- Zinc plating for corrosion-resistance (e.g. on steel).
- Zinc alloys such as brass (alloy of zinc and copper) is used in batteries.
- Zinc chloride in deodorants
- Zinc pyrithione in shampoos
- Zinc sulfide in luminescent paints
- Zinc-carbonate, Zn-gluconate as dietary supplements

Biological importance

- Considered an essential mineral
- Structural component of many enzymes such as alcohol dehydrogenase in humans or other biomolecules important in cellular and molecular processes such as Zn finger transcription factors.
- Half of the total body's Zn is present in muscle. Other major organs of the body that contain zn includes bones, skin, kidneys, testes, and prostate glands
- Zinc deficiency causes growth retardation, delayed sexual maturation, infection susceptibility, and diarrhea, etc.
- Zinc excess is associated with ataxia, lethargy, and copper and iron deficiency.

This table includes the key facts on Zn including its chemical properties, uses, and biological importance

Zinc metalloproteins are the major (~80%) reservoir of the total brain Zn while the rest is free Zn^{2+} and are histochemically detectable by Timm's sulfide-silver staining method (Frederickson and Danscher 1990). In the brain, Zn is relatively concentrated in the hippocampus and amygdala (Takeda et al. 2004). Both regions are enriched with histochemically reactive Zn^{2+} which predominantly exists in the presynaptic vesicles. Zinc homeostasis in the brain is maintained by the blood brain barrier system and is not easily disrupted by dietary Zn deficiency. Nevertheless, histochemically detectable Zn in hippocampus are susceptible to dietary Zn deficiency.

Most of the cells in the human body including neuron maintain Zn homeostasis through the regulated expression of proteins for Zn- import, export, and sequestration. Specific Zn transporters are used in certain tissues and their expression may vary with dietary Zn status and time (Dufner-Beattie et al. 2003; Kelleher and Lonnerdal 2003). Thus Zn homeostatic mechanisms appear to be tissue specific.The mechanism of exact regulation of Zn uptake from extracellular fluids (ECF) into neurons and glial cells, however, is not completely known.

Large numbers of the world's population, an estimated total of about 50%, are at risk of Zn deficiency (Brown et al. 2001). Zinc deficiency in children is a nutritional and health concern in both developing and developed countries (Black 1998; Bryan et al. 2004). Zinc deficiency results in decrease in extracellular [Zn] in the hippocampus which subsequently causes abnormal glucocorticoid secretion from the adrenal cortex. As the hippocampus is enriched with glucocorticoid receptors, the abnormal glucocorticoid secretion alters its function. Abnormal glucocorticoid secretion in Zn deficiency is associated with neuropsychological symptoms affecting cognitive performance and aggravated glutamate excitotoxicity. The decrease in Zn^{2+} pool in the peripheral tissue in Zn deficiency can also change glucocorticoid action by triggering abnormal glucocorticoid secretion.

   Alterations in Zn homeostasis in the brain is observed in Parkinson's and Alzheimer's disease (AD) as well as in transient forebrain ischemia, seizures, and traumatic brain injury. There is much evidence to show that amyloid-beta deposition in AD is induced by Zn (see review Mocchegiani et al. 2005). An elevated concentration of Zn or an excess of Zn in the brain might play a role in such pathological conditions. Indeed the exact neuropathological mechanism of either the elevated level of Zn^{2+} or its deficiency has not been completely resolved (Colvin et al. 2003; Sensi et al. 2009).

   This chapter will elaborate on the physiological importance of dietary Zn in the brain. Emphasis will be given to the mechanism of Zn homeostasis, the role of dietary Zn in brain development, and the consequences of Zn excess and/or Zn deficiency in brain pathology.

149.2 Dietary Sources of Zn and Its Bioavailability

The richest food sources of Zn (Table 149.2) are sea foods (shellfish, shrimp, lobster, crab-meat), organs and flesh of mammals and fowls (liver, meat), whole grain cereals, and some beans (Brown and Begin 1993). The total Zn content of the diet and its bioavailability, solubility in particular, in the intestinal lumen determines the amount of Zn absorbed and which can be utilized or metabolized in different organs. This also is influenced by the chemical form of Zn and the presence or absence of specific enhancers or inhibitors of Zn absorption. Amino acids such as cysteine and histidine can increase the solubility of Zn. However, some proteins such as casein have an inhibitory effect on Zn absorption. Myoinositol hexaphosphate (phytate) reduces Zn bioavailability (Soto-Quintana et al. 2003), and therefore oils, fats, and sugar are not considered good sources of Zn. Meal proteins have a positive effect on Zn absorption. In humans without excessive intake of Zn, the body burden half-time of absorbed Zn has been observed in the range between 162–500 days. After parenteral administration, half-times of Zn may vary within the range of about 100–500 days (see review Lowe et al. 2009). In spite of its great importance in human health, the amount of zinc in the diet, however, needs to be maintained properly (Table 149.3).

149.3 Blood Brain Barrier and Permeability of Zn in Brain

Both the supply of the required nutrients for proper functioning of the brain and the control of harmful substances present in the bloodstream so as to prevent them from entering the brain are done by the specialized system of capillary endothelial cells of the blood brain barrier (BBB). The transport

Table 149.2 Zinc in human diet (From Brown and Begin 1993)

Category of foods	Example of edibles
Major dietary source of Zn	
Sea foods	flesh of shellfish, shrimp, lobster, crab
Organs and flesh of mammals and fowls	liver, meat, or muscle
Whole grain cereals, vegetables	chickpeas, kidney beans, almonds
Dairy products	yogurt, milk, cheese
Inhibitors of Zn absorption	Casein
Protein	Plant oil
Oils or fats	Sugar
Carbohydrate	

Zinc is available in various food and food products. This table includes a partial list of the dietary sources of Zn. The amount of Zn, however, may vary depending on type and species

Table 149.3 Recommended daily allowance (RDA) and upper intake levels (UIL) for human Zn consumption (From Institute of Medicine, Food and Nutrition Board. Washington, DC: National Academy Press, 2001)

Age	For male RDA/UIL	For female RDA/UIL	In pregnancy RDA/UIL	During lactation RDA/UIL
0–6 months	2 mg/4 mg	2 mg/4 mg		
7–12 months	3 mg/5 mg	3 mg/5 mg		
1–3 years	3 mg/7 mg	3 mg/7 mg		
4–8 years	5 mg/12 mg	5 mg/12 mg		
9–13 years	8 mg/23 mg	8 mg/23 mg		
14-18 years	11 mg/34 mg	9 mg/34 mg	13 mg/34 mg	14 mg/34 mg
19+ years	11 mg/40 mg	8 mg/40 mg	11 mg/40 mg	12 mg/40 mg

Both the recommended amount of dietary Zn or Zn supplement and upper tolerable levels vary depending on age, gender, or stage of growth and development. This table includes the amount of Zn recommended for daily consumption and the maximum or upper tolerable limit (UIL) for different ages or conditions to maintain optimum health
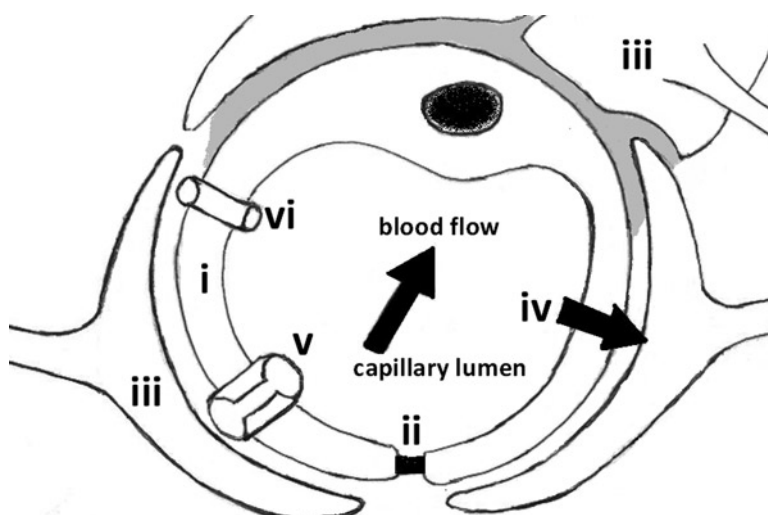
Fig. 149.1 The blood-brain barrier controls the exchange of ions including zinc, amino acids, peptides, and other substances between blood and brain. At the brain blood capillaries, the endothelium cells (i) are joined together at their edges by tight junctions (ii),which prevent water-soluble substances in the blood to enter the CSF. Most of the areas of the blood capillaries are enclosed by the astrocyte's "end-feet" (iii). Thus water-soluble substances can cross the BBB by passing directly through the walls of the cerebral capillaries made up of a lipid/protein bilayer. Fat-soluble molecules, including O_2 and CO_2, anesthetics and alcohol can pass straight through the lipids in the capillary walls (iv). Ions and amino acids can pass through using carrier proteins such as zinc import proteins (v), ion channels or pumps (vi) (Modified from Springer Image library accessed on 01 January, 2010 from http://www.springerimages.com/Images/Pharmacy/1-10.1208_s12248-008-9018-7-0)

of Zn into the brain parenchyma occurs via the BBB system (Kahn 2005). Entry of Zn into the brain is allowed through different kinds of proteins and channels on the BBB (Fig. 149.1). In other words the BBB system provides a strict regulation on Zn homeostasis in the brain and is not easily disrupted by dietary Zn (Franklin et al. 1992).

The presence of specific Zn transport sites on the brain capillary endothelial cells (Buxani-Rice et al. 1994) confirms the important regulatory role of the BBB in brain Zn homeostasis. The BBB-mediated control of Zn homeostasis in the brain is also supported by the enhanced transport of Zn across the BBB, as shown by an in vitro model of the BBB that was exposed to Zn-deficient conditions. The rate of Zn transport across the in vitro BBB model constructed using cultured porcine brain

capillary endothelial cells on porous membrane was observed to be slower when [Zn] was below 7 μmol/L and faster when it was above 30 μmol zinc/L (Lehmann et al. 2002). Notably, the zinc transport process is highly selective for Zn since none of the analogous minerals could effectively compete with zinc; besides, the zinc transfer process does not require much energy. Furthermore, metabolic inhibitors also do not influence the transport rate (Bobilya et al. 2008).

In order to maintain Zn homeostasis, brain capillary endothelial cells respond to changes in Zn status, increasing the uptake of Zn in the presence of low [Zn] in the blood and decreasing it in the presence of high [Zn] in the blood (Lehmann et al. 2002). Following its uptake, Zn can be transferred freely through the CSF and the brain ECF compartments. The reduced amount of histochemically reactive Zn in Zn deficiency suggests its reduced uptake in Zn deficiency (Takeda 2001).

149.4 Homeostasis of Zn in the Brain and Dietary Influence

The variation in the amount of Zn in different regions of the mammalian central nervous system (CNS) varies over about a fivefold range, with lower amounts generally in white matter (26–40 ppm in cortical white matter) and higher amounts in grey matter (60–90 ppm in cortical grey matter). On an average, the estimated amount of Zn in one gram of wet brain tissue is about 10μg corresponding to an average total intracellular [Zn] of about 150μM. This concentration is about 10-fold more than the serum [Zn]. On the regional distribution within the brain, the estimated total [Zn] in the hippocampus is more than 200 μM (see review Takeda and Tamano 2009), considered the highest compared to any other region (Frederickson et al. 2005). Notably, hippocampal [Zn] can be decreased significantly in dietary Zn deficiency. Among the other regions, the amygdala and neocortex contain the highest amount of Zn (Fig. 149.2).

In the ECF of the brain, Zn is either bound to low molecular weight ligands such as metalloproteins, or stay as free Zn^{2+} (see review Takeda and Tamano 2009). In the ECF, the estimated total [Zn] and
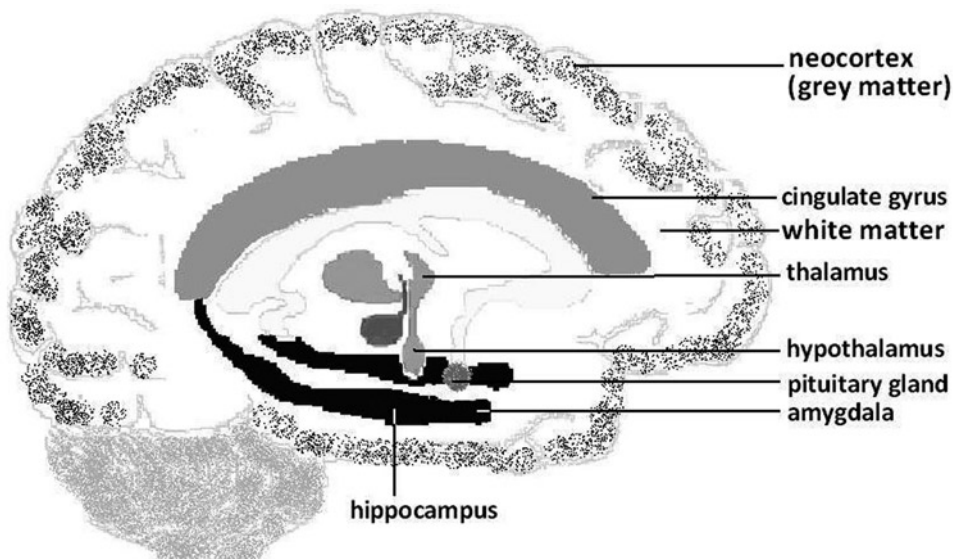
Fig. 149.2 Human brain-zinc map. The hippocampus belongs to the limbic system containing the highest concentration of zinc in the brain (*dark black area*). Other regions of the brain that contain relatively higher amount of Zn is the amygdala (*dark black area*) and grey matter neocortex (*black dotted area*)

free [Zn^{2+}] are 0.15–1 μM (Hershey et al. 1983; Weiss et al. 2000) and ~5–20 μM (Frederickson et al. 2006) respectively. About 80% of the total brain Zn is bound with Zn metalloproteins while the rest is histochemically detectable using Timm's sulfide-silver staining method (Frederickson and Danscher 1990). This is based on the observation that the removal of Zn transporter protein results in a 20% reduction of the total amount of Zn in the brain (Cole et al. 1999).

Within the brain, both the extracellualr and intracellular Zn are exchangeble. Extracellular Zn^{2+} in the brain may change because of its release from cells (Frederickson 1989; Qian and Noebels 2005), while changes in intracellular Zn^{2+} may result from oxidative stress (Frazzini et al. 2006). The concentration of rapidly exchangeable cytosolic free Zn^{2+} is estimated in the subnanomolar level. Such dynamic changes in Zn^{2+} gradients and the availability of specific Zn^{2+} binding domains suggest the importance of Zn^{2+} ions as signaling molecules. However, the signaling effects of Zn^{2+} may be mediated by intracellular or extracellular Zn^{2+} (Sensi et al. 1997).

In Zn deficiency, the level of serum Zn decreases which in turn leads to a decrease in CSF Zn. Although one week of Zn deprivation in young rats can decrease serum Zn level about 50% compared to control animals, a significant change (decrease) in extracellular Zn in the hippocampus is observed only after 4 weeks of Zn deprivation. Histochemically reactive Zn (Timm's stain) also decreases after 4 weeks of Zn deprivation. Thus only a prolonged period of Zn deficiency (4 weeks in contrast to 1 week) can cause a decrease in hippocampal Zn. Notably, extracellular Zn may lead to the decrease in histochemically reactive Zn. Extracellular Zn is also responsive to dietary Zn deficiency in other regions such as the amygdala, followed by a decrease in histochemically reactive Zn (Takeda and Tamano 2009).

The protein-bound Zn in intracellular compartments of the brain, on the other hand, may be resistant to Zn deficiency. It is possible that the response of hippocampal Zn to dietary Zn deficiency reflects that of peripheral Zn since the decrease in serum Zn may lead to the reduction of Zn^{2+} pool in peripheral tissues. It is possible that insufficient Zn^{2+} signaling in peripheral tissues is associated with activation of the hypothalamo-pituitary-adrenocortical system in Zn deficiency (Takeda and Tamano 2009).

149.5 Transport and Homeostasis of Zn in Neuron and Dietary Influence

Cells in different parts of the brain have different amounts of Zn which in turn contributes to the variable amount of Zn in different brain areas. The free [Zn^{2+}] in the cytosol from cultured neurons is estimated at subnanomolar (Weiss et al. 2000). However, Zn content in the synaptic vesicles of some neurons in the forebrain is found to be approximately >1 mM (Frederickson et al. 2005). Although intraneuronal cytosolic Zn^{2+} is in the subnanomolar or picomolar range, it is estimated to rise to micromolar levels in the proximity of axon terminals following release from synaptic vesicles that contain Zn^{2+} at millimolar range (Frederickson et al. 2005). This is most likely also the case in other intracellular compartments such as mitochondria, vesicles, and lysosomes that can take up cytosolic Zn^{2+} (Sensi et al. 2003; Colvin et al. 2006; Hwang et al. 2008; Dittmer et al. 2009).

Neurons that contain free Zn^{2+} in the vesicles of their presynaptic boutons are present both in forebrain areas (such as hippocampus, amygdala, and neocortex) and other areas of the brain (Fig. 149.2). Those neurons in the forebrain area are a subgroup of excitatory glutamatergic (or gluzinergic) neurons and in other areas they are termed Zn-enriched neurons (Frederickson and Danscher et al. 1990). Since the distribution of these neurons within the brain is not uniform, Zn distribution in the brain is also not uniform.

The exact mechanism that regulates Zn uptake from the ECF into neurons and glial cells is still not completely known. Most of the cells maintain Zn homeostasis through the regulated expression of proteins for Zn import, export, and sequestration (Table 149.4). Furthermore, Zn homeostatic

Table 149.4 Zn^{2+} transport and storage in neurons

Zn transporter(s) or storage protein	Important features
VGCCs and Ca^{2+}/Zn^{2+}-permeable AMPA receptors	Located at the plasma membrane the main routes Zn^{2+} entry into neurons
ZnT1	Located at the plasma membrane controls Zn^{2+} efflux interacts with the L-type VGCC that regulates Ca^{2+} and Zn^{2+} influx.
ZnT3	Located at the synaptic vesicles
ZnT5, ZnT6, ZnT7	Located at the golgi apparatus
ZnT5, ZnT6, ZnT7	Located at the lysozome
The Na^s/Zn^{2+} exchanger	Moves Zn^{2+} in or out of neurons depending on the Na^+ gradient
ZIP	H^+- or HCO_3-Zn^{2+} co-transporters and facilitates Zn^{2+} influx.
Ca^{2+} uniporter	Located at mitochondria
MT (MT-III)	Major Zn^{2+}-homeostatic proteins in neurons

AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid; MT, metallothionein VGCCs, voltage-gated Ca^{2+} channels; ZIP, Zinc importing protein
This table summarizes the list of major zinc transporters involved in supply and homeostasis of zinc in neurons (for detail see Ohana et al. 2009)

mechanisms appear to be tissue specific. Specific Zn transporters are used in certain tissues and its expression varies with dietary Zn status and time (Dufner-Beattie et al. 2003; Kelleher and Lonnerdal 2003). A number of Zn^{2+} transporters (ZnTs), Zn^{2+}-importing proteins (ZIPs), and buffering proteins such as the metallothioneins (MT) bind cytosolic Zn^{2+} and mediate the complex intraneuronal cytosolic Zn^{2+} homeostasis. In addition, specific gated Zn-permeable membrane-spanning channels, such as voltage-gated L-type Ca^{2+} channels, Na^+/Zn^{2+} exchangers, N-methyl-D-aspartate (NMDA) receptor gated channels, and Ca^{2+} permeable AMPA/kainate channels can also mediate the neuronal uptake of Zn. Zinc transporter proteins too regulate the efflux of Zn from neurons as well as vesicular Zn uptake. Transporters of the Zip family, which are the main membrane Zn uptake transporters, also seem to be involved in this process (reviewed in Ohana et al. 2009).

ZnTs mediate Zn^{2+} transport from the cytosol to the lumen of intracellular organelles or out of the cell. There are at least ten members of the ZnT family, most of which are ubiquitously expressed, except ZnT3 which is neuron specific and present on synaptic glutamatergic vesicles. With the exception of ZnT1, ZnTs are present on intracellular organelles such as the Golgi and the secretory vesicles of many organs (Table 149.4). Zinc Transporter 1 is expressed, synaptically and extrasynaptically, on the plasma membrane of neurons and glia. Other ZnT family members, ZnT2, ZnT4, ZnT5, and ZnT6, are also expressed in several brain regions (reviewed in Sensi et al. 2009) such as in the hippocampus, cortex, and olfactory bulb (Lee et al. 2003), and in certain cerebellar GABAergic and dopaminergic neurons (Ruiz et al. 2004). Zin Transporter 7, which probably facilitates Zn^{2+} transport from the cytoplasm into the Golgi apparatus, is moderately expressed in the brain and ZnT2, ZnT5, and ZnT6, which are associated with vesicular Zn uptake and Zn efflux in many organs, should similarly play a minor role in the brain.

149.6 Biochemistry of Zn Binding with Proteins in Brain

The knowledge of the biochemical importance of Zn dates back to 1940 with the discovery of the Zn-containing enzyme, *carbonic anhydrase*, now known to contain 1 gram atom of the metal per mole (Keilin and Mann1940). Subsequently, more than 300 such Zn containing proteins with catalytic,

structural, and other functional roles have been described. This number is more than that of any other transition or Group IIB metal (Vallee and Falchuk 1993) that is involved in biomolecules. Specific binding sites for Zn^{2+} are present on numerous proteins, including Zn^{2+} fingers on transcription factors that bind it with high affinity, and metallothioneins, from which the Zn^{2+} is easily dissociable.

Zinc binds to many proteins involved in gene regulation. The Zn finger proteins as transcription factor, Zn twists in steroid receptors, and Zn clusters in the galactose metabolism activator are well known examples. Other metalloproteins tightly binding Zn include the RING finger protein family (Freemont 1993), the tumour suppressor p53, the human growth hormone-prolactin receptor complex, and metallothionein proteins (Ebadi 1986; Vallee and Falchuk 1993). Zinc also stabilizes the 3D structure of superoxide dismutase (Salguerio et al. 2007). A partial list of Zn finger transcription factors present in different areas and types of cells in the brain is given in Table 149.5. In the brain, Zn is structurally important for reelin, a large secreted protein, implicated in the cortical development of the mammalian brain. A 2.0-Å crystal structure from the fifth and sixth reelin repeats fragment revealed the presence of Zn^{2+} bound to them (Yasui et al. 2007).

The biochemical importance of Zn lies in its role as catalytic, coactive (or co-catalytic), structural (Vallee and Falchuk 1993; MacDonald 2000), and intracellular signaling factor such as the regulation of

Table 149.5 Zinc finger transcription factors in the brain

Transcription factor	Expression site and/or function
ATBF1	• Protein is highly expressed in the midbrain and diencephalon • mRNA is highly expressed in the brainstem, mostly in embryo and neonatal brain, postmitotic neurons in the brainstem • Expression is transient and weak in the precursor cells at early neurogenesis. • Expression decreases postnatally, but remains in mature neurons • Regulation of neuronal cell maturation or region-specific central nervous system differentiation
Bcl11A/Evi9/CTIP1	• Bcl11A-S/Evi9c is widely expressed in different regions of the rat brain • Bcl11A-L/Evi9a is expressed in the cerebral cortex, hippocampus, and olfactory bulb
DRRF (Sp1 family of transcription factors)	• Highly expressed in the neural ectoderm and neural groove • Moderately expressed in the mesoderm and endoderm at the early embryonic stage. • Highest DRRF mRNA levels in olfactory bulb and tubercle, nucleus accumbens, striatum, hippocampus, amygdala, and frontal cortex. • Regulates dopaminergic neurotransmission
Egr3	• Expressed in cortex and colocalized with zif268. • Important in defining long-term, neuroplastic responses.
FOG-2	• Expressed in developing and adult heart, brain, and testis • Important cofactor for GATA-mediated transcriptional activation in cardiac and neural cell lineages.
Ik-1 and Ik-2	• Positive regulators of enkephalin gene expression in the developing striatum • Participate in regulating enkephalinergic differentiation
Lot1	• High in cerebellar granule cells, a neuronal population undergoing postnatal neurogenesis
MOK2	• *PAX3* and *IRBP* (interphotoreceptor retinoid-binding protein) genes are two potentially important target genes for the MOK2 protein.
NSM1(IA-1)	• In mouse brain, *Insm1* is strongly expressed for 2 weeks after birth but shows little or no expression thereafter. • During embryo development Cbl-associated protein may enter the nucleus through its own nuclear localization signal or by binding to INSM1.

Table 149.5 (continued)

Transcription factor	Expression site and/or function
Plag1, Plag-l2	• In the CNS and PNS • In olfactory and neuroendocrine lineages. • Might control cell fate and proliferation decisions in the developing nervous system (Oncogenes)
REST/NRSF/XBR	• Highest levels in the neurons of hippocampus, pons/medulla, and midbrain • A negative regulator rather than a transcriptional silencer of neuronal gene expression and counteracts with positive regulators to modulate target gene expression quantitatively in different cell types, including neurons.
RP58	• mRNA at E 10 in the neuroepithelium, and subsequently in the VZ of the cerebral cortex in the E12 embryo. • Strong expression in the preplate in the cerebral cortex from this stage onward. High levels of expression continue to be detected in the cortical plate and SVZ of the neocortex, hippocampus, and parts of the amygdala
Sp8	• Expressed in neurogenic regions, which gives rise to olfactory bulb interneurons at embryonic and postnatal time points and remains expressed in the calretinin-expressing and GABAergic/nondopaminergic interneurons of the glomerular layer. • Contributes to olfactory bulb interneuron diversity by regulating the survival, migration, and molecular specification of neuroblasts/interneurons.
Wt1	• The developing olfactory epithelium
Zac1(Plag family)	• Abundantly expressed in many neuroepithelia during early brain development • Regulates both apoptosis and cell cycle arrest (tumor suppressors)
Zfp423	• Expressed within the cerebellum, both in ventricular and external germinal zones. • Loss of Zfp423 results in diminished proliferation by granule cell precursors in the external germinal layer, especially near the midline, and abnormal differentiation and migration of ventricular zone-derived neurons and Bergmann glia
Zic1–5	• Precursor cells of the granule neuron and the neurons in cerebellar nuclei • Neurulation, neuronal differentiation, neural crest specification, the establishment of left-right asymmetry, and regulation of cell proliferation
Zif268 (Egr1)	• Zif268 is constitutively expressed in several parts including the temporal lobe. • Zif268 regulates neurological genes and cellular growth and proliferation genes. • Expressed in mammalian neurons during visual and fear learning, as well as in song learning in birds. • Expressed in response to cellular growth and proliferation signals by enhancing the expression of TGFβ1
ZNF536	• Most abundant in the developing central nervous system and dorsal root ganglia and localized in the cerebral cortex, hippocampus, and hypothalamic area. • Negatively regulates neuron differentiation.

This table includes a partial list of Zn finger transcription factors expressed in different sites and/or cells of the brain. Related functions of the respective transcription factors at the expression site are listed as well

cell proliferation (Hershfinkel et al. 2007). The catalytic roles of Zn include participating in the transformation of substrates by facilitating the formation of OH^- at neutral pH, or through Lewis acid catalysis. The structural role of Zn is mostly in stabilizing active tertiary peptide conformation. Notably, Zn^{2+} interacts strongly with electronegative sulfur, nitrogen, and oxygen moieties in multiple coordination geometries, and yet unlike Fe or Cu, it is not redox active under physiological conditions and thus does not promote the formation of toxic free radicals. As an extracellular signal factor Zn is involved in synaptic neurotransmission (Frederickson 1989; Vallee and Falchuk 1993). It is generally accepted that an increase in free intracellular Zn^{2+} is associated with cell death. For example, release of intracellular Zn^{2+}, triggered by formation of reactive oxygen species or by nitrosilation, induces proapoptotic molecules, e.g., p38, and activation of K^+ channels leading to cell death (McLaughlin et al. 2001; Pal et al. 2003).

149.7 The Developing Brain and Zn Status in Diet

The impact of Zn supplementation or a Zn-deficient human diet on brain development and function has not been consistent. Various dimensions of research design and a broad range of subjects varying in racial background, age, and food habits might have contributed to the observed inconsistency. However, a growing number of studies have shown the influence of maternal Zn on fetal growth and development (Goldenberg et al. 1995; Georgieff 2007; Cole and Lifshitz 2008). Daily Zn supplementation in women with relatively low plasma [Zn] in early pregnancy is associated with greater infant birth weights and head circumferences, with the effect occurring predominantly in women with a body mass index less than 26 kg/m^2 (Goldenberg et al. 1995). Very low birth weight of Canadian infants scored improved motor development when given Zn supplement (Friel et al. 1993) while low birth weight infants in Brazil (Ashworth et al. 1998) and older infants and toddlers in Guatemala (Bentley et al. 1997) and India (Sazawal et al. 1996) did not show changes in motor development. However, Zn supplementation to Zn-deficient mothers is important for proper brain development in neonates (Gibson 1994; Georgieff 2007). An adequate Zn nutriture is essential for optimal neurological development (Takeda 2001; Prasad 1997). Additional Zn intake during pregnancy results in increased neuronal proliferation in the ventricular zone of the developing brain (Azman et al. 2009). Regular consumption of more than the recommended intake, on the other hand, can have adverse effects (Ronowska et al. 2007).

149.8 Neurogenesis and Zn Supplement

Neurogenesis is a process to generate postmitoitc neuronal and glial cells from neuroepithelial stem cells. Proliferation, cell-cycle arrest, differentiation, migration, and the natural developmental death of neural precursors are well coordinated during neurogenesis (Moskowitz and Lo 2003). Optimal development of the brain depends on strict co-ordination of these events during neurogenesis. Various cell-cycle genes and transcription factors including Zn transcription factors expressed in neurons (Table 149.5) govern neurogenesis, which also determines the correct positional identity of the neural cells from the stem/progenitor cells (Araujo et al. 1990; Edenfeld et al. 2002). In most brain regions, the generation and proliferation of neurons is normally restricted to a discrete developmental period with exceptions for the regions such as hippocampus, dentate gyrus, and the subventricular zone (SVZ) of several species (Caviness 1973; Gueneau et al. 1982; Cameron et al. 1993; Kuhn et al. 1996; Gould et al. 1998; Eriksson et al. 1998; Doetsch et al. 1999), and almost all neurons are generated before early postnatal life and are generally not replaced with new ones (Rakic 1982). The ventricular zone (VZ) is the major site of proliferation and presumably produces all the cell types. A second proliferative zone, namely SVZ, also contributes large numbers of neurons to the developing cortex (Nowakowski and Rakic 1981). In addition, granule neurons are generated throughout life from a population of continuously dividing progenitor cells residing in the subgranular zone of the dentate gyrus in the rodent brain (Stanfield and Trice 1988; Kuhn et al. 1996).

In neuronal cells, Zn deficiency induces oxidative stress, alters the normal structure and dynamics of the cytoskeleton, affects the modulation of several transcription factors and induces a decreased cell proliferation and increased apoptotic death. Thus, Zn deficiency affects critical developmental events of neurogenesis (reviewed by Mackenzie et al. 2007; Nakashima and Dyck 2009). Zinc supplement on the other hand results in increased number of proliferating neurons in the VZ of the developing neocortex. This was observed in the mouse pups delivered by the mother given oral Zn supplement in drinking water during pregnancy (Azman et al. 2009). Notably, Zn is involved in

activation of enzyme systems that influence cell division and proliferation (Varrault et al. 1998; MacDonald 2000; Valente et al. 2005; Ronowska et al. 2007). During DNA synthesis, Zn affects thymidine kinase, the activity of which increases dramatically during the G1 and early S phases of the cell cycle. Zinc also influences the hormonal regulation of cell division. Insulin-like growth factor-I and the pituitary growth hormone axis are responsive to Zn status (Root et al. 1979; Roth et al. 1994).

149.9 Neuronal Apoptosis and Zn Deficiency

Zn deficiency was found to increase the expression of Zn transporters in the brain, which facilitates increased brain Zn uptake and results in the conservation of brain Zn during Zn deficiency (Chowanadisai et al. 2005). In neuronal cells, Zn deficiency induces oxidative stress, alters the normal structure and dynamics of the cytoskeleton, affects several transcription factors, and results in decreased cell proliferation and increased apoptosis. These closely associated events affect neuronal function and critical developmental events of neurogenesis when Zn availability decreases (Mackenzie et al. 2007).

In human neuronal cell model IMR-32 cells, a decrease in cellular Zn triggers mitogen-activated protein kinases (MAPKs) both in H_2O_2-independent and dependent manner. Cells grown in low Zn-containing media showed increased cell oxidants and H_2O_2 release, increased c-Jun N-terminal kinase (JNK) and p38 activation, high nuclear activator protein-1 (AP-1)-DNA binding activity, and AP-1-dependent gene expression. Increase in cellular H_2O_2 can trigger the activation of JNK and p38, leading to AP-1 activation, events that are not involved in Zn deficiency-induced apoptosis (Zago et al. 2005).

149.10 Zinc Deficiency or Excess and Brain Pathology

The homeostasis of the free Zn^{2+} pool and the mechanisms involved in controlling that homeostasis are pivotal for proper brain physiology. Acute human dietary deficiency is accompanied by CNS related Zn-reversible symptoms such as anorexia, smell and taste dysfunction, emotional and cognitive disturbances, and loss of coordination (Fig. 149.3) (Ashworth et al. 1998; Bhatnagar and Taneja 2001). Perhaps this is because Zn as a neuromodulator at excitatory synapses plays an important role in stress response and in the functionality of Zn-dependent enzymes contributing to maintaining brain compensatory capacity. Dietary Zn deficiency was also reported to affect learning and memory. Deficiency in Zn is also associated with attention deficiency/hyperactivity disorder. Age-related decline in brain functions and impaired cognitive performances could be related to dysfunctions affecting the intracellular Zn^{2+} availability (Golub et al. 1995; Takeda 2000; Takeda et al. 2008).

Zn deficiency causes abnormal glucocorticoid secretion from the adrenal cortex, which is observed prior to the decrease in extracellular [Zn] in the hippocampus. The functions of glucocorticoid receptor-rich hippocampus are changed by abnormal glucocorticoid secretion that in turn aggravates glutamate excitotoxicity in neurological diseases. Thus Zn deficiency elicits neuropsychological symptoms and affects cognitive performance (Fig. 149.3). It is possible that the decrease in Zn^{2+} pool in the peripheral tissues triggers abnormal glucocorticoid secretion. In other words, the decrease in Zn^{2+} pool may cooperate with glucocorticoid action in Zn deficiency.

Again, elevated [Zn] or Zn excess in the brain has a profound negative effect on neurological cells, which are highly susceptible to extremes in extracellular [Zn]. The exact neuropathological mechanism of elevated level of Zn^{2+} is still unclear; however, it is found to be related to the progression
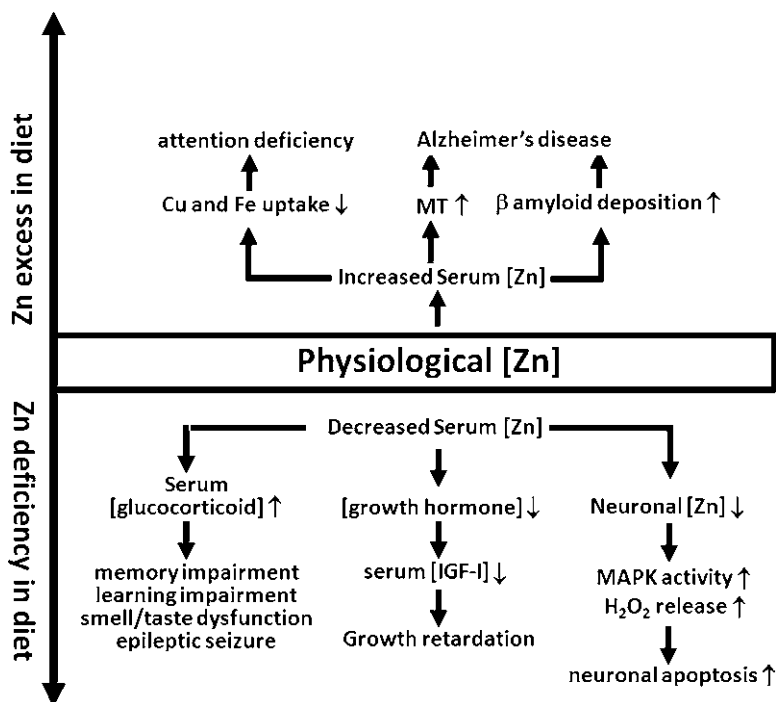
Fig. 149.3 Possible pathological consequences of dietary Zn-deficient or Zn-excess condition. In dietary Zn deficiency, serum [Zn] can be decreased leading to either increased serum glucocorticoid concentration or decreased growth hormone concentration or intracellular [Zn]. These conditions in turn may result in cognitive disturbances such as memory or learning impairment, growth retardation or neuronal apoptosis, respectively. In dietary Zn-excess condition, increased serum [Zn] can lead to decreased uptake of Cu and Fe in different organs, including the brain, or increased depositing of beta amyloid in the brain. *IGF* Insulin like growth factors I, *MAPK* mitogen activated protein kinase, ↓ decrease, increase

of AD and other neuropathologies (reviewed by Sensi et al. 2009). There is considerable evidence that amyloid-beta deposition in AD is induced by Zn, but the exact mechanism is still unclear (reviewd by Mocchegiani et al. 2005; Barnham and Bush 2008). An increased expression of MT-I and MT-II, and in some cases of MT-III (also known to be a growth inhibitory factor), is causally linked to such phenomena (Fig. 149.3). However, the protective roles of these proteins at a young age to maintain brain physiology and their functional ability in aging are not consistent. Alterations in Zn homeostasis have also been reported in Parkinson's disease as well as in transient forebrain ischemia, seizures, and traumatic brain injury. The altered Zn nutritional status of individuals with Down's Syndrome contributes to clinical complications that usually appear with their aging (Lima et al. 2010). Again, Zn metabolism is altered in the presence of Down's Syndrome (Licastro et al. 2001). Zinc supplement in diets has been tried to improve the patient's health albeit with conflicting results (Bucci et al. 2001; Blair et al. 2008).

149.11 Applications to Other Areas of Health and Disease

The importance of Zn in the biological system is remarkable and versatile. Zinc plays a pivotal role in gene expression involving cellular growth and differentiation; yet, unlike other transitional metals,

it does not cause any oxidative damage (Berg and Shi 1996). Enough is now known about the clinical and public health importance of Zn in human health and diseases. Community Zn supplementation programs among children in developing countries proved to have had a significant effect on the reduction of pneumonia (Bhutta et al. 1999). Zinc supplement has been beneficial for diarrhea prevention and childhood morbidity and mortality. Other than the brain (CNS), the epidermal, gastrointestinal, immune, skeletal, and reproductive systems are known to be affected clinically by severe Zn deficiency (Solomons 1998; Hambidge et al. 1986).

Summary Points

- The total Zn content of the diet and its bioavailability, especially its solubility in the intestinal lumen, determine the amount of absorbed Zn to be utilized or metabolized in the different organs including the brain.
- In the brain, Zn concentration is highest in the hippocampus which can decrease significantly in dietary Zn deficiency.
- The blood brain barrier system provides strict regulation on Zn homeostasis in the brain and is not easily influenced by dietary Zn.
- Zinc homeostasis is maintained through the regulated expression of proteins for Zn import, export, and sequestration.
- A multitude of Zn^{2+} transporters (ZnTs), Zn^{2+}-importing proteins (ZIPs), and buffering proteins such as the metallothioneins (MT) bind cytosolic Zn^{2+} and mediate the complex intraneuronal cytosolic free Zn^{2+} homeostasis.
- A number of Zn transcription factors are expressed in nerve cells and in different areas of the brain regulating genes involved in proliferation, differentiation, migration, and apoptosis of neurons and other cells of the brain.
- As an extracellular signal factor Zn is involved in synaptic neurotransmission.
- Additional Zn intake during pregnancy can increase neuronal proliferation at the ventricular zone of the developing brain.
- In neuronal cells, Zn deficiency induces oxidative stress, alters the normal structure and dynamics of the cytoskeleton, affects the modulation of transcription factors AP-1, NF-betaB, and NFAT and induces decreased cell proliferation and increased apoptotic death.
- Acute human dietary deficiency is accompanied by symptoms such as anorexia, smell and taste dysfunction, emotional and cognitive disturbances, and loss of coordination. Dietary Zn deficiency also has been reported to affect brain functions, including learning and memory defects.

Key Terms

Apoptosis: A form of cell death (or cell suicide) in which a programmed sequence of events leads to the elimination of cells without leaving or releasing harmful substances into the surrounding area of the dying cell(s). Apoptosis also refers to the structural changes that the cells undergo before the programmed death. Apoptosis is crucial in developing and maintaining health by eliminating old, unnecessary, and unhealthy cells. Hyperactivation and inactivation of apoptosis may result in pathological conditions. Hyperactivation may kill too many cells and inflict grave tissue damage, leading to such neurodegenerative disorders as Alzheimer's, Huntington's, and Parkinson's diseases.

Astrocyte: Astrocytes (collectively known as astroglia) are characteristic star-shaped glial cells in the CNS. Three forms of astrocytes exist in the CNS: *fibrous* (located in white matter and that physically connect the cells to the outside of the capillary wall when they are in close proximity to them), *protoplasmic* (found in grey matter tissue; they possess a larger quantity of organelles and exhibit short and highly branched cellular processes), and *radial* (disposed in a plane perpendicular to the axis of ventricles). Their functions include: biochemical support to the endothelial cells at the BBB, controlling of nutrient supply to the nervous tissue, maintenance of extracellular ion balance, and aiding in repair mechanisms of the brain and spinal cord injuries.

Blood brain barrier (BBB): The BBB is a protective network of blood vessels that filters blood flowing to the brain and separates circulating blood and cerebrospinal fluid (CSF) maintained by the choroid plexus in the CNS. Endothelial cells of the blood vessels restrict the diffusion of microscopic objects (e.g. bacteria) and large or hydrophilic molecules into the CSF, while allowing the diffusion of small hydrophobic molecules (O_2, hormones, CO_2).

Central nervous system (CNS): The CNS is one of the two major divisions of the nervous system and consists of the brain and the spinal cord. The CNS connects to sensory organs (such as the eye and ear) and other organs of the body, muscles, blood vessels, and glands through the peripheral nervous system. The CNS consists of the brain in the cranial cavity and the spinal cord in the spinal cavity.

Hippocampus: The hippocampus is named for its shape like a seahorse (From the Greek *hippos* = horse and *kampos* = a sea monster). It is a closely associated, paired structure with mirror-image halves in the left and right sides of the brain. In humans and other primates, the hippocampus is located inside the medial temporal lobe, beneath the cortical surface. The hippocampus is part of the olfactory cortex essential to the sense of smell and also helps to regulate emotion and memory. Hippocampus also plays important roles in long-term memory and spatial navigation.

Homeostasis: (from Greek: *homoios*, "similar"; and *histēmi*, "standing still"). Generally refers to the property of a system, either open or closed, that regulates its internal environment and tends to maintain a stable, constant condition. When applied to living organisms, homeostasis refers to a property of cells, tissues, and organisms that allow the maintenance and regulation of the stability and constancy needed to function properly and is maintained by the constant adjustment of biochemical and physiological pathways.

Metallothionein (MT): Metallothionein is a family of cysteine-rich, low molecular weight (3.5–14 kDa) proteins. The thiol group of MT contains cysteine residues, which represent ~20–30% of its total amino acidic residues. Both essential (such as Zn, copper, selenium) and toxic (such as cadmium, mercury, silver, arsenic) heavy metals can bind the thiol groups through the cysteine residues. MT has high affinity for Zn (1.4×10^{-13} M). There are four major isoforms (MT-I, MT-II, MT-III, MT-IV) expressed primarily in the liver and kidneys. MT expression is also evident in other tissues and organs such as blood, skin, and heart. In the brain, MT-III is known as the growth inhibitory factor. Expression of MT in different organs and tissues depends on the availability of the dietary minerals, such as Zn, copper, and selenium, and the amino acids histidine and cysteine. MT distributes intracellular Zn as Zn undergoes rapid inter- and intracluster exchange.

Neurogenesis: The process by which new nerve cells are generated i.e., production of new neurons, astrocytes, glia, and other neural lineages from undifferentiated neural progenitor or stem cells. Neurogenesis is most active during prenatal development and inactive in most areas of the adult brain.

Neuron: Neurons are cells in the nervous system including the brain, spinal cord (vertebrate), the ventral nerve cord (invertebrate), and the peripheral nerves that process and transmit information by

electrochemical signaling. A typical neuron has a cell body (soma), branching processes specialized to receive incoming signals (dendrites), and a single process (axon) that carries electrical signals away from the neuron toward other neurons or effectors. Electrical signals carried by axons are action potentials. Different types of neurons are named after their specialized structure and functions: for example, *sensory neurons* respond to touch, sound, light, and numerous other stimuli affecting cells of the sensory organs that then send signals to the spinal cord and brain; *motor neurons* receive signals from the brain and spinal cord and cause muscle contractions and affect glands; *interneurons* connect neurons to other neurons within the same region of the brain or spinal cord.

Dopaminergic neuron: Neurons that produce dopamine, a neurotransmitter produced in several areas of the brain, including the substantia nigra and the ventral tegmental area in either vertebrates or invertebrates. Dopamine is a neurohormone released by the hypothalamus mainly to inhibit the release of prolactin from the anterior lobe of the pituitary.

GABAergic neuron: Neurons that produce γ-aminobutyric acid (GABA), the chief inhibitory neurotransmitter in the mammalian CNS. It plays an important role in regulating neuronal excitability throughout the nervous system. In humans, GABA is directly responsible for the regulation of muscle tone. GABA acts at inhibitory synapses in the brain by binding to specific transmembrane receptors in the plasma membrane of both pre- and postsynaptic neuronal processes. This binding causes the opening of ion channels to allow the flow of either Cl^- ions into the cell or K^+ out of the cell. Two general classes of GABA receptor are known: $GABA_A$ in which the receptor is part of a ligand-gated ion channel complex, and $GABA_B$ metabotropic receptors, which are G protein-coupled receptors that open or close ion channels via intermediaries.

Reelin: Reelin is a protein expressed in different tissues of the body including brain, spinal cord, and blood. In the developing brain it helps to regulate neuronal migration and positioning. In the adult brain, it modulates synaptic plasticity by enhancing the induction and maintenance of long-term potentiation. It also stimulates dendrite and dendritic spine development and regulates the continuing migration of neuroblasts generated in adult neurogenesis sites like subventricular and subgranular zones.

Subventricular zone (SVZ): The subventricular zone is a paired brain structure situated throughout the lateral walls of the lateral ventricles. Along with the subgranular zone of the dentate gyrus, the SVZ serves as a source of neural stem cells in the process of neurogenesis. It harbors the largest population of proliferating cells in the adult brain of rodents, monkeys, and humans.

Synaptic vesicle: Synaptic vesicles or neurotransmitter vesicles are 40–100 nanometers in diameter, and made up of a lipid bilayer, store various neurotransmitters (NT) that are released at the synapse for synaptic transmission. The release of NTs is regulated by a voltage-dependent Ca^+ channel. At synapses, the junctional complexes between presynaptic membranes (synaptic knobs) and postsynaptic membranes (receptor surfaces of recipient neurons or effectors), synaptic transmission process signal transfer (communicate) from one neuron (affector) to other neurons (effectors).

Zinc finger transcription factor: Zinc finger transcription factors are the DNA-binding proteins, containing Zn finger domain. Zinc fingers are small protein domains, folds of which are stabilized by one or more Zn^{2+}. They coordinate Zn^{2+} with a combination of cysteine and histidine residues. Different families of Zn finger proteins can bind DNA, RNA, proteins or small molecules involved in transcription, nucleic acid polymerization, and histones.

References

Araujo DM, Chabot JG, Quirion R. Int Rev Neurobiol. 1990;32:141–74.

Ashworth A, Morris SS, Lira PI, Grantham-McGregor SM. Eur J Clin Nutr. 1998;52:223–7.

Azman MS, Wan Saudi WS, Ilhami M, Mutalib MS, Rahman MT. Nutr Neurosci. 2009;12:9–12.

Barnham KJ, Bush AI. Curr Opin Chem Biol. 2008;12:222–8.

Berg JM, Shi Y. Science. 1996;271:1081–5.

Bentley ME, Caulfield LE, Ram M, Santizo MC, Hurtado E, Rivera JA, Ruel MT, Brown KH. J Nutr. 1997;127:1333–8.

Bhatnagar S, Taneja S. Br J Nutr. 2001;85:S139–45.

Bhutta ZA, Black RE, Brown KH, et al. J Pediatr. 1999;135:689–97.

Black MM. Am J Clin Nutr. 1998;68:464S–9S.

Blair CK, Roesler M, Xie Y, Gamis AS, Olshan AF, Heerema NA, Robison LL, Ross JA. Paediatr Perinat Epidemiol. 2008;22:288–95.

Bobilya DJ, Gauthier NA, Karki S, Olley BJ, Thomas WK. Longitudinal changes in Zn transport kinetics, metallothionein and Zn transporter expression in a blood -brain barrier model in response to a moderately excessive Zn environment. J Nutr Biochem. 2008.;19:129–37

Brown KH, Bégin F. J Pediatr Gastroenterol Nutr. 1993;17:132–8.

Brown KH, Wuehler SE, Peerson JM. Food Nutr Bull. 2001;22:113–25.

Bryan J, Osendarp S, Hughes D, Calvaresi E, Baghurst K, van Klinken JW. Nutr Rev. 2004;62:295–306.

Bucci I, Napolitano G, Giuliani C, et al. Biol Trace Elem Res. 2001;82:273–5.

Buxani-Rice S, Ueda F, Bradbury MWB. J Neurochem. 1994;62:665–72.

Cameron HA, Woolley CS, McEwen BS, Gould E. Neurosci. 1993;56:337–44.

Caviness VS. J Comp Neurol. 1973;151:113–20.

Chowanadisai W, Kelleher SL, Lönnerdal B. J Nutr. 2005;135:1002–7.

Cole CR, Lifshitz F. Pediatr Endocrinol Rev. 2008;5:889–96.

Cole TB, Wenzel HJ, Kafer KE, Schwartzkroin PA, Palmiter RD. Proc Natl Acad Sci USA. 1999;96:1716–21.

Colvin RA, Laskowski M, Fontaine CP. Brain Res. 2006;1085:1–10.

Colvin RA, Fontaine CP, Laskowski M, Thomas D. Eur J Pharmacol. 2003;479:171–85.

Dittmer PJ, Miranda JG, Gorski JA, Palmer AE. J Biol Chem. 2009;284:16289–97.

Doetsch F, Caille I, Lim DA, Garcia-Verdugo JM, Alvarez-Buylla A. Cell. 1999;97:703–16.

Dufner-Beattie J, Wang F, Kuo Y, Gitschier J, Eide D, Andrews G. J Biol Chem. 2003;278:33474–81.

Ebadi M. Biol. Trace Elem Res. 1986;11:101–16.

Edenfeld G, Pielage J, Klambt C. Curr Opin Genet Dev. 2002;12:473–7.

Eriksson PS, Perfilieva E, Björk-Eriksson T, Alborn AM, Nordborg C, Peterson DA, Gage FH. Nat Med. 1998;4:1313–7.

Freemont PS. Ann N Y Acad Sci. 1993;684:174–92.

Franklin PA, Pullen RGL, Hall GH. Neurochem Res. 1992;17:767–1.

Frazzini V, Rockabrand E, Mocchegiani E, Sensi SL. Biogerontology. 2006;7:307–14.

Frederickson CJ, Giblin LJ, Krezel A, et al. Exp Neurol. 2006;198:285–93.

Frederickson CJ, Koh JY, Bush AI. Nat Rev Neurosci. 2005;6:449–62.

Frederickson CJ. Int Rev Neurobiol. 1989;31:145–238.

Frederickson CJ, Danscher G. Prog Brain Res. 1990;83:71–84.

Friel JK, Andrews WL, Matthew JD et al. J Pediatr Gastroenterol Nutr. 1993;17:97–104.

Georgieff MK. Am J Clin Nutr. 2007;85:614S–20S.

Gibson RS. Nutr Res Rev. 1994;7:151–73.

Goldenberg RL, Tamura T, Neggers Y, Copper RL, Johnston KE, DuBard MB, Hauth JC. J Am Med Assoc. 1995;274:463–8.

Golub MS, Keen CL, Gershwin ME, Hendrickx AG. J Nutr. 1995;125:2263–71.

Gould E, Tanapat P, McEwen BS, Flugge G, Fuchs E. Proc Natl Acad Sci USA. 1998;95:3168–71.

Gueneau G, Privat A, Drouet J, Court L. Dev Neurosci. 1982;5:345–58.

Hambidge KM, Casey CE, Krebs NF. Zinc. In: Metz W, editor. Trace elements in human and animal nutrition. New York: Academic Press; 1986. p. 1–37.

Hershey CO, Hershey LA, Varnes A, Vibhakar SD, Lavin P, Strain WH. Neurol. 1983;33:1350–3.

Hershfinkel M, Silverman W, Sekler I. Mol Med. 2007;13:331–6.

Hwang JJ, Lee SJ, Kim TY, Cho JH, Koh JY. J Neurosci. 2008;28:3114–22.

Keilin D, Mann T. Biochem J. 1940;34:1163–76.

Khan E. Br J Nurs. 2005;14:509–13

Kelleher S, Lonnerdal B. J Nutr. 2003;133:3378–85.

Kuhn HG, Dickinson-Anson H, Gage FH. J Neurosci. 1996;16:2027–33.

Lee JY, Kim JH, Palmiter RD, Koh JY. Exp Neurol. 2003;184:337–47.

Lehmann H, Brothwell B, Volak L, Bobilya D. J Nutr. 2002;132:2763–8.

Licastro F, Mariani RA, Faldella G, Carpenè E, Guidicini G, Rangoni A, Grilli T, Bazzocchi G. Brain Res Bull. 2001;55:313–7.

Lima AS, Cardoso BR, Cozzolino SF. Biol Trace Elem Res. Nutritional status of zinc in children with Down syndrome. 2010;133:20–8.

Lowe NM, Fekete K, Decsi T. Am J Clin Nutr. 2009;89:2040S–51S.

MacDonald RS. J Nutr. 2000;130:1500S–8S.

Mackenzie GG, Zago MP, Aimo L, Oteiza PI. IUBMB Life. 2007;59:299–307.

Maret W, Sandstead HH. Exp Gerontol. 2008;43:378–81.

McLaughlin B, Pal S, Tran MP, Parsons AA, Barone FC, Erhardt JA, Aizenman E. J Neurosci. 2001;21:3303–11.

Mocchegiani E, Bertoni-Freddari C, Marcellini F, Malavolta M. Prog Neurobiol. 2005;75:367–90.

Moskowitz MA, Lo EH. 2003;34:324–6.

Nakashima AS, Dyck RH. Brain Res Rev. 2009;59:347–73.

Nowakowski RS, Rakic P. J Comp Neurol. 1981;196:129–54.

Ohana E, Hoch E, Keasar C, Kambe T, Yifrach O, Hershfinkel M, Sekler I. Biol Chem. 2009;284:17677–86.

Pal S, Hartnett KA, Nerbonne JM, Levitan ES, Aizenman E. Neurochem Int. 2003;52:241–6.

Prasad AS. In: Connor JR, editor. Metals and oxidative damage in neurological disorders. New York: Plenum Press; 1997. p. 95–111.

Qian J, Noebels JL. J Physiol. 2005;566: 747–758

Rakic P. Neurosci Res Prog Bull. 1982;20:439–51.

Ronowska A, Gul-Hinc S, Bielarczyk H, Pawelczyk T, Szutowicz A. J Neurochem. 2007;103:972–83.

Root AW, Duckett G, Sweetland M, Reiter EO. J Nutr. 1979;109:958–64.

Roth HP, Kirchgessner M. Horm Metab Res. 1994;26:404–8.

Ruiz A, Walker MC, Fabian-Fine R, Kullmann DM. J Neurophysiol. 2004;91:1091–6.

Salgueiro MJ, Zubillaga M, Lysionek A et al. Nutr Res. 2007;20:737–55.

Sazawal S, Bentley M, Black RE, Dhingra P, George S, Bhan MK. Pediatrics. 1996;98:1132–7.

Sensi SL, Paoletti P, Bush AI, Sekler I. Nat Rev Neurosci. 2009;10:780–91.

Sensi SL, Ton-That D, Sullivan PG, Jonas EA, Gee KR, Kaczmarek LK, Weiss JH. Proc Natl Acad Sci USA. 2003;100:6157–62.

Sensi SL, Canzoniero LMT, Yu SP, Ying HS, Koh JY, Kerchner GA, Choi DW. J Neurosci. 1997;15:9554–64.

Solomons NW. Nutr Rev. 1998;56:280–1.

Soto-Quintana M, Alvarez-Nava F, Rojas-Atencio A, Granadillo V, Fernández D, Ocando A, López E, Fulcado W, et al. Invest Clin. 2003;44:51–60.

Stanfield BB, Trice JE. Exp Brain Res. 1988;72:399–406.

Takeda A, Kanno S, Sakurada N, Ando M, Oku N. J Neurosci Res. 2008;86:2906–11.

Takeda A. BioMetals. 2001;14:343–52.

Takeda A. Brain Res Rev. 2000;34:137–48.

Takeda A, Tamano H. Brain Res Rev. 2009;62:33–44.

Takeda A, Minami A, Seki Y, Oku N. J Neurosci Res. 2004;75:225–9.

Valente T, Junyent F, Auladell C. Dev Dyn. 2005;233:667–79.

Vallee BL, Falchuk KH. Physiol Rev. 1993;73:79–118.

Varrault A, Ciani E, Apiou F, Bilanges B, Hoffmann A, Pantaloni C, Bockaert J, Spengler D, Journot L. Proc Natl Acad Sci USA. 1998;95:8835–40.

Weiss JH, Sensi SL, Koh JY. Trends Pharmacol Sci. 2000;21:395–401.

Yasui N, Nogi T, Kitao T, Nakano Y, Hattori M, Takagi J. Proc Natl Acad Sci USA. 2007;104:9988–93.

Zago MP, Mackenzie GG, Adamo AM, Keen CL, Oteiza PI. Antioxid Redox Signal. 2005;7:1773–82.

Chapter 150
Dietary Copper and the Brain

Helma Antony and Ian G. Macreadie

Abbreviations

Aβ	β-Amyloid Protein
AD	Alzheimer's Disease
AI	Daily Adequate Intake
ALS	Amyotrophic Lateral Sclerosis
APP	Amyloid Precursor Protein
ATP	Adenosine Tri-Phosphate
BACE	Beta-Site APP Cleaving Enzyme
BBB	Blood–Brain–Barrier
BSE	Bovine Spongiform Encephalopathy
CJD	Creutzfeldt-Jacob Disease
CSF	CerebroSpinal Fluid
Cu	Copper
CWD	Chronic Wasting Disease
EC	Enzyme Commission number
ETIC	Endemic Tyrolean Infantile Cirrhosis
Fe	Iron
HD	Huntington Disease
ICC	Indian Childhood Cirrhosis
ICT	Idiopathic Copper Toxicosis
OHS	Occipital Horn Syndrome
PD	Parkinson's Disease
RDA	Recommended Dietary Allowance
ROS	Reactive Oxygen Species
SOD	Superoxide Dismutase
TSE	Transmissible Spongiform Encephalopathy
UL	Daily tolerable Upper intake Level

I.G. Macreadie (✉)
Bio21 Institute, University of Melbourne, 30 Flemington Road, Melbourne, VIC 3010, Australia
e-mail: ian.macreadie@gmail.com

150.1 Introduction

Copper is essential for life. It is vitally important for the body as it forms a critical component of various fundamental enzymes in the cells. These cuproenzymes (see Table 150.1) are absolutely dependent on copper for its enzymatic activity. At the molecular level, copper is required as a catalytic cofactor or prosthetic group for these metalloenzymes. The cuproenzymes include cytochrome oxidase (EC 1.9.3.1), superoxide dismutase (EC 1.13.11.11), tryptophan-2,3-dioxygenase (EC 1.13.11.11), lysine oxidase (EC 1.4.3.12), monoamine oxidase (EC 1.4.3.4), tyrosinase (EC 1.14.18.1), and dopamine-β-hydroxylase (EC 1.14.17.1).

In humans, these enzymes are required in various organs or sites and indeed some are essential in all cells. Cuproenzymes like cytochrome oxidase are an essential component of cellular respiration and are required in all cells. Other cuproenzymes are involved in iron oxidation, connective tissue formation, nerve cell function, hormone production, and pigmentation (Table 150.1). Cuproenzymes are also important for the synthesis, development and normal functioning of several physiological systems like hemopoietic, cardiovascular, nervous, skeletal, reproductive, and integumentary systems. In addition, copper plays a role as a free metal ion in some nonenzymatic activities like angiogenesis, nerve myelination, and endorphin action.

150.2 Copper in the Diet

Given that copper is essential for normal health, the dietary intake of copper is important. However, increased copper levels in the body can lead to toxicosis resulting in serious consequences (see below). Hence, it is important to consume safe and adequate amounts of copper. The previous recommended dietary allowance (RDA) of 1.5–3.0 mg of copper/day has now been reduced to 0.9 mg/day for adult men and women and 1.0–1.3 mg/day for pregnant and lactating women. For infants up to 1 year old, the daily adequate intake (AI) level is 0.2–0.22 mg/day. To avoid copper toxicity from excessive dietary intake, it is desirable not to exceed the tolerable upper intake level (UL). The UL of copper for adults is 10 mg/day. A comprehensive list of specific AIs, RDAs, and ULs for all ages can be found in Table 150.2 (Klevay 2005).

Table 150.1 Copper-containing proteins (Balamurugan and Schaffner 2006; Zatta and Frank 2007)

Enzymes/Proteins	Function
Cytochrome *c* oxidase	Energy production (electron transport chain)
Superoxide dismutase (Cu–Zn–SOD)	Protection against free radical damage
Lysyl oxidase	Strengthening connective tissue (cross-linking of collagen and elastin)
Dopamine β mono-oxygenase	Neurotransmission (catecholamine formation)
Peptidyl α amidating mono-oxygenase	Neurotransmission (pituitary peptide hormone maturation)
Amine oxidase	Hormone removal
Mono-oxygenase	Melanin formation
Ascorbate oxidase	Oxidation of ascorbate
Ceruloplasmin	Copper and iron transport (oxidation of Fe^{2+} to Fe^{3+})
Galactose oxidase	Oxidation of primary alcohols to aldehydes
Tyrosinase	Pigmentation (oxidation of phenols)

Enzymes and proteins that require copper and their biological functions are listed

Table 150.2 Dietary copper (Klevay 2005)

Age group	AI	RDA (in mg)	UL (in mg)
Infants			
0–6 months	0.20 mg or 30 μg/kg		
7–12 months	0.22 mg or 24 μg/kg		
Children			
1–3 years		0.34	1.00
4–8 years		0.44	3.00
9–13 years		0.70	5.00
Adolescents			
14–18 years		0.89	8.00
Adults			
19–70 years		0.90	10.00
Pregnant women		1.00	8.00
Lactating mothers		1.30	8.00–10.00

Recommended levels for safe and adequate copper nutrition for the different age groups are listed

AI daily Adequate Intake, *RDA* Recommended Dietary Allowance, *UL* daily tolerable Upper intake Level

150.2.1 Dietary Sources of Copper

Figure 150.1 shows some of the dietary sources of copper. High-copper containing foods such as nuts (0.2–0.5 mg/tablespoon), seeds, seafood – particularly shell fish, lobster, etc. (1.0–3.7 mg/serving), organ meats – like liver (3.8 mg/serving of beef liver) and legumes (0.2 mg/serving) are good dietary sources of copper. Substantial amounts of copper are also present in whole grains, grain products, and chocolates. Other foods like tea, milk, chicken, and potatoes contain low levels of copper. Cooking in copper vessels and drinking water from copper pipes may also offer trace amounts of copper via leaching.

150.2.2 Factors Affecting Copper Nutrition

Adequate copper nutrition also depends on the bioavailability of copper in foods and the influence of other dietary components or nutrient partners. In spite of the higher copper content of vegetarian diets compared to nonvegetarian diet, copper is less efficiently absorbed from a vegetarian diet (Hunt and Vanderpool 2001). Nevertheless, total apparent copper absorption is greater in vegetarians owing to the greater copper content of the vegetarian diet (Hunt and Vanderpool 2001). There are several other factors that affect the intestinal absorption of copper and its bioavailability. Physical and chemical food processing treatments often alter the mineral content of foods (Wapnir 1998). Long-term cooking can reduce the copper content of food considerably. Dietary components like ascorbic acid (vitamin C), zinc, calcium, molybdenum, ferrous iron, stannous tin, etc. are found to reduce copper absorption due to their copper antagonistic, chelating or copper-binding nature; whereas sodium is found to enhance copper absorption (Wapnir 1998). It has also been observed that an increased consumption of saturated and trans fats along with increased copper diet can accelerate brain aging and deteriorate cognitive function (Morris et al. 2006).
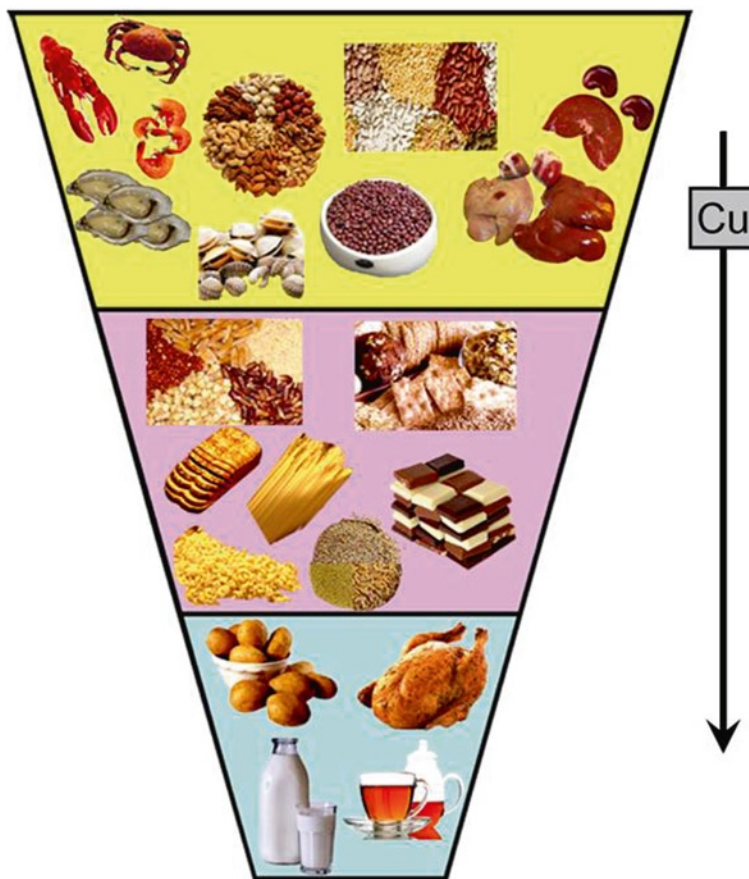
Fig. 150.1 Dietary sources of copper. Copper-containing foods are shown in decreasing order of their copper content. Foods in the upper row are rich in copper, while those in middle row contain substantial amounts of copper. Foods in the bottom row contain low levels of copper

150.3 Physiology of Copper

The physiology of copper involving its dietary intake, absorption, distribution to various tissues, and organs and its excretion is summarized in Fig. 150.2.

150.3.1 Absorption of Copper

Dietary copper uptake has been reviewed by (Linder and Hazegh-Agam 1996). Copper absorption occurs primarily via the brush border cells of the small intestine into interstitial fluid and blood (Linder and Hazegh-Agam 1996), where the copper binds to plasma proteins that carry copper. A small fraction of copper absorbed by the stomach is nutritionally insignificant (Wapnir 1998). Thus the primary site of copper absorption is considered to be the small intestine. At the level of the whole person, it is desirable for copper levels to be neither increased nor decreased. About 4 mg of copper excreted into the bile each day is mostly reabsorbed by the intestines, which in combination with dietary absorption of 0.6–1.5 mg copper, leads to a relatively constant level in the body.
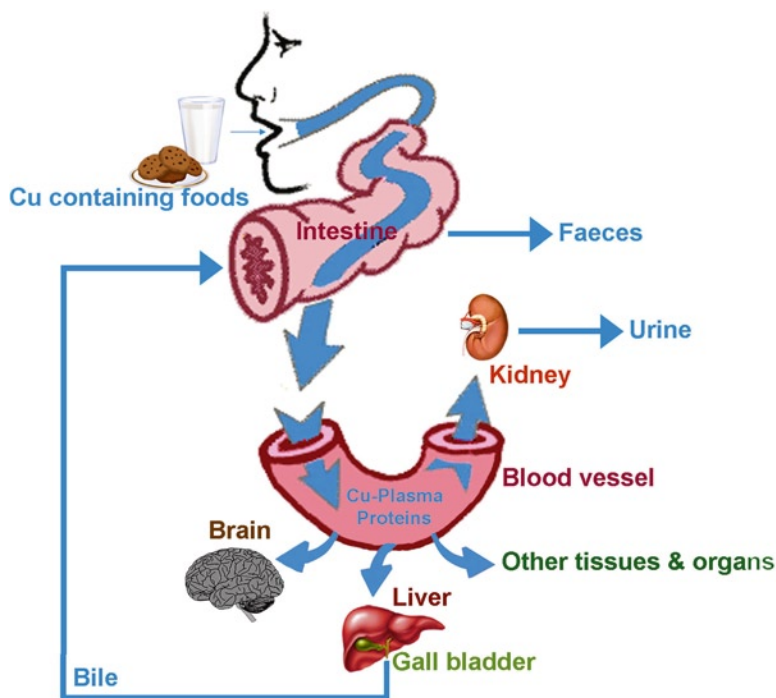
Fig. 150.2 Pathway of copper in the body. The main organs involved in copper uptake, absorption, and excretion are shown

150.3.2 Copper Transport

Copper in blood is transported in a protein-bound form to all tissues and organs (Fig. 150.2). Radiolabeled copper studies have shown that labeled copper disappeared from plasma within 2 h (Weiss and Linder 1985). The plasma-protein carriers of copper are ceruloplasmin, albumin, transcuprein, and some low molecular weight small peptides and amino acids. Of these, ceruloplasmin constitutes the nonexchangeable pool while the rest binds copper in a removable fashion to facilitate easy exchange with tissues.

(i) *Ceruloplasmin* – The major copper binding protein in blood is ceruloplasmin, which is synthesized in the liver where it binds copper. Almost 90% of the serum copper is bound to ceruloplasmin, but it is not utilized for copper transport as the bound copper is in a nonexchangeable form. Ceruloplasmin is a multicopper oxidase that requires copper for its function in the iron transport system. Ceruloplasmin oxidizes Fe^{2+} to Fe^{3+}, which then is bound by transferrin for transport. The equivalent protein in yeast is Fet3, a protein that also functions as a multicopper oxidase (see Table 150.1) (Askwith et al. 1994; de Silva et al. 1997; De Silva et al. 1995; Yuan et al. 1995). People with a total deficiency of ceruloplasmin (aceruloplasminemia) have an iron metabolism disorder and midlife dementia (Harris et al. 1995).

(ii) *Albumin* – Albumin is one of the most abundant plasma proteins. Although albumin can carry ~40 mg copper per litre of blood, it usually carries less than 1% of this amount at a time. Albumin binds copper with high-affinity via three amino acid residues at its N-terminus (Linder 2002).

(iii) *Transcuprein* – Transcuprein is a macroglobulin and is another high-affinity copper carrier found in the serum of mammals, including humans, rats, and dogs (Liu et al. 2007; Hyun and Filippich 2004; Linder 2002; Montaser et al. 1992). Both albumin and transcuprein carries 12% each of the total plasma copper and also rapidly exchanges copper with each other (Linder 2002).

(iv) *Low molecular weight fraction* – Trace amounts of copper are found bound to small peptides and amino acids in blood (Linder 2002). They are less tightly bound and increase copper content in blood directly after a meal (Zatta and Frank 2007).

150.3.3 Distribution of Copper

A healthy man of 70 kg is estimated to contain 110 mg of copper, which is constituted by 10 mg in the liver, 8.8 mg in brain, 6 mg in blood, 26 mg in skeletal muscles, and 46 mg in skeleton and bone marrow (see Fig. 150.3) (Linder et al. 1998).

 (i) *Copper in the brain* – Copper enters the brain from the bloodstream as free Cu ions via the blood–brain–barrier (BBB) and the entry is regulated by the blood-CSF barrier (Choi and Zheng
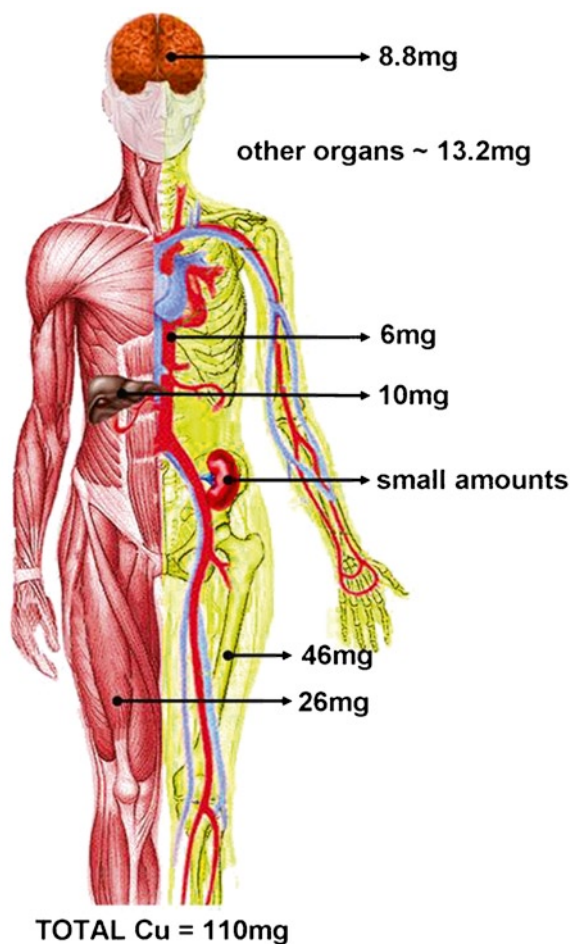
Fig. 150.3 Regional distribution of copper in the human body. Distribution of absorbed copper in different organs of the body is shown. Units are expressed in mg and the amounts are based on a healthy man with a total copper of 110 mg (Source of values: Linder et al. 1998)
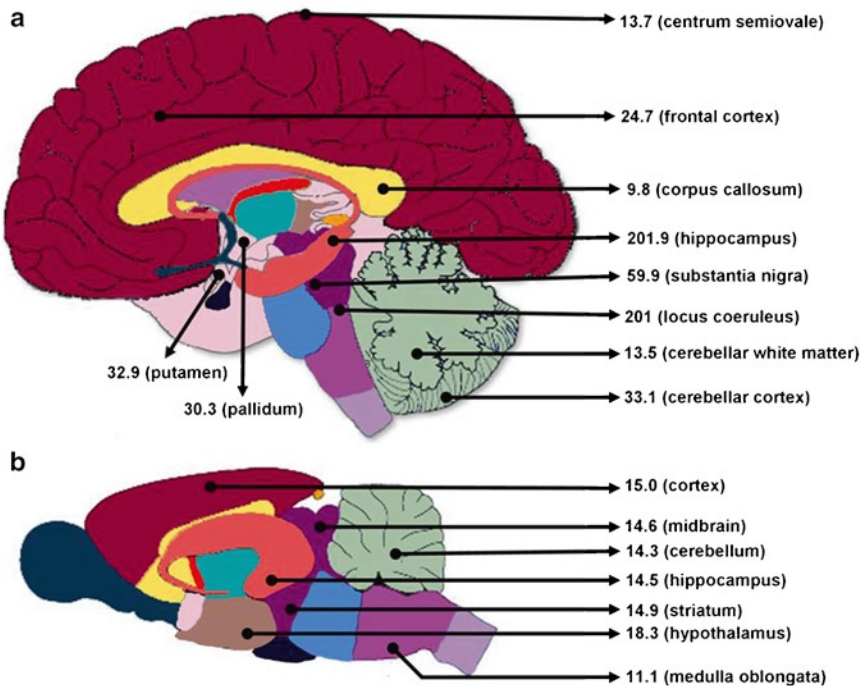
Fig. 150.4 Regional distribution of copper in the brain. Distribution of copper in different regions of (**a**) human brain and (**b**) rat brain are shown. Units are expressed as μg/g dry weight (Source of values: Prohaska 1987)

2009). While the brain contains greater amounts of copper than the blood, the concentration varies between different regions of the brain depending on age, species, environment, and genetics (see Fig. 150.4) (Zatta and Frank 2007). Compared to other animal species, the human brain has the highest copper content (Zatta and Frank 2007). The highest metal ion concentration in the adult human brain is found in substantia nigra, nucleus dentatus, putamen, and nucleus caudatus (reviewed by Speziali and Orvini 2003).

(ii) *Copper in other organs* – Most of the absorbed copper is mainly transported to the liver via enterohepatic circulation and some to the kidneys via systemic circulation. Radiolabelled copper studies show that 40% of the absorbed copper localizes in the liver by 6 h of ingestion (Weiss and Linder 1985). Though only a small amount of copper is taken to the kidneys in normal conditions, excess dietary intake can result in high levels of copper in kidneys and urine.

150.4 Copper in Cells

At the cellular level, much has been learned about the destiny of copper through basic studies of yeast genetics and cell biology. Yeast has been ideal for such studies because it is the best understood eukaryote and because it is readily genetic manipulated. In addition, gene knockouts are available for all yeast genes enabling easy and direct study of their functions. The high-level of similarity and homology between yeast and human genes aids functional identification and also often allows human gene complementation to be achieved. In the case of copper, it appears that both yeast and humans share the same pathway for the destiny of copper (shown in Fig. 150.5). The human proteins involved
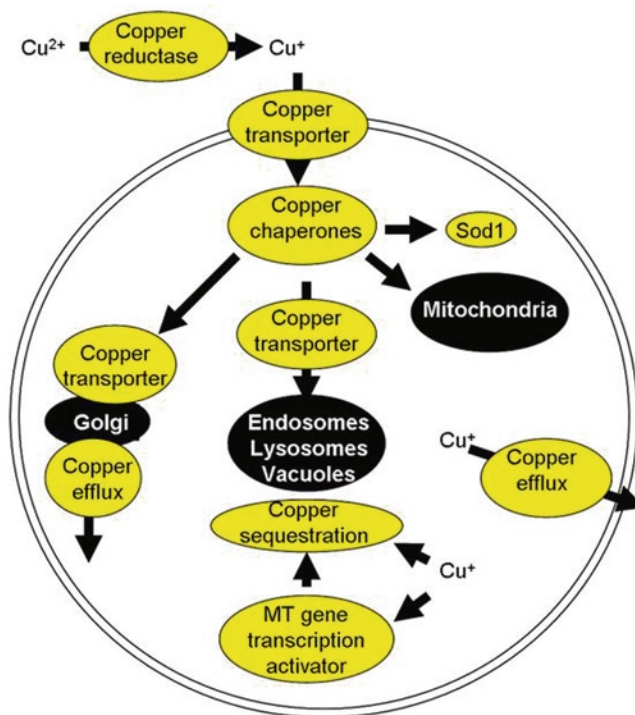
Fig. 150.5 Schematic representation of the cellular destiny of copper in eukaryotes (adapted from Macreadie 2007). The shaded ellipses represent the classes of proteins described in Table 150.3. Exogenous Cu^{2+} is reduced by a copper reductase to Cu^+ which can be transported into the cell by a membrane-spanning copper transporter. Specific chaperones carry Cu^+ to specific locations, including to Sod1, the mitochondrion and the *trans*-Golgi network. Another copper transporter delivers Cu^+ to late endosomes and lysosomes in mammals, or vacuoles in yeast. Efflux pumps and metallothionein remove or sequester excess copper. Levels of metallothionein are tightly controlled at the transcription level by a copper-sensing transcription factor that is itself a copper apothionein

in the intracellular handling of copper and the yeast equivalent proteins are summarized in Table 150.3. Several human diseases involving copper metabolism (e.g., Menkes and Wilson's disease), have also greatly aided in understanding the copper metabolism. The sections below examine copper homeostasis and the fate of copper at the cellular level.

150.4.1 Cellular Copper Homeostasis

Copper homeostasis is critical for the well-being of all organisms. Although copper is essential for the survival of many enzymes and biochemical processes that are dependent on copper for activity, excess free copper can lead to cellular toxicity. Copper toxicity is mainly brought about by the generation of aggressive free radicals via the Fenton reaction catalyzed by copper and the structural disruption of proteins via the ectopic binding of copper (Balamurugan and Schaffner 2006). Hence, all organisms, from bacteria to yeast to humans, possess complex pathways and regulatory mechanisms to control cellular uptake, transport, distribution, detoxification, and efflux of copper in order to maintain cellular homeostasis of copper (further explained below).

Table 150.3 Copper proteins in the cell (Macreadie 2007)

Function	Human proteins	Yeast proteins
Cu reduction	Steap1, Steap2, Steap3, Steap4	Fre1, Fre2
Multicopper oxidase/ Fe transport	Ceruloplasmin, Hephaestin	Fet3
Cu uptake	hCtr1, hCtr2 (late endosomes, lyzosomes)	Ctr1, Ctr3, Ctr2 (vacuoles)
Cu chaperone	Atox1, formerly called Hah1 ($\rightarrow$ ATP7A and ATP7B)	Atx1 ($\rightarrow$ Ccc2 $\rightarrow$ Fet3)
	Ccs1 ($\rightarrow$ Sod1)	Ccs1 ($\rightarrow$ Sod1)
	Cox17 ($\rightarrow$ Sco1 and Cox11)	Cox17 ($\rightarrow$ Sco1 $\rightarrow$ Cox11)
	Sco1 ($\rightarrow$ Cco)	Sco1 ($\rightarrow$ Cox2)
	Cox11 ($\rightarrow$ Cco)	Cox11 ($\rightarrow$ Cox1)
Internal Cu transport/efflux	Atp7A ($\rightarrow$ secretory pathway)	Ccc2
	Atp7B ($\rightarrow$ ceruloplasmin)	Ccc2
Cu sequestration	Metallothioneins	Metallothioneins
MT transcription factor	Mtf-1	Ace1

Major human and yeast proteins involved in copper homeostasis are listed

The arrows indicate the transfer of copper and its target proteins

150.4.2 Cellular Copper Uptake

The handling of copper in eukaryotic cells is depicted in Fig. 150.5. In the diet, copper occurs in its most oxidized form (Cu^{2+}) and requires reduction by a cell-derived copper reductase (to Cu^+) to enable transport into cells. In yeast the copper transporters, Ctr1 and Ctr2, utilize the same metalloreductase, Fre1 (Rees and Thiele 2007) which is also a ferric reductase. Another ferric reductase, Fre2, appears to have an equivalent role to Fre1. The human counterparts of Fre1, the Steap proteins, function as both cupric and ferric reductases (Ohgami et al. 2006).

The transport of copper through the plasma membrane requires a membrane-localized copper transporter which delivers the Cu^+ to a copper chaperone. In yeast, this transport occurs through a high affinity copper transporter Ctr1 (Dancis et al. 1994a, b). Human equivalents of Ctr1 and hCtr1 were identified by yeast complementation studies (Zhou and Gitschier 1997). Yeast with a defective *ctr1* gene exhibited defects in respiratory growth, iron transport, and Sod1p, all of which were rescued by the human gene, hCtr1. The overproduction of hCtr1 led to copper overload (Zhou and Gitschier 1997). A similarity search of the human proteome identified additional gene, hCtr2 (Zhou and Gitschier 1997), that is expressed in late endosomes and lyzosomes where it facilitates cellular copper uptake (van den Berghe et al. 2007). An equivalent copper transporter in yeast, Ctr2, is found exclusively on the vacuolar membrane where it controls vacuolar copper levels (Kampfenkel et al. 1995; Rees et al. 2004). It appears that Ctr2 is a nonessential vacuolar copper transporter (Portnoy et al. 2001).

150.4.3 Metallochaperones for Copper Trafficking

Unlike chaperones, metallochaperones (e.g., copper chaperones) do not facilitate protein folding. Instead, they protect the cell by binding copper with high affinity and deliver it to specific target proteins within the cell. Each copper chaperone is highly specific for its ultimate destination. Functional identification of the copper chaperones, or metallochaperones, was first made in yeast. Later studies indicated that copper chaperones were conserved from yeast to humans as three functional groups depending on their ultimate destination (reviewed by Balamurugan and Schaffner

2006). Ccs1 chaperones copper to the eukaryotic antioxidant enzyme, Cu/Zn superoxide dismutase (Sod1) in the cytosol (Culotta et al. 1997); while three copper chaperones, Cox17, Cox11 and Sco1, works together to deliver copper to cytochrome *c* oxidase (Cco) in the mitochondria (Glerum et al. 1996; Amaravadi et al. 1997; Horng et al. 2004). Atx1 is the chaperone responsible for delivering copper to the secretory pathway for cuproenzymes at the cell surface or for release (Klomp et al. 1997; Lin et al. 1997; Pufahl et al. 1997). In the Golgi, the copper from Atx1 is utilized by the copper-transporting ATPases, ATP7A and ATP7B in humans and Ccc2 in yeast. Though only yeast chaperones have been mainly cited above, the human homologs of these chaperones are described in Table 150.3.

150.4.4 Internal Copper Efflux

Internal copper efflux is accomplished by ATP-dependent transporters of the ATP7 family, also known as P-type ATPases. Insights on cellular copper efflux in humans are mainly derived from studies of Menkes disease and Wilson's disease, the two major genetically-inherited disorders of copper homeostasis (further detailed under "copper-associated diseases" below). Human cells contain two isoforms of ATPases: ATP7A (or MNK transporter) that is expressed in the mucosal cells of intestinal epithelium and most other tissues other than liver, and ATP7B (or WND transporter) which is primarily expressed in liver and certain areas of the brain (Linder 2002; Balamurugan and Schaffner 2006). Both ATPases contain six copper binding sites at the N-terminus (Zatta and Frank 2007) and are functionally stimulated by copper for trafficking (Balamurugan and Schaffner 2006). At normal or low copper, ATP7A delivers intracellular copper to enzymes in the *trans*-Golgi network (Yamaguchi-Iwai et al. 1996) but at high copper levels, ATP7A moves to the plasma membrane to perform copper efflux (Petris et al. 1996). ATP7A also plays an important role in systemic copper absorption, reabsorption of copper in kidneys and adequate copper supply to the brain (reviewed by Balamurugan and Schaffner 2006). ATP7B is functionally related to ATP7A and they also share 54% sequence similarity. At normal or low copper, ATP7B is found only in the liver where it delivers intracellular copper to apoceruloplasmin in the *trans*-Golgi network (Yamaguchi-Iwai et al. 1996); but at high copper levels, ATP7B moves copper to vesicles for delivery to the biliary caniliculus, performing copper efflux into the bile for excretion (Petris et al. 1996). Yeast cells have an equivalent pump, Ccc2, which facilitates cation transport, including copper (Yuan et al. 1995). Ccc2 is also an ATPase and it translocates copper into the trans-Golgi vesicles, where copper is then packed into the multicopper containing protein ferroxidase Fet3 (Arnesano et al. 2001).

150.4.5 Copper Sequestration and Detoxification

Since excess and free copper are toxic to cells, it is imperative that cellular mechanisms exist to sequester free intracellular copper. Healthy yeast cells maintain free copper levels at less than one free copper ion per cell (Rae et al. 1999).

Metallothioneins (also known as copper scavengers) are the cellular copper binding proteins that provide significant protection against elevated copper levels. Yeast metallothionein (Karin et al. 1984; Winge et al. 1985) is highly regulated by Ace1, a constitutively produced transcriptional activator of the yeast metallothionein gene (Buchman et al. 1989; Szczypka and Thiele

1989). In the presence of copper, Ace1 binds copper and activates transcription. In the converse situation of copper starvation, another yeast transcription factor, Mac1 acts as an intramolecular autoinhibitory domain. In human cells, heavy metal load and copper excess is handled by the transcription factor, MTF1. MTF1 is the functional analog of yeast Ace1; but they are neither related to each other nor similar in their binding sites (reviewed by Balamurugan and Schaffner 2006). In the absence of metallothionein, superoxide dismutase (SOD) plays a major protective role against copper toxicity. It is significant that some cases of amyotrophic lateral sclerosis (ALS) have defects in Cu–Zn SOD, suggesting some linkage between this form of motor neurone disease and copper metabolism. Despite the capacity of metallothioneins to store copper, they cannot perform copper efflux. For pumping out excess copper, cells depend on the afore-mentioned ATPases.

150.5 Copper-Associated Diseases

Deficient or excess copper can lead to serious disorders in many organs of the body, including brain. Depending on the origin, human disorders associated with copper can be classified into three: hereditary, chronic deficiency, and overload.

150.5.1 Hereditary Copper Diseases

Menkes disease and Wilson's disease are the two major genetically-inherited disorders of copper homeostasis resulting from mutations in the copper transporters, ATP7A (MNK transporter) and ATP7B (WND transporter) respectively. Menkes disease, an X-linked recessive disorder, is effectively a copper deficiency disease that presents with growth failure, skeletal defects, degeneration of the central nervous system, and early death (Danks 1995). Contradictorily, despite the copper deficiency in Menkes disease, the kidneys and intestinal epithelial cells in affected individuals accumulate copper, owing to the defect in copper efflux (Mercer 2001). On the other hand, Wilson's disease, an autosomal recessive disorder, is effectively a copper toxicosis disease that presents with copper accumulation in the liver and brain, leading to liver cirrhosis and neurological problems including behavioral disturbances and movement disorders. Menkes and Wilson's disease are similar in that they utilize a similar pump, but they use it in different tissues. The MNK transporter (ATP7A) is also known to be involved in placental copper transfer. Hence, abnormal gestational development and copper-deficient phenotype in fetus and newborn is observed in Menkes disease (Linder 2002). In contrast, Wilson's disease occurs only gradually after birth. Occipital Horn Syndrome (OHS), an X-linked connective tissue disorder, is a mild variant of Menkes disease caused by mutations in the Menkes gene ATP7A and presents with mild neurological disease (Mercer 2001). Another hereditary copper-associated disease is aceruloplasminemia which is caused by mutations in the ceruloplasmin gene, but it manifests as an iron accumulation disorder and does not affect copper metabolism probably due to the presence of other plasma-protein carriers for copper (Mercer 2001; Linder 2002).

Menkes disease can be treated by administering copper histidine, but success rates depend on residual Menkes protein activity. In Wilsons's diseases, treatment by Cu-chelation therapy or use of oral zinc (to reduce copper absorption from diet) is promising if disease is diagnosed prior to irreversible tissue damage (Mercer 2001).

150.5.2 Copper Deficiency Diseases

Clinical copper deficiency is rare in adults (Mercer 2001), but it can occur due to genetic predisposition, malnutrition, marginal intake of copper, reduced bioavailability (caused by excess consumption of zinc, molybdenum, chelating agents, compounds that interfere with copper absorption, etc.), patients with gastrointestinal disorders or surgical treatment such as removal/bypass of a large portion of intestine, peritoneal dialysis, etc. (Zatta and Frank 2007). At the molecular level, copper deficiency reduces the activity of SOD and other components of the oxidant defense system resulting in increased lipid peroxidation and oxidative damage to DNA and proteins (Uriu-Adams and Keen 2005). Deficiency of copper also affects the function of cuproenzymes, thereby leading to anemia, neutropenia, changes in ossification, and elevated plasma cholesterol (Zatta and Frank 2007). Severe cases display seizures. In the brain, deficiency of bioavailable copper plays a major role in the pathogenesis of many neurodegenerative diseases like Prion disease, Alzheimer's disease (AD), Huntington disease (HD), Parkinson's disease (PD), etc. (further explained in "role of copper in neurological diseases" below).

150.5.3 Copper Toxicosis

As mentioned earlier, increased amounts of copper can cause excessive oxidative stress and significant tissue damage. The oxidative stress is a consequence of the redox reactivity of copper via the Fenton reaction, i.e. production of free radicals by catalysing the reaction between superoxide anion and hydrogen peroxide. Tissue damage is caused by the structural disruption of proteins by copper and also as a result of oxidative stress (Uriu-Adams and Keen 2005). Copper toxicosis can occur as a result of copper poisoning, increased dietary intake or genetic defects. Copper poisoning reports indicate instances of accidental or deliberate ingestion of beverages contaminated with copper. Symptoms in these cases progress from abdominal pain, nausea, vomiting, headache, lethargy and diarrhea to tachycardia, respiratory difficulties, hemolytic anemia, gastrointestinal bleeding, liver and kidney failure, finally resulting in death (Hyun and Filippich 2004). Genetic copper toxicity disorders include Wilson's disease, Idiopathic copper toxicosis (ICT), Indian childhood cirrhosis (ICC), and endemic Tyrolean infantile cirrhosis (ETIC), all of which have an autosomal recessive mode of inheritance (Mercer 2001; Hyun and Filippich 2004; Balamurugan and Schaffner 2006). ICT, ICC, and ETIC are all fatal hepatic diseases. Copper contaminated milk feeds have been implicated in ICC and ETIC (Hyun and Filippich 2004; Balamurugan and Schaffner 2006). Copper toxicosis also contributes toward some neurodegenerative diseases like ALS and Creutzfeldt-Jakob disease (CJD) (Uriu-Adams and Keen 2005). In liver, copper accumulation can also occur as a consequence of chronic cholestatic liver diseases like primary biliary cirrhosis and chronic hepatitis.

150.5.4 Other Diseases Associated with Copper

Although metallic copper is insoluble, inhalation of copper dust from industrial processes can cause "copper fever" that presents with sweetish taste in mouth, dry throat, burning eyes, followed by severe headache, leukocytosis, fatigue, and catarrhic symptoms (Balamurugan and Schaffner 2006). Altered copper metabolism has also been reported in inflammation, infection, and cancer (reviewed by Linder 2002).

Key Points of Copper

- A number of essential enzymes in the cell require copper for their normal function.
- Copper is a trace element that is essential for life.
- Too little or too much is bad, but exquisite handling at the level of the cell and organs, ensures the desired homeostasis.
- We require less than 1 mg of copper per day.

150.6 Copper and the Brain

Copper contributes positively to brain development and function. Besides cytochrome *c* oxidase, which is essential for energy generation in brain, copper is utilized by dopamine β mono-oxygenase and peptidyl α amidating mono-oxygenase, both of which are important for the biosynthesis of neurotransmitters. Transport of copper across the BBB and distribution within the brain is regulated by ATP7A, the mutation of which leads to severe deficiency of copper in the brain. Bioavailability of copper is also important for normal functioning of the brain. While chronically high or low copper levels lead to major abnormalities such as Menkes or Wilson's disease, some evidence suggest that even more subtle changes in copper homeostasis have an impact on the brain, leading to some of the major late onset neurological diseases. However, more work is required to decipher the exact mechanisms of these relationships.

150.6.1 Role of Copper in Neurological Diseases

PD is the second most common neurodegenerative disorder after Alzheimer's disease, affecting both men and women over 50. PD is characterized by abnormalities of movement, such as tremor, muscular rigidity, and postural instability brought about by the degeneration of neurons in a region of the brain that controls movement. Copper affects the oligomerization of α-synuclein (Paik et al. 1999), a key protein implicated in PD. Furthermore, dopamine that is strongly associated with PD may become more toxic when it interacts with copper (Paris et al. 2001; Snyder and Friedman 1998; Spencer et al. 1994).

Prions are infectious protein particles involved in transmissible spongiform encephalopathies (TSEs), which includes CJD, scrapie, chronic wasting disease (CWD), and bovine spongiform encephalopathy (BSE). These fatal neurodegenerative diseases are caused by the misfolding of cellular prion protein PrP^c to the infective disease causing isoform, PrP^sc. Brain copper has been reported to be low in TSEs (reviewed by Legleiter et al. 2007). Furthermore, some studies indicate that human prions have copper binding sites (Brown et al. 1997; Hornshaw et al. 1995). It is speculated that the binding of copper to PrP^c may serve to stabilize the protein and allow normal function (Legleiter et al. 2007). However, this requires further research.

ALS is a progressive neurodegenerative disease that affects upper and lower motor neurons resulting in muscle weakness and atrophy. Death due to respiratory failure occurs within a short time from the onset of symptoms. The familial form of ALS is found to have a mutation in Cu–Zn SOD gene. Though one group has reported severe copper depletion of spinal cord in copper-deficient SOD, contradictory results have been reported by others (reviewed by Zatta and Frank 2007). Hence, further investigation is warranted to understand the molecular mechanism.

HD is another progressive neurodegenerative disease characterized by glutamine expansion within the N-terminus of huntingtin protein. Affected individuals undergo progressive motor, cognitive, and psychiatric deterioration. HD brain has shown an accumulation of copper and iron in the

striatum (Dexter et al. 1991). Recent studies indicate a pro-oxidant interaction between copper and huntington protein (Fox et al. 2007).

150.6.2 Copper and Alzheimer's Disease

AD is a fatal and highly debilitating progressive mental disorder that generally affects people over 65 or as young as 40–50 years. It is the most prevalent form of dementia and is characterized by severe cognitive impairment due to degeneration of brain cells that handle speech, memory, and thought. The most important protein implicated in AD is the Alzheimer's Precursor Protein (APP) from which the Aβ peptide, or β-amyloid is derived. APP has two copper binding sites, including one in the Aβ peptide sequence (Atwood et al. 1998; Hesse et al. 1994). In transgenic mice, the overexpression of APP appeared to reduce levels of copper in brains (Bayer et al. 2003; Maynard et al. 2002; Phinney et al. 2003) suggestive of APP being a copper transporter (White et al. 1998). Although APP has no yeast equivalent, it performed copper efflux in yeast (Treiber et al. 2004) as it does in brains. Two other proteins, Aplp1 and Aplp2, may also perform copper efflux since they have copper binding domains and structural similarity (Hesse et al. 1994; White et al. 1998, 1999a, b).

APP is unique among the APP/Aplp1/Aplp2 family because it is cleaved by the BACE protease (Vassar et al. 1999) and γ secretase protease to produce Aβ. Aβ exhibits neurotoxicity and is a major component of the extracellular Aβ plaques associated with AD. The extracellular plaques are a reservoir for a number of metals, including copper, and it is has been considered that the copper in these plaques may be available for the production of reactive oxygen species (ROS) which could cause neuronal loss and brain damage (Bush 2000). However, in view of the overall decline in copper levels as brains age, the alternate possibility of a build up of Aβ causing a copper shortfall, should also be considered.

150.6.3 Manipulation of Brain Copper Levels

The possibility of manipulating neuronal copper levels may lead to rational approaches to the treatment of neurological diseases. Clioquinol, a metal chelating compound, and some related compounds represent some of the most promising drugs that have been trialled to date. Clioquinol reduces plaque in mouse AD models and it appears to alter copper levels (Cherny et al. 2001). In a treatment of APP 750[SL] transgenic mice, clioquinol was shown to improve survival (Schafer et al. 2007). While clioquinol reduced serum copper levels from around 800 to around 500 μg/l, even with added copper in the diet, brain copper significantly increased, from 3.9 to 4.2 μg/g with added dietary copper. The treated mice also exhibited normal survival and improved memory, suggesting that clioquinol enabled brain copper levels to increase, and this in turn gave the positive benefit. Clioquinol also increased copper levels in yeast producing APP (Treiber et al. 2004).

Interesting results from Sparks and Schreurs show that in cholesterol-fed rabbits, increased copper led to increased deposits of Alzheimer's Aβ brain plaque (Sparks and Schreurs 2003). Plaques were induced at levels of 0.12 ppm copper in drinking water (much lower than the levels of 1.3 ppm permitted by water supply agencies). We suggest that conversely, lower cholesterol levels could lead to lower copper levels, reducing Aβ plaques. Interestingly the statins, blockbuster cholesterol-lowering drugs, appear to be the best drug to lower the incidence of AD. One particular statin, simvastatin, is

unique with respect to reducing AD (Wolozin et al. 2007). Unlike many other statins, simvastatin is lipophilic and crosses the blood–brain–barrier (BBB), so it may be expected that simvastatin would reduce cholesterol synthesis in the brain.

Finally, vaccine approaches may have some merit in animal models of AD by clearing Aβ plaque. Whether this affects brain copper has not been considered but presumably metals associated with the plaque would be removed along with plaque.

It is clear that much is now known about copper homeostasis, but there is still some way to go before we conquer neurological diseases that involve copper. It is likely that an increased understanding of copper homeostasis may help in unravelling the many important neurological diseases involving copper metabolism.

Key Points of Copper in Brain

- Copper contributes positively to brain development and function.
- Most of the major neurological disorders are due to the disruption of copper homeostasis caused by abnormal copper interactions or irregular copper metabolism.
- Manipulation of brain copper levels with compounds like clioquinol or statins could be a rational solution.

150.7 Applications to Other Areas of Health and Disease

The importance of copper in nutrition and copper homeostasis has been emphasized in this chapter. This knowledge has implications for the animal husbandry, crop management, biological control strategies, and possibly the treatment of human diseases. For example, upsetting the copper homeostasis by increasing copper levels is a strategy in antifungal control in agriculture, where copper sulphate can be applied to prevent the growth of mould, mildew, and rust fungus in crops. Likewise copper sulphate performs effectively as an algaecide in domestic swimming pools. The converse strategy, lowering copper levels, may also be a strategy to consider for impeding cell growth. Specific copper chelators such as bathocuproine sulphate can effectively inhibit the growth of cells.

Copper-deficiency in soils may also adversely affect agricultural outputs. In Australia, copper deficient soils were associated with lower wool yields in sheep. Recognizing the deficiency of copper and other trace elements in many soils have led to remedial practices such as the use of salt licks.

Detailed knowledge of copper homeostasis also provides the insights required in engineering super microbes that may help in bioremediation. For example, copper is a significant pollutant at mining sites and its removal requires novel strategies such as organisms that have increased ability to sequester copper. Metallothioneins are not limited to copper sequestration; they can sequester other metals as well.

Potentially copper homeostasis could also be altered to control cell proliferative diseases; however, lack of specificity is likely to be an issue.

Summary Points

- Copper is essential for all cells. Depletion of copper leads to loss of growth and survival.
- Copper is a cofactor for a number of cuproenzymes involved in diverse reactions.
- Excess copper can be toxic. Thus all biological systems have complex mechanisms to maintain correct copper levels.

- The fate of copper, its roles, and its biological functions has been strongly supported by studies in yeast.
- The brain may be very sensitive to copper levels which change with aging.
- Copper is a significant factor in neurodegenerative diseases, including Alzheimer's Disease.

Definitions and Explanations

Bioavailability: The amount of substance that is absorbed by the body and becomes available at the site of biological activity.

Blood–brain–barrier: A membrane barrier that separates many compounds from the brain, including various drugs, biochemicals, and macromolecules.

Copper Efflux: Outward flow of copper from the cell in the event of excess copper.

Cuproenzymes: Enzymes that require copper for their normal function.

Homeostasis: The maintenance of a constant state. Cells require homeostasis for survival, as well as for growth.

Statins: The world's largest selling prescription drugs. Although prescribed for lowering cholesterol levels they also lower the incidence of AD and PD.

Yeast studies: The yeast Saccharomyces cerevisiae is a model organism for human studies. Resources pertaining to the yeast genome can be found at www.yeastgenome.org.

References

Amaravadi R, Glerum DM, Tzagoloff A. Hum Genet. 1997;99:329–33.

Arnesano F, Banci I, Bertini F, Cantini F, Ciofi-Baffoni S, Huffman DL, O'Halloran TV. J Biol Chem. 2001;276:41365–76.

Askwith C, Eide D, Van Ho A, Bernard PS, Li L, Davis-Kaplan S, Sipe DM, Kaplan J. Cell. 1994;76:403–10.

Atwood CS, Moir RD, Huang X, Scarpa RC, Bacarra NM, Romano DM, Hartshorn MA, Tanzi RE, Bush AI. J Biol Chem. 1998;273:12817–26.

Balamurugan K, Schaffner W. Biochim Biophys Acta. 2006;1763:737–46.

Bayer TA, Schafer S, Simons A, Kemmling A, Kamer T, Tepest R, Eckert A, Schussel K, Eikenberg O, Sturchler-Pierrat C, Abramowski D, Staufenbiel M, Multhaup G. Proc Natl Acad Sci USA. 2003;100:14187–92.

Brown DR, Qin K, Herms JW, Madlung A, Manson J, Strome R, Fraser PE, Kruck T, von Bohlen A, Schulz-Schaeffer W, Giese A, Westaway D, Kretzschmar H. Nature. 1997;390:684–7

Buchman C, Skroch P, Welch J, Fogel S, Karin M. Mol Cell Biol. 1989;9:4091–5.

Bush AI. Curr Opin Chem Biol. 2000;4:184–91.

Cherny RA, Atwood CS, Xilinas ME, Gray DN, Jones WD, McLean CA, Barnham KJ, Volitakis I, Fraser FW, Kim Y, Huang X, Goldstein LE, Moir RD, Lim JT, Beyreuther K, Zheng H, Tanzi RE, Masters CL, Bush AI. Neuron. 2001;30:665–76.

Choi BS, Zheng W. Brain Res. 2009;1248:14–21.

Culotta VC, Klomp LW, Strain J, Casareno RL, Krems B, Gitlin JD. J Biol Chem. 1997;272:23469–72.

Danks DM. In: Scriver CR, Beaudet AL, Sly WM, Valle D, editors. The metabolic and molecular basis of inherited disease. McGraw-Hill: New York; 1995. pp. 2211–35.

Dancis A, Haile D, Yuan DS, Klausner RD. J Biol Chem. 1994a;269:25660–7.

Dancis A, Yuan DS, Haile D, Askwith C, Eide D, Moehle C, Kaplan J, Klausner RD. Cell. 1994b;76:393–402.

de Silva D, Davis-Kaplan S, Fergestad J, Kaplan J. J Biol Chem. 1997;272:14208–13.

De Silva DM, Askwith CC, Eide D, Kaplan J. J Biol Chem. 1995;270:1098–101.

Dexter DT, Carayon A, Javoy-Agid F, Agid Y, Wells FR, Daniel SE, Lees AJ, Jenner P, Marsden CD. Brain. 1991;114:1953–75.

Fox JH, Kama JA, Lieberman G, Chopra R, Dorsey K, Chopra V, Volitakis I, Cherny RA, Bush AI, Hersch S. PloS One. 2007;2:e334 1–12.

Glerum DM, Shtanko A, Tzagoloff A. J Biol Chem. 1996;271:14504–9.

Harris ZL, Takahashi Y, Miyajima H, Serizawa M, MacGillivray RT, Gitlin JD. Proc Natl Acad Sci USA. 1995;92:2539–43.

Hesse L, Beher D, Masters CL, Multhaup G. FEBS Lett. 1994;349:109–16.

Horng YC, Cobine PA, Maxfield AB, Carr HS, Winge DR. J Biol Chem. 2004;279:35334–40.

Hornshaw MP, McDermott JR, Candy JM. Biochem Biophys Res Commun. 1995;207:621–9.

Hunt JR, Vanderpool RA. Am J Clin Nutr. 2001;74:803–7.

Hyun C, Filippich LJ. J Exp Anim Sci. 2004;43:39–64.

Kampfenkel K, Kushnir S, Babiychuk E, Inze D, Van Montagu M. J Biol Chem. 1995;270:28479–86.

Karin M, Najarian R, Haslinger A, Valenzuela P, Welch J, Fogel S. Proc Natl Acad Sci USA. 1984;81:337–41.

Klevay LM. In: Coates PM, Blackman MR, Cragg GM, Levine M, Moss J, White JD, editors. Encyclopedia of dietary supplements. Marcel Dekker: USA; 2005. pp. 133–41.

Klomp LW, Lin SJ, Yuan DS, Klausner RD, Culotta VC, Gitlin JD. J Biol Chem. 1997;272:9221–6.

Legleiter LR, Ahola JK, Engle TE, Spears JW. Biochem Biophys Res Commun. 2007;352:884–8.

Lin SJ, Pufahl RA, Dancis A, O'Halloran TV, Culotta VC. J Biol Chem. 1997;272:9215–20.

Linder MC. In: Massaro EJ, editor. Handbook of copper pharmacology and toxicology. Humana Press: New Jersey; 2002. pp. 3–32.

Linder MC, Hazegh-Agam M. Am J Clin Nutr. 1996;63:797S–811S.

Linder MC, Wooten L, Cerveza P, Cotton S, Shulze S, Lomeli N. Am J Clin Nutr. 1998;67:965S–71S.

Liu N, Lo LS, Askary SH, Jones L, Kidane TZ, Trang T, Nguyen M, Goforth J, Chu YH, Vivas E, Tsai M, Westbrook T, Linder MC. J Nutr Biochem. 2007;18:597–608.

Macreadie IG. Eur Biophys J. 2007;37:295–300.

Maynard CJ, Cappai R, Volitakis I, Cherny RA, White AR, Beyreuther K, Masters CL, Bush AI, Li QX. J Biol Chem. 2002;277:44670–76.

Mercer JFB. Trends Mol Med. 2001;7:64–9.

Montaser A, Tetreault C, Linder M. PSEBM. 1992;200:321–9.

Morris MC, Evans DA, Tangney CC, Bienias JL, Schneider JA, Wilson RS, Scherr PA. Arch Neurol. 2006;63:1085–8.

Ohgami RS, Campagna DR, McDonald A, Fleming MD. Blood. 2006;108:1388–94.

Paik SR, Shin HJ, Lee JH, Chang CS, Kim J. Biochem J. 1999;340:821–8.

Paris I, Dagnino-Subiabre A, Marcelain K, Bennett LB, Caviedes P, Caviedes R, Azar CO, Segura-Aguilar J. J Neurochem. 2001;77:519–29.

Petris MJ, Mercer JF, Culvenor JG, Lockhart P, Gleeson PA, Camakaris J. EMBO J. 1996;15:6084–95.

Phinney AL, Drisaldi B, Schmidt SD, Lugowski S, Coronado V, Liang Y, Horne P, Yang J, Sekoulidis J, Coomaraswamy J, Chishti MA, Cox DW, Mathews PM, Nixon RA, Carlson GA, St George-Hyslop P, Westaway D. Proc Natl Acad Sci USA. 2003;100:14193–8.

Portnoy ME, Schmidt PJ, Rogers RS, Culotta VC. Mol Genet Genomics. 2001;265:873–82.

Prohaska JR. Physiol Rev. 1987;67:858–901.

Pufahl RA, Singer CP, Peariso KL, Lin SJ, Schmidt PJ, Fahrni CJ, Culotta VC, Penner-Hahn JE, O'Halloran TV. Science. 1997;278:853–6.

Rae TD, Schmidt PJ, Pufahl RA, Culotta VC, O'Halloran TV. Science. 1999;284:805–8.

Rees EM, Thiele DJ. J Biol Chem. 2007;282:21629–38.

Rees EM, Lee J, Thiele DJ. J Biol Chem. 2004;279:54221–9.

Schafer S, Pajonk FG, Multhaup G, Bayer TA. J Mol Med. 2007;85:405–13.

Snyder RD, Friedman MB. Mutat Res. 1998;405:1–8.

Sparks DL, Schreurs BG. Proc Natl Acad Sci USA. 2003;100:11065–9.

Spencer JP, Jenner A, Aruoma OI, Evans PJ, Kaur H, Dexter DT, Jenner P, Lees AJ, Marsden DC, Halliwell B. FEBS Lett. 1994;353:246–50.

Speziali M, Orvini E. In: Zatta P, editor. Metal ions and neurodegenerative disorders. World Sci: London; 2003. pp. 15–65.

Szczypka MS, Thiele DJ. Mol Cell Biol. 1989;9:421–9.

Treiber C, Simons A, Strauss M, Hafner M, Cappai R, Bayer TA, Multhaup G. J Biol Chem. 2004;279:51958–64.

Uriu-Adams JY, Keen CL. Mol Aspect Med. 2005;26:268–98.

van den Berghe PV, Folmer DE, Malingre HE, van Beurden E, Klomp AE, van de Sluis B, Merkx M, Berger R, Klomp LW. Biochem J. 2007;407:49–59.

Vassar R, Bennett BD, Babu-Khan S, Kahn S, Mendiaz EA, Denis P, Teplow DB, Ross S, Amarante P, Loeloff R, Luo Y, Fisher S, Fuller J, Edenson S, Lile J, Jarosinski MA, Biere AL, Curran E, Burgess T, Louis JC, Collins F, Treanor J, Rogers G, Citron M. Science. 1999;286:735–41.

Wapnir RA. Am J Clin Nutr. 1998;67:1054S–60S.

Weiss KC, Linder MC. Am J Physiol. 1985;249:E77–E88.

White AR, Zheng H, Galatis D, Maher F, Hesse L, Multhaup G, Beyreuther K, Masters CL, Cappai R. J Neurosci. 1998;18:6207–17.

White AR, Multhaup G, Maher F, Bellingham S, Camakaris J, Zheng H, Bush AI, Beyreuther K, Masters CL, Cappai R. J Neurosci. 1999a;19:9170–9.

White AR, Reyes R, Mercer JF, Camakaris J, Zheng H, Bush AI, Multhaup G, Beyreuther K, Masters CL, Cappai R. Brain Res. 1999b;842:439–44.

Winge DR, Nielson KB, Gray WR, Hamer DH. J Biol Chem. 1985;260:14464–70.

Wolozin B, Wang SW, Li N-C, Lee A, Lee TA, Kazis LE. BMC Med. 2007;5:20 doi:10.1186/1741-7015-5-20.

Yamaguchi-Iwai Y, Stearman R, Dancis A, Klausner RD. EMBO J. 1996;15:3377–84.

Yuan DS, Stearman R, Dancis A, Dunn T, Beeler T, Klausner RD. Proc Natl Acad Sci USA. 1995;92:2632–6.

Zatta P, Frank A. Brain Res Rev. 2007;54:19–33.

Zhou B, Gitschier J. Proc Natl Acad Sci USA. 1997;94:7481–6.

Chapter 151
Fetal–Neonatal Iron Deficiency Affects Neurotrophic Factor Expression, Neural Differentiation, and Neuroplasticity in the Rat Hippocampus

Michael K. Georgieff and Phu V. Tran

Abbreviations

BDNF	Brain-Derived Neurotrophic Factor
CNTF	Ciliary Neurotrophic Factor
Dcx	Doublecortin
Dusp4	Dual Specificity Phosphatase 4
Egr1 and 2	Early-Growth-Response-Gene 1 and 2
EGF	Epidermal Growth Factor
ERK1 and 2	Extracellular-Signal Regulated Kinase 1 and 2
FID	Formerly Iron-Deficient
GDNF	Glial-Derived Neurotrophic Factor
Hif1α	Hypoxia Inducible Factor 1α
HMGCR	3-Hydroxy-3-Methylglutaryl Coenzyme A Reductase
ID	Iron-Deficient
IS	Iron-Sufficient
LTP	Long-Term Potentiation
Mbp	Myelin Basic Protein
mTOR	Mammalian Target of Rapamycin
NGF	Nerve Growth Factor
p75^{NTR}	Neurotrophic Receptor p75
P	Postnatal Day
PARV	Parvalbumin
qPCR	Quantitative RT-PCR
TrkB	Tyrosine-Receptor Kinase B
TUNEL	TdT-Mediated biotin-dUTP Nick End Labeling

M.K. Georgieff (✉)
Department of Pediatrics, Neonatology Division & Center for Neurobehavioral Development, School of Medicine, University of Minnesota, 420 Delaware St. SE, MMC 39 (for mail), D-136 Mayo Building (for courier), Minneapolis, MN 55455, USA
e-mail: georg001@umn.edu

151.1 Introduction

151.1.1 Fetal and Neonatal Iron Deficiency Impairs Cognitive Development

Iron deficiency is one of the foremost early-life micronutrient deficiencies, affecting approximately 30–50% of preschool age children and pregnant women worldwide (WHO 2008). Late gestational and neonatal (perinatal) iron deficiency arises from four common maternal gestational conditions: severe iron deficiency anemia (IDA), placental vascular insufficiency resulting from maternal hypertension, diabetes mellitus, and cigarette smoking (Chockalingam et al. 1987; Petry et al. 1992; Sweet et al. 2001). The adverse neurobehavioral effects of early-life iron deficiency in humans and animal models are considerable and long-lasting (Lozoff and Georgieff 2006). For example, iron-deficient (ID) human newborns exhibit deficits in cognitive development that last beyond the period of iron deficiency (Nelson et al. 2000; Siddappa et al. 2004; Riggins et al. 2009). While certain developmental deficits recover with iron treatment, cognitive deficits following neonatal and early postnatal iron deficiency in humans persist up to 10 years after iron treatment (Tamura et al. 2002; Lozoff et al. 2006). Fetal and neonatal ID rodents and monkeys showed similar adverse neurobehavioral effects (Golub et al. 2006; Felt et al. 2006; Schmidt et al. 2007). The potential neural basis of these cognitive deficits continues to be an active research area; however, these effects imply an impaired hippocampus, a brain region responsible for learning and memory.

151.1.2 Fetal–Neonatal Iron Deficiency Alters Hippocampal Structure, Function, and Gene Expression in the Rat Model

In rats, fetal–neonatal iron deficiency resulted in abnormal hippocampal CA1 dendritic structure, impaired synaptic transmission, and increased susceptibility to deleterious infarction (Jorgenson et al. 2003, 2005; Rao et al., 2007). These findings support the hypothesis of an abnormal hippocampus in ID rats. The possibility of early-life ID leading to dysregulation of genes necessary for proper hippocampal development was investigated with a microarray mRNA profiling analysis (Carlson et al. 2007). This work identified alterations in salient molecular pathways involved in neuronal differentiation with most notably the Alzheimer-related gene network centered on amyloid precursor protein and the mammalian target of rapamycin (mTOR) pathway (Carlson et al. 2007, 2008). The amyloid precursor protein gene network has been implicated in cytoskeletal remodeling, cell motility and growth cone formation during hippocampal development (Guenette et al. 2006; Ikin et al. 2007). The mTOR pathway integrates external stimuli such as nutrients and growth factors and gene expression necessary for the synaptic maturation and plasticity in the hippocampus (Tang et al. 2002; Schratt et al. 2004).

151.1.3 Neurotrophic Factors Mediate Hippocampal Development and Function

Neurotrophic factors such as nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF) regulate multiple aspects of neuronal differentiation and plasticity in the hippocampus (Hennigan et al. 2007). Fetal and neonatal environments affect the expression of these neurotrophic

factors. For example, an enriched environment has beneficial effects on hippocampal function and is accompanied by increased NGF and BDNF levels, whereas an adverse environment impairs memory function and lowers NGF and BDNF expression (Pham et al. 2002; Branchi et al. 2004). In addition, neural activity such as induction of long-term potentiation (LTP), a cellular phenomenon associated with memory formation, in the rodent hippocampus rapidly increases NGF and BDNF mRNA levels (Patterson et al. 1992; McAllister et al. 1999).

The role of BDNF in mediating hippocampal function is well established, as exemplified by deficits of learning and memory in rodents with BDNF suppression or gene targeted-deletion (Korte et al. 1995; Heldt et al. 2007). BDNF is a complex gene with multiple mRNA variants containing a common protein-encoding region (Timmusk et al. 1993). BDNF signaling is mediated by tyrosine-receptor kinase B (TrkB) and p75 neurotrophic receptor (p75^{NTR}) (Chao 2003). Full-length TrkB (TrkB$_{FL}$) contains the intracellular kinase signaling domain, while several short (truncated) isoforms (TrkB$_{S}$) lack this signaling domain (Klein et al. 1990). The p75^{NTR} is a low affinity receptor that binds promiscuously to BDNF as well as other known neurotrophic factors. BDNF binding of TrkB promotes neurite outgrowth and synaptic plasticity in part through regulation of activity-dependent immediate early genes c-fos, early-growth-response-gene 1 and 2 (Egr1 and Egr2) (Alder et al. 2003; Calella et al. 2007). In contrast, BDNF binding of p75^{NTR} reduces neurite outgrowth and mediates long-term depression (Woo et al. 2005; Zagrebelsky et al. 2005).

151.1.4 Fetal–Neonatal Iron Deficiency and Hippocampal Expression of Neurotrophic Factors

The effects of fetal–neonatal iron deficiency on the expression of neurotrophic growth factors critical for hippocampal neurogenesis, differentiation and plasticity have remained unresolved. However, the abnormal hippocampal dendritic morphology and impaired neurotransmission observed in fetal–neonatal ID rats led to the hypothesis that iron deficiency would result in dysregulation of neurotrophic factors involved in hippocampal differentiation and neuroplasticity. Moreover, the persistent deficits of hippocampal-dependent tasks in formerly iron-deficient (FID) rats, that were ID during fetal–neonatal period (Felt et al. 2006; Schmidt et al. 2007), imply a long-lasting change in regulation of neurotrophic factors including BDNF. Indeed, we found evidence of diminished BDNF signaling during and after a period of iron deficiency in the rat hippocampus (Tran et al. 2008, 2009).

151.2 Fetal–Neonatal IDA Acutely Alters Expression of Neurotrophic Factors and Delays Hippocampal Neuron Differentiation

151.2.1 Increased Expression of Neurotrophic Factors During Peak Normal Neuronal Differentiation in Rat Hippocampus

Differentiation of hippocampal neurons occurs rapidly during P15 and P30 in rats (Pokorny and Yamamoto 1981; Steward and Falk 1991) with a corresponding increase in iron uptake (Siddappa et al. 2002). Quantitative measurement (real-time PCR) of messenger RNA (mRNA) for ciliary neurotrophic factor (CNTF), epithelial growth factor (EGF), glial-derived neurotrophic factor (GDNF),
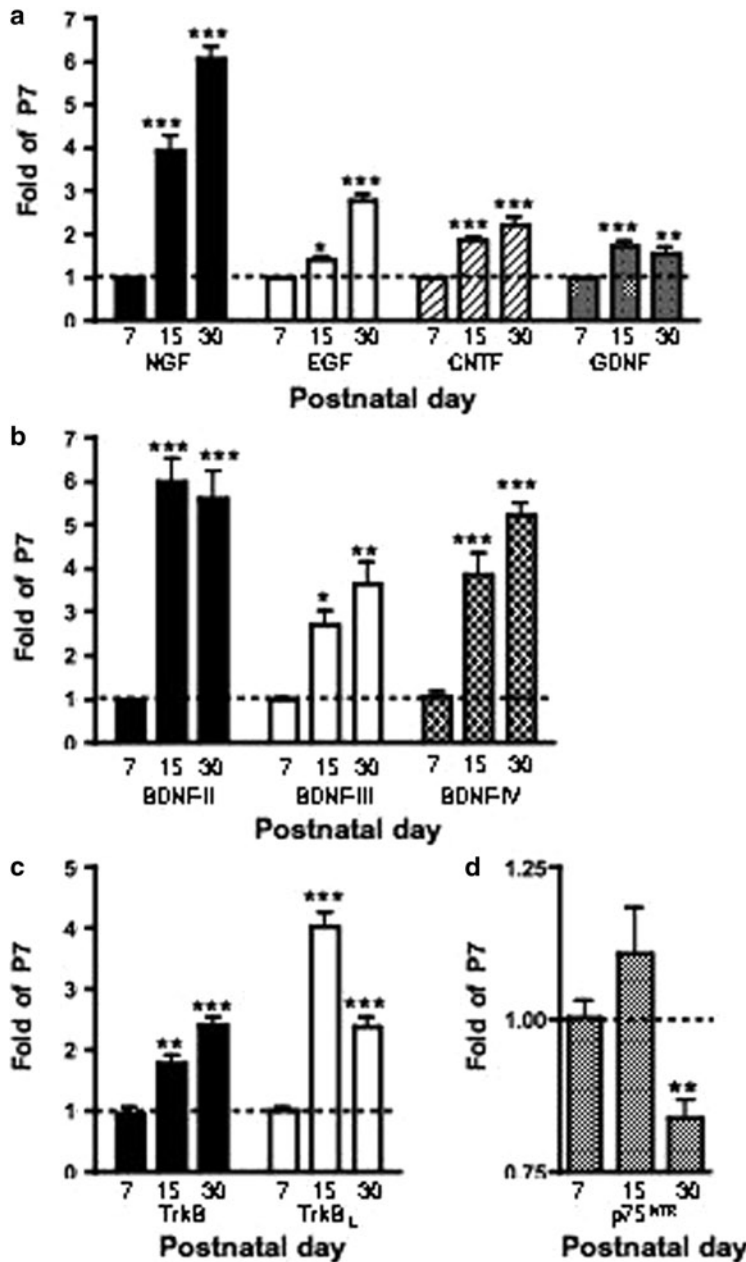
Fig. 151.1 Expression of neurotrophic factor mRNA levels at P7, P15, and P30 in the male rat hippocampus. Levels of messenger RNA (mRNA) were compared to P7, demonstrating the developmental expression of neurotrophic factors. (**a**) Nerve growth factor (NGF), EGF, CNTF, and glial-derived neurotrophic factor (GDNF), (**b**) BDNF -II, -III, and -IV, (**c**) total TrkB and TrkB full-length (TrkB$_L$), and (**d**) p75 neurotrophic receptor (p75^{NTR}). Values are means ± SEM, n = 4–6. Asterisks denote P-values as follows: *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$ (Modified and printed with permission from American Society for Nutrition)

and NGF showed higher levels at P15 and P30 compared to P7 (Fig. 151.1a). Likewise, BDNF-II, III and IV transcripts were greater at P15 and P30 compared to P7, with BDNF-II mRNA being at a negligible level compared to BDNF-III and IV in the developing rat hippocampus (Fig. 151.1b). Similar findings were also observed for BDNF receptors, TrkB and p75^{NTR} (Fig. 151.1c). Taken

together, peak expression of NGFs and their cognate receptors occurs during periods of rapid differentiation in the rat hippocampus (Tran et al. 2008). These findings are consistent with the role of neurotrophic factors in promoting neuronal differentiation and dendritic outgrowth.

151.2.2 Increased EGF, GDNF, NGF and p75^{NTR}, and Deceased BDNF Expression During Fetal–Neonatal ID in the Hippocampus

While CNTF levels were unaffected, levels of EGF, GDNF and NGF were greater in the ID compared to IS rats at P15 (Table 151.2). In contrast, iron deficiency decreased BDNF transcripts across development with a significant reduction of BDNF-III at P7 and BDNF-IV at P7 and P15 (Table 151.2). The difference was less significant between groups at P30, suggesting a normalization of expression with iron therapy. Despite lower BDNF levels, expression of its high affinity receptor TrkB was similar between ID and IS groups, suggesting an absence of an expected compensatory upregulation (Table 151.2). However, iron deficiency increased p75^{NTR} levels at P7 and P15. Collectively, iron deficiency dysregulates neurotrophic factors and associated receptors during the period of iron deficiency (Tran et al. 2008).

The reduced BDNF during periods of neural proliferation and differentiation (P7 and P15) may account for the 14% reduction in hippocampal size (Rao and Georgieff, unpublished data) and abnormal CA1 dendritic structure in older FID rats (Jorgenson et al. 2003). The effect of iron deficiency on proliferation and cell number remains unresolved with preliminary findings of increased neuronal turnover in a late gestational embryonic ID hippocampus (Lehman and Georgieff, unpublished data). Increased EGF, GDNF, NGF, and p75^{NTR} expression in the ID hippocampus suggest utilization of alternate pathways to compensate for the lower BDNF expression. Upregulation of EGF might facilitate neurogenesis and differentiation in ID hippocampus (Wong and Guillaud 2004). Likewise, GDNF could synergize with BDNF to promote neuronal survival (Erickson et al. 2001), minimizing the adverse effects of reduced BDNF. It is worthwhile to note that both EGF and GDNF mediate astrocyte proliferation and differentiation (Wong and Guillaud 2004; Chen et al. 2005). The effects of fetal–neonatal iron deficiency on astroglia development have not been fully investigated, albeit metabolomic evidence suggests increased astroglia in the ID hippocampus (Rao et al. 2003). Increased EGF and GDNF levels may affect the astroglia number as well as regulation of glutamine synthase activity (Yamada et al. 1997), in line with increased glutamine levels observed in the ID hippocampus (Rao et al. 2003). However, it is less clear what effects increased NGF and p75^{NTR} may have in the ID hippocampus. ProNGF/p75^{NTR} signaling induces neuronal apoptosis contrasting the survival effect of the mature-NGF/TrkA sig-

Table 151.1 Key facts of neurotrophic factors

1. A family of proteins classically includes nerve growth factor (NGF), BDNF, neurotrophin-3 (NT-3), and neurotrophin-4/5 (NT-4/5). These factors each bind a specific tyrosine receptor kinase (Trk) with high affinity (i.e. NGF/TrkA, BDNF/TrkB, NT-3, 4/TrkC). All bind p75 receptor with low affinity.

2. The non-classical members of neurotrophic factors include glial-derived neurotrophic factor (GDNF), CNTF, cardiotrophin-1 (CT-1), interleukin-6 (IL-6), and leukemia inhibitory factor (LIF). With the exception of GDNF, which initiates intracellular signaling by binding to the RET receptor tyrosine kinase, other factors bind and signal via G-protein coupled receptor (GPR130).

3. The role of neurotrophic factors is to regulate differentiation, growth, survival, and plasticity of both central and peripheral nervous systems.

This table describes general key facts of neurotrophic factors and their receptors. The binding of the neurotrophic factor to its cognate receptor initiates a signaling cascade that results in increased transcription and/or translation of downstream effectors

Table 151.2 Comparison of neurotrophic factor and receptor expression in the developing IS and ID rat hippocampus (Modified and printed with permission from American Society for Nutrition)

	P7		P15		P30		2-Way ANOVA P-values		
	IS	ID	IS	ID	IS	ID	Iron status	Postnatal age	Interaction
Transcript	Fold of P7 IS								
CNTF	1.0 ± 0.0^a	1.3 ± 0.1	1.9 ± 0.1^b	2.1 ± 0.2	2.2 ± 0.2^b	2.2 ± 0.2	0.11	<0.01	0.65
GDNF	1.0 ± 0.0^a	$1.8\pm0.1^*$	1.7 ± 0.1^b	$2.4\pm0.2^*$	1.5 ± 0.2^b	1.6 ± 0.2	<0.01	<0.01	0.01
EGF	1.0 ± 0.1^a	1.2 ± 0.1	1.4 ± 0.2^b	$2.2\pm0.2^*$	2.8 ± 0.33^c	2.9 ± 0.4	<0.01	<0.01	<0.01
NGF	1.0 ± 0.0^a	1.0 ± 0.1	3.8 ± 0.4^b	$5.2\pm0.5^*$	5.8 ± 0.3^c	6.5 ± 0.3	<0.01	<0.01	0.07
BDNF-III	1.0 ± 0.1^a	$0.6\pm0.0^*$	1.3 ± 0.0^b	1.1 ± 0.1	1.3 ± 0.1^b	1.0 ± 0.0	<0.01	<0.01	0.13
BDNF-IV	1.0 ± 0.1^a	$0.6\pm0.1^*$	1.7 ± 0.1^b	$1.1\pm0.1^*$	1.5 ± 0.2^b	$1.1\pm0.1^*$	<0.01	<0.01	0.96
TrkB	1.0 ± 0.1^a	1.0 ± 0.0	2.3 ± 0.3^b	2.2 ± 0.3	3.0 ± 0.2^c	2.8 ± 0.3	0.38	<0.01	0.91
TrkB$_L$	1.0 ± 0.0^a	1.2 ± 0.1	2.5 ± 0.3^b	2.3 ± 0.2	2.4 ± 0.2^b	2.9 ± 0.2	0.22	<0.01	0.14
p75	1.0 ± 0.0^a	$1.6\pm0.2^*$	1.1 ± 0.1^a	$1.9\pm0.1^*$	0.8 ± 0.0^a	0.9 ± 0.1	<0.01	<0.01	<0.01

Levels of transcript (messenger RNA) for relevant neurotrophic factors and BDNF receptors were compared between iron-sufficient (IS) control and iron-deficient (ID) hippocampi. Data were standardized to P7 value to demonstrate changes in transcript level across postnatal ages. Values are means ± SEM, $n = 4$–6. Means in a row without a common letter differ, $P < 0.05$ (a < b < c). *Asterisk denotes the difference from IS at a time, $P < 0.05$ Post-hoc Bonferroni corrected t-test

naling (Friedman 2000; Lee et al. 2001). Elevated NGF and p75[NTR] transcripts in the ID hippocampus would have predicted an increase in neuronal apoptosis. However, the observed reduction in apoptosis in postnatal ID hippocampus (Tran et al. 2008) suggests that increased NGF and p75[NTR] likely have a survival effect as seen in other studies (Bui et al. 2002; Culmsee et al. 2002). In addition, p75[NTR] is known to promote high-affinity ligand/receptor binding (e.g., BDNF/TrkB) and ligand/receptor retrograde transport (Chao 2003). The upregulation of p75[NTR] might act in a compensatory manner to promote BDNF/TrkB signaling, facilitating synaptic formation and LTP (Minichiello et al. 2002).

151.2.3 Reduced Doublecortin (Dcx) Expression is Associated with Delayed NeuN-Nuclear Accumulation in the Developing ID Hippocampus

The persistently immature form of electrophysiology (Jorgenson et al. 2005) combined with reduced NMDAR (NR2B) expression (Jorgenson and Georgieff, unpublished data) suggest an abnormal development of hippocampal glutamatergic neurotransmission in fetal–neonatal ID rats. Consistent with this effect, the level of Dcx, a microtubule-associated protein expressed in differentiating neurons (Francis et al. 1999), was reduced by 40% in the ID hippocampus at P15 (Fig. 151.2a). Dcx localization was similar in P15 IS and ID hippocampi with prominent expression in the dentate gyrus proper (Fig. 151.2b). ID rats also showed a failure of NeuN, a nuclear neuronal marker, localization to the nucleus of pyramidal neurons by P30 as seen in IS rats (Fig. 151.2c,d) (Tran et al. 2008). These findings imply a delay of neuronal maturation in the ID hippocampus during a period of rapid differentiation. Based on the increase demand of iron uptake during this developmental period (Siddappa et al. 2002), we propose that iron deficiency results in deferment of neuronal differentiation, perhaps leading to an extension of this rapid growth period, until sufficient iron replenishment. This developmental brake hypothesis is in agreement with the observed NeuN-nuclear localization in the hippocampus of iron-repleted P65 rats (Fig. 151.2e,f).
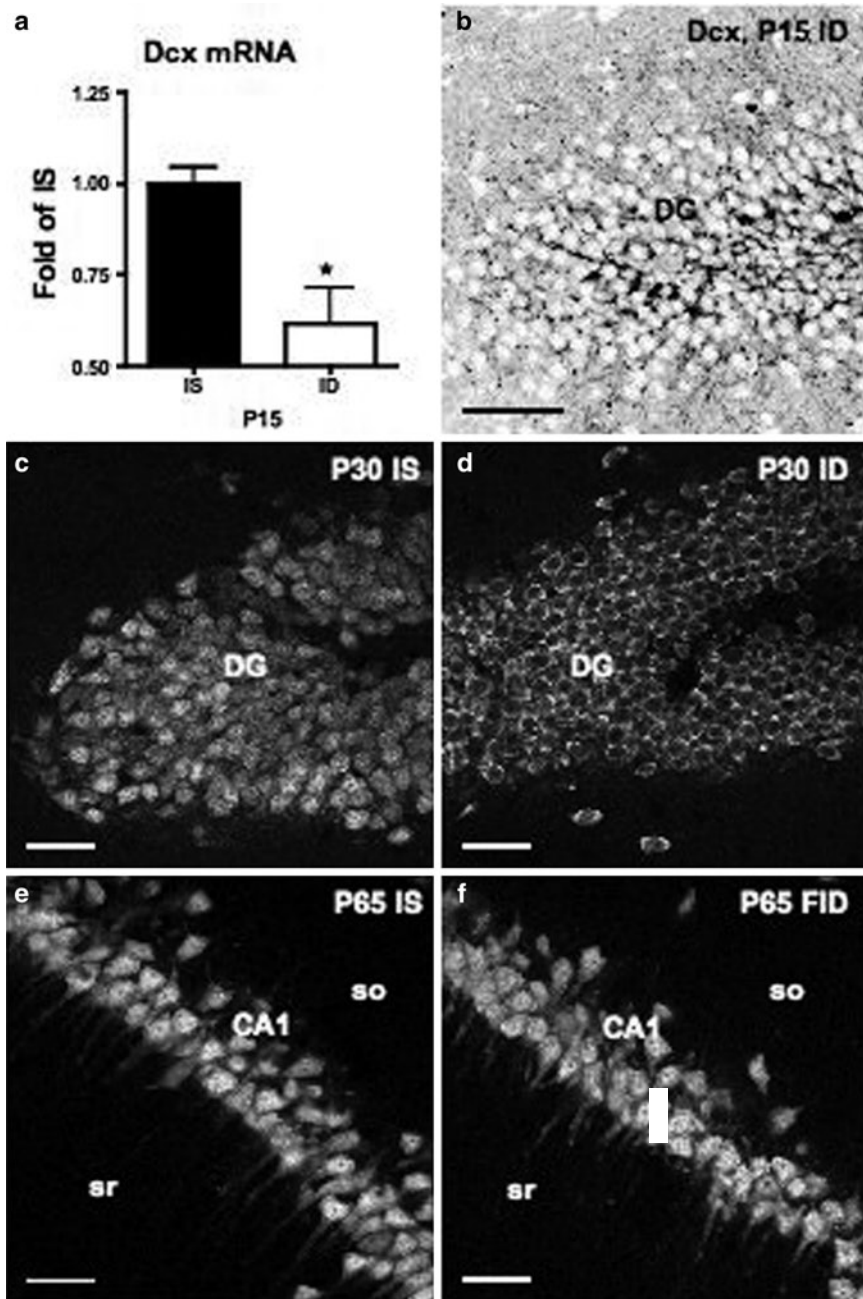
Fig. 151.2 Reduced P15 doublecortin (Dcx) expression and abnormal NeuN localization in the ID rat hippocampus. (**a**) Expression of a neuronal differentiation marker, doublecortin (Dcx), showed a significant reduction in the postnatal day (P)15 ID hippocampus compared to the IS control. Values are means ± SEM, $n = 4$–6. *$P < 0.05$, Mann-Whitney U-test. (**b**) Localization of Dcx protein in the dentate gyrus (DG) of the P15 ID rat. There was no apparent difference in Dcx localization between the IS and ID hippocampus. (**c–d**) NeuN staining in the dentate gyrus of P30 IS (**c**) and ID (**d**) hippocampi. Note the absence of NeuN in nuclei of ID neurons. Similar observations were seen in CA1 and CA3 hippocampus (data not shown). (**e–f**) NeuN staining in CA1 of P65 IS and FID rats. Note the presence of NeuN in cell nucleus. Scale bar = 50 μm

151.3 Long-Term Reduction of BDNF Activity in Adult Rats That Experienced Iron Deficiency During Fetal–Neonatal Period

The etiology of long-term the learning impairment seen in fetal and neonatal ID humans and rodent models remain largely unknown. The possibility of long-term dysregulation of neurotrophic factors and their downstream targets that regulate a cascade of molecular mediators of synaptic plasticity in FID rats was investigated (Tran et al. 2009).

151.3.1 Decreased Hippocampal BDNF and TrkB Expression in P65 FID Rats

Levels of p75^{NTR}, CNTF, CTGF, EGF, GDNF, and NGF were not different between the always IS control and FID P65 rats. However, P65 FID rats had lower levels of BDNF and its high affinity receptor TrkB (Fig. 151.3). Interestingly, truncated TrkB (TrkB$_S$) is expressed at a higher level than TkB$_{FL}$ in the control hippocampus, but not in the FID hippocampus at P65 (Fig. 151.3d). This finding
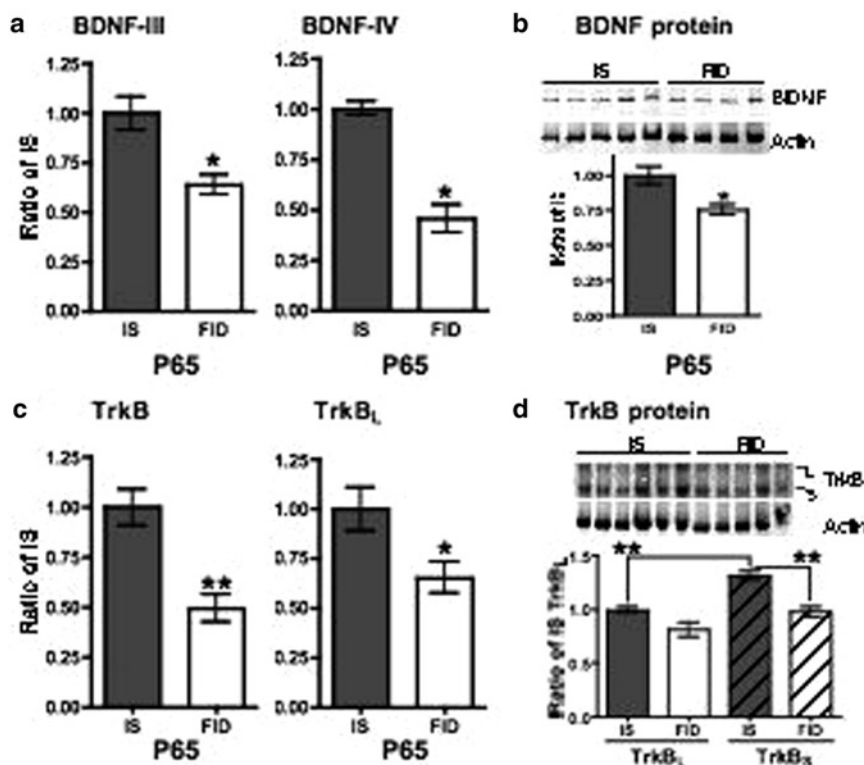
Fig. 151.3 Reduced BDNF and TrkB expression in the P65 FID hippocampus. Hippocampal expression of BDNF and TrkB receptor were compared between the control (always IS) and the formerly iron-deficient (FID) rats. Data were normalized to IS control. FID rats showed a reduced expression of BDNF and its cognate receptor TrkB. BDNF mRNA (**a**) and protein (**b**). TrkB mRNA (**c**) and protein (**d**). Values are means ± SEM, $n = 4$–6. *$P < 0.05$ and **$P < 0.01$, Mann-Whitney U-test (Modified and printed with permission from Wolters Kluwer Health)

suggests that the P65 FID hippocampus retains immature characteristics compared to the IS control hippocampus (Silhol et al. 2008). Despite having limited signaling capability, TrkB$_S$ has been implicated to negatively affect BDNF/TrkB signaling (Eide et al. 1996; Pillai and Mahadik 2008). Thus, the lower level of TrkB$_S$ in the FID hippocampus might have a compensatory effect by increasing the signaling capability of the available full-length receptor. Even with lower levels of BDNF and TrkB expressions, protein localization appeared similar in the hippocampus of both groups (Tran et al. 2009). While further ultrastructural analysis of protein localization is needed to ascertain these findings, preliminarily they imply an overall lower BDNF signaling in the hippocampus of FID rats without compromising their localization. The specific reduction of BDNF expression in FID rats suggests a more permanent change in its regulation induced by early iron deficiency. The precise mechanism awaits further investigation. One possibility may involve epigenetic modification (e.g., DNA methylation) at the BDNF gene, which was hypermethylated in rats exposed to adverse early-life environment (Roth et al. 2009).

151.3.2 Reduced Hippocampal Expression of BDNF-Activity Dependent Gene Cascades

In the postnatal brain, BDNF regulates neuronal HMGCR, the rate-limiting enzyme in cholesterol synthesis that facilitates synaptic vesicle formation (Suzuki et al. 2007). Consistent with lower BDNF activity, the level of HMGCR was decreased in P65 FID hippocampus (Fig. 151.4a), suggesting that vesicle formation may be compromised (Tran et al. 2009). Combined with a lower level of synaptobrevin I (Carlson et al. 2007), a protein involved in vesicle fusion (Schiavo et al. 1997), this finding may underlie the impaired paired-pulse facilitation and reduced synaptic efficacy seen in adult hippocampal slice preparations following recovery from fetal–neonatal iron deficiency (Jorgenson et al. 2005). Paired-pulse facilitation and LTP are important indices of neuroelectrophysiologic events during neurotransmission and LTP is widely accepted as a cellular substrate for learning and memory (Malenka 2003).

BDNF also induces the expression of c-fos, Egr1, and Egr2, which are activity-dependent immediate early transcription factors that facilitate LTP in the hippocampus (Alder et al. 2003; Rossler and Thiel 2004). Expression of these genes was also decreased in FID rats (Fig. 151.4b–d) (Tran et al. 2009). Lower c-fos expression may not only lead to a reduction in expression of genes necessary for LTP (Miyamoto 2006) but may also contribute to further reduction of BDNF expression (Dong et al. 2006), thereby leading to lesser plasticity in the hippocampus of FID rats. As expected, reduced expression of Egr1 was accompanied by lower expression of its known target genes, hif1α and Dusp4 (Berasi et al. 2006; Sperandio et al. 2009), in the hippocampus of FID rats (Fig. 151.5a,b) (Tran et al. 2009). Hif1α is an oxidative-state-dependent transcription factor that regulates chemokine (C-X-C motif) ligand 12 (Cxcl12), an important modulator of synaptic formation (Klein and Rubin 2004). Cxcl12 mRNA expression is reduced in FID rats (Carlson et al. 2007). Combined with similar long-term reductions in post-synaptic density 95 (PSD95) and calmodulin-dependent kinase IIα (CamKIIα), these changes may account for the abnormal apical dendritic length and branching in FID hippocampal neurons (Jorgenson et al. 2003; Carlson et al. 2007). DUSP4 (protein) is a dual specificity phosphatase targeting phosphorylated extracellular signal-regulated kinases 1 and 2 (ERK1 and ERK2), factors phosphorylated during formation of memory (Guan and Butch 1995; Kelly et al. 2003). Reduction of DUSP4 activity and the consequential increased level of phosphorylated ERK1/2 in FID compared to IS rats (Fig. 151.5c) could further contribute to impaired synaptic
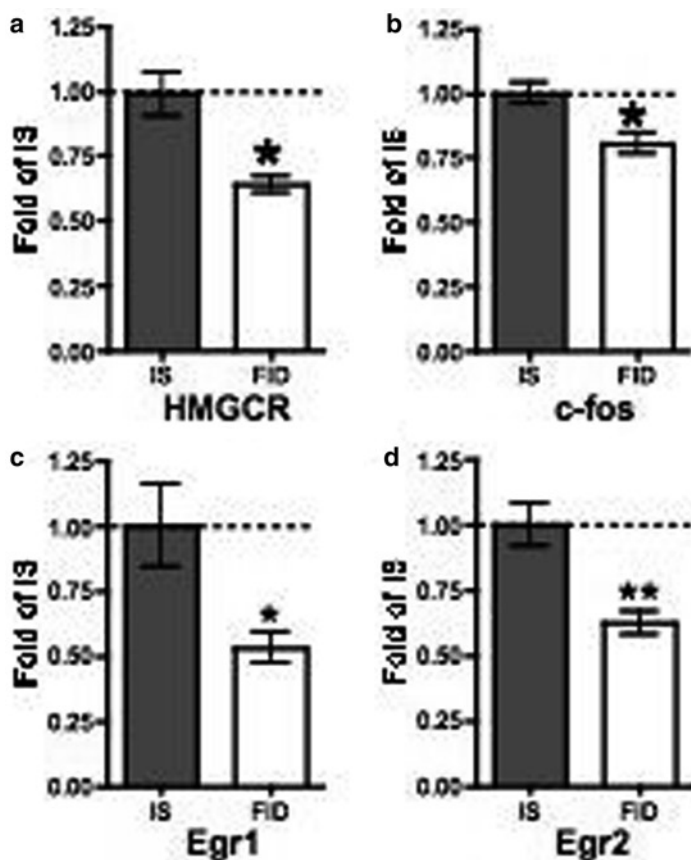
Fig. 151.4 Reduced expression of BDNF activity-dependent genes in the P65 FID hippocampus. Hippocampal expression of (**a**) HMGCR, (**b**) c-fos, (**c**) Egr1, and (**d**) Egr2 were compared between the IS control and the FID rats. FID rats showed a lower expression of these factors, consistent with a decrease in BDNF signaling. Values are means ± SEM, n = 4–6. *P < 0.05, **P < 0.01 Mann-Whitney U-test (Modified and printed with permission from Wolters Kluwer Health)

plasticity by dampening neuronal responsiveness to stimulation (Tran et al. 2009). Alternatively, sustained phosphorylation of ERK1/2 may reflect the compensatory state of the already lowered neural plasticity in FID rats. Reduced Egr2 expression resulted in lower expression of its target genes (Fig. 151.5d,e) (Tran et al. 2009), insulin-like growth factor 2 (IGF-II) and myelin basic protein (Mbp) (Gillian and Svaren 2004; Jang et al. 2006), which are important for myelin health and glial contributions to plasticity. In the adult brain, IGF-II is expressed in astroglia (Rotwein et al. 1988) and regulates myelin associated protein genes (Ye et al. 2002). Mbp is a complex gene with multiple splice variants, encoding a major component of the myelin sheath of oligodendrocytes. Decreased IGF-II and Mbp expression together may contribute to the impairment of myelination and the compromised neural transmission seen in the P65 FID hippocampus (Jorgenson et al. 2005). While whole brain Mbp expression is acutely reduced during iron deficiency (Beard et al. 2003; Clardy et al. 2006), these findings in the hippocampus of FID animals provide evidence for a long-term effect of fetal–neonatal iron deficiency on the health and function of astrocytes and oligodendrocytes.
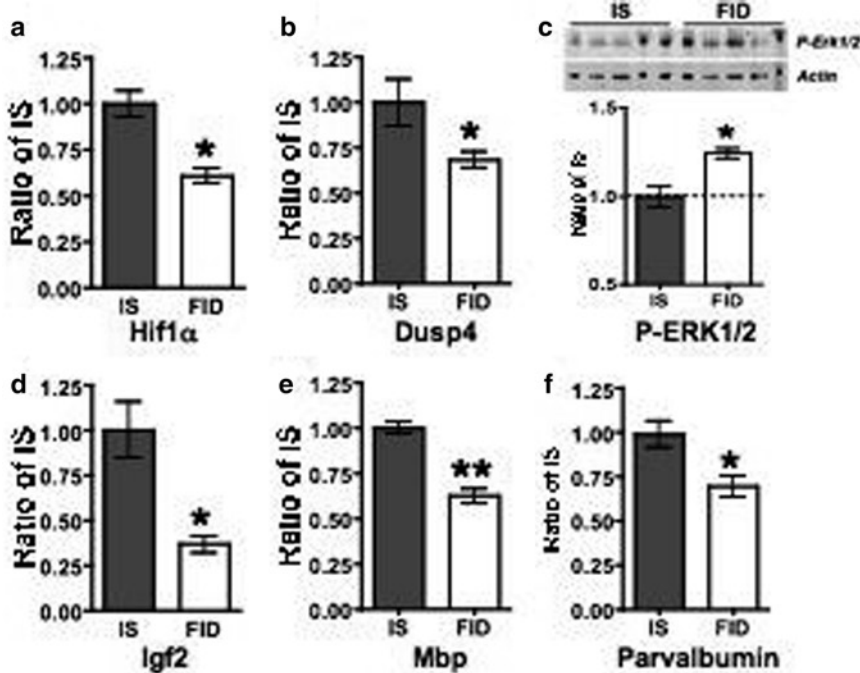
Fig. 151.5 Reduced expression of Egr1- and Egr2-target genes and parvalbumin in the P65 FID hippocampus. Assessment of Egr1 target, Hif1a (**a**) and Dusp4 (**b**), showed a lower expression in FID rats. (**c**) The increase of phosphorylated-ERK1/2 (P-ERK1/2) suggests a decrease in Dusp4 activity because Dusp4 converts P-ERK1/2 to ERK1/2. Lower transcript levels of Egr2 target, Igf2 (**d**) and Mbp (**e**), indicate a decrease in Egr2 transcriptional activity in FID rats. Together with Igf2 and Mbp, reduced parvalbumin expression (**f**) suggests impaired astroglia function in FID rats. Values are means ± SEM, $n = 4$–6. *$P < 0.05$ and **$P < 0.01$, Mann-Whitney U-test (Modified and printed with permission from Wolters Kluwer Health)

BDNF also mediates interneuron differentiation in rodent hippocampus (Marty et al. 1996; Grosse et al. 2005). More research is needed to determine comprehensively the effect of early-life iron deficiency on interneuron development. However, mRNA level of parvalbumin (PARV), a calcium-binding protein expressed in a subset of interneurons, was lower in the FID rat hippocampus (Fig. 151.5f). Whether the lower parvalbumin transcript in the FID hippocampus reflects a decrease in gene expression or a fewer number of PARV-positive (+) cells remain to be determined. It is unclear if lower BDNF expression would lead to a decrease in PARV+ cell number. Study of BDNF knock-out mice suggested a decrease of hippocampal PARV+ cell (Grosse et al. 2005); however, exogenous administration of BDNF showed no such effect in cultured rat hippocampal slice preparations (Marty et al. 1996). Nonetheless, lower parvalbumin expression might contribute to impaired plasticity in the FID rat by reducing synaptic efficacy (Jiang et al. 2004).

In summary, these findings reveal an overall diminished BDNF-mediated neural development and plasticity during and beyond iron deficiency periods. We propose that this specific effect may serve as molecular basis for the electrophysiological, morphological, and ultimately behavioral abnormalities that persist beyond the period of fetal–neonatal iron deficiency (Fig. 151.6) (Lozoff et al. 2006).
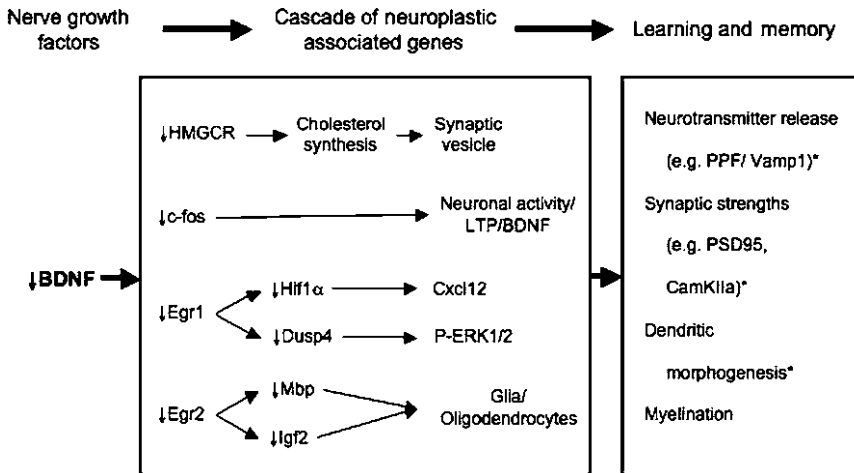
Fig. 151.6 Proposed mechanism. A possible molecular mechanism underlying a reduced BDNF activity leading to decreased neuroplasticity in FID rats. BDNF signaling regulates a cascade of factors that modulate neural plasticity, a basis of learning and memory. *Asterisk denotes previously altered factors contributing to lower synaptic plasticity (Modified and printed with permission from Wolters Kluwer Health)

151.4 Applications to Other Areas of Health and Disease

Fetal–neonatal iron deficiency is a common clinical sequela in offspring of pregnancies complicated by maternal diabetes mellitus, maternal hypertension causing intrauterine growth restriction (IUGR), maternal smoking, and severe maternal anemia. These risk groups are characterized by poorer long-term neurodevelopmental outcomes particularly in the cognitive domain suggesting that the developmental trajectory of neural circuits that support these behaviors are compromised. Long-term compromise in spite of prompt neonatal iron treatment suggests the possibility of long-term changes in regulation of the salient genes, perhaps by epigenetic mechanisms.

The lower BDNF activity induced by fetal–neonatal iron deficiency during periods of rapid neural differentiation may underlie the delay of neuronal differentiation in the developing ID hippocampus. It may also serve as the molecular basis for the morphologic and functional abnormalities seen during the period of iron deficiency. Whether these alterations are consequences of the deficit of neuronal iron or to other confounding factors in this anemia model, such as hypoxia at systemic and/or cellular levels, remain unresolved. IUGR models are also characterized by both hypoxia and iron deficiency, however, our ID model differed in terms of compensatory expression of TrkB receptor. Whereas a pig model of chronic placental insufficiency showed an obligatory increase of TrkB expression due to lower BDNF expression (Dieni and Rees 2005), we did not find such effect in ID rats. Thus, difference in TrkB finding may be attributed to the effect of ID rather than hypoxia. Despite an absence of upregulation, a greater $TrkB_L$/BDNF ratio suggests an increased availability of this TrkB isoform for BDNF binding in the ID hippocampus. This finding may be important in terms of understanding the early antecedents of adult neurological disorders characterized by reduced hippocampal function or early hippocampal degeneration. For example, Alzheimer and Parkinson's diseases are characterized by reduction of BDNF levels without compensatory increases in TrkB expression (Siegel and Chauhan 2000). The altered expression of genes involved in the pathogenesis of Alzheimer's disease as well as an increased susceptibility of brain injury in this same model supports this possibility (Carlson et al. 2007, 2008; Rao et al. 2007).

The long-term dysregulation of BDNF suggests that iron treatment alone is insufficient to attenuate the effects of iron deficiency during sensitive periods of hippocampal development, providing a role for iron in long-term programming of hippocampal BDNF. The underpinning mechanisms of this long-term effect are unknown but may be similar to those involved in the developmental origins of health and disease (Gluckman et al. 2008), including epigenetic modifications. This possibility is supported by a recent report of early-life negligence resulted in long-term down regulation of BDNF that is associated with hypermethylation of its regulatory region (Roth et al. 2009). Our results also emphasize the concept that provision of nutrients alone is inadequate to maintain optimal brain function. We propose that proper regulation of growth factors is also essential to ensure optimal utilization of nutrients. Long-term dysregulation of these growth factors may thus account for persistent abnormal function despite nutrient repletion.

In summary, our findings provide insights into a possible molecular mechanism underpinning acute and long-term cognitive deficits in fetal–neonatal iron deficiency model (Fig. 151.7). Further research is needed to determine precisely how iron regulates the expression of BDNF and its downstream effectors. While the long-term effect may be accounted by potential epigenetic modification (i.e., DNA methylation), the acute effect remains virtually unknown. We speculate that iron may have a direct role in modulating the binding of transcriptional machinery/complex at the BDNF regulatory region (Tsuji et al. 1999; Wong et al. 2005). Our data suggest that interventions that enhance BDNF activity such as exercise or selective serotonin reuptake inhibitors (Russo-Neustadt et al. 2000) may be useful as therapeutic approaches to treat long-term effects of fetal–neonatal iron deficiency, complementing iron therapy.
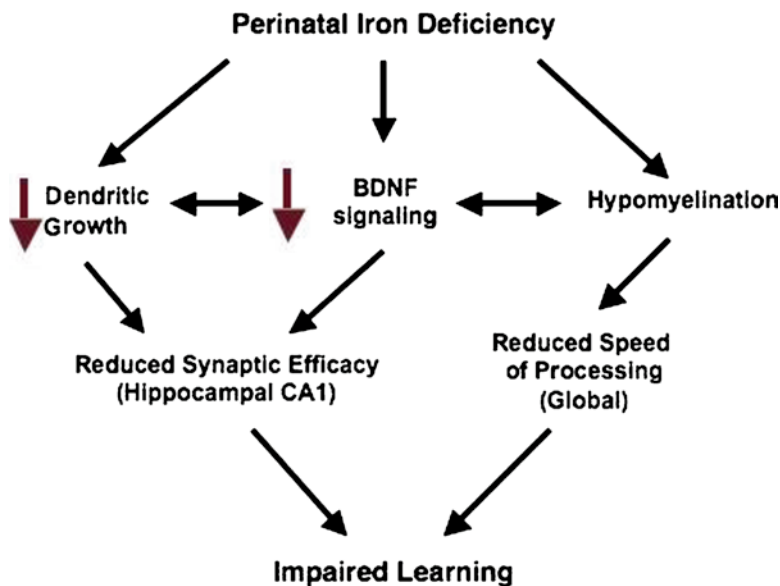
Fig. 151.7 Proposed working hypothesis. A proposed model accounting for learning impairments induced by fetal–neonatal iron deficiency. BDNF signaling affects both neuronal maturation (e.g., dendritic growth) and myelination. In turn, these processes alter synaptic efficacy and speed of neurotransmission, which ultimately contribute to learning impairments

Summary Points

- Peak expression of neurotrophic factors and their cognate receptors occurs during periods of rapid differentiation in the rat hippocampus are consistent with the role of neurotrophic factors in promoting neuronal differentiation and dendritic outgrowth.
- Fetal–neonatal iron deficiency dysregulates neurotrophic factors with specific reduction of BDNF and is associated with a delay of neuronal maturation during a period of rapid differentiation, which may reflect an extension of this rapid growth period in ID hippocampus.
- The specific reduction of BDNF expression in formerly-iron-deficient (FID) rats that were ID during early life suggests a more permanent change in its regulation. A possible underlying mechanism may involve epigenetic modification (e.g., DNA methylation) at the BDNF gene.
- Despite an absence of compensatory upregulation, an increased $TrkB_L$/BDNF ratio may maximize available BDNF signaling in the ID hippocampus. This may be important in terms of understanding the early antecedents of adult neurological disorders (e.g., Alzheimer and Parkinson's diseases) characterized by reduced BDNF and hippocampal function or early hippocampal degeneration.
- The overall diminished BDNF activity accompanied by reduced expression of a cascade of downstream factors during and beyond iron deficiency periods may serve as molecular basis for the electrophysiological, morphological, and ultimately behavioral abnormalities that persist beyond the period of fetal–neonatal iron deficiency.
- The long-term dysregulation of BDNF suggests that iron treatment alone is insufficient to attenuate the effects of iron deficiency during sensitive periods of hippocampal development, emphasizing the concept that the provision of nutrients and proper regulation of growth factors are essential to ensure optimal utilization of nutrients for brain function.

Definitions and Explanations of Key Terms

BDNF: A member of neurotrophic factors that plays critical roles in mediating neuronal proliferation, differentiation, and survival.

Dendritogenesis: A process of neural differentiation in which dendrite grows and branches into a complex pattern specifically unique to each neuronal type.

FID rats: Refers to rats that experienced iron deficiency during fetal–neonatal period, but are no longer bodily or brain ID.

Hippocampus: A brain region responsible for learning and memory that is classically organized into three subregions: CA1, CA3, and dentate gyrus.

LTP: A sustained electrophysiological activity resulting from a long-term increase of synaptic strength between two neurons, which is widely accepted as a cellular form of memory formation.

Microarray gene expression analysis: A molecular genetic technique that simultaneously assesses expression levels of thousands of genes.

Neural plasticity (neuroplasticity): The ability of neuron to adapt to its environment by altering its intracellular properties.

Quantitative (real-time) PCR: A molecular technique to measure levels of gene expression by simultaneously amplify and monitor RNA/cDNA per each thermocycle over the course of the polymerase chain reaction (PCR).

Key Points

1. Fetal–neonatal iron deficiency and cognitive development – Fetal–neonatal iron deficiency is a common clinical sequela in offspring of pregnancies complicated by maternal diabetes mellitus, maternal hypertension causing intrauterine growth restriction (IUGR), maternal smoking, and severe maternal anemia. These risk groups are characterized by poorer long-term neurodevelopmental outcomes particularly in the cognitive domain suggesting that the developmental trajectory of neural circuits that support these behaviors are compromised. According to a recent W.H.O estimate (2003), the prevalence of IDA among pregnant women and preschool age children ranges between 30% and 50% of global population worldwide.

2. Fetal–neonatal iron deficiency reduces BDNF expression and signaling – Early life iron deficiency diminishes acute as well as long-term BDNF-mediated neural development and plasticity. In turn, expression of molecular factors downstream of BDNF signaling is reduced, contributing to decreased neural maturation and plasticity. These effects may serve as molecular bases for the electrophysiological, morphological, and ultimately behavioral abnormalities during and beyond the period of fetal–neonatal iron deficiency.

References

Alder J, Thakker-Varia S, Bangasser DA, Kuroiwa M, Plummer MR, Shors TJ, Black IB. J Neurosci. 2003;23:10800–8.

Beard JL, Wiesinger JA, Connor JR. Dev Neurosci. 2003;25:308–15.

Berasi SP, Huard C, Li D, Shih HH, Sun Y, Zhong W, Paulsen JE, Brown EL, Gimeno RE, Martinez RV. J Biol Chem. 2006;281:27167–77.

Branchi I, Francia N, Alleva E. Behav Pharmacol. 2004;15:353–62.

Bui NT, Konig HG, Culmsee C, Bauerbach E, Poppe M, Krieglstein J, Prehn JH. J Neurochem. 2002;81:594–605.

Calella AM, Nerlov C, Lopez RG, Sciarretta C, von Bohlen und Halbach O, Bereshchenko O, Minichiello L. Neural Dev. 2007;2:4.

Carlson ES, Stead JD, Neal CR, Petryk A, Georgieff MK. Hippocampus. 2007;17:679–91.

Carlson ES, Magid R, Petryk A, Georgieff MK. Brain Res. 2008;1237C:75–83.

Chao MV. Nat Rev Neurosci. 2003;4:299–309.

Chen Y, Ai Y, Slevin JR, Maley BE, Gash DM. Exp Neurol. 2005;196:87–95.

Chockalingam UM, Murphy E, Ophoven JC, Weisdorf SA, Georgieff MK. J Pediatr. 1987;111:283–6.

Clardy SL, Wang X, Zhao W, Liu W, Chase GA, Beard JL, True Felt B, Connor JR. J Neural Transm Suppl. 2006;173–96.

Culmsee C, Gerling N, Lehmann M, Nikolova-Karakashian M, Prehn JH, Mattson MP, Krieglstein J. Neuroscience. 2002;115:1089–108.

Dieni S, Rees S. Exp Neurol. 2005;192:265–73.

Dong M, Wu Y, Fan Y, Xu M, Zhang J. Neurosci Lett. 2006;400:177–80.

Eide FF, Vining ER, Eide BL, Zang K, Wang XY, Reichardt LF. J Neurosci. 1996;16:3123–9.

Erickson JT, Brosenitsch TA, Katz DM. J Neurosci. 2001;21:581–9.

Felt BT, Beard JL, Schallert T, Shao J, Aldridge JW, Connor JR, Georgieff MK, Lozoff B. Behav Brain Res. 2006;171:261–70.

Francis F, Koulakoff A, Boucher D, Chafey P, Schaar B, Vinet MC, Friocourt G, McDonnell N, Reiner O, Kahn A, McConnell SK, Berwald-Netter Y, Denoulet P, Chelly J. Neuron. 1999;23:247–56.

Friedman WJ. J Neurosci. 2000;20:6340–6.

Gillian AL, Svaren J. J Biol Chem. 2004;279:9056–63.

Gluckman PD, Hanson MA, Cooper C, Thornburg KL. N Engl J Med. 2008;359:61–73.

Golub MS, Hogrefe CE, Germann SL, Capitanio JP, Lozoff B. Neurotoxicol Teratol. 2006;28:3–17.

Grosse G, Djalali S, Deng DR, Holtje M, Hinz B, Schwartzkopff K, Cygon M, Rothe T, Stroh T, Hellweg R, Ahnert-Hilger G, Hortnag H. Brain Res Dev Brain Res. 2005;156:111–26.

Guan KL, Butch E. J Biol Chem. 1995;270:7197–203.

Guenette S, Chang Y, Hiesberger T, Richardson JA, Eckman CB, Eckman EA, Hammer RE, Herz J. EMBO J. 2006;25:420–31.

Heldt SA, Stanek L, Chhatwal JP, Ressler KJ. Mol Psychiatry. 2007;12:656–70.

Hennigan A, O'Callaghan RM, Kelly AM. Biochem Soc Trans. 2007;35:424–7.

Ikin AF, Sabo SL, Lanier LM, Buxbaum JD. Mol Cell Neurosci. 2007;35:57–63.

Jang SW, LeBlanc SE, Roopra A, Wrabetz L, Svaren J. J Neurochem. 2006;98:1678–87.

Jiang B, Kitamura A, Yasuda H, Sohya K, Maruyama A, Yanagawa Y, Obata K, Tsumoto T. Eur J Neurosci. 2004;20:709–18.

Jorgenson LA, Wobken JD, Georgieff MK. Dev Neurosci. 2003;25:412–20.

Jorgenson LA, Sun M, O'Connor M, Georgieff MK. Hippocampus. 2005;15:1094–102.

Kelly A, Laroche S, Davis S. J Neurosci. 2003;23:5354–60.

Klein R, Conway D, Parada LF, Barbacid M. Cell. 1990;61:647–56.

Klein RS, Rubin JB. Trends Immunol. 2004;25:306–14.

Korte M, Carroll P, Wolf E, Brem G, Thoenen H, Bonhoeffer T. Proc Natl Acad Sci U S A. 1995;92:8856–60.

Lee R, Kermani P, Teng KK, Hempstead BL. Science. 2001;294:1945–8.

Lozoff B, Georgieff MK. Semin Pediatr Neurol. 2006;13:158–65.

Lozoff B, Beard J, Connor J, Barbara F, Georgieff M, Schallert T. Nutr Rev. 2006;64:S34–S91.

Malenka RC. Nat Rev Neurosci. 2003;4:923–6.

Marty S, Carroll P, Cellerino A, Castren E, Staiger V, Thoenen H, Lindholm D. J Neurosci. 1996;16:675–87.

McAllister AK, Katz LC, Lo DC. Annu Rev Neurosci. 1999;22:295–318.

Minichiello L, Calella AM, Medina DL, Bonhoeffer T, Klein R, Korte M. Neuron. 2002;36:121–37.

Miyamoto E. J Pharmacol Sci. 2006;100:433–42.

Nelson CA, Wewerka S, Thomas KM, Tribby-Walbridge S, deRegnier R, Georgieff M. Behav Neurosci. 2000;114:950–6.

Patterson SL, Grover LM, Schwartzkroin PA, Bothwell M. Neuron. 1992;9:1081–8.

Petry CD, Eaton MA, Wobken JD, Mills MM, Johnson DE, Georgieff MK. J Pediatr. 1992;121:109–14.

Pham TM, Winblad B, Granholm AC, Mohammed AH. Pharmacol Biochem Behav. 2002;73:167–75.

Pillai A, Mahadik SP. Schizophr Res. 2008;100:325–33.

Pokorny J, Yamamoto T. Brain Res Bull. 1981;7:113–20.

Rao R, Tkac I, Townsend EL, Gruetter R, Georgieff MK. J Nutr. 2003;133:3215–21.

Rao R, Tkac I, Townsend EL, Ennis K, Gruetter R, Georgieff MK. J Cereb Blood Flow Metab. 2007;27:729–40.

Riggins T, Miller NC, Bauer PJ, Georgieff MK, Nelson CA. Dev Sci. 2009;12:209–19.

Rossler OG, Thiel G. Am J Physiol Cell Physiol. 2004;286:C1118–29.

Roth TL, Lubin FD, Funk AJ, Sweatt JD. Biol Psychiatry. 2009;65:760–9.

Rotwein P, Burgess SK, Milbrandt JD, Krause JE. Proc Natl Acad Sci U S A. 1988;85:265–9.

Russo-Neustadt AA, Beard RC, Huang YM, Cotman CW. Neuroscience. 2000;101:305–12.

Schmidt AT, Waldow KJ, Grove WM, Salinas JA, Georgieff MK. Behav Neurosci. 2007;121:475–82.

Schratt GM, Nigh EA, Chen WG, Hu L, Greenberg ME. J Neurosci. 2004;24:7366–77.

Schiavo G, Stenbeck G, Rothman JE, Sollner TH. Proc Natl Acad Sci USA. 1997;94:997–1001.

Siddappa AJ, Rao RB, Wobken JD, Leibold EA, Connor JR, Georgieff MK. J Neurosci Res. 2002;68:761–75.

Siddappa AM, Georgieff MK, Wewerka S, Worwa C, Nelson CA, Deregnier RA. Pediatr Res. 2004;55:1034–41.

Siegel GJ, Chauhan NB. Brain Res Rev. 2000;33:199–227.

Silhol M, Arancibia S, Perrin D, Maurice T, Alliot J, Tapia-Arancibia L. Rejuvenation Res. 2008;11:1031–40.

Sperandio S, Fortin J, Sasik R, Robitaille L, Corbeil J, de Belle I. Mol Carcinog. 2009;48:38–44.

Steward O, Falk PM. J Comp Neurol. 1991;314:545–57.

Suzuki S, Kiyosue K, Hazama S, Ogura A, Kashihara M, Hara T, Koshimizu H, Kojima M. J Neurosci. 2007;27:6417–27.

Sweet DG, Savage G, Tubman TR, Lappin TR, Halliday HL. Arch Dis Child Fetal Neonatal Ed. 2001;84:F40–3.

Tamura T, Goldenberg RL, Hou J, Johnston KE, Cliver SP, Ramey SL, Nelson KG. J Pediatr. 2002;140:165–70.

Tang SJ, Reis G, Kang H, Gingras AC, Sonenberg N, Schuman EM. Proc Natl Acad Sci U S A. 2002;99:467–72.

Timmusk T, Palm K, Metsis M, Reintam T, Paalme V, Saarma M, Persson H. Neuron. 1993;10:475–89.

Tran PV, Carlson ES, Fretham SJB, Georgieff MK. J Nutr. 2008;138:2495–501.

Tran PV, Fretham SJ, Carlson ES, Georgieff MK. Pediatr Res. 2009;65:493–8.

Tsuji Y, Moran E, Torti SV, Torti FM. J Biol Chem. 1999;274:7501–7.

WHO. Micronutrient deficiencies. 2008. http://www.who.int/nutrition/topics/ida/en/index.html

Wong K, Sharma A, Awasthi S, Matlock EF, Rogers L, Van Lint C, Skiest DJ, Burns DK, Harrod R. J Biol Chem. 2005;280:9390–9.

Wong RW, Guillaud L. Cytokine Growth Factor Rev. 2004;15:147–56.

Woo NH, Teng HK, Siao CJ, Chiaruttini C, Pang PT, Milner TA, Hempstead BL, Lu B. Nat Neurosci. 2005;8:1069–77.

Yamada M, Ikeuchi T, Hatanaka H. Prog Neurobiol. 1997;51:19–37.

Ye P, Li L, Richards RG, DiAugustine RP, D'Ercole AJ. J Neurosci. 2002;22:6041–51.

Zagrebelsky M, Holz A, Dechant G, Barde YA, Bonhoeffer T, Korte M. J Neurosci. 2005;25:9989–99.

Chapter 152
Iodine and Brain Metabolism

R.H. Verheesen and C.M. Schweitzer

Abbreviations

T4	3′,5′,3,5-tetraiodo-l-thyronine or thyroxine
T3	3′,3,5-triiodo-l-thyronine or triiodothyronine
MIT	Monoiodotyrosine
DIT	Diiodotyrosine
NIS	Sodium iodide symporter
DEHAL1	Iodotyrosine dehalogenases
TH	Tyrosine hydroxylase
RDA	Recommended daily allowances
TSH	Thyrotropin
NOS	Nitric oxide synthase
Pts	6-pyruvoyltetrahydropterin synthase
WHO	World Health Organization
ICCIDD	International Council for the Control of Iodine Deficiency Disorders
UI	Urinary iodine
ADHD	Attention deficit hyperactivity disorder

152.1 Introduction

The role of iodine in brain metabolism and development has been recognized since the first half of the twentieth century. Its ability to prevent and even cure goiter was described in 1918 by Marine et al. (Marine and Kimball 1990). Soon afterwards, substantial evidence arose for its role in preventing cretinism and the deterioration of brain development (Table 152.1). It is estimated that 5–30% of the people suffering from iodine deficiency eventually suffer from neurological impairment. The latest reports on iodine deficiency published by WHO (Benoist de et al. 2004; Andersson et al. 2007). make it clear that 2 billion people continue to suffer from iodine deficiency, with Europe having the biggest proportion of people who are iodine-deficient (Andersson et al. 2007) (Table 152.2).

R.H. Verheesen (✉)

Regionaal Reuma Centrum Z.O. Brabant, Máxima Medisch Centrum, Ds. Th. Fliednerstraat 1, 5631 BM Eindhoven, The Netherlands

e-mail: rh.verheesen@mmc.nl; rhverheesen@onsbrabantnet.nl

Table 152.1 Spectrum of iodine deficiency disorders (From Andersson et al. 2007; Hetzel 1983; Stanbury et al. 1998; Laurberg et al. 2000)

Fetus	Abortions
	Stillbirths
	Congenital anomalies
	Increased perinatal mortality
	Endemic cretinism
Neonate	Neonatal hypothyroidism
	Endemic mental retardation
	Increased susceptibility of the thyroid gland to nuclear radiation
Child and adolescent	Goitre
	(Subclinical) hypothyroidism
	(Subclinical) hyperthyroidism
	Impaired mental function
	Retarded physical development
	Increased susceptibility of the thyroid gland to nuclear radiation
Adult	Goitre with its complications
	Hypothyroidism
	Impaired mental function
	Spontaneous hyperthyroidism in the elderly
	Iodine-induced hyperthyroidism
	Increased susceptibility of the thyroid gland to nuclear radiation

Effects of iodine deficiency not only a fetus-related health problem

Table 152.2 Proportion of population, and number of individuals with insufficient iodine intake in school-age children (6-12 years), and in the general population (all age groups) by WHO region, 2003

	Insufficient iodine intake (UI <100 µg/l)			
	School-age children		General population	
WHO region[a]	Proportion (%)	Total number (millions)[b]	Proportion (%)	Total number (millions)[b]
Africa	42.3	49.5	42.6	260.3
Americas	10.1	10.0	9.8	75.1
South-East Asia	39.9	95.6	39.8	624.0
Europe	59.9	42.2	56.9	435.5
Eastern Mediterranean	55.4	40.2	54.1	228.5
Western Pacific	26.2	48.0	24.0	365.3
Total	36.5	285.4	35.2	1988.7

[a]192 WHO Member States

[b]Based on population estimates in the year 2002

Thus far, iodine and its relation to brain development have been considered from a thyroid hormone point of view. Despite research during the last 40 years in this area several questions still wait for answers. In this chapter we provide a different point of view and relate iodine deficiency to the basic nutrients that are involved in iodine and thyroid metabolism. We focus on iodine, selenium, tyrosine, and vitamin D and point out their interactive relationships. By looking at the same problem from a different point of view new research and solutions could arise.

Iodine is available in the soil and recently the iodine cycle has been described in more detail. This availability in soil is probably reduced in countries with a young geographical background and in areas suffering from the latest ice age, repeated flooding, and elevated regions subject to glaciations and higher rainfalls.

152.2 Iodine and the Thyroid Hormone

152.2.1 Thyroid Hormone

Iodine is known for its role in the production of thyroid hormones. The thyroid hormone consists of two tyrosine molecules and four or three iodine molecules. The brain is known for its selectivity for thyroxin. After uptake in the brain, thyroxin is deiodinized by selenium-dependent selenodeiodinase enzymes (Kvicala and Zamrazil 2003; Kohrle 2005; Beckett and Arthur 2005).

The thyroid hormone is not only a source of iodine and tyrosine but is also a source of 3-iodothyronamines, their deiodinated products (Scanlan et al. 2004; Scanlan 2009). It is known that these 3-iodothyronamines are trace amines that overlap with classical biogenic amines, such as catecholamines and serotonin. They are capable of increasing catecholamine release.

Theoretically, this could mean that the production of 3-iodothyronamines will lead to a greater availability of the classical catecholamine. In that respect, iodine is necessary for the production of these 3-iodothyronamines and/or the binding of tyrosine.

152.2.2 Deiodination

Deiodination is a process in which deiodination enzymes are involved (Table 152.3 Iodine and brain development, Berber and Morales). As mentioned above, it is clear that the first deiodination is performed by selenium-dependent selenodeiodinase enzymes (Kohrle 2005; Beckett and Arthur 2005). These enzymes are influenced by the availability of thyroxine and triiodothyronine. In case of iodine deficiency there are several up- and downregulating mechanisms. By increasing selenodeiodinase

Table 152.3 Benefits from iodine supplementation programs (From Andersson et al. 2007; Hetzel and Maberly 1986; Levin 1987; Levin et al. 1993)

Physiologic benefits		Benefits to society
Humans	Reductions in: • Mental deficiency • Deafmutism • Spastic diplegia • Squint • Dwarfism • Motor deficiency • Goitre • Birth defects	• Higher work output • Reduced costs of medical and custodial care • Reduced educational costs (because of less absenteeism and grade repetition)
Livestock	Increases in: • Live births • Weight and meat yield • Strength for work • Health (less deformity) • Wool coat in sheep	Higher output of meat and other animal products and hence: • Profits • Higher work output of animals

Beneficial effects of iodine supplementation. Important are the effects for society as well. Noteworthy is the beneficial effect on the livestock; certainly in developing countries an important additional effect if supplementation is extended to livestock.

proteins in the brain it is, at least in the earlier stage, relatively protected from the lower T4 production (Obregon et al. 2005).

However, in the last few years it has become clear that other deiodinase proteins play an important role in the deiodination of diiodotyrosine (DIT) and monoiodotyrosine (MIT). These iodotyrosine dehalogenases (DEHAL1) have been studied only in relation to the deiodination of MIT and DIT in the thyroid. However, several studies show that their presence is not limited to the thyroid but can be found in human kidney, trachea, liver, and colon. The enzymatic deiodination is a reductive process leading to the formation of iodine and tyrosine, increasing both levels. Tyrosine itself is a known inhibitor of the process (Gnidehou et al. 2004). Since the research on the expression of the DEHAL1 in several tissues is very young it cannot be excluded that DEHAL1 is expressed in the (developing) brain. During metamorphosis in frogs, the presence of the DEHAL1 has been described in the olfactory epithelium, the nucleus infundibularis ventralis, the ventricular lining, cerebellum, in the pituitary gland, and in the mucus glands of skin (Gaupale et al. 2009). The same expression could be possible in the developing fetus. Neither studies on the effects of iodine deficiency on the expression of the gene, nor studies on the influence of iodine deficiency on the activity of the enzyme itself have been performed.

By this two-step deiodination, not only 3-iodothyronamines are formed but delivery of iodine and tyrosine into the tissues is provided as well. It is known that tyrosine is the precursor of dopamine and adrenalin, both highly important in the development and metabolism of the brain. Thyroid hormones may therefore be seen as a targeted on-demand system for catecholamine metabolism by increasing their release and also by providing the precursor itself.

152.2.3 Sodium Iodine Symporter (NIS)

In the last 10 years much research has been done on iodine uptake. The presence of the NIS was revealed in 1996. Since its discovery, many researches have been performed, predominantly related to medication development. Some interesting observations have been made. First of all, the distribution pattern of the NIS reveals that NIS is not located in the brain. Most of the NIS is present in tissues that have a direct contact to the outside world, such as the skin, salivary glands, and the stomach (Levy et al. 1998; Riesco-Eizaguirre and Santisteban 2006). Given the known interaction between bacteria and viruses and iodine it could provide a first line of defense against microorganisms. It is unlikely that the NIS is not present in the brain given the dependency of the development of the brain on iodine. Moreover, iodine uptake has been demonstrated in the ventricle system and choroid plexus, although the precise effect on the concentration of iodine in the cerebrospinal fluid and the brain tissues has not been studied thus far (Welch 1962). It could mean we have to look at the role of iodine from another perspective. By looking at iodine from a thyroid

The NIS has also been also located in the kidney, in Henle's loop. Even more important is the fact that the uptake of iodine in the kidney is dependent on the plasma sodium concentration (Spitzweg et al. 2001) (Fig. 152.1). Furthermore, the NIS could be blocked by thiocyanate and perchlorate (Fig. 152.2), the first present in cigarettes (Sande van et al. 2003; Groef de et al. 2006). This could mean that in case of strict sodium restriction or presence of per- or thiocyanate, iodine reabsorption could be impaired, leading to a high iodine excretion in the urine, but to a low presence in the body. This has implications for the availability of iodine during pregnancy and the development of the child in the smoking mother. Smoking is known to increase stillbirths, slower fetal growth, and infertility and could have a negative effect on intelligence capabilities. It may be hypothesized that these effects can be deduced to iodine deficiency.
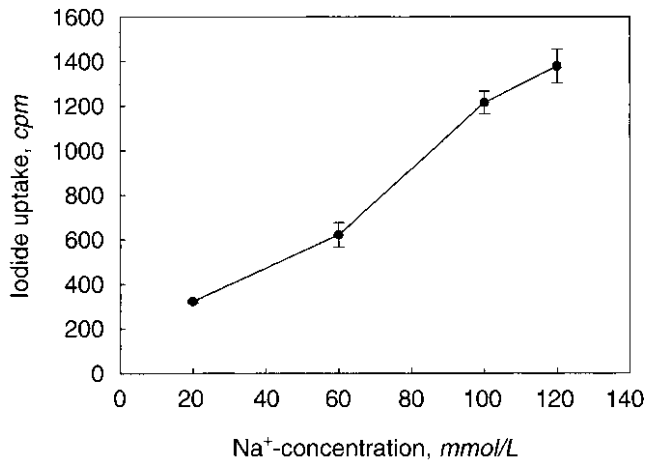
Fig. 152.1 Sodium dependency of iodide uptake by human kidney cells. Sodium dependency of iodide uptake by human kidney cells. Optimal iodide uptake is related to higher sodium levels in the kidney. The relationship with sodium restriction diets has not been investigated thus far, but could attribute to iodine deficiency (From Spitzweg et al. 2001)
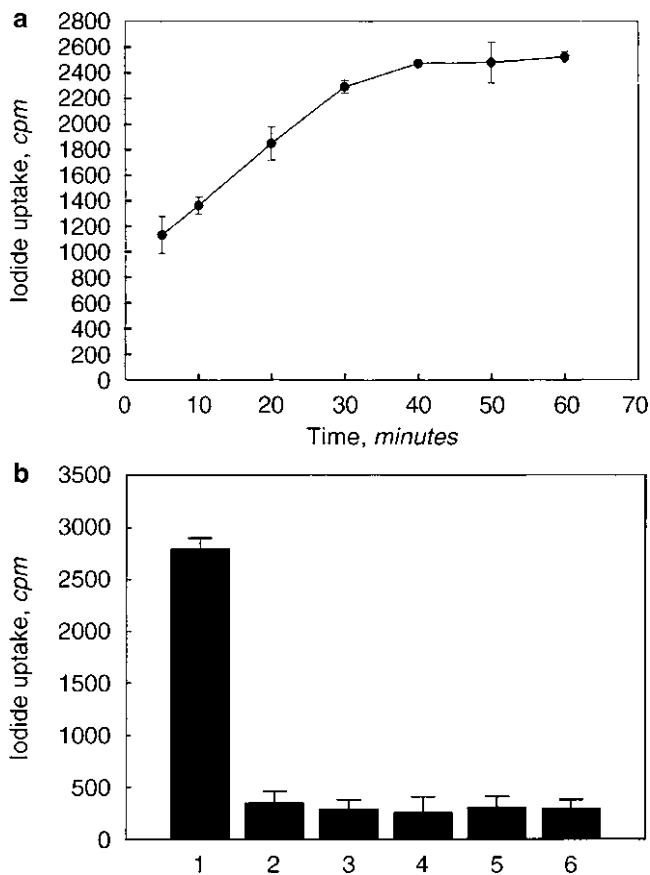
Fig. 152.2 Time course of iodine uptake by kidney cells and influence of perchlorate. Figure a shows that iodide uptake by human kidney cells is rapid and reaches maximum levels after 40 min. This is in line with the rapid iodide uptake in the stomach. Perchlorate inhibits iodide uptake by a factor of eight as can be seen in figure b. Lane 1 is normal uptake by kidney cells, lane 2 represents the same kidney cells incubated with 10 μmol/L perchlorate. Lane 3–6 are control cell lines known not to be able to take up iodine. This observation is in line with another study, which shows a similar inhibitory pattern in case of thiocyanate, abundantly present in cigarettes (From Spitzweg et al. 2001)
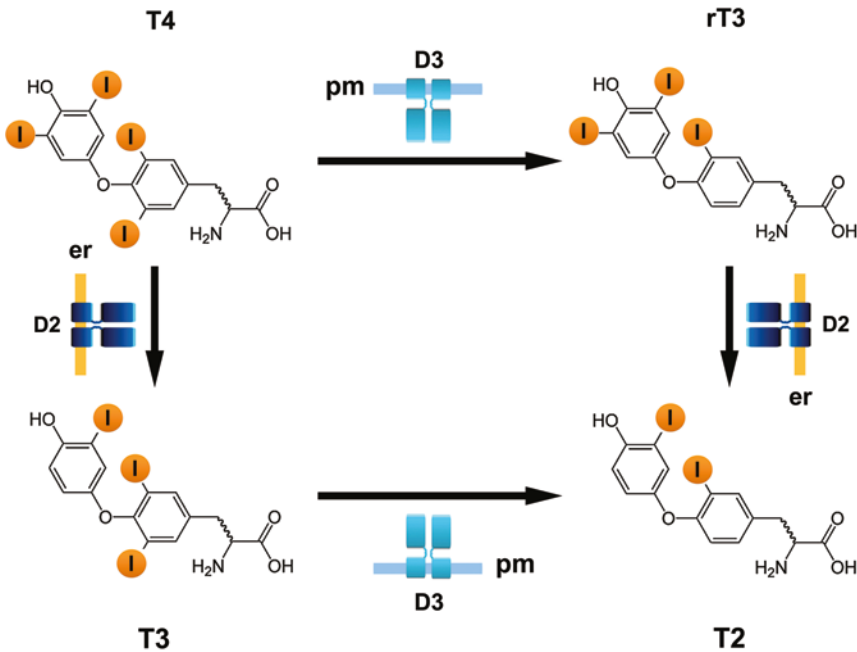
Fig. 152.3 The activating type III deiodinase (D2) catalyzes the conversion of T4 into T3. D2 also transforms rT3 into T2. Inactivating D3 transforms T4 into rT3, and T3 into T2. D3 is found in the plasmatic membrane (pm) of neurons while D2 is found in the endoplasmic reticulum (er) of astrocytes and tanycytes

152.2.4 Keypoints of Iodine Uptake by Sodium Iodide Symporter

- Iodine uptake takes place by the NIS. Its presence is not limited to the thyroid but widely distributed throughout the body.
- This observation should lead to reconsidering the recommended daily allowances (RDA), a line of thought consistent with the grounds to change the vitamin D RDA.
- Iodine uptake is negatively influenced by low sodium concentration, perchlorate, and thiocyanate. Because thiocyanate is present in cigarettes, smokers are more at risk for iodine deficiency.

152.3 Iodine and Diseases

152.3.1 Cretinism

The most dramatic effect of iodine repletion is the disappearance of cretinism and the neurological impairments in severe iodine deficiency. Before the introduction of iodine it was considered to be a disease without understanding of the mechanism. Even today the role of iodine in the development of cretinism is not fully explained. Most research concerns the measurable changes in behavior or development but not the unraveling of the mechanism itself.

The clinical manifestation depends on the degree of iodine deficiency and varies widely. Early clinical recognition is made by subnormal temperature, slow heart rate, wide fontanelles, dwarfism, and submature and sluggish behavior. Other signs include slow dentition, slow reaction time, constipation, dystonia, thick tongue and skin, and a delay in sexual development.

One of the most striking pathophysiological discrepancies is the fact that in observed cretinism there is no difference in urinary iodine excretion when compared to individuals in the same region. Moreover, a clear relationship between mental retardation and thyroid hormone levels does not seem to be present.

In the previous century some aspects of the mechanisms involved in iodine deficiency have become more apparent. In case of iodine deficiency, selenodeiodinase enzymes in the brain are upregulated, and the brain is protected against the lower production of thyroxin. The fetus is protected by upregulation of the NIS in the placenta and thus the embryo is protected at the cost of the mother. After birth too the child is protected by upregulation of the NIS in the breast in case of breastfeeding. Of course this protection is not present in the case of baby formula being used.

So it could be possible that other factors are contributing to the development of cretinism. As mentioned above, with thyroxin, tyrosine and 3-iodothyronamine are also delivered to the brain. In the process of dopamine formation out of tyrosine, tyrosine hydroxylase (TH) is the most rate-limiting step. Its activity is upregulated by vitamin D and vitamin A (Puchacz et al. 1996; Jeong et al. 2006; Gelain et al. 2007). In research we have to take other known cofactors into account, especially if it concerns widespread deficiencies, such as that of vitamin D.

If tyrosine is influencing the development of cretinism and neurological deterioration there should be clinical overlap with tyrosine–dopamine-related deficiency disorders.

152.3.2 Attention Deficit Hyperactivity Disorder (ADHD)

Recently, Vermiglio et al. showed that mothers with iodine deficiency had a greater chance that their offspring would get ADHD (Vermiglio et al. 2004). Given the fact that during pregnancy there is an upregulation of the NIS in the placenta, it is logical to suppose that the child is protected from the mother's deficiency. It would also mean that the mother will become more deficient post partum. Not only the child's iodine but also the recirculating iodine pool from the child will vanish. Given the child's protection for iodine deficiency by the upregulating NIS it is more logical to suppose that the real ADHD development takes place after birth at the moment the child starts to eat the same (iodine deficient) food the whole family takes. Just as was the case with cretinism, it is highly questionable if syndromes like ADHD have a genetic base or are just micronutrient (and thereby family) related, with the highest impact during childhood and adolescence.

It is known that iodine deficiency leads to less development of intelligence capabilities. Given the reports it could mean a decrease of IQ of 10–15 points (Bautista et al. 1982; Tiwari et al. 1996; Briel van den et al. 2000; Andersson et al. 2007). Even more important are the observed changes in social behavior (Table 152.3). Several studies point out that iodine repletion leads to a more social behavior, higher working capacity. and higher initiative level (Tiwari et al. 1996; Briel van den et al. 2000; Andersson et al. 2007).

152.4 The Role of Iodine in Brain Metabolism

Despite the fact that much literature does not concern the physiological mechanism itself we now try to explain the role of iodine. One should realize that some parts are hypothetical.

Iodine is known to be a potent antioxidant (Polley 1971; Kupper et al. 2008). It is the most simple antioxidant compared to the vitamins we know. It finds its way into the brain mostly by T4, but also by iodine uptake in the choroid plexus. Given the fact that the thyroid increases the production of T3 during iodine deficiency at the cost of T4 it means a lower iodine influx in the brain. This lower influx is counteracted by increasing the selenodeiodinase proteins.

As pointed out above, the role of iodine on the brain has thus far been discussed from the thyroid hormone perspective. It is difficult to distinguish between effects of iodine and the thyroid hormone and between thyroid hormone and tyrosine effects. In this respect, it is impossible to unravel the underlying physiological processes that account for the beneficial effects of iodine and/or tyrosine or thyroid hormones.

152.4.1 Tyrosine Effects

Studying the role of the thyroid hormone one must account for the effects of its deiodinization metabolites, iodine, 3-iodothyronamine, and tyrosine. In earlier days, thyroid hormone was, at least in part, considered a tyrosine delivery hormone. However, the idea was finally rejected based on the observation that tyrosine was widely available in the proteins present in all tissues.

It can be questioned whether that rejection was evidence-based. The fact that tyrosine is available in proteins does not have to mean that there is no need for a second delivery system. It can be even quite advantageous to have a second system, especially as we know that tyrosine is the precursor of dopamine and (nor) adrenaline. These are short-lived monoamines that have to be instantly available on several demands from several tissues. So next to a basal slowly adapting system provided for by proteins, which cannot react to individual tissue demands, it could be very ingenious to have a second swift acting system.

In this respect, it is known that the deiodination time for T4 is longer than for T3. This could explain the greater metabolic effects of T3 compared to T4. Second, the system is a post translation system and thereby a quickly adapting system. Third, by having several deiodination products, there is a buffer level within the cells, all with their own deiodination response times. T4 is slower deiodinated than T3, which in turn is slower deiodinated than DIT, which at its turn is slower deiodinated than MIT. It is even known that these products themselves can influence the thyroid-stimulating hormone (TSH) and TH (Nakano and Danowski 1959; Lutsky and Zenker 1968; Groot de and Jaksina 1969). In this way, there is an intelligent regulating system, which is not only regulated by T4 or T3 but also by its other metabolic products, next to the effectors themselves such as dopamine and adrenaline. The final metabolic reaction will depend on the total product of stimulatory and inhibitory signals.

There are not many publications about the role of tyrosine and the development of the brain. However, as being the precursor of dopamine and the amino acid thyroid hormones are made of, it could play a crucial role in brain development.

152.4.2 Tetrahydrobiopterin Deficiency

Tetrahydrobiopterin (BH4) is a crucial cofactor in the biosynthesis of catecholamines. It is encoded by the 6-pyruvoyltetrahydropterin (Pts) synthase gene. Pts knockout mice die after birth, although they develop with normal morphology in utero. However, when the mice are fed BH4, L-Dopa, and 5-hydroxyptryptophan, they survive. The mice were sacrificed and studied at 6 weeks. Qualitative

characteristics showed dwarf mice with reduced activity, dystonia, tremor, no signs of sexual maturation, hair loss, and hypothermia (Elzaouk et al. 2003). These characteristics show great overlap with the clinical features of cretinism and interestingly develop after birth. Chemical analysis showed normal serotonin and phenylalanine levels as well as normal nitric oxide synthase activity in the brain. However, the dopamine levels in the brain appeared to be only 3% of normal.

152.4.3 Tyrosine Hydroxylase Deficiency

TH is a rate-limiting enzyme involved in the synthesis of dopamine out of tyrosine. TH deficiency is a relatively rare disorder, with the severest form called infantile parkinsonism, which is mostly related to an insufficient dopamine metabolism. In the case of enzyme deficiency, the development of the syndrome is faster than in the case of a nutrient-related insufficiency, because of the compensating mechanisms occurring in the latter. Clinical symptoms of TH deficiency are lack of motion, dystonia, irritability, lack of speaking development, decreased intellectual development, low body temperature, and constipation (Eiduson 1971; Eisenhofer et al. 2003; Giovanniello et al. 2007). As with cretinism, the clinical presentation can vary greatly but there is some striking overlap with the clinical pattern of cretinism.

Given the fact that TH plays a crucial role in dopamine and adrenaline synthesis, the factors that are known to influence this enzyme have to be taken into account if we study the effects of iodine deficiency on brain development. Vitamin D is known to increase TH and vitamin D deficiency is widespread. It therefore could negatively affect the fetus if the mother is severely vitamin D deficient. Of course it will also have a negative effect on the development of the child after birth although most countries advice vitamin D supplementation, but only until the third year. Given the new insights in vitamin D, optimal levels of vitamin D supplementation are a point of discussion nowadays (Puchacz et al. 1996; Holick 2007).

152.5 Micronutrients Contributing to Iodine Deficiency

In short, the interactions between the nutrients known for their role in the iodine–tyrosine metabolism have to be mentioned. Even the earliest study on iodine and goiter by Marine et al. showed only a 60% positive effect. In those days, other nutritional influences were not known, but might account for the 40% nonresponders. The role of those other nutrients follows in brief.

Iron is crucial in the forming and functioning of peroxidases, in this case thyroid peroxidase. Thyroid peroxidase is crucial for the iodination of tyrosine (Zimmermann and Kohrle 2002).

Vitamin A is known to play an important role in the uptake of iodine by the NIS. It is known to be capable of increasing this uptake (Schmutzler 2001; Zimmermann et al. 2007).

Selenium is necessary for the formation and functioning of selenodeiodinase, which is essential for the deiodination of the thyroid hormones. It is advised not to start supplementation of selenium in case of iodine deficiency, since it can worsen or cause hypothyroidism. Nevertheless, it is widely used, not only in reform stores but also in the animal food industry. This could be harmful and give rise to increasing thyroid problems in countries with iodine deficiency. But even in countries considered to be iodine sufficient a negative effect can be expected since a median urinary iodine excretion of 100 microgram per liter could still mean a large proportion of the population being iodine deficient (Zimmermann et al. 2008).

Finally, tyrosine itself is essential for an optimal metabolism, being the precursor of catecholamines and crucial for thyroid hormone synthesis. Several studies mention the relationship between tyrosine

levels and thyroid functioning (Melmon et al. 1964; Malamos et al. 1966; Tahara et al. 1988). Optimal nutrition levels are not known.

Also, vitamin D could influence thyroid functioning. Although not widely studied, a few studies showed an interaction between vitamin D and thyroid hormones levels (Zofkova et al. 1981; Smith et al. 1989). The exact mechanism is unknown but could be related to the influence of vitamin D on TH. However, other influencing factors such as deiodinase upregulation should be studied.

In conclusion, it is clear that in our search for an optimal iodine-related metabolism all known other factors have to be taken into account as well (Verheesen and Schweitzer 2009).

152.5.1 *Keypoints of Tyrosine Metabolism in Relation to Diseases*

- Mono- and diiodotyrosine are reduced by iodotyrosine dehalogenases to iodine and tyrosine. Iodotyrosine dehalogenases are widely distributed. In developing frogs they are upregulated in the brain. Other animals have not been investigated.
- Dopamine deficiency diseases are related to a clinical picture with great similarity to cretinism.
- ADHD is treated with dopamine increasing medication. Instead of increasing dopamine by blocking its conversion, deficiency of nutrients such as iodine, tyrosine, and vitamin D leading to lower dopamine production capabilities should be investigated.

152.6 Alternative Solutions to Fight Iodine Deficiency

More than 90 years after the discovery of iodine as an essential mineral in the prevention of cretinism and hypothyroidism, 2 billion people still suffer from iodine deficiency. It is hard to believe that the strategy followed thus far will finally lead to eradication of iodine deficiency, especially if we take into account the numerous programs that have been implemented and billions of dollars that have been spent in the last decades.

Given the fact that iodine is naturally taken up by animals and plants it would be logical to increase iodine content in the soil (Steinnes 2009). Thereby it enters the natural food chain and increases the recirculation of iodine. This could lead to various profitable effects.

First, it is a far more natural way to provide enough iodine in the food chain and we are no longer dependent on one single iodine source, as in iodized salt. This single route prevention strategy is very vulnerable and depends largely on diet choices and requires a continuous very active policy. When the complete food chain is soaked with iodine many alternatives are present even when people choose to eat a very invariable diet.

Second, it has been proven that organic selenium gives rise to fewer side effects than inorganic selenium and that inorganic selenium can easily be transformed into organic selenium by plants (Broadley et al. 2006). The same phenomenon could be true for iodine. Iodine is organically bound to tyrosine, its natural partner, as is the case of iodine in seaweed. Deiodinase activity has to be present to release this bounded iodine. Furthermore, the conversion of MIT and DIT into tyrosine and iodine is inhibited by the product tyrosine itself (Gnidehou et al. 2004),thereby reducing overdose and side effects. On the other hand, the presence of thyroid antibodies could very well be related to other contributing micronutrients, especially selenium deficiency (Xu et al. 2006; Duntas 2008). Before addressing iodine as the main cause of side effects, other factors have to be taken into account

and need further investigation. In this respect, organic iodine in the form of iodotyrosine or diiodo-tyrosine could also be an attractive biomarker for individual longstanding iodine status, since it represents net iodine uptake. Measuring iodotyrosine or diiodotyrosine means that factors negatively influencing iodine uptake by the NIS have been taken into account. This is in contrast to the situation where iodine excretion in the urine is established.

Despite several reports from the WHO about increasing iodine deficiency levels, especially in developed countries, politics either do not or are slow in responding. Most countries do not follow the advice of the WHO concerning iodine supplementation in case of pregnancy and breastfeeding. Even recent advice reports from health care government agencies do not include this 6-year-old WHO directive (Health Council of the Netherlands 2008). Moreover, these countries also do not implement the directives on monitoring iodine supplementation. The case becomes worse if we are aware of the limitations of the population indicator used to define iodine sufficiency. Although some countries are regarded as iodine sufficient, up to 50% of their population can, in fact, be regarded as iodine insufficient (Zimmermann et al. 2008; Verheesen and Schweitzer 2008). However, most of these countries interpret sufficient as no deficiency at all and are not motivated to erase iodine deficiency completely. A better way to present deficiency data is by showing prevalence figures, even if they are estimated statistically. For instance, 10% of a population being deficient sounds like a good achievement, but if it means that still 27 million people are suffering from iodine deficiency (USA) it sounds like work needs to be done (Benoist de et al. 2004).

In this chapter, we chose to look at iodine and the brain from an unconventional point of view. By doing this we might find new solutions for old unresolved problems and physiological and medical questions. By studying how to nurture nature we could find a way to prevent or even change the course of diseases and syndromes without changing nature itself, and without gene therapy or by medication alone.

152.6.1 Keypoints of Alternative Strategies on Solving Iodine Deficiency

- Given the large number of children affected, the pregnancy and lactation supplementation directive from WHO should be implemented by all countries who signed the United Nations-sponsored "Declaration for the Survival, Protection and Development of Children" in 1990, before 2012.
- New iodine supplementation strategies must be considered, such as enrichment of soil.
- Iodotyrosine or diiodotyrosine could be attractive biomarkers for the individual longstanding iodine status.

152.7 Application to Other Areas of Health and Disease

Deficiencies are, even in developed countries, still widespread. History has taught us that solving severe deficiency leads to solving diseases that were thought to be heritable and untreatable, like cretinism. It showed us that genetic polymorphism is not to be blamed for diseases but environmental factors are the cause. Also mild deficiency will lead to related health problems, although not as obvious as in severe deficiencies. Iodine deficiency is by far the most widespread deficiency worldwide. It will lead to unbalanced thyroid metabolism, which theoretically, depending on the genetic polymorphism, can cause related health problems such as hypercholesterolemia, heart disease, infertility, depression, and health problems related to a disturbed tyrosine or iodine metabolism. Before changing the genetic blueprint we have to study the influence of nutrients on the expression of genes and finally diseases.

152.8 Conclusions

Based on the literature available on the role of iodine and tyrosine on the development and metabolism of the brain, several conclusions can be drawn, although some could be seen as hypothetical until more specific research on the topic is undertaken.

It is remarkable that in the case of the Pts knockout mice, the development of the fetus in utero is normal and problems begin only after birth. It could be assumed that during pregnancy the maternal delivery of catecholamines and iodine is more essential than the producing possibilities of the fetus. This could have consequences for the way we look at iodine deficiency disorders and their development. In contrast to the assumption nowadays, developmental problems could occur mainly after birth.

As with the knockout mice this could mean that the developmental disorders could very well be reduced by providing adequate levels of the required tyrosine, iodine or thyroxin. This is in line with the observations that iodine supplementation can improve the deteriorated intelligence and social behavior because of iodine deficiency. Furthermore, it is in line with the observation of the upregulated NIS in the placenta and in the breast feeding breast, the first one to prevent fetal deficiency at the cost of the mother, the second to provide optimal iodine nutrition after birth, again at the cost of the mother.

In the case of ADHD, the most effective medicine is methylphenidate. As stated, it is known to increase dopamine levels in the brain. Instead of focusing on ways to increase dopamine levels by blocking its degradation, one should focus on the possibility that essential elements in the synthesis of dopamine are lacking. Several micronutrients need to be investigated. Given the widely distributed deficiency, iodine is the most important one to investigate. In addition, the following also have to be investigated: tyrosine as being the precursor, vitamin D as being a stimulator of TH, tetrahydrobiopterin as being the cofactor for biosynthesis, vitamin A as being a second stimulator of TH, and selenium as being essential for the deiodination of thyroxin by selenodeiodinases. Since studies never focus on these specific micronutrients, no literature is available on the presence of deficiencies, let alone combinations of even very mild deficiencies that could become more relevant because of their combined existence (Verheesen and Schweitzer 2009).

The sodium symporter in the brain has not been studied, so no data are available on its presence in the various parts of the brain. Furthermore, no data are available on the effects of iodine deficiency at the NIS level. We know, however, that the distribution of the selenodeiodinases differs significantly throughout the body.

Finally, the most important concern is the fact that today iodine deficiency is still widespread. The fact that countries are characterized as developed does not guarantee that iodine deficiency has been solved, as the latest report on Europe shows (Table 152.4). Governments not only need to sign declarations, but need to execute them with the greatest efforts possible. Given the few experts involved in specific deficiencies, governments need to be willing to request for expertise from the WHO or International Council for the Control of Iodine Deficiency (ICCIDD) when they formulate

Table 152.4 Proportion of population, and number of estimated individuals with insufficient iodine intake in school-age children (6–12 years) and in the general population (all are groups) in Europe,[a] 2004

Insufficient iodine intake (UI <100 mg/l)			
School-age children		General population	
Prevalence (%)[a]	Total number (millions)[b]	Prevalence (%)[a]	Total number (millions)[b]
47.8	24.9	46.1	272

[a]Based on data from 40 countries

[b]Based on population estimates in the year 2002

and publish national guidelines. An authorization for the guidelines by the very few experts in cooperation with the leading authorities like the WHO or ICCIDD would be even more preferable. Unfortunately, national politics are very protective and have not reached that level of openness yet.

By studying the effect of iodine on the development and metabolism of the brain only as part of the thyroid hormone we could very well be missing the real effectors, tyrosine and iodine. In addition, interacting nutritional factors could be missed and not studied in relationship to each other.

Summary Points

- Iodine deficiency is the most widespread micronutrient deficiency worldwide since 1918, with 2 billion people affected anno 2007.
- To make governments better aware of the extent of the problem, the estimated number of individuals affected should be the first priority and not the overall classification based on the median urinary iodine excretion.
- Europe has the largest proportion of people affected of all WHO regions; South East Asia has the highest absolute number of individuals affected of all WHO regions.
- A biomarker for the longstanding individual iodine status is crucial to present solid prevalence data. Iodo- or diiodotyrosine could be attractive candidates since they represent the iodine level after uptake by the NIS.
- In our understanding of the physiological mechanisms of iodine deficiency, other micronutrients have to be taken into account. Most relevant nutrients are vitamin A, selenium, tyrosine, and vitamin D.
- To eliminate iodine deficiency after 90 years it is important to search for other strategies. The most logical strategy is to enrich the soil with iodine.
- To understand the side effects of iodine other contributors, especially selenium, need to be investigated since it is known for lowering thyroid peroxidase antibodies.

Explanation of Key Terms

Iodine: Member of the halogens, soluble in water, with the greatest concentrations in seawater. Seaweed and some plants are known for their high uptake of iodine.
Iodine deficiency: Iodine deficiency is characterized by a median urinary iodine excretion less than 100 microgram per liter. Goiter and elevated TSH should be regarded as a sign for longstanding inadequate iodine intake.
Deiodination: Deiodinaton of thyroid hormones is regulated by three selenodeiodinase isoforms. Deiodination of mono- and diiodotyrosine takes place by iodotyrosine dehalogenase, which is upregulated in the brain of developing frogs. In humans, selenodeiodinase and iodotyrosine dehalogenase are widely distributed.
Cretinism: Cretinism is the most severe clinical feature of iodine deficiency or congenital hypothyroidism. It leads to seriously impaired physical growth and mental development.
Sodium Iodide Symporter: The sodium iodide symporter is widely distributed throughout the body and not limited to the thyroid. In pregnancy and lactation, it is upregulated in the uterus and breasts. Iodine uptake is inhibited by perchlorate and thiocynate, next to the other halogens, bromide, and fluoride.

References

Andersson M, Benoist de B, Darnton-Hill I, Delange F. Iodine deficiency in Europe: a continuing public health problem. Geneva: World Health Organisation; 2007.

Bautista A, Barker PA, Dunn JT, Sanchez M, Kaiser DL. Am J Clin Nutr. 1982;35:127–34.

Beckett GJ, Arthur JR. J Endocrinol. 2005;184:455–65.

Benoist de B, Andersson M, Egli I, Takkouche B, Allen H. Iodine status worldwide: WHO Global Database on Iodine Deficiency. Geneva: World Health Organisation; 2004.

Briel van den T, West CE, Bleichrodt N, Vijver van de F, Ategbo EA, Hautvast JG. Am J Clin Nutr. 2000;72:1179–85.

Broadley MR, White PJ, Bryson RJ, Meacham MC, Bowen HC, Johnson SE, Hawkesford MJ, McGrath SP, Zhao FJ, Breward N, Harriman M, Tucker M. P Nutr Soc. 2006;65:169–81.

Duntas LH. Nat Clin Pract Endoc. 2008;4:454–60.

Eiduson S. UCLA Forum Med Sci. 1971;14:391–418.

Eisenhofer G, Tian H, Holmes C, Matsunaga J, Roffler-Tarlov S, Hearing VJ. FASEB J. 2003;17:1248–55.

Elzaouk L, Leimbacher W, Turri M, Ledermann B, Burki K, Blau N, Thony B. J Biol Chem. 2003;278:28303–11.

Gaupale TC, Mathi AA, Ravikumar A, Bhargava SY. Ann NY Acad Sci. 2009;1163:402–6.

Gelain DP, Moreira JC, Bevilaqua LR, Dickson PW, Dunkley PR. J Neurochem. 2007;103:2369–79.

Giovanniello T, Leuzzi V, Carducci C, Carducci C, Sabato ML, Artiola C, Santagata S, Pozzessere S, Antonozzi I. Neuropediatrics. 2007;38:213–5.

Gnidehou S, Caillou B, Talbot M, Ohayon R, Kaniewski J, Noel-Hudson MS, Morand S, Agnangji D, Sezan A, Courtin F, Virion A, Dupuy C. FASEB J. 2004;18:1574–6.

Groef de B, Decallonne BR, Geyten van der S, Darras VM, Bouillon R. Eur J Endocrinol. 2006;155:17–25.

Groot de LJ, Jaksina S. J Lab Clin Med. 1969;74:257–64.

Health Council of the Netherlands. Towards maintaining an optimal iodine intake. The Hague: Health Council of the Netherlands; 2008.

Hetzel B. Lancet. 1983;2:1126–9.

Hetzel B, Maberly G. In: Mertz C, editor. Trace elements in human and animal nutrition. New York: Academic Press; 1986. p. 139–208.

Holick MF. N Engl J Med. 2007;357:266–81.

Jeong H, Kim MS, Kim SW, Kim KS, Seol W. J Neurochem. 2006;98:386–94.

Kohrle J. Thyroid. 2005;15:841–53.

Kupper FC, Carpenter LJ, McFiggans GB, Palmer CJ, Waite TJ, Boneberg EM, Woitsch S, Weiller M, Abela R, Grolimund D, Potin P, Butler A, Luther GW, III, Kroneck PM, Meyer-Klaucke W, Feiters MC. Proc Natl Acad Sci USA. 2008;105:6954–8.

Kvicala J, Zamrazil V. Cent Eur J Public Health. 2003;11:107–13.

Laurberg P, Nohr SB, Pedersen KM, Hreidarsson AB, Andersen S, Bulow P, I, Knudsen N, Perrild H, Jorgensen T, Ovesen L. Thyroid. 2000;10:951–63.

Levin HM. In: Hetzel B, Dunn J, Stanbury J, editors. The prevention and control of iodine deficiency disorders. New York: Elsevier; 1987. p. 195–208.

Levin H, Pollitt E, Galloway R, McGuire J. In: Jamison D, editor. Disease control priorities in developing countries. New York: Oxford University Press; 1993. p. 421–451.

Levy O, Vieja de la V, Carrasco N. J Bioenerg Biomembr. 1998;30:195–206.

Lutsky BN, Zenker N. J Med Chem. 1968;11:1241–2.

Malamos B, Miras CJ, Karli-Samouilidou JN, Koutras DA. J Endocrinol. 1966;35:223–8.

Marine D, Kimball OP. J Lab Clin Med. 1990;115:128–36.

Melmon K, Rivlin R, Oates J, Sjoerdsma A. J Clin Endocr Metab. 1964;24:691–8.

Nakano M, Danowski T. Endocrinology. 1959;65:889–901.

Obregon MJ, Escobar del Rey F, Morreale de Escobar G. Thyroid. 2005;15:917–29.

Polley MJ. J Immunol. 1971;107:1493–5.

Puchacz E, Stumpf WE, Stachowiak EK, Stachowiak MK. Brain Res. 1996;36:193–6.

Riesco-Eizaguirre G, Santisteban P. Eur J Endocrinol. 2006;155:495–512.

Sande van J, Massart C, Beauwens R, Schoutens A, Costagliola S, Dumont JE, Wolff J. Endocrinology. 2003;144:247–52.

Scanlan TS. Endocrinology. 2009;150:1108–11.

Scanlan TS, Suchland KL, Hart ME, Chiellini G, Huang Y, Kruzich PJ, Frascarelli S, Crossley DA, Bunzow JR, Ronca-Testoni S, Lin ET, Hatton D, Zucchi R, Grandy DK. Nat Med. 2004;10:638–42.

Schmutzler C. Exp Clin Endocr Diab. 2001;109:41–4.

Smith MA, McHenry C, Oslapas R, Hofmann C, Hessel P, Paloyan E. Surgery. 1989;106:987–91.

Spitzweg C, Dutton CM, Castro MR, Bergert ER, Goellner JR, Heufelder AE, Morris JC. Kidney Int. 2001;59:
     1013–23.
Stanbury JB, Ermans AE, Bourdoux P, Todd C, Oken E, Tonglet R, Vidor G, Braverman LE, Medeiros-Neto G.
     Thyroid. 1998;8:83–100.
Steinnes E. Environ Geochem Health. 2009;31:523–35.
Tahara Y, Hirota M, Shima K, Kozu S, Ikegami H, Tanaka A, Kumahara Y, Amino N, Hayashizaki S, Miyai K.
     Metabolism. 1988;37:9–14.
Tiwari BD, Godbole MM, Chattopadhyay N, Mandal A, Mithal A. Am J Clin Nutr. 1996;63:782–6.
Verheesen RH, Schweitzer CM. Med Hypotheses. 2008;71:645–8.
Verheesen RH, Schweitzer CM Med Hypotheses. 2009;73:498–502.
Vermiglio F, Lo P, V, Moleti M, Sidoti M, Tortorella G, Scaffidi G, Castagna MG, Mattina F, Violi MA, Crisa A,
     Artemisia A, Trimarchi F. J Clin Endocr Metab. 2004;89:6054–60.
Welch K. Am J Physiol. 1962;202:757–60.
Xu J, Yang XF, Guo HL, Hou XH, Liu LG, Sun XF. Biol Trace Elem Res. 2006;111:229–38.
Zimmermann MB, Jooste PL, Mabapa NS, Schoeman S, Biebinger R, Mushaphi LF, Mbhenyane X. Am J Clin Nutr.
     2007;86:1040–4.
Zimmermann MB, Jooste PL, Pandav CS. Lancet. 2008;372:1251–62.
Zimmermann MB, Kohrle J. Thyroid. 2002;12:867–78.
Zofkova I, Blahos J, Bednar J. Endokrinologie. 1981;78:118–20.

Chapter 153
Riboflavin Deficiency, Brain Function, and Health

Rita Sinigaglia-Coimbra, Antonio Carlos Lopes, and Cicero G. Coimbra

Abbreviations

BBB	Brain-blood barrier
BH4	Tetrahydrobiopterin
CADCase/CSADCase	Cysteine and sulfinic acid decarboxylase
CBS	Cystathionine β-synthase
cGMP	Cyclic guanosine monophosphate
CL	Cystathionine-γ-lyase, or cystathionase
CNS	Central nervous system
CO	Carbon monoxide
CSF	Cerebrospinal fluid
EGRAC	Erythrocyte glutathione reductase activation coefficient
eNOS	Endothelial nitric oxide synthase
FAD	Flavin adenine dinucleotide
FMN	Flavin mononucleotide
GABA	γ-aminobutyric acid
GAD	Glutamic acid decarboxylase
γ-GCS	γ-glutamylcysteine synthetase
GMP	Guanosine monophosphate
GR	Glutathione reductase
GSH	Reduced glutathione
GSSG	Oxidized glutathione
GSTs	Glutathione S-transferases
H_2S	Hydrogen sulphide
HO	Heme oxygenase
HPLC	High-performance liquid chromatography
iNOS	Inducible nitric oxide synthase
MADD	Multiple acyl coenzyme A dehydrogenase deficiency
MPTP	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
MS	Methionine synthase

C.G. Coimbra (✉)
Laboratory of Clinical and Experimental Pathophysiology, Department of Neurology and Neurosurgery,
Federal University of São Paulo (UNIFESP), São Paulo SP BRAZIL
e-mail: coimbracg.nexp@epm.br

MTHFR	Methylenetetrahydrofolate reductase
NADPH	Nicotinamide adenine dinucleotide phosphate
nNOS	Neuronal nitric oxide synthase
NO	Nitric oxide
NOS	Nitric oxide synthase
PD	Parkinson's disease
PLP	Pyridoxal-5′-phosphate
PPO	Pyridoxine(pyridoxamine)-5′-phosphate oxidase
Rbf	Riboflavin
SHMT	Hydroxymethyltransferase
VDR	Vitamin D receptor

153.1 Introduction

Vitamin B2 (Rbf) is an essential micronutrient playing a key role in energy production (Hendler and Rorvik 2008). The active forms FAD and FMN act as either coenzymes or prosthetic groups in a wide diversity of biochemical reactions. Rbf deficiency has been also related to developmental abnormalities, altered iron status (ferritin iron mobilization, iron absorption and loss), cancer, visual abnormalities, neurodegeneration, and high plasma homocysteine (Powers 2003).

Nevertheless, clinical and experimental evidence compiled in this chapter support the view that the significance of Rbf deficiency for the pathophysiology and treatment of human diseases (of CNS disorders in particular) has been largely underestimated. First, current views merely consider low vitamin B2 status as a component of multiple vitamin deficiencies associated with malnutrition related to either poverty or alcoholism, because Rbf and other vitamins of the B complex share similar food sources such as whole grains, leafy green vegetables, eggs, meat, and milk (Powers 2003). Allegedly, deficiency of vitamin B2 could not occur as an isolated nutritional disorder, and the clinical consequences of multiple nutrient deficiencies would inevitably veil the specific manifestations of restricted availability of Rbf active metabolites.

Second, such views neglect the epidemiological studies by Anderson and coworkers who provided direct evidence showing that a substantial part of the world population (10–15%) carries an inherited restriction of Rbf absorption. Such restricted absorption is only balanced with a relatively high dose of Rbf (Anderson et al. 1994) repeated three to four times a day to stabilize circulating levels within the normal range throughout the 24 h (Coimbra and Junqueira 2003), suggesting increased urinary loss due to limited tubular reabsorption of Rbf from glomerular filtrate. The fundamental importance of these findings for human pathologies has been long neglected, possibly for being initially confined to the literature related to the epidemiology of malaria, against which Rbf deficiency seems to provide resistance. The data reviewed here suggest that a critical pathophysiologic role for Rbf deficiency is clearly feasible and likely, and worth research attention, particularly due to immediate implications in the prevention and therapeutic control of a wide range of prevalent human disorders like Parkinson's disease, arterial hypertension, fetal malformation and spontaneous abortion, migraine, and the full range of autoimmune diseases.

Third, a single inherited polymorphic gene disturbing cellular uptake of Rbf could explain all data related to poor absorption at the proximal ileum, low transport into red blood cells, and reduced reabsorption by proximal tubules. Anderson and coworkers provided evidence showing that the highly prevalent low vitamin B2 status is genetically determined, and suggested a polymorphic flavokinase, which catalyzes the conversion of Rbf to FMN, as a possible inherited feature responsible for the impaired cellular

uptake and trafficking of Rbf (Anderson et al. 1994). Regardless of whether or not Rbf phosphorylation is the metabolic step to blame, the polymorphic gene involved may simultaneously affect the homeostatic system reported by Spector (1980), which privileges the brain tissue with normal vitamin B2 concentrations during severe systemic deficiency. Due to the evident pathophysiologic relevance of disrupted Rbf homeostatic mechanisms in the CNS, neurologic disorders are particularly likely to develop in genetically affected individuals. Conversely, experimental attempts to replicate human neurologic disease requiring disruption of CNS mechanisms of vitamin B2 homeostasis by submitting genetically intact animals to dietary Rbf restriction may comprehensibly fail (DalPai et al. 2007).

Fourth, a wide range of metabolic pathways requires other essential micronutrients that are dependent on Rbf status, including vitamins B6 (PLP), B9 (folate), B12, and D3, which are similarly involved in numerous additional metabolic routes. Some other pathways (such as NO synthesis, HO activity, and the activity of the whole cytochrome P-450 enzyme superfamily) are doubly dependent on vitamin B2, for requiring both flavin active forms (FMN and FAD) for constant switching of critical heme enzymes to the reduced state. Furthermore, heme synthesis and degradation are also primarily or secondarily dependent on vitamin B2 status. The metabolic interdependency of these bioactive molecules significantly amplifies the spectrum of pathophysiologic phenomena potentially related to vitamin B2 deficiency, while creating direct and indirect pathways and positive feedback loops that further enhance several disease mechanisms.

153.2   Riboflavin and Its Bioactive Forms – FAD and FMN

Rbf is a water soluble light sensitive vitamin chemically named 7,8-dimethyl-10-(1′-d-ribityl-isoalloxazine), molecular formula: $C_{17}H_{20}N_4O_6$, and molecular weight: 376.4 Da (Hendler and Rorvik 2008). Originally isolated from milk in the ninth century by Wynter Blyth as a bright yellow pigment, Rbf was later recognized as a member of the vitamin B complex. Richard Kuhn in Heidelberg (1934) and Paul Karrer in Zurich (1935) almost concurrently succeeded in determining the chemical structure, and the name "riboflavin" was given to replace the variety of previous names. Soon after, Hugo Theorell (1937) and Otto Warburg and Walter Christian (1938) identified the two Rbf active forms, FMN and FAD, respectively (Massey 2000) (Fig. 153.1).
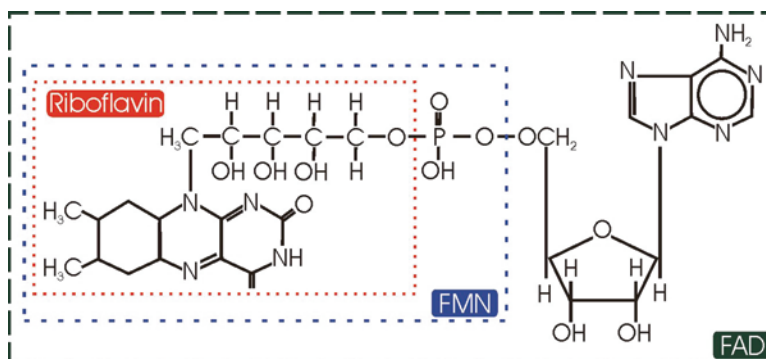
Fig. 153.1 Structure of riboflavin and its bioactive forms. Riboflavin, also known as vitamin B2, is the core of its bioactive forms – flavin mononucleotide (*FMN*) and flavin adenine dinucleotide (*FAD*). It contains a so-called "flavin ring system," an isoalloxazine ring methylated at the 7 and 8 positions, having also a d-ribityl moiety at the position 10. FMN is generated by phosphorilation at the 5′ position of ribityl group, and the addition of adenosine-5′-monophosphate yields the second bioactive form, the FAD.

153.3 Sources, Dietary Requirements, and Pharmacokinetics

Humans are not able to synthesize Rbf, and must thus obtain the vitamin from their diet. Dietary vitamin B2 is scarcely available as free Rbf, but rather mostly as FAD and FMN integrated into proteins (flavoproteins). The dietary sources of vitamin B2 are similar to those of other B vitamins. The main specific sources are milk and dairy products, which contribute to 51% of the overall intake in preschool children, 35% in schoolchildren, 27% in adults, and 36% in the elderly (Powers 2003). To a lesser extent, meat, green vegetables, and grains are also good sources of vitamin B2. UV light exposure is the most important factor impairing the bioavailability of vitamin B2 (Foraker et al. 2003).

The daily intake recommended by the World Health Organization varies from 0.3 mg for infants to 1.3 mg for adult males, being the highest requirements reserved for pregnant and lactating women (up to 1.6 mg/day). However, those recommendations do not take into account the possibility of hereditary malabsorption that may affect an average of 10–15% of the general population as suggested by Anderson and coworkers (1994), nor pathological conditions like celiac disease, malignancy or resection of the small bowel (WHO/FAO 2009). The maximal amount of Rbf that can be absorbed from a single dose is 27 mg (Zempleni 1996), which represents approximately 20 times the recommended daily dose. Therefore, humans tolerate large doses (multiple grams) given orally without toxicity – limited intestinal absorption affords protection at high intakes (Bates 1997).

The dietary bioactive forms of the vitamin (FMN and FAD) undergo hydrolysis to Rbf for absorption. Enterocytes at the proximal ileum can take up only free Rbf, which is rapidly absorbed (1.4–2.0 h) and further metabolized by specific enzymes. FAD-pyrophosphatase converts FAD to FMN, and FMN-phosphatase converts FMN to Rbf. Once within the intracellular compartment, Rbf accumulates in tissues after the resynthesis of FMN and FAD. Rbf flavokinase turns Rbf into FMN, and the enzyme FAD synthetase converts FMN to FAD (Rivlin and Pinto 2001). Intracellular FMN is either converted to FAD or integrated to flavoenzymes as a prosthetic group (covalent bounds), while FAD is mainly (covalently) incorporated into apo-flavoenzymes. Interestingly, thyroid and adrenal hormones regulate the consecutive conversions of Rbf to FMN and FMN to FAD, as well as the covalent binding of flavins to their apo-flavoenzymes (Zempleni et al. 1996).

Rbf absorption occurs through two distinct mechanisms: (1) active transport, which is dominant under low or physiologic concentrations of Rbf within the proximal ileum, and (2) passive diffusion, which becomes prominent at intraluminal Rbf concentrations above the physiological range. In addition, Ca^{++}/calmodulin, protein kinase A and G may regulate Rbf absorption (Foraker et al. 2003). The role of binding proteins in Rbf absorption and transport requires further investigation (Fig. 153.2). Several drugs (including psychotropic agents, antidepressants, chemotherapeutic and antimalarial medicines) may reduce Rbf absorption by impairing Rbf conversion into bioactive forms. It is worth noticing that all these drugs share structural similarities to Rbf. Alcohol may also impair Rbf utilization due to inhibition of both digestive and absorptive processes (Pinto et al. 1987).

Mammals have a variety of tissular and circulating Rbf binding-proteins, including albumin, immunoglobulins, and pregnancy-specific Rbf-binding proteins and Rbf kinase (White and Merril 1988), all of them endowed with high potential clinical significance. The literature has scarce information about Rbf homeostasis in the brain. Spector (1980) showed that Rbf rapidly crosses the rabbit BBB and accumulates in the brain tissue by a saturable system after phosphorylation. CSF Rbf either accumulates in brain cells or crosses the choroid plexus into the blood by a saturable, probenecid-sensitive mechanism. Rbf excretion is mainly renal, and several flavin metabolites are detectable in the urine (Zempleni et al. 1996). Further studies should address the identification of proteins
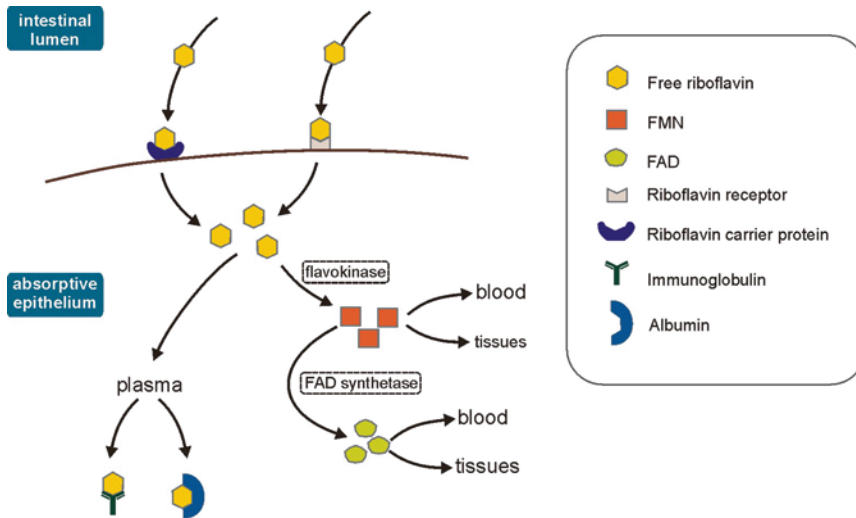
Fig. 153.2 Riboflavin absorption at the proximal ileum. Free riboflavin can be uptaken by either a receptor or a carrier protein. After uptake, riboflavin may have two possible fates: (**a**) phosphorylation to FMN by flavokinase, and then converted to FAD by FAD synthase, or (**b**) transportation to plasma. Note that small amounts of FMN may be found in blood and scarcely in tissues, while FAD is the most abundant bioactive form of vitamin B2 in blood and tissues. Part of free riboflavin is transported through the cell into the bloodstream in the unphosphorylated form, and then bound to riboflavin-binding proteins, such as albumin and immunoglobulins. *FMN* flavin mononucleotide, *FAD* flavin adenine dinucleotide

(and related gene polymorphisms) involved in uptake, trafficking, and cellular homeostasis of Rbf in humans, including at the levels of renal tubules and the BBB (Foraker et al. 2003).

153.4 Vitamin B2 Status Assessment

Although all forms of vitamin B2 (free Rbf, FMN, and FAD) are present in measurable concentrations, FAD is the main form of the vitamin found in tissues and whole blood (Powers 1999) and is therefore, most representative of total body flavin content. Although HPLC with fluorometric detection may accurately detect FAD, a functional test (EGRAC) is the method of choice for assessment of vitamin B2 status (Powers 1999). EGRAC measures saturation of the enzyme GR with its coenzyme (FAD). When vitamin B2 stores are significantly low, the addition of FAD to a sample of erythrocytes in vitro produces a percentage increase in measured enzyme activity (activity coefficient) that exceeds 15–20% (EGRAC = 1.15–1.20, respectively). Therefore, EGRAC is the ratio between enzyme activity determined with and without the addition of FAD. The larger the increase in EGRAC noted after the addition of FAD in vitro, the greater the degree of unsaturation of the apoenzyme with its cofactor and the more severe the deficiency of vitamin B2. The loss of erythrocyte FAD at an early stage in vitamin B2 deficiency makes EGRAC a sensitive method for the diagnosis of vitamin B2 deficiency (Bates 1993). EGRAC is an index independent of any uncontrolled denominator, and hence is robust as well as sensitive in practice (Bates 1987). Following bloodsampling, 31.5–84.8% of plasma FAD is hydrolyzed to FMN within 10–40 mm at 37°C (Zempleni et al. 1996). Therefore, blood should be immediately processed after sampling, and erythrocytes stored at 4.0°C for early EGRAC assessment.

153.5 Riboflavin Functions

Many key enzymes require FAD and/or FMN to catalyze a wide range of different types of reactions, particularly oxidation–reduction reactions, dehydrogenation, and oxidative decarboxylation. Most importantly, FAD and/or FMN is involved in the respiratory chain, lipid metabolism, the cytochrome P-450 system, and drug metabolism. Monoamine oxidase, sarcosine dehydrogenase, and succinate dehydrogenase are flavoproteins. Vitamin B2 also plays a role in the metabolism of essential fatty acids in brain lipids (Ogunleye and Odutuga 1989).

Complexes I and II are respectively FMN- and FAD-dependent (Nelson and Cox 2009), while flavoproteins are also responsible for oxygen reduction to hydrogen peroxide (Rivlin and Pinto 2001). Upon reduced vitamin B2 bioavailability, ATP production is selectively preserved, while the less critical FAD- or FMN-dependent metabolic pathways are impaired (Anderson et al. 1994).

Another critical feature is the influence of vitamin B2 on the glutathione system. Glutathione is a tripeptide occurring in reduced (GSH) and oxidized (GSSG) states. GSH is the major endogenous cellular antioxidant, which not only directly neutralizes free radicals, but also deactivates hydrogen peroxide molecules that result from the action of superoxide dismutase on superoxide ions. GSH is the most abundant form of glutathione under physiological conditions, and increased GSSG-to-GSH ratio becomes evident under oxidative stress. Following inactivation of free radicals or peroxides, GSH is regenerated from GSSG by the FAD-containing enzyme GSSG reductase (Hustad et al. 2002) (Fig. 153.3).

The two alternative pathways of deoxynucleotide synthesis primarily or secondarily require FAD at the expense either of FAD or GSH, respectively (Nelson and Cox 2009) (Fig.153.4), and decreased bioavailability of vitamin B2 should therefore affect DNA synthesis. Not surprisingly, the activity of the glutathione system affects the pathophysiology of cancer, regulation of apoptosis, and DNA repair (Hall 1999; Berwick and Vineis 2000; Locigno and Castronovo 2001). Vitamin B2 deficiency may affect the mitochondrial pool of GSH which in turn may affect the activities of the flavoenzymes NADPH-cytochrome P-450 reductase and NADPH-cytochrome b reductase (Hustad et al. 2002).

The GSTs comprise a super family of multifunctional enzymes widely expressed in mammalian tissue cytosols and membranes that play a pivotal role in electrophile detoxification, while protecting cells from the consequences of oxidative stress. They catalyze the conjugation of GSH with a wide
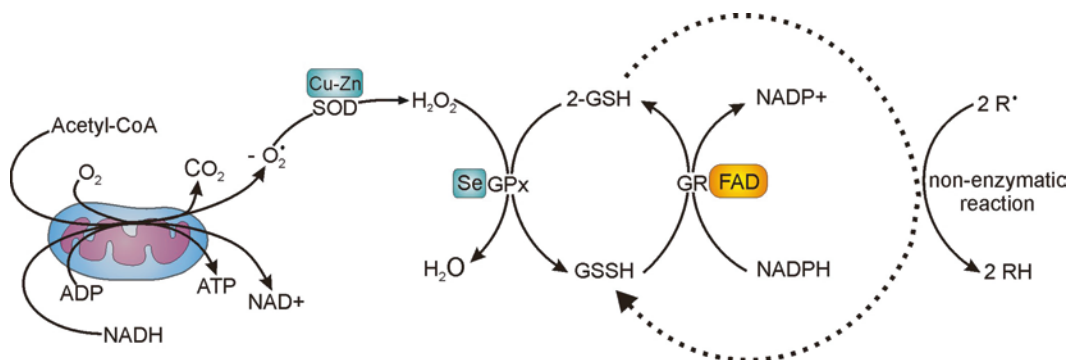
Fig. 153.3 The role of FAD on the glutathione antioxidation system. Glutathione peroxidase (*GPx*) neutralize free radicals and peroxides. The FAD-dependent enzyme glutathione redutase (*GR*) regenerates oxidized (*GSSG*) to reduced (*GSH*) glutathione. *FAD* flavin adenine dinucleotide, *SOD* superoxide dismutase, *NAD$^+$* oxidized nicotinamide adenine dinucleotide, *NADH* reduced nicotinamide adenine dinucleotide, *NADP$^+$* oxidized nicotinamide adenine dinucleotide phosphate, *NADPH* reduced nicotinamide adenine dinucleotide phosphate, *ADP* adenosine diphosphate, *ATP* adenosine triphosphate

Fig. 153.4 The role of riboflavin bioactive forms (FAD and FMN) on the cytochrome P-450 system. The microsomal cytochrome P450 receives electrons from a FAD- and FMN-containing enzyme – the NADPH-dependent cytochrome P450 reductase, where both FMN and FAD operate as prosthetic groups. *FAD* flavin adenine dinucleotide, *FMN* flavin monophosphate, *NADPH* nicotinamide adenine dinucleotide phosphate, *NADP+* nicotinamide adenine dinucleotide phosphate
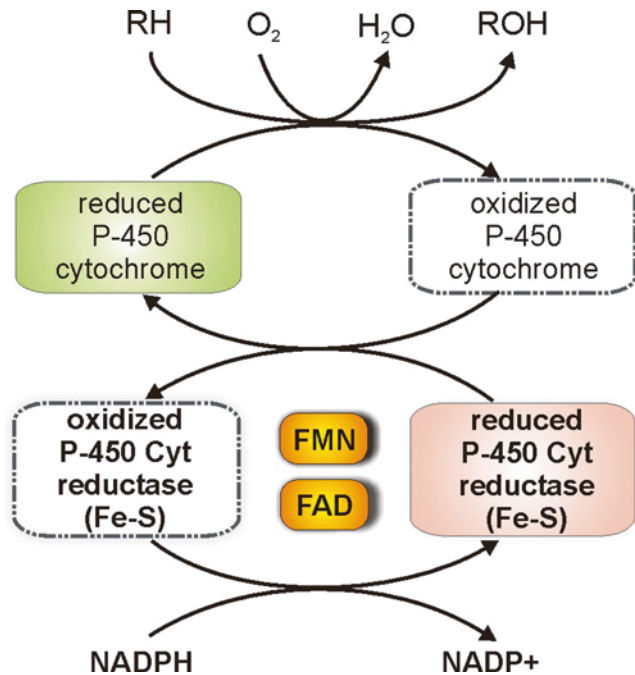
variety of exogenous and endogenous chemicals with electrophilic functional groups (e.g., products of oxidative stress, oxidized DNA and lipid molecules, environmental pollutants, xenobiotics, and carcinogens). By neutralizing the electrophilic sites, the process prevents these products from attacking macromolecules and renders them more water-soluble (Parl 2005). The impairment of GR activity by abnormally low vitamin B2 status should plausibly limit the availability of GSH required for GST activity, thereby increasing the oxidative stress.

The cytochrome P-450 is a superfamily of hemeproteins (comprising 57 human genes) that catalyze the oxidation of a wide array of lipophilic compounds such as drugs and carcinogens or endogenous compounds such as prostaglandins, fatty acids, and steroids (Nebert and Russell 2002). The microsomal cytochrome P-450 receives electrons from a FAD- and FMN-containing enzyme – the NADPH-dependent cytochrome P-450 reductase, where both FMN and FAD operate as prosthetic groups (Wang et al. 1997) (Fig. 153.4). Therefore, the whole spectrum of cytochrome P-450 reactions is impaired with vitamin B2 deficiency. That includes the metabolism of drugs, foreign chemicals (carcinogens as well), arachidonic acid and eicosanoids, cholesterol metabolism and bile acid biosynthesis, steroid synthesis and metabolism, vitamin D3 metabolism, retinoic acid hydroxylation, and the activity of other enzymes of unknown function (Nebert and Russell 2002).

The microsomal NADPH-dependent cytochrome P-450 reductase is also required to provide the reducing equivalent necessary for heme oxidation through the HO enzymatic activity (Maines 1997). HO is the only enzyme that can degrade heme (iron protoporphyrin-IX, hemin) to biliverdin, free iron, and CO. Maintaining cellular heme homeostasis, HO protects tissues against hemin-triggered oxidative stress, thereby limiting damage in diverse in vitro and in vivo models of cellular and tissue injuries. HO consists of two major isozymes: the inducible HO-1, known as heat shock protein-32 (HSP-32), and the constitutively expressed HO-2, which is highly concentrated in the brain and testes. HO-1 under basal conditions is barely detectable in the brain, but is induced in numerous conditions, such as hyperthermia, Alzheimer disease, transient and global ischemia, and subarachnoid hemorrhage (reviewed by Kim et al. 2005). By impairing the activity of the biflavin

(FMN- and FAD-dependent) enzyme NADPH-cytochrome P-450 reductase, vitamin B2 deficiency may conceivably compromise HO-dependent cytoprotective effects.

To date, tens of thousands of publications and three Nobel Laureates have unveiled and emphasized the fundamental biological importance of NO for both normal cellular and whole body physiology, and also in the pathology of many diseases, especially those related to inflammation and long term degenerative disorders. Enzymes known as NO synthases (without ATP utilization) synthesize NO from l-arginine in mammalian tissues. The activity of the three isoenzymes (eNOS, iNOS, and nNOS) requires l-arginine and NADPH, and results in the formation of citrulline and NO. NO synthesis requires not only these substrates but also the presence of calmodulin, as well as four other coenzymes/cofactors: BH4, NADPH and, particularly relevant for this discussion, the active flavins FMN and FAD (Bruckdorfer 2005). Vitamin B2 deficiency therefore, may affect the whole spectrum of metabolic pathways, physiologic and pathophysiologic phenomena related to NO.

153.6 Rbf Interactions with Pyridoxine, Folic Acid, Cobalamin, and Vitamin D

FMN and/or FAD are required for maintenance of pyridoxine (vitamin B6), folic acid (vitamin B9), and cobalamin (vitamin B12) statuses, so that vitamin B2 deficiency may lead to secondary impairment of all B6-, B9-, and B12-dependant enzyme activities. Such metabolic relationships largely amplify the spectrum of pathophysiologic implications and diseases potentially related to vitamin B2 deficiency. They provide likely explanations for the relation of vitamin B2 availability to plasma homocysteine levels, which is associated with cardiovascular disease, pregnancy complications, and cognitive impairment (Hustad et al. 2000; Skoupy et al. 2002).

A number of folate-dependent pathways related to methionine and nucleotide biosynthesis explain how folic acid may prevent neural tube and other birth defects like spina bifida, lower homocysteine and risk of cardiovascular disease, prevent several types of cancer, dementia, affective disorders, Down's syndrome, and serious conditions affecting pregnancy outcome. FAD is the cofactor for MTHFR (Fig. 153.5), which catalyzes the formation of 5-methyltetrahydrofolate – a methyl donor for homocysteine remethylation. The MTHFR C677T (cytidine to thymidine substitution at position 677) polymorphism causes alanine to be replaced by valine in the catalytic domain. This genotypic alteration affects the FAD binding and destabilizes the quaternary structure of the enzyme, making it thermolabile with approximately half-normal activity (Joshi et al. 2009), and increasing total plasma homocysteine concentrations, particularly in association with low folate status (Moat et al. 2003). Therefore, low vitamin B2 status should further impair folate-dependent pathways in individuals carrying MTHFR polymorphisms and potentiates this and other genetic susceptibilities to folic acid deficiency. Folate-dependent key physiologic roles potentially impaired in vitamin B2 deficiency, include maintenance and repair of the genome, regulation of gene expression, amino-acid metabolism, neurotransmitter synthesis, and the formation of myelin (Djukic 2007).

FMN serves as a cofactor for PPO, which catalyzes the terminal and rate-limiting step of the biosynthesis of PLP (the biologically active form of vitamin B6) from pyridoxine, the main dietary and therapeutic form of vitamin B6 (Powers 2003). PLP is a coenzyme in the catabolism of carbohydrates, fats, and proteins, and in the synthesis of hormones, red blood cells, neurotransmitters, and enzymes. PLP is a coenzyme for more than 100 enzymes involved in amino acid metabolism, including aminotransferases, decarboxylases, racemases, and dehydratases. PLP is a coenzyme for CBS (unique in having both PLP and heme as cofactors) and CL, the two enzymes involved in the transsulfuration pathway from homocysteine to cysteine (Fig. 153.5).

Fig. 153.5 FAD interactions with pyridoxine, folic acid, cobalamin. For maintenance of normal metabolism (*left panel*), the folic acid/methylcobalamin cycle needs FAD as a coenzyme for methylenetetrahydrofolate reductase (*MTHFR*) and methionine synthase (*MS*) activities. The synthesis of pyridoxal 5′-phosphate (PLP, the active form of vitamin B6) from pyridox(am)ine 5′-phosphate requires FMN, while serine hydroxymethyltransferase (*SHMT*), cystathionine-γ-lyase (*CL*, cystathionase) and cystathionine β synthase (*CBS*) are PLP-dependent enzymes and therefore, secondarily depend on FMN. Glutathione reductase (*GR*) activity requires FAD, while cysteine synthesis from homocysteine requires the consecutive activities of two PLP enzymes (CL and CBS). Hence, the levels of reduced glutathione (*GSH*, an antioxidant molecule with multiple essential metabolic functions) are doubly dependent on vitamin B2 status. The role of GSH in deoxynucleotide production (required for DNA synthesis) is explained in Fig. 153.7 and text. Upon vitamin B2 deficiency (*right panel*) all B6-, B9-, and B12-dependent enzyme activities may be impaired. "X" and "X inside the circle" respectively indicate enzyme activities primarily and secondarily inhibited under low vitamin B2 status (secondary to low PLP or methylcobalamin availability). Associated reductions of FMN-dependent SHMT activity, DNA methylation (CH$_3$DNA), deoxynucleotide production, and purine synthesis contribute to impairment of DNA repairing mechanisms under low vitamin B2 status. *GSSG* oxidized glutathione, *MT* metallothionein, *AdoHcy* adenosylhomocysteine, *SAHH* S-adenosyl homocysteine hydrolase, *Ado* adenosine, *BHMT* betaine-homocysteine methyltransferases, *Met* methionine, *MAT* methionine adenosyltransferase, *AdoMet* S-adenosyl-methionine, *MS* methionine synthase, *DHFR* dihydrofolate reductase, *TS* thymidylate synthase, *DHF* dihydrofolate, *CHTHF* methenyltetrahydrofolate, *CHOTHF* formyl tetrahydrofolate, *THF* tetrahydrofolate, *dUMP* deoxyuridine monophosphate, *dTMP* deoxythymidine monophosphate, *CH$_3$DNA* methylated DNA

PLP is also a coenzyme for δ-aminolevulinate synthase – the rate-limiting step in the biosynthesis of heme, which is incorporated as a prosthetic group to a wide variety of proteins with biologically diverse critical functions. Heme proteins include:

(a) Oxygen transport and storage proteins – hemoglobin and myoglobin;
(b) Heme redox enzymes – the cytochrome P-450 superfamily; peroxidases, catalases, and catalase-peroxidases; the dioxygenases indoleamine 2,3-dioxygenase and tryptophan 2,3-dioxygenase; the three NOS isoforms;
(c) Electron transfer proteins – cytochromes b and c;
(d) Heme sensor proteins – heme-responsive heme sensor proteins, such as the HRI system which regulates the translation of genes required for globin synthesis in red blood cells; gas-responsive heme sensor proteins such as guanylate cyclases.

The classical clinical symptoms of B6 deficiency are seborrheic dermatitis, microcytic anemia, epileptiform convulsions, insomnia, depression, and confusion (Mooney et al. 2009). By limiting the conversion of pyridox(am)ine 5′-phosphate to PLP, vitamin B2 deficiency may impair the whole wide range of PLP-dependent vital metabolic pathways (Fig. 153.5).

The enzyme MS (also known as methionine synthase reductase), which converts homocysteine to methionine, is dependent on 5-methyltetrahydrofolate as a methyl donor and on vitamin B-12 (as methylcobalamin). Vitamin B-12 plays an essential role in the methyl transfer reaction by acting as an intermediate methyl carrier between methyltetrahydrofolate and homocysteine. MS also contains both FMN and FAD as coenzymes, which are essential for maintenance of proper redox state of cobalt ions in the methylcobalamin molecule, thereby preventing inactivation of the enzyme (Olteanu and Banerjee 2001) (Fig. 153.5).

The dependency of vitamins B6, B12, and folate on FAD and/or FMN availability largely amplifies the metabolic importance of vitamin B2. For instance, Rbf deficiency may both limit the activation of vitamin B6 to PLP and inactivate methylcobalamin. Metabolic derangement of methionine and folate metabolism in this circumstance may result not only primarily from reduced MTHFR and SHMT activities, but also from oxidation of methylcobalamin secondary to Rbf deficiency.

Likewise, rather than solely resulting from decreased coenzymes (FMN and FAD) required for NOS activity, diminished NO synthesis and reduced NO-mediated biological effects in vitamin B2 deficiency may also be secondary to low PLP production by FMN-dependent PPO, which limits the synthesis of prosthetic heme to be incorporated during the assembly of NOS isoenzymes and GC (Fig. 153.6). Similarly, oxidative stress in vitamin B2 deficiency would not merely result from decreased GSH regeneration from GSSG by the FAD-dependent enzyme GSSG reductase: decreased prosthetic heme incorporation during the assembly of catalases may further aggravate oxidative stress.
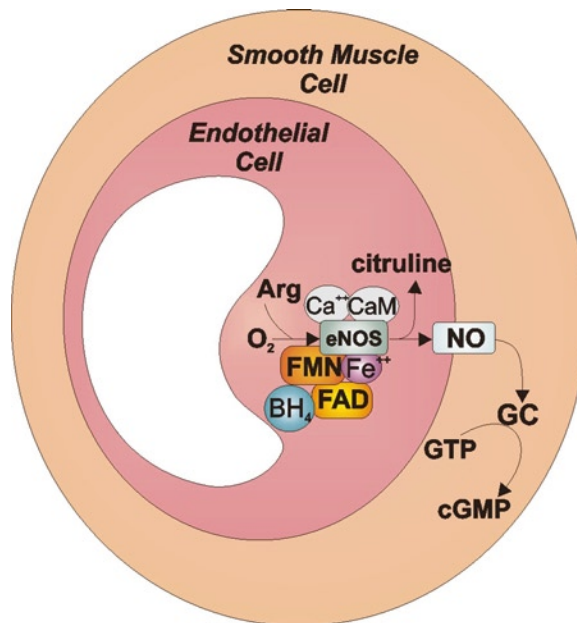
Fig. 153.6 The importance of vitamin B2 for NO production. Dependency of endothelium-derived nitric oxide (*NO*) function on vitamin B2 status. Endothelial nitric oxide synthase (*eNOS*) activity requires both active forms of vitamin B2, flavin adenine dinucleotide (*FAD*), and flavin mononucleotide (*FMN*). The vasodilatatoy effect of NO depends on guanylate cyclase (*GC*) for cGMP synthesis within smooth muscle cells. Both eNOS and GC are hemeproteins, and prosthetic heme synthesis requires the activity of pyridoxal 5′-phosphate (*PLP*)-dependent δ-aminolevulinate synthase. The synthesis of PLP (the active form of vitamin B6) from pyridox(am)ine 5′-phosphate requires FMN. Therefore, vitamin B2 deficiency may impair the vasodilatatoy effect of NO at multiple biochemical steps, including depressed eNOS activity and low availability of prosthetic heme for posttranslational incorporation into the expressed proteins eNOS and GC. *Arg* arginine, *O₂* oxygen, *Fe⁺⁺* ferrous iron, *Ca⁺⁺CaM* calcium/calmodulin complex, *BH4* tetrahydrobiopterin, *GTP* guanosine triphosphate, *cGMP* cyclic guanosine monophosphate
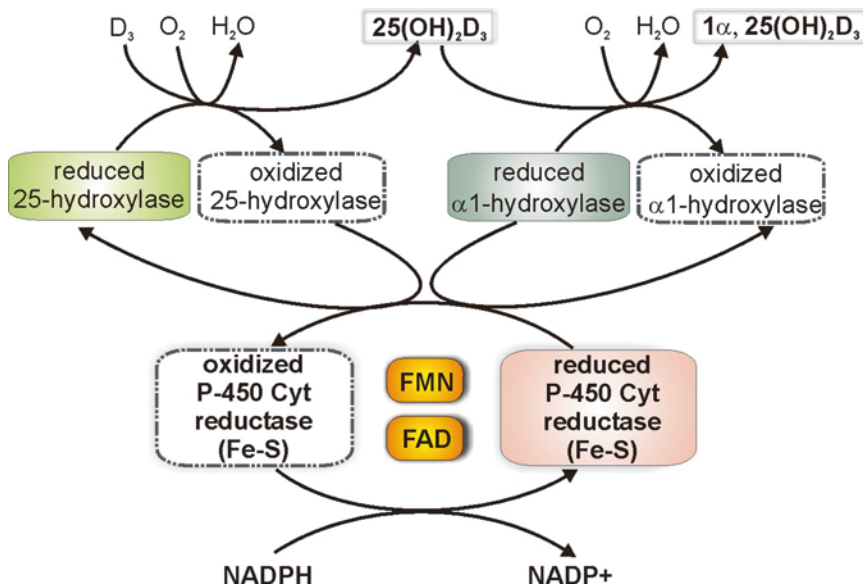
Fig. 153.7 FAD and FMN interactions with vitamin D. The deficiency of vitamin B2 bioactive forms may secondarily affect the activity of vitamin D hydroxylases. Note that enzymes 25-hydroxylase and 1α-hydroxylase are members of the cytochrome P-450 superfamily and require the activity of the flavo-enzyme NADPH-dependent cytochrome P450 reductase. *FAD* flavin adenine dinucleotide, *FMN* flavin monophosphate, *NADPH* reduced nicotinamide adenine dinucleotide phosphate, *NADP*⁺ oxidized nicotinamide adenine dinucleotide phosphate

In addition, vitamin B2 deficiency may significantly affect the activity of vitamin D hydroxylases. The enzymes 25-hydroxylase and 1α-hydroxylase are members of cytochrome P-450 superfamily. The consecutive syntheses of 25(OH)D3 (calcidiol) from cholecalciferol and 1α,25(OH)2D3 (calcitriol, the active form of Vitamin D) from calcidiol are expected to be reduced vitamin B2 deficiency. This may occur because of both decreased prosthetic heme incorporation (secondary to reduced heme synthesis due to low PLP production) to hydroxylases and limited prosthetic FMN/FAD incorporation to NADPH-dependent cytochrome P-450 reductase (Fig. 153.7).

153.7 Deficiency Consequences in Both Human and Experimental Studies

Rather than restricted to developing countries, vitamin B2 deficiency may be widespread in industrialized countries as well, where it affects both the elderly and young adults rather than occurring only in patients suffering from chronic conditions such as celiac disease, cancer, and alcoholism (Powers 2003). The importance of the work by Anderson and associates – showing that low vitamin B2 status may result from defective absorption in a relatively large number of otherwise well-nourished individuals – cannot be overemphasized. In spite of an adequate dietary intake, 10–15% of the inhabitants of London and Florence showed a low activation coefficient of two vitamin B2-dependent enzymes – GR and PPO. High doses of Rbf (24–30 mg/day for 5–8 weeks) corrected the activity of both enzymes in the affected individuals. The dependency of both FMN and FAD levels on Rbf absorption, and the normalization of the activities of both FMN- and FAD-dependent enzymes only at a high Rbf intake, taken together, are consistent with the expression of polymorphic genes related to Rbf absorption such as the flavokinase gene. The similar number of persons affected in different ethnic groups

(10–15%) indicates that these percentages may be representative of the world prevalence of genetic polymorphisms impairing Rbf absorption in the proximal ileum (Anderson et al. 1994).

Normal vitamin B2 body homeostasis also depends on a renal saturable uptake system that reabsorbs almost all the filtered micronutrient in the proximal tubule epithelial cells (Jusko and Levy 1970). Moreover, maintenance of normal EGRAC levels in vitamin B2 deficiency unrelated to dietary restriction requires the administration of high doses of Rbf at least three times a day (Coimbra and Junqueira 2003). This finding suggests an increased urinary loss of vitamin B2 in the affected individuals, implying a general impairment of uptake, trafficking, and cellular homeostasis of Rbf. In other words, a single genetic polymorphism may cause widespread changes in Rbf transport in several cell types, and underlie both malabsorption of Rbf by proximal ileum cells and impaired Rbf uptake from glomerular filtrate by proximal tubule cells. This issue has major implications for neurologic disorders as explained ahead.

The classical signs of vitamin B2 deficiency are cheilosis, angular stomatitis, glossitis, seborrheic dermatitis (Hendler and Rorvik 2008), and cataract (Powers 2003). Experimental studies in vitamin B2 deprivation in rats demonstrated disruption of iron metabolism (Powers 2003). Other studies on vitamin B2 deprivation during fetal development showed a reduction of the terminal electron transport system, increased fetal mortality and decreased fetal growth, mental retardation, and complete cessation of growth (Bates 1997; Powers 2003).

153.8 Vitamin B2 Deficiency and Neurological Diseases

The wide array of metabolic functions of FMN and FAD and their interactions with pyridoxine, folic acid, cobalamin, and vitamin D exceedingly amplify the range of human diseases potentially associated with Rbf deficiency. Additionally, the high prevalence of Rbf deficiency (probably secondary to polymorphisms of genes related to uptake, trafficking, and cellular homeostasis of vitamin B2 in humans) highly emphasizes the pathophysiologic and epidemiologic relevance of the issue.

The issues related to a highly prevalent genetic mechanism impairing cellular trafficking of Rbf in multiple tissues, possibly involving the flavokinase gene (Anderson et al. 1994), are particularly relevant for the CNS. A very efficient homeostatic system for Rbf renders the brain tissue privileged in circumstances of low dietary Rbf availability in genetically normal individuals, so that the total CNS content of vitamin B2 is preserved in contrast to other tissues (Spector 1980). The concentrations of total Rbf in plasma, CSF, and brain were 0.2, 0.1, and 8.8 2 M, respectively, in genetically normal adult rabbits (Spector 1980). Conceivably, polymorphisms of genes related to cellular uptake mechanisms may also impair the transport of Rbf across the choroid plexus epithelial cells, the main transport locus of the blood-cerebrospinal fluid barrier (Spector and Johanson 2006), thereby disrupting the activity of those powerful homeostatic mechanisms.

153.8.1 Parkinson´s Disease

Genetically impaired CNS Rbf homeostasis may underlie the predisposition to PD by enabling the activity of pathophysiologic mechanisms related to degeneration of dopaminergic nigral cells (Coimbra and Junqueira 2003). These homeostatic mechanisms would be intact in genetically normal rats and prevent the activity of similar pathophysiologic phenomena in the experimental setting (DalPai et al. 2007).

Several pathophysiologic issues related to PD may be related to disturbed Rbf homeostasis in the CNS. GSH depletion – considered an early key event in the pathogenesis of PD (Jenner et al. 1992; Schulz et al. 2000) may occur as a consequence of impaired FAD-dependent GR activity. Because humans lack efficient iron excretory mechanisms, iron excess is dealt with by increasing the synthesis of the iron-storage protein ferritin (Casey et al. 1988). Disturbed systemic (Logroscino et al. 1997) and brain (Dexter et al. 1990) iron metabolism has been reported in PD, suggesting that a selective decrease in the levels of ferritin may result in an increase in intracellular free iron, thereby enhancing free radical production (Mann et al. 1994). Indeed, vitamin B2 deficiency in rodents is associated with low circulating iron concentrations, increased iron turnover, and excretion into the intestinal lumen, which may occur in response to impaired ferritin synthesis (Powers 2003). Therefore, the consistent finding of an abnormal Rbf status in PD (Coimbra and Junqueira 2003), may help to explain the disturbed iron metabolism found in PD patients, with the underlying mechanisms possibly involving (1) impaired hemin catabolism by HO secondary to low activity of FMN- and FAD-dependent cytochrome P-450 reductase, and (2) reduced neuronal ferritin synthesis. Free iron concentrations in the cytosol increase due to impaired ferritin synthesis and/or reduced hemin catabolism associated with hydrogen peroxide accumulation due to glutathione depletion, thereby triggering the Fenton reaction, and ultimately leading to the selective formation of the potent neurotoxin 6(OH)DA in dopaminergic neurons.

Moreover, because FAD is required in both alternative pathways of deoxynucleotide synthesis (Nelson and Cox 2009) (Fig. 153.8), DNA repair and replication are expected to be disturbed by decreased Rbf bioavailability, and abnormal Rbf status may also explain the cumulative mitochondrial DNA mutations reported in PD (Di Monte 1991). In addition to mitochondrial DNA mutations, the reduced bioavailability of FMN and/or FAD required for the activity of mitochondrial complexes I and II, respectively, may further explain the impaired oxidative metabolism of PD patients (Schapira et al. 1990; Mytilineou et al. 1994; Mizuno et al. 1994).

Emotional stress may cause PD (Smith et al. 2002; Sipetic-Grujicicl et al. 2007) in individuals turned susceptible to stress-induced nigral degeneration by polymorphic genes that disturb cellular uptake and trafficking of Rbf and affect the homeostatic preservation of the vitamin stores in the CNS. Excessive dopamine concentrations in nigral cells under prolonged stressful situations (Kim et al. 2005) may cause accumulation of dopamine-derived salsolinol (Naoi et al. 2002), a potent endogenous aromatic heterocyclic amine similar to MPTP (Speciale 2002) capable of covalent binding to DNA (DNA adduct formation) and inducing degeneration of nigral cells. Additionally, exogenous aromatic heterocyclic amines absorbed from ingested meat cooked at high temperatures may contribute to Parkinsonian neurodegeneration (Collins and Neafsey 2002). Both the synthesis and catabolism of heterocyclic amines require the participation of cytochrome P-450 enzymes (Sinha and Caporaso 1997). The metabolism of (endogenous or exogenous) heterocyclic amines by cytochrome P-450 enzymes is secondarily altered in vitamin B2 deficiency due to impairment of NADPH-cytochrome P-450 reductase. Simultaneously, the vulnerability of the nervous tissue to DNA adduct formation is increased due to this and other FMN of FAD-dependent metabolic pathways, such as impaired mitochondrial DNA repair (Figs. 153.5 and 153.8), low GSH levels (Fig. 153.3), and diminished local synthesis of calcitriol (Fig. 153.7).

153.8.2 Migraine

Endothelial NO production has been implicated in the pathophysiology of migraine. This short-lived free radical is responsible for cerebral blood vessel relaxation activating guanylate cyclase and increasing cGMP in smooth muscle (reviewed by Murad 2008). Migraine-like headache is induced
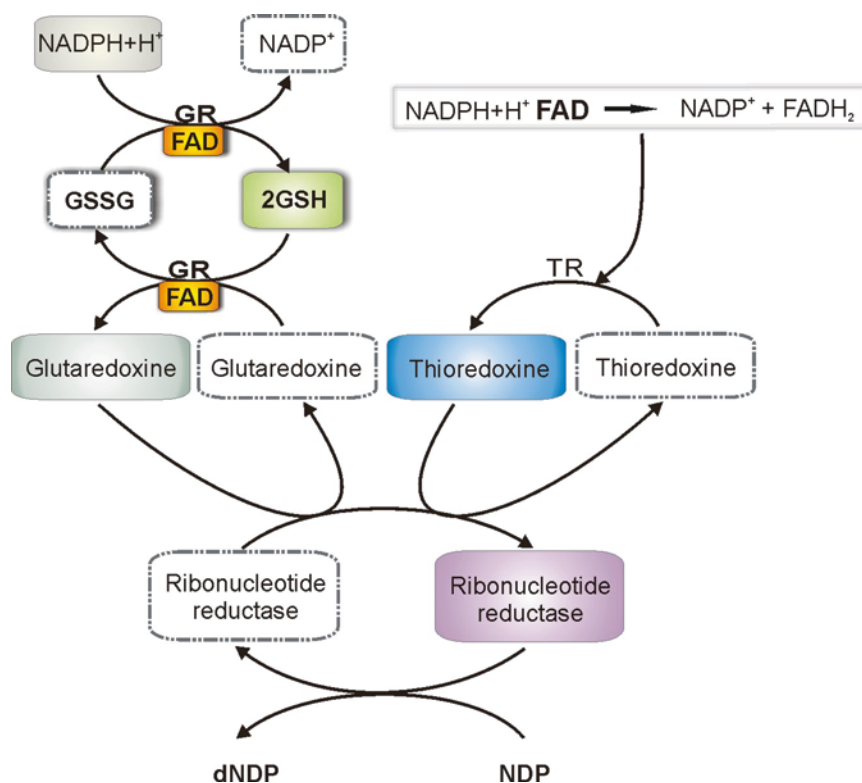
Fig. 153.8 The role of FAD in deoxynucleotide biosynthesis. *NADPH* reduced nicotinamide adenine dinucleotide phosphate, *NADP+* oxidized nicotinamide adenine dinucleotide, *FAD* flavin adenine dinucleotide, *GR* glutathione reductase, *GSH* reduced glutathione, *GSSG* oxidized glutathione, *dNDP* deoxyribonucleoside diphosphate, *NDP* ribonucleoside diphosphate

by i.v. infusions of glyceryl trinitrate (an exogenous NO donor) and histamine (which liberates NO from the vascular endothelium). Furthermore, the i.v. infusion of eNOS inhibitors effectively controls migraine attacks. These data suggest that the release of NO from blood vessels, perivascular nerve endings or from brain tissue may trigger spontaneous migraine. By reacting with superoxide, NO forms peroxynitrite, which is a highly reactive free radical that exerts noxious effects on tissues. Following interaction with superoxide, NO may cause the headache through variations of cerebral blood flow (Olesen 2008).

The synthesis of guanylate cyclase requires the incorporation of prosthetic heme, while the production of heme depends on the availability of PLP (from FMN-dependent PPO) for δ-aminolevulinate synthase activity, as mentioned elsewhere. Therefore, both adequate synthesis of NO by FMN/FAD-dependent eNOS and the triggering of intracellular signaling events by NO ultimately rely on normal vitamin B2 status. On the other hand, abnormally low vitamin B2 status with secondary impairment of GR activity should limit the availability of GSH required for elimination of peroxides, direct inactivation of reactive oxygen species, and activity of GSTs. Therefore, increased production and decreased inactivation of reactive molecules, with the consequent increase in peroxynitrite formation may enable the variations of cerebral blood flow that underlie migraine attacks. The polymorphisms of enzymes involved in FAD-dependent metabolic pathways (GSTs) and polymorphic flavo-enzymes (C677T mutation of MTHFR), respectively, correlate with susceptibility to migraine with (Kowa et al. 2000) and without (Kusumi et al. 2003) aura, supporting the relevance of vitamin B2 status for the pathophysiology of migraine.

Accordingly, several studies, including randomized control trials demonstrate that high-dose (200–400 mg) Rbf taken once a day is a well-tolerated, effective, and low-cost prophylactic treatment in children, adolescents, and adults suffering from migraine (Schoenen et al. 1998; Boehnke et al. 2004; MacLennan et al. 2008; Condo et al. 2009). Current views regard the benefits of Rbf in migraine prophylaxis as the result of a pharmacological effect, due to the high doses employed. However, the authors have not assessed the pretreatment status of vitamin B2 nor taken into consideration the seminal series of studies by Anderson and coworkers (1994) who have demonstrated a high prevalence of genetically determined Rbf malabsorption in the general population. As reviewed above, Rbf deficiency facilitates multiple pathophysiologic mechanisms of migraine; conceivably, migraine and Rbf malabsorption (with disruption of the homeostatic system for CNS flavin content) may be co-morbid conditions in a potentially large number of individuals. Furthermore, the authors have neither considered that a single dose of 27 mg saturates absorptive mechanisms, so that any excess to that dose is not actually absorbed (Zempleni 1996). Multiple daily doses of Rbf may be required for a steadily normal status of vitamin B2 (Coimbra and Junqueira 2003) that may conceivably occur in a potentially large number of migraine sufferers who could concomitantly bear genetically disturbed flavin uptake by renal proximal tubule cells increasing urinary loss of vitamin B2. A therapeutic paradigm rationalized according to current knowledge of the altered vitamin B2 dynamics may enhance the effectiveness of Rbf therapy not only in migraine prophylaxis, but also in other disorders potentially related to that genetically determined and highly prevalent metabolic defect.

153.8.3 Multiple Sclerosis, Guillain-Barré Syndrome, Myasthenia, and Other Autoimmune Disorders

Vitamin D activation requires two sequential biosynthetic steps (25-hydroxylation in hepatocytes and 1α-hydroxylation in immune cell) by mitochondrial/microsomal cytochrome P-450 enzymes, respectively 25-hydroxylases (CYP2R1, CYP27A1) and 1alpha-hydroxylase (CYP27b), yielding calcitriol, which plays a central role in maintaining immune tolerance. Vitamin D-induced immune tolerance is therefore, critically dependent on vitamin B2 status, as the activities of all cytochrome P-450 super family members require continuous restoration of their prosthetic heme to the reduced state by FAD- and FMN-containing, NADPH-dependent cytochrome P450 reductase (Wang et al. 1997) (Fig. 153.7).

During the last decades, epidemiologic studies unequivocally demonstrated a strong negative correlation between the prevalence of autoimmune diseases and the bioavailability of vitamin D, from either consumption of fish oil or sunshine exposure. Both experimental and clinical data provide evidence that the concentration of circulating 25(OH)D3 (calcidiol), which best reflects vitamin D status, critically affects the outcome of autoimmune diseases such as multiple sclerosis, systemic lupus erythematosus, rheumatoid arthritis, insulin-dependent diabetes mellitus, and inflammatory bowel disease (Correale et al. 2009; Cutolo 2009).

The active form of vitamin D (calcitriol) synthesized from circulating calcidiol by the enzyme 1alpha-hydroxylase within the immune cells maintains immunologic tolerance to self-antigens upon interaction with nuclear VDR (Bikle 2009). The expression of 1alpha-hydroxylase and VDR has been described in dendritic cells, macrophages, B cells, and activated T cells, which are, therefore, both producers and targets of calcitriol. Calcitriol changes the phenotype and the activity of the very calcitriol-producing cell (autocrine effect) and the nearby cells (paracrine effect), thereby effectively inducing tolerance to auto-antigens without causing significant immune-suppression or endocrine effects (hypercalcemia and/or hypercalciuria) (Vieth 2004).

Predisposition to autoimmune diseases due to low sunlight exposure and poor ingestion of fish oil is conceivably more prominent in individuals bearing 1alpha-hydroxylase or VDR gene polymorphisms, which respectively impair the efficiency of the enzyme and/or the affinity of VDR for its agonist (calcitriol). Accordingly, the development of auto-immune pathology related to polymorphic changes of 1alpha-hydroxylase (Pani et al. 2002) or VDR (Smolders et al. 2009), and both polymorphisms of the VDR (Smolders et al. 2009) and vitamin D metabolite levels (Smolders et al. 2008) have been linked to multiple sclerosis susceptibility and disability.

Conceivably, the administration of cholecalciferol in doses much higher than those currently recommended has a remarkable therapeutic potential in multiple sclerosis (Vieth 2004; Kimball et al. 2007; Niino et al. 2008). High levels of calcidiol may compensate for the higher Michaelis–Menten constant of a polymorphic 1alpha-hydroxylase. Similarly, a high calcidiol-to-calcitriol conversion rate provided by the effect of optimized substrate provision (to a genetically normal 1alpha-hydroxylase within the immune cells) may increase intracellular ligand levels and counteract the low binding affinity of a polymorphic VDR. However, the effect of high-dose cholecalciferol therapy in either of these circumstances may be significantly compromised by low FMN and FAD incorporation to NADPH-dependent cytochrome P-450 reductase in altered vitamin B2 status.

A low vitamin B2 status may significantly impair vitamin D metabolism for two reasons: (1) the two sequential steps of calcitriol biosynthesis require the activity of the NADPH-dependent cytochrome P-450 reductase, which (2) is doubly dependent on vitamin B2 as it uses the two active flavins (FMN and FAD) as prosthetic groups. In addition, vitamin B2 deficiency may further dysregulate the immune system by at least two other ways. First, the immune function seems to be exquisitely sensitive to changes in the intracellular GSH:GSSG ratio (Fidelus and Tsan 1987; Droge and Breitkreutz 2000), and low availability of FAD diminishes both GR activity and intracellular concentration of GSH, while increasing GSSG levels. Second, a wealth of evidence now supports the existence of extra-adrenal production of corticosteroids, particularly in the cardiovascular system and CNS, where the full array of enzymes required for the de novo synthesis of corticosteroids from cholesterol has been identified (Davies and MacKenzie 2003). The synthesis of endogenous steroids requires the activity of cytochrome P-450 enzymes (Nebert and Russell 2002), and therefore, altered vitamin B2 status could credibly favor local inflammatory and autoimmune responses in these sites.

Vitamin B2 and vitamin D statuses may similarly affect other autoimmune neurological disorders, including Guillain-Barré syndrome (acute inflammatory demyelinating polyradiculoneuropathy), myasthenia, and optic neuritis. These disorders may also respond to therapy with high doses of cholecalciferol and Rbf for the same reasons exposed here.

153.8.4 Neurodegenerative Disorders and Cell Death

Inherited low vitamin B2 status and related disruption of Rbf homeostasis in the CNS feasibly favor cell death in neurodegenerative disorders by a number of mechanisms leading to a decline in GSH/GSSG ratio (Bains and Shaw 1997). One is increased conversion of GSH to GSSG by oxidative stress (overproduction of reactive species of both oxygen and nitrogen) secondary to impairment of mitochondrial function related to low availability of FMN and FAD. Another mechanism is decreased GSH synthesis: the availability of cysteine to γ-GCS activity is the rate-limiting factor in GSH formation, and cysteine synthesis from *S*-adenosylhomocysteine is impaired in low Rbf status due to decreased PLP supply. A third mechanism is decreased reduction of GSSG to GSH by FAD-dependent GR. GSH depletion and post-translational modifications of proteins through glutathionylation

mediate apoptotic cell death triggered by a wide variety of stimuli including activation of death receptors, oxidative stress, environmental agents, and cytotoxic drugs (Franco and Cidlowski 2009). Accordingly, disturbed NO (peroxynitrite formation from superoxide and NO) and GSH metabolism may be involved in both necrotic and apoptotic phenomena related to Parkinson's disease, Alzheimer's disease, Huntington's disease, amyotrophic lateral sclerosis, multiple sclerosis, and brain ischemia (Guix et al. 2005).

Within the CNS, both microglia and neurons express 1alpha-hydroxylase and VDR, while VDR is also expressed by astrocytes and oligodendrocytes. Besides tolerance to neural auto-antigens, the local bioactivation of calcidiol into calcitriol provides a myriad of critical autocrine and paracrine benefits in the developing as well adult CNS. These include neuroprotective (through antioxidative mechanisms, neuronal calcium regulation, neuro-immunomodulation, enhanced nerve conduction and detoxification mechanisms), and neuroregenerative effects (neurogenesis stimulation, neurotrophin biosynthesis, myelination) (Garcion et al. 2002; Buell and Dawson-Hughes 2008).

Current knowledge indicates that progesterone synthesis occurs in the brain, for the brain, by neurons and glial cells in the central and peripheral nervous system of both male and female individuals. Progesterone has anticonvulsant actions, enhances mitochondrial function, neurogenesis and regeneration, promotes myelin repair, protects or reconstructs the BBB, downregulates inflammatory cascades, and limits cellular necrosis and apoptosis (reviewed by Brinton et al. 2008). According to the mechanisms explained elsewhere, a low vitamin B2 status associated with genetically determined disruption of Rbf homeostasis in the CNS may significantly impair the synthesis of calcitriol, progesterone, and other steroids in the nervous tissue.

153.8.5   Brain Ischemia and Traumatic Brain Injury

Enhanced lipolytic activity secondary to intracellular calcium overload during brain ischemia removes considerable amounts of arachidonic acid from membrane phospholipids. Reperfusion of the ischemic tissue restores oxygen supply required for the activity by the arachidonate oxygenase (prostaglandin synthetase) system, generating a sudden burst of free radical formation followed by postischemic inflammation-induced iNOS expression, with continuous production of reactive species of oxygen and nitrogen. The results include peroxidation of cellular membranes, oxidative damage to proteins and nucleic acids. The so-called "reperfusion injury" affects mitochondrial respiratory enzyme complexes and mitochondrial DNA with subsequent defects in oxidative phosphorylation, impaired ATP production, and sustained mitochondrial generation of reactive species at a rate sufficient to escape endogenous antioxidant defenses. Subsequently, peroxynitrite and hydroxyl radical production resulting from the combined effects of disturbed electron transport in the mitochondrial respiratory chain, active inflammatory processes, and failure of antioxidant defenses create a vicious cycle by further damaging lipids, nucleic acids, and proteins. This scenario of pathophysiologic events ultimately results in both necrotic and apoptotic cell death.

Conceivably, ischemia/reperfusion creates a potentially unmatched demand for numerous FNM- and/or FAD-dependent metabolic processes, including DNA resynthesis and replication (mitochondrial DNA repair), GST-mediated detoxification of oxidized DNA and lipid molecules, maintenance of the GSSG-GSH antioxidant cycle, reactions requiring NADPH-dependent cytochrome P450 reductase activity (catabolism of arachidonic acid and eicosanoids, heme degradation by HO, synthesis of steroid molecules endowed with neuroprotective and neurodegenerative actions like calcitriol and progesterone), eNOS and nNOS activities. A higher supply of vitamin B2 active forms (FMN and FAD, respectively required by complexes I and II) may plausibly improve the activity of

the electron transport chain, reducing the electron leakage and the formation of superoxide ions. Preservation of GSH levels may prevent apoptotic cell death (Franco and Cidlowski 2009).

The metabolic dependency of PLP, folate, and methylcobalamin on FMN and/or FAD availability unveils other neuroprotective and neurodegenerative enzyme activities indirectly dependent on vitamin B2 status. Rbf administration may optimize PLP synthesis and the activity of several PLP-dependent enzymes is of potential benefit in ischemia/reperfusion. The synthesis of l-cysteine by γ-GCS increases the availability of l-cysteine for GSH synthesis (Griffith 1999), thereby enhancing antioxidant defenses and antagonizing apoptosis. Rbf administration may facilitate amino acid, protein, and nucleic acid synthesis by increasing PLP availability. The PLP-dependent activity of δ-aminolevulinate synthase allows the biosynthesis of prosthetic heme required for de novo synthesis of HO, cytochrome P-450 superfamily, electron transfer proteins (cytochromes *b* and c), peroxidases, catalases, iNOS and nNOS isoforms, and guanylate cyclases, thus further enhancing antioxidant defenses, decreasing free radical production, and opposing necrotic and apoptotic pathophysiologic events. Enhancement folic acid cycle (Fig. 153.5) by Rbf administration may optimize the methylation of phospholipids, proteins, DNA, RNA, and other small molecules and critically improve cell survival in ischemia/reperfusion.

Accordingly, Rbf protects the brain tissue against brain ischemia (Betz et al. 1994) and traumatic brain injury (Hoane et al. 2005). The proposed mechanism of action is the intracellular formation of dihydroriboflavin from administered Rbf by a NADPH-dependent flavin reductase, first detected in erythrocytes 75 years ago. Dihydroriboflavin quickly reduces Fe(IV)O and Fe(V)O oxidation states of hemeproteins (implicated in tissue damage associated with ischemia and reperfusion) to Fe(III)O thus protecting cells from oxidative injury (Hultquist et al. 1993). Due to the wide range of FMN- and or FAD-dependent metabolic processes required for cell survival after ischemia/reperfusion, the protective effect of Rbf administration is not likely to be exclusively determined by increased dihydroriboflavin synthesis. Conceivably, individuals with inherited low vitamin B2 status associated with disruption of brain Rbf homeostasis may be particularly vulnerable to reperfusion injury of the nervous tissue.

153.8.6 Epilepsy and Antiepileptic Therapy

Some epileptic disorders are responsive to specific vitamins like pyridoxine and folic acid derivatives (Wolf et al. 2005). The administration PLP may result in better seizure control than pyridoxine in vitamin B6-responsive epilepsy (Hoffmann et al. 2007). PLP plays a key role in the synthesis of many neurotransmitters, particularly biogenic amines like dopamine and serotonin, and in the decarboxylation of the dominant excitatory neurotransmitter glutamate to the major inhibitory transmitter GABA in the mammalian CNS (Jansonius 1998) by serving as a coenzyme for the rate-limiting enzyme GAD (Fricke et al. 2007). Patients with an autosomal recessive defect of GAD have an imbalance of the neurotransmitters glutamate and GABA (Gospe 1998). Accordingly, GAD-knockout mice show decreased GABA transmission and increased seizure susceptibility (Asada et al. 1997); low vitamin B6 status in genetically normal humans is associated with a lowered seizure threshold (Apeland et al. 2003). Conceivably, a decreased activity of PPO (the FMN-dependent, PLP synthesizing enzyme) or abnormalities of folate metabolism may facilitate seizures. Thus, a low vitamin B2 status reduces FMN availability, which may destabilize neuronal excitability by impairing GABA synthesis.

The active form of vitamin D (calcitriol) also plays an anticonvulsant role in the brain (Siegel et al. 1984; Kalueff et al. 2005). A reduced FMN and FAD availability and incorporation to NADPH-dependent cytochrome P450 reductase may impair the hydroxylations of vitamin D to calcitriol in the brain tissue, thereby lowering the threshold for epileptic seizures.

Similarly, a number of folate-dependent metabolic roles may influence neuronal excitability, and a specific epileptic disorder responds to folic acid derivatives (Wolf et al. 2005). Folate-dependent mechanisms possibly involved in stabilization of neuronal activity include biosynthesis of the neurotransmitters serotonin, catecholamines, and melatonin (Djukic 2007), and the regulation of homocysteine concentrations (Fig. 153.5). The main route of catabolism of homocysteine is through conversion to cystathionine, catalyzed by a PLP-dependent enzyme (CBS). Cystathionine is converted to cysteine and cysteine is oxidized to cysteine sulfinic acid and subsequently, to cysteic acid. Cysteine sulfinic acid and cysteic acid are decarboxylated to hypotaurine and taurine, respectively, by another PLP-dependent enzyme (CADCase/CSADCase). The oxidation products of homocysteine (homocysteine sulfinic acid and homocysteic acid) and cysteine (cysteine sulfinic acid and cysteic acid) are excitatory sulfur amino acids and may act as excitatory neurotransmitters, whereas taurine and hypotaurine (decarboxylation products of cysteic acid and cysteine sulfinic acid) may act as inhibitory transmitters (Santhosh-Kumar et al. 1994). As discussed elsewhere, vitamin B2 deficiency impairs folate (and methylcobalamin) cycle and PLP synthesis. Vitamin B2 deficiency is expected to increase homocysteine-derived excitatory sulfur amino acids while decreasing the levels of inhibitory transmitters, hypotaurine and taurine. The result is a shift in excitatory–inhibitory balance toward a lower threshold for epileptic seizures (Fig. 153.9).

The dependency of vitamins D3 (Fig. 153.7) B6, B12, and folate on FAD and/or FMN availability (Fig. 153.5) therefore, indicates that vitamin B2 deficiency may be epileptogenic. Accordingly, high doses of Rbf abolish epileptic activities in MADD (Kmoch et al. 1995) and high prevalence of low vitamin B2 status is found in association with preeclampsia (Wacker et al. 2000) which may evolve to eclamptic convulsive seizures. The large prevalences of epilepsy (Sander 2003) and Rbf malabsorption (Anderson et al. 1994) suggest that uptake, trafficking, and cellular homeostasis of Rbf in the brain tissue may be disturbed in a significant number of epileptic individuals, and may contribute for a lower threshold for epileptic seizures (Fig. 153.9).

Taken together these data support the need for adequate diagnosis and treatment of all these vitamin deficiencies in epileptic patients to optimize seizure control. In contrast, antiepileptic drug therapy is associated with hyperhomocysteinemia (Schwaninger et al. 1999; Apeland et al. 2003) and
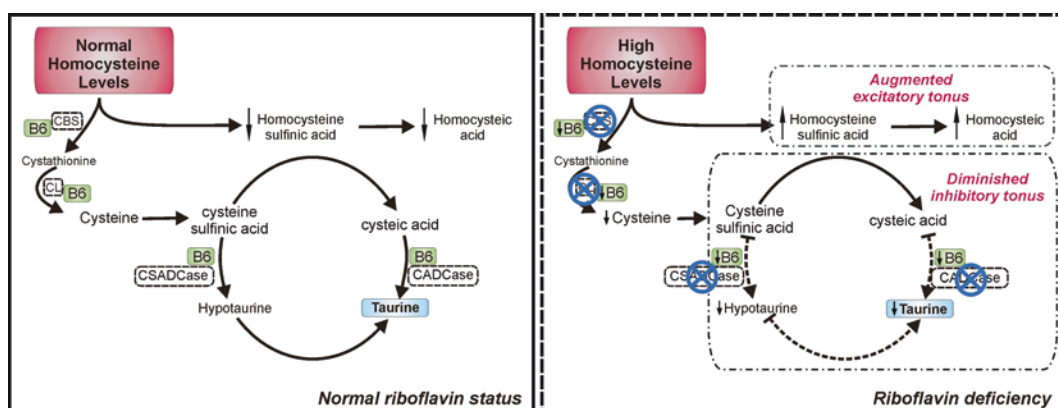
Fig. 153.9 The role of vitamin B2 status on seizure control in epileptic patients. *Left panel*: normal neuronal excitability is observed when enough flavin monophosphate is available for pyridoxal 5′-phosphate (PLP, the active form of vitamin B6) synthesis by pyridox(am)ine 5′-phosphate oxidase. *Right panel*: reduced epileptic threshold for epileptic seizures in low vitamin B2 status due to both increased levels of excitatory compounds and decreased levels of inhibitory neurotransmitters (hypotaurine and taurine). "X inside the circle" indicate enzyme activities secondarily inhibited under low vitamin B2 status (primarily due to low PLP availability). *CL* cystathionine-γ-lyase, *CBS* cystathionine β-synthase, *CADCase/CSADCase* cysteine and sulfinic acid decarboxylase
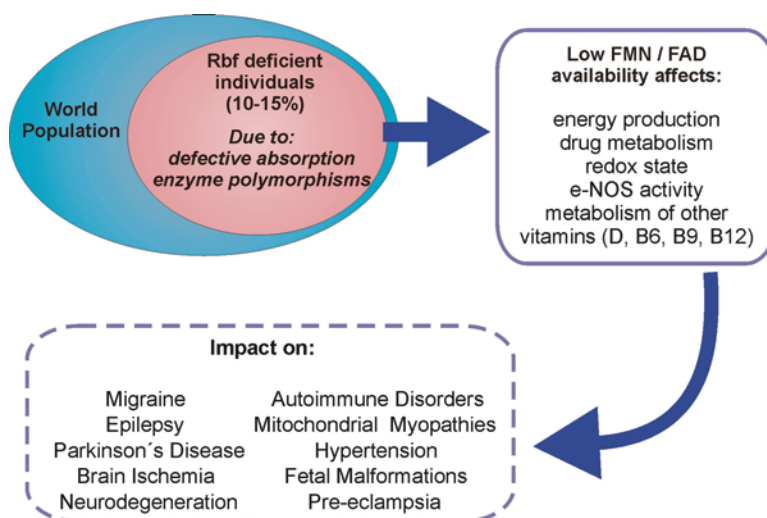
Fig. 153.10 Key facts of riboflavin. Key facts about the impact of riboflavin deficiency on human health. Riboflavin is an essential micronutrient playing a critical role in myriad of biological phenomena, including energy production, DNA replication and repair, nitric oxide synthesis, necrosis and apoptosis, drug metabolism, and antioxidant defense systems. The potential relevance of Rbf status for the pathophysiology, prevention, and treatment of a wide range of human diseases has been largely underestimated

multiple vitamin deficiencies, including those of vitamins B1, B2, B6, B12, C, D, E, beta-carotene, biotin, and folate (Krause et al. 1988; Apeland et al. 2003; Aslan et al. 2008; Nettekoven et al. 2008). Whether these metabolic changes are related to the epileptic condition or represent a pharmacologic side effect is unknown. Discussions on the relevance of vitamin supplementation to patients on anti-epileptic therapy have been usually limited to the preventive context of decreasing the risks of cardiovascular disease and birth defects (Apeland et al. 2002). Only pyridoxine supplementation for enhancing seizure control has been (barely) considered in patients on antiepileptic therapy. However, the metabolic interdependency among these vitamins, as well as their key neurophysiologic roles strongly indicate that untreated multiple vitamin deficiencies may significantly hamper the very antiepileptic effect of these drugs, leading to poor seizure control (apparent drug-resistant epilepsy) and avoidable polytherapy (Fig. 153.10).

Summary Points

- Vitamin B2 directly or indirectly participates in a much wider range of metabolic pathways than usually considered in human physiology; often the same biologic function involves FMN and/or FAD in more than one of its regulatory and integrative steps.
- The high prevalence of genetic polymorphisms related to absorption and cellular trafficking of Rbf, particularly considering the primary and secondary participation of FMN and FAD in a large number of regulatory and metabolic networks highly emphasizes the pathophysiological significance and potential therapeutic/preventive implications of unrecognized deficiency of this micronutrient.
- The interactions between the genetically determined low Rbf status and another highly prevalent inherited metabolic change – the MTHFR mutation restrictive of FAD binding (C677T) – may be of clinical relevance, since high-dose Rbf therapy may plausibly minimize the metabolic effects of that particular MTHFR polymorphism.

- The concrete possibility of a highly prevalent genetically determined disruption of Rbf homeostasis in the CNS makes the nervous tissue particularly prone to Rbf deficiency and raises higher potentially significant implications for prevention and therapy of neurologic disorders in comparison to systemic diseases.
- According to experimental evidence of benefits of Rbf treatment in models of tissue injury, the pathophysiology of cellular damage seem to set up localized higher demands for FMN and FAD required for upregulation of antioxidant, antiapoptotic and proregenerative processes dependent on Rbf metabolism.
- Future research should address the potential association between genetically determined Rbf malabsorption and disorders like migraine, neurodegenerative and autoimmune diseases, as well as in several other neurologic and systemic conditions pathophysiologically related to disturbed metabolism of lipids, amino acids, DNA, cytochrome P-450, NO, vitamin D3, HO and homocysteine metabolism;
- Whenever such association is demonstrated, further studies should investigate the dynamics (including CSF distribution) and therapeutic potential of high-dose Rbf administration in affected individuals, as well as the expression of polymorphic genes related to cellular uptake and trafficking of Rbf at the terminal ileum, proximal renal tubules, and CNS.
- Following the demonstration of low vitamin B2 status (altered EGRAC) associated with a normal dietary Rbf content, a paradigm of 30 mg three to four times a day required for maintenance of normal EGRAC throughout the 24-h period should be considered in future clinical trials aimed at investigating the therapeutic value of Rbf status normalization.

Definition Terms

Enzymes are proteins that catalyze chemical reactions in virtually all biochemical processes, requiring a substrate molecule for conversion into a product.

Cofactor is a nonproteic component that is necessary for the enzyme activity. It can be categorized into a coenzyme or prosthetic group.

Coenzyme is a cofactor of organic nature not covalently bound to the enzyme. Many coenzymes are vitamin derivatives, such as FMN and FAD.

Heme is a prosthetic group, usually an iron-containing heteroclyclic ring, the porphyrin.

Heme oxigenase is an enzyme that catalyzes the degradation of heme group, producing biliverdin, iron, and carbon monoxide.

Prosthetic group is a cofactor covalently bounded to the enzyme. It may be of organic nature, such as vitamins, or inorganic nature, like metal ions.

Synthetases are enzymes that catalyze the linkage of two molecules by using the energy derived from the ATP hydrolysis. The International Union of Biochemistry now classifies them as type 6 enzymes (ligases).

Synthases are enzymes that do not use energy from nucleoside triphosphates, differently from synthetases (see above). The Joint Commission on Biochemical Nomenclature (JCBN) dictates that the term 'synthase' may be applied to any enzyme that catalyzes synthesis (whether or not it uses nucleoside triphosphates), whereas 'synthetase' is to be used synonymously with ligase.

Microsomes are vesicles only formed from the endoplasmic reticulum in laboratory preparations for studying the metabolism of some compounds and drug interactions.

References

Anderson BB, Scattoni M, Perry GM, Galvan P, Giuberti M, Buonocore G, Vullo C. Am J Hum Genet. 1994;55:975–80.

Anderson B, Vullo C. Gut. 1994;35:1487–89

Apeland T, Mansoor MA, Pentieva K, McNulty H, Strandjord RE. Clin Chem. 2003;49:1005–8.

Asada H, Kawamura Y, Maruyama K, Kume H, Ding R, Ji FY, Kanbara N, Kuzume H, Sanbo M, Yagi T, Obata K. Biochem Biophys Res Commun. 1997;229:891–5.

Aslan K, Bozdemir H, Unsal C, Guvenc B. J Lab Hematol. 2008;30:26–35.

Bains JS, Shaw CA. Brain Res Brain Res Rev. 1997;25:335–58.

Bates CJ. World Rev Nutr Diet, Riboflavin deficiency. 1987;50:215–65.

Bates CJ, Riboflavin C. Int J Vitam Nutr Res. 1993;63:274–7.

Berwick M, Vineis P. J Natl Cancer Inst. 2000;92:874–97.

Bikle DD. Curr Osteoporos Rep. 2009;7:58–63.

Boehnke C, Reuter U, Flach U, Schuh-Hofer S, Einhaupl KM, Arnold G. Eur J Neurol. 2004;11:475–7.

Brinton RD, Thompson RF, Foy MR, Baudry M, Wang J, Finch CE, Morgan TE, Pike CJ, Mack WJ, Stanczyk FZ, Nilsen J. Front Neuroendocrinol. 2008;29:313–39.

Bruckdorfer R. Mol Aspects Med. 2005;26:3–31.

Buell JS, Dawson-Hughes B. Mol Aspects Med. 2008;29:415–22.

Casey JL, Hentze MW, Koeller DM, Caughman SW, Rouault TA, Klausner RD, Harford JB. Science. 1988;240:924–8.

Coimbra CG, Junqueira VBC. Braz J Med Biol Res. 2003;36:1409–17.

Collins MA, Neafsey EJ. Neurotoxicol Teratol. 2002;24:571–7.

Condo M, Posar A, Arbizzani A, Parmeggiani A. J Headache Pain. 2009;10:361–5.

Correale J, Ysrraelit MC, Gaitan MI. Brain. 2009;132:1146–60.

Cutolo M. Rheumatology. 2009;48:210–2.

DalPai J, Borges AA, Grassl C, Favero LA, Xavier GF, Junqueira VBC, Lopes AC, Coimbra CG, Sinigaglia-Coimbra R. Curr Top Nutr Res. 2007;5:149–55.

Davies E, MacKenzie SM. Clin Exp Pharmacol Physiol. 2003;30:437–45.

Dexter DT, Carayon A, Vidailhet M, Ruberg M, Agid F, Agid Y, Lees AJ, Wells FR, Jenner P, Marsden CD. J Neurochem. 1990;55:16–20.

Di Monte DA. Neurology. 1991;41:38–42.

Djukic A. Pediatr Neurol. 2007;37:387–97.

Droge W, Breitkreutz R. Proc Nutr Soc. 2000;59:595–600.

Fidelus RK, Tsan MF. Immunology. 1987;61:503–8.

Foraker AB, Khantwal CM, Swaan PW. Adv Drug Deliv Rev. 2003;55:1467–83.

Franco R, Cidlowski JA. Cell Death Differ.2009;16:1303–14.

Fricke MN, Jones-Davis DM, Mathews GC. J Neurochem. 2007;102:1895–1904.

Garcion E, Wion-Barbot N, Montero-Menei CN, Berger F, Wion D. Trends Endocrinol Metab. 2002;13:100–5.

Gospe SM Jr (1998) J. Pediatr. 132: 919–923

Griffith OW. Free Radic Biol Med. 1999;27:922–35.

Guix FX, Uribesalgo I, Coma M, Munoz FJ. Prog Neurobiol. 2005;76:126–52.

Hall AG. Eur J Clin Invest. 1999;29:238–45.

Hendler SS, Rorvik D. In: Hendler SS, Rorvik D, editors. PDR for nutritional supplements. Montvale: Thomson Reuters; 2008. p. 547–553.

Hoane MR, Wolyniak JG, Akstulewicz SL. J Neurotrauma. 2005;22:1112–22.

Hoffmann GF, Schmitt B, Windfuhr M, Wagner N, Strehl H, Bagci S, Franz AR, Mills PB, Clayton PT, Baumgartner MR, Steinmann B, Bast T, Wolf NI, Zschocke J. J Inherit Metab Dis. 2007;30:96–9.

Hultquist DE, Xu F, Quandt KS, Shlafer M, Mack CP, Till GO, Seekamp A, Betz AL, Ennis SR. Am J Hematol. 1993;42:13–8.

Hustad S, McKinley MC, McNulty H, Schneede J, Strain JJ, Scott JM, Ueland PM. Clin Chem. 2002;48:1571–7.

Hustad S, Ueland PM, Vollset SE, Zhang Y, Bjørke-Monsen AL, Schneede J. Clin Chem. 2000;46:1065–71.

Jansonius JN. Curr Opin Struct Biol. 1998;8:759–69.

Jenner P, Dexter DT, Sian J, Schapira AHV, Marsden CD. Ann Neurol. 1992;32:S82–7.

Joshi G, Pradhan S, Mittal B. J Neurol Sci. 2009;277:133–7.

Jusko WJ, Levy G. J Pharm Sci. 1970;59:765–72.

Kalueff AV, Minasyan A, Tuohimaa P. Brain Res Bull. 2005;67:156–60.

Kim ST, Choi JH, Chang JW, Kim SW, Hwang O. J Neurochem. 2005;95:89–98.

Kimball SM, Ursell MR, O'Connor P, Vieth R. Am J Clin Nutr. 2007;86:645–51.

Kmoch S, Zeman J, Hrebicek M, Ryba L, Kristensen MJ, Gregersen N. J Inherit Metab Dis. 1995;18:227–9.

Kowa H, Yasui K, Takeshima T, Urakami K, Sakai F, Nakashima K. Am J Med Genet. 2000; 96:762–4.

Krause KH, Bonjour JP, Berlit P, Kynast G, Schmidt-Gayk H, Schellenberg B. Drug Nutr Interact. 1988;5:317–43.

Kusumi M, Ishizaki K, Kowa H, Adachi Y, Takeshima T, Sakai F, Nakashima K. Eur Neurol. 2003;49:218–22.

Locigno R, Castronovo V. Int J Oncol. 2001;19:221–36.

Logroscino G, Marder K, Graziano J, Freyer G, Slavkovich V, LoIacono N, Cote L, Mayeux R. Neurology. 1997;49:714–7.

MacLennan SC, Wade FM, Forrest KM, Ratanayake PD, Fagan E, Antony J. J Child Neurol. 2008;23:1300–4.

Maines MD. Annu Rev Pharmacol Toxicol. 1997;37:517–54.

Mann VM, Cooper JM, Daniel SE, Srai K, Jenner P, Marsden CD, Schapira AH. Ann Neurol. 1994;36:876–81.

Massey V. Biochem Soc Trans. 2000;28:283–96.

Mizuno Y, Matuda S, Yoshino H, Mori H, Hattori N, Ikebe S. Ann Neurol. 1994;35:204–10.

Moat SJ, Ashfield-Watt PAL, Powers HJ, Newcombe RG, McDowell IFW. Clin Chem 2003;49:295–302.

Mooney S, Leuendorf JE, Hendrickson C, Hellmann H. Molecules. 2009;14:329–351.

Murad F. Can J Ophthalmol. 2008;43:291–4.

Mytilineou C, Werner P, Molinari S, Di Rocco A, Cohen G, Yahr MD. J Neural Transm Park Dis Dement Sect. 1994;8:223–8.

Naoi M, Maruyama W, Akao Y, Yi H. Neurotoxicol Teratol. 2002;24:579–91.

Nebert DW, Russell DW. Lancet. 2002;360:1155–62.

Nelson DL, Cox MM. In: Lehninger principles of biochemistry. New York: Worth Publishers; 2009. Chapters 8 and 13.

Niino M, Fukazawa T, Kikuchi S, Sasaki H. Curr Med Chem. 2008;15:499–505.

Ogunleye AJ, Odutuga AA. J Nutr Sci Vitaminol. 1989;35:193–7.

Olesen J. Pharmacol Ther. 2008;120:157–71.

Olteanu H, Banerjee R. J Biol Chem. 2001;276:35558–63.

Pani MA, Regulla K, Segni M, Krause M, Hofmann S, Hufner M, Herwig J, Pasquino AM, Usadel KH, Badenhoop K. Eur J Endocrinol. 2002;146:777–81.

Parl FF. Cancer Lett. 2005;221:123–9.

Pinto J, Huang YP, Rivlin RS. J Clin Invest. 1987;79:1343–51.

Powers HJ. Proc Nutr Soc. 1999;58:435–40.

Powers HJ. Am J Clin Nutr. 2003;77:1352–60.

Rivlin RS, Pinto JT. In: Rucker RB, Suttie JW, McCormick DB, Machlin LJ, editors. Handbook of vitamins. New York: Marcel Dekker; 2001. p. 255–274.

Sander JW. Curr Opin Neurol. 2003;16:165–70.

Santhosh-Kumar CR, Hassell KL, Deutsch JC, Kolhouse JF. Med Hypotheses. 1994;43:239–44.

Schapira AH, Cooper JM, Dexter D, Clark JB, Jenner P, Marsden CD. J Neurochem. 1990;54:823–7.

Schoenen J, Jacquy J, Lenaerts M. Neurology. 1998;50:466–70.

Schulz JB, Lindenau J, Seyfried J, Dichgans J. Eur J Biochem. 2000;267:4904–11.

Schwaninger M, Ringleb P, Winter R, Kohl B, Fiehn W, Rieser PA, Walter-Sack I. Epilepsia. 1999;40:345–50.

Siegel A, Malkowitz L, Moskovits MJ, Christakos S. Brain Res. 1984;298:125–9.

Sinha R, Caporaso N. Ann Epidemiol. 1997;7:350–6.

Sipetic-Grujicicl S, Vlajinac H, Maksiniovic J, Marinkovic J, Dzoljic E, Ratkov I, Kostic V. Parkinsonism Relat Disord. 2007;13:S35.

Skoupy S, Fodinger M, Veitl M, Perschl A, Puttinger H, Rohrer C, Schindler K, Vychytil A, Horl WH, Sunder-Plassmann G. J Am Soc Nephrol. 2002;13:1331–7.

Smith AD, Castro SL, Zigmond MJ. Physiol Behav. 2002;77:527–31.

Smolders J, Menheere P, Kessels A, Damoiseaux J, Hupperts R. Mult Scler. 2008;14:1220–4.

Smolders J, Peelen E, Thewissen M, Menheere P, Cohen Tervaert JW, Hupperts R, Damoiseaux J. Autoimmun Rev. 2009;8:621–6.

Speciale SG. Neurotoxicol Teratol. 2002;24:607–20.

Spector R. J Clin Invest. 1980;66:821–31.

Spector R, Johanson C. Pharm Res. 2006; 23:2515–24.

Vieth R. J Steroid Biochem Mol Biol. 2004;89–90:575–9.

Wacker J, Fruhauf J, Schulz M, Chiwora FM, Volz J, Becker K. Obstet Gynecol. 2000;96:38–44.

Wang M, Roberts DL, Paschke R, Shea TM, Masters BSS, Kim JJP. Proc Natl Acad Sci USA. 1997;94:8411–6.

White HB, Merril Jr AH. Ann Rev Nutr. 1988;8:279–99.

WHO – World Health Organization/FAO – Food and Agriculture Organization of the United Nations. Vitamin and mineral requirements in human nutrition. 2009.

Wolf NI, Bast T, Surtees R. Epileptic Disord. 2005;7:67–81.

Zempleni J, Galloway JR, McCormick DB. Am J Clin Nutr. 1996;63:54–66.

Chapter 154
Brain Mechanisms Involved in the Detection and Adaptation to Lysine Deficiency

Takashi Kondoh and Kunio Torii

Abbreviations

LHA   Lateral hypothalamic area
MSG   Monosodium L-glutamate
PEP   Purified egg protein
TVX   Subdiaphragmatic total vagotomy
VMH   Ventromedial nucleus of the hypothalamus

154.1 Introduction

Essential amino acids, such as L-lysine, cannot be produced by the body, and must therefore be obtained from diet in order to support growth, reproduction, and, ultimately, survival. Deficiency of a specific essential amino acid represents a relevant model to describe the overall adaptive changes in ingestive behaviors resulting from nutrient deficiency. Lysine deficiency is, arguably, one of the best models to study the adaptive changes in behavior that take place during specific nutrient deficiencies (Table 154.1). For example, while lysine is the limiting amino acid in proteins found in feed grains (Torii et al. 1987), it is not a direct precursor of any neurotransmitter in the brain. Lysine levels both in the blood and cerebrospinal fluid are high among 20 amino acids (Nishimura et al. 1995). The risk of lysine deficiency is high in low socioeconomic human populations who depend predominantly on wheat for their protein supply (Young and Pellett 1990). Rats fed a bread-based, lysine-impoverished diet based on wheat gluten, show low weight gain, reduced appetite, nervousness, and ingestion of their own body hair (Culik and Rosenberg 1958). However, rats fed lysine-supplemented bread do not show any of the above signs, and grow normally. In humans, negative nitrogen balance by consumption of wheat gluten is also observed (Bricker et al. 1945).

Deficiency of an essential amino acid affects both appetite and taste preferences for other amino acids and NaCl. Rats in nutritionally well-balanced conditions normally display strong preferences for monosodium L-glutamate (MSG; an umami substance) and L-arginine solutions (Torii et al. 1987). However, inducing states of lysine deficiency will result in concomitant abnormal patterns in both body physiology and taste preferences. In fact, when rats are restricted to a lysine-deficient diet, lysine levels in both plasma and brain decline (Mori et al. 1991a), since lysine concentrations in

K. Torii (✉)
Institute of Life Sciences, Ajinomoto Co., Inc., Suzuki-cho 1-1, Kawasaki-ku, Kawasaki 210-8681, Japan
e-mail: kunio_torii@ajinomoto.com

Table 154.1 Key features of L-lysine

1. Lysine is a basic and essential amino acid with bitter taste quality.
2. Among 20 amino acids, lysine levels in the blood and cerebrospinal fluid are high.
3. Lysine is not a direct precursor of any neurotransmitter in the brain.
4. Lysine is the first limiting amino acid in proteins of some feed grains (wheat and corn).
5. Substantial risk of lysine deficiency exists in low socioeconomic human populations who consume wheat or corn as a major protein supply.
6. Characteristic symptoms of lysine (or an essential amino acid) deficiency are reduced appetite, low weight gain, and nervousness.
7. Replete of missing nutrient will cause rapid recovery from these symptoms.

This table lists the key facts of lysine in our body or in food

plasma directly reflect the lysine content in the diet (Mori et al. 1991a). Under lysine deficiency, food intake and growth are depressed, a physiological pattern that is accompanied by increased preferences for NaCl in detriment of MSG or arginine (Torii et al. 1987). However, when offered a lysine solution, which is bitter and hence normally aversive to animals, lysine-deficient rats will robustly drink the solution, resulting in normalization of food intake levels and growth (Tabuchi et al. 1991; Torii et al. 1987, 1996). In this repleting process, their initial preference for NaCl changes towards MSG as in nondeficient rats. As the immediate licking responses to lysine solution in brief (10 s)-access tests do not increase during lysine deficiency (Markison et al. 1999), the preference for the missing amino acid appears to be learned rather than innate. In other words, learning a positive association between the taste of lysine (conditioned stimulus) and its repleting, postingestional consequences (unconditioned stimulus) is required before a lysine-deficient animal will engage in adaptive increases in lysine intake. However, the sensing mechanisms involved in detecting the deficient nutrient and the brain mechanisms regulating adaptive preferences remain poorly understood.

This review describes our current knowledge on the peripheral sensing sites, signaling pathways, and primary brain areas regulating adaptation to nutrient deficiency. We focus on lysine deficiency since this constitutes a functional working model of essential amino acid deficiency.

154.2 Changes in Food Intake, Weight Gain, and Taste Preference During Protein Deficiency

Before discussing overall changes occur during lysine deficiency, we would like to describe what happens during protein deficiency. Protein is a macronutrient essential for growth, reproduction and survival. Protein is involved not only for muscle contraction but also for numerous physiological functions since they form the constitutive material of receptors, ion channels, transporters, enzymes, immunoproteins, and transcription factors.

During low protein intake starvation, body nitrogen concentration declines to negative levels (Harper 1974). During fasting, body protein breaks down into amino acids that are used to produce energy as a replacement for glucose (Harper 1974). A characteristic symptom of Kwashiokor disease is hypoproteinemia, due to fasting-induced malnutrition; recovery takes place immediately upon treatment with a high-protein diet (Rosenberg and Rohdenburg 1952). Rats offered a low or no-protein diet show reduced food intake and reduced body weight (Mori et al. 1991a) (Fig. 154.1). Considering data from body weight measurements, the minimum percentage of protein content in diet required for normal growth in young growing rats is estimated to be 12.5% (Mori et al. 1991a) in the case of purified egg protein (PEP), an ideal protein source associated with highly efficient nitrogen storage (Forbes et al. 1958). In fact, in the choice experiments involving low (5% PEP) and
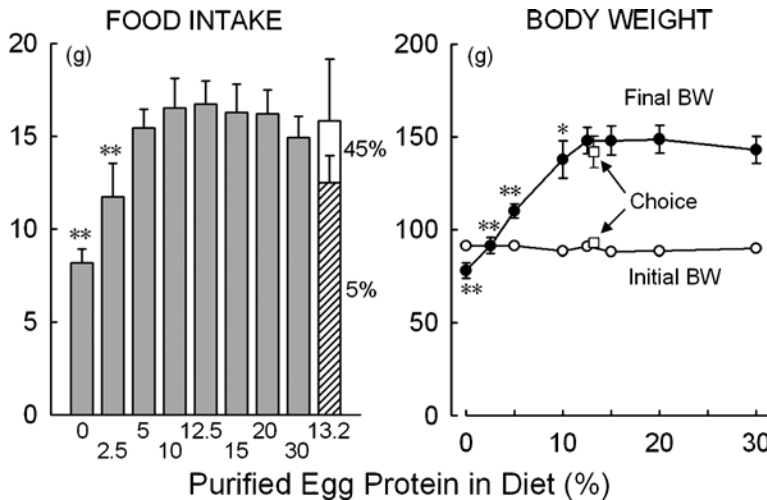
Fig. 154.1 Mean daily food intake and body weight (BW) changes in rats fed diets with various protein levels for 1 week. Rats at 4 weeks of age were fed a diet containing purified egg protein (PEP) at levels between 0% and 30%, or given a choice between 5% PEP and 45% PEP diets. Results are expressed as mean ± SD, $n = 8$. $^*P < 0.05$ and $^{**}P < 0.01$, significance compared to rats fed 20% PEP diet (control) by ANOVA followed by Dunnet's test (Reprinted from Mori et al. 1991a. With permission)

high (45% PEP) protein diets, rats tend to ingest an average of 13.2% protein content, very close to the 12.5% minimal estimate, a pattern associated with normal growth (Mori et al. 1991a).

Preferences for amino acid and NaCl solutions are also related to protein nutrition (Fig. 154.2). When dietary protein levels are normal, preference for umami taste substances such as MSG is high, suggesting that umami taste is a marker of protein ingestion (Torii et al. 1987). In contrast, preference for NaCl and glycine increases under severe protein deficiency, possibly reflecting negative nitrogen balance in the body. Glycine is effective in ameliorating low nitrogen levels under protein deficiency, suggesting a sparing effect on endogenous protein degradation (Torii et al. 1987). Therefore, preferences for certain amino acids (e.g., MSG and glycine) and NaCl depend on protein nutrition.

154.3 Lysine Deficiency and Lysine Levels in the Plasma and Brain

Some protein-rich foods contain low levels of certain amino acids. For example, wheat gluten contains low levels of lysine and methionine (20% and 17%, respectively), and corn zein is low in lysine and tryptophan (0.7% and 15%, respectively) compared to PEP (Table 154.2). Wheat flour is a major supply of plant protein for humans, and gluten is the major protein in the wheat. These proteins have been used to investigate animal ingestive behaviors associated with protein or amino acid deficiency.

Since feeding of crystalline amino acid mixture-based diets readily suppress further food intake, the protein component of a lysine-deficient diet is obtained from wheat gluten fortified with crystalline essential amino acids excluding lysine (Table 154.3). Control diets ("lysine-sufficient" diets) are fortified with crystalline lysine (L-lysine HCl). Different amounts of glutamine are added to the diets to make them isonitrogenous to a 20% PEP diet (Mori et al. 1991a). Since wheat gluten contains 20% of the total lysine levels found in PEP, a lysine-deficient diet should have 20% of the lysine levels of a control diet, rather than 0% (unless stated otherwise). This level of lysine (20% of control) is required to maintain homeostasis and avoid negative nitrogen balance in experimental animals (Torii et al. 1987).
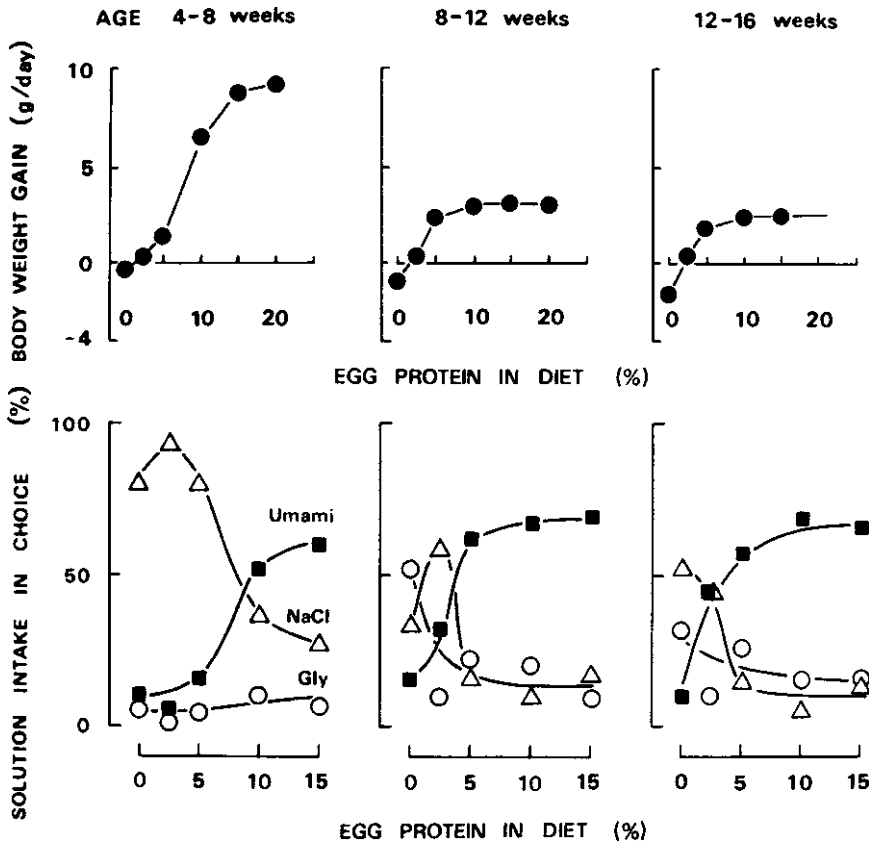
Fig. 154.2 Body weight gain (*upper*) and taste preference (*lower*) in rats fed diets with various protein levels and at various ages. Rats at 4, 8, and 12 weeks of age were fed diets containing purified egg protein at levels between 0% and 15% for 4 weeks. Averaged values of daily weight gain and percentage intake of each solution [NaCl, glycine (Gly), and umami] are shown, $n = 8$ (Reprinted from Torii et al. 1987. With permission)

The diurnal patterns of lysine concentrations in the plasma and brain are quite comparable to each other. In lysine-repleted (control) rats, lysine levels in plasma and brain are stable throughout the day (Mori et al. 1991a). In lysine-deficient rats, however, both plasma and brain lysine levels decline dramatically following onset of feeding (mainly during the dark phase since rats are nocturnal animals), but return to control levels by the end of the light phase (Fig. 154.3). During the dark phase, plasma lysine declines to near zero, but brain lysine declines to approximately one-third of control levels. Recovery of lysine levels during the light phase may reflect degradation of body proteins in order to supply amino acids to the body, especially to the brain. In fact, lysine concentrations in plasma reflect dietary lysine levels (Mori et al. 1991a) (Fig. 154.4).

154.4 Changes in Taste Preferences During Lysine Deficiency

When rats are offered diets deficient in or containing imbalanced levels of amino acids, food intake is remarkably depressed (Harper et al. 1970), followed by an attempt by animals to change their dietary source (Inoue et al. 1995). Under states of amino acid deficiency, the dietary restricted amino acid, rather than protein content, can act as the dietary stimulus to control food selection.

Table 154.2 L-Amino acid composition of whole egg protein (PEP), wheat gluten, and corn zein (Reprinted with modification from Torii et al. 1987. With permission)

L-amino acid	Concentration (% of 16 g nitrogen)		
	PEP	Wheat gluten	Corn zein
Essential amino acids			
Lysine	7.39	1.48	0.05
Methionine	3.30	0.56	1.62
Tryptophan	1.44	0.77	0.21
Phyenlyalanine	5.66	4.87	7.47
Isoleucine	5.72	3.23	3.91
Leucine	9.71	6.71	21.85
Valine	6.61	3.53	3.69
Threonine	4.83	2.46	2.81
Histidine	2.41	1.90	1.23
Nonessential amino acids			
Glutamic acid	12.84	33.58	23.81
Aspartic acid	10.08	3.13	5.70
Arginine	7.04	3.27	1.31
Serine	7.76	4.87	5.48
Alanine	6.05	2.50	10.98
Glycine	3.53	3.31	1.18
Proline	4.28	13.95	1.15
Tyrosine	4.05	3.09	5.17
Cysteine	2.30	2.82	0.34

Each protein sample was hydrolyzed and assayed for amino acid content by an automatic amino acid analyzer (micro-Kjeldahl method)

Table 154.3 Composition of lysine-sufficient (control) and lysine-deficient diets (Reprinted from Torii et al. 1987. With permission)

Composition	Experimental diets	
	Control	Lysine-deficient
Wheat gluten	24.35	24.35
L-Lysine HCl	1.35	–
L-Glutamine	0.68	1.76
L-Amino acid mixture	3.72	3.72
Corn starch	55.69	55.96
Mineral mixture	4.00	4.00
Vitamin mixture	1.00	1.00
Choline chloride	0.20	0.20
Vitamin E	0.01	0.01
Cellulose powder	4.00	4.00
Corn oil	5.00	5.00
Total	100	100
L-Lysine content in diet (%, w/w)	1.35	0.27

Each protein sample was hydrolyzed and assayed for amino acid content by an automatic amino acid analyzer (micro-Kjeldahl method). Values are shown as % of weight in each diet

Lysine deficiency drastically changes the behavioral response of rats to lysine solutions from aversion to attraction. When rats are given a lysine-deficient diet, they will select the lysine solution out of various other sapid solutions (Mori et al. 1991a; Tabuchi et al. 1991; Torii et al. 1987).

DIURNAL VARIATION OF LYSINE
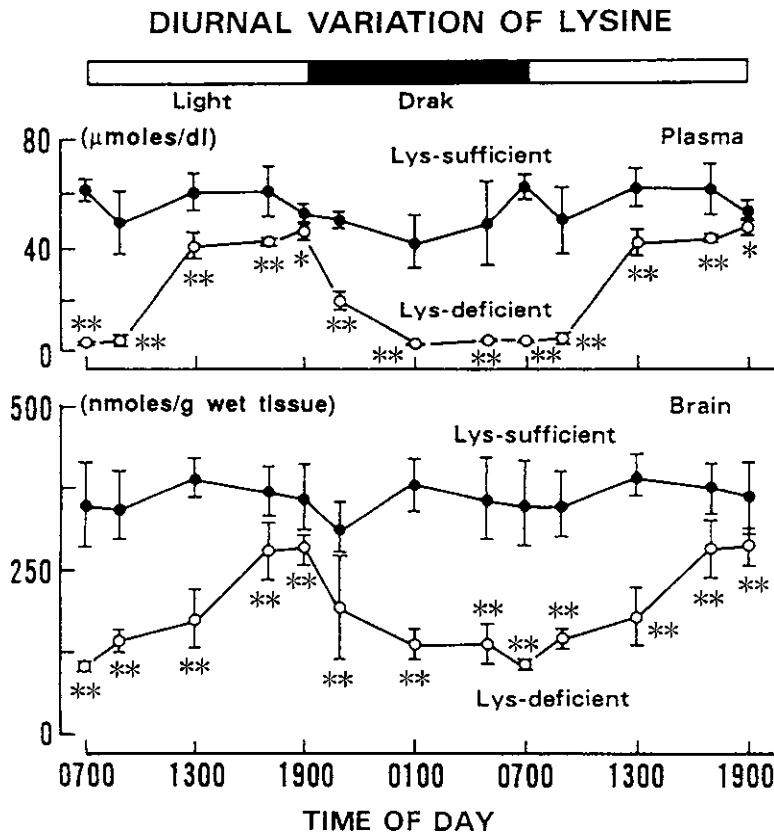
Fig. 154.3 Diurnal variation of lysine concentration in the plasma (*upper*) and brain (*lower*) under lysine-sufficient (control) and lysine-deficient conditions in rats. (**a**), in control, lysine levels in blood and brain are stable within a day. During lysine deficiency, however, lysine levels in both plasma and brain are reduced during dark period (feeding period). Lysine solution was not supplied in this experiment. Lysine concentration was assayed using an automated amino acid analyzer after deproteinization by sulfosalicylic acid. Results are expressed as mean ± SD, $n = 5$. $^*P < 0.05$ and $^{**}P < 0.01$, significance compared to control by Student's t-test (Reprinted from Mori et al. 1991a. With permission)
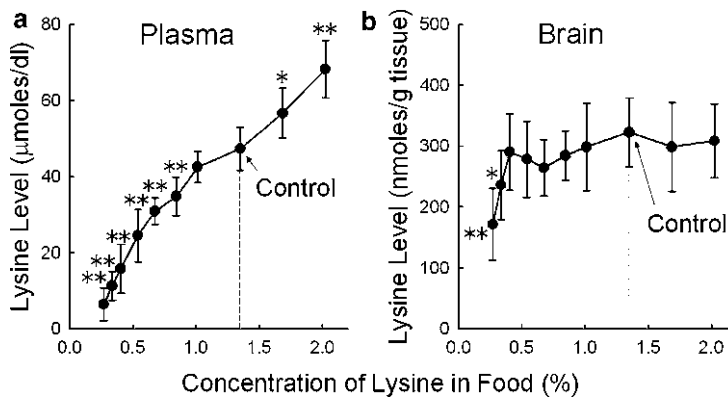
Fig. 154.4 Lysine levels in the plasma (**a**) and brain (**b**) in rats fed diets with various lysine levels. Rats at 4 weeks of age were given free access to a diet with various levels of lysine from deficiency to excess, equivalent to a lysine composition in 4–30% purified egg protein (PEP), for 8 weeks. The diet containing 1.35% lysine (equivalent to the lysine content in 20% PEP) was employed as control. Lysine solution was not supplied in this experiment. Results are expressed as mean ± SD, $n = 6$. $^*P < 0.05$ and $^{**}P < 0.01$, significance compared to control by ANOVA followed by Dunnet's test (Reprinted from Mori et al. 1991a. With permission)
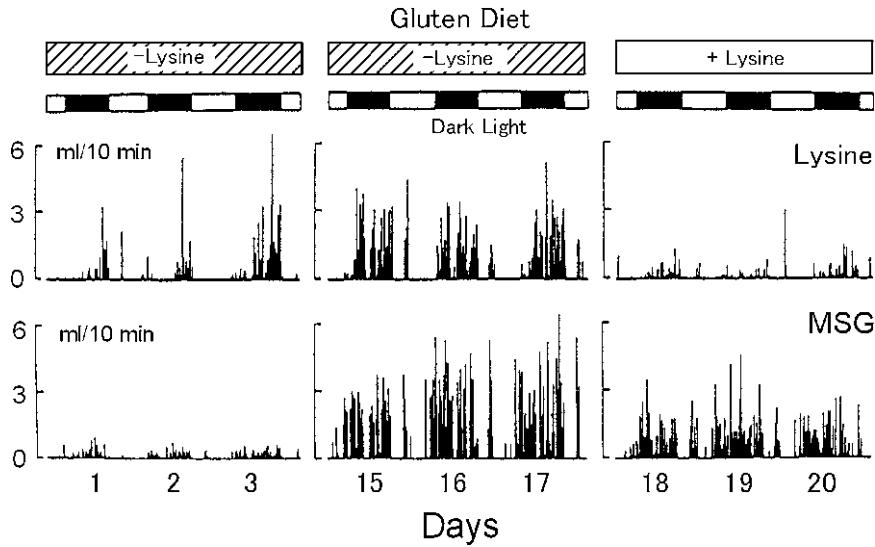
Fig. 154.5 Preference for lysine solution appears during lysine deficiency. *Upper*, intake (mL/10 min) of 0.4 M lysine solution; *Lower*, intake (mL/10 min) of monosodium L-glutamate (MSG) solution. Rats were offered lysine-deficient (– Lysine) or lysine-sufficient (+ Lysine) diets. Preference for lysine solution increased gradually during lysine deficiency and reduced rapidly after recovery from deficiency. Preference for MSG solution also appeared only when nutritive conditions are well-balanced (Reprinted from Mori et al. 1991a. With permission)

Preference for lysine solutions increase gradually during lysine deficiency and is rapidly reduced after repletion (Fig. 154.5). Preferences for MSG solution also appear only when nutritive conditions are well-balanced. Rats fed a tryptophan-deficient diet also prefer a tryptophan solution (bitter) over a saccharin solution (sweet), a choice that ameliorates their state (Mori et al. 1991b). The increased preference for a deficient nutrient is commonly observed when rats are given a diet deficient in one of the other essential amino acids (Mori et al. 1991a). These adaptive behavioral changes are considered to be learned preferences (Gietzen et al. 1992; Markison et al. 1999; Naito-Hoopes et al. 1993). In fact, lysine deficiency in rats does not seem to enhance the "palatability" of lysine as assessed by licking responses including lick rate, bout size and bout number (Markison et al. 2000). In contrast, increases in acceptance (i.e., reduction in aversion) to lysine solution are reported in lysine-deficient mice (Ninomiya et al. 1994b).

154.5 Peripheral Mechanisms

The detection of deficiency in amino acid levels will take place only after digestion of protein. Absorption of amino acids also plays an important role in sensing the levels of a deficient nutrient. Nutritional stimuli in the gut elicit hormonal release into the circulation as well as vagal activation, which are key components of the gut-brain communication. For detection of chemical compounds, specific receptors and neural coding mechanisms may exist in the gastrointestinal tract and hepatoportal region. Integration of postingestive consequences with oronasal sensory stimuli (e.g., taste, odor, and texture) occurs in the brain. Both peripheral and central mechanisms are involved in the responses observed during amino acid deficiency (Hawkins et al. 1994; Tabuchi et al. 1991).

In what follows, we describe the elevated serum levels of inhibin, a heterodimeric protein composed of α and β-subunits and a member of the transforming growth factor-β (TGF-β) superfamily, and increases in the sensitivity of hepatic vagal efferent fibers 100-fold during lysine deficiency. Behavioral aversion threshold to lysine solutions also increases 100-fold. Sensitivity of taste nerves, however, does not change under the same condition. Furthermore, in the transection of peripheral nerves, we describe the contributions of the taste and vagus nerves to the adaptive behavioral changes induced by lysine deficiency.

154.5.1 Humoral Factors

It is possible that different neurotrophic or neuromodulatory factors are released in the systemic circulation during lysine deficiency resulting in changes in sensitivity to the deficient nutrient and/or in adaptive responses. There are a number of bioactive candidates that may act at concentrations too low to be detected by most available methods. One very sensitive assay, able to detect a number of humoral factors at the femtomolar concentration range, makes use of Hydra Japonica (hydra) (Hanai 1981). Tentacle ball formation is a sign of feeding behavior in the hydra under various levels of S-methylglutathione, and inhibition of this behavior can be differentially and quantitatively observed when certain humoral factors are present along with the feeding stimulus (Hanai 1981).

Rats fed a protein-restricted diet overnight show elevated serum levels of activin A (Torii et al. 1993), a homodimeric protein composed of two inhibin β_A-subunits and a member of the TGF-β superfamily. In contrast, inhibin is increased during lysine deficiency while activin A-like activity in the serum is severely suppressed. Inhibin has opposing biological effects to activin by competing with activin for binding with its receptors and/or binding to inhibin-specific receptors (Robertson et al. 2004). Results from additional assays, i.e., radioimmunoassays for inhibin and an erythroid differentiation assay for activin A, also confirmed the release of inhibin during lysine deficiency (Torii et al. 1996). These results suggest that activin A levels in the blood plays a role in alerting the brain of amino acid imbalance, and might subsequently induce an adaptive response aimed at reversing amino acid imbalances.

154.5.2 Taste Nerve

Neurophysiological studies have shown that the chorda tympani and glossopharyngeal nerves considerably differ in their responses to various taste stimuli. For example, bitter-tasting substances, such as quinine, sucrose octaacetate, and some essential amino acids (tryptophan, phenylalanine, and histidine), elicit greater responses in the glossopharyngeal nerve compared to the chorda tympani (Ninomiya et al. 1993; Shingai and Beidler 1985). The glossopharyngeal nerve also shows greater responses to MSG, an umami substance (Ninomiya et al. 1993), suggesting that the glossopharyngeal nerve carries the main taste inputs regarding both behaviorally aversive and nutritionally important substances present in food (Ninomiya et al. 1994b).

In mice, behavioral aversion thresholds to lysine solution, which is bitter and normally aversive for animals, increase approximately 100-fold during lysine deficiency compared to the control in brief (10 s) acceptance tests (Ninomiya et al. 1994b). Licking responses to other essential amino acids (phenylalanine, leucine), quinine, and various other taste substances do not change during lysine deficiency. The increase in acceptability to lysine induced by deficiency is also observed after
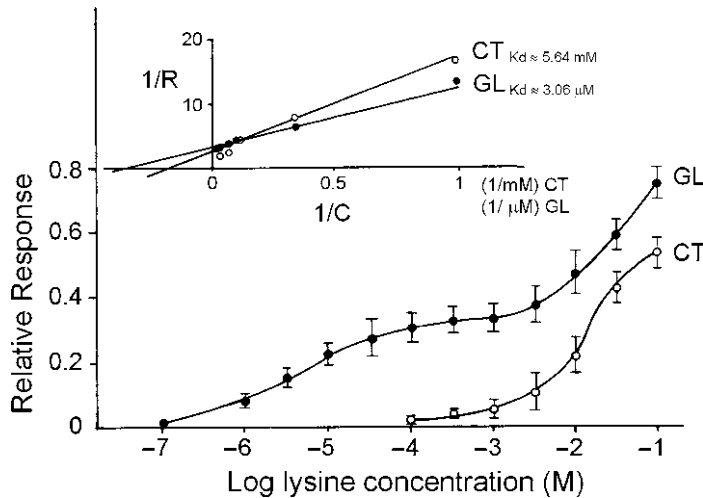
Fig. 154.6 Concentration-response relationships for lysine in the chorda tympani (CT) and glossopharyngeal (GL) nerves, and their double reciprocal plots in mice. The vertical axis represents relative responses to 0.1 M NH_4Cl as the standard stimulus. C, concentration of lysine (in mM for CT and in μM for GL). R, relative response. Results are expressed as mean ± SD, n = 8-10 (Reprinted from Ninomiya et al. 1994a. With permission)

transection of the chorda tympani while it disappears after bilateral transections of the glossopharyngeal nerve. These results suggest that taste information conveyed via the glossopharyngeal nerve plays a major role on an increase in hedonic value of lysine solution.

Neural responses to lysine are relatively larger in the glossopharyngeal nerve compared to the chorda tympani in control mice (Ninomiya et al. 1994a) (Fig. 154.6). The neural threshold for detection of a lysine solution is 2.5 log units lower in the glossopharyngeal nerve (~1.0 μM) than in the chorda tympani (~300 μM). An analysis of concentration-response relationships suggest a possibility that there are two different receptors (high- and low-affinity types) for lysine, each showing a different dissociation constant. The posterior region of the tongue would express both types, while the anterior region would express only the low-affinity type (Ninomiya et al. 1994a). Interestingly, lysine deficiency hardly affects the neural thresholds of both chorda tympani and glossopharyngeal nerves to lysine (see discussion in Ninomiya et al. 1994b), suggesting that the increased acceptance to lysine during lysine deficiency is primary mediated by the brain not by alteration of peripheral taste information.

In contrast to mice data mentioned above, rats show behavioral changes for lysine ingestion only over mM concentration range (Pritchard et al. 1982) and data from transection of taste nerves in rats point to a relatively more important role for the chorda tympani than the glossopharyngeal nerve in selecting lysine solutions during lysine deficiency (Tabuchi et al. 1996). Further studies are required to clarify the roles of these primary taste nerves in increasing preferences for deficient amino acids.

154.5.3 Vagus Nerve

The vagus nerve innervates major portions of the gastrointestinal system and is important in the control of feeding. As lysine in food normally exists in a protein-bound form, it is reasonable to assume that a peripheral lysine sensor that monitors free lysine levels following protein digestion exist in the
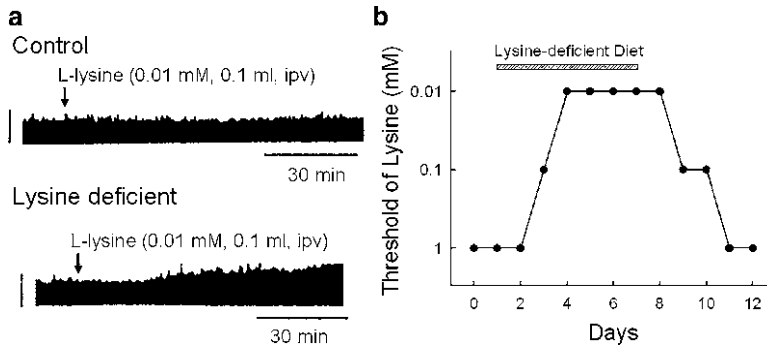
Fig. 154.7 Responses of hepatic vagal afferent fibers to lysine (**a**) and the chronological changes in lysine sensitivity (**b**) in control and during lysine deficiency. (**a**) Administration of L-lysine solution (0.01 mM, 0.1 mL) in the portal vein (ipv) increases the firing rate of the hepatic vagal afferents during lysine deficiency but not in control. Vertical bar, 60 spikes/5 s. (**b**) The threshold (the least effective concentration) of lysine changes 100-fold within 4 days both during lysine deficiency and recovery, each period from deficiency. Each data correspond to observation from one rat (Reprinted from Torii and Niijima 2001. With permission)

luminal side of gastrointestinal tract, the hepatoportal region, or in the systemic circulation. The hepatoportal region is an appropriate area for detecting amino acid levels, and abdominal vagal afferents may provide the brain with information about the current levels of dietary amino acids. Accordingly, sensitivity of hepatic vagal afferents to intraportal administrations of lysine increases 100-fold during lysine deficiency compared to control states: the lowest effective concentration of lysine to evoke hepatic vagal activity is 1 mM during lysine repletion and 0.01 mM during lysine deficiency in rats (Torii and Niijima 2001) (Fig. 154.7). Sensitivity to other L-amino acids (L-alanine and L-leucine) and D-lysine remains unchanged. To reach maximum sensitivity to lysine, 4 days of lysine restriction are required (Torii and Niijima 2001). These results indicate the existence of putative lysine sensors in the hepatoportal region that contribute to maintain amino acid homeostasis.

Recently, a receptor for basic amino acids, namely "GPRC6A" (G-protein-coupled receptor, family C, group 6, subtype A), was found in the brain and peripheral organs such as kidney, skeletal muscle, testis, and white cells (Wellendorph et al. 2004). The receptor is also evident in the mesenteric arteries (Harno et al. 2008). The receptor may contribute monitoring of lysine levels in the blood and brain. However, GPRC6A responds not only to lysine, but is a broadly-tuned sensor of other basic amino acids such as arginine, citrulline, and ornithine with EC_{50} values in the range 20–100 μM (Wellendorph et al. 2005). If there are other types of basic amino acid receptors with different ligand specificity, combination of these putative receptors may enable to monitor the lysine levels in our body.

The enhanced sensitivity of hepatic vagal afferents contributes in the identification of the deficient nutrient, and to alter preferences towards enhancing selective intake of foods containing the deficient nutrients, which prevents malnutrition and anorexia.

154.5.4 Effects of Vagotomy on Food Intake and Food Selection

The abdominal vagotomy, especially the transection of the hepatic branch, attenuates anorexia induced by an amino acid (threonine) imbalanced diet (Dixon et al. 2000), suggesting an involvement of the vagus nerve in detecting peripheral nutritional signals. To investigate the primary sensing site for lysine, Inoue et al. (1995) studied the effects of continuous lysine infusions via the intragastric, intraperitoneal, and intracerebroventricular routes on dietary choice. Rats were given a food choice between a lysine-deficient

and a protein-free diet. Previous to lysine infusions, they consumed consistently more of the protein-free compared to the lysine-deficient diet (approximately 70% versus 30% in preference, respectively). After lysine infusions via either intragastric or intraperitoneal routes, ingestion of the lysine-deficient diet increased while the intracerebroventricular infusions, within the physiological range, failed to affect food choice. Hepatic vagotomy delayed the increased preference for the lysine-deficient diet in rats injected with lysine intraperitoneally. These results implicate postabsorptive mechanisms (but not the cerebrospinal fluid) in sensing a deficient amino acid, and suggest the involvement of the hepatic vagal afferents in this sensing pathway.

154.6 Brain Mechanisms

154.6.1 Neuronal Activity in the Lateral Hypothalamic Area

The lateral hypothalamic area (LHA) is one of the most important central structures involved in feeding and drinking behaviors (Oomura 1980). LHA neurons receive information from various exogenous (visual, auditory, olfactory, and gustatory) and endogenous inputs (Ono et al. 1985; Nakamura et al. 1989; Nishino et al. 1988; Oomura et al. 1980), which are important factors regulating the ingestion and rejection of foods and fluids. Some LHA neurons respond during feeding and gustatory stimulation, and the ingestion responses are modulated by food palatability, deprivation, and satiation (Fukuda et al. 1986; Aou et al. 1991). Accordingly, it is reasonable to hypothesize that the LHA may control the selection of amino acids and NaCl under different nutritive conditions.

To evaluate the role of the LHA in the regulation of preference for amino acids and NaCl, single neuronal activity from the LHA was recorded during cue tone presentation and subsequent ingestion of various amino acids and NaCl solutions in both control and lysine-deficient rats (Tabuchi et al. 1991). Generally, LHA neurons do not discriminate between sapid solutions during ingestion. However, "MSG (umami)-specific" neurons that respond only during licking of a MSG solution are found only in control rats, whereas "lysine-specific" neurons that respond only during licking of a lysine solution were found only in lysine-deficient animals (Tabuchi et al. 1991) (Fig. 154.8). Although it is difficult to determine whether MSG-specific neurons are the same as lysine-specific neurons, these neural responses appear to be related to behavioral preferences; MSG is the most preferred solution in control and lysine is the most preferred one in lysine-deficient rats (Torii et al. 1987). Moreover, both MSG and lysine-specific neurons are localized mainly in the dorsal and lateral part of the LHA (Tabuchi et al. 1991), where gustatory pathways are traced via the pontine taste area in rats (Norgren et al. 1976). It is plausible that some LHA neurons might be related to positive reinforcement such as "satisfaction", when rats ingest a solution that is metabolically necessary for the body. These data suggest that plastic changes in neuronal responses do occur, at least in the LHA, to promote ingestion of required nutrients. The LHA may be the primary site regulating the increased preferences for deficient amino acids.

154.6.2 Microinjection in the Lateral Hypothalamic Area

Lysine levels in the brain, as well as in the blood, decreases a few hours after ingestion of a lysine-deficient diet (Mori et al. 1991a). Neurons in the LHA are more responsive to iontophoretically applied amino acids (i.e., extracellular environment) than those in thalamus or zona incerta (Wayner
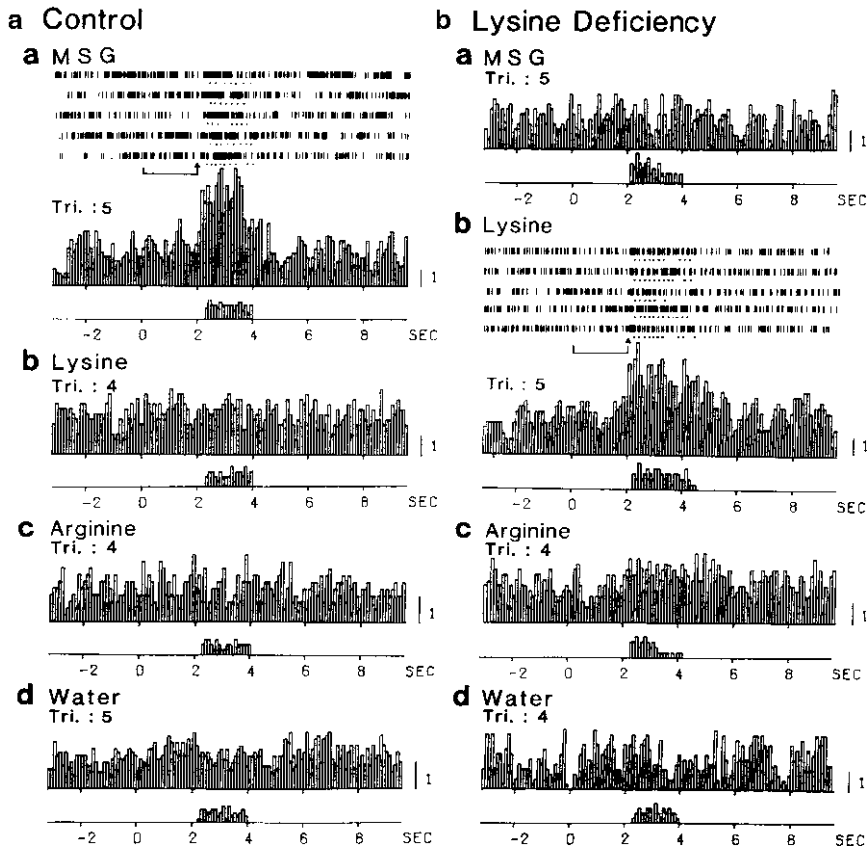
Fig. 154.8 Two examples of taste specific neurons in the lateral hypothalamic area, responding only to monosodium L-glutamate (MSG) in control (**a**) and to lysine during lysine deficiency (**b**). Rats were trained to lick solutions for 2 s licking period (2.0–4.0 s) after the end of each 2 s cue tone period (0.0–2.0 s). The neuron in (**a**) is excited during licking of MSG solution but not for any other solutions. In (**b**), the neuron is excited during licking of lysine solution but not for any other solutions. Neuronal responses to MSG in control (Aa) and to lysine during lysine deficiency (Bb) are shown by raster display (*bars*). Small dots, lick signals. Horizontal brackets, cue tone period. Arrow heads, presentation of drinking tube for licking. In each pair of averaged histograms: upper, neuronal responses; lower, lick signals; Tri, trial number. Calibration of 1 impulse per bin (100 ms) are shown at right of each upper histogram (Reprinted from Tabuchi et al. 1991. With permission)

et al. 1975). Microinjection of balanced solutions of amino acid mixture directly into the dorsolateral perifornical hypothalamus inhibited feeding in rats (Panksepp and Booth 1971). These data suggest that the LHA may be involved in the detection and recognition of deficient nutrients.

Intakes of lysine-deficient and nonprotein diets induce the release of the growth factors inhibin and activin, respectively, in the systemic circulation (Torii et al. 1993). These indicate that ingestion of lysine-deficient or nonprotein diets cause changes in blood (and possibly brain) levels of physiological factors, including inhibin and activin. These factors may be involved in the plasticity of LHA neurons regarding their responses to deficient amino acids. In addition to these peripheral changes, the β_A subunit of activin and inhibin (Torii et al. 1993) and activin receptors (Funaba et al. 1997) has been immunolocalized in a variety of brain regions including the LHA.

To investigate the roles of LHA on ingestive behavior of a deficient nutrient, rats were trained to press a bar to obtain small (50 mg) pellets of a complete diet (Hawkins et al. 1994, 1995, 1998). Rats given a lysine-deficient diet maintained a high rate of bar pressing. This behavior is reduced by (1) ad
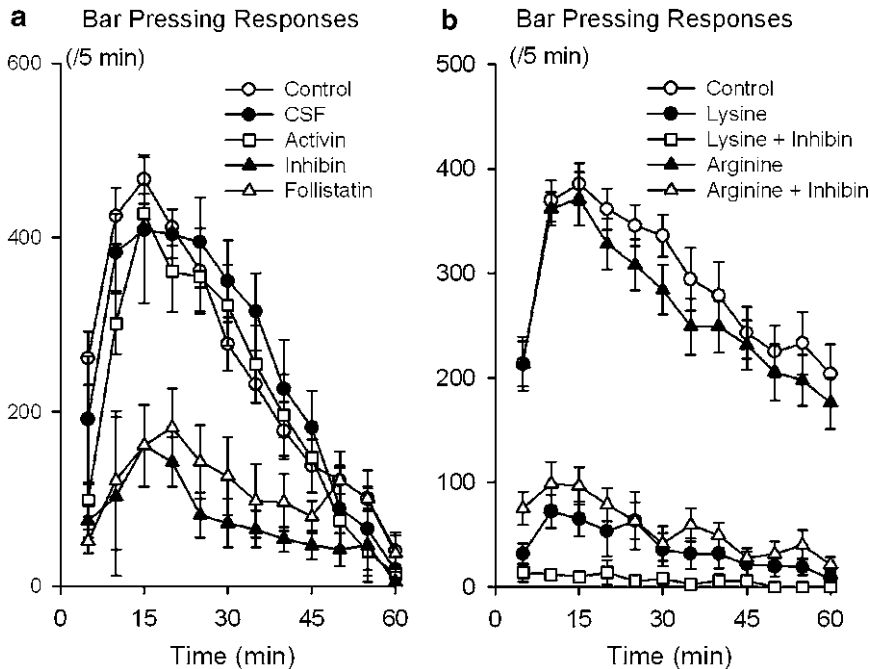
Fig. 154.9 Bar pressing behavior of lysine-deficient rats to receive complete diet (lysine-containing diet). Continuous infusions of inhibin ($P < 0.001$), follistatin ($P < 0.01$) or lysine ($P < 0.01$) into the lateral hypothalamic area reduces bar pressing behavior, while infusions of artificial cerebrospinal fluid (CSF), activin A or arginine have no effects. Results are expressed as mean ± SEM, $n = 9$ (Reprinted from Hawkins et al. 1995. With permission)

libitum access to a lysine solution, (2) intraperitoneal injections of lysine 2 h before the test session, (3) continuous infusion of a lysine solution into the LHA, (4) continuous infusion of inhibin or follistatin (activin inhibitors) into the LHA (Fig. 154.9), or (5) continuous infusion of activin antiserum into the LHA. Interestingly, infusions of lysine, inhibin, follistatin, or activin antiserum into the LHA do not ameliorate the reduced consumption of a lysine-deficient diet, suggesting the presence of different mechanisms involved in anorexia and in the preference for the missing amino acid. Neither the voluntary consumption of other solutions nor the continuous infusion of other amino acids or activin into the LHA suppressed bar-pressing behaviors. Although LHA lysine infusion decreases consumption of a concurrently available lysine solution, inhibin infusion does not change ad libitum lysine consumption. These results indicate that inhibin may work in the LHA to inhibit bar pressing to obtain a complete diet via mechanisms other than sensing lysine deficiency.

154.6.3 Norepinephrine Release in the Hypothalamus

Hypothalamic norepinephrine is involved in regulation of food intake (Bray 1993). Lysine is not a precursor of norepinephrine and does not affect norepinephrine synthesis. In control rats, norepinephrine release in the ventromedial nucleus of the hypothalamus (VMH) shows a diurnal pattern, with the lowest levels measured at the onset of the dark phase (Smriga et al. 2000a). This circadian release of norepinephrine is depressed during early lysine deficiency and ingestion of lysine solution restores the circadian pattern of norepinephrine release.

In longitudinal measurements, norepinephrine release in the VMH significantly declines within the first 24 h after the introduction of a lysine deficient diet, and the reduction of norepinephrine release persists throughout the lysine deficiency period i.e., 1 week (Smriga et al. 2000b) (Fig. 154.10). When the lysine-sufficient diet is offered, the reduced norepinephrine levels recover rapidly. The pattern of norepinephrine release is parallel to the suppression of food intake. In threonine deficient rats, increases in norepinephrine levels in homogenized VMH tissue have been reported (Gietzen et al. 1998). This increase can be attributed to reduced release of norepinephrine. Since no changes in norepinephrine release were observed in the LHA (Smriga et al. 2000b), reduced norepinephrine release in the VMH appears to be involved in both the initiation and the regulation of anorexia during lysine deficiency.
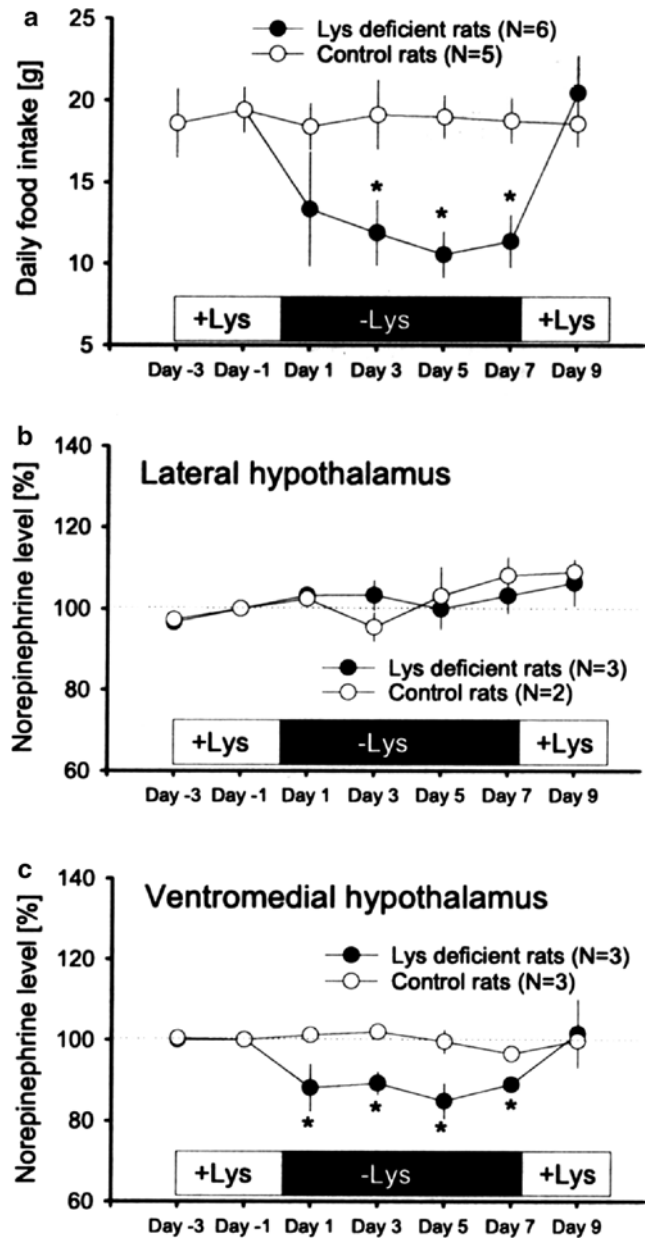
Fig. 154.10 Daily food intake (**a**), and norepinephrine release in the lateral hypothalamus (**b**) and medial hypothalamus (**c**) in rats fed lysine-deficient diet for 1 week (Day 0–7). Dietary lysine status is illustrated in each lower part of panel. +Lys, lysine-sufficient (control) diet; –Lys, lysine-deficient diet. Results are shown as percent differences from basal levels that were measured just before the introduction of lysine-deficient diet (Day -1). *$P < 0.05$, significance compared to control rats by Student's *t*-test (Reprinted from Smriga et al. 2000b. With permission)

154.6.4 Lysine Preference and Reward Circuits

The dopaminergic neurons in the ventral tegmental area have a crucial role in regulating behavioral responses to natural rewards such as sweet solutions, as well as artificial rewards such as drugs of abuse. However, lesions of the ventral tegmental area dopaminergic neurons by microinjection of 6-hydroxydopamine (a selective neurotoxin for dopaminergic neurons) do not interfere with enhanced preference for lysine during lysine deficiency, whereas the preference for sucrose is largely reduced (Shibata et al. 2009). Preferences for umami (MSG and 5'-ribonucleotides) and NaCl solutions are also unaffected by ventral tegmental area lesions. These results suggest that preferences for essential amino acids, umami, and NaCl, but not sweet, solutions operate through reward circuits that are independent of ventral tegmental area dopaminergic neurons. Contribution of dopaminergic neurons from other brain areas and the identification of the reward circuits regulating preferences for deficient nutrient must be clarified in future experiments.

154.7 Applications to Other Areas of Health and Disease

Essential amino acids are absolutely necessary for growth, reproduction, and survival. Since lysine is the limiting amino acid in proteins of some feed grains (wheat and corn), lysine deficiency is commonly found in human populations living in developing areas, where staple diet is based on such grains. Characteristic symptoms of essential amino acid deficiency include reduced appetite, low weight gain, and nervousness. Repletion of the missing nutrients will result in rapid attenuation of these symptoms. Supplementation of deficient nutrients in food is one reasonable treatment or preventive measure against nutrient deficiency. The further clarification of the mechanisms involved in the adaptation to and recovery from nutrient deficiency may provide us with significant information on how to improve the quality of our dietary choices.

Summary Points

- Lysine is a basic and essential amino acid with a bitter taste quality.
- Lysine is present at low levels in proteins found in some feed grains (wheat and corn), and hence a substantial risk of lysine deficiency exists in low socioeconomic human populations who depend predominantly on such grains for their protein supply.
- Lysine is not linked directly to the synthesis of any neurotransmitter in the brain.
- Lysine deficiency can be induced in animals upon presentation of a lysine-deficient diet.
- During lysine deficiency, lysine levels in the blood and brain decline.
- During lysine deficiency, food intake and weight gain are suppressed.
- Lysine-deficient animals display increased preferences for lysine solutions, and the consumption of which results in normalization of food intake and growth.
- During lysine deficiency, blood levels of inhibin are increased and activin A-like activity are severely suppressed.
- During lysine deficiency, aversion thresholds for lysine, but not for other bitter solutions, increase 100-fold.
- During lysine deficiency, sensitivity of primary taste nerves to lysine does not change, while the sensitivity of the hepatic vagal afferents to intraportal lysine increases 100-fold within just 4 days.
- During lysine deficiency, some LHA neurons specifically respond to the ingestion of lysine.

- Microinjection of lysine, or an activin inhibitor (inhibin, follistatin, or activin antiserum), into the LHA suppresses bar pressing behaviors to obtain lysine-containing food.
- During lysine deficiency, norepinephrine release is decreased in the VMH but does not change in the LHA.
- Lesions of the ventral tegmental area dopaminergic neurons (a reward circuit) do not interfere with enhanced preference for lysine during lysine deficiency.
- These findings indicate that signals conveyed by vagal hepatic afferent fibers play an important role in the detection of a deficient nutrient. Taste information is important in the expression of taste-guided behaviors upon association of taste information with the metabolic effects of lysine.
- Brain circuits including the lateral and medial nuclei of the hypothalamus integrate neural and humoral inputs, and regulate taste preferences for deficient nutrients. The reward circuit of the ventral tegmental area is not involved in the development of lysine preferences during lysine deficiency.

Definitions and Explanations of Key Terms

Activin: A gonadal hormone composed of two inhibin beta subunits ($\beta_A\beta_A$, $\beta_A\beta_B$, or $\beta_B\beta_B$) and belongs to the transforming growth factor-β (TGF-β) superfamily. Activin is produced in the gonads, pituitary gland, placenta, and other organs and has multiple functions including secretion of follicle-stimulating hormone and regulation of erythrocyte differentiation.

Follistatin: A monomeric autocrine glycoprotein that binds directly to both activin and inhibin through the common β subunit. Follistatin is produced by folliculostellate cells of the anterior pituitary and inhibits follicle-stimulating hormone secretion. Its primary function is binding and bioneutralization of members of the TGF-β superfamily, with primary focus on activin.

Homeostasis: Conditions under which the internal environment in the body is maintained within a stable level. Homeostasis is very important for animals to live well in a healthy condition and its disturbance may cause illness.

Inhibin: A gonadal glycoprotein closely related activin, composed of α and β subunits. Inhibin has opposing biological effects to activin such as inhibition of follicle-stimulating hormone synthesis and inhibition of gonadotropin-releasing hormone release in the pituitary gland. Inhibin is considered to compete with activin for activin receptors and/or binding to inhibin specific receptors.

Lateral hypothalamic area (LHA): One of the most important central structures involved in feeding and drinking behavior (also known as the feeding center). LHA neurons receive information from various exogenous (visual, auditory, olfactory, and gustatory) and endogenous inputs, which are important determinant for ingestion or rejection of foods and fluids, and appropriate autonomic responses.

L-Lysine: A basic and essential amino acid with bitter taste quality. Since lysine content in the wheat and corn is very low, people who eat wheat or corn as a staple food are susceptible to lysine deficiency. Lysine is not linked to levels of any neurotransmitter in the brain and hence lysine deficiency is considered as one of the best models for investigating mechanisms of nutrient deficiency.

Monosodium L-glutamate (MSG): A sodium salt of L-glutamic acid. Glutamate has multi-function involvement in perception of umami taste, intermediary metabolism, and excitatory neurotransmission. In addition, it plays important roles in activation of gut–brain axis and regulation of energy homeostasis. Several types of glutamate receptors (ionotropic and metabotropic receptors) are expressed in the body.

> **Vagus nerve:** The Xth cranial nerve that innervates the larynx, heart, lungs, and visceral organs. It consists of both afferent and efferent fibers at the abdominal levels. Several stimuli such as mechanical pressure, temperature, osmotic pressure, and chemicals alter afferent activity of the vagus nerve.
>
> **Ventral tegmental area:** An area in the midbrain implicated in drug and natural reward circuitry, motivation, cognition, drug addiction, and several psychiatric disorders. Dopaminergic cell bodies originate and their two primary efferent projections are the mesocortical (innervates the prefrontal and insular cortices) and mesolimbic (innervates septum, hippocampus, amygdala, and nucleus accumbens) pathways.
>
> **Ventromedial nucleus of the hypothalamus (VMH):** A nucleus in the hypothalamus most commonly associated with satiety (also known as the satiety center). Early studies showed that VMH lesions caused overeating and obesity in animals.

References

Aou S, Takaki A, Karádi Z, Hori T, Nishino H, Oomura Y. Brain Res Bull. 1991;27:451–5.

Bray GA. Brain Res Bull. 1993;32:537–41.

Bricker M, Mitchell HH, Kinsman GM. J Nutr. 1945;30:269–83.

Culik R, Rosenberg HR. Food Technol. 1958;12:169–74.

Dixon KD, Williams FE, Wiggins RL, Pavelka J, Lucente J, Bellinger LL, Gietzen DW. Am J Physiol Regul Integr Comp Physiol. 2000;279:R997–1009.

Forbes RM, Vaughan L, Yohe M. J Nutr. 1958;64:291–302.

Fukuda M, Ono T, Nishino H, Sasaki K. Brain Res. 1986;374:249–59.

Funaba M, Murata T, Fujimura H, Murata E, Abe M, Torii K. J Neuroendocrinol. 1997;9:105–11.

Gietzen DW, McArthur LH, Theisen JC, Rogers QR. Physiol Behav. 1992;51:909–14.

Gietzen DW, Erecius LF, Rogers QR. J Nutr. 1998;128:771–81.

Hanai K. J Comp Physiol. 1981;144:503–8.

Harno E, Edwards G, Geraghty AR, Ward DT, Dodd RH, Dauban P, Faure H, Ruat M, Weston AH. Cell calcium. 2008;44:210–9.

Harper AE. In: Henry Brown AB, editor. Protein nutrition. Springfield: Charles Thomas; 1974. p. 130–79.

Harper AE, Benevenga NJ, Wohlhueter RM. Physiol Rev. 1970;50:428–558.

Hawkins RL, Inoue M, Mori M, Torii K. Physiol Behav. 1994;56:1061–8.

Hawkins RL, Inoue M, Mori M, Torii K. Brain Res. 1995;704:1–9.

Hawkins RL, Murata T, Inoue M, Mori M, Torii K. Proc Soc Exp Biol Med. 1998;219:149–53.

Inoue M, Funaba M, Hawkins RL, Mori M, Torii K. Physiol Behav.1995;58:379–85.

Markison S, Gietzen DW, Spector AC. J Nutr. 1999;129:1604–12.

Markison S, Thompson BL, Smith JC, Spector AC. J Nutr. 2000;130:1320–8.

Mori M, Kawada T, Ono T, Torii K. Physiol Behav. 1991a;49:987–95.

Mori M, Kawada T, Torii K. Brain Res Bull. 1991b;27:417–22.

Naito-Hoopes M, McArthur LH, Gietzen DW, Rogers QR. Physiol Behav. 1993;53:485–94.

Nakamura K, Ono T, Tamura R, Indo M, Takashima Y, Kawasaki M. Brain Res. 1989;491:15–32.

Ninomiya Y, Kajiura H, Mochizuki K. Neurosci Lett. 1993;163:197–200.

Ninomiya Y, Kajiura H, Ishibashi T, Imai Y. Chem Senses. 1994a;19:617–26.

Ninomiya Y, Kajiura H, Naito Y, Mochizuki K, Katsukawa H, Torii K. Physiol Behav. 1994b;56:1179–84.

Nishimura F, Nishihara M, Mori M, Torii K, Takahashi M. Brain Res. 1995;691:217–22.

Nishino H, Oomura Y, Karádi Z, Aou S, Lénárd L, Kai Y, Fukuda A, Ito C, Min BI, Salaman CP. Brain Res Bull. 1988;20:839–45.

Norgren R. J Comp Neurol. 1976;166:17–30.

Ono T, Sasaki K, Nakamura K, Norgren R. Brain Res. 1985;327:303–6.

Oomura Y. In: Morgane PJ, Panksepp J, editors. Handbook of the hypothalamus: physiology of the hypothalamus, vol. 2. New York: Marcel Dekker; 1980. p. 557–620.

Panksepp J, Booth DA. Nature 1971;233:341–2.

Pritchard TC, Scott TR. Brain Res. 1982;253:81–92.

Robertson DM, Burger HG, Fuller PJ. Endocr Relat Cancer. 2004;11:35–49.

Rosenberg HR, Rohdenburg EL. Arch Biochem. 1952;37:461–8.

Shibata R, Kameishi M, Kondoh T, Torii K. Physiol Behav. 2009;96:667–74.

Shingai T, Beidler LM. Brain Res. 1985;335:245–9.

Smriga M, Mori M, Torii K. J Nutr. 2000a;130:1641–3.

Smriga M, Murakami H, Mori M, Torii K. Biofactors 200b;12:137–42.

Tabuchi E, Ono T, Nishijo H, Torii K. Physiol Behav. 1991;49:951–64.

Tabuchi E, Uwano T, Kondoh T, Ono T, Torii K. Brain Res. 1996;739:139–55.

Torii K, Niijima. Physiol Behav. 2001;72:685–90.

Torii K, Mimura T, Yugari Y. In: Kawamura Y, Kare MR, editors. Umami: a basic taste. New York: Marcel Dekker; 1987. p. 513–63.

Torii K, Hanai K, Oosawa K, Funaba M, Okiyama A, Mori M, Murata T, Takahashi M. Physiol Behav. 1993;54:459–66.

Torii K, Yokawa T, Tabuchi E, Murata T, Hawkins RL, Mori M, Kondoh T, Takezawa M, Ono T. In: Ono T, McNaughton BL, Molotchnikoff S, Rolls ET, Nishijo H, editors. Perception, memory and emotion: frontiers in neuroscience. Oxford: Elsevier Science; 1996. p. 467–78.

Wayner MJ, Ono T, DeYound A, Barone FC. Pharmacol Biochem Behav. 1975;3(1 Suppl):85–90.

Wellendorph P, Bräuner-Osborne H. Gene 2004;335:37–46.

Wellendorph P, Hansen KB, Balsgaard A, Greenwood JR, Egebjerg J, Bräuner-Osborne H. Mol Pharmacol. 2005;67:589–97.

Young VR, Pellet PL. Food Nutr Bull. 1990;12:289–300.

Part XXV
Anorexia Nervosa

Chapter 155
Genotypes and Phenotypes of Anorexia Nervosa

Janet Treasure, Natalie Kanakam, and Christine-Johanna Macare

Abbreviations

5HT	5-hydroxytryptamine
ACC:	Anterior cingulate cortex
AN	Anorexia nervosa
AN-R	Anorexia nervosa restricting subtype
AN-BP	Anorexia nervosa binge-purge subtype
ASD	Autistic spectrum disorders
DSM IV	Diagnostic and Statistical Manual of Mental Disorders, 4th edition
BDNF	Brain-derived neurotrophic factor
BMI	Body mass index
BN	Bulimia nervosa
COMT	Catechol-O-methyltransferase
CSF	Cerebrospinal fluid
CT studies	Computed tomography studies
CT	Constitutionally thin
DA	Dopamine
ED	Eating disorders
EDNOS	Eating disorder not otherwise specified
fMRI	Functional magnetic resonance imaging
HTR1D	Serotonin 1D receptor.
ICD-10	International Statistical Classification of Diseases and Related Health Problems 10th Revision
NICE	National Institute for Clinical Excellence

J. Treasure (✉)

Institute of Psychiatry, King's College London, London, United Kingdom
and
Department of Academic Psychiatry, Eating Disorder Research Unit, Guy's Hospital, Bermondsey Wing, SE1 9RT, London, United Kingdom
e-mail: Janet.Treasure@iop.kcl.ac.uk

OA   Object Assembly subtest
OCD   Obsessive compulsive disorder
OCPD   Obsessive compulsive personality disorders
QTL   Quantitative trait linkage
PYY   PeptideYY
SNP   Single nucleoid polymorphisms
WAIS   Wechsler Adult Intelligence Scale
WCC   Weak Central Coherence

155.1 Introduction

This chapter aims to discuss individual characteristics such as genotypes and intermediate phenotypes that increase the susceptibility to developing Anorexia Nervosa (AN). First, clinically specified phenotypes of anorexia nervosa will be outlined and the difficulties in diagnosis will be discussed. A summary of the literature relating to possible intermediate phenotypes, biomarkers, and endophenotypes relevant to AN follows. Subsequently, the methodological issues in the search for AN genotypes will be presented. Finally, the implication of these findings for health and treatments will be suggested.

155.1.1 Diagnostic Criteria

Anorexia Nervosa was first described by Gull (1873). The current DSM classification includes the following symptoms (Table 155.1):

There are two subtypes of AN: restricting (AN-R) and binge-purge type (AN-BP). The restricting subtype is characterized by behaviors of extreme and prolonged fasting and restraint. The binge-purge subtype is also defined by prolonged fasting although it is punctuated by episodes of overeating followed by behaviors to compensate for weight gain such as self-induced vomiting; the misuse of laxatives, diuretics, or enemas; and exercise.

155.1.2 Epidemiology

The onset of AN is usually reported in puberty and females are more likely to be affected than males (APA 2000). The likelihood of being diagnosed with AN at least once during lifetime is estimated at

Table 155.1 DSM IV diagnostic criteria for AN (APA 2000)

DSM IV criteria for anorexia nervosa
• Severe weight loss and maintenance of that under 85% of the expected
• Intense fear of weight gain
• Distortion of body image and overemphasis on weight as an index for self-evaluation
• Amenorrhea

These diagnostic criteria must be satisfied for AN diagnosis. At present, diagnosis is based on its visible phenotypes.

approximately 1% (Hudson et al. 2007). The annual incidence of new AN cases presenting to primary care is given in 8 out of 100,000 individuals (Hoek and van Hoeken 2003).

155.1.3 Prognosis

Mortality in AN is increased (standard mortality ratio of 6.2–10.5 (Birmingham et al. 2005; Papadopoulos et al. 2009; Lowe et al. 2001); and life expectancy reduced by 25 years for females who have suffered from AN since the age of 15 (Harbottle et al. 2008). The outcome for AN patients is poor, with only half recovering, approximately 6–10% developing a chronic condition (Berkman et al. 2007; Lowe et al. 2001), and up to 25% having poor psychosocial functioning (Wentz et al. 2009).

155.1.4 Chronic Disability

People with AN have a diminished quality of life (Mond et al. 2005). Eating disorders were placed fourth in terms of burden of disease (years of life lost through death or disability) in women aged 15–24 years (Mathers et al. 1999) with both physical and psychological comorbidity. Education in terms of attendance at school is disrupted (Byford et al. 2007). Moreover vocational functioning is impaired: 21% of cases still rely on state benefits 10–15 years after the onset of the illness (Hjern et al. 2006). Social isolation is common; social communication skills are poor (Takahashi et al. 2006) and social networks are small (Tiller et al. 1997). The costs of these disabilities are high (Su and Birmingham 2003).

155.1.5 Diagnostic Difficulties

The nosological status of the current DSM IV diagnostic criteria has been questioned (Hebebrand et al. 2004). A substantial number of patients change diagnosis over time. As many as 55% of patients who initially suffer with restrictive AN (AN-R) subsequently develop AN-BP, bulimia nervosa or eating disorder not otherwise specified (Eddy et al. 2008).

Some patients do not present with all the symptoms necessary for a diagnosis of AN according to DSM IV criteria or ICD criteria. The ICD operationalized the weight threshold as a Body Mass Index (BMI, weight in kg/height in m) below 17.5. Regular menses may occur below this threshold and medication or the contraceptive pill may make amenorrhea an unreliable diagnostic marker. Furthermore, a subgroup of patients do not fulfill the criterion of having a fear of weight gain or a distorted body image (Strober et al. 1999). Comorbidity with other psychiatric disorders can make diagnosis on the basis of phenotypes challenging. As weight loss increases, patients often present with a variety of mood and anxiety disorders. For instance, 30% of AN patients meet the criteria for Obsessive Compulsive Disorder (OCD). Also a subgroup has characteristics associated with the Autistic Spectrum Disorders (ASD). Gillberg and colleagues described 20% with an empathy disorder and social disturbances (1994). These features were predictive of poor psychosocial outcome over time (Rastam et al. 2003). Intermediate phenotypes or biomarkers may be more stable over time than illness phenotypes.

155.2 Biomarkers and Endophenotypes

Increasingly, there is an interest in intermediate phenotypes such as biomarkers (biological marker) and endophenotypes as a means to describe and identify an illness. Biomarkers are underlying cognitive or behavioral traits that are associated with a disorder, but not part of their visible presentation. They can be state or trait related. Biomarkers have a number of different applications such as being antecedent, screening, diagnostic, prognostic, or stratification markers (Ritsner and Gottesman 2009). One valuable kind of biomarker is that of an endophenotype: a heritable trait biomarker that falls on the pathway between behavior and biology (phenotype and genotype). Gottesman and Gould (2003) have defined specific criteria to be fulfilled for an endophenotype status (Table 155.2):

Although the endophenotype and biomarker concepts have been used interchangeably in the literature, Gottesman and Gould (2003) use the former when there are some signs of heritability, and biomarkers when the trait does not fulfill the criteria of genetic underpinnings. It is hoped that endophenotypes will provide a more direct association with the genotype than the phenotypes of AN (see Fig. 155.1). Recent reviews have included the concept of endophenotypes in discussions of ED etiology (Treasure et al. 2007).

Table 155.2 Endophenotype criteria (Gottesman and Gould 2003)

Endophenotype criteria
• Association with the illness in the population
• Heritability
• State-independence
• Cosegregation with the illness in families
• Presence in unaffected relatives at a higher level than in the general population

Endophenotypes are heritable trait biomarkers. The above criteria must be satisfied for the trait to be classified as an endophenotype.

Fig. 155.1 Pathway between genotype and phenotype. Intermediate phenotypes lie on the pathway between candidate genes that make an individual susceptible to anorexia nervosa (*AN*) and its visible symptoms. Potential biomarkers and endophenotypes are more directly associated with AN etiology. For example, endophenotypes such as "weak central coherence" (which refers to deficits in global processing) may be involved in causing and maintaining visible symptoms such as the inability to see the adverse consequences of extreme food restriction on physical health

Genotype: candidate genes for AN

Intermediate phenotypes: e.g. Endophenotypes such as Weak Central Coherence (a deficit in global processing)

Phenotypes: e.g. visible symptoms, such as extreme food restriction and low BMI (as specified by DSM criteria)
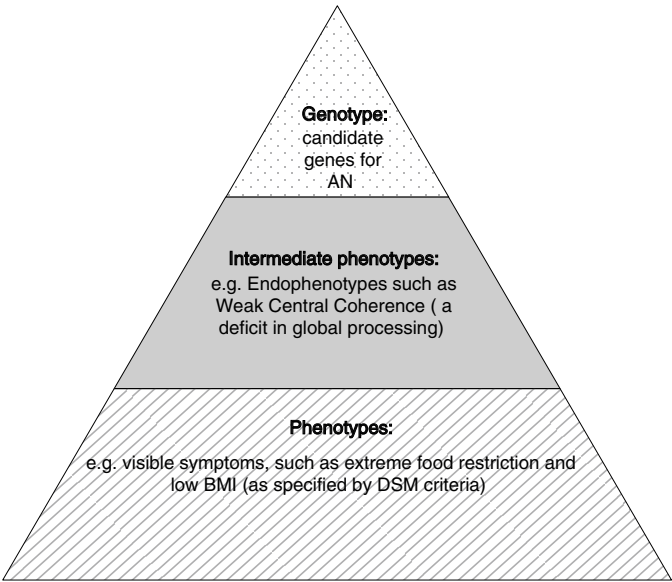
It is hoped that research to establish characteristics as intermediate phenotypes of AN will lead to a more biologically based system of classification and a more accurate understanding of causation, pathophysiology, prognosis, and treatment.

155.2.1 Distinguishing Biomarkers Associated with the Illness from Secondary Consequences of Starvation

The search for suitable biological markers in AN is complex since starvation and impaired nutrition, core elements of the disorder, have a profoundly disrupting effect on both the psychology and physiology of the individual. This causes a proliferation of biological abnormalities in the acute state. One way of trying to distinguish between the consequences of starvation and features that suggest an underlying biological vulnerability is to examine people after weight recovery. This in itself is not without problems; for example, how does one define recovery? Is it important to have a minimal duration of recovery? Is the abnormality a risk factor or a scar from the illness? Some risk factors may only occur in the context of environmental or developmental risk factors and may remain hidden. Despite these difficulties several groups have undertaken studies of biomarkers in patients after recovery. Fewer studies have taken the next step which is to examine whether the biomarkers represent a familial and genetic vulnerability.

155.3 Introduction to the Concept of Biomarkers

At present, evidence-based relevant biomarkers include (a) altered serotonin function (Kaye 2008); (b) opioid alterations (Kaye et al. 1982); (c) dopamine disturbances (Frank et al. 2005); (d) variant hormonal profiles (Germain et al. 2007); (e) alterations in brain structure (Gagel 1953; van den Eynde and Treasure 2008; Martin 1958; Roser et al. 1999); and neuropsychological endophenotypes such as (f) difficulties in set-shifting (Roberts et al. 2007; Tchanturia et al. 2004); (g) weak central coherence (Lopez et al. 2008b); and (h) social cognitive deficits (Gillberg et al. 1994).

155.3.1 Serotonin

There is growing evidence that a disturbance in serotonin function may be a biomarker involved in the etiology and pathogenesis of AN (Kaye 2008). 5HT1A receptors are increased especially in the acute state but also after recovery (Bailer et al. 2005a, b, 2007; Galusca et al. 2008), particularly in the prefrontal areas (associated with regulatory control) and the mesial temporal/subgenual areas (associated with reward). 5HT receptors in the striatum are increased in the restricting form of anorexia nervosa after recovery whereas they appear to be decreased in the binge-purge form (Bailer et al. 2004). In summary, people with eating disorders have key abnormalities in 5HT function in both the hedonic and the regulatory regions of the brain.

Dysregulation of these emotional and reward pathways not only impacts upon feeding but also contributes to a dysphoric temperament with symptoms of anxiety, obsessionality, and inhibition.

Indeed Walter Kaye has developed a hypothesis which states that, restricting food can become powerfully reinforcing since it reduces the availability of plasma tryptophan, which is a rate-limiting step in the production of 5HT. The reduced functional activity of 5HT is thought to reduce anxiety, which is in itself reinforcing (2008).

In support of this theory, positive correlations between anxiety measures used to assess harm avoidance and 5-HT2a binding have been shown in the temporal cortex (Bailer et al. 2004) and the supragenual cingulate, frontal, and parietal brain regions of recovered AN patients. This is regardless of any abnormality in overall 5-HT2a receptor activity (Bailer et al. 2007).

155.3.2 BDNF

Brain derived neurotrophic factor (BDNF), a protein, has been shown to regulate the serotonergic neurotransmitter system. BDNF is also present in the hypothalamic nuclei that are associated with weight regulation (Pelleymounter et al. 1995). Research has shown that BDNF levels are significantly decreased in people with anorexia nervosa in comparison to healthy controls (Monteleone et al. 2004) and persists into recovery (Nakazato et al. 2006).

155.3.3 Opioid

The opioidergic neurotransmitter system is also associated with regulating feeding behavior. It is thought to be implicated in the "liking" aspects of food intake and may mediate the rewarding aspects of food. Blockade of opioid receptors in rats using the opioid antagonist, naloxone, decreases consumption of more preferred and palatable foods (Glass et al. 1996). In AN higher levels of cerebrospinal fluid activity was found in those who were severely underweight in comparison to those with AN who were weight recovered, suggesting that it may be related to BMI (Kaye et al. 1982).

155.3.4 Dopamine

Dopamine-related disturbances has been related to a number of symptoms encountered in AN, such as amenorrhea, obsessive compulsive traits, hyperactivity, and weight loss (Kaye et al. 2004). This potential biomarker may also contribute to feeding behavior and to the generally anhedonic temperament in AN. Dopamine DA is a key neurochemical in the hedonic system For example, the presentation of palatable foods to fasting humans is associated with an increase in DA in the dorsal striatum (Volkow et al. 2002). Furthermore the amount of dopamine released is correlated with the amount of pleasure experienced when eating (Small et al. 2003).

Frank and colleagues (2005) demonstrated higher dopamine D2/D3 receptor binding in recovered AN subjects in the anteroventral striatum, suggesting either decreased intrasynaptic dopamine concentration or increased D2/D3 receptor density or affinity to be present in AN. This abnormality of dopamine in the hedonic system might be associated with the altered response to reward seen in AN (difficulties in differentiating between positive and negative feedback) (Wagner et al. 2007).

Moreover, in the AN group, dopamine binding potential in the dorsal caudate and dorsal putamen correlated positively with harm avoidance. This observation supports the view that the dopamine abnormalities in AN might contribute to the characteristic harm avoidance or increased physical activity (Frank et al. 2005).

155.3.5 Hormones

AN is associated with many abnormalities in the hormonal profile. Adiponectin and leptin are produced by adipose tissue and are involved in energy metabolism. Serum leptin levels were found to be severely decreased in restricting anorexics and only moderately decreased in purging anorexics. Furthermore, compared to controls, circulating levels of adiponectin were increased by 53% in purging anorexics and by 96% in restricting anorexics (Liu et al. 2008).

Other orexogenic and anorexogenic hormones which regulate appetite have been found to be important biomarkers that distinguish between AN and people who are constitutionally thin (CT). Orexogenic hormones such as ghrelin which is known to initiate appetite was found to be significantly higher in those that were CT than in people with AN. Anorexogenic hormones including PeptideYY and leptin were significantly lower in people with anorexia nervosa than in CT subjects. Interestingly, GLP-1 concentrations were significantly higher in AN than in CT subjects (Germain et al. 2007).

155.3.6 Brain Structure

Structural and metabolic changes occur in the brain during the acute phase of AN. The most consistent alteration is the reduction in brain mass. This was first suggested by postmortem findings of reduced cerebral mass with prominent sulci and small gyri (Gagel 1953; van den Eynde and Treasure 2008; Martin 1958) and later confirmed in vivo in several CT studies that additionally demonstrated enlarged ventricles (Dolan et al. 1988; Krieg et al. 1989; Palazidou et al.1990). For the most part, brain mass is restored with weight gain (Castro-Fornieles et al. 2009; McCormick et al. 2008).

155.4 Neuropsychological Endophenotypes

155.4.1 Cognitive Biomarkers

A number of cognitive deficits have been observed in AN. In particular, executive function is disrupted in the acute phase of ED. For example, Jones and collegues (1991) reported mild cognitive impairments in the domains of focusing/execution, memory, and verbal and visuospatial processing. However, most of these deficits were not present in weight recovered AN participants. Set-shifting deficits and weak central coherence are of interest in that they are associated with obsessive compulsive traits which are present before and after the acute illness phase.

155.4.2 Set Shifting

Set-shifting is one of the main aspects of executive functioning and refers to the ability to be flexible with one's mindset in adapting to new task demands or changes in situations (Miyake et al. 2000). A series of studies using a variety of neuropsychological tasks to measure this concept found that people with AN have difficulties in set-shifting in the acute state (Anderluh et al. 2003; Tchanturia et al. 2001, 2002). A meta-analytic systematic review of the literature confirmed this impairment in cognitive flexibility which was present in the various eating disorder subgroups (Roberts et al. 2007).

Women recovered from AN also demonstrate impairment in set-shifting ability but with reduced effect sizes (Tchanturia et al. 2004; Roberts et al. 2007). Examples of effect sizes across a range of set shifting tasks are shown in Table 155.3. Problems with set-shifting were also seen in the sisters of individuals with ED (Holliday et al. 2005).

Results from these studies suggest that executive function as marked by poor cognitive flexibility may be a state independent trait in some cases but that this difficulty is exaggerated during the illness phase. It does not appear to be simply a consequence of malnutrition alone since other aspects of eating disorder psychopathology such as depression and anxiety also have an impact. The limitation of a cross-sectional design to address state-independence is noted. As the recovered group had managed to overcome their AN, it is possible that they represent a different cohort than those with chronic, persistent AN.

Poor set-shifting may represent a prognostic biomarker of AN and be involved in the maintenance of the illness. Cognitive remediation therapy which addressed this deficit has been tested and proved effective (Tchanturia et al. 2006). Replication of these studies with larger samples is required as well as genetic examination to complete the exploration as to whether poor set shifting might meet the criteria for an endophenotype of some forms of ED.

155.4.3 Weak Central Coherence

Weak central coherence is another neuropsychological trait of interest because of its association with OCPD and the autistic spectrum of disorders. Central coherence is the natural cognitive

Table 155.3 Effect sizes (Cohen's *d*)* for neuropsychological tasks relating to set-shifting in AN

Task	Current AN	Recovered AN	Time	Repeat
Set-shifting				
TMT-B	0.8	0.5	5	Yes-2
WCST	0.6	0.4	10	No
Brixton	0.2	0.3	5	Yes-2
CatBat	0.6	0.4	3	No
Haptic	1.2	0.9	5	No

TMT-B (Trail Making Task, Trial B); WCST (Wisconsin Card Sorting Test); Time (Time taken in minutes to administer each task); Repeat (Can the task be repeated?); Yes, Yes-2 (have 2 versions of the task), No, ? (unsure if task can be repeated); The effect size in the table represent the mean of the published studies.
*Cohen's *d* effect sizes are understood as follows: 0 to <0.15 – negligible; >0.15–0.40 – small; >0.40–0.75 – medium; >0.75–1.10 – large; >1.10 – huge.

style of most people in adult life, and is defined as the skill of integrating large amounts of incoming information into context, gestalt, and meaning (Frith 1989). The opposite tendency, weak central coherence, is characterized by a tendency to process information in parts (detail) rather than as a whole, with relative difficulty in global or integrative processing (Happe and Booth 2008).Weak central coherence is a key component of the cognitive style in autistic spectrum disorders (ASD) (Happe and Booth 2008; Happe and Frith 2006) and has also been found in their first-degree relatives (Smalley and Asarnov 1990; Happe et al. 2001; Baron-Cohen and Hammer 1997).

Initial findings which suggested that this trait was associated with ED were found in Gillberg and collaborators' longitudinal study (1996). This cohort of early onset cases of AN were found to be persistently impaired over time on the Object Assembly subtest (OA) from WAIS. This test requires the ability to integrate pieces of information into a whole, to construct a familiar object (Gillberg et al. 1996, 2007). They also found that a subgroup of people with AN who met the criteria for ASD also had a cognitive profile resembling that found in ASD. Although the authors initially hypothesized that the poor performance in the OA was due to poor abstract thinking (Gillberg et al. 1996), they later associated their findings with weak central coherence (Gillberg et al. 2007). Our group has furthered the investigation of the weak central coherence hypothesis in people with ED with a systematic, hypothesis driven approach using a battery of tests used to measure central coherence. It was found that weak central coherence may be a feature of AN since there is superiority in tasks that require detail processing (e.g., Group/Embedded Figures and Matching Familiar Figures) and a weakness in tests that require a global strategy such as the Sentence Completion and Homograph Reading Tasks, the Rey-Osterrieth Complex Figure, and OA (Lopez et al. 2008a, b, c; Southgate et al. 2008) (see Table 155.4). A recent systematic review of the literature found some evidence supporting this account particularly for decreased global processing (Lopez et al. 2008a).

This trait has been reported also to be present in women in recovered state, with medium effect sizes for global integration and large for detail focused processing. A recent study of our group has

Table 155.4 Effect sizes (Cohen's *d*)* for neuropsychological tasks relating to weak central coherence in AN

Task	Current AN	Recovered AN	Time	Repeat
Central coherence				
D-EFT	0.5	1.0	10	Yes-2
D-GEFT	0.8		15	?
D-BD	0.0	0.2	10	?
D-MFFT	0.9		10	No
G-Rey CC	0.9	0.6	5	Yes-2
G-OA	0.6	0.6	15	No
G-Frag. Pic	1.7		10	Yes-2
G-SCT	0.7	1.2	10	No
H-HRT	0.0	0.4	10	No

EFT (Embedded Figures Task); BD (Block Design); MFFT (Efficiency Matching Familiar Figures Test); Rey CC (Rey Central Coherence Index); OA (Object Assembly); Frag. Pic. (Fragmented Pictures Task); SCT (Total Score in Sentence Completion Task); HRT (Total Score in Homograph Reading Task); Time (Time taken in minutes to administer each task); Repeat (Can the task be repeated?); Yes, Yes-2 (have 2 versions of the task), No, ? (unsure if task can be repeated). The effect size in the table represent the mean of the published studies.

*Cohen's *d* effect sizes are understood as follows: 0 to <0.15 – negligible; >0.15–0.40 – small; >0.40–0.75 – medium; >0.75–1.10 – large; >1.10 – huge.

found that weak central coherence is also present in the healthy sisters of those with AN. Using the Group Embedded Figure Test and the Rey-Osterreith Complex figure copy (central coherence index), it was found that like their AN sisters, 30 healthy sisters displayed a more detail focused processing style on both.

Thus weak central coherence appears to be a trait associated with AN. Enhanced detail function is present even in the acute phase of the illness and superiority in this skill is similar in size to that seen in cases of Asperger's Syndrome. Global integration appears to be weakened in the acute phase of the illness and deficits in this are less apparent after recovery. Thus the imbalance between local and global functioning and weak central coherence is most marked during the acute phase. This biomarker may be involved in maintaining maladaptive behaviors so that they are unable to see the "bigger picture" and ignore the severe consequences of applying a detailed thinking style to the laws of thermodynamics has on their health in terms of weight loss.

155.4.4 Social Cognition

Social cognition refers to those complex cognitive processes involved in attuning behavior to that of other people (Adolphs 1999). The study by Gillberg and colleagues suggested that a subgroup of early onset cases of AN have empathy deficits similar to those found in ASD and this was associated with poor outcome in AN (Gillberg et al. 1994). A recent review has summarized the evidence for problems in this area (Zucker et al. 2007). Traits of emotional dysregulation, social inhibition, and compulsivity are found in acute AN and persist with recovery, although to a milder degree (Holliday et al. 2006).

Women with acute AN appear to be impaired in visual and verbal recognition of emotions (Zonnevijlle-Bendek et al. 2002, 2004; Kucharska-Pietura et al. 2004). This contrasts with normal self-reported levels of empathic response (Hambrook et al. 2008). A study in our unit that administered tasks developed in the field of ASD to women with acute AN (e.g., Reading the Mind in the Voice, Films, Eyes) found large effects in all of the task domains suggesting greater difficulties in the acute state relative to a healthy comparison group (see Table 155.5). However, the deficits in the tasks particularly related to theory of mind (voice and film) were not present in people who had recovered from the illness. Our group has found that in the acute illness state, women with AN have an attentional bias to threatening social stimuli using the E-Stroop paradigm. This appears to be present albeit in an attenuated form in people recovered from the illness.

These findings suggest that emotional recognition problems which may be associated with a tendency to avoid threatening stimuli may be trait abnormality in AN whereas poor Theory of Mind is

Table 155.5 Effect sizes (Cohen's *d*) for neuropsychological tasks relating social cognition in AN

Social cognition	Current AN	Time
RMI eyes	1.1	10
RMI voice	0.8	10
RMI film	0.8	10
E-Stroop	1.6	10

RMI (Reading the Mind in the Eyes; Voice and Films); E-Stroop (Emotional Stroop Task); Time (Time taken in minutes to administer each task)

more of a state effect. Poor regulation of emotional and social stimuli possibly contributes to both causal and perpetuating factors. This has implications for the development of novel approaches to treatment.

155.4.5 Genotypes

Cultural, social, and interpersonal elements have been well recognized as having etiological significance in AN. However, increasingly, the pathogenesis of AN is investigated by looking at familial and genetic patterns. Twin studies have estimated the heritability of AN around 56% (Bulik et al. 2006). In general, relatives of those with AN have a tenfold increased risk to develop AN (Strober et al. 2000; Lilenfeld et al. 1998). These results indicate that AN has a genetic component, which makes it reasonable to go one step further and identify genes that might be involved in AN (Table 155.6).

One approach to discover genetic loci are genome-wide studies wherein large regions are mapped which then can be scrutinized further using candidate gene approaches. No previous knowledge on the genes involved in the disorder are required (Winchester and Collier 2003). Linkage studies aim to identify the genomic regions that might harbor predisposing factors for the disorder. For complex disorders such as AN, nonparametric (i.e., model-free) methods are used so that no knowledge on the mode of inheritance is needed. It is assumed that risk alleles and marker alleles will be inherited more frequently in affected relatives than expected by chance alone. The pattern of inheritance is usually compared within families with affected family members (Winchester and Collier 2003). Having identified a region, it is possible to narrow down the search space for potential candidate genes (Bulik et al. 2007). The advantage of genome-wide linkage studies is that genes with a small effect on a trait can be identified and therefore this approach offers a potential tool in investigating genes involved in complex disorders (Winchester and Collier 2003). Grice and colleagues (2002) examined the linkage of the gene coding for serotonin in families wherein two siblings were affected by an eating disorder. They found modest evidence for a linkage at marker D4S2367 and D1S3721 at chromosome 1 in a "pure" AN restricting subsample. Linkage analysis on a sample of binge-purge and restricting AN patients provided evidence for a smaller linkage peak at marker D1S3721 at chromosome 1. However, as acknowledged by the authors, these linkage peaks might also represent false positives, as the genetic makeup of AN might be composed of a large number of interacting

Table 155.6 Methodology to identify genotypes

Methodology for investigating disorder relevant genes	
Approach	Candidate gene studies
	Genome wide studies
Methodology	Linkage mapping
	Association
Types of samples	Family trios
	Case control

Relevant genes can be studied using two main approaches: candidate gene studies and genome wide studies. Within these approaches linkage or association can be studied. Types of sample include family trios, wherein families with one affected member are studied, and case-control studies wherein affected cases and matched controls are used.

loci, with each locus contributing a small effect to susceptibility, which are difficult to localize with linkage analysis (Grice et al. 2002).

In contrast to linkage studies, association studies focus on population frequency of susceptibility genes rather than heritance pattern of markers. Two types of samples are used: case control and family trios. In case control studies, affected individuals are matched and compared to healthy controls. Here, the aim is to examine patterns of differences in allelic frequency with differences in disease frequency. In family trio samples, these measures are compared within one family (i.e., mother, father, and affected child). Genes associated with key putative neuronal pathways have been examined (Bulik et al. 2007). In the following section: serotonin, dopamine, opioid systems, and the brain-derived neurotrophic factor will be discussed.

155.4.6 Serotonin

Chromosome 1 was examined closely by Bergen and colleagues(2003) who focused on region 1p36.3–34.4 and examined genes that were suggested to code for the serotonin 1D receptor. Additional evidence for the implication of a gene coding for serotonin at rs674386 SNP in AN was found (Bergen et al. 2003). Brown and colleagues (2007) reported an association between a gene encoding for HTR1D at marker rs674386 and AN. Moreover, evidence was given for an association between the restricting subtype with marker rs856510 (Brown et al. 2007). The latter results however have to be replicated in an independent sample.

Focusing on the 2A receptor, Gorwood and colleagues (2002) reviewed the evidence for an association between the rs6311 polymorphism of the HTR2A gene. Ricca and colleagues (Ricca et al. 2002) examined the −1438 G/A polymorphism, which has been located in the regions of the 5-HT2A receptor gene and has been linked to AN. In particular, an over-representation of the A allele and the AA genotypes have been documented in ANR (and BN) patients as compared to healthy controls. Interestingly, this pattern of results did not emerge in AN-BP patients who showed a similar allelic frequency as the control group (Ricca et al. 2002). Devlin and colleagues (2002) also focused on the HTR2A gene in AN patients and compared linkage of this gene in 196 families with an individual suffering from AN. This group has identified 3 regions on chromosomes 1, 2, and 12, suggestive of a linkage (markers D1S1660, DS1790 and D13S894).

The general picture with genes involved in serotonin functioning linked to AN is unclear. Overall, studies investigating genes involved in the serotonin system have been hampered by low power and a lack of replication in independent samples. Therefore, results should be interpreted with caution and replication in larger, independent samples is awaited.

155.4.7 Dopamine

The genetic basis underlying dopamine dysfunction has been examined. Gabrovsek and colleagues (2004), for instance, looked at a gene that encodes catechol-*O*-methlytransferase (COMT), which metabolizes more than 60% of dopamine especially in frontal areas. Results yielded no evidence for an association between the Val158 allele of the COMT gene and AN. The D2 receptor has been implicated in altered reward, affect, decision-making, executive control, stereotypic motor activity and decreased food ingestion in AN patients (Kaye 2008). An association was found for the rs1800497

and the rs6278 polymorphism, both polymorphisms in the gene encoding for D2 receptor, and the binge-purge subtype of AN (Bergen et al. 2005). Overall, evidence for genes involved in encoding the dopamine system involved in AN is sparse and further methodologically sound evidence is needed to draw conclusions.

155.4.8 Opioids

Bergen and colleagues (2003) examined delta opioid receptor loci in the 1p33–36 region and reported evidence for an association at 3 SNPs (8214T4C, 23340A4G, 47821A4G) for AN patients. However, as acknowledged by the authors, replications in a larger sample are needed as the current sample ($N = 191$) was underpowered. Further examination of the implication of the gene encoding for OPRD1 was added by Brown and colleagues (2007) who examined the impact of the two candidate genes previously identified by Bergen and colleagues (2003) in a case control study of AN patients. Using different SNPs than Bergen and colleagues (2003) this group found evidence for marker rs56356 with AN. Further analyses revealed a higher frequency of the C,T genotype in AN-R as compared to AN-BP patients. Patients suffering from the binge-eating/purging subtype presented with this genotype at a lower rate than controls. It was therefore tentatively suggested that this locus not only compromises susceptibility towards AN but might differentiate even between subtypes (Brown et al. 2007). Yet, it has to be kept in mind that power in this study varied between 0.63 and 0.99.

155.4.9 Brain-derived Neurotrophic Factor

Evidence for a susceptibility gene for brain-derived neurotrophic factor (BDNF) related to AN has been found. It has been suggested that this gene predisposes to AN through its impact on affective symptoms (Ribases et al. 2005). Associations have been found between the Met 66 allele, AN-R, and minimum BMI and replicated in 359 family trios.

155.5 Conclusion

Progress towards revealing potential biomarkers in AN has considerably advanced in the last decade. The search for potential genotypes, biomarkers, and endophenotypes in AN has revealed a number of features that are present in the acute state, some of which persist into recovery. The main findings in this direction highlight the involvement of altered neurotransmitters systems particularly those relating to serotonin, dopamine, BDNF, and the opiates. In addition, cognitive information processing anomalies such as weak set-shifting and central coherence may be biomarkers. The talent for perceiving detail forms part of the endophenotype in some cases of AN. Problems with executive function may arise as a secondary consequence of the illness. Difficulties in emotional recognition and avoidance of threat may be part of the trait biomarkers associated with anxiety in some cases of anorexia nervosa. Problems with social cognition with impairments in the theory of mind tasks may arise as a consequence of the illness. The trait biomarkers may be

part of the causal process that leads to the development of an eating disorder. Also in conjunction with state related markers these can form part of the maintaining processes that cause eating disorders to be stuck and less easy to recover from the longer they persist. Thus, biomarkers have implications for the prognosis of the illness. Furthermore biomarkers can inform treatment strategies (emotional, social, and cognitive remediation skills) that may reduce the duration of the illness and improve outcome. It is hoped that a deeper understanding of AN based on biomarkers and the search for endophenotypes will improve awareness, early intervention, and make for better prognosis in the long term.

155.6 Applications to Other Areas of Health and Disease

Food is one of the several natural rewards amongst others, such as sex, fluid, and social affiliation. There is evidence that the brain systems which modulate these natural rewards are also used in the processing of other rewards, such as money and material assets. Interactions between these different forms of reward can occur. Therefore, investigation into the addictive nature of extreme food restriction may inform research into other addictive behaviors.

The reward system is comprised of dopamine, opioid, and cannabinoid signaling (Cota et al. 2006). Extreme food restriction or dieting can disrupt the systems that underlie appetite motivation, increasing the reinforcing aspects of food (Epstein et al. 2003). Furthermore overactivation of the homeostatic system by extreme hunger may result in problems with regulating eating such as binge eating, emotional eating, and reduction in metabolic rate, making weight gain more likely (Lowe and Levine 2005). It may be argued that a greater understanding of AN etiology in terms of a disrupted reward system may facilitate research into the binge eating seen in bulimia nervosa and obesity.

Substance abuse disorders may also be informed by research into the reward system since this may rely on the same neuronal pathways as eating (Cota et al. 2006). Chronic food deprivation increases reward to all addictive drugs (Carr 2002). Furthermore, both eating and drugs such as cocaine and amphetamines have the same effect of increasing dopamine in the reward system (Hernandez and Hoebel 1988).

Current research findings on genotypes and phenotypes of AN can be applied to other areas of health and disease. The aforementioned serotonin and dopamine systems are known to be involved in other mental disorders such as depression and schizophrenia. Furthermore, genomic variation studies which reveal risk alleles for AN might inform other pathologies that are comorbid with AN, such as depression, anxiety disorders, and in particular obsessive compulsive disorder.

As yet clear recommendations for the effective treatment of AN have not been established. The National Institute for Clinical Excellence (NICE) guidelines state that AN patients should be treated on an outpatients basis and emphasize the combination of re-feeding with psychosocial interventions in AN, but do not specify a treatment for AN. Gaining more knowledge of the neurobiological mechanisms and genotypes is essential when designing new therapies for AN and all types of eating disorders. Treatment which addresses the stable traits of AN such as weak set-shifting and central coherence have been pioneered by our group. Cognitive remediation therapy has been developed as a pre-therapy intervention for in-patients to moderate information processing biases by strengthening flexibility in daily activities and eating rituals. This has been shown to improve the outcome of subsequent therapy interventions (Tchanturia et al. 2006; Davies and Tchanturia 2005).

Summary Points

- Diagnostic difficulties: Given the difficulties with diagnostic categories (Anderluh et al. 2009) attention should be directed toward identifying core stable traits. This will facilitate diagnosis, the creation of more accurate models of AN etiology, and enhance the search for more effective treatments.
- Biomarkers and endophenotypes: Biomarkers are traits associated with the disorder, but not part of their visible presentation. They can be state- or trait-related and may be used for screening, diagnostic, prognostic, or stratification markers. One valuable type is that of an endophenotype; a heritable trait biomarker.
- Serotonin, dopamine, and neuropsychological traits such as weak central coherence and set-shifting have been researched as potential biomarkers and endophenotypes of AN.
- Genotypes are defined as the genetic makeup of an individual. It can be described in terms of the combination of alleles at a particular locus. The locus is determined using association or linkage studies.
- Several loci have been identified and relate to serotonergic, dopaminergic, opioid, and BDNF systems. However, further research is awaited since current studies are subject to methodological limitations.

Definitions and Explanations

Anorexia nervosa: The term derives from the Greek word an-orexis which can be translated as "without appetite." The term "nervosa" is of Latin origin and indicates that the lack of food intake is due to a nervous constitution. Anorexia nervosa is one type of eating disorder that is a psychiatric illness. Individuals with this diagnosis control their body weight and often present with severe weight loss, an intense fear of weight gain, distortion of body image, and amenorrhea.

Genotypes: They contain an individual's genetic information in the form of a pair of genes.

Endophenotype: A valuable kind of biomarker is that of an endophenotype; a heritable trait biomarker that falls on the pathway between behavior and biology (phenotype and genotype). Gottesman and Gould (2003) have defined specific endophenotype criteria which include: (1) association with the illness in the population, (2) heritability, (3) state-independence, (4) cosegregation with the illness in families and (5) presence in unaffected relatives at a higher level than in the general population.

Biomarkers: They are underlying cognitive or behavioral traits associated with a disorder, but not part of their visible presentation. They can be state- or trait-related, and have a number of different applications such as being antecedent, screening, diagnostic, prognostic, or stratification markers (Ritsner and Gottesman 2009). The term biomarker is used when the trait does not fulfill the criteria of genetic underpinnings.

Phenotypes: They are the observable symptoms of a psychiatric illness, such as behavior. The AN phenotype involves a range of symptoms characterized by a disturbance of body (or self) image associated with extreme behaviors to control weight (e.g., fasting) and underweight BMI.

Key Facts of Diagnostic Difficulties in Anorexia Nervosa

1. The nosological status of the current DSM IV diagnostic criteria is suggested to lack an empirical basis. Some patients do not present with all the symptoms required for a clinical AN diagnosis. Furthermore, a substantive number of AN patients switch between diagnostic categories over the course of the illness.
2. Intermediate phenotypes such as biomarkers and endophenotypes may represent more stable characteristics of AN than illness phenotypes.
3. The search for intermediate phenotypes may lead to a more biologically based system of classification and a more accurate understanding of causation, pathophysiology, prognosis, and treatment.

Key Features of Endophenotypes and Biomarkers

1. Biomarkers are underlying cognitive or behavioral traits that are associated with a disorder, but not part of their visible presentation.
2. One valuable kind of biomarker is that of an endophenotype.
3. Gottesman and Gould (2003) use the term "endophenotype" when there are some signs of heritability, and biomarkers when the trait does not fulfill the criteria of genetic underpinnings.

Key Facts of Genotypes

1. To identify genetic loci involved in a disorder, linkage and association approaches can be used.
2. A large number of genetic loci are supposed to be involved in AN, each of which is suggested to express a small effect in the occurrence of the disorder.
3. Genetic loci relating to serotonergic, dopaminergic, and opioid systems and BDNF have been investigated in AN.
4. Research into AN genotypes should address the methodological limitations, such as population stratification and low sample sizes, which may distort results.

References

Adolphs R. Trends Cogn Sci. 1999;3:469–79.
American Psychiatric Association. Diagnostic and statistical manual of mental disorders (4th ed., text rev.). Washington, DC: Author 2000.
Anderluh M, Tchanturia K, Rabe-Hesketh S, Al E. Am J Psychiatry. 2003;160:242–7.
Anderluh M, Tchanturia K, Rabe-Hesketh S, Collier D, Teasure J. Psychol Med. 2009;39:105–14.
Bailer U, Frank G, Henry S, Al E. Arch Gen Psychiatry. 2005a;62:1032–41.

Bailer UF, Frank GK, Henry SE, Al E. Psychopharmacology (Berlin). 2005b;195:315–24.

Bailer UF, Price JC, Meltzer CC, Al E. Neuropsychopharmacology. 2004;29:1143–55.

Baron-Cohen S, Hammer J. J Cogn Neurosci. 1997;9:548–54.

Bergen AW, Van Den Bree MBM, Yeager M, Welch R, Ganjei JK, Haque K, Bacanu S, Berrettini WH, Grice DE, Goldman D, Bulik CM, Klump K, Fichter M, Halmi K, Kaplan A, Strober M, Treasure J, Woodside B, Kaye WH. Mol Psychiatry. 2003;8:397–406.

Bergen AW, Yeager M, Welch RA, Haque K, Ganjei JK, Van Den Bree MB, Mazzanti C, Nardi I, Fichter MM, Halmi KA, Kaplan AS, Strober M, Treasure J, Woodside DB, Bulik CM, Bacanu SA, Devlin B, Berrettini WH, Goldman D, Kaye WH. Neuropsychopharmacology. 2005;30:1703–10.

Berkman ND, Lohr KN, Bulik CM. Int J Eat Disord. 2007;40:293–309.

Birmingham CL, Su J, Hlynsky JA, Goldner EM, Gao M. Int J Eat Disord. 2005;38:143–6.

Brown KM, Bujac SR, Mann ET, Campbell DA, Stubbins MJ, Blundell JE. Biol Psychiatry. 2007;61:367–73.

Bulik CM, Slof-Op't Landt MC, Van Furth EF, Sullivan PF. Annu Rev Nutr. 2007;27:263–75.

Bulik CM, Sullivan PF, Tozzi F, Furberg H, Lichtenstein P, Pedersen NL. Arch Gen Psychiatry. 2006;63:305–12.

Byford S, Barrett B, Roberts C, Clark A, Edwards V, Smethurst N, Gowers SG. Br J Psychiatry. 2007;191:436–40.

Carr KD. Physiol Behav. 2002;76:353–64.

Castro-Fornieles J, Bargallo N, Lazaro L, EA. J Psychiatr Res. 2009;43:331–40. Epub 2008.

Cota D, Tschop MH, Horvath TL, Levine AS. Brain Res Rev. 2006;51:85–107.

Davies H, Tchanturia K. Eur Eat Disord Rev. 2005;13:311–6.

Devlin B, Bacanu SA, Klump KL, Bulik CM, Fichter MM, Halmi KA, Kaplan AS, Strober M, Treasure J, Woodside DB, Berrettini WH, Kaye WH. Hum Mol Genet. 2002;11:689–96.

Dolan RJ, Mitchell J, Wakeling A. Psychol Med. 1988;18:349–53.

Eddy KT, Dorer DL, Franko DL, Tahilani K, Thompson-Brenner H, Herzog DB. Am J Psychiatry. 2008;165:245–50.

Epstein LH, Truesdale R, Wojcik A, Paluch RA, Raynor HA. Physiol Behav. 2003;78:221–7.

Frank G, Bailer U, Henry S, Al E. Biol Psychiatry. 2005;58:908–12.

Frith U. Autism: explaining the enigma, Cambridge: Blackwell Science; 1989.

Gabrovsek M, Brecelj-Anderluh M, Bellodi L, Cellini E, Di Bella D, Estivill X, Fernandez-Aranda F, Freeman B, Geller F, Gratacos M, Haigh R, Hebebrand J, Hinney A, Holliday J, Hu X, Karwautz A, Nacmias B, Ribases M, Remschmidt H, Komel R, Sorbi S, Tomori M, Treasure J, Wagner G, Zhao J, Collier DA. Am J Med Genet Part B Neuropsychiatr Genet. 2004;124B:68–72.

Gagel O, Magersucht. vol. 5. Berlin: Springer. 1953.

Galusca B, Costes N, Zito NG, Peyron R, Bossu C, Lang F, Le Bars D, Estour B. Biol Psychiatry. 2008;64:1009–13.

Germain N, Galusca B, Le Roux CW, Bossu C, Ghatei MA, Lang F, Bloom SR, Estour B. Am J Clin Nutr. 2007;85:967–71.

Gillberg C, Rastam M, Gillberg C. Am Acad Child Adolesc Psychiatry. 1994;33:729–39.

Gillberg I, Rastam M, Wentz E, Al E. J Clin Exp Neuropsychol. 2007;29:170–8.

Gillberg IC, Gillberg C, Rastam M, Johansson M. Compr Psychiatry. 1996;37:23–30.

Glass MJ, Grace M, Cleary JP, Billington CJ, Levine AS. Am J Physiol Regul Integr Comp Physiol. 1996;271:217–21.

Gorwood P, Ades J, Bellodi L, Cellini E, Collier DA, Di Bella D, Di Bernardo M, Estivill X, Fernandez-Aranda F, Gratacos M, Hebebrand J, Hinney A, Hu X, Karwautz A, Kipman A, Mouren-Simeoni MC, Nacmias B, Ribases M, Remschmidt H, Ricca V, Rotella CM, Sorbi S, Treasure J. Mol Psychiatry. 2002;7:90–4.

Gottesman IL, Gould TD. Am J Psychiatry. 2003;160:636–45.

Grice DE, Halmi KA, Fichter MM, Strober M, Woodside DB, Treasure JT, Kaplan AS, Magistretti PJ, Goldman D, Bulik CM, Kaye WH, Berrettini WH. Am J Hum Genet. 2002;70:787–92.

Hambrook D, Tchanturia K, Schmidt U, Al E. Br J Clin Psychol. 2008;47:335–9.

Happe F, Briskman J, Frith U. J Child Psychol Psychiatry Allied Disciplines. 2001;42:299–307.

Happe F, Frith U. J Autism Dev Disord. 2006;36:5–25.

Happe FG, Booth RD. Q J Exp Psychol. 2008;61:50–63.

Harbottle EJ, Birmingham CL, Sayani F. Eat Weight Disord. 2008;13:e32–4.

Hebebrand J, Casper R, Treasure J, Schweiger U. J Neural Transm. 2004;111:827–40.

Hernandez L, Hoebel BG. Life Sci. 1988;42:1705–12.

Hjern A, Lindberg L, Lindblad F. Br J Psychiatry. 2006;189:428–32.

Hoek HW, Van Hoeken D. Int J Eat Disord. 2003;34:383–96.

Holliday J, Tchanturia K, Landau S, Collier DA, Treasure J. Am J Psychiatry. 2005;162:2269–75.

Holliday J, Uher R, Landau S, Collier D, Treasure J. J Pers Disord. 2006;20:417–30.

Hudson JI, Hiripi E, Pope HG, Jr., Kessler RC. Biol Psychiatry. 2007;61:348–58.

Jones BP, Duncan CC, Brouwers P, Mirsky AF. J Clin Exp Neuropsychol. 1991;13:711–28.

Kaye W. Physiol Behav. 2008;94:121–35.

Kaye W, Strober M, Jimerson D. The neurobiology of eating disorders. In: Charney, DS, Nestler EJ, editors. The neurobiology of mental illness. New York: Oxford Press; 2004.

Kaye WH, Pickar D, Naber D, Ebert MH. Am J Psychiatry. 1982;139:643–5.

Krieg JC, Lauer C, Leinsinger G, Al E. Biol Psychiatry. 1989;25:1041–8.

Kucharska-Pietura K, Nikolaou V, Masiak M, Al E. Int J Eat Disord. 2004;35:42–7.

Lilenfeld LR, Kaye WH, Greeno CG, Merikangas KR, Plotnicov K, Pollice C, Rao R, Strober M, Bulik CM, Nagy L. Arch Gen Psychiatry. 1998;55:603–10.

Liu P, Jiang Y, Chen WJ, Chang C, Lee T, Sun HS, Chuang L. Twin Res Hum Genet. 2008;11:495–504.

Lopez C, Tchanturia K, Stahl D, Al E. Psychol Med; 2008a;37:1075–84.

Lopez C, Tchanturia K, Stahl D, Al E. Int J Eat Disord. 2008b;41:143–52.

Lopez C, Tchanturia K, Stahl D, Al E. J Clin Exp Neuropsychol. 2008c;4:1–9.

Lowe B, Zipfel S, Buchholz C, Dupont Y, Reas DL, Herzog W. Psychol Med. 2001;31:881–90.

Lowe ML, Levine AS. Obes Res. 2005;13:797–806.

Martin F. Acta Neurol Belg. 1958;52:816–30.

Mathers C, Vos T, Stevenson C. MJA. 1999;172:592–6.

Mccormick LM, Keel PK, Brumm MC, Al E. Int J Eat Disord. 2008;41:602–10.

Miyake A, Friedman NP, Emerson MJ, Witzki AH, Howerter A. Cogn Psychol. 2000;41:49–100.

Mond JM, Hay PJ, Rodgers B, Owen C, Beumont PJ. Qual Life Res. 2005;14:171–8.

Monteleone P, Tortorella A, Martiadis V, Serritella C, Fuschino A, Maj M. Psychosom Med. 2004;66:744–8.

Nakazato M, Hashimoto K, Yoshimura K, Haluzik T, Shimizu E, Iyo M. Prog Neuropsychopharmacol Biol Psychiatry. 2006;30:1117–21.

Palazidou E, Robinson P, Lishman WA. Psychol Med. 1990;20:521–7.

Papadopoulos FC, Ekbom A, Brandt L, Ekselius L. Br J Psychiatry. 2009;194:10–7.

Pelleymounter MA, Culbert MJ, Wellman CL. Exp Neurol. 1995;131:229–38.

Rastam M, Gillberg C, Wentz E. Eur Child Adolesc Psychiatry. 2003;12 (Suppl 1):I78–90.

Ribases M, Gratacos M, Fernandez-Aranda F, Bellodi L, Boni C, Anderluh M, Cavallini MC, Cellini E, Di Bella D, Erzegovesi S, Foulon C, Gabrovsek M, Gorwood P, Hebebrand J, Hinney A, Holliday J, Hu X, Karwautz A, Kipman A, Komel R, Nacmias B, Remschmidt H, Ricca V, Sorbi S, Tomori M, Wagner G, Treasure J, Collier DA, Estivill X. Eur J Hum Genet. 2005;13:428–34.

Ricca V, Nacmias B, Cellini E, Di Bernardo M, Rotella CM, Sorbi S. Neurosci Lett. 2002;323:105–8.

Ritsner MS, Gottesman IL. Where do we stand in the quest for Neuropsychiatric Biomarkers and Endophenotypes and what next? In Ritsner MS, editor. The handbook of neuropsychiatric biomarkers, endophenotypes and genes. Berlin: Springer; 2009.

Roberts ME, Tchanturia K, Stahl D, Al E. Psychol Med. 2007;37:1075–84.

Roser W, Bubl R, Buergin D, Al E. Int J Eat Disord. 1999;26:119–36.

Small DM, Jones-Gotman M, Daghera A. NeuroImage. 2003;19:1709–15.

Smalley S, Asarnov R. J Autism Dev Disord. 1990;20:271–8.

Southgate L, Tchanturia K, Treasure J. Psychiatry Res. 2008;160:221–7.

Strober M, Freeman R, Lampert C, Diamond J, Kaye W. Am J Psychiatry. 2000;157:393–401.

Strober M, Freeman R, Morrell W. Int J Eat Disord. 1999;25:135–42.

Su JC, Birmingham CL. Eat Weight Disord. 2003;8:76–9.

Takahashi M, Tanaka K, Miyaoka H. Psychiatry Clin Neurosci. 2006;60:211–8.

Tchanturia K, Morris R, Anderluh M, Al E. J Psychiatr Res. 2004;38:545–52.

Tchanturia K, Morris R, Surguladze S, Al E. Eat Weight Disord. 2002;7:312–5.

Tchanturia K, Serpell L, Troop N, Al E. J Behav Ther Exp Psychiatry. 2001;32:107–15.

Tchanturia K, Whitney J, Treasure J. Weight Eat Disord. 2006;11:112–7.

Tiller JM, Sloane G, Schmidt U, Troop N, Power M, Treasure JL. Int J Eat Disord. 1997;21:31–8.

Treasure J, Lopez C, Roberts M. Pediatric Health. 2007;1:171–81.

van den Eynde F, Treasure J. Child Adolesc Psychiatric Clin N Am. 2008;18:95–115.

Volkow ND, Wang G-J, Fowler JS, Logan J, JayneM, Franceschi D, Wong C, Gatley SJ, Gifford AN, Ding Y-S, Pappas N. Synapse. 2002;44:175–80.

Wagner A, Aizenstein H, Venkatraman VK, Fudge J, May C, Mazurkewicz L, Frank GK, Bailer U, Fischer L, Nguyen L, Carter C, Putnam K, Kaye WH. Am J Psychiatry. 2007;164:1842–9.

Wentz E, Gillberg C, Anckarsater H, Gillberg C, Rastam M. Br J Psychiatry. 2009;194:168–74.

Winchester E, Collier D. Genetic aetiology of eating disorders and obesity. In Treasure J, Schmidt U, Van Furth E, editors. Handbook of eating disorders. Chichester: John Wiley & Sons; 2003.

Zonnevijlle-Bendek M, Van Goozen S, Cohen-Kettenis P, Al E. Eur Child Adolesc Psychiatry. 2002;11:38–42.

Zonnevijlle-Bendek MJ, Van Goozen S, Cohen-Kettenis P, Al E. Depress Anxiety. 2004;19:35–42.

Zucker NL, Losh M, Bulik CM, Labar KS, Piven J, Pelphrey KA. Psychol Bull. 2007;133:976–1006.

Chapter 156
Metabolic Consequences in Anorexia Nervosa

Daniel Rigaud and Marie-Claude Brindisi

Abbreviations

ACTH	Adrenocorticotropic hormone
AN	Anorexia nervosa
BMI	Body mass index
CETP	Cholesterol ester transfer protein
DIT	Diet-induced thermogenesis
ED	Eating disorder
EE	Energy expenditure
EEPA	Energy expenditure linked to physical activity
EETR	Energy expended for thermoregulation
FFM	Fat free mass
HDL-C	High density lipoprotein cholesterol
IGF1	Insulin like growth factor 1
LDL-C	Low density lipoprotein cholesterol
REE	Resting energy expenditure
TSH	Thyroid stimulating hormone
VLDL-C	Very low density lipoprotein cholesterol

156.1 Introduction

Anorexia nervosa (AN) is a chronic disease which affects eating behavior and has severe health consequences (Rigaud 2003). It is the psychiatric disease with the highest mortality rate in such young women (15–35 years old). It is the rarest, but the most severe eating disorder (ED). AN is a complex disease that includes mental, genetic, behavioral, and somatic factors. Metabolic and energetic adjustments take place in the wake of the restrictive diet and malnutrition, and the mechanisms involved in these adjustments are beginning to be understood. In this chapter, impact on energy of AN will be developed. All the components of the energy expenditure (EE) will be detailed: resting energy

D. Rigaud (✉)
Department of Endocrinology and Nutrition, CHU Le Bocage
(Dijon University Hospital), BP 77908, 21079 Dijon Cedex, France
e-mail: daniel.rigaud@chu-dijon.fr

expenditure (REE); diet-induced thermogenesis (DIT); EE linked to physical activity; thermoregulation. Then, we will pay attention to the metabolism of the different energetic substrates (protein, carbohydrates, lipids) in AN. The evolution of the body mass will be detailed, as will the physical activity and other abnormal behaviors (smoking, obsessive compulsive disorder, compulsive food intake, and bulimic crises) observed in AN. Then, we will detail the hormonal changes due to ED.

Anorexia nervosa is associated with a weight loss of more than 15% of previous weight, low weight (body mass index or BMI < 18.5 kg/m^2), impaired body image, amenorrhea, and, above all, an intense fear of gaining weight (Rigaud 2003). More than 90% of the patients see themselves as fat, even though they know they are thin. In AN, there is a voluntary restriction in fat and protein intake (Rigaud 2003). In most of the chronic cases, it is not true anorexia, i.e. a decrease in hunger feeling. On the contrary, there is a strong will to decrease food consumption because of an overpowering need to slim. In AN, the fear of gaining weight, the fear of not being able to stop the increase in body weight, and the fear of eating too much are foremost in the minds of patients.

Two clinical types of AN are described (Rigaud 2003):one is called the restrictive type and the other the binge eating type with vomiting. In the restrictive type, patients lose weight by reducing food intake and, in 50–60% of the cases, by developing hyperactivity. In the second form, patients can't bear losing control, and because they are afraid of gaining weight, they cause themselves to vomit. If they cannot vomit or lose enough weight (5–10% of cases), they use laxatives and diuretic drugs. The binge-eating/purging type represents 30–40% of AN.

Females account for 95% of cases of AN patients, of whom 75–80% are under 25 years old and 20–25% are 20–30 years old (Rigaud 2003).

Anxiety is frequent in AN. In more than 60–70% of the cases, anxiety contributes to the evolution of the disease. In around one patient in five, anxiety is a pre-existing trait of the ED. Finally, a depressive state is often seen: in one case in seven, a depressive state precedes AN; and in one case in four, a depressive state is the price to pay for going to recovery.

156.1.1 Impact on Energy: Energy Expenditure (EE) *(Table 156.1)*

Two periods are seen in AN: A restrictive period (fasting state) when high energy foods are low or absent from the patient's diet; a refeeding and/or binge-eating period, where an excessive increase in food consumption is noted, either related to binge eating episodes and/or to hypercaloric diet medically prescribed. In terms of energy metabolism, these two periods are associated with very different profiles in the four components of EE (Rigaud and Melchior 1992): REE, DIT, EE related to physical activity, and thermoregulation.

1. REE is low during the fasting state (Melchior et al. 1989; Vaisman et al. 1991; Obarzanek et al. 1994; Platte et al. 1994; Scalfi et al. 2001; Forman-Hoffman et al. 2006; Konrad et al. 2007). It is around 80–88% of normal levels when the BMI is between 16 and 18 kg/m^2, and it can be around 60–65% of normal levels if the BMI is under 12 kg/m^2. In AN, the ratio of REE to lean mass is approximately 7–14% lower (extreme values, in 87 patients) than in same-age, same-sex controls with the same lean body mass (Van Wymelbeke et al. 2004). During this chronic fasting state, the calculation of REE is as follows: weight (kg) × 0.90 (lean mass) × 28 kcal/day. When the BMI is under 10 kg/m^2 (ultimate phase of the disease), the REE can increase, almost exclusively by the oxidation of the proteins, because of a lack of usable fatty substances (Rigaud et al. 2000). An increase in REE follows the start of refeeding: An increase in REE from 12% to 20% (Rigaud et al. 2000; Van Wymelbeke et al. 2004) within the first days of starting renutrition is seen, long

Table 156.1   Key facts of energy expenditure

Energy expenditure	Is the amount of energy, measured in calories, that a person uses (e.g. during a particular activity). The energy expenditure (EE) of a man or woman over a whole day is often divided into different components, which can be individually determined. These are: resting energy expenditure (REE), diet-induced thermogenesis (DIT), physical activity (PA), and thermoregulation
Resting energy expenditure	Is the minimum amount of energy that a body requires when lying in physiological and mental rest
Diet-induced thermogenesis (DIT):	Also called postprandial thermogenesis or the thermic effect of food. This is the amount of energy utilised in the digestion, absorption, and transportation of nutrients.
Energy expenditure linked to physical activity (PA):	Is the most variable component of EE in humans. It includes the additional EE above resting metabolic rate and DIT due to muscular activity and comprises minor physical movement (such as shivering and fidgeting) as well as purposeful gross muscular work or physical exercise.
Thermoregulation	Is the ability of an organism to keep its body temperature within certain boundaries.

Key facts of EE with its different components and their definitions: Resting energy expenditure, diet-induced thermogenesis (DIT), EE linked to physical activity (PA), and thermoregulation
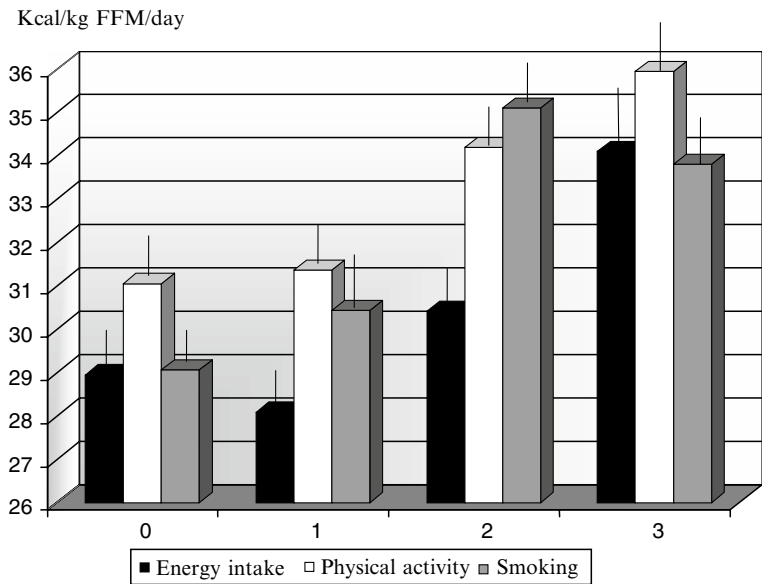
Fig. 156.1   Resting energy expenditure (REE) and level of energy intake, physical activity, and smoking. This figure shows the increase in REE according to the levels of energy intake (food intake), physical activity, and smoking behavior. When there is an increase in these factors, the REE increases too. *FFM* fat-free mass
■ *For energy intake*: "0" = before renutrition (energy intake = 830 kcal/day), "1" to "3" = during refeeding; "1" = for patients having energy intake between 1.1 and 1.3 × REE; "2" = for patients having energy intake between 1.3 and 1.8 × REE; "3" = for patients having energy intake higher than 1.8 × REE
□ *For physical activity*: "0" = none; "1" = 1 to 2 h/day; "2" = 2 to 3 h/day; "3" = >3 h/day
▨ *For smoking*: "0" = none; "1" = 1 to 5 cig/day; "2" = 6 to 10 cig/day; "3" = >10 cig/day

time before any significant increase in fat-free mass (Obarzanek et al. 1994; Platte et al. 1994; Van Wymelbeke et al. 2004; Winter et al. 2005; Konrad et al. 2007). Four factors were described to be associated with this increase in REE: smoking, having a high level of physical hyperactivity,

Fig. 156.2 Resting energy expenditure (REE) and levels of anxiety and depressed state. Level of anxiety and depressive state: 0 = none; 1 = a little; 2 = much; 3 = very much. *FFM* fat-free mass. This figure shows that when anxiety increases, there is an increase in REE, unlike depression. Indeed, when depressive state increases, we can observe a decrease in REE
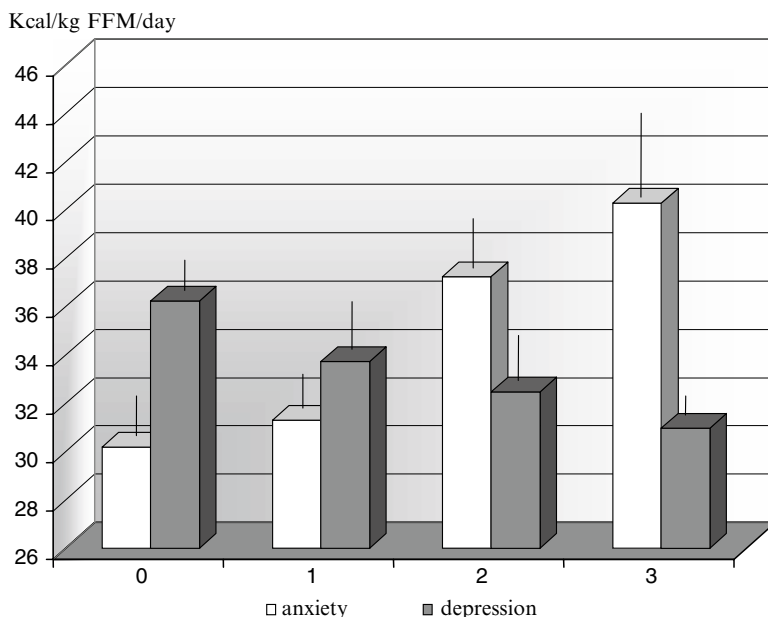
anxiety, and food intake. Conversely, depression and low food intake in the previous days decrease it (Figs. 156.1 and 156.2).

2. Diet-induced thermogenesis: A high level of DIT is observed before renutrition, compared to normal subjects (Moukaddem et al. 1997). This DIT still increases at the eighth day of renutrition, before any increase in lean body mass. In a double-blind experimental study, a 300- or 700-kcal load was given through a gastric tube. Before renutrition, DIT accounted for 36% of the 300 kcal and 26% of the 700 kcal. At the eighth day of renutrition, DIT accounted for 52% and 39% of the 300 and 700 kcal, respectively (for normal females: it was 14% and 16% for 300- and 700-kcal-loads, respectively). This increase correlates with different factors: the energy content of the meal, the fear of gaining weight, anxiety, and digestion disorders (Rigaud et al. 2007). This profile persists during renutrition; it disappears once normal weight has been reached and anxiety has disappeared. The increase in DIT during renutrition is due to the increase in food intake, and, first of all, protein intake (Fig. 156.3).

3. The EE linked to physical activity is low before renutrition (fasting period). It increases rapidly during renutrition, but it is no higher than in normal subjects with the same fat-free mass and the same level of physical activity (Rigaud et al. 1997). In fact, the increase is due to the increase in physical activity during renutrition (Kaye et al. 1988; Casper et al. 1991; Birmingham et al. 2005).Two causes explain this, a good and a bad one. The good one is that, when a severely malnourished patient is on refeeding program, his activity increases, although it was very low before refeeding. Such a behavior is seen, for example, in patients suffering from cystic fibrosis. The bad reason in AN patients is excessive exercising. Indeed, because of the fear of gaining weight, some patients engage in physical hyperactivity, and thus, largely increase their EE. This explains, in part, the slow rate of weight gain in AN (Walker et al. 1979; Dempsey et al. 1984; Leonard et al. 1996; Bossu et al. 2007). Moreover, obsessive compulsive disorders may increase EE significantly.
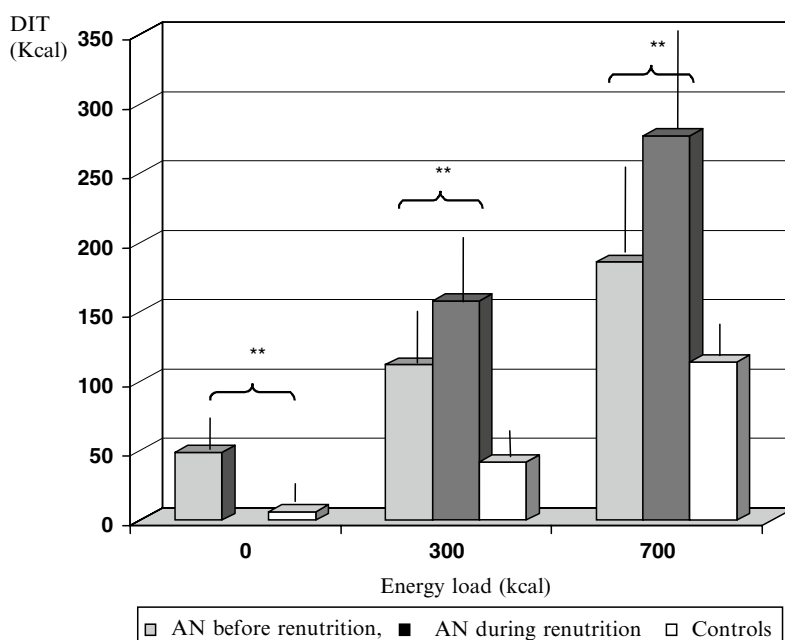
Fig. 156.3 Diet-induced thermogenesis (DIT) and energy load before and during renutrition. This study shows the increase in diet-induced thermogenesis according to the energy load before and during renutrition in 15 AN patients vs. 15 age-matched healthy women (controls). The period of renutrition corresponds to the eighth day of a renutrition program with input > 2,200 kcal/day. Loads are given in double blind manner by a nasogastric tube (0, 300 and 700 kcal in random order). This figure shows that diet-induced thermogenesis increases with the level of intragastric load

4. Energy expended for thermoregulation (EETR): it is at a low level before renutrition (fasting phase), but it increases rapidly with renutrition. Two causes explain this: the increase in thyroid hormone secretion (free T3 and T4) as soon as food intake is higher than energy needs. The increase in plasma T3 and T4 levels are noted only after the third week of renutrition. But the increase in secretion probably starts earlier, and could be responsible for the increase in REE (Onur et al. 2005). The second reason is that the body cannot store the energy (because of a lack of adipose tissue) when the fat mass is too low. This problem disappears during renutrition, well before a normal weight is reached.

156.2 Metabolism of Energetic Substrates

1. Protein metabolism: during the fasting period, a deep decrease in protein catabolism is observed, with very low nitrogen and urea 24-h urinary outputs: in 118 AN patients with a BMI of 13.4 ± 1.5 kg/m^2, the urinary nitrogen loss was 4.9 ± 0.6 g/24 h and the fecal nitrogen loss was 0.29 ± 0.6 g/24 h. This decrease in catabolism is an adaptive response to malnutrition and is due to the decrease in food intake and in hepatic and muscle protein synthesis. It does not exist during renutrition and recovery (Gniuli et al. 2001). This very low catabolism explains why markers of nutritional protein synthesized in the liver remain at a normal level for a long time (until a BMI of 12 kg/m^2 has been reached). In our study (Rigaud et al. 1989), patients with decreased plasma concentrations

of albumin, pre-albumin (transthyretin) and transferrin were AN patients with a BMI below 12 kg/m², or with an associated infectious or inflammatory disease. Moreover, the amino-acids from muscle catabolism might be used for the hepatic synthesis. Indeed, in AN, muscle mass decreases as quickly as body weight (see below).

2. Metabolism of carbohydrates: during the fasting period, low serum glucose, insulin, and C peptide levels are observed. Hypoglycemia (< 3.6 mmol/L) is found in 28% of AN patients (cohort of 487 patients hospitalized in our nutrition department, unpublished data). At the beginning of renutrition, insulin sensitivity, measured by the glycemia/insulinemia ratio is nearly always high. A decrease in fasting and postprandial serum glucose level can be observed during the first 2 weeks of renutrition. However, insulin resistance has been found during renutrition, when intakes are higher than energy needs. After a glucose load, the area under the insulin curve was reduced (3.2 ± 0.6 nmol/L/5 h in 14 AN patients and 49.6 ± 2.7 nmol/l/5 h in 12 normal patients), glucose oxidation was increased (646 ± 84 μmol/L/min vs. 368 ± 62 μmol/L/min in normal subjects), and lipid oxidation was decreased (16 ± 34 μmol/L/min, vs. 351 ± 57 μmol/L/min) (as measured by calorimetry and urinary nitrogen). Gniuli et al. found similar results (2001). This abnormal profile disappears with renutrition, well before the recovery of a normal weight.

3. Plasma lipids and lipoprotein metabolism: lipid oxidation is reduced during the fasting period. However, REE mostly depends on lipid metabolism. Lipids contribute to 22% of the REE, proteins to 16% and carbohydrates to 62% in AN (14 patients), versus 54% (lipids), 16% (proteins) and 30% (carbohydrates) in 12 normal subjects. On average, the fasting respiratory quotient is higher during fasting phase of the disease, in severely malnourished patients than in normal subjects (in 118 patients with BMI = 13.4 ± 1.5 kg/m², the respiratory quotient was 0.78 in AN patients vs. 0.71 in normal patients) (Russell et al. 2001). The reason is the increase in protein and carbohydrate oxidation, above all during renutrition. Concerning plasma lipoproteins, a decrease in cholesterol and total triglycerides is often observed (Jaguenaud et al. 1989). But, hypercholesterolemia is observed in one case in six (Rigaud et al. 2009): in 120 AN patients, a total cholesterolemia > 270 mg/100 mL was observed in 18% of cases. Low density lipoprotein-cholesterol (LDL-C), apo B, high density lipoprotein-cholesterol (HDL-C) and apo A1 levels were higher in the AN patients. Cholesterol ester transfer protein (CETP) activity is high during fasting periods in AN, partly explaining the increase in LDL-C (Ohwada et al. 2006); only denutrition and a decrease in apolipoprotein synthesis can counteract this (Jaguenaud et al. 1989). Triglycerides, which are normally low in malnutrition cases, are high in 15% of AN cases, because of a lack of lipoprotein lipase.

156.2.1 Evolution of Body Mass

AN patients want to lose fat mass, but the loss of fat-free mass and muscle mass is high (Dempsey et al. 1984; Obarzanek et al. 1994; Forman-Hoffman et al. 2006), which disturbs muscle functions (Rigaud et al. 1988; Murciano et al. 1994; Polito et al. 2000; Cuerda et al. 2007). The AN patients loss similar percentage of body weight and fat-free mass (a 15% body weight loss corresponds to a 15% fat-free mass loss). In AN patients, the fat mass represents 20–25% of body weight at the beginning of the disease and only 7–8% when their BMI is 12–14 kg/m². A decrease in cerebral grey mass and white mass are observed in AN, probably because of malnutrition. Under a BMI of 15 kg/m², hydro-sodium retention appears, with edema of the lower limbs during renutrition. This leads to

excessive weight gain, which is independent of the food intake, if a salted diet is prescribed. So, a low-salt diet is necessary as soon as BMI is under 15 kg/m^2.

156.2.2 Physical Activity

Physical hyperactivity is frequent in EDs, and particularly in AN patients (Rigaud 2003). It is observed in 35–85% of the patients. In our cohort of 487 patients followed for 10 years, physical hyperactivity was quoted in 68% of the patients with the restrictive type, and in 52% of the bulimic ones (unpublished data).

The restrictive diet and the physical hyperactivity increase each other. The activity-based anorexic rat is a very interesting model (Hillebrand et al. 2005). This model has been developed by several teams, with similar results. In this model, four groups of rats are compared: the first control group includes rats that eat normally and are put in individual cages where they can engage in limited activity. The second group has the same diet (20–21g/day) but they can go on a wheel as often as they wish. The third control group is on a low-calorie diet (–25% of the previous intake), and their cages are standard. In the experimental group, the rats receive a low-calorie diet (15–16 g of food) and can use the wheel as much as they want to. Rats eating normal diet and allowing going to the wheel increase their physical activity during few days, then less and less. Rats on a restrictive diet in standard cage do not develop physical hyperactivity. Rats on sliming diet allowed to go on the wheel, use it more often each day, and curiously decrease their restricted food intake. They lose more weight than any other rat. A recent study using a quite different model found similar results (Martin et al. 2007): when male and female rats are put on a low-calorie diet; the females lose their menstruation, take on a male hormonal profile and lose weight faster, have more stress, and engage in more physical activity than do males. So, in rats, the female predisposition to AN is seen, without the need for psychological mechanisms (which, however, does not exclude them).

156.2.3 Other Behavioral Consequences

Smoking: there is a relationship between smoking and EDs. Generally speaking, binge eating and bulimic patients smoke more and are more often dependent on tobacco (addiction), than normal subjects and restrictive AN patients. This is also true in the bulimic form of AN (binge-eating, vomiting, and low BMI). Conversely, restrictive AN patients smoke less and are less dependent on tobacco than normal subjects of the same age and sex.

Obsessive compulsive disorder: Obsessive compulsive disorder may have an effect on daily EE for two reasons: by the physical activity that they often impose (obsessive compulsive disorder for housework, cleaning, washing hands, etc.) and by the anxiety, which is often associated (obsessive-compulsive disorder patients are very frequently anxious). It must be remembered that physical hyperactivity can be considered as an obsessive compulsive disorder at least in some eating-disorder patients.

Compulsive food intake and bulimic crises: In AN patients, true bulimia is 80–100 times more frequent than compulsion without vomiting (Rigaud 2003). Bulimia means there at least two episodes a week of compulsive food intakes, without pleasure or hunger, ending with vomiting. Bulimia is six times more frequent in AN patients than in nonanorexic women. It's hard to assess the precise

risk of developing bulimic crises (binge-eating/purging episodes) in AN. Such crises occurred in 25–45% of AN patients. In our statistics (unpublished data), 31% of our 487 patients followed-up for more than 10 years developed binge-eating/purging episodes within the first 2 years. If no such crisis or vomiting is noted during the two first years, the risk of developing chronic bulimia is ten times less (4% of cases) than it is if patients exhibit such crises (36%). Almost 20–30% of the AN patients of the bulimic type do develop normal-weight chronic bulimia nervosa. On the contrary, evolution from bulimia nervosa towards the pure restrictive form of AN is very rare (6% of cases).

There are three explanations for going from the pure restrictive form to binge-eating/purging episodes: (1) frustration due to chronic food deprivation, in patients who keep the sensation of hunger and desire to eat; (2) Chronic energy deficit and various nutritional deficiencies, which lead patients to "need to eat" to avoid death; (3) An on-off response in such patients who deny the hedonic value of any sweet and savory foods. So in AN patients, cognitive restriction could be responsible for similar consequences that what is seen in obese patients on very restrictive low-calorie diet for a long time.

156.2.4 Hormonal Component

1. **Thyroid hormones**: Plasma concentrations are low during fasting; this is called the "low T3 syndrome". Thyroid hormones increase during renutrition and return to the normal level in 3–4 weeks. Normal levels of thyroid stimulating hormone (TSH) are restored at about the same time (Onur et al. 2005).
2. **Cortisol and adrenomedulla hormones**: During fasting, plasma cortisol and free urinary cortisol are often increased. Adrenocorticotropic hormone (ACTH) is high too. Physiological stress linked to the fatal risk of denutrition can explain this increase in cortisol. But physical hyperactivity increases both cortisol and ACTH. When the BMI is below 15 kg/m^2, hyperaldosteronism due to denutrition is observed.
3. **Leptin:** Leptin is reduced in AN (Polito et al. 2000; Satoh et al. 2003; Haas et al. 2005). This decrease correlates with the BMI, and may be responsible for reduced REE. But this leptin related decrease can be avoided by renutrition, because REE increases before any increase in fat mass, while leptin does not increase. When the BMI is above 18 kg/m^2, leptin increases and menstruation starts again.
4. **Adiponectin**: This is often high in AN (Pannacciulli et al. 2003). It could contribute to the increase in energy metabolism during renutrition.
5. **Ghrelin and PYY**: Their roles in EE regulation have been mentioned, but are still unclear (Misra et al. 2006).
6. **Catecholamines:** A high level of catecholamines has been found, but the results are inconsistent. They could be responsible for the increase in REE, postprandial EE, and EE linked to physical activity (Rigaud et al. 2007).

156.3 Conclusion

Understanding of the energy and metabolism components of AN and their evolution during refeeding are increasing. AN seems to be a metabolic and psycho-behavioral syndrome in which the different elements work together to perpetuate the disease. The body has a remarkable capacity to adapt to chronic fasting, but also wastes energy as soon as the patient starts eating again to build up body weight. These mechanisms of adaptation to fasting are partly known: decrease in leptin and thyroid hormone secretion, increase in cortisol secretion, reduction of the cardiac rhythm, reduction

Table 156.2 Evolution of energy needs, before and during renutrition according to the physical activity of the patient

Energy expenditure components	Restrictive AN	Restrictive + physical hyperactivity AN	Stable AN	Stable AN + physical hyperactivity	AN during renutrition	AN during renutrition plus hyperactivity
REE	924	1023	1089	1188	1353	1517
DIT	180	180	442	442	616	616
EEPA	180	260	190	280	210	290
EETR	20	20	35	35	50	55
EE weight gain	0	0	0	0	700	700
Total	**1305**	**1483**	**1756**	**1945**	**2929**	**3178**

This table describes the necessary Kcalories for a 36-kg AN patient of 1.70 m (BMI = 12.4 kg/m^2), 92% of fat-free mass (33 kg), who wants to reach a weight of 48 kg, with 86% (41 kg) of lean mass, on the measured basis of a supplement of 700 kcal/day to have a weight gain of 100 g/day. The AN patient is able to not lose weight, eating 1,300 kcal/day (for 36 kg), and she is able to not gain weight eating 1,950 kcal/day if she engages in moderate activity. In order to gain 100 g/day at 48 kg, she will need 3,200 kcal/day

AN anorexia nervosa, *REE* resting energy expenditure, *DIT* diet-induced thermogenesis, *EEPA* energy expenditure linked to physical activity, *EETR* energy expended for thermoregulation

in the body temperature, in association with a state of depression. Mechanisms involved in the increase in EE are better known too: increase in lean mass, increase in metabolic activities linked to the high energy content of meals and increased physical activity. Nearly all of the abnormalities described above are the consequences of the disease and do not seem to play a direct role in the physiopathology.

156.4 Applications to Other Areas of Health and Disease

Knowledge of the evolution of EE and its different components in AN patients will help to understand the mechanisms involved in weight gain in this disease (Table 156.2). REE should be used to know the level of food intake required to obtain the desired weight gain. For example, one can analyze the body weight gain on the basis of the need of 700 kcal/day above the daily total EE to obtain a weight gain of 100 g/day.

The measure of the EE at rest and after physical activity will be useful for a cognitive behavioral therapy. Indeed, one of the bases of the cognitive therapy is the understanding of the body's needs. The aim of this approach is to reassure AN patients and help physicians to prescribe more scientifically based therapy.

Summary Points

- In anorexia nervosa (AN), weight loss and malnutrition trigger a cascade of metabolic, hormonal, and behavioral consequences.
- A considerable decrease in energy expenditure (EE) is observed during fasting states of the disease, but refeeding and weight gain induce a marked increase in EE, including an increase in resting EE, in DIT, and in EE related to physical activity.

Definitions of Key Terms

Anorexia nervosa: Anorexia nervosa (AN) is a psychiatric diagnosis that describes an ED characterized by low body weight and body image distortion with an obsessive fear of gaining weight.

Fat-free mass: Fat-free mass is comprised of the nonfat components of the human body. Skeletal muscle, bone, and water are all examples of fat-free mass.

Body mass index (BMI): Body Mass Index is a standardized ratio of weight to height, and is often used as a general indicator of health. BMI can be calculated by dividing weight (in kilograms) by the square of height (in meters). A BMI between 18.5 and 24.9 is considered normal for most adults.

Obsessive compulsive disorder: Is a mental disorder characterized by intrusive thoughts that produce anxiety, by repetitive behaviors aimed at reducing anxiety, or by combinations of such thoughts (obsessions) and behaviors (compulsions).

Binge eating: Is a pattern of disordered eating which consists of episodes of uncontrollable overeating. It is sometimes as a symptom of binge ED. During such binges, a person rapidly consumes an excessive amount of food.

- There is a dramatic fall in protein catabolism and in glucose disposal during the fasting stages of the disease. Lipid oxidation is reduced too. During renutrition, these profiles become normal a long time before normalization of body weight.
- The loss of fat-free mass and muscle mass is high, which disturbs muscle functions.
- Physical hyperactivity is frequent in EDs, and particularly in AN patients.
- Hormonal disturbances are observed: Low T3 syndrome, increased plasma cortisol, reduced leptin level, high adiponectin level, high level of catecholamines.

References

Birmingham CL, Hlynsky J, Whiteside L, Geller J. Eat Weight Disord. 2005;10:6–9.

Bossu C, Galusca B, Normand S, Germain N, Collet P, Frere D, Lang F, Laville M, Estour B. Am J Physiol Endocrinol Metab. 2007;292:E132–7.

Casper RC, Schoeller DA, Kushner R, Hnilicka J, Gold ST. Am J Clin Nutr. 1991;53:1143–50.

Cuerda C, Ruiz A, Velasco C, Camblor M, García-Peris P. Clin Nutr. 2007;26:100–106.

Dempsey DT, Crosby LO, Pertschuk MJ, Feurer ID, Buzby GP, Mullen JL. Am J Clin Nutr. 1984;39:236–42.

Forman-Hoffman VL, Ruffin T, Schultz SK. Ann Clin Psychiatry. 2006;18:123–7.

Gniuli D, Liverani E, Capristo E, Greco AV, Mingrone G. Metabolism 2001;50:876–81.

Haas V, Onur S, Paul T, Nutzinger DO, Bosy-Westphal A, Hauer M, Brabant G, Klein H, Müller MJ. Am J Clin Nutr. 2005;81:889–96.

Hillebrand JJ, Koeners MP, de Rijke CE, Kas MJ, Adan RA. Biol Psychiatry. 2005;58:165–71.

Jaguenaud P, Malon D, Cosnes J, Réveillard V, Apfelbaum M, Rigaud D. Cah Nutr Diét. 1996;31:45–51.

Kaye WH, Gwirtsman HE, Obarzanek E, George DT. Am J Clin Nutr. 1988;47:987–94.

Konrad KK, Carels RA, Garner DM. Eat Weight Disord. 2007;12:20–26.

Léonard T, Foulon C, Samuel-Lajeunesse B, Melchior JC, Rigaud D. Appetite 1996;27:223–33.

Martin B, Pearson M, Kebejian L, Golden E, Keselman A, Bender M, Carlson O, Egan J, Ladenheim B, Cadet JL, Becker KG, Wood W, Duffy K, Vinayakumar P, Maudsley S, Mattson MP. Endocrinology 2007;148(9):4318–33.

Melchior JC, Rigaud D, Rozen R, Malon D, Apfelbaum M. Eur J Clin Nutr. 1989;43:793–9.

Misra M, Miller KK, Tsai P, Gallagher K, Lin A, Lee N, Herzog DB, Klibanski A. J Clin Endocrinol Metab. 2006;91:1027–33.

Moukaddem M, Boulier A, Apfelbaum M, Rigaud D. Am J Clin Nutr. 1997;66:133–40.

Murciano D, Rigaud D, Pingleton S, Armengaud MH, Melchior JC, Aubier M. Am J Respir Crit care Med. 1994;150:1569–74.

Obarzanek E, Lesem MD, Jimerson DC. Am J Clin Nutr. 1994;60(5):666–75.

Ohwada R, Hotta M, Oikawa S, Takano K. Int J Eat Disord. 2006;39:598–601.

Onur S, Haas V, Bosy-Westphal A, Hauer M, Paul T, Nutzinger D, Klein H, Müller MJ. Eur J Endocrinol. 2005;152:179–84.

Pannacciulli N, Vettor R, Milan G, Granzotto M, Catucci A, Federspil G, De Giacomo P, Giorgino R, De Pergola G. J Clin Endocrinol Metab. 2003;88:1748–52.

Platte P, Pirke KM, Trimborn P, Pietsch K, Krieg JC, Fichter MM. Int J Eat Disord. 1994;16(1):45–52.

Polito A, Fabbri A, Ferro-Luzzi A, Cuzzolaro M, Censi L, Ciarapica D, Fabbrini E, Giannini D. Am J Clin Nutr. 2000;71(6):1495–502.

Rigaud D. In: Marabout, editor. Les troubles du comportement alimentaire. Paris; 2003.

Rigaud D, Melchior JC. In: Lavoisier, editors. Paris: Ed Med Intern; 1992. p. 69–132.

Rigaud D, Bedig G, Merrouche M, Vulpillat M, Apfelbaum M. Dig Dis Sci. 1988;33:919–25.

Rigaud D, Sogni P, Hammel P, Melchior JC, Rozen R, Labarre C, Mignon M, Apfelbaum M. Ann Med Intern. 1989;140:86–90.

Rigaud D, Cohen B, Melchior JC, Moukaddem M, Reveillard V, Apfelbaum M. Am J Clin Nutr. 1997;65:1845–51.

Rigaud D, Hassid J, Meulemans A, Poupard AT, Boulier B. Am J Clin Nutr. 2000;72:355–62.

Rigaud D, Colas-Linhart N, Verges B, Petiet A, Moukkaddem M, Van Wymelbeke V, Brondel L. J Clin Endocrinol Metab. 2007;92(5):1623–9.

Rigaud D, Tallonneau I, Vergès B. Diabetes Metab. 2009;35:57–63.

Russell J, Baur LA, Beumont PJ, Byrnes S, Gross G, Touyz S, Abraham S, Zipfel S. Psychoneuroendocrinology 2001;26(1):51–63.

Satoh Y, Shimizu T, Lee T, Nishizawa K, Iijima M, Yamashiro Y. Int J Eat Disord. 2003;34(1):156–61.

Scalfi L, Marra M, De filippo E, Caso G, Pasanisi F, Contaldo F. Int J Obes Relat Metab Disord. 2001;25:359–64.

Vaisman N, Rossi MF, Corey M, Clarke R, Goldberg E, Pencharz PB. Eur J Clin Nutr. 1991;45:527–37.

Van Wymelbeke V, Brondel L, Brun JM, Rigaud D. Am J Clin Nutr. 2004;80:1469–77.

Walker J, Roberts SL, Halmi KA, Goldberg SC. Am J Clin Nutr. 1979;32:1396–1400.

Winter TA, O'Keefe SJ, Callanan M, Marks T. J Parenter Enteral Nutr. 2005;29:221–8.

Chapter 157
Application of Personal Construct Theory to Understanding and Treating Anorexia Nervosa

Malgorzata Starzomska and Marek Smulczyk

Abbreviations

DSM	Diagnostic and statistical manual of mental disorders
DSM-IV-TR	Diagnostic and statistical manual of mental disorders, Fourth edition, Text revision
PCP	Personal construct psychotheraphy

157.1 Introduction

Anorexia nervosa is a serious, chronic illness with significant morbidity and mortality for most patients (Kaplan 2002). This condition continues to be poorly understood and is rather mysterious (Schmidt and Treasure 2006). To be diagnosed as having anorexia nervosa according to the DSM-IV-TR (2000), a person must display: (1) Refusal to maintain body weight at or above a minimally normal weight for age and height (e.g., weight loss leading to maintenance of body weight less than 85% of that expected; or failure to make expected weight gain during the period of growth, leading to body weight less than 85% of that expected); (2) Intense fear of gaining weight or becoming fat; (3) Disturbance in the way in which one's body weight or shape is experienced, undue influence of body weight or shape on self-evaluation, or denial of the seriousness of the current low body weight; (4) In postmenarcheal, premenopausal females (women who have had their first menstrual period but have not yet gone through menopause), amenorrhea (the absence of at least three consecutive menstrual cycles). Anorexia nervosa is seen by clinicians as one of the most frustrating and undisciplinable forms of psychopathology (Blank and Latzer 2004) because of the anorectic's apparent stubbornness in the face of impending death which blocks all attempts to help her (Lemma-Wright 1994). It is no wonder that anorectic patients have retained the reputation of being difficult to help or treat. This is the most difficult problem for clinicians who try to help anorectics. Their resistance to treatment and denial of illness seem to result from the fact that anorexia nervosa provides the afflicted person with a sense of identity. Many scientists assume that anorexia nervosa is caused by impairment of healthful identity develop-

M. Starzomska (✉)
The Maria Grzegorzewska Academy of Special Education, Institute of Applied Psychology,
40 Szczesliwicka Street, 02-353 Warsaw, Poland
e-mail: eltram@life.pl

ment and failure to establish a self-definition (Stein and Corte 2007). It is highly probable that controlling and perfectionistic parents can be held responsible for impairment in the development of an independent sense of one's self as well as hindrance of autonomy (Stein and Corte 2007). Such adolescents often seek self-definition in the ability to control their body weight (Stein and Corte 2007) because this way they try to counterbalance the lack of clear identity and the accompanying feeling of impotence (Stein and Corte 2007). Thus anorexia nervosa seems to be the result of maladaptive coping with the absence of an authentic self (Stein and Corte 2007) and the search for a new, ideal identity. As a consequence, such persons begin to define their self through self-starvation (Lemma-Wright 1994) and success can be easily quantified in lost pounds, which offers immediate gratification and may explain why anorectics find it difficult to abandon weight loss (Lemma-Wright 1994). This problem is easy to notice in the following statement of a former anorectic: 'When I looked at myself in the mirror I saw someone beautiful; I saw myself … the clearer the outline of my skeleton became, the more I felt my true self to be emerging (…). Without anorexia I should have been a nothing' (Lemma-Wright 1994, p. 40). Clearly, such identity, which is also called thin (Fransella and Button 1983) or anorectic (Wojciechowska 2000), is maladaptative (Wojciechowska 2000) but for the anorectic it is highly desirable because her beliefs about weight and shape are viewed as being specifically relevant for her (Vandereycken 2006). This phenomenon, which is typical only of anorexia nervosa and refers to the sense experienced by many patients that anorexia nervosa is their identity (Tan et al. 2003a), is called egosyntonicity and it is deemed to be the condition's core feature (Crisp 2006). This specific state is very difficult to change because self-starvation can be very empowering – it offers a sense of accomplishment and self-control as well as fulfilment of the need to make autonomous decisions (Lemma-Wright 1994). Thus, anorexia nervosa is highly valued by people who suffer from it. Notably, afflicted patients sometimes call the disorder their friend (Serpell et al. 1999). It is highly probable that anorectic symptoms are maintained by beliefs about the positive function of the illness for the person (Schmidt and Treasure 2006) and that the egosyntonic nature of anorexia nervosa may be responsible for the chronicity of this condition.

157.2 Egosyntonicity Within a Cognitive Model of Anorexia Nervosa

The egosyntonicity of anorexia nervosa can be well explained and understood within a cognitive model of anorexia nervosa. Central to all cognitive theories of eating disorders is the hypothesis that beliefs and expectancies pertaining to body size and eating are biased in favor of selectively processing information related to fatness/thinness, dieting, and control of food intake or body weight. According to this hypothesis, the anorectic's beliefs and values should be treated as implicit rules which affect the way she assesses her experience of herself and her world as well as the meaning she associates with it (Lemma-Wright 1994). Thus, the primary disorder in anorexia is distortion of the individual's perception of shape and weight (Lemma-Wright 1994), and self-starvation seems to be secondary to the individual's overvalued ideas. Recently, controlled investigations of the predictions of cognitive theories of eating disorders have yielded empirical support for these theories. Vitusek and Hollon (1990) argue that the core psychopathology of anorexia nervosa results from highly organized cognitive structures that unite views of the self with beliefs about weight. These weight-related self-schemas may exert automatic effects on the processing of information and may also help to account for the clinical observation that patients frequently regard their symptoms as egosyntonic. Stein and Corte (2007) found that anorectic patients had fewer positive and more negative and highly interrelated self-schemas compared to controls and that their self-concept was associated with pathological eating- and weight-related attitudes and behaviors. The anorectic person is continuously under the influence of her malad-

aptative self-constructs that are very difficult to change. She believes that without these schemas she would lose herself because they seemingly create her sense of identity. Studies conducted by cognitive researchers have clearly revealed that egosyntonicity of anorexia can be understood in terms of cognitive self-structures which are predominantly negative and very persistent.

157.3 Egosyntonicity Within an Existential Model of Anorexia Nervosa

Some researchers underline that the most important task in the psychotherapy of anorexia nervosa is to understand the anorectic's worldview. This term was proposed by Binswanger who described various aspects of so-called being-in-the-world. This theory has its roots in the existential psychotherapeutic literature which was preoccupied with emphasizing the importance of understanding the client's experience and herself in the world (Lemma-Wright 1994).

   According to existential psychologists, although the anorectic's choice not to eat sometimes leads to death, it is the search for another life, a pursuit of attaining internally what cannot be accomplished or managed in the outer world (Lemma-Wright 1994). The anorectic's worldview seems to be dominated by control. Without control, she would be without a self, thus her unfailing perseverance essentially turns her life into a self-starvation project (Lemma-Wright 1994). Thus, according to the existentialists, anorexia nervosa is a specific solution to psychic pain. It is very important to note that existential clinicians are quite sceptical of diagnoses, for example DSM diagnoses, in general, and the diagnosis of anorexia nervosa in particular. Their primary concern is not whether the diagnosis exists but how it is used. For them, the question of so-called cure in anorexia is a controversial issue when the most important criterion appears to be weight gain. According to the existentialists, the individual who cannot find any other way of being-in-the-world than living a life of self-starvation is not necessarily cured when she starts to eat again. In our attempts to help the anorectic achieve this, we may well benefit from reminding ourselves that, as Joseph Conrad claimed, the question is not how to get cured but how to live (Lemma-Wright 1994).

   Undoubtedly, the existentialists' most important contribution to the understanding of anorexia is their critical analysis of refeeding (treated as an element of behavioral therapy) in the case of this condition.

157.4 Similarities Between Cognitive and Existential Approaches to Anorexia Nervosa

Both cognitive and existential models seem to explain the meaning of self and especially its disturbances in the etiology and maintenance of anorexia nervosa. While cognitive researchers focus on the specific maladaptive self-schemas of anorectics, existentialists focus on their worldview but both groups despair that biological therapies of anorexia are insufficient and may even have paradoxical effects because they ignore the most important feature of the disorder, namely self-disturbances. Both cognitive and existential theories strive to understand the meaning of personal identity in anorectic patients. Vitousek and colleagues (1991), cognitive researchers, explain the reasons for therapeutic difficulties during anorexia nervosa treatment partly from an existential perspective: eating disorder patients, notably anorectics, are notorious for their secrecy, making it difficult to establish communication based on mutual trust and openness. They do so by concealing their behavior, feelings, and experiences, and especially by denying that they are ill (Vitousek et al. 1991). The authors review traditional methods of entering or reconstructing the private experience and overcoming or correcting

Table 157.1 Similarities between cognitive and existential approaches to anorexia nervosa

Understanding anorexia nervosa	
In cognitive approaches	In existential approaches
Both underline that anorectics in particular are notoriously protective of their private experience.	
Both seem to explain the meaning of self and especially its disturbances in the etiology and maintenance of anorexia nervosa	
Both despair that biological therapies of anorexia are insufficient, and even have paradoxical effects, because they ignore the most important feature of the disorder, namely self-disturbances.	
Both cognitive and existential approaches adopt a similar stance with respect to anorexia nervosa in that they emphasize the importance of private experience and self-disturbance in the etiology, maintenance, and treatment of this condition	

the denial of the anorectic individual but they suggest that these methods which rely on clinical intuition, patients' testimony, and direct confrontation are likely to result in a combined perspective of clinician-researchers and their subjects (1991) so they propose a variety of alternative methods of reducing denial and distortion in patients' self-report that may prove to be more useful. Surprisingly, their terminology (internal world, private experience, etc.) is partly existential (Table 157.1).

157.5 George Kelly – Cognitivist or Existentialist?

Interestingly enough, one of the most well-known cognitive researchers, George Kelly, whose Personal Construct Theory has been successfully applied to anorexia nervosa, has been deemed an existentialist by some. Although Kelly was sceptical of phenomenology per se because of its introspective idealism and lack of clear theory and rigorous methodology and experimentation, he was convinced, just like the phenomenologists, that to understand behavior one needs to understand how a person construes reality: how he or she understands it, perceives it, and that this is more important than knowing what that reality truly is. In fact, he pointed out that everyone's view – even the hard-core scientist's – is just that: a view. This is exactly the meaning of the phenomenologist's basic principle, known as intentionality. Although Kelly's theory may sound very cognitive, with its emphasis on constructs and constructions, Kelly himself disliked being called a cognitive theorist. He maintained that his theory included the more traditional ideas of perception, behavior, and emotion. According to Boeree (2006) it is yet to be seen whether Kelly will be remembered as a phenomenologist or a cognitivist. Nevertheless it must be underlined that there are aspects of Kelly's theory that are in contradiction to phenomenology. First, Kelly was a true theory-builder whereas existential researchers tend to avoid theory. Second, he had high hopes for a rigorous methodology for psychology (Boeree 2006). Most existential researchers are much more sceptical about experimentation.

157.6 A Personal Construct Theory Framework

Personal Construct Psychology is a theory of personality developed by George Kelly in the 1950s. Kelly called his theory and philosophy constructive alternativism. His idea was that although there is only one true reality, reality is always experienced from one or another perspective, namely each person perceives the world from his/her own, completely unique vantage

point. According to Kelly, people develop internal models of reality, which he called constructs, in order to understand and explain the world around them in the same way as scientists develop theories (Kelly 1955; Hall Lindzey and Campbell 2004). Therefore, all people can be called scientists because they have constructions of their reality. Like scientists, they have theories and they improve their understanding of reality on the basis of their experiences and, like scientists, they adjust their theories to fit the facts. Constructs are usually defined by words but they can sometimes be nonverbal and very difficult to explain (http://changingminds.org/explanations/theories/personal_construct.htm).

According to Kelly, we store experience in the form of personal, usually bipolar constructs. Where there is thin, there must be fat, where there is good, there must be bad, etc. If everyone were fat, then fat would become meaningless or identical in meaning to everyone. Some people must be skinny in order for fat to have any meaning, and vice versa.

157.7 Roots and Core of Psychopathology and Psychotherapy in Personal Construct Theory

Kelly believed that a psychological disorder was any personal construction which was used repeatedly in spite of consistent invalidation. The behaviors and thoughts which occur in depression, paranoia, schizophrenia, addictions, eating disorders, and so on are examples. Such people cannot learn new ways of relating to the world. They are full of anxiety and/or hostility and other negative feelings (Kelly 1955; Hall et al. 2004).

The main method that Kellian psychotherapists use to diagnose and treat patients with various disorders or psychological problems is the repertory grid interview. Kelly derived this technique from his theory to help patients uncover their own constructs with minimal intervention or interpretation by the therapist and to reconstruct them (Kelly 1955; Hall et al. 2004; http://en.wikipedia.org/wiki/Personal_construct_psychology). In other words, Kellian psychotherapy gets the client to see things in a different way, from a new perspective. It has the following goals: to open people up to alternatives, help them to discover their freedom, and allow them to live up to their potentials (Boeree 2006). This is a noninvasive approach to psychotherapy (Kelly 1955; Hall et al. 2004). The UK Council for Psychotherapy, a regulatory body, classifies PCP therapy under Experiential Constructivism.

157.8 Repertory Grid Presentation

To create their own repertory grid (Table 157.2), patients must first name a set of ten to twenty people, called elements, likely to be of some importance in their lives. In therapy, these people are named in response to certain suggestive categories, such as "my mother," "my father," etc. Second, the therapist (or researcher) must pick out three of these at a time, and ask the patient to tell her/him which of two are similar and which one is different. Then the therapist must ask the patient to give her/him something to call the similarity and the difference. The similarity label is called the similarity pole, and the difference is called the contrast pole. Together they make up one of the constructs applied in social relations. If, for example, a girl says that both she and her mother are nervous people but her father is very calm, then nervous is the similarity pole and calm the contrast pole

Table 157.2 Elements used by 20 anorectics in Button's study

Elements 1–10	Subject's personal elements
Element 11	Me now
Element 12	Me if I was overweight
Element 13	Me as I was one year ago
Element 14	Me as I will be one year ahead
Element 15	Patient's consultant psychiatrist
Element 16	Me at the weight I would prefer to be
Element 17	Me at the sort of weight I imagine the treatment team wants me to be
Element 18	Me at what most people would call a normal weight for me
Element 19	Me as I would ideally like to be
Element 20	Me at the thinnest I've been
Element 21	Me at the heaviest I've been
Element 22	Father – if not included in the subject's personal elements
Element 23	Mother – if not included in the subject's personal elements
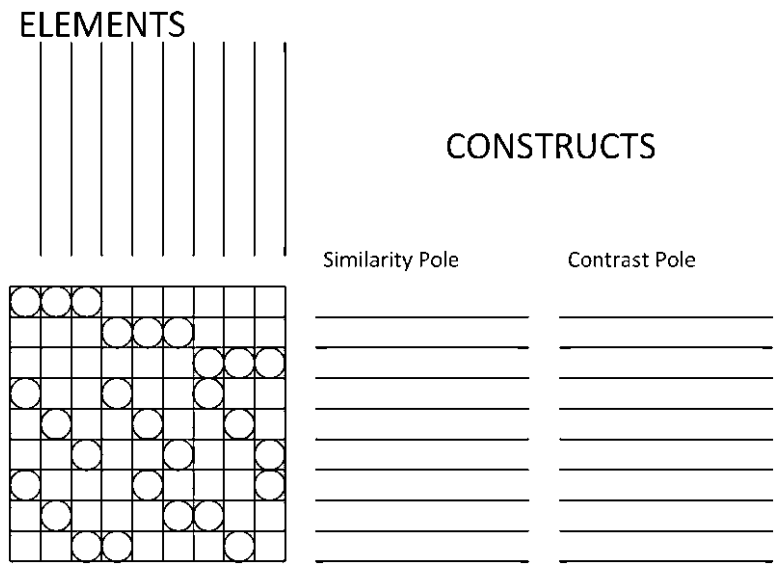
Fig. 157.1 A blank rep grid. The blank rep grid has two components, namely: elements (which correspond to important persons in one's life) and constructs (which correspond to both similarity and contrast between the elements) (Reprinted from Boeree 2006 [Online]. Available at: http://webspace.ship.edu/cgboer/kelly.html [accessed 1 June 2009]. With permission)

of the construct nervous–calm. The patient and therapist continue in this fashion, with different combinations of three, until about 20 (but sometimes fewer) contrasts are listed. The therapist, but especially the researcher, may perform certain statistical operations on the completed chart (Kelly 1955; Hall et al. 2004). The rep grid itself is a matrix where the rows represent the discovered constructs, the columns represent the elements, and cells indicate (numerically) the position of each element within each construct (Fig. 157.1). Software is available to produce several reports and graphs from these grids. In diagnostic and self-discovery applications, the therapist may encourage the patient to use constructs that refer to people's behaviors and personalities and, if necessary, to the self (Kelly 1955; Hall et al. 2004).

In therapy, the rep grid gives the therapist and client a picture of the client's view of reality that can be discussed and worked with. The rep grid is a unique test in that the client is invited to change his or her mind about it at any time. Neither is it assumed to be a complete picture of the person's mental state. It is what it is: a diagnostic tool.

Noteworthy, in research, therapists and researchers use a number of computer programs that enable measurement of the distances between constructs or elements. Thus it is possible to get a picture, created by the subjects themselves, of their world-views. It is also possible to compare the views of several people, for example a person's world-view, before and after training or therapy. Such comparisons were made in the studies described in this article (Boeree 2006).

The rep grid is an exciting tool, a creative combination of the subjective and objective side of personality research. It could be said that this technique is very attractive not only for cognitive researchers but also, due to its sensitivity to subjectivity, for methodologically oriented existentialists (Boeree 2006).

157.9 Application of Kellian Theory to Egosyntonic Aspects of Anorexia Nervosa

In 1980 Button (cited in Fransella and Button 1983) conducted a study in which he used the rep grid method. He asked 20 anorectic patients to rate 23 elements in terms of 21 constructs on a 7-point scale. It must be underlined that the constructs and elements were both specific to the individual (named: personal) and supplied by the experimenter (Tables 157.3 and 157.4).

Table 157.3 Constructs used by 20 anorectics in Button's study (Reprinted from Fransella and Button 1983. With permission)

Constructs 1–12	Subject's personal constructs
Construct 13	Very thin–very fat
Construct 14	Attractive–unattractive
Construct 15	Sexually attractive–sexually unattractive
Construct 16	Anorectic–nonanorectic
Construct 17	Eats normally–doesn't eat normally
Construct 18	Needs medical help–doesn't need medical help
Construct 19	Doesn't need psychiatric help–needs psychiatric help
Construct 20	Not physically ill–physically ill
Construct 21	Mentally ill–not mentally ill

Button construed his rep grid on the basis of the answers of 20 anorectic patients whom he asked to rate 23 elements in terms of 21 constructs on a 7-point scale. Both constructs and elements were specific to the individual (he called them personal) and supplied by the experimenter

Table 157.4 Effects of the anorectic's (thin) self construal on treatment results in Button's study

The more extremely the self (especially ideal, anorectic, thin self) was construed, the poorer the treatment outcome. The more fixed patients' views of themselves, the more resistant they were to permanent weight change.

At first follow-up a more extreme view of the self at treatment team weight and at normal weight was associated with good outcome. It therefore appears that weight maintenance after discharge is associated with the patient having a reasonably clear idea of what it means to be normal in terms of weight.

Between first and second follow-up the most significant finding was that a decrease in meaningfulness of the construct fat–thin was associated with good weight maintenance. This suggests that an important goal of therapy is to help anorectics find ways of construing themselves other than in terms of weight or fatness.

Button demonstrated that treatment outcome depends on the importance of the fat–thin construct for the anorexic patient

Results, as in the former study conducted by Fransella and Crisp in 1979, showed no evidence of denial of illness among these patients: intercorrelations between the construct anorectic–nonanorectic (its "anorectic" end) and remaining constructs supplied by the experimenter that could be named "illness" constructs (the following ends: very thin, needs medical help, mentally ill) were positive and very high, ranging between 0.95 and 0.63. Intercorrelations between the "not anorectic" end of the construct anorectic–nonanorectic and such ends of "illness" constructs as: attractive, sexually attractive, eats normally, doesn't need psychiatric help, not physically ill were negative and very high, ranging between 0.98 and 0.74. Analysis of the results showed that the present "thin self" (me now) is seen as undesirable and the "normal weight self" as desirable.

Interestingly, Button decided to take the analysis one step further by scrutinizing the relationships between the "self" elements only in terms of the personal (specific to the individual) constructs because he wanted to establish whether the dispersion of elements was simply a function of the particular constructs supplied by the experimenter (constructs 13–21, Table 157.4). Analysis of data using the same elements (Table 157.3) but different constructs (constructs 1–12, Table 157.4) revealed very similar relationships between the aforementioned elements when all constructs were used, namely self now (element 11) was not ideal (element 19) and thin (element 20), but it also revealed a new, astonishing result (compared with the analysis using all constructs), namely there was an interesting relationship between ideal self (element 19), self at treatment team, weight and self at normal weight (personal elements); ideal self was not self at treatment team and self at normal weight (Figs. 157.2 and 157.3). This
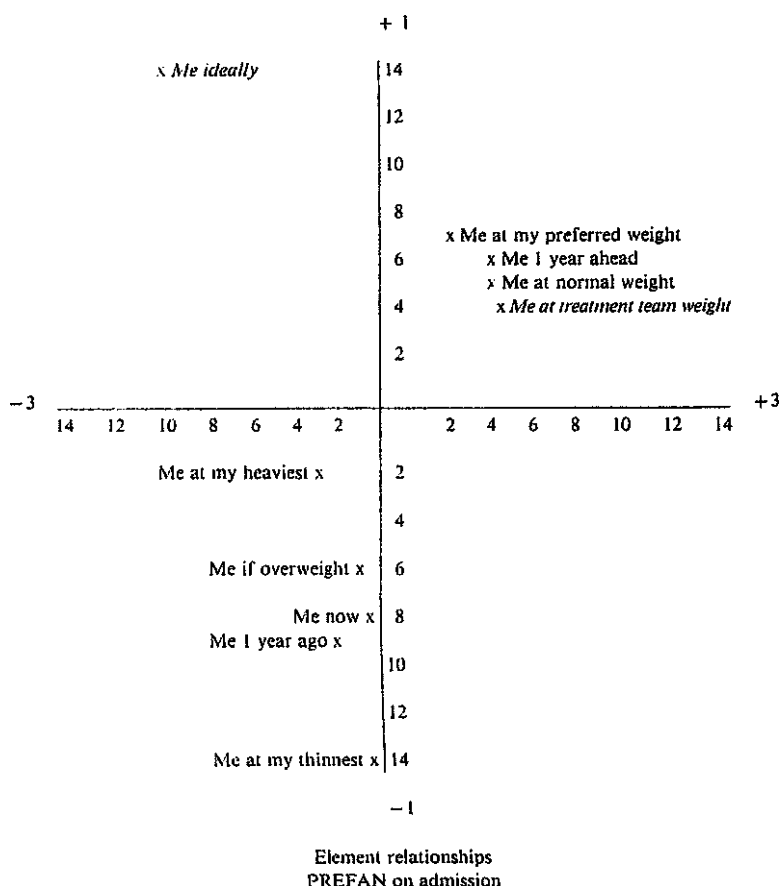
Fig. 157.2 Plot of "Self" Elements in terms of their loadings on components 1 and 2 for a group of 20 anorectic patients
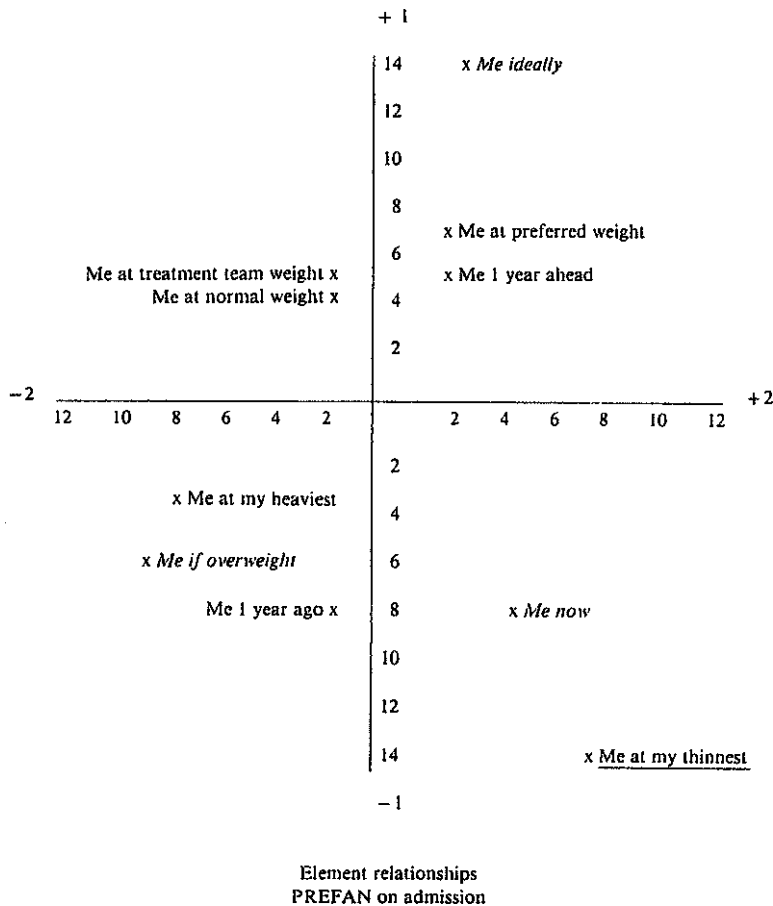
Fig. 157.3 Plot of "Self" Elements in terms of their loadings on components 1 and 3 for a group of 20 anorectc patients. Interestingly, Button decided to scrutinize the relationships between the "self" elements only in terms of the personal (specific to the individual) constructs because he wanted to establish whether the dispersion of elements was simply a function of the particular constructs supplied by the experimenter (constructs 13–21, Table 157.4). This analysis of group data using identical elements but different constructs can be performed using Slater's PREFAN program. Analysis of data using the same elements (Table 157.3) but different constructs (constructs 1–12, Table 157.4) revealed very similar relationships between the aforementioned elements when all constructs were used, namely self now (element 11) was not ideal (element 19) and thin (element 20) (Fig. 157.2), but it also revealed a new, astonishing result (compared with the analysis using all constructs), namely there was an interesting relationship between ideal self (element 19), self at treatment team, and self at normal weight (personal elements); ideal self was not self at treatment (Fig. 157.3) (Reprinted from Fransella and Button 1983. With permission)

implies that ideal self is probably closer to thin self than to medically treated self at normal weight. According to Button, this result may be a possible source of insight into the anorectic's dilemma – wanting to gain weight and be normal while at the same time sensing that this is not viable for her.

157.10 Egosyntonicity of Anorexia in the Light of Results of the Study

Disclosure of this specific ambivalence (ideal self is in contradiction to self at treatment team and self at normal weight) provides us with a real and reliable picture of anorexia: this is a condition which is inextricably linked with sense of identity, namely an anorectic person must be anorectic (i.e., thin) in

order to preserve a sense of identity (Lemma-Wright 1994) and to preserve its egosyntonic symptomatology (Vandereycken 2006). Clearly, in addition to having an anorectic (thin) self, the afflicted person also has other selves (for example, self at normal weight) but the anorectic (thin) self seems to dominate. This is why anorectics are so reluctant to accept treatment, even when they are very low in weight and at significant risk to themselves (Tan et al. 2003b). Using Kellian terms it could be said that an anorectic person is caught with her constructs down and her anxiety involves anticipations of great changes in her core (Kelly's term) constructs (interestingly, Crisp described egosyntonicity as a core feature) (1990). It is therefore understandable that she does not want to get rid of her anorexia because it constitutes her most important construct: anorectic, i.e., thin–nonanorectic, i.e., fat. Button's findings confirm that egosyntonicity (craving for an anorectic, thin identity) is the most important feature of anorexia and it is impossible to understand this condition without this phenomenon which scientists, clinicians, and lawyers dealing with capacity problems must take into account.

157.11 Effects of the Anorectic's (Thin) Self-Construal on Treatment Results

Button (1980, cited in Fransella and Button 1983) also intended to explore the effects of self-construal, in the sense of relationships between elements within specific constructs, on treatment results measured by weight maintenance. His analyses revealed that:

- The more extremely the self (especially ideal, anorectic, thin self) was construed, the poorer the outcome of treatment. The more fixed patients' views of themselves, the more resistant they were to permanent weight change.
- At first follow-up a more extreme view of the self at treatment team weight and at normal weight was associated with good outcome. It therefore appears that weight maintenance after discharge is associated with the patient having a reasonably clear idea of what it means to be normal in terms of weight.
- Between first and second follow-up the most significant finding was that a decrease in meaningfulness of the construct fat–thin was associated with good weight maintenance. This suggests that an important goal of therapy is to help anorectics find ways of construing themselves other than in terms of weight or fatness.

One statistically significant relationship of some interest was found between change in construal from time of admission to time of discharge and poor clinical outcome; this was an increase in meaningfulness of being anorectic compared with being normal weight. It was as if the girls who failed to maintain their weight came to see themselves more clearly as anorectic while in hospital. Therefore, how patients see themselves in relation to their disorder at the onset of treatment has prognostic significance. For anorectics, the more meaningful the self in relation to weight, the poorer the clinical outcome (Fransella and Button 1983). These results show that our self-image affects our behavior and may influence our proneness to change (Fransella and Button 1983) (Table 157.5).

157.12 Applications to Other Areas of Health and Disease

Results of studies on self-construal in anorexia nervosa within Personal Construct Theory may be applied to other mental disorders, or simply to problems which seem to be connected with the sense of identity. It is worth mentioning patients with anxiety disorders whose anxiety concerns a specific

Table 157.5 Key points concerning application of Personal Construct Theory to understanding and treating anorexia nervosa

Resistance to treatment and denial of illness in anorexia nervosa seem to result from the fact that anorexia nervosa provides the afflicted person with a sense of identity which is named egosyntonicity.

Personal Construct Psychology provides us with a very useful tool with which to study the egosyntonicity of anorexia nervosa, the rep grid. Studies which have used this technique show that the way patients see themselves in relation to their disorder at the onset of treatment has prognostic significance. For anorectics, the more meaningful the self in relation to weight, the poorer the clinical outcome.

Analyzing personal constructs of anorectic patients and attempts to find ways of construing themselves other than in terms of objects of fear or problems can literally change their life into easier to bear and even very successful.

Resistance to treatment and denial of illness in anorexia nervosa seem to result from the egosyntonicity of this condition, and Personal Construct Psychology provides us with a very useful tool with which to study the egosyntonicity of anorexia nervosa, the rep grid. Studies using this method have shown that the main aim in treating anorexics should be to help them find ways of construing themselves other than in terms of fatness

area of life or persons but who are not mentally disordered, only distressed about, for example, stuttering. When analyzing their personal constructs and attempts to find ways of construing themselves other than in terms of objects of fear or problems, they can literally change their life, making it easier to bear or even very successful.

157.13 Conclusion

Thanks to Button who explored various self elements, especially in anorectics, i.e., thin constructs, it is possible to understand what the term egosyntonic really means. Anorexia with its main symptom, thinness, is inseparably linked with sense of identity. As a consequence, an anorectic person is scared of life without her disorder and this phenomenon seems to be responsible for her denial of illness and resistance to treatment. It is noteworthy that both cognitive and existential models seem to explain the importance of the self and especially its disturbances in the etiology and maintenance of anorexia nervosa and both models try to explain the sense of personal identity in anorectic patients. Although some researchers stress the importance of the sense of identity in the course of anorexia nervosa, biological (mainly refeeding) and behavioral therapeutic programs are still in common use. The results of the studies presented show that the most important aim in the therapy of anorectics should be to help them find a way of self-realization that does not involve self-starvation (and sometimes death). Existential and cognitive researchers and therapists manifest considerable consensus in their analyses of this phenomenon. This aim is very ambitious and very difficult to achieve but undoubtedly worth the effort.

Summary Points

1. Anorexia nervosa is a serious, chronic illness with significant morbidity and mortality. This condition continues to be poorly understood and rather mysterious and is also seen by clinicians to be one of the most frustrating forms of psychopathology because of the anorectic's apparent stubbornness in the face of impending death which blocks all attempts to help her.
2. Resistance to treatment and denial of illness seem to result from the fact that anorexia nervosa provides the afflicted person with a sense of identity called egosyntonicity.
3. Paradoxically, both cognitive and existential models seem to explain the meaning of self and especially its disturbances in the etiology and maintenance of anorexia nervosa and both attempt to understand anorectic patients' sense of personal identity.

4. Personal Construct Psychology provides us with a very useful tool with which to study the ego-syntonicity of anorexia nervosa, the rep grid.

5. Studies which have used this technique show that the way patients see themselves in relation to their disorder at the onset of treatment has prognostic significance. In anorectics, the more meaningful the self is in relation to weight, the poorer the clinical outcome.

Definitions and Explanations of Key Terms

Anorexia nervosa: A serious psychiatric disorder characterized by distorted body image which triggers intensive self-starvation and – as a consequence – significantly diminished body weight. The very essence of this eating disorder is categorical refusal to change in conjunction with profound denial of illness.

Cognitive theories of eating disorders: Theories according to which beliefs and expectancies pertaining to body size and eating are biased in favor of selective processing of information related to fatness/thinness, dieting, and control of food intake or body weight.

Egosyntonicity: A phenomenon present in very few disorders, whose main feature is that the afflicted person derives a sense of identity from the disorder.

Personal construct theory: A theory of personality developed by George Kelly in the 1950s, based on constructive alternativism, that is, on the idea that although there is only one true reality, reality is always experienced from one perspective or another.

The repertory grid interview: The main method used by Kelly and designed on the basis of Personal Construct Theory.

References

Blank S, Latzer Y. Am J Family Therapy. 2004;32:43–54.

Boeree CG. George Kelly [Online]. Available at: http://webspace.ship.edu/cgboer/kelly.html [Accessed 1 June 2009]; 2006

Crisp A. Eur Eat Disord Rev. 2006;14:189–202.

Diagnostic and Statistical Manual of Mental Disorders. Fourth Edition. Text Revision (DSM-IV-TR). Washington, DC: American Psychiatric Association; 2000.

Fransella F, Button E. In: Darby PL, Garner DM, Garfinkel PE, Coscina DV, editors. Anorexia nervosa. Recent developments in research.New York: Alan Liss; 1983. pp. 107–16.

Hall CS, Lindzey G, Campbell J. Theories of personality.Oshawa: Crystal Dreams; 2004.

Kaplan AS. Can J Psychiatry. 2002;47:235–42.

Kelly GA. The psychology of personal constructs.New York: Norton; 1955.

Lemma-Wright AL. Starving to live. The paradox of anorexia nervosa. London: Central Book; 1994.

Personal Construct Theory [Online]. Available at: http://changingminds.org/explanations/theories/personal_construct.htm [Accessed 1 June 2009]

Personal Construct Theory [Onlin]. Available at: http://en.wikipedia.org/wiki/Personal_construct_psychology [Accessed 1 June 2009]

Schmidt U, Treasure J. Br J Clin Psychol. 2006;45:343–66.

Serpell L, Treasure J, Teasdale J, Sullivan V. Int J Eat Disord. 1999;25:177–86.

Stein K, Corte C. Eur Eat Disord Rev. 2007;15:58–69.

Tan J, Hope T, Steward A. Int J Law Psychiatry. 2003a;26:533–48.

Tan J, Hope T, Steward A, Fitzpatrick R. Int J Law Psychiatry. 2003b;26:627–45.

Vandereycken W. Eur Eat Disord Rev. 2006;14:341–51.

Vitousek KB, Hollon SD. Cogn Ther Res. 1990;14:191–214.

Vitousek KB, Daly J, Heiser C. Int J Eat Disord. 1991;10:647–66.

Wojciechowska I. In: Sucha ska A, editor. Podmiotowe i społeczno-kulturowe uwarunkowania anoreksji [The subjective and socio-cultural determinants of anorexia]. Wydawnictwo Fundacji Humaniora, Poznań; 2000. pp. 77–124.

Kelly GA. The psychology of personal constructs. New York: Norton; 1955.

Chapter 158
Comorbidity in Anorexic Adolescents: Assessment Through ASEBA System and Semistructured Interviews

Filippo Muratori, Valentina Viglione, Chiara Montalto, and Sandra Maestro

Abbreviations

AN	Anorexia Nervosa
ASEBA	Achenbach System of Empirically Based Assessment
BAI	Beck Anxiety Inventory
BDI	Beck Depression Inventory
BMI	Body Mass Index
CBCL	Child Behavior CheckList
CDI	Children's Depression Inventory
CDRS-R	Children's Depression Rating Scale Revised
DICA	Diagnostic Interview for Children and Adolescents
DSM	Diagnostic and Statistical Manual of Mental Disorders
EAT-26	Eating Attitude Test
ED	Eating Disorders
EDI-3	Eating Disorder Inventory
EXT	Externalizing
HDRS	Hamilton Depression Rating Scale
INT	Internalizing
K-SADS	Schedule for Affective Disorders and Schizophrenia for School Aged Children
MASC	Multidimensional Anxiety Scale for Children
OCD	Obsessive Compulsive Disorder
OCPD	Obsessive-Compulsive Personality Disorder
PARS	Pediatric Anxiety Rating Scale
PD	Personality Disorders
SCID-I	Structured Clinical Interview for Axis I
SCID-II	Structured Clinical Interview for Axis II
SIAB-EX	Structured Interview for Anorexic and Bulimic Disorders-Expert Form
STAI	State-Trait Anxiety Inventory
TP	Total Problem
Y-BOCS	Yale-Brown Obsessive Compulsive Scale
YSR	Youth Self-Report

F. Muratori (✉)
Division of Child Neuropsichiatry, Stella Maris Scientific Institute, University
of Pisa, IRCCS Stella Maris, Via dei Giacinti, 2-56018 Calambrone, Pisa, Italy
e-mail: filippo.muratori@inpe.unipi.it

158.1 Introduction

It is well established that individuals with eating disorders (ED) have a high rate of Axis I psychiatric comorbidity, particularly depressive and anxiety disorders broadly termed as internalizing conditions. The association between Axis II personality disorders (PD) and ED is also frequent with a prevalence of cluster C and B. Accompanying Axis I and Axis II diagnoses play an important role in the outcome of ED and in the planning of therapeutic interventions.

Although psychiatric disorders are common in ED, current literature shows an overlapping of data. In fact, many studies do not consistently consider the distinction between different types of ED; considering ED as a whole, additional axis I disorders were found in 86% by Lewinsohn et al. (2000) and Cotrufo et al. (1998), in 73% by Salbach-Andrae et al. (2008), in 74% by Milos et al. (2004), in 58% by Zaider et al. (2000), in 43% by Kennedy et al. (1994), in 66% by Geist et al. (1998). All these studies found a higher comorbidity in the binge-purging subtype than in the restricting subtype. As regards Axis II disorders, incidence varies from 90% in the study by Piran et al. (1988), to 84% by Grilo et al. (1996), and to 68% in the sample studied by Milos et al. (2004), where a prevalence of cluster C was found.

Secondly, many of these studies have examined comorbidity without considering limited ranges of age. Encompassing adolescent, young adult, and adult patients creates a loophole in the research on the specific psychiatric comorbidity of ED during adolescence when the disorder does not last for many years.

158.2 Depressive Comorbidity in Adolescent Eating Disorders

A wide range of depressive symptoms such as depressed mood, low self-esteem, and social withdrawal are very frequent in anorexic adolescents. Literature data report up to 80% of anorexic samples with a depressive disorder, especially during the acute phase of illness: depressive symptoms were found in 86% by Rastam (1992), in 62% by Smith and Steiner (1992), in 60% by Salbach-Andrae et al. (2008), in 56% by Fosson et al. (1987), and in 46% by North and Gowers (1999) and Saccomani et al. (1998). Lilenfeld et al. (1998) found high multiple lifetime comorbidity with significant differences with a control group. Herzog et al. (1992b) investigated current and lifetime comorbidity and found current comorbidity on axis I in 73% of the restricting subtype. In the study by Heebink et al. (1995), a lower level of depression and anxiety was found in younger restricting patients than in older patients.

Data on the incidence of suicide and suicidal attempts in adolescent samples are lacking (Herpertz-Dahlmann 2008); however, this varies from 10% to 20% in anorexic patients, especially combined with major depression (Bulik et al. 2008; Franko et al. 2006). In particular, in the sample studied by Bulik, around 17% of AN patients (mean age: 30 years) attempted suicide, this being significantly more evident in the purging or binging subtype.

To explain this high comorbidity between AN and depressive symptoms, some authors consider AN as a particular form of mood disorder (Alessi et al. 1989; Cooper et al. 2002; Levy and Dixon 1985). Similarly, Mouren-Simeoni MC et al. (1993), in describing a prepubertal anorexic sample, reported an association with depressive symptoms in 85% of subjects and considered prepubertal AN as a depressive equivalent. In a more recent study, Chen et al. (2009) found that dietary restraint and depressive symptoms combined at age 10 and became a risk factor for binge-eating at ages 12–14. Moreover, "dietary-depressive" subtypes (with a greater negative effect) compared to "dietary"

subtypes (with dietary restraint only) had considerably greater eating disorder behaviors. Presnell et al. (2009) revealed that depressive and bulimic symptoms contributed reciprocally to each other. In particular, they examined the reciprocal relations between the two disorders over an 8-year period, and concluded that depressive symptoms predicted increase in bulimic symptoms while bulimic symptoms predicted increase in depressive symptoms.

Other authors consider depressive symptoms as a result of a prolonged state of starvation with neuroendocrine and serotoninergic alterations (Couturier 2004).

158.3 Anxiety Comorbidity in Adolescent Eating Disorders

Anxiety disorders such as social phobia, obsessive-compulsive disorder (OCD), panic disorder, general anxiety disorder are common both in adult and juvenile anorexic samples with percentages ranging from 7% to 65% (Herzog et al. 1992b; Kaye et al. 2004). In the adolescent sample studied by Salbach-Andrae et al. (2008), anxiety disorders without OCD followed by OCD occurred in 26% and 17% respectively. Moreover, the category containing anxiety disorders without OCD was three times likely to co-occur with the AN binge eating and purging type than with the AN restrictive type. In the study by Godart et al. (2000), the most frequent lifetime anxiety disorder in its adolescent sample was social phobia (55%) followed by simple phobia (45%). In anorexic patients, food-related obsessive-compulsive symptoms arise, especially during the acute phase, such as cutting food into a certain number of pieces, counting calories, preparing meals, and setting the table in the same way. However, real OCD comorbidity with additional thought and behavior is often signaled in anorexic samples with a range from 17% to 40% (Kaye et al. 2004; Salbach-Andrae et al. 2008) and with frequent childhood onset preceding the onset of AN. Furthermore, anorexic patients show rigidity and perfectionism which are considered risk factors for obsessive disorders.

Finally, the majority of studies report the onset of anxiety disorders before the onset of an ED, supporting the possibility that anxious symptoms are a vulnerability factor for developing AN. This temporal correlation between anxiety disorders and AN has significant implications for course and treatment. In particular, since social preoccupations are very frequent in anorexic patients, many authors propose social competence training during treatment (Herpertz-Dahlmann 2008).

158.4 Personality Disorders in Adolescent Eating Disorders

The frequent association between personality traits and disorders (both in acute phase and during recovery) and ED is well described in literature. Above all, perfectionism, rigidity, and obsessiveness (cluster C) seem to be prevalent personality traits in restrictive AN patients. In the study by Thornton (Thornton and Russell 1997), 34% of an AN sample met criteria for obsessive-compulsive personality disorder (OCPD; Cluster C); Wonderlich et al. (1990) also found 60% prevalence of OCPD in 46 women with restricting subtype. Impulsivity, emotional liability, and self-aggressiveness (cluster B, Borderline Personality Disorder) are more evident in the binge eating/purging subtype of AN.

The incidence seems to decrease with the state of ED severity; for example in the study conducted by Herzog et al. (1992a), the incidence of PD in a sample of 210 nonsevere outpatients with ED was only 27%. Recent research (Thompson-Brenner et al. 2008) on ED during adolescence confirmed the results of several studies carried out on ED in adults (Claes et al. 2006; Holliday et al. 2006). Three personality subtypes were found: a high-functioning, an undercontrolled, and an avoidant/depressed

group. In particular, the high-functioning/perfectionist group showed negative associations with comorbidity and positive associations with treatment response. The Emotionally Dysregulated group was associated with externalizing Axis I and Cluster B Axis II disorders, poor school functioning, and adverse events in childhood. The Avoidant/Depressed group showed specific associations with internalizing Axis I disorders and Cluster A Axis II disorders, and poor peer relationships.

158.5 Assessment of Comorbidity in Adolescent Eating Disorders

The accurate assessment of internalizing and externalizing symptoms is a key aspect in adolescent eating disorders, where there is a tendency to deny not only anorexic behavior, but also anxiety and depression, which is very common in AN psychopathology (Viglione et al. 2006).

It is exactly for this reason that assessment with anorexic adolescent patients should be performed by a child psychiatrist having extensive experience with adolescents and sufficiently trained in psychological assessment, use of standardized measures, developmental psychology, and adolescent eating disorders. The assessment should be conducted in an office or other site where confidentiality can be ensured and where the adolescent can feel comfortable and safe. The validity of the information provided by the youth may depend on the setting and on the level of trust between the adolescent and the assessor. During the first interviews, both with the adolescent and with the parents, information should be collected on the history of eating disorders and mental health, with a focus on depression, suicidal ideation or attempts, anxiety disorders, and behavioral disorders (aggressiveness toward self and others, impulsivity, etc.); family history and school history, including academic, behavioral performance, and peer relationships.

The use of instruments is evidently required to perform standardized assessment, that is to say, to systematically, and as coherently as possible, explore the psychopathology so as to receive answers from the patients and their parents and to compare them. Psychiatric assessment instruments enable exploration of the psychopathological entity and provide a quantitative assessment in terms of severity or frequency.

The presence of comorbidity in ED is usually assessed with structured or semistructured clinical interviews, self-report questionnaires, and checklists. Nevertheless, in a recent critical review (Godart et al. 2007) it is observed that diagnostic instruments were not used in earlier studies and that, in later studies, those used varied with differences in diagnostic procedures.

The instruments more frequently used in literature to explore comorbidity in ED are: the Structured Clinical Interview for Axis I (SCID-I, Williams et al. 1992) and the Structured Clinical Interview for Axis II (SCID-II, Skodol et al. 1988) for Axis I and II diagnosis; the Hamilton Depression Rating Scale (HDRS, Williams 1988) and the Beck Depression Inventory (BDI Beck et al. 1996) for depression symptomatology; the Yale-Brown Obsessive Compulsive Scale (Y-BOCS Goodman et al. 1989), the Beck Anxiety Inventory (BAI Beck et al. 1988) and the State-Trait Anxiety Inventory (STAI Spielberger et al. 1970) for anxiety symptoms.

Studies dealing with adolescent samples make use of several specific instruments such as the Child Behavior Checklist (CBCL, Achenbach 1991) for the general psychopathology; the Schedule for Affective Disorders and Schizophrenia for School Aged Children (K-SADS, Chambers et al. 1985) or the Diagnostic interview for children and adolescents (DICA Reich 2000) for Axis I diagnosis; the Multidimensional Anxiety Scale for Children (MASC, March et al. 1999) or the Pediatric Anxiety Rating Scale (PARS, The Research Units on Pediatric Psychopharmacology anxiety study group 2002) for anxiety; the Children's Depression Inventory (CDI, Kovacs 1985) or the Children's Depression Rating Scale – Revised (CDRS – R, Overholser et al. 1995) for depression.

Table 158.1 IRCCS-Stella Maris Eating Disorder Assessment Protocol used at admission in the ED Unit

ED diagnosis	Comorbidity	Family assessment
Anamnestic interview	Kiddie-SADS (Axis I)	Family interview
Kiddie-SADS	SCID- II (Axis-II)	SCL-90
EAT-26;ChEAT	CBCL and YSR	PBI
EDI-3		
BS		
SIAB-EX		

The diagnostic instruments that we selected consider the specificity of the disorder in the young age of our patients

Kiddie-SADS Schedule for Affective Disorders and Schizophrenia for School Aged Children, *EAT-26* Eating Attitude Test (*ChEAT* Children version), *EDI-3* Eating Disorder Inventory, *BS* Binge Scale, *SIAB-EX* Structured Interview for Anorexic and Bulimic Disorders-Expert Form, *SCID-II* Structured Clinical Interview for Axis II, *CBCL* Child Behavior CheckList; *YSR* Youth Self Report, *PBI* Parental Bonding Instrument

The assessment protocol used in the Eating Disorder Program at the Stella Maris Scientific Institute was elaborated by considering the type of patients and, above all, the clinical features of the eating disorders, and the patients' young age. It is composed of: the Schedule for Affective Disorders and Schizophrenia for School Aged Children (K-SADS) for ED diagnosis and Axis I comorbidity; the Structured Clinical Interview for DSM-IV Axis II Disorders (SCID-II) for Axis II comorbidity; the Achenbach System of Empirically Based Assessment (ASEBA), in particular, the Child Behavior CheckList (CBCL) and Youth Self Report (YSR, Achenbach 1990) for general psychopathology. Naturally, instruments for assessing eating disorders are also used (EDI-3; EAT-26; SIAB-EX; Table 158.1).

158.5.1 Psychopathological Assessment Using the ASEBA System

To verify if psychopathology in adolescent anorexia is as frequent as in older samples, we assessed a sample of 43 anorexic adolescents referred to the Eating Disorder Program at the Stella Maris Scientific Institute with a mean age at admission of 14.9 (range from 10.7 to 17.8 years) and with a mean duration of illness prior to admission of 13 months (Muratori et al. 2004).

ED diagnosis and psychiatric assessment were carried out by an independent trained child psychiatrist who interviewed the child and the parents separately, using the Schedule for Affective Disorders and Schizophrenia for School Aged Children (K-SADS). The K-SADS belongs to the category of clinical diagnostic interviews which – although long – are very useful instruments (Table 158.2).

They may only be used by trained child psychiatrists and explore Axis I diagnosis (some of them also Axis II), allowing the psychiatrist to formulate diagnosis. They envisage a first nonstructured part (10–20 min) and a second semistructured part (40–60 min) during which the child psychiatrist conducts the interview according to a predefined layout. In particular, the K-SADS is a semistructured psychiatric interview based upon the diagnostic criteria of DSM-IV (Chambers et al. 1985; APA 1994) which is used to asses current and past episodes of psychopathology in children and adolescents. The K-SADS is administered by interviewing the parent(s), the child, and finally achieving summary ratings which include all sources of information (parent, child, school, etc.). At the start of the interview (first part), it is important to establish an empathic relationship, to explain the purpose of the interview, and inform the patient on the obligation of professional secrecy. Generally, if the patient is a preadolescent we interview the parents first and then the patient; instead, if the patient is an adolescent, it is important to start with the patient. In the case of discrepancies between

Table 158.2 Criteria for diagnosing adolescents anorexic syndrome (DSMIV)

Anorexia nervosa (full syndrome)

1. Refusal to maintain body weight above minimal normal weight for age and height (body weight less than 85% of the expected) or failure to achieve expected weight gain during period of growth
2. Intense fear of gaining weight or becoming fat, even though underweight
3. Disturbance in the way in which one's body weight or shape is experienced or denial of the seriousness of the current low body weight
4. In postmenarcheal females, amenorrhea of at least three consecutive menstrual cycles

Specify if Restricting subtype or Binge Eating/purging subtype

Eating disorders not otherwise specified (partial syndrome)

Eating disorders that do not meet the criteria for a AN full syndrome, for example:

1. AN criteria are met but the individual has regular menses
2. AN criteria are met except that, despite significant weight loss, the individual's current weight is in the normal range
3. Regular use of inappropriate compensatory behavior by an individual of normal body weight after eating small amounts of food

EDNOS diagnosis (partial syndromes) is very frequent in adolescent samples; furthermore, in these syndromes psychopathological and physical conditions are very serious and require a multidimensional treatment

AN anorexia nervosa

Table 158.3 Key features of Achenbach System of Emirically Based Assessment (ASEBA)

1. ASEBA gives a dimensional description of psychiatric symptomatology by elaborating an individualized profile in the various areas taken into consideration.
2. ASEBA allows psychopathological assessment by using several information sources. In fact, it may be filled in by the parents (CBCL), the youth (YSR) or the teachers (TRF: Teaching Report Form)
3. The checklist forms that are more extensively used to obtain standardized reports of child and adolescent behavior are Child Behaviour CheckList (CBCL) and Youth Self Report (YSR).
4. They contain 118 item behavioral scales which allow evaluation of a total problem score (TP), eight syndromes (withdrawn, anxious/depressed, somatic complaints, social problems, thought problems, attention problems, delinquent behavior, aggressive behavior) and two broadband groups of syndromes designated as internalizing (INT) and externalizing (EXT).
5. The last version also includes DSM-oriented scales.
6. In clinical activities, ASEBA is useful for diagnosis and for the treatment follow-up. A cut-off distinguishing clinical from non-clinical cases is defined.

In the ASEBA checklists filled in by anorexic patients and by their parents the anxious-depressed symptomatology is very evident and may cause great disturbances

parents' and child's reports, the most frequent disagreements occur in the items dealing with subjective phenomena where the parent does not know, but the child is very definite about the presence or absence of certain symptoms. This is particularly true for internalizing items such as hopelessness and suicidal ideation. Reliability, validity, administrative characteristics, and use of the K-SADS were recently reviewed (Ambrosini 2000).

Psychopathology was also studied using the Achenbach System of Empirically Based Assessment (ASEBA), in particular the Child Behavior CheckList (CBCL) and Youth Self Report (YSR). ASEBA gathers assessment data through several sources of information (it may be filled in by the parents, youth, or teachers); it provides a dimensional description of symptomatology and elaborates an individualized profile in the various areas taken into consideration. The aim is to reach a diagnostic formulation which is not focused on one or on a few symptoms, but which bears in mind the countless features of the child's/adolescent's life and of his/her complexity (Table 158.3).

The CBCL and YSR are two of the most frequently used empirically-based assessment instruments for obtaining standardized reports of children and adolescent behavior as observed by the

parents (CBCL) or self-evaluated (YSR). They contain 118 item behavioral scales which allow the evaluation of a total problem score (TP), eight syndromes (Withdrawn, Anxious/Depressed, Somatic Complaints, Social Problems, Thought Problems, Attention Problems, Delinquent Behavior, Aggressive Behavior) and two broad-band groups of syndromes designated as Internalizing (INT) and Externalizing (EXT). Internalizing score encompasses emotional disorders characterized by inhibition and overcontrol, while Externalizing score indicates the presence of attention, oppositional, antisocial, and aggressive problems. A cut-off to distinguish clinical from nonclinical cases is defined. Good reliability and validity have been reported in literature for both scales (Krol 1990). Only two symptoms of anorexia nervosa are comprised in the CBCL and YSR (no. 24: "Doesn't eat well" and no. 53: "Overeating") but they are not included in any patterns of internalizing or externalizing scales, which is of importance for our study.

Briefly, the results of our study, thanks to the use of the ASEBA, revealed that the pathological mean score on the internalizing CBCL summary scale (parents' evaluation), with 67.4% of subjects within pathological range, is highly consistent with the findings of a prevalence of affective and anxiety disorders in ED, and the percentage of subjects with psychopathological problems associated with ED are parallel to those reported in literature (Braun et al. 1994; Fosson et al. 1987; Halmi et al. 1991; Herzog et al. 1992b; Lilenfeld et al. 1998; Smith et al. 1993; Smith and Steiner 1992). Above all, on the basis of these internalizing and externalizing profiles and on the number of subjects in the clinical range, three types of adolescent anorexia emerged from our study (Fig. 158.1): (1) "normal" anorexia (32.5% of cases) with a nonclinical CBCL profile; (2) pure internalizing anorexia (51.2% of cases) with TP and INT pathological values; and mixed anorexia (16.3%) with TP, INT, and EXT pathological values. Even if both restricting and binge eating/purging subgroups are allocated in each group, the majority of both of them are represented in the pure internalizing group. The small mixed group, featuring a more severe psychopathology, highlights a type of adolescent anorexia characterized by opposition and difficulties in concentration where Internalizing symptoms are also more severe. This latter type is totally different from the pure internalizing type characterized by a lower rate of psychopathological problems and which we could call unipolar. On the basis of these psychopathological findings we could hypothesize a less severe type of ED in binge eating/purging anorexia and a more severe type in restricting anorexia; the identification of these different anorexic disorders could be of particular interest for subtyping eating disorders, for therapeutic decisions and for defining prognostic trajectory.
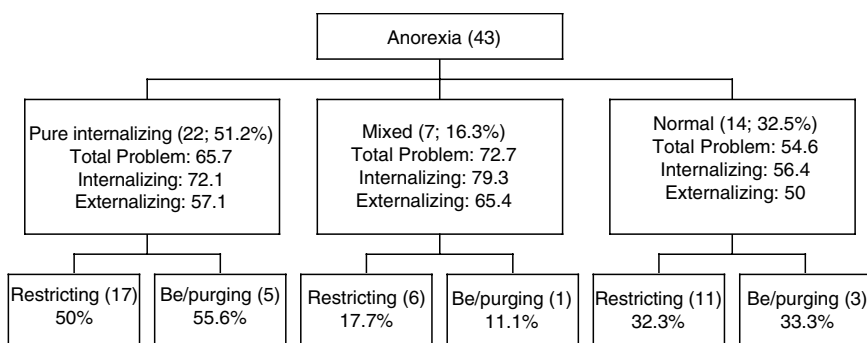
Fig. 158.1 Clinical and psychopathological characteristics at CBCL for the three types of adolescents with anorexia nervosa. The three types of anorexic groups differ on the basis of CBCL score. In fact, in the pure internalizing group, the pathological score is reached on total and internalizing global scales; in the mixed the pathological score is reached on INT and EXT scales, while in the normal group the pathological score is not reached
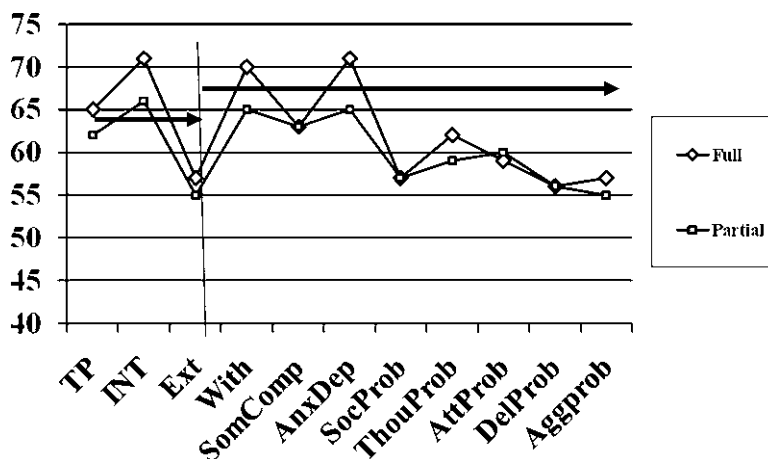
Fig. 158.2 Comparison of pscychopathological asset between full (all criteria of DSM-IV) and partial anorexic adolescent subgroups using CBCL. *Black lines* represent the clinical cutoff for global and syndrome scales. The scores of global and syndrome scales are expressed as mean values. *TP* total problems, *Int* internalizing, *Ext* externalizing, *With* withdrawn, *SomComp* somatic complaints, *AnxDep* anxious/depressed, *SocProb* social problems, *ThougProb* thought problems, *AttProb* attention problems, *Delprob* delinquent problems, *Aggprob* aggressive behavior

By comparing Full versus Partial at CBCL and YSR it is possible to assume a psychopathological continuum between full and partial syndromes, although in full syndromes anxious-depressed and concentration problems combine to represent a more disturbed anorexic adolescent (Fig. 158.2).

When comparing the Restrictive versus the Binge-eating subgroup, higher internalizing psychopathology was found in binge eating/purging subtype only at YSR (no differences at the CBCL), especially for the anxious/depressed subscale. These data seem to describe the binge eating/purging group as a group where self-reported psychopathology is specifically higher compared to that reported by parents. This is probably due to a greater difficulty by the parents in recognizing these disorders in their offspring or due to a particular way of underlining self-symptomatology by the adolescent girls.

To conclude, the use of ASEBA revealed that the amount of psychopathology in anorexia increases over time (higher mean values were found at CBCL and YSR for almost all summary and syndrome scales in the group arrived 12 months after disease onset) and suggests that it could represent a secondary complication of the illness. This finding seems a powerful argument for early intervention in adolescent ED; in fact an ongoing devious pathway can produce negative effects on many domains of functioning.

158.5.2 Psychopathological Assessment Through Semistructured Interviews

Subsequently, we investigated the incidence of personality disorders in a sample of 100 anorexic girls (mean age at admission: 14.4 years). The Kiddie-SADS was used to assess axis I comorbidity, and the SCID-II was used to asses personality disorders (PD). The Structured Clinical Interview for DSM-IV Axis II Disorders (SCID-II) is a semistructured interview for assessing DSM-IV Axis II PD through integration of the personality diagnosis in appendix B of the manual. It consists of a self-report Questionnaire and a semistructured Interview. The Questionnaire comprises 119 items for

Fig. 158.3 Axis I comorbidity in an adolescent anorexic sample using Kiddie-SADS. The anorexic adolescent sample shows a high internalizing symptomatology (depressive and anxiety disorders together: 80%). *MaD* major depression, *MiD* minor depression, *GAD* generalized anxiety disorder, SAD separation anxiety disorder

Sample
100 AN ♀
Mean Age: 14.4 ys
Mean BMI:15.6

SAD
16%

MaD
30%

GAD
43%

MiD
48%

Pure depressive disorder:34%
Pure anxiety disorder:3%
Depressive+Anxiety disorder:80%
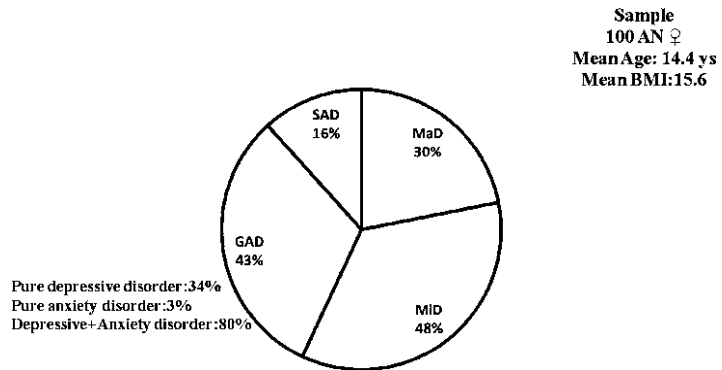
screening the ten DSM-IV PDs, in addition to the Passive-Aggressive and Depressive PDs in Appendix B of the DSM-IV. Since the Questionnaire was created for adults, we adjusted it for use with adolescents: we changed certain items, making them more suitable for the age range (for example, the term "school" was used instead of "job") but without altering their original meaning. The "yes" response to the items of the Questionnaire is reassessed in the Interview through specific questions. The answers to these questions are rated on a four-level scale. PD diagnosis is made when the number of items assessed as present (that is, presenting pathological, persistent, and diffused features) is above the cut-off determined for making diagnosis.

We confirm high axis I comorbidity also in adolescent girls with anorexia, with a prevalence of depressive and anxiety disorders. In particular, acute depressive symptoms are very frequent (Major depression: 30%; Minor Depression: 48%), as also Generalized Anxiety Disorder (43%) and Separation Anxiety Disorder (16%). Furthermore, our study highlights how 34% of the sample had a pure depressive disorder. This percentage rises to 80% if the association between depressive and anxiety disorders (46%) is considered, while only 3% of the sample had at least 1 pure anxiety disorder (Fig. 158.3).

The Kiddie-SADS is a semistructured psychiatric interview in which the items score used for the categorical diagnosis is obtained by posing the same questions separately to both parents and to the children/adolescents. In our case, therefore, the high percentage of internalizing symptoms (and in particular depressive symptoms) is the expression of both parents' and children's combined opinions. The Kiddie-SADS results are in accordance with the previous study based on CBCL and YSR data, and they seem to support the hypothesis that in anorexic girls, depressive disorder and AN are strictly connected, mutually influencing each other. Nevertheless, the high depressive values in our sample may also be considered as an expression of serious clinical and physical conditions since the mean BMI value of the sample was only 15.6.

The association with axis II comorbidity PD is also high, with values similar to those of recent studies (Milos et al. 2004). In fact, 59% of the sample had at least one PD with a prevalence of OCDP (25%) and Borderline PD (22%). It is very interesting to notice that our binge-eating subgroup also presented higher psychopathology values both in axis I and II. In particular, 88% of this subgroup had at least one PD against 53% of the restrictive subgroup, with a significantly higher value for various PDs, especially for Borderline PD (65% vs. 13%), Avoidant PD (35% vs. 11%) and Depressive PD (47% vs. 13%). We also observed that OCPD reached similar values both in the restricting and in the Binge-Eating subgroup, while there are clear differences between the full and the partial subgroup, with higher values in the first case (28% vs. 18%). Accordingly, we may assume that certain personality traits may highly favor the early onset of AN. Specifically, traits such as perfectionism, rigidity, and overcontrol may favor, together with other factors, the complete onset of the anorexic disorder, while traits such as impulsivity and emotional liability may contribute to be a defining AN quality.

158.6 Clinical Implications

It is possible to confirm the importance of psychopathological evaluation in adolescent eating disorders. The prevalence of internalizing conditions, the worst psychopathology in full syndromes and in the binge-eating/purging subtypes deserves attention when establishing treatments. Finally, the increasing psychopathology later on after the onset of the disease is of particular importance for the development of specialized services for adolescents with anorexia nervosa where early interventions, designed to change both medical and psychological issues, could prevent secondary psychopathology.

158.7 Applications to Other Areas of Health and Disease

Psychiatric assessment of adolescent pathologies is an extremely important step in clinical practice. It provides an accurate and prompt diagnosis in an age when comorbidity is extremely frequent. For this reason, a large amount of standardized interviews and self-administered scales have been identified for adolescents, in order to acquire a complete and objective description of clinical picture. Incidentally, the use of such tools is equally diffused in nonpsychiatric populations for the purpose of identifying risk factors. This aspect is particularly evident as far as Eating Disorders are regarded. Some of the tests mentioned, such as the EAT-26 or the CBCL and YSR, are often used for the screening phase in the general population.

Summary Points

- Adolescent anorexia nervosa presents high psychiatric comorbidity, as in adults.
- Depressive disorders (above all, major depression), especially during the acute phase of illness, are the most common axis I comorbidity in adolescent anorexia nervosa.
- Social difficulties as well as generalized and separation anxiety disorders are also frequent in AN.
- Obsessive–compulsive symptoms, not only food related, are often signaled in anorexic samples, with frequent onset during childhood preceding the onset of AN.
- Axis II comorbidity is frequent in adolescent anorexic samples, with a prevalence of Cluster B (especially in the binge-eating subtype) and Cluster C (especially in the restrictive subtype).

Definitions and Explanations of Key Terms

Adolescent Eating Disorders: Anorexia nervosa (AN), bulimia nervosa (BN) and EDNOS (eating disorder not otherwise specified) are all characterized by an excessive concern with weight and shape, accompanied by inadequate and irregular food intake. Many adolescents do not fulfill criteria for AN and BN but for subthreshold eating disorders (EDNOS), which are often as severe as the classical syndromes

Comorbidity: Presence of more than one diagnosis occurring in an individual at the same time. In the ED is a frequent condition that plays an important role as for diagnosis as for outcome and for planning of specific treatments.

Assessment: Evaluation of the patient for the purposes of forming a diagnosis and a treatment plan. It is very important, in clinical work with eating disorder (ED), to have a comprehensive assessment of DSM-IV comorbid disorders.

Internalizing condition: Depressive and anxiety disorders; this is the most frequent comorbidity in adolescent ED.

Personality disorders: An enduring pattern of inner experience and behavior that deviates markedly from the expectations of the culture of the individual who exhibits it. This pattern is manifested in two (or more) of the following areas: cognition, affect, interpersonal functioning, and impulse control. This diagnosis is a very frequent comorbidity in adolescent ED.

Key Points on Comorbidity in Adolescent Anorexic Disorders

High comorbidity of adolescent anorexia nervosa contributes to define specific and well-defined clinical disorders and to make therapeutic decisions more effective.

The Restrictive AN subtype is associated to higher levels of internalizing symptomatology, perfectionism, rigidity and obsessiveness (they frequently describe a Cluster C personality disorder). Impulsivity, emotional liability and self-aggressiveness (which frequently describe a Borderline Personality Disorder) are more evident in the binge eating/purging subtype of AN.

A psychopathological continuum may be assumed between full and partial syndromes.

The anxious-depressed symptomatology may cause greater disturbances in adolescents with anorexia.

The prevalence of internalizing conditions and the worst psychopathology in full syndromes and in the binge-eating/purging subtypes, deserves attention when establishing treatments. The identification of girls with anorexic partial syndrome is an opportunity to intervene at an early stage of the disorder and to improve outcome.

References

Achenbach TM. Manual for the Child behaviour Checklist/4–18 and 1991 profile. Burlington, University of Vermont department of Psychiatry; 1991a.

Achenbach TM. Manual for the Youth self-Report and 1991 profile. Burlington, University of Vermont Department of Psychiatry; 1991b.

Alessi NE, Krahn D, Brehm D, Wittekindt J. J Am Acad Child Adolesc Psychiat. 1989;28:380–4.

Ambrosini PJ. J Am Acad Child Adolesc Psychiat. 2000;39:49–56.

American Psychiatric Association. Diagnostic and statistical manual of mental disorders, 4th ed. Washington, DC: APA; 1994.

Beck AT, Epstein N, Brown G, Steer RA. J Consult Clin Psychol. 1988;56:893–7.

Beck AT, Steer RA, Ball R, Ranieri W. J Pers Assess. 1996;67:588–97.

Braun DL, Sunday SR, Halmi KA. Psychol Med. 1994;24:859–67.

Bulik C, Thornton L, Pinheiro A, Plotnicov K, Klump K, Brandt H, Crawford S, Fichter M. et al. Psychosom Med. 2008;70:378–83.

Chambers WJ, Puig-Antich J, Hirsch M, Paez P, Ambrosini PJ, Tabrizi MA. Arch Gen Psychiat. 1985;42:696–702.

Chen EY, McCloskey MS, Keenan KE. Int J Eating Disord. 2009;42:275–83.

Claes L, Vandereychen W, Luyten P, Soenens B, Pieters G, Vertommen H. J Pers Disord. 2006;20:401–16.

Cooper PJ, Watkins B, Bryant-Waugh R, Lask B. Psychol Med. 2002;32:873–80.

Cotrufo P, Barretta V, Monteleone P. Acta Psychiat Scand. 1998;98:112–5.

Couturier J. Canadian J CME. 2004; February: 81–4.

Fosson A, Knibbs J, Bryant-Waugh R, Lask B. Arch Dis Childhood. 1987;62:114–8.

Franko DL, Keel PK. Clin Psychol Rev. 2006;26:769–82.

Geist R, Davis R, Heinmaa M. Can J Psychiat. 1998;43:507–12.

Godart NT, Flament MF, Lecrubier Y, Jeammet P. Eur Psychiat. 2000;15:38–45.

Godart NT, Perdereau F, Rein Z, Berthoz S, Wallier J, Jeammet Ph, Flament MF. J Affect Disord. 2007;97:37–49.

Goodman WK, Price LH, Rasmussen SA, Mazure C, Fleischman RL, Hill KL, Heninger GR, Charney DS. Arch Gen Psychiat. 1989;46:1006–11.

Grilo CM, Levy KN, Becker DF, Edell WS, McGlashan TH. Psychiat Serv. 1996;47:426–9.

Halmi KA, Eckert E, Marchi P, Sampugnano V, Apple R, Cohen J. Arch Gen Psychiat. 1991;48:712–8.

Heebink DM, Sunday S, Halmi KA. J Am Acad Child Adolesc Psychiat. 1995;34:378–82.

Herpertz-Dahlmann B. Child Adolesc Psychiatric Clin N Am. 2008;18:31–47.

Herzog DB, Keller MB, Lavori PW, Kenny GM, Sacks NR. J Clin Psychiat. 1992a;53:147–52.

Herzog DB, Keller MB, Sacks NR, Yeh CJ, Lavori PW. J Am Acad Child Adolesc Psychiat. 1992b; 31:810–8.

Holliday J, Uher R, Landau S, Collier D, Treasure J. J Pers Disord. 2006;20:417–26.

Kaye WH, Bulik CM, Thornton L, Barbarich N, Masters K. Am J Psychiat. 2004;161:2215–21.

Kennedy SH, Kaplan AS, Garfinkel PE, Rockett W, Toner B, Abbey SE. J Psychosomatic Res. 1994;38:773–82.

Kovacs M. Psychopharmacol Bull. 1985;21:995–8.

Krol NP. J Am Acad Child Adolesc Psychiat. 1990;29:986–7.

Levy AB, Dixon KN. Int J Eating Disord. 1985;4:389–405.

Lewinsohn P, Striegel-Moore R, Seeley J. J Am Acad Child Adolesc Psychiat. 2000;39:1284–92.

Lilenfeld LR, Kaye WH, Greeno CG, Merikangas KR, Plotnicov K, Pollice C. Arch Gen Psychiat. 1998;55:603–10.

March JS, Sullivan K, Parker J. J Anxiety Disord. 1999;13:349–58.

Milos G, Spindler A, Schnyder U. Can J Psychiat. 2004;49:179–84.

Mouren-Simeoni MC, Fontanon M, Bouvard MP, Dugas M. Revue Can. de Psychaitrie. 1993; 38:51–5.

Muratori F, Viglione V, Maestro S, Picchi L. Psychopathology. 2004;37:92–7.

North C, Gowers S. Int J Eating Disord. 1999;26:386–91.

Overholser JC, Brinkman DC, Lehnert KL, Ricciardi AM. J Clin Child Adolesc Psychol. 1995;24:443–52.

Piran N, Lerner P, Garfinkel PE, Kennedy SH, Brouillette C. Int J Eat Disord. 1988;7:589–99.

Presnell K, Stice E, Seidel A, Madeley MC. Clin Psychol Psychother. 2009;16:357–65.

Rastam M. J Am Acad Child Adolesc Psychiat. 1992;31:819–29.

Reich W. J Am Acad Child Adolesc Psychiat. 2000;39:59–66.

Saccomani L, Savoini M, Cirrincione M, Verzellino F, Ravera G. J Psychosomatic Res. 1998; 44:565–71.

Salbach-Andrae H, Lenz K, Simmendinger N, Klinkowski N, Lehmkuhl U, Pfeiffer E. Child Psychiat Hum Dev. 2008;39:261–72.

Skodol AE, Rosnick L, Kellman D, Oldham JM, Hyler SE. Am J Psychiat. 1988;145:1297–9.

Smith C, Steiner H. J Am Acad Child Adolesc Psychiat. 1992;31:841–3.

Smith C, Feldman S, Nasserbakht A, Steiner H. J Am Acad Child Adolesc Psychiat. 1993;32:1237–45.

Spielberger CD, Gorsuch, RL, Lushene RE. Manual for the state-trait anxiety inventory. Palo Alto, CA: Consulting Psychologists Press; 1970.

Thompson-Brenner H, Eddy KT, Satir DA, Boisseau C, Westen D. J Child Psychol Psychiat. 2008;49:170–80.

Thornton C, Russell J. Int J Eat Disord. 1997;21:83–7.

The Research Units on Pediatric Psychopharmacology anxiety study group. J Am Acad Child Adolesc Psychiat. 2002;41:1061–9.

Viglione V, Muratori F, Maestro S, Brunori E, Picchi L. Psychopathology. 2006;39:255–60.

Williams JB. Arch Gen Psychiat. 1988;45:742–7.

Williams JBW, Gibbon M, First MB, Spitzer RL, Davis M, Borus J, Howes MJ, Kane J, Pope HG, Rounsaville B, Wittchen H. Arch Gen Psychiat. 1992;49:630–6.

Wonderlich SA, Swift WJ, Slomik HB, Goodman S. Int J Eat Disord. 1990;9:607–16.

Zaider TI, Johnson JG, Cockell S. Int J Eating Dis. 2000;28:58–67.

Chapter 159
ACTH, Cortisol, Beta Endorphin, Catecholamines, and Serotonin in Anorexia Nervosa: Implications for Behavior

Marie-Claude Brindisi and Daniel Rigaud

Abbreviations

AN	Anorexia nervosa
ACTH	Adrenocorticotropic hormone
CBG	Cortisol binding globulin
5-HIAA	5-hydroxyindolacetic acid
5-HT	5-hydroxytryptamine or Serotonin
CNS	Central nervous system
CRH	Corticotropin-releasing hormone
CSF	Cerebrospinal fluid
DHEA-S	Dehydroepiandrosterone-sulfate
ED	Eating disorder
FFA	Free fatty acid
NE	Norepinephrine
PET	Positron emission tomography
POMC	Proopiomelanocortin
SNS	Sympathetic nervous system
SPECT	Single photon emission computed tomography
SSRIs	Selective serotonin reuptake inhibitors

159.1 Introduction

Anorexia nervosa (AN) is a psychiatric disorder with a current prevalence of 1.5% and a mortality rate of 5–10%. AN is characterized by a dramatic decrease in energy and fat intake and by excessive physical exercise, which together result in physiological, biochemical, and behavioral disturbances. Excessive exercise is present in 40–80% of AN patients. In one-third to one-half of cases, AN patients control their body weight by purging, vomiting, or even laxative abuse, or by using diuretics. Two subtypes of AN have been identified: Restricting-type AN patients lose weight by pure dieting;

M.-C. Brindisi (✉)

Endocrinology and Nutrition Department, CHU le Bocage (Dijon University Hospital),
BP 77908, 21079 Dijon Cedex,
e-mail: marie-claude.brindisi@chu-dijon.fr

bulimic anorexics also restrict food, but engage in inappropriate episodic compensatory behaviors (binge-purge behavior).

Understanding of how genetic and neurobiologically mediated mechanisms contribute to the likelihood of developing eating disorders (ED) is growing. In this review, we will focus on the role of hormones, above all adrenocorticotropic hormone (ACTH) and cortisol, and neurotransmitter pathways.

159.2 Corticotrope Axis

The adrenal glands of AN patients produce more cortisol in response to ACTH than do those of normal women (Gold et al. 1986). Thus, an increase in 24h-urinary free cortisol (Bliss and Migeon 1957), and a 30% increase in plasma cortisol, with a normal nycthemeral cycle, are observed with normal levels of cortisol-binding globulin (CBG). Most studies have reported maintenance of a plasma cortisol rhythm in AN patients (Boyar et al. 1977). The rhythm of both the free salivary cortisol secretion and the plasma cortisol has been investigated by Putignano et al. (2001). The authors pointed out that the circadian rhythm was maintained in blood and saliva levels, although they reported a "flattening" of the 24-h cortisol concentration curve in AN patients as compared to controls (Putignano et al. 2001). Dos Santos et al hypothesized that this flattened daily curve of cortisol may reflect altered circadian rhythm in some, but not all of the patients included in the analysis (dos Santos et al. 2007). Sensitivity of the corticotrope axis to the inhibitory effect of a free fatty acid load (FFA) is preserved, like in healthy adult subjects (Lanfranco et al. 2006).

Most investigators have attributed the elevated level of plasma cortisol to dysfunctions in hypothalamic mechanisms that control ACTH secretion in AN patients, but the mechanisms involved have not been fully clarified. The elevated serum concentration of cortisol results partly from increased secretion, and partly from increased half-life due to malnutrition and hypometabolism; changes such as a decrease in the metabolic rate of cortisol clearance have been reported too, suggesting a dysfunction in peripheral glucocorticoid metabolism (Vierhapper et al. 1990). A nearly constant finding in AN patients is the response to ACTH, which contrasts with the weakened response to stimulation with corticotropin- releasing hormone (CRH). Moreover, CRH hypersecretion has been observed frequently in AN: patients have a high level of CRH in their cerebrospinal fluid (CSF). Studies on cortisol and ACTH responses to the dexamethasone-suppression test or the response to a competitive glucocorticoid antagonist showed abnormal cortisol suppression and high CRH secretion. Finally, CRH activates the same cerebral area as the one associated with stress and causes anorexia, an increase in motor activity, and a decrease in sexual activity. It appears that these high levels of cortisol and ACTH are secondary to weight loss, since they are normalized by weight gain. Nevertheless, they could also have a pathophysiological role, since in AN patients, low weight is associated with anxiety in 40% of the patients, true anorexia in some patients, and sexual dysfunction in most of them, which may decrease after weight gain. The hypersecretion of CRH, ACTH, and cortisol could be part of a vicious circle in AN patients, by counteracting the need to eat and increasing the risk of binge-eating in malnutrition.

The mechanisms of the flattened cortisol rhythm still need to be elucidated. Besides the effects of the central nervous system (CNS) on the hypothalamic–pituitary–adrenal axis, other factors could be involved, such as reduction in CBG levels due to the low estrogen levels and/or by the malnourished status of these patients (dos Santos et al. 2007).

A high level of cortisol is not associated with an increase in other ACTH-dependent adrenal hormones, such as dehydroepiandrosterone sulfate (DHEA-S). Sirinathsinghji and Mills (1985) demonstrated that in AN patients, hypercortisolism is observed together with a loss of DHEA-S rhythm,

and a low DHEA-S level. This situation cannot be explained by the mechanisms involved in the increase in cortisol.

This excess of cortisol could be responsible for lanugo and for the decrease in bone formation, and could also be implicated in the feeling of well-being observed in denutrition. Moreover, the size of the increase in fasting serum cortisol levels is dependent on the severity of the fasting hypoglycemia observed in these patients (Casper 1996).

159.3 Beta-endorphin

The opioid system has a direct influence on eating behavior and motor activity. It certainly plays a role in the ability of predators to catch their prey in the wild: endorphin, secreted with cannabinoids, decreases pursuit-related pain and fatigue. One may suppose that in AN patients the oversecretion of beta-endorphin enables them to deny the seriousness of their malnutrition and to endure the pain and distress related to their disease. Despite some discrepancies among studies, an increase in beta-endorphin activity has been observed in AN patients (Ericsson et al. 1996). Whereas moderately high levels of beta-endorphin stimulate feeding, higher levels allow tolerance to starvation (Hubner 1993).

Feeding blindly by a nasogastric tube induced a dose-dependent decrease in beta-endorphin and a dose-dependent increase in levels of ACTH, cortisol, norepinephrine, and dopamine in hospitalized malnourished AN patients. There was no significant change in these variables in healthy women (Rigaud et al. 2007). The decrease in the level of beta-endorphin could partly explain the abdominal discomfort, the anxiety, and the depressive state after a meal. This could also explain why some AN patients feel the need to engage in physical activity after a meal, because exercise stimulates the release of beta-endorphin. With this drop after a meal, there is a loss of the sensory benefit related to the elevated fasting level of beta-endorphin (Russell et al. 2001).

159.4 Catecholamines

159.4.1 1-Dopamine

Several symptoms of AN, such as excessive exercise, reduction in food intake, and amenorrhea have been attributed to dopamine dysfunction (Barry and Klawans 1976). Most studies have found abnormalities in peripheral and central noradrenergic activity in ill AN patients (Pirke 1996). But the results are inconsistent. For example, homovanillic acid, the major metabolite of dopamine in humans, is decreased in the CSF of AN subjects (Kaye et al. 1984). But Jimerson (1993) found normal CSF levels of dopamine in their AN patients.

By contrast, Barbato et al. (2006) showed significant increase in the eye-blink rate in their AN patients. Such an increase suggests excessive central dopaminergic activity, since the eye-blink rate is a peripheral measure of central dopaminergic activity. Moreover, a trait-related disturbance of dopamine metabolism has been shown to contribute to vulnerability to restricting-type AN (Kaye et al. 1999)

In activity-based anorexia in rats, an animal model mimicking AN, treatment with a dopaminergic antagonist inhibits anorexic behavior (Verhagen et al. 2009). This result suggests that hyperactive behavior and reduced food intake observed in anorexic patients may be treated by dopamine receptor antagonists. Antipsychotics may therefore be considered in the treatment of AN patients, when reducing an important hyperactive behavior is likely to accelerate body weight gain.

159.4.2 2-Norepinephrine

Catecholamines, especially norepinephrine (NE), are the main lipolytic hormones in human. In some studies, based on the levels of NE in plasma, urine or CSF, lower basal sympathetic nervous system (SNS) activity was found in AN patients compared with healthy controls (Pirke 1996). This contrasts with basal NE levels in subcutaneous abdominal adipose tissue which were markedly higher in AN patients than in healthy women, suggesting an increase in SNS activity in this area (Nedvidkova et al. 2004).

159.4.3 Serotonin

Serotonin (5-hydroxytryptamine, 5-HT) is a brain neurotransmitter that plays a key role in satiety (Leibowitz 1990). A lot of data are available concerning serotonin and AN. High serotonin activity could be responsible for anxiety, sleep deprivation, excessive physical exercise, true anorexia (loss of appetite), a feeling of high power, and denial of nervous and physical exhaustion (Capasso et al. 2009). In contrast, depressed serotonin activity could be responsible for a depressive mood and binge eating (symptoms frequently observed after months or years of AN). It is well known that estrogens modulate serotonergic function as well as levels of CRH; this could be why AN often begins after puberty, during late adolescence. A recent review suggested that anorexia is linked to a disturbed serotonin system (Kaye et al. 2005). Low cerebral-spinal fluid levels of the serotonergic metabolite 5-hydroxyindolacetic acid (5-HIAA) have been found in AN patients as compared to healthy women. This low level normalizes after weight gain (Kaye et al. 1988). Whether this is caused by reduction in dietary supplies of the 5-HT synthesizing amino-acid tryptophan, or by other effects of malnutrition on hormonal or neurotransmitter systems remains uncertain.

Altered brain serotonin function thus contributes to the dysregulation of appetite, mood, and impulse control in AN. A trait-related disturbance of 5-HT neuronal modulation precedes the onset of AN and contributes to premorbid symptoms of anxiety, obsessionality, and inhibition (Steiger et al. 2004). Such a dysphoric temperament may involve the inherent dysregulation of emotional and reward pathways which also mediate the hedonic aspects of feeding, thus making these individuals vulnerable to disturbed appetitive behaviors. Restricting food intake may become powerfully reinforced because it provides a temporary respite from a dysphoric mood. Puberty-related female gonadal steroids or age-related changes may exacerbate 5-HT dysregulation. Stress and/or cultural and social pressures may contribute by aggravating an anxious and obsessional temperament. AN patients may discover that reduced dietary intake, by reducing plasma tryptophan availability, is a means by which they can modulate brain 5-HT functional activity and anxiety (Kaye 2008).

Platelet monoamine oxidase activity has been proposed as an index of cerebral serotonin activity. Studies in AN patients have shown contradictory results: in 59 malnourished AN patients, platelet monoamine oxidase activity was similar to that observed in normal women. In contrast, in 35 AN patients who had recovered their normal BMI, it was 20% lower than in normal controls (Ehrlich et al. 2008). Diaz-Marsa et al. (2000) found lower than normal platelet monoamine oxidase activity in their malnourished AN patients. Biederman et al. (1984) hypothesized that this low platelet monoamine oxidase activity could be related to a depressive mood, since they found low levels in their 13 depressive AN patients, and normal levels in their 18 nondepressive AN patients, as compared with 28 matched normal control subjects. Carrasco et al. (2000) reported

that this low level was found both in bulimia nervosa patients and in patients with the binge/purging form of AN.

The efficacy of antidepressant medications in the treatment of eating disorders has been tested. Cyroheptatide, a drug with 5-HT properties has been tried to accelerate weight gain in AN. The effect of the drug was quite small (Halmi et al. 1986). Whereas antidepressants have been shown to be effective in patients with bulimia nervosa, initial studies with traditional antidepressant agents in AN patients only showed a limited benefit. Several studies have failed to demonstrate any beneficial effect of including selective serotonin reuptake inhibitors (SSRIs) in the treatment of hospitalized AN patients (Ferguson et al. 1999).

Moreover, AN patients who have recovered their normal weight often have persisting psychological symptoms that are accompanied by a significant risk of recurrent low-weight episodes. This has led to interest in studies on relapse prevention. A clinically-based, prospective, longitudinal, follow-up study failed to show any significant benefit of treatment with fluoxetine (SSRI) (Strober et al. 1997). However, recent data from a double-blind, placebo-controlled trial in weight-restored patients demonstrated that treatment with fluoxetine was associated with a reduced relapse rate and reductions in depression, anxiety, obsessions, and compulsions. This study showed that after 1 year, 10 of 16 subjects treated with fluoxetine remained well while only 3 of 19 subjects who received placebo remained well (Kaye et al. 2001).

Today, new technology using brain imaging with radioligands may lead to a better understanding of brain 5-HT neurotransmitter function and its dynamic relationship with human behavior. Up to now, single photon emission computed tomography (SPECT) and positron emission tomography (PET) studies have been used. The 5-HT2A receptor is of interest because it is thought to be involved in the regulation of feeding, mood, and anxiety, and in the action of antidepressants. Other studies of ill, underweight AN patients, which used SPECT with a 5-HT2A receptor antagonist (Audenaert et al. 2003), found a significant reduction in 5-HT2A receptor activity in the left frontal cortex, the left and right parietal cortex, and the left and right occipital cortex. These studies are consistent in that they report reduced 5-HT2A activity in cortical regions in AN, and the findings are independent of the severity of the illness. These studies raise the possibility that anorexic subtypes may share a disturbance of 5-HT2A receptor activity in the subgenual cingulate, whereas regional differences in 5-HT2A receptor activity may distinguish between ED subgroups after recovery. The subgenual cingulate is thought to play a role in emotional and autonomic responses (Freedman et al. 2000), and a disturbance in this region has been implicated in mood disorders. Mood disturbances are common in individuals with EDs, although there is some controversy as to whether EDs and mood disorders are transmitted from generation to generation independently or together (Lilenfeld et al. 1998). These data raise the possibility that some factor related to subgenual cingulated function, perhaps related to mood and autonomic modulation, creates a predisposition for anorexia.

A chapter of this book is devoted to HT1A receptor images.

159.5 Applications to Other Areas of Health and Disease

AN is a complex disease involving psychological, sociological, and neurobiological components. By understanding these mechanisms, physicians will be able to treat this eating disorder using not only dietetic and psychiatric approaches, but also chemical approaches. Nevertheless, because of the contradictions between studies and the current lack of knowledge, AN is still difficult to treat. Hopefully, as new technologies like imaging (developed in another chapter) become increasingly available, they may open doors to new therapeutic approaches (Table 159.1).

Table 159.1 Key features of biology in anorexia nervosa

1. An excess of cortisol is observed in AN with a normal nycthemeral cycle. A nearly constant finding in AN patients is the normal response to ACTH, which contrasts with the weakened response to stimulation with corticotropin- releasing hormone (CRH).
2. An increase in beta-endorphin activity has been observed in AN patients. During refeeding, there is a decrease in the level of beta-endorphin.
3. Results about catecholamines are inconsistent.
4. Low cerebral-spinal fluid levels of the serotonergic metabolite 5-hydroxyindolacetic acid (5-HIAA) have been found in AN patients as compared to healthy women. This low level normalizes after weight gain.

This table lists the different biological abnormalities observed in anorexia nervosa

Summary Points

- Anorexia nervosa (AN) is a psychiatric diagnosis that describes an eating disorder characterized by low body weight and body image distortion with an obsessive fear of gaining weight.
- AN is a complex disease including social, psychological, and biological factors.
- An excess of cortisol is observed in AN, and could be responsible for lanugo, decrease in bone formation, and in the feeling of well-being observed in denutrition.
- Oversecretion of beta-endorphin enables AN patients to deny the seriousness of their malnutrition and to endure the pain and distress related to their disease.
- Serotonin plays a key role in satiety; however, several studies have failed to demonstrate any beneficial effect of selective serotonin reuptake inhibitors (SSRIs) in the treatment of hospitalized AN patients.
- New technology using brain imaging with radioligands may lead to a better understanding of brain serotonin neurotransmitter function and its dynamic relationship with human behavior.

Definitions of Key Terms

Anorexia nervosa: Anorexia nervosa (AN) is a psychiatric diagnosis that describes an eating disorder characterized by low body weight and body image distortion with an obsessive fear of gaining weight.

Corticotrop axis: Corticotrop axis is the hypothalamic–pituitary–adrenal axis. CRH (Corticotropin-releasing hormone) from the hypothalamus stimulates ACTH (in the pituitary gland) in a pulsatile manner, and ACTH stimulates the secretion of glucocorticoids (cortisol) from the adrenal cortex.

Beta-endorphin: Beta-endorphin is an endogenous opioid peptide neurotransmitter found in the neurons of both the central and peripheral nervous system. It is a peptide 31 amino acids long, resulting from processing of the precursor proopiomelanocortin (POMC).

Catecholamines: Catecholamines are molecules that have a catechol nucleus. They include dopamine, norepinephrine and epinephrine. Epinephrine is synthesized mainly in the adrenal medulla, whereas norepinephrine is found not only in the adrenal medulla but also in the central nervous system and in the peripheral sympathetic nerves. Dopamine, the precursor of norepinephrine, is found in the adrenal medulla and in noradrenergic neurons.

Serotonin: Serotonin is a monoamine neurotransmitter. It is found extensively in the gastrointestinal tract of animals, and about 80–90% of the human body's total serotonin is located in the enterochromaffin cells in the gut, where it is used to regulate intestinal movements. The remainder is synthesized in serotonergic neurons in the central nervous system where it has various functions, including control of appetite, mood, and anger.

References

Audenaert K, Van Laere K, Dumont F, Vervaet M, Goethals I, Slegers G, Mertens J, van Heeringen C, Dierckx RA. J Nucl Med. 2003;44 (2):163–9.

Barbato G, Fichele M, Senatore I, Casiello M, Muscettola G. Psychiatry Res. 2006;142:253–5.

Barry VC, Klawans HL. J Neural Transm. 1976;38:107–22.

Biederman J, Rivinus TM, Herzog DB, Ferber RA, Harper GP, Orsulak PJ, Harmatz JS, Schildkraut JJ. Am J Psychiatry. 1984;141 (10):1244–7.

Bliss EL, Migeon CJ. J Clin Endocrinol Metab. 1957;17:766–76.

Boyar RM, Hellman LD, Roffwarg H, Katz J, Zumoff B, O'Connor J, Bradlow HL, Fukushima DK. N Engl J Med. 1977;296:190–98.

Capasso A, Petrella C, Milano W. Rev Recent Clin Trials. 2009;4:63–9.

Carrasco JL, Díaz-Marsá M, Hollander E, César J, Saiz-Ruiz J. Eur Neuropsychopharmacol. 2000;10 (2):113–7.

Casper RC. Psychiatry Res. 1996;62:85–96.

Díaz-Marsá M, Carrasco JL, Hollander E, César J, Saiz-Ruiz J. Acta Psychiatr Scand. 2000;101 (3):226–30.

dos Santos E, dos Santos J, Ribeiro RP, Rosa E Silva AC, Moreira AC, Silva de Sá MF. J Pediatr Adolesc Gynecol. 2007;20:13–8.

Ehrlich S, Franke L, Schott R, Salbach-Andrae H, Pfeiffer E, Lehmkuhl U, Uebelhack R. Pharmacopsychiatry. 2008;41 (6):226–31.

Ericsson M, Poston WS 2nd, Foreyt JP. Addict Behav. 1996;21 (6):733–43.

Ferguson CP, La Via MC, Crossan PJ, Kaye WH. Int J Eat Disord. 1999;25 (1):11–7.

Freedman LJ, Insel TR, Smith Y. J Comp Neurol. 2000;421:172–88.

Gold PW, Gwirtsman H, Avgerinos PC, Nieman LK, Gallucci WT, Kaye W, Jimerson D, Ebert M, Rittmaster R, Loriaux DL, et al. N Engl J Med. 1986;314:1335.

Halmi KA, Eckert E, LaDu TJ, Cohen J. Arch Gen Psychiatry. 1986;43 (2):177–81.

Hubner HF. In: Hubner HF, editor. Endorphins, eating disorders, and other addictive behaviors. New York: WW Norton & Company; 1993.

Jimerson DC. In: Ferrari E, Brambilla F, Solerte SB, editors. The role of central catecholamine pathways in eating disorders. Primary and secondary eating disorders: a psychonettroendocrine and metabolic approach. Oxford: Pergamon Press; 1993. p. 5944–5952.

Kaye W. Physiol Behav. 2008;94 (1):121–35.

Kaye WH, Ebert MH, Raleigh M, Lake R. Arch Gen Psych. 1984;41:350–5.

Kaye WH, Gwirtsman HE, George DT, Jimerson DC, Ebert MH. Biol Psychiatry. 1988;23:102–5.

Kaye WH, Frank GKW, McConaha C. Neuropsychopharmacology. 1999;21:503–6.

Kaye WH, Nagata T, Weltzin TE, Hsu LK, Sokol MS, McConaha C, Plotnicov KH, Weise J, Deep D. Biol Psychiatry. 2001;49 (7):644–52.

Kaye WH, Frank GK, Bailer UF, Henry SE, Meltzer CC, Price JC, Mathis CA, Wagner A. Physiol Behav. 2005;85 (1):73–81.

Lanfranco F, Gianotti L, Picu A, Giordano R, Daga GA, Mondelli V, Malfi G, Fassino S, Ghigo E, Arvat E. Eur J Endocrinol. 2006;154:731–8.

Leibowitz. SF. Drugs. 1990;39:33–48.

Lilenfeld LR, Kaye WH, Greeno CG, Merikangas KR, Plotnicov K, Pollice C, Rao R, Strober M, Bulik CM, Nagy L. Arch Gen Psychiatry. 1998;55 (7):603–10.

Nedvídková J, Dostálová I, Barták V, Papezov H, Pacák K. Physiol Res. 2004;53 (4):409–13.

Pirke KM. Psychiatry Res. 1996;62:43–9.

Putignano P, Dubini A, Toja P, Invitti C, Bonfanti S, Redaelli G, Zappulli D, Cavagnini F. Eur J Endocrinol. 2001;145:165–71.

Rigaud D, Vergès B, Colas-Linhart N, Petiet A, Moukkaddem M, Van Wymelbeke V, Brondel L. J Clin Endocrinol Metab. 2007;92 (5):1623–9.

Russell J, Baur LA, Beumont PJ, Byrnes S, Gross G, Touyz S, Abraham S, Zipfel S. Psychoneuroendocrinology. 2001;26:51–63.

Sirinathsinghji DJ, Mills IH. Acta Endocrinol. 1985;108:255–61.

Steiger H, Gauvin L, Israel M, Kin NM, Young SN, Roussin J. J Clin Psychiatry. 2004;65 (6):830–7.

Strober M, Freeman R, DeAntonio M, Lampert C, Diamond J. Psychopharmacol Bull. 1997;33 (3):425–31.

Verhagen LAW, Luijendijk MCM, Hillebrand JJG, Adan RAH. Eur Neuropsychopharmacol. 2009;19:153–60.

Vierhapper H, Kiss A, Nowotry P, Wiesnagrotzki S, Monder C, Waldhausl W. Acta Endocrinol. 1990;122:753–8.

Part XXVI
Bulimia Nervosa and Night Eating Syndrome

Chapter 160
Ethnicity in Bulimia Nervosa and Other Eating Disorders

Athena Robinson and W. Stewart Agras

Keywords Anorexia nervosa • Bulimia nervosa • Binge eating disorder • Obesity • Minorities • Treatment

Abbreviations

BMI   Body mass index
WHO   World Health Organization

160.1 Introduction

Historically, epidemiological studies of eating disorders have focused on white women and girls and relatively little research has been conducted utilizing participants from racial and ethnic minority groups (National Eating Disorder Association (NEDA) 2005). Consequently, eating disorders are often described as affecting primarily white women of high socio-economic classes (American Psychiatric Association 1993; Fairburn and Beglin 1990; Striegel-Moore and Smolak 1996). Thus, research prior to the mid-1990s typically reported that eating disorders were less common among specific minority groups in the United States including blacks, Hispanics, Native Americans, and Asian Americans (Dolan 1991; Hsu 1987; Jones et al. 1980). However, more recent empirical studies suggest that minority populations are substantially affected by disordered eating behaviors (Yanovski 2000, Streigel-Moore et al. 2003; Taylor et al. 2007).

This chapter provides a review of the occurrence of disordered eating among ethnic minority groups for anorexia nervosa, bulimia nervosa, binge eating disorder, overweight and obesity, and dieting and other forms of body disturbance. Discussion of issues related to assessment and access to treatment, and areas for future research are provided.

A. Robinson (✉)

Department of Psychiatry and Behavioral Sciences, Stanford University, School of Medicine, 401 Quarry Road, Stanford, CA 94305-5722
e-mail: athenar@stanford.edu

Table 160.1 Prevalence rates of anorexia nervosa, bulimia nervosa, binge eating disorder, and any binge eating

		Lifetime prevalence n (%)			
Reference	Sample	Anorexia nervosa	Bulimia nervosa	Binge eating disorder	Any binge eating
Streigel-Moore et al. (2003)	985 white women	15 (1.5)	23 (2.3)	27 (2.7)	–
	1061 black women	0	4 (.4)	15 (1.4)	–
Taylor et al. (2007)	5191 African American and Caribbean Black adults	7 (.17)	79 (1.49)	88 (1.66)	245 (5.08)
	Adolescents[a]	2 (.07)	5 (.40)	4 (.28)	18 (1.56)
Alegria et al. (2007)	2554 Latino adults	2 (.08)	41 (1.61)	49 (1.92)	143 (5.61)
Nicado et al. (2007)	2095 Asian American adults	2 (.08)	23 (1.09)	43 (2.04)	91 (4.35)

This table lists the prevalence rates of anorexia nervosa, bulimia nervosa (BN), binge eating disorder, and binge eating as reported by four recent studies

Rates for Alegria et al. 2007 and Nicado et al. 2007 were calculated by A. Robinson using percentage data provided in manuscripts

–Data not provided by study

[a] Only 12-month prevalence rates for adolescents provided by original paper

160.2 Prevalence Rates

Table 160.1 outlines data from four recent studies that provide prevalence estimates of anorexia nervosa, bulimia nervosa, binge eating disorder, and the presence of any binge eating among whites, blacks, Latinos, and Asian Americans. Taken together these studies suggest, with the exception of anorexia nervosa among blacks, that the rates of disordered eating behaviors among ethnic minorities are substantial.

160.2.1 Anorexia Nervosa

General anorexia nervosa prevalence estimates are approximately 0.3 among young females (Hoek 2006; Hoek and van Hoeken 2003) with crude mortality rates ranging from 5.1% to 7.4% (Herzog et al. 2000; Sullivan 1995; Crow et al. 1999) and relatively poor prognosis (Steinhausen 2002). Key features of anorexia nervosa are outlined in Table 160.2.

Prevalence rates of lifetime criteria for anorexia nervosa among 2,046 young black and white women assessed via telephone and confirmatory in-person diagnostic interviews were reported as 15 (1.5%) and 0 (0%) for white and black women respectively (Striegel-Moore et al. 2003). Another recent study interviewed a nationally representative sample of 5,191 African American and Caribbean black adults and adolescents and found that anorexia nervosa was the rarest eating disorder among African American adults and adolescents and that no single case of anorexia nervosa of at least 12-months in duration was found among Caribbean black adults (Taylor et al. 2007). Other authors echo the rarity of anorexia nervosa among black women (Hoek 2006; Mullholland and Mintz 2001). Results from the National Latino and Asian American Study (NLAAS) indicate that 2 women out of 2,554 Latinos (1,127 male, 1,427 female) met lifetime criteria for anorexia nervosa and none met current criteria for anorexia nervosa or subthreshold anorexia nervosa (Alegria et al. 2007). Lifetime and 12-month prevalence rates of anorexia nervosa among a nationally representative sample of 2,095 Asian Americans (998 male, 1,097 female) were reported as 0.08% and 0.02% for men and women respectively (Nicado et al. 2007).

Table 160.2   Key features of anorexia nervosa

Disorder	Features
Anorexia Nervosa	• Refusal to maintain body weight at or above minimum normal weight for age and height
	• Intense fear of weight gain
	• Disturbance in perception and experience of body weight and/or shape, or denial of the seriousness of low body weight
	• Amenorrhea (the absence of menstruation)

This table lists the key features of anorexia nervosa, including behavioral and cognitive symptoms and physical manifestations. Diagnostic criteria are described fully in the Diagnostic and Statistical Manual of Mental Disorders, 4th ed (DSM IV) (APA 1994)

Table 160.3   Key features of bulimia nervosa

Disorder	Features
Bulimia nervosa	• Recurrent episodes of binge eating
	• Purging behaviors (such as vomiting, laxative abuse, or compulsive exercise) used to control weight and shape
	• Self-evaluation largely based on perceptions of body shape and weight

This table lists the key features of bulimia nervosa including behavioral and cognitive symptoms. Diagnostic criteria are described fully in the Diagnostic and Statistical Manual of Mental Disorders, 4th ed (DSM IV) (APA 1994)

While firm conclusions cannot be drawn regarding the prevalence of anorexia nervosa among ethnic minority groups, data to date suggest that rates of anorexia nervosa are lower among ethnic minority groups than among their white counterparts, and are particularly low among blacks.

160.2.2 Bulimia Nervosa

General prevalence rates of bulimia nervosa have been estimated at 1% among young females (Hoek 2006). Key features of bulimia nervosa are outlined in Table 160.3.

Striegel-Moore and colleagues (2003) reported lifetime prevalence rates for bulimia nervosa among 2,046 young white and black women to be 23 (2.3%) and 4 (0.4%), respectively, and concluded that bulimia nervosa is less common among blacks than white women. Among 4997 African American and Caribbean black adults, 79 (1.49%) and 38 (0.69%) met lifetime and 12-month criteria for bulimia nervosa respectively (Taylor et al. 2007). Rates of bulimia nervosa were significantly lower among black than white college women (Gray et al. 2006) and no cases of bulimia nervosa were found among 421 black college women enrolled at a predominately white public university (Mulholland & Mintz, 2001). Alegria et al. (2007) reported a lifetime and 12-month bulimia nervosa prevalence rate of 0.08% and 0.03% respectively among a sample of 2,554 Latinos. Lifetime and 12-month prevalence rates of bulimia nervosa among 2,095 Asian American adults were 1.09% and 0.36% respectively (Nicado et al. 2007). Women from four ethnic groups (Hispanic, Asian–American, black, white) were equally likely to present behavioral symptoms of bulimia nervosa (Regan and Cachelin 2006). Similarly, a review noted bulimia nervosa rates among white women were not significantly greater than nonwhite women (Wildes et al. 2001).

160.2.3 Binge Eating Disorder

Binge eating disorder impacts approximately 2–5% of the general population (Bruce and Agras 1992) and up to 30% of weight control program participants (Spitzer et al. 1992, 1993). Key features

Table 160.4 Key features of binge eating disorder

Disorder	Features
Binge eating disorder	• Recurrent episodes of binge eating • Binge episodes are associated with some of the following: eating much more rapidly than normal, eating until uncomfortably full, eating large amounts of food when not physically hungry, eating alone due to embarrassment over food quantity consumed, and feeling depressed, guilty, or disgusted after eating • No purging behavior present

This table lists the key features of binge eating disorder including behavioral and cognitive symptoms. Diagnostic criteria are described fully in the Diagnostic and Statistical Manual of Mental Disorders, eth ed (DSM IV) (APA 1994)

of binge eating disorder are outlined in Table 160.4. The literature is in agreement that binge eating is the most prevalent disordered eating behavior among minority groups. Data from field studies reported comparable rates of binge eating disorder in white and black women (Spitzer et al. 1992, 1993) and some studies suggest that binge eating rates among black women are equal or even more common than among white women (Striegel-Moore and Smolak 2000). Similar lifetime prevalence rates of binge eating were found among adults of three minority groups: African American and Caribbean blacks at 5.08% (Taylor et al. 2007), Latinos at 5.61% (Alegria et al. 2007), and Asian Americans at 4.35% (Nicado et al. 2007).

160.2.4 Applications: Overweight and Obesity

Overweight and obesity are one of the leading causes of morbidity and mortality in the USA (US Department of Health and Human Services 2001) and obesity may be a risk factor for binge eating disorder. These conditions are particularly prevalent among some ethnic minority and immigrant groups in the USA including African–Americans and Hispanics (Centers for Disease Control (CDC) 2003). For example, Mexican American adults have reported higher rates of overweight (11% higher for males; 26% higher for females) and obesity (7% higher for males; 32% higher for females) than non-Hispanic whites. Similarly, Mexican–American adolescents aged 12–19 years reported higher rates of overweight (112% higher for males and 59% higher for females) than non-Hispanic white adolescents. Acculturation to the USA has been identified as a risk factor for obesity-related behaviors, specifically the high frequency of eating fast food and low rates of physical activity among Asian–Americans and Hispanic adolescents (Lauderdale and Rathouz 2000; Unger et al. 2004).

Overweight rates among Asian–Americans are relatively low compared to other ethnic minority groups (Lauderdale and Rathouz 2000). Whereas Asian-Americans have been found to have lower Body Mass Index (BMI), they have a higher percent body fat than whites (Wang et al. 1994). A World Health Organization (WHO) expert consultation recently reviewed evidence suggesting that Asian populations have different associations between BMI, percent body fat, and health risks than European populations and concluded that while the international BMI specifications (<18.50 = underweight, 18.50–24.99 = normal weight, 25.00–29.99 = overweight, and >30.00 = obese; WHO 2000) should be retained, the proportion of Asians with a high risk of type 2 diabetes and cardiovascular disease is substantial at BMIs lower than the existing WHO cut-off point for overweight (WHO Expert Consultation 2004).

Findings from clinic, community, and population-based studies note that binge eating disorder is associated with overweight and obesity (Bruce and Agras 1992; Fairburn et al. 2000; Smith et al. 1998, Spitzer et al. 1992; Striegel-Moore et al. 2000) and the prevalence of binge eating increases with BMI (Telch et al. 1988). Given the high rates of obesity among ethnic minority populations, experts have hypothesized that binge eating or binge eating disorder is a significant concern among

these groups (Striegel-Moore and Smolak 2000). Interestingly, a recent study found that despite white women having statistically significant higher rates of binge eating disorder than black women (2.7% vs 1.4%), black women remained significantly more likely than white women to have ever been obese and be currently obese (Striegel-Moore et al. 2003). More data on the association between overweight/obesity and binge eating disorder in minority populations is needed.

160.3 Rates of General Disordered Eating Behaviors

Key features of disordered eating behaviors are outlined in Table 160.5.

160.3.1 Among Minorities

Various studies note the presence of general disordered eating behaviors among minority populations. For example, Hispanics were found to have equal rates of eating disturbances compared to whites, while blacks, Native Americans, and Asian Americans had lower rates than whites (Crago et al. 1996). However, black females in South Africa had higher rates of eating disorder symptoms than white females (Le Grange et al. 1998; Szabo and Hollands 1997). Black college women reported less fear and discouragement concerning food and weight control than white women (Gray et al. 2006). A meta-analytic review, based on data from over 17,000 participants, indicated that as a whole, white women living in Western countries experience greater eating disturbance and body dissatisfaction than nonwhite women (Wildes et al. 2001). However, results suggested that Asian American women report similar and in some cases higher levels of disordered eating than their white counterparts. For example, Asian women, who report weighing significantly less than white women, differ from white women in having higher body dissatisfaction in the magnitude of one-third of a standard deviation.

160.3.2 Among Adolescent Minorities

Research on disordered eating behaviors and dieting among adolescents from minority groups has also challenged preexisting assumptions about the prevalence of such behaviors. Data from the 1998 Minnesota Student Survey indicated that among 9th graders, 56% of girls and 28% of boys report disordered eating behavior (i.e., one or more of the following to lose weight: fasting or skipping meals, diet pills, vomiting, laxatives, and binge eating) and that among both genders, Hispanic and Native American youth reported the highest prevalence of disordered eating (Croll et al. 2002).

Table 160.5 Key features of disordered eating

Disordered eating	• Severe restriction of food intake (may include limiting type, quantity, or frequency of consumption)
	• Compensatory behaviors used to prevent weight gain such as laxative abuse, self-induced vomiting, fasting, diuretics, diet pills, and excessive exercise
	• Intense scrutiny of body (may include repetitively analyzing self in mirrors or pinching of body parts) or purposeful avoidance of seeing body (in mirrors or when changing clothes)
	• Negative feelings about body weight and shape
	• Self-esteem and self-evaluation largely influenced by perception of body weight and shape
	• Exaggerated sense of the importance of weight and shape

This table lists examples of various behavioral and cognitive symptoms of disordered eating

Another study found few differences between ethnic groups among adolescent girls on eating disorder symptoms whereas among boys, black, Native American, Asian/Pacific Islander, and Hispanic boys reported significantly more eating disorder symptoms than white boys (Austin et al. 2008).

Dieting was found to be associated with weight dissatisfaction, perceived overweight status, and low body pride among adolescents of all ethnic groups assessed (Story et al. 1995). Perceived overweight and body dissatisfaction were found to be consistent correlates of dieting and binge eating among white, black, Hispanic, Native American, and Asian American adolescent females (French et al. 1997). Among the leanest 25% of sixth and seventh grade girls, Hispanics and Asians reported significantly more body dissatisfaction than did white girls (Robinson et al. 1996). A survey of 6,504 adolescents indicated that Asians, blacks, Hispanics, and white adolescents all reported attempting to lose weight at similar rates (32.7%, 31.9%, 36.1%, 34.9%, respectively) while 48.1% of Native American adolescents were attempting to lose weight (Kilpatrick et al. 1999).

A recent study examining family adaptability, cohesion, and satisfaction among white and ethnic minority families of adolescents seeking treatment for BN found that there were no significant differences between whites and ethnic minority patients' perceived and ideal levels of family cohesion and adaptability, or level of family functioning (Hoste et al. 2007). Likewise, there were no significant differences between white and ethnic minority parents on these same measures. In fact, both white and ethnic minority patients perceived their families to be less cohesive than did their mothers and fathers and reported lower ideal levels of cohesion than their mothers and fathers.

160.4 Treatment

Primary care physicians play a critical role as a liaison between patients and potential eating disorder treatment. Such practitioners may benefit from being more aware of recent data on the prevalence of disordered eating behaviors among ethnic minority groups and attempt to provide thorough assessments to all suspect eating disorder presentations regardless of ethnic and/or racial backgrounds. In addition, increased knowledge regarding ethnic minorities' differing worldviews, values and beliefs, patterns of acculturation, assimilation, and immigration, effects of oppression, and ethnic identity, as well as naturally occurring individual differences within eating disorder diagnostic classification could serve to augment the physician's cultural sensitivity in assessment of eating disorder symptoms and provision of appropriate treatment referrals (NEDA 2005). A recent study found that ethnic minority patients were less likely to be referred for eating disorder treatment services than white patients although once treatment was offered, treatment type did not differ (Waller et al. 2009). Race-based stereotypes about the frequency of eating disorder among minorities have been found to prevent physician detection of eating disorder symptoms in black girls (Gordon et al. 2006). Data to date suggest the necessity of a re-evaluation of assumptions regarding who is susceptible to disordered eating in order to better ensure that our efforts to combat these issues are inclusive of all (NEDA 2005). In terms of response to treatment, a recent study found that black women, compared to other ethnic groups, demonstrated greater reductions in binge eating when treated with Interpersonal Psychotherapy rather than Cognitive Behavioral Therapy (Chui et al. 2007).

Erroneous assumptions about eating disorder prevalence, cultural influence, course of illness, and access to treatment among minority persons can create referral biases and differences in service availability and access and, consequently, make it more difficult to estimate the true prevalence of eating disorders in these groups (Dolan 1991; Crago et al. 1996). Data are needed to further our understanding about disordered eating behaviors among all ethnic and racial groups in order to prevent bias in assessment, prevention, and intervention endeavors.

160.5 Areas for Further Research

There remain a variety of areas in need of further research regarding disordered eating behaviors among ethnic minorities. First, further research is needed to better understand potential variation of psychosocial risk factors for eating disorders within a minority group. For example, a recent study of Hispanic women including Dominicans, Venezuelans, Columbians, Brazilians, Puerto Ricans, Central Americans, and Mexicans found that Dominicans, Venezuelans, and Columbians had significantly higher total scores on the Psychosocial Risk Factor Questionnaire and Concern subscale than White Non-Hispanics, Central Americans, and Mexicans (George et al. 2007) and that Puerto Ricans had significant higher BMIs and ideal body image scores than Brazilians. Second, additional longitudinal studies among minority groups, perhaps assessing eating disorder symptoms and risk factors within the same cohort over time, may serve to illuminate patterns that may change across the age span. The potential influence of level of acculturation on eating disorder development and maintenance, and the relationship between overweight/obesity and binge eating disorder among various minority groups should be explored further. It is also critical to ascertain variation in minority groups' access and response to eating disorder treatment. Last, consistent use of standardized eating disorder assessment instruments can facilitate cross-study comparisons. Such research will encourage the reexamination of assumptions regarding who is susceptible to disordered eating behaviors in order to better ensure that our prevention and intervention efforts are inclusive of all, regardless of ethnic and/or racial background.

Summary Points

- Data indicate that disordered eating behaviors are notably prevalent among ethnic minorities.
- It can be tentatively concluded that anorexia nervosa is rare among blacks.
- Data are mixed on whether the rates of bulimia nervosa among ethnic minority and white females differ.
- Rates of binge eating among ethnic minorities are higher than other forms of disordered eating.
- There remain a variety of areas in need of further research regarding disordered eating behaviors among ethnic minorities.
- Further studies of eating disturbances among minority groups are needed before firm conclusions can be made about disordered eating prevalence and risk factors in such groups.

Key Terms

Anorexia nervosa: Characterized by severely limiting food intake, refusal to maintain body weight at or above minimum normal weight for age and height, and intense fear of weight gain
Bulimia nervosa: Characterized by binge eating episodes that are followed by compensatory behaviors to prevent weight gain and reduce feelings of distention resulting from the binge episode
Binge eating disorder: Characterized by binge eating episodes without associated compensatory behaviors
Binge eating: Eating episodes defined as

(a) The consumption of an unusually large amount of food within a discrete time period (e.g., eating, within a 2-h time period, an amount of food that is unambiguously large) and

(b) Accompanied by a sense of loss of control over eating (e.g., feeling loss of control over type or quantity of food consumed, or unable to stop the episode from continuing once it has begun).

Purging: Compensatory behavior used to control weight and shape. Examples include laxative abuse, self-induced vomiting, fasting, diuretics, diet pills, and excessive exercise.

Disordered eating behaviors: Weight and shape controlling/influencing behaviors including but not limited to restrictive eating, fasting, excessive dieting and exercise, binge eating, vomiting, and abuse of laxatives, diet pills, diuretics.

Body Mass Index (BMI): A ratio that relates a person's body weight to their height. The ratio is weight (in kilograms) divided by height (in meters squared). Normal weight is defined as having a BMI of 18.5 through 24.9.

Overweight/obesity: Categorization based upon BMI. Overweight and obese are defined as having a BMI of 25.00–29.99 and greater than 30.00, respectively.

Ethnic minority: For the purposes of this chapter, ethnic minority refers to a subgroup of a population defined by ethnicity and/or race such as Asian Americans and Latinos.

Prevalence: A statistical concept which refers to the proportion of individuals in a population having a particular disease at a given time.

References

Alegria M, Woo M, Cao Z, Torres M, Meng X, Striegel-Moore R. Prevalence and correlates of eating disorders in Latinos in the United States. Int J Eating Disord. 2007; 40:S15–21.

American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4th ed. Washington, DC: Author; 1994.

American Psychiatric Association. Practice guidelines for eating disorders. Am J Psychiatry. 1993;150:212–28.

Austin SB, Ziyadeh NJ, Forman S, Prokop LA, Keliher A, Jacobs D. Screening high school students for eating disorders: results of a national initiative. Prevent Chronic Dis. 2008;5 (4):A114.

Bruce B, Agras WS. Binge eating in females: a population-based investigation. Int J Eating Disord. 1992;12:365–73.

Centers for Disease Control. Health, United States, 2003: table 68. Hyattsville, MD: US. Department of Health and Human Services, CDC, National Center for Health Statistics; 2003. Available at http://www.cdc.gov/nchs/data/hus/tables/2003/03hus068.pdf.

Chui W, Safer DL, Bryson SW, Agras SW, Wilson GT. A comparison of ethnic groups in the treatment of bulimia nervosa. Eating Behav. 2007;8(4):485–91.

Crago M, Shisslak CM, Estes LS. Eating disturbances among American minority groups: a review. Int J Eating Disord. 1996;19 (3):239–48.

Croll J, Neumark-Sztainer D, Story M, Ireland M. Prevalence and risk and protective factors related to disordered eating behavior among adolescents: relationship to gender and ethnicity. J Adolescent Health. 2002;31 (2):166–75.

Crow S, Praus B, Thuras P. Mortality from eating disorders – a 5 to 10 year record linkage study. Int J Eating Disord. 1999;26 (1):97–101.

Dolan B. Cross-cultural aspects of anorexia nervosa and bulimia: a review. Int J Eating Disord. 1991;10:67–8.

Fairburn CG, Beglin SJ. Studies of the epidemiology of bulimia nervosa. American Journal of Psychiatry. 1990;147:401–408.

Fairburn CG, Cooper Z, Doll HA, Norman P, O'Conner M. The natural course of bulimia nervosa and binge eating disorder in young women. Arch Gen Psychiatry. 2000;57:659–65.

French S, Story M, Neumark-Sztainer D, Downess B, Resnick M, Blum R. Ethnic differences in psychosocial and health behavior correlates of dieting, purging, and binge eating in a populations-based sample of adolescent females. Int J Eat Disord. 1997;22 (3):315–22.

Herzog DB, Greenwood DN, Dorer DJ, Flores AT, Ekeblad ER, Richards A, Blais MA, Keller MB. Mortality in eating disorders: a descriptive study. Int J Eating Disord. 2000;28 (1):20–6.

Hoek HW. Incidence, prevalence and mortality of anorexia nervosa and other eating disorders. Curr Opin Psychiatry. 2006;19 (4):389–94.

Hoek HW, van Hoeken D. Review of the prevalence and incidence of eating disorders. Int J Eating Disord. 2003;34 (4):383–96.

Hoste RR, Hewell K, LeGrange D. Family interaction among white and ethnic minority adolescents with bulimia nervosa and their parents. European Eating Disorders Review. 2007;15:152–158.

Hsu LKG. Are the eating disorders becoming more common in Blacks? Int J Eating Disord. 1987;6:113–24.

George VA, Erb AF, Harris CL, Casazza K. Psychosocial risk factors for eating disorders in Hispanic females of diverse ethnic background and non-Hispanic females. Eat Behav. 2007;8:1–9.

Gordon KH, Brattole MM, Wingate LR, Joiner TE. The impact of client race on clinician detection of eating disorders. Behav Ther. 2006;37 (4):319–25.

Gray JJ, Ford K, Kelly LM. The prevalence of bulimia in a black college population. Int J Eat Disord. 2006;6:733–40.

Jones DJ, Fox MM, Babigian HM, Hutton HE. Epidemiology of anorexia nervosa in Monroe County, New York: 1960–1976. Psychosom Med. 1980;42:551–8.

Kilpatrick M, Ohannessian C, Bartholomew J. Adolescent weight management and perceptions: an analysis of the National Longitudinal study of Adolescent Health. J Sch Health. 1999;69:148–52.

Lauderdale DS, Rathouz PJ. Body mass index in a US national sample of Asian Americans: effects of nativity, years since immigration and socioeconomic status. International Journal of Obesity and Related Metabolic Disorders. 2000;24:1188–1194.

Le Grange D, Telch CF, Tibbs K. Eating attitudes and behaviors in 1435 South African Caucasian and non-Caucasian college students. Am J Psychiatry. 1998;155:250–4.

Mullholland AM, Mintz LB. Prevalence of eating disorders among African American women. J Counsel Psychol. 2001;48:111–6.

National Eating Disorder Association. Eating disorders in women of color: explanations and implications. National Eating Disorder Association. 2005: www.nationaleatingdisorders.org

Nicado EG, Hong S, Takeuchi DT. Prevalence and correlates of eating disorders among Asian Americans: results from the National Latino and Asian American Study. Int J Eat Disord. 2007;40:S22–6.

Regan PC, Cachelin FM. Binge eating and purging in a multi-ethnic community sample. International Journal of Eating Disoders. 2006;39:523–526.

Robinson TN, Killen JD, Litt IF, Hammer LD, Wilson DM, Haydel KF, Hayward C, Taylor CB. Ethnicity and body dissatisfaction: are Hispanic and Asian girls at increased risk for eating disorders? J Adolescent Health. 1996;19:384–93.

Smith DE, Marcus MD, Lewis CE, Fitzgibbon M, Schreiner P. Prevalence of binge eating disorder, obesity, and depression in a biracial cohort of young adults. Ann Behav Med. 1998;20:227–32.

Spitzer RL, Devlin MJ, Walsh BT, Hasin D, Wing RR, Marcus MD, Stunkard A, Wadden T, Yanovski S, Agras WS, Nonas C. Binge eating disorder: a multisite field trail of the diagnostic criteria. Int J Eat Disord. 1992; 11:191–203.

Spitzer RL, Yanovski S, Wadden T, Wing R, Marcus MD, Stunkard A, Devlin M, Mitchell J, Hasin D, Horne RL. Binge eating disorder: Its further validation in a multisite study. Int J Eat Disord. 1993;13:137–53.

Steinhausen HC. The outcome of anorexia nervosa in the 20th century. Am J Psychiatry. 2002;159:1284–93.

Story M, French S, Resnick M, Blum R. Ethnic/racial and socioeconomic differences in dieting behaviors and body image perceptions in adolescents. Int J Eat Disord. 1995;18 (2):173–9.

Striegel-Moore R, Dohm FA, Kraemer HC, Taylor CB, Daniels S, Crawford PB, Schreiber GB. Eating disorders in black and white women. Am J Psychiatry. 2003;160:1326–31.

Striegel-Moore R, Smolak L. The role of race in the development of eating deisorders. In: Smolak L, Levine MP, Striegel-Moore R, editors. The developmental psychopathology of eating disorders. Mahwah: Lawrence Erlbaum Associates; 1996.

Striegel-Moore R, Smolak L. The influence of ethnicity on eating disorders in women. In Eisler RM, Hersen M, editors.Handbook of gender, culture, and health. Mahwah: Lawrence Erlbaum Associates; 2000. p. 227–254.

Striegel-Moore RH, Wilfley DE, Pike KM, Dohm FA, Fairburn CG. Recurrent binge eating in Black American women. Arch Fam Med. 2000;9:83–7.

Sullivan PF. Mortality in anorexia nervosa. Am J Psychiatry. 1995;152:1073–4.

Szabo CP, Hollands, C. Factors influencing eating attitudes in secondary girls in South-Africa – a preliminary study. S Afr Med J. 1997;87 (4):531–4.

Taylor JY, Caldwell CH, Baser RE, Faison N, Jackson JS. Prevalence of eating disorders among blacks in the National Survey of American Life. Int J Eat Disord. 2007;40: S10–4.

Telch CF, Agras WS, Rossiter EM. Binge eating increases with increasing adiposity. Int J Eat Disord. 1988;7:115–9.

Unger JB, Reynolds K, Shakib S, Spruijt-Metz D, Sun P, Johnson CA. Acculturation, physical activity, and fast-food consumption among Asian American and Hispanic adolescents. J Community Health. 2004;29:467–81.

US Department of Health and Human Services. The Surgeon General's call to action to prevent and decrease overweight and obesity. Rockville: US Department of Health and Human Services, Public Health Service, Office of the Surgeon General; 2001.

Waller G, Schmidt U, Treasure J, Emanuelli F, Alenya J, Crockett J, Murray K. Ethnic origins of patients attending specialist eating disorders services in a multiethnic urban catchment area in the United Kingdom. Int J Eat Disord. 2009;42:459–463.

Wang J, Thornton JC, Russell M, Burastero S, Heymsfield S, Pierson RN. Asians have lower body mass index (BMI) but higher percent body fat than do whites: Comparisons of anthropometric measures. Am J Clin Nutr. 1994;60:23–8.

Wildes JE, Emery RE, Simons AD. The roles of ethnicity and culture in the development of eating disturbance and body dissatisfaction: A meta-analytic review. Clin Psychol Rev. 2001;21 (4):521–51.

WHO Expert Consultation. Appropriate body-mass index for Asian American populations and its implication for policy intervention strategies. Lancet. 2004;363:157–163.

World Health Organization. Obesity: preventing and managing the global epidemic. Report of a WHO consultation, WHO Technical Report Series 854. Geneva: World Health Organization; 2000.

Yanovski SZ. Eating disorders, race, and mythology. Arch Fam Med. 2000;9:88.

Chapter 161
Dyscontrol in Women with Bulimia Nervosa: Lack of Inhibitory Control over Motor, Cognitive, and Emotional Responses in Women with Bulimia Nervosa

Sonia Rodríguez-Ruiz, Silvia Moreno, M. Carmen Fernández, Antonio Cepeda-Benito, and Jaime Vila

Abbreviations

AN	Anorexia nervosa
BN	Bulimia nervosa
ANR	Anorexia nervosa restrictive-type
ANBP	Anorexia nervosa binge/purging-type
BNP	Bulimia nervosa purging-type
BNNP	Bulimia nervosa non-purging-type
CDR	Cardiac defense response
DSM IV TR	Diagnostic and Statistical Manual of Mental Disorders, fourth edition
ED	Eating disorders
FCQ-T	Food Craving Questionnaire-Trait
GNG	Go/No-Go task
HRV	Heart rate variability
IAPS	International Affective Picture System
IGT	Iowa Gambling Task
SAM	Self-Assessment Manikin
SMR	Startle motor reflex

161.1 Introduction

The cardinal feature of bulimia nervosa (BN) is bouts of uncontrolled food intake (binges). During bingeing, individuals ingest large amounts of food while experiencing an uncontrollable desire to eat. Individuals with BN tend to be highly concerned or dissatisfied with their body shape and, as a consequence, repeatedly display compensatory behaviors aimed at preventing weight gain. Compensatory behaviors include purging, excessive exercise, dietary restraint, or fasting between periods of binge eating (APA 2000).

S. Rodríguez-Ruiz (✉)

Departamento de Personalidad, Evaluación y Tratamiento Psicológico, Facultad de Psicología, Universidad de Granada, Campus de la Cartuja s/n, 18071, Granada, Spain
e-mail: srruiz@ugr.es

Individuals with BN are characterized by obsessiveness and perfectionism and by their greater impulsivity in comparison to anorexia nervosa (AN) patients (Fairburn 1995). BN patients also tend to be emotionally unstable, experience strong food cravings (Cepeda-Benito and Gleaves 2001), and be prone to substance abuse, sensation seeking, and antisocial behaviors (Rosval et al. 2006; Ortega-Roldán et al. 2009).

161.2 Loss of Control Over Eating and Sexual Behaviors in Women with Bulimia Nervosa

There are reasons to suspect that BN also has an impact on women's sexuality. First, the biological effects of severe dietary restrictions lead directly to dysfunctions of the reproductive system, affecting secondary sexual characteristics (Pirke 1995). Moreover, it seems plausible that individuals who are not comfortable with their bodies, such as individuals with eating disorders, will have difficulties in deriving pleasure from sexual activity (Wiederman and Pryor 1997). Finally, eating and sexual activity are highly self-reinforcing behaviors controlled by the primary appetitive motivational circuit in the brain: the mesolimbic dopaminergic system (Koch and Schnitzler 1997). This neurophysiological circuit may explain why women with AN seem to be able to go on without food and sex so consistently (Zuckerman 1994), whereas women with BN go through cycles of restriction and loss of control over both appetitive behaviors.

Published empirical research confirms that women with eating disorders (ED) tend to face disorder-specific sexual difficulties throughout their lives (Wiederman and Pryor 1997). Inadequate body weight in women with AN compromises the presence of secondary postpubertal characteristics and leads to a childlike appearance. Women with BN are more dissatisfied with their body image than women with AN, but BN individuals are able to maintain normal body weight and also engage more frequently in sexual activity than women with AN (Cash and Deagle 1996). Compared to controls, women with BN report more sexual activity and more pressure to "perform" sexually (Katzma and Wolchick 1984), as well as greater sexual dissatisfaction. This association between increased sexual activity and sexual dissatisfaction in women with BN seems to parallel their pattern of binge eating and subsequent dysphoria.

Based on clinical observations, several authors have suggested that impulsivity and loss of control seem to be the central clinical features that discriminate between BN and AN (Matsunaga et al. 2000). Zerbe (1993) has speculated that loss of control over eating prompts individuals with BN to attempt, in vain, to gain external approval through promiscuous behavior with new partners (see also Troop 1998). Interested in this hypothesis, we recently tested the extent to which women with BN and healthy controls differed in their reactivity to food images and erotic pictures (Rodríguez et al. 2007a). Women with (n = 24) and without (n = 24) BN observed a set of food and erotic pictures, together with neutral and unpleasant ones, all selected from the *International Affective Picture System* [IAPS]. Participants rated their feelings while viewing the pictures using the *Self-Assessment Manikin* [SAM] scales: valence (pleasant–unpleasant), arousal (activated–relaxed), and control (dominant–dominated). In comparison to women without BN, women with BN responded to the erotic and food pictures with lower scores in valence and control (see Fig. 161.1). These results suggest that women with BN experience less pleasure and control over both food and sexual impulses than healthy individuals.

The finding by Rodríguez et al. (2007a) of similar reactivity to erotic and food pictures is not surprising given that both eating and sexual behaviors are controlled by the same brain circuit (Bradley and Lang 2007). According to these authors, there are two primary motivational circuits

Fig. 161.1 Food and sexual-related stimuli used to test the emotional reactivity of women with bulimia nervosa (*BN*). Food images and erotic stimuli retrieved from the Internet with similar content to the International Affective Picture System (*IAPS*) pictures used in the study of Rodríguez et al. (2007a). Food and erotic pictures were rated by women with bulimia nervosa as less pleasant and controllable than women without bulimia nervosa

in the brain: the appetitive and the defensive. The appetitive circuit is mediated by the mesolimbic dopaminergic system (nucleus accumbens) and its activation is signaled by approach/consumption behaviors. The defensive circuit is mediated by the amygdala and other subcortical areas (e.g., stria terminalis, ventral tegmental area, and paraventricular hypothalamus, among others) and its activation results in avoidance/defense behaviors. For the majority of people, eating and sexuality are two basic gratifying activities that reflect the exclusive activation of appetitive mechanisms. However, sexual and food-related stimuli seem to evoke dyscontrol and negative mood in women with BN, an effect congruent with the simultaneous co-activation of aversive and appetitive motivations (Bradley 2000). Co-activation of both circuits would lead to a typical approach–avoidance conflict, explaining the observed reduction in pleasure and control in both eating and sex observed in individuals with BN.

The dyscontrol hypothesis also predicts that increased sexual activity leads to increased sexual dissatisfaction in women with BN. It has been suggested that individuals with BN use sexual activity instrumentally as a means of obtaining approval (Zerbe 1993) or of assuring continuity in their relationships (Katzma and Wolchick 1984). Some authors consider eating disorders the result of a faulty coping mechanism aimed at resolving unpleasant emotional states (Troop 1998). That is, women with BN may attempt to gain emotional relief and control by bingeing, or becoming sexually promiscuous. However, bingeing, like promiscuity, increases rather than decreases the feelings of dyscontrol and dissatisfaction.

161.3 Impulsivity and Impairment of Decision-making in Women with Bulimia Nervosa

Whereas the cognitive and behavioral symptoms that characterize eating disorders have been researched since the beginning of the nineteenth century, our understanding of the neuropsychological characteristics of individuals with eating disorders is restricted to research conducted mostly over the past two decades. Neuropsychological research in this area aims to explore the possible implication of neural dysfunctions in the etiology of ED (Duchesne et al. 2004). The general symptoms that characterize ED have been associated with damage in the right frontal and parietal lobes. This finding was supported by reports of cerebral hypoperfusion in parietal, temporal, and right frontal lobes of patients with BN purging-type (BNP) and AN restrictive-type (ANR). Images of high-calorie food were associated with anomalous activity in the ventromedial prefrontal cortex and anterior cingulate cortex of patients with BN and AN (Uher et al. 2004). Thus, the presence of functionally altered cortical (cognitive) and subcortical (emotional) areas in the brain are congruent with some of the most frequent problems reported by BN patients: deficits in selective attention and in executive function related to poor inhibitory control (Figs. 161.2 and 161.3).
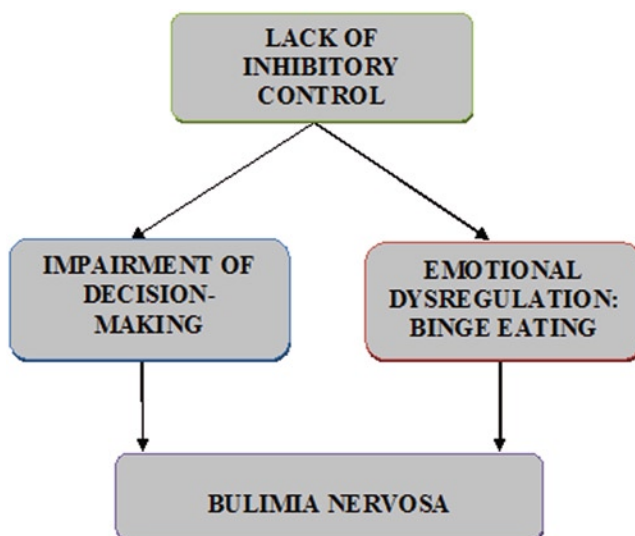
Fig. 161.2 Relationship between impulsivity, decision-making, and emotional dysregulation in bulimia nervosa. The poor inhibitory control shown by bulimia nervosa patients suggests that impulsivity may be a central and distinctive component of the disorder, mediating emotionally guided decision-making and binge eating behavior as demonstrated by Ortega-Roldán et al. (2009)
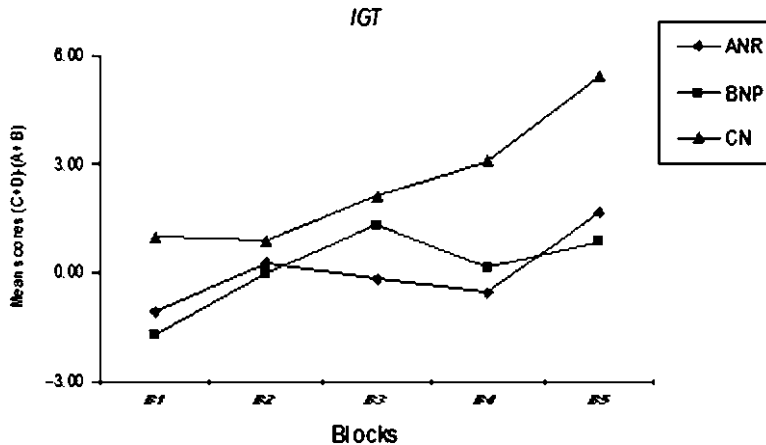
Fig. 161.3 Decision-making impairment in bulimia nervosa. The overall IGT performance of Bulimia Nervosa-Purging patients (*BNP*) was significantly worse than the one of the Anorexia Nervosa-Restrictive patients (*ANR*) or controls, which may be a consequence of their poor learning from rewards and punishments received during the course of the task (Reprinted from Ortega-Roldán et al. 2009. With permission)

The cognitive behavioral model of ED hypothesizes that ED symptoms are precipitated and maintained by maladaptive thoughts and dysfunctional assumptions about food. Research using the emotional *Stroop task* (Black et al. 1997) found higher interference and lower inhibitory control in bulimia and anorexia nervosa participants than in controls when presented words related to food, body shape, and weight (Fassino et al. 2002). Studies using the *Go/No-Go task* (Newman et al, 1985) to examine inhibitory control in ED patients have found greater impulsivity (see Table 161.1) in patients with BN and AN bingeing/purging type (ANBP), compared to patients with AN restrictive-type (ANR), and individuals without ED (Rosval et al. 2006). Finally, studies using the *Iowa Gambling Task* (IGT) (Cavedini et al. 2004; Davis et al. 2004) have found impairment of decision-making function (see Table 161.2) in individuals with AN, BN, and obesity, reflected by their inability to successfully perform the task.

The above findings on impulsivity, a key factor in emotionally triggered binge eating (Nederkoorn et al. 2004), prompted our team to examine the relationships between impulsivity, emotion, and decision-making in women with BN ($n = 14$), ANR ($n = 22$), and controls ($n = 29$) (Ortega-Roldán et al. 2009). Participants carried out two tasks: the IGT and an affective version of the Go/No-Go task. The IGT imitates real-life decision-making by means of a card game that evaluates the capacity to balance immediate rewards with long-term negative consequences. The affective version of the Go/No-Go task is a measure of motor impulsivity, since the participant must inhibit a behavioral response (pressing a key) to affect-related stimuli. Participants also completed a set of questionnaires on cognitive impulsivity, mood state, anxiety, and food craving. The results showed that patients with BN performed considerably worse in the IGT and Go/No-Go task than both AN and control participants. In addition, the results indicated that BN and AN patients performed differently in the Go/No-Go task, with BN participants showing greater cognitive impulsivity, more negative mood, and greater anxiety and food craving than AN participants. The poor inhibitory control shown by BN patients suggests that impulsivity may be a central and distinctive component of the disorder, mediating emotionally guided decision-making and binge eating behavior.

The lower performance in the IGT of BN than AN may be related to the different nature of both disorders. AN individuals may derive strong short-term reinforcement from successfully avoiding food intake, such as a reduction in their fear of becoming fat, at the expense of the long-term negative

Table 161.1 Key features of impulsivity

1. Impulsivity has been defined as the inability to think over when confronting a conflictive situation, resulting in failure to anticipate the consequences of one's actions, a rushed style when making decisions, difficulties in planning one's future behavior, and/or inability to exert self-control
2. Motor (or behavioral) impulsivity has been distinguished from cognitive (or choice) impulsivity
3. Motor impulsivity is equivalent to lack of response inhibition
4. Cognitive impulsivity is considered the inability to weigh the consequences of immediate and future events and, consequently, delay gratification
5. Motor impulsivity has been measured with a variety of instruments such as the Go/No-Go, reversal learning tasks, continuous performance tests, or stop tasks
6. Cognitive impulsivity has been measured using decision-making tasks such as the Iowa Gambling Task
7. Motor impulsivity is associated with impairments to the dorsolateral prefrontal cortex
8. Cognitive impulsivity is associated with impairments to the ventromedial prefrontal cortex

This table lists the key features of impulsivity, including the definition of impulsivity, the differentiation between motor and cognitive impulsivity, the measurement and the location of brain impairments for each type of impulsivity

Table 161.2 Key facts of decision-making

1. The generic structure of decision-making involves three independent processes:
(a) Appraisal of the stimuli or options
(b) Selection or execution of an action
(c) Evaluation of the experience or outcome of the choices that were made
2. Each of these stages may be differentially affected by various psychological and neural factors
3. When pleasurable or aversive events are confronted in one's immediate circumstances, appropriate somatic states are generated via activation of subcortical circuitry, and these emotions are subconsciously remembered for future occurrences of the same stimuli
4. The orbitofrontal cortex, in particular, is critical for activating feelings or emotional states from "thoughts" about rewarding or punishing events that are not currently present in one's environment
5. The behavioral deficits of the impaired decision-making are typically caused by an inability to advantageously assess future consequences
6. Poor decision-making is a core symptom of certain mental health problems such as drug dependence, mania, and some forms of eating disorder

This table lists the key facts of decision-making including the processes involved, the psychological and neural factors that influence these processes, the behavioral deficits of the impaired decision-making, and the affected populations

consequences of their behavior, i.e., severe physical and psychosocial impairments. Similarly, BN individuals appear to succumb to binge and purging impulses, arguably to escape negative emotional states, causing an unhealthy, long-term cycle of extreme dieting, bingeing, and purging.

On the other hand, the results obtained with the *Go/No-Go* task support the hypothesis that patients with BN have greater motor and cognitive impulsivity than patients with AN. Thus, our findings support the notion that lack of impulsivity diagnostically differentiates AN from BN.

161.4 Loss of Control Evoked by Dietary Restraint, Food Craving, and Binge Eating in Women with Bulimia Nervosa

Women with BN not only show risk-behaviors (e.g., multiple sexual relationships) and impulsivity, they also experience very intense food cravings (Fig. 161.4). Craving has been defined as a state of strong desire to consume a given substance. Food craving has been linked to binge eating in women with BN, increased food consumption in restrained eaters, early dropout from weight-loss treatments, overeating in obese individuals, and lifetime prevalence rates of BN (Cepeda-Benito and
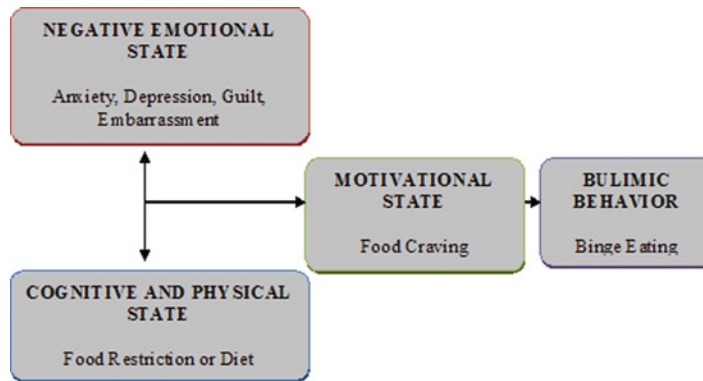
Fig. 161.4 Relationship between emotional states, dietary restraint, and food craving in bulimia nervosa. This model (Moreno et al. 2009a) proposes that a negative emotional state (such as anxiety, depression, guilt, embarrassment…) and a cognitive and physical state (associated with food restriction) are required to provoke a motivational state of food craving. The food craving might be a trigger of the binge eating as a typical behavior of bulimia nervosa patients

Gleaves 2001). The experience of craving has often been conceptualized as an "irresistible demand" for a substance and having a craving equates with losing control over the craved substance (e.g., Gendall et al. 1997).

Researchers have postulated that food craving plays an instrumental role in the development and maintenance of binge-eating behavior (e.g., Heatherton and Polivy 1992). For example, the starvation/dietary restraint model explains that dietary restraint practices produce a state of strong food craving that provokes a loss of control over eating (i.e., binge eating; Cepeda-Benito and Gleaves 2001).

However, it has also been reported that energy deprivation does not always precede food cravings and binge eating (Hill et al. 1991). Specifically, negative emotions such as anger, fear, or sadness have been found to increase binge eating among BN individuals, as well as in people diagnosed with Binge Eating Disorder (Agras and Telch 1998).

BN patients use binge eating to seek relief from their negative moods (anxiety, sadness, boredom…), but overeating also produces negative emotions as a consequence of the recognition of their inability to maintain control over their intake (Cavallo and Pinto 2001). Thus, food deprivation allows BN individuals to escape the negative affect produced by excessive consumption of food, and it may also be a maladaptive response to cope with other negative aspects of their daily lives. From this perspective, dieting may be considered a self-regulatory mechanism to reduce both the negative affect elicited by food intake and the fear of gaining weight (Mann and Ward 2004).

The effects of emotions on eating have been studied extensively, but less research has been conducted on how negative emotions modulate food craving responses as potential mediators of overeating (Waters et al. 2001). In order to better understand the relationship between negative mood and food craving, we asked women with BN ($n = 21$) and healthy controls ($n = 21$) to refrain from eating and drinking (except water) for 20 h (see Moreno et al. 2009a). Participants were asked to complete several self-report measures at different time intervals to assess mood, anxiety, and food craving. After the 20-h fasting period, all participants were allowed to eat as much as they wanted from a breakfast buffet. The number or calories and the portion of carbohydrates, proteins, and fats consumed were estimated for each participant by weighing the food and counting the servings remaining in the buffet.

The results showed that food deprivation increased food cravings in both BN and healthy controls, but that the effect was considerably greater in the BN participants. The results also demonstrated that emotional state and craving fluctuated together throughout the period of deprivation in both groups. Initially, food deprivation increased craving and negative mood in both BN and control

participants. However, as the fasting period increased, food craving was associated with higher negative mood and anxiety in healthy individuals, but with improved mood and reduced anxiety in participants with BN. Finally, although BN and healthy participants did not differ in the amount of food consumed, food cravings and caloric intake were positively correlated just in BN participants.

Together, our findings support several hypotheses put forth by numerous authors. The observed increase in craving as a direct result of fasting is congruent with the hypothesis that food deprivation increases the desire to eat and may lead to binge eating (Hill et al. 1991). This conclusion is further strengthened by the finding that craving and food intake were correlated in BN but not in healthy participants. That is, BN patients appeared to be particularly vulnerable to the effects of food cravings on food intake. The observation that prolonged fasting reduced negative emotions in women with bulimia nervosa support our earlier conclusion that women with BN escape negative emotional states through fasting (Mann and Ward 2004).

We also studied the nature of the relationship between dietary restraint and loss of control over eating in AN and BN participants (Moreno et al. 2009b). It was hypothesized that food craving would be highly prevalent in individuals known to have marked tendencies to temporarily restrain their diets but lose control over eating (BN participants), but would be rare in individuals with marked tendencies to restrain food intake but not break their diets (AN participants). Using the Discriminatory Factor Analysis (DFA) on the *Food Craving Questionnaire-Trait* (Cepeda-Benito et al. 2000) to differentiate between women diagnosed with ANR, ANBP, BNP, and BNNP, we found that patients with ED who reported very low levels of food craving were accurately classified as individuals with AN, whereas patients with ED that reported high levels of food craving were accurately classified as individuals with BN (Fig. 161.5).
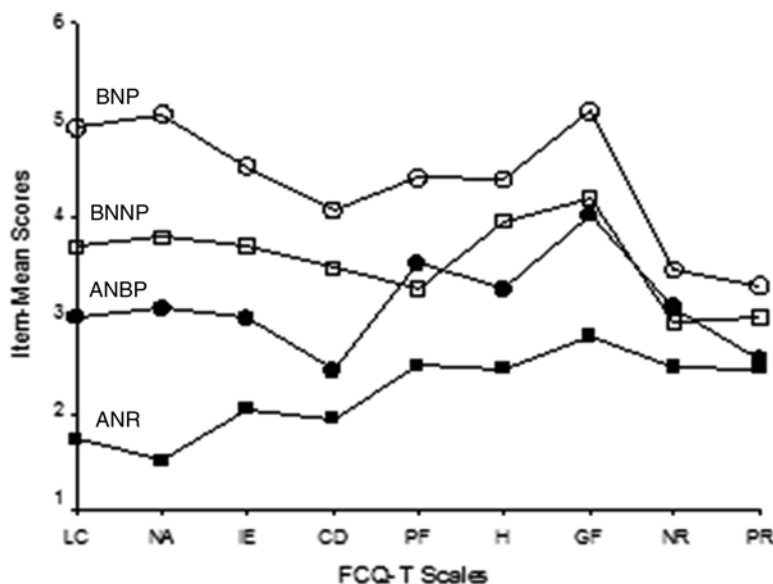
Fig. 161.5 Food Craving Questionnaire-Trait (*FCQ-T*) scales for the different types of Eating Disorders. Mean scores of the nine scales of the Food Craving Questionnaire-Trait (*FCQ-T*) for Anorexia Nervosa-Restrictive (*ANR*), Anorexia Nervosa-Binge/Purging (*ANBP*), Bulimia Nervosa-Non-Purging (*BNNP*), and Bulimia Nervosa-Purging (*BNP*) participants. The order of scale presentation is Lack of Control over Eating (*LC*), Negative Affect (*NA*), Intentions to Eat (*IE*), Cue-Dependent Eating (*CD*), Preoccupation with Food (*PF*), Hunger (*H*), Guilty Feelings (*GF*), Negative Reinforcement (*NR*), and Positive Reinforcement (*PR*). Clearly, ANR patients reported the lowest levels of food cravings across the board, followed in ascending order by ANBP, BNNP, and BNP participants (Reprinted from Moreno et al. 2009b. With permission)

Overall, the above findings suggest that dietary restraint does not lead to food craving in individuals with AN. Food craving is associated with binge eating only in women diagnosed with BN. This result is congruent with the observation by Cepeda-Benito and Gleaves (2001) that a positive association between dietary restraint and food craving is confined to unsuccessful dieters.

161.5 Lack of Inhibitory Control on Physiological and Emotional Processes in Women with Bulimia Nervosa

Heart Rate Variability (HRV) has recently attracted the interest of scientists as an index of autonomic and emotional regulation. Thayer and Lane (2000) proposed a model of neurovisceral integration in which a network of neural structures associated with emotional and autonomic regulation is related to HRV via connections from the prefrontal cortex to the amygdala, and from the amygdala to the sympathetic and parasympathetic innervations of the heart. Numerous authors have found a negative association between vagally-mediated HRV and poor psychological and physiological functioning, including conditions characterized by a lack of impulse control, i.e., cravings (Ingjaldsson et al. 2003; Rodríguez-Ruiz et al. 2009). Experimental data also support a relationship between HRV and emotional regulation. High vagally-mediated HRV has been associated with larger orienting responses but faster habituation to nonthreat stimuli, whereas low HRV has been related to a failure to habituate (hypervigilance) and to greater defensive reactions (Thayer and Lane 2000).

The modulation of defensive reflexes also offers an interesting paradigm to examine autonomic and emotional regulation in BN. The magnitude of defense reflexes, such as the *startle motor reflex* and the *cardiac defense response* elicited by a brief acoustic probe stimulus, is augmented during viewing of unpleasant and threatening pictures and is reduced while viewing pleasant images (see Bradley 2000 and Vila et al. 2007, for review). The phenomenon has been explained, according to the *motivational priming hypothesis* (Lang 1995), as due to the congruence or incongruence between the emotional state induced by the pictures (positive versus negative) and the type of reflex being elicited (appetitive versus defensive): defensive reflexes are augmented if the organism is in a negative emotional state and reduced if the organism is in a positive emotional state.

Several studies have examined the modulation of defensive reflexes in people with eating disorders. Drobes et al. (2001) used this methodology to evaluate the affective state evoked by food stimuli in women who suffer from binge eating. The results showed that women who suffer from binge eating displayed an increased startle reflex when presented with food pictures. Nevertheless, some verbal, behavioral, and psychophysiological responses were consistent with an appetitive motivational reaction to food pictures, while other responses were consistent with a defensive one. Rodríguez et al. (2005) also found that the experience of chocolate craving included both appetitive (inhibition of the cardiac defense) and aversive (potentiation of the startle reflex) components. These findings suggested that the motivational circuits (appetitive and defensive) in women with bulimic symptomatology would be co-activated by food stimuli (Konorski 1967; Lang 1995).

Similarly, Mauler et al. (2006) studied the modulation of the eye-blink startle reflex while viewing food pictures in women without ED and those with BN (both groups under food deprivation and nondeprivation, respectively). Their findings showed a greater magnitude of the startle reflex to food pictures in women suffering from BN. However, food pictures did not elicit greater skin conductance responses in women with BN. These findings suggest that food pictures instead of provoking a typical fear response mediated by the sympathetic nervous system (*flight*) seem to provoke a disgust or anxiety response mediated by the parasympathetic nervous system. In addition, the startle reflex potentiation upon presentation of food pictures in patients with BN was attenuated by food deprivation, a

finding also reported by Rodríguez et al. (2007b). Thus, a period of successful food restriction might create a sense of control over food and this may render it less threatening.

Overall, the above findings are congruent with the observation that food deprivation increases craving but reduces negative mood in BN participants (Moreno et al. 2009a). This observation suggests that negative affect primed by food cues might motivate dietary restraint to ameliorate the negative affect associated with food intake in women with BN. It could be argued that individuals with BN make food less threatening by demonstrating control over their consumption through restrained eating.

Nevertheless, it has been reported that the above findings are also modulated by individual differences in emotional regulation indexed by HRV. Rodríguez-Ruiz et al. (under review) found that food cues evoked negative emotional responses, comparable to those elicited by unpleasant stimuli, in deprived individuals with BN and low HRV. Participants with BN and low HRV exhibited a substantial potentiation of their blink response magnitudes to all stimulus categories (see Fig. 161.6),

Fig. 161.6 Food, pleasant, neutral, and unpleasant stimuli used to examine the physiological reactivity of women with bulimia nervosa (*BN*). Food, pleasant, neutral, and unpleasant stimuli retrieved from Internet with similar content to the International Affective Picture System (*IAPS*) pictures used in the study of Rodríguez-Ruiz et al. (under review).
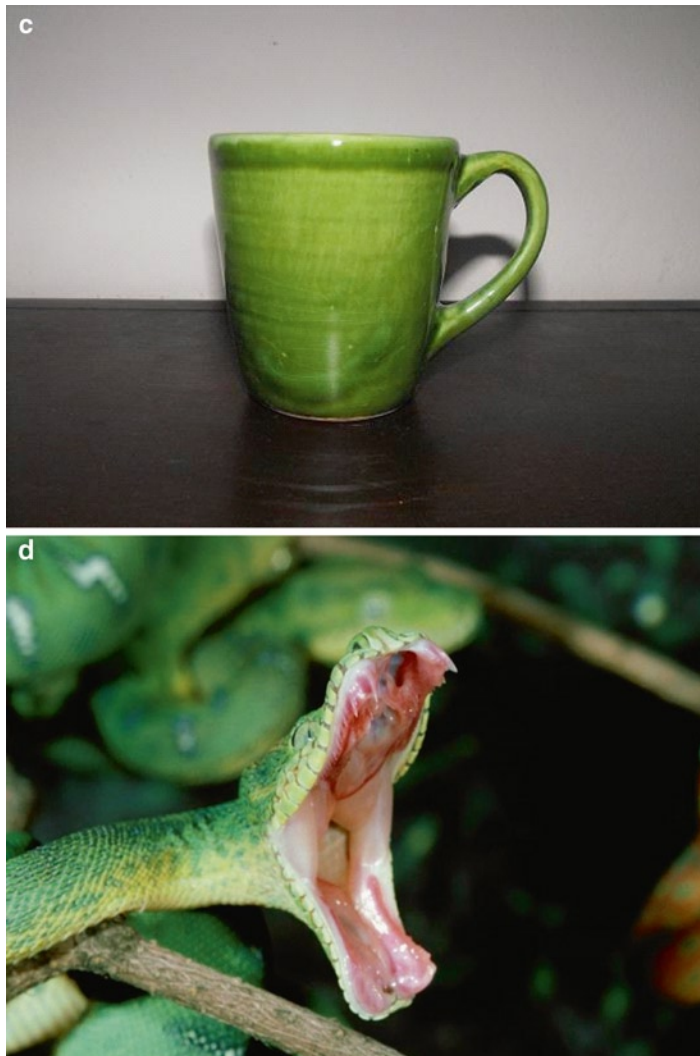
Fig. 161.6 (continued) All pictures provoked in women with bulimia nervosa and low HRV a greater eye-blink startle compared to those with bulimia nervosa and high heart rate variability (*HRV*), although food pictures evoked a blink response almost comparable to the augmentation that could be observed during the viewing of unpleasant emotional stimuli

although food pictures evoked a blink response almost comparable to the augmentation that could be observed during the viewing of unpleasant emotional stimuli. Deprived participants with BN and low HRV also labeled their feelings associated with food cues as more disgusting and uncontrollable than deprived participants with BN and high HRV and control participants.

Thus, our results confirm the inverse association between vagally-mediated HRV and psychological functioning (Thayer and Lane 2000). To sum up, HRV appears to modulate defensive reactions to food in BN individuals, supporting the hypothesis that poor emotional and autonomic regulation plays a role in the observed lack of inhibitory control in BN.

161.6 Applications to Other Areas of Health and Disease

The research reviewed in this chapter has potential applications. For example, IGT could become a useful tool for the assessment and treatment of ED patients. IGT provides an individual profile on the decision-making process of the individual and could be used to enhance the patient's awareness of the nature of his/her disease and improve patients' motivation for treatment compliance. IGT can also serve as a pre- and post-treatment measure to evaluate treatment outcome. IGT may be also useful in the detection of individuals at risk for ED. Finally, the data indirectly support the presence of neurological deficits in ED, with probable involvement of the frontal lobe, indicating that neuropsychological rehabilitation might be an appropriate treatment for these patients.

The clinical implications of the research on dietary restraint, food craving, and emotion in BN are twofold. First, it would be advisable, in the context of cue-exposure therapy, to elicit craving by means of manipulation other than mere food exposure and include strategies to modulate affective states, feelings of control over eating, and motivation to consume or avoid foods. The goal would be to elicit and extinguish the underlying craving factors that are most relevant to bingeing (e.g., negative affect and lack of control). Second, the effectiveness of cue exposure therapy might be increased if exposure is combined with physiological techniques aimed at improving emotional and autonomic regulation in patients with BN, as well as in patients with disorders characterized by lack of control (e.g., drug addiction). A number of nonpharmacological techniques have been used to increase HRV, including breathing training and HRV biofeedback (Lehrer et al. 1999). HRV biofeedback has been proposed as a powerful tool to help individuals learn emotional and autonomic self-regulation skills (Nolan et al. 2005).

Summary Points

- Impulsivity and loss of control seem to be the central clinical features that discriminate between bulimia and anorexia nervosas
- In our studies the women with bulimia nervosa experience lack of pleasure and control over both food-related and sexual impulses
- They showed significant motor impulsivity and an impairment of decision-making abilities based on short-term consequences, more negative mood, anxiety, and food craving than women with anorexia nervosa
- Prolonged fasting increased food craving and reduced negative emotions in women with bulimia nervosa since they escape from negative emotional states by fasting
- The positive association between dietary restraint and food craving is confined to unsuccessful dieters who lose control over eating as do women with bulimia nervosa
- In our studies the women with bulimia nervosa and low heart rate variability labeled their feelings associated with food cues as more disgusting and uncontrollable than women with bulimia nervosa and high heart rate variability
- To be effective, treatment interventions for bulimia nervosa must combine not only behavioral and neuropsychological approaches, but also physiological techniques aimed at improving emotional and autonomic regulation.

Definitions

International Affective Picture System [IAPS]: (Lang et al. 1999). The IAPS is an instrument for the study of emotion in laboratory settings. The IAPS is an instrument under continuous development created by the Center for the Study of Emotion and Attention, under the direction of Professor Peter J. Lang, at the University of Florida. It includes over 800 color photographs, in slide and digitalized format, belonging to different semantic categories: animals, nature scenes, house objects, naked people, erotic couples, human faces, mutilated bodies, weapons, food, sports, etc.

Self-Assessment Manikin [SAM]: (Lang 1980). The SAM is a universally applied instrument consisting of three pictographic nonverbal scales (valence, arousal, and control or dominance). It does not require language and is therefore easy to administer. The instrument provides information for each picture on three general emotional dimensions: valence (pleasant–unpleasant), arousal (activated–relaxed) and control (dominant–dominated).

Stroop task: (Stroop 1935). The Stroop task is a classic experimental paradigm to examine the Stroop interference effect, a measure of word reading's influence upon color naming. The procedure involves naming the color of a color word presented visually using the same or different color. The interference is quantified in terms of increase in reaction time to color naming when noun and presentation color are incongruent compared to the condition, in which they are congruent. The task demands resolution of a conflict between two competing tendencies, that of reading versus naming.

Go/No-Go task [GNG]: (Newman et al. 1985). The GNG is a computerized measure of motor impulsivity in which participants must try to inhibit their responses to certain stimuli, with the number of errors and false alarms indicating motor impulsivity.

Iowa Gambling Task [IGT]: (Bechara et al. 1994). The IGT is a computerized task that imitates a card game and is made up of 100 trials. Participants choose a card from one of four virtual decks (A, B, C, and D). Depending on the deck selected in each trial, the person gains (reward) or loses (punishment) symbolic money. Two of the decks, A and B, generate losses in the long term because, although profits are higher, so too are the losses. The other two decks, C and D, generate a profit in the long-term because the losses are smaller. The IGT score is calculated by subtracting the number of cards selected from decks A and B from the number of cards selected from decks C and D in each of the 5 blocks of 20 trials that comprise the task.

Food Craving Questionnaire-Trait [FCQ-T]: (Cepeda-Benito et al. 2000). The FCQ was created consistent with the theory that food cravings can arise from and be expressed as both physiologically and psychologically mediated processes. Using confirmatory Factor Analyses (CFA), the FCQ-T has yielded excellent fit indices for a nine-factor solution (e.g., Moreno et al. 2009b). The nine factor derived scales of the FCQ-T measure cravings experienced as or associated with: (1) *Positive Reinforcement*; (2) *Negative Reinforcement*; (3) *Cue-dependent Eating*; (4) *Feelings of Hunger*; (5) *Preoccupation with Food*; (6) *Intentions to Eat*; (7) *Lack of Control*; (8) *Negative Affect*; and (9) *Guilty Feelings*. The FCQ-T instructs participants to indicate how frequently each statement "would be true for you in general" using a six point scale that ranges from 1 (*Never* or *Not Applicable*) to 6 (*Always*). Full-scale and factor-scale totals can be calculated by simply adding the corresponding item scores.

Startle motor reflex [SMR]: (Lang 1995). The SMR is a pattern of motor activation elicited by sudden intense stimulation. The SMR in humans is based on the psychophysiological recording via the electromyography (EMG) of the orbicularis oculi muscle. The pattern and magnitude of the response can be obtained through both raw EMG and filtered EMG.

Cardiac defense response [CDR]: (Vila et al. 2007). The CDR is a complex pattern of heart rate changes to an intense acoustic stimulus with accelerative and decelerative components that appear in an alternate sequential order (acceleration–deceleration–acceleration–deceleration) during the 80 s following the presentation of the stimulus.

References

Agras WS, Telch CF. Behav Ther. 1998;29:491–503.

American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4th ed. Text revision. Washington, DC: Author; 2000.

Bechara A, Damasio AR, Damasio H, Anderson SW. Cognition. 1994;50:7–15.

Black CM, Wilson GT, Labouvie E, Heffernan K. Int J Eat Disord. 1997;22:329–33.

Bradley MM. In: Cacioppo JT, Tassinary LG, Berntson GG, editors. Handbook of psychophysiology. New York: Cambridge University Press; 2000. p. 602–642.

Bradley MM, Lang PJ. In: Cacioppo JT, Tassinary LG, Berntson GG, editors. Handbook of psychophysiology. 3rd ed. New York: Cambridge University Press; 2007.

Cash TF, Deagle EA. Int J Eat Disord. 1996;22:107–25.

Cavallo DA, Pinto A. Eat Behav. 2001;2:113–27.

Cavedini P, Bassi T, Ubbiali A, Casolari A, Giordani S, Zorzi C, Bellodi S. Psychiatry Res. 2004;127:259–66.

Cepeda-Benito A, Gleaves D. In: Hetherington M, editor. Food cravings and addiction. Leatherhead: Surrey; 2001. p. 3–29.

Cepeda-Benito A, Gleaves DH, Williams TL, Erath ST. Behav Ther. 2000;31:151–73.

Davis C, Levitan RD, Muglia P, Bewell C, Kennedy JL. Obesity Research. 2004;12:929–35.

Drobes DJ, Miller EJ, Hillman CH, Bradley MM, Cuthbert BN, Lang PJ. Biol Psychol. 2001;57:153–77.

Duchesne M, Mattos P, Fontenelle LF, Veiga H, Rizo L, Appolinaro JC. Rev Bras Psiquiatr. 2004;26:107–17.

FairburnCG. In: Brownell KD, Fairburn CG, editors. Eating disorders and obesity: a comprehensive handbook. New York: Guildford Press; 1995.

Fassino S, Pieró A, Daga GA, Leombruni P, Mortara P, Rovera GG. Int J Eat Disord. 2002;31:274–83.

Gendall KA, Joyce PR, Sullivan PF. Appetite. 1997;28:63–72.

Heatherton TF, Polivy J. In: Crowther J, Hobfall SE, Stephens MAP, Tennenbaum DL, editors. The etiology of bulimia: the individual and familial context. Washington, DC: Hemisphere; 1992. p. 135–155.

Hill AJ, Weaver CFL, Blundell JE. Food craving, dietary restraint and mood. Appetite. 1991;17:187–97.

Ingjaldsson JT, Laberg JC, Thayer JF. Biol Psychiatry. 2003;54:1427–36.

Katzma MA, Wolchick SA. J Consult Clin Psychol. 1984;52:423–8.

Koch M, Schnitzler HU. Behav Brain Res. 1997;89:35–49.

Konorski J. Integrative activity of de brain: an interdisciplinary approach. Chicago: University of Chicago Press; 1967.

Lang PJ. In: Sidowski JB, Johnson JH, Williams TA, editors. Technology in mental health care delivery systems. Norwood: Ablex; 1980. p. 119–137.

Lang PJ. Am Psychol. 1995;50:372–85.

Lang PJ, Bradley MM, Cuthbert BN. The international affective picture system: technical manual and affective ratings. Gainesville: The Center for Research in Psychophysiology, University of Florida; 1999.

Lehrer P, Sasaki Y, Saito Y. Psychosom Med. 1999;61:812–21.

Mann T, Ward A. J Abnorm Psychol. 2004;113:90–8.

Matsunaga H, Kiriike N, Iwasaki Y, Miyata A, Matsui T. Int J Eat Disord. 2000;27:348–52.

Mauler BI, Hamm AO, Weike, AI, Tuschen-Caffier B. J Abnorm Psychol. 2006;115:567–79.

Moreno S. Rodríguez-Ruiz S, Fernández-Santaella MC. ?Qué es el ansia por la comida? Manuales Prácticos. Madrid: Pirámide; 2009a.

Moreno S, Warren CW, Rodríguez S, Fernández M.C., Cepeda-Benito A. Appetite. 2009b;52:588–94.

Nederkoorn C, Van Eijs Y, Jansen A. Pers Individ Differ. 2004;37:1651–8.

Newman J, Widom C, Nathan S. J Pers Soc Psychol. 1985;48:1316–27.

Nolan R, Kamath MV, Floras JS, Stanley J, Pang C, Picton P, Young QR. Am Heart J. 2005;149:1137.

Ortega-Roldán B, Rodríguez S, Moreno S, Morandé G, Fernández MC. In: Chambers N, editor. Binge eating: psychological factors, symptoms, and treatment. New York: Novascience; 2009.

Pirke KM. In Brownell KD, Fairburn CG, editors. Eating disorders and obesity: a comprehensive handbook. New York: Guildford Press; 1995.

Rodríguez-Ruiz S, Ruiz-Padial E, Vera MN, Fernández, MC, Anllo-Vento L, Vila J. J Psychophysiol. 2009;23:95–103

Rodríguez-Ruiz S, Moreno S, Guerra PM, Fernández MC, Vila J. J Psychophysiol. [under review].

Rodríguez S, Fernández MC, Cepeda-Benito A, Vila J. Biol Psychol. 2005;70 (1):9–18.

Rodríguez S, Mata JL, Lameiras M, Fernández MC Vila J. Eur Eat Disord Rev. 2007a;15 (3):231–9.

Rodríguez S, Mata JL, Moreno S, Fernández MC, Vila J. Psicothema. 2007b;19:30–6.

Rosval L, Steiger H, Bruce K, Israël M, Richardson J, Aubut M. Int J Eat Disord. 2006;39:590–3.

Stroop JR. J Exp Psychol Gen. 1935;18:643–62.

Thayer JF, Lane RD. J Affect Disord. 2000;61:201–16.

Troop NA. Eur Eat Disord Rev. 1998;6:229–37.

Uher R, Murphy T, Brammer MJ, Dalgleish T, Phillips ML, Ng VW, Andrew CM, Williams SCR, Campbell I, Treasure J. Am J Psychiatry. 2004;161:1238–46.

Vila J, Guerra P, Muñoz MA, Vico C, Viedma MI, Delgado LC, Perakakis P, Kley E, Mata JL, Rodríguez S. Int J Psychophysiol. 2007;66 (3):169–82.

Waters A, Hill A, Waller G. Behav Res Ther. 2001;39:877–86.

Wiederman MW, Pryor T. Int J Eat Disord. 1997;22:395–401.

Zerbe KJ. The body betrayed: Women, eating disorders, and treatment. Washington, DC: American Psychiatric Press; 1993.

Zuckerman M. Behavioral expressions and biosocial bases of sensation seeking. New York: Cambridge University Press; 1994.

Chapter 162
Experiences of Women with Bulimia Nervosa

Kathryn Proulx

Abbreviations

CBT	Cognitive behavioral treatment
DBT	Dialectical behavioral treatment
DSM IV TR	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision.
EMDR	Eye movement desensitization and reprocessing

162.1 Introduction

The following chapter reflects qualitative data collected as part of a broader study that sought to understand how college-age women with bulimia nervosa experienced participating in a Mindfulness-Based Eating Disorder Treatment Group (Proulx 2008). In that phenomenological study, six college-age women who met the DSM-IV-TR criteria for bulimia nervosa (APA 2000) were interviewed prior to the group by the researcher. Initial data was collected and self-portraits were completed. Then the participants attended an 8-week mindfulness group designed and facilitated by the researcher. Journal data was collected during the group and the researcher kept notes for each group. When the group was completed, the researcher again interviewed each participant to explore their experience of the group. Final self-portraits were completed at that time. In addition to having bulimia nervosa for several years, participants also had comorbid mood or anxiety disorders and some were taking psychotropic medications. None of the participants met DSM-IV-TR criteria for substance abuse or Dissociative Identity Disorder (Table 162.1).

162.2 Bulimia Nervosa

In response to the cultural idealization of thinness, over 50% of adolescent girls think they are overweight and consequently diet (Fisher et al. 1995). Moreover, 5–10 million adolescent girls and women in the USA are estimated to struggle with eating disorders (National Eating Disorders Association 2006). Bulimia nervosa occurs in 1–4% of American college-age women (APA 2000).

K. Proulx (✉)

Mental Health Services, University of Massachusetts, Hills North, Amherst, MA 01103
e-mail: kproulx@nursing.umass.edu

Table 162.1 Key features of bulimia nervosa

- Recurrent episodes of binge eating characterized by both:
    1. Eating, in a discrete period of time (e.g., within any 2-h period), an amount of food that is definitely larger than most people would eat during a similar period of time and under similar circumstances
    2. A sense of lack of control over eating during the episode, defined by a feeling that one cannot stop eating or control what or how much one is eating
- Recurrent inappropriate compensatory behavior to prevent weight gain
    1. Self-induced vomiting
    2. Misuse of laxatives, diuretics, enemas, or other medications
    3. Fasting
    4. Excessive exercise
- The binge eating and inappropriate compensatory behavior both occur, on average, at least twice a week for 3 months.
- Self evaluation is unduly influenced by body shape and weight.
- Gradually binge eating becomes a response to emotional upset. It functions to reduce stress and is triggered by such emotions as anxiety, anger, and depression.

This table lists key criteria of bulimia nervosa as identified by the Diagnostic and Statistical Manual of Mental Disorders

Bulimia nervosa typically begins with a fear of weight gain and the need for dieting (Fairburn and Cooper 1982; Pipher 1994). Self-imposed starvation eventually leads to binge eating in 30–50% of patients with anorexia nervosa referred for treatment (Garfinkel et al. 1980; Hsu et al. 1979). The gradual breakdown of self-control and the emergence of binge eating typically occur about 9 months after the initiation of dieting (Garfinkel et al. 1980).

An episode of binge eating is characterized by eating, within a 2-h period of time, an amount of food that is definitely larger than most people would eat during a similar period of time in similar circumstances (APA 2000). Individuals with bulimia nervosa experience a sense of lack of control over their eating during the episode including the feeling either that one cannot stop eating, control how much one is eating, or control the type of foods eaten. Recurrent inappropriate compensatory behaviors include self-induced vomiting, the misuse of laxatives, diuretics, diet pills, medications, fasting, and excessive exercise. Individuals with bulimia nervosa are often normal weight or overweight, making it a hidden disorder.

Gradually, the eating binges get separated from mealtime or desire for food and become more and more a response to emotional upset. Once bulimia is entrenched, it functions to reduce stress and is triggered by such emotions as anxiety, anger, and depression. Over time, the behavior takes on a life of its own where eventually pleasure and normal interpersonal relationships are replaced by compulsion, secrecy, and guilt. According to Bruch (1988), the drive for excessive thinness experienced by young women with bulimia nervosa acts as a "cage" that constricts their psychological growth and the development of a genuine self.

Many women with bulimia nervosa are disconnected from their bodies and feelings, rendering them easily influenced by cultural pressures and peer expectations (Brown and Gilligan 1992; Pipher 1994). These women experience low self-esteem, anxiety, depression, and interpersonal difficulties (Bruch 1988).

162.3 Methodological Considerations

This chapter will focus on the phenomenology of living with bulimia nervosa as it emerged thematically from the qualitative data. Data analysis was completed from a phenomenological, interpretive Hermeneutic perspective (Husserl 1913/1983; Van Manen 1990), which included my own process of

self-reflection throughout every aspect of the study (Drew 1999, 2001, 2004). Once the data from the initial assessments, interview transcripts, self portraits, and journals were closely examined and highlighted, common themes were identified and then synthesized into an integrated whole.

162.4   Thematic Analysis of Living with Bulimia Nervosa

This section will present themes that emerged from the data analysis related to the participants' sense of self, coping skills, and interpersonal relationships. The first theme, "Waging War on a Fragile Self," is divided into two major subsections. The first subsection entitled the "Fragile Self" describes how the participants see themselves and reveals the highly judgmental quality of their attitudes towards themselves. The second subsection in this theme entitled "Waging War as a Means of Gaining Control" addresses how the participants try to cope with the day-to-day stress experienced in their lives. Family and cultural influences on identity and women's roles are imbedded within these themes. The names of the six participants: Ana, Kelley, Rena, Sophia, Eva, and Ruth as they appear below are fictitious to preserve their confidentiality.

162.5   Waging War on a Fragile Self

162.5.1   The Fragile Self

Each of the participants identified that their experience of themselves felt fragmented and incongruent. Their sense of self changed in different environments and seemed to vacillate between extremes. They internalized the media images of beauty and strove to achieve this standard of thinness as the most important measure of self worth and success.

Because of their high degree of disconnection from themselves, they were unable to receive accurate feedback from their bodies. They unanimously experienced self-loathing and distorted body perceptions. The commonalities of their experiences related to self are organized as follows: Hiding the truth, Hating myself, Distorting my body, and Keeping me from where I want to be.

162.5.1.1   Hiding the Truth: I Am Not Who I Seem On the Outside

Kelley is a graduate student who has experienced symptoms of bulimia nervosa for approximately 14 years (Fig. 162.1). Her problems with eating and body image began following a motor vehicle accident that immobilized her for several months. She abruptly went from having been very physically active to total inertia and began to gain weight. As she reflects on her first self-portrait in which she drew two separate images of herself, she comments that the two images are "polar opposites of me." "There is the completely horrible, ugly, fat way I feel inside which is also the way I think that other people see me now, and a 19 year old version of me that is thin, pretty, perfect, very put together, and confident."

In her initial self-portrait Kelley draws two completely separate versions of herself reflecting her sense of "being split within myself, like there are multiple versions of me in here."

Rena, a college junior with a performance major, describes herself as being made up of "sunshine and happiness which is the ultimate of what I want from life, as well as fatigue and depression, which

Fig. 162.1 Kelley's self portrait. This figure represents Kelley's first self-portrait. The left image represents the idealized, thin confident self and the right image is the horrible, ugly, fat, totally devalued self

is a plague on my life and not so good." She points out that in her first self-portrait, love was surrounding her but was outside of her. Her focus was on being thin, pretty, and perfect in order to attract the prince who would provide her with love so she could feel sunny and happy evermore.

She was hoping for a man to feed her the love she craved so she could feel good about herself (Fig. 162.2). She believed that in order for any man to love her, she had to be thin and beautiful. When a man would hurt or reject her she would blame herself and think, "What did I do wrong? What's wrong with me? Look at my stomach, that's why it all went wrong."

Before the start of one group, Rena verbally told me she was having a very stressful day and was feeling quite depressed, all the while smiling, laughing, and impeccably dressed and groomed. Her affect and appearance were incongruent with her verbal description of how she was feeling and how she had experienced her day.

Sophia, a graduating senior, has had problems with bulimia nervosa since middle school. She is interested in Buddhism and feminism and so remarks about her "inability to find a middle ground", a topic she has been writing about all semester. She sees herself as "vacillating between extremes and torn between all the dichotomies of life." Sophia approaches every interpersonal situation with pre-planned ideas of "who I think I am and how I think I ought to act or how I've got to be." She adds, "When I am in a room with a bunch of people I would become those people. They envelop me instead of me being able to stay grounded in myself. I don't feel a core self."

Ruth is a junior student experiencing some academic problems this semester due to her mood instability and problems with focus and concentration. Out of all the women, Ruth was the most apprehensive about participating in a group. She had never joined a group before and indicated that her greatest fear was "hearing about my problem coming out of someone else's mouth." Secrets are really important to Ruth, which is why she was so apprehensive about coming to the group. She had

Fig. 162.2 Rena's self portrait. This figure represents Rena's first self-portrait. It depicts her belief that she must be thin, pretty, and perfect in order to attract the prince whose love would bring her happiness. She is dependent on external sources for validation and love

never told anyone about her eating disorder. She was ambivalent about keeping her secrets in that, although her secrets made her feel special, they also kept her separate from others. She worked hard at presenting herself as happy, funny, outgoing, and competent but expressed the following in her journal: "Fucking body. Fucking secrets. DO YOU UNDERSTAND THAT I AM NOT ON THE OUTSIDE THIS PERSON ON PAPER – DO YOU UNDERSTAND? I like who I am on the outside; I love myself. I am a very good person. Nobody knows. My mom knows about my anxiety and depression, but I still have my fucking secrets (bulimia, cutting), even from her."

Ana, a graduate student, who continues to live with her abusive parents admits, "I have to be two different people, like I am one person inside the house with my family but as soon as I step outside the house, I become somebody else, like I have to smile." Ana recognizes that she so urgently wants "approval from authority figures and peers that I won't rock the boat or stir up trouble for fear that people won't respect or like me." The outcome is that she sacrifices getting her needs met or creating authentic connections in her life, especially with herself. She is frustrated with herself, "I need to find myself in me but I don't know how to do that. I don't know how to be happy in myself." With respect to connections with others she describes, "I always tried to hide myself behind my hair…so people wouldn't see my face (Fig. 162.3)."

Eva was an undergraduate freshman and the youngest member of the group with a history of trauma, depression, and bulimia nervosa. She was experiencing significant emotional distress over the first 3 weeks of the group, frequently tearful and, on one occasion, needing to be seen at urgent care at the health service for symptoms of anxiety. Of all the participants, Eva was perhaps the least

Fig. 162.3 Ana's self portrait. This figure represents Ana's first self-portrait. It demonstrates her preoccupation with weight and how her sense of self is totally connected to her external appearance

verbal about her experience in the group but as you will see below her initial self-portrait is quite remarkable with respect to the experience of self-fragmentation (Fig. 162.4).

It is evident from Eva's self-portrait that she experienced herself as fragmented, disconnected, and barely held together.

162.5.1.2 Hating Myself

All the participants believed their sense of self worth was entirely contingent on perfectionistic standards of accomplishment and external validation and approval from others. The women were consistently self-critical and judgmental and felt the need to constantly compare themselves to others.

Ruth describes her tendency towards self-criticism, "I'm sooo hard on myself… I bash, I bash, I bash…I'll say, Damn, I should have done that. And then all the would've, could've, should've cross my mind. I am judging myself without even thinking about it."

Eva explains that she is "overly self-critical" and describes "a constant barrage of negative self-talk such as 'You know you're not doing this right'." Or "Why can't I do it correctly?" She adds that if she falls short of her goals or self-expectations, she is "devastated." Her self worth is reliant on her accomplishments, primarily in the academic realm. She is generally unaccepting of her body shape and size and feels self-conscious about her appearance.

Rena was a performer who had several shows at the end of the semester. These were very stressful experiences for her. She shared that she is very critical of her performances so that, even if people she admires complement her, she continues to doubt and degrade her abilities. "I can never say I'm

Fig. 162.4 Eva's self portrait. This figure represents Eva's first self-portrait. It clearly depicts the fragility of Eva's sense of self

proud of my performance because there's always something wrong with it." She uses words such as "heferly" and "walrus" to describe her body size, even if others reassure her she is attractive.

Both Ruth and Ana had actresses on their original self-portraits reflecting the cultural image of what is valued as real beauty. Actresses in our culture set the standards for beauty and the ideal towards which women should strive. The actresses on their posters (Elizabeth Taylor, Katherine Hepburn, Renee Zellweiger) were thin, beautiful, glamorous women whom Ruth and Ana actually resembled (Fig. 162.5).

162.5.1.3   Distorting the Body

The women objectified their bodies as a "thing" to be "controlled and manipulated". They regarded their bodies as nonself, thereby justifying their regular abuse of their bodies. By placing their highly judgmental focus on their objectified bodies, they were distracted from the painful underlying emotional turmoil they felt powerless to change. As the women strove to meet self-imposed, perfectionistic standards, their level of stress rose, which they then took out on their objectified body, creating a never-ending cycle of self-dissatisfaction, failure, and guilt.

In reflecting on her first self-portrait in which she depicts two distinctly separate selves (Fig. 162.1), Kelley notes that in the right hand self representation,

> I didn't even have a neck because I just did not feel at all connected to my body. I could not feel anything; I was just numb. I perceived it more like the Michelin Tire man, the one that's like a stack of tires, like a snowman. That's kind of how I felt, like a series of ripples of fat stacked together or something. But I was missing any connection between my body and mind.

Kelley remembers that while some people may not like what they see when they look in a mirror, she took it one step further, "When I looked in the mirror I would simply say that isn't me." She totally

Fig. 162.5 Part of Ruth's self portrait (**a**). Part of Ana's self portrait (**b**). These figures display components of Ruth and Ana's Self-portraits related to their idealization and identification with glamorous movie stars who are held as the standard of beauty in our culture

refused to have a conscious connection with her body. She further illustrates her disconnection from her body by recounting this story, "A couple of years ago I wanted to know what I looked like to other people so I actually took pictures of myself without my head because I didn't want to know that it was me." She adds that she has no pictures of herself after the age of 23.

Following a body scan, Ruth commented that if her stomach could talk with her it would say, "You hurt me with all you put me through." Her response was "You know, I'd think about my stomach as another unit, a thing, not a part of me."

In looking at her first self-portrait (Fig. 162.2), Rena remembers that she deliberately left off her body because "There is so much more I can think and laugh about without having to worry about the thing that's attached to my head." She confesses she had thoughts of "just wanting to get a knife and cutting off her abdomen" she hated it so much.

In exploring with Ana ways that she could begin to nurture herself more she observed,

> I guess I don't recognize my body as being important or valid. I know that my body needs to be taken care of and that it doesn't deserve all the treatment from my parents and myself, its just so much easier for me to be caring to somebody else.

162.5.1.4 Keeping Me from Where I Want To Be

As the participants reflected on their earlier self-portraits, significant insights emerged regarding the depths of their inner emptiness and emotional fragility, inability to tolerate the intensity of their emotions, and unending fears of not being good enough or lovable. Although each of these women was

Fig. 162.6 Part of Ruth's self portrait (**a**). This figure was included in Ruth's initial self-portrait. Ruth felt that her bipolar disorder and intense moods interfered with her ability to reach her full potential and created problems in her relationships
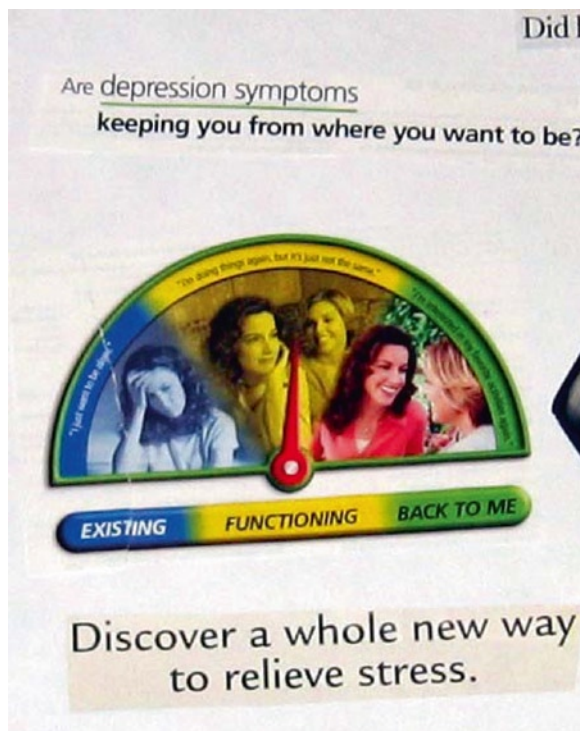
obsessively focusing on body shape and size, controlling all aspects of eating and exercise, they clearly felt out of control and overwhelmed on an emotional level.

The women identified experiencing very intense emotions that were difficult to regulate and that interfered with their functioning at times. Anxiety was a common emotion that frequently escalated to the level of panic. Most of the women had been treated for symptoms of depression. One woman had bipolar disorder. Several women had experienced significant traumatic events in their lives. The angry feelings experienced by the women were primarily viewed as negative and frightening. Participants also identified guilty feelings, for not being good daughters, for displeasing others, or in response to their own anger.

In her initial self-portrait (Fig. 162.6), Ruth poses the question: "Are depression symptoms keeping you from where you want to be?" She worries,

> that question will go with me for the rest of my life. Right now it's keeping me from where I want to go. It kept my grandmother from going where she wanted to go. Sometimes I just break down uncontrollably and I can't…I lose all control, and that's really scary. In the past I would take out my anger and frustration on the people closest to me, like my family. I would beat them with words and I felt so bad afterwards.

Eva shared with the group that she has problems managing her anger. When faced with conflict within her family she would become very angry and retreat to her room, slamming the door and turning off communication. During family therapy she learned how to be assertive and has found that helpful. She has had problems with depression since age 16 and there is a maternal family history of depression as well. During the time of the mindfulness group, Eva was having symptoms of panic, which was making it difficult for her to sit through class, thereby interfering with her schoolwork.

Sophia recalls being an angry, difficult child and that she frequently expressed her anger through head-banging behaviors. She first experienced depression as a high school sophomore, which

included irritability and self-harming behaviors. She describes being abusive to her boyfriend at the time. In addition, Sophia experiences problems with social anxiety that can culminate in panic attacks. Her mother also has a history of depression and eating disorder. As a result of her experiences within her family and her own depression, anxiety, and bulimia, Sophia had difficulty feeling positive about herself and establishing healthy relationships. She often felt that she lost herself in relationships with others.

> If you threw me in a room with a bunch of people and they were the only people I had to interact with, I am afraid that I would become those people, and that's really scary. Especially when lets say, it's a room full of misogynists, which leaves me hating myself. That's why I fear looking at magazines and stuff like that, because I feel like it will envelop me, instead of me being able to take a position against it.

Rena has experienced symptoms of depression since seventh grade marked by extreme self-criticism and thoughts of hopelessness such as "life is not worth living." She also can become highly anxious and experience panic attacks. Rena's mother and maternal extended family have been treated for depression. Rena recognizes that the level of self-hatred and self-criticism she experiences can have a detrimental effect on her performance and will hinder her career aspirations.

Kelley tracks the onset of her depression to her father's unexpected death by motor vehicle accident. Her father's death was very difficult for Kelley and she continues to harbor guilt feelings. Her anxiety and depression have kept her feeling dependent and inadequate. She admits there is a part of her that is terrified of finishing her degree and beginning a professional career beyond the university. Because of this, she delayed her comprehensive exams and remained in an abusive relationship for quite some time.

Ana experiences intense feelings of grief and sadness for the childhood she did not have within her abusive family. She often blames herself for the abuse and explains,

> I feel like the abuse is my fault, like I haven't been that good to my parents; or like I'm betraying them if I get angry about the way they treat me. The anger goes inside and that's what like goes to the eating and stuff because there's no other place for it. Usually my parents focus their abuse on me and I take some pride in the fact that this protects my two younger brothers; but if my brothers do something really crazy and my parents focus on them, I feel guilty since I'm the oldest and should protect them.

Ana also experiences symptoms of panic when her mother is berating her for long periods of time. She typically turns her emotions against herself rather than externalizing them. She is desperate for approval from others so avoids conflict as much as possible. She has learned to experience pleasure somewhat vicariously by observing others having fun, with little expectation of experiencing happiness for herself.

162.5.2 Waging War as a Means of Gaining Control

This second subsection of the theme describes the strategies used by the participants to cope with stress in their daily lives. Their choice of coping methods is connected to their experience of themselves as described above. Although in the short term the strategies they used helped to lower the intensity of their emotional turmoil, over time these choices perpetuated their sense of fragmentation, ineffectiveness, and lack of control within themselves and within the world. Their experiences are synthesized as follows: Numbing out; Going into Trance; Binging; Purging; Weighing, Measuring and Constantly Comparing; Cutting; and Abusing Alcohol and Pot.

162.5.2.1 Numbing Out

Many of the participants unconsciously used denial rather than face the emotional pain of their situations, particularly in relation to family dysfunction and past trauma. Being aware of and facing

emotional pain is very difficult for all of us, but for the women in this study who experienced a fragmented, inadequate sense of self, it was especially overwhelming.

Sophia experienced a great deal of emotional numbness to create an illusion of calm. She became aware of this emotional numbness while completing self-awareness assignments in the group. In attempting to notice pleasant and unpleasant events she recognized that she does not allow herself to experience any emotions at all. She explained,

> Numbness is not in and of itself a bad thing. It's sort of like a placid thing. It becomes problematic when something is being covered up or isn't being handled. Its harder to notice problems when things are placid, so then a variety of symptoms may emerge such as anxiety, depression, and bulimia nervosa.

Sophia used a great deal of numbing out to avoid her angry, sad feelings about her family situation. She did not feel comfortable with those feelings and preferred to feel nothing.

162.5.2.2 Going into Trance

Going into trance is another way that participants unconsciously tried to manage powerful, unpleasant feelings. When the stress of a situation was sufficiently high, an alternate mode of consciousness took over to protect them from the painful feelings of their current experience.

In describing her choice of spiral as a representation of herself, Sophia explained, "the spiral characterizes the experience of a drowning kind of hypnotic thing, like falling into a tunnel, and where your mind goes away (Fig. 162.7)."

Fig. 162.7 Sophia's self portrait. This figure represents Sophia's self-portrait. She describes that the spirals represent her tendency to use dissociation to cope with stress. Several of the women describe dissociation as part of the binge–purge cycle

In situations where she experiences extreme emotional distress such as when her mother is verbally abusing her or she experiences personal rejection, Ana described the following,

> When I get very wound up there's something inside me that I feel like is not even me, that automatically sets in and I can't stop it. Its like I go into a trance and binging is all I can think about. Nothing's satisfied until the binge is over. The trance takes over and everything else stops.

Ana has not found a way to stop the trance from occurring. Nor has she found anything that soothes her as completely as a binge when she is feeling her worst emotionally.

162.5.2.3 Binging

Several of the participants identified that when they felt stressed, they frequently binged. Binging with food was self-soothing. Binges were frequently anticipated in advance and a great deal of time and energy went into the planning. Social opportunities were passed up if they would interfere with the binge. Guilt and shame commonly followed the binge, triggering the urge to purge or to socially isolate.

Ana has occasional success with delaying the urge to binge but she notes that there are times when she wants to binge and will consciously choose to binge because she has been unable to find anything else that is as self-soothing. She is aware that the urge to binge is associated with stress and remembers that she started eating instead of crying during high school. "My mother was always big on appearances so when I began to wear mascara in high school I stopped crying because I had to look good and crying would cause my mascara to run." Moreover,

> I didn't want my parents to have the satisfaction of seeing me cry. I knew they had control over everything I did and I didn't want them to have control over me too. I guess I always thought of crying as weakness and once my parents knew how to get to me they would use it against me over and over. I didn't want to give them something else to hurt me with. With eating, once I cleaned up all the food, they never noticed.

Ana knows the locations of many grocery stores between school and home. She will buy food in the store and eat it secretly in her car. She worries what her roommate thinks when large quantities of food come into the dorm room and quickly disappear.

Ruth describes the previous week as follows,

> I didn't stop eating and throwing up one after the other. I couldn't sit still, I didn't sit while I ate, I jumped around fidgeting, scrounging around in my cabinets looking for more to eat. Right now, I don't have enough money to eat normally, never mind to binge with. I sneak into the dining halls and go crazy.

When Kelley feels anxious and depressed she goes to fast food restaurants, buys large quantities of fast food, isolates in her apartment, and eats and sleeps for an entire weekend. She will cancel social obligations, not do any work, and stay in bed around the clock. If friends come to her door she won't let them in because all the food wrappers are visible. Other times she will purchase large quantities of food at the grocery store, spread it out on her bed, and eat is as fast as she can. Kelley bakes desserts in large quantities, which she rarely eats but just keeps in her apartment or sends to relatives.

When Sophia feels stressed she isolates in her room and eats large quantities of whatever food is available, although she prefers sugary foods and carbohydrates such as ice cream, cake, or cereal. She eats until she literally feels ill and then stays alone until the gastric symptoms subside. She alternates between the extremes of binging and restricting and struggles to achieve moderation. Sophia shared her story of buying an entire cake for herself in preparation for a binge. She had the bakery write "happy birthday Joe" on the top of the cake so that if she ran into a classmate, she then had a story to hide her true purpose. She remembers occasions even in middle school where she would binge on food on returning home from having been out socially with friends.

162.5.2.4 Purging

Purging refers to the compensatory behaviors participants used to rid their body of the food or calories resulting from a binge. The two main purging behaviors that the women reported using were inducing vomiting or compulsive, rigorous exercise. Each of these will be described below.

162.5.2.5 Vomiting

Each of the participants acknowledged that stress and anxiety led to purging behaviors. Purging generally followed eating, and was not always in response to a binge. Just the sensation of food in the stomach could result in purging. For most participants, vomiting was cyclical in relation to stress levels and could occur following every meal. Following the initial lowering of anxiety that resulted from vomiting, guilt and shame frequently ensued. The women felt isolated by their secret behaviors. For some vomiting could occur spontaneously with minimal or no inducement.

On spring break Ruth went home to visit her family. She and her mother went to a tearoom for lunch and Ruth ate tiny tea sandwiches, scones, and drank tea. She wrote in her journal,

> Such a nice place and what do I do? I got up to the bathroom and threw it up! Then what? The toilet didn't flush the vomit away (which Ruth has perfected over the years). Then I noticed a sign *Antique Plumbing*. Blah, Blah, Shit! What do I do?!!! Panic. People are outside waiting! Waiting! I wait until the water stops hissing and flush a second time but still lettuce is floating on top. I try to sift it out with my fingers, but still a few left. Why didn't I throw up in the garbage? Sometimes I do that. Throw up in paper towel and stick it under wads of used towels. I flush a third time and walk out. Panicky that people next in line will know. Will they say something? My hands are shaking; itty-bitty shakes that rattle my teacup. My chest is aching, pressure.

Ruth has been purging since high school. Her eating symptoms began as restricting (anorexia) but then she switched to binging and purging since the effects of bulimia could be hidden from her mother. Her binging and purging episodes may be correlated with her mood swings. There are stretches of time when she purges multiple times a day at least following every meal alternating with a period of time when she is not binging or purging at all or only a few times per week. Generally if she is eating more than she would like, she will purge. If her eating is restricted, there is less need to purge.

As a performer, there are times when Rena cannot purge since this adversely affects her performance. At times, she has performances daily over the course of a week. She relates that, "As soon as my performances are over, the first thing I do after I eat is just purge." She notes that when she feels very stressed she finds it difficult to tolerate the feeling of food in her stomach. Usually purging will alleviate the feeling and lower her stress. At those times when it is not possible for her to purge, she may then engage in self-mutilation as an alternative means of lowering her stress.

Kelley has purged for so long, it happens reflexively with minimal stimulation. Just brushing her teeth results in vomiting. She has to warn her dentist to use a light touch or she vomits in the chair. Kelley tends to vomit every morning on awakening without any noticeable precipitant. On one occasion she began to wretch in my office while exploring deeply emotional issues related to her fears of taking care of herself as an adult.

162.5.2.6 Exercising

An alternative way to purge is through excessive exercise. The goal is enhanced body shape and lowered weight, rather than health. The workouts have a compulsive, frantic quality to them, so if they are missed or shortened, the women experience feelings of guilt and failure.

Ana exercises excessively and compulsively. Prior to the mindfulness group she was jogging on a treadmill at home for 10 miles or 3 h daily. Occasionally she jogged twice a day. Missing a workout created tremendous guilt and anxiety.

Kelley described herself as "rigid" in regards to her exercise routine. She would not allow herself a day off and would only work out on a certain piece of equipment. If someone else were using the equipment, she would either pressure that individual to give up "my machine" or leave the gym angry and resentful. She could never override her need to go the gym for any reason.

Rena was forcing herself to go to the gym in order to work out at the end of a full day of classes during which time she had only eaten "lightly." She confides, "The exercising I do now is like punishing myself, really it is. I've never really liked going to the gym. I watch the clock and it's just a pain. Even while doing Palates I have to be distracted by music or some kind of dance moves."

Eva historically was a gymnast and was a member of the crew team at school. Practice for crew was daily and entailed hours of grueling exercise and rowing beginning in the early morning hours before dawn. She was used to being very physically active which had reduced her need to restrict or purge. Eva decided to drop crew because playing a sport and academic pressures had overwhelmed her. With less physical activity, her eating and purging markedly increased.

162.5.2.7 Weighing, Measuring, and Constantly Comparing

Each of the participants was obsessively preoccupied with their body shape and size. They compulsively weighed themselves, scrutinized themselves, compared themselves to others, and counted calories and fat content in their diet.

As Rena puts it,

> Beauty, I'm obsessed with beauty and any achievement thereof. That, together with the perfectionist in me, grows eating disorders. I want to be like a Barbie doll but I can't because, even at my thinnest, I have a certain size bone. I wake up in the morning and I'm just like 'Oh gosh you look awful' because I'm expecting to see a size 4 in the mirror, but I'm a size 10 or 12."

She historically has counted carbohydrates, fat, and calories, and measured and weighed herself after grueling exercise workouts.

Kelley is preoccupied with her appearance and weight. She was so unhappy with her body that she would only use the exercise machine at the gym that was located in the corner next to the wall away from the mirrors. That way neither she nor anyone else could see her while she exercised. She tended to weigh herself frequently at home and at the gym and would set specific weight loss goals for herself. Her standard of comparison was her own body image at age 16. She has cycles where she restricts her food intake and exercises regularly alternating with loss of control of her eating resulting in binging and purging.

Sophia reveals that she is really neurotic about her diet.

> If I eat pizza it has to be completely blotted and then I pick half the cheese off. I have so many habits in terms of food. It has to do with the fact that I am not accepting of a certain weight. I chronically buy clothing that is too small for me and then I have nothing nice to wear.

162.5.2.8 Cutting

Sometimes, as an alternative to purging, women in the M-BED Group turned to self-mutilation to reduce intolerable levels of stress and anxiety. While some of the women were continuing to use cutting to lower emotional distress, others had used it in the past, but had stopped.

 In her journal, Rena wrote about what these episodes were like for her,

I was feeling tired and weak from a long day of classes, followed by an hour of exercise with nothing to eat. While I was undressing to take a shower, I happened to glance in the mirror and had never looked so disgustingly fat. I freaked out and began to hyperventilate. All I could focus on was my walrus-sized gut. I didn't know what to do. There was nothing in my stomach to throw up, so I cut my wrist. What I really wanted to do was to cut my stomach open and drain out whatever was in there making me fat!!! I HAVE to be thin.

Only a few days later Rena again viewed herself in the mirror and judged herself to be "incredibly, disgustingly fat." She again "freaked out" and began to have a panic attack. She was feeling all alone and unable to accept her body size. She could not throw up because of a performance the following day. All she could think of was to hurt herself. She cut herself with a pair of scissors and with a piece of glass hoping that "draining my blood might make me thinner." She wrote in her journal, "My mind is out of control and I want to destroy all my mirrors and murder any humans who decided thin was desirable."

Sophia had a history of cutting herself in high school but has not had recent self-harming behaviors. Like wise, Ruth had cut her arms between the ages of 12–14 but not recently. In fact, Ruth had an angry reaction to the group's discussion of Rena's cutting behavior. Ruth wrote in her journal "When I hear the mention of cutting I cringe, I feel ill to my stomach." She obsesses about a visible scar on her arm from a time she cut herself at age 14. This scar is very upsetting to her because she feels people who see it know her secret (similar to the lettuce floating in the toilet).

162.5.2.9 Abusing Alcohol and Pot

In another attempt at lowering stress and anxiety, two of the women used marijuana and alcohol to relax and numb intense emotion. Ruth relates that she was a "little pothead" during high school and that now she drinks, "to have fun and to make myself happy." While drinking last year, Ruth had an unwanted sexual experience about which she continues to feel angry and taken advantage of (Fig. 162.8).

Fig. 162.8 Part of Ruth's self portrait (C). This figure represents a part of Ruth's initial self-portrait. It reveals her tendency to rely on alcohol and drugs to cope with stress. At the bottom, she refers to her unwanted sexual experience and her residual guilt, shame, and anger

Sophia was not very academically motivated when she started college. She was still struggling with depression and ended up partying with drugs and alcohol through freshman year. After counseling and a medical withdrawal in her sophomore year, Sophia stopped using drugs and alcohol, realized she had nothing in common with her old friends, and transferred to a college that could better meet her academic and social needs.

162.6 Implications for Recovery from Bulimia Nervosa

Human vulnerability and suffering is an existential given (Chodron 1997; Clemence 1966; Peck 1978). This human "wound" (Todres 2004), common to us all, can serve as a vehicle for hardening (becoming psychologically defended) and closing off to relational life or softening (remaining vulnerable and open) and extending empathy as the great connector to relational life on behalf of humanity's shared "wound" (Salzberg 1997; Todres 2004; Welwood 2000). It is clear that in response to their human vulnerability, these six women were experiencing extremes in their thoughts, feelings, and behavior. They felt worthless, unlovable, inadequate, powerless, victimized, angry, sad, and numb. They were out of touch with their authentic selves, their bodies, and their personal needs. The women could not trust themselves or others to meet their needs because their needs were perceived as being either too great or altogether unimportant. Because they were so disconnected from their inner selves and because of their underlying, negative beliefs about themselves, the women experienced great difficulty regulating their extreme feelings, causing their behaviors to become out of control. Based on their temperaments, family experiences, and cultural expectations, they developed a belief system that if they achieved the perfect body size and shape, they would be seen as successful and loveable. In response to this belief system, they adopted the coping behaviors of restricting eating, which then progressed to binging and purging. When controlling food and purging activities were insufficient or unavailable, many of the women resorted to cutting themselves to obtain relief from their excruciating feelings and self-loathing. The women's thoughts, feelings, and behaviors were aimed at control, self-sufficiency, and completeness in response to their internal sense of lack of control, dependency, and incompleteness. They had grown to hate their personal experience of vulnerability and human need, closing off to authentic relational life with self and other.

Binging and purging, as private and secret activities, isolated them from others, creating a deep sense of loneliness. The women experienced shame regarding their behaviors, further lowering their self worth. In the mean time, they engaged in a driven and endless pursuit of external achievements, abusive or sexualized relationships, and culturally defined beauty in a futile effort to feel lovable.

162.7 Application for Other Areas of Health and Disease

Bulimia nervosa reflects an underlying disorder of self and, as such, effective treatment requires a trauma-informed, interdisciplinary, integrated approach that restores both physiological and psychological health. Because of the serious medical risks associated with bulimia nervosa, consistent medical and nutritional monitoring and education are central to recovery. Concurrent with these interventions, a phase model of psychotherapeutic treatment is essential that includes cultivating a therapeutic relationship, providing ongoing psychoeducation, building a positive support system, and developing nonharming coping skills. Depending on the severity of the symptoms and the presence of comorbid disorders, additional therapies that may be helpful to the recovery process include mindfulness-based approaches (Proulx 2008), sensorimotor approaches (Ogden et al. 2006), ego

state work (Seubert 2008), Eye Movement Desensitization and Reprocessing (EMDR) (Forgash and Copeley 2008; Shapiro 2009), dialectical behavioral treatment (Linehan 1993), and cognitive behavioral treatment (Fairburn et al. 1993). Up to 40% of women with bulimia nervosa do not respond to traditional treatments and symptoms can become chronic with deleterious medical, psychological, and social outcomes (Fairburn et al. 1992; Stice 1999). Bulimia nervosa is a mind-body disorder that responds best to the active collaboration of many healthcare disciplines.

Summary Points

- The women in this study with bulimia nervosa lacked connection with their inner selves as well as their bodies.
- They experienced deep self-loathing and were highly self-critical.
- They sense of lovability became related to the achievement of external, cultural ideals of beauty, thinness, and perfection.
- The symptoms of bulimia, which originated as a way to control body size and shape, became a coping strategy for lowering stress and regulating emotion.
- The addictive coping cycle compounded feelings of shame and guilt and was cloaked in secrecy and isolation.
- In up to 40% of women with bulimia nervosa, the condition can become chronic, with significant medical sequelae.
- To be effective, treatment interventions for bulimia nervosa must not only address health and nutritional concerns, but also the lack of self-connection, self-compassion, and effective coping strategies that are not self-harming.

Definitions

Cognitive behavioral therapy: A therapy developed by Beck that is aimed at changing maladaptive, distorted thoughts and behaviors to lower depression and anxiety. Relaxation and deep breathing exercises are emphasized behaviorally.

Dialectical behavioral treatment: An empirically tested, cognitive-behavioral treatment approach developed by Marsh Linehan to assist individuals with symptoms of borderline personality disorder to improve the quality of their lives by learning how to regulate emotions, tolerate emotional distress, and improve their interpersonal effectiveness.

Ego state therapy: A therapeutic approach developed by Watkins & Watkins that identifies and connects with all parts of the personality for the purpose of relieving symptoms and healing conflicts. Ego states formed in childhood trauma may function maladaptively in present life situations. Ego state therapy helps the healthier, core parts of the self to collaborate with and reparent the immature, wounded parts of the self.

EMDR: Eye Movement Desensitization and Reprocessing is a therapeutic intervention developed by Francine Shapiro that utilizes dual stimulation to activate the information processing system allowing individuals to transform dysfunctionally stored traumatic events into a normal narrative memory that is no longer disturbing.

Hermeneutic phenomenology: a philosophy and qualitative research methodology that attempts to understand the internal world or lived experience of human beings by "going to the things themselves." The researcher approaches the phenomenon with rigorous self- awareness and an

open mind in order to more deeply understand and accurately interpret the specific phenomenon. It is based on the beliefs of Husserl, Heidegger, Gadamer, and Merleau-Ponty.

Mindfulness: Paying attention to one's moment-to-moment experience with an attitude of non-judgment. Derived from Buddhist mediation practices and adapted to Western culture as a life style that has been shown to lower stress and depression.

Sensorimotor approaches: Based on the belief that traumatic experience disrupts the body's physiological and emotional regulation, these approaches advocate for working with the body's own defensive systems, autoregulatory patterns, and adaptive responses to promote reconnection with the body.

References

American Psychiatric Association (APA). Diagnostic and statistical manual of mental disorders. 4th ed. Text revision. Washington, DC: Author; 2000.

Brown LM, Gilligan C. Meeting at the crossroads. New York: Ballantine Books; 1992.

Bruch H. Conversations with anorexics. New York: Basic Books; 1988.

Chodron P. When things fall apart: Heart advice for difficult times. Boston: Shambhala Publications; 1997.

Clemence M. AJN. 1966;66:500–5.

Drew N. In: Polifroni EC, Welch M, editors. Perspectives on philosophy of science in nursing: An historical and contemporary anthology. Philadelphia: Lippincott, Williams, & Wilkins; 1999. p. 263–272.

Drew N. ANS. 2001;23:16–31.

Drew N. ANS. 2004;27:215–23.

Fairburn CG, Agras WS, Wilson GT. In: Anderson GH, Kennedy SH, editors. The biology of feast and famine: relevance to eating disorders. San Diego: Academic; 1992. p. 317–340.

Fairburn CG, Cooper PJ. BMJ. 1982;284:1153–5.

Fairburn CG, Marcus MD, Wilson GT. In: Fairburn CG, Wilson GT, editors. Binge eating: nature assessment, and treatment. New York: The Guilford Press; 1993. p. 361–404.

Fisher M, Golden NH, Katzman, DK et al. J Adol Health. 1995;16: 420–37.

Fogash C, Copeley M (eds). Healing the heart of trauma and dissociation with EMDR and ego state therapy. New York: Springer Publishing Company; 2008.

Garfinkel PE, Moldofsky H, Garner DM. Arch Gen Psych. 1980;37:1036–40.

Hsu LKG, Crisp AH, Harding B. Lancet. 1979;i:61–5.

Husserl E. Ideas pertaining to a pure phenomenology and to a phenomenological philosophy, first book (F. Kersten, Trans.). Boston: Kluwer Academic Publishers; 1983. (Original work published 1913)

Linehan M. Cognitive-behavioral treatment of borderline personality. NewYork: Guilford Press; 1993.

National Eating Disorders Association. General eating disorders information: facts for activists. 2006. Retrieved 23 Mar 2006 from http://www.edap.org/p.asp?WebPage_ID=320&Profile_ID=95634.

Ogden P, Minton K, Pain C. Trauma and the body: a sensorimotor approach to psychotherapy. New York: W W Norton; 2006.

Peck MS. The road less traveled. New York: Simon & Schuster; 1978.

Pipher M. Reviving Ophelia: saving the selves of adolescent girls. New York: Ballantine Books; 1994.

Proulx K. Eat Dis. 2008;16:52–72.

Salzberg S. Loving kindness: the revolutionary art of happiness. Boston: Shambhala Publications; 1997.

Seubert A. The courage to feel: a practical guide to the power and freedom of emotional honesty. West Conshohocken: Infinity; 2008.

Shapiro R, editor. EMDR solutions II: for depression, eating disorders, performance and more. New York: WW Norton; 2009.

Stice E. J Clin Psych. 1999;55:675–83.

Todres L. Indo-Pac J Phenomenol. 2004;4:1–12.

Van Manen M. Researching lived experience: human science for an action sensitive pedagogy. Ontario: Althouse Press; 1990.

Welwood J. Toward a psychology of awakening. Boston: Shambhala Publications; 2000.

Chapter 163
The Night Eating Syndrome: An Overview

Jennifer D. Lundgren

Abbreviations

AN	Anorexia Nervosa
BED	Binge Eating Disorder
BN	Bulimia Nervosa
NEDQ	Night Eating Diagnostic Questionnaire
NEQ	Night Eating Questionnaire
NES	Night Eating Syndrome
NESHI	Night Eating Syndrome History and Inventory
SCID	Structured Clinical Interview for the DSM
SRED	Sleep-related Eating Disorder
SSRI	Selective Serotonin Reuptake Inhibitor

163.1 Introduction

Night Eating Syndrome (NES) is a delay in the circadian pattern of food intake, manifested by evening hyperphagia (consuming ≥ 25% of the total daily food intake after the evening meal) and/or nocturnal awakenings accompanied by ingestions of food (O'Reardon et al. 2004). First recognized by Stunkard and colleagues (1955), research on the nosology, etiology, pathophysiology, and treatment of NES has advanced over the past decade. This chapter will provide an overview of NES, including a brief history of its conceptualization over the past 50 years, its prevalence and comorbidity, hypothesized etiology and pathophysiology, its consequences and treatment, and will end with a review of future directions needed to further characterize the nutritional, behavioral, and neurobiological aspects of NES (Table 163.1). Other chapters in this section will review in detail the current status of the neurobiological and neuroendocrine aspects of NES.

J.D. Lundgren (✉)

Department of Psychology, University of Missouri-Kansas City, 4825 Troost Avenue, Ste. 124, Kansas City, Missouri, 64110, USA

e-mail: lundgrenj@umkc.edu

Table 163.1 Key facts of NES

Diagnosis	NES research diagnostic criteria have been developed and should be used in future studies to diagnose NES
Prevalence and comorbidity	The prevalence of NES in the general population is low (around 1.5%) and increases with adiposity and psychiatric symptoms
Etiology	The etiology of NES is unknown, but likely involves behavioral/functional (i.e., night eating serves to help someone sleep), nutritional, neuroendocrine, and pathophysiological mechanisms
Health implications	Studies of the relationship between NES and obesity are equivocal, although certain populations may be at higher risk for weight gain due to night eating (e.g., those who are already obese or taking weight promoting medications). More research is needed on the health implications of NES
Assessment and treatment	Validated assessment measures and efficacious treatments exist for NES. Individuals with NES should be referred for treatment to a qualified healthcare provider

NES night eating syndrome

Table 163.2 Comparison of 1955 and 1999 NES diagnostic criteria

Symptom domain	1955 NES criteria[a]	1999 NES criteria[b]
Evening hyperphagia	Consumption of large amounts of food in the evening and night; at least 25% of total calories for the day during the period following the evening meal	Evening hyperphagia ≥ 50% of total daily energy after the evening meal
Sleep disturbance	Sleeplessness, at least until midnight, more than half of the time	Awakening at least once a night
Nocturnal ingestions	–	Consumption of snacks during the awakenings
Morning hunger	Morning anorexia with negligible food intake at breakfast	Morning anorexia, even if the person eats breakfast
Duration	–	At least 3 months
Other diagnoses	–	Person cannot receive a diagnosis of NES if they meet criteria for BN or BED

This table compares the 1955 and 1999 proposed diagnostic criteria for NES

NES night eating syndrome, *BED* binge eating disorder, *BN* bulimia nervosa

[a]Criteria cited in Stunkard et al. (1955)

[b]Criteria cited in Birketvedt et al. (1999)

163.2 History of Night Eating Syndrome

NES was first described in 1955 as a disorder of morning anorexia, evening hyperphagia, and insomnia, usually accompanied by depressed mood and stressful life circumstances (Stunkard et al. 1955). Table 163.2 shows the original diagnostic criteria outlined by Stunkard and colleagues (1955).

NES did not receive much research or clinical attention until the 1990s, coinciding with increasing rates of obesity and the search for factors related to excessive weight gain. In 1999, Birketvedt and colleagues added awakenings with ingestions of food (*nocturnal ingestions*), increased the percent of food consumed after the evening meal from 25% to 50% (*evening hyperphagia*), and added duration and rule out criteria to those originally described in 1955 (see Table 163.2 for a comparison of the diagnostic criteria). Additionally, they noted that NES affects both obese and nonobese persons, which is an observation that has become more important as discussions of the clinical significance of NES have ensued.

163.3 Current Conceptualization of NES

As research has advanced our understanding of NES, the diagnostic criteria for NES have continued to evolve, making comparisons across studies difficult. In an effort to move NES research forward based on current research evidence, the First International Night Eating Symposium (April 26, 2008, Minneapolis, MN) was held to reach a consensus on a set of provisional research diagnostic criteria for NES and to discuss a roadmap for future NES research. Approximately 20 researchers in the areas of eating disorders, obesity, and sleep attended the meeting and contributed to the development of the proposed research diagnostic criteria presented in Table 163.3.

These criteria offer the most comprehensive conceptualization of NES to date. The first criterion reflects the notion that NES is at its core a disorder of eating and circadian rhythm. This is manifested by either the consumption of an unusually large percent of the total daily food intake in the evening hours after the evening meal (*evening hyperphagia*) and/or the consumption of food upon awakening in the middle of the night (*nocturnal ingestions*). Figures 163.1 and 163.2 demonstrate the differences in eating patterns of individuals diagnosed with NES compared to weight matched controls.

O'Reardon and colleagues (2004) found that obese persons with NES did not consume significantly more total daily calories than weight matched controls, but they did have a strikingly different circadian pattern of food intake (Fig. 163.1). Weight matched controls showed typical increases in food consumption during the lunch and supper hours, whereas night eaters had a steady food intake that continued until 6:00 a.m. the following morning. There were no significant differences in sleep onset or offset times, indicating that the circadian sleep pattern is not delayed in parallel with the food intake delay, but the night eaters did report significantly more awakenings per night (1.5 vs. 0.5 awakenings).

Table 163.3 2009 Proposed research diagnostic criteria

Symptom domain	Diagnostic criterion
Eating pattern	I. The daily pattern of eating demonstrates a significantly increased intake in the evening and/or night-time, as manifested by one or both of the following:
	(A) At least 25% of food intake is consumed after the evening meal
	(B) At least two episodes of nocturnal eating per week
Awareness of eating behavior	II. Awareness and recall of evening and nocturnal eating episodes are present
Associated mood, hunger, and sleep features	III. The clinical picture is characterized by at least three of the following features:
	(A) Lack of desire to eat in the morning and/or breakfast is omitted on four or more mornings per week
	(B) Presence of a strong urge to eat between dinner and sleep onset and/or during the night
	(C) Sleep onset and/or sleep maintenance insomnia are present four or more nights per week
	(D) Presence of a belief that one must eat in order to initiate or return to sleep
	(E) Mood is frequently depressed and/or mood worsens in the evening
Distress/impairment in functioning	IV. The disorder is associated with significant distress and/or impairment in functioning
Duration	V. The disordered pattern of eating has been maintained for at least 3 months
Other diagnoses or Medical conditions	VI. The disorder is not secondary to substance abuse or dependence, medical disorder, medication, or another psychiatric disorder

This table shows the 2009 proposed research diagnostic criteria for NES. These criteria are comprehensive and based on more recent research than those presented in 1955 and 1999 (see Table 163.2)

Cumulative Caloric Curves For Controls vs. NES Participants
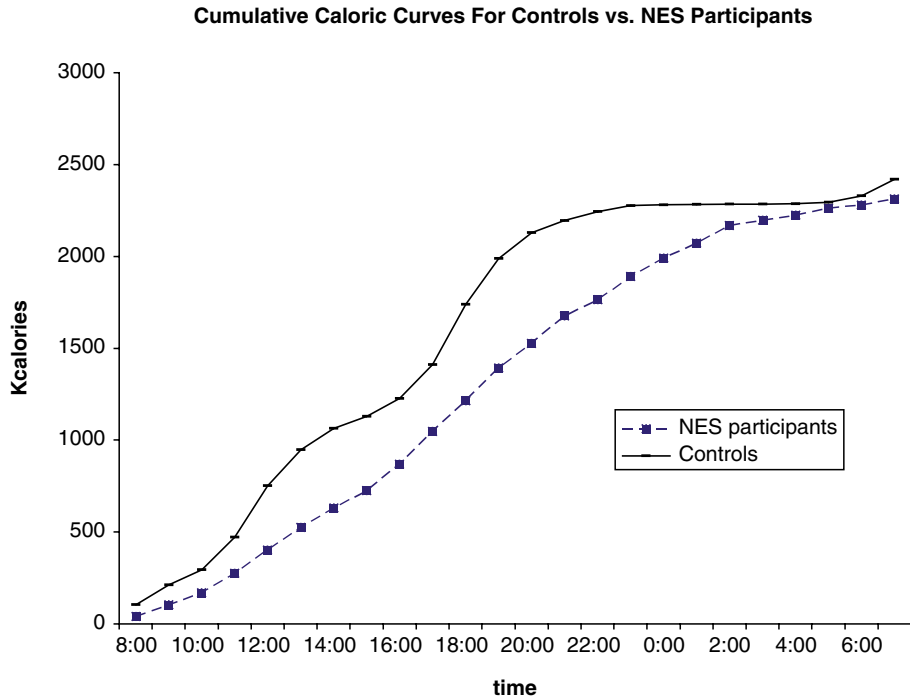
Fig. 163.1 Comparison of 24-h food patterns of obese persons with NES and weight-matched controls. This figure illustrates the significantly different circadian patterns of food intake between obese persons with night eating syndrome and weight matched controls, although the total caloric intake is not significantly different over 24 h (Reprinted with permission)
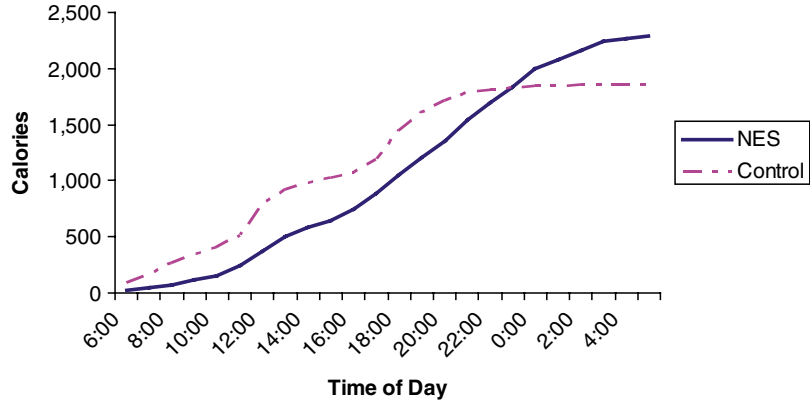
Fig. 163.2 Comparison of 24-h food patterns of non-obese persons with NES and weight-matched controls. This figure illustrates the significantly different circadian pattern of food intake between nonobese persons with night eating syndrome and weight matched controls. Total daily caloric intake is significantly greater for the group with night eating syndrome (Reprinted with permission)

Lundgren and colleagues (2008a) found nearly identical patterns of delayed circadian food intake in nonobese night eaters compared to weight matched controls (Fig. 163.2). Nonobese night eaters, compared to weight matched controls, however did consume significantly more total calories per day (night eater = 2284.5 kcal; control = 1856.2 kcal). Nonobese night eaters had significantly more nocturnal awakenings and ingestions of food than did controls.

Currently, only evening hyperphagia *or* nocturnal ingestions are necessary to meet the first proposed NES diagnostic criterion. This criterion was left intentionally broad because further research is needed clarify the relationship between these two manifestations of the circadian delay of food intake, and because individuals often report both behaviors. For example, Lundgren and colleagues (2008a) found that 84% of nonobese individuals with NES met criteria for both evening hyperphagia *and* nocturnal ingestions of food. In another study of night eating in women diagnosed with bulimia nervosa (BN), however, Lundgren and colleagues (2008b) found that only 14% of BN patients with night eating features reported both behaviors. More research is needed to clarify this core criterion.

The second criterion (Table 163.3), that awareness and recall of evening and nocturnal eating episodes are present, was proposed to differentiate NES from parasomnias such as sleep-related eating disorder (SRED) (Howell et al. 2009). Persons with SRED can consume food in the middle of the night, do so while in a sleep-walking state, and often consume nonfood items. Although persons with NES occasionally report a lack of full awareness with nocturnal ingestions of food, they must report awarness and recall of the nocturnal eating episodes in general.

At least three of five additional features must be present in order for one to receive a diagnosis of NES (Table 163.3). These include a lack of morning hunger or omission of food in the morning, a strong urge to eat either after dinner or upon awakening in the middle of the night, difficulty falling or staying asleep at night, presence of a belief that one must eat in order to return to sleep, and mood that is frequently depressed and that may worsens in the evening hours.

Evidence of problems with morning hunger, morning food omission, and sleep disturbance in individuals with NES is presented in Figs. 163.1 and 163.2. Anecdotal evidence and that collected with self-report instruments, such as the night eating questionnaire (NEQ; Allison et al. 2008) suggest that many persons with NES experience a strong urge to eat after dinner or upon awakening in the middle of the night. Allison and colleagues (2004) noted several different themes associated with these urges, including cravings for specific foods, anxiety and agitation, distress about sleep disruption, and feeling compelled to eat/needing to feel full to sleep.

Similarly, some persons with NES feel that they must eat in order to fall asleep initially or to fall back asleep after a nocturnal awakening. Again, this is assessed with the NEQ (Allison et al. 2008) and is often described as a function of night eating for some who suffer from NES (Allison et al. 2004).

Night eating syndrome is associated with mood disturbance in some individuals. Stunkard and colleagues (1955) noted this disturbance in their original description of NES and several studies have confirmed that night eaters have high rates of comorbid mood disorders and increased scores on depression measures (Gluck et al. 2001; de Zwaan et al. 2006; Lundgren et al. 2008a). Interestingly, persons with mood disorders are not necessarily at increased risk for NES (Lundgren et al. 2006). A recent SPECT study has provided preliminary evidence that the pathophysiology of NES and MDD is distinct (Lundgren et al. 2009), and will be reviewed in a later chapter.

Finally, the night eating and associated features must cause distress and impairment, be present for at least 3 months, and not be better explained by another psychiatric diagnosis, medical condition, or medication/substance. The conditions which are frequently comorbid with NES, in addition to mood disorders, will be reviewed below.

163.4 Prevalence of NES

The prevalence of NES varies substantially depending on the criteria used to diagnose it and the population under study. To date, no studies have examined the prevalence of NES using the recently proposed research diagnostic criteria (Table 163.3). Studies using previous criteria have provided a general sense of the magnitude of NES in the general population, among obese individuals, and

Table 163.4 Prevalence of NES

Population	Prevalence (%)	Citation
General population	1.5	Rand et al. (1997)
	1.6	Striegel-Moore et al. (2006)
	5.7	Colles et al. (2007)
	2.2–7.1	Lundgren et al. (in press a)
Special populations:		
Weight loss seeking	6	Stunkard et al. (1996)
Bariatric surgery	16	Adami et al. (2002)
Diabetes	9	Allison et al. (2006)
Psychiatric	27	Rand et al. (1997)
	3.8	Allison et al. (2007)
	9.7	Morse et al. (2006)
	12.3	Lundgren et al. (2006)
	25	Lundgren et al. (in press b)

This table shows the prevalence of night eating syndrome in several populations

among other psychiatric populations, such as those with eating disorders and severe mental illness (Table 163.4).

Variability in prevalence is due to differences in assessment measures, diagnostic criteria, and populations.

Prevalence of night eating in the general population has been reported at 1.5% (Rand et al. 1997) to 7.1% (Lundgren et al. 2010a). Prevalence rates in special populations suggest ranges of 6% (Stunkard et al. 1996) to 16% (Adami et al. 2002) in weight loss samples of class I and II obesity. Among bariatric surgery candidates, the range in prospective interview studies is 9% (Allison et al. 2006) to 27% (Rand et al. 1997); Allison and colleagues (2007) found a prevalence of 3.8% among older adults in a large multicenter study of type 2 diabetes (Allison et al. 2007).

Three studies have examined the prevalence of night eating in other psychiatric populations. Lundgren and colleagues (2006) found a prevalence of 12.3% in two university outpatient psychiatric clinics which included patients with a variety of Axis I and Axis II psychiatric disorders. In a sample of weight loss seeking individuals with serious mental illness (schizophrenia, bipolar disorder, and severe major depressive disorders), the prevalence of NES was striking at 25% (Lundgren et al. 2010b). It is unlikely that participants grossly over-reported night eating behavior in this sample, as only 5.9% of participants met the criteria for binge eating disorder (BED) (Lundgren et al. 2010b). Finally, Lundgren, Shapiro, and Bulik (2008b) reported that nearly half of women seeking outpatient treatment for BN reported evening hyperphagia, nocturnal ingestions of food, or both core symptoms of NES. These later prevalence studies suggest that much research on the comorbidity of NES, especially the temporal relationship of night eating to other psychiatric symptoms is needed.

163.5 Comorbidity of NES

163.5.1 Medical Comorbidity

The most commonly studied medical comorbidity of NES is obesity (Stunkard et al. 1955, 1996; Colles et al. 2007; Lundgren et al. 2010a) and early descriptions of NES suggested that it was a pathway to obesity. Andersen and colleagues (2004) found that endorsement of the question "Do

you get up at night to eat?" prospectively predicted weight gain among obese women in the Danish MONICA study. Recently, Lundgren and colleagues (2010a) found that nocturnal eating, but not evening hyperphagia, was associated with obesity in a sample of community adults.

Not all studies have supported a relationship between NES and obesity. Using large national databases Striegel-Moore and colleagues (2005, 2006) did not find an increased risk of obesity with night eating; these studies, however, were not designed to assess NES specifically, but were based on 24-h food record data. More recent research, however, has suggested that obesity may only be associated with NES in certain populations. For example, psychiatric outpatients with NES were nearly five times more likely to be obese than the non-night eating outpatients (Lundgren et al. 2006). Discrepancies in studies examining the comorbidity of NES and obesity suggest that more work, using similar diagnostic criteria, is needed to understand the relationship between NES and obesity.

163.5.2 Psychiatric Comorbidity

High rates of psychiatric comorbidity have been noted among persons diagnosed with NES. Lifetime prevalence of Axis I disorders assessed by the Structured Clinical Interview for the DSM (SCID) is high among those with NES. Lundgren and colleagues found that 74% of night eaters, compared with 18% of controls had at least one comorbid Axis I diagnosis (Lundgren et al. 2008a). Mood disorders are common and NES has been related to high rates of lifetime diagnosis for major depressive disorder at 52.6% (Lundgren et al. 2008a), 55.7% (de Zwaan et al. 2006), and 57.1% (Boseck et al. 2007). Lundgren and colleagues (2008a) also found high rates of anxiety disorders among NES patients (47.4%).

Fewer studies have examined the comorbidity of NES among psychiatric samples. Lundgren and colleagues (2006) examined the prevalence of NES in psychiatric outpatients with a variety of diagnoses. In this sample, the only diagnoses to co-occur with NES were current and lifetime histories of substance use disorders. Participants prescribed atypical antipsychotics were more likely to be diagnosed with NES compared to those not prescribed this class of medication, but in this study serious mental illness was not associated with NES. In a follow-up to this study, Lundgren and colleagues (2010b) found that obese adults with serious mental illness who were prescribed psychotropic medications were at risk of NES, with nearly 25% of the sample meeting criteria. Combined, these studies suggest that there is perhaps a synergistic effect of obesity, medication use, and psychiatric symptoms that increase risk of night eating behavior.

The relationship of NES to other eating disorders has also been investigated. The comorbidity of BED and NES ranges from 5% to 20% (Stunkard et al. 1996; Geliebter 2002, Allison et al. 2005b, 2007; Striegel-Moore et al. 2005). Few studies have examined the relationship between NES and anorexia nervosa (AN) or BN. Lundgren and colleagues (2008b) found that 35.5% of women seeking outpatient treatment for BN reported evening hyperphagia of at least 25% of their caloric intake after dinner, and 19.3% reported eating at least half of their intake after dinner. It is unclear, however, whether their reported evening hyperphagia is distinct from evening binge eating episodes. More striking, however, is that 38.7% of the patients with BN reported at least occasional nocturnal ingestions, while 12.9% reported eating during awakenings at least half of the time. More research is needed to clarify the relationship of NES to these other eating disorders.

163.6 Hypothesized Causes of NES and Potential Pathophysiology

The causes of NES are unknown and hypothesized explanations include behavioral/functional (i.e., night eating serves to help someone sleep), nutritional, neuroendocrine, and pathophysiological. From a behavioral level of explanation, the onset of NES is often associated with a life stressor (Allison et al. 2004; Stunkard et al. 2006) and the function of night eating behavior could be to calm someone who experiences difficulty with sleep onset and/or maintenance and help him or her return to sleep. In a review of common thoughts experienced by persons with NES, Allison and colleagues (2004) point out that many people with NES have a core belief that they must eat in order to return to sleep. This explanation is informative for behavioral and cognitive-behavioral treatments for NES, but alone do not explain the development of NES.

Early hypotheses involving nutritional deficits or carbohydrate craving were suggested by Birketvedt and colleagues (1999). They found that the proportion of carbohydrates consumed during night eating episodes was greater than during the day and that the carbohydrate to protein ratio was 7:1 during nocturnal ingestions. More recent data have not supported such differences in the proportion of macronutrient content of foods consumed during the night versus the day (Allison et al. 2005a).

Neuroendocrine and pathophysiological abnormalities have been noted among persons with NES. These will be reviewed in detail in later chapters.

163.7 Consequences and Clinical Significance of NES

Although NES research has progressed significantly in the past decade, there are lingering questions about the consequences of evening and nocturnal eating. Specifically, questions have been raised about its *clinical significance*, given that late evening dinners and midnight snacking are normative in different cultures. The clinical significance of NES has been challenged even more as studies on NES and obesity have been equivocal (see above) and because earlier versions of NES diagnostic criteria did not specify that distress or impairment in functioning due to night eating be present for a diagnosis. The most recently proposed criteria (Table 163.4) have included such specifiers. Other than obesity, the two primary health consequences of NES that have been reported in the literature are diabetic complications and poor oral health.

Morse and colleagues (2006) examined night eating in individuals with Type I and II diabetes. They found that patients with NES were less adherent with their nutrition and exercise plans, as well as glucose monitoring. Night eaters' had higher A1C values and were more likely to have diabetes complications than non-night eaters. No studies have reported the prevalence of metabolic syndrome among persons with NES, and more research is needed to replicate Morse and colleagues' findings.

In a recent study, nocturnal ingestions of food, but not evening hyperphagia, predicted poor oral health on a variety of oral heath indices (Lundgren et al. 2010a). Specifically, nocturnal eating was a significant predictor of the number of missing teeth, periodontal disease, and active tooth decay.

163.8 Assessment and Treatment of NES

Assessment of NES can be aided with the help of self-report inventories, interviews, and food records. A description of common NES assessment measures is presented in Table 163.5. The NEQ (Allison et al. 2008) is a brief self report inventory which assesses the pattern and timing of food

Table 163.5 Commonly used NES assessment measures

Measure	Description
Night Eating Questionnaire (NEQ)	14-item self report inventory which assesses the pattern and timing of food intake, hunger and cravings for food, and mood and sleep difficulties. Administration time is approximately 5 min. Published in Allison et al. (2008)
Night Eating Syndrome History and Inventory (NESHI)	Semi-structured, unpublished interview available from Drs. Albert Stunkard and Kelly Allison at the University of Pennsylvania. This interview assesses current eating behavior, cravings, sleep patterns, and mood, as well as the history and precipitating NES factors. Administration time is approximately 30 min
Night Eating Diagnostic Questionnaire (NEDQ)	Similar to the NEQ, this brief measure provides information on one's eating patterns, sleep, and mood, as well as diet and weight history. It has recently been revised to reflect proposed research diagnostic criteria, and can be obtained from its authors (Gluck et al. 2001). Administration time is approximately 5 min
Food Record	Prospective food records which assess the timing of food intake, type of food consumed, and amount of food consumed and which can be helpful in identifying night eating patterns and in confirming night eating behavior. Week-long food records are preferred as they provide more stable estimates of night eating behavior than 1–2 day records or recalls
Dietary Recall	Dietary recalls assess the timing, type, and amount of food consumed retrospectively and typically focus on the previous 24-h. Recalls can be helpful in assessing very recent night eating behavior, but are less useful than prospective food records at assessing night eating behavior for longer periods of time
Actigraphy	Actigraphy can be used to assess patterns of activity and sleep. Actigraphs can be purchased through commercial suppliers and are useful in research studies to verify nocturnal awakenings

This table shows assessment measures that are available for screening and diagnosing NES
NES night eating syndrome

intake, hunger and cravings for food, and mood and sleep difficulties. The NEQ can be used as a symptom or screening measure, and a score of 30 or greater is suggestive of NES (Allison et al. 2008). The Night Eating Diagnostic Questionnaire (NEDQ) (Gluck et al. 2001) is useful in establishing a diagnosis of NES. It has recently been revised to reflect the proposed NES diagnostic criteria (Table 163.3) and can be obtained from its authors.

For a more thorough assessment of one's current and past night eating patterns, the Night Eating Syndrome History and Inventory (NESHI) can be used. It is an unpublished, semi-structured interview that assesses the current and past symptoms of NES, precipitating factors, familial night eating patterns, and treatment attempts. It can be obtained from its authors, Drs. Kelly Allison and Albert Stunkard at the University of Pennsylvania.

Finally, food and sleep records, dietary recalls, and actigraphy are essential in documenting eating and sleeping patterns in both research and clinical contexts. Food records and sleep records can be used to establish antecedents of night eating and treatment targets. Actigraphy is helpful in verifying nocturnal ingestions of food and in studying sleep/activity patterns.

With the increased research interest in NES over the past decade, several promising therapies have been developed and tested. Three studies have found that the selective serotonin reuptake inhibitor (SSRI), sertraline, significantly reduces evening hyperphagia, night-time awakenings, and nocturnal ingestions of food, as well as body weight (O'Reardon et al. 2004, 2006; Stunkard et al. 2006). These studies were the impetus for examining the role of serotonin transporter in the development and maintenance of NES, which is reviewed in a later chapter.

Cognitive behavioral therapy has also shown promise for treating NES. In a pilot study patients have shown a benefit, including a weight loss of 3 kg for completers, which is comparable to that seen with sertraline (Allison et al. 2010a). The combination of pharmacotherapy and psychotherapy has not been tested; this may prove to be a useful approach in the future.

Investigators have also reported some success with progressive muscle relaxation (Pawlow et al. 2003), paroxetine (Miyaoka et al. 2003), and light therapy (Friedman et al. 2002). Further research is necessary to confirm these findings and to determine whether behavioral weight loss treatment would be effective for reducing weight and NES symptoms.

163.9 Future Directions

As can be concluded from the review of NES above, the research community is just starting to develop a knowledge base of the causes and correlates of NES. Several research initiatives are underway to further characterize NES, including the standardization and testing of the newly proposed NES Research Diagnostic Criteria (Allison et al. 2010b; Table 163.4). As these new criteria are being tested, several aspects of NES are in need of more research, including its health implications, its relationship to other eating disorders, obesity, and sleep disorders, its pathophysiology, and its treatment. Later chapters in this section will review state-of-the-art findings on the neuroendocrine aspects of NES as well as recent research on the potential role of serotonin transporter in its pathophysiology. Significantly more research is needed in these areas as well to further understand and treat NES.

163.10 Applications to Other Areas of Health and Disease

Research on NES has significant implications for other areas of health, including obesity and eating disorders, sleep disorders, metabolic syndrome, and oral heath. As reviewed above, the impact of night eating on obesity has potentially serious consequences for certain populations, especially those with serious mental illness. Given the potential for weight gain that so many antipsychotic medications have, it is crucial to understand why night eating is so prevalent in this population. Similarly, the field is only now beginning to study night eating in the context of other eating disorders. The data reviewed above regarding night eating in women with BN suggests that there is potentially much more overlap between NES and other eating disorders than previously suspected. This has implications for the diagnosis and treatment of not only NES, but of BN and, potentially, AN as well.

Although not reviewed in detail in this chapter, the relationship between NES and sleep disorders is understudied. Both sleep and eating disorder researchers would benefit from improved communication and collaboration when studying night eating. There is likely much that both fields can share with one another to further understand the neurobiology of NES and other eating-related sleep disorders, such as SRED.

Finally, as this chapter points out, much work is needed on further understanding the health implications of NES. Preliminary studies have suggested that NES puts one at increased risk for metabolic disturbance and poor oral health. Future studies are needed to replicate and extend these findings so that they can better inform weight management, endocrine, and dental professionals.

Summary Points

- Night Eating Syndrome (NES) is a disorder of circadian rhythm manifested by the core criteria of evening hyperphagia and/or nocturnal ingestions of food.
- Research diagnostic criteria for NES have recently been proposed and should be tested in future NES research.
- NES is rare among the general population, but its prevalence increases with obesity and among persons with psychiatric symptoms.
- The etiology of NES is unknown, but research on behavioral and neuroendocrine causes, as well as the role of the serotonin system, is underway.
- Assessments and treatments for NES are available and should be disseminated more broadly, despite limitations in known pathophysiology.

Definition of Key Terms

Night eating syndrome: A disorder of the circadian pattern of food intake, manifested by evening hyperphagia and/or nocturnal awakenings accompanied by ingestions of food.
Evening hyperphagia: The consumption of an unusually large amount of food after the evening meal. Current NES diagnostic criteria suggest that the consumption of 25% or more of one's total daily calories after supper constitutes evening hyperphagia.
Nocturnal awakenings: Awakening in the middle of the night after sleep onset.
Nocturnal ingestions of food: Consuming food upon awakening in the middle of the night after sleep onset.

References

Adami GF, Campostano A, Marinari GM, Ravera G, Scopinaro N. Nutrition 2002;18:587–9.

Allison KC, Stunkard AJ, Thier SL. Overcoming night eating syndrome: a step-by-step guide to breaking the cycle. Oakland: New Harbinger; 2004.

Allison KC, Ahima RS, O'Reardon JP, Dinges DF, Sharma V, Cummings DE., Heo, M, Martino N, Stunkard AJ. J Clin Endocrinol Metab. 2005a;90:6214–7.

Allison KC, Grilo CM, Masheb RM, Stunkard AJ. J Consult Clin Psychol. 2005b;73:1107–15.

Allison KC, Wadden TA, Sarwer DB, Fabricatore AN, Crerand C, Gibbons L, Stack R, Stunkard AJ, Williams N. Obesity 2006;14:77S–82S.

Allison KC, Crow S, Reeves RR, West DS, Foreyt JP, DiLillo VG, Wadden TA, Jeffery RW, Van Dorsten B, Stunkard AJ, and the Eating Disorders Subgroup of the Look AHEAD Research Group. Obesity 2007;15:1285–91.

Allison KC, Lundgren JD, O Reardon JP, Sarwer DB, Wadden TA, Stunkard AJ. Eat Behav. 2008;9:62–72.

Allison KC, Lundgren JD, O'Reardon JP, Moore RH, Stunkard AJ. Am J Psychotherapy. 2010a;64:94-106.

Allison .C, Lundgren JD, O'Reardon JP, Geliebter A, Gluck M, Vanai P, Mitchell JE, Schenck CH, Howell MJ, Crow SJ, Engel S, Latzer Y, Tzischinsky O, Mahowald MW, Stunkard AJ. 2010b;43:2414–247.

Andersen GS, Stunkard AJ, Sorensen TIA, Pedersen L, Heitman BL. Int J Obesity. 2004;28:1138–43.

Birketvedt G, Florholmen J, Sundsfjord J, Osterud B, Dinges D, Bilker W, Stunkard AJ. JAMA 1999;282:657–63.

Boseck JJ, Engel SG, de Zwaan M, Allison KC, Crosby RD, Mitchell JE. Int J Eat Disord. 2007;40:271–6.

Colles S L, Dixon JB, O'Brien PE. Int J Obesity. 2007;31:1722–30.

de Zwaan M, Roerig DB, Crosby RD, Karaz S, Mitchell JE. Int J Eat Disord. 2006;39:224–32.

Freidman S, Even C, Dardennes R, Guelfi JD. Am J Psychiatry. 2002;159:875–6.

Geliebter A. Appetite 2002;38:1–3.

Gluck M E, Geliebter A, Satov T. Obesity Res. 2001;9:264–7.

Howell M, Crow S, Schenck C. Sleep Med. 2009;13:23–34.

Lundgren JD, Allison KC, Crow S, Berg KC, Galbraith J, Martino NS, O'Reardon JP, Stunkard AJ. Am J Psychiatry. 2006;163:156–8.

Lundgren JD, Allison KC, O'Reardon JP, Stunkard AJ. Eat Beh. 2008a;9:343–51.

Lundgren JD, Shapiro JR, Bulik C. Eat Weight Disord. 2008b;13:171–5.

Lundgren JD, Amsterdam J, Newberg A, Allison KC, Wintering N, Stunkard AJ. Eat Weight Disord. 2009;14:45–50.

Lundgren JD, Smith B, Williams K, Spresser C, Harkins P, Zolton L. General Dentistry. 2010a;58:163.

Lundgren JD, Rempfer MV, Brown CE, Goetz J, Hamera E. Psychiatry Res. 2010b;175: 233–236.

Miyaoka T, Yasukawa R, Tsubouchi K, Miura S, Shimizu Y, Sukegawa T, Maeda T, Mizuno S, Kameda A, Uegaki J, Inagaki T, Horiguchi J. Int Clin Psychopharmacol. 2003;18:175–7.

Morse SA, Ciechanowski PS, Katon WJ, Hirsch IB. Diabetes Care. 2006;29:1800–4.

O'Reardon JP, Stunkard AJ, Allison KC. Int J Eat Disord. 2004;35:16–26.

O'Reardon JP, Ringel BL, Dinges DF, Costello Allison K, Rogers NL, Martino NS, Stunkard AJ. Obes Res. 2004;12:1789–96.

O'Reardon JP, Allison KC, Martino NS, Lundgren JD, Heo M, Stunkard AJ. Am J Psychiatry. 2006;163:893–8.

Pawlow LA, O'Neil PM, Malcolm RJ. Int J Obes Relat Metab Disord. 2003;27:970–8.

Rand CSW, Macgregor MD, Stunkard AJ. Int J Eat Disord. 1997;22:65–9.

Striegel Moore RH, Dohn FA, Hook JM, Schreiber GB, Crawford PB, Daniels SR. Int J Eat Disord. 2005;37:200–6.

Stunkard AJ, Berkowitz R, Wadden T, Tankirut C, Reiss E, Young L. Int J Obes Relat Metab Disord. 1996;20:1–6.

Striegel-Moore RH, Franko DL, Thompson D, Affenito S, Kraemer HC. Obes Res. 2006;14:139–47.

Stunkard AJ, Allison KC, Lundgren JD, Martino NS, Heo M, Etemad B, O'Reardon JP. J Clin Psychiatry. 2006;67:1568–72.

Stunkard AJ, Grace WJ, Wolff HG. Am J Med. 1955;9:78–86.

Part XXVII
Metabolic Syndrome
and Non-obese Overweight

Chapter 164
Metabolic Syndrome as a Disorder of the Brain with Its Origins in the Perinatal Period

Undurti N. Das

Abbreviations

PUFAs	Polyunsaturated fatty acids
EFAs	Essential fatty acids
IL	Interleukin
TNF	Tumor necrosis factor
ROS	Reactive oxygen species
NO	Nitric oxide
CRP	C-reactive protein
CHD	Coronary heart disease
NF-κB	Nuclear factor kappaB
IkBα	Inhibitor kappaB alpha
NADPH	Nicotinamide adenine dinucleotide phosphate
G6P	Glucose-6-phosphate
TBSA	Total body surface area
NPY	Neuropeptide Y
AgRP	Agouti-related peptide
POMC	Pro-opiomelanocortin
MSH	Melanocyte stimulating hormone
CART	Cocaine and amphetamine-regulated transcript

164.1 Introduction

The various components of the metabolic syndrome include: dyslipidemia, hypertension, hyperglycemia, insulin resistance, polycystic ovary syndrome, fatty liver, cholesterol gallstones, asthma, sleep disturbances, and some forms of cancer.

The incidence of metabolic syndrome is increasing and by the year 2010, in the United States alone there may be about 50–75 million people with the disease. An early stage of the metabolic

U.N. Das (✉)
UND Life Sciences 13800 Fairhill Road, #321, Shaker Heights, OH, 44120, USA
Jawaharlal Nehru Technological University, Kakinada- 533 003, Andhra Pradesh, India
e-mail: Undurti@hotmail.com

Table 164.1 Key features of metabolic syndrome

 I. Key clinical features are:
    1. Abdominal obesity
    2. Insulin resistance
    3. Hyperlipidemia
    4. Hypertension
    5. Type 2 diabetes mellitus
    6. Atheroslcerosis
    7. Decreased heart rate variability

II. Key biochemical features are:
    1. Hyperinsulinemia and hyperglycemia
    2. Low plasma endothelial nitric oxide levels
    3. Low plasma adiponectin levels
    4. Hyperleptin emia
    5. Low plasma levels of antioxidants
    6. High plasma levels of lipid peroxides and resistin
    7. Elevated plasma ADMA (asymmetrical dimethyl arginine)
    8. Elevated plasma IL-6, TNF-α, MIF (macrophage migration inhibitory factor), HMGB-1
      (high mobility group box-1), hs-CRP (high sensitive –reactive protein), and adhesion molecules
    9. Low plasma BDNF and visfatin
  10. Low plasma GLP-1 (glucagon-like peptide-1) and gastric inhibitory polypeptide (GIP)

syndrome is characterized by insulin resistance restricted to muscle tissue whereas adipose tissue is not resistant to insulin (Grundy et al. 2004). This explains why exercise is beneficial in the prevention and treatment of insulin resistance since it decreases insulin resistance and enhances glucose utilization in the muscles. In addition, exercise is anti-inflammatory in nature (Table 164.1) (Das 2004, 2006a).

164.2 Low-grade Systemic Inflammation Occurs in Metabolic Syndrome

Obesity, insulin resistance, hypertension, hyperlipidemia, and coronary heart disease (CHD) are all associated with low-grade systemic inflammation since plasma levels of C-reactive protein (CRP), tumor necrosis factor-α (TNF-α), and interleukin-6 (IL-6), markers of inflammation, are elevated (reviewed in Das 2008), whereas anti-inflammatory molecules adiponectin, IL-4, IL-10, and eNO (endothelial nitric oxide) are decreased in these conditions (Das 2002a). The exact reason why low-grade systemic inflammation occurs in metabolic syndrome is not clear. But it is interesting to note that glucose is pro-inflammatory whereas insulin is anti-inflammatory in nature.

164.3 Glucose Can Initiate and Perpetuate Inflammation

Hyperglycemia is one of the major components of the metabolic syndrome, and metabolic syndrome is a low-grade systemic inflammatory condition; it is therefore likely that hyperglycemia has proinflammatory actions. Glucose ingestion (75 g in 300 mL water) in healthy human subjects resulted in an increase in intranuclear nuclear factor kappaB (NF-kB) binding, the reduction of inhibitor kappaB alpha (IkBα) protein, and an increase in the activity of inhibitor kappaB kinase (IKK) and the expression of IKKalpha and IKKbeta, the enzymes that phosphorylate IkBα in mononuclear cells.

Glucose intake caused an increase in the expression of TNF-α messenger RNA in mononuclear cells. Membranous p47(phox) subunit, an index of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase expression and activation, also increased after glucose intake (Aljada et al. 2004, 2006). These data are consistent with the prediction that hyperglycemia initiates and perpetuates inflammation.

Rat pancreatic islets or clonal rat BRIN BD11 β cells incubated with 16.7 mmol/L glucose for 1 h produced significantly increased amounts of free radicals that were inhibited by NADPH oxidase inhibitor (Morgan et al. 2007). Pre-exposure of U937 histiocytes to high glucose concentrations markedly increased the lipopolysaccharide-induced secretion of proinflammatory cytokines--> and chemokines and the cellular inducible nitric oxide level compared with pre-exposure to normal glucose (Nareika et al. 2007). Similarly, exposure of human microvascular endothelial cells to various concentrations of glucose from low to physiological levels (0–5 mmol/L), production of G6P (glucose-6-phosphate), lactate, NAD(P)H, and CO_2 increased as expected, while oxygen consumption rate was reduced. These changes were found to be oxidative stress mediated endothelial inflammation induced by excess glucose as a result of G6P accumulation (Sweet et al. 2009). These results clearly suggest that glucose is proinflammatory in nature.

164.4 Hyperglycemia Induces Oxidative Stress in Adipose and β Cells

It is interesting that hyperglycemia induced adipose tissue developed severe insulin resistance and produced a number of acute phase reactants at high levels (Lin et al. 2001) that is mediated by the induction of reactive oxygen species (ROS). Hyperglycemia induced a significant increase in ROS in adipocytes isolated from streptozotocin-treated diabetic mice. Hyperglycemia-induced proinflammatory response in adipose tissue was reduced significantly by agents that lower the mitochondrial membrane potential, or by overexpression of uncoupling protein 1 or superoxide dismutase. On the other hand, hyperpolarization of the mitochondrial membrane, such as overexpression of the mitochondrial dicarboxylate carrier resulted in increased ROS formation and decreased insulin sensitivity, even under normoglycemic conditions (Lin et al. 2005). These results highlight the importance of ROS production in adipocytes and the associated insulin resistance and inflammatory response.

Both hyperglycemia and the proinflammatory cytokine IL-1β induced up-regulation of c-Myc and heme-oxygenase-1 in β cells. Hyperglycemia stimulated islet (β cell) c-Myc and heme-oxygenase-1 expression without affecting NF-kB activity or iNOS and IkBα mRNA levels. Fas mRNA levels only increased after prolonged incubation with 30 mmol/L glucose. Short (such as overnight) exposure to hydrogen peroxide mimicked the effects of hyperglycemia on heme-oxygenase-1 and c-Myc mRNA levels without activating NF-kB, while the antioxidant N-acetyl-L-cysteine inhibited the stimulation of heme-oxygenas-1 and c-Myc expression by 30 mmol/L glucose and/or hydrogen peroxide. These results suggest that hyperglycemia and hydrogen peroxide do not activate NF-kB in cultured rat islets, suggesting that the stimulation of islet c-Myc and heme-oxygenase-1 expression by 30 mmol/L glucose results from activation of a distinct, probably oxidative, stress-dependent signaling pathway (Elouil et al. 2005). Thus, hyperglycemia-induced proinflammatory event in different cells may follow different pathways. This proposal is supported by the observation that both TNF-α and glucocorticoid dexamethasone-induced insulin resistance is associated with enhanced levels of ROS, and methods designed to suppress ROS generation improves insulin resistance in obese, insulin-resistant mice and restored glucose homeostasis (Houstis et al. 2006). Since insulin resistance is one of the hallmarks of obesity, type 2 diabetes mellitus, and the metabolic syndrome, it suggests that ROS plays a significant role in these conditions. Hyperglycemia induces

oxidative stress not only in pancreatic β cells and adipose tissue but also in endothelial cells. This enhanced oxidative stress in endothelial cells could be responsible for endothelial dysfunction seen in metabolic syndrome.

164.5 Insulin Is Anti-inflammatory in Nature

In contrast, insulin has anti-inflammatory properties (Das 2000, 2001). Insulin suppresses the production of proinflammatory cytokines, ROS, MIF (macrophage migration inhibitory factor), and augments the production of anti-inflammatory cytokines and eNO. In thermally injured rats (30% total body surface area, TBSA), insulin administration significantly decreased dose dependently serum proinflammatory cytokines IL-1β at 1, 5, and 7 days, IL-6 at 1 day, MIF at 5 and 7 days, and TNF at 1 and 2 days after injury when compared with controls. Insulin increased anti-inflammatory cytokines IL-2 and IL-4 at 5 and 7 days after trauma and IL-10 at 2, 5, and 7 days after trauma when compared with controls. Proinflammatory signal transcription factors STAT-5 and C/EBP-beta mRNA were significantly decreased 1 and 2 days post-trauma; insulin increased anti-inflammatory signal transcription factor mRNA expression of SOCS-3 and RANTES 7 days after the injury (Jeschke et al. 2002). These data lend support to the original hypothesis (Das 2000, 2001) that insulin attenuates the inflammatory response and thus restores systemic homeostasis that could be critical for organ function and survival in critically ill patients. Furthermore, insulin significantly improved hepatic protein synthesis by increasing albumin and decreasing c-reactive protein; decreased the hepatic inflammatory response signal cascade by decreasing hepatic proinflammatory cytokines mRNA and proteins IL-1β and TNF levels; and increased hepatic cytokine mRNA and protein expression of IL-2 and IL-10 at a pretranslational level when compared with controls in rats that received thermal injury. Insulin increased hepatocyte proliferation along with Bcl-2 concentration, while decreasing hepatocyte apoptosis along with decreased caspases-3 and -9 concentration and thus improved liver morphology ($P < 0.05$). Thus, insulin attenuates the inflammatory events (Kelin et al. 2004). Similar results have been noted in thermally injured children who received insulin (Jeschke et al. 2004).

High-dose insulin treatment (short-acting insulin 1 IU/kg/h with 30% glucose 1.5 ml/kg/h administered separately) that was targeted to maintain blood glucose levels at 6.0–8.0 mmol/L produced a significant fall in C-reactive protein and free fatty acid levels postoperatively in patients with unstable angina pectoris who underwent urgent coronary artery bypass surgery. Though the proinflammatory cytokine response [interleukin-6 (IL-6), interleukin-8 (IL-8) and TNF-α] levels did not differ between the insulin group and the controls and no beneficial effects on myocardial injury were detected, these results suggested that high-dose insulin treatment has potential anti-inflammatory properties independent of its ability to lower blood glucose levels (Koskenkari et al. 2006). Similar attenuation of the systemic inflammatory response was noted in infants undergoing cardiopulmonary bypass who received intensive insulin therapy (Gu et al. 2008).

In a nonhyperglycemic mouse model of endotoxemia, continuous administration of a low dose of human insulin induced phosphorylation of Akt in muscle and adipose tissues but did not exacerbate lipopolysaccharide (LPS)-induced hypoglycemia. Insulin decreased plasma levels of IL-6, TNF-α, monocyte chemotactic protein 1 (MCP1)/JE, and keratinocyte chemoattractant, and decreased mortality. The PI3K inhibitor wortmannin abolished the insulin-mediated activation of Akt and the reduction of chemokine and interleukin-6 levels suggesting that insulin reduces LPS-induced inflammation in a PI3K/Akt-dependent manner without affecting blood glucose levels (Kidd et al. 2008). In a study designed to evaluate whether insulin attenuates TNF-α induction in acute myocardial ischemia/reperfusion

injury both in vitro and in vivo, we observed that insulin inhibited ischemia-reperfusion-induced TNF-α production through the Akt-activated and eNOS-NO-dependent pathway (Li et al. 2008). These results strongly suggest that insulin has cardioprotective and prosurvival effects in the critically ill and, in general, possesses cytoprotective actions. But it should be noted that in some studies the protective effect of intensive insulin therapy in patients after cardiac surgery could not be related to a change in cytokine balance from a proinflammatory to an anti-inflammatory pattern (Hoedemaekers et al. 2005). This discrepancy in the results could be attributed to the differences in the study population, the insulin protocol used, and the underlying clinical conditions.

The fact that glucose and insulin have opposite actions on inflammation and since food intake is regulated by the hypothalamus, a function that is possible only if the hypothalamus is able to sense blood glucose levels and regulate gut function and insulin secretion, it is likely that the glucose-sensing mechanism of the hypothalamus may involve ROS signaling. Vagus seems to facilitate cross-talk among the gut, adipose tissue, pancreas, and hypothalamus, while cytokines modulate hypothalamic neuronal firing rate. In addition, the presence of insulin receptors in the brain and the known interactions between insulin, ROS, cytokines, and glucose homeostasis (as discussed above) suggest that hypothalamus function is regulated by ROS. For a better understanding of the existence of low-grade systemic inflammation in metabolic syndrome and the role played by hypothalamus in glucose homeostasis, it is important to briefly review the role of the hypothalamus in food intake and glucose homeostasis.

164.6 Hypothalamus Regulates Food Intake

Appetite is controlled by an appetite stimulating neuropeptide Y (NPY), an agouti-related peptide (AgRP), and the appetite inhibitory molecules pro-opiomelanocortin (POMC), the precursor for α-melanocyte stimulating hormone (α-MSH), and cocaine and amphetamine-regulated transcript (CART), which are expressed within the hypothalamus and act together to regulate energy balance. NPY is predominantly localized in the hypothalamic arcuate nuclei (ARC) and NPY neurons project to the paraventricular nucleus (PVN), dorsomedial nucleus (DMN), the perifornical region, and the lateral hypothalamic area (LHA) (Grove and Smith 2003). NPY neurons respond to alterations in the concentrations of plasma glucose, insulin, and leptin. Increased food intake increases the circulating concentrations of leptin that are sensed by the leptin receptors expressed on ARC and DMN neurons leading to a fall in hypothalamic NPY mRNA that results in decreased food intake. AgRP that is coexpressed with NPY in the ARC is an endogenous antagonist of anorexigenic melanocortin receptors MC3-R and MC4-R in the PVN and other hypothalamic regions. α-MSH is an endogenous anorexigenic peptide that acts on the melanocortin receptors to suppress food intake. CART, localized within the POMC neurons in the hypothalamus, also suppresses food intake (McMillen et al. 2005).

164.7 Appetite Regulatory Centers Develop During the Perinatal Period

Hypothalamic appetite regulatory centers develop predominantly during the perinatal period. For instance, NPY is present within the fetal ARC from as early as 14.5 days gestation; NPY/AgRP projections between the ARC and DMN develop around 10–11 days after birth whereas NPY containing projections to the PVN develop around 15–16 days (Grove and Smith 2003; McMillen et al. 2005). Hence, factors that influence the growth and development of the brain will have a significant

impact on the development of appetite regulatory centers that, in turn, could determine food intake in later life.

For instance, postnatal over nutrition in rats led to an increased early weight gain and fat deposition, hyperphagia, obesity, hyperleptinemia, hyperglycemia, hyperinsulinemia, and insulin resistance. These indices of the metabolic syndrome were accompanied by decreased mean areas of neuronal nuclei and cytoplasm within the PVN, VMN, and ARC and a significant increase in the number of NPY containing neurons within the ARC, and decreased immunostaining for both POMC and α-MSH (McMillen et al. 2005; Davidowa et al. 2003; Fahrenkrog et al. 2004). In contrast, when rats are undernourished during the perinatal period the offspring develop significant hyperphagia and obesity when maintained on a high fat diet and showed an increase in the relative mass of retroperitoneal fat. Thus, the amount and type of food consumed during the suckling period determines food intake and preferences in later life.

The neuropeptides NPY, AgRP, POMC, and CART showed significant changes in their concentrations in the hypothalamic nuclei of fetal sheep in response to intrafetal infusion of glucose between 130 and 140 days of gestation by which time these peptides are highly expressed (Muhlhausler et al. 2005). These results suggest that neuropeptides that regulate appetite centers and their responses to stimuli are "programmed" in the fetal and perinatal stages of development. This ultimately influences the dietary preferences and the development of obesity and the metabolic syndrome in later life. This implies that early life feeding pattern and growth "program" the hypothalamic centers and their neurotransmitters that could have a life-long impact on food intake and thus influence the future development of the metabolic syndrome in a given subject.

164.8 Ventromedial Hypothalamic Lesion Produces Features of Metabolic Syndrome

Hyperphagia and excessive weight gain, fasting hyperglycemia, hyperinsulinemia, hypertriglyceridemia, and impaired glucose tolerance, which are features of the metabolic syndrome are seen when the ventromedial hypothalamus (VMH) is injured in rats (Axen et al. 1994; Keno et al. 1994). Intraventricular administration of antibodies to neuropeptide Y (NPY) abolished the hyperphagia and *ob* mRNA (leptin mRNA) in these animals, suggesting that enhanced NPY is responsible for hyperphagia and obesity seen in VMH lesioned animals, and the *ob* gene is upregulated even in nongenetically obese animals (Dube et al. 1995; Funahashi et al. 1995). Paraventricular, ventromedial (VMH), and lateral hypothalamic areas showed increased NPY concentrations in streptozotocin-induced diabetic rats. These diabetic animals also showed a significant decrease in extracellular concentrations of noradrenaline (NA), serotonin (5-HT), and their metabolites. and a pronounced increase in extracellular GABA, in the VMH. Long-term infusion of norepinephrine plus serotonin into the VMH impairs pancreatic islet function inasmuch as VMH norepinephrine and serotonin levels are elevated in hyperinsulinemic and insulin-resistant animals (reviewed in Das 2008). Streptozotocin-induced diabetes caused an increase in NA concentrations in the PVN with a concurrent increase in serum corticosterone and an increase in the concentrations of NA, dopamine, and serotonin in the ARC. It also increased NA concentrations in the lateral hypothalamus, VMH, and suprachiasmatic nucleus that reverted to normal with insulin treatment, while leptin treatment was ineffective (Das 2008).

The activity of glucokinase (GK), the critical glucose sensor of pancreatic β cells, is high in the arcuate nucleus; moderate or low in the ventromedial nucleus, lateral hypothalamic area, and paraventricular nucleus; and very low in the cortex. GK activity and GK mRNA level in the arcuate

nucleus of streptozotocin-treated rats were lower than those of control rats, suggesting that prolonged hyperglycemia induced by diabetes decreased the activity of GK in the arcuate nucleus. This decrease in glucokinase activity in the hypothalamic neurons may interfere with the central regulatory mechanisms of insulin secretion by pancreatic β cells. Thus, hypothalamic neurons and neurotransmitters and GK play a critical role in the regulation of insulin secretion and in the pathobiology of the metabolic syndrome, suggesting that the latter may very well be a disorder of the brain (Das 2008).

164.9 Insulin and Insulin Receptors in the Brain

Brain is rich in insulin receptors especially in the olfactory bulb, the hypothalamus, and the pituitary, and insulin signaling has a role in the regulation of food intake, neuronal growth, and differentiation; it also regulates neurotransmitter release and synaptic plasticity in the CNS (Wan et al. 1997; Bruning et al. 2000; Hill et al. 1986). Insulin infusion into the VMN and PVN increased body temperature and energy expenditure and reduced food intake (Menendez and Atrens 1991; McGowan et al. 1992). Infusion of insulin-specific antibodies or antisense oligonucleotides directed against the insulin receptor in the third ventricle reduced hepatic sensitivity to circulating insulin and increased hepatic glucose production, suggesting that insulin in the brain regulates liver glucose metabolism (McGowan 1992). IRS-2 is abundant in the arcuate nucleus, and insulin administration induced tyrosine phosphorylation of IRS-2 and increased the production of phosphatidylinositol 3,4,5-trisphosphate (PI_3). Mice lacking IRS-2 in the hypothalamus exhibited hyperphagia and enhanced body fat deposition (Lin et al. 2004). ICV insulin infusion blocked the effects of both fasting and streptozotocin-induced diabetes to increase expression of NPY mRNA in the arcuate nucleus, while insulin increased hypothalamic POMC mRNA content. The melanocortin receptor antagonist, blocked the ability of ICV (intracerebroventricular) insulin to suppress food intake (Benoit et al. 2002). Subthreshold doses of insulin and leptin showed additive effects on short-term food intake, while both insulin and leptin suppressed NPY/AgRP neurons in the arcuate nucleus and concomitantly activated POMC/CART neurons. These results suggest that there is a cross talk between insulin and leptin apart from sharing the common ability to suppress anabolic, while activating catabolic, regulatory neurocircuitry.

164.10 Mechanism(s) of Action of Insulin in the Brain

Insulin activates ATP-sensitive K^+ channels (K_{ATP} channels) of hypothalamic neurons, especially in the mediobasal hypothalamus (Spanswick et al. 2000). Activation of K_{ATP} channels is suppressed by increased intracellular ATP levels in response to oxidation of glucose or other substrates. This raises intracellular concentrations of K^+, leading to membrane depolarization and increased firing rate. Thus, glucose-excited neurons are those that are activated (i.e., depolarized) by increased local concentrations of glucose. However, some studies showed that these effects are not seen at physiological glucose levels, suggesting that these neurons are downstream of NPY and POMC neurons and potentially play an integrating role for peripheral and central energy homeostasis. Leptin, like insulin, activates K_{ATP} channels in glucose-responsive hypothalamic neurons (Mirshamsi et al. 2004). Glucose-responsive neurons from Zucker fatty (*fa/fa*) rats that develop obesity, which have a leptin receptor mutation, are insensitive to both insulin and leptin. This may explain why ICV insulin inhibits neither food intake nor NPY gene expression in these *fa/fa* rats.

GLUT-4 and GLUT-8, the glucose transporters, and glucokinase, the glucose sensor of the β-cell, are present in several areas of the brain. In the arcuate nucleus, >75% of NPY-positive neurons express glucokinase (Lynch et al. 2000). Intracarotid glucose infusions increased hypothalamic glucokinase expression (Dunn-Meynell et al. 2002), suggesting that glucokinase could function as a glucose-sensor in both glucose-responsive (also referred to as glucose-excited) and glucose-sensitive (also referred to as glucose-inhibited) neurons. Since many glucokinase-expressing neurons coexpress K_{ATP} channels, and coexpression of GLUT-4 with insulin receptor mRNA is reported in glucose-responsive neurons, interactions among glucose-sensors, K_{ATP} channels and various neuropeptides is expected.

Thus, insulin interacts with neuropeptides and regulates food intake that may have relevance to the development of obesity and metabolic syndrome. Disruption of the neuron-specific insulin receptor gene (NIRKO) in mice increased food intake, developed diet-sensitive obesity with increases in body fat and plasma leptin levels, insulin resistance, hyperinsulinemia and hypertriglyceridemia, features that are seen in metabolic syndrome without interfering with the development of brain and neuronal function (Bruning et al. 2000) lending strong support to the concept that a decrease in the number of insulin receptors, deficiencies in the functioning of insulin receptors, and insulin lack or resistance in the brain leads to the development of metabolic syndrome even when the pancreatic β cells are normal (Table 164.2). This is further supported by the observation that intraventricular injection of insulin inhibits food intake (McGowan et al. 1992).

Food-deprivation induced increase in NPY levels in the paraventricular nucleus (PVN) returned to the control range following insulin injections, which did not alter blood glucose levels. Both insulin and insulin-like growth factor-II (IGF-II) decreased the release of NPY in a dose dependent fashion from the PVN *in vitro*, suggesting that the site of insulin action on the hypothalamic NPY network is at the level of NPY nerve terminals and that both insulin and IGF-II decrease NPY release from the PVN (Sahu et al. 1995). Since NPY is a potent orexigenic signal and as insulin and IGF-II decrease hypothalamic NPY, it is suggested that presence of adequate amounts of insulin, insulin receptors, and IGF-II in the brain reduces appetite, and thus controls obesity and hyperglycemia. This interaction among insulin (and insulin receptors), IGF-II, and neuropeptides depends on the health of the neurons in the brain, their receptors, and the presence of adequate synaptic connections among them.

Plasma concentrations of proinflammatory markers are increased in metabolic syndrome. These proinflammatory molecules: TNF-α, IL-6, and CRP, cause endothelial dysfunction. Mice with targeted disruption of eNOS are not only hypertensive and insulin resistant but also showed features of the metabolic syndrome such as hyperlipidemia, hyperleptinemia, hyperuricemia, and hyperfibrinogenemia and glucose intolerance but were not obese (Cook et al. 2003). These features are similar to those seen in the NIRKO mice. Since insulin stimulates the production of eNO and inhibits TNF-α production (Das 2008) and NIRKO mice show several features of the metabolic syndrome, it is postulated that a decrease in the number of insulin receptors, defects in the functioning of insulin receptors, and insulin lack or resistance in the neuronal cells lead to the development of

Table 164.2 Neuron-specific insulin receptor knockout (NIRKO) mice

1. Brain is rich in insulin receptors
2. Insulin and insulin receptors are necessary for normal growth and development of the brain
3. Insulin is also essential for neuronal growth and synapse formation
4. Insulin receptors in the brain are particularly rich in the hypothalamus
5. When these neuron-specific insulin receptors are knocked out by genetic manipulation these animals develop all the features of the metabolic syndrome
6. This suggests that insulin receptors in the brain have the ability to signal pancreatic β cells to secrete adequate amounts of insulin as the situation demands.

metabolic syndrome even when pancreatic β cells are normal. Thus, metabolic syndrome could be a disorder of the brain.

But the major question is: "When and how is metabolic syndrome initiated?" Evidence is available that suggests that the metabolic syndrome may have its origins in the perinatal period.

164.11 Perinatal Programming of the Metabolic Syndrome

Stimuli or insults induced during the perinatal period can have lifetime consequences and is called "programming". Hormonal signals or nutritional factors may serve as programming stimuli. Smallness and thinness at birth, continued slow growth in early childhood, followed by acceleration of growth so that height and weight approach the population means is considered as the most unfavorable growth pattern that results in fetal adaptations that may programme the development of metabolic syndrome in later life (Das 2008). This implies that perinatal nutrition is a crucial determinant of adult diseases. Since the development of brain occurs during the period between second trimester to 5 years of age and again during adolescence, it is likely that nutrition during these periods plays a significant role in this process. Factors that are essential for brain growth and development, regulation of synapse formation, and neurotransmission include: polyunsaturated fatty acids (PUFAs) and their metabolites, various cytokines, insulin and various neuropeptides, and monoaminergic neurotransmitters.

164.12 Essential Fatty Acids

Essential fatty acids (EFAs) are important constituents of all cell membranes. EFAs confer on membranes properties of fluidity and thus determine and influence the behavior of membrane-bound enzymes and receptors. There are two types of naturally occurring EFAs in the body, the ω-6 series derived from *cis*-linoleic acid (LA, 18:2) and the ω-3 series derived from α-linolenic acid (ALA, 18:3). LA and ALA are converted to their respective long-chain metabolites and several eicosanoids that have significant biological actions (see Fig. 164.1 for metabolism). The long-chain metabolites of EFAs (also called as polyunsaturated fatty acids, PUFAs) can give rise to both pro- (such as prostaglandins, thromboxanes, and leukotrienes) and anti-inflammatory (such as lipoxins, resolvins, protectins, and maresins) molecules. Hence, the balance between these mutually antagonistic compounds could determine the final outcome of the disease process.

164.13 PUFAs, Insulin, and Acetylcholine Function as Endogenous Neuroprotectors

Human infants accumulate PUFAs such as arachidonic acid (AA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA) from maternal/placental transfer, consumption of human milk, and synthesis from LA and ALA. AA regulates energy metabolism in the cerebral cortex by stimulating glucose uptake in cerebral cortical astrocytes and enhances acetylcholine (Ach) release in the brain (Das 2002b). DHA also enhances cerebral ACh levels and improves learning ability in rats. ACh modulates long-term potentiation and synaptic plasticity in neuronal circuits and interacts with dopamine

Fig. 164.1 Metabolism of essential fatty acids. Resolvins, protectins, lipoxins, and maresins formed from PUFAs have anti-inflammatory actions and participate in the resolution of inflammation. Neuroprotectin D_1 formed from DHA has anti-inflammatory and cytoprotective actions. EPA can be converted to DHA. DHA can be retroconverted to EPA
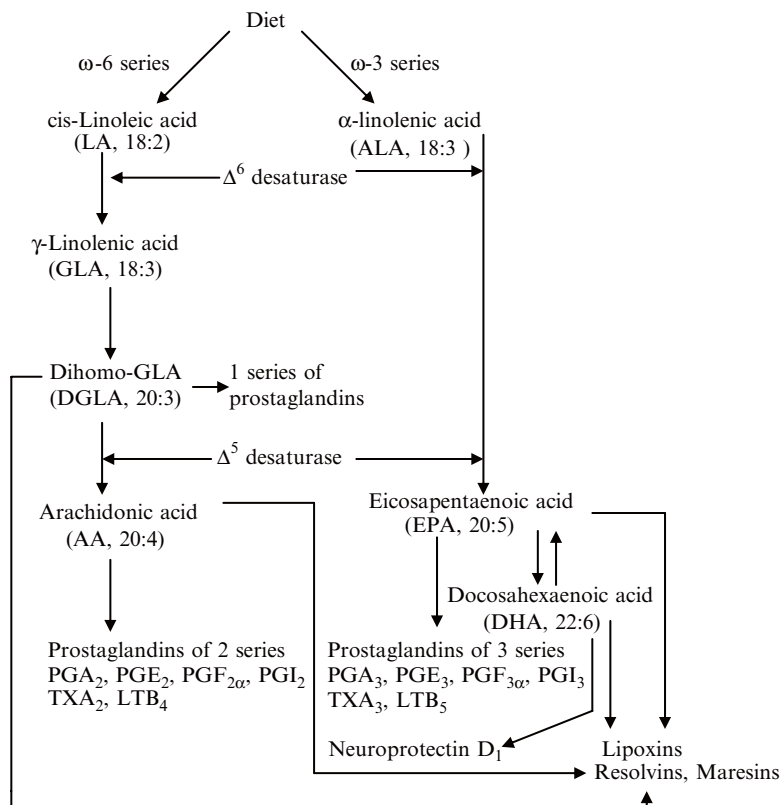
receptor in the hippocampus. In obesity, a decrease in the number of dopamine receptors or dopamine concentrations occurs and obesity is common in type 2 diabetes and metabolic syndrome (reviewed in Das 2008).

Insulin augments the activities of desaturases, enzymes involved in the desaturation and elongation of LA and ALA to their respective long-chain metabolites, and this increases the formation of AA, EPA, and DHA. Insulin-like growth factor-1 (IGF-1), insulin and AA, EPA, and DHA antagonize neuronal death induced by TNF-α and thus show neuroprotective and cytoprotective actions (reviewed in Das 2008). Furthermore, PUFAs are potent inhibitors of IL-6 and TNF-α production (Kumar and Das 1994), and they also regulate superoxide anion generation and enhance the production of eNO. NO is anti-inflammatory in nature and quenches superoxide anion. IGF-I and insulin enhance ACh release from rat cortical slices. ACh inhibits the synthesis and release of TNF-α both in vitro and in vivo and thus, has anti-inflammatory actions and is also a potent stimulator of eNO synthesis. These data suggest that insulin enhances the formation of PUFAs that, in turn, enhance ACh levels in the brain and inhibit the production of TNF-α. Thus, insulin, ACh, and PUFAs suppress TNF-α production and augment the synthesis of eNO. ACh and eNO are not only neuroprotective in nature but also interact with other neurotransmitters. Thus, insulin, ACh, and PUFAs protect brain from insults induced by TNF-α and other molecules. In addition, incorporation of significant amounts of PUFAs into the cell membranes increases their fluidity that, in turn, enhances the number of insulin receptors on the membranes and the affinity of insulin to its receptors. Thus PUFAs can attenuate insulin resistance (Das 2008).

Since human brain is rich in AA, EPA, and DHA, one of their important functions in the brain could be to ensure the presence of adequate number of insulin receptors and protect

neurons from insults. Hence, it is reasonable to propose that when adequate amounts of PUFAs are not incorporated into the neuronal cell membranes during growth and development it may cause a defect in the expression or function of insulin receptors in the brain that could lead to the development of metabolic syndrome as seen in the NIRKO mice. Furthermore, systemic injections of insulin in rats resulted in an increase in extracellular ACh in the amygdala (Hajnal et al. 1998). ACh modulates dopamine release that, in turn, regulates appetite. As already discussed above, ACh inhibits the production of proinflammatory cytokines (IL-1, IL-2 and TNF-α) in the brain and thus protects the neurons from neurotoxic injury.

AA and DHA activate syntaxin.-->3, a plasma membrane protein that has an important role in the growth of neurites (Darios and Davletov 2006). AA, DHA, and EPA bind to RAR-RXR, LXR, FXR and other nuclear receptor heterodimers and thus modulate development of the brain.

164.14   TNF-α, AA/EPA/DHA, Insulin, and Neuronal Growth and Synapse Formation

Perinatal supply of ω-3 fatty acids influences brain gene expression later in life and is critical to the development and maturation of several brain centers that are specifically involved in the regulation of appetite and satiety. Supplementation of AA and EPA/DHA increased the expression of serotonin receptor in the hypothalamus (Berger et al. 2002). 5-HT$_4$ receptor increases in expression have been shown to augment hippocampal acetylcholine outflow. It was reported that AA and EPA/DHA feeding enhanced the expression of POMC in the hippocampus, suggesting that AA/EPA/DHA influence appetite and satiety and thus control energy metabolism.

TNF-α produced by glial cells enhances synaptic efficacy by increasing surface expression of AMPA receptors. Continued presence of TNF-α is required for preservation of synaptic strength at excitatory synapses (reviewed in Das 2008). TNF-α production is suppressed by EPA/DHA, whereas excess TNF-α induces apoptosis of neurons. Insulin is not only needed for neuronal growth and differentiation and synaptic plasticity in the CNS but also stimulates the formation of AA/EPA/DHA and suppresses TNF-α production. Both insulin and AA/EPA/DHA stimulate eNO formation. This close interaction and feedback regulation among TNF-α, EPA/DHA, insulin, and neuronal growth and synapse formation suggests that growth of neurons and synaptic formation will be optimum only when all these factors are present in physiological concentrations. In contrast, when AA/EPA/DHA concentrations are suboptimal, TNF-α levels tend to be high. High TNF-α concentration are neurotoxic and hence could cause damage to VMH neurons that could lead to the development of the metabolic syndrome.

164.15   Maternal Diet Influences Fetal Leptin Levels

Low birth weight is associated with high prevalence of metabolic syndrome in later life (reviewed in Das 2008). Babies with low birth weights have 10 times greater chance of developing metabolic syndrome compared to those whose birth weight was normal. In addition, postnatal nutrition and growth also play a role in the development of metabolic syndrome in later life. Maternal protein restriction or increased consumption of saturated and/or trans-fatty acids and energy rich diets (maternal overnutrition) during pregnancy decrease the formation of PUFAs. Perinatal protein depletion leads to almost complete absence of activities of the enzymes in fetal liver and placenta that are

necessary for the elongation and desaturation of LA and ALA. Thus, both protein deficiency and high-energy diet leads to maternal and fetal deficiency of EPA, DHA, and AA.

A diet rich in PUFAs increases leptin levels in diet-induced obese adult rats, suggesting that variation in the type of diet during pregnancy and lactation might significantly modulate fetal and neonatal growth and development by leptin-associated mechanisms since leptin influences NPY/AgRP and POMC/CART neurons and their connections (reviewed in Das 2008). Plasma leptin levels were found to be low in the lactating dams fed an EFA-deficient diet and their suckling pups compared with controls. The suckling pups showed decreased concentrations of leptin even in their adipose tissue, suggesting that maternal EFA deficiency can produce a decrease in leptin levels in several tissues, possibly even in the hypothalamus. These low leptin levels during the perinatal period alter NPY/AgRP and POMC/CART homeostasis that may lead to the hypothalamic "body weight/appetite/satiety set point" set at a higher level that is long-lasting and potentially irreversible onto adulthood. Thus, maternal malnutrition, low perinatal PUFAs, and consequent low leptin concentrations could lead to the development of metabolic syndrome in adulthood (Das 2008).

164.16 Gastric Bypass-induced Weight Loss Could be due to Changes in the Hypothalamic Neuropeptides and Monoamines

If it is true that metabolic syndrome is a disorder of the brain, then it is necessary to show that diet-induced obesity and weight loss are due to changes in hypothalamic neuropeptides and monoamines. Roux-en-gastric bypass (RYGB) and other bariatric operations are being increasingly adopted to induce weight loss. RYGB produces on an average 49–65% weight loss within 2–5 years and ameliorates diabetes, hyperlipidemia, and other obesity-related metabolic abnormalities. In order to understand the molecular mechanisms involved in weight loss and amelioration of metabolic abnormalities in diet-induced obese animals that shed weight after RYGB operation, we developed a surgical rat model of human RYGB (Meguid et al. 2004; Middleton et al. 2004 and Xu et al. 2004).

Weight loss achieved by RYGB and PF (pair fed rats that received the same amount of diet that RYGB animals consumed) in obese rats was accompanied by a decrease in NPY in ARC, pPVN (parvocellular part of paraventricular nucleus of hypothalamus), and mPVN (magnocellular part of PVN) and an increase in α-MSH in ARC, pPVN, and mPVN compared with obese controls. 5HT-$_{1B}$-receptor in pPVN and mPVN increased in RYGB and PF compared to obese control (Romanova et al. 2004). Thus, weight loss seen after RYGB and diet control in PF groups is due to specific changes in hypothalamic peptides. Serotonin innervation is widely present in the hypothalamus and it innervates NPY neurons both in the ARC and PVN. Serotonin suppresses food intake. Hence, weight loss seen in RYGB and PF groups could be attributed to alterations in the concentrations of specific hypothalamic signaling peptides that regulate appetite, food intake, and satiety.

Even in tumor bearing anorectic rats, which showed significant weight loss due to tumor burden, similar results were seen: an increase of serotonin in PVN and VMN and a concomitant decrease of dopamine in PVN, VMN, and LHA (lateral hypothalamus), and of NPY in LHA, VMN, and PVN; a decrease in NPY in ARC and of POMC (proopiomelanocortin) in ARC and PVN (Romanova et al. 2004; Ramos et al. 2004); these abnormalities reverted to normal after tumor resection. Even the concentrations of IL-6 and TNF-α that were found to be elevated in ARC in tumor-bearing rats reverted to near normal in tumor-bearing rats that were fed fish oil (a rich source of EPA and DHA). In addition, a significant decrease in the concentrations of NPY and POMC in ARC were noted in fish oil fed nontumor-bearing rats, indicating that EPA/DHA regulate the levels of hypothalamic neuropeptides and monoamines.

164.17 Conclusions

Based on the preceding discussion, it is evident that availability of adequate amounts of EPA, DHA, and AA during the perinatal period is crucial to prevent the development of metabolic syndrome in later life. This could be in the form of supplementation of PUFAs to pregnant and lactating women, adequate breast-feeding to the newborn, followed by EPA, DHA, and AA supplementation to infants, children, and adolescents. The negative correlation noted between breast-feeding and insulin resistance and type 2 DM supports this view since human breast milk contains significant amounts of PUFAs. When infants receive inadequate amounts of PUFAs, optimal neural development is unlikely. As a result, the development, expression, and maintenance of NPY/AgRP, POMC/CART neurons, and insulin receptors will be defective; plasma, tissue, and hypothalamic concentrations of leptin will be inadequate, whereas the concentrations of proinflammatory cytokine TNF-α will be high, which may affect neuronal plasticity. A high TNF-α level may result in inadequate development of the critical hypothalamic neurons predisposing to the development of metabolic syndrome as seen in the NIRKO mice, VMH lesioned rats, and Lep^{ob}/Lep^{ob} mice. Thus, a marginal deficiency of PUFAs during the critical phases of fetal and infant growth can have a major effect on subsequent health. This is analogous to the observation that DHA deficiency in the perinatal period results in hypertension in later life, even when animals were subsequently replete with this fatty acid (Weisinger et al. 2001).

PUFAs also regulate food intake by modulating the concentrations of endogenous lipids *N*-acyl-ethanolamine (NAEs, anandamide) and 2-acylglycerols, and the ligands of cannabinoid (CB) receptors. These polyunsaturated NAEs bind to CB1 and CB2 (cannabinoid) receptors and regulate food intake. Furthermore, defective leptin signaling elevated hypothalamic levels of endocannabinoids in obese *db/db* and *ob/ob* mice and Zucker rats. Leptin treatment reduced anandamide and 2-arachidonoyl glycerol concentrations in the hypothalamus. EPA and DHA modulate leptin gene expression and levels both *in vitro* and *in vivo*. This suggests that PUFAs, endocannabinoids, and leptins act in concert with neurotransmitters NPY/AgRP and POMC/CART to control food intake, obesity, and metabolic syndrome.

Direct support to the concept that unsaturated fatty acids regulate hypothalamic neurons involved in the control of food intake and energy homeostasis comes from the observation that infusion of oleic acid (18:1 ω-9) in the third ventricle resulted in a marked decline in plasma insulin concentration and a decrease in the plasma glucose concentration compared with control within 1 h from the start of the infusion (Obici et al. 2002), suggesting that intracerebroventricular (ICV) oleic acid enhances insulin sensitivity. These results confirm that unsaturated fatty acids decrease systemic insulin levels and markedly stimulate insulin action on glucose homeostasis. Oleic acid suppressed the rate of glucose production by activating K_{ATP} channels in the hypothalamus similar to leptin and insulin.

Fatty acid synthase inhibitors reduced food intake and hypothalamic NPY mRNA levels (Loftus et al. 2000) by increasing the concentration of malonyl CoA, an inhibitor of the entry of long-chain CoAs into the mitochondria via inhibition of the activity of the enzyme carnitine palmitoyl-transferase-1. This results in elevation of cytoplasmic long-chain fatty acyl CoAs and diacylglycerol that play a role in signaling to the cells about the availability of fuels. Malonyl-CoA mediates nutrient-stimulated insulin secretion in the pancreatic β cell. Since glucose-sensing neurons and β cells have several similarities, such as expression of glucokinase and the ATP-sensitive K^+ channels, it is likely that malonyl-CoA may also signal fuel status in the hypothalamic neurons as it would in the β cells. In addition, both fatty acid synthase inhibitors and ICV injection of oleic acid inhibited hypothalamic expression of NPY, indicating that PUFA content of the hypothalamic neurons regulates the expression of NPY and other neuropeptides and, thus, modulates food intake, glucose homeostasis, and the development of metabolic syndrome.

Regulation of ATP-sensitive K$^+$ channels seems to be a common pathway by which nutrients modulate neuronal sensing of fuels. A primary increase in hypothalamic glucose levels lowers blood glucose through inhibition of glucose production and this effect of glucose requires its conversion to lactate followed by stimulation of pyruvate metabolism, which activates ATP-sensitive K$^+$ channels. Pyruvate has antioxidant and anti-inflammatory actions (pyruvate inhibits NF-κB activation, TNF-α, IL-6, MIF, and HMGB1 production) and is an insulin secretagogue (Das 2006b). This implies that glucose and pyruvate influence neuronal glucose sensing by a free radical dependent process since both modulate free radical generation.

Although ATP production and consequent closure of ATP-sensitive K$^+$ channels and calcium influx is considered as the main metabolic signal for this purpose, glucose-excited signaling in β cells and hypothalamic neurons is not totally dependent on ATP generation. In some hypothalamic arcuate neurons, ATP-sensitive K$^+$ channels function independent of ATP level and glucose-independent depolarization might occur through an ATP-sensitive channel-independent mechanism. Transient increase in glucose metabolism generates NADH and FADH$_2$ from the mitochondria and their use increases superoxide anion production (also called mitochondrial reactive oxygen species, mROS). Hypothalamic slices *ex vivo* exposed to 5–20 mmol/L glucose generated ROS. Glucose-induced increased neuronal activity in arcuate nucleus and insulin release are suppressed by antioxidants, suggesting that the brain glucose-sensing mechanism involves ROS signaling (reviewed in Das 2008). This is supported by the observation that ATP-sensitive K$^+$ channels control transmitter release in dorsal striatum through an H$_2$O$_2$-dependent mechanism and as several ROS-sensitive and nonselective cationic channels are known to exist. It is likely that glucose-sensing mechanisms could be similar, if not identical, in glucose responsive cells: pancreatic β cells and hypothalamic neurons. Thus, hypothalamic pyruvate, a metabolite of glucose metabolism; ROS; and PUFAs not only play a significant role in the regulation of nutrient sensing by hypothalamic neurons and β cells, but may interact among themselves. Ghrelin-induced feeding behavior that is controlled by arcuate neurons that coexpress NPY/AgRP also seem to be mediated by free radicals (Andrews et al. 2008). Thus, free radicals seem to be the common mechanism by which ghrelin, NPY/AgRP, glucose, and insulin (and possibly POMC neurons) act on hypothalamus to bring about their actions on food intake, satiety, appetite, and finally glucose homeostasis (Fig. 164.2).

Peripheral tissues (such as muscle, adipose cells, etc.), pancreatic β cells, and the hypothalamic neurons need to communicate with each other to maintain energy homeostasis. For instance, immediately after food intake gut peptides such as ghrelin, cholecystokinin (CCK), etc., are released that interact with hypothalamic neurons and signal hunger and satiety sensations. CCK reduces food intake by acting at CCK-1 receptors on vagal afferent neurons. Leptin mRNA has been reported in vagal afferent neurons, some of which also express CCK-1 receptor, suggesting that leptin, alone or in cooperation with CCK, might activate vagal afferent neurons and influence food intake via a vagal route. A much higher prevalence of CCK and leptin sensitivity amongst cultured vagal afferent neurons that innervate stomach or duodenum than there was in the overall vagal afferent population was reported. Almost all leptin-responsive gastric and duodenal vagal afferents also were sensitive to CCK. Leptin, infused into the upper GI tract arterial supply, reduced meal size, and enhanced satiation evoked by CCK, indicating that vagal afferent neurons are activated by leptin, and that this activation participates in meal termination by enhancing vagal sensitivity to CCK (reviewed in Das 2008). Injection of adeno-associated viral vectors encoding leptin (rAAV-lep) rAAV-lep injection increased hypothalamic leptin expression in the complete absence of peripheral leptin in *ob/ob* mice; suppressed body weight and adiposity; voluntarily decreased dark-phase food intake; suppressed plasma levels of adiponectin, TNF-α, free fatty acids, and insulin concomitant with normoglycemia and elevated ghrelin levels for an extended period. Leptin administration rapidly decreased plasma gastric ghrelin and adipocyte adiponectin but not TNF-α level, thereby demonstrating a
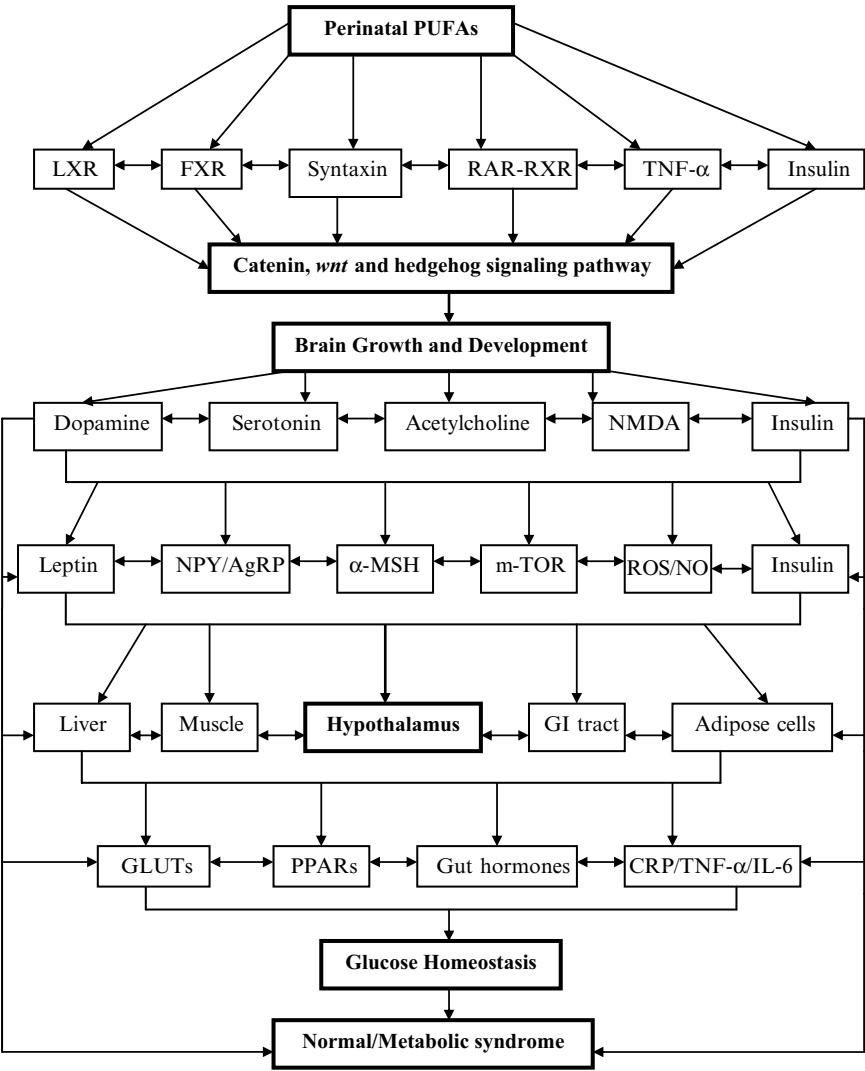
Fig. 164.2 Scheme showing the relationship among PUFAs and various tissues and factors involved in the pathobiology of the metabolic syndrome

peripheral restraining action of leptin on the secretion of hormones of varied origins. Whereas ghrelin administration readily stimulated feeding in controls, it was completely ineffective in rAAV-lep-treated wt mice. Thus, leptin expressed locally in the hypothalamus counteracted the central orexigenic effects of peripheral ghrelin, suggesting that leptin and ghrelin interact with each other and thus regulate energy homeostasis and metabolism. It was reported that incubation of the hypothalamic explants with ghrelin significantly increased NPY and AGRP mRNA expression, suggesting that ghrelin and NPY interact with each other. Ghrelin facilitates both cholinergic and tachykininergic excitatory pathways, consistent with activity within the enteric nervous system and possibly the vagus nerve (reviewed in Das 2008). These evidences suggest that sympathetic and parasympathetic (especially vagus nerve) nerves carry messages from the peripheral tissues and β cells to the hypothalamus and *vice versa* where all the messages are integrated, codified, and relayed to the target tissues to maintain overall energy balance (Fig. 164.3).
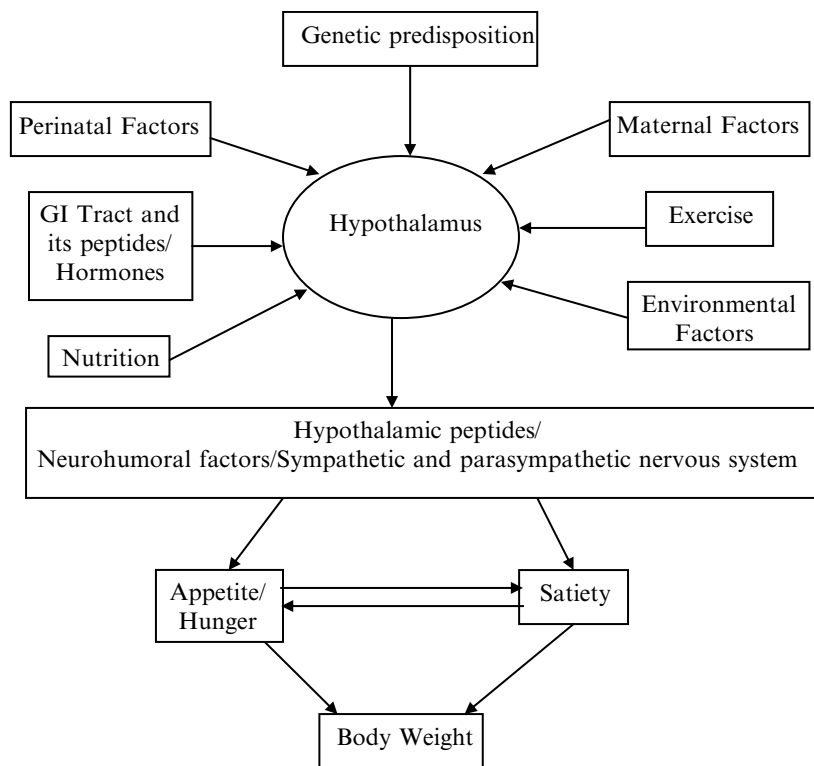
Fig. 164.3 Scheme showing the simplified relationship between genetic factors, maternal factors, diet, GI tract, and hypothalamus to body weight

This is supported by the observation that adenovirus-mediated expression of PPAR-γ2 in the liver induces acute hepatic steatosis while markedly reducing peripheral adiposity, changes that were accompanied by increased energy expenditure and improved systemic insulin sensitivity. Interestingly, hepatic vagotomy and selective afferent blockage of the hepatic vagus reversed these changes, whereas thiazolidinedione, a PPAR-γ agonist, enhanced these changes (reviewed in Das 2008). Thus, a neuronal pathway consisting of the afferent vagus from the liver and efferent sympathetic nerves to adipose tissues is involved in the regulation of energy expenditure, systemic insulin sensitivity, glucose metabolism, and fat distribution between the liver and the periphery. In this context, it should be noted that proinflammatory cytokine production is regulated by the efferent vagus nerve. Acetylcholine (ACh), the principal vagal neurotransmitter, has been shown to inhibit the production of TNF, IL-1, MIF, and HMGB1, and activation of NF-κB expression (reviewed in Das 2008). Since ACh is both a neurotransmitter and regulates serotonin, dopamine, and other neuropeptides, whereas PUFAs influence ACh release and insulin sensitivity (Das 2008), it is clear that a complex network of interaction(s) exists among all these molecules in the regulation of energy homeostasis. Furthermore, brain insulin resistance exists in peripheral insulin resistance, especially in regions subserving appetite and reward; exercise enhanced the sensitivity of hypothalamus to the actions of leptin and insulin and the appetite-suppressive actions of exercise are mediated by the hypothalamus (Das 2008). These evidences emphasize the role of hypothalamus in the pathobiology of metabolic syndrome.

Summary Points

- The incidence of metabolic syndrome is assuming epidemic proportions in almost all countries in the world.
- Low-grade systemic inflammation occurs in metabolic syndrome.
- Glucose has proinflammatory actions while insulin is anti-inflammatory in nature.
- The anti-inflammatory nature of insulin suggests that hyperinsulinemia seen in insulin resistance may be a protective phenomena and this also explains its cardioprotective and cytoprotective actions.
- The hypothalamic centers that regulate appetite, food intake, and satiety are formed during the fetal period; enhanced maternal and early perinatal nutrition programs the hypothalamic centers and this influences food preferences in later life.
- Features of metabolic syndrome are seen when ventromedial hypothalamus is damaged suggesting that it could be a disorder of the brain.
- Insulin receptors are present in the brain and intracerebroventricular injection of insulin reduces food intake and suppresses NPY/AgRP and activates POMC/CART neurons.
- Insulin activates K_{ATP} channels in the neurons and modulates the levels of reactive oxygen species and nitric oxide, and thus regulates glucose homeostasis.
- PUFAs are essential for brain growth and development and modulate the production and actions of acetylcholine, dopamine and other neurotransmitters and monoamines. PUFAs are also neuroprotective in nature.
- Maternal diet influences plasma leptin levels that, in turn, modulates NPY/AgRP and POMC/CART homeostasis
- Gastric bypass and diet restriction induced weight loss could be due to alterations in hypothalamic neuropeptides and monoamines.

Key Points

- Glucose is needed for the energy needs of all tissues of the body.
- Glucose needs to enter the cell for its conversion to ATP (adenosine triphosphate), the main source of energy to all cells of the body.
- Insulin has the property to push glucose into the cells.
- Insulin to produce its actions binds to its receptor, insulin receptor, which leads to the generation of a series of signals that bring about the actions of insulin in the cell.
- Once the glucose enters the cell, though its receptors called GLUT (glucose transporters) receptors plasma glucose levels decrease.
- When glucose fails to enter the cell due to a defect in insulin action and abnormalities in GLUTs, plasma glucose will increase while the cells are starved of glucose.
- Insulin is produced by pancreatic β cells in response to food intake and increase in plasma glucose levels.
- Failure to produce adequate amounts of insulin leads to inadequate utilization of glucose by cells and this results in an increase in plasma glucose. Called hyperglycemia, this is a key feature of type 2 diabetes mellitus and the metabolic syndrome.
- Other features associated with metabolic syndrome are obesity, abnormities in plasma lipid levels, and low-grade inflammation.

- Metabolic syndrome is considered a low grade systemic inflammatory condition.
- Hyperglycemia enhances the production of free radicals, and proinflammatory cytokines.
- Insulin shows anti-inflammatory actions.
- Lesions of the ventromedial hypothalamus (VMH) in experimental animals produce all the features of the metabolic syndrome
- Neuron-specific insulin receptor knockout (NIRKO) mice also show many features of the metabolic syndrome.
- Mice with targeted disruption of endothelial nitric oxides synthase (eNOS) are not only hypertensive and insulin resistant but also show features of the metabolic syndrome.
- The brain is rich in insulin receptors, including the hypothalamus.
- Administration of insulin into the hypothalamus reduces food intake and plasma glucose.
- Hypothalamic centers that regulate food intake, appetite, and satiety are formed during the perinatal period.
- Maternal diet and perinatal nutrition programs the hypothalamic centers, hypothalamic neuropeptides, and monoamines.
- Polyunsaturated fatty acids (PUFAs) are essential for brain growth and development and can modulate the production of leptin and other neuropeptides.
- Intraventricular administration of oleic acid decreases food intake, reduces plasma glucose and leptin levels, and ameliorates diabetes mellitus.
- Cross-talk among gut, liver, pancreas, and hypothalamus occurs through vagal fibers.
- Acetylcholine, the principal vagal neurotransmitter, shows anti-inflammatory actions and regulates various hypothalamic monoamines.
- Insulin, PUFAs, and acetylcholine enhance endothelial nitric oxide generation, and have anti-inflammatory and neuroprotective actions.
- Glucose, insulin, and PUFAs act on K_{ATP} channels in glucose-responsive hypothalamic neurons.
- Brain glucose-sensing mechanism involves reactive oxygen species (ROS) signaling that act on ATP-sensitive K^+ channels.
- The strategy of providing adequate PUFAs during the perinatal period may prevent the development of the metabolic syndrome by suppressing low-grade systemic inflammation, ensuring the presence of adequate number of insulin receptors in the brain, and adequacy of hypothalamic neuropeptides and monoamines.

References

Aljada A, Ghanim H, Mohanty P, Hofmeyer D, Chaudhuri A, Dandona P. Metabolism. 2006;55:1177–85.

Aljada A, Mohanty P, Ghanim H, Abdo T, Tripathy D, Chaudhuri A, Dandona P. Am J Clin Nutr. 2004;79:682–90.

Andrews ZB, Liu Z-W, Wallingford N, Erion DM, Borok E, Friedman JM, Tschop MH, Shanabrough M, Cline G, Shulman GI, Coppola A, Gao X-B, Horvath TL, Diano S. Nature. 2008;454:846–51.

Axen KV, Li X, Fung K, Sclafani A. Am J Physiol. 1994;266 (3 Pt 2):R921–8.

Benoit SC, Air EL, Coolen LM, Strauss R, Jackman A, Clegg DJ, Seeley RJ, Woods SC. J Neurosci. 2002;22:9048–52.

Berger A, Mutch DM, German JB, Roberts MA. Lipids Health Dis. 2002;1:2.

Bruning JC, Gautam D, Burks DJ, Gillette J, Schubert M, Orban PC, Klein R, Krone W, Muller-Wieland D, Kahn CR. Science. 2000;289:2122–5.

Cook S, Hugli O, Egli M, Vollenweder P, Burcelin R, Nicod P, Thorens B, Scherrer U. Swiss Med Wkly. 2003;133:360–3.

Darios F, Davletov B. Nature. 2006;440:813–7.

Das UN. Diabetologia. 2000;43:1081–2.

Das UN. Nutrition. 2001;17:409–13.

Das UN. Exp Biol Med. 2002a;227:989–97.

Das UN. Lancet. 2002b;360:490.

Das UN. Nutrition. 2004;20:323–6.

Das UN. Eur Heart J. 2006a;27:1385–6.

Das UN. Nutrition. 2006b;22:965–72.

Das UN. Curr Nutr Food Sci. 2008;4:73–108.

Davidowa H, Li Y, Plagemann A. Eur J Neurosci. 2003;18:613–21.

Dube MG, Kalra PS, Crowley WR, Kalra SP. Brain Res. 1995;690:275–8.

Dunn-Meynell AA, Routh VH, Kang L, Gaspers L, Levin BE. Diabetes. 2002;51:2056–65.

Elouil H, Cardozo AK, Eizirik DL, Henquin JC, Jonas JC. Diabetologia. 2005;48:496–505.

Fahrenkrog S, Harder T, Stolaczyk E, Melchior K, Franke K, Dudenhausen JW, Plagemann A. J Nutr. 2004;134:648–54.

Funahashi T, Shimomura I, Hiraoka H, Arai T, Takahashi M, Nakamura T, Nozaki S, Yamashita S, Takemura K, Tokunaga K, et al. Biochem Biophys Res Commun. 1995;211:469–75.

Grove KL, Smith MS. Physiol Behav. 2003;79:47–63.

Grundy SM, Brewer Jr B, Cleema JI, Smith SC, Lenfant C for the conference participants. NHLBI/AHA conference proceedings. Circulation. 2004;109:433–8.

Gu CH, Cui Q, Wang YY, Wang J, Dou YW, Zhao R, Liu Y, Wang J, Pei JM, Yi DH. Cytokine. 2008;44:96–100.

Hajnal A, Pothos EN, Lenard L, Hoebel BG. Effects of feeding and insulin on extracellular acetylcholine in the amygdala of freely moving rats. Brain Res. 1998;785:41–8.

Hill JM, Lesniak MA, Pert CB, Roth J. Neuroscience. 1986;17:1127–38.

Hoedemaekers CW, Pickkers P, Netea MG, van Deuren M, Van der Hoeven JG. Crit Care. 2005;9:R790–7.

Houstis N, Rosen ED, Lander S. Nature. 2006;440:944–8.

Jeschke MG, Einspanier R, Kelin D, Jauch KW. Mol Med. 2002;8:443–50.

Jeschke MG, Klein D, Herndon DN. Ann Surg. 2004;239:553–60.

Keno Y, Tokunaga K, Fujioka S, Kobatake T, Kotani K, Yoshida S, Nishida M, Shimomura I, Matsuo T, Odaka H, et al. Metabolism. 1994;43:32–7.

Kidd LB, Schabbauer GA, Luyendyk JP, Holscher TD, Tilley RE, Tencati M, Mackman N. J Pharmacol Exp Ther. 2008;326:348–53.

Klein D, Shubert T, Horch RE, Jauch KW, Jeschke MG. Ann Surg. 2004;240:340–9.

Koskenkari JK, Kaukoranta PK, Rimpilainen J, Vainionpaa V, Ohtonen PP, Surcel HM, Juvonen T, Ala-Kokko TI. Acta Anaesthesiol Scand. 2006;50:962–9.

Kumar SG, Das UN. Prostaglandins Leukotr Essen Fatty Acids. 1994;50:331–4.

Li J, Zhang H, Wu F, Nan Y, Ma H, Guo W, Wang H, Ren J, Das UN, Gao F. Crit Care Med. 2008;36:1551–8.

Lin X, Taguchi A, Park S, Kushner JA, Li F, Li Y, White MF. J Clin Invest. 2004;114:908–16.

Lin Y, erg AH, Iyengar P, Lam TK, Giacca A, Combs TP, Rajala MW, Du X, Rollman B, Li W, Hawkins M, Barzilai N, Rhodes CJ, Fantus IG, Brownlee M, Scherer PE. J Biol Chem. 2005;280:4617–26.

Lin Y, Rajala MW, Berge JP, Moller DE, Barzilai N, Scherer PE. J Biol Chem. 2001;276:42077–83.

Loftus TM, Jaworsky DE, Frehywot GL, Townsend CA, Ronnett GV, Lane MD, Kuhajda FP. Science. 2000;288:2379–81.

Lynch RM, Tompkins LS, Brooks HL, Dunn-Meynell AA, Levin BE. Diabetes. 2000;49:693–700.

McGowan MK, Andrews KM, Grossman SP. Physiol Behav. 1992;51:753–66.

McMillen IC, Adam CL, Muhlhausler BS. J Physiol. 2005;565:9–17.

Meguid MM, Ramos EJB, Suzuki S, Xu Y, George ZM, Das UN, Hughes K, Quinn R, Chen C, Marx W, Cunningham PRG. J Gastrointestinal Surg. 2004;8:621–30.

Menendez JA, Atrens DM. Brain Res. 1991;555:193–201.

Middleton FA, Ramos EJB, Xu Y, Diab H, Zhao X, Das UN, Meguid MM. Nutrition. 2004;20:14–25.

Mirshamsi S, Laidlaw HA, Ning K, Anderson E, Burgess LA, Gray A, Sutherland C, Ashford ML. BMC Neurosci. 2004;5:54.

Morgan D, Oliveira-Emilio HR, Keane D, Hirata AE, Santos da Rocha M, Bordin S, Curi R, Newsholme P, Carpinelli AR. Diabetologia. 2007;50:359–69.

Muhlhausler BS, Adam CL, Marracco EM, Findlay PA, Roberts CI, McFarlane JR, Kauter KG, McMillen IC. J Physiol. 2005;565:185–95.

Nareika A, Maldonado A, He L, Game BA, Slate EH, Sanders JJ, London SD, Lopes-Virella MF, Huang Y. J Periodontal Res. 2007;42:31–8.

Obici S, Feng Z, Morgan K, Stein D, Karkanias G, Rossetti L. Diabetes. 2002;51:271–5.

Ramos EJB, Suzuki S, Meguid MM, Laviano A, Sato T, Chen C, Das UN. Surgery. 2004;136:270–6.

Romanova I, Ramos EJB, Xu Y, Quinn R, Chan C, George ZM, Inui A, Das UN, Meguid MM. J Am Coll Surg. 2004;199:887–95.

Sahu A, Dube MG, Phelps CP, Sninsky CA, Kalra PS, Kalra SP. Endocrinology. 1995;136:5718–24.

Spanswick D, Smith MA, Mirshamsi S, Routh VH, Ashford ML. Nat Neurosci. 2000;3:757–8.

Sweet IR, Gilbert M, Maloney E, Hockenbery DM, Schwartz MW, Kim F. Diabetologia. 2009;52:921–31.

Wan Q, Xiong ZG, Man HY, Ackerley CA, Braunton J, Lu WY, Becker LE, MacDonald JF, Wang YT. Nature. 1997;388:686–90.

Weisinger HS, Armitage JA, Sinclair AJ, Vingrys AJ, Burns PL, Weisinger RS. Nat Med. 2001;7:258–9.

Xu Y, Ramos EJB, Middleton F, Romanova I, Quinn R, Chen C, Das UN, Inui A, Meguid MM. Surgery. 2004;136:246–52.

Chapter 165
Schizophrenia and the Metabolic Syndrome

Jared Edward Reser

165.1 Introduction

It has been well known for at least 2 decades that schizophrenia is associated with excess mortality, premature death, and increased standard mortality from both natural and unnatural causes (Allebeck 1989). Patients with schizophrenia are at high risk of death from unnatural causes such as suicides and accidents; however, unnatural causes do not account for even half of the excess mortality. It is increasingly recognized that patients with schizophrenia are at increased risk for natural causes of death, primarily life-shortening illnesses (Marder et al. 2004). Epidemiological data have for decades evinced that natural causes afflict patients with schizophrenia much earlier than they do people in the general population. In fact, one meta-analysis concluded that at least 60% of the excess mortality in patients with schizophrenia is attributable to physical illness (Brown 1997). This well-received study also found that only 28% of the excess mortality is attributable to suicide and only 12% to accidents, leaving even more room than initially expected for the contribution of illness. Individuals with schizophrenia have been shown to die younger from a variety of cardiovascular, infectious, gastrointestinal, respiratory, urogenital, and metabolic conditions. It is not clear if there is a common contributing pathological factor that underlies these epidemiological correlations. Probably the best candidate for such a unifying factor is the metabolic syndrome, a cluster of commonly comorbid metabolic derangements that tend to exacerbate one another and tend to afflict individuals with schizophrenia. It is not clear why the metabolic syndrome is relatively prevalent in populations with schizophrenia, but taken together, various points of evidence regarding this association are beginning to elucidate how the two are related and what can be done in regard to prevention.

Most medical professionals do not think of the metabolic syndrome when they hear the word schizophrenia. Schizophrenia is a psychiatric diagnosis that is characterized by abnormalities in the perception or expression of reality. It can present in different ways but commonly manifests as auditory hallucinations, paranoid or bizarre delusions, or disorganized speech and thinking. The impairment in sensory gating, emotional inhibition, and the organization of complex behaviors cause individuals with schizophrenia to have significant impairments in social and occupational abilities. Onset of symptoms typically occurs in young adulthood with between 0.4% and 0.6% of the worldwide population affected (Bhugra 2006). It has become clear that the psychological symptoms are accompanied by a variety of somatic symptoms and health issues. In a study of over 168,000 affected

J.E. Reser (✉)
University of Southern California, Psychology Department, SGM 501, 3620 South McClintock Ave.,
Los Angeles, CA 90089-1061, USA
e-mail: jared@jaredreser.com; reser@usc.edu

Table 165.1 The key features of schizophrenia

Thought	Hallucinations, delusions, paranoid ideation, bizarre thinking
Behavior	Disorganized speech, emotional outbursts, social and occupational dysfunction, long term unemployment, homelessness, poverty
Causes	Both genetic and environmental, high heritability, stress, prenatal stress, drug abuse, social disadvantage
Brain physiology	Increased dopamine activity in the mesolimbic pathway, hypometabolic states in the prefrontal and temporal cortices and hippocampus
Comorbid conditions	Major depression, anxiety disorders, metabolic disorders, substance abuse

The key features of schizophrenia with selected aspects

patients in Sweden, schizophrenia was associated with an average life expectancy of approximately 80–85% of that of the general population (Hannerz et al. 2001). It is currently thought that a large proportion of this excess mortality can be attributed to metabolic disease.

Before the explicit ties to the metabolic syndrome were made, it was noted by epidemiologists that cardiovascular disease plays a large role in the premature deaths of schizophrenic patients. It was estimated that cardiovascular disease was responsible for as much as 50% of the excess mortality (Osby et al. 2000). Moreover, nearly 20% of deaths in schizophrenia can be attributed to ischemic heart disease, the most common cause of death in both sexes (Newman and Bland 1991). Today it is thought that even though there may be many contributing factors to cardiovascular disease in schizophrenia (such as cardiac arrhythmia and toxic cardiomyopathy), the major contributing factors may be metabolic disturbances – shared, common comorbidities in cardiovascular disease and schizophrenia. Since this realization, it has been well documented that individuals with schizophrenia are markedly susceptible to a specific group of metabolic disturbances that tend to present together in human and animal populations as the metabolic syndrome. It is thought that susceptibility to metabolic disease may be due to many different aspects common to schizophrenia, the most probable include inactive lifestyle, poor dietary choices, severe stress, and the side effects of psychotropic medications (Wirshing and Meyer 2003) (Table 165.1).

165.2 The Metabolic Syndrome in Schizophrenia

The metabolic syndrome has been a significant construct in the field of cardiology and endocrinology for at least 2 decades, but has become of interest to a variety of different fields in the last decade because of the ongoing, worldwide epidemic of obesity and diabetes. The metabolic syndrome is comprised of a group of clinical features that include atherogenic dyslipidemia (low high density lipoprotein (HDL) and elevated fasting triglycerides), hypertension, increased abdominal or visceral adiposity, and impaired fasting glucose or diabetes mellitus (Expert Panel on Detection 2001) (Table 165.2).

In 2005, the Adult Treatment Panel III of the National Cholesterol Education Program defined diagnosis as the presence of three or more of the five states listed in Table 165.3. The International Diabetes Federation, the European Group for the Study of Insulin Resistance, the World Health Organization, and others have each identified unique sets of diagnostic criteria. This disparity in diagnostic definition has created some concern and confusion; however, all three systems are relatively similar. There is broad overlap between the definitions, especially those of the World Health Organization and National Cholesterol Education Program. These similarities led researchers to find that, using data from the third National Health and Nutrition Examination Survey, NCEP and WHO criteria led to identical diagnoses for a group of 8,608 subjects in 86.2% of subjects. Not surprisingly,

Table 165.2 The key features of the metabolic syndrome

Obesity	Increased total body fat, abdominal or central fat distribution, increased visceral fat
Insulin resistance	Hyperinsulinemia
Dyslipidemia	Hypertriglyceridemia, decreased HDL cholesterol, increased LDL cholesterol
Impaired glucose tolerance	Type 2 diabetes mellitus
Hypertension	High or deranged blood pressure

The defining disorders of the metabolic syndrome and their components

Table 165.3 Criteria for the metabolic syndrome

Increased waist circumference	>102 cm in men, >88 cm in women
Elevated triglycerides	>150 mg/dl or 1.7 mmol/l
Decreased HDL cholesterol	<40 mg/dl in men, <50 mg/dl in women
Blood pressure	>130/85 mgHg or active treatment for hypertension
Fasting glucose	>110 mg/dl or active treatment for hyperglycemia

The National Cholesterol Education Program's criteria for diagnosis of the metabolic syndrome and their defining measures. Three of the five risk factors must be present for a diagnosis

differences in susceptibility to individual features caused the prevalence estimates between the two definitions to differ for some subpopulations, including sex and race (Ford and Giles 2003). It is not known if schizophrenia is another subpopulation whose prevalence might be affected arbitrarily by differences in susceptibility to certain features over others, although it is certainly possible.

The metabolic syndrome is highly prevalent in the general population. Based on the estimates derived from the third National Health and Nutrition Examination Survey it is thought that around 47 million people in the US meet the diagnostic criteria (Ford and Giles 2003). The age-adjusted prevalence in the US is 23.7% with the lowest prevalence of 6.7% for individuals between the ages of 20 and 29 and the highest prevalence of 43.5% for individuals aged 60 and higher. Both schizophrenia and a closely related psychiatric illness, schizoaffective disorder, are associated with a drastically increased risk for the metabolic syndrome and together have an age-adjusted prevalence of 42.6% for males and 48.5% for females (Cohn et al. 2004). Ethnicity as a predictor persists even after controlling for age, BMI, and socioeconomic status. For instance, Hispanics have the highest age adjusted prevalence of 31.9%. The age adjusted prevalence for schizophrenia is thought to be above 40%, significantly higher than the highest prevalence by ethnicity (Cohn et al. 2004).

McEvoy et al. (2005) confirmed in a large and well-controlled study that the metabolic syndrome is much more prevalent in patients with schizophrenia than among individuals from the general population, even after controlling for body mass and a variety of demographic variables. The order of the significance of this finding persuaded researchers to state that schizophrenia patients may represent a patient population with one of the highest metabolic syndrome prevalence rates of the major patient groups studied today. This study also showed that female patients with schizophrenia may constitute one of the subpopulations most vulnerable to central obesity and type 2 diabetes mellitus. Despite this and other fine studies in this area, there is no consensus about the prevalence of the metabolic syndrome in schizophrenia, in it subsets, or in associated psychotic disorders. It will be very informative to have the cross-sectional, longitudinal, and component feature data, and this may be available in a more reliable form in the near future.

The etiology of the metabolic syndrome, like that of schizophrenia, is still mysterious and controversial. There are a large number of secondary factors, aside from the key features, that are closely associated with the metabolic syndrome (Ryan and Thakore 2002), see Table 165.4. A review of these by Hansen (1999) identifies a wide assortment including: autonomic neuropathy, altered adipose tissue

Table 165.4 Secondary associations with the metabolic syndrome

Adipose tissue abnormalities: hyperleptinemia, altered lipoprotein lipase activity
Alcohol consumption
Pituitary adrenal abnormalities: hypercoritisolemia, impaired glucocorticoid receptor function
Reduced physical activity
Reduced ability to cope with stress, elevated stress hormone levels
Genetic predisposition, high heritability
Smoking
Increased food intake: hyperphagia, increased dietary fat content
Sex hormone abnormalities

A brief list of some of the secondary abnormalities associated with the diagnosis of the metabolic syndrome

physiology, difficulty coping with stress, excess alcohol consumption, hypercortisolemia, hyperphagia, impaired glucocorticoid receptor function, increased dietary fat content, reduced growth hormone, reduced physical activity, sex hormone abnormalities, and smoking. Factor analyses of the key and secondary features suggest that there is no unifying etiological feature (Zimmet et al. 1999). Many of these features are known to be quite commonplace in schizophrenia (Ryan and Thakore 2002). There has been very little research though, on whether populations of nonschizophrenic individuals with the metabolic syndrome exhibit symptoms particular to schizophrenia.

Individuals with schizophrenia may have increased risk for the metabolic syndrome because of patterns of unhealthy lifestyle choices common to schizophrenia and other psychotic disorders. Heavy alcohol (Mortensen and Juel 1993) and cigarette (Masterson and O'Shea 1984) use, along with poor diet, high fat consumption, lack of exercise and low physical activity (Brown et al. 1999) are all strongly associated with schizophrenia and have been for decades. These lifestyle factors are also powerful risk factors for the metabolic syndrome. It is clear that there is an increased need for lifestyle therapy intervention in this population. Diminishing substance abuse and increasing physical activity have long been treatment goals in schizophrenia therapy designed to ameliorate the psychological symptoms and improve mood. Now it is obvious that these goals will do more for this population than previously appreciated because they will also help to treat the metabolic symptoms.

It is becoming clear that the high prevalence of the metabolic syndrome in schizophrenia is due to more than just the behavioral propensities of patients or the antipsychotic drugs that the majority of patients have been prescribed. Several family history studies, and even decades old historical studies have found weighty, positive associations between schizophrenia and diabetes. Studies have also shown that first episode drug-naïve patients have an increased prevalence of central obesity, impaired fasting glucose, and insulin resistance suggesting that metabolic disturbances may be an inherent genetic component of the schizophrenia phenotype (de Leon and Diaz 2007; Spelman et al. 2007). Some well controlled studies have even shown that diabetes is more common in patients not taking antipsychotics than in those that were receiving them (Mukherjee et al. 1996). This represented powerful evidence suggesting that the association between schizophrenia and the metabolic syndrome is due to more than just the commonly accepted environmental influences. Some recent articles have even stated explicitly that there is evidence indicating that, "patients with schizophrenia might have an inherent predisposition towards the metabolic syndrome in a similar manner seen with certain ethnic groups" (McEvoy et al. 2005). In fact, genes responsible for schizophrenia and the metabolic syndrome seem to transmit together across generations. There is an increased frequency of the metabolic syndrome in the nonschizophrenic relatives of patients with schizophrenia (Mukherjee et al. 1989). Also, many of the individual facets of the metabolic syndrome have been closely tied to first episode or drug naïve schizophrenia as Table 165.5 demonstrates.

Table 165.5 Metabolic disorders and schizophrenia

Cardiovascular disease	Kendrick (1996); Davidson (2002) Ryan and Thakore (2002)
Insulin resistance	Felker et al. (1996); Ryan and Thakore (2002); Ristow (2004)
HPA axis up-regulation	Walker et al. (1996); Walker and Diforio (1997)
Metabolic syndrome	Ryan and Thakore (2002); Heiskanen et al. (2003)
Obesity	Allison et al. (1999); Davidson (2002)

A list of some of the features of the metabolic syndrome that have been associated with drug naïve or first episode schizophrenia

165.3 Schizophrenia and Diabetes

Studies indicate that diabetes mellitus may be twice as prevalent in schizophrenia (14%) as it is in the general population (7%) (Dixon et al. 2000). Additionally, impaired glucose tolerance and insulin resistance are also more common (Jeste et al. 1996). It is still not clear to what extent schizophrenia and diabetes present comorbidly because of shared genetic backgrounds, or if they are associated environmentally through weight gain. Prior to the onset of schizophrenia, there is not strong evidence for preexisting obesity (Weiser et al. 2004), an observation which provides some support for the latter assumption given that susceptibility of children and adults to the metabolic syndrome increases with worsening obesity. This does not necessarily detract from the significance of genetic contribution though, especially since individuals with schizophrenia are more likely to have obese parents. Furthermore, some studies have shown that even though there may not be a predisposition towards obesity prior to onset, it seems there is a prodromal predisposition for visceral adiposity (Zhang et al. 2004). It is possible that this inclination becomes fully expressed as obesity and diabetes after onset due to epigenetic factors, lifestyle, medications or interactions between all three.

The number of published prevalence studies of the metabolic syndrome in schizophrenia patients is not large, but it documents that the association is probably larger than the association between schizophrenia and diabetes mellitus (Heiskanen et al. 2003; Basu et al. 2004). Why this might be is unclear. The association between diabetes mellitus and schizophrenia has come under scrutiny recently because of new data associating atypical antipsychotics (also known as second generation antipsychotics) with new onset diabetes and the dangerous state of diabetic ketoacidosis (American Diabetes Association et al. 2004). Atypical antipsychotics have been known to work well to alleviate the symptoms of schizophrenia, and other forms of psychosis, but have received negative attention in the literature because of the significant weight gain liabilities associated with certain drugs (Meyer 2001).

165.4 Antipsychotic Medications

Atypical antipsychotics have been immensely effective in treating schizophrenia. Ironically though, they have been implicated in greatly accelerating the progression of the metabolic syndrome. More specifically, they have been heavily associated with cardiac irregularities, dyslipidemia, glucose intolerance, and weight gain (Ryan and Thakore 2002). The proportion of patients on antipsychotics with the metabolic syndrome ranges between 20% and 60% and in most cases is double the prevalence in the general population (De Hert et al. 2006; Haupt 2006). The evidence is the strongest for clozapine and olanzapine (Shirzadi and Ghaemi 2006) and suggestive but weaker for other antipsychotics (Newcomer and Haupt 2006).

It has been difficult for researchers to come to conclusions about the adverse effects of antipsychotics without the much needed randomized, controlled trials with prospective designs. Prior antipsychotic treatment and other medications confound the findings of many of the studies. Recent studies done with first episode schizophrenia avoided some of these confounds because all of the participants were drug naïve and had no prior antipsychotic prescription. One such study, using historic data, found that even though there was no difference in prevalence of the metabolic syndrome between first episode schizophrenics from 15–20 years ago compared with first episode moderns, the incidence of the metabolic syndrome was three times higher in the modern group that took atypical antipsychotics compared to the historic group that took first-generation antipsychotics (Hert et al. 2008). A number of findings have reinforced the consensus that first generation antipsychotics were far less likely to lead to metabolic complications. Another first episode study compared individual medications and showed that the test groups receiving olanzapine had the highest prevalence of the metabolic syndrome at 20–25%, followed by risperidone at 9–24% and finally haloperidol at 0–3% (Saddichha et al. 2008). Other studies have identified clozapine as being among the worst of these agents.

There are still many unknowns in this arena but fortunately there are also some thoughtful articles aimed at educating health professionals about what is known. The American Diabetes Association published a consensus paper on antipsychotic drugs and metabolic outcome that provides clear and helpful guidelines for health monitoring and medication selection for patients needing atypical antipsychotic drugs (American Diabetes Association et al. 2004). Despite many strong findings, it is important to point out that the influence of antipsychotic drugs comprises only a piece of this puzzle. As stated earlier, metabolic abnormalities have consistently been associated with schizophrenia even before the era of antipsychotic medications (Raphael 1921; Homel et al. 2002).

165.5 Schizophrenia and Cardiovascular Disease

As stated earlier, cardiovascular disease is one of the primary causes of morbidity and mortality in patients with schizophrenia (Meyer and Nasrallah 2003). Patients are known to commonly exhibit several different markers for cardiovascular risk. Both individuals treated with atypical antipsychotics and those who are drug free have a high propensity for platelet aggregation differences which makes them more likely to produce thrombus. Thrombus production is crucial during wound healing but overproduction can lead to life-threatening pathology including myocardial infarction. Exactly why and how this increased platelet aggregation occurs is unclear. Other unhealthy cardiac features that are associated with schizophrenia include: abnormal heart variation, prolonged phase of cardiac depolarization, decreased variations in cardiac rate, high sinus rhythm resting heart rate, long periodicity of endogenous ultradian rhythm of heart rate, and others. Interestingly, most of these features were abnormal in both individuals treated with antipsychotic drugs and those that were never treated. These findings lead one to conclude that there are multiple sources of evidence for abnormal autonomic control of heart rate, each of them related to cardiovascular risk, and many of them particular to the condition of schizophrenia specifically because they seem to be independent of the effects of antipsychotic medication.

The autonomic basis for these cardiovascular effects may be related to the extreme liability of both the sympathetic and parasympathetic divisions of the autonomic nervous system in untreated schizophrenia. It has been found that treatment with antipsychotic drugs actually has the effect of normalizing these swift autonomic swings. Such major autonomic dysregulation in untreated individuals could be inextricably tied to the development of the metabolic syndrome for several reasons including the following three: insulin is known to stimulate sympathetic activity, habitually elevated

Table 165.6   Therapeutic intervention for the metabolic syndrome

Obesity	Behavior modification, caloric restriction, regular exercise
Atherogenic diet	Reduce trans fats, saturated fats, dietary cholesterol and total fat
Cigarette smoking	Complete smoking cessation
Low HDL	Advise adding fibrate or nicotinic acid to diet
Hypertension	Lifestyle therapy, advise antihypertensive drugs
High LDL	Advise LDL cholesterol lowering drugs
Elevated glucose	Lifestyle therapy, advise hypoglycemic agents
Physical inactivity	Sixty minutes of moderate-intensity exercise daily
Prothrombotic state	Advise low-dose aspirin therapy

A very brief summary of clinical recommendations for individual facets of the metabolic syndrome

levels of sympathetic activity induce insulin resistance in skeletal muscle, increased sympathetic tone is associated with obesity and visceral fat deposition. The autonomic dysregulation may also lead to risk factors for the metabolic syndrome via a separate route. Chronic arousal of the sympathetic branch of the autonomic nervous system causes upregulation in the hypothalamic-pituitary-adrenal axis which in turn increases levels of circulating cortisol. Chronically elevated cortisol levels, a major finding in schizophrenia, influence and accelerate, at multiple etiologic stages, insulin resistance, abdominal obesity and dyslipidemia. An article by Rosmond and Bjorntorp (2000) provides compelling support for the wealth of evidence tying autonomic and hypothalamic-pituitary-adrenal axis dysregulation to risk factors for the metabolic syndrome.

Physician efficacy in moderating lifestyle risk factors for cardiovascular disease such as physical activity, diet and smoking can be very low even in healthy populations. Due to their psychological symptoms such as high levels of emotion and low capacity for inhibition, influencing lifestyle factors is probably more difficult in populations of patients with psychiatric histories, especially ones with schizophrenia. This makes it even more important to treat the other risk factors: hyperlipidemia, obesity, and glucose intolerance. In other words, because patients with schizophrenia can be relatively resistant to lifestyle therapy, the medications and the role of the prescribing physician are of upmost importance. There are a daunting number of antihypertensive, hypoglycemic, and cholesterol lowering drugs to keep track of, each with multiple contraindications and implications for medication evaluation. Table 165.6 summarizes some of the major therapeutic interventions for individual features of the metabolic syndrome, including behavioral goals and medications. These are forms of intervention that any medical professional treating schizophrenia should be aware of.

165.6   Applications to Other Areas of Health and Disease

It is clear that patients with schizophrenia are susceptible to a variety of medical illnesses and that these are responsible for a large proportion of the excess mortality observed. A large proportion of these disturbances map on neatly to the various features of the metabolic syndrome. It is not obvious whether the metabolic disorders are an integral part of schizophrenia or whether both are caused by a third, unidentified mechanism. The close association probably has at least a small genetic foundation and is further exacerbated by unhealthy lifestyle choices and the commonly prescribed antipsychotics. The existence of serious metabolic disease in schizophrenia has major implications for public health. It is very important that mental health professionals are made cognizant of the metabolic issues in patients with schizophrenia and instructed in how to address them proactively. Serious efforts should

be made to instruct and educate psychologists and psychiatrists to investigate, recognize, and actively monitor metabolic conditions in their patients with schizophrenia as well as readily refer these patients to primary care physicians. It is also important to increase awareness among psychiatrists of the fact that these conditions can be iatrogenically exacerbated during antipsychotic therapy.

A great deal of evidence suggests that the existence of the metabolic syndrome in schizophrenia, as in other populations, is contingent upon a high fat diet and living in a Westernized culture (Thakore et al. 2002). The metabolic syndrome is reaching pandemic proportions worldwide and this is thought to be closely related to the absence of physical exercise and abundant and cheap supply of calorie dense foods. Another chapter in this book, "Nutrition, Behavior and the Developmental Origins of the Metabolic Syndrome," discusses how immoderate eating habits and reductions in physical activity have the capacity to greatly exacerbate metabolic disturbances in humans from Westernized cultures. Now that we no longer forage throughout the day for lean meats, fruit and vegetables we are susceptible to obesity and metabolic disease, just like laboratory animals that are caged and fed ad libitum. Many of the topics highlighted by that chapter, including the Westernization of diet, the genetic associations between different metabolic abnormalities, the discussion of "thrifty genotypes" and the influences of epigenetic programming may also be relevant to the present discussion.

There are several well refined animal models of schizophrenia. Most of these induce schizophrenic symptoms in rats or mice by using the same cues thought largely responsible for inducing schizophrenia in humans stress and hypercortisolemia. Rats that are stressed, either prenatally or postnatally, exhibit many of the fundamental symptoms of schizophrenia including impulsivity, habituation deficits, sensory gating deficiencies and reduced hippocampal size. There is truly a paucity of research on the metabolic abnormalities in these animals and the present literature on schizophrenia and the metabolic syndrome has all but ignored this model. Researching the metabolic features of the animal models of schizophrenia should be far less expensive and easier to control and manipulate than many of the current studies looking at these features in humans. Of course, further studies with people are urgently needed as well though, and an emphasis should be placed on drug-naïve, longitudinal designs.

Comprehensive reviews in clinical endocrinology have established that, as our population ages, the metabolic syndrome will be an increasingly important concern. The incidence of schizophrenia does not increase with advancing age yet very little is known about the incidence of the metabolic syndrome in aging individuals with a past diagnosis of schizophrenia. As this chapter has illustrated, we know a good deal but there are still many unknowns. The formulation of treatment standards for the metabolic syndrome remains a highly contentious topic even in individuals without schizophrenia. Increasing the efficacy of lifestyle therapy, decreasing the metabolic disturbances associated with antipsychotics and disentangling people from their genetic propensities for schizophrenia and the metabolic syndrome all remain formidable and complicated problems for the future. It is clear; however, that the careful monitoring of metabolic health in patients with schizophrenia, especially those on atypical antipsychotics, could help markedly in early detection and prevention of the metabolic syndrome.

Summary Points

- Schizophrenia is a life-shortening illness with excess mortality attributable to increased frequency of specific natural and unnatural causes.
- Schizophrenia carries increased risk of a variety of metabolic disorders.
- High visceral fat, type 2 diabetes mellitus and cardiovascular disorders occur with increased frequency in schizophrenia.

- Unhealthy lifestyle, poor diet and lack of exercise probably contribute to the metabolic syndrome and metabolic abnormalities in schizophrenia.
- An inherent susceptibility to stress and elevated levels of cortisol probably exacerbate both psychiatric and metabolic disturbances.
- Atypical, or second generation, antipsychotics have been largely implicated in the onset of obesity, diabetes mellitus and the exaggeration of metabolic complications.
- New findings in this literature have important implications for public health and the treatment of schizophrenia.

Definitions

Antipsychotics: Medications used to treat schizophrenia or other psychotic conditions often manipulating dopamine function to decrease hallucinations, delusions, and other symptoms. Also referred to as neuroleptic drugs.

Dyslipidimia: A disruption of the levels of lipids in the blood. In western societies, most dyslipidemias are hyperlipidemias; an elevation of lipids often due to diet, lifestyle or prolonged elevations of insulin.

Glucose tolerance: The ability of the body to adapt to a relatively large dose of glucose. This ability is usually diminished in diabetics and is used to diagnose diabetes mellitus. A fasting subject ingests around 75 g of glucose and blood glucose is measured at intervals. In diabetics the concentration is higher and takes longer to return to baseline value.

Hypercortisolemia: A state marked by elevated levels of circulating cortisol, an essential glucocorticoid steroid hormone, the major hormone secreted by the adrenal glands.

Hyperglycemia: A complex metabolic condition characterized by high levels of blood glucose in the circulation, usually a result of insufficient or ineffective insulin production in either type 1 or type 2 diabetes mellitus.

Hyperphagia: An abnormal appetite or increased consumption of food, often associated with abnormalities in the hypothalamus.

Hypertension: High blood pressure or force of blood on the vessel walls of the arteries.

Hypothalamic-Pituitary-Adrenal axis: This is a neuroendocrine system in the body responsible for regulating stress physiology. Brain areas that sense threat, signal the hypothalamus which communicates hormonally to the pituitary which in turn signals the adrenal glands to secrete adrenaline and cortisol.

Insulin resistance: A condition in which cells, especially those comprising muscle, fat and liver tissue, fail to be properly receptive to the messages of the hormone insulin. Because insulin promotes the extraction of glucose from the blood, allowing cells to meet their metabolic needs, insulin resistance is associated with elevated levels of blood glucose.

Metabolic syndrome: A combination of metabolic disorders that commonly present together and increase the risk of developing diabetes and cardiovascular disease.

Schizophrenia: A group of psychotic disorders characterized by impairments in sensory gating, emotional inhibition and the organization of complex behaviors.

Visceral fat: The accumulation of fat around the internal organs of the torso. It is associated with the "apple shape," belly fat, central obesity and a high waist to hip ratio.

References

Allebeck P. Schizophrenia Bull. 1989;15:81–9.

Allison DB, Fontaine KR, Heo M. J Clin Psychiat. 1999;60:215–20.

American Diabetes Association, American Psychiatric Association, American Association of Clinical Endocrinologists, North American Association for the Study of Obesity. J Clin Psychiat. 2004;65:267–72.

Basu R, Brar JS, Chengappa KNR, John V, Parepally H, Gershon S, Schlicht P, Kupfer D. Bipolar Disord. 2004;6:314–8.

Bhugra D. PLoS Med. 2006;2:372–3.

Brown S. Brit J Psychiatry. 1997;171:502–508

Brown S, Birtwistle J, Roe L, Thompson C. Psychol Med. 1999;29:697–701.

Cohn T, Prud'homme D, Steiner D, Kameh H, Remington G. Can J Psychiat. 2004;49:753–60.

Davidson M. J Clin Psychiat. 2002;63:5–11.

De Hert M, van Eyck D, De Nayer A. Int Clin Psychopharmacol. 2006;21:S11–5.

De Leon J, Diaz FJ. Schizophr Res. 2007;96:185–97.

Dixon L, Weiden P, Delahanty J, Goldberg R, Postrado L, Lucksted A, Lehman A. Schizophrenia Bull. 2000; 26:903–12.

Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. JAMA. 2001;285:2486–97.

Ford ES, Giles WH. Diabetes Care. 2003;26:575–81.

Felker B, Yazel JJ, Short D. Psychiat Serv. 1996;47:1356–63.

Gothelf D, Falk B, Singer P. Am J Psychiat. 2002;159:1055–7.

Hannerz H, Borgå P, Borritz M. Public Health. 2001;115:32837.

Hansen BC. Ann NY Acad Sci. 1999;829:1–24.

Haupt DW. Eur Neuropsychopharmacol. 2006;16:S149–55.

Heiskanen T, Niskanen L, Lyytikainen R, Saarinen PI, Hintikka J. J Clin Psychiat. 2003;64:575–9.

Hert MD, Schreurs V, Sweers K, Van Eyck D, Hanssens L, Sinko S, Wampers M, Scheen A, Peuskens J, van Winkel R. Schizophrenia Res. 2008;101:295–303.

Homel P, Casey D, Allison DB. Schizophrenia Res. 2002;55:277–84.

Jeste DV, Gladsjo JA, Lindamer LA, Lacro JP. Schizophrenia Bull. 1996;22:412–30.

Kendrick T. Br J Psychiat. 1996;169:733–9.

Marder SR, Essock SM, Miller AL, Buchanan RW, Casey DE et al. Am J Psychiat. 2004;161:1334–49.

Masterson E, O'Shea B. Brit J Psychiat. 1984;43:643–9.

McEvoy JP, Meyer JM, Goff DC, Nasrallah HA, Davis SM, Sullivan L, Meltzer HY, Hsiao J, Stroup TS, Lieberman JA. Schizophrenia Res. 2005;80:19–32.

Meyer JM. J Clin Psychiat. 2001;62:27–34.

Meyer JM, Nasrallah HA. Medical illness and schizophrenia.Washington, DC: American Psychiatric Press; 2003.

Mortensen PB, Juel K. Brit J Psychiat. 1993;163:183–9.

Mukherjee S, Schnur DB, Reddy R. Lancet. 1989;1:495.

Mukherjee S, Decina P, Bocola V, Saraceni F, Scapicchio PL. Compr Psychiat. 1996;37:68–73.

Newcomer JW, Haupt DW. Can J Psychiat. 2006;51:480–91.

Newman SC, Bland RC. Can J Psychait. 1991;36:239–45.

Osby U, Correia N, Brandt L, Ekbom A, Sparen P. Schizophrenia Res. 2000;45:21–8.

Raphael RP. Arch Neurol Psychiat. 1921;5:687–709.

Reser JE. Med Hypotheses. 2007;69:383–94.

Ristow M. J Mol Med. 2004;82:510–29.

Rosmond R, Bjorntorp P. J Intern Med. 2000;247:188–97.

Ryan MC, Thakore JH. Life Sci. 2002;71:239–57.

Saddichha S, Manjunatha N, Ameen S, Akhtar S. Schizophrenia Res. 2008;101:266–72.

Shirzadi AA, Ghaemi SN. Harv Rev Psychiat. 2006;14:152–64.

Spelman LM, Walsh PI, Sharifi N, Collins P, Thakore JH. Diabet Med. 2007;24:481–5.

Thakore JH, Mann JN, Vlahos I, Martin A, Reznek R. J Int Assoc Study Obesity. 2002;26:137–41.

Walker EF, Diforio D. Psychol Rev. 1997;104:667–85.

Walker EF, Neumann C, Baum KM, Davis D, Diforio D, Bergman A. Dev Psychopathol. 1996;8:647–55.

Weiser M, Knobler H, Lubin G, Nahon D, Kravitz E, Caspi A, Noy S, Knobler HY, Davidson M. J Clin Psychiat. 2004;65:1546–9.

Wirshing DA, Meyer JM. In: Meyer JM, Nasrallah H, editors. Medical illness and schizophrenia.Washington, DC: American Psychiatric Press; 2003. pp. 39–58.

Zhang ZJ, Yao ZJ, Liu W, Fang Q, Reynolds GP. Brit J Psychiat. 2004;18:58–62.

Zimmet P, Boyko EJ, Collier GR, De Courten M. Ann NY Acad Sci. 1999;892:25–44.

Chapter 166
Nutrition, Behavior, and the Developmental Origins of the Metabolic Syndrome

Jared Edward Reser

Abbreviations

LDL   Low density lipoprotein
FOAD   Fetal origins of adult disease

166.1 Introduction

A handful of unifying perspectives have guided theory and even research related to the metabolic syndrome and its associated abnormalities. A broad look at the most popular of these adds another dimension to the clinical knowledgebase that we have and also helps us to better characterize findings and unknowns. This chapter will take such an approach and attempt to highlight some of the outstanding perspectives in an attempt to reconcile the metabolic syndrome with the goals and frame of reference of this book. First, of course, it is important to have a handle on what the metabolic syndrome represents nosologically and why it can be such a difficult construct to get a firm grip on.

The metabolic syndrome is a combination of medical disorders that present in a clustered fashion and result in increased risk for cardiovascular disease and diabetes. Also known as syndrome x, and the insulin resistance syndrome, this multifactorial disease was identified over 80 years ago but has shown a striking increase, worldwide, in the last 2 decades. The rise in international prevalence and clinical interest is closely associated with the global epidemic of obesity and diabetes; however, the metabolic syndrome includes other comorbid disorders, including cardiovascular disease. Symptoms and features include: glucose intolerance (type 2 diabetes, impaired glucose tolerance or impaired fasting glycemia); high blood pressure (hypertension); central obesity (visceral adiposity); increased LDL cholesterol; and dyslipidemia (elevated triglycerides) (Table 166.1). These conditions have a tendency to co-occur in individuals more often than they present alone. For this reason, they have been grouped into the encompassing diagnosis of the metabolic syndrome which is known to present in a variety of different ways in different people. Partly because the constellation of metabolic abnormalities can be slightly different for virtually every person, there is still some contention over which features are central etiologically.

J.E. Reser (✉)
University of Southern California, Psychology Department, SGM 501, 3620 South McClintock Ave.
Los Angeles, CA 90089-1061, USA
e-mail: jared@jaredreser.com; reser@usc.edu

Table 166.1 The key features of the metabolic syndrome

Obesity	Increased total body fat, abdominal or central fat distribution, increased visceral fat
Insulin resistance	Hyperinsulinemia
Dyslipidemia	Hypertriglyceridemia, decreased HDL cholesterol, increased LDL cholesterol
Impaired glucose tolerance	Type 2 diabetes mellitus
Hypertension	High or deranged blood pressure

The defining disorders of the metabolic syndrome and their components

Table 166.2 Diagnosis of the metabolic syndrome

Increased waist circumference	>102 cm in men, >88 cm in women
Elevated triglycerides	>150 mg/dL or 1.7 mmol/L
Decreased HDL cholesterol	<40 mg/dL in men, <50 mg/dL in women
Blood pressure	>130/85 mgHg or active treatment for hypertension
Fasting glucose	>110 mg/dL or active treatment for hyperglycemia

The National Cholesterol Program requires that at least three of the above five criteria be met for a diagnosis of the metabolic syndrome

In 2005 the Adult Treatment Panel III of the National Cholesterol Education Program (2001) defined diagnosis as three or more of five states listed in Table 166.2. The International Diabetes Federation, the European Group for the Study of Insulin Resistance, and the World Health Organization, and others have each identified unique sets of diagnostic criteria. This disparity in diagnostic definition has created some concern and confusion, although all three systems are relatively similar.

Making comparisons of prevalence for different populations is difficult because different published studies utilize different diagnostic criteria, although a standardized, international definition should abet these difficulties. Sex and ethnic origin predict large amounts of variation in prevalence. The prevalence is also highly age-dependent. Prevalence in the USA (in the national health and nutrition examination survey) increased from 7% in participants between the ages of 20 and 29 to 44% in participants between 60 and 69 (Ford et al. 2002). The majority of diagnoses are given to older, obese individuals who have a degree of insulin resistance. Until recently, the metabolic syndrome was regarded as a disease of old age, yet now, with increasing rates of obesity and diabetes in young people, it is commonly diagnosed in children. As in adults, susceptibility of children to the metabolic syndrome increases with worsening obesity.

The etiology and pathophysiology of the metabolic syndrome are extremely complex and have only partially been elucidated. Currently, it is debated whether obesity or insulin resistance is the cause of the metabolic syndrome, or if it can be attributed to a more obscure metabolic derangement (Table 166.3). The disorder, like its features, is highly heritable, and the large genetic component helps health practitioners to identify at-risk individuals if their family medical history is known. The main treatments include calorie restriction and dieting, physical exercise, and occasional drug prescription. The individual diseases that make up the metabolic syndrome are usually treated individually; diuretics and ACE inhibitors for hypertension, cholesterol drugs for elevated LDL cholesterol, and triglyceride levels and various drugs for insulin resistance. More information about treatment and clinical recommendations is given in Table 166.4.

The prevalence of the metabolic syndrome has increased severalfold in the last few decades. In these same decades, fast food and processed foods have become internationally ubiquitous, and physical exercise has been engineered out of our daily routines. It is clear that the metabolic syndrome is a product of the modern environment which has done much to increase sedentary behavior and the overconsumption of unhealthy foods. It is thought that humans were not "designed" to live this type of lifestyle, which is to say that we were not naturally selected to have genes that prepare us for it. Our hunting and gathering ancestors were probably only rarely afflicted by such unhealthy lifestyles or their metabolic consequences.

Table 166.3   Behavior and the metabolic syndrome

Pituitary adrenal abnormalities: hypercortisolemia, stress behavior
Reduced physical activity, sedentariness
Reduced ability to cope with stress, elevated stress hormone levels
Substance abuse: smoking, alcohol, others
Increased food intake: hyperphagia, increased dietary fat content
Sex hormone abnormalities

A brief list of some of the behavioral abnormalities closely associated with the metabolic syndrome

Table 166.4   Therapeutic intervention for the metabolic syndrome

Obesity	Behavior modification, caloric restriction, regular exercise
Atherogenic diet	Reduce trans fats, saturated fats, dietary cholesterol, and total fat
Cigarette smoking	Complete smoking cessation
HDL	Advise adding fibrate or nicotinic acid to diet
Hypertension	Lifestyle therapy, advice antihypertensive drugs
LDL	Advice LDL cholesterol-lowering drugs
Elevated glucose	Lifestyle therapy, advice hypoglycemic agents
Physical inactivity	60 min of moderate-intensity exercise daily
Prothrombotic state	Advice low dose aspirin therapy

A very brief summary of clinical recommendations for the individual disorders of the metabolic syndrome

166.2   The Thrifty Genotype

The same genes that cause humans to be susceptible to diabetes, heart disease, and obesity in modern times may have protected us from starvation and famine during ancestral times. This hypothesis was first put forward in 1962 by James Neel in an article entitled: "Diabetes mellitus: a 'thrifty' genotype rendered detrimental by 'progress.'" Neel coined the phrase "thrifty genotype" referring to the probably very large complement of genes that would have helped our ancestors' metabolisms to be economical and prudent with the foods that they hunted and gathered (Neel 1982). Not only did their meals contain a smaller proportion of sugar and fat, but our ancestors also had to engage in prolonged physical activities to obtain them. Interestingly, adopting a "paleolithic diet" consisting primarily of fruit, vegetables, and meat is an increasingly popular dietary regimen. Neel pointed out that not only are our bodies engineered to expect a different diet, but they are also probably expecting extreme food shortages, something modern people only very rarely encounter. His thesis, refined in subsequent articles, was that adaptations that allowed organisms to minimize metabolism and providently lay down fat reserves would produce a survival advantage during periods of nutritional scarcity (Neel 1999). A good deal of research has indicated that the environment of human adaptedness, and wild environments in general, are marked by periods of "boom and bust" where periods of plenty are interspersed among periods of food shortage or famine. This concept was initially generated to allow an evolutionary explanation for the existence of diabetes, but has since been generalized toward the metabolic syndrome and become widely adopted. The mainstay of this conceptual standpoint is that our inherited propensity for energy conservation probably only translates into obesity and metabolic disease in modern times and may have protected individuals, particularly those with the "thriftiest genotypes" from starvation in ancestral times (Table 166.5).

Thrifty benefits have been attributed to the individual components of the metabolic syndrome. A smaller, weaker, yet less energy-expensive heart may confer the ability to minimize energy expenditure in the heart in order to mitigate the risk of starvation (Barker 1998; Barker et al. 2002). In modern times people that express this once adaptive phenotype no longer enjoy the benefits because the excess of fat and cholesterol consumed by these individuals puts a serious strain on their "thrifty" heart, making

Table 166.5 Diet and behavior, then and now

Prehistoric foraging individual	Modern day individual
Caloric uncertainty	Caloric stability
Moderate to high physical activity	Low physical activity
Dietary balance	Dietary excess
Insulin sensitivity in muscle cells	Insulin resistance in muscle cells
Metabolic efficiency	Metabolic dysregulation
Reproductive advantage	Presumed reproductive disadvantage

A comparison of health and ecological features between a typical forager and modern individual on a Westernized diet with an inactive lifestyle

them susceptible to heart or cardiovascular disease (Ridley 2003). A similar tradeoff is presumed to exist for insulin signaling. The beta cells of the pancreas release insulin in response to carbohydrate intake facilitating the metabolism of carbohydrates. An exaggerated pancreatic response (seen in the metabolic syndrome) results in hyperinsulinemia (high circulating levels of insulin) that leads to increased lipogenic activity and ultimately the storage of fats in adipose tissue. Such metabolic tendencies for increased adiposity may have helped individuals in the past to be frugal with fats and to store more fat, yet today they lead to obesity. Type 2 diabetes mellitus has been characterized as a disorder that is a prototypic example of this kind of evolutionary tradeoff. It has been thought for decades now that, on a cellular and organ system level, the disorder represents a thrifty condition – insulin resistance – that would have only rarely manifested as disease in the ancestral environment, because at that time individuals had no access to refined sugar or processed foods. The current literature holds that insulin resistance, brought about by genes for type 2 diabetes, represents a finely tuned physiological state and that its cellular and molecular pathways have been refined by natural selection over millions of years to help organisms conserve blood sugar. Insulin causes cells to rapidly take up blood sugars and increase the rate of their cellular processes thereby increasing total metabolic output. The defective insulin receptors, seen in cells of people with insulin resistance, might have helped to conserve these blood sugars in the past, but now that our diets feature dramatically higher levels of refined sugar; insulin resistance results in blood sugar levels that are vastly too high. Elevated blood sugar, hyperglycemia, can cause a variety of systemic and organ problems through the glycation and damaging of important biomolecules, seen frequently in diabetes. In all of these examples, biological mechanisms malfunction badly once they are forced to face our unhealthy modern diets (Table 166.6). It is now thought that many individual physiological pathways involved in the metabolic syndrome may represent ancient methods of energy conservancy (Eriksson et al. 2001).

Population genomics has identified some very interesting trends in geographic susceptibility to the metabolic syndrome, which provide corroborating evidence for the thrifty genotype theory. This widely accepted interpretation emphasizes that populations of preagricultural, foraging individuals who live in areas where, until recently, food has been relatively unpredictable have much higher prevalence of thrifty genes (Neel 1982). The traits that these genes code for probably helped these individuals survive during prolonged periods of scarcity or were maintained because historically these individuals were not exposed to high calorie diets (Valencia et al. 1999). Today, the incidence of the metabolic disease remains highest among populations where an economy of foraging existed until recently. Unfortunately, people in these areas such as Native Americans, Aboriginal Australians, and Pacific Islanders have an unusually high prevalence of the metabolic syndrome now that they have been exposed to the modern "diet of affluence." This genetic variation between human populations is akin to other known forms of anthropological adaptation to environment. Unknown to many, there are several examples of selective pressures acting on humans even in the last 50,000 years. Lactase persistence is one example, where populations in Europe and elsewhere

Table 166.6 Medical risks associated with a westernized diet

Metabolic state	Implications for foragers	Implications for moderns
Adiposity	Healthy fat retention	Excessive fat retention
Insulin resistance	Healthy levels of blood sugar	Excessive levels of blood sugar
Beta cell Responsiveness	Metabolism of carbohydrates	Hyperinsulinemia
Thrifty heart	Healthy, efficient heart	Heart burdened by high body fat
Glucose intolerance	Normoglycemia	Hyperglycemia

A comparison between a typical forager and an obese modern individual with respect to the end result of individual metabolic states

retained the ability to digest lactose into adulthood because of the domestication of cattle and the importance of the ability to derive calories from milk.

The Pima Indians in Arizona and the Nauru people from the Micronesian South Pacific Islands appear to have particularly thrifty genotypes (Dowse et al. 1991). Both populations are thought to have endured repeated episodes of food shortage and starvation. They live and have long lived in relatively isolated, unpredictable, and in the case of the Pima, desolate areas. Fascinatingly, the Nauru people have traveled among remote islands in the Pacific during many, several-week-long canoe voyages. Historical accounts attest that many individuals in these canoes died of starvation during the trips, perhaps creating a Nauru founder population of highly starvation adapted people. When exposed to a Western lifestyle in the twentieth century, obesity and type 2 diabetes increased drastically in the Pima and Nauru. For some time, these two groups had among the highest age and sex-adjusted incidence rates of type 2 diabetes, around 25 per 1,000 people per year for the Pima (Schulz et al. 2006).

A variety of animal studies echo these genographic studies in humans. Diabetes commonly afflicts zoo animals, and an epidemic has been described of captive populations of primates, whose lifestyle approximates the sedentary, high-calorie lifestyle of First World urban humans (Diamond 2003). Ecological support for the thrifty genotype hypothesis comes from studies with leptin-deficient (ob/ob) and leptin receptor-deficient (db/db) mice (Coleman 1979). Heterozygous animals, which have a significant tendency toward obesity and diabetes when fed ad libitum, survived longer during fasting than the wild-type animals, even when matched for body weight. This trend has been observed outside of the laboratory too. Certain animals that are well adapted to frequent food shortages, such as desert mammals, show increased susceptibility to the features of the metabolic syndrome when they are able to feed ad libitum. The Israeli sand rat is a prime example. It is highly predisposed to developing metabolic disease including insulin resistance, obesity, and diabetes when put on the western lab rat diet. The symptoms reverse quickly when its food is restricted or it is placed back in its natural environment (Haines et al. 1965). Fascinatingly, it is known that the facets of the metabolic syndrome in humans, including diabetes, can be reversed by diet, exercise, and weight loss. This decline and even disappearance of diabetes symptoms happened to thousands of Parisians during the 1870–1871 famine associated with the siege of Paris (Zimmet 1997).

Even though the thrifty gene hypothesis has been challenged in its particulars, the aspects discussed here have been well accepted in the medical and ethological literatures. The thrifty genotype model is not meant to account for all instances of metabolic disease, but does seem to offer a high degree of explanatory power for the metabolic pandemic of modern times. Far from being a liability, a tendency to be fine tuned for having a lower metabolism would have been an asset to survival in the Plio-Pleistocene because it would have helped individuals to conserve calories. That individual species, or some individuals within a species, have this tendency has important biomedical ramifications, and further research and experimentation in this area should help to clarify the underpinnings and tradeoffs involved in energy homeostasis. Several successful animal models, like the ones mentioned,

are thought to have helped to elucidate some of the key genes and pathways involved in impaired energy balance regulation. Interestingly, the genes that one is born with are not the only predisposing factors, as the next section will illustrate; the environment can play a large role as well.

166.3 The Developmental Origins of the Metabolic Syndrome

It is now widely accepted that the risk for a number of metabolic diseases may be affected by circumstances before birth. Professor David Barker and colleagues have produced a large amount of data, since 1994, showing that low birth weight increases susceptibility to noninsulin-dependent diabetes mellitus, hypertension, and coronary heart disease (Barker 1998) later in life. By analyzing epidemiological data for cohorts whose birth records are available, and following these individuals into adulthood, Barker, Hales and others have shown that birthweight, length, body proportions, and placental weight are highly associated with later metabolic disease incidence (Philips 1998) or risk factors for those diseases (hypertension, glucose intolerance, hyperlipidemia) (Barker, 1994, 1998). In addition to having increased adipose tissue mass in adulthood, low birth weight individuals have a tendency to store adipose tissue centrally and have a lower lean mass. Reduced muscle has been reported to contribute heavily to a lowered basal metabolic rate and is expected to reduce capacity for exercise (Kensara et al. 2005). These associations between birth size and disease are often apparent from childhood, hold in a large number of different populations, and have given rise to the term "fetal origins of adult disease" (FOAD) (Law and Shiell 1996; McKeigue 1997).

The biological changes responsible for metabolic alterations are attributed to epigenetic programming, also called phenotypic plasticity. Epigenetic programming occurs when an environmental cue creates a change in gene expression. Even small changes in gene expression and protein regulation, early on, can cause large phenotypic changes with time. Developmental geneticists closely adhere to the idea that a single genotype can give rise to, or canalize, a variety of different phenotypes depending on the programming effects of the early environment. Intrauterine programming is a well-established biological phenomenon, and there are many well-known examples, affecting organisms from plants to humans. In this case, an environmental stimulus, experienced during gestation, is thought to lead to impaired fetal growth and diminution in size at birth, although "catch-up" growth in childhood is the norm. This stimulus or cue also leads to altered homeostatic mechanisms such as the regulation of blood pressure or insulin sensitivity, which in turn results in susceptibility to the metabolic syndrome later in life. Exactly what this cue or stimulus is, has been open to debate. The majority of models in this literature point to undernutrition (Langley 1997) but some emphasize the contribution of other forces, such as placental dysfunction, or excessive fetal exposure to glucocorticoids.

Evidence for undernutrition as the underlying, environmental stimulus in this association comes from three sources: (1) the aforementioned epidemiological associations; (2) animal models; and (3) historical pseudo-experiments. Birth weight is readily altered in experimental animals by manipulating maternal nutrition during fetal development. A reliable way to decrease a rat's size at birth is by reducing the proportion of protein in the diet of their pregnant mothers. Like humans and other mammals, these rats show catch-up growth in youth, but soon thereafter exhibit tendencies toward obesity, elevated blood pressure (Langley and Jackson 1994), and impairments in glucose tolerance (Desai et al. 1995). Glucose intolerance seen in low-protein exposed offspring is contributed to by a reduction in pancreatic beta cell mass, reduced insulin secretion, and peripheral tissue insulin resistance. These symptoms are worsened by the presence of obesity in an additive manner (Petry et al. 1997) and, as in humans, worsened symptoms lead to reduced longevity in rats and mice (Ozanne and Hales 2004).

Restriction of total calories during pregnancy, without respect to protein composition, has been shown to result in rat offspring that are hyperphagic, hyperinsulinemic, obese, hypertensive, and significantly less physically active (Harding 2001). Again, analogous to what we see in our own species, these symptoms are accentuated by a highly palatable or high-fat diet later in life. High levels of catch-up growth after early deprivation have been shown to be related to skeletal muscle insulin resistance, reduced thermogenesis, and increased insulin sensitivity in adipose tissue (Cettour-Rose et al. 2005). Another parallel in this domain that is directly relevant to human health is the finding that diets of saturated fats lead to detrimental effects on glucose homeostasis in fetally deprived rats whereas diets containing polyunsaturated fatty acids had beneficial effects (Siemelink et al. 2002). Similar studies designed to reduce maternal nutrition during pregnancy have led to comparable results in rats, mice, guinea pigs, and sheep.

Peripheral signals that indicate the size of adipose stores such as circulating factors and the hormone leptin are received and integrated by the central nervous system, primarily at the hypothalamus and brainstem. If adipose stores are sufficient or large, changes in these signaling systems, such as the increase in leptin hormone, induce the nervous system to inhibit feeding and promote energy expenditure. Offspring of undernutrition pregnancies have been shown to demonstrate leptin insensitivity, high body weight, and increased food intake in adult life (Harding 2001). Whether early food restriction acts at the level of the hypothalamus to predispose to this "thrifty behavior" is currently not clear. There is very little doubt though that maternal undernutrition in animals leads to diminished size, altered behavior, and permanent alterations in metabolism, and that this is consistent with disease susceptibility observed in human studies.

The second source of evidence for the efficacy of maternal undernutrition in the programming of the metabolic syndrome comes from historical pseudo-experiments. A popular example, the Dutch Hunger Winter, was a season of extreme food shortage in the Netherlands between 1944 and 1945. Ravelli and colleagues compared data on 300,000 19-year-old males that were born before, during, or after this famine (Ravelli et al. 1976). The study revealed that the nutritional limitations imposed by severe nutritional deprivation lead to offspring with reduced birth size, and increased risk of glucose intolerance, and obesity in adult life. The cohorts that were most affected were the offspring of the mothers whose first two trimesters of pregnancy coincided with the famine. Similar historical pseudo-experiments, with well documented medical data that are consistent with the findings of the Dutch Hunger Winter, have occurred in Asia and elsewhere.

Another body of literature has taken this programming concept a step further and attributed adaptive or evolutionary value to sensitivity to programming (Barker et al. 2002). Evolutionary significance has been attributed to the programming that occurs due to nutritional deprivation, and even to altogether different programming models, such as early life stress. Neonatal rats, when exposed to various stressors, show permanent changes in hypothalamic structure and systemic responses to stress (Barbazanges et al. 1996; Francis et al. 1996) and these responses have been characterized as representing predictive actions to better prepare the animal for predation risk and environmental adversity (Zhang et al. 2004). In a similar manner, the thrifty phenotype hypothesis contends that the permanent changes in metabolic homeostasis represent evolutionarily adaptive programming that decreases susceptibility to starvation.

166.4 The Thrifty Phenotype

It is clear that Hales and Barker, like Neel before them, appreciated the evolutionary implications of their hypotheses. They explicitly proposed that this metabolic response to a nutritionally poor early environment was a predictive, adaptive response that would maximize chances of surviving postnatally in conditions of ongoing deprivation. Also, like Neel, they appreciated the fact that this prediction represents a

tradeoff and is subject to being inaccurate. If, unexpectedly, the postnatal environment provides plentiful nutrition these individuals will be at increased risk of metabolic disease.

The phenotypic characteristics of many organisms ranging from plants to insects to mammals are known to show plastic responses to environmental events, many of which are thought to represent adaptive, defensive responses, or reproductive strategies (Via and Lande 1985). This phenotypic plasticity through differential gene expression is often cued by maternal condition and is known to create profound alterations in the phenotypes of developing organisms. The thrifty phenotype hypothesis (Hales and Barker 1992, 2003 2001) has been used widely by researchers from different disciplines to interpret studies showing that maternal malnutrition is a strong risk factor for the metabolic syndrome (Wells). According to this hypothesis, phenotypes that are programmed by prenatal malnutrition to express low metabolic rates enjoy a survival advantage under deprived circumstances; however, if such a thrifty fetus is born into an environment marked by nutritional abundance, it will face increased risk of negative health consequences (Bateson et al. 2004). Conversely, robust phenotypes that express larger size and rapid metabolism are thought to increase reproductive success when resources are more plentiful, but are more susceptible to starvation if exposed to nutritional shortage. Specialists now believe that the association between maternal malnourishment and the offspring's proclivity for a low metabolism is adaptive specifically because the mother's deprived condition during pregnancy is often predictive of the environment into which the fetus will be born. It has been established that many animals share similar metabolic responses to environmental cues and this requires us to concede that our own tendency to react plastically may derive from phylogenetically earlier forms because of a shared evolutionary history (Crespi and Denver 2005).

Epigenetic processes are the biological basis for programming effects. Chemicals such as acetyl or methyl groups attach themselves to promoter regions of genes in specific tissues. Fine and intricate control of gene expression has been taken to suggest that the programming effects have been maintained through evolution because of their adaptive advantage rather than representing maladaptive effects of developmental disruption such as teratogenesis (Hanson and Gluckman 2008). It has been shown that, in animals, these epigenetic effects, for instance DNA methylation, can be passed down to successive generations along with the altered phenotypic expressions. In fact, due to alterations in the epigenome that are maintained during the creation of gametes, the effects of early life undernutrition may be transmitted to subsequent generations without repetition of the immediate insult in the second generation (Drake and Walker 2004). Many researchers believe that there may be an adaptive advantage in long term intergenerational programming, and that information about a grandparent's environment will help a developing animal in its "environmental forecasting."

Many fully grown animals are well known to demonstrate consistent adaptive responses to starvation that help to minimize energy expenditure, even of the order of a few days. Starvation evokes several immediate physiological changes, the most dramatic of which include suppression of metabolic rate, increased adiposity, reduction of thyroid and growth hormone levels, a reduction in fertility (through the suppression of gonadal function), and an increased activation of the hypothalamic–pituitary–adrenal axis (Schwartz et al. 1995; Flier 1998). Unlike animals programmed prenatally for thrift though, these predictive metabolic measures reverse largely after the animal resumes its normal diet. It is also well accepted that seasonal cycles of metabolic alterations occur in hibernating mammals. Many animals that hibernate are insulin insensitive for months before they go into hibernation and exhibit increased adiposity. When they wake up in the spring they are lean and insulin sensitive once again (Scott and Grant 2006). These other examples of phenotypic plasticity are comparable to intrauterine programming in many ways and researchers could potentially learn much from contrasting these models.

The brains of experimental animals that were exposed to early nutritional deprivation seem to be buffered from growth restriction in moderate cases, but can show definite changes in severe ones.

Reductions in the number of cells in certain regions as well as in synapses and white matter evince that programming effects, that may involve thrift, take place in the brain as well. Recent studies using imaging techniques show that gray matter is reduced in humans subjected to intrauterine growth restriction, and that catch up growth may not occur (Tolsa et al. 2004). The present author has offered explanatory hypotheses for these and related observations elsewhere (Reser 2006). It is possible that a large number of different metabolic and organ systems may be affected by epigenetic programming involving predictive adaptive responses. Further, integrative research, incorporating the viewpoints from different levels of biological and medical analysis, should help to provide a clearer picture of what we refer to today as "thrift."

166.5 Applications to Other Areas of Health and Disease

The thrifty genotype hypothesis posits that certain human genes that are associated with increased risk for metabolic disease today were naturally selected in the past because they helped their bearers to be more "thrifty" with energy stores. According to this hypothesis, phenotypes that express low metabolic rates enjoy a survival advantage under deprived circumstances. However, they face increased risk of negative health consequences when sugars and fats are artificially abundant, as they are in many countries today. The thrifty phenotype hypothesis posits that all of us have windows of susceptibility to thrifty programming that enable us to create permanent readjustments in homeostatic systems in an obsolete attempt to aid survival.

Today, the costs of the metabolic syndrome are well documented and well understood, but the prehistoric, defensive manifestations are obscured, at least at first glance, because of discrepancies between the ancestral environment and the modern environment. Many traits that are known to have been defensive in the ancestral environment are now seen as maladaptive in the present (an "environmental mismatch") and the science of evolutionary medicine attempts to identify and characterize these traits. Researchers have identified many such "pathological" conditions such as anxiety, cystic fibrosis, diarrhea, fever, inflammation, pain, sneezing, sickle cell anemia, and vomiting and have helped to show that they actually represent evolved defenses that would have promoted survival and the likelihood of reproductive success (Williams and Nesse 1998).

The merits of the thrifty genotype and phenotype hypotheses include the implications that they generate for understanding past, current, and future trends in disease (Pollard). The historical and evolutionary forces that are apparent are still largely abstract when measured against our biomedical knowledge, and it is clear that during our journey of reconciling the two, they will continue to influence and provide predictions for each other. The notion that the human genome bears witness to past struggles for survival against starvation allows us a new context within which to view the responses of the human body. A person's physiological response to dieting will reflect our ancestors' adaptive responses to seasonal hunger, just as their response to abundant calories and fats will reflect our ancestors' beneficial responses to harvest seasons. Furthermore, the thrifty phenotype hypothesis informs us that early, prenatal effects and even effects that were inherited from grandparents can cause the same anachronistic responses.

The cause of fetal malnutrition in present day populations is different from what it used to be. In the ancestral past the majority of examples of fetal malnutrition and intrauterine growth restriction probably would have come from starvation. Today, especially in affluent countries, it primarily stems from circulatory problems that are secondary to uteroplacental dysfunction, a relatively rare but epidemiologically constant condition. These modern fetuses, restricted by uteroplacental dysfunction, misinterpret their situation and prepare for nutritional scarcity when they will, in fact, encounter the opposite scenario.

Anthony Philipps explains that these findings have important implications for obstetrics and prenatal nutrition. It is imperative that circulatory assessments be made earlier in pregnancy, that more reliable ways to ascertain placental villous blood flow are developed, and that more sophisticated fetal growth measures are devised and used widely.

The identification and mapping of both thrifty genes and epigenetic markers will help to evaluate these hypotheses, but more importantly, will help inform medical research. Many critical aspects remain to be explored: (1) Where are the alleles for thrifty genes? (2) At what points during development do these windows of susceptibility exist? (3) What are the signaling pathways through which an environmental cue is translated into a developmental response? (4) Which developmental responses persist beyond a single generation and how? (5) How long do we have to wait, and how many people have to die prematurely from the metabolic syndrome for natural selection to remove the thrifty genes from our gene pool?

The observations discussed here have been extensively replicated and the theories discussed have been widely espoused but both are – and perhaps for good reason – still discussed, questioned, and debated. Many of these observations are not invariable and the causal pathways are still quite far from being transparent. It is thought that the concepts of the "thrifty genotype" and "thrifty phenotype" can be consistent and reconciled with one another. Sometimes, though, it is clear that they are mutually exclusive explanatory alternatives such as when it is not known if a low birth weight is inherited or acquired. Validity and applicability of these hypotheses is certainly open for dispute. Thrifty genes may not be identified for decades and even given the recent advances in genetic analysis are a rather nebulous concept today. One would assume that thrifty alleles would influence processes such as lipolysis, fuel oxidation, and skeletal muscle glucose metabolism, but it is difficult to say. The 2007 genome-wide association studies on type 2 diabetes mellitus provided promising data, and more refined genetic tools will provide a more complete picture of the genetic and epigenetic complexity of the metabolic syndrome.

Animal models are not always directly comparable to the human situation, but should continue to offer insight into mechanism. Long-term studies in humans are expensive and time-consuming but they will help to clarify the pertinent issues too. It is evident that this line of research has major ramifications for public health policy. Health care funding may be more prudently spent on informing and improving pregnancy care rather than on the contingent metabolic disorders which manifest decades later and cost many times more to treat. If overeating and sedentary behavior are determined during prenatal development to the degree that this literature implies, this may explain why public health initiatives to improve exercise and dieting in adults with metabolic symptoms are largely ineffective.

There is a large literature that addresses these concepts from different angles, and much is known about the similarities in predisposition for metabolic disease between people and animals (Gluckman and Hanson 2004). There is still much that is unknown though, and whether the broad, ultimate, evolutionary hypotheses have to be largely altered or just fine tuned, it is becoming clear that metabolic disease may very simply stem from the fact that our behavior, diet, and nutrition are so different from the way they used to be.

Summary Points for the Developmental Origins of the Metabolic Syndrome

- The metabolic syndrome represents a cluster of metabolic derangements that are risk factors for obesity, type 2 diabetes mellitus, and cardiovascular disease.
- There is currently a worldwide epidemic of obesity and diabetes that is due to unhealthy eating and poor exercise. These are probably issues that our hunting and gathering ancestors would rarely have been exposed to, because they were probably rarely exposed to excess, but commonly exposed to famine.

- The human gene pool probably contains many thrifty genes that would have helped our ancient ancestors to survive food shortages and starvation. For example, a tendency to efficiently take up ingested fats into fat stores would have increased the likelihood of survival.
- The physiological states that cause us to be susceptible to facets of the metabolic syndrome probably all had ecological utility in the past. This is supported by animal models.
- Many mammals and it seems humans too can be programmed for thrift if they are exposed to severe undernutrition early in development. This programming may be a predictive adaptive response to environmental cues signaling that the environment is nutritionally poor.
- The thrifty phenotype that is created from these programming effects is highly susceptible to metabolic disease.
- Future findings in this literature should have serious implications for public health and the treatment of the metabolic syndrome.

Definitions

Dyslipidemia: Refers to a disruption of the levels of lipid in the blood. In western societies, most dyslipidemias are hyperlipidemias; an elevation of lipids, often due to diet, lifestyle, or prolonged elevations of insulin.

Glucose tolerance: The ability of the body to adapt to a relatively large dose of glucose. This ability is usually diminished in diabetics and is used to diagnose diabetes mellitus. A fasting subject ingests around 75 g of glucose, and blood glucose is measured at intervals. In diabetics the concentration is higher and takes longer to return to baseline value.

Genotype: The genetic constitution of a cell or organism. The genotype contains the information, in the form of DNA, which dictates how the cell or organism develops and interacts with its environment.

Hypercortisolemia: High amounts of circulating cortisol, an essential glucocorticoid steroid hormone, and the major hormone secreted by the adrenal glands.

Hyperglycemia: A complex metabolic condition characterized by high levels of blood glucose in the circulation, usually a result of insufficient or ineffective insulin production in either type 1 or type 2 diabetes mellitus.

Hyperphagia: Refers to an abnormal appetite or increased eating of food, often associated with abnormalities in the hypothalamus.

Hypertension: High blood pressure or force of blood on the vessel walls of the arteries.

Hypothalamic–pituitary–adrenal axis: This is a neuroendocrine system in the body responsible for regulating stress physiology. Brain areas that sense threat signal the hypothalamus, which communicates hormonally to the pituitary which hormonally signals the adrenal glands to secrete adrenaline and cortisol.

Insulin resistance: A condition in which cells, especially those comprising muscle, fat, and liver tissue fail to be properly receptive to the messages of the hormone insulin. Because insulin promotes the extraction of glucose from the blood, allowing cells to meet their metabolic needs, insulin resistance is associated with elevated levels of blood glucose.

Metabolic syndrome: A combination of metabolic disorders that commonly present together, and increase the risk of developing diabetes and cardiovascular disease.

Phenotype: An observable characteristic of an organism, such as a trait, property, or behavior. Phenotypes develop from the interaction between an organism's genes and its environment.

Visceral fat: The accumulation of fat around the internal organs of the torso. It is associated with the "apple shape," belly fat, central obesity, and a high waist to hip ratio.

References

Barbazanges A, Piazza PV, Le Moal M, Maccari S. J Neurosci. 1996;16:3943–9.

Barker DJP. Fetal Maternal Med Rev. 1994;6:71–80.

Barker DJP. Mothers, babies and health in later life. London: Churchill Livingstone; 1998.

Barker D, Eriksson J, Forsen T, Osmond C. Int J Epidemiol. 2002;31:1235–9.

Bateson P, Barker D, Clutton-Brock T, Deb D, D'Udine B, Foley R, Gluckman P, Godfrey K, Kirkwood T, Mirazon Lahr M, McNamara J, Metcalfe N, Monaghan P, Spencer H, Sultan S. Nature 2004;430:419–21.

Cettour-Rose P, Samec S, Russell AP, Summermatter S, Mainieri D, Carrillo-Theander C. Diabetes 2005;54:751–6.

Coleman D. Science 1979;203:663–5.

Crespi EJ, Denver RJ. Am J Hum Biol. 2005;17:44–54.

Desai M, Crowther NJ, Ozanne SE, Lucas A, Hales CN. Biochem SocTrans. 1995;23:31–5.

Diamond J. Nature2003;423:599–602.

Dowse GK, Zimmet PZ, King H. Diabetes Care. 1991;14:968–74.

Drake AJ, Walker BR. J Endocrinol. 2004;180:1–16.

Eriksson J, Forsen T, Tuomilehto J, Osmond C, Barker D. Br Med J. 2001;322:949–53.

Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. JAMA 2001;285:2486–97.

Flier JS. J Clin Endocrinol Metab. 1998;83:1407–13.

Ford ES, Giles WH, Dietz WH. JAMA 2002;287:356–9.

Francis D, Diorio J, LaPlante P, Weaver S, Seckl JR, Meaney MJ. Ann NY Acad Sci. 1996;794:136–52.

Gluckman P, Hanson M. Trends Endocrinol Metab. 2004;15:183–7.

Haines H, Hackel D, Schmidt-Nielsen K. Am J Physiol. 1965;208:297–300.

Hales CN, Barker DJ. Diabetologia 1992;35:595–601.

Hales CN, Barker DJ. Br Med Bull. 2001;60:5–20.

Hanson MA, Gluckman PD. Basic Clin Pharmacol. 2008;102:90–3.

Harding, JE. Int J Epidemiol. 2001;30:15–23.

Kensara OA, Wootton SA, Phillips DI, Patel M, Jackson AA, Elia M. Am J Clin Nutr. 2005;82:980–7.

Langley-Evans SC. J Hypertens.1997;15:537–44.

Langley SC, Jackson AA. Clin Sci. 1994;86:217–22.

Law CM, Shiell AW. J Hypertens. 1996;14:935–41.

McKeigue P. In: Kuh D, Ben-Shlomo Y, editors. A life course approach to chronic disease epidemiology. Oxford: Oxford University Press; 1997. p. 78–100.

Neel JV. Am J Hum Genet. 1962;14:353–62.

Neel JV. In: Kobberling J, Tattersall R, editors. The genetics of diabetes mellitus. Amsterdam: Academic; 1982. p. 137–47.

Neel JV. Nutr Rev. 1999;57:2–9.

Nesse R, Williams G. Sci Am. 1998;279:58–65.

Ozanne SE, Hales CN. Nature 2004;427:411–2.

Petry CJ, Ozanne SE, Wang CL, Hales CN. Clin Sci Lond. 1997;93:147–52.

Phillips DI. Diabetes Care. 1998;21:150–5.

Pollard TM. Western diseases: an evolutionary perspective. Cambridge UK: Cambridge University Press; 2008. p. 5–9.

Ravelli, GP, Stein ZA, Susser MW. N Engl J Med. 1976;295:349–53.

Reser JE. Med Hypotheses. 2006;67:529–44.

Ridley M. Nature via nurture: genes experience and what makes us human. New York: Harper Collins; 2003.

Scott EM, Grant PJ. Diabetologia 2006;49:1462–6.

Schulz LO, Bennett PH, Ravussin E, Kidd JR, Kidd KK. Diabetes Care. 2006;29:1866–71.

Schwartz MW, Dallman MF, Woods SC. Am J Physiol. 1995;269:949–57.

Siemelink M, Verhoef A, Dormans JA, Span PN, Piersma AH. Diabetologia 2002;45:1397–403.

Tolsa CB, Zimine S, Warfield SK, Freschi M, Rossignol AS, Lazeyras F, Hanquinet S, Pfizenmaier M, Huppi PS. Pediat Res. 2004;56:131–8.

Valencia M, Bennett P, Ravussin E, Esparza J, Fox C, Schulz L. Nutr Rev. 1999;57:55–7.

Via S, Lande R. Evolution 1985;39:505–22.

Vickers MH, Breier BH, McCarthy D, Gluckman PD. Am J Physiol Endocrinol Metab. 2000;279:83–7.

Wells J. J Theor Biol. 2003;7:221:143–61.

Zhang T, Parent C, Weaver I, Meaney M. Ann NY Acad Sci.2004;1032:85–103.

Zimmet P. In: Fischer E, Moller G, editors. The medical challenge: complex traits. Munich: Piper; 1997. p. 55–110.

Chapter 167
The Relationship Between Television Viewing and Overweight and Obesity in Young Children: A Review of Existing Explanations

Vickii B. Jenvey

Abbreviations

ABS	Australian Bureau of Statistics
BMI	Body Mass Index
kg	Kilogram
kgs	Kilograms
m	Meter
m^2	Meter squared
TV	Television
WHO	World Health Organization
$\geq$	Greater than or equal to
$>$	Greater than
$<$	Less than

167.1 Introduction

Data collected worldwide point to an increase in childhood overweight and obesity. Studies in both developed and developing countries [for example, Australia (Bauer 2002) and Peoples' Republic of China (PRC) (Jiang et al. 2006)] show that the proportion of children who can be considered obese has continued to increase over the past three decades. It is often proposed that outcomes of early obesity can predispose children to life-long health problems, including the early onset of Type II diabetes, and early onset of risk factors associated with the later-life development of cardiovascular disease (Teran-Garcia et al. 2008). Additionally, obesity in early childhood has been linked to ostracism and early development of low self-esteem (Schmitz et al. 2002), with the critical factor being peer acceptance (Iobst et al. 2009). Parallel to this rise in overweight and obesity among children of all ages is the apparent increase in sedentary leisure pursuits, such as watching television (TV), surfing the Internet, and playing computer games, because of increased access to all forms of electronic media. Watching TV is a low-level activity and is ubiquitous among young children in both developed and developing countries (see, for example, Larson and Verma 1999). For Australian children's TV consumption see for example, Jenvey (2003) in which

V.B. Jenvey (✉)
School of Psychology, Psychiatry, Monash University, Building 17, Clayton, Victoria 3800, Australia
e-mail: vickii.jenvey@monash.edu.au

Australian children's usual play and leisure patterns in different social contexts were surveyed, and the Australian Bureau of Statistics (ABS) Survey of Australian children's usual leisure activities (ABS 2004). It is not surprising, therefore, that researchers have attempted to identify an association between TV viewing and increasing levels of obesity among children in those countries. While some studies have investigated relationships between the amount of time children spend accessing all forms of electronic media (computers, computer games, electronic games, TV, and watching DVDs) (for a review, see Marshall et al. 2004), the majority of research has focused on adverse health outcomes associated with frequent TV viewing by children from an early age (Anderson et al. 1998; Landhuis et al. 2008).

167.2 Children Who Are Overweight and Obese

Obesity is assessed by calculating body mass index (BMI). To calculate children's BMI, their weight and height are measured, and BMI is derived from dividing children's weight (in kilograms) by their height (in meters squared). Children whose BMI is more than or equal to 25 kg/m^2 are classified as overweight or obese if BMI is more than or equal to 30 kg/m^2 (Cole et al. 2000). Children's weight and height are compared with established international norms, so that meaningful comparisons of children's growth can be made across different countries (Bar-On 2002). There are separate norms for boys and girls, and each child's weight and height are compared with norms established for children of the same age. While BMI provides a quick and internationally agreed-upon means of determining which children can be classified as overweight or obese, other parameters of children's growth should be considered to determine obesity [World Health Organization (WHO) 1995]. In addition to weight and height, measurement of children's mid-upper arm circumference and skin fold thickness (subscapular and mid-upper arm) should be taken to ascertain, respectively, children's muscle mass and fat stores (WHO 1995). Table 167.1 displays recommended anthropometric measures to most reliably characterize children's growth relative to a normative sample.

Consistency or change in children's and youth's BMI measures throughout development continue to be used as dependent measures to investigate associations between amount of TV viewing and obesity in early childhood. Despite this widespread practice, other researchers point to the inappropriateness of BMI measure to detect individual gains in body mass that result from inherited differences in body composition and bone structure among different ethnic groups. Additionally, even successive BMI measures do not adequately characterize individual differences in children's growth rates, particularly during the early childhood period (Lloyd et al. 2009).

Table 167.1 Anthropometric measures used to characterize overweight and obesity in early childhood

Anthropometric measure	Utility and source
Body Mass Index (BMI)	Efficient, shorthand way to characterize growth/ changes in growth in young children (Weight/Height^2) (Cole et al. 2000)
Mid-upper-arm circumference	Measures muscle mass – better to characterize changes in young children's growth over time (Kanda et al. 1997)
Skin fold thickness (Triceps, Subscapular)	Argued to be most reliable measure of young children's fat stores (WHO Expert Committee 1995)

This table displays the most commonly used and internationally agreed upon measures to characterize changes in children's growth over time, including measures of children's height, weight, muscle mass, and fat stores

167.3 Amount of Time Children Spend Watching Television

In a cross-national investigation of children's leisure pursuits it was found that time spent by children of different ages, including young children 5–8 years, in different countries ranged between 1.5–2.5 h/day (Larson and Verma 1999). Australian parents report similar amounts of TV viewing (average of 15 h/week) among their children, including preschool and early school-age children (Wake et al. 2003). This latter study also included time spent in computer-based activity, which was still less than the time spent watching TV. Additionally, results from a survey of frequency and type of leisure activities of a sample of more than two million 5–15 year-old Australian children (ABS 2004) showed that watching TV and videos was the most popular leisure activity of young Australians, with 98% of children engaged in that activity during their leisure time. In a 2-week period during school term, children spent, on average, 22 h per fortnight watching TV and videos. Time spent watching TV and videos exceeded time spent in other leisure pursuits such as reading or playing electronic games (8 h/fortnight) and more physically active pursuits such as bike riding (6 h/ fortnight) or skateboarding and rollerblading (5 h/fortnight).

When these data are considered in addition to time spent by children accessing other more recent forms of computer-based activities, it is reasonable to assume that young children are spending a sizeable proportion of their leisure time in sedentary, electronic media consumption. In fact, children persist in TV viewing even with the advent of more personalized, interactive media such as Internet and computer games. Thus, time spent accessing these more recent forms of electronic media occurs *in addition to* time spent watching TV (Roberts et al. 1999; ABS 2004). Owing to the fact that TV has been part of children's leisure for several decades, there is a larger body of research investigating the impact of TV viewing on young children's development than exists on more recent forms of computer-based technology taken up by contemporary children. Table 167.2 shows estimated daily or weekly TV viewing among children from different countries.

167.4 Potential Adverse Impact of Watching Television on Young Children's Growth and Development

It is argued that the amount of time young children spend watching TV, displaces time that otherwise might be spent in more physically active leisure pursuits (Dietz and Gortmaker 1985). The second concern is related to the program and advertisement content of TV watched by young children. Television content said to be associated with adverse developmental outcomes for children include programs containing advertisements for food products of poor nutritional quality, which are placed strategically during peak viewing times by children (Kelly et al. 2008; Taras et al. 1989). A third hypothesis proposes an interaction of sedentariness of TV viewing and susceptibility of young children to the persuasive intent

Table 167.2 Estimated hours of television (TV) viewing in early childhood

Estimates of hours of TV viewing	Population and source
22 h/fortnight	Australian children 5–15 years (ABS 2004)
1.5–2.5 h/day	Cross-national comparison (Larson and Verma 1999)
15 h/week	Australian children 3–6 years (Wake et al. 2003)

This table summarizes research estimates (in hours) of amount of time spent by children watching TV across different populations. Estimates are fairly consistent across different populations of children worldwide

Table 167.3 Main explanations and underlying processes associating time spent watching (TV) in early childhood and the development of overweight and obesity

Explanation and source	Proposed underlying processes
Energy displacement (Dietz and Gortmaker 1985)	Time spent watching TV supplants time available for more physically active leisure activities, and energy intake (in the form of food) exceeds energy expenditure (in the form of physical activity) and results in overweight and obesity
Exposure to saturation amounts of TV advertisements for foods of poor nutritional quality (Wilson et al. 1999)	Amount of time spent watching TV ensures high level of exposure to certain food products.
	Young children become familiar with the product brands and pester parents, who, in turn, buy those products, to be eaten by their children
In addition to energy displacement, young children's cognitive immaturity impedes detection of the persuasive intent of the food advertisements (Kelly et al. 2008)	Reduction in physical activity relative to energy requirements coupled with an increase in consumption of food products advertised on TV. Such products consistently high in saturated fats, sugars and excessive amounts of salt.
	Young children, because of their cognitive immaturity are susceptible to the persuasive intent of the advertisements

This table outlines the three main explanations of associations between amount of TV viewed by young children and the development of overweight and obesity in childhood. Specifically three main explanations are (a) energy displacement, (b) cognitive immaturity of young children and their susceptibility to persuasive intent of advertisements for *snack* and *junk* foods, and (c) combination of energy displacement and vulnerability to persuasive messages in *snack* and *junk* food advertisements broadcast during children's TV programs

of advertisements for foods of poor nutritional quality, that are frequently advertised during designated children's TV viewing time (Kelly et al. 2008). Each of these explanations will be discussed more fully in the following sections, and they are presented in Table 167.3.

167.5 Relationship Between Young Children's Television Viewing and Low Physical Activity Levels

A relationship has been found among overweight and obesity, hours of TV viewing, and reduced physical activity among young (3–6 years-old) children (Jago et al. 2005). The more time children spent watching TV, the more overweight or obese they were, and this effect was more pronounced among older children (6–7 years-old) in the cohort. Researchers explained these findings by proposing that TV viewing supplants time spent in physical activity, thereby leading to reduced energy expenditure relative to energy intake, and the development of obesity (Jago et al. 2005). Key features of the energy displacement hypothesis are presented in Table 167.4.

On the other hand, Jackson, Djafarian, Stewart and Speakman (2009) found an association between increased hours of TV viewing and elevated body fatness among preschool children, but this association was not mediated by reduced physical activity. A weak but statistically significant association was found between hours of TV viewing and reduced physical activity among 3–4-year-old children (DuRant et al. 1994), while another study showed no relationship between physical activity and TV viewing among Mexican children living in Mexico City (Hernandez et al. 1999). Thus, there is a lack of consistency in findings from one study to another. In a follow-up study in adolescence of the potential adverse developmental outcomes of TV viewing in early childhood in two cohorts of children in Massachusetts and Kansas, USA, Anderson, Huston, Schmitt, Linebarger and Wright (2001) found no relationship between frequent TV viewing in early childhood and the development of obesity in adolescence. In fact, the single weak but statistically significant relationship was found between

Table 167.4 Key features of energy displacement hypothesis

- Increased time spent in early childhood in sedentary leisure activity of watching TV
- Increased time watching TV occurs at expense of other physical activity
- Children with increased sedentary behavior require lower energy consumption (food), but food intake remains same
- Food intake exceeds daily requirements for decreased physical activity
- Overweight and obesity result from energy intake exceeding energy expenditure

This table outlines one explanation of underlying mechanism by which children develop overweight and obesity in early childhood. Increased hours spent watching TV reduces time available for more physical activities, yet food consumption remains constant, leading to surplus energy intake to energy requirements, in turn resulting in development of overweight and obesity

amount of sedentary behavior (hours spent TV viewing) during adolescence for girls but not boys. The authors interpreted these results as further evidence of findings from multiple studies that females become more sedentary than males during adolescence. Consequently, time that could potentially be taken up with more active leisure pursuits becomes displaced with TV watching for adolescent girls (Anderson et al. 2001).

These equivocal results are not surprising, given the problem that, in large-scale epidemiological studies of factors that contribute to children's and adolescents' growth, it has been difficult to establish a link between physical inactivity and overweight and obesity (see: for example: Krassas et al. 2001, Hernanadez et al. 1999). What is overlooked in these studies is that TV viewing in early childhood does not always displace all forms of physical activity, and young children have been shown to maintain relatively stable levels of physical activity in addition to watching quite a few hours of TV during their usual leisure times (Rey-Lopez et al. 2008). Absence of a clear relationship between time spent watching TV and overweight and obesity among children in these different studies is likely to be linked to methods adopted commonly for data collection of the amount and type of participants' leisure activities. Many of the studies required children or their parents to keep a diary of their daily activities [e.g. Anderson et al. (2001) (early childhood phase of study); Wake and Hesketh 2003], while other samples of children's activity levels are derived from a short-term and an ultimately limited sample of children's regular activity (e.g. ABS 2004). Retrospective diary methods of information gathering have the potential problem of social desirability bias. That is, children and parents report what they should be doing rather than what they are actually doing, and often diaries are completed retrospectively, sometimes several days after a reported activity took place. Further, many studies that investigate links between amount of TV viewing and overweight and obesity in children and youth rely on measurements of TV viewing time that do not report the psychometric properties of the measure used, how the measure was administered, and how data were coded and tabulated. Such methodological problems inevitably compromise the reliability and validity of results that report statistically significant associations between TV viewing and activity levels (Bryant et al. 2007). Perhaps data collection daily at home or school, completed by children themselves, their parents, or their teachers, in the presence of researchers, might overcome problems with diaries completed retrospectively after too much time has elapsed. Such methods are, however, potentially intrusive into family or school life, are very labor-intensive, and dictate large research budgets. Other potential methodological problems include differences in the way children's activity levels are characterized in the different studies. The diverse behaviors of which children's physical activity is comprised has led researchers to recommend that activities be stratified as high activity (e.g. running; jumping, team sports), medium activity (e.g. walking round school playground during recess), and low activity (e.g. occasional movements during play activity) (Goran et al. 1997). Other researchers note that the intensity of the activity may also affect the amount of energy expended during an activity (Strauss et al. 2001).

Contradictory findings should also be considered in light of evidence that the same young children who report that their usual play activity is watching TV when at home alone or in the company of siblings and friends also report that they engage in vigorous outdoor-active play, such as riding bicycles, playing sports, and other physically active games, such as chasey or rough-and-tumble play (Jenvey 2003). It should be noted that children reported less time spent in more vigorous physical activity but also reported that their physical activity was more intense (Jenvey 2003). Moreover, the results of a large-scale survey of Australian children's leisure activities (ABS 2004) support Jenvey's (2003) findings. In the ABS survey, although young children (5–8 year-olds) spent a lot of leisure time in sedentary activities, mainly watching TV, playing computer games, and accessing the Internet, more than 60% of that age group also participated in organized sports and cultural activities, that included learning and practicing folk dancing (ABS 2004).

Larson (2001) notes that even young contemporary children from both developed and developing countries have far more leisure time than children of previous generations, whose time was taken up with household chores and contributing to income-generating activities. Increased technological assistance reduced repetitive manual labor associated with feeding, transportation, and providing a suitable home for children. When many children in developing countries were no longer needed to contribute to such activities, they had more free time available for all forms of leisure activity. Subsequently, children in developing countries also began to spend more of their leisure time watching TV (Larson 2001).

Additional research evidence indicates that certain inherited propensities to develop high leptin levels and fat-mass are implicated in the development of obesity in early childhood (Comuzzie et al. 2003). This latter finding indicates that some children will be more susceptible to early-onset obesity, and low levels of physical activity will have differential developmental outcomes for children according to their inherited predispositions.

Thus, a direct relationship between inactivity resulting from frequent TV viewing in early childhood and the development of obesity is not clearly established. Other factors, such as amount and type of all leisure activities each child engages in, and the level and intensity of the physical activity, together with inherited propensities that differentially predispose some children to the development of obesity in early childhood need also to be taken into account when attempting to ascertain the reasons for increasing levels of obesity among young children worldwide. As well as the amount of time children spend watching TV, it is also important to consider the content of the TV that young children watch.

167.6 Food Advertisements During Designated Children's Television Time and Amount and Type of Food Consumed by Young Children

Before considering the processes by which young children are influenced by advertisements on TV, it is important to consider just how many food advertisements are placed during times when young children are most likely to be watching. As much as 30% of non-program content during children's designated TV time in both Australia (Wilson et al. 1999) and New Zealand (Hill et al. 2006) contains advertisements for food, and the types of products advertised are of poor nutritional quality. That is, food types that are commonly referred to as "snack foods" that can be purchased in attractive packaging at supermarkets and "fast foods" made and sold at fast food outlets are frequently advertised during designated children's TV times. The types of foods advertised to Australian and New Zealand children on TV are similar to products advertised during peak periods of children's viewing in USA (see, for example, Kuribyashi et al. 2001; Harrison and Marske 2005) and for advertisement content on British TV during times of peak viewing by young children (for example, Pine and Nash

Table 167.5 Estimates of proportion of children's television (TV) programs that contain food advertisements

Proportion of food advertisements/children's TV programs[a]	Population and source
Approx. 30% of programs	New Zealand children (Wilson et al. 1999)
Approx. 30% of programs	Australian children (Hill et al. 2006).
Approx. 35% of programs	US children (Kuribyashi et al. 2001)
>25% of programs	British children (Pine and Nash 2003)

This table summarizes research estimates (as percentage of total TV program time), the proportion of designated children's TV programs that contain advertisements for *snack* and *junk* foods and which are broadcast in four different English-speaking populations. Proportional estimates show consistently high proportion of programme content in four different developed countries

[a]In all estimates, majority of food products advertised were most likely to contain levels of salt, saturated fats, and sugars that exceeded recommended daily allowances for children in target age ranges

2003). Table 167.5 summarizes estimates of the level of exposure of children to televised food advertisements across different child populations.

The foods advertised during children's TV programs were more likely to contain levels of salt, saturated fats, and sugars that exceeded recommended daily allowances for children of the ages in the target audiences (Harrison and Marske 2005). They also advertised highly processed foods that were low in dietary fiber (Kuribyashi et al. 2001). The latter compared the contents of food advertisements placed in Saturday morning children's programs with contents of food advertisements placed in Saturday evening adult programs across four free-to-air US TV stations. When the food types advertised during periods of peak viewing by children were compared with types of food products advertised during periods of peak viewing by adults, it was found that there were more food commercials shown during the peak (early morning) children's program hours; they were more repetitious and took up a higher proportion of the overall program time than food advertisements screened in the evenings during prime-time adult programming. Overall, food products advertised during Saturday morning programs, a period of peak viewing by young children, contained significantly higher levels of sugar and saturated fat than products advertised during Saturday evening programs, when the majority of the audience was adult (Kuribyashi et al. 2001).

While it is important to establish the frequency of exposure of young children to certain food types while they watch TV, it is equally important to consider how such advertising might affect children's food preferences, eating patterns, and general nutrition. Evidence from research in different countries indicates that both amount and type of food provided to young children by their parents, grandparents, and even older siblings are the most significant influence on the development of food preferences and eating patterns in early childhood (Cullen et al. 2000). Thus, if parents usually purchase and consume *snack foods* and *junk foods*, then such foods will be readily available to children in their homes. Messages contained in advertising content might reinforce young children's preference to consume foods available already in their home. Even when young children respond to the persuasive intent of the advertisements, it is not clear how young children might then influence their parents to purchase foods advertised on TV, if such foods are not usually provided by their parents or other family members in their homes. Taras, Sallis, Patterson, Nader and Nelson (1989) did show a more direct link between young children's exposure to certain food advertisements on TV and the types of foods they consumed. Mothers of 3–8 year-olds completed a questionnaire on children's TV viewing patterns and the nature of their requests for certain food products commonly advertised on TV (Taras et al. 1989). The more often children saw programs containing advertisements for certain food types, the more frequently they requested that their parents purchase the products. Different relationships were found for exposure to sporting goods advertisements and children's requests for sporting goods. The more time children spent watching TV generally, the less frequently they requested that their parents purchase sporting goods promoted in advertisements

they viewed on TV. The design of this study did not control for other potential confounds in the data. For example, children who watch a lot of TV are also exposed to advertisements for all sorts of products, but the type of food advertised (mostly snack, and processed packaged food) is relatively cheap, when compared with toys, sporting goods, and other products also advertised frequently during children's TV programs. Perhaps the more snack food that was requested by children, purchased subsequently by parents, and thus consumed by children occurred because of its cheapness relative to other advertised products (e.g. toys and sporting goods).

Additionally, there was no mention of how frequently parents succumbed to their children's demands to purchase products they saw advertised on TV. This is often referred to as the "pester factor", and is apparently one of the intentions of advertising that targets young children. Nevertheless, while advertisers identify its existence, and it is asserted that children's demands play a role in parents' response to their children's requests for certain products, there is little evidence to support this view-point (Jenvey and Jenvey 2003). It is likely that parents who monitor what their young children watch on TV would be far more vigilant about responding to their children's requests for the types of foods advertised (Jenvey and Jenvey 2003). Yet, few studies have surveyed parents of young children about this issue. A second omission from Tallis et al.'s (1999) study was information about the availability of those foods in children's households. Results of other studies show that types of foods available in young children's households, together with their parents' own consumption of food of poor nutritional quality, have a significant role in shaping the food preferences and diet of their young children (Guidetti and Cavazza 2008).

It is proposed that the psychological processes that underlie children being influenced by the media about food, attitudes to food, diet, and exercise involve the dual processes of imitation and modeling (Bandura 1986). At first, children tend to imitate the behaviors of influential adults in their environment. Reinforcement of behaviors of influential others occurs vicariously. Children are rewarded by watching others being rewarded, and are likely to use these people as models upon whom they can base their own behavior, in the expectation that they themselves will be rewarded directly for similar behavior. This process explains why children might show a preference for food advertised on TV, especially if the food is endorsed by popular TV characters, or high profile media, or sporting personalities. This process is understood well by corporate marketers, and is one of the reasons why popular actors, sporting and other media personalities are used for both questionable advertising campaigns (e.g. junk foods advertisements targeted at young children), as well as more prosocial campaigns that contain community service messages (e.g. support programs for child cancer sufferers and road safety campaigns).

Imitation and modeling also explain why parents, and mothers especially, act as important role models in the development of children's food preferences and eating habits. There is evidence to support the influence of parent's modeling both healthy and unhealthy eating habits and food preferences (Guidetta and Cavazzo 2008). Among young 3–8 year-old children, parents or immediate family members are the most significant role models for children's behaviors (Black et al. 2001; Cullen et al. 2000), and this understanding of the importance of parents and even grandparents modeling appropriate nutrition and exercise habits for their offspring has been incorporated into successful intervention programs to improve infant and young children's nutrition and physical activity, as well as to prevent or reverse the early onset of overweight and obesity (Black et al. 2001). Furthermore, in an epidemiological study of factors that contribute to fruit and vegetable consumption by 6–12-year-olds, the most significant predictors of fruit and vegetable consumption by children were, in order, the provision of fruits and vegetables in children's homes, parents' intake of fruit and vegetables, and parents' knowledge of childhood nutrition and dietary recommendations (Blanchette and Brug 2005). In this study, children's TV viewing, including exposure to televised food advertisements and the availability of

convenience food at children's schools were less significant predictors of the amount of fruits and vegetables children consumed (Blanchette and Brug 2005).

Thus, these latter factors were far less predictive of poor nutrition than parental factors, and they formed a complex of other factors related to both availability of snack foods in places other than children's homes and, less significantly, to passive TV consumption and exposure to food advertisements, the content of which are not fully described in the study.

Thus, the extent to which young children are influenced by this mode of advertising is still dependent upon: (a) whether parents provide such food for their children, (b) whether parents also model those poor dietary preferences, and (c) how well young children are able to persuade their parents to purchase the snack foods and junk foods frequently advertised on TV which are not usually present in children's households.

A consideration of other cognitive processes of young children may also explain why young, preschool, and early school-aged children may be more susceptible to the persuasive intent of TV advertisements for certain types of food products. It is often the case that advertisements are embedded in thematically related children's TV programs, and that their persuasive intent is not obvious to young children (Kunkel and McIlrath 2003). It has been demonstrated that young children (< 4–5 years) have difficulty distinguishing advertising content from program content on TV, and that they do not understand the persuasive intent of the advertisements (Kunkel and McIlrath 2003). Characteristics of young children's cognition are shown in Table 167.6.

As children mature cognitively, however, they begin to understand the persuasive intent of advertisements (Oates et al. 2002). Nevertheless, these authors noted that, in their study, a sizeable proportion (approximately 25%) of 10-year-olds were unaware of the persuasive intent of advertisements (Oates et al. 2002). What is important to understand is what differentiated the 25% of 4–5 year-olds, who understood the persuasive intent of advertisements from the 75% who did not. Similarly, it is important to find out why 25% of 10-year-olds still did not yet understand the persuasive intent of advertisements, when compared with the majority of their age group, who readily understood the persuasive intent of advertisements. To determine the validity of these findings, it is important to consider whether the minority of 10-year-olds who remain susceptible to the persuasive intent of TV commercials had other cognitive delays, for example, in perspective taking or global cognitive functioning. Additionally, there is no report of whether the group of 10-year-olds watched TV alone or in the company of adults or other children, who might have afforded them opportunities to discuss the content and function of advertisements they watched so that they could develop a more critical response to what they watch on TV.

It is a much-replicated finding that TV advertising, the intent of which is to influence young children to persuade their parents to purchase and consume products such as *snack* or *junk* foods, is placed frequently during programs that attract large numbers of child viewers (Kunkel and McIlrath 2003). There is also evidence that very young children are often unaware that the intent of advertisements is to

Table 167.6 Key features of cognitive immaturity of 3–6-year-olds

- Children's thinking characterized by primitive, pre-logical thinking
- Self-centered perspective that makes them unable to see events from another's viewpoint
- Have literal interpretation of what they see and hear
- What they view on TV is taken at face value
- Respond to content in advertisements and are unable to determine that the persuasive message only represents viewpoint of person or character in advertisement

This table outlines how young children, because of their stage of cognitive development, are unable to detect the intention of food advertisements to influence young children to purchase and consume products advertised

persuade children to themselves purchase and consume their products or to demand that their parents purchase such products. It has yet to be established, however, that there is a direct link between types of products advertised to children during children's TV programs, and parents' purchase and children's consumption of such food products to explain the development of overweight and obesity in many young children. It appears more likely that young children begin to consume nutritionally poor food in certain households where such foods are already available and where parents do not monitor what their young children watch on TV. Additionally, evidence is still needed to show that parents, older siblings, or grandparents are more responsive to young children's requests to buy junk foods, and those foods then are consumed by children instead of more nutritious foods. It is also critical to find out whether young children, who develop poor eating habits and food preferences from being exposed to excessive advertising of *junk* food when they watch TV, are also less likely to engage in physically active leisure pursuits that, in turn, leads to the development of early onset of obesity. Time displaced by watching TV may lead to reduced engagement in physical activity together with increased exposure to junk food advertisements and increases in parents' purchase of such foods *may* result in children eating more nutritionally poor food at the expense of more nutritionally appropriate food. This explanation suggests a multidimensional process rather than a one-dimensional process that leads to early and sustained development of overweight and obesity in early childhood.

Despite the plausibility of the different explanations reviewed, results from research investigating an association between TV and other passive media consumption and early onset of overweight and obesity in young children have been equivocal. Researchers have yet to delineate clearly the underlying mechanisms that link TV viewing with the development of overweight and obesity in early childhood. Methodological shortfalls in existing research include an over-reliance on BMI to characterize children's growth. Other studies lack adequate data on all leisure activities of children, the level and intensity of children's physical activities and reliable and valid documentation of children's TV viewing time. Within the family context there is a lack of information about the amount and type of food parents provided to their young children, including snacks; existing nutritional practices within families; parents' own eating habits and food preferences; and parents' level of physical activity. Table 167.7 summarizes recurrent methodological and conceptual shortfalls in existing research.

How increased TV viewing may be linked to the development of overweight and obesity and thereby the diseases that result from the onset of overweight and obesity in early childhood has yet

Table 167.7 Conceptual and methodological shortfalls of each explanation

Explanation	Conceptual problems	Methodological problems
Energy displacement	Characterizing and measuring typical activity in children	Need measures of all activities and their intensity
	Valid and reliable measure of time spent watching television (TV)	Need reliable and valid method of data collection for amount of time spent watching TV
Exposure to saturation amounts of TV advertisements for foods of poor nutritional quality	Establishing a link between children's awareness of products advertised and their requests to parents to buy same products	Find out whether products already purchased by parents and available in home
		Distinguish between knowledge of product and frequency of purchase
Energy Displacement + Cognitive Immaturity of Young Children	How reduced physical activity co-occurs with susceptibility to persuasive intent of advertisements	Measuring activity levels and children's cognition appropriately

This table lists, some of the recurrent conceptual and methodological shortfalls in existing research on each of the three main explanations that link TV viewing to the development of overweight and obesity in young children

Model of Potential factors that contribute vto overweight and obesity in early childhood

FAMILY FACTORS

Genetic Propensities
Ethnicity and Culture

Parents Encouragement and Modelling
of Amount and Type of Food
Parent's own Diet and Nutriton

Parent's Physical and Sedentary Activities

CHILD FACTORS

Inherited Propensities
Body Composition and Growth Rate

Food Preferences and Eating Habits

Physical Activities
Duration Level and Intensity

Time Spent in Sedentary Activity
Time Spent Viewing Television

GROWTH and DEVELOPMENT

Comparisons with Normative Development
Height and Weight
Muscle Mass and Fat Stores
Overweight
Obesity

TELEVISION PROGRAM CONTENT

Television Advertisement Content
eg. Junk and Snack Foods

Child's Level of Cognitive Maturity
Understanding of Persuasive Intent
of Television Advertisements

Fig. 167.1 There are several potential biological, behavioral and social factors, in addition to excessive TV watching, that impact on children's growth and development, resulting in overweight and obesity

to be delineated. In Fig. 167.1, a multidimensional model is proposed to explain potential factors that best explain the underlying processes that make some young children more vulnerable to the development of overweight and obesity in early childhood.

Factors identified in Fig. 167.1 should be investigated within one study of a representative sample of young children, and the use of longitudinal research design would also overcome some of the underlying conceptual and methodological shortfalls in research to date. Using a multidimensional model as the basis for future investigations of processes by which young children become overweight and obese would then permit researchers to investigate interactions among variables and identify pathways that lead to the onset of overweight and obesity in early childhood.

Existing research tends to focus on a limited number of variables to investigate relationships between TV watching in early childhood and the development of overweight and obesity. Children do not develop in isolation, and their growth and development is not only affected by inherited propensities and individual behavioral differences but also their family and other social contexts in which growth and development take place.

167.7 Applications to Other Areas of Children's Health and Disease

There is conflicting evidence of an association between time young children spend watching TV and contemporaneous or later-onset development of overweight and obesity. Additionally, existing physiological and cognitive models are not yet able to characterize the processes through which TV viewing contributes to overweight and obesity in early and later stages of development. Thus, any suggested applications of research findings reviewed in this chapter to other areas of young children's health and disease remain tentative. Potential applications of research to other areas of children's health and disease are shown in Table 167.8.

It should be noted, however, that there is almost as much evidence showing no association between TV viewing and overweight and obesity during early childhood. If advertising agencies can produce advertisements that actually do influence young children to buy and consume food products of poor nutritional quality and to develop preferences for such food products, then similar advertising strategies could be implemented to promote more healthy food preferences for young children. For example, advertisements could be developed to persuade children, for example, to eat more healthy foods

Table 167.8 Potential applications to other areas of health and disease in young children

Behaviors associated with television (TV) viewing	Health and well-being	Disease
Increased sedentariness and reduced physical activity	May lead to overweight and obesity	May be related to early symptoms of cardiovascular disease
		Joint and muscular-skeletal problems
		Onset of diabetes
Energy consumption disproportionate to energy requirement	May lead to overweight and obesity	May be related to early symptoms of cardiovascular disease
		Joint and muscular-skeletal problems
		Onset of diabetes
Body image and self-esteem difficulties	May lead to adverse psychological effects related to overweight and obesity	Potential future mental health problems
Over-exposure to TV advertisements for *junk* and *snack* foods	May lead to poor diet, if types of food then consumed by children	Dietary imbalances
		Poor nutrition and later-life health problems
Susceptibility to persuasive intent of advertisement for food of poor nutritional quality	May lead to poor diet, if types of food then consumed by children	Dietary imbalances
		Poor nutrition and later- life health problems
Young children's susceptibility to persuasive intent of advertisements for food of poor nutritional quality	Cognitive strategies used in advertisements to persuade children about nutritionally poor products could be harnessed by health authorities to promote the attractiveness of appropriate foods to young children	Promotion of healthy eating at a young age
		Reduction of overweight and obesity in early childhood
		Potential reduction of future diseases linked to overweight and obesity

This table outlines some of the potential applications to other areas of children's health of research in which an association between amount of TV viewing in early childhood and the onset of overweight and obesity. Caution is recommended, because of the contradictory findings in existing research. Potential applications of findings to the promotion of healthy eating and preventative programs are listed

or to promote knowledge about good nutrition, adequate levels of physical activity, and alternative activities to occupy leisure hours that might otherwise be spent by young children watching TV.

167.8 Conclusion

The ubiquity, frequency, and sedentary nature of TV viewing that occupies a sizeable proportion of young children's leisure time in both developed and developing countries is considered by many researchers to be implicated in the increasing percentage of young children worldwide who are overweight and obese. Three commonly proposed explanations of the underlying processes that link TV viewing to the development of obesity in young children were evaluated. There were inconclusive findings to support the proposal that TV viewing displaces time available for more vigorous activity, reduced energy expenditure relative to energy intake, and the development of early-onset overweight or obesity. Additionally, there was inconclusive evidence to support the proposition that all young children are susceptible to persuasive intent of advertisements for food products of poor nutritional quality that appear frequently during children's TV, and that, arguably, contribute to unhealthy food preferences and eating patterns which predispose young children to the early onset of obesity. An interaction of energy displacement and susceptibility to develop preferences for unhealthy foods advertised when young children are most likely to be watching TV was identified as a more plausible explanation of the proposed link between TV watching and obesity in young children, but more

evidence is needed to support an interactive explanation. It was recommended that future research address both conceptual and methodological shortfalls in existing studies and a proposed multidimensional model to investigate all potential factors that contribute to the development of overweight and obesity in early childhood. Potential applications to other areas of children's health and disease were also discussed.

Summary Points

- Apparent increase in obesity at all stages of development. Increasing proportion of young (3–6 year-old) children overweight and obese. Trends in overweight and obesity found in diverse populations of children worldwide. Trend evident in developed and developing countries.
- Ubiquity of TV viewing as leisure activity among younger age group, documented in both developed and developing countries. This finding represents one of the main reasons for investigating any association between amount of time young children spend watching TV and the development of overweight and obesity in early childhood.
- Three main explanations proposed for linking amount of TV viewing with overweight and obesity in early childhood. These are: (1) Energy displacement explanation; (2) Cognitive immaturity of young children explanation; and (3) Combination of energy displacement and cognitive immaturity of young children.
- *Energy displacement* explanation: Time spent watching TV supplants time spent in other more physically active leisure, especially vigorous physical activities that require greater energy expenditure. Energy consumed (by food) exceeds energy required (for less physical activity and increased sedentariness), which in turn leads to early onset of overweight and obesity.
- *Cognitive immaturity* of young children (< 6 years) makes them more susceptible than older children to the persuasive intent of advertisements for *snack* and *junk* foods that are frequently broadcast during TV programs designed for and watched by very young children. Snack and junk foods are highly processed and contain proportions of saturated fats and sugar that far exceed recommended daily allowances in young children's diets. Marketers develop food products and packaging designed to influence children's food preferences and to encourage young children to pester parents to purchase such foods. Buying these products and regularly including them in daily food intake can lead to dietary imbalance, resulting in overweight and obesity when young children consume *snack* and *junk* foods at expense of other food groups. It is argued that younger children are more susceptible to such advertisements because they have difficulty in discriminating between TV content and advertising content, and thus remain unable to detect the persuasive pitch in advertisements because of self-centered cognition.
- *Energy displacement and cognitive immaturity of young children, in concert*, lead to preferences for and consumption of more processed, fat and sugar-laden foods of the types commonly advertised during designated children's TV programs. Increased sedentariness compounds adverse outcomes of poor food choices, leading to more rapid development of overweight and obesity.
- *Persuasive Intent of Advertisements*: Content of the advertisements often contain subtle and covert messages, designed to take advantage of young children's cognitive immaturity, especially in their inability to grasp the intentions or viewpoint of another, including intentions or viewpoints of real or fictitious characters who appear in food products marketed to children during children's TV programs. This leaves young children unable to determine that they are being persuaded, for example, to eat a certain type of food.
- While each of three explanations has some plausibility, evidence in support of all three is equivocal. Some studies report a significant association between TV viewing and development of

overweight and obesity in early childhood. However, several recent studies report no significant association between times spent watching TV or frequency of exposure to advertisements for *snack* and *junk* foods. Contradictory findings can be attributed to both conceptual and methodological shortfalls in many existing studies.

- One of the main methodological problems is the widespread use of BMI, measured at different periods during children's early development to characterize overweight and obesity of children across developmental periods. Besides measuring children's weight relative to their height compared with children of same age and sex, international expert committees recommend measuring children's skin fold thickness (to characterize fat stores) and upper arm and calf circumferences (to assess children's muscle mass). In addition, differences in growth rates on all parameters vary according to children's ethnicity and inherited predispositions, which are often omitted from studies.

- Other methodological shortfalls relate to how the potential range of all children's activities are measured, and whether intensity of physical activity is accounted for. The way in which TV viewing is measured often is not reported, and daily food intakes often are recorded retrospectively via parents' completing a questionnaire.

- There is a dearth of information that directly assesses associations between the actual types of foods advertised on TV and children's requests to parents to purchase those foods. Additionally, there is a lack of information about whether snack and junk foods are readily available in households, whether they are provided usually by parents for children to eat, or whether parents themselves eat such foods in the presence of their young children. There is also a near-absence in studies to investigate parents' and other family members' food preferences and eating habits and how much TV other family members watch.

- A multidimensional model is proposed to investigate more comprehensively the myriad of potential interacting factors that contribute to the development of overweight and obesity in young children. Within such a research model, factors that need to be considered are: (a) the inherited propensities of children that might contribute to increased fat stores; (b) differences in rate and dimensions of growth among different ethnic groups between and within populations; (c) the amount and types of foods provided in children's homes by their parents, together with parents own food preferences, eating habits, and exercise regimens; and (d) the use of valid and reliable measures to quantify children's TV viewing and food consumption.

- Only when methodological and conceptual shortfalls in existing studies are addressed in future research can there be an adequate understanding of the processes that lead to overweight and obesity in early childhood. Once process is delineated, then there will be potential applications of such findings to develop intervention and prevention programs to reduce adverse health outcomes associated with the development of overweight and obesity in young children. Such programs should adopt a multipronged approach to address all potential contributing factors.

- *Intervention and Prevention*: To improve general cardiovascular fitness and to increase bone density; reduce risk of later development of cardiovascular problems; Type II diabetes and kidney disease. To intervene or prevent certain psychological problems associated with overweight and obesity in childhood, including early onset of depression; problems with body image and self-esteem; and to prevent social isolation and withdrawal from activities with peers. In relation to advertising *snack* and *junk* foods during children's TV programs, public health programs could be implemented to reduce advertising hours and scrutinize content for advertisements shown during TV programs aimed at young children. Additionally, if advertisements were shown to be capable of promoting nutritious food preferences and sensible eating habits as well as to educate young children about appropriate nutrition.

Definitions and Explanations of Key Terms

Body mass index: Represents a shorthand way of characterizing children's growth. It is calculated after obtaining height and weight, and height is divided by weight squared to yield a BMI value that can be compared with normative values for child's age and sex. Is argued to be a problematic measure when used to characterize growth changes in children, especially during early childhood, as it does not take into account body types of different ethnic groups

Mid-upper arm circumference (MUAC): Recommended as indicative of children's growth. Measures muscle mass. Measured by finding median point between child's shoulder and elbow. Measured using flexible tape measure. Value is compared with normative data. Comparatively low measures, when compared with normative group can indicate protein malnourishment in young children.

Skin fold thickness: Considered reliable index of children's fat stores. Special calipers are used to measure (in cms/mms) children's fat mass from under their upper arm and just below their scapula. Subscapular skin fold argued to be the best indication of children's fat stores, and when compared with normative data can indicate under- or over-nourishment.

Imitation: Young children learn behaviors, which become stable over time, firstly by imitating models of those behaviors displayed by people deemed to be important in children's lives (role models), and parents are often the most powerful role models whom young children imitate. Additionally, influential or well-known figures also act as behavioral models for children to imitate. This explains why young children are likely to imitate behaviors, even opinions or beliefs expressed in advertisements featuring well-known personalities. If such models, for example, are seen by young children to eat certain food products or express a favorable opinion about a food product, then young children will tend to imitate that behavior (eat the product, if available or adopt the same opinion about a product that is expressed in the food advertisement. Reinforcement to repeat and stabilize such behaviors occurs through vicarious reinforcement (i.e. watching role models being reinforced for their behaviors).

Modeling: A more pervasive behavior than direct imitation. Young children begin to generalize behaviors initially imitated to other wider contexts. For example, preferences for, or opinions about, certain food products that are modeled by influential role models, in TV food advertisements, will be repeated by children, firstly in the context of the food advertisement but later in other contexts.

Cognitive immaturity of 3–6 year-olds: Young children are said to be cognitively immature, because their cognition is perception-dominated and egocentric.

Persuasive intent of advertisements: Content of the advertisements often contain subtle and covert messages designed to take advantage of young children's cognitive immaturity, especially in their inability to grasp the intentions or viewpoint of another, including, intentions or viewpoints of real or fictitious characters, who appear in food products marketed to children during children's TV programs. This leaves young children unable to determine that they are being persuaded, for example, to eat a certain type of food.

Key Points About Associations Between Television Viewing by Young Children and Development of Overweight and Obesity

- There is evidence of worldwide increase in proportion of young children (3–6 year old) who are overweight or obese compared with children of earlier generations.
- Trend exists in both developed and developing countries.

- Much replicated finding that most common free time activity of children worldwide, including younger children, is watching TV. Trend identified in both developed and developing countries. Thus, children's TV viewing patterns frequently targeted in research investigation as contributory factor in the development of overweight and obesity among young children.
- Apparent association between TV viewing and overweight and obesity explained in terms of three probable mechanisms: (1) Increased sedentariness, with attendant energy displacement. (2) Over-exposure to persuasive advertisements for food products of poor nutritional quality that are screened during designated children's TV programs. (3) Young children's cognitive immaturity renders them more susceptible to the persuasive intent contained in advertisements for snack and junk foods frequently broadcast when they watch TV. This exposure said to affect young children's food preferences and eating habits, leading to dietary imbalances associated with development of overweight and obesity.
- Studies yield mixed results when attempting to identify association between TV viewing-overweight and obesity.
- Reasons for conflicting findings attributable to conceptual and methodological problems in research studies to date.
- Conceptual problems include how best to characterize and measure children's growth parameters over time, especially during early childhood.
- BMI, most commonly used measure, has been criticized because it does not account for ethnic differences in growth patterns, and is not fully sensitive to subtle growth changes in early childhood.
- Methods for collecting TV viewing consistently lack adequate reliability and validity, thereby confounding studies' results.
- How best to characterize all activities, in addition to children's TV viewing during early childhood is still to be determined.
- Methods for collecting food consumption often are unreliable because they are collected retrospectively and are subject to social desirability bias.

References

Anderson RE, Crespo CJ, Bartlett SJ, Cheskin KM, Pratt M. JAMA 1998;279:938–42.

Anderson DR, Huston AC, Schmitt KL, Linebarger DL, Wright JC. Monogr Soc Res Child Dev. 2001;66:1–47.

Australian Bureau of Statistics. Children's participation in leisure cultural and activities, Australia. 2004. http://www.abs.gov.au/ausstats/abs@nsf/b06660592430724fca2568b5007b8619/0b14d8. Retrieved 12/02/06.

Bandura A. Social foundations of thought and action: a social cognitive theory. New Jersey: Prentice-Hall; 1986.

Bar-On ME. Arch Dis Child. 2002;83:289–92.

Baur LA. Asia Pac J Clin Nutr. 2002;11:524–8.

Black MM, Siegal E, Abel Y, Bentley ME. Pediatrics 2001;107:e67. http://www.pediatrics.org.cgi/content/full/107/e67. retrieved 10/09/07

Blanchette L, Brug J. J Hum Nutr Diet. 2005;18:431–43.

Bryant MJ, Lucove JC, Evenson, K.R, Marshall S. Obes Rev. 2007;8:197–209.

Cole TJ, Belizzi MC, Flegal KM Dietz WH. Br Med J. 2000;320:1240–3.

Comuzzie AG, Mitchell BD, Cole S, Martin LJ, Hsueh WC, Rainwater DL, Almasy L, Stern MP, Hixson J, MacCluer JW, Blangero J. Hum Biol. 2003;75:635–46.

Cullen KW, Baranowski T, Rittenberry L, Olvera N. Health Educ Res. 2000;15:81–590.

Dietz WH, Gortmaker SL. Pediatrics 1985;75:807–11.

DuRant RH, Baronowski T, Johnson M, Thompson WO. Pediatrics 1994;94:49–455.

Freedman DS, Dietz WH, Srinivasan SR Berenson GS. Pediatrics 1999;103:1175–82.

Goran MI, Hunter G, Nagy, TR, Johnson R. Int J Obes. 1997;21:171–8.

Guidetti M, Cavazzo N. Appetite 2008;50:83–90.

Harrison K, Marske AL. Am J Public Health. 2005;95:1568–74.

Hernandez B, Gortmaker SL, Colditz GA, Petersaon KE, Laird NM, Parra-Cabrera D. Int J Obes. 1999;23:845–54.

Iobst EA, Ritchley PN, Nabors LA, Stutz R, Ghee K, Smith DT. Int J Obes. 2009;52:1–7.

Jackson DM, Djafarian K, Stewart J, Speakman JR. Am J Clin Nutr. 2009;89:1031–6.

Jago R, Baranowski T, Baranowski JC, Thompson D, Greaves KA. Int J Obes. 2005;29:557–64.

Jenvey VB. Australian children's toy and play preferences: 1989–2005. In: Berg LE, Nelson A, Svensson K, editors. Toy research in late twentieth century: toys in educational and sociocultural contexts. Stockholm: SITREC, Swedish Institute of Technology; 2003a. p. 105–21.

Jenvey VB, Jenvey HL. Family, other sociocultural and media influences on preschool children's nutrition: a review and recommendations for intervention. Canberra: Department of Health and Ageing; 2003b.

Jiang J, Rosenqvist U, Wong H, Greiner, T, Ma Y, Toschke A. Int J Pediatr Obes. 2006;1:103–8.

Kanda A, Watanabe, Y, Kawaguchi T. Pub Health. 1997;111:29–32.

Katzmarzyk PT, Malina RM, Song TM, Bouchard C. J Adolesc Health. 1998;23:318–25.

Kelly B, Hattersley L, King L, Flood V. Health Promot Int. 2008;23:337–44.

Krassas GE, Tzotzas T, Tsametis C, Konstantinidis T. J Pediatr Endocrinol Metab. 2001;14:1327–33.

Kunkel D, McIlrath M. In: Palmer EL, Young BM, editors. The faces of televisual media: teaching violence, selling to children. 2nd ed. Mahwah: Lawrence Erlbaum; 2003. p. 287–300.

Kuribayashi A, Roberts MC, Johnson RJ. Child Health Care. 2001;30:309–22.

Landhuis CE, Poulton CE, Welch D, Hancox R. Pediatrics 2007;120:532–7.

Larson RW. Curr Dir Psychol Sci. 2001;10:160–4.

Larson RW, Verma S. Psychol Bull. 1999;125:701–36.

Lloyd LJ, Langley-Evans SC, McMullen S. Int J Obes. 2009. E-published 12/05/09. Retrieved 16/05/09.

Marshall SJ, Biddle SJH, Gorley T, Cameron N, Murdey I. Int J Obes Relat Metab Disord. 2004.

Oates C, Blades M, Gunter B. J Consum Behav. 2002;1:238–45.

Piaget J. Play, dreams and imitation in childhood. New York: W. Norton; 1962.

Pine KJ, Nash A. J Dev Behav Pediatr. 2003;24:219–24.

Rey-Lopez JP, Vincente-Rodriguez G, Biosca M, Moreno LA. Nutr Metab Cardiovasc Dis. 2008;18:242–51.

Roberts D, Foeher U, Rideout V, Brodie M. Kids and media @ the new millennium: a comprehensive analysis of children's media use. Washington, DC: The Henry Kaiser Foundation; 1999.

Ross JG, Pate RR, Casperson CJ, Danberg CL, Svilar M. Int J Phys Educ Recr Dance. 1987;58:85–92.

Schmitz KH, Leslie A, Lytle RD, Phillips GA, Murray DM, Birnbaum A, Kubik MY. Prev Med. 2002;34:266–78.

Strauss RS, Rodzilsky D, Burack G, Colin M. Arch Pediatr Adolesc Med. 2001;155:897–902.

Taras HL, Sallis JF, Patterson TL, Nader PR. J Dev Behav Pediatr. 1989;10:176–80.

Terran-Garcia M, Rankinen T, Bouchard C. J Appl Physiol. 2008;105:988–1001.

Wake M, Hesketh K, Waters E. J Paediatr Child Health. 2003;39:130–4.

World Health Organisation (WHO) Expert Committee on Anthropometry. Geneva: WHO; 1995.

Wilson N, Quigley R, Mansoor O. Aust NZ J Public Health. 1999;23:647–50.

Wilson N, Signal L, Nicholls S, Thomson G. Prev Med. 2006;42:96–101.

Chapter 168
The Dopamine Transporter Gene (DAT1) in Obesity and Binge Eating Disorders

Karen Wight, Caroline Reid-Westoby, and Caroline Davis

Abbreviations

AD(H)D	Attention deficit/(hyperactivity) disorder
BED	Binge eating disorder
BMI	Body mass index
DAT	Dopamine transporter
DAT1	Dopamine transporter gene
DSM-IV-TR	Diagnostic Statistical Manual of Mental Disorders – Fourth Edition
RDS	Reward deficiency syndrome
UTR	Untranslated region
VNTR	Variable number tandem repeat

168.1 Introduction

Experts have often attributed escalating obesity rates to a clash between our genes – adapted to survive seasonal food shortages or possible famines in times past – and the current abundant food environment (Cummings and Schwartz 2003; Peters 2003). According to the *thrifty genotype hypothesis*, obesity can be viewed as a natural response to our modern surroundings with its excess of energy sources (Cummings and Schwartz 2003; Peters 2003). We have a biological drive to eat beyond caloric need when food is available and to store energy as fat, as this would have been beneficial years ago, leading to improved chances of survival when food was scarce. Nowadays, this inherent motivation is problematic, given that the availability, variety, and portion sizes of food have greatly increased (Jeffery and Utter 2003; Nestle 2003) – factors associated with higher caloric intakes and elevated obesity rates (Nestle 2003).

Despite drastic changes to our environment, some individuals are able to maintain a healthy weight. It is critical to determine what differentiates this fraction of the population from the large and escalating proportion who chronically overeat. The various forms of overeating are derived from one of two separate drives according to the *homeostatic–hedonic model* – motives based on needing food and

K. Wight (✉)
Faculty of Health, York University, 223 Bethune College, 4700 Keele Street, Toronto, Canada
and
Centre for Addiction and Mental Health, University of Toronto, Toronto, Canada
e-mail: kapatte@yorku.ca

motives based on wanting food, respectively (Saper et al. 2002). The involvement of the hypothalamic pathways in the former has long been recognized; whereas, less is known about *hedonic* or *non-homeostatic eating*, which refers to eating for reasons other than caloric need, such as emotional states ("comfort eating") or environmental cues (e.g., seeing others eating, the sight and smell of food stimuli). Experts believe the action of the neurotransmitter *dopamine* on the brain's *common reward pathway* is primarily accountable for hedonic motivations for food intake, with the opioid system playing a more minor role. Individual variations in the tendency to overeat can be attributed – at least in part – to the genetically determined action and availability of dopamine. Among the dopamine-related genes studied, the gene encoding the dopamine transporter (DAT1) has received particular attention in relation to eating behavior. The purpose of this chapter is to review the literature on the role of the DAT1 in obesity and binge eating disorders.

168.2 Binge Eating

Reward-based motivations seem to overpower homeostatic drives in some individuals, given the frequent snacking, binge eating, and higher caloric intakes seen among many obese individuals despite their adequate energy stores. *Binge eating* represents an extreme phenotype of hedonic over-eating and is a significant risk factor for substantial weight gain over time (Fairburn et al. 2000). It is defined as the consumption of an abnormally large amount of food within a limited time span in the absence of physical hunger, and is associated with feelings of loss of control. Individuals typically engage in binge eating when alone because they often feel embarrassed and guilty about their behavior. Binge eating represents a defining behavioral symptom of both *binge eating disorder* (BED) and *bulimia nervosa.*

According to the Diagnostic Statistical Manual of Mental Disorders – Fourth Edition (DSM-IV-TR; see Table 168.1), BED is characterized by regular binge episodes (2–3/week) for a minimum of 6 months, without the use of compensatory behaviors such as purging, excessive exercise, diet pills, laxatives and/or diuretics for the purpose of weight loss, as often associated with bulimia nervosa (American Psychiatric Association 2000). Individuals with the disorder also tend to overeat through-out the day in addition to their binge episodes, and as a result, are usually obese – defined as having a

Table 168.1 Diagnostic criteria for binge eating disorder (Created from DSM-IV-TR criteria APA 2000)

A. Recurrent episodes of binge eating. An episode is characterized by:
- Eating, in a discrete period of time (e.g., 2 h), and amount of food that is definitely larger than most people would eat in a similar period of time under similar circumstances
- Feelings of loss of control over the amount or the type of food being consumed during the episode (e.g., feeling one cannot stop eating)

B. Binge eating episodes associated with at least three of the following:
- Eating alone because of feelings of embarrassment regarding eating
- Eating large quantities of food when not feeling physically hungry
- Eating until feeling uncomfortably full
- Eating much more rapidly than normal
- Feelings of disgust with oneself, depression, and/or guilt after a binge

C. Marked distress regarding binge eating

D. Binge eating occurs, on average, at least 2 days a week for 6 months

E. The binge eating is not associated with regular use of inappropriate compensatory behaviors, such as purging, fasting or excessive exercise, and does not occur exclusively during the course of bulimia nervosa or anorexia nervosa

Body Mass Index (BMI) over 30 kg/m^2. In a longitudinal study of BED, the proportion of obese individuals rose from 22% to 39% over 5 years – validating binge eating as a significant risk factor for substantial weight gain over time (Fairburn et al. 2000). At a weight loss clinic, as many as 30% of obese attendees met diagnostic criteria for BED (Striegel-Moore and Franko 2003; Yanovski 2003). Current opinion varies on how individuals with BED differ from obese adults who do not binge eat. A recent study found no difference between the groups on many personality variables, leading to the speculation that the distinction exists at the biobehavioral level (Davis et al. 2008).

Much of our understanding of BED stemmed from research on bulimia nervosa, as the former represents a relatively modern phenomenon. Bulimia nervosa is also characterized by recurrent episodes of binge eating; however, unlike BED sufferers, individuals with bulimia nervosa engage in extreme weight-control behaviors, such as self-induced vomiting, strict dieting, and the misuse of laxatives or diuretics (Fairburn et al. 2000). Bulimia nervosa patients are typically of normal body weight as a result of compensatory acts. Many of the underlying mechanisms for binge eating in bulimia nervosa resemble those contributing to BED.

Among both BED and bulimia nervosa sufferers, negative affect (e.g., anxiety, depression) has been acknowledged as a primary risk factor for binge eating (Stice et al. 2000). Largely accounting for the susceptibility to such depressive and anxious states associated with binge eating are genetically determined levels of brain neurotransmitters. Similarly, the brain neurotransmitters play a role in impulsivity and impulse control disorders – such as substance abuse, pathological gambling, conduct disorder, and attention deficit/(hyperactivity) disorder (AD[H]D) – which are often comorbid with binge eating disorders (Blum et al. 2000). A genetic contribution to binge eating is also suggested in twin studies testing for a familial transmission of the behavior (Bulik et al. 2003; Reichborn-Kjennerud et al. 2004). Moreover, candidate genes association studies support the role of certain genes in a predisposition to binge eating disorders. To date, the bulk of this research has focused on the genes contributing to the dopamine reward system.

168.3 Dopamine

The dopamine system is involved in several motor activities and cognitive functions. Dopamine neurons in the *mesolimbic* and *mesocortical* pathways – considered the brain's reward system – originate in the ventral tegmental area and, respectively, project to limbic structures including the nucleus accumbens and amygdala, and to the frontal cortex (Koob 1992; see Fig. 168.1). Along the mesolimbic pathway, dopamine is responsible for regulating our emotional capacity to feel pleasure and our desire and motivation to seek out rewarding experiences (Berridge 2003). The pleasure felt in response to these experiences reinforces certain behaviors and directs attention to relevant environmental cues by associating them with feelings of reward (Blum et al. 1996). Dopamine release in the nucleus accumbens (the "reward centre" of the brain) acts to promote an appetitive/approach response to reward cues that are contingent on carrying out a specific action (Nicola et al. 2005). For example, inactivation of the ventral tegmental area (the major dopaminergic input to the striatum) abolishes neuronal firing in the nucleus accumbens and reward-seeking responses to reinforcing stimuli such as food (Yun et al. 2004). These responses can also be reduced by administration of dopamine receptor antagonists (Nicola et al. 2005). On the other hand, a stimulant injection in the nucleus accumbens potentiates dopamine release and reward-related behavioral responding (Zangen et al. 2006).

Similar to the majority of bodily systems, dopamine response varies considerably across individuals (Davis and Fox 2008). In the case of the mesocorticolimbic pathways, those with inherently higher levels of dopamine availability are likely to have a larger hedonic capacity and a stronger
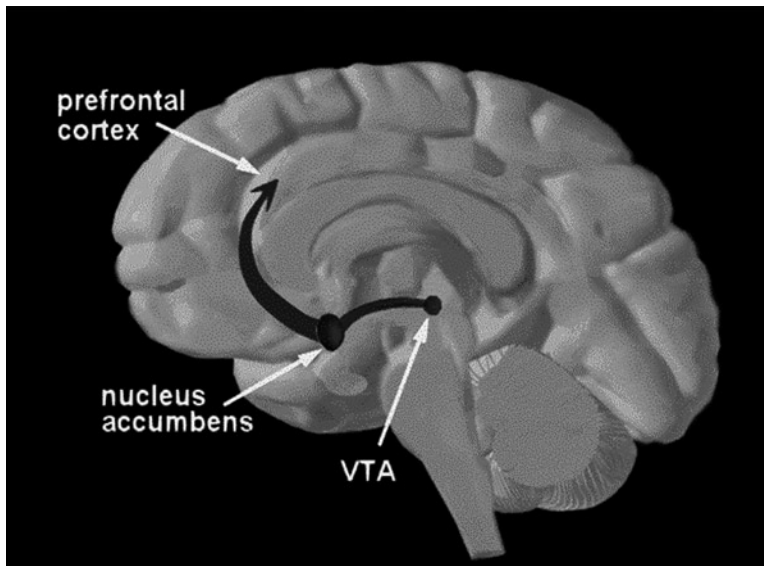
Fig. 168.1 Common reward pathway. All rewarding stimuli (e.g., food, sex) activate the same brain pathway: the mesolimbic pathway from the ventral tegmental area (*VTA*) to the nucleus accumbens, as well as the corticolimbic pathway from the nucleus accumbens up to the prefrontal cortex (Image adapted from National Institution on Drug Addiction (*NIDA*) at www.drugabuse.gov. NIDA cites this image as public domain and copyright permissions not required)

motivation to approach potentially pleasurable outcomes (Davis et al. 2004). In other words, they may experience greater pleasure from rewards, such as food, and therefore engage in more behaviors that will lead to its acquisition and consumption. Alternatively, a sluggish dopamine system is reflected in an anhedonic demeanor and a relative insensitivity to reward (Depue and Collins 1999).

Reduced dopamine availability is believed to place some individuals at increased risk of addictive behaviors according to the *reward deficiency syndrome* (RDS) (Blum et al. 2000). Basically, due to a breakdown in the brain "reward cascade," these individuals are said to require a "dopamine-fix" to feel good, and therefore, they are more likely to seek out stimuli that increase available dopamine such as illicit drugs (e.g., cocaine). The subcortical brain's response to reward does not appear to differentiate among being provoked by illicit drugs, natural reinforcers such as food or sex, or behavioral addictions such as gambling or shopping (Kelley et al. 2005). Nowadays, relative to drugs of abuse, highly caloric food represents an easily accessible, inexpensive, and reliable method to boost a sluggish dopamine system (Wang et al. 2004), and as a result, is one of the most common forms of self-medication (Davis et al. 2004).

The high comorbidity established clinically between substance-related and binge eating disorders supports the hypothesis of a shared biological basis. Moreover, chronic drug abuse and binge eating share many physiological and behavioral similarities, leading some experts to argue that non-homeostatic overeating is also appropriately modeled as an addictive behavior (Davis et al. 2004; Wang et al. 2004). Therefore, based on the RDS theory, researchers speculate dysfunctional dopamine availability due to variations in dopamine genes may predispose individuals to binge eating behaviors.

However, conflicting evidence suggests that an *elevated* dopamine signal also places individuals at risk for binge eating due to a stronger appetitive response to food cues. Consistent with these data, women who have high sensitivity to reward (and likely greater dopamine availability) were found to

report stronger food cravings (Franken and Muris 2005) and are more likely to overeat and binge eat (Davis and Fox 2008; Davis et al. 2004) compared with their less hedonic counterparts. Some experts propose that, similar to the response seen in substance abuse addicts, a downregulation may occur among obese individuals as their brain's way of compensating for chronically elevated dopamine levels produced by overeating, and this may account for the conflicting findings of low dopamine levels (Davis et al. 2004). Considering both theories, Davis and Fox (2008) suggest a dual vulnerability for overeating where low or high dopamine availability confers risk – albeit, in different individuals and perhaps with different levels of severity. Indisputably, several routes to obesity and binge eating exist, and are based on various biological vulnerability factors, including variations in the dopamine system.

168.4 Dopamine Transporter

Dopamine availability is highly polygenic, and primarily determined by the affinity and density of the dopamine transporters (DATs) and receptors, and the amount of dopamine synthesized and secreted into the synapse (Need et al. 2006). The DAT is a member of a family of sodium (Na$^+$) and chlorine (Cl$^-$) ion-dependent neurotransmitter transporters that is highly expressed in the human striatum and prefrontal cortex where it regulates the duration of dopamine activity (see Fig. 168.2; Cragg and Rice 2004). Specifically, as a membrane-spanning protein, the DAT functions by binding to dopamine to clear it from the synapse and transport it back into the neuron. Therefore, a greater density of DAT is believed to predict less dopamine reaching the postsynaptic cell (Table 168.2).

The human DAT1 gene (SLC6A3) that encodes for the DAT protein has been mapped to the short arm of chromosome 5 (5p15.3) and carries 15 exons (Giros et al. 1992; Vandenbergh et al. 1992).
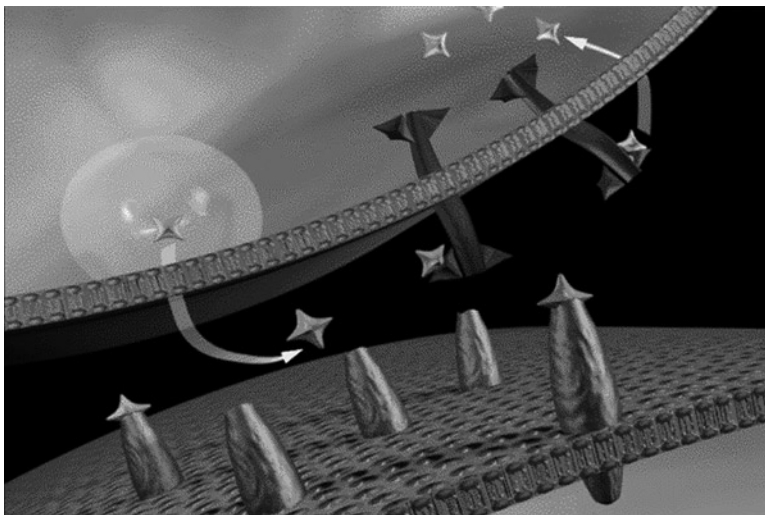
Fig. 168.2 Dopamine transporter at synapse. As synaptic vesicles release dopamine into the synapse, some dopamine binds to the dopamine receptors on the postsynaptic neuron and some of the neurotransmitter is transferred back into the presynaptic neuron by the dopamine transporters (*DATs*). (Image adapted from National Institution on Drug Addiction (*NIDA*) at www.drugabuse.gov NIDA cites this image as public domain and copyright permissions not required)

Table 168.2 Key features of the dopamine transporter (DAT)

	Dopamine transporter (DAT)
Form:	Membrane-spanning protein and member of family of Na$^+$ and Cl$^-$ ion-dependent neurotransmitter transporters
Location:	Highly expressed in human striatum and prefrontal cortex
Function:	Regulates the duration and strength of the DA signal
Action:	Binds to DA to clear it from synapse and transport it back into the presynaptic neuron
Predicted effect on DA levels:	Greater density of DAT → ↑ DA reuptake → ↓ DA availability

DA dopamine, *Na$^+$* sodium, *Cl$^-$* chlorine

Table 168.3 Key features of the dopamine transporter gene (DAT1)

	Dopamine transporter gene (DAT1; SLC6A3)
Form:	Carries 15 exons; highly polymorphic
Location:	Short arm of chromosome 5 (5p15.3)
Function:	Encodes DAT protein
Key polymorphism:	Functional 40-base pair VNTR in 3′ UTR in exon 15
Predicted effect on DA levels:	10-repeat → ↑ DAT binding site density → ↓ DA availability (Relative to 9-repeat)

DA dopamine, *DAT* dopamine transporter

Of the polymorphisms identified, a 40-base pair *variable number of tandem repeat* (VNTR) in the 3′ untranslated region (3′ UTR) in exon 15 has been the most extensively studied (Fuke et al. 2001; Heinz et al. 2000; Mill et al. 2002). VNTR polymorphisms are series of altered fragment lengths that are related to each other by sequences of variable number of tandem repeated DNA segments in an interval between two restriction sites. For this VNTR, repeat numbers vary from 3 to 13, with the 9- and 10-repeat alleles occurring with the greatest frequency in the majority of human populations (Giros et al. 1992; Vandenbergh et al. 1992).

Although there have been some inconsistent findings concerning the functional effect of the DAT1 VNTR polymorphism, it is generally agreed upon that the 10-repeat variant is associated with particularly efficient DATs (Mill et al. 2002). According to the best available evidence, the 10-repeat variant yields an approximately 50–90% elevated DAT binding site density in comparison to the 9-repeat allele (VanNess et al. 2005). That is, the 10-repeat variant produces a greater amount of DAT protein, diminishing activity in the dopamine pathways due to heightened transportation of dopamine from the synapse back into the presynaptic neuron. For this reason, the 10-repeat variant has been considered the "high-risk" allele for certain psychiatric syndromes and conditions, and widely investigated due to its central role in the regulation of striatal dopamine availability – a crucial determinant of motivation (Table 168.3) (Yang et al. 2007).

Evidence supports a shared genetic causative mechanism between binge eating and substance dependence involving the dopaminergic system. As mentioned above, the DAT is the main mechanism for dopamine clearance from the synapse in dopaminergic neurons found in the midbrain. Researchers have established a relationship between the DAT1 genetic variants and individual differences in vulnerability to addictive behaviors including smoking (Jorm et al. 2000), alcohol dependence and withdrawal (Sander et al. 1997), and cocaine abuse (Crits-Christoph et al. 2008). The DAT1 has also recently been linked to compulsive overeating and obesity (Epstein et al. 2004).

168.5 DAT1, Obesity, and Binge Eating

Consuming a well-prepared dish is among the most enjoyable experiences in life, and because humans find food so rewarding, we are strongly motivated to acquire it. If feeding were exclusively regulated by homeostatic mechanisms, most people would likely be at their ideal body weight, and would view eating in similar ways to breathing, for example, as an essential but uninteresting part of life. However, many individuals consume more food than is required for survival and compelling evidence suggests that individual differences in food reinforcement play a role in overeating and subsequent obesity. The reinforcing value of food is associated with dopaminergic system activity (Epstein et al. 2007). In fact, consumption of food causes a rise in dopamine levels (Hernandez and Hoebel 1990).

Altering brain dopamine levels has been found to affect eating, where dopamine agonists generally diminish caloric intake (Leddy et al. 2004) and dopamine antagonists increase consumption and body weight (Wellman 2005); although, there is great individual variation in the population in response to these drugs (Davis et al. 2007). In line with this direction of evidence, some genetic studies report that genotypes and alleles associated with *lower* dopamine availability are overexpressed among obese individuals. For instance, in a sample of participants with an African American background, the likelihood of obesity was 5.16 times greater among individuals possessing the homozygous 10-repeat genotype of the DAT1 3′ UTR VNTR compared to that of the 9/9 or 9/10 genotypes; although, no association was found among non-Hispanic white participants (Epstein et al. 2002). Similarly, Epstein et al. (2004) found that participants who demonstrated high levels of food reinforcement (as assessed by a behavioral choice questionnaire) and possessed the 10/10 genotype had significantly greater caloric intakes in a food consumption task compared to subjects in the other groups. However, subjects in these studies were regular smokers and this limits the generalizability of the findings. Long-term tobacco exposure results in an upregulation of DAT activity (Li et al. 2004), which leaves less available dopamine and can increase sensitivity to food reinforcement. Therefore, these findings may not be replicable among participants without a history of smoking. To this effect, a study conducted recently among a larger sample of nonsmokers did not find any significant association between the DAT1 and energy intake, or between the DAT1 and food reinforcement (Epstein et al. 2007).

In contrast, some evidence suggests that obese individuals possess *higher* levels of dopamine availability. For example, using single position emission computational topography (SPECT) to measure striatal DAT availability among 50 healthy volunteers, Chen et al. (2008) found a significant negative association between age and BMI with striatal DAT availability, and BMI was the only significant predictor for DAT density. In other words, higher BMIs predicted lower DAT density, which in turn, is associated with greater dopamine levels. Elevated dopamine availability is believed to lead to greater hedonic capacity and a stronger motivation to approach food. In support of this theory, obese individuals have been reported to find food more rewarding compared to their leaner counterparts (Saelens and Epstein 1996). Specific to binge eating, a case-control study of Japanese women found an excess of short alleles (7- and 9-repeats) of the DAT 3′ UTR VNTR among patients with clinically significant binge eating behaviors (Shinohara et al. 2004). These results suggest that a strong dopamine signal, due to a decrease in the DAT protein, increased the reinforcing value of food, leading to a tendency to binge eat.

In order to test the appetitive response to elevated dopamine levels, many studies have used stimulant medications. The DAT is of specific interest in these studies as it represents the primary site of action of psychomotor stimulants such as cocaine, methylphenidate, and amphetamines, which bind to the transporters, thereby inhibiting the reuptake of dopamine into the cell and increasing its availability in the synapse. In particular, response to methylphenidate – better known by the brand name

Table 168.4 A proposed theory of associations among the dopamine transporter, the dopamine signal, and psychobehavioral response (Adapted from first printing in Davis et al. 2007)

10-repeat allele	↑ DAT Protein → ↓ synaptic DA	Increased risk for AD(H)D and therapeutic response to methylphenidate; increased response to exogenous stimulants
9-repeat allele	↓ DAT Protein → ↑ synaptic DA	Increased risk for binge eating
↓ DA signal	↓ Hedonic tone and ↓ sensitivity to reward	Increased risk for drug addiction
↑ DA signal	↑ Hedonic tone and ↑ sensitivity to reward	Increased risk for overeating

DA dopamine, *DAT* dopamine transporter

Ritalin and the most common treatment for AD(H)D – has often been studied and results generally indicate that ingestion of a small oral dose of the drug increased desire to eat in response to palatable food cues among human participants (Volkow et al. 2002). However, very high stimulation of dopamine pathways produced by chronic drug abuse typically curbs appetite (Cochrane et al. 1998). The same effect is seen in animal studies where drugs causing a substantial rise in dopamine induce anorexia (Bina and Cincotta 2000; Kuo 2002).

To further examine this relationship, Davis and colleagues (Davis et al. 2007) conducted the first study testing the suppression of appetite due to methylphenidate in relation to DAT1 genotype variation. Participants' "favorite snack" was provided as a food cue to judge appetite ratings. The results revealed that individuals with BED possessing at least one copy of the 9-repeat allele had a significant decrease in appetite ratings in response to the methylphenidate, in comparison to control participants with the 9-repeat variants or to BED and controls with the 10/10 genotype – all three of whom had negligible differences in appetite ratings between drug and placebo conditions. Results support the role of genetic factors influencing dopamine availability in regulating appetitive response to methylphenidate. A study by Leddy et al. (2004) also revealed a varied response to methylphenidate in a small sample of obese adults. Following a large dose of the drug, participants were fairly equally divided among showing a large decrease, a small or moderate decrease, or even an increase in caloric intake, and these effects did not correlate with initial body weight.

Some experts interpret the varied DAT relationship with obesity and binge eating to indicate that dopamine activation and subjective response have an inverted-U relationship (Volkow et al. 1999). That is, a moderate boost in dopamine levels is believed to foster appetitive motivation; whereas, the opposite may occur with greater augmentation to very high dopamine levels, causing a suppression effect in the case of eating (Davis et al. 2007). Davis et al. (2007) have proposed that such a nonlinear relationship would assist in understanding some of the apparent contradictions in the literature regarding the relationship between dopamine activation and eating behavior. Evident variations in dopamine availability and responses to dopamine-related medications have important implications for obesity and binge eating treatment. Further examination of the dopamine-eating behavior relationship will assist in allowing better targeting of interventions to individual susceptibility (Table 168.4).

168.6 Implications for Treatment of Binge Eating and Obesity

Behavioral neurogenetic research has begun, and will continue, to enhance our understanding of individual susceptibility to binge eating and obesity in order to develop effective treatment and prevention efforts. This chapter has reported evidence highlighting the heterogeneity of obesity in terms of its diverse risk pathways, despite a long history of researchers and clinicians regarding all obese individuals as one homogeneous group. For this reason, individualized treatment approaches are

required and should be determined by factors such as the causes and forms of overeating, biological contributors, and comorbid conditions. Individuals engaging in binge eating represent one subgroup requiring specialized interventions.

Treatment for binge eating in bulimia nervosa typically includes antidepressant medications to target the negative affect and comorbid mood disorders that often underlie and trigger binge behaviors. In terms of general obesity treatments, and of particular relevance, some of the weight loss medications endorsed by the US Food and Drug Administration stimulate norepinephrine and dopamine release in a manner similar to methylphenidate (Rucker et al. 2007). The studies discussed above indicate that the effectiveness and appropriate dosages of these pharmaceutical treatments are largely dependent on patients' baseline dopamine availability and genetic makeup. This chapter focuses on the role of the DAT; however, dopamine availability and drug response depends on variations in several related genes. In the future, with a greater understanding of the polygenic contributors to dopamine availability and treatment response, genetic testing may allow for better targeting of appropriate medications and dosages.

Large-scale clinical trials support the success of some of these drugs in reducing food intake and cravings, and fostering significant long-term weight loss (Rucker et al. 2007). Although, while these medications may be effective among some individuals in controlling eating behavior, the drawback is that they operate on the same systems which moderate mood. This is particularly concerning considering the high prevalence of depression and anxiety disorders found among patients with bulimia nervosa, BED and obesity. For this reason, some of these medications have recently been removed from the market.

In terms of implications for non-pharmacological interventions, other naturally rewarding but healthier activities should be encouraged. For instance, social activities, sex, and exercise are associated with a moderate increase in dopamine. Greater positive reinforcement should be given to individuals for engaging in healthy eating and physical activities. The recently increased attention in controlling food advertising is also promising as commercials often conceptualize high-fat or fast foods as treats or rewards, and therefore, likely enhance the motivation to eat them and the reinforcing value derived from their consumption. Moreover, the food consumed today has progressively moved toward high sugar and processed fare, some of which resembles drugs more closely than the natural whole foods our ancestors consumed. In fact, highly palatable, high-fat foods provoke a larger increase in dopamine relative to the consumption of healthier foods (Berridge 2003). Tackling our obesogenic environment is a necessary but particularly difficult route, and results will not likely be evident for several years. Currently, one of the most promising approaches appears to be first treating the comorbid disorders, such as depression and AD(H)D, which may contribute to, or exacerbate, binge eating.

168.7 Applications to Other Areas of Health and Disease: AD(H)D

The DAT1 has also been implicated in AD(H)D – a lifespan disorder characterized by developmentally age-inappropriate signs of impulsiveness, inattention, and/or hyperactivity (APA 2000). Relatively recently, it has been recognized that AD(H)D and obesity often coexist (Agranat-Meged et al. 2005). The occurrence of AD(H)D is especially high among individuals with Class III or morbid obesity (BMI > 40 kg/m^2), representing almost half of the sample in one study (42.6%) (Altfas 2002). Adding to the problem is the particular difficulty these individuals have adhering to weight loss programs – as evidenced by the greater clinic visits and longer treatment duration found among adults with AD(H)D attending a weight loss program relative to their non-AD(H)D counterparts (Altfas 2002). Among children with AD(H)D, the prevalence of overweight and obesity is also

significantly greater than the age-matched population. For instance, in a study of obese school-aged children, over half (57.7%) suffered from co-morbid AD(H)D (Agranat-Meged et al. 2005).

Recent reports indicate that overeating, and binge eating in particular, moderate the relationship between AD(H)D and obesity (Davis et al. 2006). Adults with AD(H)D were found to have a higher prevalence of BED compared to the general population (Mattos et al. 2004), and similarly, a sample of adolescents with AD(H)D was more likely to engage in binge eating than controls (Neumark-Sztainer et al. 1995). AD(H)D symptoms could plausibly predispose individuals specifically to binge eating.

The comorbidities suggest that symptoms or biological factors associated with the disorder increase the risk of weight gain and binge eating. Genetic and neuroimaging research generated the dopamine-dysfunction hypothesis for the etiology of AD(H)D, leading some researchers to propose the AD(H)D-obesity link partially results from sub-optimal dopamine levels (Davis et al. 2006). In support of this theory, several reports indicate that DAT density is approximately 70% greater in AD(H)D cases compared to healthy controls (Yang et al. 2007). In addition, numerous studies and meta-analyses have reported a significant association between the 10-repeat variant of the DAT1 VNTR in the 3′ UTR and the disorder (e.g., Yang et al. 2007), leading to its designation as the "high-risk allele" for AD(H)D; although, there has been some conflicting evidence.

Similar to the varied appetitive response to methylphenidate, the DAT1 appears to regulate treatment response to methylphenidate among AD(H)D patients. Studies indicate the poorest response occurs among individuals homozygous for the 9-repeat allele, whereas the best treatment response is associated with the 10/10 genotype (Bellgrove et al. 2005). As discussed above, the greater effectiveness of treatment in 10-repeat individuals is proposed to occur because it ameliorates a hypodopaminergic state mediated by DAT1. Results have direct implications for treatment approaches for AD(H)D, as well as for the binge eating behaviors found among many of these patients. Awareness of the association and the biological mechanisms will assist in obesity prevention among individuals diagnosed with AD(H)D, and obesity and binge eating treatment among individuals whose previous efforts have been hindered by AD(H)D symptoms.

168.8 Conclusion

The strong links with weight gain and the serious medical and psychiatric morbidities associated with binge eating and related disorders, indicate the behavior demands further exploration. Binge eating emerged in our society relatively recently, in part as a response to environmental factors, such as the altered food composition, decline of family meals, and increased depression rates. There is little doubt that the environment plays an important role in sustaining, if not increasing, current obesity and overeating rates. Nevertheless, not everyone in our obesogenic environment regularly overeats or has difficulty maintaining a healthy weight, suggesting that gene-environment interactions are likely to contribute to individual vulnerability.

The purpose of this chapter was to discuss the role of the DAT1 – encoding the protein responsible for regulating the strength and duration of the dopamine signal, and one of several genes that have been linked to food intake and body weight. Dopamine is an important and necessary neurotransmitter involved in eating behavior. Without it, we would have little motivation to eat because doing so would provide us little pleasure, as witnessed in rat gene knock-out studies. Hedonic motivations often appear to overpower homeostatic mechanisms regulating energy consumption, leading to consumption beyond caloric need. Based on this evidence, interventions aimed at regions within the reward system will likely be required to control eating behavior among individuals engaging in binge eating in order to achieve and maintain a healthy body weight. To date, a comprehensive strategy to address obesity and/or binge

eating disorders has yet to be established; although, recent and continuing advances in molecular genetics and neuroscience have greatly improved our understanding of the physiology of energy intake and have brought us closer to developing effective treatments. In the future, using a genetic approach to study eating behavior may enable us to identify susceptible individuals and allow for early intervention to prevent binge eating and weight gain, as well as their many comorbid disorders.

Summary Points

- Binge eating represents an extreme form of hedonic overeating and is defined as the consumption of an abnormally large amount of food in a limited time span in the absence of hunger. Binge eating is a central symptom of both bulimia nervosa and BED.
- Bulimia nervosa is characterized by recurrent episodes of binge eating and extreme weight-control behaviors such as purging, dieting, excessive exercise, and/or diet pill, laxative or diuretic use; whereas, individuals with BED engage in regular binge eating without the use of compensatory behaviors and are typically obese as a result.
- Evidence indicates a genetic contribution to predisposition to binge eating and associated disorders, with the majority of neurogenetic research focusing on the role of the brain neurotransmitter dopamine.
- Dopamine is responsible for regulating our motivation to seek out rewarding experiences and directing attention to relevant environmental cues by associating them with feelings of reward or pleasure.
- The action of dopamine on the brain's "Common Reward Pathway" is primary accountable for hedonic motivations for eating. Dopamine availability along these pathways varies considerably across individuals in the population, and this variation is believed to be partly attributable for individual differences in the tendency to binge eat.
- Two routes are evidenced to lead to bingeing. Based on the RDS model, individuals engage in compulsive overeating as a means to self-medicate low dopamine levels; whereas, a conflicting theory proposes that high dopamine levels are to blame as they cause a greater hedonic capacity and motivation to eat. Dopamine availability is highly polygenic and largely determined by factors including the affinity and density of dopamine transporters and receptors.
- The DAT is expressed in the striatum and prefrontal cortex, where it regulates the strength and duration of the dopamine signal by binding to synaptic dopamine and transporting it back into the neuron.
- The DAT1 gene that encodes the DAT protein contains a functional VNTR polymorphism in the 3′ UTR with the 10- and 9-repeat alleles occurring with the greatest frequency in the general population.
- The 10-repeat variant is associated with an elevated DAT binding site density (i.e., heightened dopamine reuptake and therefore, lower dopamine availability) compared to DATs encoded by the 9-repeat variant.
- In support of the RDS theory, some evidence indicates the 10-repeat allele – associated with lower dopamine availability – is overexpressed among obese individuals; although, more research is required as existing literature is likely confounded by the influence of comorbid smoking behaviors.
- In contrast, women engaging in binge eating behaviors were found to have a higher prevalence of the 9-repeat allele, which has also been associated with higher BMIs.
- An inverted-U relationship is hypothesized between dopamine availability and subjective response, based on studies using stimulant medications to boost dopamine in order to test the appetitive effect. That is, a moderate rise in dopamine levels is believed to increase appetite, whereas, very high dopamine augmentation likely suppresses eating.

Definitions of Key Terms

Binge eating: Binge eating is defined as the consumption of an amount of food that is unquestionably larger than most people would eat under normal circumstances within a discrete period of time (i.e., less than 2 h; APA 2000).

Binge eating disorder (BED): BED is characterized by recurrent episodes of binge eating (2–3 times per week for a minimum of 6 months) without the use of inappropriate compensatory behaviors, such as self-induced vomiting, misuse of laxatives or diet pills, fasting, or excessive exercising (APA 2000).

Bulimia nervosa: Bulimia nervosa is an eating disorder characterized by binge eating and inappropriate compensatory methods to prevent weight gain. In order to meet diagnostic criteria, a person must engage in binge eating and compensatory behaviors on average at least twice a week for the past 3 months (APA 2000).

Dopamine: Dopamine is a neurotransmitter that plays an important role in motivation and pleasure. Dopamine is characterized as a catecholamine (a molecule that acts as a neurotransmitter and/or hormone). It affects brain processes that control movement, emotional response, and ability to experience pleasure and pain.

Common reward pathway: Also referred to as the *mesocorticolimbic* pathway, the Common Reward Pathway is a circuitry in the brain that regulates and activates behaviors necessary for survival, such as feeding, sex, and maternal behavior. This pathway also underlies the development and maintenance of addictions.

Dopamine transporter (DAT): The DAT is a membrane-spanning protein that binds to synaptic dopamine. The DAT clears dopamine from the synapse, reuptaking it back into the presynaptic neuron, which ultimately leads to the termination of the dopamine signal.

DAT1 gene: The human DAT1 gene (SLC6A3) encodes for the DAT protein. It has been mapped to the short arm of chromosome 5 (5p15.3) and carries 15 exons. The gene is highly polymorphic, containing a functional VNTR in the 3′ UTR which is associated with DAT density.

Reward Deficiency Syndrome (RDS): According the RDS theory, deficient levels of dopamine in the reward pathways of the brain leave individuals susceptible to engaging in addictive behaviors as a means of increasing available dopamine.

Hedonic/non-homeostatic eating: As opposed to homeostatic eating, hedonic eating refers to food consumption driven by reasons other than survival, for example, to comfort emotional states (e.g., boredom, depressed mood) or for enjoyment in social situations.

Thrifty Gene hypothesis: The Thrifty Gene hypothesis postulates that genes predisposing individuals to overeating and obesity evolved because they were once beneficial. The ability to store excess energy as fat in times of food abundance was advantageous in order to increase one's chances of survival during times of famine.

Variable Number Tandem Repeat (VNTR): A VNTR is a gene polymorphism where a sequence of nucleotides is repeated a number of times in an interval between two restriction sites, causing different fragment lengths. The number of times the sequence is repeated varies within the population.

References

Agranat-Meged AN, Deitcher C, Goldzweig G, Leibenson L, Stein M, Galili-Weisstub E. Int J Eat Disord. 2005;37:357–9.

Altfas JR. BMC Psychiatry. 2002;2:9.

American Psychiatric Association. Diagnostic and statistical manual. 4th ed. Text revision. Washington, DC: American Psychiatric Association Press; 2000.

Bellgrove MA, Hawi Z, Kirley A, Fitzgerald M, Gill M, Robertson IH. Neuropsychopharmacology. 2005;30:2290–7.

Berridge KC. Brain Cogn. 2003;52:106–28.

Bina KG, Cincotta AH. Neuroendocrinology. 2000;71:68–78.

Blum K, Braverman ER, Holder JM, Lubar JF, Monastra VJ, Miller D, Lubar JO, Chen TJ, Comings DE. J Psychoactive Drugs. 2000;32 (Suppl. i–iv):1–112.

Blum K, Sheridan PJ, Wood RC, Braverman ER, Chen TJ, Cull JG, Comings DE. J R Soc Med. 1996;89:396–400.

Bulik CM, Sullivan PF, Kendler KS. Int J Eat Disord. 2003;33:293–8.

Chen PS, Yang YK, Yeh TL, Lee I-H, Yao WJ, Chiu NT, Lu RB. NeuroImage. 2008;40(1):275–9.

Cochrane C, Malcolm R, Brewerton T. Addict Behav. 1998;23:201–7.

Cragg SJ, Rice ME. Trends Neurosci. 2004;27:270–7.

Crits-Christoph P, Newberg A, Wintering N, Ploessl K, Gibbons MB, Ring-Kurtz S, Gallop R, Present J. Drug Alcohol Depend. 2008;98:70–6.

Cummings DE, Schwartz MW. Annu Rev Med. 2003;54:453–71.

Davis C, Fox J. Appetite. 2008;50:43–9.

Davis C, Levitan RD, Kaplan AS, Carter J, Reid C, Curtis C, Patte K, Hwang R, Kennedy JL. Prog Neuropsychopharmacol Biol Psychiatry. 2008;32:620–8.

Davis C, Levitan RD, Kaplan AS, Carter J, Reid C, Curtis C, Patte K, Kennedy JL. Neuropsychopharmacology 2007;32:2199–206.

Davis C, Levitan RD, Smith M, Tweed S, Curtis C. Eat Behav. 2006;7:266–74.

Davis C, Strachan S, Berkson M. Appetite. 2004;42:131–8.

Depue RA, Collins PF. Behavioral and Brain Sciences. 1999;22:491–569.

Epstein LH, Jaroni JL, Paluch RA, Leddy JJ, Vahue HE, Hawk L, Wileyto EP, Shields PG, Lerman C. Obes Res. 2002;10:1232–40.

Epstein LH, Temple JL, Neaderhiser BJ, Salis RJ, Erbe RW, Leddy JJ. Behav Neurosci. 2007;121:877–86.

Epstein LH, Wright SM, Paluch RA, Leddy JJ, Hawk LW, Jr., Jaroni JL, Saad FG, Crystal-Mansour S, Shields PG, Lerman C. Am J Clin Nutr. 2004;80:82–8.

Fairburn CG, Cooper Z, Doll HA, Norman P, O'Connor M. Arch Gen Psychiatry. 2000;57:659–65.

Franken IH, Muris P. Appetite. 2005;45:198–201.

Fuke S, Suo S, Takahashi N, Koike H, Sasagawa N, Ishiura S. Pharmacogenomics J. 2001;1:152–6.

Giros B, el Mestikawy S, Godinot N, Zheng K, Han H, Yang-Feng T, Caron MG. Mol Pharmacol. 1992;42:383–90.

Heinz A, Goldman D, Jones DW, Palmour R, Hommer D, Gorey JG, Lee KS, Linnoila M, Weinberger DR. Neuropsychopharmacology. 2000;22:133–9.

Hernandez L, Hoebel BG. Brain Res Bull. 1990;25:975–9.

Jeffery RW, Utter J. Obes Res. 2003;11 (Suppl.):12S–22S.

Jorm AF, Henderson AS, Jacomb PA, Christensen H, Korten AE, Rodgers B, Tan X, Easteal S. Am J Med Genet. 2000;96:331–4.

Kelley AE, Schiltz CA, Landry CF. Physiol Behav. 2005;86:11–4.

Koob GF. Trends in Pharmacological Science. 1992;13:177–84.

Kuo DY. J Biomed Sci. 2002;9:126–32.

Leddy JJ, Epstein LH, Jaroni JL, Roemmich JN, Paluch RA, Goldfield GS, Lerman C. Obes Res. 2004;12:224–32.

Li LB, Chen N, Ramamoorthy S, Chi L, Cui XN, Wang LC, et al. J Biol Chem. 2004;279:21012–20.

Mattos P, Saboya E, Ayrao V, Segenreich D, Duchesne M, Coutinho G. Rev Bras Psiquiatr. 2004;26:248–50.

Mill J, Asherson P, Browes C, D'Souza U, Craig I. Am J Med Genet. 2002;114:975–9.

Need AC, Ahmadi KR, Spector TD, Goldstein DB. Ann Hum Genet. 2006;70:293–303.

Nestle M. J Am Diet Assoc. 2003;103:39–40.

Neumark-Sztainer D, Story M, Resnick MD, Garwick A, Blum RW. Arch Pediatr Adolesc Med. 1995;149:1330–5.

Nicola SM, Taha SA, Kim SW, Fields HL. Neuroscience. 2005;135:1025–33.

Peters JC. Obes Res. 2003;11 (Suppl.):7S–11S.

Reichborn-Kjennerud T, Bulik CM, Tambs K, Harris JR. Int J Eat Disord. 2004;36:307–14.

Rucker D, Padwal R, Li SK, Curioni C, Lau DC. BMJ. 2007;335:1194–9.

Saelens BE, Epstein LH. Appetite. 1996;27:41–50.

Sander T, Harms H, Podschus J, Finckh U, Nickel B, Rolfs A, Rommelspacher H, Schmidt LG. Biol Psychiatry. 1997;41:299–304.

Saper CB, Chou TC, Elmquist JK. Neuron. 2002;36:199–211.

Shinohara M, Mizushima H, Hirano M, Shioe K, Nakazawa M, Hiejima Y, Ono Y, Kanba S. J Psychiatry Neurosci. 2004;29:134–7.

Stice E, Akutagawa D, Gaggar A, Agras WS. Int J Eat Disord. 2000;27:218–29.

Striegel-Moore RH, Franko DL. Int J Eat Disord. 2003;34 (Suppl.):S19–29.

Vandenbergh DJ, Persico AM, Hawkins AL, Griffin CA, Li X, Jabs EW, Uhl GR. Genomics. 1992;14:1104–6.

VanNess SH, Owens MJ, Kilts CD. BMC Genet. 2005;6:55.

Volkow ND, Wang G-J, Fowler JS, Logan J, Gatley SJ, Gifford A, Hitzemann R, Ding Y-S, Pappas N. American Journal of Psychiatry. 1999;156:1440–3.

Volkow ND, Wang GJ, Fowler JS, Logan J, Franceschi D, Maynard L, Ding YS, Gatley SJ, Gifford A, Zhu W, Swanson JM. Synapse. 2002;43:181–7.

Wang GJ, Volkow ND, Thanos PK, Fowler JS. J Addict Dis. 2004;23:39–53.

Wellman PJ. Curr Drug Targets. 2005;6:191–9.

Yang B, Chan RC, Jing J, Li T, Sham P, Chen RY. Am J Med Genet B Neuropsychiatr Genet. 2007;144B:541–50.

Yanovski SZ. Int J Eat Disord. 2003;34 (Suppl.):S117–20.

Yun IA, Wakabayashi KT, Fields HL, Nicola SM. J Neurosci. 2004;24:2923–33.

Zangen A, Solinas M, Ikemoto S, Goldberg SR, Wise RA. J Neurosci. 2006;26:4901–7.

Chapter 169
Feeding and Satiety Signals in Prader-Willi Syndrome: Relation to Obesity, Diet, and Behavior

Maithe Tauber, Emmanuelle Mimoun, Patrick Ritz, and Gwenaelle Diene

Abbreviations

AgRP	Agouti-Related Peptide
AP	Area Postrema
ARC	Arcuate Nucleus
BBB	Blood Brain Barrier
BMI	Body Mass Index
CNS	Central Nervous System
DMH	Dorsomedial Hypothalamus
FISH	Fluorescence In Situ Hybridization
fMRI	Functional MRI
FTT	Failure to Thrive
GH	Growth Hormone
GHR	Ghrelin Receptor
GnRH	Gonadotrophin Releasing Hormone
IQ	Intelligence Quotient
mPFC	Medial Prefrontal Cortex
MRI	Magnetic Resonance Imaging
NA	Nucleus Accumbens
NPY	Neuropeptide Y
NTS	Nucleus Tractus Solitarius
OFC	Orbitofrontal Cortex
OXM	Oxyntomodulin
PFC	Pre Frontal Cortex
PP	Pancreatic Polypeptide
PVN	Paraventricular Nucleus
PWS	Prader-Willi Syndrome
PYY	Peptide YY
UPD	UniParental Disomy

M. Tauber (✉)

Centre de référence du syndrome de Prader-Willi, Hôpital des Enfants, 330 av de Grande Bretagne, TSA 70034, 31059 Toulouse Cedex 9, France

e-mail: tauber.mt@chu-toulouse.fr

VMH   Ventromedial Hypothalamus
VTA   Ventral Tegmental Area
VTA   Ventral Tegmental Area

169.1 Introduction

Prader-Willi syndrome (PWS) is a complex multisystem genetic disorder that arises from the lack of expression of paternally inherited imprinted genes on chromosome 15q11-q13. The syndrome has characteristic phenotypes (Gunay-Aygun et al. 2001), including severe neonatal hypotonia, early onset of hyperphagia, and the development of morbid obesity, short stature, hypogonadism, learning disabilities, behavioral problems, and psychiatric disturbances with severe consequences that pose difficult management issues for patients, families, and caregivers. Recent epidemiological surveys have estimated the lower limit of birth incidence at about 1 in 30,000, and the population prevalence at about 1 in 50,000. Other recent studies have highlighted the high rates and varied causes of morbidity and mortality throughout the natural history of the disease, mainly due to obesity complications (Schrander-Stumpel et al. 2004; Tauber et al. 2008). Early diagnosis and an integrated multidisciplinary approach improve quality of life, prevent complications (particularly childhood obesity), and prolong life expectancy (Bachere et al. 2008).

169.2 Diagnosis of PWS

In the past few years, the diagnosis has been increasingly made during the first months of life. As clinical signs vary with age, the diagnostic criteria from Holm et al. (Holm et al. 1993) have been modified to improve the description of the signs that should lead to genetic testing (see Table 169.1) (Gunay-Aygun et al. 2001).

There are different methods for confirming the diagnosis and identifying the genetic subtype using peripheral blood lymphocytes. DNA methylation analysis is the only technique that can both confirm and reject the diagnosis of PWS and should therefore be the initial investigation of choice. Parental samples are not required for this analysis. If DNA methylation analysis shows only a maternal pattern, then PWS is confirmed. Further methods may then be performed to determine the genetic subtype and to guide genetic counseling, particularly with regard to the risk of recurrence. Fluorescence In Situ

Table 169.1 Indications for DNA testing (Copyright 2008, the Endocrine Society)

Age at assessment	Features sufficient to prompt DNA testing
Birth to 2 years	• Hypotonia with poor suck
2–6 years	• Hypotonia with a history of poor suck
	• Global developmental delay
	• Short stature and/or growth failure associated with accelerated weight gain[a]
6–12 years	• Hypotonia with a history of poor suck (hypotonia often persists)
	• Global developmental delay
	• Excessive eating (hyperphagia, obsession with food) with central obesity if uncontrolled
13 years through adulthood	• Cognitive impairment, usually mild mental retardation
	• Excessive eating (hyperphagia, obsession with food) with central obesity if uncontrolled
	• Hypothalamic hypogonadism and/or typical behavior problems (including temper tantrums and obsessive-compulsive features)

[a]This item was added by the authors (Goldstone et al. 2008)
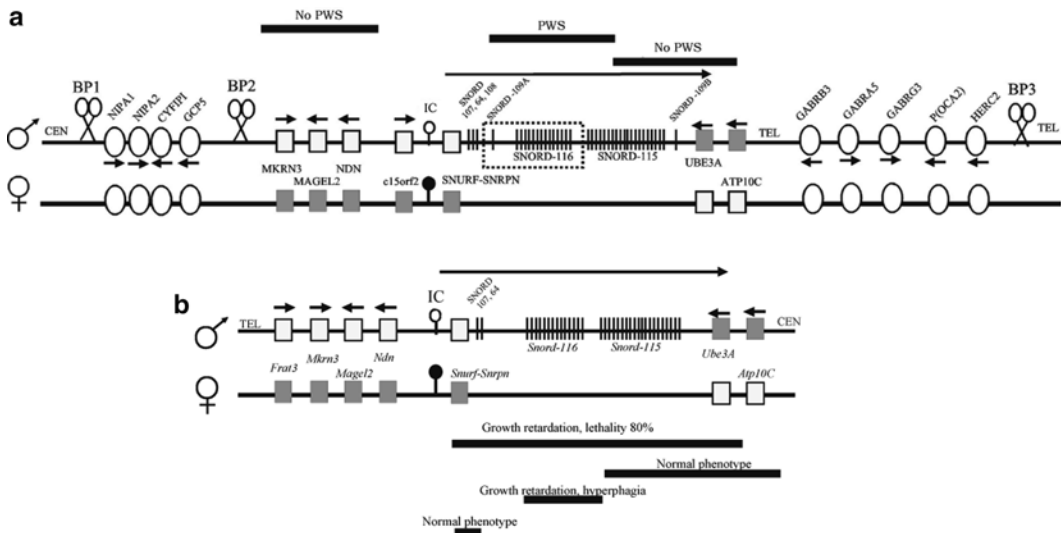
Fig. 169.1 PWS chromosomal region on 15q11-q13 (not to scale) (**a**) and murine orthologous region (**b**). Imprinted genes are white boxes (paternal allele expressed) and grey boxes (maternal allele expressed) and nonimprinted genes are white ovals. Vertical bars indicate snoRNA C/D genes. BP1, BP2, and BP3 indicate common breakpoint (BP) regions for deletions: type I deletions are between BB1 and BP3, and type II deletions are between BP2 and BP3. Arrows indicate transcription direction and horizontal black bars represent some informative deletions. Empty and plain circles indicate, respectively, the hypo- and hypermethylated region overlapping imprinting center (IC). A frame indicates the minimal critical region likely to contain a gene of major interest for PWS (SNORD116 cluster)

Hybridization (FISH) and high-resolution chromosome analysis can detect chromosome 15q11-q13 deletions in PWS.

As a whole, 70% of patients present with a deletion, 25% with maternal uniparental disomy (UPD), 1–3% with imprinting defects, and the remaining few with translocation involving chromosome 15. Most cases are sporadic but a high recurrence risk is associated with imprinting defects.

Figure 169.1 shows the complexity of the chromosomal PWS region in man (A) and mouse (B).

169.3   Description of Nutritional Phases

The two classical phases: PWS has been classically described as having two phases: (1) poor feeding and frequent failure to thrive in infancy (FTT), and (2) onset of hyperphagia leading to obesity (Gunay-Aygun et al. 2001). Phase 1 occurs from birth to early infancy when infants with PWS have severe hypotonia and a poor ability to suck and often require tube feeding. FTT refers to the lack of weight gain despite normal calorie intake. Phase 2 is described as beginning between 1 and 6 years, usually between 2 and 4 years (Gunay-Aygun et al. 2001). Recent examination of the natural history suggests a more complex progression leading to four main nutritional phases with subphases in the first two (McCune H 2005).

169.3.1   Four Nutritional Phases

Not all PWS individuals go through all the phases and subphases, which may be further altered by the use of GH (see Sect. 169.7).

In the first phase, the infant is hypotonic and is not yet obese. Subphase 1a consists of feeding difficulties with or without FTT. In subphase 1b, the infant grows steadily along a growth curve, at a normal rate.

In the second phase, which occurs between 18 and 36 months of age, body weight and BMI start to increase very rapidly. In subphase 2a, the child's weight increases in such a way that it crosses one, two, or more weight percentiles without a significant increase in calorie intake. In subphase 2b, the child increases his or her daily calorie intake, becomes more autonomous and turns overweight or obese, and displays an abnormally increased interest in food. Still, the appetite is not insatiable and unrelenting as it is in phase 3.

Phase 3 starts as early as 3 years of age or as late as 15 years. This is the classical phase that most people typically associate with PWS, with aggressive food-seeking and markedly reduced satiety. Patients in phase 3 have delayed meal termination and require significantly greater calorie intake to experience loss of hunger compared with those without PWS.

In phase 4, an individual may still have an increased appetite, but it is not as aggressive and unrelenting as previously observed and seems to occur only in a subset of adults typically after 30 years of age.

169.4 Eating Behavior and Food Preferences

Children with PWS present a particular meal pattern with a slower initial eating rate but much longer meal duration and nondecelerating eating curves. They are also distinguished by an early return of hunger after the previous meal, with early meal initiation. These findings were demonstrated by Lindgren et al. (Lindgren et al. 2000) using an elegant protocol to study nine subjects with PWS (compared with obese and normal weight subjects). These subjects were served a copious lunch on a hidden scale built into a table and connected to a computer. The authors concluded that the eating behavior of patients with PWS might be due to decreased satiation rather than increased hunger.

Given free access to food, patients with PWS will consume approximately three times more than control subjects, according to Zipf and Bernston (Zipf and Berntson 1987). These authors examined food intake patterns in ten patients with PWS and nine age- and weight-matched obese children by making standard chicken-salad sandwich quarters continuously available for one hour. Moreover, this overeating occurs despite delayed gastric emptying, leading to extremely morbid obesity.

Exploring food preferences, Fieldstone et al. (Fieldstone et al. 1997) elaborated a taste test with three types of foods (high carbohydrate, high protein, and high fat) reduced to spread consistency. PWS subjects preferred high carbohydrate foods over high protein foods and high protein foods over high fat foods. Moreover, the preference for high carbohydrate foods was significantly higher in PWS subjects than in obese controls. In addition, PWS patients are more likely than controls with and without mental retardation to eat nonfood items (pica) and contaminated foods and to make inappropriate food combinations.

Overall, the drive for food remains a life-long source of stress for individuals with PWS and their families. Complications of obesity remain the major cause of deaths in adults with PWS in relation with cardiovascular or respiratory failures. These patients are also at risk of choking due to a swallowing defect combined with their abnormal voracity or gastric perforation after consuming high quantities of food, even in the absence of obesity (Stevenson et al. 2007).

169.5 Evaluation of Hyperphagia and Feeding Disorders in Patients with PWS

Measuring hyperphagia in PWS has long been a research challenge. The abnormal feeding behavior in PWS includes a morbid obsession with food, food stealing, money stealing to buy food, hoarding and foraging, pica behavior, reduced satiety, and early return of hunger after the last meal (Goldstone 2004).

As described above, the first studies on PWS eating behavior provided unlimited access to food to patients and measured the number of sandwich quarters consumed. This methodology was questioned, and specific questionnaires were subsequently developed. In 2003, Russell and Oliver (Russell and Oliver 2003) proposed a 16-item informant-based Food Related Problem Questionnaire with three subscales (preoccupation with food, impairment of satiety, and other food-related 'challenging' behavior) for people with PWS. More recently, Dykens et al. (Dykens et al. 2007) developed a 13-item Hyperphagia Questionnaire to be filled out by parents or caregivers. The development of this questionnaire sets a landmark for future research on the eating behavior of patients with PWS (see article by Dykens in chapter 2.1). It also provides insight into the connections between the various behavioral features of the syndrome, as well as the connections between behavioral and neuronal or biochemical features.

Further research should focus on the role of maladaptive behaviors or emotional problems in the manifestation of hyperphagia in PWS and the mechanisms associated with individual variability, including genetic subtypes, neurobiological factors, emotional functioning, development and aging, and therapeutic interventions.

169.6 Mechanisms Involved in Hyperphagia and Feeding Problems

169.6.1 Feeding and Satiety Signals

PWS has been described as a genetic hypothalamic syndrome, although the phenotype and pathophysiology of the so-called hypothalamic dysfunction have yet to be reported in detail. The necdin gene, which is located in the 4 Mbp PWS chromosomal region, has been clearly implicated in preventing apoptosis of hypothalamic gonadotrophin-releasing hormone (GnRH) neurons. The Magel 2 gene (another candidate gene close to necdin in the PWS region) seems to be involved in hypocretin regulation and sleep control, with an involvement of hypothalamic neurons. Nevertheless, paternal deletion of the three genes – necdin, MKRN-3, and Magel 2 – does not result in the PWS phenotype in humans (Kanber et al. 2009).

Recently, the major components of the distributed neural system controlling food intake and energy balance were extensively reviewed. Over the past 10 years, the limited view of a few mainly hypothalamic centers has gradually been modified by evidence of a much more complex and distributed system including various corticolimbic areas. It is now recognized that cognitive, hedonic, and emotional neural processes play important roles in energy intake and expenditure and in the resulting energy balance, and that hormones modulate many of these processes. This model fits very well with what is known about the integrated dysfunctions in PWS that encompass the hypothalamus and brain regions involved in cognitive, social, and affective processes.

169.6.2 Elevated Ghrelin Levels in PWS

The most striking and specific defect in the satiety signals in PWS is the high circulating level of the orexigenic stomach-derived hormone ghrelin. Ghrelin is a 28-amino acid acylated peptide, first isolated from stomach in 1999, with a strong orexigenic effect, and it is the most potent GH secretagogue through its hypothalamic actions. Ghrelin is now considered a pleiotropic hormone with various secreting organs (duodenum, pancreas, pituitary, hypothalamus, testis, ovary, bone, and cartilage) and a wide range of target tissues depending on its acylation status (hypothalamus, stomach and gut, pancreas, adipose and cardiovascular tissues, testis, ovaries, and muscle), acting through distinct receptors (Hosoda et al. 2006). A specific enzyme, Gastric O acyl transferase (GOAT), was recently reported to be involved in ghrelin acylation and may have an important regulatory role. In addition, the ghrelin antisense strand gene GHRLOS, a recently reported candidate non-coding RNA gene, may have a regulatory and functional role in the ghrelin axis.

There are two reservoirs of ghrelin: the gastrointestinal tract and the central nervous system (CNS). Most circulating ghrelin is released by the stomach into the general circulation and can cross the blood–brain barrier (BBB) in a highly regulated process (Banks et al. 2002). In the CNS, ghrelin is produced in the major site for feeding regulation, the arcuate nucleus (ARC), and by a group of neurons adjacent to the third ventricle between four hypothalamic nuclei: dorsomedial (DMH), ventromedial (VMH), paraventricular (PVN), and ARC. Interestingly, these neurons also express ghrelin receptor GHR1a, which specifically binds acylated ghrelin. Receptors have also been identified in other areas such as the dorsovagal complex which includes nucleus tractus solitary (NTS), area postrema (AP), and dorsal motor nucleus of the vagus. In these areas, the density of GHRs is higher in fasting rats than in fed ones. The vagal nerve obviously plays a crucial but not mandatory role in driving the central actions of ghrelin (Date et al. 2002).

Regarding its role at the level of the ARC, ghrelin demonstrated opposite effects to leptin, another hormone involved in the control of food intake and energy homeostasis that is secreted by adipocytes and acts on the same hypothalamic neurons (Schwartz and Morton 2002). Ghrelin increases NPY and AgRP release. Leptin also plays a role in neuronal plasticity and particularly in the implementation of neuronal pathways in early life; its levels appear to be normal in people with PWS.

Circulating ghrelin levels have been shown to be low in obesity, suggesting that conversely to leptin, there is no ghrelin resistance in obesity. Individuals with PWS, unlike those with other known causes of obesity, have hyperghrelinemia (Cummings et al. 2002; Haqq et al. 2003; Tauber et al. 2004), which could explain at least two major endocrine dysfunctions observed in these patients: obesity and GH deficiency (described in 40–100% of the patients and explaining the short stature). GH deficiency could be explained by ghrelin resistance, whereas obesity could result from a preserved action of ghrelin on appetite centers, possibly due to different receptors or modulators. Nevertheless, ghrelin levels were reported to be negatively correlated with visceral adiposity, fasting insulin, and the homeostasis model assessment insulin resistance index (Goldstone et al. 2005) in adults with PWS. Ghrelin levels decreased with age, in controls, and in patients with PWS (Cummings et al. 2002; Haqq et al. 2003). Most of the studies documented an inverse correlation between ghrelin levels and BMI in the individuals with PWS (Haqq et al. 2003; Tauber et al. 2004). Our group recently described the changes in plasma ghrelin over the course of life in PWS and controls and showed that ghrelin dysregulation in PWS occurs very early in life and precedes the onset of obesity (Feigerlova et al. 2008). Thus, plasma ghrelin levels were high from birth to adulthood in patients with PWS, regardless of age, but the physiological decrease with age was preserved.

Recent data suggest that ghrelin does more than regulate energy homeostasis and that it is involved in the gustatory pathways, locomotor activity, dopamine/serotonin reward networks, and neuronal plasticity.

Ghrelin acts on hippocampal neurons to induce the formation of new synapses in the CA1 region correlated with enhanced spatial learning. Ghrelin-deficient mice exhibited impaired spatial learning that was corrected by ghrelin administration (Diano et al. 2006). These findings are consistent with the idea that ghrelin is involved in the appetitive phase of ingestive behavior, when it is important to find food in the environment. It is plausible that the ghrelin-induced changes in hippocampal function facilitate the recall of stored representations of prior experience with food. This is indicated by human subjects reporting a vivid, plastic image of their preferred meal upon intravenous ghrelin infusion. In addition, ghrelin activates dopamine neurons in the ventral tegmental area (VTA), increases dopamine turnover in the nucleus accumbens, and directly stimulates food intake when locally administered to the VTA. As local ghrelin receptor blockade in the VTA blunted rebound feeding following fasting, these observations suggest that enhancement of reward processing in the mesolimbic dopamine system is an integrated part of endogenous ghrelin orexigenic action (Olszewski et al. 2007).

While the well-known preprandial rise and postprandial fall in plasma ghrelin levels initially supported the hypothesis of a physiological role for ghrelin in meal initiation in humans, these more recent data favor a role of ghrelin in meal anticipation as shown in Fig. 169.2 (Frecka and Mattes 2008).

In humans, ghrelin bursts occur after the peak of hunger, and are related to habitual meal patterns (Frecka and Mattes 2008) and contents. Ghrelin levels may rise in anticipation of eating rather than eliciting feeding. These findings support the implementation of regular schedules for meal times and meal contents to control the eating behavior of patients with PWS. Ghrelin has been shown to be involved in food searching, food storage, foraging, and hoarding in hamsters.

Ghrelin also interacts with other important neuro-hormones possibly involved in PWS: lateral hypothalamic orexin neurons appear to mediate the orexigenic effects of ghrelin, and intra cerebro ventricular ghrelin activates magnocellular ocytocin neurons (Olszewski et al. 2007). Ghrelin may also support feeding driven by energy needs rather than reward (Bomberg et al. 2007).

Although somatostatin acutely suppresses plasma ghrelin concentrations in PWS patients, appetite is not reduced. A recent study found no benefit on weight or appetite in PWS from chronic administration of a long-acting somatostatin analogue (De Waele et al. 2008). This may suggest that early high
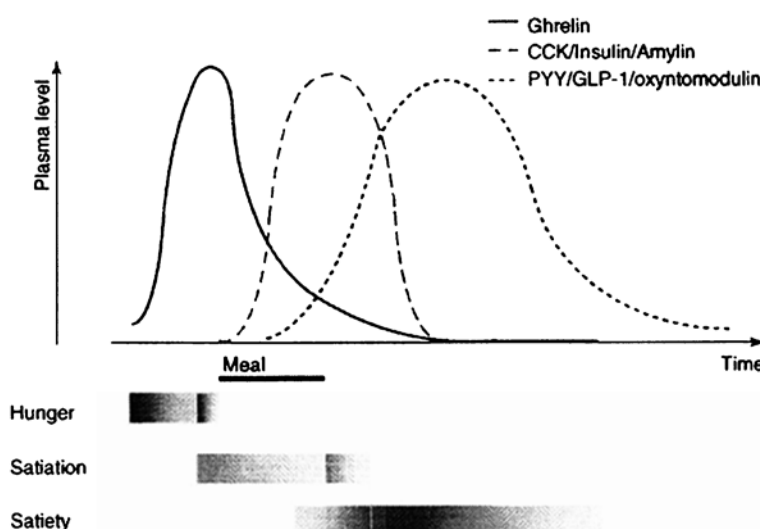
Fig. 169.2 Evolution of ghrelin, CCK, insulin, amylin, PYY, GLP-1, and OXM in humans before, during, and after mealtime

ghrelin levels set up an abnormal tuning for food seeking and anticipation of meals in patients with PWS, which cannot then be turned off. An alternative explanation could be that hyperghrelinemia is secondary to a primary defect that is not corrected by somatostatin. Recent evidence in human subjects suggests that both peptide YY (PYY) and oxyntomodulin (OXM, a product of differential processing of proglucagon in brain and gut) suppress circulating concentrations of ghrelin when given peripherally, whereas pancreatic polypeptide (PP) has no effect (Batterham et al. 2003a) Table 169.4.

169.6.3 Decreased Levels of Pancreatic Polypeptide

Levels of the anorexigenic gut hormone PP are reduced in PWS (Goldstone 2004). PP was discovered in 1975 and isolated from chicken pancreatic extracts. It is a 36-amino-acid peptide and a member of the PP-fold peptide family (also including NPY and PYY). The PP-fold family binds to receptors Y1–Y6, but PP binds with greatest affinity to the Y4 and Y5 receptors. It is produced in the endocrine type F cells, which are located in the peripheries of the pancreatic islets. Pancreatic polypeptide cannot cross the BBB and thus its central effects may be mediated in regions where the BBB is incomplete, such as the hypothalamus, AP, and adjacent brainstem areas (Katsuura et al. 2002). The release of PP appears to require an intact vagal cholinergic reflex. Peptide YY inhibits fluid and electrolyte secretion in the small bowel and delays intestinal meal transport. It may act as an "ileal brake," slowing gastric emptying and intestinal transit, so that nutrients can be absorbed in the small bowel. In humans, intravenous infusion of PP reduced food intake by 21.8% at a free-choice buffet, but did not affect gastric emptying (Batterham et al. 2003b).

Basal PP levels are elevated in anorexia nervosa, and in patients with advanced malignant disease. People with PWS had a blunted PP response to meals and short-term infusions of peripheral PP given to these subjects were shown to reduce subsequent food intake by 12% (Berntson et al. 1993). More recently, further evidence of PP's role in weight regulation came from a prospective study in Pima Indians. PP meal profiles were measured at baseline, and at a 5-year follow-up, and then correlated with change in weight. An increase in postprandial PP levels was associated with decreased weight gain, but surprisingly high fasting PP levels were associated with increased weight gain (Koska et al. 2004). These results suggest that different receptors may be activated. The precise role of PP in appetite regulation is not yet resolved. PP may be involved in the pathophysiology of obesity and dysregulation of body weight via effects on the parasympathetic nervous system.

Interestingly, the two main abnormal signals, one orexigenic (ghrelin) and the second involved in satiety control (PP), may explain the major feeding disturbances described in people with PWS. Part of their action requires an intact vagal nerve reflex and they both regulate gastric emptying. Both hormones are elevated in anorexia nervosa. A decreased parasympathetic tone has long been described in PWS together with a defect in gastric emptying and other gut dysfunctions possibly related to these hormone dysfunctions.

Besides a permanent state of hunger, people with PWS have disturbances in the anticipation of hunger and the representation of meal content, combined with satiety signal abnormalities involving the hypothalamus, corticolimbic networks, and the vagal system.

Table 169.2 summarizes the findings of studies on hypothalamic neuropeptides and their signaling inputs in PWS. It seems likely that in addition to these hormonal abnormalities in PWS, there are overriding brain defects, including hypothalamic, which lead to resistance to peripheral satiety signals (Goldstone 2004). The possibility of therapeutic avenues for reducing hyperphagia in PWS may depend on the existence of relative rather than absolute resistance to peripheral satiety signals.

Table 169.2 Summarized findings of studies on hypothalamic neuropeptides and their signalling inputs in PWS (Adapted from *Trends in Endocrinology and Metabolism*, Vol 15, Prader-Willi syndrome: advances in genetics, pathophysiology and treatment, pages 12–20. Copyright (2004) with permission from Elsevier)

• Normal leptin secretion	• Normal distribution and colocalization of neuropeptide Y (NPY) and agouti-related protein (AgRP) in infundibular nucleus (INF).
• Long isoform leptin receptor mRNA expressed in lymphocytes	
• Increased fasting plasma ghrelin	• Normal increase in NPY, measured by either immunocytochemical (ICC) staining or mRNA expression, or AGRP (ICC staining) in INF during illness.
• Reduced postprandial secretion of pancreatic polypeptide (PP)	
• Reduced fasting and postprandial insulin secretion	
• Normal cholecystokinin (CCK) secretion	• Reduced NPY (ICC or mRNA expression) in INF, compared with control, but not non-PWS obese adults, corrected for the duration of premorbid illness.
• Normal distribution of oxytocin and vasopressin neurons in the paraventricular nucleus (PVN).	
• Reduced number of total (38%) and oxytocin (42%)-containing neurons in the PVN.	• Normal AGRP (ICC staining) in INF, compared to control and non-PWS obese adults, corrected for the duration of premorbid illness.
• Normal number of neurons containing cocaine and amphetamine-regulated transcript (CART) in the INF, PVN, and lateral hypothalamic area (LHA).	• Deficiency of POMC-containing neurons in INF, CART-neurons in INF, PVN, and LHA is not complete.

169.6.4 Dysregulation of Serotonin Receptors

Sno RNAs located in the chromosomal region of PWS (Fig. 169.1) are candidate genes for the disease. It has been hypothesized that the Sno RNA HB-52 negatively regulates editing of the 5HT-2C receptor pre-RNA. Indeed, this post transcriptional regulation of this serotonin receptor involved in cognition and cessation of feeding changes its activity. The lack of editing in PWS through the increasing intrinsic activity of the receptor may explain some of the features of this disease. A recent study performed in a mouse model (PWS IC +/−) seems to confirm this hypothesis, although the link with the lack of Sno RNA HB 52 was not established in the publication (see below the chapter on animal models).

169.6.5 Abnormalities in Hypothalamus Histology

Quantitative neuroanatomical studies of postmortem human hypothalamic tissue from patients with PWS in the Netherlands Brain Bank have yet to find any pathological abnormalities in orexigenic neuropeptide Y or agouti-related protein, anorexigenic POMC neurons or GH-releasing hormone neurons in the infundibular nucleus, or orexin/hypocretin neurons in the lateral hypothalamus. Nevertheless, interpretation may be complicated by small numbers and the effects of premortem illness (Goldstone et al. 2003). However, appropriate changes in neuropeptide Y, agouti-related protein, and GH-releasing hormone were found in PWS subjects in cases of illness, obesity, and exogenous GH therapy. This suggests normal neuronal function in their response to alterations in peripheral signals. Cerebrospinal fluid orexin concentrations have nevertheless been reported to be low in cases of PWS with hypersomnia (Nevsimalova et al. 2005). Reduced immunostaining of processed vasopressin, its processing enzyme, prohormone convertase 2, and its molecular chaperone polypeptide 7B2 has also been found in the PVN and supraoptic nucleus of hypothalami from subjects with PWS, though diabetes insipidus is not a recognized clinical problem (Gabreels et al. 1998).

The total and oxytocin cell number is reduced in the hypothalamic PVN of adults with PWS, which may play a primary causative role in hyperphagia. Oxytocin and the PVN have anorexigenic roles in rodents. A 29% reduction in PVN oxytocin neurons was also seen in necdin knockout mice, though these mice are not obese (Muscatelli et al. 2000). Interestingly, oxytocin is an anorexigenic hormone with other newly described actions, particularly regarding social skills, trust, and pair bonding. Peripheral levels are normal although there was discordant data on oxytocin in CSF levels (Fig. 169.3).

169.6.6 Recent Neuroimaging Data

Several morphological neuroimaging abnormalities have been described in PWS: according to Miller et al. (Miller et al. 2007a), ventriculomegaly (100% of 20 patients with PWS aged 3 months to 39 years), decreased volume of brain tissue in the parietal-occipital lobe (50%), sylvian fissure

Hyperghrelinemia.   Pancreatic Polypeptide Targets   Regulation of Food Intake
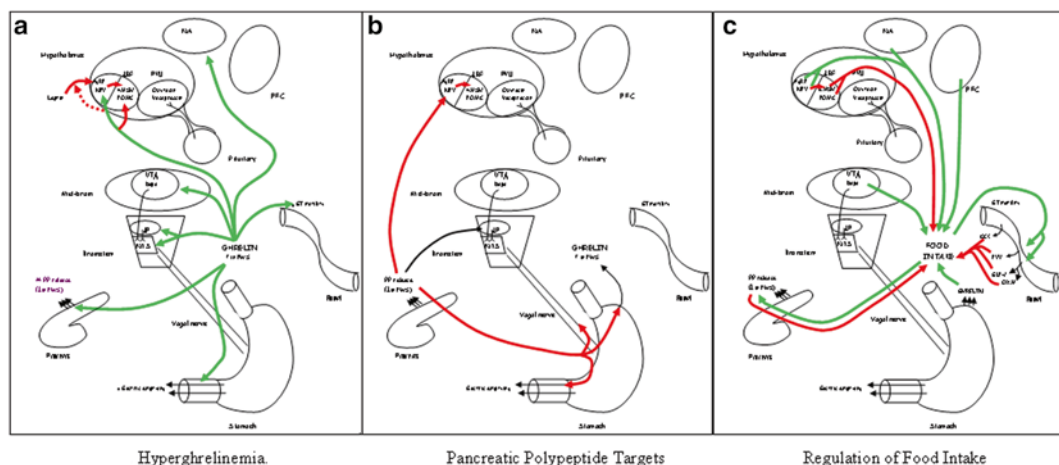
Fig. 169.3 Features of feeding and satiety regulation. *Green arrows* stand for stimulation. *Red arrows* stand for inhibition. Sets of three black arrows stand for secretion. The *nucleus accumbens* (NA) is a collection of neurons within the forebrain that is thought to be involved in the reward circuit, and by which neuronal activity is modulated by dopaminergic input from the ventral tegmental area (VTA). The *prefrontal cortex* (PFC) is the anterior part of the frontal lobes of the brain. (**a**) Hyperghrelinemia. Ghrelin is secreted mainly by the stomach, but also by duodenum, pancreas, hypothalamus, testis, ovary, bone, and cartilage. Patients with PWS have greatly increased circulating levels of ghrelin. The effects of ghrelin on eating behavior are mediated via the arcuate nucleus (ARC) and the solitary tract nucleus (NTS) to merge in the hypothalamus. There, ghrelin opposes the actions of leptin through disinhibition of second line neuropeptides such as neuropeptide Y (NPY) and agouti gene-related peptide (AgRP). Ghrelin activates dopamine neurons in the ventral tegmental area (VTA) and increases dopamine turnover in the nucleus accumbens. Ghrelin also partly exerts its effect through vagal afferent loops. It increases fasting gastro-intestinal motility and the rate of gastric emptying. In PWS, it is hypothesized that a peripheral resistance to ghrelin opposes its stimulating actions (represented by # in the figure), which fits with clinical observations (patients with PWS have decreased GI motility, delayed gastric emptying and decreased PP release). (**b**) Pancreatic Polypeptide Targets. The inhibitory effect of PP on food intake might be indirect and regulated via vagal input to the stomach, pancreas, and other gastrointestinal organs. PP could also enter the brain to bind to AP and influence the adjacent nuclei, such as NTS and Dorso-Medial Nucleus to inhibit gastric emptying, which in turn suppresses food intake. Patients with PWS have reduced PP release both basally and postprandially. PP infusion in subjects with PWS reduced the levels of ghrelin. (**c**) Food Intake Regulation. Peripheral injection of PP inhibits food intake in both humans and mice. In Prader-Willi subjects, intravenous (i.v.) infusion of PP was reported to increase serum PP levels and significantly reduce food intake. GLP-1 is secreted within the circulation by the L-cells of the intestine, together with PYY and OXM; this secretion is stimulated by food intake. CCK is released by the I-cells of the intestine. These peptides all regulate negatively food intake. The ARC appears to be necessary for the stimulatory action of ghrelin on food intake

polymicrogyria (60%), and incomplete insular closure (65%) were found on 3D MRI scans, compared with 21 normal weight sibling controls and 16 individuals with early-onset morbid obesity of unknown etiology. On volumetric MRI, the same author (Miller et al. 2009) found that patients with PWS had smaller cerebellar volumes than a control group of 15 siblings. In several other studies, subjects with PWS had a higher prevalence of pituitary morphological abnormalities than did control subjects, without correlation with hormonal deficiencies (Tauber et al. 2000).

These abnormalities may play a role not only in cognitive, behavioral and neuroendocrine defects in PWS, but in hyperphagia as well. Indeed, recent functional neuroimaging techniques such as positron emission tomography and functional MRI (fMRI) in PWS have revealed abnormal brain activation patterns in corticolimbic structures, such as the amygdala and the prefrontal, orbitofrontal (OFC), and insular cortex, in response to food stimuli after ingestion of oral glucose or a meal (Shapira et al. 2005; Holsen et al. 2006; Miller et al. 2007b). These patterns suggest abnormal reward and motivational responses to food that may underlie the hyperphagia in individuals with PWS.

Hypothalamus dysfunction seems to be central in hyperphagia and underlies other abnormal functioning in PWS (temperature dysregulation, sleep–wake cycle abnormalities, and metabolic and endocrine disorders (Dimitropoulos and Schultz 2008)). Dimitropoulos et al. performed fMRIs on nine individuals with PWS (8–38 years old) IQ- and BMI-matched to ten controls, all in a hunger state, while they performed perceptual discrimination tasks on pictures of pairs of objects and high- or low-calorie foods. The authors showed that patients with PWS displayed a greater activation in the bilateral hypothalamus and right amygdala than controls for high-calorie foods. The OFC was more activated by high-calorie than low-calorie foods in the PWS subjects. The authors thus concluded to a hyper-activation of neural circuitry involving motivation, reward, taste, and food-seeking behaviors (hypothalamus, amygdala, OFC).

The lack of satiety in patients with PWS has also been investigated through fMRI (Shapira et al. 2005) by examining the regions related to satiation (insula, ventromedial prefrontal cortex, and nucleus accumbens). The activation of these regions was delayed after a glucose oral load in PWS patients compared with obese and lean controls. Hyperphagia thus appears to be linked to at least two mechanisms, since patients with PWS (vs. healthy weight controls) who were presented with visual food stimuli after eating a meal showed hyperfunction in limbic and paralimbic regions that drive eating behavior (e.g., the amygdala) and in regions that regulate food intake (e.g., the medial prefrontal cortex (mPFC)) (Holsen et al. 2006) (see article by Ogura in chapter 2.5).

In conclusion, although it has been clearly established that reward and motivation neural pathways and satiety dysfunction are involved in PWS hyperphagia, evidence has gradually emerged that the eating behavior of the patients with PWS arises from a complex mechanism combining insufficient neural development, hormonal dysfunctions, and an overall behavioral disorder involving psychiatric manifestations of the syndrome. In addition to the universal presence of the propensity to overeating and compulsive and ritualistic behaviors, people with PWS show pronounced emotional liability, and a striking inability to control their emotions, which predisposes them to temper outbursts. The frequent anger is often in response to frustration and to the feeling of not being understood, and it may be due to disturbances in understanding others, which in turn could be related to theory of mind and empathy.

169.6.7 Data from Animal Models

Most of the models that reproduce the genetic defects of PWS result in severe growth defect, feeding difficulties, and high lethality within the first days of life. However, surviving mice do not become obese.

Ding et al. (Ding et al. 2008) recently reported a new mouse model with great homologies with the PWS phenotype, but without the occurrence of obesity. This Snord116del mouse model seems to reproduce the abnormal feeding behavior and endocrine disorders described in humans with PWS. The hyperphagia of these mice is associated with prolonged meal times, pointing to a delay in meal termination that is most likely due to an inability to sense satiety. Interestingly, they also have elevated ghrelin, high insulin sensitivity, and low IGF-1, with growth delay that develops soon after birth. They may also have abnormal GH release though this has not been proved.

The authors concluded that the primary mechanism for hyperphagia in PWS is not a defect in energy homeostasis control, but in sensing satiety. They further concluded that the higher cognitive regions of the brain, such as the mPFC, which is involved in interpreting the incentive values of food, and those involved in planning complicated schemes to obtain food, may be changed secondary to the prolonged perception of hunger/lack of satiety. This is in line with the hypothesis developed by Holland (Holland et al. 2003) and with our own hypothesis on the impact of early hypergrhelinemia in the development and implementation of satiety circuits (Feigerlova et al. 2008).

Another interesting finding was reported by Doe et al. (Doe et al. 2009) using the imprinted centre deletion model. The authors studied abnormal editing of the 5HT2C receptor and alterations in its effect. Indeed, mice show impulsive responding, increased locomotor activity, and reactivity to palatable foodstuffs. Use of drugs confirmed the role of this serotonin receptor in these alterations.

The link between the lack of snoRNA genes and abnormal editing has yet to be proven. Although two patients have been described with the PWS phenotype and deletion of snoRNA HB85 (Sahoo et al. 2008; de Smith et al. 2009), an effect of snoRNA HB52 cannot be completely eliminated.

169.7 Management of Hyperphagia and Obesity

Obesity management in people with PWS involves strict and permanent environmental control, with early institution of a low-calorie, well-balanced diet, with regular exercise, rigorous supervision, restriction of access to food and money (after consideration of the legal and ethical obligations), and appropriate psychological and behavioral counseling for the patient and family. Early discussion with parents about the inevitability of hyperphagia, even during infancy, is essential to prepare them for the need to prevent obesity by setting firm limits and strictly controlling the food environment and the daily schedule (hour and contents of the meals). As an example of how important these steps can be, a young institutionalized adult declared that her anxiety and insomnia were improved the day she learned that the kitchen would be locked at night instead of simply being watched by a guardian who could possibly be away from his post for a short time. This aspect of management should thus be reemphasized at every visit, for our opinion is that total autonomy with regards to food is impossible and unrelated to the IQ of the patients.

Anecdotally, pharmacological treatment, including the available anorexigenic agents, has not been of benefit in treating hyperphagia, though there are few published placebo-controlled studies. Studies of the potential benefits of newer agents such as endo-cannabinoid antagonists were awaited in PWS, but recent concerns about psychiatric side effects led to withdrawal of these drugs. Restrictive bariatric surgery, such as gastric banding or bypass, has not been shown to reduce hyperphagia or achieve long-term weight reduction and is associated with unacceptable morbidity and mortality (Scheimann et al. 2008). While some of the studies of biliopancreatic diversion have reported successful weight loss, complications from the resulting intestinal malabsorption were frequent. Intragastric balloons are a risk for these patients and deaths have been reported (Grugni et al. 2008).

Physical activity in PWS is significantly reduced and is related to obesity, hypersomnolence, and persistent reduced lean mass and poor muscle tone. The resting metabolic rate is reduced relative to body size and this is related to the abnormal body composition, which further contributes to a reduction in 24-h energy expenditure (van Mil et al. 2000). Increased physical activity and exercise programs are beneficial in improving body composition in PWS.

169.8   GH Effects on Obesity and Body Composition

Body composition studies have shown both increased body fat and reduced muscle in PWS from infancy to adulthood (Carrel et al. 2004) with a selective relative reduction in visceral adiposity in PWS adults of both sexes (Goldstone et al. 2001). This may explain the relative hypoinsulinemia and normal triglyceride levels, with preservation of insulin sensitivity and protective elevation in adiponectin levels in these patients given their overall obesity.

GH treatment is routinely used for short stature in children with PWS in the USA, and since 2000 for treatment of short stature or abnormal body composition in Europe. As the age at diagnosis has markedly decreased in the past few years and is currently 3 months, the age for starting GH treatment has also decreased. Only a few publications have reported the possible benefits of early treatment on motility scores, cognitive function, and increased head circumference (Festen et al. 2008). The main effects of GH are the improvement in height, velocity, and adult height; the maintenance of lean body mass; and better control of BMI with a decrease in fat mass. It may also delay the occurrence of nutritional phase 3. By modifying the body shape of these children and increasing their motility, GH improves their socialization and, in some of them, lowers depressions scores (Whitman et al. 2002). Part of the GH effects may be related to the decrease in ghrelin under GH treatment (Hauffa and Petersenn 2008). Figure 169.4 shows the effect of GH in a boy who started treatment at 7 years with secondary normalization of BMI and body shape.

The benefits of GH cannot be obtained without integrated multidisciplinary care (Table 169.3).
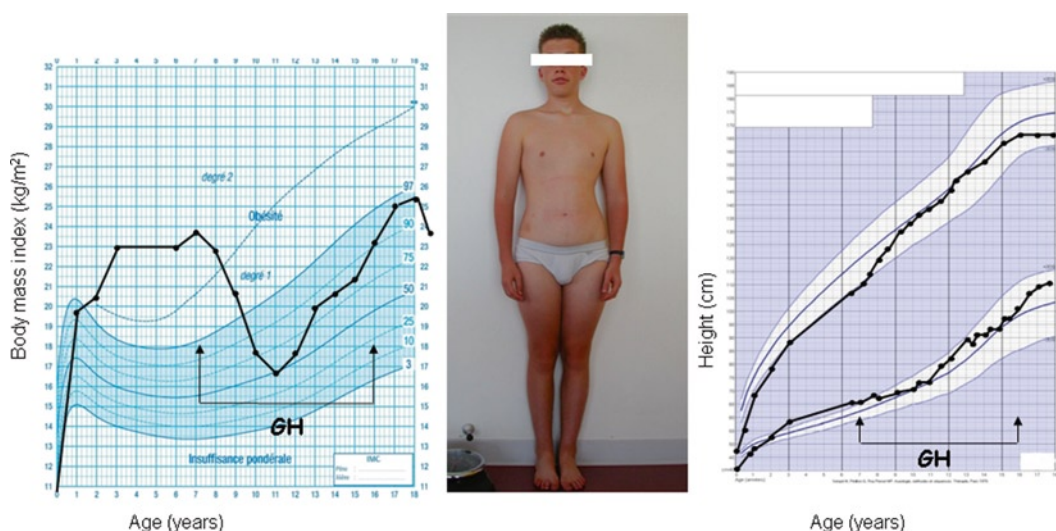
Fig. 169.4 Evolution of BMI chart, growth curve, and body shape in a boy with PWS treated by GH from the age of 7

Table 169.3 Ideal multidisciplinary team for children and adults with PWS (Copyright 2008, the Endocrine Society)

For children	For adults
Neonatologist	
Medical Geneticist[a]	Medical Geneticist[a]
Paediatric Endocrinologist[a]	Endocrinologist/Diabetologist[a]
Neuropediatrician	Gynaecologist/Urologist[a]
Speech and language specialist	Cardiologist
ENT specialist	
Psychiatrist[a]	Psychiatrist[a]
Orthopaedist[a]	Orthopaedist[a]
Surgeon (for orchidopexy)	
Pneumologist	Pneumologist
Sleep disorder specialist	Sleep disorder specialist
Dentist	
Ophthalmologist	
Gastroenterologist	Gastroenterologist
Dietician[a]	Dietician[a]
Speech therapist	
Physical therapist	Physical therapist
Psychologist[a]	Psychologist[a]
Social worker[a]	Social worker[a]

[a]Indicates those particularly involved in transition

Figure 169.5 shows the effects of GH in a boy with PWS with morbid and uncontrolled obesity at 2 years due to poor family compliance with the diet. GH treatment was started in order to try to control the BMI, which nevertheless continued to increase with the aggravation of obstructive sleep apneas. This prompted us to stop the GH treatment and focus on parental guidance. Thanks to the strong collaborative work of all the caregivers, particularly the psychiatrist, family compliance was obtained. The child lost weight, normalized his BMI, and corrected his sleep respiratory disorder, and therefore resumed GH treatment.

Interruption of GH treatment at growth completion is required in most countries, though it may have a deleterious effect on BMI and body composition. Continuing GH in the adult is based on the potential benefits to bone mineralization, body composition, and maintenance of lean mass and muscular function. The effect on quality of life is difficult to prove, however, given the lack of an appropriate evaluation tool.

169.9 Transition from Childhood to Adolescence and Adulthood

The transition phase from childhood to adolescence and adulthood is of great importance in these patients. During the transition appointment, medical issues and psychosocial aspects concerning the patient are discussed. In the case of young adults, the emphasis is put on issues related to the processes of adolescence such as puberty, choice of profession, daily activities, relationships, and sexuality.

The prevalence of obesity in adults with PWS who received GH treatment in childhood is significantly reduced compared with those who did not receive it (personal data).

In conclusion, studies are needed to improve our knowledge of the natural history of hyperphagia and feeding disturbance in patients with PWS. Ongoing research on feeding and satiety signals such as ghrelin, PP, and ocytocin will help to unravel the mechanisms of the feeding behavior in these patients.

Fig. 169.5 Evolution of BMI in a young boy: effects of reinforced multidisciplinary care in a context of compliance difficulties
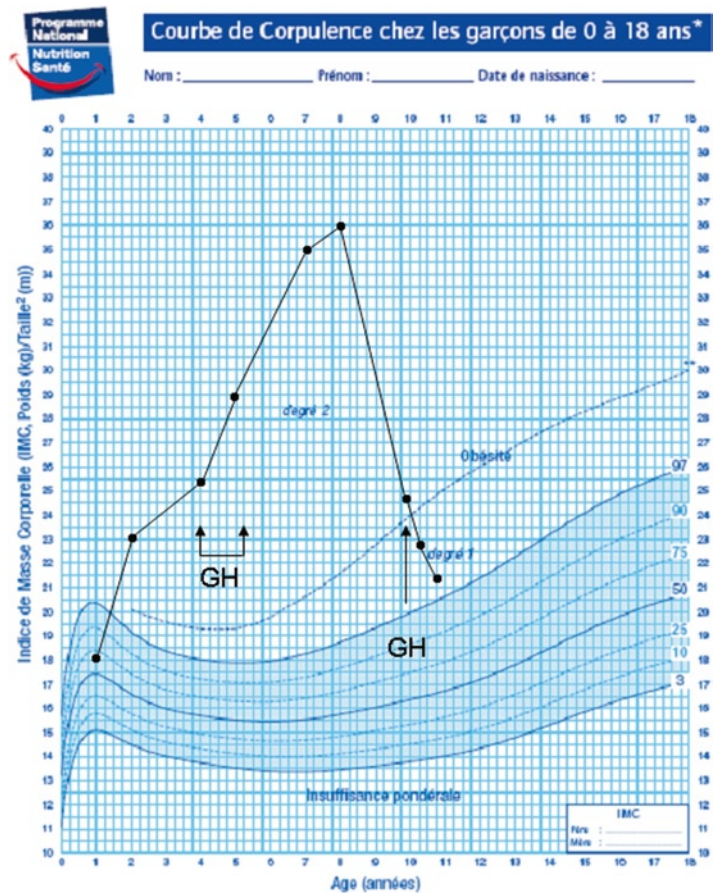
Table 169.4 Key facts of ghrelin

Circulating gut peptide

Orexigenic

Stimulate growth hormone secretion

Acylated in the Serine 3 amino acid

Circulating ghrelin increases before meals and decreases after

Low levels in obese people vs. controls

Elevated levels in PWS and anorexia

Balance between leptin and ghrelin at the level of arcuate nucleus neurons in the hypothalamus

Table 169.5 Key facts of growth hormone

GH is a peptide secreted by the anterior pituitary under hypothalamic control (GHRH, ghrelin, and somatostatin)

Induces somatic growth before cartilage fusion

Acts on different tissues: adipose tissue, muscles, bone

Has metabolic effects (lipid, glucose metabolisms), anabolic effect

GH secretion is decreased in some children having short stature. Treatment increases height and normalizes adult height

GH treatment is based on daily subcutaneous injections

Functional neuroimaging may open new perspectives on pathophysiology and treatment. Last, the effects of early diagnosis, the outcomes of GH treatment, and multidisciplinary care need to be analyzed properly in order to determine the best possible care for patients with PWS (Tables 169.4 and 169.5).

169.10 Applications to Other Areas of Health and Disease

Acquiring knowledge in hormones and signals controlling food and satiety signals in PWS may open new perspectives on pathophysiologics and therapeutical issues for persons with nonsyndromic obesity.

Summary Points

- *Two main features* characterize hyperphagia in PWS: a reduced satiety and an early return of excessive hunger.
- *Two main hormonal dysfunctions* might explain hyperphagia: hyperghrelinemia and decreased pancreatic polypeptide.
- *Oxytocin deficit* may be involved in hyperphagia.
- *Two neuronal networks* may be involved in the eating behavior of PWS: the cortico-limbic structures implied in reward mechanisms and the paralimbic regions that drive food behavior.
- *Better characterization of eating behavior* will help understanding hyperphagia pathophysiology and defining treatment goals.
- *Data on animal models* are insufficient to explain human clinical and biological findings.
- It is likely that the implementation of *early diagnosis, multidisciplinary care, and GH treatment* altogether will optimize patients' quality of life.

Definitions and Explanations of Key Terms

Hyperphagia: Eating disorder in which an individual eats abnormally large amounts of food in little time.

Orexigenic: Hormones that trigger a desire to eat. Ghrelin is the only real orexigenic peptide, since AgRP and NPY release is related to ghrelin activity.

Satiety: Time during which an individual does not feel the desire to eat. Satiety is related to the sensation of fullness without being tantamount to it. PP, CCK, GLP-1 and OXM are peptides which release triggers a satiety feeling.

Hypothalamic syndrome: Although there is no consensus definition of the hypothalamic syndrome, it is usually described as the collection of appetite disorders, hyperphagia and obesity, or anorexia, thirst abnormalities, tiredness, temperature dysregulation, sleep disorders, and behavioral difficulties. In the course of evolution, endocrine abnormalities usually develop, characterized by hyperprolactinemia and pituitary deficits (gonadotrophic, somatotropic, corticotropic, and thyrotropic). Central precocious puberty can also occur. Several causes can be involved: tumors, genetic syndromes such as Prader-Willi, infectious or inflammatory diseases, and idiopathic.

Reward networks: Collection of brain structures which attempts to regulate and control behavior by inducing pleasurable effects. It principally involves the mesolimbic (which goes from the ventral tegmental area via the medial forebrain bundle to nucleus accumbens, where mainly dopamine is released) and the mesocortical pathway (which connects the ventral tegmentum to the cerebral cortex).

References

Bachere N, Diene G, Delagnes V, Molinas C, Moulin P, Tauber M. Horm Res. 2008;69:45–52.

Banks WA, Tschop M, Robinson SM, Heiman ML. J Pharmacol Exp Ther. 2002;302:822–7.

Batterham RL, Cohen MA, Ellis SM, Le Roux CW, Withers DJ, Frost GS, Ghatei MA, Bloom SR. N Engl J Med. 2003a;349: 941–8.

Batterham RL, Le Roux CW, Cohen MA, Park AJ, Ellis SM, Patterson M, Frost GS, Ghatei MA, Bloom SR. J Clin Endocrinol Metab. 2003b;88:3989–92.

Berntson GG, Zipf WB, O'Dorisio TM, Hoffman JA, Chance RE. Peptides. 1993;14:497–503.

Bomberg EM, Grace MK, Wirth MM, Levine AS, Olszewski PK. Neuroreport. 2007;18:591–5.

Carrel AL, Moerchen V, Myers SE, Bekx MT, Whitman BY, Allen DB. J Pediatr. 2004;145:744–9.

Cummings DE, Clement K, Purnell JQ, Vaisse C, Foster KE, Frayo RS, Schwartz MW, Basdevant A, Weigle DS. Nat Med. 2002;8:643–4.

Date Y, Murakami N, Toshinai K, Matsukura S, Niijima A, Matsuo H, Kangawa K, Nakazato M. Gastroenterology. 2002;123:1120–8.

de Smith AJ, Purmann C, Walters RG, Ellis RJ, Holder SE, Van Haelst MM, Brady AF, Fairbrother UL, Dattani M, Keogh JM, Henning E, Yeo GS, O'Rahilly S, Froguel P, Farooqi IS, Blakemore AI. Hum Mol Genet. 2009;18:3257–65.

De Waele K, Ishkanian SL, Bogarin R, Miranda CA, Ghatei MA, Bloom SR, Pacaud D, Chanoine JP. Eur J Endocrinol. 2008;159:381–8.

Diano S, Farr SA, Benoit SC, McNay EC, da Silva I, Horvath B, Gaskin FS, Nonaka N, Jaeger LB, Banks WA, Morley JE, Pinto S, Sherwin RS, Xu L, Yamada KA, Sleeman MW, Tschop MH, Horvath TL. Nat Neurosci. 2006;9:381–8.

Dimitropoulos A, Schultz RT. J Autism Dev Disord. 2008;38:1642–53.

Ding F, Li HH, Zhang S, Solomon NM, Camper SA, Cohen P, Francke U. PLoS ONE. 2008;3:e1709.

Doe CM, Relkovic D, Garfield AS, Dalley JW, Theobald DE, Humby T, Wilkinson LS, Isles AR. Hum Mol Genet. 2009;18:2140–8.

Dykens EM, Maxwell MA, Pantino E, Kossler R, Roof E. Obesity (Silver Spring). 2007;15:1816–26.

Feigerlova E, Diene G, Conte-Auriol F, Molinas C, Gennero I, Salles JP, Arnaud C, Tauber M. J Clin Endocrinol Metab. 2008;93:2800–5.

Festen DA, de Lind van Wijngaarden R, van Eekelen M, Otten BJ, Wit JM, Duivenvoorden HJ, Hokken-Koelega AC. Clin Endocrinol (Oxf). 2008;69:443–51.

Fieldstone A, Zipf WB, Schwartz HC, Berntson GG. Int J Obes Relat Metab Disord. 1997;21:1046–52.

Frecka JM, Mattes RD. Am J Physiol Gastrointest Liver Physiol. 2008;294:G699–707.

Gabreels BA, Swaab DF, de Kleijn DP, Seidah NG, Van de Loo JW, Van de Ven WJ, Martens GJ, van Leeuwen FW. J Clin Endocrinol Metab. 1998;83:591–9.

Goldstone AP. Trends Endocrinol Metab. 2004;15:12–20.

Goldstone AP, Thomas EL, Brynes AE, Bell JD, Frost G, Saeed N, Hajnal JV, Howard JK, Holland A, Bloom SR. J Clin Endocrinol Metab. 2001;86:4330–8.

Goldstone AP, Unmehopa UA, Swaab DF. Clin Endocrinol (Oxf). 2003;58:743–55.

Goldstone AP, Patterson M, Kalingag N, Ghatei MA, Brynes AE, Bloom SR, Grossman AB, Korbonits M. J Clin Endocrinol Metab. 2005;90:2681–90.

Goldstone AP, Holland AJ, Hauffa BP, Hokken-Koelega AC, Tauber M. J Clin Endocrinol Metab. 2008;93:4183–97.

Grugni G, Crino A, Bosio L, Corrias A, Cuttini M, De Toni T, Di Battista E, Franzese A, Gargantini L, Greggio N, Iughetti L, Livieri C, Naselli A, Pagano C, Pozzan G, Ragusa L, Salvatoni A, Trifiro G, Beccaria L, Bellizzi M, Bellone J, Brunani A, Cappa M, Caselli G, Cerioni V, Delvecchio M, Giardino D, Ianni F, Memo L, Pilotta A, Pomara C, Radetti G, Sacco M, Sanzari A, Sartorio A, Tonini G, Vettor R, Zaglia F, Chiumello G. Am J Med Genet A. 2008;146:861–72.

Gunay-Aygun M, Schwartz S, Heeger S, O'Riordan MA, Cassidy SB. Pediatrics. 2001;108:E92.

Haqq AM, Farooqi IS, O'Rahilly S, Stadler DD, Rosenfeld RG, Pratt KL, LaFranchi SH, Purnell JQ. J Clin Endocrinol Metab. 2003;88:174–8.

Hauffa BP, Petersenn S. Clin Endocrinol (Oxf). 2009;71:155–6.

Holland A, Whittington J, Hinton E. Lancet. 2003;362:989–91.

Holm VA, Cassidy SB, Butler MG, Hanchett JM, Greenswag LR, Whitman BY, Greenberg F. Pediatrics. 1993;91:398–402.

Holsen LM, Zarcone JR, Brooks WM, Butler MG, Thompson TI, Ahluwalia JS, Nollen NL, Savage CR. Obesity (Silver Spring). 2006;14:1028–37.

Hosoda H, Kojima M, Kangawa K. J Pharmacol Sci. 2006;100:398–410.

Kanber D, Giltay J, Wieczorek D, Zogel C, Hochstenbach R, Caliebe A, Kuechler A, Horsthemke B, Buiting K. Eur J Hum Genet. 2009;17:582–90.

Katsuura G, Asakawa A, Inui A. Peptides. 2002;23:323–9.

Koska J, DelParigi A, de Courten B, Weyer C, Tataranni PA. Diabetes. 2004;53:3091–6.

Lindgren AC, Barkeling B, Hagg A, Ritzen EM, Marcus C, Rossner S. J Pediatr. 2000;137:50–5.

McCune H, Driscoll DJ, Prader-Willi syndrome. In: Ekvall SW, Ekvall VF, eds. Pediatric nutrition in chronic diseases and developmental disorders, 2nd ed., New York: Oxford University press: 2005, pp. 128–32.

Miller JL, Couch JA, Schmalfuss I, He G, Liu Y, Driscoll DJ. Am J Med Genet A. 2007a;143:476–83.

Miller JL, James GA, Goldstone AP, Couch JA, He G, Driscoll DJ, Liu Y. J Neurol Neurosurg Psychiatry. 2007b;78:615–9.

Miller JL, Couch J, Schwenk K, Long M, Towler S, Theriaque DW, He G, Liu Y, Driscoll DJ, Leonard CM. Dev Neuropsychol. 2009;34:272–83.

Muscatelli F, Abrous DN, Massacrier A, Boccaccio I, Le Moal M, Cau P, Cremer H. Hum Mol Genet. 2000;9:3101–10.

Nevsimalova S, Vankova J, Stepanova I, Seemanova E, Mignot E, Nishino S. Eur J Neurol. 2005;12:70–2.

Olszewski PK, Bomberg EM, Martell A, Grace MK, Levine AS. Neuroreport. 2007;18:499–503.

Russell H, Oliver C. Br J Clin Psychol. 2003;42:379–92.

Sahoo T, del Gaudio D, German JR, Shinawi M, Peters SU, Person RE, Garnica A, Cheung SW, Beaudet AL. Nat Genet. 2008;40:719–21.

Scheimann AO, Butler MG, Gourash L, Cuffari C, Klish W. J Pediatr Gastroenterol Nutr. 2008;46:80–3.

Schrander-Stumpel CT, Curfs LM, Sastrowijoto P, Cassidy SB, Schrander JJ, Fryns JP. Am J Med Genet A. 2004;124A:333–8.

Schwartz MW, Morton GJ. Nature. 2002;418:595–7.

Shapira NA, Lessig MC, He AG, James GA, Driscoll DJ, Liu Y. J Neurol Neurosurg Psychiatry. 2005;76:260–2.

Stevenson DA, Heinemann J, Angulo M, Butler MG, Loker J, Rupe N, Kendell P, Cassidy SB, Scheimann A. J Pediatr Gastroenterol Nutr. 2007;45:272–4.

Tauber M, Barbeau C, Jouret B, Pienkowski C, Malzac P, Moncla A, Rochiccioli P. Horm Res. 2000;53:279–87.

Tauber M, Conte Auriol F, Moulin P, Molinas C, Delagnes V, Salles JP. Horm Res. 2004;62:49–54.

Tauber M, Diene G, Molinas C, Hebert M. Am J Med Genet A. 2008;146:881–7

van Mil EA, Westerterp KR, Gerver WJ, Curfs LM, Schrander-Stumpel CT, Kester AD, Saris WH. Am J Clin Nutr. 2000;71:752–6.

Whitman BY, Myers S, Carrel A, Allen D. Pediatrics. 2002;109:E35.

Zipf WB, Berntson GG. Am J Clin Nutr. 1987;46:277–81.

Chapter 170
Insulin and Clinical Eating Disorders in Diabetes

Masato Takii

Abbreviations

IDDM	Insulin-dependent diabetes
AN	Anorexia nervosa
DSM-III	Diagnostic and Statistical Manual of Mental Disorders, Third Edition
DSM-III-R	Diagnostic and Statistical Manual of Mental Disorders, Revised Third Edition
BN	Bulimia nervosa
ED-NOS	Eating disorder not otherwise specified
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition
ICB	Inappropriate compensatory behavior in order to prevent weight gain
BED	Binge-eating disorder
DKA	Diabetic ketoacidosis
NIDDM	Non-insulin-dependent diabetes

170.1 Introduction

Type 1 diabetes is a disease characterized by a total absence of insulin production because the pancreatic β cells have been destroyed by an autoimmune mechanism. Problems associated with the regulation of blood sugar and the long-term complications are well known. An eating disorder is a disease in which a person has an abnormal eating behavior associated with an excessive fixation on body weight. Because type 1 diabetes patients who develop an eating disorder have great difficulty maintaining a therapeutic dietary regimen and often place priority on weight control over metabolic control, they face severe obstacles to proper diabetes control. As with eating disorders in the general population, an eating disorder concurrent with type 1 diabetes is most commonly seen in young women.

The research on the concurrence of an eating disorder and type 1 diabetes has been done since about 1980, mostly in Europe and North America. Empirical studies in this field have focused on the prevalence of eating disorders, poor metabolic control, the high risk of diabetic long-term complications, and nonadherence to the diabetes treatment regimen through behaviors such as insulin omission.

M. Takii (✉)
Department of Psychosomatic Medicine, Graduate School of Medical Sciences, Kyushu University,
3-1-1 Maidashi, Higashi-ku, Fukuoka, 812-8582, Japan
e-mail: Takii@cephal.med.kyushu-u.ac.jp

Table 170.1 Key features of type 1 diabetes

1. Type 1 diabetes results from extremely decreased insulin production by the pancreas because the beta cells (insulin secretion cells) are destroyed by an autoimmune mechanism.
2. The main treatment for type 1 diabetes is to supply extrinsic insulin. Persons with type 1 diabetes must take supplementary insulin by injections for the rest of their lives.
3. The onset age of type 1 diabetes is usually young, most often in childhood or the adolescent period, and the onset is fairly rapid.
4. Various self-care efforts are necessary for patients to maintain good glycemic control and to prevent diabetes-related complications.
5. Because the burden of having this severe disease and the requirements of managing it are often too heavy for young patients, they tend to have psychological and behavioral problems.
6. These problems lead to a deterioration of the metabolic control of the diabetes and to early onset of long-term diabetic complications that severely affect the quality of life of the patients.

This table lists the key facts of type 1 diabetes including the etiology by an autoimmune mechanism, the necessity of insulin supplementation for treatment, the young onset age of the disease, the difficulty of controlling it, and the risk for psychological/behavioral and medical problems

This report focuses on current findings and theories related to the epidemiology, clinical condition, mechanism of the onset of the eating disorder, and the treatment approach for patients with clinical eating disorders concurrent with type 1 diabetes. In addition, studies of eating disorders complicated with type 2 diabetes will be introduced.

The Department of Psychosomatic Medicine at Kyushu University specializes in the treatment of both eating disorders and diabetes. Diabetes patients who have psychological problems are referred from all over Japan. Over the past 15 years, we have treated more than 150 type 1 diabetes patients with a concurrent clinical eating disorder. Studies done in our department concerning the clinical condition and treatment of these patients are described in this chapter.

Also discussed are self-destructive behaviors associated with insulin omission and poor insulin manipulation, which are often deeply related to eating disorders and are among the most severe problematic behaviors of diabetes patients (Table 170.1).

170.2 Epidemiology/Clinical Condition

170.2.1 Early Review

Marcus and Wing (1990) did a literature review of the clinical condition of 57 patients with an eating disorder concurrent with insulin-dependent diabetes (IDDM). A summary is as follows:

1. Co-occurrence of these disorders is common.
2. The diagnosis of IDDM occurs before that of an eating disorder in the preponderance (90%) of the cases.
3. Ninety-five percent of the cases of eating disorders among IDDM patients have occurred in women.
4. Sixty-two percent of eating-disordered IDDM patients reported deliberate manipulation of insulin to promote weight loss. Regular elimination of insulin doses would be predicted to have negative consequences for glycemic control.
5. Poor glycemic control was reported in 75% of patients with eating disorders, and major diabetic complications may be prevalent as well.
6. The relationship between diabetes and anorexia nervosa (AN)/bulimia shows a kind of synergism in which one disorder worsens the other and where successful therapeutic interventions may consequently prove exceedingly difficult.

170.2.2 Prevalence of the Eating Disorders of Type 1 Diabetes Patients

A relatively large number of studies investigating the prevalence of the eating disorders of patients with type 1 diabetes have been published since late 1980s (Steel et al. 1987; Rodin et al. 1991; Fairburn et al. 1991; Peveler et al. 1992; Jones et al. 2000). Whether or not eating disorder frequency was higher in female patients of type 1 diabetes than nondiabetic peers was controversial.

Relatively more studies suggested that eating disorder frequency is higher in women with type 1 diabetes than in women in general (Steel et al. 1987; Rodin et al. 1991). For example, Rodin et al. (1991) reported a diagnosis of an eating disorder for 13- to 18-year-old women with type 1 diabetes in 13% of their sample (103 cases), based on DSM-III criteria (AN 1% and bulimia 12%) and in 5% of the sample based on the more severe DSM-III-R criteria (American Psychiatric Association 1987) (all bulimia nervosa (BN)).

Other studies have found that the eating disorder frequency does not differ from that of women in general (Fairburn et al. 1991; Peveler et al. 1992). Fairburn et al. (1991) diagnosed eating disorders in 11% of 54 women with IDDM aged 17–25 years (BN 5.5% and "eating disorder not otherwise specified (ED-NOS)" 5.5%) and in 7.5% of nondiabetic, control women (BN 3% and ED-NOS 4.5%) based on DSM-III-R criteria. No significant difference was found between the groups. ED-NOSs were defined as eating disorders other than AN or BN.

The differences in prevalences may have been because of differences in the method of diagnosis, the eating disorder diagnostic criteria, and/or the sample. The DSM-IV diagnostic criteria (American Psychiatric Association 1994) for the first time accepted insulin omission as an "inappropriate compensatory behavior in order to prevent weight gain" (ICB), which is necessary for a diagnosis of BN. The use of the earlier criteria may have led to underestimation of the prevalence of the eating disorders of type 1 diabetes patients (Affenito and Adams 2001).

Jones et al. (2000) conducted a large, multisite case-controlled study of 356 girls aged 12–19 years with type 1 diabetes and 1,098 case-matched controls. They used a two-stage design with both self-report questionnaires and structured diagnostic interviews of eating disorders and found that eating disorders that met the DSM-IV diagnostic criteria were 2.4 times more common in girls with diabetes (5 BN cases and 31 ED-NOS cases) than in their nondiabetic peers (10% vs 4%).

170.2.3 Classification of the Eating Disorders Associated with Type 1 Diabetes

Research indicates that eating disorders associated with binge eating, such as BN and binge-eating disorder (BED), are the most common types of eating disorders among girls with diabetes and that restricting eating disorders are much less common conditions (Jones et al. 2000; Affenito et al. 1997). BED is classified as an ED-NOS. Although BN and BED have frequent binge eating in common, the primary difference between BN and BED is the regular use of an ICB by BN patients, such as insulin omission, self-induced vomiting, misuse of laxatives, fasting, or excessive exercise (American Psychiatric Association 1994).

In a meta-analysis, Nielsen (2002) reported that although AN was not increased in females with type 1 diabetes compared with their nondiabetic peers, BN (OR = 2.9), ED-NOS (OR = 1.8), and subthreshold eating disorders (OR = 1.9) were increased.

Since 1994, we have treated 158 type 1 diabetes patients with clinical eating disorders: 151 female and 7 male. The classification of the eating disorders of female patients, based on DSM-IV, were

Table 170.2 Demographic and clinical features of female type 1 diabetes patients with bulimia nervosa (BN), with binge-eating disorder (BED), and without an eating disorder (CONTROL) (Adapted from Takii et al. 1999)

	BN (N = 22)	BED (N = 11)	CONTROL (N = 32)	P
Age (years)	23.2 ± 4.4	24.8 ± 7.5	23.9 ± 3.8	NS
Onset of DM (years)	14.5 ± 5.4	20.1 ± 8.2	15.9 ± 5.9	NS
Duration of DM (years)	8.7 ± 5.7	4.7 ± 1.8	7.9 ± 5.5	NS
Onset of BE (years)	18.2 ± 4.2	22.4 ± 7.0	(-)	<0.05
Duration of BE (years)	5.0 ± 3.9	2.5 ± 1.6	(-)	<0.05
BMI (kg/m^2)	21.6 ± 2.5	23.6 ± 2.7	20.7 ± 2.2	<0.05[a]
HbA1c (%)	12.3 ± 2.6	9.7 ± 2.1	6.2 ± 0.8	<0.0001[b]
Retinopathy (%)	40.9	0.0	6.3	<0.001
Neuropathy (%)	45.4	9.0	6.3	<0.005
EDI	93.5 ± 26.9	57.4 ± 25.0	36.2 ± 15.3	<0.0001[b]
SDS	53.3 ± 7.2	42.8 ± 7.2	37.1 ± 6.8	<0.0001[b]
Trait-Anxiety scale in STAI	58.9 ± 7.1	47.9 ± 9.0	42.2 ± 8.3	<0.0001[c]
Any co-occurring mental disorder	18 (81.8%)	5 (45.5%)	ND	<0.05
GAF	45.7 ± 7.7	56.5 ± 8.8	ND	<0.001

Female type 1 diabetes patients with bulimia nervosa (BN) have the most severe medical consequences of diabetes, psychopathology related to eating disorders, and general psychological disturbances; those without eating disorders (CONTROL) have the least; and those with binge-eating disorder (BED) are between BN and CONTROL

DM type 1 diabetes, *BE* binge eating, *EDI* eating disorder inventory, *SDS* self-rating depression scale, *STAI* state-trait anxiety inventory, *GAF* global assessment of functioning, *ND* not determined

Data are means ± SD. NS, $p > 0.05$

Differences were determined by one-way ANOVA followed by Bonferroni's adjusted t-test or by chi-square test

[a] BED > BN and CONTROL

[b] BN > BED > CONTROL

[c] BN > BED and CONTROL

100 cases of BN (66.2%), 35 cases of BED (23.2%), 11 cases of AN (7.3%), and five cases of ED-NOS other than BED (3.3%). Of the 11 cases of AN, only 1 was the restricting type, with the remaining 10 the binge-eating/purging type. For males, one case of BN (14.3%) and six cases of BED (85.7%) were found. Although the high proportion of binge-eating-associated eating disorders was similar to previous studies, the preponderance of BN patients may reflect sample bias because of the urgent necessity to give specialized treatment for the patient's severe medical condition: BN patients with type 1 diabetes have been shown to have the most severe medical problems in comparison with patients with other eating disorders such as BED, as will be presented in the following sections (Takii et al. 1999) (Table 170.2).

170.2.4 Psychopathological Aspects

170.2.4.1 Psychopathology Associated with the Eating Disorder

For young women with type 1 diabetes, some studies have shown that the psychopathology related to the eating disorder is more pronounced than for persons without diabetes (Rosmark et al. 1986; Fairburn et al. 1991).

Our research has shown that type 1 diabetes patients with a clinical eating disorder manifest significantly more severe eating disorder psychopathology than patients with an episode of binge eating but without a clinical eating disorder (abnormal eating habits), and that patients with abnormal

eating habits manifest significantly more severe eating disorder psychopathology than patients with normal eating habits (Tsukahara et al. 2009).

We also reported that female type 1 diabetes patients with BN had a significantly more severe eating disorder psychopathology than patients with BED and that patients with BED had a significantly more severe eating disorder psychopathology than patients without eating disorders (Takii et al. 1999) (Table 170.2).

170.2.4.2 General Psychopathology

Mood disorders have been reported to be common in patients with an eating disorder (Kennedy et al. 1994). They are also common in patients with diabetes (Talbot and Nouwen 2000). Vila et al. (1995) found that almost half of the 52 teenaged girls with type 1 diabetes and an eating disorder also reported significant depressive symptoms.

Our research has shown that type 1 diabetes patients with a clinical eating disorder had significantly more severe depression, anxiety, and diabetes-related distrust than patients with abnormal eating habits and that patients with abnormal eating habits had significantly more severe psychopathology than patients with normal eating habits (Tsukahara et al. 2009).

We also reported that female type 1 diabetes patients with BN manifested significantly more severe depression, anxiety, a higher rate of co-occurring mental disorders, and poorer psychosocial functioning than patients with BED and that patients with BED were significantly more depressive than patients without eating disorders (Takii et al. 1999) (Table 170.2).

170.2.5 Behavioral Problems

170.2.5.1 Noncompliance

Rodin et al. (1991) reported that patients with an eating disorder reported significantly more noncompliance with almost all aspects of their diabetes treatment, such as testing of blood and urine, taking insulin on schedule, following a dietary plan, maintaining blood sugar, fitting exercise into the treatment plan, and remembering to do everything specified for controlling IDDM.

170.2.5.2 Insulin Omission

Insulin omission is a problematic behavior in which diabetes patients deliberately omit or reduce their insulin dosage. Many studies have focused on the rates of insulin omission of female diabetes patients, the extreme disturbance of insulin omission to metabolic control, and the relationship between insulin omission and eating disorders (Rodin et al. 1991; Polonsky et al. 1994; Biggs et al. 1994; Affenito et al. 1997; Takii et al. 1999, 2002a, 2008; Goebel-Fabbri et al. 2008).

Polonsky et al. (1994) reported that 31% of women with IDDM reported intentional insulin omission and that approximately half of them reported omitting insulin for weight-management purposes (weight-related omitters). Weight-related omitters evidenced significantly greater psychological distress, poorer regimen adherence (including more frequent omission), poorer glycemic control, and higher rates of long-term diabetic complications than did non-weight-related omitters or nonomitters. Non-weight-related omitters tended to fall between weight-related omitters and nonomitters on most measures of psychological functioning, adherence, and glycemic control.

In a meta-analysis, Nielsen (2002) reported that insulin omission is increased when eating disorders coexist with type 1 diabetes (OR = 12.6).

As mentioned above, the DSM-IV diagnostic criteria (American Psychiatric Association 1994) have for the first time accepted insulin omission as an ICB, which is necessary for the diagnosis of BN. According to the criteria, insulin omission or reduction at least twice a week could be considered an ICB by BN patients. However, we found that, when type 1 diabetic females with BN omit insulin, they nearly always do it more frequently and in a more extreme way: omission of at least one-quarter of the prescribed insulin (Takii et al. 2002a, 2008). We define this degree of insulin omission as "severe insulin omission."

170.2.5.3 ICBs (Purging Behaviors) of Type 1 Diabetes Patients with an Eating Disorder

Rodin et al. (1991) reported the methods of inducing weight loss used by adolescent females with IDDM with and without an eating disorder. Of 13 patients with an eating disorder by DSM-III criteria, 7 (54%) omitted insulin, 9 (69%) dieted, 4 (31%) self-induced vomiting, 3 (23%) did extreme exercise to lose weight, and 1 (8%) abused laxatives. Of the 90 patients without an eating disorder, 5 (6%) omitted insulin, 30 (33%) dieted, 4 (4%) did self-induced vomiting, 17 (19%) did extreme exercise to lose weight, and 1 (1%) abused laxatives.

In a study of 55 female patients with BN, we reported that 44 (80.0%) did severe insulin omission, (omission of at least one-quarter of the prescribed insulin) 27 (49.1%) did self-induced vomiting, and 11 (20.0%) abused laxative (Takii et al. 2002a). In classifying the patients by type of ICB, we found that 22 patients did only severe insulin omission, 22 did both severe insulin omission and another ICB, and 11 did not engage in severe insulin omission but had another ICB. Table 170.3 shows a comparison of the clinical characteristics of these three groups and a group of female BED patients. We found that type 1 diabetic females with BN are not a homogenous group and that they can be classified into three distinctive subgroups by type of ICB. Individuals with severe insulin omission and another ICB (BN-IP) had the most severe medical problems, such as the poorest metabolic control and the highest rate of diabetic complications, and had severe psychological/behavioral pathology. Individuals without severe insulin omission and with another ICB (BN-NI) manifested the highest psychological distress. Individuals with only severe insulin omission (BN-I) had comparatively mild distress despite having the poorest metabolic control. The apparent comparative lack of distress of patients with only severe insulin omission as an ICB may largely result from taking the easy way of reducing their body weight, insulin omission, as an avoidance mechanism.

170.2.6 Medical Problems

170.2.6.1 Poor Glycemic Control

Many studies have shown that HbA1c levels are significantly higher in type 1 diabetes patients with an eating disorder than in patients without (Marcus and Wing 1990; Affenito et al. 1997; Rydall et al. 1997; Takii et al. 1999; Jones et al. 2000; Rodin et al. 2002; Goebel-Fabbri et al. 2002). For example, among 356 adolescent females with type 1 diabetes, Jones et al. (2000) reported that the HbA1c of 36 who had eating disorders (9.4 ± 1.8%) was significantly higher than that of the other patients (8.6 ± 1.6%). We reported that the HbA1c of 22 type 1 diabetic females with BN (12.3 ± 2.6%) was significantly higher than that of 11 female patients with BED (9.7 ± 2.1%), and that the HbA1c of

Table 170.3 Demographic and clinical features of female type 1 diabetes patients categorized by type of bulimia nervosa (BN) and binge-eating disorder (BED) (Adapted from Takii et al. 2002a. Copyright 2002 by the American Diabetes Association, Inc.)

	BED	BN-I	BN-IP	BN-NI	p
N	24	22	22	11	
Age (years)	25.2 ± 5.4	22.3 ± 4.4	23.7 ± 4.7	22.3 ± 3.1	NS
Onset of type 1 diabetes (years)	17.5 ± 8.1	15.9 ± 5.8	13.1 ± 5.4	14.0 ± 4.4	NS
Duration of type 1 diabetes (years)	7.1 ± 5.7	6.4 ± 3.8	10.5 ± 7.0	8.3 ± 5.1	NS
Onset of eating disorder (years)	21.7 ± 5.7	17.9 ± 4.5	17.5 ± 3.6	17.9 ± 2.3	<0.01[a]
Duration of eating disorder (years)	3.5 ± 3.1	4.2 ± 3.5	6.3 ± 4.0	4.4 ± 3.0	NS
BMI (kg/m²)	24.1 ± 2.6	22.1 ± 2.7	20.4 ± 2.2	22.3 ± 2.7	<0.0001[b]
HbA1c (%)	9.8 ± 1.7	12.4 ± 2.1	13.0 ± 3.1	9.7 ± 2.4	<0.0001[c]
Neuropathy (%)	16.7	28.6	72.7	54.5	<0.001
Retinopathy (%)	8.3	19.0	54.5	45.5	<0.005
Nephropathy (%)	8.3	4.8	27.3	0	<0.05
EDI	63.9 ± 24.6	85.8 ± 35.9	93.7 ± 26.9	103.1 ± 25.2	<0.005[d]
SDS	44.5 ± 7.3	48.5 ± 8.3	53.4 ± 10.0	55.8 ± 8.2	<0.001[e]
STAI-T	50.9 ± 9.8	53.5 ± 9.5	59.5 ± 10.4	62.5 ± 9.3	<0.005 [e]
MPS	99.1±17.7	92.5 ± 23.0	102.3 ± 16.6	122.8 ± 25.0	<0.05[f]

Female type 1 diabetes patients with bulimia nervosa (BN) are not a homogenous group. They can be classified into three distinctive subgroups by type of inappropriate compensatory behavior in order to prevent weight gain

BED Binge-eating disorder, *BN* bulimia nervosa, *BN-I* BN-insulin omission, *BN-IP* BN-insulin omission/other purging, *BN-NI* BN-no insulin omission, *EDI* eating disorder inventory, *SDS* self-rating depression scale, *STAI* state-trait anxiety inventory, *MPS* multiple-dimension perfectionism scale (Frost)

Data are means ± SD. NS, $p > 0.05$

Differences were determined by one-way ANOVA followed by Bonferroni's adjusted t-test or by chi-square test

[a]BED > BN-I, BN-IP, BN-NI

[b]BED > BN-I, BN-IP

[c]BN-I, BN-IP > BED, BN-NI

[d]BN-I, BN-IP, BN-NI > BED

[e]BN-NI > BED, BN-I; BN-IP>BED

[f]BN-NI > BED, BN-I, BN-IP

patients with BED was significantly higher than that of patients without an eating disorder (6.2 ± 0.8%) (Takii et al. 1999) (Table 170.2).

170.2.6.2 Factors Related to the Exacerbation of Glycemic Control

We examined the psychological/behavioral predictors of elevated HbA1c of females with type 1 diabetes and BN or BED by multiple regression analysis (Takii et al. 1999). "Severe insulin omission" was found to be the factor most predictive of a higher HbA1c level, with a large amount eaten (2,000+ calories) in one binge-eating session the next most predictive.

170.2.6.3 Short- and Medium-term Complications

Unstable and poor metabolic control (so-called brittle diabetes), recurrent diabetic ketoacidosis (DKA), and severe hypoglycemic attacks easily occur in diabetes patients with a concurrent eating disorder (Rodin and Daneman 1992) and are likely to be associated with the need for more frequent

hospitalization (Glasgow et al. 1991). Because most eating disorders are accompanied by binge eating and insulin omission, it is natural that these patients have extreme hyperglycemia. Female type 1 diabetes patients who have frequently repeated DKA can be strongly suspected of severe insulin omission associated with a severe eating disorder. An irregular diet or the irregular use of insulin injections (based on excessive attachment to body weight) often lead to unstable metabolic control, which can in turn lead to severe hypoglycemic attacks. However, in our experience, severe hypoglycemia attacks are not often seen in type 1 diabetes patients with a clinical eating disorder.

170.2.6.4 Long-term Complications

A considerable number of studies have indicated that a concurrent eating disorder or disordered eating can lead to an increased risk of the long-term complications of diabetes (Steel et al. 1987; Affenito et al. 1997; Rydall et al. 1997; Takii et al. 1999; Goebel-Fabbri et al. 2002).

In a meta-analysis, Nielsen (2000) reported that a coexisting eating disorder with type 1 diabetes increases the overall common odds ratio for retinopathy to 4.8. Of the various problematic behavioral factors related to eating disorders, we found the duration of severe insulin omission (omission of at least one-quarter of the prescribed insulin) to be the factor most closely associated with the retinopathy and nephropathy of type 1 diabetic females with clinical eating disorders (Takii et al. 2008). As mentioned above, severe insulin omission is the factor most predictive of the HbA1c of patients with concurrent type 1 diabetes and an eating disorder (Takii et al. 1999). The duration of severe insulin omission was related to the duration of poorest glycemic control. This finding may help patients who deliberately omit insulin to become aware of the medical risks of insulin omission.

170.2.7 Longitudinal Course of an Eating Disorder in Diabetes

Reports related to the long-term course of eating disorders and disordered eating by patients with type 1 diabetes are rare. Rydall et al. (1997) reported the 4- to 5-year course of type 1 diabetic females who were 12–18 years old at study entry. Intentional omission or underdosing of insulin and dieting for weight loss increased in prevalence from baseline to follow-up. Binge eating, self-induced vomiting, and dieting for weight loss tended to persist at follow-up if they were present at base line. Herpertz et al. (2001) assessed a sample of 36 diabetic patients with an eating disorder (type 1 diabetes: $n = 13$, Type 2 diabetes: $n = 23$) over a period of about 2 years. They reported that the eating disorder tended to persist over time, with a considerable shift within the different types of eating disorders. Nielsen et al. (2002) combined information from earlier studies to estimate mortality and reported a standardized mortality rate of 4.06% for type 1 diabetes, 8.86% for AN, and 14.5% for concurrent cases.

170.2.8 Eating Disorders Complicated with Type 2 Diabetes

In comparison with studies of eating disorders concurrent with type 1 diabetes, such studies of type 2 diabetes patients are rare. Herpertz et al. (1998) reported that although there was no difference in the prevalence of all eating disorders between IDDM (36.3 ± 10.6 years of age) and non-insulin-dependent

diabetes (NIDDM) (54.2 ± 8.1 years of age) (point prevalence 5.5% vs 6.5%, lifetime prevalence 10.0% vs 9.9%), the prevalence of BN was higher in IDDM patients (point prevalence 1.5% vs 0.3%, lifetime prevalence 3.2% vs 1.9%) and BED was more frequent in NIDDM patients (point prevalence 1.8% vs 3.7%, lifetime prevalence 2.6% vs 5.9%). They also reported that type 2 diabetes patients with an eating disorder showed a greater psychopathology compared to patients without an eating disorder and that the diagnosis of an eating disorder did not seem to have a special influence on glycemic control (Herpertz et al. 2000). Papelbaum et al. (2005) reported that 20% of patients with type 2 diabetes (52.9 ± 6.8 years of age) displayed an eating disorder, that BED was the predominant eating disorder diagnosis (10%), and that the presence of an eating disorder was associated with a significant increase in the frequency of anxiety disorders.

170.3 The Mechanism of Eating Disorder Onset

170.3.1 Various Etiological Factors Peculiar to Type 1 Diabetes

Eating disorders are generally considered to have multiple etiologies including biological, psychological, familial, cultural, and social factors. Along with these general factors, many hypotheses have been proposed for the relationship between type 1 diabetes and the onset of an eating disorder. For example, "chronic dietary restraint" (Marcus and Wing 1990; Rodin and Daneman 1992; Polonsky 1996; Daneman et al. 1998; Goebel-Fabbri et al. 2002), "weight gain associated with appropriate diabetes self-care" (Marcus and Wing 1990; Rodin and Daneman 1992; Polonsky 1996; Daneman et al. 1998; Goebel-Fabbri et al. 2002), "uniquely effective forms of purging (insulin omission)" (Marcus and Wing 1990; Rodin and Daneman 1992; Polonsky 1996; Daneman et al. 1998; Goebel-Fabbri et al. 2002), "altered family dynamics" (Marcus and Wing 1990; Anderson 1990; Rodin and Daneman 1992; Maharaj et al. 1998), "greater prevalence of depressed and fluctuating moods" (Marcus and Wing 1990; Polonsky 1996; Goebel-Fabbri et al. 2002), "effects of type 1 diabetes on psychological development" (Marcus and Wing 1990), and "feeling out of control" (Schwartz et al. 2002). However, except for a few studies (Maharaj et al. 1998; Schwartz et al. 2002), empirical support is lacking.

The factors Marcus and Wing (1990) reported as the reasons that patients with type 1 diabetes would be vulnerable to eating disorders are as follows.

1. Factors related to the treatment of type 1 diabetes, such as being required to focus on diet and limit weight gain, weight gain by insulin therapy and good glycemic control, and the presence of a purging behavior peculiar to diabetes called insulin omission.
2. Type 1 diabetes may affect the psychological well-being of adolescents. Diabetes can interfere significantly with adolescent development by affecting body image, causing feelings of being different, and/or exacerbating dependence/independence conflict.
3. A family relationship such as a tendency among some parents to be overprotective or overinvolved with their youngster, rigidity, and a lack of conflict resolution.
4. Effects of chronic stress caused by chronic disease, which lead to lower self-esteem, affect body image, feelings of mastery or competence, necessitate changes in diet, and/or affect family environment.

Daneman et al. (1998) developed a model demonstrating how diabetic-related factors, such as weight gain after the initiation of insulin treatment or intensive diabetes management, dietary restriction for the nutritional management of diabetes, and insulin omission, interact to lead to

eating disorders. Furthermore, in an empirical study, Maharaj et al. (1998) found that the eating disturbances of adolescent girls with diabetes are associated with significantly more family dysfunction. Diabetic girls with eating disturbances reported less support, poorer communication, and less trust in their relationships with their parents than did diabetic girls without eating disturbances. Schwartz et al. (2002) reported that a lower sense of overall control and a lower sense of bodily control were both directly related to more severe eating-disordered symptoms.

170.3.2   The "Compulsive Self-care → Binge Eating" Hypothesis

We have proposed two etiology hypotheses. Figure 170.1 shows the "Compulsive self-care → binge eating" hypothesis. There is tremendous social pressure on diabetes patients to limit the amount of food they eat and to not become fat, which may lead them to feel cornered and cause them to endure serious distress. Such thoughts can be enhanced by well intentioned, but poorly considered diabetes education. If the patient is overly conscientious and the family is too strict, the patient may feel trapped and that they must engage in overly strict diabetes management. These patients often do compulsive self-care for a period of time after the onset of diabetes. During this time, they are often treated like "honor students" by the medical staff.

However, frustration gradually increases, and the patient becomes unable to tolerate the strict regimen. Binge eating often starts without a special trigger and escalates quickly. Furthermore, weight gain by the binge eating causes a fear of becoming fat, which often leads to inappropriate compensatory behaviors in order to prevent weight gain (ICB), such as insulin omission and self-induced vomiting.
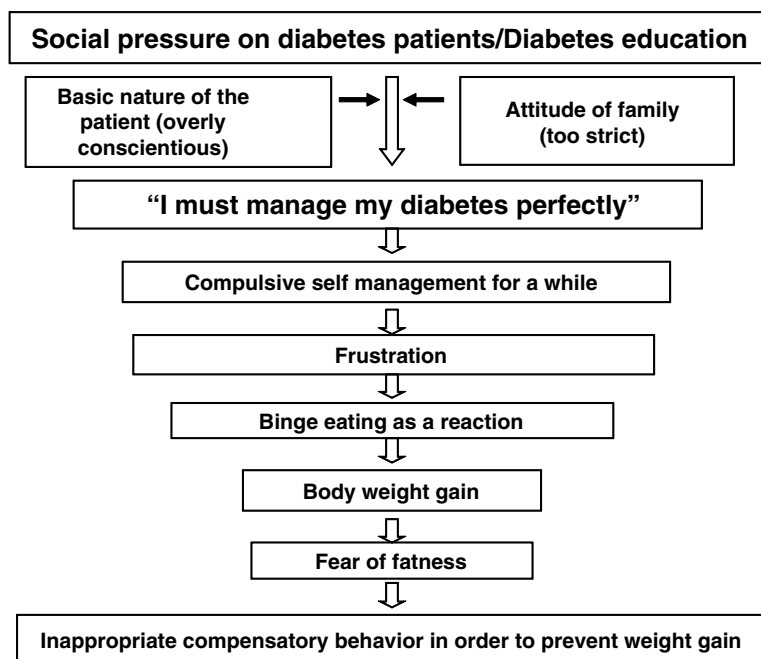
Fig. 170.1 The "Compulsive self-care → binge eating" hypothesis. This figure shows the flow of how female patients with type 1 diabetes who initially engage in compulsive self-care begin to binge and develop an eating disorder

170.3.3 Trauma Hypothesis

We have also developed what we call our Trauma hypothesis. The age at which type 1 diabetes begins most frequently, from infancy to the adolescent years, is a time when the self is not yet well formed. The patients have not developed adult mechanisms to cope with stress in general. At this critical time, the patient is suddenly confronted by a serious disease and the need to face a strict self-care regimen, which often leaves the patient overwhelmed by the diabetes. Unless the patient is able to accept and control it, the diabetes may be experienced with remarkable pain. For these distressed young patients, key people surrounding them sometimes fail to give effective psychological support and, on the contrary, they may take an attitude lacking in understanding; scolding and blaming.

Because of a lack of understanding of type 1 diabetes, diabetes patients are often subject to prejudice, discrimination, and special handling, which can be quite hurtful to the patient. This can lead to feelings of ineffectualness, despair, and a sense of guilt for not being able to deal with the diabetes. Suffering from a sense of alienation and/or feeling of isolation with no outside assistance, diabetes patients may develop severe trauma.

The eating disorder may give the patient relief from this state of despair. It gives the patient a perverted psychological structure in which they no longer care about anything but body weight/shape. Moreover, because the patient thinks about nothing else while they eat binge, they are temporarily freed from stress.

170.4 Self-destructive Behaviors Associated with Insulin Self-administration

By the proper self-administration of insulin, the quality of life and the treatment outcome of patients with type 1 diabetes can be remarkably improved. However, while there are patients who are able to accept this powerful drug and to manage it for the betterment of their life, there are patients who do not use sufficient insulin (insulin omission) or who use insulin extremely inadequately, which can cause serious medical problems (self-destructive behaviors). The most miserable psychosocial problems of type 1 diabetes patients are self-destructive behaviors such as recurrent diabetic ketoacidosis (DKA), frequent severe hypoglycemia, and brittle diabetes (Rubin and Peyrot 1992; Schade et al. 1985). These behaviors are often deeply associated with insulin manipulation. Self-destructive behaviors seem to coincide with severe psychosocial disturbance; either individual psychopathology (Schade et al. 1985), family dysfunction (White et al. 1984), or both (Golden et al. 1985). Self-destructive behaviors and eating disorders probably overlap to a significant degree; both clinical conditions are deeply associated with insulin manipulation (Table 170.4).

170.4.1 Recurrent Diabetic Ketoacidosis

As mentioned above, a comparatively high percentage of female patients with type 1 diabetes omit or reduce insulin to control body weight. Furthermore, some patients with a concurrent clinical eating disorder inject much less insulin than prescribed by the doctor, and they often seem to be on the threshold of DKA. In such cases, DKA will develop from only a slight precipitant, such as an insulin

Table 170.4 Key features of self-destructive behaviors

1. Type 1 diabetes patients sometimes exhibit self-destructive behaviors that result in recurrent diabetic ketoacidosis, frequent severe hypoglycemic attacks, and brittle diabetes.
2. These behaviors are often done with insulin manipulation including insulin omission and overdosing.
3. These behaviors lead to extreme instability of glycemic control, life-threatening episodes, and frequent hospitalizations.
4. These behaviors seem to coincide with severe psychological disturbance of individual psychopathology, family dysfunction, or both.
5. The main reason for these behaviors seems to be an intention to escape from an environment with much stress and to gain the concern of others by creating a serious physical condition that requires hospitalization.
6. Self-destructive behaviors and eating disorders probably overlap to a significant degree; both clinical conditions are deeply associated with insulin manipulation.

This table lists the key factors involved in self-destructive behaviors including the types of these behaviors, the etiological role of insulin manipulation, medical outcomes, psychological disturbance of the patient and family, the patient's psychological intention to engage in these behaviors, and the overlap between eating disorders

resistance increase by a worsened physical situation (sick day), failure to inject the insulin at the proper time because of failure to bring an injection device or by loss of their precarious mental balance because of mental instability. Moreover, patients may repeat DKA in order to escape from severe psychosocial disturbances.

170.4.2 Frequent Severe Hypoglycemic Attacks

Frequent severe hypoglycemic attacks can be caused by the intentional injection of too large a quantity of insulin for the purpose of escaping from the stresses of life. When patients who are psychologically immature and susceptible to stress are continually exposed to a harsh and hopeless environment, it is natural in a sense to escape by taking advantage of their disease. Feeling that they have no place in the family, through hospital admission they can escape form the family and the vicious cycle of family problems. However, even in cases in which the environment is not so terrible, extremely psychologically immature patients often cause repeated, severe hypoglycemia in order to escape from the pressures of diabetes and their life in general by causing themselves to lose consciousness.

170.4.3 Brittle Diabetes

Brittle diabetes overlaps widely with recurrent DKA and frequent severe hypoglycemic attacks. It is defined as "unexplained large changes in blood glucose concentration" (Woodyatt 1934) or "unable to maintain a normal lifestyle because of frequent disruptions secondary to severe hyperglycemic and/or hypoglycemic episodes" (Schade et al. 1985). In their study of brittle diabetes and recurrent DKA, Schade et al. (1985) reported that most type 1 diabetic patients who were thought to have brittle diabetes or insulin resistance were afterward found to have omitted insulin or had poor insulin manipulation. They also reported that, of 30 patients, eight were diagnosed with factitious disease and eight malingering. The most common causes of these self-destructive behaviors seem to be (1) to escape from an environment with much stress and difficulty, (2) severe personality disorder, and (3) insulin omission because of anxiety to weight gain (Fig. 170.2).
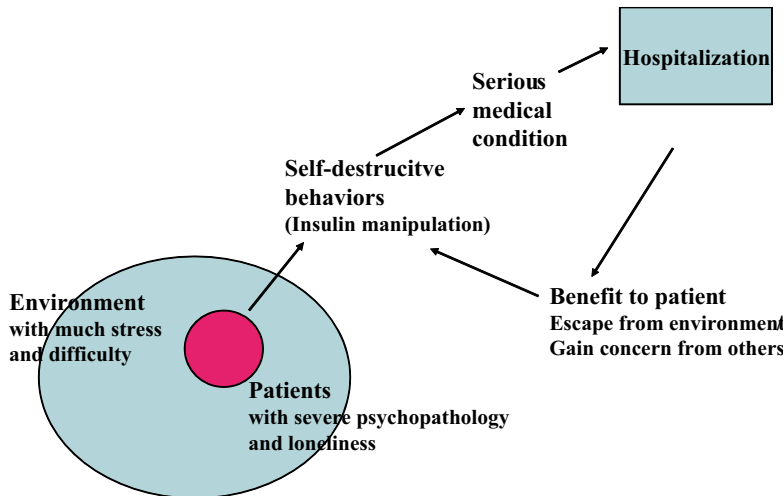
Fig. 170.2 The mechanism of the self-destructive behaviors of diabetes patients. Self-destructive behaviors include recurrent diabetic ketoacidosis, frequent severe hypoglycemia, and brittle diabetes. An intention to escape from an environment with much stress and to gain concern from others by creating a serious physical condition that requires hospitalization seems to be the main reason for the self-destructive behaviors of diabetes patients

170.4.4 Management

Patients tend to hide their problematic behaviors because of an intensive sense of guilt or a fear of being criticized or deserted by people significant to them. Even when the medical staff suspect insulin misapplication, the patient may strongly deny it and the family may show strong resistance to admitting it. As a result, an unexplained inability to control blood glucose can often be attributed to insulin resistance. It is important that the medical staff recognize this psychological problem and recommend psychological treatment by a mental health specialist.

170.5 Treatment Approach for Type 1 Diabetes Patients with Eating Disorders

170.5.1 Treatment for the Clinical Eating Disorders of Patients with Type 1 Diabetes

Previous studies have indicated the difficulties of dealing with type 1 diabetes patients with eating disorders and the urgent necessity for developing effective treatments (Marcus and Wing 1990; Rubin and Peyrot 1992). However, interventions specifically for these patients have rarely been reported, and most have been case studies. Peveler and Fairburn (1992) provided a detailed description of management and outcome, in a report of the treatment of a series of six females with type 1 diabetes and BN in which they used modified cognitive–behavioral therapy for BN, mainly on an outpatient basis. Although the treatment usually resulted in improved eating habits and glycemic control, the success rate was lower than for nondiabetic BN patients. Moreover, the improved glycemic control of their patients seems to have been insufficient to prevent long-term complications.

170.5.2 Psychoeducation Program for Type 1 Diabetes Patients with Disturbed Eating

Several group psychoeducation programs for patients with disturbed eating attitudes, not clinical eating disorders, have also been reported. Olmsted et al. (2002) evaluated the effect of a six-session psychoeducation program for young women with type 1 diabetes and disordered eating attitudes and behaviors that included a "nondeprivational" approach and recommendations that all types of foods be eaten in normal amounts. Compared with a treatment-as-usual group, the psychoeducation group was associated with a reduction in eating disturbance, but not with improvement in the frequency of insulin omission or HbA1c levels. Alloway et al. (2001) reported that a six-session group psychoeducation program, which is based on a program for BN and subclinical bulimia that was modified slightly to adapt to type 1 diabetes, was no more effective than a wait-list control group for treating subclinical disordered eating by women with type 1 diabetes.

170.5.3 Treatment for Type 1 Diabetes Patients with Clinical Eating Disorders in the Department of Psychosomatic Medicine, Kyushu University

We have acquired much experience in the treatment of type 1 diabetes patients with clinical eating disorders, having treated more than 150 of such patients, referred from throughout Japan, from 1994 to 2009. The majority were engaged in recurrent binge eating, either BN or BED. We reported that patients with BN clearly showed more severe psychological and medical pathology than patients with BED (Takii et al. 1999). This finding of pathological difference may be useful for developing a comprehensive treatment system that allows intervention to be tailored to the pathological severity of the individual patient. We have developed two forms of intervention: "outpatient counseling at first visit" (Takii et al. 2002b) and "integrated inpatient therapy" (Takii et al. 2003).

170.5.3.1 Outpatient Counseling at First Visit

Each patient underwent "outpatient counseling at first visit". The main purpose of the counseling is to empathize with the patient's distress from living with diabetes and to reduce the stress associated with their self-care regimen. Table 170.5 presents a summary of the elements of "outpatient counseling at first visit".

   After the first visit, the patient returns to the referring physician for follow-up treatment. We reported that a great majority of the 10 BED patients significantly improved their eating pathology and glycemic control with a single session of our "outpatient counseling at first visit" as a turning point (Takii et al. 2002b) (Fig. 170.3). The reasons for this surprisingly good response are that these patients originally had mild psychopathology: Their binge eating was to a considerable extent due to the stress of the strict food regimen for the diabetes and their fixation on body weight/shape was comparatively mild. This counseling is performed for about 3 h by a doctor familiar with this area. The patients, for the first time since having developed type 1 diabetes, feel that they are understood deeply and accepted by significant others. They are given hope that they can live with diabetes through knowing how to more easily control it, in contrast with what they had previously thought. We tell them that type 1 diabetes is a disease in which there is no problem except that no insulin is produced and that they can gain good glycemic control only by proper insulin injection, without having to engage in a

Table 170.5 A summary of the elements of "outpatient counseling at first visit"

1. Bring out feelings about diabetes by listening for a sufficient amount of time that the patient gets a feeling of "validation" (to be deeply understood and accepted by the therapist).

2. Help the patient recover from the injured self-esteem. "It is very natural to be worried about diabetes and to long for eating when one's food is restricted".

3. Contradict too pessimistic an image of diabetes and present a hopeful and acceptable image of it. "Type 1 diabetes is no more than a deficiency of endogenous insulin. It is possible to have excellent glycemic control without special dietary/exercise therapy, if insulin is injected properly".

4. Teach the patient the importance of finding the easiest and most suitable diabetes self-care. "The patient cannot keep up excessive dieting or over exercising".

5. Encourage recovery/improvement of communication between the patient and family members, especially the mother.

6. Not demand that the patient attend our hospital as an outpatient or be hospitalized.

The main purpose of the counseling is to empathize with the patient's distress from living with diabetes and to reduce the stress associated with their self-care regimen
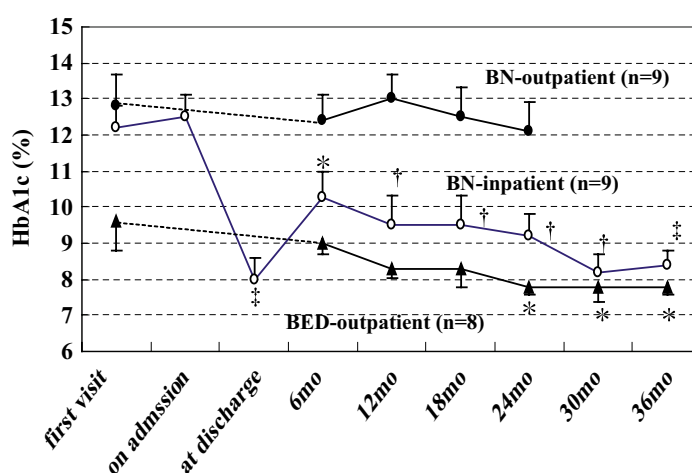
Fig. 170.3 HbA1c course of BN patients who had "Integrated inpatient therapy", BN patients who did not, and BED patients who did not. In BN patients who had the inpatient therapy (BN-inpatient:○), the HbA1c levels at discharge, 6, 12, 18, 24, 30, and 36 months after discharge were significantly lower than at first visit. In BED patients who did not have inpatient therapy (BED-outpatient: ▲), the HbA1c levels at 24, 30, and 36 months after first visit were significantly lower than at first visit. In BN patients who did not have the inpatient therapy (BN-outpatient:●), HbA1c level was not different between the first visit and any follow-up. All patients had "Outpatient counseling at first visit." Data are means ± S.E. *$p < 0.05$, †$p < 0.01$, ‡$p < 0,001$ (Adapted from Takii et al. 2002b. Copyright 2002 by Elsevier Science B.V.)

strict dietary regimen. Patients who are able to have such an experience through our counseling can relatively easily change their attitudes toward food/body weight and diabetes.

After a period of observation by the referring physician, patients without sufficient improvement are encouraged to undergo "integrated inpatient therapy" in our hospital. We reported that none of 19 patients with BN showed sufficient improvement at this stage, and nine agreed to undergo "integrated inpatient therapy" (Takii et al. 2003) (Fig. 170.3).

170.5.3.2 Integrated Inpatient Therapy

The main points of this inpatient therapy are (1) to rest the mind and body in a supportive and lenient but regulated ward environment, (2) revision of cognitions and behaviors such as fixed ideas about diet and body weight or poor eating behaviors (3) acceptance of diabetes based on the experience

that good glycemic control can be obtained without oppressive effort, and (4) the repair of family relationships based on insights by the patient. Table 170.6 presents a summary of the elements of our "Integrated Inpatient Therapy" (Takii et al. 2003).

On the day of admission, the patient is encouraged to decide the initial caloric intake, with the understanding that she should be able to and will be expected to eat the whole meal. In the conflict between the fear of becoming fat and the desire to eat, the patients waver considerably, but eventually most choose a comparatively small amount of food, such as 1,400 kcal a day. Similarly, the initial insulin injection dose is decided in consultation with the patient. In general, to eat all of the supplied meal is the easiest way for patients with an eating disorder to eat successfully.

However, in spite of the agreement, the majority of patients at first tend to leave part of the meal because of over-concern about body weight. The therapist calls the patient's attention to the fact that strict dieting is what has led to continued binge eating and instructs her not to leave any food uneaten. If the patient continues to resist eating all of her meal, the therapist does not advance to the next step of the treatment schedule: The patient's struggle to eliminate avoidance behaviors is the most important element of the inpatient treatment.

Even with this intervention, some patients regress from time to time when the meal is increased, either by leaving part of the meal or by secretly decreasing the insulin dose. The therapist must be aware of and stop this type of avoidance and again explain the rational behind eating the full portion

Table 170.6 A summary of the elements of "Integrated inpatient therapy" for type 1 diabetes patients with an eating disorder (Adapted from Takii et al. 2003. Copyright 2003 by Elsevier Inc.)

 I. Recovery period for the mind and body
   a. Recovery from mental and physical fatigue and depression
   b. Normalization of biorhythms
 II. Modification of behaviors and cognition
   a. Improvement of eating behavior
     Therapist control stage
       Decision, by the patient, of the initial calorie intake and insulin dose
       Completely and regularly eating meals
       Not eating snacks or confectioneries
       Incremental increases in the volume of the meal (200 kcal at a time) to a suitable-sized hospital meal (approximately 40 kcal/kg standard body weight each day)
     Patient control stage
       Free ingestion training
       Snack training
       Eating out training
       Staying at home training
   b. Promoting glycemic control competence
     Self-measurement of blood glucose
     Self-injection of insulin
     Practical coaching and training in adjustment of the insulin dose
   c. Modification of cognitive aspects
     Individual counseling
     Group therapy for eating disorders
III. Restoration of family relationships
   a. Spontaneous restoration process
   b. Family counseling
   c. Coaching family members: especially in how to understand and cope with the patient

In therapist control stage, patients are guarded from their eating disorder psychopathology by the therapeutic framework. In patient control stage, by phased removals of hospital staff control, the patient has to face by herself the stimuli that led her to eating disorder-related behaviors and she has to control her mind and behavior

and injecting the full dose of decided insulin. Through the process of making patients stick to their agreements on eating and insulin injection, they come to learn that they can control their body weight and diabetes with a normal food intake, that there is no need of food restriction, or to engage in a purging behavior, and that there will be good changes such as recovering a feeling of timely hunger and fullness, contrary to their expectations.

In therapist control stage, patients are guarded from their eating disorder psychopathology by the therapeutic framework, such as eating all of the food supplied, the prohibition of purging behaviors, not eating snacks, and the relatively restricted life in the hospital. In patient control stage, by phased removals of hospital staff control, the patient has to face by herself the stimuli that led her to eating disorder-related behaviors and she has to control her mind and behavior. These phased removals of control are as follows. (1) Free ingestion training: as the restriction that the patient must completely eat the meal is lifted, she must choose how much and what kind of food she eats; (2) Snack training: training in self-control in eating snack foods; (3) Eating out training: allowing the patient to eat in restaurants; and (4) Staying at home training: rehearsal for living in her own family/community circumstance. Although the patient often suffers setbacks, becoming unstable and/or having failures, including binge eating, these experiences are very good practical learning opportunities that help the patient face and overcome problems. The therapist does not allow the patient to escape from problems, but helps her attain a deep understanding and coaches her as to how to overcome them.

Along with a decreasing fixation on food and body weight, the patient often comes to reflect on herself, the relationship between significant people and herself, and her association with diabetes. The introspective environment of the ward and counseling twice a week facilitate the process. The patient comes to communicate with parents by letters and telephone calls (their place of residence is generally far from the hospital), which leads to a spontaneous restoration process for the family relationship. The therapist follows the process and holds family counseling to facilitate the process. The experience of being able to control diabetes without any special hardships tends to lead the patient to reconcile themselves to their diabetes.

After discharge from our hospital, the patients again return to the referring physician. We reported that the HbA1c levels of nine BN patients who underwent the inpatient therapy were significantly lower at discharge, 6, 12, 18, 24, 30, and 36 months after discharge than at first visit (Takii et al. 2003) (Fig. 170.3). Moreover, the patients had significantly lower psychological test scores related to eating disorder psychopathology, depressiveness, and anxiety; a reduced frequency and amount of binge eating; and fewer patients exhibited purging behaviors at 36 months after discharge than at first visit (Takii et al. 2003). Ten BN patients who did not undergo the inpatient therapy had no significant psychological/behavioral or medical improvement (Takii et al. 2003) (Fig. 170.3).

The effectiveness of the "integrated inpatient therapy" for type 1 diabetes patients with BN can be largely attributed to the therapeutic framework and intervention of the therapist, which block the avoidance behaviors against becoming fat. Because type 1 diabetes patients with BN have such an extreme fixation on body weight/shape, the therapeutic framework and intervention of a therapist, which block the avoidance behaviors, are essential in the treatment of type 1 diabetes patients with BN.

170.5.3.3   Long-term Psychotherapy and Adjustments of the Patient's Circumstances

Although most type 1 diabetes patients with BN respond to the integrated inpatient therapy, some patients who have marked psychopathology tend to regress repeatedly, in spite of multiple episodes of inpatient therapy. The marked psychopathology includes severe personality disorder, trauma, and a marked delay of psychological/emotional development: For some patients, it seems as if their psychological development stopped after they developed type 1 diabetes. It is difficult for such
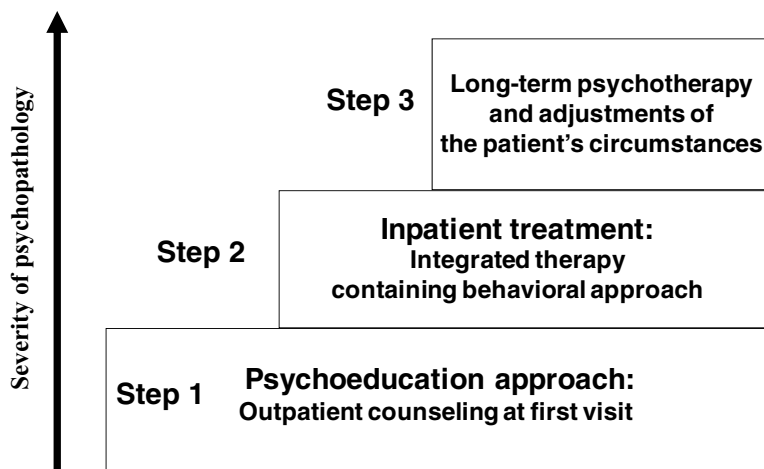
Fig. 170.4 Step-by-step treatment system for type 1 diabetes patients with a clinical eating disorder according to the severity of psychopathology. The number of steps necessary for successful treatment depends on the severity of the patient's psychopathology

patients to improve their eating disorders and control of diabetes without a reduction of their extreme psychopathology. It is important for the therapist to persevere in offering long-term psychotherapy and to strive to adjust the family circumstances to facilitate the patient's psychological growth.

Figure 170.4 shows the step-by-step treatment system of our department for type 1 diabetes patients with a clinical eating disorder, which is done according to the severity of patient's psychopathology.

170.6 Early Awareness and the Prevention of Eating Disorders by Type 1 Diabetes Patients

The treatment of diabetes patients with eating disorders has been reported to be extremely difficult. Moreover, even if the treatment is successful, huge expenditures of time and energy are required before the eating disorder and diabetic control become sufficiently improved. Prevention is much preferable to treatment.

Marcus and Wing (1990) suggested that emotional support and effective information in the context of a sound relationship may prevent problems as well as ameliorate mildly disturbed eating behavior. They emphasized that it is crucial to promote the development of a strong therapeutic relationship in which patients are encouraged to discuss their concerns about body shape and weight. They also indicated that diabetes patients need sound information about weight regulation and that adolescent IDDM patients need special help in learning to eat and drink in social situations, with a view to minimizing feelings of being different.

Rodin et al. (2002) suggested that current diabetes treatment approaches, which emphasize normalizing eating behavior and matching insulin administration to caloric intake, may lessen the experience of deprivation and reduce the risk of eating disturbances. From the suspicion that eating disorders are often not recognized in the diabetes clinic setting, they recommended that health-care professionals who treat young women with type 1 diabetes maintain a high index of suspicion for the presence of an eating disturbance, particularly among those who present with persistently poor metabolic control, repeated episodes of diabetic ketoacidosis, and/or weight and body shape concerns.

Rapaport et al. (1996) listed the following potential markers for the development of an eating disorder by a patient with diabetes: Frequent diabetic ketoacidosis, elevated HbA1c, anxiety about – or avoidance of – being weighed, frequent and severe hypoglycemia, nonadherence, brittle diabetes, delay in puberty or sexual maturation or failure to grow, bingeing with food or alcohol, and severe stress in the family. These markers are of special concern among young women.

We recently reported that the development of type 1 diabetes in preadolescence or adolescence seems to place girls at risk for the subsequent development of AN or BN (Takii et al. in print). Careful attention should be paid to these high-risk patients.

References

Affenito SG, Adams CH. Nutr Rev. 2001;59:179–82.

Affenito SG, Backstrand JR, Welch GW, Lammi-Keefe CJ, Rodriguez NR, Adams CH. Diab Care. 1997;20:182–4.

Alloway SC, Toth EL, Mccargar LJ. Can J Diet Pract Res. 2001;62:188–92.

American Psychiatric Association. Diagnostic and statistical manual of mental disorders. Revised 3rd edn. Washington, DC: American Psychiatric Association; 1987.

American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4th edn. Washington, DC: American Psychiatric Association; 1994.

Anderson BJ. In: Holmes CS, editor. Neuropsychological and behavioral aspects of diabetes. New York: Springer-Verlag; 1990. p. 85–101.

Biggs MM, Basco MR, Patterson G, Raskin P. Diab Care. 1994;17:1186–9.

Daneman D, Olmsted M, Rydall A, Maharaj S, Rodin G. Horm Res. 1998;50:79–86.

Fairburn CG, Peveler RC, Davies B, Mann JI, Mayou RA. BMJ. 1991;303:17–20.

Glasgow AM, Weissberg-Benchell I, Tynan WD, Epstein SF, Driscoll CD, Turek J, Beliveau E. Pediatrics. 1991;88:98–104.

Goebel-Fabbri AE, Fikkan J, Connell A, Vangsness L, Anderson BJ. Treat Endocrinol. 2002;1:155–62.

Goebel-Fabbri AN, Fikkan J, Franko DL, Pearson K, Anderson BJ, Weinger K. Diab Care. 2008;31:415–9.

Golden MP, Herrold AJ, Orr DP. J Pediatr. 1985;107:195–200.

Herpertz S, Wagener R, Albus C, Kocnar M, Wagner R, Best F, Schleppinghoff BS, Filz H-P, Förster K, Thomas W, Mann K, Köhle K, Senf W. J Psychosom Res. 1998;44:503–15.

Herpertz S, Albus C, Lichtblau K, Kohle K, Mann K, Senf W. Int J Eat Disord. 2000;28:68–77.

Herpertz S, Albus C, Kielmann R, Hagemann-Patt H, Lichtblau K, Köhle K, Mann K, Senf W. J Psychosom Res. 2001;51:673–8.

Jones JM, Lawson ML, Danemann D, Olmsted MP, Rodin G. BMJ. 2000;320:1563–6.

Kennedy SH, Kaplan AS, Garfinkel PE, Rockert W, Toner B. J Psychosom Res. 1994;38:773–82.

Maharaj SI, Rodin GM, Olmsted MP, Daneman D. J Psychosom Res. 1998;44:470–90.

Marcus MD, Wing RR. In: Holmes CS, editor. Neuropsychological and behavioral aspects of diabetes. New York: Springer-Verlag; 1990. p.102–121.

Nielsen S. Eur Eat Disorders Rev. 2002;10:241–54.

Nielsen S, Emborg C, Molbak AG. Diab Care. 2002;25:309–12.

Olmsted MP, Daneman D, Rydall AC, Lawson ML, Rodin G. Int J Eat Disord. 2002;32:230–9.

Papelbaum M, Appolinário JC, Moreira RO, Ellinger VCM, Kupfer R, Coutinho. Res Bras Psiquiatr. 2005;27:135–8.

Peveler RC, Fairburn CG, Boller I, Dunger D. Diab Care. 1992;15:1356–60.

Peveler RC, Fairburn CG. Int J Eat Disord. 1992;11:45–53.

Polonsky WH. In: Powers MA, editor. Handbook of diabetes medical nutrition therapy. 2nd edn. Sudbury: Jones & Bartlett Publishers; 1996. p. 585–601.

Polonsky WH, Anderson BJ, Lohrer PA, Aponte JE, Jacobson AM, Cole CF. Diab Care. 1994;17:1178–85.

Rapaport WS, LaGreca AM, Levin P. In: Anderson BJ, Rubin RR, editors. Practical psychology for diabetes clinicians. Alexandria: American Diabetes Association;1996. p. 133–141.

Rodin G, Craven J, Littlefield C, Murray M, Daneman D. Psychosomatics. 1991;32:171–6.

Rodin GM, Daneman D. Diab Care. 1992;15:1402–12.

Rodin GM, Olmsted MP, Rydall AC, Maharaj SI, Colton PA, Jones JM, Biancucci LA, Daneman D. J psychosom Res. 2002;53:943–9.

Rosmark B, Berne C, Holmgren S, Lago C, Renholm G, Sohlberg S. J Clin Psychiatry. 1986;47:547–50.

Rubin RR, Peyrot M. Diab Care. 1992;15:1640–57.

Rydall AC, Rodin GM, Olmsted MP, Devenyi RG, Daneman D. N Engl J Med. 1997;336:1849–54.

Schade DS, Drumm DA, Duckworth WC, Eaton RP. Diab Care. 1985;8:12–20.

Schwartz SA, Weissberg-Benchell J, Perlmuter LC. Diab Care. 2002;25:1987–91.

Steel JM, Young RJ, Lloyd GG, Clarke BF. Br Med J. 1987;294:859–62.

Takii M, Komaki G, Uchigata Y, Maeda M, Omori Y, Kubo C. J psychosom Res. 1999;47:221–31.

Takii M, Uchigata Y, Nozaki T, Nishikata H, Kawai K, Komaki G, Iwamoto Y, Kubo C. Diab Care. 2002a;25:1571–5.

Takii M, Uchigata Y, Komaki G, Nozaki T, Kawai K, Nishikata H, Kawai H, Morioka K, Iwamoto Y, Kubo C. In: Sivik T, Byrne D, Lipsitt D, Christodoulou G, Dienstfrey H, editors. Psycho-neuro-endocrino-immunology. Amsterdam: Elsevier Science; 2002b. p. 291–296.

Takii M, Uchigata Y, Komaki G, Nozaki T, Kawai H, Iwamoto Y, Kubo C. J Psychosom Res. 2003;55:349–56.

Takii M, Uchigata Y, Tokunaga S, Amemiya N, Kinukawa N, Nozaki T, Iwamoto Y, Kubo C. Int J Eat Disord. 2008;41:259–64.

Takii M, Uchigata Y, Kishimoto J, Morita C, Hata T, Nozaki T, Kawai K, Iwamoto Y, Sudo N, Kubo C. Pediatr Diabetes. In print.

Talbot F, Nouwen A. Diab Care. 2000;23:1556–62.

Tsukahara S, Uchigata Y, Ishido K, Takii M, Iwamoto Y. J Jpn Diab Soc. 2009;52:13–21.

Vila G, Robert JJ, Nollet-Clemencon C, Vera L, Crosnier H, Rault G, Jos J, Mouren-Simeoni MC. Eur Child Adolesc Psychiatry. 1995;4:270–9.

White K, Kolman ML, Wexler P, Polin G, Winter RJ. Pediatrics. 1984;73:749–55.

Woodyatt RT. In: Cecil RL, editor. A textbook of medicine. 3rd edn. Philadelphia: W. B. Saunders Company; 1934. p. 628.

Chapter 171
Comparing Abnormal Eating Behavior in Type 1 and 2 Diabetic Patients

Patrick Ritz, Monelle Bertrand, and Hélène Hanaire

Abbreviation

ED-NOS   Eating disorder not otherwise specified

171.1 Introduction

Diabetes is classically divided into type 1 and type 2. Type 1 diabetes concerns less than 10% of diabetic people, who are typically young, thin, with an intense endocrine pancreatic failure. To closely regulate plasma glucose concentrations within narrow limits, the treatment is an obligatory complex schedule of multiple daily insulin injections and a mandatory monitoring of carbohydrate intake and of capillary blood glucose, to adjust insulin doses. Type 2 diabetes affects the vast majority of diabetic people, and is closely associated to overweight and obesity. The pathophysiology of type 2 diabetes is a combination of endocrine pancreatic failure (making insulin injections necessary during the course of the disease) and insulin-resistance, which is closely associated to fat intake, low physical activity, genetic background, and increased fat mass. The basis of the treatment of type 2 diabetes is the control of body weight through adaptation of the diet, and of physical activity, which remains necessary even when drugs are prescribed.

It is therefore obvious that patients suffering from diabetes have to change their predisease diet. Furthermore, diabetes affects patients who have "learned" to behave with food and eating, and an important question is to ask whether diabetes itself and/or diabetes care affects eating behavior. Indeed, diabetes management does place emphasis on strict dietary adherence, which could reinforce pre-existing "abnormal" eating behavior or indeed promote them in otherwise normal eating behavior patients (Goodwin et al. 2003). This review summarizes the knowledge about "abnormal" eating behavior in type 1 and type 2 diabetic patients. It is obvious from this literature search that the definitions used vary between authors. It sometimes crosses over with other concerns (such as body shape and image in adolescents) so that "insulin omission" is also considered in "eating behavior." It is also noticeable that most of the information come from a limited number of authors, studying mostly young females, with very little known about young males.

P. Ritz (✉)
Unité de Nutrition, CHU Larrey, TSA 30030, F-31059 Toulouse cedex 9, France
e-mail: Ritz.p@chu-toulouse.fr

171.2 Definitions of "Abnormal" Eating Behavior

171.2.1 DSM Criteria

Strictly speaking, "abnormal" eating behavior can be approached as eating behavior disorders. Those are based on the diagnostic criteria proposed by the DSM panel of the American Psychiatric Association Tables 171.1 and 171.2 (APS 1994). Binge eating is one such disorder. It refers to the episodic consumption of an objectively large quantity of food that is accompanied by a loss of control during the consumption. When no such loss of control is felt, it is termed episodic overeating. It can be distinguished from bulimia nervosa by the absence of frequent inappropriate compensatory

Table 171.1 Diagnostic criteria of bulimia nervosa

- Recurrent episodes of binge eating characterized by both:
    1. Eating, in a discrete period of time (e.g., within any 2-hour period), an amount of food that is definitely larger than most people would eat during a similar period of time and under similar circumstances
    2. A sense of lack of control over eating during the episode, defined by a feeling that one cannot stop eating or control what or how much one is eating
- Recurrent inappropriate compensatory behavior to prevent weight gain
    1. Self-induced vomiting
    2. Misuse of laxatives, diuretics, enemas, or other medications
    3. Fasting
    4. Excessive exercise
- The binge eating and inappropriate compensatory behavior both occur, on average, at least twice a week for 3 months.
- Self evaluation is unduly influenced by body shape and weight.
- The disturbance does not occur exclusively during episodes of anorexia nervosa.

Type
- Purging type: During the current episode of bulimia nervosa, the person has regularly engaged in self-induced vomiting or the misuse of laxatives, diuretics, or enemas.
- Nonpurging type: During the current episode of bulimia nervosa, the person has used inappropriate compensatory behavior but has not regularly engaged in self-induced vomiting or misused laxatives, diuretics, or enemas.

This table describes the clinical traits for the diagnosis pf bulimia nervosa according to DSM IV

Table 171.2 Diagnostic criteria of EDNOS (eating disorders not otherwise specified) (Adapted from APS, 2000)

Eating disorder not otherwise specified includes disorders of eating that do not meet the criteria for any specific eating disorder.
1. For female patients, all of the criteria for anorexia nervosa are met except that the patient has regular menses.
2. All of the criteria for anorexia nervosa are met except that, despite significant weight loss, the patient's current weight is in the normal range.
3. All of the criteria for bulimia nervosa are met except that the binge eating and inappropriate compensatory mechanisms occur less than twice a week or for less than 3 months.
4. The patient has normal body weight and regularly uses inappropriate compensatory behavior after eating small amounts of food (e.g., self-induced vomiting after consuming two cookies).
5. Repeatedly chewing and spitting out, but not swallowing, large amounts of food.

Binge-eating disorder is recurrent episodes of binge eating in the absence if regular inappropriate compensatory behavior characteristic of bulimia nervosa. It is often, but not always, associated with obesity symptoms.

Night eating syndrome includes morning anorexia, increased appetite in the evening, and insomnia. Often obese, these patients can have complete or partial amnesia for eating during the night.

This table describes the clinical traits for the diagnosis of eating disorders not otherwise specified according to DSM IV

behaviors, whether purging (vomiting, excessive laxative and diuretic use) or nonpurging (excessive exercise, intentional fasting), both of which are characteristic of bulimia (Dingemans et al. 2002).

171.2.2 Other Definitions Arising from the Type 1 Diabetes Literature

Gary Rodin and coauthors (Colton et al. 2004) from the Department of Psychiatry, Toronto (Canada) have extensively studied behaviors in young type 1 females and have extended the definition to include fasting and dieting; self-induced vomiting; the abuse of laxatives, diet pills, diuretics, and other medications; and the use of intense, excessive exercise for weight control. The psychological traits and symptoms include preoccupation with body weight and shape, distortions of body image, and severely disturbed attitudes toward food, calories, and eating.

More specifically, they described eating disorder not otherwise specified (ED-NOS) and subthreshold eating disorders. A specific aspect of the definition of ED-NOS concerns diabetic patients (item 5), probably because weight concerns are very important in type 1 diabetic patients in whom body weight increases dramatically as a consequence of diabetes care (Colton et al. 2004).

ED-NOS is defined in the situations where there are:

1. All the criteria for anorexia nervosa except for amenorrhea; or
2. All the criteria for anorexia nervosa except the subject does not report a fear of weight gain or does not report a disturbance in the way in which their body weight and/or shape is experienced; or
3. All the criteria for bulimia nervosa except that the subject does not report self-evaluation being unduly influenced by shape and/or weight; or
4. All the criteria for bulimia nervosa except that the frequency of binge-eating and purging behavior occurred at least once per week for 3 months, or two times per week over the previous 4 weeks; or
5. An individual regularly engages in inappropriate compensatory behavior in the absence of binge eating (e.g., recurrent self-induced vomiting or insulin omission for shape and weight control at least one time per week for the past 3 months, or twice weekly over the previous 4 weeks); or
6. An individual engages in recurrent episodes of objective binge eating (at least one time per week for the past 3 months, or twice weekly over the previous 4 weeks).

Subthreshold eating disorders are defined in situations where:

1. An individual engages in occasional (three or more times) binge eating, and/or purging over the past 3 months; or
2. An individual whose self-evaluation is unduly influenced by shape or weight, and who regularly engages in extreme dietary restraint (<500 kcal/day); or
3. An individual whose self-evaluation is unduly influenced by shape or weight, and who regularly engages in intense, excessive exercise for the purpose of weight control (at least five times weekly) over the past 3 months.

171.2.3 Definitions from Obesity and Type 2 Literature

In the obesity literature, eating behavior has also been defined with tools assessing dietary restraint, disinhibition, hunger, and emotional and external eating patterns (Mela 1996).

Dietary restraint refers to the intention to restrict and control food intake to attain or maintain a desirable body weight. It can be assessed by questions such as "I often stop eating before being fully

satisfied in order to control the amount of food I eat". Disinhibition refers to overeating associated with a loss of control during eating and can be addressed by questions such as "Sometimes what I'm eating is so good I continue on eating even if I'm not hungry". Hunger represents perceived hunger sensations and can be assessed by questions such as "I cannot go on a diet for the simple reason that I get too hungry".

Emotional and external eating refers to the fact that compared with their lean counterparts, obese human subjects are argued to be more reactive to external cues (time, presence of food, situational effects, etc.) and less sensitive to internal hunger and satiety signals than their lean counterparts. According to this view, high external responsiveness would, given an environment of an easily accessible, abundant, and highly palatable food supply, encourage overeating and, hence, the development of obesity.

171.3 Description of "Abnormal" Eating Behavior and Type 1 Diabetes

Gary Rodin and coauthors have produced a large number of studies (Colton et al. 2004; Jones et al. 2000; Rodin et al. 2002; Colton et al. 2007a, b; Rydall et al. 1997; Olmsted et al. 2002) on eating behavior and type 1 diabetes. They mostly studied young type 1 diabetic females. An important concern in these women is that diabetes care leads to weight gain, as reflected by BMI being greater in diabetic women than in controls (22.7 vs. 20.6 kg/m²; Jones et al. 2000). According to Rodin and colleagues this raises preoccupations about body size and shape and leads to an adjustment of eating behaviors in order to deal with these concerns.

In the two largest reports from this group (on more than 350 individuals aged 12–19 years), DSM criteria are present with an odd-ratio of 2.4 as compared to control subjects (Jones et al. 2000; Rodin et al. 2002). There were no people suffering from anorexia nervosa and very few from bulimia (although with an odds ratio of 3 vs. controls). A total of 10% of the subjects (vs. 4% in the controls) are presenting DSM or ED-NOS criteria. The odds ratio of subthreshold eating disorders is 1.9 versus controls. Binge eating occurs in 3% of the patients (vs. 0.3% in controls; Colton et al. 2004), a figure also reported by Peveler et al. (5% in adult type 1 diabetic women, 2005).

In a smaller group of patients (n = 101) with similar BMIs as controls, the prevalence of ED-NOS is 8% and about eight times more frequent that in controls (Colton et al. 2004). If all eating behavior abnormalities are considered, about 20% of these young diabetic people are concerned (Colton et al. 2007a). Dieting in the month preceding the evaluation occurs in 15%, intense exercise in 10% (ten times more than in controls; Colton et al. 2004).

These data are summarized in Table 171.3.

It appears that diabetes care itself promotes "abnormal" eating behaviors since from this 20% figure, there are 10% more new cases after 1 year follow-up (Colton et al. 2007b) and the prevalence is close to 49% after 5 years of follow-up (Colton et al. 2007a). These follow-up data are summarized in Table 171.4.

Another cohort of 90 women (both adults and adolescents) was studied by Peveler et al. in England (Peveler et al. 2005). They found 8 out of 57 subjects presenting with either DSM or ED-NOS or subthreshold eating behavior disorders. It is noticeable that adult women omitted significantly more insulin injections to control weight (37%) than adolescents (15%). This figure was 1% in preteens, 11–14% in adolescents, and about 33% of the young adults studied by Rodin (2002). The 8–12 years follow-up of the British group told that insulin omission was stable in adults but doubled in adolescents (Peveler et al. 2005). Jones et al. showed that insulin omission was closely associated with "abnormal" eating behavior, since the prevalence was 42% in persons with disturbed eating patterns

Table 171.3 Prevalence of eating disorders in type 1 diabetes subjects

Reference	N subjects	Compared to	Full DSM IV (% of group)	AN (N)	BN (N)	BED (N)	EDNOS (N)	IO (N)	SIV (N)	Laxative abuse (N)	Males (N)	Dieting (N)
Peveler et al. (2005)	54 young adults		8%	1	3	3	1	20	6	6	0	
Peveler et al. (2005)	33 young adolescents		8%	0	0	0	0	5	2	0	0	
Herpetz et al. (1998)	341	Controls	5%	1	5	6	6	2			153	
Jones et al. (2000)	361	Controls	10%	0	3	108	32	39	7	2	0	12
Colton et al. (2004)	101	Controls	11%	0	0	3	8	2	0	0	0	11

This table describes the prevalence of eating disorders in the cohorts of patients with type 1 diabetes published in the literature

N is the number of observations in the cohort

AN anorexia nervosa, *BN* bulimia nervosa, *BED* binge eating disorder, *EDNOS* eating disorder not otherwise specified, *IO* insulin omission, *SIV* self induced vomiting

Definitions are given in Tables 171.1 and 171.2

Table 171.4 Progression of eating disorders in type 1 diabetes subjects at follow-up

Reference	N subjects at follow up/initial number	Compared to	Full DSM IV	AN (N)	BN (N)	BED (N)	EDNOS (N)	IO (N)	SIV (N)	Laxative abuse (N)	Males (N)
Peveler et al. (2005)	37/54 young adults	12 years later		1/1	1/3	1/3	0/1	21/20	7/6	8/6	0
Peveler et al. (2005)	26/33 young adolescents	8 years later	10/8	0/01/0	0/0	0/0	1/0	10/5	4/2	2/0	0
Colton et al. (2007a)	126	5 years later	13		3	6	3	3	3		

This table describes the progression of eating disorders in the cohorts of patients with type 1 diabetes published in the literature

N is the number of observations in the cohort

Data are compared to that existing in the initial cohort, the best comparator for Colton et al. is the data from the same author in Table 171.3

AN anorexia nervosa, *BN* bulimia nervosa, *BED* binge eating disorder, *EDNOS* eating disorder not otherwise specified, *IO* insulin omission, *SIV* self induced vomiting

Definitions are given in Tables 171.1 and 171.2

(Rodin et al. 2002). Similarly, self-induced vomiting doubled in adolescents (2–4 out of 33 subjects); while it was stable in adults (6 in 57 persons; Peveler et al. 2005).

"Abnormal" eating behaviors are also related to mood disorders that may be secondary to diabetes and/or its complications, which make it difficult to tell which is the chicken from the egg (Rodin et al. 2002). Although there may be a "genetic" component is these behaviors, Rodin et al. (2002) have shown that mothers of these adolescents bring them less support, and that the subjects show less trust in the relationship with their parents than patients without disturbed behaviors.

These "abnormal" behaviors are important to diagnose because they are associated with poorer metabolic control (9.4% glycated hemoglobin, vs. 8.6% in patients without "abnormal" eating behaviors), greater risk of ketoacidosis, and microvascular complications. In particular, diabetic

retinopathy is present in 84% of patients with an "abnormal" eating behavior, and 24% of patients without (Rodin et al. 2002; Rydall et al. 1997).

Treatment of "abnormal" eating behavior has been rarely studied. Rodin and colleagues show that a 6-session psychoeducation program improves signs of ED-NOS but not insulin omission or metabolic control (Olmsted et al. 2002).

Data in males are scarce. Ryan et al. (2008) report 43 type 1 diabetic subjects, with 27 males. No patient, male or female, met the full DSM criteria. However, over one-quarter (26%) of males presented with disordered eating behavior, either overeating or binge eating. It is noticeable that patients were older than in other cohorts. Of all patients exhibiting disordered behavior, 22% reported occasionally fasting or exercising excessively to lose weight; however, these episodes were infrequent and considered normal. Herpertz (1998) reported data from 143 German male subjects, with a lower prevalence of disturbed behaviors than in females (that was reported to be 10.8–16.9%; DSM plus ED-NOS criteria).

171.4 Comparison of "Abnormal" Eating Behavior in Type 2 and Type 1 Diabetes

Goodwin et al. (2003) in their assessment of 3,000 primary care patients observed that an eating disorder (based on DSM-IV criteria) was the only psychological condition associated with an increased diabetes risk. Goodwin et al. (2003) also found that diabetes was the only disease of the seven most common diseases evaluated that carried significantly increased odds of developing an eating disorder. Reports of "abnormal" eating behavior in type 2 diabetes suggest that binge eating has ranged between 5% and 21% and that the percentage of patients meeting full DSM criteria has ranged between 1.5% and 26% (Mannucci et al. 2002; Kenardy et al. 1994; Papelbaum et al. 2005; Crow et al. 2001). Observed overeating and binge-eating rates were 27% in French males and 11% in women mildly higher than those observed in other European diabetic populations (Ryan et al. 2008). This was higher than the prevalence in the French nondiabetic population, although caution should be taken with this information since the diabetic sample was rather small (n = 96). Mannucci et al. reported rates of full DSM criteria in 2.5% of type diabetes patients (similar to that in non diabetic or obese Italian patients), and binge eating in 7.5% females and 2.6% males (2002). Herpertz in Germany showed a 6.5–9% prevalence of DSM plus ED-NOS criteria (1998). Such rates may, however, be lower than rates observed in the United States (Kenardy et al. 1994; Papelbaum et al. 2005; Crow et al. 2001) but given the heterogeneity of measurements tools used across these studies it is difficult to compare results meaningfully (Table 171.5).

One-quarter of the Diabetes Prevention Program cohort of patients at risk for type 2 diabetes (n = 274) was studied by Delahanty et al. (2002) and showed a binge-eating rate of 19%.

Type 2 diabetic patients are significantly more dietary restrained than type 1 diabetic patients. Restraint was found to increase in line with BMI (Ryan et al. 2008; Herpetz et al. 1998). Dietary disinhibition score was generally low and similar between diabetic groups as it was for hunger (Ryan et al. 2008). It is noteworthy that both reported disinhibition and hunger were significantly higher in patients with "abnormal" eating behavior than in those without, while dietary restraint was similar. However, dietary restraint increases from the diagnosis to after 6 months in type 1 diabetic patients (Ritz 2008).

Although dietary restraint is not regarded as a DSM or ED-NOS criteria, the restraint theory proposes that increased restraint can facilitate the development of unusual eating habits as a result of stress incurred by the need to control body weight. In diabetic patients, any food intake may be considered to be a result of the "balance between their desire to eat and their wish to diet." A lapse in this self-control (a disinhibition effect) – for whatever reason – can result in overeating. In contrast to "normal" eaters,

Table 171.5 Prevalence of Binge eating in patients at risk or with type 2 diabetes

Reference	% of cohort without Binge eating	% of cohort with episodic over-eating	% of cohort with Binge eating
Delahanty et al. (2002)	59	22	19
Ryan et al. (2008) – Men	73	9	18
Ryan et al. (2008) – Women	74	0	11
Manucci et al. (2002)	94.7		5.3
Herpetz et al. (1998)			2.5–3.4

This table describes the prevalence of binge eating in the published cohorts of type 2 diabetic patients

who are influenced by a sophisticated internal regulatory system that modulates external factors such as smell to initiate or end food intake, restrained eaters try to dominate all external factors. As a result, the food intake of restrained eaters becomes uncontrolled and unrelated to either their appetite or nutritional requirements. This situation, with its eventual subsequent disinhibition, could result in periods of significant overeating. Golay et al. (2001) emphasized the importance of using food diaries to reveal patients' eating habits as well as the need to help them to understand what a meal is and to reestablish a regular eating pattern.

171.5 Conclusion

"Abnormal" eating behaviors are prevalent in both type 1 and type 2 diabetic subjects. In type 1 subjects, classical criteria of DSM and ED-NOS are more prevalent than in the general population, and progress with the disease during adolescence to reach high rates in adults. Other less classical behaviors related to body size and shape concerns develop with the course of the disease, such as insulin omission or self-induced vomiting. Since these behaviors are associated with greater complication rates and poorer metabolic control, they should be searched systematically. Indeed, omitting the diagnosis leads to lack of treatment, although more research is needed about therapeutic approaches. The possibility of a gender effect warrants further exploration in larger patient cohorts. In type 2 patients, binge eating and overeating appear to be frequent and can be subject to specific approaches such as cognitive and behavioral therapy (Golay et al. 2001).

Dietary restraint, disinhibition, and hunger rates are high in both type 1 and type 2 patients. These parameters have been associated in a complex bidirectional relationship with body-weight management. Whether the systematic evaluation of those parameters should be performed remains a matter of debate.

All the studies reported have used somewhat different definitions of "abnormal" eating behaviors, and different tools to address prevalence. Future studies should pay attention to these aspects in order to compare data from different cohorts.

The authors display no conflict of interest between them and with industrial partners related to this work.

Summary Points

- Disordered eating behavior is frequent in type 1 diabetic patients.
- Disordered eating behavior is associated with a higher rate of microvascular complications in type 1 diabetic patients.
- Disordered eating behavior is related to dysregulation of body shape and image in type 1 diabetic patients.

- Disordered eating behavior is characterized by other traits in type 1 diabetic patients, such as intense exercise practice and self-induced vomiting to control body shape and image.
- Disordered eating behavior is probably underdiagnosed in type 1 diabetic patients
- Disordered eating behaviors are different in type 1 and type 2 diabetic patients
- Binge eating disorder is the most frequent disorder in type 2 diabetic patients
- Emotional eating, dietary restraint, and disinhibition are eating behaviors that are often observed in obese patients. Whether they are more frequent in diabetic obese patients remains to be established.

Definitions

Type 1 diabetes: A metabolic disorder characterized by an autoimmune aggression of the pancreatic cells producing insulin. Symptoms are those of hyperglycemia (polyuria, thirst) and those of insulin deficiency (weight loss, muscle mass loss). Patients require exogenous insulin as a treatment.

Microvascular complications: In all types of diabetes chronic hyperglycemia damage small vessels. Organs such as the eyes, the kidney, and nerves are damaged.

Self-induced vomiting: This is a symptom specific of type 1 diabetes. Some patients act so as to vomit in the wish that it will help controlling body weight.

Insulin omission: Voluntary omission of the treatment with insulin

The Diabetes Prevention Program: A trial design to prevent type 2 diabetes by lifestyle modifications (healthy diet, reduction of body weight, increase in physical activity).

References

American Psychiatric Association (APS). Diagnostic and statistical manual of mental disorders. 4th ed. Washington, DC: American Psychiatric Association; 1994.

American Psychiatric Association (APS). Diagnostic and statistical manual of mental disorders. 4th ed, text rev. Washington, DC: American Psychiatric Association; 2000.

Colton P, Olmsted M, Daneman G, Rydall A, Rodin G. 2004;27:1654–9.

Colton P, Olmsted M, Daneman G, Rydall A, Rodin G. Diabetes Care. 2007a;30:2861–2.

Colton P, Olmsted M, Daneman G, Rydall A, Rodin G. Diabet Med. 2007b;24:424–9.

Crow S, Kendall D, Praus B, Thuras P. Int J Eat Disord. 2001;30:222–6.

Delahanty LM, Meigs JB, Hayden D, Williamson DA, Nathan DM, and THE DPP RESEARCH group. Diabetes Care. 2002;25:1992–8.

Dingemans AE, Bruna MJ, van Furth EF. Int J Obes Relat Metab Disord. 2002;26:299–307.

Golay A, Fossati M, Volery M, Rieker A. Diabetes Metabol. 2001;27:71–7.

Goodwin RD, Hoven CW, Spitzer RL. Int J Eat Disord. 2003;33:85–91.

Herpetz S, Albus C, Wagener R, Kocnar M. Comorbidity of diabetes and eating disorders. Diabetes Care. 1998;21:1110–5.

Jones JM, Lawson ML, Daneman D, Olmsted MP, Rodin G. Brit Med J. 2000;320:1563–6.

Kenardy J, Mensch M, Bowen K, Pearson SA. Diabetes Care. 1994;17:1197–9.

Mannucci E, Tesi F, Ricca V, Pierazzuoli E, Barciulli E, Moretti S. Int J Obes Relat Metab Disord. 2002;26:848–53.

Mela DJ. Proc Nutr Soc. 1996;55:803–8.

Olmsted MP, Daneman C, Rydal AC, Lawson ML, Rodin G. Int J Eat Disord. 2002;32:230–9.

Papelbaum M, Appolinario JC, Moreira Rde O, Ellinger VC, Kupfer R, Coutinho WF. Rev Bras Psiquiatr. 2005;27:135–8.

Peveler RC, Bryden KS, Neil HAW, Fairburn CG, Mayou RA, Dunger DB, Turner HM. Diabetes Care. 2005;28:84–8.

Rodin GM, Olmsted MP, Rydall AC, Maharaj SI, Colton PA, Jones JM, Biancucci LA, Daneman D. J Psychosomatic Res. 2002;53:943–9.

Ryan M, Gallanagh J, Livingstone MB, Gaillard C, Ritz P. Diabet Metabol. 2008;34:581–6.

Rydall AC, Rodin GM, Olmsted MP, Devenyi RG, Daneman D. N Engl J Med. 1997;336:1849–54.

Chapter 172
Binge Eating in Overweight and Obese Individuals with Type 2 Diabetes

Amy A. Gorin, Heather M. Niemeier, and Anna Schierberl Scherr

Abbreviations

NIDDM	Non-insulin-dependent diabetes mellitus
BED	Binge eating disorder
HbA_{1c}	Glycosylated hemoglobin
NIH	National Institutes of Health
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, 4th Edition

172.1 Introduction

Type 2 diabetes, or non-insulin-dependent diabetes mellitus (NIDDM), is a chronic metabolic disorder that results from the body's inability to produce or effectively use insulin. While serious complications such as cardiovascular disease, retinopathy, neuropathy, and nephropathy can occur, successful management is possible through medication, healthy lifestyle choices, and weight loss when indicated. Because of the link between dietary choices and the development and management of diabetes, understanding disordered eating patterns in this patient population is clinically relevant. This chapter focuses on binge eating – one of the most common forms of disordered eating – and its relationship with type 2 diabetes.

172.2 Binge Eating: Definitions and Prevalence

Binge eating disorder (BED) is characterized by recurrent binge eating episodes during which an individual consumes a large amount of food in a relatively short period of time and feels a loss of control over eating (American Psychiatric Assocation (APA) 1994). Accompanying characteristics may include eating rapidly, eating until feeling uncomfortably full, eating large amounts of food when not physically hungry, eating alone because of embarrassment about how much food is being consumed, and feeling disgusted, depressed, or guilty after overeating. To meet diagnostic criteria as

A.A. Gorin (✉)
Department of Psychology, Center for Health, Intervention, and Prevention, University of Connecticut,
2006 Hillside Road, Storrs, CT 06269-1248, USA
e-mail: amy.gorin@uconn.edu

defined by the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) (APA 1994), binge eating episodes must occur on average two or more times per week for a period of 6 months or more and must occur in the absence of compensatory behaviors such as purging, fasting, or excessive exercise.

BED is present in approximately 1–5% of the general population (Hay 1998; de Zwaan 2001; Striegel-Moore and Franco 2003; Hudson et al. 2007) and is much more common in individuals who are overweight or obese than in normal-weight individuals (Fairburn et al. 1998; Dingemans et al. 2002). While the exact prevalence of BED in obese adults is unknown, a recent study with a community sample found that 16% of obese individuals screened positive for BED (Grucza et al. 2007) and there is some evidence that binge eating is more likely to be present as the degree of obesity increases (Telch et al. 1988; de Zwaan 2001; De Freitas et al. 2008). Some of the highest rates of BED have been found among overweight and obese individuals seeking weight-loss treatment, with rates between 20% and 30% often reported (de Zwaan 2001; Dingemans et al. 2002; Castellini et al. 2008).

Given that the vast majority of individuals with type 2 diabetes are overweight or obese, it is not surprising that binge eating rates in this population are also elevated (Wing et al. 1989; Herpertz et al. 1998; Crow et al. 2001; Kenardy et al. 2001; Mannucci et al. 2002; Meneghini et al. 2006; Allison et al. 2007; Gorin et al. 2008). In a sample of 215 women with type 2 diabetes, 21% reported binge eating at least once per week and 14% met diagnostic criteria for BED (Kenardy et al. 2001). More recent work examining the connection between binge eating and diabetes has come from Look AHEAD, an National Institutes of Health (NIH)-funded multisite, randomized, controlled trial examining the long-term effect of intentional weight loss on cardiovascular disease in overweight and obese individuals with type 2 diabetes. At study entry, 11.7% of the 5145 Look AHEAD participants self-reported having one or more binge eating episodes in the prior 6 months and 2.6% met diagnostic criteria for BED (Gorin et al. 2008). In a subsample of 845 participants who underwent more formal diagnostic interviews, 1.4% were found to meet the full BED criteria (Allison et al. 2007). These numbers illustrate some important points (Table 172.1). First, there is often a discrepancy in BED rates when comparing self-report assessments to standardized diagnostic interviews, with higher BED rates typically found with self-report questionnaires (Streigel-Moore and Franco 2003). Second, many

Table 172.1 Issues to consider in evaluating research on binge eating

Diagnosis via self-report vs. clinical interview	Inconsistencies in the prevalence of BED across studies often are due to differences in assessment methods. Self-report questionnaires, while often briefer and more cost-effective than other methods, may yield higher rates of binge eating than more stringent, structured, interview-based methods (Striegel-Moore and Franco 2003). Brief self-report measures, however, may be more practical in clinical settings and for repeated use when tracking individuals longitudinally.
Binge eating disorder vs. Binge eating behavior	The DSM-IV criteria for BED require an average of 2 binge episodes per week over a 6 month period. Many researchers have suggested that this frequency criterion is arbitrary and that subthreshold cases are equally important to study. Thus, some researchers have expanded their investigations to include as binge eaters any individuals who report binge eating behavior regardless of frequency.
Community vs. treatment-seeking samples	Much of the work on binge eating has been done on overweight and obese individuals presenting for weight-loss treatment, a population with much higher rates of binge eating than found in the general public. Studies on treatment-seeking samples may confound the psychological and physical risk of binge eating with the negative effects of excessive weight. More research on both community and clinical samples is needed to understand the unique impact of binge eating on health.

This table outlines issues that need to be considered when examining research on binge eating. Research findings will be influenced by whether a binge eating diagnosis is made via self-report or clinical interviews, whether the research focuses on binge eating disorder or binge eating behavior more broadly defined, and whether the study includes a community sample or treatment-seeking individuals.

individuals engage in binge eating at subthreshold levels, making binge eating one of the most common forms of disordered eating in overweight and obese individuals with and without type 2 diabetes. Finally, rates of binge eating may vary according to whether the investigation focuses on a clinical or community sample, with the highest rates typically observed in weight loss-seeking samples.

172.3 Demographic, Psychological, and Health Risk Factors Associated with Binge Eating

Overweight and obese individuals who binge eat tend to be younger and are more likely to be college educated than their non-binge eating peers (Wing et al. 1989; Sherwood et al. 1999; Kenardy et al. 2001; Meneghini et al. 2006; Gorin et al. 2008). In treatment-seeking samples, BED is also more likely to be diagnosed in women than in men (Hay 1998; Grucza et al. 2007); however, this gender difference is smaller than that observed in other eating disorders and in community samples in which equivalent rates are often found (Striegel-Moore and Franco 2003; Grucza et al. 2007). Binge eating is present across racial and ethnic groups (Taylor et al. 2007; Nicado et al. 2007), with some evidence that Caucasian and African-American individuals are more prone to binge eating than other ethnicities, a trend that has emerged in both diabetic and nondiabetic samples (Meneghini et al. 2006; Gorin et al. 2008; Allison et al. 2007, Striegel-Moore and Franco 2008).

In addition to demographic differences, the psychological profiles of binge eaters tend to differ from their non-binge eating peers. Binge eating is often accompanied by body image disparagement, interpersonal difficulties, and low levels of self-esteem (Kuehnel and Wadden 1994; Eldredge et al. 1998; Striegel-Moore et al. 1998), perhaps creating a vulnerability for the development of other psychological disorders. Indeed, there is a high degree of comorbidity between binge eating and depressive disorders. Telch and Stice (1999) found that women with BED were twice as likely as weight-matched non-BED women to have a lifetime prevalence of major depressive disorder (49% vs. 28%, respectively) and these findings have been replicated by others (e.g., Kolotkin et al. 1987; Mussell et al. 1995). Connections between binge eating and bipolar disorder, anxiety disorders, and substance abuse have also been reported (Swinbourne and Touyz 2007; Wildes et al. 2008). In addition to elevated risk of many Axis I disorders, individuals who binge eat appear more likely to have a lifetime prevalence of a personality disorder (Telch and Stice 1999).

On indicators of physical health, binge eating is associated with increased adiposity, which may result in a higher risk of developing weight-related health problems such as type 2 diabetes, increased blood pressure, high cholesterol, gallbladder disease, gastrointestinal issues, and so on for those who binge eat (e.g., Telch et al. 1988; Herpertz et al. 1998; Cremonini et al. 2009). While excessive weight is assumed to be the pathway linking binge eating with negative health outcomes, some initial studies suggest that binge eating and body weight exert independent negative effects on health (e.g., Kenardy et al. 2001; Cremonini et al. 2009). Specific to type 2 diabetes, Kenardy and colleagues (2001) found a relationship between binge eating severity and HbA_{1c} levels that remained significant even after controlling for body weight and exercise habits (see Table 172.2). A similar relationship was reported by Meneghini et al. (2006). In a sample of 140 obese diabetics, binge eaters had worse glycemic control and, among individuals who reported binge eating, there was a positive correlation between binge eating severity and HbA_{1c} levels. However, there are some conflicting reports regarding binge eating and its association with glycemic control. Ryan and colleagues (2008), for example, found that binge eating status was not associated with HbA_{1c} among 94 adults with diabetes. Similarly, in Look AHEAD, we found no difference between binge eaters and non-binge eaters in HbA_{1c} levels or on other diabetes-specific measures such as diabetes treatment regimens (Gorin et al. 2008). With

Table 172.2 Key features of HbA$_{1c}$: glycosylated hemoglobin

1. Glycosylated (or glycated) hemoglobin (HbA$_{1c}$) is produced in red blood cells when blood sugar attaches to hemoglobin
2. A HbA$_{1c}$ blood test identifies the average plasma glucose concentration over the prior 2–3 months, serving as a good indicator of diabetes management
3. Higher HbA$_{1c}$ values suggest higher levels of blood glucose. Levels between 4 and 6% are considered normal, however, among individuals with diabetes, levels at or below 7% are often considered ideal
4. Higher HbA$_{1c}$ levels, particularly over an extended period of time, indicate greater risk of developing diabetes complications
5. Individuals with type 2 diabetes should have their HbA$_{1c}$ tested at least two times a year

This table lists the key facts of HbA$_{1c}$ when used as a measure of diabetes control

Table 172.3 Key facts about binge eating in community and clinical samples

Prevalence	• Binge eating disorder is found in 1–5% of community samples
	• Unlike other eating disorders, nearly equal rates of binge eating are found in men and women
	• The highest rates of binge eating are typically found in overweight and obese individuals presenting for weight-loss treatment
	• Overweight and obese individuals who have type 2 diabetes have rates of binge eating that are on par to the general overweight and obese population
Related comorbidities	• Individuals who binge eat tend to have higher rates of depressive disorders, personality disorders, and more issues with self-esteem and body image
	• Binge eating is associated with weight gain over time and consequently with increased risk of weight-related comorbidities
	• In overweight and obese individuals with type 2 diabetes, binge eating is associated with worse reported physical health but is not consistently associated with glycemic control
Treatment options	• If an individual who binge eats is also overweight or obese and wants to lose weight, a lifestyle management program that promotes weight loss through behavioral strategies is likely to both reduce binge eating behaviors and produce modest weight loss
	• In individuals with type 2 diabetes, recent evidence suggests that binge eating is not associated with weight-loss outcomes unless the behavior begins or persists during treatment
	• In individuals with and without type 2 diabetes, binge eating should be monitored throughout weight-loss treatment and additional support should be provided if the behavior continues
	• Additional treatment options for binge eating are cognitive behavioral treatment, interpersonal therapy, dialectical behavior therapy, and some antidepressants

Key features of binge eating, including prevalence rates, commonly associated psychological and physical comorbidities, and treatment options are described in this table

over 5,000 participants, this is the largest and most representative study conducted to date examining the diabetes–binge eating connection. While the link between binge eating and glycemic control is questionable, several studies suggest that overweight and obese diabetes patients who binge eat self-report worse physical health than their non-binge eating counterparts (e.g., Kenardy et al. 2001; Gorin et al. 2008; Table 172.3).

172.4 Treating Overweight and Obese Patients Who Binge Eat

There is debate in the eating disorders and obesity literatures about how best to approach treatment in individuals who present with both binge eating and excessive weight. The primary question is whether binge eating needs to be addressed prior to initiating a weight-loss program (DeAngelis 2002). Those who advocate treating binge eating first often express concerns that the highly structured nature of
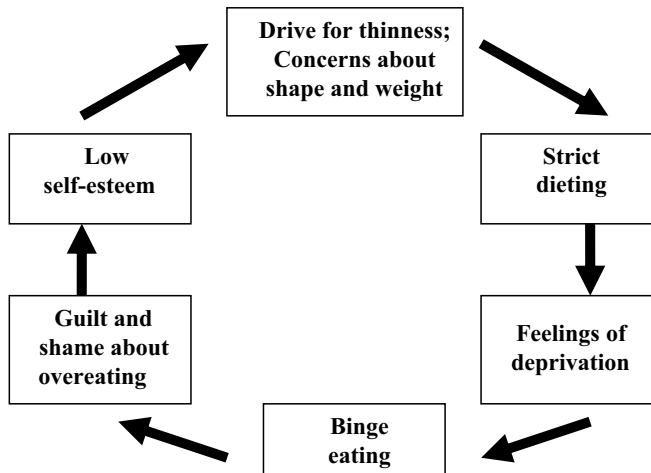
Fig. 172.1 Cognitive behavioral model of binge eating. This figure outlines the cognitive behavioral model of binge eating in which binge eating is believed to result from a cycle of concerns about weight and shape, strict dieting, and deprivation that leads to binge episodes followed by feelings of guilt and decreased self-esteem

behavioral weight-loss treatment will exacerbate binge eating in individuals with a predisposition for the behavior (e.g., Kenardy et al. 2001). This concern is consistent with the cognitive behavioral model of binge eating (Fig. 172.1), which conceptualizes binge eating as a result of a vicious cycle that begins with a thinness-obsessed culture that creates excessive concerns about weight and shape. In individuals predisposed to binge eating, these concerns lead to strict dieting and unrealistic food rules, which are impossible to maintain. Lack of adherence to these self-imposed rules leads to an abstinence violation effect, in which a small lapse in dieting gives way to a loss of control over eating and binge eating. Behavioral weight-loss treatment and its emphasis on caloric restriction, physical activity prescriptions, and increased attention to eating and weight through self-monitoring of food intake, physical activity, and frequent self-weighing may appear contraindicated for those patients engaging in binge eating.

There is some empirical evidence to suggest that binge eaters do not respond as well to weight-loss treatment and have poorer compliance than non-binge eaters. Pagoto and colleagues (2007) recently reported that binge eating was associated with poorer weight-loss outcomes among individuals participating in a hospital-based structured lifestyle program. Clinically significant weight losses were achieved by 37% of non-binge eaters compared to only 16% of individuals who reported binge eating at the start of treatment. Others have found that individuals who binge eat tend to report more extensive weight-loss histories, greater difficulties with weight control, and more unhealthy weight control practices than their non-binge eating peers, findings have emerged in both diabetic and nondiabetic samples (Venditti et al. 1996; Sherwood et al. 1999; Johnsen et al. 2003).

While findings such as these are concerning, most of the available evidence suggests that behavioral weight-loss treatment does not exacerbate or precipitate binge eating (Wadden et al. 2004; Butryn and Wadden 2005), that binge eating status is not associated with weight-loss outcomes (Sherwood et al. 1999; Teixeria et al. 2005; Delinsky et al. 2006), and that binge eating may in fact improve with weight-loss treatment (Wing et al. 1989; National Task Force 2000). For example, to examine whether behavioral weight-loss approaches precipitate binge eating, Wadden et al. (2004) randomly assigned 123 obese women reporting no binge eating at baseline to a 1,000 kcal diet using liquid meal replacement, a 1,200–1,500 kcal diet using conventional foods, or a nondieting program. Following treatment, there were no differences between the groups on binge eating behavior and

those in the active weight-loss programs lost more weight and reported less depression than those in the nondieting condition. Furthermore, in a study of participants in a self-help program for weight loss with a relatively high prevalence of self-reported binge eating (41% of participants), Delinsky and colleagues (2006) found no relationship between binge eating and weight-loss outcomes. Indeed there is evidence that participation in behavioral weight loss can improve binge eating behavior (e.g., Agras et al. 1994; Porzelius et al. 1995). Given that weight loss is a cornerstone of effective diabetes management, this is welcome news for binge eaters with type 2 diabetes.

The most recent evidence to suggest that behavioral weight-loss treatment is appropriate for individuals with type 2 diabetes has come out of the Look AHEAD study. In this trial, overweight and obese individuals with type 2 diabetes were randomly assigned to an intensive lifestyle intervention or to a diabetes support and education control condition. The goals of the lifestyle intervention (modeled after the Diabetes Prevention Program) were to produce a mean weight loss of ≥7% of initial weight through caloric restriction and increased physical activity (Wadden et al. 2006). Binge eating behavior was assessed prior to starting the program and 1 year later. We found that about 10% of participants reported binge eating in the 6 months prior to starting the program and that the majority of these individuals (67%) were no longer engaging in binge eating at the 1-year follow-up. We also found that very few individuals, less than 4%, started binge eating during the first year of treatment, suggesting as others have found that behavioral weight-loss treatment does not generally lead to initiation of binge eating behavior (National Task Force on Prevention and Treatment of Obesity 2000; Butryn and Wadden 2005). Finally, we found that binge eating interfered with weight loss only in the small minority of participants for whom binge eating started, or persisted during treatment (see Fig. 172.2). The attenuated weight losses in those who started or continued to binge eat during treatment likely reflect the smaller decreases in caloric intake achieved in these individuals (Fig. 172.3).

Taken together, the findings from Look AHEAD further confirm the current recommendations (National Task Force on Prevention and Treatment of Obesity 2000) that individuals who binge eat
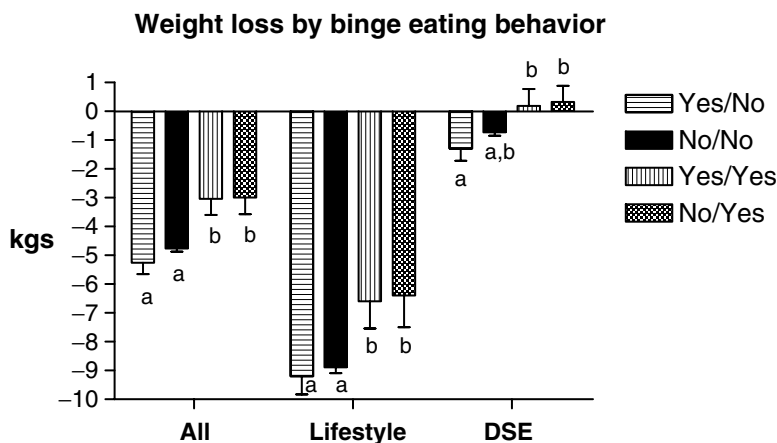
Fig. 172.2 One-year weight loss by binge eating status in overweight and obese individuals with type 2 diabetes participating in the Look AHEAD trial. This figure shows the amount of weight loss (means and standard deviations) overweight and obese individuals with type 2 diabetes achieved in the Look AHEAD trial. Individuals who reported binge eating at baseline but not at year 1 lost just as much weight as individuals who were not binge eating at either time point and lost more weight than those who reported binge eating at only year 1 or who were binge eating at baseline and year 1. Yes/No = reported binge eating at baseline but not 1-year; No/No = did not report binge eating at either time point; Yes/Yes = reported binge eating at both time points; No/Yes = did not report binge eating at baseline but did at 1-year (Originally published in Gorin et al. (2008, 1450). Copyright 2008, American Medical Association. All rights reserved)
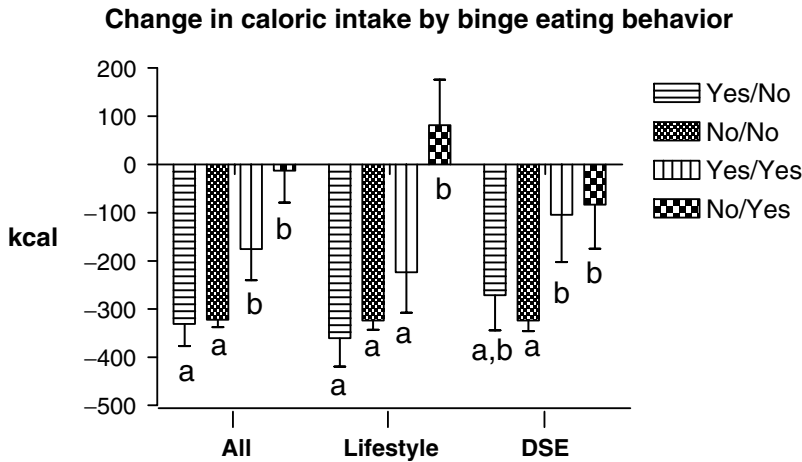
Fig. 172.3 One-year change in reported caloric intake by binge eating status in overweight and obese individuals with type 2 diabetes participating in the Look AHEAD trial. This figure shows changes in caloric intake (means and standard deviations) reported by overweight and obese individuals with type 2 diabetes in the Look AHEAD trial. Individuals who reported binge eating at baseline but not at year 1 decreased their daily intake just as much as individuals who were not binge eating at either time point and decreased their daily intake more than those who reported binge eating at only year 1 or who were binge eating at baseline and year 1. Yes/No = endorsed binge eating at baseline but not 1-year; No/No = did not endorse binge eating at either time point; Yes/Yes = endorsed binge eating at both time points; No/Yes = did not endorse binge eating at baseline but did at 1-year (Originally published in Gorin et al. (2008, 1451). Copyright 2008, American Medical Association. All rights reserved)

should not be discouraged from entering behavioral weight-loss programs. However, it is important to note that individuals who continued to binge eat and those who started to binge eat during treatment did not fare as well. Thus, it would appear useful to assess binge eating throughout treatment, not simply at entry into a program, and provide additional support as needed. Treatments for binge eating with proven effectiveness include several psychotherapies (cognitive behavioral, interpersonal, and dialectical behavior therapy) and antidepressants (Vocks et al. 2009), which may be considered as a supplement or alternative to behavioral weight-loss treatment.

172.5 Applications to Other Areas of Health and Disease

Binge eating is found in a large percentage of overweight and obese individuals with and without type 2 diabetes. If presenting for weight loss, these individuals are best served by a structured lifestyle modification program, with improvements likely to occur in both binge eating and weight status. Moreover, the modest weight losses of 5–10% of initial body weight typically produced by behaviorally based lifestyle modification programs will likely improve overall health parameters. Known benefits of weight losses of this size include a significant reduction in the likelihood of developing type 2 diabetes and hypertension and improvements in diabetes control, urinary incontinence, hyperlipidemia, and overall quality of life (e.g., Diabetes Prevention Program Research Group 2002; Subak et al. 2009). While psychotherapy and pharmacotherapy options have also been shown to be effective in treating binge eating (Vocks et al. 2009), these alternatives do not produce weight loss, which is an important component of successful diabetes management.

Summary Points

- Binge eating is one of the most common forms of eating pathology. Rates range from 1–5% in the general population to 20–30% in individuals entering weight-loss treatment. Binge eating rates in overweight and obese individuals with type 2 diabetes appear similar to the general overweight and obese population.
- Binge eating, by leading to excessive weight gain, may be associated with many obesity-related physical comorbidities such as hypertension and dyslipidemia. In overweight and obese individuals with type 2 diabetes, binge eating is associated with worse self-reported physical health but is not consistently associated with glycemic control.
- There is disagreement about how to treat overweight binge eaters. Some believe that the structured format of behavioral weight-loss treatment is inappropriate for this population. However, research suggests that most individuals who binge eat stop doing so during weight-loss treatment and have outcomes equivalent to non-binge eaters.
- Specific to type 2 diabetes, a recent study found that binge eating was only associated with poorer weight-loss outcomes if an individual started, or continued, to binge eat during a behavioral weight-loss program.

Definition of Key Terms

Binge eating disorder: Disorder recognized as a diagnosis of further study in the American Psychiatric Association's DSM-IV. Characterized by recurrent episodes of binge eating (eating a large amount of food in a discrete period of time while feeling a loss of control) and a lack of compensatory behaviors.

Behavioral weight-loss treatment: A structured lifestyle modification program, typically offered in academic clinics or university-based practices, which provides diet and physical activity prescriptions supported by training in key behavioral techniques such as self-monitoring, stimulus control, problem solving, and goal setting.

Diabetes Prevention Program: A landmark study published in 2002 demonstrating that a behaviorally based weight-loss program that produced modest weight losses (approximately 7% of initial body weight) and increased moderate intensity physical activity was more effective than metformin in reducing the risk of developing type 2 diabetes.

Look AHEAD trial: An ongoing randomized, controlled trial sponsored by NIH that is examining the long-term effects of intentional weight loss on cardiovascular outcomes in individuals with type 2 diabetes. Over 5,000 participants are enrolled in this 12-year, 16-center study (www.lookaheadtrial.org).

References

Agras WS, Telch CF, Arnow BA, Eldredge K, Wilfley DE, Raeburn SD, Henderson J, Marnell M. Behav Ther. 1994;25:209–38.

Allison KC, Crow SJ, Reeves RR, West DS, Foreyt JP, DiLillo VG, Wadden TA, Jeffery RW, Van Dorsten B, Stunkard AJ. Obesity 2007;15:1287–93.

American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4th ed. Washington, DC: Author; 1994.

Butryn ML, Wadden TA. Int J Eat Disord. 2005;37:285–93.

Castellini G, Lapi F, Ravaldi C, Vannacci A, Rotella CM, Faravelli C, Ricca V. Compr Psychiatry. 2008;49:359–63.

Cremonini F, Camilleri M, Clark MM, Beebe TJ, Locke GR, Zinsmeister AR, Herrick LM, Talley NJ. Int J Obes. 2009;33:342–53.

Crow S, Kendall D, Praus B, Thuras P. Int J Eat Disord. 2001;30:222–6.

DeAngelis T. Monit on Psych. 2002;33.

De Freitas SR, Appolinario JC, Souza ADM, Sichieri R. Int J Eat Disord. 2008;41:471–8.

Delinsky SS, Latner JD, Wilson GT. Obesity 2006;14:1244–9.

de Zwaan M. Int J Obes. 2001;25:S51–5.

Diabetes Prevention Program Research Group. N Engl J Med. 2002;346:393–403.

Dingemans AE, Bruna MJ, van Furth EF. Int J Obes. 2002;26:299–307.

Eldredge KL, Locke KD, Horowitz LM. Int J Eat Disord. 1998;23:383–90.

Fairburn CG, Doll HA, Welch SL, Hay PJ, Davies BA, O'Connor ME. Arch Gen Psychiatry. 1998;55:425–32.

Giovanni C, Lapi F, Ravaldi C, Vannacci A, Rotella CM, Faravelli C, Ricca V. Compr Psychiatry. 2008;24:359–63.

Gorin AA, Niemeier HM, Hogan P, Coday M, Davis C, Dilillo VG, Gluck ME, Wadden TA, West DS, Wlliamson D, Yanovski SZ. Arch Gen Psychiatry. 2008;65:1447–55.

Grucza RA, Przybeck TR, Cloninger CR. Compr Psychiatry. 2007;48:124–31.

Guerdjikova AI, McElroy SL, Kotwal R, Keck PE Jr. Eat Weight Disord. 2007;12:e19–23.

Hay P. Int J Eat Disord. 1998;2:371–82.

Herpertz S, Albus C, Wagener R, Kocnar M, Wagner R, Henning A, Best F, Foerster H, Schulze Schleppinghoff B, Thomas W, Kohle K, Mann K, Senf W. Diabetes Care. 1998;21:1110–6.

Hudson JI, Hiripi E, Pope HG Jr, Kessler RC. Biol Psych. 2007;61:348–58.

Johnsen LA, Gorin A, Stone AA, le Grange D. Eat Behav. 2003;3:295–305.

Kenardy J, Mensch M, Bowen K, Green B, Walton J, Dalton M. Eat Behav. 2001;20:222–6.

Kolotkin RL, Revis ES, Kirkley BG, Janick L. J Consult Clin Psych. 1987;55:872–6.

Kuehnel RH, Wadden TA. Int J Eat Disord. 1994;15:321–9.

Mannucci E, Tesi F, Ricca V, Pierazzuoli E, Barciulli E, Moretti S, Di Bernardo M, Travaglini R, Carrara S, Zucchi T, Placidi GF, Rotella CM. Int J Obes. 2002;26:848–53.

Meneghini LF, Spadola J, Florez H. Diabetes Care. 2006;29:2760.

Mussell MP, Mitchell JE, Weller CL, Raymond NC, Crow SJ, Crosby RD. Int J Eat Disord. 1995;17:395–401.

National Task Force on Prevention and Treatment of Obesity. Arch Intern Med. 2000;160:2581–9.

Nicado EG, Hong S, Takeuchi DT. Int J Eat Disord. 2007;40:S22–6.

Pagoto S, Bodenlos JS, Kantor L, Gitkind M, Curtin C, Ma Y. Obesity 2007;15:2557–9.

Porzelius LK, Houston C, Smith M, Arfkin C, Fisher E. Behav Ther. 1995;26:119–34.

Ryan M, Gallanagh J, Livinstone MB, Gaillard C, Ritz P. Diabetes Metab. 2008;34:581–6.

Sherwood NE, Jeffery RW, Wing RR. Int J Obes Relat Metab Disord. 1999;23:485–93.

Striegel-Moore RH, Franko DL. Int J Eat Disord. 2003;34:S19–29.

Striegel-Moore RH, Franko DL. Ann Rev Clin Psych. 2008;4:305–24.

Striegel-Moore RH, Wilson GT, Wilfley DE, Elder KA, Brownell KD. Int J Eat Disord. 1998;23:27–37.

Subak LL, Wing R, West DS, Franklin F, Vittinghoff E, Creasman JM, Richter HE, Myers D, Burgio KL, Gorin AA, Macer J, Kusek JW, Grady D; PRIDE Investigators. N Engl J Med. 2009;360:481–90.

Swinbourne JM, Touyz SW. Eur Eat Disord Rev. 2007;15:253–74.

Taylor JY, Caldwell CH, Baser RE, Faison N, Jackson JS. Prevalence of eating disorders among blacks in National Survey of American Life. Int J Eat Disord. 2007;40:S10–4.

Teixeria PJ, Going SB, Sardinha LB, Lohman TB. Obes Rev. 2005;6:43–65.

Telch CF, Stice E. J Consult Clin Psych. 1999;66:768–76.

Telch CF, Agras WS, Rossiter EM. Int J Eat Disord. 1988;23:7–15.

Venditti EM, Wing RR, Jakicic JM, Butler BA, Marcus MD. J Consult Clin Psych. 1996;64:400–5.

Vocks S, Tuschen-Caffier B, Pietrowsky R, Rustenbach SJ, Kersting A, Herpertz S. Int J Eat Disord. 2009.

Wadden TA, Foster GD, Sarwer DB, Anderson DA, Gladis M, Sanderson RS, Letchak RV, Berkowitz RI, Phelan S. Am J Clin Nutr. 2004;80:560–8.

Wadden TA, West DS, Delahanty L, Jakicic J, Rejeski J, Williamson D, Berkowitz RI, Kelley DE, Tomchee C, Hill JO, Kumanyika S, Look AHEAD Research Group. Obesity 2006;14:737–52.

Wildes JE, Marcus MD, Fagiolini A. Psychiatry Res. 2008;161:51–8.

Wing RR, Marcus M, Epstein L, Blair E, Burton L. Int J Eat Disord. 1989;8:671–9.

Part XXX
Nutrient Excess and Toxicity

Chapter 173
High Blood Glucose and Damage to Neuronal Tissue

Robert R. Miller Jr.

Abbreviations

AChE	Acetylcholine esterase
BDNF	Brain-derived neurotrophic factor
ChAT	Choline acetyltransferase
DHA	Docosahexaenoic acid
10-FTHF DH	10-formyltetrahydrofolate dehydrogenase
10-FTHF hydrolase	10-formyltetrahydrofolate hydrolase
GDNF	Glial cell line-derived neurotrophic factor
GFAP	Glial fibrillary acidic protein
GLUTS	Glucose transporters
HoCys	Homocysteine
5-Methyl THF	5-methyltetrahydrofolate
NTDs	Neural tube defects
NMDA	N-methyl-D-aspartate
SAH	S-adenosylhomocysteine
SAM	S-adenosylmethionine
STZ	Streptozocin
TBARS	Thiobarbituric acid reactive substances
T1D	Type-1 diabetes
T2D	Type-2 diabetes

173.1 Introduction

Type-1 diabetes (T1D; insulin-dependent), type-2 diabetes (T2D; non-insulin-dependent), and gestational diabetes can damage and impair the nervous system. Type-1 and type-2 diabetics have a 25-fold increase in the risk of retinopathy-associated blindness (Wolff 1993), a 4- to 12-fold increased risk of stroke and ischemia-induced cerebral damage (Scott et al. 1999; Bemur et al. 2007), and

R.R. Miller Jr. (✉)
Biology Department, Hillsdale College, 278 N. West St., Dow Science 213,
Hillsdale, MI 49242-1205, USA
e-mail: bob.miller@hillsdale.edu

approximately 50% of all type-1 and type-2 diabetics undergo some form of neuropathy (Negi et al. 2008). Among the various risk factors associated with stroke and ischemia, both mild and severe hyperglycemia within 24 h of the onset of cerebral ischemia exacerbates cerebral damage and increases mortality (Lanier 1999).

Hertz (2008) has recently reviewed how glucose is used as virtually the only metabolic fuel in adult neurons, astrocytes, and oligodendrites. Glucose-6-phosphate is anaerobically metabolized to pyruvate via glycolysis. Because neurons and oligodendrites lack pyruvate decarboxylase, astrocytes must convert pyruvate to acetyl coenzyme-A and then aerobically convert acetyl coenzyme-A to α-ketobutyrate. Under aerobic conditions, astrocytes supply neurons with α-ketobutyrate so neurons can complete aerobic respiration via the Kreb's cycle, or the astrocytes can convert α-ketobutyrate to glutamate and then decarboxylate glutamate to glutamine. Astrocytes then release glutamine to nearby neurons and neurons deaminate the incorporated glutamine to glutamate. Neurons can use glutamate as a neural transmitter, which when released, activates nearby N-methyl-D-aspartate (NMDA) receptors and opens Ca^{+2} channels.

During ischemia, astrocytes, oligodendrites, and neurons convert pyruvate to lactate (acidosis). Because of oxygen-debt, neurons are unable to oxidatively deaminate glutamate to α-ketobutyrate and release excessively high glutamate levels and overstimulate nearby neurons via NMDA receptors (Hertz 2008). Coupled with the overstimulation of NMDA receptors and increased cytoplasmic Ca^{+2} levels, changes in the nearby microvascular system are observed associated with local inflammatory responses that include neutrophil recruitment and the formation of reactive oxygen species (oxygen radicals, hydroxyl radicals, and peroxynitrite radicals). Reactive oxygen species can be generated by enhanced neutrophil NADPH oxidase and xanthine oxidase activities and by activation of neuronal nitrous oxide synthase. Any Fe^{+2}-containing enzyme, such as a cytochrome released from mitochondria into the cytoplasm of cells undergoing apoptosis, or any enzyme that produces H_2O_2 can potentially generate hydroxyl radicals (HO^-) at the expense of oxygen radicals (O^-). This is especially true if the newly produced H_2O_2 cannot be converted to H_2O and O_2 by either catalase or glutathione peroxidase. As H_2O_2 levels increase, H_2O_2 can decompose into HO^- via the Harber–Weiss reaction (Miller 2004).

$$H_2O_2 + Fe^{+2} \rightarrow OH^- + HO^- + Fe^{+3} \rightarrow \text{Fenton Reaction}$$

$$+Fe^{+3} + 2O^- \rightarrow Fe^{+2} + O_2 \rightarrow \text{Reduction of ferricion}$$

$$H_2O_2 + 2O^- \rightarrow OH^- + HO^- + Fe^{+3} \rightarrow \text{Harber-Weiss reaction}$$
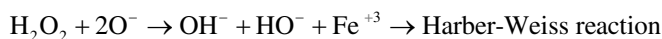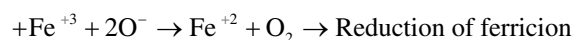
All of these events initiate oxidative stress, oxidative damage via membrane lipid peroxidation, necrosis, apoptosis, mitochondrial involvement, and have recently been reviewed (Wolff 1993; Gonzalez-Zulueta et al. 1998; Vincent et al. 2005; Negi et al. 2008; Bemur et al. 2007; Norenberg and Rao 2007; Hertz 2008; Friedlander 2009). This article will review articles largely excluded from these reviews.

173.2 Type-1 Diabetes: Cognitive Impairment, Neuropathy, and Astrogliosis

Type-1 diabetic children, who suffer prolonged periods of hyperglycemia and momentary episodes of hypoglycemia, exhibit cognitive deficits (Northam et al. 2001; Hershey et al. 2005) and regional differences in brain anatomy as compared to nondiabetics (Sharma et al. 2003; Perantie et al. 2007).

Hershey et al. (2005) reported deficits in spatial memory as a function of hypoglycemia in type-1 diabetic children as compared to controls, and Malone et al. (2008) reported reduced neuron dendritic branching, reduced spine density within the parietal cortex, and hyperglycemia-induced spatial memory deficits in streptozocin (STZ)-treated rats. Exposure of rats to STZ, an agent that destroys pancreatic β-cells, caused reductions in hippocampus-dependent spatial learning, which was associated with hyperglycemia-induced increased brain sorbitol levels, increased brain inositol levels, and decreased brain taurine levels in male rats as compared to controls (Malone et al. 2008). Type-2 diabetics may also have abnormally low taurine levels in brain due to enhanced excretion of taurine (Sankarasubbaiyan et al. 2001). Beauguis et al. (2008) reported elevated expression of hypothalamic hormones, including oxytocin and vasopressin, and elevated plasma glucocorticosteroid levels, and astrogliosis within the hippocampus of STZ-injected female mice. Astrogliosis was measured by the induction of glial fibrillary acidic protein (GFAP) and is associated with neuropathy (Beauguis et al. 2008).

By the use of magnetic resonance imaging, Sharma et al. (2003) demonstrated reduced brain volume in adults (18–50 years old) who suffered T1D for a period exceeding 10 years as compared to controls. Also by use of magnetic resonance imaging, Perantie et al. (2007) reported smaller gray matter volume in the left temporal region in diabetic children (7–17 years old) who suffered from periods of severe hypoglycemia as compared to hypoglycemia-naive diabetic peers. Reduced gray matter within the left superior temporal and angular gyri has been reported in adults who suffered from T1D (Musen et al. 2006) and this same region of the human brain has been associated with episodic memory (Cabeza et al. 2004). Meanwhile, hyperglycemia in type-1 diabetic children was associated with reduced gray matter in the right cuneus and precuneus, reduced white matter in the right posterior parietal region, and increased gray matter volume in the right prefrontal lobes as compared to nondiabetic siblings (Perantie et al. 2007).

Neurons express GLUT-3 (glucose transporter-3), while astrocytes express GLUT-1 and GLUT-2. Consequently, nerves, retina, and kidneys will undergo an intense hyperglycemia-induced D-glucose influx in type-1 and type-2 diabetics because GLUT-1, GLUT-2, and GLUT-3 are insulin-insensitive as compared to GLUT-4 (Anderson et al. 2001). This D-glucose influx causes sorbitol synthesizes by the polyol pathway during neuropathy because hexokinase, which normally converts glucose to glucose-6-phosphate, becomes saturated and excess glucose is then converted to sorbitol via aldose reductase. The polyol pathway and subsequent formation of glycated proteins (advanced glycation end products; Wolff 1993) is active during diabetic retinopathy (Sun et al. 2006; Negi et al. 2008) and Sun et al. (2006) reported that the use of an aldose reductase inhibitor (ARI-809) ameliorated the severity of diabetic retinopathy.

173.3 Type-1 Diabetes: Peripheral Neuropathy and Glial Cell Line-Derived Neurotrophic Factor (GDNF)

Gastrointestinal dysfunction occurs in many diabetics and gastrointestinal tract motility changes involve losses of peripheral neurons (neuropathy). Increased apoptosis rates have been observed in neurons within dorsal root ganglion in STZ-treated rats (Guo et al. 2004) and the neuropathy has been associated with a reduction in neurotrophic factors (Leinninger et al. 2004). One such neurotrophic factor is GDNF. After being released by glial cells, GDNF binds to Ret tyrosine kinase receptors on neuron membranes and stimulates MAPK (Mitogen-Activated Protein Kinase) and P13K signaling pathways. Activation of the P13K pathway causes phosphorylation of Akt and inhibits the translocation of the forkhead box O3a (FOXO3a) transcription factor, which blocks apoptosis by inhibiting the transcription of the proapoptotic genes *Bim* and *Puma* (Srinivasan et al. 2005;

Anitha et al. 2006). Anitha et al. (2006) reported increased apoptosis rates in myenteric neurons, reduced Akt-phosphorylation in myenteric neurons, and delayed gastric emptying (increased intestinal transit time) in STZ-treated diabetic rats, and these hyperglycemia-related events were reversed with exogenous GDNF.

173.4 Type-1 Diabetes: Acetylcholine

The neural transmitter acetylcholine plays an essential role in learning and memory within the basalis magnocellularis and activates cholinergic innervation to the neocortex (Winkler et al. 1995). Thus, choline uptake, enzymes that modulate acetylcholine levels, and acetylcholine receptors are of interest. Mooradian (1987) reported that choline transport across the blood–brain barrier is reduced in STZ-induced diabetic rats. Type-1 and type-2 diabetic mothers have significantly lower plasma choline phosphoglyceride docosahexaenoic acid (DHA) levels in umbilical cords and in circulating red blood cells of pregnant women as compared to nondiabetic mothers (Min et al. 2005a, b). Improved spatial cognition with dietary DHA supplementation was associated with increased *Fos* expression within the CA1 nucleus within the hippocampus of nondiabetic rats (Tanabe et al. 2004), and a significant correlation coefficient between blood DHA levels and Peabody Picture Vocabulary Test scores (a test of listening comprehension and vocabulary acquisition) (r = 0.46; $p < 0.018$) was observed in healthy 4-year-old children (Ryan and Nelson 2008).

Once choline enters, neurons convert choline to acetylcholine via choline acetyltransferease. However, choline acetyltransferase (ChAT) activities were reduced in the hippocampus of STZ-treated rats as compared to controls (Blokland and Jolies 1993; Terwel et al. 1995). Terwel et al. (1995) observed decreased septum masses as hippocampal ChAT activities decreased in STZ-treated rats, and Blokland and Jolies (1993) reported impaired spatial discrimination performances as hippocampal ChAT activities decreased in STZ-treated rats. While Welsh and Wecker (1991) failed to report significant differences in choline or acetylcholine levels in either the striatum or hippocampus within brain slices obtained from STZ-injected rats, reduced release of acetylcholine in striatal slices of STZ-injected rats was reported.

Not only is the synthesis and release of acetylcholine reduced within the hippocampal region of STZ-treated rats, the degradation of acetylcholine to acetate and choline via acetylcholine esterase (AChE) is inhibited in STZ-treated (Ashokkumar et al. 2006) and alloxan-treated rats (Khandkar et al. 1995; Ghareeb and Hussen 2008). Like STZ, alloxan kills pancreatic β-cells and induces T1D. Ashokkumar et al. (2006) reported that brain AChE activities decreased as brain thiobarbituric acid reactive substances (TBARS) levels increased in STZ-treated rats. TBARS are a measure of oxidative stress and are lipid peroxidation intermediates. Ghareeb and Hussen (2008) reported that brain glutathione-S-transferase activities decreased as brain membrane-bound and soluble-AChE activities decreased in alloxan-treated rats. Oxidative stress is also supported by Ates et al. (2007) who reported increased lipid peroxidation levels, as measured by malondialdehyde, increased nitric oxide levels, and reduced glutathione levels in the hippocampus, cortex, cerebellum, brain stem, and spinal cord of STZ-treated rats as compared to controls. Administering the antioxidant, resveratrol, ameliorated hyperglycemia-induced oxidative stress in STZ-treated rats (Ates et al. 2007). Kamboj et al. (2008) reported that *N*-acetylcysteine attenuated hyperglycemia-induced decreased glutathione levels, decreased total thiol levels, and decreased AChE activities within the cerebral cortex, cerebellum, and brain stem of STZ-treated rats as compared to controls. *N*-acetylcysteine is a precursor of cysteine and exerts antioxidant effects by either reacting directly with electrophiles or by facilitating the generation of the antioxidant, glutathione (Song et al. 2004). Kamboj et al. (2008) also reported

cognitive deficits and reduced activities of several antioxidant enzymes including superoxide dimutase, catalase, and glutathione reductase within the cerebral cortex, cerebellum, and brain stem in STZ-treated rats as compared to controls. Thus, the loss of the "cholinergic phenotype" in the brains of type-1 diabetics correlates with the generation of reactive oxygen species and oxidative stress.

173.5 Type-2 Diabetes: Acetylcholine

Gautam et al. (2009) recently demonstrated that the failure of acetylcholine to stimulate brain neuronal M3 muscuranic acetylcholine receptors caused pronounced hypoplasia of the anterior pituitary gland. They produced brain-specific M3 muscuranic acetylcholine receptor knockout mice that exhibited a dwarf phenotype, abnormally small anterior pituitary glands, and reduced ability to synthesize and release serum growth hormone, prolactin, and gonadotropic hormone. Treatment of these M3 receptor-deficient knockout mice with CJC-1295, a synthetic gonadotropic hormone-releasing factor, restored normal pituitary size and serum gonadotropic hormone levels. Thus, acetylcholine and M3 muscuranic acetylcholine receptors within the hypothalamus play a role in the development of anterior pituitary.

While anterior pituitary development requires cholinergic neurons and the stimulation of M3 muscuranic acetylcholine receptors, overstimulation of M3 muscuranic acetylcholine receptors within the peripheral nervous system is associated with T2D. Most animals that model T2D, as reflected by obesity and hyperinsulinemia, have increased vagal cholinergic activities and are mediated by G-protein-coupled muscuranic receptor subtypes (M1–M5) within the parasympathetic nervous system (Caulfield and Birdsall 1998). Gautam et al. (2006) mimicked T2D by inducing obesity, glucose intolerance, and insulin resistance in male $M3R^{-/-}$ and $M3R^{-/-}ob^{-/-}$ mice by either feeding mice high-fat diets or by destroying glucose-receptive neurons in the ventromedial nucleus of the hypothalamus with gold thioglucose. The $M3R^{-/-}$ mice lacked G-protein coupled M3 muscuranic receptors and the $M3R^{-/-}ob^{-/-}$ mice lacked M3 muscuranic receptors and were also leptin deficient. In all experimental animals, the lack of M3 muscuranic receptors protected animals against overeating, hyperglycemia, hyperinsulinemia, and all mice lacking M3 muscuranic receptors had increased fatty acid β-oxidation rates. Thus, while fetal and neonatal animals may require M3 muscuranic receptor stimulation for anterior pituitary development, antagonists of peripheral M3 muscuranic receptors may help control T2D.

173.6 Type-2 Diabetes: Cognitive Impairment and Neuropathy

Individuals who suffer from T2D frequently exhibit insulin resistance, leptin resistance, hypertriglyceridemia, and obesity (Van Gaal et al. 1999; Ma et al. 2002; Margetic et al. 2002). Plasma leptin levels were correlated to plasma insulin levels, cholesterol levels, and triglyceride levels in 107 elderly women (67–78 years old) and the correlation coefficients (r) were 0.56 ($p \leq 0.001$), 0.23 ($p \leq$ 0.05), 0.25 ($p \leq 0.01$), respectively (Zamboni et al. 2004). Elevated circulating triglyceride levels among individuals suffering from T2D have been associated with poor cognitive performance (Perimuter et al. 1988). Insights into this complex and poorly understood set of relationships have come from studying lean and obese mice. Triolein (a triglyceride) injected directly into the brains of lean *CD-1* male mice impaired the NMDA receptor-mediated maintenance of hippocampal long-term synaptic potential as measured by three different measures of cognitive paradigms. The injection of free-palmitate into brains failed to induce cognitive deficits. Meanwhile, lowering blood triglyceride levels, through the administration of gemfibrozil, reversed cognitive impairments and improved

measures of oxidative stress in the brains of obese mice. Thus, hypertriglyceridemia somehow inhibits hippocampal long-term potentiation by blocking NMDA receptor activation and NMDA receptor-induced Ca^{+2} influxes into neurons (Farr et al. 2008).

173.7 Type-2 Diabetes: BDGF and VGF

Some individuals have a predisposition in developing T2D and this predisposition may involve brain-derived neurotrophic factor (BDNF). BDNF is a member of the neurotrophin family that includes nerve growth factor, neurotrophin-3, and neurotrophin-4/5 (Skup 1994; Barbacid 1995; Lewin and Barde 1996; Lindsay et al. 1994). BDNF promotes neurite outgrowth, provides tropic support for neurons in both the central and peripheral nervous system, and has been successfully used in the treatment of several neurological disorders (Sendtner et al. 1996; Yuen et al. 1996) and the injection of BDNF into obese mice ameliorated hyperglycemia (Ono et al. 1997; Tonra et al. 1999; Nakagawa et al. 2000). The recent creation of the transgenic mouse strain, *Timo⁻/⁻*, has resulted in reduced and disrupted hippocampal *Bdnf* expression and is associated with obesity and hyperglycemia (Sha et al. 2007). Recently, the injection of BDNF into predisposed obese and hyperglycemic mice (*db⁻/⁻*), which possess abnormal leptin receptors, blocked the onset of T2D (Yamanaka et al. 2008). Thus, reduced *Bdnf* expression appears associated with the onset of T2D.

VGF (nonacronymic protein) was originally identified as a neutrophin-regulated gene product in PC12 cells (Levi et al. 1985) and is robustly induced by BDNF and neurotrophin-3 and marginally induced by fibroblast growth factors and insulin (Levi et al. 1985, 2004; Salton et al. 2000). In the rat brain, VGF isoforms are distributed throughout the brain, spinal cord, and pancreas with very high abundance in the hypothalamus and hippocampus (Chakraborty et al. 2006). Interest in VGF grew markedly after VGF-deficient mice were created that are lean, hypermetabolic, and resistant to obesity (Hahm et al. 1999). Targeted deletion of the *Vgf* gene, through the creation of several strains of knock-out mice, promoted reduced circulating blood glucose and reduced circulating insulin levels in leptin-deficient *ob⁻/⁻* mice and in *MCR4⁻/⁻* mice, who fail to express hypothalamic melanocortin-4-receptors (Watson et al. 2005). Watson et al. (2005) hypothesized that VGF-ablation induced greater glucose use, greater insulin sensitivity, and obesity-resistance in mice predisposed to T2D.

Vgf gene expression produces *Vgf*-mRNA and a VGF precursor protein that is processed, cleaved, and secreted through a regulated pathway into a number of VGF peptides/isoforms (Chakraborty et al. 2006). Bartolomucci et al. (2006) isolated TLQP-21, which is a VGF-peptide, from rat brains. Surprisingly, chronic injection of TLQP-21 into the brains of rats fed high-fat diets, reduced circulating leptin levels and caused reduced body mass as compared to rats fed only high-fat diets (Bartolomucci et al. 2006). Thus, VGF-derived peptides may up- or downregulate appetite, metabolism, and leptin resistance through complex signaling pathways and are dependent on the presence of VGF isoform.

173.8 Gestational Diabetes

Neural tube defects (NTDs) are the most common abnormality seen within a fetus during gestational diabetes and a major source of neonatal mortality (Becerra et al. 1990; Ramos-Arroyo et al. 1992). Spina bifida, which is a failure of the neural tube to fuse in posterior regions, is the most common form of NTDs and is observed in infants of diabetic mothers (McLeod and Ray 2002). After neural tube fusion, the proliferation of neuroepithelial cells, the outward migration of cells, the differentiation of both neural tube cells and neural crest cells, and cell death via apoptosis of nonfunctional neurons follow.

Gao and Gao (2007) reported that STZ-induced gestational diabetes caused decreased cell prolifieration, as measured by bromodeoxyuridine incorporation into proliferating cells, and increased apoptosis rates in neuroepithelial cells within embryonic mouse spinal cords. Apoptosis was measured by terminal deoxynucleotidyl transferase-mediated dUTP nick end-labeled DNA fragments (TUNEL), and by monitoring activated caspase-3 levels via Western blots. Previously, Reece et al. (1985) observed decreased numbers of mitotic cells throughout the neuroepithelium but with a predominance at the site of failed neural tube closure in rat embryos cultured in male rat serum containing high D-glucose (7,500 mg/L) levels as compared to controls cultured with less glucose (1,250 mg/L).

A high incidence of congenital NTDs and reduced levels of *Pax-3* mRNA have been reported in mouse embryos collected from hyperglycemic dames whose diabetes was induced with either STZ or phlorizen treatments (Fine et al. 1999). *Pax-3* codes for a transcription factor necessary for neural tube development and reduced *Pax-3* expression was associated with apoptosis, as measured by TUNEL-labeled DNA fragments, within the neuroepithelium of mouse neural tubes (Fine et al. 1999). Jia et al. (2008) recently isolated and cultured neural progenitor cells from the cerebral cortex of mouse embryos (stage 12.2). When the neural progenitor cells were cultured in medium that contained high D-glucose levels (45 mM), increased reactive oxygen species levels, increased Annexin-V levels, and increased nuclear cAbl and p53 levels were observed as compared to control cells cultured in medium that contained less D-glucose (25 mM). Activated Annexin-V promotes membrane blebbing during apoptosis by carrying phosphatidylserine from the cytoplasmic side of the cell membrane to the external side of the cell membrane. Meanwhile, c-Abl is a Src-related nonreceptor tyrosine kinase that can move from the cytoplasm to the nucleus via actin cytoskeletal filaments. Nuclear c-Abl appears to contribute to p53-dependent apoptosis (Yuan et al. 1996).

173.9 Gestational Diabetes: Arachidonic Acid

Gestational diabetes is associated with abnormally low arachidonic acid levels and DHA levels in maternal red blood cells and umbilical cords (Min et al. 2005b). Because the n-3 isomer of arachidonic acid (20:4, n-3) can be elongated and desaturated to DHA (22:6, n-3) (Reitz 1992) and because the n-6 isomer of arachidonic acid (20:4, n-6) can be metabolized to a wide variety of potent signaling compounds, known as prostaglandins (Anggard and Samuelsson 1965), maternal deficiencies in arachidonic acid (both 20:4, n-3 and 20:4, n-6) may have profound effects on fetal development. In response to this hypothesis, subcutaneous injections of arachidonic acid into pregnant STZ-treated rats failed to alter maternal blood glucose levels, maternal weight gain, or embryonic weights. However, the incidence of NTDs was reduced from 11% to 3.8% ($p < 0.005$), the frequency of cleft palate was reduced from 11% to 4% ($p < 0.005$), and the incidence of micrognatha was reduced from 7% to 0.8% ($p < 0.001$) as compared to controls (Goldman et al. 1985). Unfortunately, it is unclear whether Goldman et al. (1985) injected the n-3 isomer of arachidonic acid, the n-6 isomer of arachidonic acid, or a mixture of both isomers (n-3 and n-6).

173.10 Gestational Diabetes: Increased Fetal Brain Insulin-Binding Sites

Insulin, insulin receptors, and glucose transporters (GLUTs) exist within the brain (Baskin et al. 1987; Schwartz et al. 1992). In order to test the effect of gestational diabetes on the density of insulin receptors, the density GLUTs, and the frequency of GLUTs within various regions of the embryonic rat brain, Leloup et al. (2004) implanted catheters into the jugular veins of pregnant mice and infused

the dames with either saline or 30% glucose solutions for a period of 48 h. Just before birth (21.5 days), the infusions were halted and rat fetuses were removed by cesarean sections. The major result was an increased density of insulin receptors in the ventromedial hypothalamus, the arcuate nucleus, the lateral hypothalamus, and in extrahypothalamic areas within the ventromedial hypothalamus in fetal brains obtained from hyperglycemic dames as compared to controls. Among the predominant neural GLUTs identified were GLUT-1 (endothelial and glial cells) and GLUT-3 (neuronal cells). GLUT-2 and GLUT-4 were also identified but at lower levels on astrocytes and neurons within the hypothalamus and spinal cord. The authors concluded that the effect of gestational diabetes was on the density of insulin receptors within the specific fetal brain areas and not on the GLUTs because no relationship could be found between GLUT densities and hyperinsulinism within specific areas of the fetal brain (Leloup et al. 2004).

173.11 Embryonic Diabetes: Apoptosis, Lipid Peroxidation, and Homocysteine

We have also been studying the effects of hyperglycemia in developing chick embryos (Miller et al. 2005; Coes et al. 2008; Miller et al. 2009). For some, this seems like an unlikely choice of animal to model a human condition. However, unlike the mammalian embryo, the avian embryo (cleidoic egg) is a closed system that offers the ability to solely observe embryonic responses to a teratogen as compared to combined maternal responses, fetal responses, and maternal-to-fetal transport systems. It has also been argued that adult birds may naturally reflect a hyperglycemic condition as compared to mammals (Hazelwood 1986). This last argument is partially based on the normally high, at least by mammalian standards, avian serum D-glucose levels (2,000–2,500 mg/L) (Hazelwood 2000).

We have made chick embryos hyperglycemic by injecting D-glucose, L-glucose, or pig anti-insulin antibodies into the air sac of fertile chicken eggs during the first 3 days of avian development. Controls were injected with avian saline (0.72% NaCl, v/v) (Miller et al. 2005; Coles et al. 2008; Miller et al. 2009). After incubation, we collected blood, brains, and livers from embryos at 11 days (theoretical stage 37; Hamburger and Hamilton 1951) and at 18 days of development (theoretical stage 44; Hamburger and Hamilton 1951). Chicks normally hatch in 21 days. Thus, 11 days of chick development is comparable to mid-second trimester and 18 days of development is comparable to mid-third trimester of human development. Our injection period of the first 3 days of chick development (E_{0-2}) is comparable to 0–38 days of human development (≤5.4 weeks). Early pregnancy factor can be detected in maternal serum 24–48 h after fertilization, while human chorionic gonadotropin levels within maternal urine cannot be detected until the second week of human pregnancy corresponding with implantation (Nahhas and Barnea 1990). Hence, our injection period in chick embryos corresponds to before and shortly after most women learn of their pregnancies.

The injection of either exogenous D-glucose or L-glucose, concentrations ranging from 9.29 to 18.58 μmol/kg egg, caused embryonic hyperglycemia, reduced embryo masses, and reductions in the % living chick embryos at 18 days of development (Miller et al. 2005). Also noted were increased serum alanine transaminase activities (a marker of liver trauma), increased hepatic caspase-3 activities (a marker of apoptosis), increased hepatic liver lipid hydroperoxides levels, and decreased arachidonic acid (20:4, n-6) levels within hepatic membrane phospholipids of all embryos injected with either exogenous D-glucose or L-glucose as compared to controls. Also noted was decreased DHA (22:6, n-3) levels within hepatic membrane phospholipids when eggs were injected with 18.58 μmol D-glucose/kg egg, 9.29 μmol L-glucose/kg egg, or 18.58 μmol L-glucose/kg egg as

compared to controls. The hyperglycemia-induced reductions in long-chain polyunsaturated membrane fatty acids, increased hepatic lipid hydroperoxide levels, and increased hepatic caspase-3 activities all indicate hyperglycemia-induced apoptosis and membrane lipid peroxidation within hepatic membranes.

Within chick brains at 18 days of development, decreased brain masses, increased brain caspase-3 activities (indicating apoptosis), and increased brain lipid hydroperoxides levels were all observed in exogenous D-glucose- or L-glucose-treated embryos as compared to controls. While the authors did not monitor the effects of hyperglycemia on brain membrane fatty acid composition, it appears likely that hyperglycemia-induced increased apoptosis rates and hyperglycemia-induced lipid peroxidation occurred in developing chick brains at 18 days of development (theoretical stage 44; Hamburger and Hamilton 1951) (Miller et al. 2005).

These observations were extended into an earlier developmental stage (11 days of development; theoretical stage 37; Hamburger and Hamilton 1951). L-glucose (9.29 μmol/kg egg) was injected into the air sac of fertile chicken eggs during the first 3 days of embryonic development (E_{0-2}), which promoted embryonic hyperglycemia, reduced embryo viability, increased membrane lipid peroxidation, increased brain homocysteine (HoCys) levels, and decreased S-adenosylmethionine (SAM)/S-adenosylhomocysteine (SAH) ratios at 11 days of development (Coles et al. 2008). Exogenous L-glucose, which inhibits GLUTs from binding endogenous D-glucose, caused a 1.7-fold increase in serum D-glucose levels ($p \leq 0.05$), a 1.4-fold decrease in percentage of living embryos ($p \leq 0.05$), a 1.1-fold decrease in embryo masses ($p \leq 0.05$), and a 1.4-fold decrease in embryonic brain masses ($p \leq 0.05$) as compared to controls. Exogenous L-glucose also caused a 3.8-fold increase in brain lipid hydroperoxide levels, a 1.9-fold ($p \leq 0.05$) decrease in Σ unsaturated/saturated brain membrane fatty acids ratios, and a 1.8-fold ($p \leq 0.05$) decrease in Σ long-chain/short-chain membrane fatty acids ratios as compared to controls. L-glucose-treated embryos had decreased levels of brain membrane arachidonic acid (20:4, n-6) and DHA (22–6, n-3) as compared to controls ($p \leq 0.05$). These observations are consistent with the hypothesis of hyperglycemia-induced brain membrane lipid peroxidation (Coles et al. 2008).

Exogenous L-glucose also caused a 12-fold increase in brain HoCys levels, a 2.5-fold decrease in SAM levels, and a twofold increase in SAH levels as compared to controls ($p \leq 0.05$) at 11 days of chick development. These hyperglycemia-induced alterations in HoCys, SAM, and SAH levels indicate methylation difficulties and were somewhat attenuated by exogenous folic acid (181.2 μmol/kg egg) (Coles et al. 2008). Hyperglycemia-induced hyperhomocysteinemia is also of great interest because HoCys is both an agonist and antagonist to the NMDA receptor (Lipton et al. 1997) and hyperhomocysteinemia has been observed in both type-1 (Khare et al. 2005) and type-2 diabetics (Onat et al. 2008).

Because hyperglycemia-induced membrane lipid peroxidation was observed in embryonic chick livers (Miller et al. 2005) and brains (Coles et al. 2008), it is tempting to test whether an exogenous antioxidant can ameliorate hyperglycemia-induced membrane lipid peroxidation. The antioxidant, resveratrol, ameliorated hyperglycemia-induced oxidative stress in STZ-treated rats (Ates et al. 2007). While other exogenous antioxidants may work, it is unlikely that exogenous resveratrol can ameliorate membrane lipid peroxidation and increased apoptosis rates within developing chick embryos. Hancock and Miller (2006) reported that while moderate (2.95 nmol/kg egg) to high levels of exogenous *trans*-resveratrol (29.50 nmol/kg egg) attenuated ethanol-induced decreased brain membrane arachidonic acid (20:4, n-6) and DHA (22-6, n-3) levels as compared to controls, these same dosages of *trans*-resveratrol failed to attenuate ethanol-induced increased brain lipid hydroperoxide levels and increased brain caspase-3 activities (Hancock and Miller 2006).

While *trans*-reveratrol is an antioxidant, *trans*-resveratrol also inhibits angiogenesis. *Trans*-resveratrol inhibited bovine endothelial cell growth by inhibiting fibroblast growth factor-2 induced phosphoryation of MAP kinases in a dose-dependent manner (Brakenhielm et al. 2001). In vivo studies using chick embryos, demonstrated that discs containing 1–100 mg per disc of *trans*-resveratrol produced avascular zones within chick chorio-allantoic membranes (Brakenhielm et al. 2001). The dosages of Brakenhielm et al. (2001) (1–100 µg of *trans*-resveratrol/disc) are similar to the dosages used by Hancock and Miller (2006). Interestingly, hyperglycemia-induced increased brain HoCys levels in developing chick brains (Coles et al. 2008) may also be a threat to the developing blood–brain barrier because HoCys is also known to inhibit endothelial cell proliferation and acts as an antiangiogenic molecule (Nagai et al. 2001; Rodriquez-Nieto et al. 2002).

173.12 Embryonic Diabetes: Homocysteine Metabolism and Oxidative Stress

The knowledge of hyperglycemia-induced increased brain and hepatic HoCys levels (Coles et al. 2008) was alarming to us because we have previously demonstrated that exogenous HoCys caused increased apoptosis rates (as measured by increased caspase-3 activities), increased brain membrane lipid peroxidation rates (as measured by increased levels of brain lipid hydroperoxides and decreased brain membrane long-chain polyunsaturated fatty acid levels), and decreased chick embryo viability at 11 days of development (Miller et al. 2003, 2006). We reported that exogenous HoCys-induced reductions in brain SAM/SAH ratios were partially attenuated by exogenous glycine (Miller et al. 2006). Elevated HoCys levels can cause oxidative stress because two HoCys molecules can undergo auto-oxidation and form a dimer (HoCys:oxidized disulfide) by liberating two hydrogen ions and two electrons. In doing so, hydrogen peroxide and hydroxyl radicals can be generated (Hayden and Tyagi 2004) and these reactive oxygen species can promote membrane lipid peroxidation and subsequent necrosis and apoptosis (Miller 2004).

HoCys is metabolized by the transsulfuration pathway and by the remethylation pathway (Fig. 173.1). In the remethylation pathway, methylcobalamine, which receives the methyl group from SAM, 5-methyltetrahydrofolate (5-methyl THF), or betaine (trimethyl glycine), methylates HoCys to methionine. Methionine is subsequently converted to SAM (Selhub 1999). Hence, folate deficiencies inhibit the remethylation of HoCys to methionine and cause hyperhomocysteinemia and have been associated with a variety of pathological problems (Carmel and Jacobson 2001), and folate deficiencies are well associated with increased incidence of NTDs (Boyles et al. 2006). Many methylases within a cell use SAM as the methyl donor. So as methylase activities continue during hyperhomocysteinemia, SAM levels decline while SAH levels increase (Selhub 1999). Consequently, NTDs may be caused by hyperhomocysteinemia and not by folate deficiencies.

Two enzymes in the remethylation pathway are 10-formyltetrahydrofolate dehydrogenase (10-FTHF DH) and 10-formyltetrahydrofolate hydrolase (10-FTHF hydrolase) (Fig. 173.2). Both enzymes catalyze the conversion of 10-formyltetrahydrofolate to CO_2 and tetrahydrofolate (THF). The difference between the two enzymes is that 10-FTHF DH requires NADPH while 10-FTHF hydrolase does not require NADPH. In the glycine cleavage system within the remethylation pathway, T-protein requires THF as a coenzyme and synthesizes N^5,N^{10}-methylenetetrahydrofolate, which is converted to the methyl donor, 5-methyl THF (Kikuchi 1973; van der Put et al. 2001). Low 5-methyl THF levels could not only inhibit the remethylation of HoCys to methionine, but also alter SAM/SAH levels because methionine is used to produce SAM, SAM is converted to SAH, and SAH is hydrolyzed to HoCys (Selhub 1999).

HoCys is also removed in the transsulfuration pathway (Fig. 173.1). The first and irreversible reaction is catalyzed by a pyridoxal-5'-phosphate (vitamin B_6) containing enzyme, cystathionine
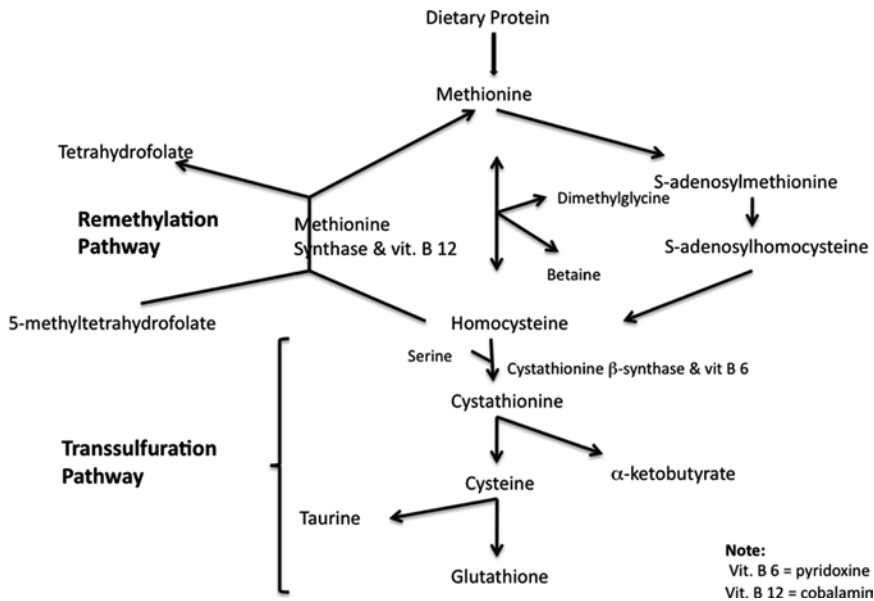
Fig. 173.1 Homocysteine removal via remethylation and transsulfuration pathways. *Vit. B6* pyridoxine, *Vit. B12* cobalamin

β-synthase that condenses serine and HoCys to form crystathionine. Cystathionine is subsequently hydrolyzed by another pyridoxial-5'-phosphate containing enzyme, cystathionine γ-synthase, thus forming α-ketobutyrate and cysteine and excess cysteine is converted to taurine (Selhub 1999). Thus, as cystathionine β-synthase activity decreases and the rest of the transsulfuration pathway slows, increased HoCys levels and decreased taurine levels are observed.

We have recently studied whether embryonic hyperglycemia reduces the enzymatic activities of two enzymes in the remethylation pathway, 10-FTHF DH and 10-formyltethydrofolate hydrolase (10-FTHF hydrolase) (Fig. 173.2) and whether embryonic hyperglycemia slows the transsulfuration pathway, as measured by brain and hepatic taurine levels (Fig. 173.1). We injected white Leghorn chicken eggs with either 9.29 μmol L-glucose/kg egg (avian saline was the solvent) or avian saline (0.72% NaCl, w/v) during the first 3 days of avian development (E_{0-2}). At 11 days of development (theoretical stage 37; Hamburger and Hamilton 1951), blood from chorio-allantoic vessels was collected and serum isolated by centrifugation ($10,000\times$ g for 1 min). The mass of each chick embryo was measured followed by decapitation. Brains and livers were excised, tissue mass measured, and stored at $-80°C$ for subsequent biochemical analysis. Serum D-glucose levels were measured according to Coles et al. (2008) and brain and hepatic taurine levels were measured by high performance liquid chromatography as described by Barnett et al. (2009). The enzymatic activities of brain and hepatic 10-FTHF DH and 10 FTHF hydrolase activities were also measured according to Barnett et al. (2009).

Exogenous L-glucose injected into early chick embryos (E_{0-2}) caused serum D-glucose levels to increase by approximately 2.6 fold ($p < 0.0001$) at 11 days of development (Table 173.1). Presumably, L-glucose inhibited the GLUTs from binding and transporting d-glucose from the developing circulatory system into cells. L-glucose-induced hyperglycemia was also associated with reduced embryo masses ($p \leq 0.0001$) and reduced brain masses ($p = 0.006$) as compared to controls. However, L-glucose-induced hyperglycemia was not associated with reduced hepatic mass or reduced % living embryos as compared to controls (Table 173.1) (Miller et al. 2009).
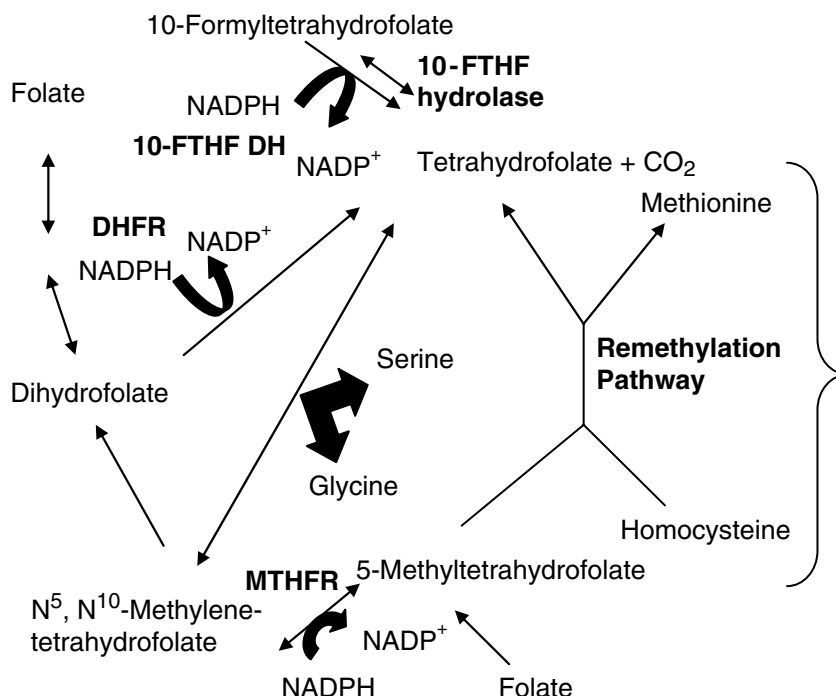
Fig. 173.2 The remethylation pathway and folate metabolism. *10-FTHF DH* 10-formyltetrahydrofolate dehydroge-nase, *10-FTHF hydrolase* 10-formyltetrahydrofolate hydrolase, *MTHFR* N^5,N^{10}-methylenetetrahydrofolate reductase, *DHFR* dihydrofolate reductase

Exogenous L-glucose-induced hyperglycemia caused approximately a 2.4-fold reduction in brain 10-FTHF DH activities ($p = 0.0035$) and a 2.5-fold reduction in hepatic 10-FTHF DH activities ($p = 0.0035$) as compared to controls (Table 173.2). Hyperglycemia failed to significantly affect either brain or liver 10-FTHF hydrolase activities. When serum D-glucose levels were correlated to brain 10-FTHF activities, the Pearson product moment (r) was -0.56 [F = (1, 13) 5.89; $p = 0.03$] (Fig. 173.3). When serum D-glucose levels were correlated to hepatic 10-FTHF activities, the Pearson product moment (r) was -0.55 [F = (1, 13) 5.63; $p = 0.04$] (Miller et al. 2009) (Fig. 173.4).

Exogenous L-glucose-induced hyperglycemia also caused approximately a 1.8-fold reduction in brain taurine levels ($p \leq 0.007$) and a 2.0-fold reduction in hepatic taurine ($p < 0.01$) as compared to controls (Table 173.2). When serum D-glucose levels were correlated to brain taurine levels, the Pearson product moment (r) was -0.60 [F = (1, 12) 6.68; $p = 0.02$] (Fig. 173.5). When serum d-glucose levels were correlated to hepatic taurine levels, the Pearson product moment (r) was -0.61 [F = (1, 9) 5.40; $p = 0.045$] (Fig. 173.6). Thus, exogenous l-glucose-induced hyperglycemia is inhibiting both the remethylation and the transsulfuration pathways in embryonic chick brains and livers at 11 days of development (Miller et al. 2009).

Table 173.1 The effect of exogenous L-glucose on chick embryo viability at 11 days of development

	Controls (avian saline)	Exogenous L-glucose (9.29 μmol/kg egg)	Statistical analyses
% living embryos	80.11 ± 6.95% $N = 4$ different sets of injections where 16–20 eggs were injected during each set	81.89 ± 10.85% $N = 4$ different sets of injections where 16–20 eggs were injected during each set	$t = 0.28$ df = 6 $p = 0.79$
Embryo mass (g)	3.367 ± 0.196 g $N = 12$	2.873 ± 0.291 g $N = 12$	$t = 4.62$ df = 22 $p \leq 0.0001$
Liver mass (mg)	54 ± 7 mg $N = 12$	52 ± 13 mg $N = 12$	$t = 0.33$ df = 22 $p = 0.74$
Brain mass (mg)	607 ± 71 mg $N = 12$	497 ± 92 mg $N = 12$	$t = 3.09$ df = 22 $p = 0.006$
Serum D-glucose levels	1112.65 ± 256.25 mg/L (6.18 ± 1.52 mM) $N = 12$	2915.12 ± 735.12 mg/L (16.18 ± 4.08 mM) $N = 12$	$t = 6.49$ df = 22 $p < 0.0001$

Fertile white Leghorn chicken eggs were injected with approximately 25 μL of either avian saline (0.72% NaCl) or 9.29 μmol L-glucose/kg egg in avian saline during the first 3 days of development (E_{0-2}) into the air sac of each egg. After sealing each injection sight with paraffin wax, all embryos were incubated in a forced air incubator at 37.5°C and turned every 4 h with the humidity ranging from 70% to 90%. At 11 days of development (theoretical stage 37, Hamburger and Hamilton 1951), blood was collected from chorio-allantoic blood vessels and serum isolated by centrifugation (10,000× g for 1 min). The mass of each chick embryo was determined followed by decapitation. Brains and livers were excised, tissue mass measured, and stored at –80°C for subsequent biochemical analysis. Serum D-glucose levels were measured according to Coles et al. (2008).
Data presented as mean ± standard deviation

Table 173.2 The effects of exogenous L-glucose on brain and hepatic taurine levels, brain and hepatic 10-formyltetrahydrofolate dehydrogenase (10-FTHF DH), and 10-formyltetrahydrofolate hydrolase (10-FTHF hydrolase) activities at 11 days of development

	Controls (avian saline)	Exogenous L-glucose (9.29 μmol/kg egg)	Statistical analyses
Brain 10-FTHF DH activities (μmol/min/mg brain protein)	6.31 ± 2.50 $N = 9$	2.57 ± 2.13 $N = 9$	$t = 3.42$ df = 16 $p = 0.0035$
Hepatic-10 FTHF DH activities (μmol/min/mg hepatic protein)	6.32 ± 2.50 $N = 9$	2.57 ± 2.10 $N = 9$	$t = 3.42$ df = 16 $p = 0.0035$
Brain 10-FTHF hydrolase activities (μmol/min/mg brain protein)	2.37 ± 0.69 $N = 10$	2.36 ± 0.94 $N = 13$	$t = 0.04$ df = 21 $p = 0.97$
Hepatic-10 FTHF hydrolase activities (μmol/min/mg hepatic protein)	2.23 ± 1.65 $N = 10$	3.14 ± 2.51 $N = 11$	$t = 0.97$ df = 19 $p = 0.34$
Brain taurine levels (nmol/mg brain)	1.89 ± 0.74 $N = 7$	1.04 ± 0.22 $N = 8$	$t = 3.20$ df = 13 $p \leq 0.007$
Hepatic taurine levels (nmol/mg liver)	10.69 ± 3.63 $N = 6$	5.48 ± 2.29 $N = 6$	$t = 5.21$ df = 10 $p < 0.01$

Brain and hepatic taurine levels were measured by high-performance liquid chromatography as described by Barnett et al. (2009). The enzymatic activities of brain and hepatic 10-FTHF DH and 10-FTHF hydolase were measured according to Barnett et al. (2009)
Data presented as mean ± standard deviation

Fig. 173.3 The relationship
between brain 10-formyl
tetrahydrofolate dehydroge-
nase (10-FTHF DH) activities
and serum D-glucose levels in
embryonic chicks at 11 days
of development. $r = -0.56$
[$F = (1, 13)$ 5.89; $p = 0.03$],
$y = 6.977 - 0.001$ (X);
$R^2 = 0.312$
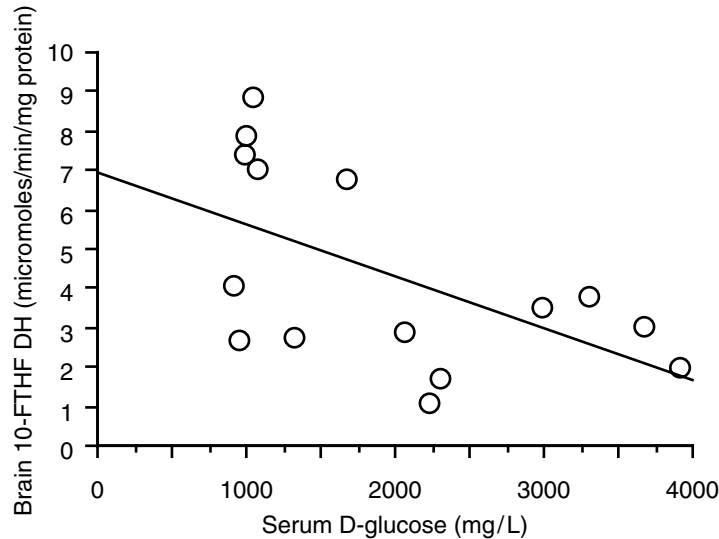
$r = -0.56$ [$F = (1, 13)$ 5.89; $p = 0.03$]

$y = 6.977 - 0.001$ (X); $R^2 = 0.312$

Fig. 173.4 The relationship
between hepatic 10-formyl
tetrahydrofolate dehydroge-
nase (10-FTHF DH) activities
and serum D-glucose levels in
embryonic chicks at 11 days
of development. $r = -0.55$
[$F = (1, 13)$ 5.63; $p = 0.04$],
$y = 6.395 - 0.0001$ (X);
$R^2 = 0.302$
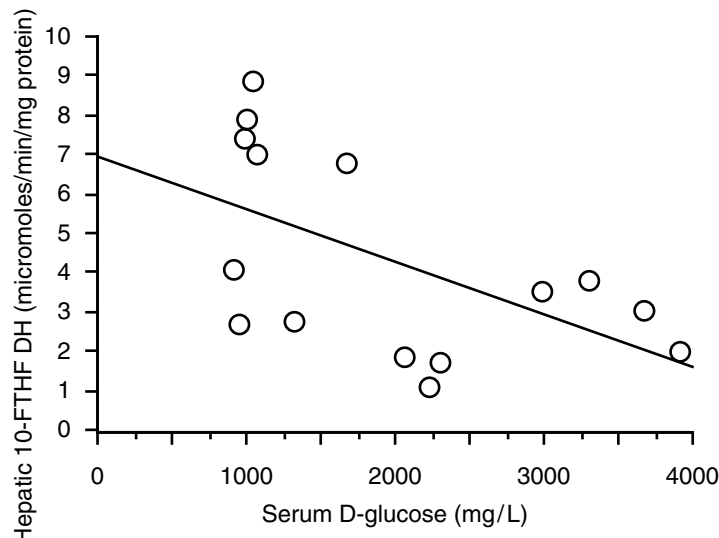
$r = -0.55$ [$F = (1, 13)$ 5.63; $p = 0.04$]
$y = 6.395 - 0.0001$ (X); $R^2 = 0.302$

Hyperglycemia-induced inhibition of the remethylation and transsulfuration pathways explain increased brain and hepatic HoCys levels within embryonic chicks (Coles et al. 2008). This also raises questions as to whether exogenous 5-methyl THF or taurine ameliorates hyperglycemia-induced hyperhomocysteinemia, oxidative stress, and apoptosis in embryonic brains and livers.

Fig. 173.5 The relationship between brain taurine levels and serum D-glucose levels in embryonic chicks at 11 days of development. $r = -0.60$ [$F = (1, 12)$ 6.68; $p = 0.02$], $y = 2.236 - (3.837 \times 10^{-4}) X$; $R^2 = 0.358$

r = –0.60 [F = (1, 12) 6.68; p = 0.02]

y = 2.236 –(3.837 X 10^{-4}) X; R^2 = 0.358

Fig. 173.6 The relationship between hepatic taurine levels and serum D-glucose levels in embryonic chicks at 11 days of development. $r = -0.61$ [$F = (1, 9)$ 5.40; $p = 0.045$], $y = 12.799 - (0.002) X$; $R^2 = 0.375$
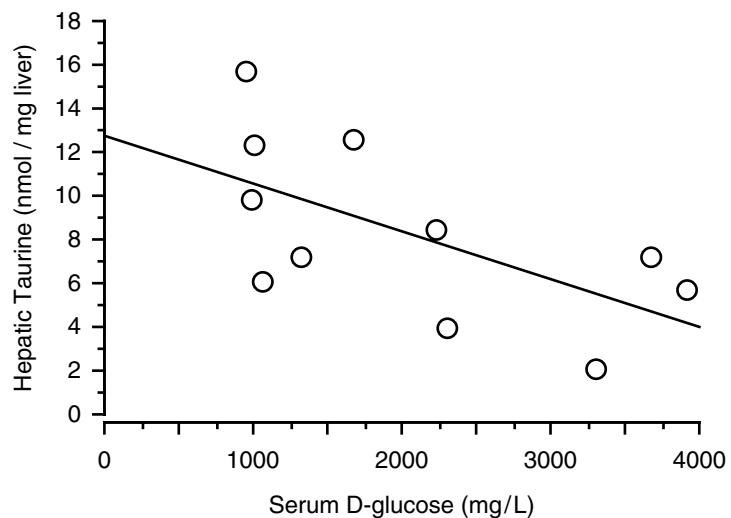
r = –0.61 [F = (1, 9) 5.40; p = 0.045]

y = 12.799 –(0.002) X; R^2 = 0.375

Chen et al. (1998) reported that taurine is essential for proliferation and neurite extension when culturing human fetal neurons isolated from the cerebral hemispheres in glial-free media and the folate pathway is well associated with the prevention of NTDs (Boyles et al. 2006).

173.13 Applications to Other Areas of Health and Disease

Oxidative stress, enhanced rates of apoptosis, and elevated HoCys levels are also observed in the brains of alcoholics and the brains of fetuses exposed to alcohol. Hyperhomocysteinemia is also seen in a number of serious and debilitating diseases (Carmel and Jacobson 2001) and exogenous HoCys is teratogenic in at least embryonic chicks (Miller et al. 2003, 2006). Consequently, exploring the regulation of folate metabolism; the regulation of the transsulfuration pathway; the use of antioxidants; the use of exogenous folates and possibly taurine; and a better understanding of how neurotrophic factors regulate developing neurons may not only provide us with a better understanding of the physiology and development of the nervous system, but may provide important clinical insights into several serious and debilitating diseases.

Summary Points

- Type-1 and type-2 diabetics have increased risk of ischemia-induced vascular damage. During oxygen-deprivation (ischemia), neurons are unable to convert glutamate to α-ketobutyrate and release excessively high glutamate levels. This causes increased cytoplasmic Ca^{+2} levels, increased reactive oxygen species levels, increased oxidative-stress, increased membrane lipid peroxidation, and apoptosis.
- Type-1 diabetics (insulin-dependent) exhibit spatial and episodic memory deficits and are associated with neuropathy within the hippocampus, hypothalamus, and possess reduced gray matter within the temporal lobes.
- Peripheral neuropathy in STZ-treated rats causes reduced (GDNF) levels, reduced activation of Ret tyrosine kinase receptors, and increased apoptosis rates.
- Type-1 diabetics (insulin-dependent) have reduced choline acetyltransferease activities, reduced AChE activities, and reduced acetylcholine levels and are associated with oxidative stress within the hippocampus and cerebral cortex (Table 173.3).
- During fetal/neonatal development, acetylcholine must stimulate brain neuronal M3 muscuranic acetylcholine receptors in order to prevent an underdevelopment of the anterior pituitary gland. However, the lack of M3 muscuranic acetylcholine receptor activation protects against the onset of type-2 (non-insulin-dependent) diabetes.

Table 173.3 Key features of neuropathy in type-1 diabetics

1. Neuropathy can occur as a result of momentary oxygen deprivation during ischemia-induced vascular damage and type-1 and type-2 diabetics are prone to ischemia-induced vascular damage.
2. During oxygen deprivation, neurons cannot convert glutamate to α-ketobutyrate and overstimulate nearby neurons with excessively high levels of glutamate via the N-methyl-D-aspartate receptor.
3. During neuropathy, reactive oxygen species are produced causing oxidative-stress and are seen during necrosis and apoptosis.
4. Oxidative stress causes membrane lipid peroxidation and is observed during necrosis and apoptosis.
5. Reduced utilization of cholinergic neurons is seen during oxidative stress and is associated with cognitive deficits.
6. Reduced levels of a tropic factor, such as glial cell line derived-neurotrophic factor, has been observed in peripheral neuropathy in streptozocin (STZ)-treated rats.
7. Elevated levels of circulating homocysteine in type-1 diabetics and decreased brain taurine levels are seen in STZ-treated rats.

This table lists key facts associated with neuronal damage (neuropathy) in type-1 diabetics and animals used to model type-1 diabetes

- Type-2 diabetics (non-insulin-dependent) are frequently obese, insulin-resistant, leptin-resistant, have elevated circulating triglycerides levels, and exhibit poor cognitive performance. Recent injection of triglycerides into the brains of lean mice impaired the NMDA receptor-mediated maintenance of hippocampal long-term synaptic potential (Table 173.4).
- Reduced and disrupted expression of hippocampal *BDNF* is associated with the onset of T2D. While VGF (nonacronymic protein)-deficient mice tend to resist the onset of T2D, exogenous TLQP-21 (a VGF isoform) reduced circulating leptin levels and ameliorated obesity in mice.
- Gestational diabetes stimulates c-Abl- and p53-induced signaling, reduced *Pax-3* expression, and increases apoptosis rates within mouse neural tube neuroepithelial cells.
- Gestational diabetes is frequently associated with abnormally low maternal arachidonic acid (20:4, n-3 and 20:4, n-6) and DHA (22:6, n-3) levels. Meanwhile, exogenous arachidonic acid injected into STZ-treated pregnant rats ameliorated the frequency of gestational diabetes-induced NTDs (Table 173.5).
- Gestational diabetes in pregnant rats caused increased density of insulin receptors within the ventromedial hypothalamus and lateral hypothalamus of fetal rats brains. However, no relationship between the densities of various GLUTs to hyperinsulinemia within various regions of the fetal brain was observed.
- Hyperglycemia in embryonic chicks has been induced and is associated with increased membrane lipid peroxidation rates, increased apoptosis rates, decreased SAM/SAH, and elevated HoCys levels within embryonic brains and livers.

Table 173.4 Key features of neuropathy in type-2 diabetics

1. Neuropathy can occur as a result of momentary oxygen deprivation during ischemia-induced vascular damage and type-1 and type-2 diabetics (T2D)are prone to ischemia-induced vascular damage.
2. During oxygen deprivation, neurons cannot convert glutamate to α-ketobutyrate and overstimulate nearby neurons with excessively high levels of glutamate via the *N*-methyl-D-aspartate receptor.
3. During neuropathy, reactive oxygen species are produced causing oxidative-stress and are seen during necrosis and apoptosis.
4. Oxidative stress causes membrane lipid peroxidation and is observed during necrosis and apoptosis.
5. Overstimulation of M3 muscuranic acetylcholine receptors in the peripheral nervous system has been associated T2D.
6. Reduced levels of a tropic factor, such as brain-derived neurotrophic factor, have been observed in obese, hyperglycemic mice.
7. Elevated levels of circulating homocysteine and the overexcretion of taurine are seen in type-2 diabetics.

This table lists key facts associated with neuronal damage (neuropathy) in type-2 diabetics and animals used to model T2D

Table 173.5 Key features of neuropathy in gestational (embryonic) diabetics

1. Neuropathy can occur before the vascular system fully develops because neuralation begins prior to angiogenesis.
2. While embryonic-derived neurons can undergo in vitro glutamate toxicity, the exact role of glutamate and the *N*-methyl-D-aspartate receptor in gestational/embryonic diabetes is unclear.
3. During neuropathy, reactive oxygen species are produced causing oxidative stress and are seen during necrosis and apoptosis.
4. Oxidative stress causes membrane lipid peroxidation and is observed during necrosis and apoptosis.
5. The role of acetylcholine and acetylcholine receptors during gestational (embryonic) neuropathy is unclear.
6. While reduced levels of tropic factors are possible, exact roles in embryonic neuropathy are unclear.
7. Elevated homocysteine levels and decreased taurine levels are seen in brains and livers of hyperglycemic chick embryos.

This table lists key facts associated with neuronal damage (neuropathy) in animals used to model gestational (embryonic) diabetes

- Elevated embryonic HoCys levels are teratogenic, cause NTDs, stimulate oxidative stress, and stimulate apoptosis in developing chick brains. In chicks, hyperglycemia-induced brain HoCys levels correlate with a hyperglycemia-induced inhibition of the folate-mediated remethylation pathway and inhibited taurine synthesis via the transsulfuration pathway.
- Oxidative stress, enhanced apoptosis rates, and elevated HoCys levels are observed in the brains of alcoholics and in embryonic brains exposed to alcohol. Consequently, exploring the regulation of folate metabolism and the transsulfuration pathway may provide us with a better understanding of hyperglycemia-induced neuropathy and alcohol-induced neuropathy.

Definitions of Key Terms

Apoptosis: Apoptosis and necrosis are two different forms of cell death and can occur at the same time. Necrosis begins with increased membrane fluidity via membrane lipid peroxidation and can be initiated by reactive oxygen species. The ultimate loss of cell membrane integrity spreads to all eukaryotic membranes and results in a total failure of all organelles, inhibition of protein synthesis, and random DNA fragmentation. Apoptosis, sometimes referred as genetically programmed cell death, is dependent on protein synthesis and utilizes a number of proteins including Annexin-V, poly(ADP-ribose)polymerase (PARP), and a number of caspases. PARPs deplete the NAD^+ pool by adding a poly-A tail to DNA fragments and can be detected by deoxynucleotidyl transferease-mediated dUTP nick end-labeled DNA fragments (TUNEL). Apoptosis can be initiated from outside the cell (extrinsic pathway) or inside the cell (intrinsic pathway). While complex, the extrinsic pathway begins with a receptor-ligand interaction at the cell membrane level or a lack of a tropic factor leaving a vacant binding-site on a membrane receptor. This initiates a signal transduction cascade that activates a number of initiator caspases and transcription factors. Ultimately, the activation of Bcl-2 proapoptotic signals, reactive oxygen species, and increased cytoplasmic Ca^{+2} levels activate Bcl-2 family proteins on the outer mitochondrial membrane. Once Bcl-2 family proteins are activated, the intrinsic pathway begins where mitochondria release cytochrome-c and Ca^{+2} into the cytoplasm. This activates the cytoplasmic protein Apaf-1 that binds and activates procaspase-9 and procaspase-3. Procaspase-3 is activated to caspase-3.

Caspase-3: Caspase-3 is a "killer" caspase and a protease. It will bind and cleave any protein that has a DEVD (aspartate-glutamate-valine-aspartate) domain. Whether apoptosis is initiated by the extrinsic pathway, which spreads to the intrinsic pathway, or initiated by direct activation of the intrinsic pathway, caspase-3 is activated and it's enzymatic activity level and/or presence is a convenient measurement of apoptosis rates.

Homocysteine: HoCys is a non-protein-coding amino acid. It is teratogenic in chick embryos and causes both apoptosis and membrane lipid peroxidation. Elevated levels of HoCys are seen in a number of debilitating disorders and can be caused by folate deficiencies and/or inhibition of the transsulfuration pathway.

Ischemia: Type-1 and type-2 diabetics have a 4- to 12-fold increased risk of stroke and ischemia-induced cerebral damage. As the microvascular system becomes occluded, downstream oxygen and glucose levels are momentarily depleted prompting necrosis and energy depletion of downstream cells. Inflammation of the occluded microvascular system is partially due to neutrophil recruitment causing enhanced neutrophil NADPH oxidase and xanthine oxidase activities and the production of reactive oxygen species. Increased oxidative stress is thought to exacerbate ischemia-induced cerebral damage and can promote apoptosis in nearby cells (Bemur et al. 2007).

Lipid peroxidation: Reactive oxygen species can cleave polyunsaturated fatty acids into shorter-chain fatty acids and toxic aldehydes and affect membrane integrity (fluidity).

> **Oxidative stress:** Membrane lipid peroxidation and increased apoptosis rates can ultimately kill cells undergoing oxidative stress. Oxidative stress is exacerbated by decreased levels of antioxidants, such as glutathione, and reduced antioxidant enzyme activity levels. Antioxidant enzymes include superoxide dimutase, catalase, glutathione peroxidase, and glutathione-*S*-transferase.
>
> **Reactive oxygen species:** Reactive oxygen species include oxygen radicals, hydroxyl radicals, and peroxynitrite radicals. During ischemia, reactive oxygen species can be generated by enhanced neutrophil NADPH oxidase and xanthine oxidase activities and by activation of neuronal nitrous oxide synthase.

References

Anderson MS, Flowers-Ziegler J, Das UG, Hay WH Jr, Devaskar SU. Am J Regulatory Integrative Comp Physiol. 2001;281:R1545–52.

Anggard E, Samuelsson B. J Biol Chem. 1965;240:3518–21.

Anitha M, Gondha, C, Sutliff R, Parasadanian A, Mwangi S, Sitaraman SV, Srinivasan S. J Clin Invest. 2006;116:344–56.

Ashokkumar N, Pari L, Ramkumar K. Basic Clin Pharm Toxicol. 2006;99:246–50.

Ates O, Cayli SR, Yucel N, Altinoz E, Kocak A, Akif Durak M, Turkoz Y, Yologlu S. J Clin Neuroscience. 2007;14:256–60.

Barbacid M. Curr Opin Cell Biol. 1995;7:148–55.

Barnett RK, Booms, SL, Gura T, Gushrowski M, Miller RR Jr. Comp Biochem Physiol. 2009;150C:107–12.

Bartolomucci A, La Corte G, Possent R, Locatelli V, Rigamonti AE, Torsello A, Bresciani E, Bulgarelli I, Rizzi R, Pavone F, D'Amato FR, Severini, C, Mignogna G, Giorgi A, Schinina ME, Ela G, Brancia C, Ferri G-L, Ciani B, Pascuuci T, Dell'Omo G, Muller EE, Levi A, Moles A. Proc Natl Acad Sci USA. 2006;103:14584–9.

Baskin DG, Figleicz DP, Woods SC, Pore DJ, Dorsa DM. Ann Rev Physiol. 1987;49:335–47.

Beauguis J, Homo-Delarche F, Revsin Y, De Nicola AF, Saravia F. Neuroimmunomodulation 2008;15:61–7.

Becerra JE, Khoury MJ, Cordero, JF, Erickson JD. Pediatrics 85:1–9.

Bemur C, Ste-Marie L, Montogomery J. Neurochem Int. 2007;50:890–904.

Blokland A, Jolies J. Pharmacol Biochem Behav. 1993;44:491–4.

Boyles, AL, Billups, AV, Deak KL, Siegel DG, Mehltretter L, Slifer SH, Bassuk AG, Kessler JA, Reed MC, Nijhout AF, George TM, Enterline DS, Gilbert JR, Speer MC. Env Health Perspect. 2006;114:1547–52.

Brakenhielm E, Cao R, Cao Y. FASEB J. 2001;15:1798–800.

Cabeza R, Prince SE, Daselaar SM, Greenberg DL, Budde M, Dolcos F, Labar KS, Ruben DC. J Cogn Neurosci. 2004;16:1583–94.

Carmel R, Jacobson DW, editors. Homocysteine in health and disease. UK: Cambridge University Press; 2001.

Caulfield MP, Birdsall NJM. Pharmacol Rev. 1998;50:270–90.

Chakraborty TR, Tkalych O, Nanno D, Garcia AL, Devi LA, Salton SRJ. Brain Res. 2006;1089:21–32.

Chen X-C, Pan Z-L, Liu D-S, Han X. Adv Exp Med Biol. 1998;442:397–403.

Coles NW, Weaver KR, Walcher BN, Adams ZF, Miller RR Jr. Comp Biochem Physiol. 2008;150B:338–43.

Farr SA, Yamada, KA, Butterfield DA, Abdul HM, Xu L, Miller NE, Banks WA, Morley JE. Endocrinology 2008;149:2628–36.

Fine EL, Horal M, Chang TI, Fortin G, Locken MR. Diabetes 1999;48:2454–62.

Friedlander RM. New Engl J Med. 2009;348:1365–75.

Gao O, Gao YM. Int J Dev Neurosci. 2007;25:349–357.

Gautam D, Gavrilova O, Jeon J, Pack S, Jou W, Cui Y, Li JH, Wess J. Cell Metab. 2006;4:363–75.

Gautam D, Jeon J, Starost MF, Han S-J, Hamdan FF, Cui Y, Parlow AF, Gavrilova O, Szalayova I, Mezey E, Wess J. Proc Natl Acad Sci USA. 2009;106:6398–403.

Ghareeb DA, Hussen HM. Neurosci Lett. 2008;436:44–7.

Goldman AS, Baker L, Piddington R, Marx B, Herold R, Egler J. Proc Natl Acad Sci USA. 1985;82:8227–31.

Gonzalez-Zulueta M, Ensz, Mukhina G, Lebrovitz RM, Zwacka RM, Engelhardt JF, Oberly LW, Dawson LW, Dawson VL, Dawson TM. J Neurosci. 1998;15:2040–55.

Guo C, Quobatari A, Shangguan Y, Hong S, Wiley JW. Neurogastroenterol Motil. 2004;16:355–45.

Hahm S, Mizuno TM, Wu J, Wisor JP, Priest, CA, Kozak CA, Boozer CN, Peng B, McEvoy RC, Good P, Kelley KA, Takahashi JS, Pintar JE, Roberts, JL, Mobbs CV, Salton SRJ. Neuron 1999;537–48.

Hamburger V, Hamilton HL. J Morphol. 1951;88:49–92.

Hancock ML, Miller RR Jr. Nutr Neurosci. 2006;9:121–9.

Hayden MR, Tyagi SC. J Nutr. 2004;3:4–36.

Hazelwood RL. In: Ouellet H, editor. ACTA XIX Congress Intl. Ornithologia, vol. 2. Ottawa: University of Ottawa Press; 1986. p. 2223–33.

Hazelwood RL. In: Whittow GL, editor. Sturkie's avian physiology. 5th ed. San Diego: Academic; 2000, p. 539–55.

Hershey T, Perantie DC, Warren SL, Zimmerman EC, Sadler M., White NH. Diabetes Care. 2005;28:2372–7.

Hertz L. Neuropharmacology 2008;55:289–309.

Jia DY, Liu HJ, Wang FW, Liu SM, Ling EA, Liu K, Hao AJ. Neurosci Lett. 2008;440:27–31.

Kamboj SS, Chopra K, Sandhir R. Metab Brain Dis. 2008;23:427–43.

Khandkar M, Jee E, Parmar D, Katare. Biochem J. 1995;307:647–9.

Khare A, Shetty S, Ghosh K, Mohanty D, Chatterjee S. Athersoclerosis 2005;180:375–80.

Kikuchi G. Mol Cell Biochem. 1973;1:101–14.

Lanier WL. Can J Anesth. 1999;46:R46–51.

Leinninger GM, Vincent AM, Feldman EL. J Peripher Nerv Sys. 2004;9:26–53.

Leloup C, Magnan C, Alquier T, Mistry S, Offer G, Arnaud E, Kassis N, Ktorza, Penicaud L. Pediatr Res. 2004;56:263–7.

Levi A, Eldridge JD, Paterson BM. Science 1985;229:393–5.

Levi A, Ferri GL, Watson E, Possenti R, Salton SR. Cell Mol Neurobiol. 2004;24:517–33.

Lewin GR, Barde YA. Annu Rev Neurosci. 1996;19:289–317.

Lindsay RM, Wiegand SJ, Altar CA, DiStefano PS. Trends Neurosci. 1994;17:182–90.

Lipton SA, Kim WK, Choi YB, Kumar S, D'Emilia DM, Rayuda PV, Arnelle DR, Stamler JS. Proc Natl Acad Sci USA. 1997;94:5923–8.

Ma XH, Muzumdar R, Yang XM, Gabriely I, Berger R, Barzilai N. J Gerontol Med Sci. 2002;57A:B225–31.

Malone JI, Hanna S, Saporta S, Mervis RF, Park CR, Chong L, Giamond DM. Pediatr Diabetes. 2008;9:531–9.

Margetic S, Cazzola C, Pegg GG, Hill RA. Int J Obes. 2002;26:1407–1433.

McLeod L, Ray JG. Community Genet. 2002;5:33–9.

Mooradian AD. Diabetes 1987;36:1094–7.

Miller RR Jr. In: Preedy VR, Watson RR, editors. Alcohol in disease: nutrient interactions and dietary intake. Boca Raton: CRC; 2004. p. 339–64.

Miller RR Jr, Leanza CM, Phillips EE, Blacquiere KD. Comp Biochem Physiol. 2003;136B:521–32.

Miller RR Jr, Burum AL, Leithart ME, Hart JD. Comp Biochem Physiol. 2005;141B:323–30.

Miller RR Jr, Hay CM, Striegnitz TR, Honsey LE, Coykendall CE, Blacquiere KD. Comp Biochem Physiol. 2006;144C:23–33.

Miller RR Jr, Coleman K, Yearsley S. 2009; Unpublished data.

Min Y, Lowy C, Ghebremeskel K, Thomas B, Offley-Shore B, Crawford M. Am J Clin Nutr. 2005a;82:1162–8.

Min Y, Lowy C, Ghebremeskel K, Thomas B, Crawford M. Diabet Med. 2005b;22:914–20.

Musen G, Lyoo KL, Sparks C, Ryan CM, Jimerson DC, Jacobson AM. Diabetes 2006;55:326–33.

Nagai Y, Tasaki H, Takatsu H, Nihei SI, Yamashita K, Nakashima Y. Biochem Biophys Res Commun. 2001;281:726–31.

Nahhas F, Barnea E. Am J Reprod Immunol. 1990;22:105–8.

Nakagawa T, Tsuchida A, Itakura Y, Nonmura T, Ono M, Hirota F, Inoue T, Nakayama C, Taiji M, Noguchi H. Diabetes 2000;49:436–44.

Negi G, Kumar A, Sharma SS. Current Res Inf Pharm Sci. 2008;9:62–8.

Norenberg MD, Rama Rao KV. Neurochem Int. 2007;50:983–97.

Northam EA, Anderson PJ, Jacobs R, Hughes M, Warne GL, Werther GA. Diabetes Care. 2001;24:1541–6.

Onat A, Hergenc G, Kucukdurmaz Z, Can G, Ayhan E, Bulur S. Clin Nutr. 2008;27:732–9.

Ono M, Ichihara J, Nonomura T, Itakura Y, Taiji M, Nakayama C, Noguchi H. Biochem Biophys Res Acta. 1997;238:633–7.

Perantie DC, Wu J, Koller JM, Lim A, Warren SL, Black KJ, Sadler M, White NH, Hershey T. Diabetes Care. 2007;30:2331–7.

Perimuter LC, Nathan DM, Goldfinger SH, Russo PA, Yates J, Larkin M. J Diabetes Complicat. 1988;2:210–3.

Ramos-Arroyo MA, Rodriquez-Pinella E, Cordero JF. Eur J Epidemiol. 1992;8:503–8.

Reece EA, Pinter E, Leranth CZ, Garcia-Segura M, Sanyal K, Hobbins, JC, Mahoney MJ, Naftolin JC. Teratology 1985;32:363–73.

Reitz RC. In: Watson RR, Watzl B, editors. Nutrition and alcohol. Boca Raton: CRC; 1992. p. 191–204.

Rodriquez-Nieto A, Chavarria T, Martinez-Poveda B, Sanchez-Jime, AR, Medina, MA. Biochem Biophys Res Commun. 2002;293:497–500.

Ryan AS, Nelson EB. Clin Pediatr. 2008;20:1–8.

Salton SR, Ferri GL, Hahm S, Snyder SE, Wilson AJ, Possenti R, Levi A. Front Neuroendocr. 2000;21:199–219.

Sankarasubbaiyan S, Cooper C, Heilig CW. Am J Kidney Dis. 2001;37:1039–43.

Schwartz MW, Figlewicz DP, Baskin DG, Woods SC, Porte DJ. Endocr Rev. 1992;13:387–414.

Scott JF, Robinson GM, French JM, O'Connell JE, Alberti KGMM, Gray CS. Stroke 1999;30:703–99.

Sendtner M, Holtman B, Hughes RA. Neurochem Res. 1996;21:831–41.

Sha H, Xu J, Tang J, Ding J, Gong J, Ge X, Kong D, Gao X. Physiol Genomics. 2007;31:252–63.

Sharma JBR, Lee D, Hachinski V, Chan RKT. Neurology 2003;60(Suppl1):A26C.

Selhub J. Annu Rev Nutr. 1999;19:217–46.

Skup MH. Acta Neurobiol Exp. 1994;54:81–94.

Song M, Kellum JA, Kaldas H, Fink MP. J Pharmacol Exp Ther. 2004;308:307–16.

Srinivasan S, Anitha M, Mwangi S, Heuckeroth RO. Mol Cell Neurosci. 2005;29:118–33.

Sun W, Oates PJ, Coutcher JB, Gerhardinger C, Lorenzi M. Diabetes 2006;55:2757–62.

Tanabe Y, Hashimoto M, Sugioka K, Maruyama M, Fujii Y, Hagiwara R, Hara T, Hossain SM, Shido O. Clin Exp Pharmacol Physiol. 2004;31:700–3.

Terwel D, Prickaerts J, Meng F, Jolies J. Eur J Pharmacol. 1995;287:65–71.

Tonra JR, Ono M, Liu X, Garcia K, Jackson C, Yancopoulos GD, Wiegand SJ, Wong V. Diabetes 1999;48:588–94.

van der Put NMJ, van Straaten HWM, Trijbels FJM, Blom HJ. Exp Biol Med. 2001;226:243–70.

Van Gaal LF, Wauters M, Mertens IL, Considine RV, De Leeuw IH. Int J Obes RelatMetab Disord. 1999;23(Suppl 1):29–36.

Vincent AM, McLean LL, Backus C, Feldman EL. FASEB J. 2005;19:638–640.

Watson E, Hahm S, Mizuno TM, Windsor J, Montgomery C, Scherer PE, Mobbs CV, Salton SRJ. Endocrinology. 2005;146:5151–5163.

Welsh B, Wecker L. Neurochem Res.1991;16:453–60.

Winkler J, Suhr ST, Gage FH, Thal LJ, Fisher LJ. Nature 1995;375:484–7.

Wolff SP. Br Med Bull. 1993;49:642–52.

Yamanaka M, Itakura Y, Tsuchida A, Nakagawa T, Taiji M. Biomedical Res. 2008;29:147–53.

Yuan ZM, Huang Y, Fan MM, Sawyers C, Kharbanda S, Kufee D. J Biol Chem. 1996;271:26457–60.

Yuen EC, Howe CL, Li Y, Holtzman, DM, Mobley WC. Brain Dev. 1996;18:362–8.

Zamboni M, Zoico E, Fantin F, Panagiota Panourgia M, Di Francesco V, Tosoni P, Solerte B, Vettor R, Bosello O. J Gerontol Med Sci. 2004;59A:396–400.

Chapter 174
Neurological Aspects of Dietary Lead

Kim M. Cecil and Diana M. Lindquist

Abbreviations

ADHD	Attention-deficit hyperactivity disorder
ALAD	γ-aminolevulinic acid dehydratase
BE	Belgium
CANTAB	Cambridge Neuropsychological Test Automated Battery
CDC	Centers for Disease Control
CNS	Central nervous system
DE	Germany
DK	Denmark
dL	Deciliter
EPA	Environmental Protection Agency of the United States
EU	European Union
FAO	The Joint Food and Agriculture Organization of the United Nations
FDA	Food and Drug Administration of the United States
FI	Finland
FR	France
GFR	Glomerular filtration rate
HOME	Home Observation for Measurement of the Environment
HE	Greece
IgE	Immunoglobulin E
IQ	Intelligence Quotient
IR	Ireland
IT	Italy
LTP	Long-term potentiation

K.M. Cecil (✉)
Cincinnati Children's Environmental Health Center at the Cincinnati Children's
Hospital Medical Center, Departments of Radiology, Pediatrics, Neuroscience and Environmental Health,
University of Cincinnati College of Medicine, Cincinnati, OH, USA
and
Cincinnati Children's Hospital Medical Center, Department of Radiology/Imaging
Research Center MLC 5033, 3333 Burnet Avenue, Cincinnati, OH 45229, USA
e-mail: kim.cecil@cchmc.org

μg	Microgram
kg	Kilogram
MRI	Magnetic resonance imaging
MRS	Magnetic resonance spectroscopy
NMDA	*N*-methyl-D-aspartate
NO	Norway
PKC	Protein Kinase C
ppb	Part per billion
PT	Portugal
PTTI	Provisional Total Tolerable Intake
PTWI	Provisional Tolerable Weekly Intake
SE	Sweden
TEL	Tetraethyl lead
TML	Tetramethyl lead
TSH	Thyroid-stimulating hormone
UK	United Kingdom
US	United States
WHO	World Health Organization

174.1 Introduction

For millennia, lead exposure has harmed human health. While lead is found naturally within the Earth's crust, anthropogenic activities have resulted in widespread contamination of the environment (air, water and soil). Since the late 1970s, public health agencies and associated governmental efforts have dramatically increased the awareness of the toxicity of this element and provided regulation for common sources of lead exposure in a majority of the world's population. The most widely recognized efforts in reduction are associated with elimination of lead additives from the production of paint and petroleum products (gasoline, petrol). However, diet remains a significant source of lead exposure for humans within the modern, industrialized urban centers to the remote Brazilian Amazon. We will review how dietary lead exposures can arise from the ingestion of water, food, vitamins, supplements, pharmaceuticals, and traditional remedies. Lead contamination can occur at any step upon transferring these items from source to the consumer including the contamination of raw materials and implements involved in the preparation, processing, handling, and transport of these items (Table 174.1).

Table 174.1 Dietary sources of lead

- Contaminated drinking water arises from lead contaminated municipal water systems and from leaded pipes and plumbing, often within older homes.
- Food and other ingested items have significant lead levels after grown in lead-contaminated soil or in regions near sources of airborne lead particle emissions such as smelters, incinerators or roads with automobiles using leaded gasoline.
- Contamination of food and other ingested items may occur during the processing, preparation, handling by the producers, and transport to the consumer.
- Contamination of food and beverages may occur after being prepared on leaded cookware, served on lead glazed pottery, ceramics, and crystal and stored in lead-contaminated containers.
- Traditional medicines, pharmaceuticals, supplements, and vitamins are prepared or contaminated with leaded source materials.
- Ingestion of nonfood items related to pica activity provides another source of dietary lead.

This table provides an overview of common sources of lead found in ingested items

Table 174.2 Health effects associated with lead exposure (Adapted from ATSDR 2007)

System	Effect	Vulnerable population
Cardiovascular	Increased risk for hypertension	Adult, General
Developmental	Decrease birth length, stature, head circumference; Delayed sexual maturation	Pediatric, General
Endocrinological	Elevated TSH	Adult, Occupational
Gastrointestinal	Colic	Pediatric, General
Hematological	Decreased ALAD activity	Mixed Age and Source
Immunological	Increased serum IgE	Pediatric, General
Musculoskeletal	Dental caries and bone loss	Mixed Age, General
Neurological	Impaired motor skills, cognition, IQ, attention, executive functioning, social behavioral skills	Pediatric, General
Renal	Decreased GFR	Adult, General
Reproductive	Decreased fertility	Male, Adult Occupational

Lead exposure affects numerous systems within the human body. The effects listed in the table vary in their reversibility. The general population, particularly children, is vulnerable due to multiple sources of lead within the environment.

A number of factors modulate how dietary sources of lead harm the body. Factors such as the form (organic versus inorganic) of lead, age of a person, nutritional status of the individual, and pregnancy influence lead absorption.

Neurological aspects have been examined in cellular and animal models. Complex mechanisms of neurotoxicity are known. For human studies, epidemiologic cohorts have been established and longitudinally monitored to explore cognitive and neurobehavioral aspects of low, moderate, and high lead exposure levels.

While the focus of this work is on the neurological aspects of dietary lead, it is important to recognize that once lead is in the bloodstream, the systemic effects are largely independent of the source whether ingested or inhaled, but rely on the bioavailability pertaining to dose. Lead exposure affects all the major systems within the human body (Table 174.2).

Finally, this review will summarize future directions of research and public policy. Increasing numbers of studies find that low-level lead exposure is associated with adverse cognitive effects. These effects warrant continued action toward identifying sources and reducing lead levels in the environment that potentially threaten human health via ingestion or inhalation.

174.2 Dietary Sources and Intake of Lead

Lead levels within food itself are quite variable due to heterogeneous distribution of lead deposited within the soil and water, the contamination during open shipping of raw items and during processing, the transfer of lead from contaminated storage containers and plastic food wrappers with painted decals, and the transfer from inadequately glazed or heavily worn cookware and ceramic serving dishes. Dietary intake also depends upon cultural practices and individual diet. National regulations regarding lead usage and the practices monitoring compliance can also influence the amount of lead available for dietary consumption. Food lead concentrations have decreased dramatically in most nations primarily due to the reduction of airborne lead emissions and the prohibition of lead solder in storage cans, especially in milk for infant formula. Yet, in 2009 approximately 19 countries continue to use leaded petroleum products. Examining blood lead exposure models at levels above and below the contemporary action level of 10 µg/dL remains relevant toward understanding lead toxicity

Table 174.3 National statistics for dietary intake of lead from food (Adapted from Moschandreas et al. 2002; Marti-Cid et al. 2008; ATSDR 2005; UNEP 2008; EU SCOOP 2004)

Nation State(s)	Average dietary intake in µg/kg of body weight per day	Population
Australia	0.06–0.39	Adult males 25–34 years
	0.02–0.35	Adult females 25–34 years
	0.02–0.43	Boys 12 years
	0.01–0.34	Girls 12 years
	0.03–0.93	Toddlers 2 years
	0.01–1.19	Infant 9 months
Burkina Faso	0.9	52 µg Pb per day for 60 kg average weight
European Union	0.6	42 µg Pb per day for 70 kg average weight
Finland	0.24	17 µg Pb per day for 70 kg average weight
Mexico	3.5	3 µg/kg lead in food
Poland	1.48	Males 103.5 µg Pb per day for 70 kg average weight; 88.5 µg Pb per day for 60 kg average weight
Spain	0.644–0.85	Adult male assuming 70 kg living in Catalonia
USA	0.918	Males over 55 years
	0.895	Males over 20 years
	0.890	Males 13–19 years
	0.946	Females over 55 years
	0.920	Females over 20 years
	0.824	Females 13–19 years
	1.164	Children 7–12 years
	1.952	Children 1–6 years
	3.117	Non-nursing infants
	1.009	US population

This table provides a composite of national statistics reporting contemporary levels of lead intake for individuals in select nations obtained from dietary sources

in all populations. As lead is not degradable and thus, land is the ultimate repository, lead contamination continues to threaten many populations.

The United Nations Environment Program estimated that in 1987 the global average daily intake of lead was about 80 µg/day from food and 40 µg/day from drinking water. More recently, the joint Food and Agriculture Organization of the United Nations (FAO) and World Health Organization Expert Committee on Food Additives established a provisional tolerable weekly intake (PTWI) of 25 µg/kg of body weight, which is the equivalent of 3.5 µg/kg of body weight per day (WHO 2000). Examples of contemporary national estimates of daily intake of lead via food are shown in Table 174.3.

174.2.1 Levels of Lead in Raw Foods

In the European Union, data from national surveys of the adult population find that the major sources of dietary intake include bakery wares, cereals, fruits, vegetables, and beverages (Table 174.4). Levels of dietary lead intake for children were 6–15% above that of adults (not shown).

National surveys tend to focus on adult populations. Children may have lower absolute values of dietary lead intake; however, given their lower body weights, they may have a larger lead burden as they drink more fluids, eat more food, and breathe more air per kg of body weight.

In edible plants, lead contamination may occur from surface deposition of particulate matter or from the soil via the root system using direct foliar uptake and translocation within the plant.

Table 174.4 Daily intake (μg/day) of lead by adults from EU National Surveys (Adapted from EU SCOOP 2004)

Food	UK	DE	NO	BE	DK	FI	FR	HE	IT	IR	PT	SE	Mean
Bakery and cereals	4.0	6.0	2.2		2.35	0.08	9.63	3.2	4.35		0.53	1.43	3.4
Beverage	14	9.7	10.1	18.7	8.61	0.48	13.7		4.2		12.2	1.17	8.9
Cheese, yogurt condensed, powdered milk	0.48	1.3	0.062	0.74	0.19				1.94			0.25	0.71
Confectionary		0.39	0.04		0.74						0.031		0.30
Crustaceans, bivalves, cephalopods			1.2	0.08		0.04	0.79	2.03		0.35	0.51		0.71
Eggs	0.04	0.70	0.42		0.03	0.19	0.12		0.14			0.08	0.21
Fats and oils	0.14	0.74			0.6				0.22		.48		0.44
Fish and fish products	0.28	0.36	0.97		0.16	0.48	0.70	13.8	1.27	0.34	2.22	0.066	1.9
Fruits and vegetables	4.98	14	1.51	17.4	3.98	1.72	25.2	0.29	16.7		117	0.69	18
Meat	1.23	11	3.24		0.99	1.25	1.83	4.21	2.82	0.42		0.74	2.8
Milk, milk products	0.28		0.93	0.95	0.59	2.1	0.32	1.38	0.91			0.3	0.87
Offal	0.09	0.16	0.066	0.01		0.14	0.14	0.23	1.17		0.15		0.24
Ready to eat	0.02		0.008										0.01
Salts and spices		2.2					3.92						3.0
Sweeteners	1.0	0.65	0.047	0.04		0.02	0.47				0.17	0.023	0.30
Sum per Nation	27	47	21	38	18	7	57	25	34	1.1	133	5	**42**

This table provides the amount of lead determined in national surveys of products consumed by adults within the European Union. The data were collected during different periods in the 1990s and 2000s and vary due to study methodology, regional and cultural factors

The bioavailability of lead within the soil depends on pH, amount of organic matter present, amount of additives (i.e. limestone) within the soil, soil moisture levels, cation exchange capacity, and the forms of lead in the soil. For a majority of raw foods, lead is present at low concentration levels. However, contamination during production and processing is responsible for enhanced lead intake via dietary sources. While cocoa beans have the lowest reported values for a raw food, manufactured cocoa and chocolate products have among the highest values reported for all foods (Rankin et al. 2005). Atmospheric emissions of lead particulates contaminate shells, which protect the raw cocoa bean quite well from lead. However, as the beans are harvested, sun dried, and processed, contamination of the cocoa bean can occur upon mixing with the shells. Subsequent transport, distribution, and product formulations also allow for further lead contamination.

In a remote, riverside population within the Brazilian Amazon, with no known documented source of environmental or occupational lead, Barbosa and colleagues found 57% of participants had blood lead levels equal to or higher than 10 µg/dL (Barbosa et al. 2009). The mean blood lead levels were 13.1 ± 8.5 µg/dL (males 15.3 µg/dL vs females 7.9 µg/dL). Upon investigating, the villages with the highest exposures had two sources of lead: the production of farinha and hunting. The artisanal production of farinha (flour) from manioc requires roasting the pulp over fire on metal plates that contain leaded alloy. The young men spend several hours stirring the pulp, inhaling lead vapors, and ultimately consuming the farinha with produced food. Raw manioc had a mean lead concentration of 0.017 µg/g $\pm$ 0.016 (range 0.003–0.04 µg/g) while that for farinha was 0.19 µg/g $\pm$ 0.10 (range 0.09–0.38 µg/g). The lead exposure from hunting arises from contamination of the game from bullets with leaded alloys.

174.2.2 Transfer of Lead to Food from Children's Hands

For Western societies, there is at least a century of human industrialized activity, which produced pervasive contamination of air, soil, and water. Airborne lead particles from industrial sources continue to be deposited in soil and water, and thus, enter the food supply. Household lead contamination occurs in homes previously painted (interior and/or exterior) with leaded paint and/or situated near major highways as the deposition of lead particulates from decades of leaded petroleum product emissions contaminate the soil. In 2000, 1.2 million housing units in the United States with low-income families having children under 6 years of age were reported with deteriorated paint, dust, or bare soil contaminated with lead (Jacobs et al. 2002). Young children, especially toddlers, obtain leaded dust on their hands as they crawl, learn to walk, fall, and move about their residential environment. Freeman demonstrated that children with previously elevated lead levels transferred significant amounts of lead dust to their food (Freeman et al. 2001) by handling food items with their hands. The residential environment, the parents and children's hygiene habits influence the amounts of dietary lead exposure.

174.2.3 Pica Activity

Pica activity, the consumption of nonfood items, particularly in children and pregnant women, greatly increases the risk of lead intake. Pica activity is attributed to cultural and low socioeconomic factors as well as nutritional deficiencies. For children engaging in pica behavior, the soil ingestion rate may be as high as 5 g/day. Blood lead levels ≥ 10 µg/dL in children 6–71 months of age have been associated with yard soil containing lead concentrations exceeding 500 mg/kg (ATSDR 2007).

174.2.4 Lead Contamination of Water

Another dietary source of lead is water used for drinking and in the preparation of beverages, particularly coffee, tea, and infant formulas. Within the United States (US), the Environmental Protection Agency (EPA) monitors municipal water supplies. In 1991, the EPA set an action level for lead in tap water at 0.015 mg/L (15 ppb) with estimates that less than 1% of the public water systems have water entering the distribution system at levels above 5 µg/L (ATSDR 2007). Lead in US drinking water potentially contributes 10–20% of total lead exposure in young children. Lead found in US drinking water is usually derived from corrosion of lead pipes, lead-based solder, and brass, chrome, or bronze plumbing fixtures with older residences. Lead corrosion can occur with soft, acidic water (low pH) and by increasing the dissolved oxygen demand. The temperature and length of time that drinking water resides in a pipe alters the lead concentration within the water. Studies found that 57% of public school buildings in Philadelphia in 2000 and 2001, as well as 22% reported in Seattle during 2004, had lead water levels exceeding recommended levels (Bryant 2004; Sathyanarayana et al. 2006). Lanphear et al. found that children who lived in housing with a water lead concentration greater than 5 ppb had blood lead concentrations that were 20% (1 µg/dL) higher than children living in housing with water lead concentrations below 5 ppb (Lanphear et al. 2002). In Washington DC, increased levels of lead in drinking water were found when the municipal utility changed the disinfectant from free chlorine to chloroamine, which precipitated out lead from leaded plumbing. The incidence of blood lead levels exceeding 10 µg/dL for children less than 30 months increased more than four times (Edwards et al. 2009). Lead in drinking water may be a significant contributor to lead burdens, especially in persons with elevated blood lead levels where no paint or soil source of contamination is found (Levin et al. 2008).

174.2.5 Lead in Traditional Medicines

Traditional medicines, herbal remedies, and other supplements often contain significant amounts of lead either contaminated in processing or directly included in the formulation of the product. Karri et al. found 76 case reports of lead encephalopathy associated with traditional medicine published between 1966 and February 2007 (Karri et al. 2008). For 95% of the reports, the patients involved were infants and young children with outcomes that included death (11%) and residual neurological deficits (21%). Such products are listed in Table 174.5 along with their intended benefit and regional origin. The amounts of lead within the products are variable.

174.2.6 Standards for Lead Intake

The US Food and Drug Administration provisional total tolerable intake levels (PTTI) currently set for young children, for adults, and for pregnant and lactating women are 6, 62.5, and 25 µg/day, respectively. Mindak et al. determined the lead content of 324 multivitamin–mineral products and found that an overall median value for lead exposure was 0.576 µg/day (Mindak et al. 2008). The estimated median and maximum lead exposures varied for young children (less than or equal to 6 years) at 0.123 and 2.88 µg/day, older children (7 years and over) at 0.356 and 1.78 µg/day, adult women at 0.842 and 4.92 µg/day, and for pregnant and lactating women at 0.845 and 8.97 µg/day. In another study, the concentration of lead found in 95 major dietary supplements with an emphasis on botanical-based products, ranged from 20 to 48,600 µg/kg with a median concentration of 403 µg/kg. (Dolan et al. 2003) For 11 products, the lead levels would exceed the tolerable lead intakes for children

Table 174.5 Traditional medicines, herbal remedies and supplements with lead (Adapted from CT 2009 and NY 2009)

Traditional medicines and herbal products	Uses and conditions treated	Region of origin
Albayalde	Vomiting, colic, apathy, lethargy	Mexico, Central America
An Kung Niu Huan Wan (Peaceful Palace Ox Gallstone Pill	Vertigo, delirium, high fevers, measles, restlessness	China
Anzroot	Gastroenteritis	Middle East
Azarcon, also known as Alarcon, Maria Luisa, Coral, Rueda	Gastrointestinal symptoms	Mexico
Ba Bow Sen	Hyperactivity and nightmares in children	China
Bal Chamcha	Problems w/liver, digestion, teething, milk intolerance, irregular stools, colic, regurgitation, bloating, parasites, poor sleep, poor dentition, myalgia	India
Bal Jivan	Baby tonic	India
Bala Goli/Fita	Dissolved in "gripe water"; used for stomach ache	India
Bala Guti	Children's tonic	India
Bala Sogathi	Growth of children, teething, cough, cold, fever, and diarrhea	India
Balguti Kesaria	Tonic tablets for infants with sudha and gold rickets, coryza, cough griping, skin roughness, worms, and dental problems	India
Bao Ning Dan	Traditional remedy for acne, pain, and removing toxins	China
Bezoar Sedative Pills	High grade fever, encephalitis, inflammation, infection, infantile convulsions, and viral meningitis	China
Bint Al Zahab	Diarrhea, colic, constipation, general neonatal use	Middle East, Iran
Bokhoor	Fumes calm infants	Saudia Arabia
Cebagin	Teething powder	Middle East
Chuifong tokuwan	Joint pain, arthritis	Asia
Cordyceps	Hypertension, diabetes, bleeding	China
Deshi Dewa	Fertility	India
Emperor's Tea Pill	Maintain body's natural balance	China
Farouk	Teething powder	Saudi Arabia
Ghasard also known as Ghazard and Qhasard	Aid digestion	India
Greta	Digestive problems	Mexico, Central America
Hai Ge Fen	Gastrointestinal ailments	China
Hepatico Extract	Healthy liver and regularity	China
Jambrulin	Diabetes, sugar control	India
Jeu Wo Dan	Cast dressing	China
Kandu	Intestinal problems	Asian
Kohl also known as Kajal and Surma	Eye cosmetic; Infant eye treatment; skin infections, navel of newborns	Middle East, Africa, South Asia, India
Koo Sar, Koo Soo	Menstrual cramps	Hong Kong
Liga	Digestive and stomach problems	Mexico
Litargirio	Deodorant/antiperspirant	Dominican Republic
Lu Shen Wan	Mumps, fever, infections, sore throat	China
Maha Yograj Guggul	Musculo-skeletal disorders	India
Mahalakshmi Vilas Ras with gold	Cold related symptoms, blood deficiency, wound healing, asthma	India
Mahayogaraj Guggulu	Rheumatic pain	India

(continued)

Table 174.5 (continued)

Traditional medicines and herbal products	Uses and conditions treated	Region of origin
Mahayogaraj Guggulu with silver and Makardhwaj	Rheumatic pain, bile, pigmentation disorders, blood purification, eye problems, weakness	India
Molleja de Pollo Molida	Stomach ache	Mexico
Murrah, al-murrah	Colic, stomach aches, diarrhea	Saudi Arabia
Navratna Rasa	General debility, rickets, calcium deficiency	India
Pay-loo-ah	Rash and high fever	Southeast Asia
Po Ying Tan	Childhood complaints	China
Qing Fen	Cast dressing, pain	China
Rueda	Colic, calm children	China
Santrinj	Teething powder	Saudi Arabia
Sundari Kalp	Menstrual health	India
Saoot	Eye injury, teething, navel of newborns	Middle Eastern
Surma	Teething powder	India
Swarna Mahayograj Guggulu with gold	Rheumatism, gas, cerebrovascular accident, menstrual cycles, menopause, progesterone deficiency, mental disorders, fertility	India
Tibetan Herbal Medicine	Mental retardation	Tibet, India
White Peony Scar Repairing Pills	Scars	Hong Kong
Zhui Feng Tou Gu Wan/ Zhiufeng Tougu Wan	Bone ailments, joint pain, numbness	China

This table provides a reference of traditional medicines, herbal remedies, and supplements known to have significant lead concentrations, their intended usage, and region of origin

and women of child-bearing age. In a survey of lead concentrations in 45 pharmaceutical products by Kauffman, the average mass of lead ingested by the consumer was 0.22 µg/day (Kauffman et al. 2007). The highest lead containing product, a calcium antacid and supplement, was estimated to deliver a maximum daily lead mass of 2.7 µg/day. Lead contamination of calcium supplements has been reported in several studies with older studies tending to find greater lead levels (Bourgoin et al. 1993; Ross et al. 2000; Scelfo and Flegal 2000; Kim et al. 2003). However, overuse of supplements with "safe lead levels" can result in lead intake in excess of current tolerable limits, particularly in vulnerable populations such as children, pregnant, and lactating women.

174.3 Factors Influencing Lead Absorption Within the Body

Lead can be characterized as organic or inorganic depending upon the chemical form. Organic complexes such as tetraethyl lead (TEL) and tetramethyl lead (TML), added to petroleum products for usage as antiknock agents in automobile engines, decompose into trialkyl and dialkyl lead compounds such as lead halides and ammonium lead halides upon atmospheric release and exposure to sunlight. These compounds further react with the air, water, and soil in the environment to produce inorganic forms, which are likely to be ingested as inorganic lead alloys and lead salts. Nearly all forms of lead from anthropogenic sources that are released to soil are inorganic lead compounds. Inorganic lead compounds can be inhaled and swallowed depending on the particle size. In the human body, inorganic lead is metabolized upon forming ligand complexes with amino acids, non-protein thiols, and various proteins (ATSDR 2007). Inorganic lead can be measured in tissues, blood, serum, urine, sweat, saliva, breast milk, cerebrospinal fluid, bone, nails, teeth, and hair.

174.3.1 Nutritional Modifiers

Nutritional factors are often mentioned as important modifiers of the metabolism and toxicity of lead. Essential elements, such as calcium, iron, and zinc, interact with lead as demonstrated in studies of both animal models and humans. These interactions are complex and inter-related. Evidence in the literature (see review (Ros and Mwanri 2003)) supports the nutritional statements listed in Table 174.6; however, some concepts remain controversial.

A recent clinical trial found that for mild-to-moderately lead-poisoned children with sufficient dietary calcium, further supplementation aimed at providing 1,800 mg of calcium per day had no effect on the change in blood lead levels (Markowitz et al. 2004). Another trial evaluated the efficacy of iron and/or zinc supplementation on cognitive performance in school children living in a lead-contaminated city (Rico et al. 2006). For 6 months, children were given 30 mg of iron, 30 mg of zinc, both or placebo daily. At three time points (baseline, end of the trial, and 6 months after the supplementation trial ended) children were evaluated with cognitive tests of memory, attention, visual–spatial abilities, and learning. Among the groups, no consistent or persistent differences in cognitive performance were found. The existing evidence does not support the usage of dietary interventions as a key strategy for a reduction in childhood lead exposure (Ballew and Bowman 2001).

There is a large body of literature supporting the concept that children absorb more lead than adults. Specifically, water-soluble lead absorption appears to be higher in appropriately nourished children than adults, 40–50% versus 3–10%, respectively (ATSDR 2007). However, the fact that blood lead levels rise may be related to bone turnover associated with growth rather than increased absorption within the gastrointestinal tract.

174.3.2 Lead Mobilization from Bone

Without current exposure, women's blood lead levels may rise from the mobilization of lead from bone, which occurs during times of physiological stress such as pregnancy, and lactation in response to calcium demands of the developing fetus and nursing infant (Manton 1985; Gulson et al. 1998). Since lead readily crosses the placenta, fetal lead exposure can be significant and related to adverse postnatal outcomes (reduced birth weight and gestational age, postnatal mental retardation, and impaired neurobehavioral development) as fetal blood lead concentration is highly correlated with

Table 174.6 Nutritional features associated with ingested lead

- Lead ingested during fasting is absorbed at a much higher rate than lead ingested with a regular food intake.
- Retention of lead in children is important due to more rapid gastric emptying times.
- Calcium inhibits the absorption of lead in mammals by binding to and displacing lead from common mucosal carriers in the intestinal tract, though it is short-lived, as calcium must be present with lead.
- Calcium deficiency mobilizes lead from the bone and distributes it via the blood to soft tissues, thereby increasing the concentration of lead in critical organs, particularly the brain.
- For experimental animals, iron deficiency increases lead absorption from the intestinal tract. In humans, the relationship is uncertain.
- Lead and iron compete for critical binding sites; lead further aggravates the features of iron deficiency.
- Iron deficiency and lead toxicity both adversely affect cognitive development. Children with elevated blood lead levels should also be evaluated for iron deficiency, as those at risk for one are likely to be at risk for the other.
- Blood lead levels and activity of zinc-containing heme enzymes, such as ALAD, are inversely related indicating lead can replace zinc in these systems.

The table summarizes how calcium, iron, and zinc influence dietary lead absorption and concentration levels

maternal levels (Goyer 1990). Calcium supplementation at levels of 1200–1,500 mg/day is recommended for pregnant and nursing women. For postmenopausal women and those with osteoporosis, bone mineral resorption can cause lead stored in the bones to be released into the blood.

174.4 Neurological Impact of Lead Exposure

174.4.1 Mechanisms of Action

The neurological impact of lead exposure has been examined in humans, animals, and in vitro systems for several decades (see reviews by Lidsky and Schneider 2003; Toscano and Guilarte 2005; Garza et al. 2006). Significant advancements have been made to our understanding of how lead exerts neurotoxicity to humans and animals. Multiple toxic mechanisms of action for lead are present in the brain, which are often variable in presentation, overlapping in function and opposing in dose–effect relationships. These mechanisms are listed in Table 174.7 (Garza et al. 2006). A common factor among many of these mechanisms is the ability of lead to mimic calcium. In both the developing and adult brain, the ability of lead to substitute for calcium allows selective passage into the brain across the blood–brain barrier. As mentioned previously, intrinsic factors (age, sex, etc.), genetic mechanisms of metal transport, nutritional factors, and dosage factors (form, concentration, duration, and timing) can modulate the lead concentration that reaches the human brain. Lead exposure during distinct periods of neurodevelopment can produce different effects. Chronic "low-level" exposure may also produce different effects from acute "moderate to high-level" exposures. Such modulation of factors can influence human outcomes and contribute to contradictory findings in model systems. While many animal models employ a dietary ingestion method for lead dosing, the majority of human epidemiological studies assume the primary exposure source is inhalation. The neurological aspects of lead exposure are dependent on exposure source as bioavailability modulates dose.

Many contemporary studies have sought to unravel the molecular and biochemical underpinnings associated with the cognitive and behavioral deficits associated with lead exposure. In children, the cognitive and behavioral effects of early, developmental lead exposure are now regarded as irreversible. Animal models, rats, and nonhuman primates with blood lead concentrations on the order of 10–15 μg/dL demonstrate deficits in learning, which are similar to those observed in children associated with lead exposure (Rice 1996; Cory-Slechta 2003).

Table 174.7 Neurotoxic effects and mechanisms of action for lead in the brain

- Apoptosis
- Calcium competition and substitution
- Disruption of calcium homeostasis
- Lipid peroxidation
- Alterations in neurotransmitter synthesis, storage, and release
- Excitotoxicity
- Alterations in the expression and operation of receptors
- Interference with second messenger systems
- Interference with mitochondrial metabolism
- Damage to the oligodendroglia and astroglia
- Zinc substitution in zinc-mediated processes

This table details the mechanisms of action found associated with lead toxicity in model systems

174.4.2 Protein Kinase C

In models of acute exposure, lead directly stimulates Protein Kinase C (PKC) activity at picomolar levels, which are 4–5 orders of magnitude greater than the action of calcium (Markovac and Goldstein 1988). Tomsig and Suszkiw subsequently found that lead, depending on the concentration range, was capable of both activating and inhibiting the enzyme (Tomsig and Suszkiw 1995). PKC influences synaptic transmission via synthesis of neurotransmitters, ligand-receptor interactions, conductance of ion channels, and dendritic branching. Evidence suggests that lead targets the γ-isoform of PKC, a calcium-dependent, neuron-specific isozyme of PKC involved in long-term potentiation, memory function, and spatial learning.

174.4.3 Neurotransmitters: Cholinergic, Dopaminergic, and Glutamatergic

Neurotransmitter systems, particularly cholinergic, dopaminergic, and glutamatergic, have important roles in brain development and cognitive function. Lead exposure decreases neurotransmission. For chronically lead-exposed animals, upregulation of cholinergic, dopaminergic, and glutamatergic receptors are generally consistent with findings of diminished presynaptic function.

Within the central nervous system (CNS), activity within the cholinergic neurons projecting from the basal region of the forebrain to the hippocampus is key for memory and learning activities. Lead blocks the evoked release of acetylcholine and diminishes cholinergic system function. Bielarczyk and colleagues found depression of choline acetyltransferase activity in the cortex and hippocampus of young adult rats exposed to lead only during early development (Bielarczyk et al. 1996). The study also found decreased functional cholinergic innervation in the hippocampus. These reported denervation-like effects in the hippocampus could represent an important factor in long-term learning and cognitive impairments following developmental exposure to low levels of lead (Bielarczyk et al. 1996).

The dopaminergic and glutamatergic systems play a role in many aspects of cognitive functioning including attention, impulsivity, flexibility, learning, and memory. Based on studies of rodents and nonhuman primates, it has been known for some time that the dopamine system is particularly sensitive to lead (Cory-Slechta 1995). Lead may impair regulation of dopamine synthesis and release. The prefrontal cortex has the highest concentration of dopamine of all cortical areas and is the region primarily involved with cognitive and executive functions. For the glutamatergic system, chronic developmental lead exposure increases the threshold of long-term potentiation (LTP) induction with a biphasic dose–effect relationship, and decreased magnitude of LTP. Decreases in stimulated glutamate release are a significant factor contributing to lead-induced changes in LTP. Alterations in the N-methyl-D-aspartate (NMDA) subtype of glutamate receptor can produce deficits in synaptic plasticity that affect learning and memory (Toscano and Guilarte 2005). Developmental lead exposure is able to modify NMDA receptor subunit expression, subunit composition, and synaptic localization resulting in activity changes for calcium-sensitive signaling pathways.

174.4.4 Neurological Symptoms Associated with Lead Encephalopathy

In humans with frank lead encephalopathy, blood lead levels typically exceed 70 μg/dL and manifest with initial symptoms that include headache, loss of memory, hallucinations, muscle tremors, ataxia, dullness, poor attention span, and irritability. At these blood lead levels and above, gastrointestinal

distress and other systemic features can also be present. As the condition worsens, seizures, paralysis, coma, and death can occur. In fatal cases, histopathological features include cerebral edema, perivascular glial proliferation, altered capillaries, and neuronal damage consistent with hypoxic–ischemic injury.

Exposures at blood lead levels exceeding 40 µg/dL, typically found in adults with occupational lead exposure, can produce symptoms including headache, malaise, altered mood state, fatigue, lethargy, forgetfulness, irritability, dizziness, and paresthesia. In addition to these features, a significant number of studies have reported neuropsychological effects such as disturbances in manual dexterity, reaction time, visual–motor performance, and cognitive performance.

174.4.5 Pediatric Epidemiological Studies

Human epidemiological studies in children assume that the majority of lead exposure arises from inhalation of automotive emissions and the ingestion of dust from paint residues. However, one study of children demonstrated convincing dose–response deficits in cognitive abilities of lead exposure arising from drinking water (Fulton et al. 1987).

174.4.6 Epidemiological Studies and Intelligence Quotient

Needleman and colleagues investigated pediatric low-level lead exposure in children from Chelsea and Somerville, Massachusetts. This study documented cumulative exposure to lead using a measurement of lead in deciduous teeth, assessed confounding factors, and employed multivariate statistical procedures. Needleman and colleagues reported a covariate-adjusted difference in child IQ of approximately 4.5 points between groups "high" and "low" in tooth lead (Needleman et al. 1979). Teacher ratings of children's behavior in the classroom indicated more behavioral problems and academic difficulties among children with higher concentrations of lead. Many cohort studies were developed to verify these findings and refine study design (i.e. employ blood lead measures). Subsequently, a number of meta-analyses have established that lead is robustly associated with dose-related declines in IQ (Needleman and Gatsonis 1990; Pocock et al. 1994; Schwartz 1994). Lanphear and colleagues conducted a pooled analysis of seven prospective studies that were started prior to 1995 (Lanphear et al. 2005). The analysis involved 1,333 children with complete data on confounding factors used in the multivariable analyses. A significant number ($N = 244$) of children with blood lead concentrations that never exceeded 10 µg/dL were included in the analysis. The participating sites included Boston, MA; Cincinnati, OH; Cleveland, OH; Kosovo, Yugoslavia; Mexico City, Mexico; Port Pirie, Australia; and Rochester, NY. The primary outcome measure was full-scale IQ assessed in school-age children with the Wechsler scales (mean age of testing was 7 years). The median lifetime average blood lead concentration was 12.4 µg/dL (5th–95th percentile 4.1–34.8 µg/dL). The mean IQ of all children was 93.2 (SD 19.2). Multivariable regression analysis resulted in a six-term model including the log of concurrent blood lead, study site, maternal IQ, a measure of caretaking quality (Home Observation for Measurement of the Environment (HOME)), birth weight, and maternal education. Using a log-linear model, the study's authors estimated a decrement of 1.9 points (95% CI 1.2, 2.6) in full-scale IQ for a doubling of concurrent blood lead. However, the IQ point decrements associated with an increase in blood lead from 1 to 10 µg/dL were 6.2 points (95% CI 3.8, 8.6) compared to 1.9 points (95% CI 1.2, 2.6) with an increase in blood lead from 10 to 20 µg/dL. The individual effect estimates indicated steeper slopes in cohorts with lower blood lead levels.

In the Rochester Lead Study analyses using only children with peak blood lead levels less than 10 µg/dL found for each 1 µg/dL increase in concurrent blood lead levels was associated with a statistically significant, covariate-adjusted 1.8 point decline in IQ at 5 years of age (Canfield et al. 2003a). Nonlinear semiparametric smoothing revealed a covariate-adjusted decline of more than 7 IQ points up to 10 µg/dL of childhood average blood lead, whereas a more gradual decline of 2.5 points was associated with an increase in blood lead from 10 to 20 µg/dL.

174.4.7 Neuropsychological Deficits in Pediatric Lead Cohorts

Cognitive abilities, such as attention and executive functions, language, memory and learning, and visuospatial processing have been explored in association with lead exposure. Two of these abilities, attention/executive functions and visual–spatial skills, have demonstrated convincing evidence of diminishment associated with lead exposure (Table 174.8).

174.4.8 Attention Skills

Bellinger and colleagues examined a subset of the Chelsea and Somerville cohorts at 19–20 years of age with a battery of attentional measures (Bellinger et al. 1994). Higher tooth lead concentrations were significantly associated with poorer scores on the Focus-Execute and Shift factors of the battery, supporting the notion that early lead exposure is associated with poorer executive/regulatory functions thought reliant on frontal or prefrontal regions of the brain. Canfield and colleagues evaluated executive functioning and learning in the Rochester Lead Study cohort using the Shape School Task with embedded protocols requiring inhibition and attention switching mental sets (Canfield et al. 2003b). The mean blood lead level at 48 months was 6.5 µg/dL (range 2–21) with 80% of the children below 10 µg/dL. Following covariate adjustment, blood lead concentration at 48 months was negatively associated with children's focused attention, naming efficiency, and inhibition of

Table 174.8 Lead-associated findings reported from pediatric epidemiological cohorts of low-to-moderate lead exposure

- Decreased measures of general intelligence
- Deficits in tests of visual–spatial skills
- Impaired performance on tests of spatial working memory
- Increased errors on test of visual–motor integration
- Impaired performance on tests of spatial memory span
- Increased time required for tests of manual dexterity
- Increased numbers of errors and false alarms on continuous performance test
- Impaired performance on tests of cognitive flexibility
- Deficits with short-term memory
- Impaired performance on test requiring inhibition of automatic responding
- Impaired performance on tests of attention and attention switching
- Decreased academic school performance
- Increased externalizing behaviors, aggressive behaviors, disruptive behaviors
- Increased teacher and parent rankings for hyperactive behavior
- Increased antisocial, delinquent behaviors

This table summarizes the neurobehavioral deficits found from published studies of childhood lead exposure

automatic responding. Children with higher blood lead levels also completed fewer phases of the task and knew fewer color and shape names. At 6 years of age, the Working Memory and Planning protocols from the Cambridge Automated Neuropsychological Test Battery (CANTAB) were administered to assess mnemonic and executive functions (Canfield et al. 2004). Following covariate adjustment, children with higher blood lead concentrations showed impaired performance on tests of spatial working memory, spatial memory span, cognitive flexibility, and planning as indexed by tests of intradimensional and extradimensional shifts and an analogue of the Tower of London task. At 16 years of age, a comprehensive neuropsychological battery was administered to Cincinnati Lead Study participants (Ris et al. 2004). Childhood blood lead levels in the Cincinnati cohort were high with 30% of the cohort having at least one blood lead concentration in excess of 25 µg/dL during the first 5 years of life. After covariate adjustment, the strongest association between lead exposure and cognitive performance was found for attention factor scores derived from a principal components analysis with the findings more prominent among male subjects.

In 1943, Byers and Lord reported problems with attention and aggression in their patients who recovered from acute lead encephalopathy (Byers and Lord 1943). Needleman reported that disturbances in behavior and social conduct are prototypical sequela among victims of lead poisoning (Needleman 2004). Parents frequently report that following recovery from an episode of acute poisoning their child's behavior changed dramatically, and became restless, aggressive, impulsive, and inattentive. In the Yugoslavian prospective study, concurrent blood lead levels were significantly associated with parent ratings on the Destructive Behaviors subscale of the Achenbach CBCL upon covariate adjustment (Wasserman et al. 1998).

Lead levels measured in blood and/or teeth have been associated with teacher ratings of hyperactive behavior, attentional and behavioral problems in many studies (Needleman et al. 1979; Fergusson et al. 1988; Silva et al. 1988; Thomson et al. 1989). Using data from the National Health and Nutrition Examination Survey (1999–2002), Braun and colleagues examined the available blood lead concentrations for 4,704 subjects 4–15 years of age, 4.2% of whom were reported to have ADHD and stimulant medication use (Braun et al. 2006). Following covariate adjustment, higher blood lead concentrations were significantly associated with ADHD. Subjects with blood lead levels > 2 µg/dL were four times more likely to have a diagnosis of ADHD and be on stimulant medication. Braun and colleagues determined that nationally lead exposure accounts for 290,000 excess cases of ADHD in US children.

174.4.9 Visual–Motor Integration Skills

Studies employing specific measures of visual–motor integration skills, such as the Developmental Test of Visual Motor Integration, the Bender Visual-Motor Gestalt Test, demonstrate strong evidence linking deficits with early lead exposure (Winneke et al. 1990; Dietrich et al. 1993; Baghurst et al. 1995; Wasserman et al. 2000). Ris and colleagues observed a significant association between prenatal maternal blood lead levels and deficits in visual–spatial and constructional skills as indexed by Visual-Constructional factor scores for Cincinnati Lead Study participants at 16 years (Ris et al. 2004).

174.4.10 Neuroimaging

Several case reports describe neuroimaging features associated with lead encephalopathy arising from the use of traditional medicines and occupational exposures (Mani et al. 1998; Atre et al. 2006; Karri et al. 2008). In general, blood lead levels within the encephalopathic range can produce focal

lesions with abnormal signal, calcified lesions, and edema. The distribution of the lesions is variable, but encompasses every brain lobe, including gray and white matter structures.

For children exposed to lead at low-to-moderate levels, "clinical" neuroimaging modalities (i.e. computerized tomography and magnetic resonance imaging (MRI)) provide very little insight into lead-associated injury responsible for cognitive deficits. Trope and colleagues performed MRI and MRS studies on a sample of 16 subjects with a history of elevated blood lead levels (23–65 µg/dL) prior to 5 years of age (Trope et al. 2001). The average time of evaluation was 8 years. Compared to age-matched controls composed of siblings or cousins without a history of undue lead exposure (i.e., ≤10 µg/dL), lead-exposed subjects exhibited a significant reduction in *N*-acetyl aspartate:creatine ratios within frontal cortical gray matter. *N*-acetyl aspartate is a metabolite shown to decrease in processes that involve decreased neuronal and axonal functioning and loss.

Using volumetric MRI, Cecil and colleagues also examined a subset of the Cincinnati Lead Study cohort (Cecil et al. 2008). In studies of 157 subjects between the ages of 19 and 24 years, analyses of whole-brain MRI revealed significant decreases in brain volume associated with childhood blood lead concentrations. Following adjustment for other significant covariates including age at time of imaging and birth weight, the most affected regions were within the frontal gray matter, specifically the anterior cingulate cortex and ventrolateral prefrontal cortex, which are areas associated with executive functions, including mood regulation, decision-making, and interpretation of sensory inputs. Areas of lead-associated gray matter volume loss were larger for males.

Using functional MRI, the influence of childhood lead exposure on language function was examined in a subset of 42 young adults from the Cincinnati Lead Study (Yuan et al. 2006). Subjects performed an integrated verb generation/finger-tapping paradigm. Higher childhood average blood lead levels were significantly associated with reduced activation in Broca's area, a recognized region of speech production in the frontal lobe of the left hemisphere. Higher blood lead levels were also associated with increased activation in the right temporal lobe, the homologue of Wernicke's area, which is associated with speech perception. These associations were statistically significant following adjustment for covariate including birth weight, and marijuana usage as assessed by a positive urine screen. Lead exposure during childhood reorganizes the brain circuitry responsible for language function in a striking, dose-dependent fashion.

174.5 Future Directions of Research and Policy

174.5.1 Research

The complex mechanisms of lead toxicity require further elucidation. Questions remain such as: (a) is there any "safe" level or threshold of exposure? (b) at what ages are humans, specifically children, most vulnerable to lead? (c) can dietary modifications and pharmaceutical interventions help to minimize the neurotoxic effects of lead? As we uncover more about the "normal" functioning of brain systems with emerging imaging technologies, we will also have the opportunity to study how lead perturbs cellular networks, as lead affects numerous neural systems.

Controlled trials of environmental interventions aimed at reducing an existing lead exposure source are necessary to offer options to exposed populations. Continued research understanding the low-level effects of lead exposure needs to be coupled with studies of concurrent exposures to other prevalent neurotoxicants. Examination of the current action level, 10 µg/dL, to possibly lower levels for children is important based upon emerging evidence of low-level lead exposure effects.

Table 174.9 Steps for reducing the harmful effects of lead exposure

- Remediate lead-contaminated soil, especially where children play and where food items are grown.
- Removal or abatement of leaded paint in homes.
- Removal of leaded dust from homes with frequent cleaning.
- Removal of cookware and storage containers containing lead.
- Replace water system lines to homes, plumbing, and pipes within homes.
- Provide nutritious diets with appropriate amounts of iron, zinc, and calcium.
- Provide appropriate monitoring of lead hazards in homes, schools, and other places where children play.
- Eliminate leaded additives in petroleum products, paint, jewelry, cosmetics, and other consumer items in all nations.
- Eliminate usage of traditional medicines, and supplements, which purposely include lead within the formulation.
- Minimize production of industrial materials containing lead.

This table summarizes actions that can be employed to minimize lead exposure

174.5.2 Policy Implications

Lead continues to threaten significant numbers of the world's population, as it remains present in several sources. The goal must be the prevention of lead exposure in all populations (Table 174.9). Elimination of lead additives to petroleum products and paint needs to be enacted in all nations. Primary prevention strategies to eliminate lead hazards in homes and workplaces must be implemented. Lead paint residues, particularly within dust and soil, are often found in the homes located in older, urbanized centers. Screening of high-risk, older housing units in urbanized centers for leaded paint and plumbing is needed to prevent exposure. Lead abatement, while costly, could provide greater savings in special education, medical, and crime-related costs. Lead added to paint continues to be found in toys and other consumer products. Support for regulations and resources for enforcements of existing standards must be strengthened.

Severe restrictions on industrial and all nonessential uses of lead will greatly minimize occupational exposures in addition to the general population. Uniform lead limits are also needed to insure the lowest achievable exposure to lead from pharmaceutical and dietary supplement products (Kauffman et al. 2007).

174.6 Applications to Environmental Neurotoxicants and Human Health

The decades of research in the field of lead neurotoxicity have demonstrated that exposure to lead is associated with neurological and neurobehavioral disorders in adults and children. Exposure to lead during infancy and childhood produces essentially irreversible deficits in cognition, attention, executive functions, intelligence, learning, memory, and increases in externalizing behavioral problems. The success in reducing environmental lead sources was difficult to achieve. Novel approaches with genetics, imaging, and epidemiological statistical modeling developed for investigating lead exposures offer tremendous potential to other toxicants. Confirmed and suspected ubiquitous toxicants such as mercury, traffic-related exhaust particles, tobacco smoke, polychlorinated biphenyls, pesticides, and some plastics may be responsible for human morbidities and disease in children and adults. Applying the lessons learned from lead to existing and emerging toxicants could improve the lives of significant numbers within the world's population.

174.7 Key Facts of Lead Toxicity

- Lead exposures have decreased dramatically due to the elimination of lead additives in petroleum products, paint, and lead solder in food cans.
- Lead remains a health threat as it remains present in our environment, in dust, land and water. Food grown in contaminated soil, handled by children living in home environments with lead dust from leaded paint residues and water obtained from leaded plumbing continue to serve as a source for potential lead exposure in children.
- Traditional medicines, herbal remedies, and supplements can contain significant amounts of lead.
- Factors such as age, sex, fasting status, nutritional deficiencies such as zinc and iron deficiency and pregnancy status for women modulate the amount of lead that enters the blood stream and ultimately, the brain.
- Human epidemiological studies find significant cognitive, neuropsychological, and motor deficits related to blood lead levels, even at levels below the currently set action level of 10 μg/dL.

Summary Points

- Despite efforts to reduce human exposure, lead contamination, particularly via dietary sources, remains a significant global health problem.
- Dietary lead exposures can arise from the ingestion of contaminated water, food, vitamins, supplements, pharmaceuticals, and traditional remedies.
- Lead contamination can occur at any step upon transferring these items from source to the consumer including the contamination of raw materials and implements involved in preparation, processing, handling, and transport of consumed items.
- Factors such as the form (organic versus inorganic) of lead, age of a person, nutritional status of the individual, and pregnancy influence lead absorption.
- Complex mechanisms of lead neurotoxicity are implicated from in vitro, animal, and human epidemiological studies.
- Meta-analyses of pediatric epidemiological cohorts have established that lead is robustly associated with dose-related declines in IQ.
- Recent advanced neuroimaging studies suggest gray matter neuronal volume loss and reorganization of function associated with low-to-moderate childhood lead exposure.

Definition and Explanations of Key Terms

Anthropogenic: Processes or materials are those derived from human activities
Cognitive: Process of thinking, comprehension, reasoning, learning, or understanding
Covariate: It is a variable that is possibly predictive of outcome under study
Epidemiological: Study of factors affecting the health of populations
Executive functions: Processes for planning, cognitive flexibility, abstract thinking, rule acquisition, initiating appropriate actions and inhibiting inappropriate actions, and selecting relevant sensory information
Hippocampus: A structure within the limbic system of the brain thought responsible for long-term memory and spatial navigation

> **Long-term potentiation:** Major cellular mechanism responsible for memory and learning as neurons simultaneously communicate.
>
> **Neuropsychological:** Refers to brain processes and behaviors relating to mental and behavioral functions
>
> **Neurotoxic:** An agent which adversely acts on nerve cells
>
> **Toxicant:** A chemical compound introduced into the environment by human activity that has an affect on organisms

References

Agency for Toxic Substances and Disease Registry (ATSDR). Toxicological Profile for Lead, Atlanta: US Department of Health and Human Services; 2005.

Agency for Toxic Substances and Disease Registry (ATSDR). Toxicological Profile for Lead, Atlanta: US Department of Health and Human Services; 2007.

Atre AL, Shinde PR, Shinde SN, Wadia RS, Nanivadekar AA, Vaid SJ, Shinde RS. Am J Neuroradiol. 2006;27:902–3.

Baghurst PA, McMichael AJ, Tong S, Wigg NR, Vimpani GV, Robertson EF. Epidemiology. 1995;6:104–9.

Ballew C, Bowman B. Nutr Rev. 2001;59:71–9.

Barbosa F, Jr., Fillion M, Lemire M, Passos CJ, Rodrigues JL, Philibert A, Guimaraes JR, Mergler D. Environ Res. 2009;109:594–9.

Bellinger D, Hu H, Titlebaum L, Needleman HL. Arch Environ Health. 1994;49:98–105.

Bielarczyk H, Tian X, Suszkiw JB. Brain Res. 1996;708:108–15.

Bourgoin BP, Evans DR, Cornett JR, Lingard SM, Quattrone AJ. Am J Public Health. 1993;83:1155–60.

Braun JM, Kahn RS, Froehlich T, Auinger P, Lanphear BP. Environ Health Persp. 2006;114:1904–9.

Bryant SD. J Toxicol Clin Toxicol. 2004;42:287–94.

Byers RK, Lord EE. AMA Am J Dis Child. 1943;66:471–94.

Canfield RL, Gendle MH, Cory-Slechta DA. Dev Neuropsychol. 2004;26:513–40.

Canfield RL, Henderson CR, Jr., Cory-Slechta DA, Cox C, Jusko TA, Lanphear BP. New Engl J Med. 2003a;348:1517–26.

Canfield RL, Kreher DA, Cornwell C, Henderson CR, Jr. Child Neuropsychol. 2003b;9:35–53.

Cecil KM, Brubaker CJ, Adler CM, Dietrich KN, Altaye M, Egelhoff JC, Wessel S, Elangovan I, Hornung R, Jarvis K, Lanphear BP. PLoS Med. 2008;5:e112.

Cory-Slechta DA. Annu Rev Pharmacol Toxicol. 1995;35:391–415.

Cory-Slechta DA. Child Neuropsychol. 2003;9:54–75.

CT. Ethnic and Ayurvedics Products Containing Lead. Connecticut: Department of Public Health; 2009. Available at http://www.ct.gov/dph/lib/dph/environmental_health/lead/pdf/Ethinc-Ayurvedics_Products.pdf.

Dietrich KN, Berger OG, Succop PA. Pediatrics. 1993;91:301–7.

Dolan SP, Nortrup DA, Bolger PM, Capar SG. J Agric Food Chem. 2003;51:1307–12.

Edwards M, Triantafyllidou S, Best D. Environ Sci Technol. 2009;43:1618–23.

EU SCOOP. Assessment of the Dietary Exposure to Arsenic, Cadmium, Lead and Mercury of the Population of the EU Member States. Reports on Task for Scientific Cooperation. Report of Experts Participating in Task 3.2.11. Directorate-General Health and Consumer Protection. European Commission, Brussels. 2004. Available at http://ec.europa.eu/food/food/chemicalsafety/contaminants/scoop_3-2-11_heavy_metals_report_en.pdf.

Fergusson DM, Fergusson JE, Horwood LJ, Kinzett NG. J Child Psychol Psychiatry. 1988;29:811–24.

Freeman NC, Sheldon L, Jimenez M, Melnyk L, Pellizzari E, Berry M. J Expo Anal Environ Epidemiol. 2001;11:407–13.

Fulton M, Raab G, Thomson G, Laxen D, Hunter R, Hepburn W. Lancet. 1987;1:1221–6.

Garza A, Vega R, Soto E. Med Sci Monit. 2006;12:RA57–65.

Goyer RA. Environ Health Persp. 1990;89:101–5.

Gulson BL, Mahaffey KR, Jameson CW, Mizon KJ, Korsch MJ, Cameron MA, Eisman JA. J Lab Clin Med. 1998;131:324–9.

Jacobs DE, Clickner RP, Zhou JY, Viet SM, Marker DA, Rogers JW, Zeldin DC, Broene P, Friedman W. Environ Health Persp. 2002;110:A599–606.

Karri SK, Saper RB, Kales SN. Curr Drug Saf. 2008;3:54–9.

Kauffman JF, Westenberger BJ, Robertson JD, Guthrie J, Jacobs A, Cummins SK. Regul Toxicol Pharmacol. 2007;48:128–34.

Kim M, Kim C, Song I. Food Addit Contam. 2003;20:149–53.

Lanphear BP, Hornung R, Ho M, Howard CR, Eberly S, Knauf K. J Pediatr. 2002;140:40–7.

Lanphear BP, Hornung R, Khoury J, Yolton K, Baghurst P, Bellinger DC, Canfield RL, Dietrich KN, Bornschein R, Greene T, Rothenberg SJ, Needleman HL, Schnaas L, Wasserman G, Graziano J, Roberts R. Environ Health Persp. 2005;113:894–9.

Levin R, Brown MJ, Kashtock ME, Jacobs DE, Whelan EA, Rodman J, Schock MR, Padilla A, Sinks T. Environ Health Persp. 2008;116:1285–93.

Lidsky TI, Schneider JS. Brain. 2003;126:5–19.

Mani J, Chaudhary N, Kanjalkar M, Shah PU. J Neurol Neurosurg PS. 1998;65:797.

Manton WI. Br J Ind Med. 1985;42:168–72.

Markovac J, Goldstein GW. Nature. 1988;334:71–3.

Markowitz ME, Sinnett M, Rosen JF. Pediatrics. 2004;113:e34–9.

Marti-Cid R, Llobet JM, Castell V, Domingo JL. Biol Trace Elem Res. 2008;125:120–32.

Mindak WR, Cheng J, Canas BJ, Bolger PM. J Agric Food Chem. 2008;56:6892–6.

Moschandreas DJ, Karuchit S, Berry MR, O'Rourke MK, Lo D, Lebowitz MD, Robertson G. J Expo Anal Environ Epidemiol. 2002;12:233–43.

Needleman H. Annu Rev Med. 2004;55:209–22.

Needleman HL, Gatsonis CA. JAMA. 1990;263:673–8.

Needleman HL, Gunnoe C, Leviton A, Reed R, Peresie H, Maher C, Barrett P. N Engl J Med. 1979;300:689–95.

NY. Imported herbal medicine products known to contain lead, mercury or arsenic. Department of Health and Mental Hygiene. The City of New York, 2009. Available at http://www.nyc.gov/html/doh/downloads/pdf/lead/lead-herb-almed.pdf.

Pocock SJ, Smith M, Baghurst P. BMJ. 1994;309:1189–97.

Rankin CW, Nriagu JO, Aggarwal JK, Arowolo TA, Adebayo K, Flegal AR. Environ Health Persp. 2005;113:1344–8.

Rice DC. Environ Health Persp. 1996;104 (Suppl 2):337–51.

Rico JA, Kordas K, Lopez P, Rosado JL, Vargas GG, Ronquillo D, Stoltzfus RJ. Pediatrics. 2006;117:e518–27.

Ris MD, Dietrich KN, Succop PA, Berger OG, Bornschein RL. J Int Neuropsychol Soc. 2004;10:261–70.

Ros C, Mwanri L. Asia Pac J Clin Nutr. 2003;12:388–95.

Ross EA, Szabo NJ, Tebbett IR. JAMA. 2000;284:1425–9.

Sathyanarayana S, Beaudet N, Omri K, Karr C. Ambul Pediatr. 2006;6:288–92.

Scelfo GM, Flegal AR. Environ Health Persp. 2000;108:309–13.

Schwartz J. Environ Res. 1994;65:42–55.

Silva PA, Hughes P, Williams S, Faed JM. J Child Psychol Psychiatry. 1988;29:43–52.

Thomson GO, Raab GM, Hepburn WS, Hunter R, Fulton M, Laxen DP. J Child Psychol Psychiatry. 1989;30: 515–28.

Tomsig JL, Suszkiw JB. J Neurochem. 1995;64:2667–73.

Toscano CD, Guilarte TR. Brain Res Brain Res Rev. 2005;49:529–54.

Trope I, Lopez-Villegas D, Cecil KM, Lenkinski RE. Pediatrics. 2001;107:1437–42.

UNEP. Draft final review of scientific information on lead. Geneva, Switzerland: United Nations Environment Programme, Chemicals Branch; 2008.

Wasserman GA, Musabegovic A, Liu X, Kline J, Factor-Litvak P, Graziano JH. J Pediatr. 2000;137:555–61.

Wasserman GA, Staghezza-Jaramillo B, Shrout P, Popovac D, Graziano J. Am J Public Health. 1998;88:481–6.

WHO. Evaluation of certain food additives and contaminants, Vol. 896. Geneva: WHO; 2000.

Winneke G, Brockhaus A, Ewers U, Kramer U, Neuf M. Neurotoxicol Teratol. 1990;12:553–9.

Yuan W, Holland SK, Cecil KM, Dietrich KN, Wessel SD, Altaye M, Hornung RW, Ris MD, Egelhoff JC, Lanphear BP. Pediatrics. 2006;118:971–7.

Chapter 175
Diet- and Mercury-induced Visual Loss

Cian E. Collins

Abbreviations

EPA   The Environmental Protection Agency
MR   Magnetic resonance
SCDS   The Seychelles Child Development Study
VEP   Visual evoked potential

175.1 Introduction

Mercury is a heavy metal emitted into the atmosphere from both natural (such as volcanoes) and human sources (power plants, mining, waste incineration etc.) (http://www.epa.gov/mercury).

Atmospheric mercury in rainwater enters lakes and oceans, where microbial activity converts inorganic mercury into organic methylmercury. Methylmercury is readily absorbed and actively transported into tissues. Thus, methylmercury bioaccumulates in aquatic food chains and concentrations are magnified through the food chain. Larger, longer-living predators (e.g. swordfish, shark) have higher tissue concentrations, while smaller or shorter-lived species (e.g. shellfish, salmon) have very low concentrations. (http://www.epa.gov/mercury/report.htm)

Our knowledge of the effects of methylmercury poisoning on a population is based on two well-known industrial accidents. Industrial pollution of Minamata Bay, Japan in the 1950s poisoned local fish stocks and when local people consumed these contaminated fish, they suffered extensive neurological damage including paraplegia, ataxia, paresthesias, confusion, and in some cases, death (Tsubaki and Takahashi 1986). Visual symptoms reported include sudden bilateral blindness, constricted visual fields, and poor night vision. Seed grain contaminated by mercury mistakenly made its way into the food chain in Iraq in the 1970s and caused similar acute and chronic effects (more than 6000 people hospitalized, 459 deaths, and extensive neurological defects). (Bakir et al. 1973)

C.E. Collins (✉)
Princess Alexandra Eye Pavilion, Chalmers Street, Edinburgh EH3 9HA
e-mail: collinscian@btinternet.com

175.2 Neurological Findings

In adult monkeys and humans, methylmercury exposure has been linked to constriction of the visual field and abnormal color vision (Korogi et al. 1994). Korogi et al performed MR imaging of the brains of patients with known Minamata disease. The visual cortex, the cerebellar vermis and hemispheres, and the postcentral cortex were significantly atrophic. MR also demonstrated lesions in the calcarine area, cerebellum, and postcentral gyri. Korogi et al later looked at the striate cortex in patients with known Minamata disease and visual field constriction. They found a correlation between the visual field defect and the extent of dilatation of the calcarine fissure. (Korogi et al. 1997).

Ventura et al (Ventura et al. 2004) have reported on electrophysiological findings in patients with a history of mercury intoxication. Full-field ERGs showed that scotopic, photopic, peripheral, and midperipheral retinal functions were affected, and the multifocal ERGs indicated that central retinal function was also significantly depressed.

Electrophysiological testing of workers exposed to mercury vapors found a significant reduction of Visual Evoked Potential (VEP) latency, especially for the N75. (Urban et al. 2003) Further work completed in 2003 identified greater color confusion, greater errors on color, testing and an increased frequency of type III dyschromatopsias (blue–yellow confusion axis) in comparison with the control group. Cavalleri et al (Cavalleri and Gobba 1998) studied a group of workers with high levels of urinary mercury and found a dose-related impairment of color discrimination. Following changes to their work practices, mercury levels 12 months later had fallen to one-tenth of the previous levels and their color vision had returned almost to normal.

Neurological recovery after removal of the source of mercury is variable. Color vision impairment as a result of occupational mercury exposure was noted to be irreversible in one large study (Feitosa-Santana et al. 2008). Mercury-exposed patients had significantly worse color discrimination ($p < 0.02$) than controls, as evaluated by the size of MacAdam's color discrimination ellipses and color discrimination thresholds along protan, deutan, and tritan confusion axes. These changes persisted and were unchanged three years later. Other symptoms such as peripheral neuropathies have been noted to persist with little improvement, even up to 30 years later, after prolonged occupational exposure to inorganic mercury(Letz et al. 2000)

175.3 Children and Mercury Exposure

Children with raised blood mercury concentrations have been studied for changes in visual function testing. Saint-amour et al (Saint-Amour et al. 2006), examining preschool Inuit children living in Nunavik Northern Quebec, reported similar reduced VEP latency to those found in mercury-exposed workers. Many seaside communities depend on fish as a major food source. A large study by Davidson et al. (1998) followed 711 mother and child pairs in the Seychelles over a 5-year period from pregnancy through childhood. Using 6 age-appropriate test of neurodevelopment, no adverse effect was found to be associated with a raised hair mercury level of 6.5 ppm (US average is quoted as 0.47–3.8 ppm).

175.4 Pregnancy and Mercury Exposure

Methylmercury crosses the placenta, and fetal exposure correlates with maternal exposure. Following the Minamata and Iranian disasters, marked neurodevelopmental abnormalities were found in children exposed in-utero to very high levels of mercury. 'Gochfeld 2003' Very high doses

of methylmercury have been associated with mental retardation, poor motor function, ataxia, and seizures (Harada 1995).

In the mid-1980s, 2 large cohort studies were initiated: one in the Republic of Seychelles called the Seychelles Child Development Study (SCDS) (Van Wijngaarden et al. 2006) and the other in the Faeroe Islands. (Myers and Davidson 1998) In the Seychelles study, of a total of 46 primary end points, only one end point showed a possible adverse association with prenatal methylmercury exposure. The Faeroes study reported adverse associations between prenatal methylmercury exposure and tests of memory, attention, language, and visual–spatial perception measured at 7 years of age.

Seafood species are also rich dietary sources of selenium. Selenium may reduce tissue accumulation of mercury in fish and humans. (Seppanen et al. 2000) The protective effect of selenium may partly account for conflicting results of studies of mercury exposure and neurodevelopmental indexes in children. (Raymond and Ralston 2004)

175.5 Chronic Diet-related Exposure

We recently published an unusual case of diet-related mercury poisoning resulting in visual loss in a 36-year-old man of Caribbean origin living in the UK. (Saldana et al. 2006) His unexplained neurological symptoms (peripheral neuropathies, reduced visual acuity, central scotomas) were eventually linked to his raised blood mercury levels at 13.9 µg/l. The Environmental Protection Agency (EPA) quotes the US average blood mercury to be 1.3 µg/l (http://www.epa.gov/waterscience/fishadvice/advice.html). He underwent electrophysiological testing and multifocal visual evoked potential showed almost abolition of the central responses in both eyes. Multifocal ERG also showed mild reduced amplitudes and delayed responses.

His liking for imported Caribbean fish known to be high in mercury levels (3 or 4 red snapper fish, every day) was identified as the likely source and his change in diet has to date produced little improvement.

A previously published case-report highlights a 53 year-old woman with similar dietary exposure. She had been eating fresh fish between 6 and 12 times per week for more than 10 years and ate swordfish at least twice a week. Her hair mercury levels measured 67.8 ppm (US average is quoted as 0.47–3.8 ppm). She initially presented to her doctor with skin erythema, and later developed stomatitis, headaches, and tinnitus. (Risher John 2004) No further details were provided as to her progress after reducing exposure to mercury.

175.6 Applications to Other Areas of Health and Disease

The EPA states the reference dose, (ie the allowable upper limit of daily intake) for methylmercury of 0.1 ug/kg per day, which is 50 µg/wk for a 70-kg woman. This was calculated from the lower 95% confidence limit at which gestational exposure to mercury may produce abnormal neurological test scores, multiplied by a 10-fold uncertainty factor. The EPA also has published a focused advisory for women of childbearing age, nursing mothers, and young children. (http://www.epa.gov/waterscience/fishadvice/advice.html)

The advisory specifically advises such individuals to avoid shark, swordfish, golden bass, and king mackerel (each containing >50 µg methylmercury per serving); to eat up to 12 oz/wk (two average meals) of a variety of fish and shellfish lower in mercury; and to consult local advisories for locally caught freshwater fish. However, a recent Lancet article showed mothers who consumed more than the US recommendations (340 g or three portions per week) had children who scored better on tests of fine motor, communication, and social skills. (Myers and Davidson 2007)

A large review published in JAMA highlighted the benefits of regular fish consumption (1–2 servings per week of oily fish) in adults (Mozaffarian and Rimm 2006). It identified the reduction in risk of coronary death by 36% and total mortality by 17%.

Summary

- Many studies have tried to identify whether the known benefits of a diet rich in seafood are outweighed by the dangers posed by methyl mercury.
- Large studies on childhood neurodevelopment in communities with a high rate of fish consumption show conflicting results depending on the type of neurological tests used.
- Overall, it is felt that any adverse effects of methylmercury are likely to be minimal alongside the known nutritional advantages of fish oils and omega-3 in a child's neurodevelopment.
- Fish consumption in adults has been shown to confer significant cardiovascular health benefits. Studies suggest people may be avoiding fish consumption due to the risks of methylmercury toxicity and may miss out on the known health benefits of fish consumption.
- Visual changes associated with mercury exposure depend on the duration and degree of exposure.
- Toxic effects on the brain and optic pathways are unfortunately likely to be irreversible.
- Diet-related visual loss is extremely rare and is not a risk to people who keep within the common-sense guidelines

---

Definitions

Inorganic mercury: A heavy metal found in the environment, which is nontoxic and cannot be absorbed in this form

Methylmercury: When mercury is converted into this organic form it can be absorbed and accumulated in tissues resulting in toxicity

Minamata disease: Called after the Minamata area in Japan where it was first described, it is a broad spectrum of neurological disorders caused by exposure to high doses of methylmercury.

Neurodevelopmental testing: A complex series of tests that compare many neurological functions (such as memory, language, motor function and spatial awareness) in subjects with expected age-matched levels in a control population.

Electrophysiological testing: Visual stimuli are introduced to the patient and the electrophysiological responses produced by the photoreceptors are measured by contact skin probes around the eyes. These findings are compared to expected average responses in a control population.

Key facts on mercury exposure and vision

1. Most significant cases of visual loss are as a result of industrial accidents, where there was exposure to very high levels of methylmercury.
2. Most people will only be exposed to methylmercury in any significant quantities if they consume seafood.
3. Certain fish (e.g. those higher up the food chain) will have considerably higher levels of methyl mercury than those short-lived species
4. Recommended guidelines suggest 1–2 servings of oily fish will provide most people with the beneficial effects without being at risk of methylmercury toxicity.

References

Bakir F, et al. Methylmercury poisoning in Iraq. Science. 1973;181:230–41.

Cavalleri A, Gobba F. Color vision impairment in workers exposed to neurotoxic chemicals fabriziomaria Gobba1, Alessandro Cavalleri. Neurotoxicology. 1998;24(2003):693–702.

Davidson G, et al. Effects of prenatal and postnatal methylmercury exposure from fish consumption on neurodevelopment: outcomes at 66 months of age in the Seychelles Child Development Study. JAMA. Feb 17 1998;280(8):701–7.

Feitosa-Santana C, et al. Irreversible color vision losses in patients with chronic mercury vapor intoxication. Vis Neurosci. May-Jun 2008;25(3):487–91.

Gochfeld M. Cases of mercury exposure, bioavailability and absorption. Ecotoxicol Environ Saf. 2003;56:174–9.

Harada M. Minamata disease: methylmercury poisoning in Japan caused by environmental pollution. Crit Rev Toxicol. 1995;25(1):1–24, Review.

Korogi Y, Takahashi M, Shinzato J, Okajima T. Am J Neuroradiol. Sep 1994;15(8):1575–8.

Korogi Y, Takahashi M, Hirai T, Ikushima I, Kitajima M, Sugahara T, Shigematsu Y, Okajima T, Mukuno K. Representation of the visual field in the striate cortex: comparison of MR findings with visual field deficits in organic mercury poisoning (Minamata disease). Am J Neuroradiol. Jun-Jul 1997;18(6):1127–30.

Letz R, Gerr F, Cragle D, et al. Residual neurologic deficits 30 years after occupational exposure to elemental mercury. Neurotoxicology. 2000;21:459–74.

Mozaffarian D, Rimm EB. Fish intake, contaminants, and human health: evaluating the risks and the benefits. JAMA. Oct 18 2006;296(15):1885–99.

Myers GJ, Davidson PW. Prenatal methylmercury exposure and children: neurologic, developmental, and behavioral research. Environ Health Perspect. 1998 Jun;106(Suppl 3):841–7, Review.

Myers GJ, Davidson PW. Maternal fish consumption benefits children's development. Lancet. Feb 17 2007;369(9561):537–8.

Raymond LJ, Ralston NV. Mercury: selenium interactions and health implications. Seychelles Med Dent J. 2004;7:72–7.

Risher JF. Too much of a good thing (fish): methylmercury case study. J Environ Health. Jul/Aug 2004;67(1):9–14.

Saint-Amour D, et al. Alterations of visual evoked potentials in preschool Inuit children exposed to methylmercury and polychlorinated biphenyls from a marine diet. Neurotoxicology. 2006;27:567–78.

Saldana M, Collins C, Gale R, Backhouse O. Diet-related mercury poisoning resulting in visual loss. Br J Ophthalmol. 2006;90: 1432–4.

Seppanen K, Kantola M, Laatikainen R, et al. Effect of supplementation with organic selenium on mercury status as measured by mercury in pubic hair. J Trace Elem Med Biol. 2000;14:84–87.

Tsubaki T, Takahashi H. (editors) Recent advances in minimata disease studies: methylmercury poisoning in Minimata and Nigiita, Japan. Tokyo, Japan; 1986.

Urban P, Gobba F, Nerudova J, Lukas E, Cabelkova Z, Cikrt M. Color discrimination impairment in workers exposed to mercury vapor. Neurotoxicology. 2003 Aug;24(4–5):711–6.

US Environmental Protection Agency. Controlling power plant emissions: emissions progress. Washington: US Environmental Protection Agency; 2009a. http://www.epa.gov/mercury.

US Environmental Protection Agency. Mercury Study report to Congress. Washington: US Environmental Protection Agency; 2009b. http://www.epa.gov/mercury/report.htm.

US Environmental Protection Agency. What you need to know about mercury in fish and shellfish. Washington: US Environmental Protection Agency; 2009c. http://www.epa.gov/waterscience/fishadvice/advice.html.

Van Wijngaarden E, Beck C, Shamlaye CF, Cernichiari E, Davidson PW, Myers GJ, Clarkson TW. Benchmark concentrations for methyl mercury obtained from the 9-year follow-up of the Seychelles Child Development Study. Neurotoxicology. 2006 Sep;27(5):702–9.

Ventura DF, Costa MT, Costa MF, et al. Multifocal and full field electroretinogram changes associated with colour-vision loss in mercury vapour exposure. Visual Neurosci. 2004;21:421–9.

Chapter 176
Soy, Tofu and Brain Function in the Elderly

Amina Yesufu-Udechuku, Tri Budi W. Rahardjo, and Eef Hogervorst

Abbreviations

AD	Alzheimer's disease
Aβ	Amyloid beta
CASI	Cognitive abilities screening instrument
CI	Cognitive impairment
CVFT	Category verbal fluency test
DHEAS	Dehydroepiandrosterone sulphate
E	Estrogen
E2	17 β-Estradiol
ER	Estrogen receptor
ERα	Estrogen receptor alpha
ERβ	Estrogen receptor beta
FDA	Food and Drug Administration
FFQ	Food Frequency Questionnaire
HAAS	Honolulu Asia Aging Study
LDH	Lactate De-Hydrogenase
MMSE	Mini Mental Status Examination
MRI	Magnetic Resonance Imaging
P	Progesterone
RCT	Randomized Controlled Trials
ROS	Reactive Oxygen Species
SOPHIA	Soy and Postmenopausal Health In Aging Study
SWAN	Study of Women's Health Across the Nation
UK	United Kingdom
USA	United States of America
VaD	Vascular dementia

E. Hogervorst (✉)
School of Sport, Exercise and Health Sciences, Loughborough University,
Ashby Road, Loughborough, Leicestershire, United Kingdom
e-mail: E.Hogervorst@lboro.ac.uk

176.1 Introduction

Dementia is characterized by severe cognitive decline, which impacts on daily living (American Psychiatric Association 1994). Its most common form is Alzheimer's disease (AD). Dementia is on the increase with an increasing aging population, particularly in developing countries. The human and economic costs of dementia are high and it is therefore important that cheap and easily adaptable preventive measures are identified. Given its biological plausibility (see Sect. 176.8), eating soy could be a potential preventive measure against cognitive impairment. This chapter describes the effect that phytoestrogens have on the brain and cognitive function in the elderly. The incidence of AD is lower in East Asian countries than in Western populations (see Sect. 176.9). Furthermore, East Asian populations consume significantly more soy in their daily diets. It has thus been hypothesized that these observed differences in AD prevalence can be attributed, in part, to the isoflavone-rich diets in Japan and China compared to the USA and Europe and the potential positive effects that isoflavones can have on the brain. However, other healthy lifestyle choices (e.g., consumption of fruit and vegetables, less alcohol consumption, more exercise and a lower body mass index, etc.) could also attribute to lower AD risk in these countries. In this chapter, we review the biochemistry of phytoestrogen, the food it occurs in and its effect on the brain using data derived from animal and cell culture studies, as well as data from observational and treatment studies in humans.

176.2 Soy, Tofu and Phytoestrogens

The soybean is an important part of the diet in East Asian countries, with increasing popularity in Western countries (see Table 176.1). Soy is used in the production of a number of food products, with the most well known being tofu (see Table 176.2). Soy foods contain varying quantities of phytoestrogens.

Phytoestrogens are naturally occurring polyphenolic molecules found in plants. Phytoestrogens are found in abundance in the soybean (and soybean-based products such as tofu) as well as other fruits, vegetables, grains, legumes and clover (Kurzer and Xu 1997). Phytoestrogens, or plant hormones, are very similar to estrogens (E) in their physiochemical and physiological properties (Murkies et al. 1998; Setchell 1998; Kurzer and Xu 1997). The Food Standards Agency (FSA) defined phytoestrogens as 'any plant substance or metabolite that induces biological responses in

Table 176.1 Key facts of soy

1. The soybean is an oilseed that is an important source of protein and vegetable oil and contains omega-3 fatty acids, alpha-Linolenic acid, and is the richest source of isoflavones.
2. Oil (20%) and protein (40%) account for approximately 60% of the weight of the soybean, with the remainder consisting of carbohydrate (35%) and approximately 5% ash (Mohamed and Xu 2003).
3. The majority of the compounds in the soybean are heat-stable, which makes the soybean suitable for high-temperature cooking to produce tofu, soymilk and textured vegetable protein (Mohamed and Xu 2003).
4. Soy-based foods have been eaten in Asian societies for over 1,000 years and are an important part of everyday diet (Murkies et al. 1998).
5. Soy is used to make foods such as tofu, tempe miso, natto as well as other products such as soy milk and soy sauce (Murkies et al. 1998).
6. Soy consumption is substantially higher in Asian societies than in Western countries with populations in Japan, Taiwan and Korea consuming approximately 20–150 mg/day from a variety of soy-based foods, compared to a much lower (approximately 1–3 mg/day) intake in Western populations (Murkies et al. 1998)

This table shows the key facts about soy which includes its composition, origins and uses in diet

Table 176.2 Key facts of Tofu

1. Tofu is of Chinese origin, although the exact origins and discovery have not been confirmed.
2. Tofu is made by coagulating soy milk from the soy-bean curd and using salt or acid coagulants. This is then formed into blocks and processed in a variety of ways to form different types and textures.
3. Tofu is relatively bland in taste and therefore picks up flavours easily. Because of this, it is used in Asian cooking in a wide variety of ways including soups, stews, stir-fries, eaten raw or stuffed with other fillings.
4. Although it originated from China, the spread of Buddhism (which places high importance on proteins and has a strict vegetarian diet) meant that tofu was then introduced into the diet in Korea, Japan, and other parts of East Asia, such as Indonesia, in the late eighth century.
5. In Western countries, tofu was not well known until the middle of the twentieth century with increasing popularity and adoption of vegetarian diets. It is not eaten widely but is popular amongst vegetarians, and promoted as a 'healthy superfood'.
6. Tofu contains isoflavones (a type of phytoestrogen) primarily in the aglycone form which previous research has shown has effects on the human brain similar to that of estrogen (a natural sex hormone).
7. The effects of consuming tofu on brain function are not fully known with studies reporting both positive and negative effects.
8. The effects of tofu consumption on the brain have been attributed to the high quantities of isoflavones (a type of phytoestrogen which mimics the effects of natural estrogen) as well as possibly other chemicals (e.g., formaldehyde) added in the processing of tofu which may be toxic to the brain.
9. It is possible that age, gender, quantity consumed and habitual intake may influence if tofu consumption has a protective or negative effect on cognitive function.

This table lists the key facts about tofu explaining its origins, the differences between populations in its consumption and its effects on cognitive function

vertebrates and can mimic or modulate the actions of endogenous, usually by binding to estrogen receptors' (FSA 2002). Es are naturally occurring hormones that promote secondary female sex characteristics and fertility. However, their role in also maintaining cognition in older women and men is now disputed, despite basic sciences data supporting their potential protective effects on the brain (see book edited by Hogervorst et al., 2009). The role of phytoestrogens in protecting the brain is less well investigated and this chapter aims to review the existing evidence available.

176.3 Phytoestrogen Classification

Phytoestrogens can be classified into three main categories; lignans, coumestans, and isoflavones. The most potent estrogenic aglycone isoflavones, and those mostly discussed in the current chapter, are daidzein and genistein (Fig, 176.1).

Isoflavones resemble estrogens in their heterocyclic phenol structure. The location of the hydroxyl groups allows binding to the estrogen receptor (ER) protein, and the A and C rings of isoflavones are similar to the A and B rings of 17β-estradiol (E2), the most potent E (Ganora 2008).

176.4 Application to Other Areas of Health and Disease

Before we discuss the possible effects of isoflavones on the brain and cognition, it may be important to highlight other more researched benefits (or potential increased risks) of phytoestrogen consumption. East Asians (who show high consumption of soy products) and Western populations show different prevalence rates for certain health conditions (Adlercreutz 1990), which could indirectly impact on cognitive health and risk of secondary dementias (APA 1994). Table 176.3 briefly describes some of these areas of research findings.
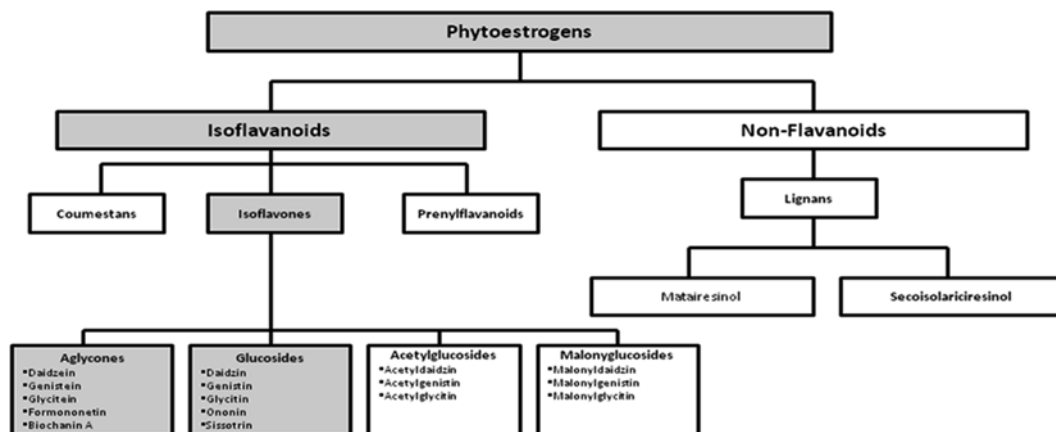
Fig. 176.1 Classification of phytoestrogens. This figure shows the classification of phytoestrogens. This chapter focuses on the isoflavones aglycones and glucosides
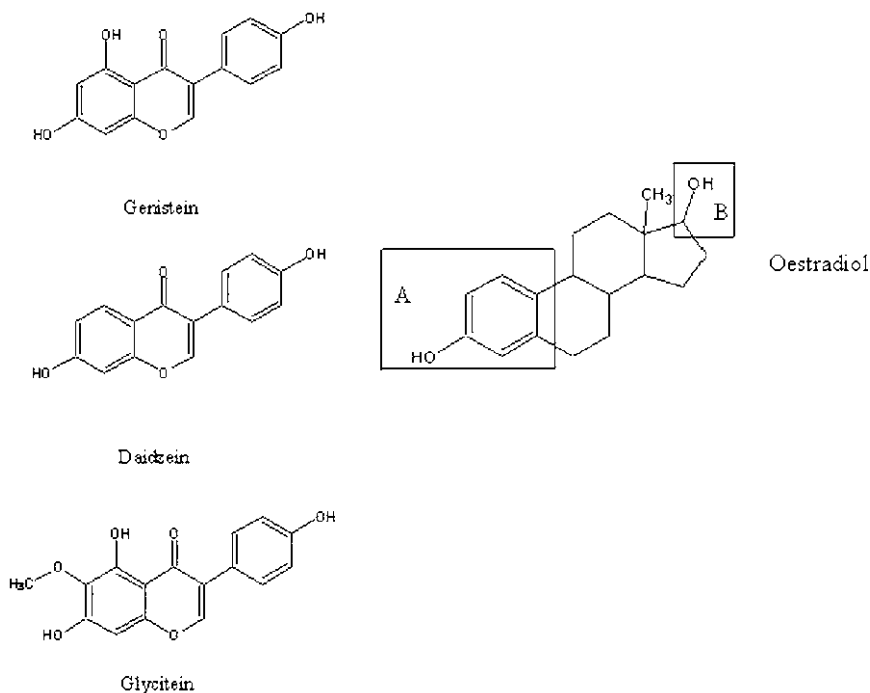
Fig. 176.2 Chemical similarities of aglycone isoflavones and oestradiol. Figure shows the structure of 17β-oestradiol, as well as the aglycone isoflavones genistein, daidzein, and glycitein. Aglycone isoflavone structures possess the phenolic (A) and hydroxyl (B) moieties also seen in estradiol, with a similar distance between the two groups (FSA 2002)

Table 176.3 Application to other areas of health and disease

- Asian population having a lower prevalence and incidence of some cancers, e.g., breast cancer (Wu et al. 2008) and prostate cancer (Dhom 1991).
- High soy intake has been associated with lower incidence of breast cancer (Wu et al. 2008) and prostate cancer (Coward et al. 1993).
- Concern has recently arisen from the reports of in vitro and animal studies finding an *increased* risk of breast cancer with soy isoflavones (Ju et al. 2006).
- Geographic differences in cardiovascular health have also been positively linked to soy intake (Azadbakht et al. 2007), as has a low prevalence of osteoporosis (Chiechi et al. 2002), and some menopausal symptoms (Maskarinec 2003).
- However, most research into the health effects of phytoestrogens has been on the basis of animal models and in vitro cell culture studies with only limited clinical assessments (see Knight and Eden 1996).

This table lists some other areas of health and disease which have shown cross-cultural variation and been linked to soy intake

176.5 Biological Mechanisms Explaining Neuroprotective Effects of Phytoestrogens

A number of studies have shown neuroprotective effects of isoflavones on various biological mechanisms. For full reviews see Murkies et al. (1998); Setchell (1998); and Adlercreutz and Mazur (1997). Isoflavones (and coumestans) thus have the ability to bind to the ERs in the mammalian body, but with less affinity than E2. They have shown greater binding to the ER-beta (ERβ) than the ER-alpha (ERα) receptor sites and can moderately interfere with the endogenous E-responsive signalling (Fitzpatrick 2003). On the other hand, genistein initiates greater gene transcription of ERα compared to ERβ, and also has the ability to bind to the progesterone (P) and androgen receptors (Fitzpatrick 2003) In postmenopausal women, who have very low levels of endogenous estrogens, phytoestrogens have greater potential to bind to ER than in premenopausal women, whose endogenous estrogens levels are much higher which renders greater competition for ER sites (Kuiper et al. 1998). Phytoestrogens can thus behave as estrogenic antagonists in environments with high levels of estrogens (e.g., during the ovulatory phase in premenopausal women), but can act as estrogenic agonists in low estrogenic environments (e.g., in postmenopausal women) (see Boettger-Tong et al. 1998; Murkies et al. 1998).

Although a great deal of attention has been paid to effects of phytoestrogens on peripheral systems, research is limited concerning the influence of phytoestrogens on the nervous system and cognitive function (Linford and Dorsa 2002; Halbreich and Kahn 2000) Phytoestrogens can directly protect the brain and act upon mechanisms thought to be implicated in Alzheimer's disease (AD, the most common form of dementia), such as the formation of tangles by tau protein phosphorylation and accumulation of the toxic amyloid-beta (Aβ) in plaques (Kim 2000). Phytoestrogens have been found to demonstrate a neuroprotective effect by attenuating tau protein phosphorylations (Kim et al. 2000), and by protecting cells against Aβ-induced apoptosis (self-programmed cell death) (Bang et al. 2004). The hippocampus is thought to be implicated in early AD (Reitz et al. 2009). Phytoestrogens have been found to regulate choline acetyltransferase, nerve growth factor, and brain-derived neurotrophic factor in the hippocampus, and also in the frontal cortex of female rats (Pan et al. 1999), which also is thought to play an important role in cognitive aging (see, e.g., Isingrini and Taconnat 2008).

Genistein and daidzein have also been found to protect hippocampal and cortical neurons against several forms of induced neurotoxicity (Occhiuto et al. 2008; Sonee et al. 2004). In an in vivo rat model study (Zeng et al. 2004), genistein reversed Abeta25–35-induced apoptosis and related cell pathology. Abeta25–35-induced apoptosis is associated with an increase in intracellular levels of

free Ca^{2+}, the accumulation of reactive oxygen species (ROS), and the activation of caspase-3 and is further characterized by loss of cell viability and neuronal DNA fragmentation. Trieu et al. (1999) reported that cerebral lesions in mice caused by singlet-oxygen-induced cerebral strokes were reduced by 44% with genistein treatment compared to controls, supporting the potential antioxidant effects of soy isoflavones. Genistein was also found to increase the activity of anti-oxidant enzymes (Lee et al. 2005) and has earlier also been shown to have antioxidant effects on neurons exposed to free radical damage (Lee et al. 2005).

We must note that although these studies distinctly show neuroprotective qualities of genistein, other studies have reported that genistein can also induce apoptosis and damage in neurons. The association between phytoestrogens and brain function may therefore not be linear (e.g., more is always better). For example, Choi and Lee (2004) reported that rats consuming a very large dose of genistein (20 mg/day) showed an increase in lactate dehydrogenase (LDH), a marker of neuronal damage, in brain tissue, which was not the case for rats on low genistein regimes (2 mg/day). DNA fragmentation was seen in both treatment groups. It must be noted that these amounts of genistein given to rats in these studies would far exceed the normal amount of isoflavones that are given to human participants in treatment trials or eaten in a normal daily diet. For example, assuming a rat weighed approximately 300 mg and the average human weighs approximately 60 kg, a rat being given a dose of 2 mg/day is then the equivalent of giving a human 1,200 g/day of genistein. As we have previously discussed, even in populations where isoflavone consumption is very high (e.g. 100 mg/day = 0.1 g/day), this toxic dosage would equate to over 12,000 times the quantity of normal daily consumption.

176.6 Different Soy Foods and their Composition

Many databases have been developed to list the isoflavone content of soy foods (Beecher et al. 2000; Horn-Ross et al. 2000). A summary is given in Table 176.4. Soy is the richest source of genistein, is abundant in daidzein, and is the only source of glycitein (Zhao and Brinton 2007). The estrogenic effect of soy has been attributed to genistein and daidzein, as well as the daidzein metabolite, equol. Equol has high estrogenic activity. However, there are individual (genetic) and cross-cultural differences in the ability (or lack of it) to produce equol in the intestines (see discussion). The soy-bean is cultivated and processed in different ways to make products from its different components, and this can have a significant effect on the pharmacokinetics and pharmacodynamics of isoflavones. For example, consumption of tempe (which contains approximately 50% aglycone) was found to result in higher serum peak levels of genistein than 15% aglycone textured vegetable protein. However, soymilk (which also contains ≈ 15% aglycone) was absorbed quicker and reached peak plasma levels faster than both tempe and textured vegetable protein (Cassidy et al. 2006). Alcohol extraction and acid precipitation reduces the isoflavone content of soy protein and the soybean can be altered in its levels of fibre, fat, phytic acid and saponin content by the processing methods used to make the end-product (Oakenfull 2001; Potter 1995)

176.7 Safety and Availability of Dietary Phytoestrogens

Currently, dietary phytoestrogens are a billion-dollar business at least partly accounted for by the fact that four out of five middle-aged women use herbal remedies and dietary supplements, with or without prescription drugs, on a regular basis in order to treat health problems associated with aging. Isoflavones are readily available, either over the counter, or as ingredients in (fortified) foods (Bloedon et al. 2002; Setchell et al. 2001).

Table 176.4   Soy food isoflavone content

Product	Aglycone (microgram per gram)			
	Daidzein	Genistein	Glycitein	Total
Traditional soy foods				
Roasted soybeans ♦	563	869	193	1625
Tofu ♦	146	162	29	337
Tempe ♦	273	320	32	625
Miso (soy bean paste) ♦	272	245	77	593
Natto (fermented soybeans)) ◊				
Soy milk (liquid from boiled pureed soybeans) ◊	50	63	ns	ns
Soy Sauce◊	2	6	ns	ns
Second-generation soy foods				
Soy hotdog ♦	34	82	34	150
Soy bacon ♦	28	69	24	122
Tempe burger ♦	64	196	30	289
Flat noodle ♦	9	37	39	85
Soy parmesan ♦	15	8	41	65
Foods containing soy flour or protein and other foods				
White bread ◊	7	8	ns	ns
Wholegrain bread ◊	2	1	ns	ns
Canned tuna ◊	4	7	ns	ns
Doughnuts ◊	20	32	ns	ns
Pancakes ◊	13	14	ns	ns
Soy/"veggie" Burgers ◊	30	20	ns	ns
Coffee ◊	0.5	tr	ns	ns
"Power"-type bars ◊	18	33	ns	ns
Pizza ◊	2	2	ns	ns

This table shows the quantities of the aglycones genistein, daidzein and glycitein, in the most common soy-based foods. Please note: ns = not stated; tr = trace defined as ≤25 μg/100g (the authors minimum level of reliable detection); ♦ = data sourced from Wang and Murphy (1994); ◊ = data sourced from Horn-Ross et al. (2000)

The US Food and Drug Administration (FDA) recently allowed the food industry to state that soy protein can protect and promote a healthy heart, focusing on its isoflavone and protein content (US Food and Drug Administration 1999). This has resulted in a flooding of the food markets with soy products and supplements, as well as an expected further increase in the sale and use of these compounds. This is worrying as the full implications of soy manufacturing processes or efficacy are not fully understood. In fact, the scarce and conflicting information regarding the metabolism and bioavailability of phytoestrogens in itself should be enough to cause concern over its promotion as a 'health food'. Furthermore, a trend towards manufactured isoflavone supplements, as opposed to isoflavone in a more natural form through isoflavone-rich foods, may have further implications for health.

176.8   East Versus West: Cultural Differences in Soy Consumption and Phytoestrogen Levels

Soy-based foods have been eaten in Asian societies for over 1,000 years and are an important part of everyday diet, thus their consumption is much higher than in Western countries. Populations in Japan, China, Taiwan and Korea are estimated to consume approximately 20–150 mg/day of isoflavones,

Table 176.5 Eastern versus Western intake of isoflavones

Country	Study	Mean intake (mg/day)		
		Isoflavones	Daidzein	Genistein
Japan	Kimira et al. (1998)	39.46	4.62	52.12
Japan	Arai et al. (2000)	NR	16.4	30.1
Finland	Valsta et al. (2003)	0.79	NR	NR
USA	Horn-Ross et al. (2000)	NR	1.28	1.48
Holland	Boker et al. (2002)	NR	0.15	0.16
USA	de Kleijn et al. (2001)	1.54	0.39	0.7

NR not reported
Table gives an example of average isoflavone intake in some Eastern and Western countries as published by a selection of studies

usually from a variety of soy food sources (Murkies et al. 1998), compared to the average American who consumes only 1–3 mg/day (Barnes et al. 1995). Table 176.5 displays findings from various studies which assessed Eastern and Western soy consumption.

In Japan, soy foods and supplements are heavily promoted as "natural" sources of Es with beneficial effects for women and as having a positive influence on healthy aging, therefore soy intake in that part of the world is especially high. The most common types of soy foods eaten in Japan are tofu, miso, natto (Arai et al. 2000), and fried tofu (Wakai et al. 1999). Among the Chinese, Chen et al. (1999) found that the majority (96.7%) of women of a Shanghai sample (*n* = 60) ate soy foods at least once a week (median intake of soy foods = 100.6 g/day). Although many of these samples were small in size (less than 100 participants), the same finding was reported across studies, associating high phytoestrogen intake with East Asian communities. For instance, in our Indonesian study (*n* = 719) virtually everyone ate tofu and tempe (65% of the sample ate tofu at least once a day and 67% ate tempe at least once a day), (Hogervorst 2008).

In the West, most of the phytoestrogens consumed are lignans (de Kleijn et al. 2001; Horn-Ross et al. 2000), whereas isoflavone intake in Western countries is low compared to that in East Asian countries. Isoflavones are derived mainly from second-generation soy foods such as tofu, doughnuts, soy milk, white bread, pancakes or waffles, canned tuna and coffee (Horn-Ross et al. 2000).

176.9 Cross-cultural Dementia Prevalence

If consumption of phytoestrogens is different and if soy can affect the brain, one would expect differences in dementia prevalence in East Asian countries (such as Japan and China) and Western populations (such as the USA or Europe) in the prevalence of cognitive disorders and dementia. This is indeed found to be the case. This difference is not found for all-cause dementia, which seems to be similar across Japan, China and the West (Zhao and Brinton 2007), but specifically for the most common subtypes of dementia, AD and Vascular Dementia (VaD) (Zhao and Brinton 2007). AD rates are lower in Japan and China, and its prevalence is ~2.5 times higher in Western populations. Whereas AD is more prevalent in Western societies than VaD (~2.2 fold), AD and VaD rates in Japan and China are more similar (for an excellent review on this topic see Zhao and Brinton 2007).

The difference between East and West in AD prevalence has thus been hypothesized to be attributed to the isoflavone-rich diets in Japan and China compared to the USA and Europe and

the potential positive effects that isoflavones can have on the brain. However, other healthy lifestyles (e.g., consumption of fruit and vegetables, less alcohol consumption, more exercise and a lower body mass index, etc.) could also attribute to lower AD risks in these countries. Studies investigating the association between soy and cognition in the elderly in more detail are described below.

176.10 Observational Studies of Soy Consumption and Cognitive Function

Observational studies assessing the relationship between isoflavone and cognitive function have been few and far between, and have also reported conflicting results. These studies have investigated the relationship between phytoestrogen consumption and various aspects of cognitive function in Western countries with postmenopausal women of non-East Asian descent, older men and postmenopausal women of East Asian descent (Rice et al. 2000; White et al. 2000) as well as multi-ethnic populations younger than 50 years of age (Ostatníková et al. 2007; Huang et al. 2006; Celec et al. 2005).

176.10.1 Observational Studies in Non-Asian Western Populations

Kreijkamp-Kaspers et al. (2007) assessed the effects of habitual intake of low quantities of phytoestrogens through diet on cognition. The sample consisted of 301 Dutch postmenopausal women aged between 60 and 75 years. These were volunteers from an ongoing cohort study assessing nutrition and cancer, as well as a breast screening program, who had a wide range of phytoestrogen intake. A Food Frequency Questionnaire (FFQ) was utilized to compile information on consumption of food containing phytoestrogens. Furthermore, to evaluate approximate levels of phytoestrogens consumed, the researchers assigned a value to the various phytoestrogens (in mg per 100 g of food or drink). The foods were then divided into seven groups based on this phytoestrogen 'score' (see de Kleijn et al. 2001 for methods used), and a median phytoestrogen content was assigned to each group to avoid over- or underestimation of phytoestrogen consumption. In this sample, median intake per day of lignans ranged from 0.65 to 2.29 mg/day, whereas for isoflavones this was 0.18–14.64 mg/day, although the middle two quartiles were significantly lower than the highest (0.34 and 2.99 mg/day). The researchers reported no significant differences between the effects of various levels of isoflavone intake on cognitive tests of memory, processing speed, or executive functions. However, a significant association was found between high lignan intake and processing capacity and speed, as well as executive function.

In the same Dutch sample, Franco et al. (2005) investigated the effects of isoflavones and lignans of the levels found in a typical Western diet on cognitive performance using only the Mini Mental Status Examination (MMSE). However, in these analyses, the investigators were interested in differences between women who had experienced a longer (20–30 years) versus a shorter (8–12 years) period since menopause (postmenopausal time span). They also included natural menopause as a factor that might have affected the relationship between phytoestrogen intake and cognitive function. No significant association was found between isoflavone intake and cognitive function as measured by the MMSE. However, and more pronounced in women with longer postmenopausal time span, a significant association was found between higher lignan intake and better cognitive performance. The authors speculated that this stronger association in women with longer postmenopausal time span could be due to the older age, or other age-related mechanisms, which could have mediated the

relationship. However, it must be noted that mean isoflavone intake was very low (0.14 mg/day) in this sample and was substantially lower than those observed in Japanese and Chinese samples showing significant (negative) associations which are discussed below in 176.10.2.

176.10.2   Observational Studies in East-Asian Western Populations

Two large-scale epidemiological studies have assessed the relationship between phytoestrogen consumption, specifically tofu, and cognitive function, in Asian-Americans living in Western communities. These are the Honolulu Asia Ageing Study (HAAS) (White et al. 2000) and the Kame Project (Rice et al. 2000) although the latter has only been published as a peer-reviewed abstract, to our knowledge.

176.10.2.1   The Honolulu Asia Ageing Study

The largest study of the effect of phytoestrogen on cognitive function in both men and women has been the Honolulu Asia Ageing Study (HAAS), consisting of 3,734 Japanese-American participants, aged 70–90 years and living in Hawaii, USA (White et al. 2000). The investigators reported that (contrary to expectations based on its biological plausibility) high midlife soy consumption had a negative association with late life cognitive function. The study found that men aged 71 and above, as well as their wives, who had consumed tofu more than twice a week in midlife and in old age, had a higher risk of dementia and lower cognitive function, but also lower brain weight and more ventricular enlargement than those who consumed less tofu. For example, for men with the lowest tofu intake, the percentage of participants with cognitive impairment (CI) was identified as 4%, as compared to men with the highest tofu intake where 19% had CI. Also, in the low tofu intake group, low brain weight was seen in 12% of cases, compared to 40% of men in the highest tofu intake category. Data suggested that there may be a dose-dependent effect of tofu consumption, i.e., that increased tofu consumption was associated with poorer cognitive function.

The strength of the HAAS study lies in its' coverage of a wide time-span of dietary assessment (data were collected in two assessments, up to nine years apart). Also, some data were collected in midlife, approximately 20 years before cognitive evaluation and magnetic resonance imaging (MRI) scans. However, and as with studies using this methodology, it is unclear if tofu consumption itself was responsible for dementia risk, or whether high tofu intake was an indication of some other unfavourable exposure. For example, the men with high tofu intake, and hence a more traditional diet, were more likely to come from impoverished backgrounds and may have experienced more childhood deprivation which could be related to brain development and later life cognitive function (see also Whalley et al. 2000). In addition, a high-tofu diet could be an indication of a specific dietary pattern that may be harmful to the brain, but separating the individual elements of this diet in order to isolate the contributing factors may prove very difficult. Although these results are of great interest, they were limited, as relatively few subjects consumed very high levels of tofu and confidence intervals around the estimates of effect presented were wide, indicating little precision of results (Grodstein et al. 2000).

176.10.2.2   The Kame Project

The Kame Project (Rice et al. 2000) consisted of Japanese-American men ($n = 634$) and women ($n = 767$) living in Washington State, USA, who were aged 65 years and above. Cross-sectional results

showed an association between having a lower cognitive score, as measured by the Cognitive Abilities Screening Instrument (CASI, the same test was also used in the HAAS to identify CI), and high tofu consumption (>3 times a week) as opposed to moderate (1–2 times a week) or low consumption (<1 time a week). In stratified analyses, this negative association remained significant only for women who were hormone replacement users (but not for those who were not hormone users, elderly men or those who consumed moderate to low amounts of tofu). The investigators also found longitudinally (although no overall association was found between tofu consumption and 2 year change of CASI score), that those with modest tofu consumption showed the greatest improvements in CASI scores. These data suggest that there may be optimal levels of phytoestrogens, perhaps interacting with age, gender and E levels. It must be noted that in this and the HAAS study, the investigators did not assess total isoflavone exposure, but only estimated tofu intake. This may be problematic as the authors pointed out that tofu accounted for only approximately half of soy-based isoflavones consumed by this particular population.

176.10.3 Observational Studies in Premenopausal Women

Other observational studies have assessed the relationship between phytoestrogen consumption and cognitive function in premenopausal women. In the Study of Women's Health Across the Nation (SWAN) (Huang et al. 2006), a sub-group of 195 Japanese and 185 Chinese women who were living in the USA and were between 42 to 52 years of age were assessed for this relationship. Various tests of episodic memory, working memory and processing speed were used to assess cognitive function. The investigators found no association between genistein intake (as calculated from the FFQ) and cognitive function. The authors surmised that the effects might only be present in women who are in low-estrogenic states (i.e., postmenopausal women). Comparisons with the other studies mentioned above are difficult, as optimal genistein and daidzein levels were investigated using tertiles, rather than reported in weekly intake of tofu, as in the previous studies mentioned (Rice 2000; White 2000). Furthermore, although the participants were of Japanese and Chinese origin, with higher isoflavone intake than other Western non-Asian populations, mean genistein and daidzein intakes were still only 6.79 and 4.68 μg for Japanese women, and 3.53 and 1.74 μg for Chinese women. An intake of approximately 45,000 μg of isoflavones is needed to significantly affect follicular phase and menstrual cycle length in premenopausal women (Cassidy et al. 1995). Therefore, it is possible that the finding of no association in this study could in part be due to the levels of isoflavone not being sufficiently high enough to have an impact on cognitive function. This could also explain a lack of significant findings in the Kreijkamp-Kaspers study described above. For instance, a 100 g size serving of tofu, which is typical of an Asian diet (see Chen et al. 1999), is equivalent to 33,700 μg, which, when eaten daily, might affect human fertility, physiology and hence possibly the brain, although the exact dosage at which this occurs (if it does) is not entirely clear. This is further complicated as different sources and forms of phytoestrogens were used in the various studies.

176.10.4 Discussion of Findings from Observational Studies

It is hypothesized that the lack of any significant findings in studies assessing Western populations could thus be due to the very low levels of isoflavones consumed in these populations. The participants in Kreijkamp-Kaspers (2007) observational study had at a maximum dietary intake of 15mg/day

of soy isoflavones. This is only a quarter or half of that consumed by Japanese women living in Japan, but it was higher than that reported in other Caucasian women living in Western countries (e.g., Franco et al. 2005). This suggests there may be a dose effect and/or an effect of habitual intake, and that the lack of significance in the studies not finding an association may be due to the lower habitual intake of isoflavones consumed.

In line with previous suggestions and theory, the findings from observational studies (whether the association is a positive one, a negative one or no association has been found) thus suggest that an optimal level of phytoestrogens may be needed in order to maintain cognitive function in the middle-aged, but not in the elderly (>65 years of age) in whom high tofu consumption could be negatively associated with cognitive function. However, these studies relied on self-report FFQ, which may not be the most reliable single indicator of soy intake (especially in samples with a very low phytoestrogen intake). There is also a potential problem when comparing studies due to the differences in the type of food questionnaires used. For example, some used dietary self-report methods (recall vs. active food diary), which may cause a problem in distinguishing between cause and effect (i.e., those with cognitive impairment not remembering their intake), as well as introducing biases, such as the 'healthy-user' bias (e.g., eating soy as part of a healthy diet and/or lifestyle). In addition, in these studies, no actual endogenous phytoestrogen levels were measured.

176.11 Soy Consumption and Cognitive Function in an Elderly Indonesian Sample: Findings from our Indonesian Pilot Study

We assessed the relationship between soy intake and cognitive function in an elderly Indonesian sample. The results of the study revealed that tofu and tempe were the most common forms of soy consumed in this sample. We also measured isoflavone levels using saliva samples from the participants. See Table 176.6 for mean soy intake and salivary isoflavone levels.

In our Indonesian sample, similar to findings by White (2000) and Rice (2000), we also reported a negative association between high daily or more tofu intake and memory in participants over the age of 68 years (see Fig. 176.3) (Hogervorst et al. 2008). On the other hand, we found that participants between 52 and 68 years of age appeared to have optimal genistein levels relating to optimal memory function, whereas participants older than 68 years of age with high genistein levels exhibited lower cognitive performance and an increased risk of dementia (Hogervorst et al. 2009) (see Fig. 176.4). This suggests that the role of phytoestrogens on cognitive function may be modified by age and gender.

Another novel finding was that high tempe intake, in the same analyses, was positively associated with cognitive function. We suggested that a possible reason for this could be due to different processing methods used to make these two types of soy foods. Formaldehyde is reported to be added to tofu in Indonesia and can create oxidative damage to frontal cortex and hippocampal tissue (Gurel et al. 2005). Tempe could potentially protect against formaldehyde-induced damage through its antioxidant effects (Rilantono et al. 2000).

However, a pilot study carried out by the University of Indonesia in Jakarta, Depok recently found no trace of formaldehyde in various tofu samples bought in Jakarta (data unpublished). An alternative hypothesis is that the fermentation process used to make tempe can produce folate (Ginting and Arcot 2004) which is known to have protective effects in the brain (Smith 2002) This may be similar to findings of an interaction between estrogens and folate found before, where women who had high

Table 176.6 Frequency and quantity of soy foods eaten and salivary isoflavone levels in our Indonesian sample

Type of food eaten daily or more	Number of Participants (%)
Soy of any type	511 (71)
Tofu (daily or more)	479 (67)
Tempe (daily or more)	491 (68)
Mean Weekly Intake	Mean ± SD
Tofu	9.3 (6.9)
Tempe	9.5 (6.8)
Salivary Phytoestrogen Levels (ppm)	Mean ± SD
Genistein	0.021 (0.009)
Daidzein	0.043 (0.016)
Glycitein	0.041 (0.027)

Table shows the intake of soy foods as well as the mean salivary isoflavone levels for the whole sample. The figures show the number and percentage *[N(%)]* of participants whom eat these foods at least once a day. The table also shows the mean (and standard deviation or SD) number of times the food are eaten a week. The mean (and SD) salivary isoflavone levels are also displayed
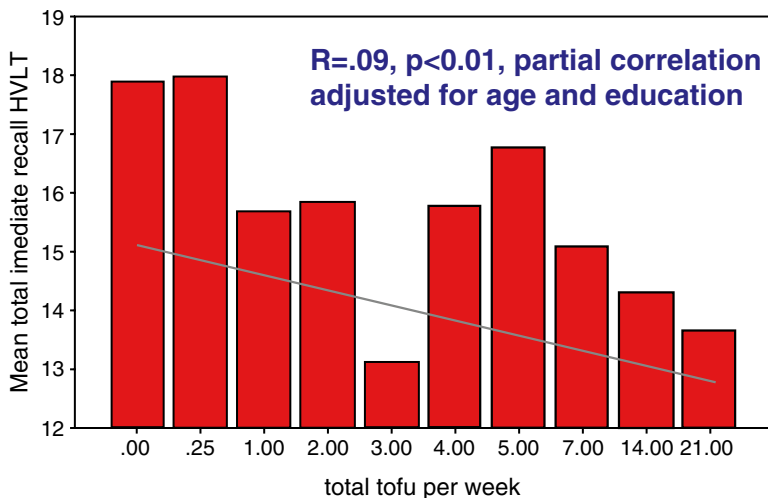
Fig. 176.3 Weekly Tofu intake and memory Score on the Hopkins Verbal Learning Test (HVLT) in an Elderly Indonesian Population. Figure shows the quantity of tofu eaten on a weekly basis in our elderly Indonesian sample plotted against scores on the HVLT verbal memory test. As can be seen a weekly tofu intake increase was associated with lower memory scores

levels of estrogens, but also high levels of folate did not score below the cut-offs scores on the MMSE for dementia (Hogervorst and Smith 2002). These associations need to be investigated in more detail in future studies.

Clearly, observational studies can introduce systematic bias and ultimately treatment studies carry more weight in disentangling cause and effect of (dietary) phytoestrogens versus cognitive outcomes. These studies are thus discussed in more detail in the next section.
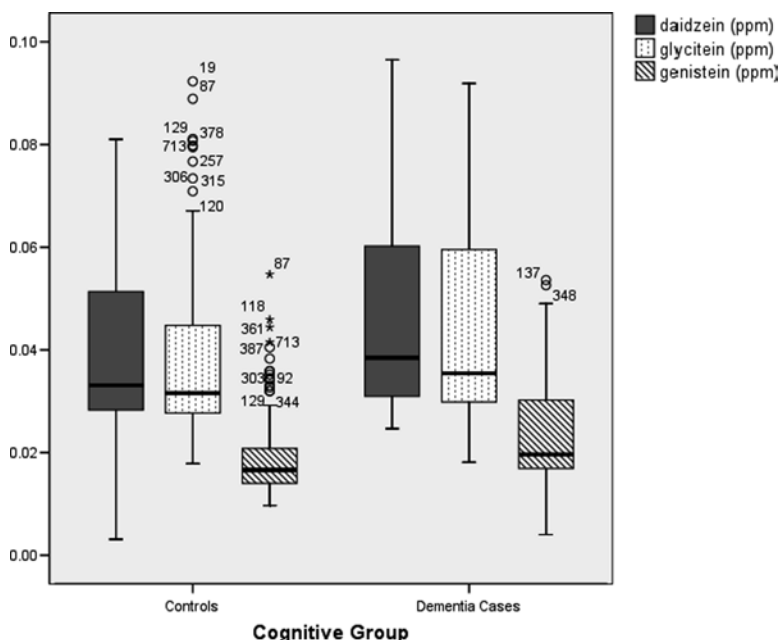
Fig. 176.4 Salivary phytoestrogen levels for the possible dementia cases and control cases in an elderly Indonesian population. Figure shows levels of the phytoestrogens daidzein, genistein and glycitein stratified by possible dementia cases and control cases. Genistein and glycitein levels were significantly higher in cases than in controls ($p < 0.05$)

176.12 Treatment/Intervention Studies in Postmenopausal Women

See Table 176.7 for a summary of all human phytoestrogen treatment studies.

There have been ten randomized placebo-controlled intervention studies (randomized controlled trials or RCTs) assessing the effects of soy isoflavone supplementation on various aspects of cognitive function (see Table 176.7). Of these, eight have assessed postmenopausal women only, of which seven were in Western populations (Fournier et al. 2007; Casini et al. 2006; File et al. 2005; Howes et al. 2004; Kreijkamp-Kaspers et al. 2004; Duffy et al. 2003), and one in a Hong Kong sample (Ho et al. 2007). Another study has assessed older men and postmenopausal women (Gleason et al. 2009) and the tenth study has been with premenopausal women and young men in a UK sample (File et al. 2001). Furthermore, two very short-term (1 week) prospective intervention studies, also with premenopausal women and young men have also been conducted (Ostatníková et al. 2007; Celec et al. 2005).

176.12.1 RCTs Reporting Positive Effects of Isoflavone Consumption on Cognitive Function

Four of the studies assessing postmenopausal women reported beneficial effects of isoflavone treatment on cognitive function (Casini et al. 2006; Duffy et al. 2003; Kritz-Silverstein et al. 2003; File 2005). Two were from the same group of investigators and separately assessed the effects of 60 mg total isoflavones per day on cognitive function, using the same cognitive test battery with postmeno-

Table 176.7 Human intervention studies of soy isoflavones and cognitive function

Study	Location	Design	Duration	Participant Variables	Intervention	Cognitive Measures	Outcomes
Gleason et al. (2009)		RDBP, P	6 months	$n = 30$ healthy PMW and men Mean age = 74.3 years (Placebo) and 73.0 (Isoflavone)	1. Soy supplement – 100 mg total isoflavones/day 2. Placebo	Verbal and visuospatial memory – Buschke Selective Reminding test, Paragraph Recall, Rey Complex Figure test, Visual Spatial Learning test) Language – Boston Naming test Language Fluency – FAS, animal fluency Visual-motor function – Rey Complex Figure test copy, Grooved Pegboard Executive function – Stroop Color Word test, Mazes and Trail Making Test B	Plama Dadizein and Genistein ↑ with isoflavone consumption Isoflavone ↑ visual spatial memory, construction, verbal fluency, speed dexterity; Placebo ↑ executive function; → verbal memory
Ho et al. (2007)	Hong Kong, China	RDBP, P	6 months	$n = 176$ (168 completed) healthy PMW Mean age = 63.5 years (55–76 years) Exclusion criteria: HT in previous 6 months	1. Soy supplement – 80 mg total isoflavones/day 2. Placebo	Learning & Memory Tests: Hong Kong Learning List Test, Rey-Osterrieth Complex Figure Test, WMS-R Executive function: Trail-Making Test, Verbal Fluency Test Verbal fluency: Boston Naming Task Attention and Concentration: Digit Span test Motor Control: Finger Tapping test Language: Boston Naming test Visual Perception: Rey-Osterrieth Copy Trial Global Cognition and Dementia: MMSE	0/15 measures were significantly improved

(continued)

Table 176.7 (continued)

Study	Location	Design	Duration	Participant Variables	Intervention	Cognitive Measures	Outcomes
Fournier et al. (2007)	Pullman, USA	RDBP, P	16 weeks	n = 79 healthy PMW	1. Soy milk – 72 mg total isoflavone/day (37 mg genistein, 31 mg daidzein, 4 mg glycitein)	Working memory: Digit Ordering, Color Matching	0/16 measures were significantly improved
				Mean age = 56.1 years (48–65 years), 1–35 years beyond menopause (mean 7.7 years)	2. Soy supplement – 70 mg total isoflavone/day (33mg genistein, 30 mg daidzein, 7 mg glycitein)	Memory Recall & Recognition: Benton Visual Retention Test, Visual Pattern Recognition	
				Exclusion criteria: HT in previous 6 months	3. Placebo	Memory span (working memory): Forward Digit Span, Corsi Block-Tapping	
						Selective attention: Stroop Test	
Casini et al. (2006)	Milan and Rome, Italy	RDBP, CO	6 months	n = 76 PMW	1. Soy supplement – 60 mg total isoflavone/day (40–45% genistein, 40–45% daidzein, 10–20% glycitein)	Psychomotor performance: Digit Symbol test	↑ 6/8 measures of all three cognitive aspects
				Mean age = 49.5 years; >1 year of meno-pause (mean 5.7 years)	2. Placebo	Immediate auditory attention and mental flexibility: Digit Span test Distractibility and visual inattentive-ness: Visual Scanning Test	↑ Self-rated mood
				Exclusion criteria: HT use in previous 8 weeks, presence or history endocrino-logical disorders, use of psychoactive medication		Other non-cognitive measures: Mood, Participant Condition Preference	↑ Preference to isoflavone treatment (n = 49)

Study	Location	Design	Duration	Sample	Intervention	Cognitive measures	Results
File et al. (2005)	London, UK	RDBP, P	6 weeks	$n = 50$ healthy PMW Mean age 58 years (51–66 years); >1 year beyond menopause (mean = 9.1 years, 66% >5 years) Exclusion criteria: HT in previous 12 months	1. Soy supplement – 60 mg total isoflavone/day 2. Placebo	Short-term non-verbal memory: CANTAB Short and long-term verbal memory: Logical memory & Recall Wechsler (revised) Long-term episodic memory: Picture Recall Verbal Fluency & Semantic Memory: Category Fluency Sustained Attention: PASAT Mental Flexibility (simple and complex rule reversal): IDED-CANTAB Planning Ability: SoC CANTAB	↑ Short-term nonverbal memory, mental flexibility, planning ability → Short & long term verbal memory, long-term episodic memory, verbal fluency & semantic memory, sustained attention
Kreijkamp-Kaspers et al. (2004)	Utrecht, Netherlands	RDBP, P	12 months	$n = 175$ PMW Mean age 66.6 years (60–75 years); >1 year of menopause (mean 18 years) Exclusion criteria: HT in previous 6 months, estrogen related health conditions	1. Soy protein Supplement – 99 mg total isoflavone/day (52 mg genistein, 41 mg daidzein, 6 mg glycitein) 2. Placebo	Verbal episodic memory: Rey Auditory Verbal Learning test Visual memory: The Doors test Short-term/working memory: Digit Span test Verbal Fluency: Boston Naming Task Global cognition & dementia: MMSE Complex attention: Trail Making Test, Digit Symbol Substitution test Other non-cognitive measures: Depression (Geriatric Depression Scale), Verbal Intelligence (Dutch Adult Reading Test), Bone Mineral Density, Plasma Lipids	→ On 16 cognitive measures

Table 176.7 (continued)

Study	Location	Design	Duration	Participant Variables	Intervention	Cognitive Measures	Outcomes
Howes et al. (2004) ❤	New South Wales, Australia	RP, P	6 months	n = 30 PMW Age > 60 years	1. Aglycone Isoflavone extract from red clover (25 mg formononetin 2.5 mg biochanin, < 1 mg daidzein & genistein) 2. Placebo	Visuo-spatial intelligence: Block Design Verbal Memory Digit Recall	→ On all cognitive measures
Duffy et al. (2003)	London, UK	RDBP, P	12 weeks	n = 33 healthy PMW Mean age = 57.8 years (50–65 years); >1 year of menopause (mean 8.1 years) Exclusion criteria: HT in previous 12 months, use of antibiotics in previous 3 months, use of psychoactive medication, smoking	1. Soy supplement – 60 mg total isoflavone/day 2. Placebo	Short term verbal episodic memory: Logical Memory & Recall WMS-R Short term non-verbal episodic memory: DMTS-CANTAB Long term episodic memory: Picture Recall Verbal Fluency & Semantic Memory – Category Generation Frontal Lobe Functioning (mental flexibility & simple rule reversal) – IDED – CANTAB Frontal Lobe Functioning (planning ability) – SoC-CANTAB Sustained Attention – PASAT Other Non-Cognitive Measures: Mood (Bond & Lader Mood Questionnaire)	→ Short-Term Verbal & Non-Verbal Memory; Verbal Fluency & Semantic Memory ↑ Long-Term Episodic Memory; Sustained Attention; Mental Flexibility; Planning Ability

Author (year)	Location	Design	Duration	Sample	Intervention	Cognitive measures	Outcomes
Kritz-Silverstein et al. (2003) ❤	San Diego, USA	RDBP, P	6 months	n = 53 healthy PMW; Mean age = 60.7 years (55–74 years); >2 years of menopause (mean 10.9 years); Exclusion criteria: current HT users	1. Soy supplement – 110 mg total isoflavones/day; 2. Placebo	Short and long-term memory: Logical memory & recall Wechsler; Verbal fluency & semantic memory: Category Fluency; Visuomotor tracking & attention: Halstead-Reitan Trails A & B	→ Short & Long Term Memory; Trail A; ↑ Verbal Fluency & Semantic Memory; Trail B
Ostatnikova (2007)	Bratislava, Slovak Republic	STPI	1 week	n = 86 PRMW and young men (54 females & 32 males); Age range 18–25 years; Exclusion criteria: use of hormonal contraceptives	1. 2 g/kg per day soybeans	Mental rotation: Sub-section of Amthauer Intelligence test (non-verbal); Spatial visualization: Sub-section of Smith & Whetton intelligence scale (non-verbal); Other Non-Cognitive Measures: Salivary Testosterone, Plasma Estradiol	↑ Mental Rotation & Spatial Visualization
Celec et al. (2005)	Bratislava, Slovak Republic	STPI	1 week	n = 16 PRMW; Mean age = 23.4 years	900 g soybean to be eaten with one week (1,080.0–3,780.0 mg isoflavones)	Mental rotation: Sub-section of Amthauer Intelligence test (non-verbal); Spatial visualization: Sub-section of Smith & Whetton intelligence scale (non-verbal); Other Non-Cognitive Measures: Salivary and Plasma Testosterone & Estradiol	↑ Mental Rotation & Spatial Visualization

(continued)

Table 176.7 (continued)

Study	Location	Design	Duration	Participant Variables	Intervention	Cognitive Measures	Outcomes
File et al. (2001)	London, UK	RP	10 weeks	$n = 27$ PRMW and young men (15 males and 12 females)	1. High soy diet (100 mg total isoflavones/day)	Attention: DSS, DC test, PASAT	↑ Short-Term Non-Verbal Memory; Short-Term Verbal Memory; Long-Term Verbal Memory; Long-Term Episodic Memory; Mental Flexibility Females only
				Mean age = 25 years	2. Low soy diet (0.5 mg total isoflavones/day)	Immediate episodic memory: Short story (WMS-R)	↑ Frontal Function; Planning Ability
						Short-term non-verbal memory: DMTS-CANTAB	→ Verbal Fluency & Semantic Memory; Sustained Attention
						Long-term episodic memory: Picture Recall	
						Semantic memory: Category Generation Task	
						Mental flexibility (simple and complex rule reversal): IDED-CANTAB	
						Planning ability: SoC CANTAB	
						Frontal function: Letter Fluency	
						Intelligence: NART-R	
						Other non-cognitive measures: Depression (HAD)	
						Mood (Bond & Lader Mood Questionnaire)	

Table shows the study details of human intervention trials assessing the effects of isoflavone consumption on cognitive function. NB: ♥ = Full Paper could not be accessed, only abstract; ↑ = Improvement in performance; → = No change in performance; *CANTAB* Cambridge Neuropsychological Test; Automated Battery, *CBLC* Community Based Longitudinal Cohort Study, *CO* Crossover Design, *CS* Cross-Sectional, *DC* Digit Cancellation Test, *DMTS* Delayed Matching to Sample Test (part of CANTAB), *DSS* Digit-Symbol Substitution, *HAD* Hospital Anxiety & Depression Scale, *HT* Hormone Therapy, *IDED* Attentional Set Shifting, *MMSE* Mini Mental Status Examination, *NART-R* National Adult Reading Test revised version, *P* Parallel Design, *PASAT* Paced Auditory Serial Addition Test, *PMW* Postmenopausal Women, *PRMW* Premenopausal Women, *RDBP* Randomized, double-blind placebo-controlled, *RP* Randomized, placebo-controlled, *SoC* Stockings of Cambridge, *STPI* Short Term Prospective Intervention Study, *WMS-R* Wechsler Memory Scale – Revised

pausal women aged 50–66 years in the UK for a duration of 6 weeks (File et al. 2005) and 12 weeks (Duffy et al. 2003). The investigators found that 60 mg/day isoflavone equivalent was beneficial for cognitive function as assessed by memory tests, as well as on tests of frontal lobe function, such as those assessing mental flexibility and planning ability.

Around the same time as the UK studies were published, the Soy and Postmenopausal Health in Aging Study (SOPHIA) (Kritz-Silverstein et al. 2003) data from the USA were disseminated. This study had also included postmenopausal women aged 55–74 years. However, a higher dose (110 mg/day) of isoflavones was used and for a much longer duration of 6 months. A learning effect was observed over time in both the placebo and isoflavone treatment group, showing improvements in all five cognitive tests used. This improvement was larger in the isoflavone groups for four tests, and significantly greater (23% as opposed to 3%) for the Category Fluency test, even after controlling for age and education. Furthermore, in analysis stratified by age, those in the younger age group (50–59 years) taking the isoflavone supplement showed a greater improvement than those on placebo on a test of visuospatial tracking and attention (Trails B). This effect was not observed in the older group (60–74 years), again suggesting that not only could isoflavones have a beneficial effect on verbal memory in postmenopausal women, but also that the effect of isoflavones may be greater for peri-menopausal women than for those who are older and had already experienced menopause. This would be in line with our observational data and those of E studies (Hogervorst et al. 2009). Similarly, another RCT (Casini et al. 2006) reported that postmenopausal women (with a mean age of 49.5 years and an average 5.7 years since menopause), who were given 60 mg/day equivalent of isofla-vones as aglycones for a duration of 6 months showed an improvement in cognitive ability, as measured by three cognitive tests, as well as improved mood. When asked, the participants also generally showed a preference for phytoestrogen over placebo (64%). This study has particular value because it provides support for the possible role of phytoestrogens in alleviating or reversing psychological ailments associated with menopause, such as mood and quality of life. Gleason et al. (2009) investi-gated the effects of 100 mg/day soy isoflavone for a duration of 6 months on cognitive function for both men and women aged 62–89 years. Cognitive function was tested at month 1, 3 and 6 and the investigators reported that the isoflavones group showed greater improvements in visual-spatial memory, construction, verbal memory and speed dexterity. However, the placebo group were faster on two tests of executive function. There was no significant effect on verbal memory for either group. Interestingly, although plasma genistein and daidzein levels showed a rise with increasing isoflavone supplementation, equol levels did not and none of the samples were equol producers. This is important as some investigators have suggested that equol, a highly estrogenic metabolite derived from daidzein in some, but not all, humans, is the most potent derivative for maintaining brain func-tion through its strong estrogenic effects. This study would suggest that this is not necessarily the case. However, the small sample size in this study ($n = 30$) must be taken into consideration.

176.12.2 RCTs Reporting No Effects of Isoflavone Consumption on Cognitive Function

Four studies failed to show any significant effect of isoflavone supplementation on various aspects of cognitive function with postmenopausal women (Fournier et al. 2007; Ho et al. 2007; Howes et al. 2004; Kreijkamp-Kaspers et al. 2004). Using aglycone isoflavone extracts from red clover, (Howes et al. 2004) investigated the effects of 25 mg/day of predominantly biochanin A (which contains less than 2 mg daidzein and genistein) for a duration of 6 months and found no significant effects on tests of visuospatial intelligence and verbal memory in postmenopausal women. The dose used may have

thus been too low and, in addition, the women included in this study were all older than 60 years of age. In a study of the longest duration of all RCTs carried out in this area, Kreijkamp-Kaspers et al. (2004) investigated the effects of 12 months of soy protein containing 99 mg equivalent of total isoflavone per day (52 mg genistein, 41 mg daidzein, and 6 mg glycitein) on cognitive function (and other health indicators) in postmenopausal women aged 60–75 years in the Netherlands. No effect of isoflavones supplementation was found on a large number of cognitive tests (see Table 176.2 for full list). However, it must be noted that compared to the earlier reported positive studies, these participants were much older on average (66 years of age), had been menopausal for longer (mean of 18 years), and 19% were also using cholesterol-lowering and antihypertensive medication. Similarly, Ho et al. (2007) did not find any effects of 6 months supplementation with 80 mg/day soy isoflavones on quality of life, as well as various cognitive functions. They had also included postmenopausal women with an average age of 63.5 years, who were also 13.8 years since menopause, on average. Interestingly, this latter study was the only study of a population who habitually ate soy as part of their daily diet (Hong Kong Chinese) and who had a mean dietary intake of 20 mg/day isoflavones. It is thus also possible that no effect was found in this study due to the higher habitual intake of soy in the sample, which could have potentially reduced group differences (Ho et al. 2007).

These data taken together would suggest that age of women, duration of treatment, habitual intake and years since menopause could explain differences found between studies. This reasoning is very similar to that for E treatment (Hogervorst et al. 2009). However, in a US-based study of postmenopausal women with a mean age of 56.1 years, and with an average of 8 years since menopause (Fournier et al. 2007), researchers also found no significant effects of either 72 mg/day total isoflavones (from soy milk) or 70 mg/day total isoflavone (via a soy isoflavone supplement) on various cognitive abilities, including selective attention, working or visuospatial short- or long-term memory when compared to placebo. On the other hand, the large variability in age since menopause (Zhao and Brinton 2007) in this group may have been responsible for a lack of significant findings.

176.13 Dose Effect of Phytoestrogens in a Pilot RCT

In a pilot RCT study (Yesufu 2009) we assessed the 24-h dose effect of phytoestrogens on verbal episodic (word lists) and semantic memory (Category Fluency) in postmenopausal women between 45 to 65 years of age. See Table 176.8 for inclusion and exclusion criteria and Fig. 176.5 for procedure. Participants had been instructed to take one of the allocated pills (half the dose) 24 hours before the morning of testing immediately upon waking, and the other half of the dose immediately before going to bed on the night before testing (10 hours before testing) to obtain maximal phytoestrogen levels. This was done to investigate the potential 24-hour dendritic sprouting effects of E (Woolley and McEwen 1993). Timing of ingestion of the dosages was based on findings by Setchell et al. (2003), who reported the terminal half-life (the interval required for the quantity to decay to half its initial value) of daidzein and genistein to be approximately 8–10 hours. In this pilot study, fifteen participants successfully completed the study. Due to subject drop out (unrelated to side effects), cells were unbalanced and there was an uneven number of participants in each treatment group (placebo $n = 6$; 30 mg, $n = 5$; 100 mg $n = 4$).

Table 176.9 below describes the sample demographics. The mean age of the participants was 55.47 ± 5.74 (range 49–65 years). Most participants had achieved secondary or university level education ($n = 6$ and $n = 8$, respectively), and only one participant had a primary level education. The majority of participants were Caucasian ($n = 12$). Nearly half the sample was currently using medication ($n = 7$), but the majority of participants did not smoke ($n = 14$) and exercised on a regular basis ($n = 14$), indicating a healthy lifestyle. No significant difference was observed between treatment

Table 176.8 Inclusion and exclusion criteria for pilot randomized controlled trial

Inclusion criteria	Exclusion criteria
Aged 45–65 years old	Use of supplementary hormones (including hormonal contraception within the last 3 months)
Good health as assessed by self-report questionnaire	
Postmenopausal (women): last menses longer than 6 months ago	Use of antibiotics in previous 6 months
Surgical or natural Menopause	Previous history of thrombosis
	Benign or malignant growths
	History of breast, ovarian or endometrial cancer
	Psychiatric disorder (e.g., clinical depression)
	Pregnancy
	Dementia (e.g., Alzheimer's disease)
	Epilepsy
	Vision/ear/hearing problems
	Dyslexia
	Premenopausal women
	Regular soy food consumers

This table shows the study inclusion and exclusion criteria for participants in the pilot Randomised Controlled Trial (RCT)
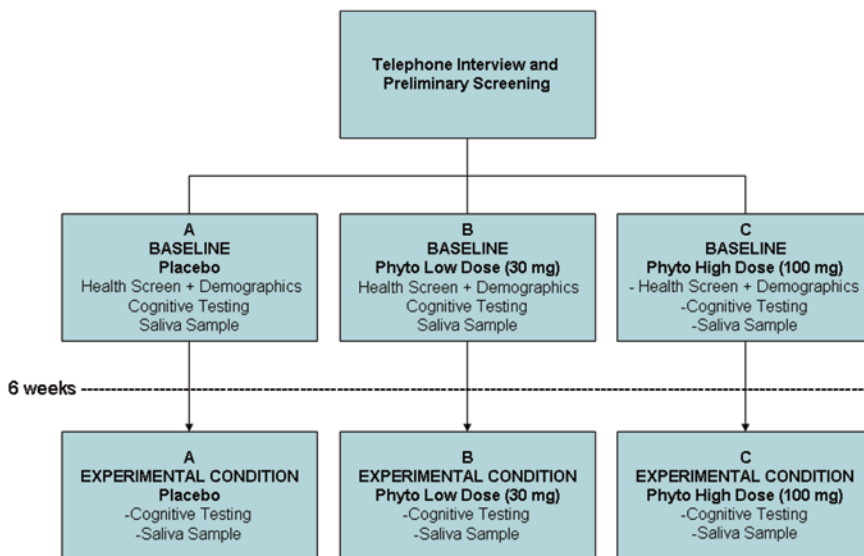
Fig. 176.5 Randomized Controlled Trial (RCT) procedure. This figure shows the recruitment and test procedure for the RCT. After initial telephone screening, participants were allocated to one of the three treatment groups. Baseline data was collected. After a time period of 6 weeks, the participants consumed their treatment or placebo pills and completed the same test battery again

groups in educational attainment, ethnicity, medication use, smoking and exercise. Unfortunately, due to randomization, participants in the 30 mg group were significantly older (61 ± 4.30 years of age) than the participants in the 100 mg (50 ± 1.16 years of age) and placebo (54.50 ± 4.60 years of age) groups [$F(14) = 9.10$, df = 2, $p = 0.004$].

We found a positive effect of 100 mg total equivalent of isoflavones, as opposed to the 30 mg or placebo treatment on verbal Category Fluency (number of animals in 90 s) (see Fig. 176.6) controlling for

Table 176.9 Pilot randomized controlled trial sample demographic variables

Demographic variables	Whole group	Placebo	30 mg	100 mg	Critical value	df	p value
N	15	6	5	4			
Age, mean ± SD	55.47 (5.74)	54.60 (4.59)	61.00 (4.30)	50.0 (1.15)	9.1	2	0.004*
Education, N (%)					2.82	4	ns
Primary	1 (6.7)	1 (16.7)	0 (0)	0 (0)			
Secondary	6 40.0)	2 (33.3)	3 (60.0)	1 (25.0)			
University or higher	8 (53.3)	3 (50.0)	2 (40.0)	3 (75.0)			
Profession							
Higher manager, admin, professional	1 (6.7)	0 (0)	0 (0)	1 (25.0)	6.83	8	ns
Intermediate – Manager, admin, professional	5 (33.3)	2 (33.3)	1 (20.0)	2 (50.0)			
Supervisory or clerical, junior manager, admin or professional	5 (33.3)	2 (33.3)	2 (40.0)	1 (25.0)			
Student	1 6.7)	1 (16.7)	0 (0)	0 (0)			
State Pensioner, no other earner, causal or lowest grade worker	3 (20.0)	1 (16.7)	2 (40.0)	0 (0)			
Ethnicity							
Caucasian	12 (80.0)	4 (66.7)	1 (16.7)	1 (16.7)	2.58	4	ns
Asian	2 (13.3)	4 (80.0)	1 (20.0)	0 (0)			
Black	1 (6.7)	4 (100)	0 (0)	0 (0)			
On medication at present							
Yes	7 (46.7)	2 (33.3)	4 (66.7)	1 (25.0)	3.42	2	ns
No	8 (53.3)	4 (80.0)	1 (20.0)	3 (75.0)			
Do you smoke?							
Yes	1 (6.7)	0 (0)	0 (0)	1 (25.0)	2.95	2	ns
No	14 (93.3)	6 (100.0)	5 (100.0)	3 (75.0)			
Do you exercise on a regular basis?							
Yes	14 (93.3)	6 (100.0)	4 (80.0)	4 (100.0)	2.14	2	ns
No	1 (6.7)	0 (0)	1 (20.0)	0 (0)			

This table displays the differences between treatment groups in demographic variables. Univariate ANOVA analyses were used to assess the differences between groups in age and chi-square analyses for all other categorical variables. NB: Critical value refers to F = ANOVA, χ^2 = chi-square; p Value = significance; df = degrees of freedom; * Correlation is significant at the 0.01 level (2-tailed); ns = correlation is not significant

age and BMI [F (14) = 4.057, df = 2, p = 0.05]. Analyses exhibited no baseline differences between groups (which had been done six weeks earlier at enrolment). The 100-mg treatment group showed more improvement than the 30-mg group, who also showed greater improvement than the placebo group ($p = 0.05$).

Women in our RCT isoflavone study (participant recruitment is ongoing) were on average younger (mean age 55 years) than those in previous studies reporting no effect or detrimental effects of phytoestrogen consumption. Due to similarities between the sex hormone E and naturally occurring phytoestrogens, this positive effect on cognitive function was expected, as this finding is in line with the 'window of opportunity' theory for estrogens (Gibbs 2006; Henderson et al. 2005; Pinkerton and Henderson 2005). This theory suggests beneficial effects of E on cognition in recently menopausal

Fig. 176.6 Change in baseline score for the Category Verbal Fluency Test (CVFT). This figure shows the 'change in baseline score' using box plots (with medians) between test session 1 and test session 2 on the CVFT for each treatment group
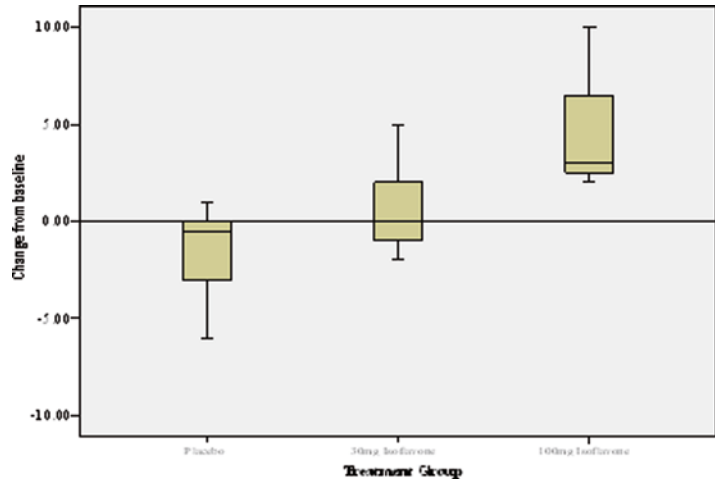
women only and is substantiated by basic science and human observational data. While our results reported are preliminary, they are also similar to other reports finding positive effects of phytoestrogen intake on the Category Fluency test (Kritz-Silverstein et al. 2003). Also reflective of our study was that Kritz-Silverstein et al. (2003) did not find any significant effects on other types of verbal memory either (e.g., story and verbal list recall were also assessed in our study). This may indicate that, similar to estrogenic findings, phytoestrogens may also have test-specific effects. Interestingly, the two longitudinal studies investigating menopausal change on cognition also show the largest differences on the same verbal Fluency task, which may thus be very sensitive to fluctuations in estrogenic metabolite levels (Fuh et al. 2006; Thilers et al. 2006).

176.14 Discussion

It is thought that diet and nutrition could play an important part in age-related health issues, such as cancer, cardiovascular disease, and to maintain cognitive function and prevent AD (American Institute for Cancer Research 1997). In this modern day and age we have turned to dietary supplements as a quick and easy way to obtain the nutrition we believe maintains and promotes good health. Therefore, the dietary supplement industry is now a multi-billion-dollar business based on studies such as those described in this review. However, a worrying increase in hormone-dependent health issues has been observed. Consequently, soy isoflavones have been suggested as a natural alternative to manufactured hormones, such as E, and have already been endorsed as being protective for cardiovascular health (US Food and Drug Administration 1999). The labelling of a product as 'natural' does not necessarily confirm its safety (Ernst 2002) and relatively little is known about the biological behaviours of soy isoflavones in the human body. Furthermore, the effects of a plant hormone in its natural state is not necessarily the same as that of when it is capsulated or has been extracted and processed to create a tablet form (Fitzpatrick 2003). Human phytoestrogen trials have evaluated many health issues (e.g., menopausal symptoms, cardiovascular markers, cancer, bone density and cognitive function), but clinical data remain limited and a discrepancy can be seen between studies in vitro and in vivo, across various in vivo clinical trials as well as observational studies. There are a few possible explanations for discrepancies between studies and reasons why comparing them may be complicated.

176.14.1 Differences Between Studies

176.14.1.1 Bioavailability and Metabolism of Isoflavones

Various composition and structural make-up differences between different types, products and sources of soy isoflavones may affect their in vivo pharmacodynamics in the human body (see Kano et al. 2006). This begins with the initial growth process and response to external stimuli (which may cause the molecules of the soy plant to develop in certain ways that result in more complex phytoestrogen profiles (Zhao and Brinton 2007) and ends in the processing, storage and preparation of foods. This is especially a problem as the intervention studies to date have used various different sources and types of soy isoflavones. Some studies used isolated isoflavones, while others used intact soy protein. As can be seen from Table 176.2, phytoestrogen trials vary in the make-up of their administered phytoestrogens. Variability in composition of the soy used leads to the issue of differences in bioavailability of compounds between studies and hence the possible differences in their overall effect on health. This degree of variation needs to be taken into consideration when comparing and contrasting studies, as well as when forming conclusions based on the findings of these studies.

Knowledge about the bioavailability of ingested isoflavones is of paramount importance as it enables an understanding of the way in which the chemical forms of isoflavones have a positive biological effect on the human body, i.e., their efficacy (Zubik and Meydani 2003) and allows for an evaluation of their safety. However, this knowledge, particularly in reference to the bioavailability of genistein and daidzein as a result of the form consumed (aglycone or glucoside), is in the main part incomplete, contradictory and inconclusive, particularly in human studies, making it difficult to establish firm recommendations with regards to the optimal dosage to maintain health and optimal function.

176.14.1.2 The Effects of Dose and Habitual Intake

As discussed, soy isoflavones may have different estrogenic effects, which could also be dose-dependent, but the effective dose to maintain cognitive function has not been found. Linford and Dorsa (2002) reported that very high concentrations of genistein are toxic to neurons, suggesting optimal and non linear levels. Zeng et al. (2004) reported that the neuroprotective effects of genistein are mediated by two mechanisms dependent on dose. The first one is at a nonmolar level, in which genistein protects neurons via an ER-mediated pathway. The second involves a micromolar level in which genistein behaves as an antioxidant. For instance, treatment with 50 µmol/L did not attenuate neuronal apoptosis induced by the endoplasmic reticulum calcium-ATPase inhibitor thapsigargin and actually enhanced apoptosis of cells, whilst low concentrations of genistein ameliorated apoptosis of neurons. In contrast, another study found that the same dose of genistein did protect HCN1-A and HCN2 cells from death (Sonee et al. 2004). The dose administered could thus greatly influence the efficacy and safety, by either being too low to have a noticeable effect on cognitive function, (e.g., in the SWAN study, Huang et al. 2006), or by being too high over a long exposure period and resulting in possible safety issues, which have not yet been investigated in sufficient detail. Dose, but also tissue-specific issues (see Sect. 176.3) thus need to be considered when assessing different types of health benefits of the isoflavones.

The RCTs to date all tended to use large quantities of daily administered isoflavones, which exceed the amount of daily isoflavone consumed in food in a typical Asian diet. No guidelines exist to assist in this decision and the reasons for this are not at all clear, as they are not based on any known pharmacokinetics of isoflavones. Although a possible influence of dose was found in

our RCT, confusion still exists as to whether there is a linear relationship between bioavailability and increasing dose (Setchell et al. 2003; Setchell et al. 2003; Bloedon et al. 2002). Setchell et al. (2003) and Setchell (2000) reported a positive correlation between isoflavone intake and peak concentrations of daidzein and genistein, although this was nonlinear. The same relationship has been seen between bioavailability and intake, with urine analyses showing that, over a 4-day period, a doubling of the dose of isoflavones did not double the total recovery (Setchell et al. 2003). This indicates that consuming a greater quantity of isoflavones does not necessarily result in higher quantities of isoflavones being metabolized, which may reflect a possible saturation or storage effect. Further studies assessing the optimal dosage of isoflavones in tandem with both bioavailability and cognitive function are required in order to have a clearer understanding about the relationship between these factors. The observational studies have not shed any light on this either as amount consumed was not weighted or analyzed. They did, however, suggest that intake of tofu more than 2/3 times a week could already have detrimental associations with cognitive function in the elderly.

The implication of habitual intake of isoflavones is an issue all on its own and may impact on many factors relating to bioavailability (Slavin et al. 1998; Adlercreutz et al. 1982). The regularity of isoflavone consumption could also be of some importance. Significant effects, protective or detrimental, have been reported in populations who regularly consume large amounts of isoflavones (e.g., the HAAS and Kame project), whereas no associations have been found in other sample populations treated with phytoestrogens and/or those who consumed very low and infrequent quantities of isoflavones through their diets. Setchell et al. (2003) suggests that eating soy foods regularly through the day may be more effective for maintaining high serum phytoestrogen levels, and hence may be more beneficial (or detrimental to the elderly as reflected in our Indonesian sample) than eating soy once a day or once a week. However, in a soy treatment study assessing bioavailability as a result of chronic exposure to soy isoflavones over a 10-week period, no difference was found between midpoint and endpoint concentrations of isoflavones in plasma, urine and faeces, which suggests that there were no significant effects of habitual intake (Wiseman et al. 2004). On the other hand, this study may have been too short to appropriately assess 'habitual' intake effects.

176.14.1.3   Characteristics of the Study Population: Age and Menopausal Status

Variations in some characteristics of the study participants (e.g., habitual consumption) may thus influence the effect of isoflavones on cognitive function. Similar to the findings with E, data suggest that it is also possible that age, menopausal status and endogenous hormonal profile may have an impact on the effect of soy isoflavone on cognitive function (Zhao and Brinton 2007). Interestingly, most RCTs finding no, or a negative (e.g., seen in two tests in Gleason et al. 2009), effect of isoflavone treatment on cognitive function had included participants older than 60 years of age (Ho et al. 2007; Howes et al. 2004; Kreijkamp-Kaspers et al. 2004), similar to the observational studies finding negative associations in those over 65 years of age (Rice et al. 2000; White et al. 2000; Hogervorst 2008). Beneficial effects of soy isoflavones were mainly seen for women who were within 10 years of the onset of menopause (bar Gleason et al. 2009) and/or those who had been treated for less than a year with a high dosage, which is also similar to effects seen in E treatment studies (Hogervorst 2006).

Another possible difference between the pre- and postmenopausal studies is the duration of supplementation, as the premenopausal studies tended to use much shorter treatment regimes than the postmenopausal treatment trials (Lu and Anderson 1998; Slavin et al. 1998; Lu et al. 1995). Similar to the effects of E treatment, positive effects of treatment on cognition may be limited up to 2–6 months (Hogervorst et al. 2009).

176.14.1.4 Characteristics of the Study Population: Genetics Determining Phytoestrogen Metabolism

Genetic factors could further influence the metabolism of isoflavones, i.e., due to differences in intestinal microfloral populations (Rowland et al. 1999). It is possible that the colonic microfloral environments of American participants (Zubik and Meydani 2003) may have a higher capacity to hydrolyze glucosides than those of Japanese samples (Izumi et al. 2000), and thus metabolize glucosides better, resulting in these being less bioavailable in the American participants (Zubik and Meydani 2003). Furthermore, the presence of other foods in the digestive system and the composition of those foods may also be factors to consider (Zubik and Meydani 2003). For instance, food-deprived animals were found to absorb isoflavones faster than fed animals (Piskula 2000). In the Izumi et al. (2000) and Zubik and Meydani (2003) studies, participants were fed foods with a different composition matrix before isoflavone consumption, affecting the quantities of aglycones and glucosides, which may have accounted for some of the discrepancies between the studies on cognition which were reviewed earlier.

Another factor causing variation between individuals that has relatively recently been recognized is equol. As previously stated, equol is a metabolite of the isoflavone daidzein produced by gut microflora. Equol's binding ability is of similar strength to genistein, and it has been found to be three times as estrogenic as its parent daidzein in an endometrial tumour line (Markiewicz et al. 1993). Variations exist between animals and humans, as well as between various human populations in the proportion of people who have the ability to produce equol. Due to the variability in gut microflora, only 20–35% of a Western population can produce equol (Wiseman et al. 2004; Morton et al. 1994). It is possible that the effects of isoflavones on various endogenous systems are mediated by the variable of being an equol producer or not (Zhao and Brinton 2007) and, possibly, by age affecting equol production (Frankenfeld et al. 2004). Therefore, equol may be a major player in the effect of soy consumption in the human body, and the failure of human intervention studies to account for this could result in marked differences in individuals' responses to soy consumption. On the other hand, positive effects of soy were also found in a population of non-equol producers (Gleason et al. 2009). This would suggest that other aglycones could mediate the positive effect on cognition (e.g., genistein, and daidzein itself).

176.14.1.5 Other Differences Between Studies

Another factor that needs to be considered when comparing studies and drawing conclusions from the results of RCTs is the types of cognitive tests used. The Fluency test seemed to be particularly sensitive to estrogenic effects (menopausal transition, RCTs with E and phytoestrogens), as well as possibly some specific executive function tests. However, not all studies used the same tests, which makes comparisons complicated. Again, these issues are very similar to those found in studies of the effects of E on the brain (Hogervorst 2009).

176.15 Concluding Remarks

To summarize our research, to our knowledge, we were the first to assess the intake of different types of soy products, as well as endogenous isoflavone levels, in relation to cognitive function in our Indonesian observational study (Hogervorst et al. 2008). In addition, we (Yesufu 2009) were the first to find a beneficial effect of a 24-hour high dose isoflavone supplement (100 mg equivalent of total

intake of isoflavones), as opposed to low 30 mg total intake or placebo on Verbal Fluency. Woolley and McEwen (1993) reported that the increase in dendritic sprouting as a result of high levels of Es peaked at two and three days and then decreased over the preceding 7 days. Taking these findings into consideration, with data suggesting optimal levels in the young and middle aged and negative effects of consuming tofu more than two/three times weekly in the elderly, it could be suggested that intermittent intake may be the most favourable regime to render positive effects on the brain in women who are younger than 65 years of age.

To date, most studies assessing the health effects of soy isoflavones have run into conflict and disagreement. Undeniably, there is a huge gap in our knowledge about the effects of phytoestrogens, partly due to the lack of well-controlled large clinical studies. The optimal dose at which a positive effect will be observed is unknown, as well as the toxicity of high doses of isoflavones in humans. The duration of consumption needed to detect if any effect exists, and at what point long-term intake becomes detrimental in whom, is also unclear. Other factors such as genetic/ethnic and environmental variables, isoflavone metabolism and equol production, gender, age and menopausal status, all need to be taken into consideration. Therefore, future studies should aim at addressing these issues and at arriving at a consensus about methodological standards (e.g., type of cognitive test used, isoflavones measurements, etc.) which should be used in order to make the studies more directly comparable. Taking all these points into consideration, the evidence to date is not sufficient to make any recommendations about the use of dietary intake of soy isoflavones to address any human health issues at present. Further focused research needs to be conducted in order to arrive at more definitive conclusions.

Summary Points

- Phytoestrogens are found in abundance in a variety of foods, such as fruits, vegetables and grains. However, very high concentrations can be found in soy. When consumed, they can mimic the effect of estrogens in the body.
- Phytoestrogen consumption has been promoted as beneficial on various health aspects. However, the isoflavone content can vary between different soy foods as a result of their growth process, production and the form they are consumed in. This can affect their metabolism, as well as their effect on the human body.
- It has been suggested that a diet rich in isoflavones (genistein and daidzein) could be implicated in the lower prevalence of Alzheimer's disease in East Asian countries compared to Western countries. East Asian countries consume greater quantities of isoflavones than Western countries from more traditional soy foods, such as tofu and tempe.
- Previous research assessing the relationship between isoflavones and cognition is limited and the effects are not well understood, partly due to conflicting reports from previous studies. Basic cell research has reported both neuroprotective and neurotoxic (but only in very high dosages) effects of genistein and daidzein on biological mechanisms implicated in dementia.
- Observational studies assessing the relationship between isoflavone consumption through diet and cognitive function have either found no relationship in Western populations consuming low levels of isoflavones, or a detrimental effect of high tofu consumption (>2–3/week) in older East Asian populations. This suggests that an optimal level may be required to maintain cognitive function.
- In our observational study in Indonesia, we also reported a negative relationship between high (daily) tofu intake and cognitive function. A positive relationship was observed between high tempe intake and cognitive function in the same analyses. We suggest that processing differences (formaldehyde added to tofu and folate as a by-product of tempe production) may be implicated in these findings.

- However, our results only pertained to women over 68 years of age. This suggests that the effects of phytoestrogens on cognitive function may be modified by age and gender. Participants between 52–68 years appeared to have optimal genistein levels, which was associated with better memory function. However, those over 68 years of age with high genistein levels had lower cognitive scores and a higher risk of dementia.
- Ten RCTs have also assessed this relationship in postmenopausal men and women. Some of these studies have reported beneficial effects on various cognitive functions in women and men. However, others did not find any effect. The data suggests that the duration of treatment (6 months or less), age of women (<65 years), years since menopause and possibly habitual intake could potentially explain differences found between studies.
- Preliminary results of our pilot RCT assessed the 24-hour effects of isoflavone consumption on verbal episodic and semantic memory in postmenopausal women with a mean age of 55 years. We found a positive effect of 100 mg isoflavones (compared to 30 mg or placebo) on verbal Category Fluency. This reflects previous studies reporting a protective effect of high intake in postmenopausal women.
- We propose that possible reasons for discrepancies seen between studies could be due to differences in types and sources of isoflavones (affecting bioavailability and metabolism), dose and the effect of habitual intake, duration of treatment, types of cognitive test used (not all are sensitive), as well as characteristics of the study population (age, internal hormonal status, and genetic factors affecting metabolism).
- To our knowledge, we were the first to assess soy intake and endogenous isoflavone levels in the same sample. We are also the first, to our knowledge, to find beneficial effects of isoflavones on verbal semantic memory after 24 hours. Future research is needed to identify a possible optimal dose at which a positive effect of isoflavones can be observed on cognitive function.

Definition and Explanations of Key Terms or Words

Phytoestrogen: A plant hormone which is physiologically and physiochemically similar to estrogen

Cognition: Mental capacity (Literally 'knowing'), the ability to process information; this includes perception, learning and memory, language and higher executive functions, including complex (but not simple) psychomotor reaction times

Isoflavone: A type of phytoestrogen in the form of glucosides (a sugar group attached to the main part of the molecule which makes it water soluble). When consumed isoflavones can be found in the form of aglycones (no sugar group attached)

Equol: A metabolite of the isoflavone daidzein produced by gut microflora

Estradiol: Most potent estrogen

Estrogenic: A substance which has a biological effect which is similar to that of estrogen

Anti-estrogenic: A substance which competes with estrogens to bind to receptor sites and hence blocks the activity of estrogen

Bioavailability: The part of a substance that remains after it has been digested, absorbed and metabolized by the human body

Agonist: A substance that binds to a receptor and hence affects it's functioning

Antagonist: A chemical that blocks the binding of another chemical to its receptor in an organism without binding to the receptor itself

Pharmacokinetic: The process by which a substance is absorbed, distributed, metabolized and eliminated by the body

Pharmacodynamic: The actions or effects of a substance on a living organism

References

Adlercreutz H. Scan J Clin Lab Inv. 1990;201:3–23.

Adlercreutz H, Fotsis T, Heikkinen R, Dwyer JT, Woods M, Goldin BR, Gorbach SL. Lancet. 1982;2:1295–9.

Adlercreutz H, Mazur W. Ann Med. 1997;29:95–120.

American Institute for Cancer Research. Food nutrition and the prevention of cancer. Washington: World Cancer Research Fund. 1997

American Psychiatric Association. Diagnostic and statistical manual of mental disorders, 4th ed. (DSM-IV) Washington, DC: American Psychiatric Association; 1994.

Arai Y, Uehara M, Sato Y, Kimira M, Eboshida A, Adlercreutz H, Watanabe S. J Epidemiol. 2000; 10 (2):127–35.

Azadbakht L, Kimiagar M, Mehrabi Y, Esmaillzadeh A, Padyab M, Hu FB, Hu FB, Willett WC. Am J Clin Nutr. 2007;85:735–41.

Bang OY, Hong HS, Kim DH, Kim H, Boo JH, Huh K, Mook-Jung I. Neurobiol Dis. 2004;16:21–8.

Barnes S, Peterson TG, Coward L. J Cell Biochem Suppl. 1995; 22:181–7.

Beecher GR, Bhagwat S, Haytowitz D, Holden JM, Murphy PA. J Nutr. 2000;130:666S.

Bloedon LT, Jeffcoat AR, Lopaczynski W, Schell MJ, Black TM, Dix KJ, Thomas BF, Albright C, Busby MG, Crowell JA, Zeisel SH. Am J Clin Nutr. 2002;76:1126–37.

Boettger-Tong H, Murthy L, Chiappetta C, Kirkland JL, Goodwin B, Adlercreutz H, Stancel GM, Mäkelä S. Environ Health Perspect. 1998;106:369–73.

Boker LK, Van der Schouw YT, De Kleijn MJ, Jacques PF, Grobbee DE, Peeters PH. J Nutr. 2002;132:1319–28.

Casini ML, Marelli G, Papaleo E, Ferrari A, D'Ambrosio F, Unfer V. Fertil Steril. 2006;85:972–8.

Cassidy A, Bingham S, Setchell K. Br J Nutr. 1995;74:587–601.

Cassidy A, Brown JE, Hawdon A, Faughnan MS, King LJ, Millward J, Zimmer-Nechemias L, Wolfe B, Setchell KD. J Nutr. 2006;136:45–51.

Celec P, Ostatnikova D, Caganova M, Zuchova S, Hodosy J, Putz Z, Bernadic M, Kúdela M. Gynecol Obstet Invest. 2005;59:62–6.

Chen Z, Zheng W, Custer LJ, Dai Q, Shu XO, Jin F, Franke AA. Nutr Cancer. 1999;33:82–7.

Chiechi LM, Secreto G, D'Amore M, Fanelli M, Venturelli E, Cantatore F, Valerio T, Laselva G, Loizzi P. Maturitas. 2002;42:295–300.

Choi EJ, Lee BH. Life Sci. 2004;75:499–509.

Coward LN, Barnes C, Setchell KD, Barnes S. J Agric Food Chem. 1993;41:1961–7.

de Kleijn MJ, van der Schouw YT, Wilson PW, Adlercreutz H, Mazur W, Grobbee DE, Jacques PF. J Nutr. 2001;131:1826–32.

Dhom G. In: Voight KD, Knabbe C, editors. Endocrine dependent tumors. New York: Raven Press; 1991. pp. 1–42.

Duffy R, Wiseman H, File SE. Pharmacol Biochem Be. 2003;75:721–9.

Ernst E. Ann Intern Med. 2002;136:42–53.

File SE, Hartley DE, Elsabagh S, Duffy R, Wiseman H. Menopause. 2005;12:193–201.

File SE, Jarrett N, Fluck E, Duffy R, Casey K, Wiseman H. Psychopharmacology. 2001;157:430–6.

Fitzpatrick LA. Maturitas. 2003;44:S21–9.

Fournier LR, Ryan Borchers TA, Robison LM, Wiediger M, Park JS, Chew BP, McGuire MK, Sclar DA, Skaer TL, Beerman KA. J Nutr Health Ageing. 2007;11:155–64.

Franco OH, Burger H, Lebrun CE, Peeters PH, Lamberts SW, Grobbee DE, Van Der Schouw. J Nutr. 2005;135:1190–5.

Frankenfeld CL, Atkinson C, Thomas WK, Goode EL, Gonzalez A, Jokela T, Wähälä K, Schwartz SM, Li SS, Lampe JW. Exp Biol Med (Maywood). 2004;229:902–13.

FSA. COT WOrking group on phytoestrogens draft report. Retrieved August 18, 2008, from http://www.food.gov.uk/ multimedia/webpage/phytoreportworddocs; 2002***

Fuh JL, Wang SJ, Lee SJ, Lu SR, Juang KD (2006). Maturitas. 53: 447–453

Ganora L. (2008) Phyoestrogens. Retrieved August 16, 2008, from http://www.herbalchem.net/Introductory.htm***

Gibbs RB. In: Rasgun NL, editor. The effects of estrogen on brain function. Baltimore: John Hopkins Press; 2006. pp. 9–45.

Ginting E, Arcot J. J Agric Food Chem. 2004;52:7752–8.

Gleason CE, Carlsson CM, Barnet JH, Meade SA, Setchell KD, Atwood CS, Johnson SC, Ries ML, Asthana S. Age Aging. 2009;38:86–93.

Grodstein F, Mayeux R, Stampfer MJ. J Am CollNutr. 2000;19:207–9.

Gurel A, Coskun O, Armutcu F, Kanter M, Ozen OA. J Chem Neuroanat. 2005;29:173–8.

Halbreich U, Kahn LS. Expert Opin Pharmacother. 2000;1:1385–98.

Henderson VW, Benke KS, Green RC, Cupples LA, Farrer LA, MIRAGE Study Group. J Neurol Neurosurg Psychiatry. 2005;76:103–5.

Ho SC, Chan AS, Ho YP, So EK, Sham A, Zee B, Woo JL (2007) Menopause. 14: 489–499

Hogervorst E. In: Rasgun NL, editor. Effects of estrogen on brain function. Baltimore: John Hopkins University Press; 2006. pp. 46–78.

Hogervorst E, Yesufu A, Sadjimim T, Kreager P, Rahardjo TB. In: Hogervorst E, Henderson AS, Brinton-Diaz R, Gibbs R (eds.) Hormones, cognition and dementia. New York: Cambridge University Press; 2009.

Hogervorst E, Henderson V, Brinton-Diaz R, Gibbs R. Hormones cognition and dementia. Edinburgh: Cambridge University Press; (2009 in press) (Chapter 13) 121–122.

Hogervorst E, Sadjimim T, Yesufu A, Kreager P, Rahardjo TB. Dement Geriatr Cogn. 2008;26:50–7.

Hogervorst E, Smith AD. Neuro Endocrinol Lett. 2002;23:155–60.

Horn-Ross PL, Barnes S, Lee M, Coward L, Mandel JE, Koo J, John EM, Smith M. Cancer Causes Control. 2000;11:289–98.

Horn-Ross PL, Lee M, John EM, Koo J. Cancer Causes Control. 2000;11:299–302.

Howes JB, Bray K, Lorenz L, Smerdel P, Howes LG. Climacteric. 2004;7:70–7.

Huang MH, Luetters C, Buckwalter GJ, Seeman TE, Gold EB, Sternfeld B, Greendale GA. Menopause. 2006;13:621–30.

Isingrini M, Taconnat L. Rev Neurol (Paris). 2008;164:S91–5.

Izumi T, Piskula MK, Osawa S, Obata A, Tobe K, Saito M. The Journal of Nutrition. 2000;130(7):1695–1699.

Ju YH, Allred KF, Allred CD, Helferich WG. Carcinogenesis. 2006;27:1292–9.

Kim H, Xia H, Li L, Gewin J. BioFactors. 2000;12:243–50.

Kimira M, Arai Y, Shimoi K, Watanabe S. J Epidemiol. 1998;8:168–75.

Knight DC, Eden JA. Obstet Gynecol. 1996;87:897–904.

Kreijkamp-Kaspers S, Kok L, Grobbee DE, de Haan EH, Aleman A, Lampe JW van der Schouw YT. JAMA. 2004;292:65–74.

Kreijkamp-Kaspers S, Kok L, Grobbee DE, de Haan EH, Aleman A, van der Schouw YT. J Gerontol A-Biol. 2007;62:556–62.

Kritz-Silverstein D, Von Muhlen D, Barrett-Connor E, Bressel MA. Menopause. 2003;10:196–202.

Kuiper GG, Lemmen JG, Carlsson B, Corton JC, Safe SH, van der Saag PT, van der Burg B, Gustofsson JA. Endocrinology. 1998;139:4252–63.

Kurzer MS, Xu X. Annu Rev Nutr. 1997;17:353–81.

Lee YB, Lee HJ, Sohn HS. J Nutr Biochem. 2005;16:641–9.

Linford NJ, Dorsa DM. Steroids. 2002;67:1029–40.

Lu LJ, Anderson KE. Am J Clin Nutr. 1998;68:1500S–4S.

Lu LJ, Grady JJ, Marshall MV, Ramanujam VM, Anderson KE. Nutr Cancer. 1995;24:311–23.

Markiewicz L, Garey J, Adlercreutz H, Gurpide E. J Steroid Biochem Mol Biol. 1993;45:399–405.

Maskarinec G, Singh S, Meng L, Franke AA. Cancer Epidem Biomark. 1998;7:613–9.

Maskarinec S. Nutrition Bytes. 2003;9:5.

Mohamed A, Xu J. Food Chem. 2003;83:227–36.

Morton MS, Wilcox G, Wahlqvist ML, Griffiths K. J Endocrinol. 1994;142:251–9.

Murkies AL, Wilcox G, Davis SR. J Clin Endocrinol Metab. 1998;83:297–303.

Oakenfull D. J Nutr. 2001;131:2971–2.

Occhiuto F, Zangla G, Samperi S, Palumbo DR, Pino A, De Pasquale R, Circosta C. Phytomedicine. 2008;15:676–82.

Ostatníková D, Celec P, Hodosy J, Hampl R, Putz Z, Kúdela M. Fertil Steril. 2007;88:1632–6.

Pan Y, Anthony M, Clarkson TB. Proc Soc Exp Biol Med. 1999;221:118–25.

Pinkerton JV, Henderson VW. Semin Reprod Med. 2005;23:172–9.

Piskula MK. J Nutr. 2000;130:1766–71.

Potter SM. J Nutr. 1995;125:606S–11S.

Reitz C, Honig L, Vonsattel JP, Tang MX, Mayeux R. J Neurol Neurosurg Psychiatry. 2009;80:715–21.

Rice MM, Graves AB, McCurry SM, Gibbons L, Bowen J, McCormick W, Larson EB (2000) Third international symposium on the role of soy in preventing and treating chronic disease, Washington, DC, Oct 31–Nov 3, 1999, Vol. 130, p. 676S.

Rilantono LI, Yuwono HS, Nugrahadi T. Clin Hemorheol Microcirc. 2000;23:113–7.

Rowland I, Wiseman H, Sanders T, Adlercreutz H, Bowey E. Biochem Soc Trans. 1999;27:304–8.

Setchell KD. Am J Clin Nutr. 1998;68:1333S–46S.

Setchell KD. (2000) Absorption and metabolism of soy isoflavones-from food to dietary supplements and adults to infants J Nutr. 2000;130:654S–5S.

Setchell KD, Brown NM, Desai P, Zimmer-Nechemias L, Wolfe BE, Brashear WT, Kirschner AS, Cassidy A, Heubi JE. J Nutr. 2001;131:1362S–75S.

Setchell KD, Brown NM, Desai PB, Zimmer-Nechimias L, Wolfe B, Jakate AS, Creutzinger V, Heubi JE. J Nutr. 2003;133:1027–35.

Slavin JL, Karr SC, Hutchins AM, Lampe JW. The American Journal of Clinical Nutrition, 68(6 Suppl), 1998;1492S–1495S.

Smith AD (2002) Am. J. Clin. Nutr. 75: 85–786

Sonee M, Sum T, Wang C, Mukherjee SK. Neurotoxicology. 2004;25:885–91.

Thilers PP, Macdonald SW, Herlitz A. Psychoneuroendocrinology. 2006;31:565–76.

Trieu VN, Dong Y, Zheng Y, Uckun FM. Radiat Res. 1999;152:508–16.

US Food and Drug Administration. Federal Register. 1999;64:57699–733.

Valsta LM, Kilkkinen A, Mazur W, Nurmi T, Lampi AM, Ovaskainen ML, Korhonen T, Adlercreutz H, Pietinen P. Br J Nutr. 2003;89:S31–8.

Wang HJ, Murphy P. J Agr Food Chem. 1994;42:1666–73.

Wakai K, Egami I, Kato K, Kawamura T, Tamakoshi A, Lin Y, Nakayama T, Wada M, Ohno Y. Nutr Cancer. 1999;33:139–45.

Whalley LJ, Starr JM, Athawes R, Hunter D, Pattie A, Deary IJ. Neurology. 2000;55:1455–9.

White LR, Petrovitch H, Ross GW, Masaki K, Hardman J, Nelson J, Davis D, Markesbery W. J Am Coll Nutr. 2000;19:242–55.

Wiseman H, Casey K, Bowey EA, Duffy R, Davies M, Rowland IR, Lloyd AS, Murray A, Thompson R, Clarke DB. Am J Clin Nutr. 2004;80:692–9.

Woolley CS, McEwen BS. J Comp Neurol. 1993;336:293–306.

Wu AH, Yu MC, Tseng CC, Pike MC. Br J Cancer. 2008;98:9–14.

Yesufu A. Demographic and modifiable risk factors for age related cognitive impairment and possible dementia. Loughborough University Library; 2009.

Zeng H, Chen Q, Zhao B. Free Radic Biol Med. 2004;36:180–8.

Zhao L, Brinton RD. Expert Rev Neurother. 2007;7:1549–64.

Zubik L, Meydani M. Am J Clin Nutr. 2003;77:1459–65.

Chapter 177
Nutritional Risk in the Elderly with Cognitive Impairment: A Far Eastern Perspective

Kang Soo Lee and Chang Hyung Hong

Abbreviations

AD	Alzheimer's disease
ADL	Activities of daily living
IADL	Instrumental activities of daily living
K-MMSE	Korean version of mini mental state examination
MCI	Mild cognitive impairment
NCF	Normal cognitive function
NSI	Nutrition screening initiative

177.1 Introduction

The 2005 data from the Korea National Statistical Office indicates that by 2018, Korea would become an aged society in which the elderly population, i.e., persons aged more than 65 years, would comprise 14% of the total population. As a result, problems pertaining to the welfare and health of the elderly have become a national concern. With the increase in the elderly population, the incidence of chronic geriatric diseases is also on the rise. Nutrition and diet have gradually become important from the perspective of prevention of geriatric diseases and promotion of the health of the elderly. If malnutrition refers to dietary intake in reference to dietary needs, intakes of several nutrients have been shown to be inadequate among those living in the community. However, diet is only one indicator of nutritional status of elderly people and probably not the best given the methodological assessment issues. Therefore, other indicators such as anthropometric, hematological, biochemical and immunological indices, health conditions and diseases need to be considered in addition in the evaluation of nutritional health. Many efforts have been directed to discovering factors influencing the nutritional status of elderly people to identify people with poor nutritional status or those who are at high risk of nutritional problems. Based on these factors, some simple and easy to apply nutritional assessment tools such as nutrition screening initiative checklist have been developed.

Malnutrition is one of the most prevalent problems in the elderly that is easily overlooked. The nutritional state of the elderly is threatened by several factors including the followings: tooth loss or

C.H. Hong (✉)
Department of Psychiatry and Ajou Institute of Aging, Ajou University School of Medicine,
San 5, Wonchun-dong, Youngtong-gu, Suwon-si, 443-749, Korea
e-mail: antiaging@ajou.ac.kr

masticatory difficulty; deterioration of physiological functions, including the weakening of digestion and absorption; loss of gustation; effect of medications used for treating various ailments; smoking; habitual drinking; decreased activity; living alone; depression due to death of a spouse; psychological factors such as feelings of neglect; financial difficulties due to reduction in income; and environmental factors (Brownie 2006). Consequently, there is insufficient intake of food by the elderly and the utilization rate in the body also becomes lower; thus, there is a high predisposition to a nutritional risk state. Through various studies, it has been shown that the nutritional state of elderly Koreans is generally not good (Kim et al. 1997; Cho et al. 1997). In particular, the level of malnutrition is higher in the elderly residing in social welfare institutions and the low-income elderly residing at home, and it is known that the nutritional intake state is poor in the elderly who evaluate their own health as being poor or as having more clinical symptoms of diseases (Son et al. 1996; Song et al. 1995).

There is growing attention in the relationships between aging, nutritional status, and cognitive function. Research in this filed has tended to focus on advanced old age, although many of the causal pathway implicated may operate over a much longer period from early life. Nutrition has been found to be associated with cognitive impairment and dementia in older populations. The nutritional risk level of the elderly is associated with cognitive function (Pearson et al. 2001). Impairment of cognitive functions related to the basic activities of daily living (ADL) has been reported to be more rapid over a 1-year follow-up period in malnourished subjects (Vellas et al. 2005). An increased interest in this field has led to the formulation of varied hypotheses regarding the correlation between nutritional factors and cognitive impairment (Donini et al. 2007).

177.2 Nutrition and Alzheimer's Dementia

Nutrition Screening Initiative (NSI) checklist has been developed as part of the US Nutrition Screening Initiative, a collaborative effort between the American Dietetic Association, the American Academy of Family Physicians and the National Council on the Aging, Inc. The NSI checklist is the first step in a two-tiered approach to screening and assessment. The checklist is designed to enhance the older person's understanding of the determinants of nutritional well-being and promote the consideration of nutritional problems by health professionals. This self-administered awareness tool is intended for the public and may need a follow-up by professionals for further nutritional and health assessments. The checklist includes 10 Yes/No items that are given different weights associated with the nutritional well-being of older people. The checklist is not meant to be a clinical diagnostic tool but should predict overall perceived health status and identify persons whose estimated nutrient intakes fall below the recommended dietary allowances (Table 177.2).

Table 177.1 Key features of K-MMSE: Korean Mini Mental State Examination

1. The MMSE developed by Folstein et al. (1975) is the most widely used instrument for measuring global cognitive performance and for identifying individuals with cognitive dysfunction
2. The MMSE, variously modified and translated into several languages, has been used successfully in several independent cross-national studies of dementia epidemiology
3. The original MMSE was somewhat modified in the development of the K-MMSE in order to adapt it to the cultural background in Korea
4. The total K-MMSE score was calculated by summing the correct responses to all the K-MMSE sub items
5. The test scores ranged from 0 to 30
6. A Korean study in the community defined the cutoff point of K-MMSE score during the screening of dementia as 17/18 points

Table 177.2   Key features of nutrition screening Initiative checklist

1. The Nutrition Screening Initiative checklist comprises 10 questions that were designed such that their answer would be "yes" or "no."
2. Based on the evaluation standard for the nutritional risk level, 0–2 points were assigned to a good nutritional state; 3–5 points, moderate nutritional risk state; and more than 6 points, high nutritional risk state.
3. In case of good nutritional state, recheck your nutritional score in 6 months
4. If you are at moderate nutritional risk, see what can be done to improve your eating habits and life style. Recheck your nutritional score in 3 months
5. If you are at high nutritional risk, bring this checklist the next time you see your doctor or other qualified health and social service professional. Ask for help to improve your nutritional health.
6. The NSI checklist is influenced by the type of family members living together, diseases, financial condition, age, physical health condition, and its effects on cognitive function
7. Question 1 (yes = 2 point): I have an illness or condition that made me change the kind and/or amount of food I eat. Question 2 (yes = 3 point): I eat fewer than 2 meals per day. Question 3 (yes = 2 point): I eat few fruits or vegetables or milk products Question 4 (yes = 2 point): I have 3 or more drinks of beer, liquor or wine almost every day. Question 5 (yes = 2 point): I have tooth or mouth problems that make it hard for me to eat. Question 6 (yes = 4 point): I don't always have enough money to buy the food I need. Question 7 (yes = 1 point): I eat alone most of the time. Question 8 (yes = 1 point): I take 3 or more different prescribed or over-the-counter drugs a day. Question 9 (yes = 2 point): Without wanting to, I have lost or gained 10 lb in the last 6 months. Question 10 (yes = 2 point): I am not always physically able to shop, cook, and/or feedmyself.

Nutritional status is potentially important in the etiology of cognitive impairment and dementia. Dementia is associated with weight loss, which precedes the onset of the clinical syndrome and accelerates around the time of diagnosis. Specific nutritional deficits such as vitamin B12 and folate deficiency are recognized to be important potential risk factors, and other dietary factors such as caloric intake and fish consumption have also been implicated as modifying risk. Epidemiological (Masaki et al. 2000; Engelhart et al. 2002) and laboratory studies (Cotman et al. 2002; Kruman et al. 2002) have demonstrated that antioxidants, which are found in abundance in fresh fruits and vegetables, are associated with cognitive function. In addition, it has been reported that nutritional substances or food stuffs such as fish, vitamin, and a moderate amount of alcohol decrease the risk for dementia and Alzheimer's disease (AD) (Kalmijn et al. 1997, 2004; Luchsinger and Mayeux 2004). Several studies have clearly demonstrated that nutritional factors are linked with AD, both as risk or protective factors in the onset of the disease and as elements that are capable of modifying the disease course (Donini et al. 2007). Although dietary intervention is capable of minimizing or preventing weight loss (Franzoni et al. 1996), patients at particular risk of malnutrition are not detected quickly enough; therefore, nutritional screening tools should be included in the multidimensional geriatric evaluation that must be performed in every elderly patient.

177.3 Nutrition and Mild Cognitive Impairment

In 1999, Petersen et al. proposed clinical MCI criteria including essentially preserved activities of daily living. In 2003, Petersen et al. revised original criteria as one including clinical judgment for assessing people of low education and for ADL performance. In terms of the criterion of preserved activities of daily living, the CSHA study found intact ADL to be unnecessary for case definition but the validity of the ADL criterion were also challenged in the other study. These reflect that MCI represents a condition with multiple sources of heterogeneity. Key methodological factors differing

across studies of MCI include (1) the fact of MCI diagnoses being assigned on a case-by-case basis in a consensus conference of expert clinicians or assigned purely objectively using neuropsychological, functional, and medical data; (2) the extent to which non-demented older subjects with memory deficits are distinguished from those with cognitive deficits in non-memory domains; (3) the extent to which those with isolated deficits in one cognitive domain are distinguished from those with impairment in multiple cognitive domains; (4) the test score "cutoff" used to define cognitive impairment; (5) the use of norms that adjust for age and other background factors such as years of school, sex, and race/ethnicity; (6) the extent to which subjective memory complaints are considered as a requirement for the diagnosis of MCI; and finally, (7) follow-up diagnosis being made with the knowledge of prior diagnostic status.

Difficulties remain in defining the boundaries between normal ageing and MCI, and between MCI and mild dementia. An international working group on MCI formulated specific recommendations for certain criteria, including: (1) the individual is neither normal nor demented; (2) there is evidence of cognitive deterioration, shown by either objectively measured decline over time or subjective report of decline by self or informant in conjunction with objective cognitive deficits; and (3) activities of daily life are preserved and complex instrumental functions are either intact or minimally impaired. Considering the special situation that low educational level and simple life style are frequent in the Korean rural community, there are many subjects who are neither normal nor demented and whose complex instrumental functions are impaired. Findings of epidemiological studies have shown that subtle difficulties in the performance of everyday activities are common in individuals with MCI. If limitations on complex ADL were present in patients with MCI, the assessment of impairments in everyday life might provide useful complementary information to establish the diagnosis of the syndrome. The use of combined tests has shown to be a promising procedure in order to increase the accuracy of mild dementia diagnoses, as for instance the combination of a cognitive test with a functional evaluation test. An approach that combines both domains of information is often part of a comprehensive clinical assessment and appears, from the present data, to be valuable in prediction of clinical course as well. However, until now no specific instruments for evaluating complex ADL in MCI have been proposed. So, there is a need for a consensus regarding the degree of functional decline that can be considered acceptable in the frame of MCI definition.

Mild cognitive impairment (MCI) defines a transitional stage between normal aging and dementia (Petersen et al. 2001) and reflects a clinical situation where a person has complaints about memory loss and shows objective evidence of cognitive impairment but exhibits no evidence of dementia (Burns and Zaudig 2002). Not many studies have prospectively addressed the role of putative risk factors for MCI. Three short-term longitudinal studies, carried out in subjects with MCI, identified older age, low education, being African American, presence of ApoE 4, cortical atrophy at neuroimaging, signs or symptoms of vascular diseases and depression as risk factors. In a recent 3-year prospective study, the authors found that a previous diagnosis of psychosis, hip fracture and polypharmacy increased the risk of cognitive impairment in non-demented subjects, independent of subsequent development of dementia. Furthermore, three long-term prospective studies described midlife alcohol drinking, elevated serum cholesterol, high diastolic blood pressure, ApoE4, and white matter hyperintensities as risk factors for MCI in late life. In the absence of sensitive and specific biomarkers, risk profiles are of great importance in identifying individuals with the highest probability of incipient disease. To the extent that MCI represents preclinical AD, risk factors for AD should also be risk factors for MCI development or progression. That this degree of correspondence has not been found again reflects the heterogeneity of MCI. These might well represent reversible comorbid conditions, other than neurodegeneration, that caused or contributed to the cognitive impairment, for example, depression, heart failure, anticholinergic drug use (Ganguli 2006).

Over the last decade few studies have examined nutritional risk and low weight in the community-living older adult population. Multifactorial issues that contribute to nutritional risk and malnutrition make it difficult to study. It is apparent that weight loss and nutritional risk are common in this population and can be associated with adverse outcomes. The results of many studies carried out in recent years ascertained that nutritional factors are linked with dementia, especially with AD, both as risk or protective factors in the onset of the disease and elements able to modify the course of the disease (Donini et al. 2007). But in the case of MCI, antioxidant trials are underway, aiming to prove that vitamin E, selegiline, and Ginkgo Biloba slow or stop MCI to AD conversion (Brenner 2003; Mecocci et al. 2004); however, another trial (Petersen et al. 2005) failed to demonstrate a benefit from vitamin E. This approach is in line with previous studies on preceding concepts on MCI with cognitive stimulants and nootropics (Levy 1994; Lockhart and Lestage 2003). The results have been consistently disappointing and in contrast with neurobiological data, which have always been in favor of the role of free radicals and reactive oxygen species in cell death and dementia onset (Qin et al. 2006).

177.4 Nutrition and Functional Status in the Elderly

At the beginning of the disease course, there may be an alteration of nutritional status. This alteration may be explained by a change in dietary intake due to the inability to carry out complex tasks in daily life (e.g., difficulty in shopping, preparing meals, or selecting food). A change in the instrumental activities of daily living (IADL), which assesses independence in performing complex tasks in daily life, is sometimes one of the first signs of the disease. The original criteria for MCI provided for intact ADL, but the current recommendations indicate that the basic ADL should be mainly preserved, and that a "minimal impairment" in IADL may be accepted (Winblad et al. 2004). Recent data suggest that the inclusion of IADL restriction in MCI criteria improves the prediction of subsequent dementia as well as the stability of the MCI condition over time (Peres et al. 2006). Although no consensus has been reached about what composes an ADL restriction in MCI, functional impairments in MCI are focused on the area of instrumental ADL (IADL) tasks – such as managing finances or using a telephone. As IADL tasks are definitely more cognitively demanding tasks than basic ADL tasks, they are more likely to be vulnerable to early cognitive decline due to MCI. Loss in the ability to complete IADL tasks can be among the earliest signs of MCI, even though global functional impairment would still be unnoticeable. Moreover, recent studies suggest that MCI patients with IADL impairment are at higher risk of progression to dementia in the future. MCI patients have significantly worse IADL ratings compared with cognitively unimpaired controls, and those with IADL impairment experience more rapid functional decline and are more likely to convert to dementia compared with those MCI patients without IADL problems. Therefore, an assessment of the completion of IADL tasks in MCI is potentially of great interest, and could serve as a major criterion for differentiating MCI and cognitively normal elderly. Impaired IADL is a strong prognosticator of progression to dementia, with the risk increasing as a function of the number of impaired IADL tasks, particularly specific IADL tasks (e.g., telephone, transport, medication, and finances) in MCI patients, the conversion rate being almost four times higher.

Because functional and nutritional statuses are interrelated, functional impairment can also increase the risk of poor nutrition in MCI. Many of the identified nutritional risk factors of malnutrition are based on functional competencies such as mobility, depression, cognition, food shopping, and food preparation. Considering MCI has little known risk factors and minimal impairment in IADL, nutritional risk assessment will be helpful.

177.5 Nutritional Risk and Cognition: A Far Eastern Perspective

177.5.1 Nutritional Risk and Cognitive Impairment

Elderly Korean people have a low level of education because the sociopolitical circumstances during their childhood and adolescence hindered their access to formal schooling, and the availability of public education was generally lower during the time period between the Second World War and the Korean War. Although the K-MMSE equals the scoring of the MMSE reported by Folstein, considering the special situation that low educational level are frequent in the Korean rural community, the low K-MMSE scores in the MCI subjects could not suggest that these patients may meet criteria for dementia. Another normative study of the K-MMSE in the elderly showed that education level had a greater effect on the K-MMSE than age and sex (Table 177.1).

The MMSE developed by Folstein is the most widely used instrument for measuring global cognitive performance and for identifying individuals with cognitive dysfunction. The elderly exhibit a high prevalence of cognitive dysfunction that may influence their test performance, and therefore their normative data may differ from those in younger subjects. The MMSE, variously modified and translated into several languages, has been used successfully in several independent cross-national studies of dementia epidemiology. The MMSE was modified and translated into Korean by Kang, and the resulting K-MMSE has been widely used in clinical evaluations and research involving patients with dementia in Korea. The original MMSE was somewhat modified in the development of the K-MMSE in order to adapt it to the cultural background in Korea; however, the K-MMSE still shares all of the limitations of the original MMSE. Temporal orientation was assessed according to the two methods used to calculate year and time in Korea: the solar and lunar years. The words "airplane," "pencil," and "pine tree" were used in the memory assessment, with their associated sounds. Serial sevens (sequential subtraction of 7 from 100) were performed to assess the attention of each patient. The repetition phrase item, "no ifs, ands, or buts," was modified to "seeing is believing" with vowel sounds. The three-stage command was modified to "turn the paper over, fold it in half, and give it to me." The total K-MMSE score was calculated by summing the correct responses to all the KMMSE sub items. The test scores ranged from 0 to 30.

The original K-MMSE score was lower in the moderate or high nutritional risk state group of elderly subjects living in the community when compared with the good nutritional state group of elderly subjects. A Korean study in the community defined the cutoff point of K-MMSE score during the screening of dementia as 17/18 points; the sensitivity and specificity of the findings were 91% and 86%, respectively (Kim et al. 2003). Based on these results, we defined cognitive impairment as the group that had a K-MMSE score lower than 17 points, and cognitive non-impairment was defined as the group that had a K-MMSE score higher than 18 points. In the good nutritional state group, the percentage of subjects demonstrating cognitive function impairment was only 13.9%, whereas it was 27.0% in the moderate nutritional risk state group or the high nutritional risk state group. This suggests that malnutrition state is associated with an impairment of cognitive function (Tables 177.3 and Fig 177.1).

This is in agreement with the findings reported in a study of 627 elderly individuals (Pearson et al. 2001). Although the interrelationship between cognitive impairment and nutritional risk are complex and reciprocal; cognitive impairment recedes malnutrition or vice versa. Recent research demonstrates that altered nutritional status appear to predict the severity and progression of cognitive impairment (Vellas et al. 2005). These findings underscore the importance of systematic nutritional assessment at the time of diagnosis and during the follow-up of cognitive impairment cases, especially in those with dementia, in order to implement nutritional intervention as soon as it is deemed necessary (Gillette-Guyonnet et al. 2007). To examine whether cognitive function differs depending

Table 177.3 The relationship between nutritional risk and Mini Mental State Examination in the Far Eastern community elderly subjects (Reprinted from Lee et al.2009. With permission)

K-MMSE score	Good nutritional state (NSI[a] score ≤ 2), n (%)	Moderate or high nutritional risk (NSI[a] score > 2), n (%)	p^b
>17	1485 (86.1)	615 (73.0)	<0.0001
≤17	239 (13.9)	228 (27.0)	

[a]Nutritional Screening Initiative

[b]Chi-square test

Chi-square analysis was performed to assess the risk for cognitive impairment based on the presence or absence of nutritional risk. Table 177.2 shows that the relative frequency of cases with cognitive impairment was higher in the moderate or high nutritional risk level group when compared with that observed in the good nutritional state group ($x^2 = 66.1$, d.f. = 1, $p < 0.0001$)
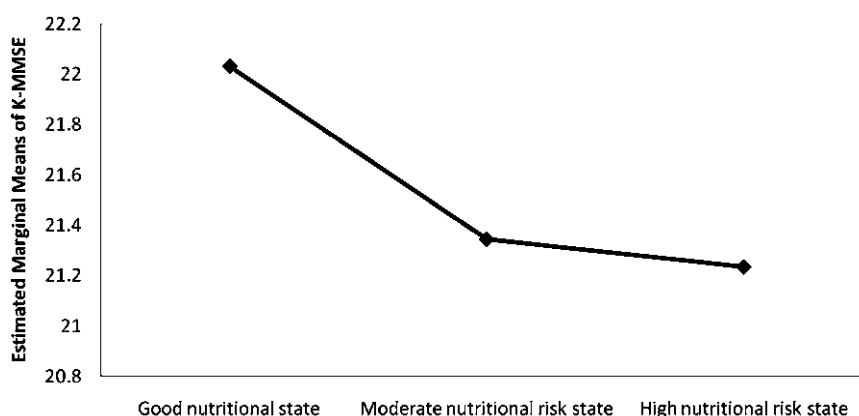
Fig.177. 1 Estimated marginal means of Mini Mental State Examination according to the nutritional risk in the Far Eastern community elderly subjects. Multiple logistic regression analysis was performed to assess the risk for cognitive impairment based on the presence or absence of nutritional risk after adjustment for age, sex, and educational level. General Linear Model (GLM) univariate analysis was performed, and GLM profile plots were plotted as shown in this figure (Reprinted from Lee et al. 2009. With permission)

on the responses to the ten questions in the NSI checklist, we compared the response rate of NSI checklist items in the low and high K-MMSE groups. It was observed that the low K-MMSE group responded more frequently to the following two items after adjustment of age, sex, education: (1) "I have tooth or mouth problems that make it difficult for me to eat," (2) "I am not always physically able to shop, cook, and feed myself." Tooth problems are not simply limited to oral problems. Additionally, they are not limited by their association with the socio-economic and education levels, lifestyle, and smoking history; they are also related to diverse physical conditions such as the presence of cardiopulmonary diseases. It has been reported that there is an association between most oral problems and lower cognitive function (Avlund et al. 2004). However, the results cannot confirm whether the presence of tooth and other oral problems resulted in malnutrition and consequently impairment in cognitive function, whether cognitive impairment was caused by other factors that led to tooth and oral problems, or whether cognitive impairment resulted in changes in the lifestyle that induced tooth and oral problems. The same problem was also applied to other questions.

177.5.2 Nutritional Risk and Mild Cognitive Impairment

The frequency of MCI was higher in the moderate or high nutritional risk state group of elderly subjects living in a community when compared with the group of elderly subjects in a good nutritional state. In the good nutritional state group, the percentage of MCI subjects was only 47.0%, whereas it was 61.1% in the moderate or high nutritional risk state group. One study showed that the K-MMSE score was lower in the moderate or high nutritional risk state group of elderly subjects living in the community when compared with the good nutritional state group of elderly subjects. In line with this concept, the nutritional risk state is associated with an MCI (Table 177.4).

However, the interrelationships between MCI and nutritional risk are complex and reciprocal; MCI precedes malnutrition or vice versa. On the one hand, nutritional risk influences risk factors or outcomes of MCI. Recent research demonstrates that an altered nutritional status appear to predict the severity and progression of cognitive impairment (Vellas et al. 2005). These findings underline the systematic nutritional assessment in MCI. On the other hand, mild changes in discrete IADLs in MCI increase nutritional risk. By analyzing the functional characteristics of subjects with MCI collected in the ReGAl study, it was found that subjects with MCI had more severe IADL disability than cognitively healthy elderly controls, particularly with regard to shopping, self-administration of drugs, and handling finances. These IADL disabilities were significantly associated with the degree of cognitive impairment, but not with somatic comorbidity. Similarly, in another study (Perneczky et al. 2006), it was found that MCI patients are limited in everyday tasks that involve either memory (i.e., finding things at home, keeping appointments, and remembering information from a conversation or from television) or complex reasoning (i.e., checking bank account, shopping). When compared the response rate of the NSI checklist items in the MCI and NCF elderly groups to examine whether MCI results in different responses to the ten questions in the NSI checklist. The MCI group responded more frequently to the following two items after the adjustment of age, sex, and education: (1) "I do not always have enough money to buy the food I need" and (2) "I am not always physically able to shop, cook, and feed myself (Table 177.5)." Items (1) and (2) generally reflect financial abilities and physical abilities. Because the "yes" response rate to item (1) was too low, the interpretation of the result has limitations. But financial abilities cognitively demand IADLs that are vital to independent functioning in a community (Marson et al. 2000), and they are very sensitive to mild AD (Earnst et al. 2001; Wadley et al. 2003). Financial skills are multidimensional, and they encompass an array of judgmental, conceptual, and pragmatic skills. They have been shown to be affected in the early stages of dementia. The nutritional state is also not limited by the association with the socio-economic and education levels, lifestyle, and

Table 177.4 Multiple logistic regression analysis for mild cognitive impairment with nutritional risk in the Far Eastern community elderly subjects (Reprinted from Lee et al. 2009. With permission)

	β (SE)	p	OR (95% CI)
Intercept	−0.28 (1.44)	0.846	–
Nutritional risk (NSI score ≥ 3)	0.12 (0.06)	0.032	1.13 (1.01–1.26)
Age (year)	0.004 (0.02)	0.849	1.14 (1.10–1.17)
Sex: male	0.24 (0.24)	0.319	1.28 (0.79–2.06)
Education (year)	−0.23 (0.08)	0.007	0.798 (0.679–0.939)
K-SGDS score	0.03 (0.03)	0.317	1.028 (0.974–1.086)

K-SGDS Korean short form Geriatric Depression Scale, *SE* standard erro, *OR* odds ratio, *CI* confidence interval

The nutritional risk increased the risk of mild cognitive impairment (OR = 1.13, 95% CI = 1.01–1.26) after the adjustment for age, sex, educational level, and geriatric depression score

Table 177.5 Relationship between mild cognitive impairment and nutrition screening initiative checklist (ten items) in the Far Eastern community elderly subjects (Reprinted from Lee et al. 2009. With permission)

Items (weighted score)		NCF elderly n (%)	MCI n (%)	p	Odds ratio (OR)
F1. I have an illness or condition that made me change the kind and/or amount of food I eat. (2)	Yes	23 (9.7)	37 (14.6)	0.10	Unadjusted OR = 0.627 (0.361–1.092)
	No	214 (90.3)	216 (85.4)		Adjusted OR = 1.563 (0.890-2.744)
F2. I eat fewer than two meals per day. (3)	Yes	2 (0.8)	3 (1.2)	0.71	Unadjusted OR = 0.709 (0.117–4.282)
	No	235 (99.2)	250 (98.8)		Adjusted OR = 1.532 (0.243–9.658)
F3. I eat few fruits or vegetables or milk products. (2)	Yes	1 (0.4)	4 (1.6)	0.20	Unadjusted OR = 3.791 (0.421–34.165)
	No	236 (99.6)	249 (98.4)		Adjusted OR = 4.717 (0.496–44.832)
F4. I have three or more drinks of beer, liquor, or wine almost every day. (2)	Yes	6 (2.5)	10 (4.0)	0.38	Unadjusted OR = 1.584 (0.567–4.429)
	No	231 (97.5)	243 (96.0)		Adjusted OR = 1.503 (0.513–4.404)
F5. I have tooth or mouth problems that make it hard for me to eat. (2)	Yes	118 (49.8)	135 (53.4)	0.43	Unadjusted OR = 1.154 (0.809–1.645)
	No	119 (50.2)	118 (46.6)		Adjusted OR = 0.963 (0.662–1.400)
F6. I don't always have enough money to buy the food I need. (4)	Yes	2 (0.8)	12 (4.7)	0.01	Unadjusted OR = 5.851(1.295–26.423)
	No	235 (99.2)	241 (95.3)		Adjusted OR = 6.006 (1.316–27.398)
F7. I eat alone most of the time. (1)	Yes	33 (13.9)	40 (15.8)	0.56	Unadjusted OR = 1.161 (0.705–1.913)
	No	204 (86.1)	213 (84.2)		Adjusted OR = 1.064 (0.635–1.782)
F8. I take 3 or more different prescribed or over-the-counter drugs a day. (1)	Yes	20 (8.4)	21 (8.3)	0.96	Unadjusted OR = 0.982 (0.518–1.862)
	No	217 (91.6)	232 (91.7)		Adjusted OR = 1.169 (0.608–2.247)
F9. Without wanting to, I have lost or gained 10 lb in the last 6 months. (2)	Yes	3 (1.3)	3 (1.2)	0.94	Unadjusted OR = 0.936 (0.187–4.684)
	No	234 (98.7)	250 (98.8)		Adjusted OR = 1.325 (0.258–6.807)
F10. I am not always physically able to shop, cook and/or feed myself. (2)	Yes	38 (16.0)	65 (25.7)	0.01	Unadjusted OR = 1.811 (1.158–2.831)
	No	199 (84.0)	188 (74.3)		Adjusted OR = 1.647 (1.025–2.648)

NCF normal cognitive function, *MCI* mild cognitive impairment

The mild cognitive impairment group responded more significantly than the normal cognitive function elderly groups in the following two items: (1) "I do not always have enough money to buy the food I need" and (2) "I am not always physically able to shop, cook, and feed myself" ($p = 0.01$; $p = 0.001$, respectively). Those participants with economic problem or physical disability were significantly more likely than those are not to develop mild cognitive impairment (with economic problem adjusted OR = 6.006, 95% CI = 1.316–27.398; with physical disability adjusted OR = 1.647, 95% CI = 1.025–2.648) after adjustment for age, sex, and education

smoking history; it is also related to diverse physical conditions such as the presence of cardiopulmonary diseases. This finding is consistent with the results of previous study that the low cognitive function group (less than the score of K-MMSE 17) responded more frequently to item (1).

177.6 Applications to Other Areas of Health and Disease

Although dietary intervention is capable of minimizing or preventing weight loss, patients at particular risk of malnutrition are not detected quickly enough; therefore, nutritional screening tools should be included in the multidimensional geriatric evaluation that must be performed in every elderly patient.

Because functional and nutritional statuses are interrelated, functional impairment can also increase the risk of poor nutrition in mild cognitive impairment (MCI). Many of the identified nutritional risk factors of malnutrition are based on functional competencies such as mobility, depression, cognition, food shopping, and food preparation. Considering MCI has little known risk factors and minimal impairment in IADL, nutritional risk assessment will be helpful.

Summary Points

- Mini Mental State Examination score was lower in the moderate or high nutritional risk state group of elderly subjects living in the community when compared with the good nutritional state group of elderly subjects.
- The frequency of Mild Cognitive Impairment was higher in the moderate or high nutritional risk state group of elderly subjects living in a community when compared with the group of elderly subjects in a good nutritional state.
- Nutritional factors are linked with Alzheimer's disease, both as risk or protective factors in the onset of the disease and as elements that are capable of modifying the disease course.
- Considering Mild Cognitive Impairment has little known risk factors and minimal impairment in Instrumental Activities of Daily Living, nutritional risk assessment will be helpful.
- Nutrition screening tools should be included in the multidimensional geriatric evaluation that must be performed in every elderly patient.

Key Terms

Mild cognitive impairment: This is a transitional stage between normal aging and dementia and reflects a clinical situation where a person has complaints about memory loss and shows objective evidence of cognitive impairment but exhibits no evidence of dementia.

Nutrition screening initiative: The checklist comprises ten questions that were designed such that their answer would be ''yes'' or ''no.'' 0–2 points were assigned to a good nutritional state; 3–5 points, moderate nutritional risk state; and more than 6 points, high nutritional risk state.

References

Avlund K, Holm-Pedersen P, Morse DE, Viitanen M, Winblad B. Gerodonotology. 2004;21:17–26.
Brenner SR. Arch Neurol. 2003;60:292–303.
Brownie S. Int J Nurs Pract. 2006;12:110–8.
Burns A, Zaudig M. Lancet. 2002;360:1963–5.
Cotman CW, Head E, Muggenburg BA, Zicker S, Milgram NW. Neurobiol Aging. 2002;23:809–18.
Cho HS, Oh BH, Kim KS, Kim KW, Park JY, Lee HR, Yoo GJ. J Kor Geriatr. 1997;1(2):120–139.
Donini LM, De Felice MR, Cannella C. Arch Gerontol Geriatr. 2007;44:143–53.
Earnst KS, Wadley VG, Aldridge TM, Steenwyk AB, Hammond AE, Harrell LE, Marson DC. Aging Neuropsychol Cogn. 2001;8:109–19.
Engelhart MJ, Geerlings MI, Ruitenberg A, Van Swieten JC, Hofman A, Witteman JC, Breteler MM. Neurology. 2002;12:1915–21.

Franzoni S, Frisoni GB, Boffelli S, Rozzini R, Trabucchi M. J Am Geriatr Soc. 1996;44:1366–70.

Ganguli M. Alzheimer Dis Assoc Disord. 2006;20:52–7.

Gillette-Guyonnet S, Abellan Van Kan G, Alix E, Andrieu S, Belmin J, Berrut G, Bonnefoy M, Brocker P, Constans T, Ferry M, Ghisolfi-Marque A, Girard L, Gonthier R, Guerin O, Hervy MP, Jouanny P, Laurain MC, Lechowski L, Nourhashemi F, Raynaud-Simon A, Ritz P, Roche J, Rolland Y, Salva T, Vellas B, International Academy on Nutrition and Aging Expert Group. J Nutr Health Aging. 2007;11:38–48.

Kalmijn S, Launer LJ, Ott A, Witteman JC, Hofman A, Breteler MM. Ann Neurol. 1997;42:776–82.

Kalmijn S, Van Boxtel MP, Ocke M, Verschuren WM, Kromhout D, Launer LJ. Neurology. 2004;62:275–80.

Kim MY. J Kor Commu Health Nur Academic Soc. 1997;11(2):94–105.

Kim JM, Shin IS, Yoon JS, Lee HY. J Kor Neuropsychiatr Assoc. 2003;42:124–30.

Kruman II, Kumaravel TS, Lohani A, Pedersen WA, Cutler RG, Kruman Y, Haughey N, Lee J, Evans M, Mattson MP. J Neurosci. 2002;22:1752–62.

Lee KS, Cheong HK, Kim EA, Kim KR, Oh BH, Hong CH. Arch Gerontol Geriatr. 2009;48:95–9.

Levy R. Int Psychogeriatry. 1994;6:63–8.

Lockhart BP, Lestage PJ. Exp Gerontol. 2003;38:119–28.

Luchsinger JA, Mayeux R. Lancet Neurol. 2004;10:579–87.

Marson DC, Sawrie SM, Snyder S, McInturff B, Stalvey T, Boothe A, Aldridge T, Chatterjee A, Harrell LE. Arch Neurol. 2000;27:877–84.

Masaki KH, Losonczy KG, Izmirlian G, Foley DJ, Ross GW, Petrovitch H, Havlik R, White LR. Neurology. 2000;54:1265–72.

Mecocci P, Mariani E, Cornacchiola V, Polidori MC. Neurol Res. 2004;26:598–602.

Pearson JM, Schlettwein-Gsell D, Brzozowska A, Van Staveren WA, Bjornsbo K. J Nutr Health Aging. 2001;5:278–83.

Peres K, Chrysostome V, Fabrigoule C, Orgogozo JM, Dartigues JF, Barberger-Gateau P. Neurology. 2006;67:461–6.

Perneczky R, Pohl C, Sorg C, Hartmann J, Tosic N, Grimmer T, Heitele S, Kurz A. Int J Geriatr Psychiatry. 2006;21:158–62.

Petersen RC, Thomas RG, Grundman M, Bennett D, Doody R, Ferris S, Galasko D, Jin S, Kaye J, Levey A, Pfeiffer E, Sano M, Van Dyck CH, Thal LJ. N Engl J Med. 2005;352:2379–88.

Petersen RC, Doody R, Kurz A, Mohs RC, Morris JC, Rabins PV, Ritchie K, Rossor M, Thal L, Winblad B. Arch Neurol. 2001;58:1985–92.

Qin B, Cartier L, Dubois-Dauphin M, Li B, Serrander L, Krause KH. Neurobiol Aging. 2006;27:1577–87.

Son SM, Park YJ, Koo JO, Mo SM, Yoon HY, Sung CJ. Kor J Commu Nutr. 1996;1:79–88.

Song YS, Chung HK, Cho MS. Kor J Nutr. 1995;28:1100–1166.

Vellas B, Lauque S, GilletteGuyonnet S, Andrieu S, Cortes F, Nourhashemi F, Cantet C, Ousset PJ, Grandjean H, REAL.FR Group. J Nutr Health Aging. 2005;9:75–80.

Wadley VG, Harrell LE, Marson DC. J Am Geriatr Soc. 2003;51:1621–6.

Winblad B, Palmer K, Kivipelto M, Jelic V, Fratiglioni L, Wahlund LO, Nordberg A, Backman L, Albert M, Almkvist O, Arai H, Basun H, Blennow K, De Leon M, DeCarli C, Erkinjuntti T, Giacobini E, Graff C, Hardy J, Jack C, Jorm A, Ritchie K, Van Duijn C, Visser P, Petersen RC. J Intern Med. 2004;256:240–6.

Chapter 178
Aluminium in the Diet, Cognitive Decline and Dementia

Vincenza Frisardi, Vincenzo Solfrizzi, Patrick G. Kehoe, Bruno P. Imbimbo, Gianluigi Vendemiale, Antonio Capurso, and Francesco Panza

Abbreviations

AD	Alzheimer's Disease
VaD	Vascular dementia
MCI	Mild Cognitive Impairment
NFT	Neurofibrillary tangles
SP	Senile plaque
AβPP	Amyloid-β protein precursor
CAA	Cerebral amyloid angiopathy
CNS	Central nervous system
BBB	Blood-brain barrier
Al	Aluminium
SOD	Superoxide dismutase
RR	Relative risk
OR	Odds ratio
MTP	Mitochondrial transition pore
HEDTA	Hydroxyethylethylenediaminetriacetic acid
ER	Endoplasmic reticulum
ROS	Reactive oxygen species
Zn	Zinc
TCA	Tricarboxylic acid
Ca	Calcium
Mg	Magnesium
ALS	Amyotrophic lateral sclerosis
TPN	Total parenteral nutrition
FDA	Food and Drug Administration

V. Frisardi (✉)
Department of Geriatrics, Center for Aging Brain, Memory Unit, University of Bari, Bristol, UK
e-mail: vfrisardi@yahoo.com

178.1 Introduction

178.1.1 Dementia and Predementia Syndromes

In westernised countries, Alzheimer's disease (AD) and vascular dementia (VaD) are the most common forms of dementia, with estimated incidences of 70% and 15% of all dementia, respectively (Table 178.1). In elderly people, AD is the primary neurodegenerative disorder defined by a loss of memory associated with a progressive deterioration of other cognitive functions that must also contribute to significant decline in a person's level of everyday functioning, eventually to disability and finally contributing to death in a period of time that can range from 2 to 20 years (Table 178.1). After the age of 60 years, the prevalence of AD doubles every 5 years, increasing from a prevalence of 1% among those 60–64 years old to about 40% among those aged 85 years and above (Vickers et al. 1999). Thus, with recent improvements in life expectancy and as a result of increased aging population, AD has become a major public health consideration because of its consequence in terms of social and emotional costs. AD is characterised by two major anatomo-pathological features, intraneuronal protein clusters composed of paired helical filaments consisting of hyperphosphorylated forms of tau protein [neurofibrillary tangles (NFTs)], and extracellular protein aggregates [senile plaques (SPs)]. The SPs contain a diverse array of constituents but the main one being a toxic amyloid β (Aβ) peptide that accumulates most likely as a result of misprocessing of the Aβ protein precursor (AβPP) by β- and γ-secretases as well as reduced levels of clearance of Aβ through the blood-brain barrier (BBB) from the brain (Bell and Zlokovic 2009) and its degradation by a variety of Aβ degrading enzymes within the brain (Miners et al. 2008; Banks et al. 1997). In turn, Aβ aggregates into a variety of molecular configurations (Irvine et al. 2008) which contribute to a pathogenic cascade ultimately leading to neuronal loss. Amongst the various molecular configurations that Aβ can

Table 178.1 Key features of dementia syndromes

1. Dementia is a syndrome definite by impairments in memory and other cognitive functions that are severe enough to cause significant decline from a previous level of social and occupational functioning

2. AD is the most common dementia and primary neurodegenerative disorder in the elderly, gradually leading to a complete psychological and physical dependency and finally to death within one to two decades

3. The diagnosis of AD is essentially a clinical one, and it is based on a typical clinical picture and findings, with a set of clinical criteria often used in research

4. Cognitive function declines over time, and the diagnosis of AD can be considered when the patient has impairments in memory and at least in one other cognitive function (executive dysfunction, agnosia, aphasia, apraxia), severe enough to cause impairment in social or occupational functioning

5. In advanced AD, common symptoms include also confusion, behavioural and gait disturbances, and the patients are increasingly dependent on others in activities of daily living

6. Another common form of dementia is VaD, its clinical presentation varies greatly depending on the causes and location of cerebral damage

7. Large-vessel disease leads commonly to multiple cortical infarcts and a multifocal cortical dementia syndrome

8. Small-vessel disease, usually resulting from hypertension and diabetes, causes periventricular white matter ischemia and lacunar strokes characterised clinically by subcortical dementia with frontal lobe deficits, executive dysfunction, slow information processing, impaired memory, inattention, depressive mood changes, slowing of motor function, Parkinsonian features, small-step gait, urinary disturbances and pseudobulbar palsy

9. The characteristic neuropsychological profile of VaD is believed to include frequently early impairment of attention and executive control function, with slowing of motor performance and information processing, while episodic memory is relatively spared compared to that in AD

This table lists the key facts of dementia syndromes including clinical pictures and criteria of Alzheimer's disease (AD) and vascular dementia (VaD), the most common dementia syndromes

form, including soluble monomers, dimers and oligomers, increasingly complex aggregations are suggested to be more toxic than monomeric forms (Permanne et al. 2002).

Although the 'amyloid cascade hypothesis' is one of the more commonly upheld and cited hypotheses, AD is also recognised to involve a combination of genetic and environmental factors. Moreover, a significant comorbidity of AD and cerebrovascular disease has been demonstrated, suggesting that cerebrovascular disruption may be an important contributor to, and feature of, AD and supporting views of possible pathological and clinical overlap between AD and VaD (Gold 2003; Jellinger 2003). In fact, it has been shown that the major forms of Aβ peptides (Aβ 1–40 and Aβ 1–42) may cause vascular lesions. Cerebral amyloid angiopathy (CAA), which involves the deposition of Aβ 1–40 in the cerebrovascular system and is a major risk factor for stroke, is one such example. CAA is normally present in the majority of AD cases but is only present (in less severe forms) in approximately 30% of non-demented elderly (Love et al. 2009). Other examples include the occurrence of Aβ associated lesions in the arterioles of some animal models (Rhodin et al. 2003), similar to those observed in the brain of AD patients and which may represent the initial phase of a vascular inflammatory response associated with CAA (Banks et al. 2006).

Recently, the term 'predementia syndrome' was proposed to describe all conditions associated with age-related deficits in cognitive function that are reported in the literature. This included a mild stage of cognitive impairment based on a model of normality and pathological characteristics that were considered to be predictive of early stages of dementia (Panza et al. 2006) (Table 178.2). Mild cognitive impairment (MCI) is, at present, the most widely used term to identify non-demented aged persons with a mild memory or cognitive impairment that is not considered to be explained by any recognised medical or psychiatric disorder and which is not severe enough to cause impairment as might be more typically attributed to dementia (Table 178.2). Moreover, 12% of MCI patients develop dementia within 1 year (Panza et al 2005) a prevalence that increases to 20% over 3 years (Petersen et al. 2001). Recently, in the Italian Longitudinal Study on Aging (ILSA), a population-based study involving a sample of 5,632 individuals aged 65–84 years, a progression rate to dementia of MCI of 3.8/100 person-years was found (Solfrizzi et al. 2004). Nevertheless, at present, it still questionable whether these entities are a manifestation of normal aging, are clinically distinguishable from dementing syndromes, or, are part of a continuum with dementia.

Table 178.2   Key features of predementia syndromes

1. The term 'predementia syndromes' identifies all conditions with age-related deficits in cognitive function reported in the literature, including a mild stage of cognitive impairment based on a normality model and pathological conditions considered predictive or early stages of dementia

2. Among predementia syndromes, MCI is, at present, the most widely used term to indicate non-demented aged persons with a mild memory or cognitive impairment that cannot be accounted for any recognised medical or psychiatric condition

3. The general criteria for MCI include: (a) memory complaint, (b) objective memory disorder, (c) absence of other cognitive disorders or repercussions on daily life, (d) normal general cognitive function, (e) absence of dementia

4. MCI definitions can be broadly classified as amnestic (aMCI) and nonamnestic (naMCI)

5. There is now ample evidence that MCI is often a pathology-based condition with a high rate of progression to AD, and aMCI, with a central role for memory disorder and with relative preservation of other cognitive domains, was identified as the predementia syndrome for AD

6. aMCI can be subdivided into a single domain subtype with a pronounced memory deficit or a multiple domain subtype that includes memory impairment along with some impairment in other cognitive domains such as language, executive function, and visuospatial skills

7. The other major MCI subtype is naMCI, which similarly can be subdivided into single and multiple domain subtypes

This table lists the key facts of predementia syndromes including diagnostic criteria and clinical classification of mild cognitive impairment (MCI), the most common predementia syndrome

Table 178.3 Key features of aluminium

1. Aluminium is a nonessential metal present in 8% of the Earth's crust
2. Aluminium has no known function in living cells and produces some toxic effects in elevated concentrations
3. The toxicity of aluminium can be traced to deposition in bone and the central nervous system, which is particularly noticeable in patients with reduced renal function
4. In very high doses, aluminium can cause neurotoxicity, and is associated with altered function of the blood-brain barrier
5. Present studies have not convincingly demonstrated a causal relationship between aluminium and AD. Nevertheless, some studies suggested aluminium exposure as a risk factor for AD, as some brain senile plaques have been found to contain increased levels of the metal

AD Alzheimer's disease

This table lists the key features of aluminium including definition, general health effects, and current research findings on the aluminium and AD

178.1.2 Neurotoxicity of Aluminium and Other Metals

Although knowledge of the pathophysiology of AD has greatly increased during recent decades, and new therapeutic approaches have been proposed, AD is still a chronic and incurable disease, and its causal mechanisms remain unclear. In recent years, interest in the potential role of metals such as iron, copper and zinc, among other trace redox-active transition metals, in the pathogenesis of AD, has grown considerably (Todorich and Connor 2004). The hypothesis that aluminium (Al) exposure is related to AD has prompted several studies and, at present, the relationship is still unresolved and under investigation (Table 178.3). The potential role of Al as a mediator of neurotoxicity was suggested more than 100 years ago after Dollken reported his work with Al in experimental studies on animals (Dollken 1897). Al neurotoxicity was first reported in humans at the beginning of the 1970s when neurodegeneration in patients undergoing chronic hemodialysis was observed (Wills and Savory 1983). The hypothesis that Al could be involved in the pathogenesis of AD arose when Al was detected in SPs and NFTs in brain tissue from AD patients (Crapper et al. 1973). Subsequently, several studies have reported that higher intake of Al increases the production of Aβ in transgenic APP mice (Praticò et al. 2002; El-Rahman 2003). Although further research supported these findings, the role of Al remains controversial, because several other investigations did not find any relationship between Al exposure and risk of AD. In this chapter, we examine the possible role of dietary exposure to Al from drinking water or foods in modulating the risk of age-related changes in cognitive function, predementia and dementia syndromes, as well as the possible molecular epidemiological mechanisms behind the observed associations.

178.2 Environmental Exposure to Aluminium, Including Drinking Water, in Cognitive Decline and Dementia

Al is a non-essential metal present in 8% of the Earth's crust. It is a lightweight, silvery white, soft, malleable metal derived from the refining and smelting of cryolite and bauxite ore (Miessler 2003). Al is omnipresent in everyday life, and may enter the human body in many ways such as the environment, diet or drugs. Several pathological conditions that involve neurobehavioral changes have been reported among the workers involved in the Al industry such as shipbuilding, petroleum processing, and rubber industry. In particular, the potential relationship between Al body burden and CNS function was studied in Al welders where a threshold level for adverse effects was suggested (Riihimäki et al. 2000). In this context, low-exposure and high-exposure groups were defined according to Al concentrations

measured in serum (S-Al) and urine (U-Al) and were examined with a neuropsychological test battery. This neuropsychological testing revealed a circumscribed negative dose-dependent effect associated with increased Al body burden, mainly in tasks demanding complex attention, the processing of information using working memory and the analysis and recall of abstract visual patterns. This study indicated that the body burden threshold for adverse effect approximates to a U-Al value of 4–6 micromol/l and an S-Al value of 0.25–0.35 micromol/l among Al welders (Riihimäki et al. 2000). Further evidence in support of the potential of Al-mediated toxicity in humans comes from observations made of the widespread practise of glue sniffing among teenagers (Akay et al. 2008). Here the investigators compared the S-Al of glue sniffing groups and healthy control adolescents and they computed Al levels of different commercial glue preparations (i.e., metal and plastic containers). The S-Al was found to be 63.29 ± 13.20 in glue sniffers compared with 36.7 ± 8.60 ng/ml in control subjects ($P < 0.001$) (Akay et al. 2008).

Unlike occupational exposures, environmental exposure to Al is inevitable or less easy to avoid. The principal route of metal exposure is through diet (food/drinking water) and inhalation of Al as fine particles. It has been estimated that the dietary intake of Al can range from 3 to 30 mg/day, and varies with the composition of the food eaten, country of residence, age and sex (World Health Organization 1997). In the USA, the total dietary Al intake estimates for adult men and women are 8–9 and 7 mg/day, respectively (Pennington and Schoen 1995). The metal can be taken from food (both naturally occurring Al and its additives), from cookware, utensils and food wrappings, containers (including Al drink cans), and from water, aerosols and dusts. However, dietary absorption of Al consumed from food is small (less than 1% of ingested Al is absorbed) if compared with the amounts consumed through the use of Al containing antacids that may provide doses of 50–1,000 mg/day (Reinke et al. 2003). Similarly, the bioavailability of Al from water is higher than from food (0.3% vs 0.1%, respectively); yet, due to differences in daily Al intake, drinking water contributes considerably less to the total Al body burden (Yokel and Florence 2006).

Since Al is used extensively as a coagulant in water treatment, to reduce the number of small particles or as a flocculation agent to remove organic substances and improve the colour of the water, the issue of safe levels of Al in drinking water is of considerable interest to public health officials and regulatory agencies (Flaten 2001). However, other elements present in drinking water, such as fluoride, copper, zinc, iron could also have an effect on cognitive impairment or influence the Al neurotoxicity. Some epidemiological studies, but not all, suggest that silica could be protective against Al damage, because it reduces the oral absorption of Al and/or enhances Al excretion (Gillette-Guyonnet et al. 2005).

The World Health Organization (1997) has recommended that Al concentrations in drinking water should not exceed 0.2 mg/l. The US Environmental Protection Agency set 0.05 mg/l as a limit in 1985, but the European Union has more recently recommended 0.05 mg/l as a guideline with a maximum permissible level of 0.2 mg/l (Shcherbatykh and Carpenter 2007). Numerous epidemiological studies reported their investigations of the relationship between exposure to Al from drinking water and risk of AD (Flaten 2001). The first attempts to relate the actual levels of Al in drinking water to AD were made in 1986, when two parallel Norwegian studies reported higher mortality from dementia (from all causes) in areas with high Al concentration in drinking water (Vogt 1986). A cross-sectional investigation conducted a few years later in England and Wales found that among all other causes of dementia the risk of AD was 1.5 times higher in districts where the mean Al concentration in drinking water exceeded 0.11 mg/l, compared to the districts where Al concentrations were less than 0.01 mg/l (Martyn et al. 1989) (Table 178.4). In the same period, another ecological study conducted in Canada reported an excess of dementia mortality from the north shore of Bonavista Bay; a phenomenon that could be explained only by high Al concentration in the drinking water (165 mg/l) and low pH (5.2) in that area, because no other differences in sex, age or other parameters could be found (Frecker 1991) (Table 178.4).

Table 178.4 Principal cross-sectional studies on the relationships between dietary aluminium (Al) from drinking water and dementia (i.e., Alzheimer's disease, AD)

References	Setting and study design	Subjects	Aluminium assessment	Cognitive functions assessment	Results and conclusions
Longitudinal studies					
Martyn et al. (1989) United Kingdom	Cross-sectional study	1,203 patients with dementia aged under 70 years; 445 (37%) of these subjects had probable AD by 88 country districts data	Al concentrations in water were obtained from water authorities and water companies	Indirect measures by computed tomography scan records	Among all other causes of dementia, the risk of AD was 1.5 times higher in districts where the mean Al concentration in drinking water exceeded 0.11 mg/l, compared to the districts where Al concentrations were less than 0.01 mg/l
Frecker (1991) Canada	Ecological study; 1985 and 1986 survey data from the province of Newfoundland	399 persons dead between 1985 and 1986	Detailed analysis of untreated drinking water samples collected in June and October 1986 from six communities in Bonavista Bay	Indirect measures by death certificates based census population, the prevalence of dementia at death for 1985 and 1986	The highest Al concentration is recorded in the area with the highest dementia mortality
Neri and Hewitt (1991) Canada	Case-control study	2,232 patients aged 55 years or over	Water quality data from the Water Quality Surveillance Programme of the Ontario Ministry of the Environment	Hospital discharge data with a diagnosis of dementia or presenile dementia	The relative risks associated with the consumption of drinking water containing Al concentrations of <0.01, 0.01–0.1, 0.1–0.199 and >0.200 mg/l were estimated to be 1.00, 1.13, 1.26 and 1.46, respectively
McLachlan et al. (1996) Canada	Case-control study; 830 brains of healthy controls and those with neurodegenerative diseases were donated by next of kin to the CBTB between 1981 and 1991, who, at the time of death, were Ontario residents.	680 brains analyzed which 385 with pathological or clinical diagnosis of AD and 295 controls	Al of public drinking water at last residence before death at the first moment; in the second moment Al of 10-year weighted residential exposure prior to death	Histopathologically verified AD	Elevated risk for AD associated with higher levels of Al (>0.1 mg/l) (OR = 1.7, 95% CI 1.2–2.5). For an Al concentration in drinking water of 0.125 mg/l, the OR for risk of AD was 3.6 (95% CI 1.4–9.9); at 150 mg/l the OR was 4.4 (95% CI 0.98–20), and at 0.175 mg/l it was 7.6 (95% CI 0.98–61)

CBTB Canadian Brain Tissue Bank

This table lists the principal findings of cross-sectional clinical, ecological and epidemiological studies on the relationships between dietary Al from drinking water and dementia (i.e., AD), including setting, study design, and Al and cognitive assessment used. OR = Odds Ratio; 95% CI = 95% confidence internal

A case-control study conducted in Ontario, Canada, described dose–response relationships between the Al content of drinking water and risk of AD, using hospital discharge data with a diagnosis of dementia or presenile dementia (Neri and Hewitt 1991) (Table 178.4). The relative risks (RR) associated with the consumption of drinking water containing Al concentrations of < 0.01, 0.01–0.1, 0.1–0.199 and > 0.200 mg/l were estimated to be 1.00, 1.13, 1.26 and 1.46, respectively. Subsequent re-analysis of the data adjusted for age and sex confirmed a stronger dose–response relationship for those over 75 years of age (Smith 1995). Another Canadian investigation studied the relationship between Al, fluoride and other constituents in drinking water and cognitive function (Forbes et al. 1995). The research project was based on the Ontario Longitudinal Study of Aging, where 2,000 men have been followed for about 30 years. Analysis of the data showed that men living in areas with high Al and low fluoride concentrations in drinking water were about three times more likely to have some form of cognitive impairment than those individuals living in the areas with low Al and high fluoride levels (Forbes et al. 1995). The same authors in a previous analysis confirmed that both neutral pH, relatively low Al concentrations, and relatively high fluoride concentrations in drinking water decreased the odds of cognitive impairment by a factor of five (Forbes et al. 1994). Al concentration in drinking water at last residence before death was used as the measure of exposure in a case-control study conducted on autopsy-verified material comparing the patients with AD and controls without brain pathology (McLachlan et al. 1996) (Table 178.4). The results reported elevated risks for histopathologically verified AD associated with higher levels of Al [odds ratios (OR) = 1.7, 95% CI 1.2–2.5, for a level of Al > 0.1 mg/l]. For an Al concentration in drinking water of 0.125 mg/l, the OR for risk of AD was 3.6 (95% CI 1.4–9.9); for 0.150 mg/l, the OR was 4.4 (95% CI 0.98–20); and for 0.175 mg/l, it was 7.6 (95% CI 0.98–61). Despite the fact that results were seemingly biased by selection criteria, the study had several methodological strengths, including the diagnostic quality of the data (McLachlan et al. 1996) (Table 178.4).

In France, a geographic association between Al and silica and cognitive decline or dementia was reported, utilizing the data from the Personnes Agèes QUID (PAQUID) cohort study. In this study, 3,777 subjects aged 65 years and above who were living at home in either a rural or an urban area in southwestern France were followed for up to 8 years, recording all new cases of dementia and AD (Rondeau et al. 2000). In each residential area, the range and mean exposure to Al (0.001–0.459 mg/l, median 0.009 mg/l) and silica (4.2–22.4 mg/l) from drinking water were recognised. The analysis of data adjusted for age, gender, educational level, place of residence, and wine consumption revealed that the risk of dementia was higher for individuals who lived in areas with high levels of Al in water (mean concentration >0.1 mg/l) compared with people residing in areas with Al levels less than 0.1 mg/l (RR: 1.99; 95% CI: 1.20–3.28, $P = 0.007$). Higher silica concentrations (11.25 mg/l), adjusted for age and gender, were associated with a reduced risk of dementia (RR: 0.71; 95% CI: 0.56–0.91, $P = 0.007$) (Rondeau et al. 2000) (Table 178.5). The adjusted RR of AD for individuals exposed to drinking water with Al concentration > 0.10 mg/l was 2.14 (95% CI: 1.21– 3.80, $P = 0.007$). The risk of AD was reduced in the presence of high concentrations of silica (RR: 0.73; 95% CI: 0.55–0.99, $P = 0.04$), and the authors concluded that a concentration of Al in drinking water above 0.1 mg/l may be a risk factor for dementia and AD although no dose-response effect was found (Rondeau et al. 2000) (Table 178.5). Recently, the same group revisited this topic with more precise data on daily Al and silica intake in a larger cohort followed for 15 years adding 400 subjects from the Aluminum-Maladie d'Alzheimer (ALMA+) cohort to the 3,777 elderly subjects from the PAQUID study (Rondeau et al. 2009) (Table 178.5). In this recent study, two measures of exposure to Al and silica were taken into account: geographic and individual exposure from daily consumption of tap water (including water used in making tea, coffee, soup or alcoholic drinks) and bottled water (spring or mineral). Of the whole sample, only 1,925 subjects were considered because they were free of cognitive impairment at baseline and had reliable water consumption data. Whereas geographic exposure

Table 178.5 Principal longitudinal studies on the relationships between dietary aluminium (Al) and dementia (i.e., Alzheimer's disease, AD and vascular dementia, VaD), or predementia syndromes (i.e., age-related cognitive decline, ARCD) in older people

References Longitudinal studies	Setting and study design	Subjects	Aluminium assessment	Cognitive functions assessment	Results and conclusions
Rondeau et al. (2000) France	Longitudinal study (8 years of follow-up); subjects from PAQUID study	3,777 subjects aged 65 years and older	In each residential area the range and mean exposure to Al (0.001–0.459 mg/l, median 0.009 mg/l) and silica (4.2–22.4 mg/l) from drinking water were recorded	MMSE and other cognitive tests; standardised questionnaire for dementia's diagnosis (DSM III revised criteria); NINCDS/ADRDA criteria for AD; Hachinski score for VaD	The risk of dementia was higher for individuals who lived in areas with high levels of Al in water (>0.1 mg/l) compared with people residing in areas with Al levels less than 0.1 mg/l (RR = 1.99, 95% CI = 1.20–3.28). Higher silica concentrations (>11.25 mg/l), were associated with a reduced risk of dementia (RR = 0.71, 95% CI 0.56–0.91). The adjusted RR of AD for individuals exposed to Al concentration >0.10 mg/l was 2.14 (95% CI 1.21–3.80); the risk of AD was reduced in the presence of high concentrations of silica (RR = 0.73, 95% CI 0.55–0.99). No dose-response effect was found
Gillette-Guyonnet et al. (2005) France	Cross-sectional and longitudinal study (7 years of follow-up); multicentre study (EPIDOS)	7,598 women aged >75 years	Questionnaire relative to the daily consumption of tap water and mineral water and the brand of mineral water most frequently consumed	SPMSQ considering women cognitively normal with a score >8; MMSE and Grober and Buschke test; dementia was diagnosed by DSM IV and AD diagnosed by NINCDS/ADRDA criteria.	An inverse association between silica intake from drinking water and AD was found. Women with AD were 2.7 times as likely to have a low daily silica intake (<4 mg/day). However, this study does not show any evidence for aluminium as a risk factor for AD

| Rondeau et al. (2009) France | Longitudinal study (15 years of follow-up); subjects living in 91 drinking-water districts in southern France (PAQUID Cohort), and subjects living at home in one of the 14 drinking-water areas in southwestern France (ALMA+ Cohort) | 1,677 subjects aged 65 years or over (PAQUID cohort), and 248 subjects aged 75 years or over (ALMA+ cohort) | Two kinds of drinking water indicators for Al and silica: (1) geographic exposure measure; (2) individual measure by the questionnaire on daily consumption of tap water and bottled water | MMSE and other cognitive tests; standardised questionnaire for diagnosis of dementia (DSM III revised criteria); NINCDS/ADRDA criteria for AD; Hachinski score for VaD; cognitive decline was analyzed in both the PAQUID and the ALMA+ cohorts; dementia and AD were investigated only in the PAQUID cohort | The risk of dementia was higher for subjects with a high daily Al intake (for >0.1 mg/day; $RR = 2.26$; $P = 0.049$). Conversely, an increase of 10 mg/day in silica intake reduced the risk of dementia (adjusted $RR = 0.89$; $P = 0.036$). Using the geographic measure of tap-water exposure, Al or silica concentrations were no more associated with the risk of AD, although the tendencies were similar |

This table lists the principal findings of longitudinal clinical and epidemiological studies on the relationships between dietary Al (from drinking water or foods) and dementia (i.e., AD and VaD) or predementia syndromes (i.e., ARCD) in older people, including setting, study design, and Al and cognitive assessment used

PAQUID Personnes agées Quid, *MMSE* Mini Mental State Examination, *DSM III Diagnostic and Statistical Manual of Mental Disorders, Third Edition*, *DSM III* Diagnostic and Statistical Manual of Mental Disorders, Third Edition, *NINCDS/ADRDA* National Institute of Neurological and Communicative Disorders and Stroke/Alzheimer's Disease and Related Disorders Association, *DSM IV* Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, *RR* relative risk, *EPIDOS Study* Epidemiology of Osteoporosis Study, *SPMSQ* Short Portable Mental Status Questionnaire, *ALMA+* Aluminium-Maladie Alzheimer

to Al or silica from tap water was not associated strongly with dementia, given that other territorial factors could influence cognitive decline, the conclusions of the study were that cognitive decline became greater over time in subjects with a higher daily intake of Al from drinking water (>0.1 mg/day; adjusted RR =2.26; P = 0.005). Moreover, about silica intake, an increase of 10 mg/day was associated with a reduced risk of AD (adjusted RR = 0.89, P = 0,036) (Rondeau et al. 2009) (Table 178.5).

Recently, new evidence has come to the fore in support of the Al-AD hypothesis. First, a case of a 58-year-old woman with a rapidly progressive, fatal neurological illness, who, at autopsy, showed dramatic Aβ deposition of cerebral cortical and leptomeningeal blood vessels, modest numbers of NFTs and Lewy bodies, and evidence of very high Al content in affected brain regions. This neurological injury is potentially linked to Al exposure from drinking water. In fact, this woman was exposed, along with other 20,000 people, to high concentrations of Al in their water supplies, in excess of 500–3,000 times the limit of 0.2 mg/l. (Exley and Esiri 2006). Second, a very recent report that compared baseline and follow-up composition of drinking water and the level of cognitive function and possible risk of AD in women taking part in the Epidemiology of Osteoporosis Study (EPIDOS) found that a low silica concentration was associated with low cognitive performance at baseline. Further multivariate analysis including potential confounding factors showed that women with AD appeared to have been exposed to lower amounts of silica at baseline, suggesting a protective role against AD of silica in drinking water (Gillette-Guyonnet et al. 2005) (Table 178.5).

On balance, all epidemiological studies of Al in drinking water are more or less open to critique, particularly considering the difficulty in producing high-quality data for exposure and especially for the disease (Lovell et al. 1996). A fundamental difficulty in the interpretation of the epidemiological studies indicating increased risk for AD with increased Al concentrations in drinking water is that even at high concentrations (0.1–0.4 mg/l), drinking water accounts for less than 5% of total daily Al intake. Moreover, in contrast with the findings of these epidemiological studies and evidence against the Al-AD hypothesis is the fact that many studies examining antacid exposure that involves 1000-fold higher exposure to Al compared to drinking water or diet and AD, have been largely negative (Lione 1985). Similarly, other studies did not support any association between Al in drinking water and AD. Wettstein and colleagues (1991) compared the cognitive functions of two groups of elderly, long-term residents of Zurich, who lived in two different areas: one, with high Al concentration in drinking water (> 0.10 mg/l), and the other with relatively low Al levels (<0.01 mg/l). The authors found no substantial differences in cognitive impairment between these two groups (Wettstein et al. 1991). However, a limitation of this study was that the methodology relied on only two sources of drinking water, and thus the bioavailability of Al was likely different in the two water sources. Another study that compared 106 men with AD, 99 men with other dementias, 226 men with brain cancer, and 441 men with other diseases of the nervous system reported no association between the prevalence of AD and higher Al concentrations in drinking water (Martyn et al. 1997). In this context, all subjects aged up to 75 years old and the analysis performed employed three different measurements of exposure. No association between AD and either higher Al or lower silica concentrations in drinking water was found and this study represents perhaps some of the strongest evidence against the idea of causal relationship between Al exposure and AD.

178.3 Aluminium in Food and Cognitive Decline

Unlike a lot of studies about drinking water and AD, little investigations have attempted to measure the possible association between Al in food and cognitive decline, most likely due to significant variability in Al content in food and the difficulty to accurately measure levels of exposure and in turn absorption

from food. Yet, dietary intake of Al remains the largest route of exposure, since Al consumption from foods is typically ten-fold greater than that from drinking water (Saiyed and Yokel 2005). Al in the food supply comes from natural sources including the natural composition of the food itself, water used in food preparation, and food additives. Some foods, known as Al accumulators (e.g., herbs, tea leaves) may naturally contain more than 5 mg/g of this metal. Intake of dietary Al is higher in the USA than in other countries due to widespread use of Al-containing food additives (Flaten 2001; Saiyed and Yokel 2005). One pilot study that interviewed close relatives about dietary intake of patients in a geriatric centre, with special attention to foods high in Al (such as American cheese, chocolate pudding, doughnuts, pancakes or muffins), showed the crude OR of 2.0 (*P* value = 0.19) for daily intake of any such high-Al foodstuffs and OR of 8.6 adjusted for total caloric intake, body mass index, education and intake of vitamins A, C and E (Rogers and Simon 1999). Some subcategories of food containing Al additives were also examined; however, due to the smaller samples in these subgroups, the resulting ORs were not statistically significant, except for one food category containing waffles, pancakes, biscuits, muffins and cornbread or corn tortillas. Although interesting, these results require reproducing in other studies with larger samples sizes and more rigorous design.

Several studies have explored the link between tea consumption and risk of AD since it has been known that Al is naturally present in tea leaves. The reported concentration of Al is 0.3% in older leaves and about 0.01% in younger ones (Rao 1994). Typical tea infusions contain 50 times as much as Al as do infusions from coffee. Levels of Al in tea infusions are commonly in the range of 2–6 mg/l (Rao 1994), and thus may contribute up to 50% of the total daily Al intake in the countries with high consumption and small intake of Al from other sources (Pennington1987; Saiyed and Yokel 2005). In a case-control study (Forster et al. 1995), comparing cases of clinically diagnosed presenile dementia of the Alzheimer's type and controls matched for age and sex, exposure to Al from tea was not a significant risk factor for dementia (the OR for dementia among people consuming more than four cups of tea a day was 1.4; 95% CI: 0.8–2.6). Similarly, no relationship was found between exposure to Al from drinking water, or medicinal sources. A case-control study completed in Canada produced a similar OR for the risk of AD (1.4; 95% CI: 0.86–2.28); however, the serving amount of tea was not specified (Canadian Study of Health and Aging 1994). An Australian case-control study (Broe et al. 1990), also reported an OR of 1.42 (95% CI: 0.93–2.17) while another study found no significant relationship between tea consumption and AD (adjusted OR: 0.7, *P*-value = 0.69). In the latter there was a suggestion that the absence of association may be due to loss of Al during the tea processing and binding of Al to organic compounds, possibly lemon juice (Rogers and Simon 1999). In summary, it would seem that despite relatively high Al content and high dietary consumption, the role of tea as a dietary source of Al in development of AD or similar pathologies remains controversial.

178.4   Possible Mechanisms of Aluminium Neurotoxicity

Although there is compelling evidence in support of a central role of Aβ (including from genetic studies) and tau protein in the pathogenesis of AD, there have been some residual questions whether these abnormalities are causative of the disease or secondary to another etiologic factor (Neve and Robakis 1998). Many lines of evidence have focused on the role of oxidative stress mechanisms and free radical damage in AD pathogenesis (Grant et al. 2002) (Fig. 178.1). Whether oxidative damage increases Aβ peptide production or vice versa is still unresolved. There is ambiguous evidence on the hypothetical molecular mechanisms that might explain Al involvement in the aetiology and pathogenesis of AD. Several experimental models have strongly supported the involvement of Al as a secondary modifying factor or risk factor in the pathogenesis of AD (Bharathi et al. 2008) (Fig. 178.2). There is
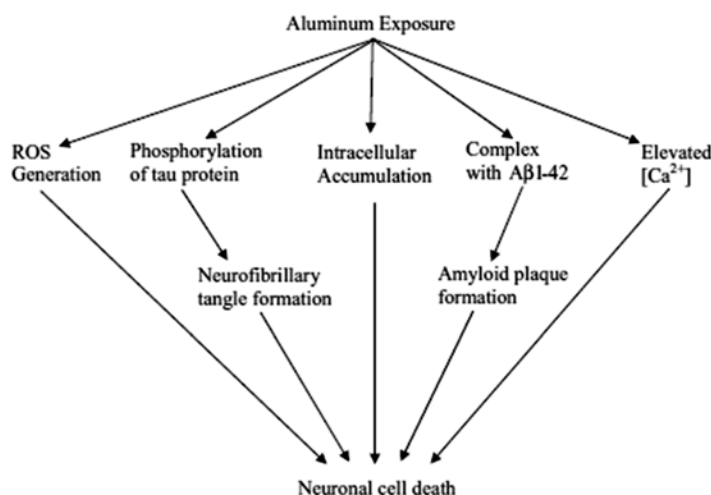
Fig. 178.1 Possible mechanisms whereby aluminium exposure causes neuronal cell death and lead to Alzheimer's disease. This figure shows major hypothesised pathways whereby aluminium exposure leads to neuronal cell death and Alzheimer's disease including aluminium-induced oxidative stress, accumulation of amyloid β (Aβ), phosphorylation of tau protein, elevation of [Ca²⁺], complex with Ab1–42 peptide, and intracellular accumulation of aluminium (From Shcherbatykh and Carpenter 2007. With permission)

also evidence that Al may alter the normal processing of AβPP and as such the dynamics of Aβ production (Garruto and Brown 1994), via reduced solubility of aluminium-Aβ 1–42 complexes, as well as increased precipitation of β-sheets (Exley 2006) and facilitated Aβ transport across the BBB (Yokel 2006). Several studies suggest that Aβ and oxidative stress are causally linked and Al enhances Aβ production leading to Aβ aggregation into oligomeric forms (Bondy and Kirstein 1996) which might influence the early-onset of AD or its progression (Fig. 178.1).

An appealing feature of the oxidative stress hypothesis for neurodegenerative diseases is that cumulative oxidative damage over time could account for the late-life onset and the slowly progressive nature of such disorders (Shcherbatykh and Carpenter 2007). With the development of transgenic techniques in neuroscience, new research approaches have emerged. It has been demonstrated that chronic dietary administration of Al can increase Aβ levels and accelerate SP deposition in an animal model of AD-like amyloidosis with an exacerbation of brain lipid peroxidation (Praticò et al. 2002). This phenomenon could be limited by addition of the antioxidant addition (vitamin E). Other investigators have shown that exposure to Al affects different neuronal areas, and that melatonin protects against the Al-induced cellular damage (Esparza et al. 2003).

Various mechanisms have been suggested to explain the Al toxicity, taking into account that many biological reactions, if altered, can have profound cellular consequences, eventually contributing to neuronal cell death. The major sites of localisation of these important reactions are mitochondria, lysosomes and the nucleus in the cell; therefore Al toxicity can be mediated across a number of cellular compartments (Dobson et al. 1998). Al could play a role in neurodegeneration by increasing oxidative stress because as a non-redox active metal it may increase the redox active iron concentration in brain, mainly through a Fenton reaction. Al is simultaneously an activator of superoxide dismutase (SOD) and an inhibitor of catalase, and this leads to an increase in the production of hydroxyl radicals (Good et al. 1996). Apoptosis or programmed cell death, which plays a role in normal development and maintenance of tissue homeostasis, is also believed to be the general mechanism by which Al toxicity is mediated in cells. Mitochondrial changes
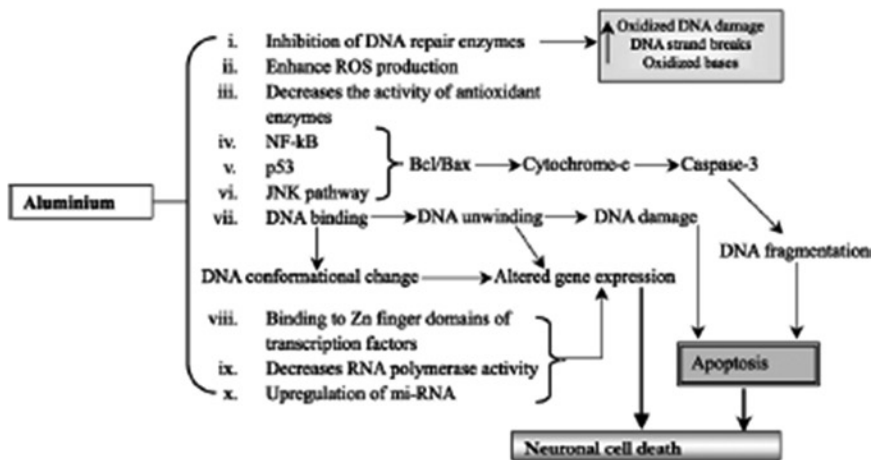
Fig. 178.2 Synopsis of principal mechanisms of neurotoxicity linked to aluminium exposure. This figure shows aluminium (Al) to be one of the principal causes of neurotoxicity, including modulation of inhibition of DNA repair enzymes, enhancement of ROS production, decrease of the activity of antioxidant enzymes, alteration of NF-kB, p53, JNK pathway, DNA binding. Al also binds to Zn finger domains of transcription factors, thereby decreasing RNA polymerase activity and upregulating mi-RNA. All these events lead to genomic instability and cell death (From Bharathi et al. 2008. With permission)

following cytotoxic stimuli represent a primary event in apoptotic cell death. Al has also been demonstrated to accumulate in neurons, where it inhibits the sodium $(Na)^+$/calcium $(Ca)^{2+}$ exchange mechanisms and thereby mediates the accumulation of mitochondrial Ca^{2+} (Bharathi et al. 2008) (Fig. 178.1). This increase in intra-mitochondrial Ca^{2+} levels in turn leads to an opening of the mitochondrial transition pore (MTP), with cytochrome c (an important apoptotic factor) release and subsequent apoptosis resulting from the activation of the caspase family of proteases (Dewitt et al. 2006) (Fig. 178.2).

Although mitochondrial alterations may represent an important step in the apoptotic process, other evidence supported the endoplasmic reticulum (ER) role in regulating this cell death and ER homeostasis changes due to Al. The ER is the major reservoir for calcium and is the main site of the apoptotic mediators including members of the Bcl-2 family of proteins, Bcl-2 and Bcl-XL. Al induces a redistribution of the apoptosis-regulatory proteins within the ER, resulting in Bax being elevated in the ER compared with the cytosol and mediating the reduction of Bcl-2 (D'mello et al. 1994) (Fig. 178.2). Therefore, Al mediates a specific type of apoptosis which is independent from other mitochondrial-targeted apoptotic signals. Moreover, since Al is a Lewis base, it might bind to oxygen donors generated in the cell and binds to vital biomolecules such as nucleic acids, phosphate groups of ATP and/or phosphorylated proteins and carboxylic groups of the molecules (Lankoff et al. 2006). Thus, Al could facilitate genotoxicity, through modification of DNA repair processes and conformational changes that cause DNA to unwind all of which increase the likelihood of DNA damage and changes to gene expression that might lead to neuronal cell death in AD. Further evidence in support of this are reports of Al-mediated decrease of the levels of mRNA from genes of endogenous antioxidant enzymes (Gonzalez-Muñoz et al. 2008). This may be the result of interference with the binding of transcription factors, such as factor IIIA to its corresponding zinc finger domains and in turn inhibition of gene expression (Hanas and Gunn 1996)

The biogenesis of NFTs remains an important question in understanding Alzheimer's neuropathology. Al promotes phosphorylation of the tau protein, the microtubular-associated protein that

accumulates into NFTs making it less soluble and increasing the likelihood that the protein will aggregate (Li et al. 1998) (Fig. 178.1). Thus, Al could act to promote the development of NFTs. However, an important consideration is that NFTs are associated with a number of diseases such as dementia pugilistica and other diseases where the causes remain unclear (Bharathi et al. 2008). Furthermore, studies have reported that Al kills isolated neurons secondary to its intracellular accumulation, and that the cell death is neither secondary to generation of reactive oxygen species (ROS) nor accumulation of intracellular calcium. This is despite the capability of Al to cause an elevation in both (Tuneva et al. 2006), suggesting that Al could be directly toxic to some intracellular processes. Considering numerous studies about Al neurotoxicity, Kawahara proposed a comprehensive hypothesis regarding the implications of Al and other trace metals in the pathogenesis of AD (Kawahara 2005) (Fig. 178.3).

Recently, a study investigated the effects of Al on behaviour, neurological function and morphology, using Al-maltolate administered to rabbits via the intracisternal route (Bharathi et al. 2008). The authors concluded that Al caused neurotoxicity in a multifaceted way by modulating the inhibition of DNA repair enzymes, the enhancement of ROS production, the decrease in the activity of antioxidant enzymes, and the alteration in apoptotic pathways as NF-kB, p53 and JNK (Fig. 178.2). Al was also found to bind to Zn finger domains of transcription factors, thereby decreasing RNA polymerase activity and gene expression and also upregulating micro-RNA. All these events lead to genomic instability and cell death. Common mechanisms such as failure in protein folding mechanisms have not yet been fully explored but offer possible models for further testing, particularly where circulating or intracellular forms of these proteins, complexed to Al may be toxic, and work in addition to other primary causes of the neuronal cell death (Bharathi et al. 2008).

178.5 Possible Alzheimer's Disease Treatment Linked to the Aluminium Hypothesis

Metal ligand-based therapeutic approaches for the treatment of AD have been suggested, given the growing number of epidemiological investigations that have identified Al and other metals (especially zinc and copper) as possible risk factors for this disease (Fig. 178.4). Therefore, if metals play a potential role as a cofactor in the pathogenesis of AD, removal of these from the brain might hypothetically modulate neuronal damage and progression of the AD process (Domingo 2006). Among these drugs, the use of fluoride and chelating agents were strong candidates. It was well known that fluoride ions bind with high affinity to Al, while desferrioxamine, an iron chelator, was also shown to be an effective chelating agent for Al.

Desferrioxamine (deferoxamine, DFOA) usually used for the treatment of iron overload, was first employed to enhance Al removal in 1980, and it has been the most effective and safest Al chelator for long-term use and has produced a striking improvement in a patient with severe dialysis encephalopathy (Ackrill et al. 1980). However, the authors noted that both fluoride and chelating agents could have systemic side effects. Due to the high affinity of DFOA for Al ($K = 1,022$), this chelating agent has also been successfully applied to the therapy of Al overload, including the treatment of dialysis encephalopathy (Swartz 1985; Milne et al. 1983), however, important side effects have been reported, including increased susceptibility to infectious diseases, ocular and auditory toxicity, audiovisual neurotoxicity and developmental toxicity if used for prolonged periods at excessive doses (Domingo 1996). The hypothesis that DFOA might slow the clinical progression of the dementia associated with AD was tested in a small study, which
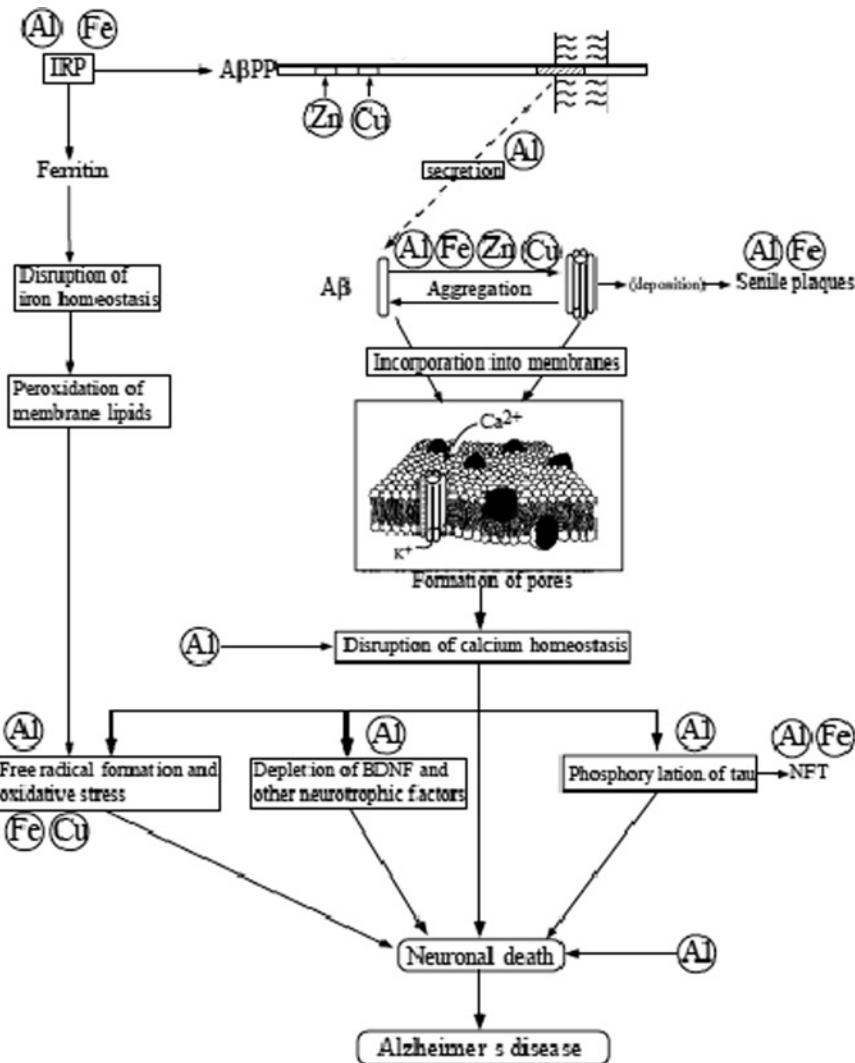
Fig. 178.3 Hypothesis regarding the implications of aluminium (Al) and other trace metals in the pathogenesis of Alzheimer's disease (AD). Al binds to iron regulatory protein (IRP) and influences the expression of amyloid β protein precursor (AβPP) as well as ferritin. Abnormal expression of AβPP will lead to the increased amount of amyloid β (Aβ). Normally secreted Aβ is degraded by various proteases. However, Aβ which is aggregated in the presence of trace metals, including Al, zinc (Zn), iron (Fe), and copper (Cu), could be resistant to proteases and accumulates in the brain. The aggregated Aβ could be easily incorporated into membranes resulting in the formation of ion channels. The abnormal calcium influx through amyloid channels cause the phosphorylation of tau, the depletion of neurotrophic factors such as brain-derived neurotrophic factor (BDNF), and the formation of free radicals, and finally induces neuronal death. Al implicates these neurodegenerative pathways by inhibition of BDNF-induced increase in intracellular calcium levels, by accelerating the phosphorylation of tau, and by stimulating iron-induced lipid peroxidation. Meanwhile, abnormal expression of ferritin caused an altered concentration of free iron ions, and thus, will cause oxidative damage and membrane lipid peroxidation. These events also finally lead to neuronal death. Various genetic and environmental factors may contribute to these pathways. It is possible that Al and other metals are implicated in various stages of these degenerative processes and finally link to the pathogenesis of AD (From Kawahara 2005. With permission)
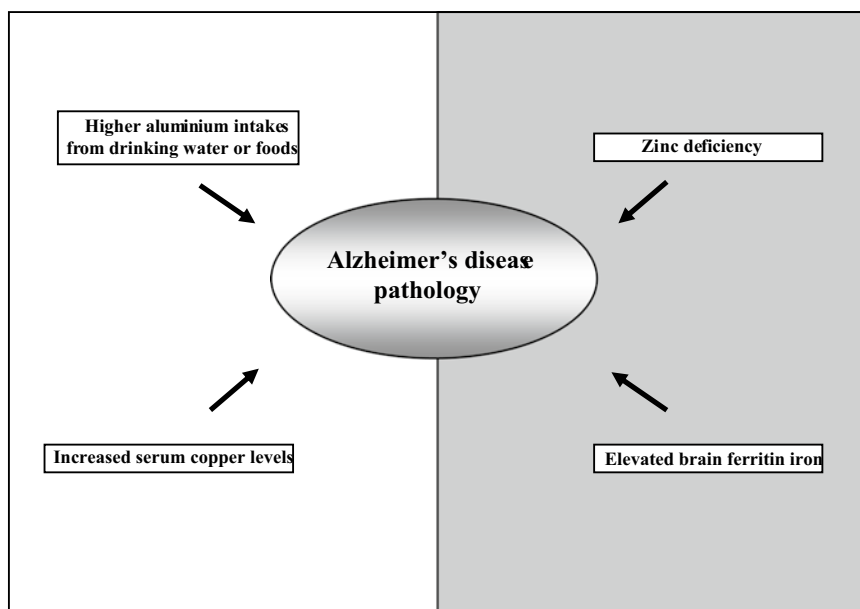
Fig. 178.4 Synopsis of the evidence on the possible effects of metals on Alzheimer's disease pathology. This figure shows the suggested impact of various metals on Alzheimer's disease pathology including aluminium, zinc, copper and iron

investigated 48 patients with probable AD, who were randomly assigned to receive DFOA (125 mg intramuscularly twice daily, 5 days per week, for 24 months), oral placebo (lecithin), or nontreatment (i.e., normal care) (McLachlan et al. 1991). No significant differences in baseline measures of intelligence, memory or speech ability existed between the groups. Activities of daily living were also assessed and video recorded at 6, 12, 18 and 24 month intervals. DFOA administration was associated with a significant reduction in the rate of decline of daily living skills as assessed by both group means and variances, while differences in the rate deterioration of patients receiving either placebo or nontreatment were noted. The mean rate of decline was twice as rapid for the nontreatment group while appetite and weight loss, which was found to be reversible by temporary suspension of DFOA, were the only reported side effects (Kruck et al. 1990). These findings (McLachlan et al. 1991) proved controversial, particularly in relation to the statistical analyses of the results as well as the use of lecithin as placebo, which was administered orally while DFOA was injected intramuscularly (Domingo 2006). Experimental studies on rabbits showed that although a partial reversal of Al-induced neurodegeneration by DFOA was observed, pretreatment of the animals with this chelator was not protective against Al-induced NFT-associated pathology. One possible explanation could also be that the therapeutic effects of DFOA were partly due to mechanisms other than chelation, such as inhibition of free radical formation or inflammation (McLachlan et al. 1991).

To date, ten natural and synthetic Al(III) ligands and chelators (fluoride, maltol, citrate, EDTA, hydroxyurea, dihydroxyacetone, salicylate, ascorbate, DFOA and Feralex-G), have been investigated alone or in combination (Kruck et al. 2004) for their ability to remove Al(III) from intact human brain cell nuclei, following preincubations with the respective compounds. Although nuclear-bound Al(III) was found to be resistant to removal, the combination of ascorbate plus Feralex-G was found to be particularly effective in removing Al(III) from the nuclear matrix. The mechanism proposed by

authors (Kruck et al. 2004), called molecular shuttle chelation, might provide a useful pharmacotherapy in the potential treatment of Al(III) overload. Nonetheless, DFOA has been the only Al chelator successfully tested in the palliative treatment of AD and while it is the main stay of iron and Al chelation therapy, the high cost of this drug, the need for parenteral administration, and various side effects observed have been considered reasonable justification to pursue an orally effective, cheaper and less toxic chelating agent than DFOA where BBB permeability of the compound would be particularly useful in AD.

There are, however, many other effective chelators of trivalent ions available that might already be exerting protective effects through the chelation of Al (House et al. 2004). Among a number of these chelating agents tested in animal models, the most promising were the 1-alkyl-3-hydroxy-2-methylpyrid- 4-ones, and particularly the compound 1,2-dimethyl-3- hydroxypyrid-4-one (deferiprone, L1) (Domingo 1996). Until recent years, aminoacridines have been the group of drugs most frequently used to improve cognitive functions in AD patients. It was even hypothesised that, in addition to the enhancement in cholinergic transmission, their metabolite might chelate Al, thereby offering an additional benefit by diminishing the Al body burden, but these claims have not been substantiated (Domingo 1996).

The possible effects of combined treatments using chelating agents to remove Al from the body have also been investigated based on the rationale that they might be more efficient than monotherapy. In a study of rats, the therapeutic efficacy of combined administration of citric acid and *N*-2 hydroxyethylethylenediaminetriacetic acid (HEDTA) was measured on the extent to which blood and brain Al concentrations and parameters indicative of haematological disorders as well as brain oxidative stress were altered (Flora et al. 2003). In contrast to DFOA, which is unable to enter the brain, HEDTA which is BBB-permeable resulted in a moderate decrease in rat brain Al concentration. The authors concluded that HEDTA could be a potential antidote for Al overload. However, in order to achieve an optimum effect of chelation therapy, administration of citric acid and HEDTA would be recommended (Flora et al. 2003). In previous studies, injection of citrate following parenteral Al administration depleted tissue Al concentrations (Domingo 2006); however, citrate may be able to increase or decrease Al accumulation, depending on the relative concentrations of Al and citrate within different compartments in the organism (Yokel et al. 1996). Research into this topic continues but it remains to be seen whether this possible therapeutic route might be of any practical importance.

178.6 Applications to Other Areas of Health and Disease

Al, as a known environmental toxicant, has been linked to a variety of pathological conditions such as dialysis encephalopathy, osteomalacia as well as AD. However, its precise role in the pathogenesis of these disorders is not fully understood. Studies using hepatocytes as a model system have examined the impact of Al on aerobic energy production and found that Al-exposed hepatocytes were characterised by lipid and protein oxidation and a dysfunctional tricarboxylic acid (TCA) cycle. Thus Al toxicity was suggested to promote a dysfunctional TCA cycle and impede ATP production, events that may contribute to various Al-induced abnormalities (Mailloux et al. 2006). Al has also been associated with other neurodegenerative diseases and, along with decreased levels of Ca and magnesium (Mg), is suspected to contribute to the pathogenesis of amyotrophic lateral sclerosis (ALS) and Parkinson's disease–related dementia (Shiraki and Yase 1991). The existence of Al in NFTs of patients with ALS/Parkinsonism dementia was also reported at the beginning of the 1960s, when epidemiological surveys in both Kozagawa and Hobara foci

revealed the characteristics of Kii ALS as follows: younger age at onset, especially men, familial clustering and presence of Alzheimer's NFTs (Kawahara 2005). Other environmental studies showed that extremely low levels of Ca and Mg in rivers adjacent to the birthplaces of ALS patients inversely and significantly correlated with high mortality rates, Al content, and densities of hippocampal NFTs (Kawahara 2005). Similarly, in experimental animals, low Ca and Mg, but high Al content in diet led to a neuronal loss with axonal swellings and chromatolysis (Kawahara 2005). Recently, a significant loss of dopaminergic neurons was identified exclusively in the substantia nigra of 1-year-old rats derived from colonies fed a low Mg diet over two generations (Kawahara 2005). Overall, some of these interactions may point to a predisposition to develop ALS/Parkinsonism dementia but which are precipitated by their environmental exposures and supporting suggestions that the aetiologies of these conditions are the result of gene-environment interactions (Kawahara 2005).

Dialysis encephalopathy was found to be caused by Al in dialysis solution or Al-containing pharmacological compounds in hemodialysis patients (Alfrey et al. 1976). A more recent case report has demonstrated that Al-containing cement used in bone reconstruction surgery caused fatal encephalopathy (Reusche et al. 2001). There have also been cases of encephalopathy that have developed in dialysis patients after they took Al-containing antacids. The Japanese Ministry of Health, Labour and Welfare recommended that patients on dialysis or with kidney failure should not use Al-containing antacids.

The lipophilic nature of the organic Al salt is a critical determinant of toxicity (Campbell et al. 2001). Human cell lines of neural origin were utilised to study the effect of lipophilic Al acetylacetonate and non-lipophilic Al sulfate on cell proliferation and viability. Although analysis of Al species in the cell culture media demonstrated that there are positively charged Al species present in solutions prepared with both Al salts, only the Al acetylacetonate salt caused changes in cell proliferation and viability. Neuroblastoma (SK-N-SH) cells were also more susceptible to decreased cell proliferation although the lipophilic Al salt was more toxic to the glioblastoma (T98G) cells. While the toxicity of Al acetylacetonate was inhibited in the T98G cells by the addition of phosphate, the same treatment did not reverse cell death in the SK-N-SH cells. Thus, the mechanism of Al toxicity appears to be different in the two cell lines and it is possible that the most susceptible cell type for Al is glial but when these cells are compromised, then there may be a secondary impact upon the neuronal population that eventually leads to neurodegeneration (Campbell et al. 2001).

The Al contamination of total parenteral nutrition (TPN) solutions is a matter of great concern. Bishop et al. reported that the neurological development of premature infants who had received a TPN solution containing a high level of Al was impaired compared with infants who had received an Al-depleted TPN solution (Bishop et al. 1997). Considering that Al in TPN solutions is highly bioavailable and that the renal function of infants is impaired, the Al contamination of TPN solutions could cause serious brain damage. The US Food and Drug Administration (FDA), the North American Society for Pediatric Gastroenterology and Nutrition (Klein et al. 1998), and other societies have recommended the reduction of the contamination of Al in parenteral solutions.

178.7 Conclusions

AD is widely accepted as a multifactorial disease, and genetic as well as environmental factors play significant roles in its pathogenesis. The involvement of Al in the pathogenesis of AD cannot be discarded, especially when there are many reports suggesting links between Al and the Aβ hypothesis

Table 178.6 Key points of clinical and epidemiological studies on the relationships between dietary aluminium (Al) and dementia or predementia syndromes

A. In recent years, an increasing body of epidemiological evidence suggested potential role of metals in the pathogenesis of Alzheimer's Disease (AD). In particular, the aluminium (Al) neurotoxicity has been established, beginning from its presence discovered in the senile plaques and neurofibrillary tangles, the principal histopathological hallmarks of AD
B. Al may enter the human body from several sources, especially from drinking water and food consumption. The epidemiological evidence supporting this association is somewhat stronger for exposure to Al from drinking water, as compared to food. However, other elements present in drinking water, such as fluoride, copper, zinc or iron could also have an effect on cognitive impairment or influence the Al neurotoxicity
C. Metal ligand-based therapeutic approaches for treatment of AD have been suggested, given the growing number of epidemiological investigations that have identified Al and other metals (especially zinc and copper) as possible risk factors for this disease, opening a new route to disease-modifying treatment of AD

This table lists the principal features of clinical and epidemiological studies on the relationships between dietary Al and dementia (i.e., AD), or predementia syndromes (i.e., age-related cognitive decline)

in AD. Overall, the results of molecular epidemiological investigations have suggested an association between chronic exposure to Al and risk of AD. This possible association is biologically plausible and likely to be of moderate significance and may be modified by other inorganic substances, like silica (Rondeau et al. 2000). The evidence supporting this association is stronger for exposure to Al from drinking water, compared to food (Table 178.6). However, this association does not yet satisfy all of Hill's criteria for causation (Hill 1965). Therefore, future studies require stronger methodological designs in order to fully test the validity of previous positive findings and to demonstrate dose–response relationships between Al and AD risk. This might provide new routes to the treatment of AD, with a disease-modifying effect, as opposed to the predominantly symptomatic approaches currently in use.

Summary Points

- An increasing body of molecular epidemiological evidence suggests the potential role of metals in the pathogenesis of Alzheimer's Disease (AD).
- Aluminium (Al) neurotoxicity, in particular, has been identified due to its presence in the senile plaques and neurofibrillary tangles that are the principal neuropathological hallmarks of AD.
- Epidemiological evidence supporting association between Al and AD is stronger for exposure to Al from drinking water, compared to exposure from food, although other elements present in drinking water, such as fluoride, copper, zinc or iron could also have an effect on cognitive impairment or influence any Al-mediated neurotoxicity.
- Metal ligand–based therapeutic approaches that might offer treatment for AD have been suggested, following the epidemiological evidence supporting the involvement of Al and other metals (especially zinc and copper) as possible risk factors for this disease
- The therapeutic efficacy of combined administration of citric acid and N-2 hydroxyethyl-ethylenediaminetriacetic acid (HEDTA) in decreasing blood and brain Al concentrations, other adverse haematological parameters, and brain oxidative stress has been investigated but further research is required to identify whether it can truly offer practical or clinical application.

Definitions

Aluminium: is a nonessential metal present in 8% of the Earth's crust. Despite its natural abundance, aluminium has no known function in living cells and produces some toxic effects in elevated concentrations. Its toxicity can be traced to deposition in bone and the central nervous system, which is particularly noticeable in patients with reduced renal function. In very high doses, aluminium can cause neurotoxicity, and is associated with altered function of the blood-brain barrier

Dementia: is a syndrome defined by impairments in memory and other cognitive functions that are severe enough to cause significant impairment and decline from a previous level of social and occupational functioning

Alzheimer's disease neuropathology: Alzheimer's disease is characterised by a number of pathological hallmarks, the most common being intraneuronal protein clusters composed of paired helical filaments including hyperphosphorylated tau protein (neurofibrillary tangles), and extracellular protein aggregates (senile plaques). The senile plaques are the result of either increased processing of the amyloid-β (Aβ) protein precursor by β- and γ-secretases or reduced degradation of clearance of the resultant toxic Aβ peptide that forms and in turn aggregates and initiates a pathogenic cascade that leads to neuronal loss

Predementia syndrome: this term identifies all conditions with age-related deficits in cognitive function, including a mild stage of cognitive impairment based on a model of normality or also due to pathological conditions considered predictive or early stages of dementia

Mild cognitive impairment (MCI): is a clinical label that includes non-demented aged persons with memory impairment that is more pronounced than what would be expected normal for that age but not severe enough as to cause significant disability

---

References

Ackrill P, Ralston AJ, Day JP, Hodge KC. Lancet. 1980;2:692–3.

Alfrey AC, LeGendre GR, Kaehny WD. New Engl J Med. 1976;294:184–8.

Akay C, Kalman S, Dündaröz R, Sayal A, Aydýn A, Ozkan Y, Gül H. Basic Clin Pharmacol Toxicol. 2008;102:433–6.

Banks WA, Kastin AJ, Maness LM, Banks MF, Shayo M, McLay RN. Ann N Y Acad Sci. 1997;826:190–9.

Banks WA, Niehoff ML, Drago D, Zatta P. Brain Res. 2006;1116:215–21.

Bell RD, Zlokovic BV. Acta Neuropathol. 2009;118:103–13.

Bharathi, Vasudevaraju P, Govindaraju M, Palanisamy AP, Sambamurti K, Rao KSJ. Indian J Med Res. 2008;128:545–56.

Bishop NJ, Morley R, Day JP, Lucas A. New Engl J Med. 1997;336:1557–61.

Bondy SC, Kirstein S. Mol Chem Neuropathol. 1996;27:185–94.

Broe GA, Henderson AS, Creasey H, McCusker E, Korten AE, Jorm AF, Longley W, Anthony JC. Neurology. 1990;40:1698–707.

Campbell A, Hamai D, Bondy SC. Neurotoxicology. 2001;22:63–71.

Canadian Study of Health and Aging. Neurology. 1994;44:2073–80.

Crapper DR, Krishnan SS, Dalton AJ. Science. 1973;180:511–3.

Dewitt DA, Hurd JA, Fox N, Townsend BE, Griffioen KJ, Ghribi O, Savory J. J Alzheimers Dis. 2006;9:195–205.

D'mello SR, Anelli R, Calissano P. Exp Cell Res. 1994;211:232–8.

Dobson CB, Day JP, King SJ, Itzhaki RF. Toxicol Appl Pharmacol. 1998;152:145–52.

Döllken V. Arch Exp Pathol Pharmacol. 1897;98–120.

Domingo JL. Adverse Drug React Toxicol Rev. 1996;15:145–65.

Domingo JL. J Alzheimers Dis. 2006;102 (3):331–41.

El-Rahman SS. Pharmacol Res. 2003;47:189–94.

Esparza JL, Gomez M, Romeu M, Mulero M, Sanchez DJ, Mallol J, Domingo JL. J Pineal Res. 2003;35:32–9.

Exley C. J Alzheimer Dis. 2006;10:173–7.

Exley C, Esiri MM. J Neurol Neurosurg Psychiatry. 2006;77:877–9.

Flaten TP. Brain Res Bull. 2001;55:187–96.

Flora SJ, Mehta A, Satsangi K, Kannan GM, Gupta M. Comp Biochem Physiol C Toxicol Pharmacol. 2003;134:319–28.

Forbes WF, McAiney CA, Hayward LM, Agwani N. Can J Aging. 1994;13:249–67.

Forbes WF, Lessard S, Gentleman JF. Can J Aging. 1995;14:642–56.

Forster DP, Newens AJ, Kay DWK, Edwardson JA. J Epidemiol Community Health. 1995;49:253–8.

Frecker MF. J Epidemiol Community Health. 1991;45:307–11.

Garruto RM, Brown P. Lancet. 1994;343:989–99.

Gillette-Guyonnet S, Andrieu S, Nourhashemi F, de la Guéronnière V, Grandjean H, Vellas B. Am J Clin Nutr. 2005;81:897–902.

Grant WB, Campbell A, Itzhaki RF, Savory J. J Alzheimers Dis. 2002;4:179–89.

Gold G. Int Psychogeriatr. 2003;15 Suppl 1:111–4.

Gonzalez-Muñoz MJ, Meseguer I, Sanchez-Reus MI, Schultz A, Olivero R, Benedí J, Sánchez Muniz FJ. Food Chem Toxicol. 2008;46:1111–8.

Good PF, Werner P, Hsu A, Olanow CW, Perl DP. Am J Pathol. 1996;149:21–8.

Hanas JS, Gunn CG. Nucleic Acids Res. 1996;24:924–30.

Hill AB. Proc R Soc Med. 1965;58:295–300.

House E, Collingwood J, Khan A, Korchazkina O, Berthon G, Exley C. J Alzheimers Dis. 2004;6:291–301.

Irvine GB, El-Agnaf OM, Shankar GM, Walsh DM. Mol Med. 2008;14:451–64.

Jellinger KA. J Alzheimers Dis. 2003;5:247–50.

Kawahara M. J Alzheimer Dis. 2005;8:171–82.

Klein GL, Leichtner AM, Heyman MB. J Pediatr Gastroenterol Nutr. 1998;27:457–60.

Kruck TP, Fisher EA, McLachlan DR. Clin Pharmacol Ther. 1990;48:439–46.

Kruck TP, Cui JG, Percy ME, Lukiw WJ. Cell Mol Neurobiol. 2004;24:443–59.

Lankoff A, Banasik A, Duma A, Ochniak E, Lisowska H, Kuszewski T, Gó d S, Wojcik A. Toxicol Lett. 2006;16:27–36.

Li W, Kenneth KY, Sun W, Paudel HK. Neurochem Res. 1998;23:1467–76.

Lione A. Pharmacol Ther. 1985;29:255–85.

Love S, Miners S, Palmer J, Chalmers K, Kehoe P. Front Biosci. 2009;14:4778–92.

Lovell MA, Ehmann WD, Markesbery WR, Melethil S, Swyt CR, Zatta PF. J Toxicol Environ Health. 1996;48:637–48.

Martyn CN, Osmond C, Edwardson JA, Barker DJP, Harris EC, Lacey RF. Lancet. 1989;333:61–2.

Martyn CN, Coggon DN, Inskip H, Lacey RF, Young WF. Epidemiology. 1997;8:281–6.

Mailloux RJ, Hamel R, Appanna VD. J Biochem Mol Toxicol. 2006;20:198–208.

McLachlan DRC, Bergeron C, Smith JE, Boomer D, Rifat SL. Neurology. 1996;46:401–5.

McLachlan DR, Dalton AJ, Kruck TP, Bell MY, Smith WL, Kalow W, Andrews DF. Lancet. 1991;337:1304–8.

Miessler G, Tarr D. Inorganic chemistry. Prentice Hall. 2003;720.

Milne FJ, Sharf B, Bell P, Meyers AM. Clin Nephrol. 1983;20:202–7.

Miners JS, Baig S, Palmer J, Palmer LE, Kehoe PG, Love S. Brain Pathol. 2008;18:240–252.

Neri LC, Hewitt D. Lancet. 1991;338:390.

Neve RL, Robakis NK. Trends Neurosci. 1998;21:15–9.

Panza F, D'Introno A, Colacicco AM, Capurso C, Del Parigi A, Caselli RJ, Pilotto A, Argentieri G, Scapicchio PL, Scafato E, Capurso A, Solfrizzi V. Am J Geriatr Psychiatry. 2005;13:633–44.

Panza F, D'Introno A, Colacicco AM, Capurso C, Parigi AD, Capurso SA, Caselli RJ, Pilotto A, Scafato E, Capurso A, Solfrizzi V. Neurobiol Aging. 2006;27:933–40.

Pennington JA. Food Addit Contam. 1987;5:161–232.

Pennington JA, Schoen SA. Food Addit Contam. 1995;12:119–28.

Permanne B, Adessi C, Fraga S, Frossard MJ, Saborio GP, Soto C. J Neural Transm Suppl. 2002;62:293–301.

Petersen RC, Doody R, Kurz A, Mohs RC, Morris JC, Rabins PV, Ritchie K, Rossor M, Thal L, Winblad B. Arch Neurol. 2001;58:1985–92.

Praticó'D, Uryu K, Sung S, Tang S, Trojanowski JQ, Lee VM. FASEB J. 2002;16:1138–40.

Rao KSJ. Nahrung. 1994;5:533–7.

Reinke CM, Breitkreutz J, Leuenberger H. Drug Saf. 2003;26:1011–25.

Reusche E, Pilz P, Oberascher G, Lindner B, Egensperger R, Gloeckner K, Trinka E, Iglseder B. Hum Pathol. 2001;32:1136–40.

Riihimäki V, Hänninen H, Akila R, Kovala T, Kuosma E, Paakkulainen H, Valkonen S, Engström B. Scand J Work Environ Health. 2000;26:118–30.

Rhodin JA, Thomas TN, Clark L, Garces A, Bryant M. J Alzheimers Dis. 2003;5:275–86.

Rogers MAM, Simon DG. Age Ageing. 1999;28:205–9.

Rondeau V, Commenges D, Jacqmin-Gadda H, Dartigues JF. Am J Epidemiol. 2000;152:59–66.

Rondeau V, Jacqmin-Gadda H, Commenges D, Helmer C, Dartigues JF. Am J Epidemiol. 2009;169:489–96.

Saiyed SM, Yokel RA. Food Addit Contam. 2005;22:234–44.

Shcherbatykh I, Carpenter DO. J Alzheimer Dis. 2007;11:191–205.

Shiraki H, Yase Y. In: Pierre J Vinken, HL Klawans, GW Bruyn, JM De Jong, editors. Diseases of the motor system. Handbook of clinical neurology 15. Amsterdam: Elsevier Health Sciences; 1991. p. 273–300.

Smith LF. Environmetrics. 1995;6:277–86.

Solfrizzi V, Panza F, Colacicco AM, D'Introno A, Capurso C, Torres F, Grigoletto F, Maggi S, Del Parigi A, Reiman EM, Caselli RJ, Scafato E, Farchi G, Capurso A. Neurology. 2004;63:1882–91.

Swartz RD. Am J Kidney Dis. 1985;6:358–64.

Todorich BM, Connor JR. Ann NY Acad Sci. 2004;1012:171–8.

Tuneva J, Chittur S, Boldyrev AA, Birman I, Carpenter DO. Neurotox Res. 2006;9:1–8.

Vickers JC, Dickson TC, Adlard PA, Saunders HL, King CE, McCormack G. Prog Neurobiol. 1999;60:139–65.

Vogt T (1986) Water quality and health. Study of a possible relation between aluminum in drinking water and dementia (published in Norwegian with English summary). Sociale Og Okonomiske Studier 61, Statistisk Sentralbyra Oslo-Kongsvinger, pp. 60–63.

Wettstein A, Aeppli J, Gautschi K, Peters M. Int Arch Occup Environ Health. 1991;63:97–103.

World Health Organization (WHO)/IPCS. Environ Health Criteria. 1997;194:1–152.

Wills RR, Savory J. Lancet. 1983;2:29–34.

Yokel RA, Ackrill P, Burgess E, Day JP, Domingo JL, Flaten TP, Savory J. J Toxicol Environ Health. 1996;48:667–83.

Yokel RA, Florence RL. Toxicology 2006;227:86–93.

Yokel RA. J Alzheimers Dis. 2006;10:223–53.

Chapter 179
Dietary Fatty Acids, Cognitive Decline, and Dementia

Vincenzo Solfrizzi, Vincenza Frisardi, Cristiano Capurso, Alessia D'Introno,
Anna M. Colacicco, Gianluigi Vendemiale, Antonio Capurso, and Francesco Panza

Abbreviations

AD   Alzheimer's disease
VaD   Vascular dementia
MCI   Mild cognitive impairment
ARCD   Age-related cognitive decline
AACD   Aging-associated cognitive decline
UFA   Unsaturated fatty acids
MUFA   Monounsaturated fatty acids
PUFA   Polyunsaturated fatty acids
LA   Linoleic acid
ALA   α-linolenic acid
DHA   Docosahexaenoic acid
EPA   Eicosapentaenoic acid
APOE   Apolipoprotein E
ARA   Arachidonic acid

179.1 Introduction

179.1.1 Dementia and Predementia Syndromes

Dementia is estimated to affect approximately 6% of the population aged 65 and older, the prevalence increasing exponentially with age, to 40–70% at the age of 95 years and over. In Western countries, the most common forms of dementia are Alzheimer's disease (AD) (Table 179.1) and vascular dementia (VaD) (Table 179.2), with respective frequencies of 70% and 15% of all dementias (Qiu et al. 2007). AD is an age-related progressive neurodegenerative disorder with an enormous unmet medical need, characterized by relatively slow chronic but progressive impairment in cognition, behavior, and functionality. The number of people suffering from AD is rising quickly because there are no effective

V. Solfrizzi (✉)
Department of Geriatrics, Center for Aging Brain, Memory Unit,
University of Bari, Policlinico, Piazza Giulio Cesare, 11, 70124 Bari, Italy
e-mail: v.solfrizzi@geriatria.uniba.it

Table 179.1 Key features of Alzheimer's disease (AD)

1. AD is the most common dementia and primary neurodegenerative disorder in the elderly
2. AD gradually leads to a complete psychological and physical dependency and finally to death within one to two decades
3. The neuropathology of AD involves aberrant protein processing and is characterized by the presence of both intraneuronal protein clusters composed of paired helical filaments of hyperphosphorilated tau protein (NFTs), and extracellular protein aggregates (SPs)
4. The diagnosis of AD is essentially a clinical one, and it is based on a typical clinical picture and findings, with a set of clinical criteria often used in research
5. From a clinical point of view, AD is a slow, progressive disease that most often starts with episodic memory impairment. However, the patients with preclinical AD show deficits in several cognitive areas, including executive function, verbal and visuospatial abilities, attention, and perceptive speed
6. Cognitive function declines over time, and the diagnosis of AD can be considered when the patient has impairments in memory and at least in one other cognitive function (executive dysfunction, agnosia, aphasia, apraxia), severe enough to cause impairment in social or occupational functioning
7. In advanced AD, common symptoms include also confusion, behavioral and gait disturbances, and the patients are increasingly dependent on others in activities of daily living

NFTs neurofibrillary tangles, *SPs* senile plaques
This table lists the key facts of AD including neuropathological hallmarks, clinical criteria for diagnosis, and the natural history of the disease

Table 179.2 Key features of vascular dementia (VaD)

1. The clinical presentation of VaD varies greatly depending on the causes and location of cerebral damage
2. Large-vessel disease leads commonly to multiple cortical infarcts and a multifocal cortical dementia syndrome
3. Small-vessel disease, usually resulting from hypertension and diabetes, causes periventricular white matter ischemia and lacunar strokes characterized clinically by subcortical dementia with frontal lobe deficits, executive dysfunction, slow information processing, impaired memory, inattention, depressive mood changes, slowing of motor function, Parkinsonian features, small-step gait, urinary disturbances and pseudobulbar palsy
4. The term Vascular Cognitive Disorder (VCD) has been recently proposed and it would become the global diagnostic category for cognitive impairment of vascular origin
5. VCD would include the group of syndromes and diseases characterized by cognitive impairment resulting from a cerebrovascular etiology
6. The main categories of VCD are Vascular Cognitive Impairment (VCI) (i.e., vascular CIND and vascular MCI), VaD, and mixed AD plus CVD. previously termed "mixed dementia"
7. Dementia is defined as executive control deficit producing loss of function for instrumental activities of daily living, while mixed AD plus CVD is defined as preexisting AD worsened by stroke (equivalent to prestroke dementia)
8. VCI is a term referred to all forms of mild to severe cognitive impairment associated with CVD, including vascular CIND and vascular MCI, e.g., predementia syndromes with a presumed primary vascular basis
9. The characteristic neuropsychological profile of VCI is believed to include frequently early impairment of attention and executive control function, with slowing of motor performance and information processing, while episodic memory is relatively spared compared to that in AD

CIND cognitive impairment no dementia, *MCI* mild cognitive impairment, *AD* Alzheimer's disease, *CVD* cerebrovascular disease
This table lists the key features of VaD including clinical and neuropathological classification, and the clinical picture of the disease

treatments for the disorder available. Clinical and epidemiological research has also focused on the identification of risk factors that may be modified in predementia syndromes, at a preclinical or early clinical stage of dementing disorders. The umbrella term "predementia syndromes" includes the transitional phase between mild nondisabling cognitive decline and disabling dementia, an ambiguous diagnostic period during which it is unclear whether mild cognitive deficits predict incipient dementia or not. In fact, the clinical label identifies all conditions with age-related deficits in cognitive function reported in the literature, including a mild stage of cognitive impairment based on a normality model

and pathological conditions considered predictive of early stages of dementia (Panza et al. 2005). Such predementia syndromes have been defined for AD and partly for VaD, but have not yet been operationalized for other specific forms of dementia. Therefore, the term "predementia syndromes" includes different conditions and, among them, MCI is at present the most widely used term to indicate non-demented aged persons with no significant disability and a mild memory or cognitive impairment, which cannot be explained by any recognized medical or psychiatric condition (Panza et al. 2005). At present, the term mild cognitive impairment and its abbreviation MCI have frequently been used in studies on the preclinical phases of dementia, although with differing and inconsistent definitions (Petersen et al. 1999, 2001; Winblad et al. 2004) (Table 179.3). There is now ample evidence that MCI is often a pathology-based condition with a high rate of progression to AD (Panza et al. 2005). Therefore, MCI has also been identified as the predementia syndrome for AD. The more recently proposed multiple subtypes of MCI were intended to reflect the heterogeneity of different types of dementia. Actually, the recent subclassifications of MCI according to its cognitive features [dysexecutive MCI and amnestic-MCI (aMCI), or aMCI and non-amnestic MCI (naMCI): single-domain aMCI and multiple-domain aMCI or single-domain naMCI and multiple-domain naMCI] (Winblad et al. 2004), clinical presentation [MCI with parkinsonism, cerebrovascular disease (CVD), depressive symptoms, behavioral and psychological symptoms], or probable etiology (MCI-AD, vascular MCI, or MCI-Lewy body dementia) (Gauthier et al. 2006) all represent an attempt to control this heterogeneity. A critical review has recently made in Stockholm and then in Montreal, in order to define a new consensus on MCI (Winblad et al. 2004). Furthermore, different diagnostic criteria have been proposed for other predementia syndromes, and the terms age-related cognitive decline (ARCD) (American Psychiatric Association 1994) (Table 179.4) and aging-associated cognitive decline (AACD) (Levy 1994) (Table 179.5) have been recently proposed to distinguish individuals with mild cognitive disorders associated with aging, also non-pathological, from noncognitively unimpaired individuals.

Table 179.3 Key features of mild cognitive impairment (MCI)

1. MCI is, at present, the most widely used term to indicate non-demented aged persons with a mild memory or cognitive impairment that cannot be accounted for any recognized medical or psychiatric condition
2. The general criteria for MCI include: a) memory complaint, b) objective memory disorder, c) absence of other cognitive disorders or repercussions on daily life, d) normal general cognitive function, e) absence of dementia
3. MCI definitions can be broadly classified as amnestic (aMCI) and nonamnestic (naMCI)
4. There is now ample evidence that MCI is often a pathology-based condition with a high rate of progression to AD, and aMCI, with a central role for memory disorder and with relative preservation of other cognitive domains, was identified as the predementia syndrome for AD
5. aMCI can be subdivided into a single domain subtype with a pronounced memory deficit or a multiple domain subtype that includes memory impairment along with some impairment in other cognitive domains such as language, executive function, and visuospatial skills
6. The other major MCI subtype is naMCI, which similarly can be subdivided into single and multiple domain subtypes

AD Alzheimer's disease
This table lists the key features of MCI including diagnostic criteria, and clinical classification

Table 179.4 Key features of age-related cognitive impairment (ARCD)

1. ARCD is defined by the DSM-IV as "an objectively identified decline in cognitive functioning consequent to the aging process that is within normal limits given the person's age
2. At present, there are no defined diagnostic criteria for ARCD or other operational definition
3. Few epidemiological studies using this definition have been conducted

DSM IV Diagnostic and Statistical Manual of Mental Disorders, fourth edition
This table lists the key features of MCI including definition, and current research issues on this clinical entity.

Table 179.5 Key features of aging-associated cognitive decline (AACD)

1. In 1994 a task force of the International Psychogeriatric Association (IPA) in collaboration with the World Health Organization (WHO) proposed diagnostic criteria for AACD

2. In these clinical diagnostic criteria, patients score at least one SD below age and education-based standards (e.g., by reference to norms for elderly people) on neuropsychological tests assessing multiple cognitive abilities (memory and learning, attention and concentration, thinking, language, and visuospatial functioning)

3. In the AACD criteria there is no age restriction: though the cognitive decline is more prevalent in old age, its onset may occur earlier in life

SD standard deviation

This table lists the key features of AACD focusing on clinical diagnostic criteria

179.1.2 *Possible Prevention of Dementia and Predementia Syndromes*

The causes of predementia syndromes and dementia are at present unknown. However, some studies have suggested that these conditions may be prevented (Solfrizzi et al. 2006a, 2008). The role of the diet in cognitive decline has not been extensively investigated, with a few data available on the role of macronutrient intake in the pathogenesis of predementia and dementia syndromes (Solfrizzi et al. 2006a, 2008). Since several dietary factors affect the risk of cardiovascular disease, it can be assumed that they also influence the risk of dementia. Some recent studies have suggested that dietary fatty acids may play a role in the development of cognitive decline associated with aging or dementia (Solfrizzi et al. 2005). This concept is further supported by recent evidence that certain diets have been associated with a lower incidence of AD. In fact, antioxidants, dietary fatty acids, and micronutrients appear to have a role, and evidence is at least suggestive that diets rich in fruits and vegetables and other dietary approaches may permit a beneficial effect on the risk of dementia (Solfrizzi et al. 2006a, 2008).

Fatty acids can be categorized briefly into saturated fatty acids (SFA) and unsaturated fatty acids (UFA). SFA, such as stearic acid, is present in products such as meat, dairy products, cookies, and pastries. Monounsaturated fatty acids (MUFA) are most frequently consumed in olive oil. The principal series of polyunsaturated fatty acids (PUFA) are *n*-6 [i.e., linoleic acid (LA)] and *n*-3 [i.e., α-linolenic acid (ALA), docosahexaenoic acid (DHA), and eicosapentaenoic acid (EPA)]. In our Mediterranean dietary pattern, the main sources of *n*-6 PUFA are vegetable oils, while the principal sources of *n*-3 PUFA are fatty fish (salmon, tuna, and mackerel). In fact, olive oil contains 70–80% MUFA (oleic acid) and 8–10% PUFA (6–7% linoleic acid and 1–2% a-linolenic acid) (Solfrizzi et al. 2005). In this chapter, we examine the possible role of dietary fatty acids in modulating the risk of age-related changes in cognitive function, predementia, and dementia syndromes, as well as the possible mechanisms behind the observed associations. Furthermore, we review current evidence on dietary fatty acid supplementation in predementia and dementia syndromes.

179.2 Dietary Fatty Acids in Predementia Syndromes

179.2.1 *Cross-sectional Studies*

Recently, an increasing number of epidemiological and clinical studies have addressed the link between UFA intake and cognitive function, most being cross-sectional (Solfrizzi et al. 2005). In the last years, the study approach was to associate single micro- or macronutrients to ARCD, MCI, AD, or VaD. In this picture, several hallmarks of the Mediterranean diet were linked to increased risk or to a protective effect against cognitive impairment (Panza et al. 2004). The typical dietary pattern of a Mediterranean

diet is characterized by high intakes of vegetables, fruits and nuts, legumes, cereals, fish, and MUFA, relatively low intakes of meat and dairy products, and moderate consumption of alcohol. In fact, higher levels of consumption of olive oil are considered the hallmark of the traditional Mediterranean diet.

In a cross-sectional French study, a positive relationship was found in elderly women between lipid intake and the Mini Mental State Examination (MMSE) score, which evaluates global cognitive functions. A positive relationship was also found between PUFA intake and mobility in elderly men, and between functional variables and alcohol intake in the whole sample. The response rate of this study was very low (around 50%) and these findings, contradictory to the results of the subsequent studies, were explained by the authors with the fact that high intakes of these dietary factors can be considered as an indicator of a better health status (Pradignac et al. 1995) (Table 179.6). Another cross-sectional study from Spain showed that the older subjects with a lower intake of MUFA, SFA, and cholesterol, and higher intakes of total calories, fresh fruit, carbohydrate, thiamine, foliate, vitamin C, and minerals (iron and zinc) had the best performance in global cognitive tests, with a statistical significance after adjustment for age and sex (Ortega et al. 1997) (Table 179.6).

As seen above, MUFA, consequent to the high consumption of extra-virgin olive oil, represent the most important fats in the Mediterranean diet. Cumulative evidence suggests that extra-virgin olive oil may have a role in the protection against cognitive decline, besides coronary disease and several types of cancer, because of its high levels of MUFA and polyphenolic compounds. In the older subjects of the Italian Longitudinal Study on Aging (ILSA), which followed a Mediterranean dietary pattern, total fat is 29% of energy, with a high consumption of olive oil (46 g/d), an MUFA energy intake of 17.6% of total energy, 85% of which is derived from olive oil, and an SFA intake of only 6% (Solfrizzi et al. 1999) (Fig. 179.1). The cross-sectional association between dietary macronutrients and cognitive impairment was examined in elderly subjects aged 65–84 years from the ILSA. After adjustment for educational level, the odds ratios (ORs) of cognitive decline (MMSE score < 24) decreased exponentially with the increase of MUFA energy intakes. Furthermore, selective attention performances were independently associated with MUFA intake (Solfrizzi et al. 1999) (Table 179.6). Recently, in another Northern Italian cross-sectional study on older subjects, the Progetto Veneto Anziani (Pro.V.A. study), in a multiple regression analysis, age and educational level accounted for 29.6% of the MMSE variance, while the contribution of the other variables considered [low-density lipoproteins (LDL) cholesterol, diastolic blood pressure, MUFA, and PUFA] was almost negligible. The authors acknowledged that these results were limited by the fact that total energy intake, which is known to be reduced in patients with cognitive impairment, was not considered, and by the fact that the study was a cross-sectional survey (Manzato et al. 2003). Recently, in the Doetinchem Cohort Study, after adjusting for age, gender, education, alcohol consumption, smoking, and energy intake, higher dietary cholesterol was associated with an increased risk of impaired memory function and cognitive flexibility cognitive function, whereas higher SFA intake was associated, although not significantly, with a 15% to 19% increased risk of impairment in memory function, psychomotor speed, and cognitive flexibility. Fatty fish and marine *n*-3 PUFA consumption were significantly associated with a 19% to 28% decreased risk of global cognitive function impairment and psychomotor speed. These associations appeared to be independent of differences in cardiovascular risk factors (Kalmijn et al 2004) (Table 179.6).

179.2.2 Longitudinal Studies

To our knowledge, there is an increasing number of longitudinal epidemiological studies on the association between fatty acids and cognitive functioning (Kalmijn et al. 1997a; Hende et al. 2003; Morris et al. 2004, 2005a; Solfrizzi et al. 2005, 2006a, b; Psaltopoulou et al. 2008; Eskelinen et al. 2008;

Table 179.6 Principal cross-sectional studies on the relationships between dietary fatty acids and predementia syndromes in older people

Cross-sectional studies

Reference	Setting and study design	Subjects	Dietary assessment	Cognitive outcomes	Results and conclusions
Pradignac et al. (1995)	Cross-sectional, population based	441 subjects aged >65 years	Evaluation of dietary intake	MMSE, Geronte scale for the assessment of daily living activities	In men, alcohol intake was associated with improved functional and cognitive parameters, while PUFA intake only with functional status. In women, lipid intakes were related to better cognitive performance. Overweight in both sexes was associated with an improvement in functional status
Ortega et al. (1997)	Cross-sectional	260 subjects aged 65–90 years	Evaluation of dietary intake with a weighed-food record for 7 consecutive days, and biochemical assays	MMSE, PMSQ	A diet poor in fatty acids, saturated fatty acids, and cholesterol, but rich in carbohydrates, fibers, vitamins (folates, vitamins C and E, and β-carotene, and minerals [zinc and iron) seems to improve cognitive skills
Solfrizzi et al. (1999)	Cross-sectional, population based	278 subjects, 65–84 years old	Evaluation of dietary intake with a 77-item FFQ	MMSE, DCT, and BSRT	Inverse relationship between MUFA intake and cognitive decline. Significant inverse association between MUFA intakes and selective attention. No association was found between nutritional variables and episodic memory
Manzato et al. (2003)	Cross-sectional, population based	191 subjects aged □ 65 years	Evaluation of plasma phospholipid fatty acid composition	MMSE: subjects with a score between 10 and 17 versus subjects with a score between 28 and 30	Cognitive functioning are affected mainly by age and education, not by dietary fatty acids
Kalmijn et al. (2004)	Cross-sectional, population based	1,613 subjects, 45–70 years old	Evaluation of fatty fish, total fat, cholesterol, SFA MUFA, PUFA (n-6 and n-3) dietary intakes with a 178-item FFQ	Concurrent to the dietary assessment, the VVLT, the CST, an abbreviated SCWT, the LDST, a CFT were administrated	Fatty fish and marine n-3 PUFA consumption was associated with a reduced risk and intake of cholesterol and saturated fatty acids with an increased risk of impaired cognitive function in this middle-aged population

Nurk et al. (2007)	Cross-sectional, population based	2,031 subjects, 70–74 years old	Evaluation of dietary intakes with a 169-item FFQ	Six cognitive tests were administered: m-MMSE, m-DST, m-BD; KOLT; TMT-A, and the S-task of the COWAT	Consumers of fish and fish products had better cognitive function than did non-consumers. The associations between fish and fish product intake and cognition were dose-dependent. The effect of fish on cognition differed according to the type of fish and fish product consumed
Dangour et al. (2009)	Randomized clinical trial (24 months)	867 subjects, 70–79 years old from 20 general practices in England and Wales.	Evaluation of fish consumption variable that took into account both frequency and type of fish consumption	A standardized battery of cognitive tests: CVLT; subjective memory assessment; 3 tests of prospective memory; story recall (immediate and delayed); verbal fluency; letter cancellation; location memory (immediate and delayed); symbol-letter substitution; digit span forwards and backwards; simple and choice reaction time	High levels of fish consumption are associated with better cognitive function in later life. Furthermore, there was an apparent linear trend for increased cognitive function across the five-item fish consumption variable, with highest cognitive function levels found in those individuals who report eating the largest amount of fatty, as opposed to white fish

This table lists the principal findings of cross-sectional clinical and epidemiological studies on the relationships between dietary fatty acids and predementia syndromes (i.e., age-related cognitive decline, ARCD, and mild cognitive impairment, MCI) in older people, including the setting and study design, and the dietary and cognitive assessment used. *FFQ* food frequency questionnaire, *MMSE* Mini-Mental State Examination (global cognitive functioning), *PMSQ* Pfeiffer's Mental State Questionnaire (global cognitive functioning), *DCT* Digit Cancellation Test (selective attention), *PUFA* = polyunsaturated fatty acids, *MUFA* = monounsaturated fatty acids; *SFA* = saturated fatty acids; *VVLT* = Visual Verbal Learning Test (verbal memory), *CST* Concept Shifting Task (mental processing speed), *SCWT* Stroop Color Word Test (selective attention), *LDST* Letter Digit Substitution Test (perceptual-motor speed), *CFT* Category Fluency Test (semantic memory), *m-MMSE* modified Mini-Mental State Examination (global cognitive functioning), *m-DST* modified Digit Symbol Test (perceptual speed), *m-BD* modified Block Design (visuo-spatial and motor skills), *KOLT* Kendrick Object Learning Test (episodic memory), *TMT-A* Trail Making Test, part A (executive function), S-task of the *COWAT* the abridged version of the Controlled Oral Word Association Test (access to semantic memory), *CVLT* Californian Verbal Learning Test (verbal memory)
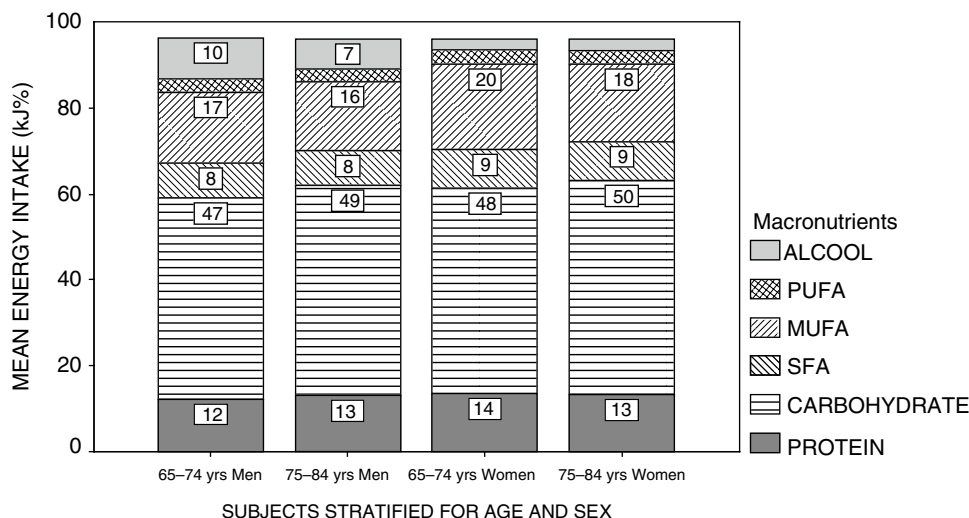
Fig. 179.1 Mean energy intakes from the Italian Longitudinal Study on Aging (*ILSA*). This figure shows the distribution of mean energy intakes (%), stratified for age and gender of the ILSA (Casamassima, Bari, Italy), first prevalence Survey, 1992–1993

Vercambre et al. 2009) (Table 179.7), indicating a crucial need for prospective studies that could confirm initial observations. In particular, one of these prospective studies, the Zutphen Study of 476 men aged 69–89 years, found that high linoleic acid intake was positively associated with cognitive impairment in elderly subjects only in one cross-sectional study after an adjustment for age, education, cigarette smoking, alcohol consumption, and energy intake. High fish consumption, tended to be inversely associated with cognitive impairment and cognitive decline at 3-year follow-up, but not significantly (Kalmijn et al. 1997a) (Table 179.7). Furthermore, in the cohort of the Etude du Viellissement Arteriel (EVA) Study, moderate cognitive decline (a > 2-point of MMSE decrease) and erythrocyte membrane fatty acid composition were evaluated in 264 elderly subjects aged 63–74 years, during a 4-year follow-up. In this study, a lower content of *n*-3 PUFA was significantly associated with a higher risk of cognitive decline. After adjusting for age, gender, educational level and initial MMSE score, stearic acid and total *n*-6 PUFA were consistently associated with an increased risk of cognitive decline. Moreover, a lower content of *n*-3 PUFA was significantly associated with cognitive decline, but after adjustment, this association remained significant only for DHA, and not for EPA (Hende et al. 2003) (Table 179.7). Findings from the CHAP on 2,560 persons aged 65 years and older, showed that in a large population-based sample, a high intake of saturated and trans-unsaturated fat was associated with a greater cognitive decline over a 6-year follow-up. Intake of MUFA was inversely associated with cognitive change among persons with good cognitive function at baseline and among those with stable long-term consumption of margarine, a major food source. Slower decline in cognitive function was associated with higher intake of PUFA, but the association appeared to be due largely to its high content of vitamin E, which shares vegetable oil as a primary food source and which is inversely related to cognitive decline. Finally, cognitive change was not associated with intakes of total fat, animal fat, vegetable fat, or cholesterol (Morris et al. 2004) (Table 179.7). In the same CHAP sample on 3,718 persons aged 65 years and older, high copper intake was associated with a significantly faster rate of cognitive decline but only among persons who also consumed a diet that was high in saturated and trans fats in a 6-year follow-up (Morris et al. 2005a) (Table 179.7). Moreover, in a total of 732 men and women aged 60 years or older, participating

Table 179.7 Principal longitudinal studies on the relationships between dietary fatty acids and predementia syndromes in older people

Reference	Setting and study design	Subjects	Dietary assessment	Cognitive outcomes	Results and conclusions
Longitudinal studies					
Kalmijn et al. (1997a)	Longitudinal, population based (3 years)	476 subjects, aged 69–89 years	Evaluation of dietary intake with the cross-check dietary history method	Cognitive impairment defined as a MMSE score <25 points and cognitive decline as a drop of >2 points of MMSE over a 3-year period	High linoleic acid intake (PUFA) was positively associated with cognitive impairment. High fish consumption was inversely associated with cognitive impairment
Hende et al. (2003)	Longitudinal, population based (4 years)	246 subjects aged 63–74 years	Evaluation of fatty acid composition in erythrocyte membranes	MMSE score with a >2-point of decrease in a 4-year follow-up	Inverse association between cognitive decline and the ratio of *n-3* to *n-6* PUFA in erythrocyte membranes
Morris et al. (2004)	Longitudinal, population based (6 years)	2,560 subjects, aged 65 years and older	Evaluation of dietary intake with a 139-items FFQ	Cognitive change at 3-year and 6-year follow-ups measured with the EBT of Immediate and Delayed Recall, the MMSE, and the SDMT	A diet high in saturated and *trans*-unsaturated fat or low in non-hydrogenated unsaturated fats may be associated with cognitive decline among older people
Morris et al. (2005a)	Longitudinal, population based (6 years)	3,718 subjects, aged 65 years and older	Evaluation of dietary intake with a 139-items FFQ	Cognitive change at 3-year and 6-year follow-ups measured with the EBT of Immediate and Delayed Recall, the MMSE, and the SDMT	High copper intake was associated with a significantly faster rate of cognitive decline, but only among persons who also consumed a diet that was high in saturated and trans fats
Morris et al. (2005b)	Longitudinal, population based (6 years)	3,718 subjects, aged 65 years and older	Evaluation of dietary intake with a 139-items FFQ	Cognitive change at 3-year and 6-year follow-ups measured with the EBT of Immediate and Delayed Recall, the MMSE, and the SDMT	Dietary intake of fish was inversely associated with cognitive decline over 6 years. There were no consistent associations with the *n-3* fatty acids, although the effect estimates were in the direction of slower decline

(continued)

Table 179.7 (continued)

Reference	Setting and study design	Subjects	Dietary assessment	Cognitive outcomes	Results and conclusions
Solfrizzi et al. (2006a)	Longitudinal, population based (8.5 years)	278 subjects, 65–84 years old from a cohort of 5,632 subjects	Evaluation of MUFA and PUFA dietary intakes with a 77-item FFQ	MMSE	High MUFA, PUFA, and total energy intake were significantly associated with a better cognitive performance in time. The association between high MUFA, PUFA intakes and cognitive performance remained robust even after adjustment for potential confounding variables such as age, sex, educational level, CCI, BMI, and total energy intakes
Solfrizzi et al. (2006b)	Longitudinal, population based (2.6 years)	278 subjects, 65–84 years old from a cohort of 5,632 subjects	Evaluation of MUFA and PUFA dietary intakes with a 77-item FFQ	Incident MCI. Diagnostic criteria for MCI: 1.5 SDs below mean age and education adjusted on the MMSE and 10th percentile below age and education adjusted on memory test, without SMC and intact ADL/IADL	Dietary fatty acids intakes were not associated with incident MCI. However, high PUFA intake appeared to have borderline nonsignificant trend for a protective effect against the development of MCI that may be important.
van Gelder et al. (2007)	Longitudinal, population based (5 years)	210 subjects,70–89 years old	Information about habitual food consumption was collected using the cross-check dietary history method	MMSE	Fish consumption was associated with less subsequent 5-y cognitive decline than was no fish consumption. Furthermore, a dose-response relation was noted between the combined intake of EPA and DHA and cognitive decline, which suggests that a higher intake of EPA plus DHA was associated with less cognitive decline
Psaltopoulou et al. (2008)	Longitudinal, population based (median 8 years)	732 subjects, 60 years or older	Evaluation of dietary intakes with a 150-item FFQ. A dietary composite score (MeDi score) evaluated adherence to Mediterranean diet	MMSE	No significant association between MeDi score and MMSE scores, whereas a statistically significant inverse association was found between MMSE performance and some individual dietary components, such as seed oil or PUFA intakes

| Vercambre et al. (2008) | Longitudinal, population based (13 years) | 4,809 elderly women, 76–82 years old | Evaluation of dietary intakes with a 208-item FFQ | DECO and IADL | Elderly women that were reported by informants to have undergone recent cognitive decline, 13 years previously, lower intakes of poultry, fish, and animal fats, as well as higher intakes of dairy desserts and ice-cream. They had lower habitual intakes of dietary fiber and n-3 PUFA, but a higher intake of retinol. Elderly women that were reported by informants to be functionally impaired had, in the past, lower intakes of vegetables and vitamins B2, B6 and B12 |
| Eskilinen et al. (2008) | Longitudinal, population based (21 years) | 1,449 subjects aged 65–80 years | Evaluation of dietary intakes with a 208-item FFQ | The Mayo Clinic AD Research Center criteria were applied for diagnosing MCI; MMSE, CFT, PPBt, LDST, episodic memory with immediate word recall tests; executive function with the Stroop test, and prospective memory with a task by Einstein | Elevated SFA intake at midlife was associated with poorer global cognitive function and prospective memory and with an increased risk of MCI. High intake of PUFA was associated with better semantic memory. Frequent fish consumption was associated with better global cognitive function and semantic memory. Higher PUFA/SFA ratio was associated with better psychomotor speed and executive function |

This table lists the principal findings of longitudinal clinical and epidemiological studies on the relationships between dietary fatty acids and predementia syndromes (i.e., age-related cognitive decline, ARCD, and mild cognitive impairment, MCI) in older people, including the setting and study design, and the dietary and cognitive assessment used

MMSE Mini-Mental State Examination (global cognitive functioning), *PUFA* polyunsaturated fatty acids, *FFQ* food frequency questionnaire, *EBT* East Boston Memory test (immediate and delayed episodic memory), *SDMT* Symbol Digit Modalities Test (perceptual-motor speed), *MUFA* monounsaturated fatty acids, *CCI* Charlson comorbidity index, *BMI* body mass index, *SMC* subjective memory complaint, *ADL* activities of daily living, *IADL* instrumental activities of daily living, *EPA* eicosapentaenoic acid, *DHA* docosahexaenoic acid, *DECO* DEtérioration Cognitive Observée scale (observed cognitive deterioration), *CFT* Category Fluency Test (semantic memory), *PPBt* Purdue Peg Board task (psychomotor speed), *LDST* Letter Digit Substitution Test (perceptual-motor speed)

in the European Prospective Investigation into Cancer and Nutrition (EPIC), Greece cohort, and residing in the Attica region, 6–13 years follow up showed that seed-oil consumption may adversely affect cognition, whereas adherence to the Mediterranean diet, as well as intake of olive oil, MUFA, and SFA exhibited weakly positive but not significant associations (Psaltopoulou et al. 2008) (Table 179.7). Finally, 4.809 elderly women (born between 1925 and 1930) were studied in a French longitudinal cohort, the Etude Epidémiologique de Femmes de la Mutuelle Générale de l'Education Nationale (E3N) study. Elderly women participating in the E3N cohort who were reported by informants to have undergone recent cognitive decline had, 13 years previously, lower intakes of poultry, fish, and animal fats, as well as higher intakes of dairy desserts and ice-cream. They had lower habitual intakes of dietary fiber and *n*-3 PUFA, but a higher intake of retinol. Furthermore, elderly women who were reported by informants to be functionally impaired had, in the past, lower intakes of vegetables and vitamins B2, B6, and B12 (Vercambre et al. 2009) (Table 179.7). More recently, in the Cardiovascular Risk Factors, Aging and Dementia (CAIDE) Study from eastern Finland, abundant SFA intake from milk products and spreads at midlife was associated with poorer global cognitive function and prospective memory and with an increased risk of MCI in average follow-up period of 21 years after adjusting for demographic and vascular factors, other fats, and apolipoprotein E (APOE). On the contrary, high PUFA intake was associated with better semantic memory. Also frequent fish consumption was associated with better global cognitive function and semantic memory. Further, higher PUFA/SFA ratio was associated with better psychomotor speed and executive function (Eskelinen et al. 2008) (Table 179.7).

Therefore, on the basis of the previous significant suggestions (Solfrizzi et al. 2005), we tested further the hypothesis that high MUFA and PUFA intakes may protect against the development of cognitive impairment over time in a median follow-up of 8.5 years of the ILSA. The major finding of this study was that high MUFA, PUFA, and total energy intake were significantly associated with a better cognitive performance in time (Figs. 179.2 and 179.3). Total energy intake should be considered

Fig. 179.2 Cognitive profile across time for total energy intake from the Italian Longitudinal Study on Aging (*ILSA*). This figure shows the mean observed Mini-Mental State Examination (*MMSE*) score profile across time for total energy intake (<11,330 kJ/day and ≥11,330 kJ/day at the beginning of the study), ILSA, 1992–2001. The *squared symbols* and *solid line* represent the mean observed MMSE scores for total energy intake, respectively, computed using all observations (*n* = 278 subjects), while the squared symbols and short dashed line represent the mean MMSE scores for total energy intake, computed data from 95 subjects with complete observations
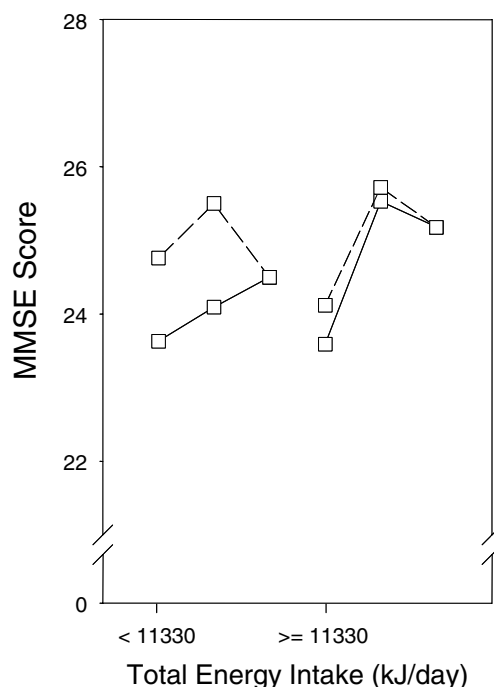
Fig. 179.3 Cognitive profile across time for monounsaturated fatty acids (*MUFA*) intake from the Italian Longitudinal Study on Aging (*ILSA*). This table Mean observed MMSE score profile across time for daily MUFA intake (<53.1 g/day and ≥53.1 g/day at the beginning of the study), ILSA, 1992–2001. The *circle symbols* and *solid* represent the mean observed MMSE scores for MUFA intake, respectively, computed using all observations (*n* = 278 subjects), while the circle symbols and short dashed line represent the mean MMSE scores for MUFA intake, computed data from 95 subjects with complete observations
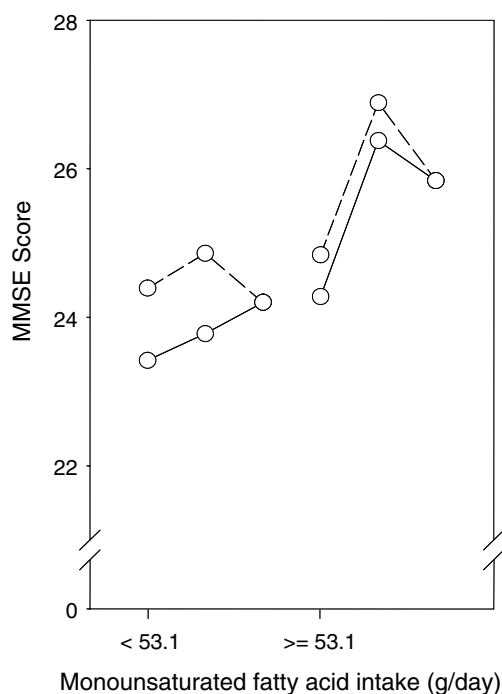
an important confounder of diet-ARCD relationships and, as we proposed in our methodological approach, suggesting that association between macronutrient intake and cognitive decline should be adjusted by total energy intake. No other individual dietary component of our study population was significantly associated with cognitive impairment in time (Solfrizzi et al. 2006a) (Table 179.7). The association between high MUFA, PUFA intakes, and cognitive performance remained robust even after adjustment for potential confounding variables such as age, sex, educational level, Charlson comorbidity index, body mass index, and total energy intakes (Solfrizzi et al. 2006a). Finally, recent findings from the ILSA demonstrated that while dietary fatty acids intakes were not associated with incident MCI, high PUFA intake appeared to have a borderline nonsignificant trend for a protective effect against the development of MCI (Solfrizzi et al. 2006b) (Table 179.7).

179.2.3 Fish Consumption and Cognitive Decline

Epidemiological observational studies reporting associations of fish consumption with cognitive function have shown mixed results; some cross-sectional and longitudinal studies have reported a positive association with higher fish consumption (Morris et al. 2005b; van Gelder et al. 2007; Nurk et al. 2007; Dangour et al. 2009), while others have found no association (Kalmijn et al. 1997a) (Tables 179.6 and 179.7). Fish, particularly fatty fish (e.g., herring, mackerel, salmon, or trout), is the principal source of *n*-3 PUFA in the Mediterranean diet. Very recently, the baseline data from the Older People And *n*-3 Long-chain polyunsaturated fatty acid (OPAL) study, a double-blind randomized placebo-controlled trial examining the effect of daily supplementation with 700 mg *n*-3 PUFA on cognitive performance in healthy older persons aged 70–79, suggested that higher fish consumption is associated with better cognitive function in later life (Dangour et al. 2009) (Table 179.6).

In the Chicago Health and Aging Project (CHAP), dietary intake of fish was inversely associated with cognitive decline over 6 years of follow-up. In this cohort, there was little evidence that the *n*-3 PUFA were associated with cognitive change (Morris et al. 2005b) (Table 179.7). Furthermore, in the Zutphen Elderly Study, fish consumers had significantly less 5-year subsequent cognitive decline than did non-consumers. A linear trend was observed for the relation between the intake of EPA + DHA and cognitive decline, and an average difference of 380 mg/day in EPA plus DHA intake was associated with a 1.1-point difference in cognitive decline (van Gelder et al. 2007) (Table 179.7). Finally, findings from the Hordaland Health Study suggested that subjects whose mean daily intake of fish and fish products was >10 g/day had significantly better mean test scores and a lower prevalence of poor cognitive performance than did those whose intake was <10 g/day. The associations between total intake of seafood and cognition were strongly dose dependent; and the effect was more pronounced for non-processed lean fish and fatty fish (Nurk et al. 2007) (Table 179.6).

179.3 Dietary Fatty Acids and Dementia

179.3.1 Cross-sectional Studies

In 1997, for the first time, a strong dietary link to AD was suggested (Grant 1997) (Table 179.8). The primary finding of this cross-sectional ecological study was that fat and total caloric supply have the highest correlations with AD prevalence rates. In addition, a combination of fat and fish consumption is found to reduce the prevalence of AD in the European and North American countries, i.e., one calorie of fish was found to counter the effects of approximately 4.3 calories of fat. As with most studies of this type, there are a number of potential caveats. In particular, the results of analyses of food supply data with prevalence data that are applied to specific populations should be viewed with caution. However, these ecological evidences were in agreement with various recent epidemiologic studies (Grant 1999).

One of the most interesting findings of a recent study on VaD risk factors conducted on the cohort of the Honolulu-Asia Aging Study (HAAS), in 3,385 older Japanese subjects, was the protective effect of a Western diet against the development of VaD (Ross et al. 1999) (Table 179.8). Oriental populations from Asian countries are known to be more prone to stroke and VaD. A traditional Western diet is high in animal fat and protein and low in complex carbohydrates, compared to the traditional Japanese diet, which is high in complex carbohydrates and low in animal fat and protein. This is an interesting approach in which dietary patterns, not only single micro- or macronutrients, are considered in explaining the possible role of diet in cognitive decline. The mechanism by which an oriental diet leads to VaD remains speculative. The higher risk of stroke could probably be referred to the lower intake of animal fat and protein. As these findings do not allow analysis of separate nutrients, a hypothesis could be that more fat intake may stabilize the integrity of smaller intracranial arterioles, while the quantity and quality of dietary protein may affect small vessel pathology. Furthermore, the increased risk of VaD and stroke in Japan may well be due to the high sodium intake, in the form of soy sauce, pickled fish, etc.

179.3.2 Longitudinal Studies

The possible relationship between dietary fatty acids intake and risk of dementia and AD has been evaluated in a series of longitudinal studies. In fact, the finding that total dietary fat is a possible risk factor for the development of AD has been reported in the Rotterdam Study, although not at a

Table 179.8 Principal cross-sectional studies on the relationships between dietary fatty acids and dementia, or vascular dementia (VaD), or Alzheimer's disease (AD)

Reference	Setting and study design	Subjects	Dietary assessment	Dementia diagnosis	Results and conclusions
Cross-sectional studies					
Grant (1997)	Ecological cross-sectional	18 community-wide studies conducted after 1979 (≥65 years old)	Evaluation of the components of the national diets	Prevalence of AD diagnosed with various clinical criteria	The primary finding is that fat and total caloric supply have the highest correlations with AD prevalence rates. In addition, fish consumption is found to reduce the prevalence of AD in the European and North American countries
Ross et al. (1999)	Cross-sectional, population based	3,734 Japanese American men aged 71 to 93	Evaluation of vascular risk factors, dietary habits, and questionnaire on supplementary vitamin E and C use and alcohol intake	Diagnosis of dementia, VaD (ADDTC criteria), and stroke without dementia	The antioxidant vitamin E and unknown factors related to a Western diet, high in animal fat and protein and low in complex carbohydrates, as opposed to an Oriental diet may be protective against developing VaD

This table lists the principal findings of cross-sectional ecological and epidemiological studies on the relationships between dietary fatty acids and dementia, or VaD, or AD, including the setting and study design, and the dietary and cognitive assessment used
ADDTC California Alzheimer's Disease Diagnostic and Treatment Centers

statistically significant level. In the same study, fish consumption was confirmed to reduce AD risk and LA was inversely correlated with AD. This study suggested that an elevated intake of lipids and saturated fat increased the risk for dementia with a cerebrovascular component (Kalmijn et al. 1997b) (Table 179.9). The cohort of the Rotterdam Study was reexamined in a 6-year follow-up, and a high intake of total fat, saturated fat, trans fat, and cholesterol and low intake of MUFA, PUFA, *n*-6 PUFA, and *n*-3 PUFA were not associated with an increased risk of dementia or its subtypes (Engelhart et al. 2002) (Table 179.9). The discrepancy in comparison with the results of the first study was explained by the authors by the shorter follow-up (2.1 years) and a consequent smaller number of incident cases of dementia. Moreover, other limitations of the Rotterdam study included the potential for confounding by intake of other types of fat (e.g., intake of trans fat is associated with both intakes of MUFA and SFA), and the potential for nonlinear associations, with associations of the extremes of intake.

Finally, the findings of the reexamined cohort of the Rotterdam Study are at odds with several recent studies (Luchsinger et al. 2002; Barberger-Gateau et al. 2002; Morris et al. 2003a, b; Laitinen et al. 2006; Barberger-Gateau et al. 2007) (Table 179.9). In fact, a 4-year cohort study in New York, the Washington Heights-Inwood Columbia Aging Project, found that dietary fat was an important risk factor for AD for those with the APOE ε4 allele, but not for those without that allele (Luchsinger et al 2002). Luchsinger and colleagues did not find associations with individual types of fat, but like the Rotterdam study, failed to control for other types of fat, which may have confounded the observed findings. They also confirmed previous ecological findings on the possible role of cereals as a risk reduction factor (Grant 1997).

Furthermore, findings coming from the Personnes Agees QUID (PAQUID) study, a population-based study conducted in France on 1,674 subjects aged 68 years and over, with no apparent dementia at baseline, showed that participants who ate fish or seafood at least once a week had a significantly lower risk of dementia (age and sex adjusted hazard ratio of 0.66, 95% CI: 0.47–0.93) in the 7 subsequent years. After adjusting for education, the hazard ratio was almost unchanged (0.73), but the 95% CI (0.52–1.03), slightly overlapping 1.00, indicated that higher education regarding regular consumption explains in part the protective effect of weekly fish or seafood consumption against dementia. Moreover, in this study no significant association between meat consumption and the risk of dementia was found for weekly consumers, with only a borderline significance for developing AD (hazard ratio: 0.68, 95% CI: 0.47–1.01) (Barberger-Gateau et al. 2002) (Table 179.9).

More recently, two studies from the cohort of the CHAP, increased the evidence of a strict linkage between dementia and fatty acid intake (Morris et al. 2003a, b) (Table 179.9). In fact, in this cohort of 815 subjects, aged 65 years and older, after a mean follow-up of 3.9 years, 131 persons developed AD. A high intake of saturated fat and trans-unsaturated fat may be associated with a higher risk of AD; while a high intake of *n*-6 PUFA and MUFA may be protective against AD (Morris et al. 2003a). Furthermore, in the same cohort, a higher intake of *n*-3 PUFA and weekly fish consumption may reduce the risk of incident AD. In fact, in this study, people who ate fish once or more times in a week had a relative risk for AD of 0.4: the absolute risk reduction was about 9.5% (Morris et al. 2003b). More recently, in the CAIDE Study, after an average follow-up of 21 years, moderate intake of PUFA at midlife decreased the risk of dementia, whereas SFA intake was associated with an increased risk, only among the APOE ε4 carriers (Laitinen et al. 2006) (Table 179.9) (Fig. 179.4). Finally, data from the Three-City Study demonstrated that a diet rich in fish, *n*-3 rich oils, fruits, and vegetables could contribute to decreasing the risk of dementia and AD in older persons whereas consumption of *n*-6 rich oils could exert detrimental effects when not counterbalanced by sufficient *n*-3 intake. These effects seem more pronounced among APOE ε4 non-carriers (Barberger-Gateau et al. 2007) (Table 179.9).

Table 179.9 Principal longitudinal studies on the relationships between dietary fatty acids and dementia, or vascular dementia (VaD), or Alzheimer's disease (AD)

Reference	Setting and study design	Subjects	Dietary assessment	Dementia diagnosis	Results and conclusions
Longitudinal studies					
Kalmijn et al. (1997b)	Longitudinal, population based (2.1 years)	5,386 subjects aged 55 and older	Evaluation of dietary intakes with a 170-item FFQ	Diagnosis of AD (NINCDS-ADRDA criteria), VaD (NINDS-AIREN criteria), or dementia with a vascular component	High intakes of total fat, saturated fat, and cholesterol were associated with an increased risk of dementia. Dementia with a vascular component was most strongly related to total fat and saturated fat. Fish consumption was inversely related to incident dementia, and in particular to AD
Engelhart et al. (2002)	Longitudinal, population based (6 years)	5,395 subjects aged 55 and older	Evaluation of dietary intakes with a 100-item FFQ	Diagnosis of dementia (DSM-III-R criteria), AD (NINCDS-ADRDA criteria), and VaD (NINCDS-AIREN criteria)	High intakes of total fat, saturated fat, trans fat, and cholesterol and low intake of MUFA, PUFA, n-6 PUFA, and n-3 PUFA were not associated with an increased risk of dementia, AD, or VaD
Luchsinger et al. (2002)	Longitudinal, population based (4 years)	980 subjects, mean age: 75.3±5.8 years	Evaluation of dietary intake with a 61-item FFQ	Diagnosis of prevalent dementia (DSM-IV criteria) and incident AD (NINCDS-ADRDA criteria)	Higher intake of calories and fats may be associated with higher risk of AD in subjects carrying the apolipoprotein E □4 allele
Barberger-Gateau et al. (2002)	Longitudinal, population based (7 years)	1,674 subjects aged 68 years and over	Evaluation of frequency of consumption of meat and fish and seafood: from daily to never	Diagnosis of incident dementia, including AD (DSM-III-R criteria)	Elderly people who consumed fish [rich in PUFA] or seafood at least once a week are at lower risk of dementia, including AD
Morris et al. (2003a)	Longitudinal, population based (3.9 years)	815 subjects, aged 65 years and older	Evaluation of dietary intake with a 154-item FFQ	Incident diagnosis of AD (NINCDS-ADRDA criteria)	High intake of saturated and trans-unsaturated fats may be associated with higher risk of AD; while high intake of n-6 PUFA and MUFA may be protective against AD
Morris et al (2003b)	Longitudinal, population based (3.9 years)	815 subjects, aged 65 years and older	Evaluation of dietary intake with a 154-item FFQ	Incident diagnosis of AD (NINCDS-ADRDA criteria)	Higher intake of n-3 PUFA and weekly fish consumption may reduce the risk of incident AD

(continued)

Table 179.9 (continued)

Reference	Setting and study design	Subjects	Dietary assessment	Dementia diagnosis	Results and conclusions
Huang et al. (2005)	Longitudinal, population based (5.4 years)	5,201 participants, aged 65 years and older	Evaluation of dietary intake with a 99-item FFQ	Incident diagnosis of dementia (DSM-IV criteria) and AD (NINCDS-ADRDA criteria)	Fatty fish, such as tuna or "other fish" was associated with a lower risk of developing dementia and AD with a dose-response relationship, whereas lean, fried fish was not. Those without an APOE ε4 allele had a 35–45% lower risk with consumption of fatty fish, whereas there was little or no difference for APOE ε4 allele carriers
Schaefer et al. (2006)	Longitudinal, population based (9.1 years)	488 participants from a sample of 899 individuals, median age: 76.0 years	Evaluation of dietary intake with a 125-item FFQ and plasma phosphatidylcholine DHA content	Incident diagnosis of dementia (DSM-IV criteria) and AD (NINCDS-ADRDA criteria)	Higher dietary intakes of DHA and fish did not result protective against all cause dementia and AD. A protective effect of higher plasma DHA was observed against the risk of all cause dementia but not for AD
Laitinen et al. (2006)	Longitudinal, population based (21 years)	1,449 subjects aged 65–80 years	Evaluation of dietary intake with a 154-item FFQ	Incident diagnosis of AD (NINCDS-ADRDA criteria)	Moderate intake of PUFA at midlife was protective, whereas a moderate intake of SFA may increase the risk of dementia and AD, especially among APOE ε4 carriers.
Barberger-Gateau et al. (2007)	Longitudinal, population based (4 years)	9,294 subjects, aged 65 years and older	Evaluation of dietary intakes with a FFQ	Incident diagnosis of dementia (DSM-IV criteria) and AD (NINCDS-ADRDA criteria)	Frequent consumption of fruits and vegetables, fish, and n-3 rich oils may decrease the risk of dementia and AD, especially among APOE ε4 non-carriers

This table lists the principal findings of longitudinal clinical and epidemiological studies on the relationships between dietary fatty acids and dementia, or VaD, or AD, including the setting and study design, and the dietary and cognitive assessment used.

FFQ food frequency questionnaire, *NINCDS-ADRDA* National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association, *NINCDS-AIREN* National Institute of Neurological and Communicative Disorders and Stroke and the Association Internationale pour la Recherche at l'Enseignement en Neurosciences, *DSM-III-R* Diagnostic and Statistical Manual of Mental Disorders, third edition revised, *PUFA* polyunsaturated fatty acids, *MUFA* monounsaturated fatty acids, *DSM-IV* Diagnostic and Statistical Manual of Mental Disorders, fourth edition, *APOE* apolipoprotein E, *DHA* docosahexaenoic acid
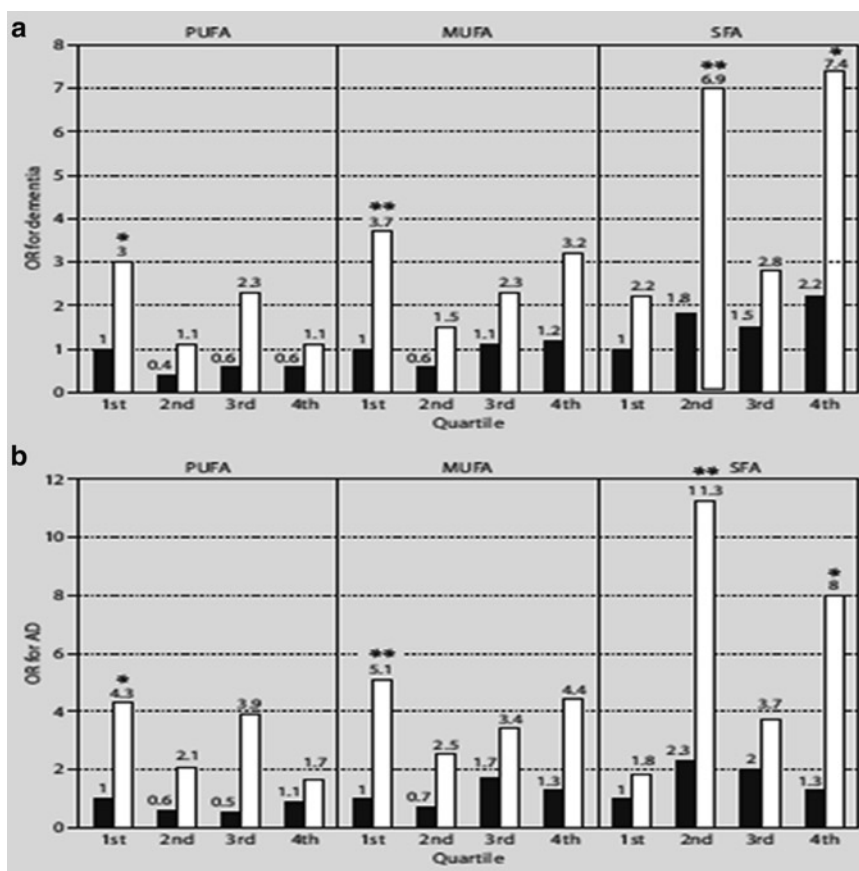
Fig. 179.4 Combined effects of apolipoprotein E (*APOE*) ε4 carrier status and midlife polyunsaturated fatty acids (*PUFA*), monounsaturated fatty acids (*MUFA*), and saturated fatty acids (*SFA*) consumptions in spreads and the risk of dementia (**a**) and Alzheimer's disease (*AD*) (**b**). This figure lists analyses adjusted for age, sex, education, follow-up time, other subtypes of fat from spreads and milk, APOE ε4 and midlife systolic blood pressure (*SBP*), body mass index (*BMI*), cholesterol, smoking, and late-life history of myocardial infarction, stroke and diabetes; *$p < 0.05$, **$p < 0.01$ when compared to the reference group (first fat quartile and APOE ε4 non-carrier); = APOE ε4 non-carriers; = APOE ε4carriers (Reprinted from Laitinen et al. 2006. With permission)

179.3.3   Fish Consumption and Dementia

A lower risk of incident dementia in subjects consuming more fish has nevertheless been reported in several other independent prospective cohort studies (Barberger-Gateau et al. 2002; Morris et al. 2003b; Huang et al. 2005; Barberger-Gateau et al. 2007) (Table 179.9). In particular, data from the Cardiovascular Health Cognition Study (CHCS) showed that consumption of fatty fish more than twice per week was associated with a reduction in risk of dementia by 28%, and AD by 41% in comparison to those who ate fish less than once per month. Stratification by APOE ε4 showed this effect to be selective to those without the ε4 allele (Huang et al. 2005) (Table 179.9). Only one prospective study has not shown a significant benefit of higher fish intake and risk of AD (Schaefer et al. 2006) (Table 179.9). This study was based on a subsample of 488 participants representing about 25% of the main cohort of the Framingham Heart Study in which both dietary DHA intakes were

calculated and plasma DHA measurements made. A protective effect of higher plasma DHA was observed against the risk of all cause dementia but not for AD. Higher dietary intakes of DHA and fish did not result protective against dementia and AD. This negative finding for AD per se may have been due to a lack of statistical power because the 50% risk reduction for AD in subjects who consumed fish more than twice a week was almost statistically significant (95% CI 0.20–1.27; P=0.14). Furthermore, several studies suggest that APOE polymorphism may inhibit or prevent the beneficial effect of fish in reducing the risk of cognitive decline in the elderly. Two recent prospective studies indicate that ApoE4 carriers are not protected against dementia by higher fish intake (Huang et al. 2005; Barberger-Gateau et al. 2007) (Table 179.9). Therefore, despite these contrasting findings, there is now considerable evidence suggesting that fatty acid intake and fish consumption may influence dementia and AD risk, but the direction (protection or risk) and the level of this effect remain unclear. In fact, based on the current evidences from human and animal studies, it is not possible to make definitive dietary recommendations in relation to the AD risk on fish consumption and the lower intake of saturated fat from meat and dairy products. Furthermore, individuals who consume a diet high in fruits and vegetables as well as nuts or fish would probably have other lifestyle characteristics that might be effective in reducing AD or VaD risk (e.g., physical activity). However, a high consumption of fats from fish, vegetable oils, vegetables, and nuts should be encouraged because this dietary advice is in accordance with recommendations for lowering the risk of cardiovascular disease, obesity, diabetes, and hypertension.

179.4 Dietary Fatty Acid Supplementation in Predementia and Dementia Syndromes: Is It the Case for a Treatment?

The increasing epidemiological evidence of an association between a reduced risk of AD and a diet high in *n*-3 PUFA and fish consumption (Panza et al. 2004), is further supported by recent findings that certain diets have been associated with a lower incidence of predementia syndromes (Solfrizzi et al. 2006a, b). Two randomized clinical trials (RCT), using an *n*-3/*n*-6 fatty acid compound on 100 AD patients and a supplementation with DHA on 20 nursing home residents with VaD found improvements in mood, cooperation, appetite, sleep, ability to navigate in the home, and short-term memory in the AD-treated group (Yehuda et al. 1996) and improved cognitive scores in the VaD-treated group (Terano et al. 1999) (Table 179.10).

Recently, Freund-Levi and colleagues found that, in 204 patients with moderate AD, the supplementation with DHA and EPA (for a total dose of 1,720 mg DHA/600 mg EPA) for 6 months (OmegAD Study) did not delay the rate of cognitive decline but, in the group of 32 patients with the most mild AD (MMSE >27, Clinical Dementia Rating Score 0.5–1), *n*-3 PUFA supplementation slowed the decline in MMSE scores (Freund-Levi et al. 2006) (Table 179.10). After the treatment period, all the subjects received open label *n*-3 PUFA for another 6 months. The subjects in the placebo group of these very mild AD patients also showed a statistically significant slowing of decline when they were switched to treatment between 6 and 12 months, suggesting that *n*-3 PUFA might be of benefit to slow the progression of the disease in MCI or very mild AD (Freund-Levi et al. 2006). Furthermore, this supplementation did not result in marked effects on neuropsychiatric symptoms in mild to moderate AD patients except for possible positive effects on depressive symptoms and agitation symptoms in subgroups. In fact, there were positive effects on depressive symptoms in non-APOE ε4 carriers and in non-APOE ε4 carriers on agitation symptoms (Freund-Levi et al. 2008) (Table 179.10).

At present, the effect of arachidonic acid (ARA) and DHA (240 mg/day), after a 90-day supplementation, on MCI, organic brain lesions, or AD showed a significant improvement of the immediate

Table 179.10 Principal clinical trials on polyunsaturated fatty acid (PUFA) supplementation in patients with mild cognitive impairment (MCI), vascular dementia (VaD), Alzheimer's disease (AD), and age-related cognitive decline (ARCD)

Reference	Participants	Intervention and duration of exposure	Outcome measures	Effects of interventions
Terano et al. (1999)	20 elderly nursing home residents with VaD	A single dose of 4.3 g of DHA was administered; dose effect was not assessed. The duration of exposure was 12 months	Cognitive functioning was evaluated using HDS-R and MMSE scores at baseline, and after 3, 6, and 12 months	Baseline HDS-R and MMSE scores were 15 to 22, consistent with mild to moderate dementia. HDS-R and MMSE scores improved in the DHA-treated group but not among patients who were not treated with DHA. Comparisons between groups were significant at 3 and 6 months for the HDS-R and at 6 months for the MMSE
Freund-Levi et al. (2006)	204 patients with mild to moderate AD and with acetylcholine esterase inhibitor treatment and a MMSE >15 points	A single dose of 1.7 g of DHA plus 0.6 g of EPA was administered. The duration of exposure was 6 months placebo-controlled and 6 months open for both groups	Primary outcome measures: MMSE and ADAS-cog. Secondary outcome measures: was global function as assessed with the CDR	Administration of n-3 PUFA in patients with mild to moderate AD did not delay the rate of cognitive decline according to the MMSE or ADAS-cog. However, positive effects were observed in a small group of patients with very mild AD (MMSE >27 points)
Kotani et al. (2006)	21 patients with mild cognitive dysfunction (12 MCI patients with supplementation and 9 MCI patients with placebo), 10 patients with organic brain lesions, and 8 patients with AD	A single dose of 240 mg/day of ARA and DHA, or 240 mg/day of olive oil (placebo). The duration of exposure was 3 months	The cognitive functions were evaluated using Japanese version of RBANS at two time points: before and 90 days after the supplementation	The MCI group with supplementation showed a significant improvement of the immediate memory and attention score. Organic group showed a significant improvement of immediate and delayed memory. However, there were no significant improvements of each score in AD and MCI placebo groups
Freund-Levi et al. (2008)	204 patients with mild to moderate AD and with acetylcholine esterase inhibitor treatment and a MMSE >15 points	A single dose of 1.7 g of DHA plus 0.6 g of EPA was administered. The duration of exposure was 6 months placebo-controlled and 6 months open for both groups	Neuropsychiatric symptoms were measured with NPI and MADRS. Care givers' burden and activities of daily living (DAD) were also assessed.	No significant overall treatment effects on neuropsychiatric symptoms, on activities of daily living or on caregiver's burden were found. However, significant positive treatment effects on the scores in the NPI agitation domain in APOE ε4 carriers and in MADRS scores in non-APOE ε4 carriers were found.

Table 179.10 (continued)

Reference	Participants	Intervention and duration of exposure	Outcome measures	Effects of interventions
Chiu et al. (2008)	23 patients with mild to moderate AD and 23 patients with MCI	n-3 PUFA 1.8 g/day in monotherapy or placebo (olive oil). The duration of exposure was 24 weeks	Global clinical function measured with CIBIC-plus, cognitive function with ADAS-cog and MMSE, depressive symptoms with HDRS	This supplementation may improve global clinical function (CIBIC-plus) in MCI patients relative to placebo. No associations were found between randomization group and ADAS-cog, MMSE or HDRS scores
Van de Rest et al. (2008a)	Independently living individuals (n = 302) aged ≥ 65 years CES-D score < 16 MMSE score > 21	A single dose of 1,800 mg/day EPA+DHA (n = 96), 400 mg/day EPA+DHA (n = 100), or placebo capsules (n = 106); the duration of exposure was 26 weeks	Changes in mental well-being were assessed as the primary outcome with the CES-D, MADRS, GDS-15, and HADS-A	Treatment with neither 1800 mg nor 400 mg EPA+DHA differentially affected any of the measures of mental well-being after 13 or 26 weeks of intervention compared with placebo
Van de Rest et al. (2008b)	Independently living individuals (n = 302) aged ≥ 65 years CES-D score < 16 MMSE score > 21	A single dose of 1,800 mg/day EPA+DHA (n = 96), 400 mg/day EPA+DHA (n = 100), or placebo capsules (n = 106); the duration of exposure was 26 weeks	Cognitive performance was assessed using an extensive neuropsychological test battery that included the cognitive domains of attention (SC-WT; fWDST), sensorimotor speed (TMT-A), memory (WLT; bWDST), and executive function (TMT-B; VFT)	There were no significant differential changes in any of the cognitive domains for either low-dose or high-dose fish oil supplementation compared with placebo; an effect of EPA–DHA supplementation in subjects who carried the APOE ε4 allele was also found, but only on the cognitive domain of attention

This table lists the principal findings of clinical trials on PUFA supplementation in patients with MCI, VaD, AD, and ARCD, including the intervention and duration of exposure, and the outcome measures used

DHA docosahexaenoic acid, *HDS-R* Hasegawa's Dementia rating scale, *MMSE* Mini-mental State Examination, *EPA* eicosapentaenoic acid, *ADAS-cog* cognitive portion of the Alzheimer Disease Assessment Scale, *CDR* Clinical Dementia Rating Scale, *ARA* arachidonic acid, *RBANS* Repeatable Battery for Assessment of Neuropsychological Status, *NPI* Neuropsychiatric Inventory, *MADRS* Montgomery Asberg Depression Scale, *DAD* Disability Assessment for Dementia, *APOE* apolipoprotein E, *CIBIC-plus* Clinician's Interview-Based Impression of Change Scale, *HDRS* Hamilton Depression rating Scale, *DRS-2* Dementia Rating Scale 2, *CDT* Clock Drawing Tests, *ADCS-ADL* Alzheimer's Disease Cooperative Study–Activities of Daily Living, *CES-D* Center for Epidemiologic Studies Depression Scale, *GDS-15* 15-item Geriatric Depression Scale, *HADS-A* Hospital Anxiety and Depression Scale, *SC-WT* Stroop Color–Word Test, *fWDST* forward test of the Wechsler Digit Span Task, *TMT-A* Trail Making Test version A, *WLT* Word Learning Test, *bWDST* backward test of the Wechsler Digit Span Task, *TMT-B* Trail Making Test version B, *VFT* Verbal Fluency Test

memory and attention score for MCI patients, and a significant improvement of immediate and delayed memories for patients with organic brain damages (Kotani et al. 2006) (Table 179.10). Finally, the preliminary results from a 24-week, randomized, double-blind placebo-controlled study on 23 participants with mild or moderate AD and 23 with MCI randomized to receive *n*-3 PUFA 1.8 g/day or placebo (olive oil), suggested that his supplementation may improve global clinical function, as measured by Clinician's Interview-Based Impression of Change scale which included caregiver-supplied information (CIBIC-plus), relative to placebo. No associations were found between the randomization group and ADAS-cog, MMSE, or Hamilton Depression rating Scale scores. Levels of EPA on erythrocyte membrane, were associated with cognitive function, measured by ADAS-cog, in these patients (Chiu et al. 2008) (Table 179.10). However, in a secondary analysis, participants with MCI showed more improvement of ADAS-cog than those with AD associated with *n*-3 PUFA administration (Chiu et al. 2008), which support recent reports showing that PUFA supplementation could be more beneficial on cognition in people with very mild AD (Freund-Levi et al. 2006) or MCI Kotani et al. 2006) than in AD patients (Table 179.10).

A few years ago, a Cochrane review concluded that there was a growing body of evidence from biological, observational, and epidemiological studies that suggested a protective effect of *n*-3 PUFA against dementia. However, the Cochrane review team was unable to locate a single published randomized controlled trial on which to base recommendations for the use of dietary or supplemental *n*-3 PUFA for the prevention of cognitive impairment or dementia (Lim et al. 2006). However, very recently, a randomized, double-blind, placebo-controlled trial on 302 cognitively healthy (MMSE score > 21) individuals aged 65 years or older investigated the possible impact of *n*-3 PUFA on the mental well-being and cognitive performance of nondepressed (CES-D score < 16), older individuals (van de Rest et al. 2008a, b) (Table 179.10). In this RCT, participants were randomly assigned to 1.800 mg/d EPA–DHA, 400 mg/d EPA–DHA, or placebo capsules for 26 weeks. In older Dutch subjects, no effect of daily supplementation with low or high doses of EPA-DHA on mental well-being as assessed by depression and anxiety questionnaires was found (van de Rest et al. 2008a). Furthermore, there were no significant differential changes in any of the cognitive domains (attention, sensorimotor speed, memory, and executive function) for either low-dose or high-dose fish oil supplementation compared with placebo (van de Rest et al. 2008b). However, an effect of EPA–DHA supplementation in subjects who carried the APOE-ε4 allele was found, but only on the cognitive domain of attention (van de Rest et al. 2008b). Fish oil may be beneficial in these subjects who are most sensitive to developing dementia. These two substantially negative studies on ARCD may be explained by the samples investigated (nondepressed and noncognitively impaired older subjects). Further trials in depressed patients or ε4-carriers with MCI are needed. Finally, there is another ongoing RCT with cognitive endpoints of *n*-3 PUFA supplementation in healthy cognitively intact older persons. The OPAL study is a double-blind randomized placebo-controlled trial examining the effect of daily supplementation with 700 mg *n*-3 PUFA (500 mg DHA and 200 mg EPA) for 24 months on cognitive performance in healthy older persons aged 70–79 with good cognitive function (MMSE equals or greater than 24 out of 30 points at baseline), who are recruited from 20 primary care practices (Dangour et al. 2006). The OPAL study was completed at the end of 2007 and its findings will be published shortly. Thus, epidemiological evidence has suggested a possible association between PUFA (particularly, *n*-3 PUFA) and reduced risk of cognitive decline and dementia. However, due to the small number of studies that inform this topic, further research is necessary before a strong conclusion can be drawn. Some recent RCTs assessed the cognitive or functional effect of *n*-3 PUFA supplementation on patients with VaD, AD, MCI, or ARCD in cognitively unimpaired older subjects. These RCTs suggested a positive effect of this intervention only in very mild AD or MCI patients, or in subgroups (e.g., APOE-e4 carriers) for cognitive performance in nondemented subjects or for neuropsychiatric symptoms in mild to moderate AD patients. On the basis

of these evidences, we strongly suggest also for predementia syndromes, a high-risk condition for progression to dementia of vascular and degenerative origin, intervention trials using measures of dietary supplementation similar to the OmegAD Study to determine if such supplements will slow cognitive decline.

179.5 Dietary Unsaturated Fatty Acids and Cognitive Decline: Possible Mechanisms

179.5.1 Monounsaturated Fatty Acids and Cognitive Decline

Different pathways could contribute to the neuroprotective as well as the neurotrophic properties of UFA. As seen above, in the older subjects of the ILSA, there was a high consumption of olive oil, with an MUFA energy intake of 17.6%, 85% of which was derived from olive oil (Solfrizzi et al. 1999) (Fig. 179.1). In our population, the prolonged protection of MUFA intake against age-related changes in cognitive functions may be linked to the relevant quota of antioxidant compounds in olive oil, including low-molecular-weight phenols (Solfrizzi et al. 2005). In fact, animal studies suggested that diets high in antioxidant-rich foods, such as spinach, strawberries, and blueberries, rich in anthocyanins and other flavonoids may be beneficial in slowing age-related cognitive decline (Solfrizzi et al. 2005). The possible role of antioxidant compounds from olive oil do not diminish or otherwise alter the argument concerning the fatty acids, because this is only a possible explanation of the role of MUFA on age-related cognitive changes in our population, in which MUFA intake derived for a large part from olive oil.

The neuroprotective effects of dietary UFA could rely on their impact on membrane architecture. In fact, UFA have an important role in maintaining the structural integrity of neuronal membranes, determining the fluidity of synaptosomal membranes and thereby regulating neuronal transmission. Furthermore, essential fatty acids can modify the activity of certain membrane-bound enzymes (phospholipase A2, protein kinase C, and acetyltranferase), and the function of the neurotransmitters' receptors. Finally, free fatty acids, lipid metabolites, and phospholipids modify the function of membrane proteins including ion channels (Solfrizzi et al. 2005). Moreover, fatty acid composition of neuronal membranes in advancing age demonstrated an increase in MUFA content and a decrease in PUFA content (Solfrizzi et al. 2005). *n*-3 PUFA increase membrane fluidity by replacing *n*-6 PUFA and cholesterol from the membrane (Solfrizzi et al. 2005) maintaining an optimal membrane fluidity as obligatory for neurotransmitter binding and signaling within the cell (Solfrizzi et al. 2005). There is also evidence associating a dietary deficiency of *n*-3 PUFA with changes in cortical dopoaminergic function (Solfrizzi et al. 2005) (Fig. 179.5).

179.5.2 Polyunsaturated Fatty Acids and Cognitive Decline

In adult rats, learning and cognitive behavior are related to brain DHA status, which, in turn, is related to the levels of the dietary *n*-3 PUFA (Moriguchi et al. 2000). In fact, administration of DHA seems to improve learning ability in β-amyloid (Aβ)-infused rats (Hashimoto et al. 2005) and inhibit decline in avoidance learning ability in the AD model rats, associated with an increase in the cortico-hippocampal *n*-3/*n*-6 ratio, and a decrease in neuronal apoptotic products (Hashimoto et al. 2002).
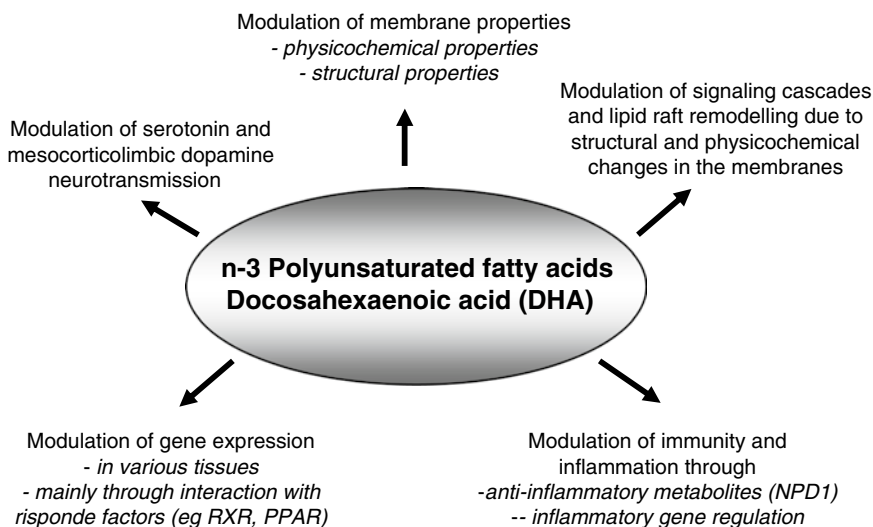
Fig. 179.5 Synopsis of the neuroprotective properties of *n*-3 polyunsaturated fatty acids (*PUFA*) and docosahexaenoic acid (*DHA*). This figure lists various possible molecular mechanisms of *n*-3 PUFA and DHA linked to their neuroprotective properties including modulation of membrane properties, serotonin, and dopamine neurotransmission, signaling cascades and lipid raft remodeling, gene expression, and immunity and inflammation (Modified from Florent-Béchard et al. 2007. With permission)

Similarly, recent studies showed that dietary DHA in an aged AD mouse model could be protective against Aβ production, deposition in plaques and cerebral amyloid angiopathy (Lim et al. 2005; Hooijmans et al. 2007), and increases cerebral blood volume (Hooijmans et al. 2007). In other transgenic AD mouse models, DHA also protects against dendritic pathology (Calon et al. 2004) and prevents neuronal apoptosis induced by soluble Aβ peptides (Florent et al. 2006), increases synaptic protein and phospholipid densities (Cole et al. 2005; Wurtman et al. 2006), and inhibits degradative endopeptidase activities (Park et al. 2003). Some experimental evidence has suggested that essential *n*-3 PUFA effectively lower Aβ production in transgenic mice, as reported in studies from several laboratories (Lim et al. 2005; Cole et al. 2005; Oksman et al. 2006). Yet, plaque burden was reduced in only one study using aged transgenic mice, following 3 months DHA enriched diet (Lim et al. 2005), but not in several other studies that started dietary intervention at a much younger age (Oksman et al. 2006; Hooijmans et al. 2007).

Furthermore, DHA, given its unique structural properties, could allow of the modification of the architectural properties of the membrane, especially the distribution and the abundance of lipid raft microdomains (Florent-Béchard et al. 2007). Lipid rafts are liquid ordered sphingomyelin-rich cholesterol-rich PUFA-poor microdomains. DHA and PUFA enrichment is known to be accompanied by lateral phase separation and local lipid redistribution, subtle membrane remodeling and selective displacement of proteins (Florent-Béchard et al. 2007) (Fig. 179.5). By changing the organization and/or composition of the lipid rafts, DHA could directly modify many signaling pathways such as those initiated at the plasma membrane (Florent-Béchard et al. 2007) (Fig. 179.5).

It is well known that PUFA of both *n*-3 and *n*-6 families control gene expression in a variety of tissues including liver and adipose tissue. However, the underlying mechanisms of the direct effects of dietary PUFA-induced differential gene expression pattern in the brain have been addressed by few studies (Florent-Béchard et al. 2007). Gene regulation by PUFA can occur through interactions with specific or nonspecific ligands such as transcription factors like peroxysome proliferator-activated

receptors (PPAR) or retinoid X receptor (RXR) that directly modulate the expression of target genes (Florent-Béchard et al. 2007) (Fig. 179.5). The direct effects of PUFA on gene regulation might be one of the clues to understand the beneficial effects of the *n*-3 PUFA on the nervous system.

Several clinical and epidemiological studies have identified beneficial effects of PUFA for a variety of inflammatory diseases, yet without mechanistic explanations for these beneficial effects. Resolvins and protectins are recently identified molecules that are generated from *n*-3 PUFA precursors and can orchestrate the timely resolution of inflammation in model systems. In fact, DHA also serves as a precursor for the biosynthesis of additional bioactive counter-regulatory lipid mediators. For (neuro)protectin D1 (N)PD1 formation, DHA is rapidly released for conversion to 17S-hydroxy-DHA that serves as a biosynthetic precursor (Serhan et al. 2006). In AD, NPD1 biosynthesis is activated by soluble APP-α (Lukiw et al. 2005). In this disorder, levels of DHA, NPD1, and 15-lipoxygenase (15-LOX) are selectively decreased in the hippocampus, providing a plausible mechanism for decreased neuroprotection in AD: less inhibition of apoptosis and subsequently, increased neuronal cell death (Lukiw et al. 2005) (Fig. 179.5). In a placebo-controlled randomized trial, the OmegAD study, AD patients treated with DHA-rich dietary supplements had reduced release of interleukin (IL)-1b, IL-6 and granulocyte colony-stimulating factor from peripheral blood mononuclear cells (Vedin et al. 2008).

The *n*-3 PUFA from fish may be inversely associated with dementia because it lowers the risk of thrombosis, stroke, cardiovascular disease, and cardiac arrhythmia, reducing the risk of thromboembolism in the brain and consequently of lacunar and large infarcts that can lead to VaD and AD (Solfrizzi et al. 2005). Furthermore, the *n*-3 PUFA may be important as lipids in the brain, particularly for the possible influence of DHA on the physical properties of the brain that are essential for its function (Solfrizzi et al. 2005). Furthermore, fish oil was a better source than α-linolenic acid for the incorporation of *n*-3 PUFA into rat brain phospholipid subclasses (Solfrizzi et al. 2005). On the contrary, high linoleic acid intake (*n*-6 PUFA) may increase the susceptibility of LDL cholesterol to oxidation, which makes it more atherogenic, even if the association between linoleic acid and atherosclerosis is controversial (Solfrizzi et al. 2005). Therefore the ratio of dietary *n*-3/*n*-6 PUFA intake may influence the potential role of PUFA on cognitive decline and dementia, the optimal ratio of *n*-6/*n*-3 should be <5:1 (de Lorgeril et al. 1998). Finally, a high dietary intake of SFA and cholesterol increases the risk for cardiovascular disease, and therefore for cognitive decline, VaD, and AD (Solfrizzi et al. 2008). On the contrary, treatment for 4 weeks with a Mediterranean-inspired diet rich in *n*-3 PUFA decreased blood lipids in healthy individuals with a low-risk profile for cardiovascular disease, with a beneficial effect also on vascular function and oxidative stress (Ambring et al. 2004).

179.6 Applications to Other Areas of Health and Disease

About 50–60% of the dry weight portion of the human brain consists of lipids. PUFA constitute approximately 35 percent of that lipid content (Lauritzen et al. 2001). *n*-3 PUFA, particularly EPA and DHA, play important roles in the development and maintenance of normal central nervous system structure and function. Along with the *n*-6 PUFA, ARA, DHA is a major constituent of neuronal membranes, making up about 20% of the brain's dry weight (Yehuda et al. 1999). Synapses contain a high concentration of DHA, which appears to play a role in synaptic signal transduction (Jones et al. 1997). The metabolic pathways of the essential fatty acids that play an important role in neuronal signal transduction and release of these fatty acids is involved in the phospholipase A2 cycle following activation of various neurotransmitter receptors. DHA is also important for normal cognitive development. In addition, the anti-inflammatory compounds for which DHA is a precursor may

function in the brain to protect against ischemic damage. PUFA in general play important roles in structural and functional maintenance of neuronal membranes, neurotransmission, and eicosanoid biosynthesis (Lauritzen et al. 2001; Tapiero et al. 2002), as well as in the maintenance of membrane fluidity and flexibility and in the modulation of ion channels, receptors, and ATPases. The importance of PUFA in the maintenance of adequate membrane rigidity is evidenced by the loss of fluidity that follows decrease in PUFA (Bourre et al. 1991), leading to changes in the orientation and function of receptors and ion channels, such as calcium and sodium channels.

Several lines of research have suggested that the high ratio of *n*-6 PUFA to low levels of *n*-3 PUFA currently consumed in occidental countries promotes a number of chronic diseases. Whether or not the relatively high intake of *n*-6 PUFA independently contributes to this problem is currently uncertain (Richardson 2003). Because of the slow rate of elongation and further desaturation of the essential fatty acids, the importance of PUFA to many physiological processes, and the overwhelming ratio of *n*-6 PUFA to *n*-3 PUFA in the average occidental diet, nutrition experts are increasingly recognizing the need for humans to augment the body's synthesis of *n*-3 PUFA by consuming foods that are rich in these compounds. According to data from two population-based surveys, the major dietary sources of *n*-3 PUFA in the US population are fish, fish oil, vegetable oils (principally canola and soybean), walnuts, wheat germ, and some dietary supplements, and the primary dietary sources of *n*-6 PUFA are meats and dairy products. These surveys, the Continuing Food Survey of Intakes by Individuals 1994–98 (CSFII) and the third National Health and Nutrition Examination (NHANES III) 1988–94 surveys, are the main sources of dietary intake data for the US population.

Other studies specifically addressed the association of *n*-3 PUFA consumption with risk or incidence of particular neurological diseases other than dementia, e.g., the incidence of multiple sclerosis (MS) (Ghadirian et al. 1998; Zhang et al. 2000), the risk of Parkinson's disease (PD) (Chen et al. 2003), and the risk of cerebral palsy (Petridou et al. 1998). The relationship between dietary intake of *n*-3 PUFA and incidence of MS was assessed in two reports; one pooled data from two large cohorts of women from the Nurses' Health Study (NHS) and the Nurses' Health Study II (NHS II) (Zhang et al. 2000), and the other used a case-control design (Ghadirian et al. 1998). The prospective cohort study assessed the effect of *n*-3 PUFA in terms of fish consumption, fish *n*-3 PUFA, ALA, EPA, and DHA. ALA was associated with a reduced risk of MS in both cohorts that did not reach statistical significance. Intakes of *n*-3 PUFA, EPA, or DHA were not associated with MS incidence. The case-control study evaluated 197 incident MS cases and 202 age-, sex- and neighborhood-matched controls and found no significant association between fish consumption and risk of MS overall. However, fish consumption was significantly associated with a lower risk of MS in females only (Ghadirian et al. 1998).

The relationship between dietary intake of *n*-3 PUFA and incidence of PD was assessed in one report that pooled data from two large prospective cohorts, the Health Professionals Follow-up Study and the NHS (Chen et al. 2003). This study assessed the effect of *n*-3 PUFA in terms of *n*-3 fats from fish, ALA, EPA, and DHA over a 6- to 8-year period. There was no significant association between fish *n*-3 PUFA, ALA, EPA, or DHA intake and risk of PD. In a pooled analysis of men and women across two cohorts, ALA was associated with a reduced risk of developing PD (RR = 0.65, 95% CI 0.46, 0.91 for comparison of highest to lowest quintiles of risk). Among women, there was a significant trend but no significant risk reduction for any individual quintile of consumption. This finding is particularly noteworthy given the statistical power of the Health Professionals Follow-up Study and the NHS and the longitudinal analysis of dietary intake in these studies.

One study evaluated the effects of maternal dietary intake on the risk of cerebral palsy in offspring in a case-control study of 91 cases of cerebral palsy identified from statistics of hospitals and rehabilitation centers in Greece and 246 neighborhood controls (Petridou et al. 1998). Mothers of cases and controls were interviewed about their dietary habits during pregnancy using a food-frequency

questionnaire. Consumption of fish once a week throughout pregnancy was associated with a lower risk of cerebral palsy compared with no fish intake.

In the Mediterranean countries, the principal source of MUFA is olive oil, probably the most representative food in the traditional Mediterranean diet. The hypocholesterolemic effect of the isoenergetic substitution of dietary MUFA for SFA first generated interest in MUFA-rich fats, which include olive, canola, and high-oleic sunflower oils. However, olive oil has additional biological effects, related in part to MUFA but also to minor components, particularly antioxidant phenolics. Virgin olive oil, a pure olive juice, is particularly rich in phenolics. Increasing epidemiologic and clinical evidences suggest that MUFA as a nutrient, olive oil as a food, and the Mediterranean diet as a food pattern have beneficial effects on obesity, the metabolic syndrome, and diabetes (Perez-Jimenez et al. 2005). A Mediterranean diet rich in virgin olive oil and virgin olive oil per se have been shown to improve classical and novel cardiovascular risk factors, such as lipid profiles, blood pressure, postprandial lipemia, endothelial dysfunction, oxidative stress, inflammation, and thrombosis (Perez-Jimenez et al. 2005). Limited epidemiologic evidences from Mediterranean countries suggest that dietary MUFA and/or olive oil intake might protect against breast, colorectal and prostate cancer. Experimental cellular studies have provided new evidences on the potential protective effect of virgin olive oil on cancer (Perez-Jimenez et al. 2005).

179.7 Conclusions

Recently, several studies have suggested that an increase of SFA could have negative effects on cognitive functions. Furthermore, a clear reduction of risk for cognitive decline has been found in population samples with elevated fish consumption, high intake of MUFA and PUFA, particularly *n*-3 PUFA (Fig. 179.6). Recent findings have demonstrated that while dietary fatty acid intakes were not associated with incident MCI, high PUFA intake appeared to have a borderline nonsignificant trend
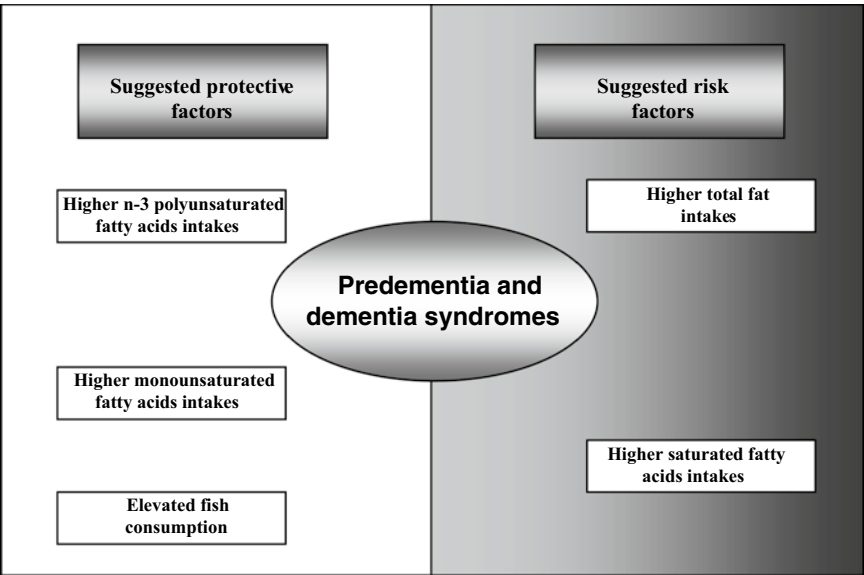
Fig. 179.6 Synopsis of the evidence on the possible effects of dietary fatty acids on predementia and dementia syndromes. This table lists the key possible effects of dietary fatty acids on predementia and dementia syndromes including *n*-3 polyunsaturated fatty acids, monounsaturated fatty acids, saturated fatty acids (*SFA*), and fish consumption

Table 179.11 Key points of studies on the relationships between dietary fatty acids and predementia and dementia syndromes

A. An increasing body of epidemiological evidence suggests that elevated saturated fatty acids (SFA) could have negative effects on age-related cognitive decline (ARCD). On the contrary, a reduction of risk for dementia and mild cognitive impairment (MCI) has been found in population samples with elevated fish consumption, high intake of monounsaturated fatty acids (MUFA) and polyunsaturated fatty acids (PUFA), particularly *n*-3 PUFA

B. Recent findings from clinical trials with *n*-3 PUFA supplementation have shown efficacy on depressive symptoms in non-apolipoprotein E (APOE) ε4 carriers, and on cognitive symptoms only in very mild Alzheimer's disease (AD) subgroups, MCI patients, and cognitively unimpaired subjects non-APOE ε4 carriers

C. The evidence coming from clinical trials together with epidemiological findings support the idea that *n*-3 PUFA may play a role in maintaining adequate cognitive functioning in predementia syndromes, but not when the AD process has already taken over. Therefore, at present, no definitive dietary recommendations on fish and unsaturated fatty acids consumption or lower intake of saturated fat in relation to the risk for predementia and dementia syndromes are possible

This table lists the principal features of clinical and epidemiological studies on the relationships between dietary fatty acids and predementia (MCI and ARCD) and dementia syndromes (AD and vascular dementia), including findings of clinical trials on PUFA supplementation in these patients

for a protective effect against the development of MCI. Nonetheless, at present, no definitive dietary recommendations on fish and UFA consumption or lower intake of saturated fat in relation to the risk for dementia and cognitive decline are possible (Table 179.11). In fact, in a recent randomized controlled trial, *n*-3 PUFA supplementation did not influence cognitive functioning during a follow-up of 6 months except in a small group of patients with very mild AD and for possible positive effects on depressive symptoms in non-APOE ε4 carriers. These data together with epidemiological evidence support the idea that *n*-3 PUFA may have a role in the primary and maybe secondary prevention of the disease but not when the disease process has already taken over. However, high levels of consumption of fats from fish, vegetable oils, and vegetables should be encouraged because this dietary advice is in accordance with recommendations for lowering the risk of cardiovascular disease, obesity, diabetes, and hypertension. Therefore, epidemiological studies on the association between diet and cognitive decline suggested a possible role of fatty acids intake in maintaining adequate cognitive functioning and possibly in preventing or delaying the onset of dementia, both of degenerative or vascular origin. Appropriate dietary measures or supplementation with specific macronutrients might open new ways for the prevention and management of cognitive decline and dementia (Solfrizzi et al. 2008).

On the other hand, Scarmeas and colleagues, using an inclusive dietary score (MeDi score) but studying a population with a substantial difference in dietary habits in comparison with Greek (EPIC) (Psaltopoulou et al. 2008) and Italian (ILSA) (Solfrizzi et al. 2006a, b) cohorts, found that higher adherence to the Mediterranean diet is associated with a trend for reduced risk of incident MCI and with reduced risk of MCI progression to AD (Scarmeas et al. 2009). The use of diet-scoring systems such as the MeDi score has undeniable advantages in understanding the role of diet in chronic disease (Solfrizzi et al. 2006c). They may account for the complex biological interactions between different components of a composite dietary pattern, such as a Mediterranean diet, that may be difficult to detect in analyses focusing only on individual components (Trichopoulou et al. 2006). These contrasting findings about the impact of MeDi score or individual macronutrients on ARCD or MCI may suggest an approach not confined only to cognitive skills but extended to functional status and comorbidity. However, we should not renounce a priori the work for a correct estimate of the validity of the MeDi score for cognitive impairment as a criterion. In fact, the evidence about the role of the whole Mediterranean diet on cognitive decline are still scarce (Psaltopoulou et al. 2008; Scarmeas et al. 2009). Therefore, in future studies, it would be indicated, along with measuring this effect by a dietary composite score, also to report the estimates and the impact of the individual components

of the diet. In a very recent re-analysis from the ILSA cohort, we showed that high PUFA were associated with reduced risk of incident MCI among who consumed a low MUFA/SFA ratio intake (Solfrizzi et al. 2009). Therefore, it should be advisable to include PUFA in the MeDi score as individual macronutrient (such as MUFA/SFA ratio), among the components presumed to be beneficial, in evaluating the relationship between adherence to Mediterranean diet and ARCD or MCI. In fact, while an increasing body of evidence suggested that elevated fish consumption and high intake of *n*-3 PUFA may be protective against ARCD and MCI, the traditional Cretan diet, although strongly dependent on high olive oil intake, was never centered on fish consumption. In this context, *n*-6 PUFA could potentially exert some health benefits. In fact, in a Mediterranean diet, some foods are rich in *n*-6 PUFA (e.g., walnuts, almonds, hazelnuts), while other foods, although poor in *n*-6 PUFA, are highly consumed such as cereals, legumes, and, in less amount, some types of meat (pork), and poultry. Furthermore, olive oil contains n–6 and n–3 PUFA in a ratio of 10:1. Therefore, it should be advisable to include PUFA in the MeDi score as individual macronutrient (such as MUFA/SFA ratio), among the components presumed to be beneficial, in evaluating the relationship between adherence to Mediterranean diet and ARCD or MCI (Solfrizzi et al. 2009).

Summary Points

- Dietary and vascular factors are associated with increasing risk of predementia and dementia syndromes.
- Among different dietary patterns, adherence to a traditional Mediterranean diet was associated with a significant reduction in risk for Alzheimer's disease (AD).
- Among dietary factors, a clear reduction of risk of cognitive decline has been found in a population sample with a high intake of polyunsaturated fatty acids (PUFA) and monounsaturated fatty acids (MUFA).
- Cumulative evidence has suggested that elevated saturated fatty acids (SFA) could have negative effects on age-related cognitive decline (ARCD).
- Recent findings have demonstrated that while dietary fatty acids intakes were not associated with incident mild cognitive impairment (MCI), high PUFA intake appeared to have a borderline non-significant trend for a protective effect against the development of MCI.
- Recent findings from clinical trials with *n*-3 PUFA supplementation, showing efficacy on cognitive and depressive symptoms only in very mild AD subgroups or MCI, suggest a possible role of fatty acid intake in maintaining adequate cognitive functioning and possibly for the prevention and management of cognitive decline and dementia.

Definitions

Unsaturated and saturated fatty acids: Unsaturated fat is fat or fatty acid in which there are one or more double bonds in the fatty acid chain. A fat molecule is monounsaturated if it contains one double bond, and polyunsaturated if it contains more than one double bond. Whendouble bonds are formed, hydrogen atoms are eliminated. Thus,saturated fat is "saturated" with hydrogen atoms.

Dementia: This is a syndrome defined by impairments in memory and other cognitive functions that are severe enough to cause significant decline from a previous level of social and occupational functioning.

Predementia syndrome: This term identifies all conditions with age-related deficits in cognitive function, including a mild stage of cognitive impairment based on a normality model and pathological conditions considered predictive of early stages of dementia

Mild cognitive impairment (MCI): This is a clinical label that includes non-demented aged persons with memory impairment and no significant disability.

Age-related cognitive decline (ARCD): This is defined as an objectively identified decline in cognitive functioning consequent to the aging process that is within normal limits given the person's age, but there are no defined diagnostic criteria, and few epidemiological studies using this definition have been conducted.

References

Ambring A, Friberg P, Axelsen M, Laffrenzen M, Taskinen MR, Basu S, Johansson M Clin Sci. 2004;106:519–25.

American Psychiatric Association Committee on Nomenclature and Statistics. Diagnostic and statistical manual of mental disorders. Washington, DC: American Psychiatric Association; 1994.

Barberger-Gateau P, Letenneur L, Deschamps V, Peres K, Dartigues JF, Renaud S. BMJ. 2002;325:932–3.

Barberger-Gateau P, Raffaitin C, Letenneur L, Berr C, Tzourio C, Dartigues JF, Alperovitch A. Neurology. 2007;69:1921–30.

Bourre JM, Dumont O, Piciotti M, Clement M, Chaudiere J, Bonneil M, Nalbone G, Lafont H, Pascal G, Durand G. In: Simopoulos AP, Kifer RR, Martin RE, Barlow SM, editors. Health effects of omega-3 polyunsaturated fatty acids in seafoods. Vol. 66. Karger/Basel/Switzerland: World Rev. Nutr. Diet.; 1991. p. 103–117.

Calon F, Lim GP, Yang F, Morihara T, Teter B., Ubeda O, Rostaing P, Triller A, Salem N, Ashe KH, Frautschy SA, Cole GM. Neuron. 2004;43:633–45.

Chen H, Zhang SM, Hernan MA, Willett WC, Ascherio A. Am J Epidem. 2003;157:1007–14.

Chiu CC, Su KP, Cheng TC, Liu HC, Chang CJ, Dewey ME, Stewart R, Huang SY. Prog Neuropsychopharmacol Biol Psychiatry. 2008;32:1538–44.

Cole GM, Lim GP, Yang F, Teter B, Begum A, Ma Q, Harris-White ME, Frautschy SA. Neurobiol Aging. 2005;26 (Suppl 1):133–6.

Dangour AD, Clemens F, Elbourne D, Fasey N, Fletcher AE, Hardy P, Holder GE, Huppert FA, Knight R, Letley L, Richards M, Truesdale A, Vickers M, Uauy R. Nutr J. 2006;5:20.

Dangour AD, Allen E, Elbourne D, Fletcher A, Richards M, Uauy R. J Nutr Health Aging 2009;13:198–202.

de Lorgeril M, Salen P, Martin JL, Monjaud I, Boucher P, Mamelle N. Arch Intern Med. 1998;158:1181–7.

Engelhart MJ, Geerlings MI, Ruitenberg A, Van Swieten JC, Hofman A, Witteman JC, Breteler MM. Neurology. 2002;59:1915–21.

Eskelinen MH, Ngandu T, Helkala EL, Tuomilehto J, Nissinen A, Soininen H, Kivipelto M. Int J Geriatr Psychiatry. 2008;23:741–7.

Florent S, Malaplate-Armand C, Youssef I, Kriem B, Koziel V, Escanye M-C, Fifre A, Sponne I, Leininger-Muller B, Olivier J-L, Pillot T, Oster T. J Neurochem. 2006;96:385–95.

Florent-Béchard S, Malaplate-Armand C, Koziel V, Kriem B, Olivier JL, Pillot T, Oster T. J Neurol Sci. 2007;262:27–36.

Freund-Levi Y, Eriksdotter-Jönhagen M, Cederholm T, Basun H, Faxén-Irving G, Garlind A, Vedin I, Vessby B, Wahlund LO, Palmblad J. Arch Neurol. 2006;63:1402–8.

Freund-Levi Y, Basun H, Cederholm T, Faxén-Irving G, Garlind A, Grut M, Vedin I, Palmblad J, Wahlund LO, Eriksdotter-Jönhagen M. Int J Geriatr Psychiatry. 2008;23:161–9.

Gauthier S, Reisberg B, Zaudig M. Lancet. 2006;367:1262–70.

Ghadirian P, Meera J, Ducic S, Shatenstein B, Morisset R, Jain M. Int J Epidem. 1998;27:845–52.

Grant WB. Alzheimers Dis Rev. 1997;2:42–55.

Grant WB. J Alzheimers Dis. 1999;1:197–201.

Hashimoto M, Hossain S, Shimada T, Sugioka K, Yamasaki H, Fujii Y, Ishibashi Y, Oka J, Shido O. J Neurochem. 2002;81:1084–91.

Hashimoto M, Tanabe Y, Fujii Y, Kikuta T, Shibata H, Shido O. J Nutr. 2005;135:549–55.

Hende B, Ducimitiere P, Berr C. Am J Clin Nutr. 2003;77:803–8.

Hooijmans CR, Rutters F, Dederen PJ, Gambarota G, Veltien A, van Groen, T, Broersen LM, Lütjohann D, Heerschap A, Tanila H, Kiliaan AJ. Neurobiol Dis. 2007;28:16–29.

Huang TL, Zandi PP, Tucker KL, Fitzpatrick AL, Kuller LH, Fried LP, Burke GL, Carlson MC. Neurology. 2005;65:1409–14.

Jones C, Arai T, Rapoport S. Neurochem Res. 1997;22:663–70.

Kalmijn S, Feskens EJ, Launer LJ, Kromhout D. Am J Epidemiol. 1997a;145:33–41.

Kalmijn S, Launer LJ, Ott A, Witteman JC, Hofman A, Breteler MM. Ann Neurol. 1997b;42:776–82.

Kalmijn S, van Boxtel MP, Ocke M, Verschuren WM, Kromhout D, Launer LJ. Neurology. 2004;62:275–80.

Kotani S, Sakaguchi E, Warashina S, Matsukawa N, Ishikura Y, Kiso Y, Sakakibara M, Yoshimoto T, Guo J, Yamashima T. Neurosci Res. 2006;56:159–64.

Laitinen MH, Ngandu T, Rovio S, Helkala E-L, Uusitalo U, Viitanen M, Nissinen A, Tuomilehto J, Soininen H, Kivipelto M. Dement Geriatr Cogn Disord. 2006;22:99–107.

Lauritzen L, Hansen HS, Jorgensen MH, Michaelsen KF. Prog Lipid Res. 2001;40:1–94.

Levy R. Int Psychogeriatrics. 1994;6:63–8.

Lim GP, Calon F, Morihara T, Yang F, Teter B, Ubeda O, Salem Jr N, Frautschy SA, Cole GM. J Neurosci. 2005;25:3032–40.

Lim WS, Gammack JK, Van Niekerk JK, Dangour A (2006) Cochrane Database Syst. Rev: CD005379.

Luchsinger JA, Tang MX, Shea S, Mayeux R. Arch Neurol. 2002;59:1256–63.

Lukiw WJ, Cui JG, Marcheselli VL, Bodker M, Botkjaer A, Gotlinger K, Serhan CN, Bazan NG. J Clin Invest. 2005;115:2774–83.

Manzato E, Roselli della Rovere G, Zambon S, Romanato G, Corti MC, Sartori L, Baggio G, Crepaldi G. Aging Clin Exp Res. 2003;15:83–6.

Moriguchi T, Greiner RS, Salem N. J Neurochem. 2000;75:2563–73.

Morris MC, Evans DA, Bienias JL, Tangney CC, Bennett DA, Aggarwal N, Schneider J, Wilson RS. Arch Neurol. 2003a;60:194–200.

Morris MC, Evans DA, Bienias JL, Tangney CC, Bennett DA, Wilson RS, Aggarwal N, Schneider J. Arch Neurol. 2003b;60:940–6.

Morris MC, Evans DA, Bienias JL, Tangney CC, Bennett DA, Wilson RS. Neurology. 2004;62:1573–9.

Morris MC, Evans DA, Tangney CC, Bienias JL, Schneider JA, Wilson RS, Scherr PA. Arch Neurol. 2005a;63:1085–8.

Morris MC, Evans DA, Tangney CC, Bienias JL, Wilson RS. Arch Neurol. 2005b;62:1849–53.

Nurk E, Drevon CA, Refsum H, Solvoll K, Vollset SE, Nygård O, Nygaard HA, Engedal K, Tell GS, Smith DA. Am J Clin Nutr. 2007;86:1470–8.

Oksman M, Iivonen H, Hogyes E, Amtul Z, Penke B, Leenders I, Broersen L, Lutjohann D, Hartmann T, Tanila H. Neurobiol Dis. 2006;23:563–72.

Ortega RM, Requejo AM, Andres P, Lopez-Sobaler AM, Quintas ME, Redondo MR, Navia B, Rivas T. Am J Clin Nutr. 1997;66:803–9.

Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, Kokmen E. Arch Neurol. 1999;56:303–8.

Petersen RC, Doody R, Kurz A, Mohs RC, Morris JC, Rabins PV, Ritchie K, Rossor M, Thal L, Winblad B. Arch Neurol. 2001;58:1985–92.

Petridou E, Koussouri M, Toupadaki N, Youroukos S, Papavassiliou A, Pantelakis S, Olsen J, Trichopoulos D. Br J Nutr. 1998;79:407–12.

Panza F, Solfrizzi V, Colacicco AM., D'Introno A, Capurso C, Torres F, Del Parigi A, Capurso S, Capurso A. Public Health Nutr. 2004;7:959–63.

Panza F, D'Introno A, Colacicco AM, Capurso C, Del Parigi A, Caselli RJ, Pilotto A, Argentieri G, Scapicchio PL, Scafato E, Capurso A, Solfrizzi V. Am J Geriatr Psychiatry. 2005;13:633–44.

Perez-Jimenez F, Alvarez de Cienfuegos G, Badimon L, Barja G, Battino M, Blanco A, Bonanome A, Colomer R, Corella-Piquer D, Covas I, Chamorro-Quiros J, Escrich E, Gaforio JJ, Garcia Luna PP, Hidalgo L, Kafatos A, Kris-Etherton PM, Lairon D, Lamuela-Raventos R, Lopez-Miranda J, Lopez-Segura F, Martinez-Gonzalez MA, Mata P, Mataix J, Ordovas J, Osada J, Pacheco-Reyes R, Perucho M, Pineda-Priego M, Quiles JL, Ramirez-Tortosa MC, Ruiz-Gutierrez V, Sanchez-Rovira P, Solfrizzi V, Soriguer-Escofet F, de la Torre-Fornell R, Trichopoulos A, Villalba-Montoro JM, Villar-Ortiz JR, Visioli F. Eur J Clin Invest. 2005;35:421–4.

Park IH, Hwang EM, Hong HS, Boo JH, Oh SS, Lee J, Jung MW, Bang OY, Kim SU, Mook-Jung I. Neurobiol Aging. 2003;24:637–43.

Pradignac A, Schlienger JL, Velten M, Mejean L. Aging Clin Exp Res. 1995;7:67–74.

Psaltopoulou T, Kyrozis A, Stathopoulos P, Trichopoulos D, Vassilopoulos D, Trichopoulou A. Public Health Nutr. 2008;11:1–9.

Qiu C, De Ronchi D, Fratiglioni L. Curr Opin Psychiatry. 2007;20:380–5.

Richardson AJ. Scand J Nutr/Naringsforskning. 2003;47:92–8.

Ross GW, Petrovitch H, White LR, Masaki KH, Li CY, Curb JD, Yano K, Rodriguez BL, Foley DJ, Blanchette PL, Havlik R. Neurology. 1999;53:337–43.

Schaefer EJ, Bongard V, Beiser AS, Lamon-Fava S, Robins SJ, Au R, Tucker KL, Kyle DJ, Wilson PW, Wolf PA. Arch Neurol. 2006;63:1545–50.

Serhan CN, Gotlinger K, Hong S, Lu Y, Siegelman J, Baer T, Yang R, Colgan SP, Petasis NA. J Immunol. 2006;176:1848–59.

Solfrizzi V, Panza F, Torres F, Mastroianni F, Del Parigi A, Venezia A, Capurso A. Neurology. 1999;52:1563–69.

Solfrizzi V, D'Introno A, Colacicco AM, Capurso C, Del Parigi A, Capurso S, Gadaleta A, Capurso A, Panza F. Exp Gerontol. 2005;40:257–70.

Solfrizzi V, Colacicco AM, D'Introno A, Capurso C, Torres F, Rizzo C, Capurso A, Panza F. Neurobiol Aging. 2006a; 27:1694–704.

Solfrizzi V, Colacicco AM, D'Introno A, Capurso C, Del Parigi A, Capurso SA, Argentieri G, Capurso A, Panza F. Exp Gerontol. 2006b;41:619–27.

Solfrizzi V, Capurso C, D'Introno A, Colacicco AM, Capurso A, Panza F. J Am Geriatr Soc. 2006c;54:1800–2.

Solfrizzi V, Capurso C, D'Introno A, Colacicco AM, Frisardi V, Santamato A, Ranieri M, Fiore P, Vendemiale G, Seripa D, Pilotto A, Capurso A, Panza F. J Nutr Health Aging. 2008;12:382–6.

Solfrizzi V, Frisardi V, Capurso C, D'Introno A, Colacicco AM, Chiloiro R, Dellegrazie F, Di Palo A, Capurso A, Panza F. J Am Geriatr Soc. 2009;57:1944–6.

Scarmeas N, Stern Y, Mayeux R, Manly JJ, Schupf N, Luchsinger JA. Arch Neurol. 2009;66:216–25.

Tapiero H, Nguyen Ba G, Couvreur P, Tew KD. Biomed Pharmacother. 2002;56:215–22.

Terano T, Fujishiro S, Ban T, Yamamoto K, Tanaka T, Noguchi Y, Tamura Y, Yazawa K, Hirayama T. Lipids. 1999;34(suppl):S345–6.

Trichopoulou A, Orfanos P, Norat T, Bueno-de-Mesquita B, Ocké MC, Peeters PH, van der Schouw YT, Boeing H, Hoffmann K, Boffetta P, Nagel G, Masala G, Krogh V, Panico S, Tumino R, Vineis P, Bamia C, Naska A, Benetou V, Ferrari P, Slimani N, Pera G, Martinez-Garcia C, Navarro C, Rodriguez-Barranco M, Dorronsoro M, Spencer EA, Key TJ, Bingham S, Khaw KT, Kesse E, Clavel-Chapelon F, Boutron-Ruault MC, Berglund G, Wirfalt E, Hallmans G, Johansson I, Tjonneland A, Olsen A, Overvad K, Hundborg HH, Riboli E, Trichopoulos D. BMJ. 2006;330:1329–30.

van Gelder BM, Tijhuis M, Kalmijn S, Kromhout D. Am J Clin Nutr. 2007;85:1142–7.

van de Rest O, Geleijnse JM, Kok FJ, van Staveren WA, Hoefnagels WH, Beekman AT, de Groot LC. Am J Clin Nutr. 2008;88:706–13.

van de Rest O, Geleijnse JM, Kok FJ, van Staveren WA, Dullemeijer C, Olderikkert MG, Beekman AT, de Groot CP. Neurology. 2008;71:430–8.

Vedin I, Cederholm T, Freund Levi Y, Basun H, Garlind A, Faxén Irving G, Jönhagen ME, Vessby, B, Wahlund LO, Palmblad J. Am J Clin Nutr. 2008;87:1616–22.

Vercambre MN, Boutron-Ruault MC, Ritchie K, Clavel-Chapelon F, Berr C. Br J Nutr. 2009;102:419–27.

Winblad B, Palmer K, Kivipelto M, Jelic V, Fratiglioni L, Wahlund LO, Nordberg A, Backman L, Albert M, Almkvist O, Arai H, Basun H, Blennow K, de Leon M, DeCarli C, Erkinjuntti T, Giacobini E, Graff C, Hardy J, Jack C, Jorm A, Ritchie K, van Duijn C, Visser P, Petersen RC. J Intern Med. 2004;256:240–46.

Wurtman RJ, Ulus IH, Cansev M, Watkins CJ, Wang L, Marzloff G. Brain Res. 2006;1088:83–92.

Yehuda S, Rabinovtz S, Carasso RL, Mostofsky DI. Int J Neurosci. 1996;87:141–9.

Yehuda S, Rabinovitz S, Mostofsky DI. J Neurosci Res. 1999;56:565–70.

Zhang SM, Willett WC, Hernan MA, Olek MJ, Ascherio A. Am J Epidem. 2000;152:1056–64.

Chapter 180
Nutritional Issues for Older People and Older People with Dementia in Institutional Environments

Angela B. Kydd

Abbreviations

BAPEN   British Association for Parenteral and Enteral Nutrition
ENHA   European Nutrition for Health Alliance

180.1 Introduction

Nutrition has always been a factor in the care of ill people and chapters on nutrition were commonplace, and still are, in nursing textbooks. In the field of gerontology, authors such as Potter and Perry (1993:1094) suggest that when treatments or therapies were lacking, care relied heavily on the *preparation and administration* of food to maintain the body's strength and fight disease. Later nursing texts, for example, Ebersole et al. (2008), devote a chapter to nutrition and again emphasize the importance of ensuring that patients take adequate fluids and diet. The authors stress the problems associated with poor nutrition and provide strategies to ensure that all patients have the opportunity to eat well by giving them assistance and by providing them with an atmosphere conducive to eating. It appears to be simple; people need adequate food and fluids to maintain and to restore health. However, on further exploration of factors affecting the nutritional needs of older people, providing an environment conductive to eating and making mealtimes special are an essential part of nutritional care.

    This chapter highlights the problems of poor nutrition for an ever increasing ageing population who are in institutions (hospital or care home). It goes on to examine why, when there are so many directives for, and standards on, good nutritional care, frail older people and people with dementia are failing to have their nutritional needs met. The conclusion centres on the fact that directives and standards are aimed at managers and qualified staff, yet the direct care of serving food and assisting with meals is carried out by care assistants who have no knowledge of best practices (Table 180.1).

A.B. Kydd (✉)
School of Health Nursing and Midwifery, University of the West of Scotland, Hamilton Campus, Almada Street, Hamilton, Lanarkshire, ML3 0JB, UK
e-mail: angela.kydd@uws.ac.uk

Table 180.1 Key facts of ageing

- Ageing is a complex, natural process potentially involving every molecule, cell and organ in the body.
- In its broadest sense, ageing merely refers to changes that occur during the lifespan and is marked by time.
- Chronological ageing is not a disease, but biological ageing involves internal and external factors that negatively impact on an individual's system
- As individuals grow older, they do lose functional reserve, which means that their bodies do lose the ability to compensate when threatened by disease or hardship
- The term Frailty is common, but there is no consensus on its definition, apart from that it is caused by many factors including anorexia and weight loss and is a state of vulnerability
- Poor nutrition is recognised as one of the physical factors leading to frailty

This table illustrates the difference between chronological age, marked by years, and biological age, marked by factors that negatively impact on an individual's bodily functions. It highlights the important of maintaining an older person's nutritional status as poor nutrition can compromise an individual's ability to combat disease

Table 180.2 Three calls to action from the European Nutrition for Health Alliance (2005)

Action	Recommendation
1	Malnutrition is 'alive and killing'. It must be recognised as a disease in its own right
2	The high prevalence of malnutrition can no longer be tolerated. It is a serious social and economic issue with significant repercussions for individuals and society as a whole
3	Every stakeholder needs to take ownership and action to address the problem. Malnutrition occurs across all settings. Targeted actions are needed to address the root causes of malnutrition and empower individuals to foster 'well nutrition' for themselves

The calls to action were drawn from discussions and recommendations from the ENHA 2005 conference. In identifying malnutrition as a disease, the onus is on stakeholders to see this as a condition that needs treating as much as any other disease or disorder

180.2 The Extent of the Problem of Poor Nutrition in Older People

There is high incidence of malnutrition in the older age groups. This is a cause for major concern and more worryingly, not a new concern. Addressing poor nutrition has been on the health and social care agenda for many years. The statistics make depressing reading.

In 2005, the European Nutrition for Health Alliance (ENHA) published an inaugural conference report which stated that 46% of all hospitalized patients in Europe are malnourished on admission to hospital. The figure rises to 50% for those over the age of 60. The report stated that as one third of all Europeans will be over 60 in 2050, malnutrition is a serious problem and a critical issue for Europe. The recommendations from the conference are presented in Table 180.2.

Statistics from Age Concern England (2006) show a higher incidence, with estimates that 60% of people over 60 are at risk of becoming malnourished.

Prevalence of malnutrition does increase with age (ENHA 2005) but malnutrition is not a normal part of ageing. For those who are not in ill health, a healthy diet can result in many years of active life into old age (Department of Health 2001). Indeed, many people over the age of 65 are healthy and living full lives, with only 7% being classed as "frail" (Fried et al. 2004).

180.3 The Increase in the Numbers of Frail Older People in the UK

The prevalence of frailty increases up to 40% in persons aged 85 and over, and given the dramatic increase of the oldest-old population (those 85 and over), frailty is becoming increasingly common (Table 180.3).

Table 180.3 The ageing population

Year	Population over 65 (%)	Those aged 65–74 (%)	Those aged 75–84 (%)	85 years or older (%)
2006	16.4	8.9	5.5	2
2021	19.2	10.4	6.3	2.5
2051	24.4	10.7	8.8	4.9

Figures from the Office of Health Economics (2009) to illustrate the projected percentage increase in the numbers of frail older people in the United Kingdom (UK)

The incidence of dementia also increases with age. Approximately 2% of persons aged over 65 have some form of dementia, but prevalence rises to 20% in those over 80. In terms of numbers, this means there are currently 670,000 people with dementia in the UK, and this figure is expected to rise to nearly 1,000,000 by 2021 (Barratt 2004). If the above projections are realized, this figure is set to double in 2050.

These statistics have serious implications when coupled with the statistics on the number of older people thought to be malnourished.

180.4 Malnutrition in Institutions

In the early 1990s attention was paid to the fact that older people in institutional care were not having their nutritional needs met. A wealth of publications resulted. In 1991, the Committee on Medical Aspects of Food Policy [COMA] found that nearly 50% of people in care had nutrient deficiencies. In 1992 COMA reported that further research needed to be carried out on the nutritional needs of frail older people. The King's Fund Centre report (Lennard-Jones 1992) suggested the benefit of treating poor nutritional states would only be realised when nutritional assessment on every patient was routine.

In 1995, the Caroline Walker Trust recommended that all older people entering residential care accommodation should have their nutritional needs assessed in the first week after admission, and should be monitored regularly thereafter. This recommendation was reiterated in 1996 by BAPEN. In 1997 the publication *Hungry in Hospital* by the Association of Community Health Councils in England and Wales (ACHEW) identified the need for nurses to assess nutritional status and ensure that frail older people received adequate nutrition. Yet a National study by Finch et al. (1998) reported that of 412 people over the age of 65 living in institutions, 16% of men and 15% of women were underweight.

Currently, there are many recommendations of how to address the problem of poor nutrition of older people in institutions. In 2003, BAPEN developed a valid and reliable nutritional screening tool to identify people who were underweight and those at risk of under-nutrition; the Malnutrition Universal Screening Tool (MUST). Standards to address the nutritional needs of older people in institutions were published by the Nutrition Advisory Group for Elderly People (NAGE) (2005), the Food Standards Agency (2006) and the Commission for Social Care Inspection (2006) in England and NHS Quality Improvement Scotland (2003) and the Care Commission in Scotland (2009).

Best practices and standards for good nutritional care, *all* include the need for qualified and unqualified staff to recognize both the physical and psychosocial aspects of mealtimes and the importance of food and fluids. These have been outlined in Table 180.4 and expanded below.

However, life in institutions frequently centre on the routine tasks to be performed, and rather than be seen as an enjoyable way to break up an otherwise long day, mealtimes are treated as a task to be accomplished at certain times.

Table 180.4 Intrinsic and extrinsic risk factors for malnutrition in care

Domain	Examples of intrinsic risk factors	Examples of extrinsic risk factors
Physical	Arthritic	Fasted prior to surgery
	In pain	Inability to use utensils
	Xerostomia (dry mouth)	Medicines given prior to mealtimes
	Oral thrush or mouth ulcers	Food not hot/cold enough
	Poorly fitting dentures	
	Sensory loss	
	Constipated	
	Nauseated	
	Side effects of medication	
	Difficulties with chewing/swallowing	
Psycho-social	Depression	Dislikes people sharing the table
	Confusion	Poor relationship with staff
	Delirium	Noisy environment
	Dementia	Untrained staff
	Feeling rushed/anxious, frightened/ withdrawn/stressed/agitated	Dislikes food
		Food not suitable for the individual
	Not able to recognize food	Meal served in unsuitable surroundings such as a clinical area with urinals/vomit bowls in sight
	Unable to move food from plate to mouth	
	Unable to accept current situation	
	Dining area not conducive to eating	No sense of occasion

Physical and psychosocial considerations as risk factors for malnutrition

180.5 Meals in Institutions

The recommendations and standards of good nutritional care stress the importance of the intrinsic and extrinsic factors associated with mealtimes and food, yet meals served in institutions are still reported to be an unpleasant experience. Sadly, early literature of life in institutions such as Goffman (1961) on *block treatment* and Miller and Gwynne (1971) on *warehousing* is found in more current literature such as institutional disrespect (Kitwood 1997) and lack of personalised care (Kydd 2006; Kerr et al. 2008).

180.5.1 The Social Environment

The social aspect of meals should not be underestimated, yet mealtimes in some institutions can be anti-social. Staff can appear like wardens, overseeing patients eating, and the environment can be noisy and alarming. Studies (e.g., Mathey et al. 2001; Desai et al. 2007) have shown that when institutionalised mealtimes were changed to more homely environments, the results showed improved food consumption and therefore improved nutritional status in older people. Providing a homely environment includes providing a set dining area, matching crockery, a nicely set table, with glasses for water and a water jug.

180.5.2 Institutional Food

Whilst the social environment of mealtimes is important, so are the food and fluids. Some foods served in institutions can be difficult to eat and fluids are not always offered or available. Some food might be unpalatable or culturally inappropriate for the individual (Kayser-Jones 2000), the

Table 180.5 Personalised strategies to promoting eating

Strategies to increase appetite	Reason
Provide balanced meals	To avoid constipation
Offer a favourite alcoholic drink before the meal (if medications permit)	To stimulate appetite
Do not give medications directly before a meal	The taste can put individuals off their food
Allow the person to eat when hungry	Food is more enjoyable
Encourage physical activity where possible	To work up an appetite
Find out what the individual's favourite foods are	To enhance enjoyment
Encourage the individual to eat one type of food before moving on to the next	To avoid confusion when tastes and textures change
To ascertain which meal should be the largest	To fit in with the individuals pattern of eating
Allow enough time to help individuals to the table or to sit alone if that is their preference	To avoid individuals feeling rushed
Ensure that individuals have their dentures and their mouth is clean	
Ensure that each individual has assistance at hand should they require it	To avoid people becoming frustrated with the effort of trying to manage their food
Provide seasonal food and temperature appropriate foods	Soups are more appetising in the winter and ice-cream in the summer

The above strategies are basic requisites to provide a person-centred approach to care

packaging may be difficult to open (Healthcare Commission 2007), or the portions too big (Vivanti et al. 2008). Antecedents to meals such as medications given just before meals can negatively affect food consumption (de Graaf 1994; Stratton et al. 2003) and strategies to enhance appetite, such as an aperitif before main meals are a rare occurrence. Examples of such strategies are given in Table 180.5.

180.5.3 Institutional Living

Routines within institutions can pose threats to promoting each individual's nutritional status. For example, staff shortages at mealtimes can mean that the individuals who need assistance may not get the help they require (Crogan and Scultz 2000). Timing of meals is also important. Food is usually prepared in one main kitchen and meals are given at set times. Unless such foods are prescribed, it is not easy for staff to provide fortified foods or snacks outside of the normal routine mealtimes. Individuals have different times of day to have their main meals and may not be able to eat a large meal at the times served in the institution. Many older people will have lived alone before being admitted into an institution and will have developed eating habits to suit themselves. Focussing on an individual's past routines and personalising care needs should be at the heart of good care and this has to include nutritional care, which must be person centred and have the explicit aim of helping individuals to maintain their own nutritional needs (European Nutrition for Health Alliance 2005). This can be a problem especially at night time when food is not usually available (Kerr et al. 2008).

Table 180.6 outlines some of the considerations necessary to ensure that individuals get the maximum benefit from meals within an institutional setting.

Table 180.6 Considerations at mealtimes

Area	Action	Examples of evidence
Personal care	Well fitting dentures, mouth care, choice of menu, choice of person to sit with (if appropriate)	Barratt (2004)
The social environment of mealtimes	The environment should be homely, the table set nicely and the environment should be calm and non confrontational	Mathey et al. (2001); Desai et al. (2007)
Communal eating	Consideration given to those people who wish to eat alone and those who prefer company	Barratt (2004)
Crockery and cutlery	Disabilities should be minimized. Cutlery and crockery designed to help people eat their food	Marshall (1996); Bartlett (2000)
The food	The food should be identifiable and culturally appropriate for the individual. It should be easy for the individual to eat. Small and nutrient rich	Kayser-Jones (2000); Healthcare Commission (2007); Vivanti et al. (2008)
Time of meal	Personal preferences for meals or snacks	Barratt (2004)
Time of and type of medications	Medications should not be given immediately before meals if possible. Knowledge of drugs/side effects that may affect appetite needs to be included in nutritional assessment and reviewed regularly	de Graaf et al. (1994); Stratton et al. (2003)
The Assistance required	Help should be available to give time to all patients who require assistance	Crogan and Scultz (2000)
Staff training	Staff need to be trained in how to ensure patients receive adequate nutrition	Castellanos et al. (2000); Chang and Lin (2005)

The areas of concern are not exhaustive but serve to illustrate the multifactorial nature of the antecedents to meals and mealtimes

180.5.4 Staff Attitudes

Institutionalised ageism, explained by Bender (2003: 121) as a way of treating everyone in the same manner, serves to devalue the individual. Bender (2003) states that any expressions of preference or individuality are seen as complaints and patients' requests are frequently ignored. People who are physically dependent are more vulnerable to being treated this way and yet these are the people in most need of help. A study by Sormunen et al. (2007) found that the greater the dependence of the resident in a care home, the greater the number of inappropriate treatments they received, and of the inappropriate treatments, a quarter of these occurred during mealtimes, with staff talking over patients and performing tasks for people that the individuals could still do for themselves if given time.

180.6 The Extent of the Problem of Poor Nutrition in People with Dementia

All of the issues of poor nutrition as described above are all relevant to people with dementia living in institutions, but this client group are at greater risk from dehydration and malnutrition (Castellanos et al. 2003). One of the symptoms of dementia is weight loss and is associated with the disease

process, poor quality of life and morbidity and mortality (Smith and Greenwood 2008). However, weight loss is also associated with age-related physical problems and psychosocial behaviours of people with dementia in care, and the behaviours and attitudes of staff.

180.7   The Need to Train Frontline Staff

In order to identify people who need extra calories, staff need to be trained and frontline staff who give direct help with meals are usually care assistants, who have little training in the nutritional care of frail older people and older people with dementia (Watson 1997). Training care staff has been shown to have positive effects on the nutritional status of older people with dementia, as staff need to be aware of the multiple factors involved in presenting, serving and assisting people to eat the food offered (Chang and Lin 2005). The challenges in providing adequate nutrition to people with dementia can lie in knowledge of how dementia affects a person's neuromuscular ability to take food to their mouths, chew and swallow (Ikeda et al. 2002), their perceptual difficulties of recognizing food and/or utensils (apraxia), or their ability to identify objects by name (aphasia). They may also lack the cognitive ability to initiate and/or maintain an effective way of eating (Chang and Roberts 2008). This can make following instructions impossible for them, and may lead to confrontations between staff and the individual at mealtimes. Such individuals can have difficulty communicating their likes, dislikes and their lack of comprehension verbally, which can cause them to feel frustrated and incapable, resulting in them communicating their dislikes with aggressive behaviours. In turn, staff who have no training in caring for people with dementia will not view the distress, but will view the individual as a 'problem'. This lack of understanding of what the person with dementia is experiencing can lead to negative attitudes and negative or diminished social interaction with the individual. This treatment depersonalises the individual, leading to what Kitwood (1998) termed 'malignant social psychology'.

Person-centred care, espoused by Kitwood (1997), centres on seeing the person and not the dementia. Promoting independence in eating is preferable and various strategies can be used to promote food intake. Marshall (1996), in writing on mealtimes in institution, speaks of disabling environments and suggests that people could be given greater assistance with eating independently if they had utensils and crockery that compensated for their disabilities.

Table 180.7 illustrates activities and actions to promote an individual's nutritional status.

180.8   Applications to Other Areas of Health and Disease

People who are ill have a compromised nutritional status. Poor nutrition can be the cause of health problems, ranging from relatively minor ailments such as constipation to more serious problems such as anaemia, osteoporosis, coronary heart disease and declining mental health (The Caroline Walker Trust 2004). Malnutrition can exacerbate illness (British Association for Parenteral and Enteral Nutrition [BAPEN] 2006) and prevent recovery from illnesses. The human cost of malnutrition is high, resulting in lengthy hospital stays, poor quality of life and malnutrition can have serious consequences for frail older people (Crogan and Pasvogal 2003). The public cost on disease-related malnutrition is also high; with a projected spend of over £7 billion per annum in 2007 in the UK (BAPEN 2009).

Table 180.7 Activities and actions to ensure adequate nutrition

Activity	Action
Valid nutritional assessment	Medical and nursing staff to ascertain any causes for poor appetite that can be treated, such as pain, illness, side effects from medications, depression
Educating staff, especially those involved in direct care	To provide staff training on food and nutrition for older people and older people with dementia
Providing easy to eat foods at regular times that individual patients like	The social aspects of mealtimes help people orientate to time of day and mix with other residents
Provide high calorie snacks at regular intervals between meals	Foods such as muffins, cakes scones, malt loaf, cheese and biscuits
Provide finger foods	Foods and for people who have compromised manual dexterity and that can be eaten independently. These foods are also suitable for people who find it difficult to sit still while eating.
Offer fortified foods or food supplements when adequate food cannot be taken	Food should always be offered first, food can be fortified and supplements given but not instead of meals.

Assessment is essential in order to follow through on the actions. Meals should be treated as an enjoyable experience. Food should be acceptable, fortified if necessary and supplements given to augment calorific intake

180.9 Conclusion

This chapter highlights that the importance of providing good nutritional care for older people has been well documented in the many recommendations and standards written by experts in Europe and the UK. However, if these standards are to be implemented, they have to be taught to those involved in the direct care of mealtimes. Frontline staff who deal with meals have to not only be aware of the importance of maintaining an individual's nutritional status, but they need to be taught that ensuring good nutrition is more than a physical requirement, it involves knowing that the psychosocial aspects of meals play a major part in helping older people and older people with dementia to maintain dignity, independence and a sense of enjoyment at mealtimes.

Summary Points

- Malnutrition in older people and older people with dementia is a critical issue.
- Recommendations and standards are not being carried out in many institutions.
- Training is essential for staff who provide meals to people in institutional care.
- Frontline staff are usually untrained people who have little knowledge of the strategies that can be used to ensure adequate nutrition.
- Mealtimes involve physical and psychosocial interventions.

Definitions of Key words

Malnutrition: The cellular imbalance between the supply of nutrients and energy and the body's demand for them to ensure growth, maintenance and specific functions. This can result in weight gain or weight loss

Nutrients: Foods that contain the elements necessary for bodily functions. The six categories of nutrients are water, carbohydrates, proteins, lipids, vitamins and minerals.

Undernutrition: When nutrient intake falls below that necessary to sustain health and well-being and results in weight loss.

Fortified drinks: Fluids that have extra nutrients in them.

Finger foods: Foods that can be eaten without the need for crockery or cutlery.

Nutritional screening tool: An assessment carried out to assess people at risk of undernutrition and/or malnutrition.

References

Age Concern. Hungry to be heard: The scandal of malnourished older people in hospital. England, London: Age Concern; 2006.

Association of Community Health Councils in England and Wales [ACHEW]. Hungry in hospital. London: ACHEW; 1997.

Barratt J. Rev Clin Geront. 2004;14:247–51.

Bartlett R. J Dem Care. Sept/Oct2006 ;33–36.

Bender M. Explorations in dementia. London: Jessica Kingsley Publications; 2003

British Association for Parenteral and Enteral Nutrition [BAPEN] (1996) BAPEN, Maidenhead

British Association for Parenteral and Enteral Nutrition [BAPEN]. The MUST Report: Nutritional Screening of Adults: A multi-disciplinary responsibility. Redditch: BAPEN; 2003

British Association for Parenteral and Enteral Nutrition [BAPEN]. Malnutrition among older people in the Community: Policy Recommendations for Change. A UK Policy Report by the European Nutrition for Health Alliance, BAPEN and the International Longevity Centre – UK. BAPEN, Redditch; 2006.

British Association for Parenteral and Enteral Nutrition [BAPEN]. Nutrition Screening Survey in the UK in 2008. Hospitals, care homes and mental health units. A Report by BAPEN, Redditch; 2009.

Care Commission. Eating well in care homes for older people. Dundee: Scottish Commission for the Regulation of Care; 2009

Castellanos V, Silver H, Gallagher-Allred C, Smith T. Nutrition issues in the home, community and long term care setting. Nut Clin Pract. 2003;18:21–36.

Chang C, Lin L. Effects of a feeding skills training programme on nursing assistants and dementia patients. J Clin Nurs. 2005;14:1185–92.

Chang C, Roberts B. Feeding difficulty in older adults with dementia. J Clin Nurs. 2008;17:2266–74.

Commission for Social Care Inspection. Highlight of the day? – improving meals for older people in care homes. 2006. Available at http://www.csi.org.uk/PDF/highlight_of_day.pdf

Committee on Medical Aspects of Food Policy [COMA]. Dietary Reference Values for Food Energy and Nutrients for the United Kingdom (Report on Health and Social Subjects No 41). The Stationery Office, London; 1991.

Committee on Medical Aspects of Food Policy [COMA]. The Nutrition of Elderly People. (Report on Health and Social Subjects No 43) The Stationery Office, London; 1992.

Crogan N, Pasvogal A. J Gerontol A Biol Sci Med Sci. 2003;58:159–64.

Crogan N, Schultz J. J Nurses Staff Dev. 2000;16:216–21.

de Graaf C, Polet P, van Staverton W. J Gerontol. 1994;49 (3):93–9.

Department of Health. National standards framework for older people, London: Department of Health; 2001.

Department of Health. Standards for better health. London: Department of Health; 2004.

Desai J, Winter A, Young K, Greenwood C. J Am Diet Assoc. 2007;107:808–14.

Ebersole P, Hess P, Touhy T, Jett K, Luggen A. Toward healthy aging: human needs and nursing response. 7th ed. Missouri: Mosby Elsevier; 2008. Chap. 9, pp. 194–265.

European Nutrition for Health Alliance. Malnutrition within an ageing population: a call for action. Report on the Inaugural Conference of the European Nutrition for Health Alliance, 14 Sept 2005. Available at http://www.european-nutrition.org/files/pdf_pdf_34.pdf

Finch S, Doyle W, Lowe C, Bates C, Prentice A, Smithers G. National diet and nutrition survey. People aged 65 years and over, 1994–1995. Volume 1: Report of the diet and nutritional survey. The Stationery Office, London; 1998.

Fried L, Furrucci L, Darer J, Williamson J, Anderson G. J Gerontol A Biol Sci Med Sci. 2004;59:255–63.

Food Standards Agency. Food served to older people in residential care. 2006. Available at http://www.food.gov.uk/healthiereating/nutritioncommunity/care

Goffman E. Asylums: essays in the social situation of mental patients and other inmates. New York: Hawthorne; 1961.

Healthcare Commission. Caring for dignity: a national report for dignity in care of older people while in hospital. London: Commission for Healthcare Audit and Inspection; 2007.

Ikeda M, Brown J, Holland A, Fukuhara R, Hodges J. J Neurosurg Psych. 2002;73:371–6.

Kayser-Jones J. Nursing homes: long term care management. 2000;49:56–59, 113–114.

Kerr D, Wilkinson H, Cunningham C. Supporting older people in care homes at night. Edinburgh: Joseph Rowntree Foundation; 2008.

Kitwood T. Dementia reconsidered: the person comes first. Philadelphia: Open University Press; 1997.

Kitwood T. J Clin Ethic. 1998;9:23–34.

Kydd A. Life in limbo: delayed discharge from a policy and patient perspective. PhD thesis, Aberdeen: University of Aberdeen; 2006.

Lennard-Jones J. A positive approach to nutrition as treatment. London: Kings Fund Centre; 1992.

Marshall M. 'I Can't Place This Place at All': working with people with dementia and their carers. Birmingham: Venture; 1996.

Mathey M, Vanneste V, de Graaf c, de Groot L, van Stavaren W. Prev Med. 2001;32:416–23.

NHS Quality Improvement Scotland. Food, fluid and nutritional care in hospitals. Edinburgh: NHS QIS; 2003.

Office of Health Economics. OHE compendium. 20th ed. 2009. Available from http://www.ohe.org/page/knowledge/schools/appendix/aging_population.cfm

Potter P, Perry A. Fundamentals of nursing. 3rd ed. London: Mosby-Year Book; 1993.

Smith K, Greenwood C. Nestle Nutr Works Se. 2008;27:381–403.

Sormunen S, Topo P, Elonieme-Sulkava U. Aging Ment Health. 2007;11:246–55.

Stratton R, Green C, Elia M. Disease-related malnutrition: an evidenced based approach to treatment. Oxford: CABI publishing; 2003.

The Caroline Walker Trust. Eating well for older people. London: The Caroline Walker Trust; 1995.

The Caroline Walker Trust. Eating well for older people. 2nd edn. London: The Caroline Walker Trust; 2004.

Vivanti A, Banks M, Aliakbari J, Suter M, Hannah-Jones M, McBride E. Nutr Diet. 2008;65:36–40.

Watson R. Undernutrition, weight loss and feeding difficulty in elderly patients with dementia: a nursing perspective. Rev Clin Geront. 1997;7:317–26.

Watson R, Manthorpe J, Stimpson A. Learning from carer's experiences: helping older people with dementia to eat and drink. Nursing Older People. 2003;14:23–27.

Part XXXII
Alcohol

Chapter 181
Diffusion Tensor Imaging of the Brain in Fetal Alcohol Spectrum Disorder

Catherine Lebel, Carmen Rasmussen, and Christian Beaulieu

Abbreviations

ALIC	Anterior limb of the internal capsule
CC	Corpus callosum
CSF	Cerebro-spinal fluid
CST	Corticospinal tract
DTI	Diffusion tensor imaging
FA	Fractional anisotropy
FAS	Fetal alcohol syndrome
FASD	Fetal alcohol spectrum disorder
IFO	Inferior fronto-occipital fasciculus
ILF	Inferior longitudinal fasciculus
MD	Mean diffusivity
MRI	Magnetic resonance imaging
NBD: AE	Neurobehavioral disorder: alcohol exposed
pFAS	Partial Fetal Alcohol Syndrome
PLIC	Posterior limb of the internal capsule
ROI	Region of interest
SE: AE	Static encephalopathy: alcohol exposed
SFO	Superior fronto-occipital fasciculus
SLF	Superior longitudinal fasciculus
TBSS	Tract-based spatial statistics
UF	Uncinate fasciculus
VBM	Voxel-based morphometry
WISC	Weschler intelligence scale for children
WRAT	Wide range test of achievement

C. Beaulieu (✉)

Department of Biomedical Engineering, 1098 Research Transition Facility, University of Alberta, Edmonton, Alberta T6G 2V2, Canada

e-mail: christian.beaulieu@ualberta.ca

181.1 Introduction

Fetal alcohol syndrome (FAS) is a condition referring to a specific set of growth, cognitive, behavioral and facial abnormalities associated with prenatal alcohol exposure. It was first described in the late 1960s and early 1970s (Jones and Smith 1973; Lemoine et al. 1968), and is now estimated to affect anywhere between 0.3 and 2 individuals per 1,000 live births (Abel and Sokol 1986; May and Gossage 2001; Sampson et al. 1997). Individuals with FAS demonstrate characteristic facial abnormalities such as a smooth philtrum, short palpebral fissures, and a thin upper lip (Astley 2004; Sampson et al. 1997). Common brain malformations revealed by postmortem studies include microcephaly, ventriculomegaly, a small cerebellum, and malformations or agenesis of the corpus callosum (Clarren et al. 1978; Jones and Smith 1973; Peiffer et al. 1979). Children and adults with FAS may also demonstrate a wide variety of cognitive and behavioral problems including motor delays, and deficits of executive functioning, attention, memory, reading, and mathematics (Jacobson and Jacobson 2002; Mukherjee et al. 2006).

However, not all individuals with prenatal alcohol exposure demonstrate the same extent of symptoms, and it is now known that there is a wide range of outcomes associated with prenatal alcohol exposure. Although poorly understood, the extent and timing of prenatal alcohol consumption likely plays a major role in creating this spectrum; there are also differences in genetic susceptibility (Streissguth and Dehaene 1993). Fetal alcohol spectrum disorder (FASD) is the umbrella term used to describe the various developmental disorders associated with prenatal alcohol exposure. The prevalence of FASD is higher than FAS since it includes additional disorders, and is estimated at up to 1% of live births in North America (May and Gossage 2001; Sampson et al. 1997). FASD is the leading known cause of mental retardation (Abel and Sokol 1986).

There are a variety of methods for diagnosing the various disorders falling under the FASD umbrella; however, the 4-digit diagnostic code is an increasingly popular technique due to its consistency and reproducibility (Astley 2004). The 4-digit diagnostic code ranks diagnostic information in the areas of growth deficiency, facial phenotype, brain dysfunction, and alcohol use. The magnitude of expression of each feature is ranked independently on a 4-point Likert scale: 1 reflects complete absence of the typical FAS feature, 4 reflects a strong "classic" presence of the FAS feature. To meet the criteria for FASD, individuals must have a brain dysfunction score of 2 or higher and confirmed alcohol exposure, as indicated by alcohol use scores of 3 (some risk) or 4 (high risk). Diagnoses falling under the FASD umbrella can be grouped into four broad categories, which are (in order of most severe to least severe): FAS, partial FAS (pFAS), static encephalopathy: alcohol-exposed (SE:AE), and neurobehavioral disorder: alcohol-exposed (NBD:AE). Individuals diagnosed with FAS, the most severe end of the FASD spectrum, display serious structural and functional brain abnormalities (brain code of 3 or 4), growth deficiencies (rank 2–4), and the full FAS phenotype of thin upper lip, smooth philtrum, and short palpebral fissures. SE:AE is the diagnosis given to subjects who have significant structural and/or functional brain abnormalities at a level of 3 or 4, but are lacking the growth deficiencies and facial features of FAS. When individuals have static encephalopathy and most, but not all, of the growth deficiencies and facial features of FAS, they are given the diagnosis of partial FAS (pFAS). Subjects with NDB:AE still have brain abnormalities, but they are ranked 2 and are less severe than for those with static encephalopathy. The accurate diagnosis and characterization of FASD subjects is challenging, yet is a key part of imaging studies to ensure appropriate analysis and interpretation of quantitative brain parameters.

181.2 Brain Abnormalities in FASD

Early studies of children with prenatal alcohol exposure used autopsies to identify several structural brain abnormalities caused by neuronal and glial migration errors (Clarren et al. 1978; Jones and Smith 1973; Peiffer et al. 1979). These malformations include microcephaly, a small cerebellum, agenesis of the corpus callosum, and ventriculomegaly. However, autopsy studies are limited by the number of available subjects and represent a skewed sample, since only the most severely alcohol-affected subjects die during infancy or early childhood. Brain imaging techniques such as magnetic resonance imaging (MRI) make it possible to noninvasively assess the teratogenic effects of alcohol in vivo, thus allowing for much larger sample sizes with a wide range of severities. Also, since MRI does not use ionizing radiation, it is a safe modality to investigate children.

MRI and other neuroimaging studies have shown many different structural abnormalities in individuals with FASD (Riley and McGee 2005). Conventional MRI can provide excellent contrast among the major brain tissues (white matter, cortical gray matter and deep gray matter) and allows for measurements of volume, thickness, and density. Individuals with FASD demonstrate total brain volume reductions, as well as reductions of all major tissue components (Archibald et al. 2001; Astley et al. 2009). Children with FASD have thicker cortical gray matter than healthy children, particularly in the parietal and temporal lobes (Sowell et al. 2008b). Deep gray matter structures have been shown to be particularly affected in FASD, demonstrating especially reduced volumes (Archibald et al. 2001; Astley et al. 2009) and abnormal metabolic rates (Cortese et al. 2006; Fagerlund et al. 2006). Abnormalities in the corpus callosum, the largest brain white matter tract, are common across imaging studies, with a variety of malformations reported (Bookstein et al. 2001; Peiffer et al. 1979). Diffusion tensor imaging provides an excellent way of further studying the white matter, as it provides measures of microstructure not available via conventional imaging methods, and diffusion tensor imaging studies have revealed widespread brain abnormalities in individuals with FASD, highlighting many of the same regions identified by previous MRI studies and suggesting even more widespread damage.

181.3 Diffusion Tensor Imaging

Diffusion tensor MRI (DTI) is an advanced imaging technique that uses the mobility of water molecules to infer the state of the underlying tissue microstructure (Basser et al. 1994; Le Bihan 2003); its key features are summarized in Table 181.1. While the concept was first described 15 years ago, its applications have greatly expanded to study a myriad of brain disorders over the last 5 years (Assaf and Pasternak 2008; White et al. 2008). DTI is sensitive to the Brownian motion of water molecules (i.e., so-called diffusion). When the diffusion of water molecules is unhindered, or encounters randomly oriented barriers, motion occurs equally in all directions and is termed isotropic diffusion (see Fig. 181.1a). However, oriented barriers asymmetrically hinder diffusion, imposing a directionality on water motion; this is termed anisotropic diffusion (see Fig, 181.1b). The axonal membranes and myelin sheaths contained in the highly ordered fiber bundles of brain white matter form barriers to diffusion perpendicular to axons, while allowing water diffusion to occur unhindered parallel to the axons (Beaulieu 2002). A direct relationship between a specific tissue compartment (e.g., myelin) and a measured diffusion parameter, while desirable, is fraught with difficulty given the complexity of neural fibers (the reader is referred to the review article by Beaulieu (2002), for a more in-depth discussion).

Table 181.1 Key features of diffusion tensor imaging (DTI)

1. Diffusion tensor imaging (DTI) is a noninvasive, quantitative magnetic resonance imaging technique sensitive to the Brownian motion (i.e., diffusion) of water molecules.
2. Diffusion occurs differently in an unrestricted medium (e.g., cerebrospinal fluid), tissue with randomly oriented barriers to diffusion (e.g., gray matter), and tissue with highly oriented barriers to diffusion (e.g., white matter). DTI can measure the diffusion in different brain areas and provide information about tissue microstructure.
3. DTI is typically conduced on MRI scanners with magnetic field strengths of 1.5 or 3 T.
4. Typical DTI sequences range from 5 to 10 min in length and measure diffusion along 6–30 different directions.
5. Raw DTI images are processed to provide important quantitative measures of tissue microstructure, including fractional anisotropy (FA) and mean diffusivity (MD).
6. DTI can be used to investigate healthy development, as well as abnormalities in many different diseases and conditions.

This table lists the key features of diffusion tensor imaging (DTI), including how images are acquired and why they are useful
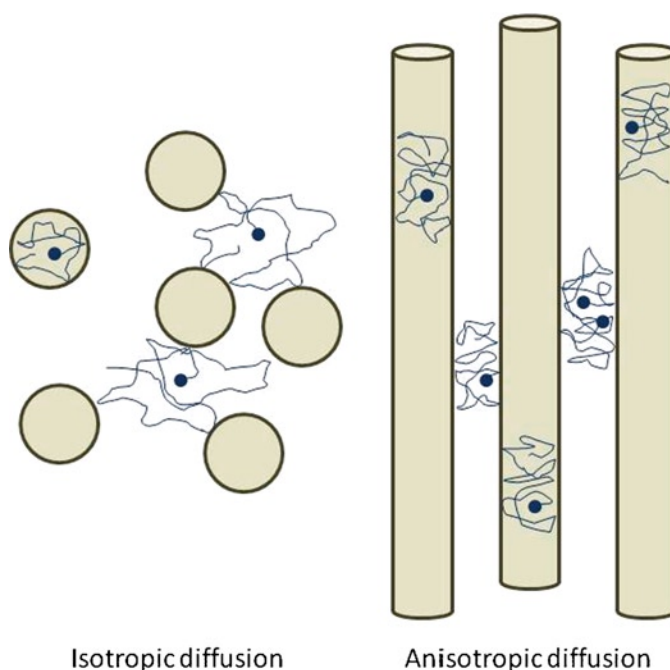
Fig. 181.1 Isotropic and anisotropic diffusion. Isotropic diffusion occurs in a fluid either without barriers (e.g., in a cup of coffee or cerebrospinal fluid), or one with randomly oriented barriers to diffusion, (e.g., gray matter). Anisotropic diffusion occurs when there are oriented barriers to diffusion, such as brain white matter, in which the axonal membranes and myelin sheaths hinder diffusion perpendicular to axons

In cerebrospinal fluid (CSF), there are no barriers and diffusion is rapid and isotropic. Brain gray matter, which contains dendrites, neuronal cell bodies, and glial cells, presents barriers to diffusion that are mostly randomly oriented. However, deep gray matter structures such as the thalamus and putamen exhibit some degree of anisotropy. Figure 181.1 shows examples of isotropic diffusion (e.g., in CSF or gray matter) and anisotropic diffusion (in white matter).

DTI allows for the characterization of diffusion in all directions in each voxel within the brain. DTI measures diffusion in at least six noncollinear directions using diffusion-sensitizing gradients to create a tensor model that fully characterizes diffusion within a voxel. From this tensor, three eigenvalues may be calculated, representing the magnitude of diffusion in the primary diffusion

direction (assumed to be oriented along the white matter tract) called parallel or axial diffusivity, and the magnitude of diffusion in two directions orthogonal to that called perpendicular or radial diffusivity. While it is possible to calculate the primary diffusion direction regardless of its orientation relative to the diffusion-sensitizing gradients, one of the major weaknesses of the tensor model occurs in areas where two or more white matter fiber bundles oriented in different directions overlap.

The two most commonly used DTI parameters are fractional anisotropy (FA) and mean diffusivity (MD). The overall magnitude of diffusion is measured by MD, which is simply the average of the three eigenvalues. The directionality, or anisotropy, of diffusion is most often assessed using FA (Basser 1995). FA varies from 0 to 1, with 0 representing completely isotropic diffusion and 1 representing highly anisotropic diffusion. FA is generally thought of as a measure of white matter integrity, with lower FA values indicative of reduced myelination, less densely packed axons, or some combination of the two. One method of visualizing isotropic and anisotropic diffusion is an ellipsoid. The three eigenvalues of the diffusion tensor (representing diffusivity in the primary direction and two orthogonal directions) form the three axes of the ellipsoid and the overall size of the ellipsoid gives an indication of MD. Isotropic diffusion is represented as a sphere, while more anisotropic diffusion is represented as a more elongated ellipsoid. Figure 181.2 shows an FA map and an MD map, and gives the diffusion ellipsoids and FA and MD values for several different brain regions. In general, anisotropy is high within brain white matter due to its highly ordered nature (white matter appears bright in Fig. 181.2a), while CSF exhibits virtually no anisotropy (appears dark in Fig. 181.2a). The deep gray matter structures exhibit some anisotropy, albeit to a much lesser degree than brain white matter. MD is generally quite uniform across the non-infant brain parenchyma (Fig. 181.2b), but is much higher in the CSF.
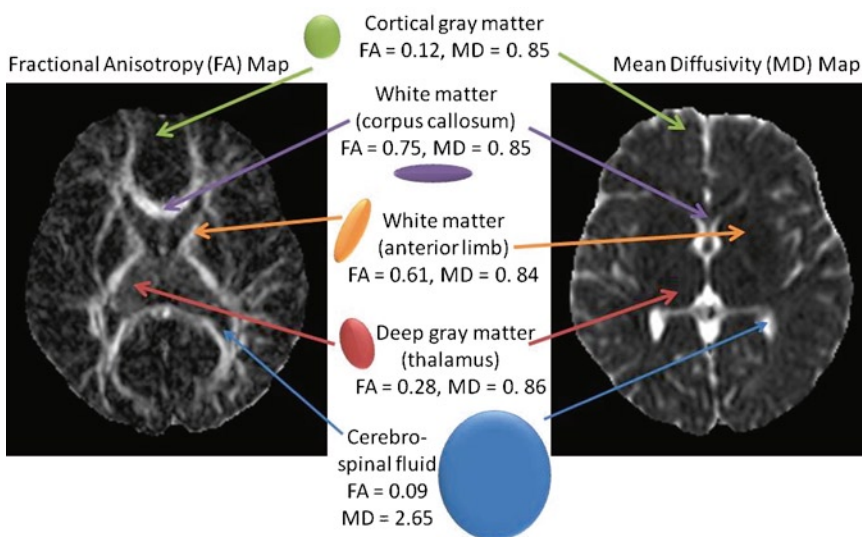
Fig. 181.2 Fractional anisotropy and mean diffusivity maps. Fractional anisotropy (*FA*, *left*) and mean diffusivity (*MD*, units of 10^{-3} mm^2/s, *right*) maps are shown for two axial slices in a 9-year-old boy with Fetal alcohol spectrum disorder (*FASD*). On the FA map, structures with high FA (white matter) appear bright, indicating greater directionality of water diffusion, while those with low FA (gray matter and cerebrospinal fluid) appear dark. On the MD map, regions with more rapid diffusion (i.e., molecules displace further in the same amount of time) are bright. Diffusion ellipsoids demonstrating the probability of diffusion in each direction are shown for voxels in five different areas reflecting a range of FA values as well as a much higher MD for cerebrospinal fluid than the brain tissue whose MD is rather uniform between gray and white matter (unlike FA)

Fig. 181.3 Diffusion
tractography. Five examples
of white matter pathways that
can be virtually reconstructed
and visualized using diffusion
tractography are shown: the
superior and inferior
longitudinal fasciculus, the
superior and inferior
fronto-occipital fasciculi and
the uncinate fasciculus
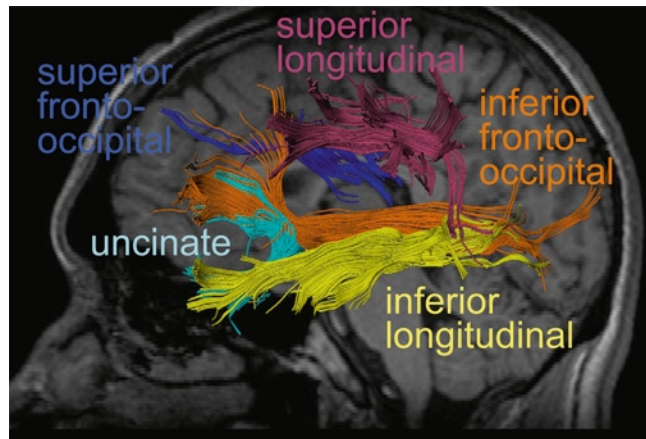
There are three primary techniques for analyzing DTI data: region-of-interest (ROI) analysis, tractography, and voxel-based morphometry (VBM). With ROI analysis, the investigator manually defines areas on two-dimensional images to extract diffusion parameters for specific structures. ROI analysis is generally quite straightforward to conduct, and can be performed on any structure that is readily visible on two-dimensional images. Tractography is a method of virtually reconstructing and visualizing white matter fiber tracts, essentially creating three-dimensional volumes of interest (Basser et al. 2000; Conturo et al. 1999; Jones et al. 1999; Mori et al. 1999). With tractography, the user defines seeding and target regions to start and constrain the fiber tracts, and then an algorithm uses the primary direction of diffusion within each voxel and the FA values to trace out white matter fibers in the brain. Once the fiber bundles have been delineated, FA and MD can be measured along the entire tract, or any smaller portion of it. Figure 181.3 shows an example of some of the white matter pathways that can be reconstructed using tractography.

The third commonly used analysis method for DTI data is VBM, which examines the entire brain without relying on user-defined regions for ROI analysis or tractography (Ashburner and Friston 2000). VBM normalizes each subject's brain to a template and looks at each voxel individually across the group. VBM allows for both group comparisons and correlations with other variables. Tract-based spatial statistics (TBSS) is a form of VBM specifically designed for analysis of DTI data, which examines only the central portion of white matter fibers (Smith et al. 2006). The sensitivity of DTI to microstructural changes within brain tissue makes it an excellent method for studying brain differences in FASD. The following section discusses the published studies that have used DTI to investigate brain abnormalities within FASD.

181.4 DTI Studies of FASD

Although DTI cannot yet be used as a diagnostic tool, it can nonetheless provide valuable information about brain abnormalities in FASD. There are seven previously published DTI studies of FASD or prenatal alcohol exposure (Fryer et al. 2009; Lebel et al. 2008a; Li et al. 2009; Ma et al. 2005; Sowell et al. 2008a; Wozniak et al. 2006, 2009), using a variety of methods and including subjects with a range of ages and disorders related to prenatal alcohol consumption. Table 181.2 summarizes the key details for each of the seven studies. Six studies compared one group of children or young

Table 181.2 DTI studies of prenatal alcohol exposure

Study	Number of subjects	Age range	DTI protocol	Analysis method	Findings
Fryer et al. (2009)	15 alcohol-exposed (9 FAS, 6 unspecified alcohol-exposed) 12 control	8–18 year	3 T GE 7 min 15 directions $b = 2,000$ s/mm²	TBSS of white matter ROI of CC	↓FA in ant, post, sup CR, forceps major, R SLF; R UF; R SFO; ↓FA in body CC ↑FA in R PLIC, R cing ↑MD in L ALIC, L sup frontal lobe ↓MD in R ant CR, R forceps major Alcohol-exposed compared to controls
Lebel et al. (2008a)	24 FASD (2 FAS, 3 SE:AE, 8 NBD:AE, 11 unspecified FASD) 95 control	5–13 year	1.5 T Siemens 6 min 6 directions $b = 1,000$ s/mm²	Tractography of 10 white matter tracts ROIs of 4 deep gray matter structures	↓FA in splenium CC, ILF, SLF, R cing, globus pallidus, L thalamus ↑MD in IFO, R CST, R ILF, globus pallidus, R putamen, R thalamus ↓MD in genu CC FASD compared to control
Li et al. (2009)	57 alcohol-exposed (29 nondysmorphic, 28 dysmorphic) 25 control	19–27 year	3 T Siemens 10 min 12 directions $b = 1,000$ s/mm²	TBSS of white matter ROI of CC	↓FA in isthmus, splenium CC ↑MD in isthmus CC
Ma et al. (2005)	9 FAS 7 control	18–25 year	3 T Siemens 7 min 12 directions $b = 1,000$ s/mm²	ROI of CC	Dysmorphics compared to controls ↓FA in genu, splenium CC ↑MD in genu, splenium CC FAS compared to controls
Sowell et al. (2008a)	17 FASD (4 FAS, 5 pFAS, 7 NBD:AE, 1 unspecified FASD) 19 control	7–15 year	1.5 Siemens[a] 6 directions $b = 1,000$ s/mm²	VBM of white matter	↓FA in splenium CC, R temporal lobe FASD compared to control

(continued)

Table 181.2 (continued)

Study	Number of subjects	Age range	DTI protocol	Analysis method	Findings
Wozniak et al. (2006)	14 FASD (5 pFAS, 5 SE:AE, 4 NBD:AE) 13 control	10–13 year	3 T Siemens 5 min 12 directions $b = 1,000$ s/mm^2	ROI of CC	↑MD in isthmus CC FASD compared to controls
Wozniak et al. (2009)	33 FASD (8 FAS, 23 pFAS, 2 SE:AE) 19 control	10–17 year	3 T Siemens 6 min 30 directions $b = 1,000$ s/mm^2	Tractography of CC	↓FA in posterior midbody, isthmus, splenium CC FASD compared to controls

[a]No scan time provided

The seven previous studies examining the effects of prenatal alcohol exposure on brain structure using DTI are outlined below

adults prenatally exposed to alcohol ($n = 9$–33) to healthy controls ($n = 7$–95) whereas one study subdivided participants into three groups: alcohol-exposed with dysmorphia, alcohol-exposed without dysmorphia, and controls ($n = 28, 29, 25$, respectively). In total, the previous studies cover an age range of 5–27 years. It is not surprising that there are no studies examining older individuals with FASD, since FASD disorders are relatively new and the diagnosis of adults is more difficult and less common than in children. One advantage of studying children is that it provides a glimpse of brain abnormalities that are more likely to be caused by prenatal alcohol exposure rather than by a lifetime of adaptation to particular difficulties.

One of the most important things to consider in a study of FASD is the severity of the subjects included. Structural brain abnormalities have been shown to vary with the severity of diagnosis, with subjects classified as FAS or pFAS having more severe abnormalities than those with SE:AE, who have more abnormalities than those with NBD:AE (Astley et al. 2009). Most studies included a mix of subjects, although one study (Ma et al. 2005) included only subjects with FAS, the most severe disorder on the FASD spectrum, and another (Wozniak et al. 2006) included only subjects with less severe FASD (no subjects in their study had FAS). The study by Li et al. (2009) subdivides the 57 subjects with prenatal alcohol exposure into those with dysmorphia (the facial features associated with FAS) and those without. The subjects in the Li et al. (2009) study were never formally assessed for diagnosis of FASD; however, those in the dysmorphic group had characteristic FAS facial abnormalities, as well as confirmed prenatal alcohol exposure, suggesting that they are likely to fall under either the FAS or pFAS diagnostic categories, depending on the severity of the growth, brain, and facial abnormalities. Although the non-dysmorphic subjects had confirmed alcohol exposure, they were not assessed for the other features of FASD (growth deficiency and central nervous system abnormalities), so they may have symptoms meeting the criteria for diagnoses of SE:AE or NBD:AE, or may not. The study by Fryer et al. (2009) included nine subjects (60%) with FAS, and mentions that all subjects had substantial prenatal alcohol exposure, but does not confirm an FASD diagnosis for the remaining six subjects. The remaining studies used only subjects with a confirmed diagnosis of FASD, but with varying levels of severity; the percentage of subjects with full-blown FAS ranged from 8–60%. Thus, there is a wide range of symptom severity among studies, which should be taken into account when comparing the findings. In addition, confounds such as other drug use during pregnancy and abuse or neglect may be of particular concern in an FASD population. Unfortunately, information about these potential confounds, as well as exact timing and amount of alcohol use during pregnancy, is often unavailable.

Although it is not possible to assess image quality when studies do not show raw diffusion images or the processed FA maps from which they are measuring diffusion parameters, the imaging protocols used by all the DTI FASD studies appear adequate. In general, the protocols were fairly similar, with the number of diffusion encoding directions ranging from 6–30 (with 6 of 7 studies using 15 or fewer), the DTI protocols were 5–10 min in length, and all but one used a b-value of 1,000 s/mm^2. The magnetic field strength was 1.5 T for two of the studies; 3 T MRI scanners were used for the other five studies. The image analysis methods varied, with several studies using a combination of methods. Five studies used ROI analysis on select regions, three used VBM (two of those using TBSS specifically) of all the white matter, and two used tractography of a priori defined white matter tracts.

Three of the DTI studies of FASD (Ma et al. 2005; Wozniak et al. 2006, 2009) examined only the corpus callosum, likely because it is a large, important, and straightforward-to-measure structure that is known from autopsy and conventional imaging studies to be affected in FASD. Three of the studies examined all brain white matter using VBM (Fryer et al. 2009; Li et al. 2009; Sowell et al. 2008a), and one (Lebel et al. 2008a) used tractography to study 10 major white matter tracts and ROI analysis to examine 4 deep gray matter regions. All studies measured FA changes, and all but one (Sowell et al. 2008a) also assessed MD values.

Although there have been relatively few studies of FASD using DTI, there are some convergent results. The findings common to several studies likely point to the most consistently affected structures across individuals with FASD regardless of age, diagnosis severity, etc. Figure 181.4 shows the regions observed to have significantly different FA values between subjects with prenatal alcohol exposure and healthy controls. The corpus callosum, particularly the posterior portion, is consistently reported to be highly affected by FASD. The posterior corpus callosum (the splenium and isthmus were defined differently among the studies, so they have been lumped together for the purpose of this review) had significantly lower FA values in FASD subjects in five of seven studies.
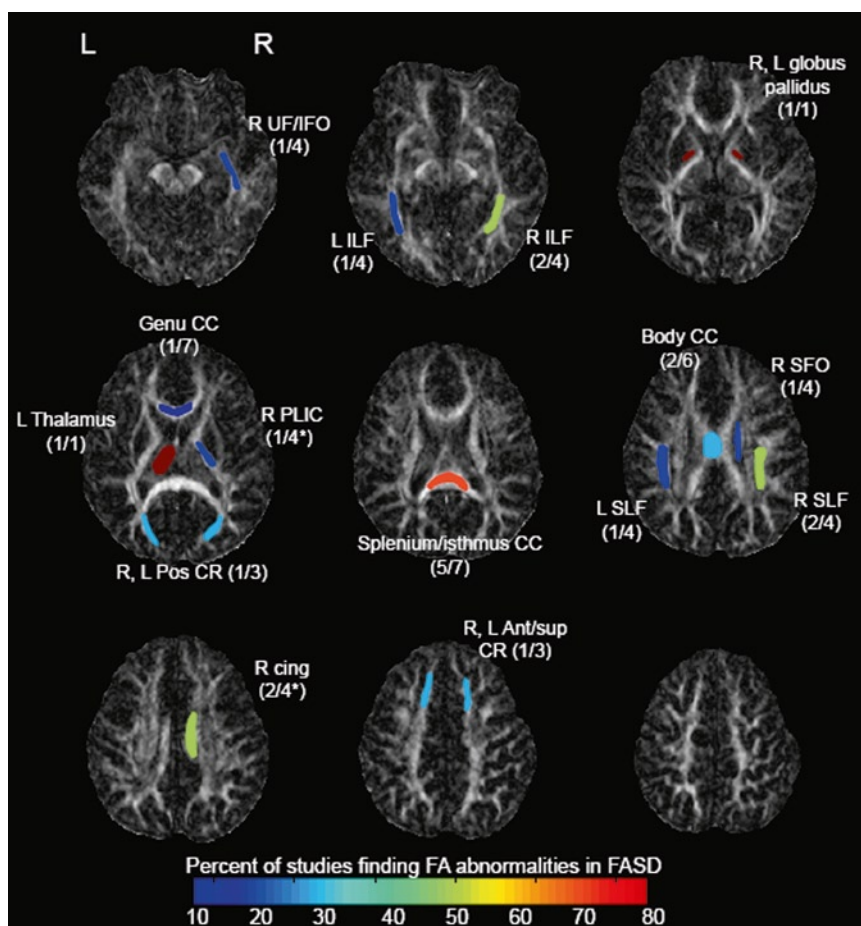
Fig. 181.4 Structures demonstrating fractional anisotropy abnormalities in Fetal alcohol spectrum disorder (*FASD*). Structures that have shown significant fractional anisotropy (*FA*) differences between subjects with prenatal alcohol exposure and healthy controls are shown overlaid on an FA map of a 9-year-old boy with FASD. Structures are colored according to the percentage of studies that has shown differences in that particular area. Structures are also listed with the number of studies showing differences and the total number of studies examining that particular area. For all regions, the alcohol-exposed group showed lower FA than controls, except for regions marked with an asterisk (*, the right PLIC and R cingulum), for which one of the studies showed increased FA in the alcohol-exposed group. *ALIC/PLIC* anterior/posterior limb of the internal capsule, *ant* anterior, *CC* corpus callosum, *cing* cingulum, *CR* corona radiata, *IFO/SFO* inferior/superior fronto-occipital fasciculus, *ILF/SLF* inferior/superior longitudinal fasciculus, *sup* superior, *UF* uncinate fasciculus, *WM* white matter

Other consistent FA abnormalities include three temporal connections: the right inferior and superior longitudinal fasciculi, and the right cingulum, which were each significantly different in two studies (out of the four that examined these areas). Several studies have demonstrated an anterior-to-posterior trend of maturation in the corpus callosum during healthy childhood development, with the splenium maturing later than the genu (Giedd et al. 1999b; Thompson et al. 2000). Also, the white matter in the temporal lobe is known to be late-developing, in terms of both white matter volume (Giedd et al. 1999a), and diffusion parameters of white matter tracts that connect there (Lebel et al. 2008b; Zhang et al. 2007). Therefore, it appears that the latest maturing structures in the brain seem to be the most affected by prenatal alcohol consumption. It is not clear why these regions may be more vulnerable to the teratogenic effects of alcohol.

Other portions of the brain display less consistent FA abnormalities. Two of six studies observed lower FA in the body of the corpus callosum (Wozniak et al. (2009) found differences specifically in the posterior midbody), while the remaining structures pictured in Fig. 181.4 were found to be abnormal in only one of the three to four studies investigating them. The deep gray matter structures were only measured by Lebel et al. (2008a), so it is impossible to assess the consistency of these DTI findings. The structures found to be abnormal in only one study, or those that were only examined by one study, will need to be further investigated to determine whether they are consistent among those with FASD or perhaps a unique feature of the particular population of subjects used in one study.

Abnormalities of MD are shown in Fig. 181.5. Although many of the same regions were highlighted in the FA findings, including the corpus callosum, inferior longitudinal fasciculus, and several deep gray matter structures, the MD results seem less consistent than the abnormal FA findings. The only structures observed to have abnormal MD values in more than one study were the genu and splenium of the corpus callosum. There are some conflicting reports, such as one study observed higher MD in the genu of adolescents with FAS (Ma et al. 2005), while another observed lower MD in the genu of FASD children (Lebel et al. 2008a).

Analysis of Figs. 181.4 and 181.5 suggests the right hemisphere of the brain is more affected than the left hemisphere. Although some structures demonstrate bilateral differences between subjects with FASD and controls (the globus pallidus for FA and MD, anterior and posterior corona radiata for FA, inferior fronto-occipital fasciculus for MD), and some demonstrate differences only in the left hemisphere (thalamus for FA differences, superior frontal white matter, anterior and posterior limbs of the internal capsule, and left inferior longitudinal fasciculus for MD only), more abnormalities are apparent in the right hemisphere. Figures 181.4 and 181.5 show ten structures for which the differences are either present only in the right hemisphere, or are more consistent there (i.e., detected by more studies). While most volumetric studies do not report hemispheric differences, an earlier study using conventional T_1-weighted MRI reported more prominent differences in the left hemisphere of children and adolescents with FASD (Sowell et al. 2001). The development of brain asymmetry is poorly understood, although it can be affected by many different genes and drugs (Levin 2005). Clearly, there are some interesting asymmetries present in FASD, but the reasons for this are not clear at present.

Previous studies have reported temporal and parietal lobe abnormalities in FASD populations, showing increased cortical gray matter thickness (Sowell et al. 2008b) and decreased volume in the parietal lobe (Archibald et al. 2001). Although the parietal area did not have an unusually large number of regions demonstrating diffusion abnormalities (only the superior longitudinal fasciculus, a frontal-parietal-temporal connection showed FA differences between FASD and controls), the temporal lobe shows many changes. In fact, three of the four studies examining the temporal lobe found differences here. Three temporal areas or connections to them were found to be abnormal in at least two studies: the superior longitudinal fasciculus (SLF), the inferior longitudinal fasciculus (ILF, an occiptial-temporal connection), and the cingulum (frontal-temporal). The uncinate fasciculus (UF), another frontal-temporal connection was found to be abnormal by one study. Another region that
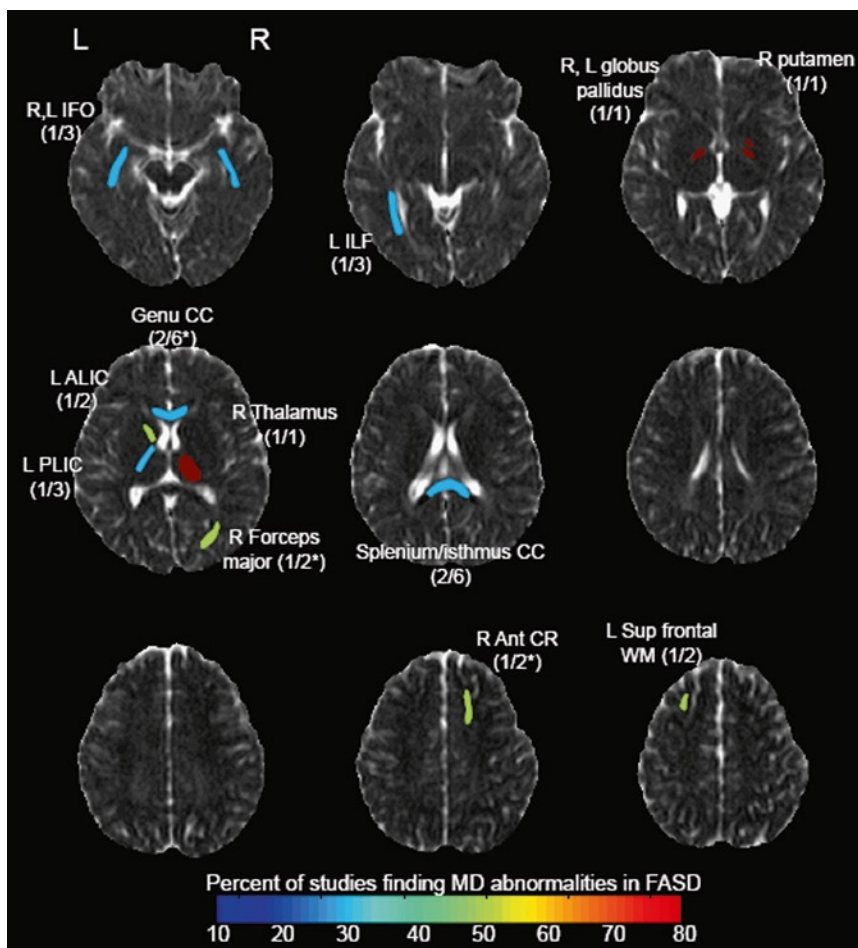
Fig. 181.5 Structures with mean diffusivity abnormalities in Fetal alcohol spectrum disorder (*FASD*). Structures that have shown significant mean diffusivity (*MD*) differences between subjects with prenatal alcohol exposure and healthy controls are shown overlaid on an MD map of a 9-year-old boy with FASD. Structures are colored according to the percentage of studies that has shown differences in that particular area. Structures are also listed with the number of studies showing differences and the total number of studies examining that particular area. For all regions, the alcohol-exposed group showed higher MD than controls, except for regions marked with an asterisk (*, the genu CC, forceps major, anterior coronal radiata), for which one of the studies showed decreased MD in the alcohol-exposed group. Abbreviations are the same as for Fig. 181.4.

seems to be commonly different amongst these studies is the frontal region: the UF, SLF, cingulum, inferior and superior fronto-occipital fasciculi (IFO, SFO), and the anterior corona radiata, all connect to this area. Since the frontal lobe is involved in impulse control and executive functioning, both of which many FASD individuals have difficulty with, these frontal connection abnormalities make sense.

Volumetric and metabolic imaging studies have reported major changes in the deep gray matter structures, which are the relay stations of the brain; in particular the caudate nucleus has been implicated (Archibald et al. 2001; Cortese et al. 2006; Mattson et al. 1996). However, only one DTI study to date has examined the deep gray matter structures, where it was demonstrated that the thalamus, putamen, and globus pallidus had significant differences of diffusion parameters in FASD. In contrast to the volumetric and metabolic studies, significant DTI differences were not observed in the caudate nucleus between groups (Lebel et al. 2008a). Further studies are needed to determine whether these
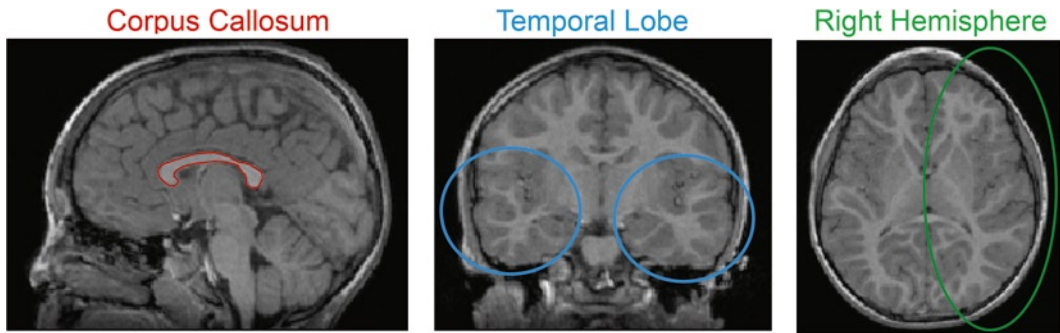
Fig. 181.6 Regions commonly reported to be abnormal in DTI studies of FASD. Abnormalities in the corpus callosum, temporal lobes, and the right hemisphere of individuals with fetal alcohol spectrum disorder (*FASD*) have been reported by many, but not all, diffusion tensor imaging (*DTI*) studies of FASD

diffusion differences are robust and appear in other FASD populations, which would be interesting given the sensitivity of deep gray matter structures to prenatal alcohol exposure in terms of their size and function. Agreement of diffusion changes with volumetric and functional abnormalities in these areas would suggest that they are highly sensitive to prenatal alcohol exposure in many ways, while a disparity between volumetrics and diffusion parameters may indicate a preservation of tissue microstructure, even while overall volume was reduced.

One interesting line of study will be age-related changes within FASD populations. It is well known that diffusion parameters across the brain change with age during childhood and adolescence (Lebel et al. 2008b; Schmithorst et al. 2002); however, the developmental trajectory for FASD is unknown. To date, the DTI studies of children with FASD (age-related DTI changes will be most prominent in children and adolescents) have had relatively small sample sizes ($n = 14$–24), which limit their ability to detect possible changes. Large sample sizes, wide age ranges, and an assortment of analysis techniques will be required to accurately model development trajectories, which are often nonlinear and contain considerable scatter. Lebel et al. (2008a) conducted an exploratory analysis to examine age-related changes of diffusion parameters in FASD compared to the trajectory of development in healthy controls. While there were insufficient FASD subjects to properly fit a curve, in structures with significant differences between children with FASD and healthy controls, the FASD group seemed to follow a similar pattern to the healthy controls, but with most FASD subjects located on one side of the best-fit curve. Another study tested correlations between FA and age in all subjects (FASD group and controls combined) and found no significant correlations (Fryer et al. 2009); however, this may not be unexpected given the small sample size ($n = 15$ FASD, $n = 12$ control).

Despite the relatively small number of studies examining diffusion parameters in FASD, the corpus callosum, temporal lobe, and right hemisphere emerge as consistently abnormal (see Fig. 181.6). Future studies may highlight additional areas and may help elucidate reasons as to why these particular areas are most affected by prenatal alcohol exposure.

181.5 Links to Cognition and Behavior

Children, adolescents, and adults with FASD often have a variety of cognitive and behavioral impairments that may include motor delays, attention deficits, and difficulties with language, learning, memory, and mathematics (Jacobson and Jacobson 2002; Mattson and Riley 1998). Many studies have linked cognitive abilities to brain microstructure as assessed by DTI in healthy populations and

Table 181.3 DTI studies examining correlations with cognitive measures

Study	Number of subjects	Cognitive measures	Brain regions	Findings
Lebel et al. (2008a)	24 FASD	NEPSY (6 subtests) WMTB: Digit, Block Recall WJ III: Quantitative Concepts WRMT: Word ID CREVT	10 white matter tracts 4 deep gray matter structures	No significant correlations
Ma et al. (2005)	9 FAS 7 controls	WISC-III Full-scale IQ	Genu CC Splenium CC	Full-scale IQ – FA in genu and splenium Processing speed – FA in genu and splenium (correlations were across entire group, not in the FAS group alone)
Sowell et al. (2008a)	17 FASD	WRAT reading scores Visuomotor integration	7 regions in temporal lobe, splenium, brainstem	Visuomotor integration – splenium FA
Wozniak et al. (2009)	33 FASD	WISC-IV or WAIS-III: Verbal Comprehension, Perceptual Organization, Working Memory, Processing Speed	Genu CC Splenium CC	Working memory – FA genu and MD splenium Perceptual organization - MD splenium

This table outlines details of the four previous studies that have tested for correlations between cognitive measures and DTI parameters in subjects with prenatal alcohol exposure

other abnormal conditions (Barnea-Goraly et al. 2005; Deutsch et al. 2005; Schmithorst et al. 2005). However, little is known about the relationship between brain structure, cognition, and behavior in FASD. Out of the seven previous studies examining FASD using DTI, four report looking at correlations between brain structure, as assessed by DTI parameters, and cognitive measures. The results of the correlations in these studies are presented in Table 181.3. Although FA is a nonspecific measure, lower FA is suggestive of reduced myelination and/or decreased axonal density; basically, lower FA is interpreted or hypothesized to be linked with weaker white matter integrity. Since white matter forms the brain connections necessary for proper and efficient cognitive function, it is logical that weaker connections would be associated with cognitive deficits. Therefore, positive correlations are expected between cognition and/or behavior scores and FA measures. Brain regions where correlations occur may indicate some degree of specificity related to a certain cognitive task. Significant correlations imply that the variety of cognitive and behavioral difficulties in individuals with FASD is associated with the level of brain abnormalities, and that the more difficulties an individual has with the task, the more abnormal their brain structure is likely to be. Similarly, negative correlations of cognitive scores with MD would be expected, given the higher MD in children with FASD (i.e., freer water diffusion, reflecting fewer microstructural barriers). However, correlations are not causal and may also simply be due to the fact that both the brain area and cognitive measure in question are particularly affected by prenatal alcohol exposure, rather than that they are related to each other. Therefore, although correlations between brain structure and cognition can be extremely useful for understanding FASD, they must be interpreted with caution.

Lebel et al. (2008a) examined correlations between FA and MD in ten different white matter tracts identified with tractography and four deep gray matter structures (ROI) of children with FASD and ten

different cognitive measures: six subtests of the NEPSY measuring neuropsychological functioning, Working Memory Test Battery (WMTB) digit and block recall tests, the Woodcock-Johnson III Tests of Achievement Quantitative Concepts subtest, and the WRMT Word ID, and the Comprehensive Receptive and Expressive Vocabulary Test. None of the correlations between diffusion parameters and cognitive measures were significant after correction for multiple comparisons. However, given the high number of comparisons (10 cognitive scores × 14 brain regions), the correction was strict and more targeted analyses may be needed. Furthermore, correlations between cognitive scores and diffusion parameters are most often found in small areas that are a subsection of a tract, and averaging over an entire white matter tract may mask correlations that exist in smaller subsections of the tract.

Ma et al. (2005) correlated both FA and MD with the WISC-III full-scale IQ and processing speed scores. A significant linear relationship was observed for both processing speed and full-scale IQ measures with FA in the corpus callosum (both genu and splenium). These correlations, however, were only observed across the entire group (nine FAS, seven controls) and were not present in the FAS group alone. Two caveats must be noted,however: first, the sample size was quite small ($n = 9$ for FAS subjects), so the absence of significant correlations may be simply due to reduced power; and second, the cognitive scores used in the correlations were obtained approximately 5 years prior to imaging. Although the authors mention that these types of scores tend to be stable over adolescence, this is a potential confound.

In a study of 33 children and adolescents with FASD, Wozniak et al. (2009) correlated diffusion parameters in the genu and splenium of the corpus callosum with verbal comprehension, perceptual organization, working memory, and processing speed. A significant positive correlation was observed between working memory and FA in the genu; significant negative correlations were reported between splenium MD and both perceptual organization and working memory.

Another study examined correlations between FA and visuo-motor integrations and Wide Range Achievement Test (WRAT) reading scores (Sowell et al. 2008a). FA values were measured in the splenium, bilateral brainstem, and two regions of the temporal lobe in each hemisphere. Significant positive correlations were observed between the visuomotor integration scores and FA in the splenium within the FASD group. No significant correlations were observed between FA and reading scores.

Clearly, connecting diffusion abnormalities with cognitive difficulties in FASD is an important area of research and very little is currently known. Ultimately, linking specific structural brain abnormalities in FASD with cognition, behavior, and brain function will provide clues as to the causes of certain deficits and may lead to more effective treatments of such difficulties in the future.

181.6 Summary

In summary, the seven previous DTI studies of FASD point to several consistent structural brain abnormalities between children, adolescents, and young adults with FASD and healthy controls: the corpus callosum, in particular the posterior region; the temporal lobes, and the right hemisphere. The corpus callosum and temporal lobe findings are in good agreement with other imaging and autopsy studies. To date, only a few studies have examined cognition-brain structure correlations within individuals with FASD, but they do point to relationships between the cognitive and behavioral deficits observed in FASD and the underlying brain microstructure. Future research examining brain abnormalities, cognitive score-diffusion parameter correlations, and developmental trajectories within FASD will provide a much more detailed understanding of this unfortunately prevalent but preventable disorder.

Summary Points

- Fetal alcohol spectrum disorder (FASD) is a developmental disorder associated with prenatal alcohol exposure.
- Individuals with FASD have a variety of cognitive, behavioral, and neurological brain deficits, including structural brain damage.
- Diffusion tensor imaging (DTI) is an excellent method of examining tissue microstructure, especially in white matter tracts.
- DTI has been used in seven previous studies to examine abnormalities in children, adolescents, and young adults prenatally exposed to alcohol.
- Consistent findings of these studies include abnormalities of the corpus callosum (especially the posterior section), temporal lobes, and right hemisphere
- Four of these studies have examined correlations between cognitive measures and DTI parameters, demonstrating significant relationships between brain structure and visuomotor integration, perceptual organization and working memory in individuals with FASD.

Definitions

Fractional anisotropy (FA): An important diffusion tensor imaging parameter reflecting the directionality of diffusion. FA varies from 0 (isotropic diffusion) to 1 (completely anisotropic diffusion). FA is often considered to be a measure of "white matter integrity".

Mean diffusivity (MD): Another important diffusion tensor imaging parameter representing the average diffusivity (i.e., mobility) of water occurring in the tissue.

Tractography: A diffusion tensor image analysis technique that uses the primary diffusion direction and anisotropy to trace out white matter connections and provide visualization of the pathways in vivo. Tractography is often used to analyze the FA and MD of specific white matter tracts.

White matter tracts: Bundles of axons connecting spatially segmented brain regions. These are necessary for efficient brain communication and proper cognitive function. One or more white matter tracts are often abnormal in various diseases or conditions.

Fetal alcohol spectrum disorder (FASD): The umbrella term describing the various disorders associated with prenatal alcohol exposure. Individuals with FASD may have a variety of behavior, cognitive, and brain abnormalities.

References

Abel EL, Sokol RJ. Lancet. 1986;2:1222.

Archibald SL, Fennema-Notestine C, Gamst A, Riley EP, Mattson SN, Jernigan TL. Dev Med Child Neurol. 2001;43:148–54.

Ashburner J, Friston KJ. Neuroimage. 2000;11:805–21.

Assaf Y, Pasternak O. J Mol Neurosci. 2008;34:51–61.

Astley SJ. Diagnositc guide for fetal alcohol spectrum disorders: the 4-digit diagnostic code. Seattle: Fetal Alcohol Syndrome Diagnostic and Prevention Network, University of Washington; 2004.

Astley SJ, Aylward EH, Olson HC, Kerns K, Brooks A, Coggins TE, Davies J, Dorn S, Gendler B, Jirikowic T, Kraegel P, Maravilla K, Richards T. Astley Alcohol Clin Exp Res. 2009;33:1671–89.

Barnea-Goraly N, Eliez S, Menon V, Bammer R, Reiss AL. Brain Res Cogn Brain Res 2005;25:735–40.

Basser PJ. NMR Biomed. 1995;8:333–44.

Basser PJ, Mattiello J, LeBihan D. Biophys J. 1994;66:259–67.

Basser PJ, Pajevic S, Pierpaoli C, Duda J, Aldroubi A. Magn Reson Med. 2000;44:625–32.

Beaulieu C. NMR Biomed. 2002;15:435–55.

Bookstein FL, Sampson PD, Streissguth AP, Connor PD. Teratology. 2001;64:4–32.

Clarren SK, Alvord EC, Jr, Sumi SM, Streissguth AP, Smith DW. J Pediatr. 1978;92:64–7.

Conturo TE, Lori NF, Cull TS, Akbudak E, Snyder AZ, Shimony JS, McKinstry RC, Burton H, Raichle ME. Proc Natl Acad Sci USA. 1999;96:10422–7.

Cortese BM, Moore GJ, Bailey BA, Jacobson SW, Delaney-Black V, Hannigan JH. Neurotoxicol Teratol. 2006;28:597–606.

Deutsch GK, Dougherty RF, Bammer R, Siok WT, Gabrieli JD, Wandell B. Cortex. 2005;41:354–63.

Fagerlund A, Heikkinen S, Autti-Ramo I, Korkman M, Timonen M, Kuusi T, Riley EP, Lundbom N. Alcohol Clin Exp Res. 2006;30:2097–104.

Fryer SL, Schweinsburg BC, Bjorkquist OA, Frank LR, Mattson SN, Spadoni AD, Riley EP. Alcohol Clin Exp Res. 2009;33:514–21.

Giedd JN, Blumenthal J, Jeffries NO, Castellanos FX, Liu H, Zijdenbos A, Paus T, Evans AC, Rapoport JL. Nat Neurosci. 1999a;2:861–3.

Giedd JN, Blumenthal J, Jeffries NO, Rajapakse JC, Vaituzis AC, Liu H, Berry YC, Tobin M, Nelson J, Castellanos FX. Prog Neuropsychopharmacol Biol Psychiatry. 1999b;23:571–88.

Jacobson JL, Jacobson SW. Alcohol Res Health. 2002;26:282–6.

Jones DK, Simmons A, Williams SC, Horsfield MA. Magn Reson Med. 1999;42:37–41.

Jones KL, Smith DW. Lancet. 1973;2:999–1001.

Le Bihan D. Nat Rev Neurosci. 2003;4:469–80.

Lebel C, Rasmussen C, Wyper K, Walker L, Andrew G, Yager J, Beaulieu C. Alcohol Clin Exp Res. 2008a;32:1732–40.

Lebel C, Walker L, Leemans A, Phillips L, Beaulieu C. Neuroimage. 2008b;40:1044–55.

Lemoine P, Harousseau H, Borteyru JP, Menuet JC. Ouest Med. 1968;21:476–82.

Levin M. Mech Dev. 2005;122:3–25.

Li L, Coles CD, Lynch ME, Hu X. Li Human Brain Mapp. 2009;30:3265–74.

Ma X, Coles CD, Lynch ME, Laconte SM, Zurkiya O, Wang D, Hu X. Alcohol Clin Exp Res. 2005;29:1214–22.

Mattson SN, Riley EP. Alcohol Clin Exp Res. 1998;22:279–94.

Mattson SN, Riley EP, Sowell ER, Jernigan TL, Sobel DF, Jones KL. Alcohol Clin Exp Res. 1996;20:1088–93.

May PA, Gossage JP. Alcohol Res Health. 2001;25:159–67.

Mori S, Crain BJ, Chacko VP, van Zijl PC. Ann Neurol. 1999;45:265–9.

Mukherjee RA, Hollins S, Turk J. J R Soc Med. 2006;99:298–302.

Peiffer J, Majewski F, Fischbach H, Bierich JR, Volk B. J Neurol Sci. 1979;41:125–37.

Riley EP, McGee CL. Exp Biol Med (Maywood). 2005;230:357–65.

Sampson PD, Streissguth AP, Bookstein FL, Little RE, Clarren SK, Dehaene P, Hanson JW, Graham JM, Jr. Teratology. 1997;56:317–26.

Schmithorst VJ, Wilke M, Dardzinski BJ, Holland SK. Radiology. 2002;222:212–8.

Schmithorst VJ, Wilke M, Dardzinski BJ, Holland SK. Hum Brain Mapp. 2005;26:139–47.

Smith SM, Jenkinson M, Johansen-Berg H, Rueckert D, Nichols TE, Mackay CE, Watkins KE, Ciccarelli O, Cader MZ, Matthews PM, Behrens TE. Neuroimage. 2006;31:1487–505.

Sowell ER, Johnson A, Kan E, Lu LH, Van Horn JD, Toga AW, O'Connor MJ, Bookheimer SY. J Neurosci. 2008a;28:1313–9.

Sowell ER, Mattson SN, Kan E, Thompson PM, Riley EP, Toga AW. Cereb Cortex. 2008b;18:136–44.

Sowell ER, Thompson PM, Mattson SN, Tessner KD, Jernigan TL, Riley EP, Toga AW. Neuroreport. 2001;12:515–23.

Streissguth AP, Dehaene P. Am J Med Genet. 1993;47:857–61.

Thompson PM, Giedd JN, Woods RP, MacDonald D, Evans AC, Toga AW. Nature. 2000;404:190–3.

White T, Nelson M, Lim KO. Top Magn Reson Imaging. 2008;19:97–109.

Wozniak JR, Mueller BA, Chang PN, Muetzel RL, Caros L, Lim KO. Alcohol Clin Exp Res. 2006;30:1799–1806.

Wozniak JR, Muetzel RL, Mueller BA, McGee CL, Freerks MA, Ward EE, Nelson ML, Chang PN, Lim KO. Wozniak Alcohol Clin Exp Res. 2009;33:1825–35.

Zhang J, Evans A, Hermoye L, Lee SK, Wakana S, Zhang W, Donohue P, Miller MI, Huang H, Wang X, van Zijl PC, Mori S. Neuroimage. 2007;38:239–47.

Chapter 182
Neuronal Cell Migration in Fetal Alcohol Syndrome

Tatsuro Kumada, Yutaro Komuro, Ying Li, Yoav Littner, and Hitoshi Komuro

Abbreviations

FAS	Fetal alcohol syndrome
FASD	Fetal alcohol spectrum disorders
EGL	External granular layer
ML	Molecular layer
PCL	Purkinje cell layer
IGL	Internal granular layer
WM	White matter
NMDA	N-methyl-D-aspartate
cAMP	Cyclic AMP
cGMP	Cyclic GMP
AC	Adenylyl cyclase
PKA	Protein kinase A
PDE	Cyclic nucleotide phosphodiesterases
PKC	Protein kinase C
CaMKII	Ca^{2+}/calmodulin-dependent protein kinase II
PP1	Protein phosphatase 1
MAPK	Mitogen-activated protein kinase
PI$_3$K	Phosphoinositide 3-kinase
BrdU	5-bromo-2′-deoxy-uridine

182.1 Introduction

Prolonged exposure to alcohol during gestation and lactation correlates with a pattern of abnormal development in newborns (Lemoine et al. 2003; Sokol et al. 2003; Goodlett et al. 2005). Jones and Smith (1973) called this developmental disturbance "fetal alcohol syndrome" (FAS). The disturbance of the central nervous system is the most serious feature of FAS (Marcus 1987; Riley and

H. Komuro (✉)
Department of Neurosciences/NC30, Lerner Research Institute,
The Cleveland Clinic Foundation, 9500 Euclid Avenue, Cleveland, OH 44195, USA
e-mail: komuroh@ccf.org

McGee 2005). For example, microencephaly is common among FAS patients (Wisniewski et al. 1983). Several aspects of the developmental program are involved in the alcohol-induced malformation of the brain (Jones 1988; Coulter et al. 1993; Guerri 2002). Among them, the most striking abnormalities appear to involve the impairment of neuronal cell migration (Miller 1986, 1993). Recent studies indicate the role of the Ca^{2+} and cyclic nucleotide signaling pathways in the alcohol-induced abnormal migration of immature neurons (Kumada et al. 2006). In this chapter, we focus on cellular mechanisms by which alcohol impairs the migration of immature neurons in the developing brain.

182.2 Maternal Alcohol Exposure Affects Brain Development of Fetuses and Children

Alcohol is presently the most common chemical teratogen causing malformation and mental deficiency in humans (Clarren and Smith 1978; Clarren et al. 1978). Maternal exposure to alcohol may not lead to full expression of FAS but rather may result in a variety of less pronounced dysmorphic, cognitive, and behavioral effects, often termed "fetal alcohol spectrum disorders" (FASD). The world incidence of FAS is estimated as approximately 1.9 per 1,000 live births, while the incidence of FASD is thought to be as high as 1 in 100 live births (Committee on Substance Abuse 1993). The most serious feature of FAS is disturbance of the central nervous system (Clarren and Smith 1978; Clarren et al. 1978, 1990). Microcephaly is present in nearly all cases, and this reflection of disturbed brain growth is accompanied by delayed neurologic development in approximately 90% of the cases (Wisniewski 1983). Particular defects of speech and language development are also evident (Marcus 1987). In addition to serious cognitive deficits, a far-reaching and pervasive state of disability is induced by behavioral disturbances, impaired communication skills, and maladaptive social function, manifested by lack of reciprocal friendships, impulsive behavior, anxiety and dysphoria. Children with FAS also show neurological signs associated with cerebellar damage such as delayed motor development, problems with fine tasks, and ataxia (Coffin et al. 2005; Manzardo et al. 2005). The most common abnormality observed in the brain of FAS patients is a leptomeningeal neuroglial heterotopia that assumes the form of a sheet of aberrant neuronal and glial cells covering portions of the cerebral, cerebellar, and brain stem surfaces (Clarren and Smith 1978; Clarren et al. 1978). Aberrations of brain stem and cerebellar development, in large part related to faulty cell migration, have also been especially frequent, along with the migrational disturbances of schizencephaly and polymicrogyria (Peiffer et al. 1979). Disordered midline prosencephalic formation – e.g., agenesis of the corpus callosum, septo-optic dysplasia, and incomplete holoprosencephaly – has also been documented (Coulter et al. 1993). Therefore, multiple aspects of central nervous system development can be affected by alcohol exposure, including proliferation, migration, differentiation, and synapse formation.

182.3 Animal Models for Studying the Effects of Alcohol Exposure on Brain Development

Due to the obvious limitations on human studies, animal models of FAS have been used to further document the phenomenon of alcohol-induced defects in brain development and to study underlying mechanisms. Pre- and/or neonatal exposure to alcohol also induces long-term neuromorphologic, neurochemical and behavioral changes in experimental animals (Sakata-Haga et al. 2001;

Dikranian et al. 2005). Some of these changes were observed in humans, and thus led to the identification of FAS. In mice and rats, the early postnatal period is equivalent to fetal development in humans, and alcohol exposure causes a reduction of their brain weight, especially in the cerebellum (Kornguth et al. 1979; Sakata-Haga et al. 2001; Dikranian et al. 2005). The alcohol-exposed rats are hypoactive during treatment and exhibit a reduction in cerebellar Purkinje cell numbers, especially in the early maturing lobules (Bauer-Moffet and Altman 1975). Furthermore, the number of granule cells in the internal granular layer (IGL) of the cerebellum is significantly reduced in the alcohol-treated animals (Borges and Lewis 1983), suggesting that alcohol affects the migration of cerebellar granule cells to the IGL. Moreover, prenatal exposure of alcohol-induced morphological defects in the rat cerebral cortex, including heterotopia and disorganized cortical architecture, suggest abnormal migration (Kotkoskie and Norton 1988). In the rat cerebrum, prenatal alcohol exposure delays the migration of early generated neurons to the deep cortical layers by 2 days, and the migration of late generated neurons to the upper cortical layers by 4–6 days (Miller 1993). Alcohol exposure also reduces the speed of neuronal cell migration in the rat cerebrum (Siegenthaler and Miller 2004).

182.4 Migration of Cerebellar Granule Cells as a Model of Neuronal Cell Migration

To examine mechanisms by which alcohol affects neuronal migration, the cerebellum of the early postnatal mouse is used as a model system, since exposure to alcohol induces quantitative morphological changes in the rodent cerebellum (Bauer-Moffet and Altman 1975; Borges and Lewis 1983). Furthermore, the defined neuronal cytoarchitecture and the small number of neuronal types in the cerebellum provide an ideal system for determining cellular and molecular mechanisms of neuronal migration (Komuro and Rakic 1998b; Komuro and Yacubova 2003). Specifically, the migration of granule cells has been intensively examined, and it has become apparent that the mechanisms underlying granule cell migration are utilized during the migration of immature neurons in other brain regions (Yacubova and Komuro 2003; Komuro and Kumada 2005). Therefore, this review is based on studies of the migration of cerebellar granule cells. Interestingly, cerebellar granule cells alter the mode, rate and direction of migration as they traverse different cortical layers of the cerebellum (as schematically presented in Fig. 182.1).

At the top of the external granular layer (EGL), granule cell precursors proliferate every 18–20 h. After their final mitosis, granule cells remain in the EGL for 24–48 h before initiating their radial migration across the molecular layer (ML) (Komuro et al. 2001). During this latent period, granule cells tangentially migrate within the middle and bottom of the EGL (Komuro et al. 2001). At the middle of the EGL, coinciding with the extension of two uneven horizontal processes oriented parallel to the longitudinal axis of the folium, granule cells start to migrate tangentially in the direction of the larger process. Their morphology and speed of movement change systematically with their position within the EGL (Komuro et al. 2001). The speed of movement is fastest (~14.8 μm/h) in the middle of the EGL, when granule cells have two short horizontal processes. As granule cells elongate their somata and extend longer horizontal processes at the bottom of the EGL, they move at a reduced speed (~12.6 μm/h). At the interface of the EGL and the ML where granule cells migrate at the slowest speed (~4.1 μm/h), their somata round, and then begin to extend couples of descending processes into the ML. After the stationary period, granule cells abruptly extend a single vertical process and initiate the transition from tangential to radial migration, reshaping their rounded somata into a vertically elongated spindle.
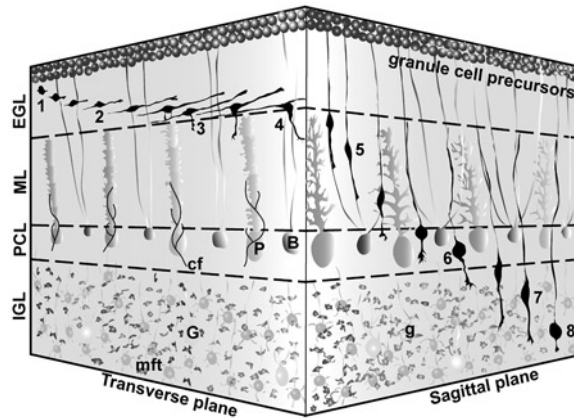
Fig. 182.1 A three-dimensional representation of granule cell migration from their birthplace, the external granular layer (*EGL*), to their final destination, the internal granular layer (*IGL*), in the developing cerebellum. 1, Extension of two uneven horizontal processes near the top of the EGL; 2, Tangential migration in the middle of the EGL; 3, Development of vertical processes near the border between the EGL and the molecular layer (*ML*); 4, Initiation of radial migration at the EGL-ML border; 5, Bergmann glia-associated radial migration in the ML; 6, Stationary state in the Purkinje cell layer (*PCL*); 7, Glia-independent radial migration in the IGL; 8, Completion of migration in the middle or bottom of the IGL. Abbreviations: *P* Purkinje cell, *B* Bergmann glia, *G* Golgi cell, *g* postmigratory granule cell, *cf* climbing fiber, *mft* mossy fiber terminal

In the ML, granule cells have vertically elongated cell bodies, thin trailing processes, and more voluminous leading processes, and migrate radially along Bergmann glial processes (Komuro and Rakic 1995). In this layer, the speed of granule cell movement depends critically on the age of the cerebellum (Komuro and Rakic 1995). The average speed of migration in the ML increases systematically from 9.6 μm/h in the cerebellum of postnatal 7-day-old mice to 18.0 μm/h in postnatal 13-day-old mice. Consequently, granule cells traverse the developing ML within a relatively constant time period (10–11 h) despite the doubling in width of the layer during the second week of postnatal life. The movement of granule cells in this layer is characterized by alternations of short stationary phases with movement in a forward or backward direction. The net displacement of granule cells depends on the duration and frequency of these phases as well as on the speed of movement.

Upon entering the Purkinje cell layer (PCL), granule cells detach from the processes of Bergmann glial cells, and the shape of their cell bodies abruptly transforms from a vertically elongated spindle to a sphere (Komuro and Rakic 1998a). The rounded somata significantly slow their movement, and stop completely in the PCL. The somata remain stationary in the PCL for an average of 115 min, with times ranging from 30–220 min (Komuro and Rakic 1998a). However, highly motile lamellipodia and filopodia develop at the distal portion of the leading process, suggesting that the tips of leading processes actively search for potential guidance cues. After a prolonged stationary period, granule cells in the PCL begin to re-extend their somata and leading processes. During this transformation, granule cells gradually accelerate the speed of migration and cross the border between the PCL and the internal granular layer (IGL).

In the IGL, granule cells migrate radially toward the bottom of the IGL without an association with glial cells at a speed comparable to that observed in the ML (Komuro and Rakic 1998a). The long axis of their somata remains oriented perpendicular to the PCL-IGL boundary line during this radial migration. Interestingly, once the tip of a leading process approaches the IGL-white matter (WM) border, their somata become rounded again. Thereafter, granule cells gradually slow their

migration and stop movement near the IGL-WM border (Komuro and Rakic 1998a). In early postnatal mouse cerebella, the majority of granule cells complete their migration at the bottom stratum of the IGL.

In vitro studies with the use of real-time observation of granule cell migration in acute cerebellar slices reveal that in the P10 mouse cerebellum, granule cells first move tangentially about 220 μm in the EGL, and then migrate radially about 250 μm to reach their final position in the IGL (Komuro and Yacubova 2003). The average transit time of granule cells is 25.0 h in the EGL, 9.8 h in the ML, 5.2 h in the PCL, and 11.1 h to attain their final position in the IGL (Yacubova and Komuro 2003). Therefore, granule cells move from the top of the EGL through the ML and PCL to their final position in the IGL within about 2 days (average, 51 h).

182.5 Alcohol Exposure Reduces the Speed of Granule Cell Migration In Vitro

To determine whether and how alcohol exposure affects the migration of cerebellar granule cells, first, the relation between the doses of alcohol exposure and the effects on granule cell migration was examined. Real-time observation of cell movement in cerebellar slices obtained from postnatal (P) 10-day-old mice indicate that the administration of 100 mM ethanol immediately slows the tangential migration of granule cells in the EGL (Kumada et al. 2006). Pharmacologically relevant concentrations of ethanol are based on blood-ethanol concentrations attained by alcohol consumption in humans (Jones 1988). Since ethanol readily crosses the placental and blood brain barriers, and diffuses rapidly into all aqueous compartments of the body, these levels would readily be found in cases of alcohol consumption during pregnancy (West et al. 1994). The effects of ethanol on the speed of granule cell migration in the cerebellar slices of P10 mice are dose dependent (Fig. 182.2). Although 2.5 mM ethanol fails to alter the speed of granule cell movement, 10 mM ethanol (equivalent to blood ethanol level <50 mg/dL) significantly decreases the speed to 62% (EGL), 76% (ML), and 82% (IGL) of the control value. In the presence of 50 mM ethanol, the speed is further reduced to 40% (EGL), 55% (ML), and 62% (IGL) of the controls. Finally, when 100 mM ethanol is added, movement declines to 35% (EGL), 50% (ML), and 56% (IGL) of the control. It is noteworthy that the vulnerability of granule cells to ethanol exposure decreases as granule cells migrate from the

Fig. 182.2 Ethanol slows the migration of granule cells in the acute slices of the early postnatal mouse cerebella. Effects of different doses (0–100 mM) of ethanol on the speed of granule cell migration among three different cortical layers (the EGL, ML and IGL) of the early postnatal mouse cerebellum. Bar is S.D.
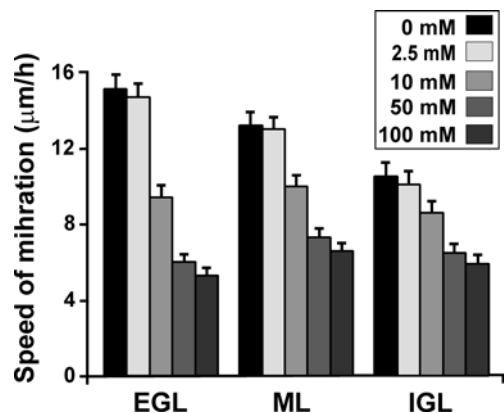
Fig. 182.3 Ethanol directly inhibits the migration of isolated granule cells in the microexplant cultures of the early postnatal mouse cerebella. Dose-dependent reduction of the speed of granule cell migration in the microexplant cultures of P3 mouse cerebella by an acute exposure of ethanol (0–200 mM). Bar is S.D.
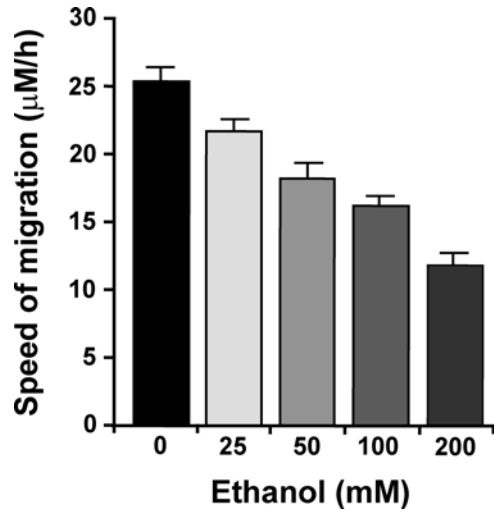
EGL to the IGL (Fig. 182.2). The changing vulnerability suggests that the stage of differentiation (or maturation) is critical in producing the harmful effects of ethanol on granule cell migration.

Ethanol may alter the motility of granule cells directly or indirectly by modifying the surrounding environment. For example, ethanol exposure affects the development and functions of glia, which in turn may alter granule cell motility (Shetty and Phillips 1992). To determine whether ethanol directly affects granule cell migration, microexplant cultures of P0-P3 mouse cerebella, in which isolated granule cells actively migrate in the absence of cell–cell contact, are used (Yacubova and Komuro 2002; Kumada et al. 2009). The addition of 100 mM ethanol slowed the migration of isolated granule cells from 43.2 to 18.3 μm/h, even though ethanol did not affect the extension of the leading process or the morphological features of the process (Kumada et al. 2006). Furthermore, application of ethanol at concentrations ranging from 25 to 200 mM appreciably slows the movement of isolated granule cells (Fig. 182.3). The average speed of granule cell movement is reduced to 85% (25 mM ethanol), 71% (50 mM ethanol), 63% (100 mM ethanol), and 46% (200 mM ethanol) of the control (Kumada et al. 2006). These results indicate that ethanol directly acts on granule cell migration in a dose-dependent manner.

182.6 Alcohol Exposure Reduces the Frequency of Spontaneous Ca^{2+} Spikes in Migrating Granule Cells

How does alcohol slow the migration of granule cells? Although the effects of alcohol are initially believed to arise from alcohol-induced perturbations in the order of membrane lipids, the effects on membrane lipids are actually quite small at clinically relevant concentrations (Peoples et al. 1996).

However, even low levels of alcohol can modulate the functions of voltage-gated and ligand-gated Ca^{2+} channels by binding to a hydrophobic pocket on the proteins (Walter and Messing 1999). This suggests that alcohol may affect the intracellular Ca^{2+} levels of migrating granule cells. This is intriguing because granule cell migration is highly sensitive to changes in intracellular Ca^{2+} levels and Ca^{2+} signaling (Komuro and Rakic 1992, 1993, 1996; Kumada and Komuro 2004; Komuro and Kumada 2005). Indeed, the use of a Ca^{2+} indicator dye revealed that administration of ethanol significantly

Fig. 182.4 Ethanol action on Ca^{2+} spikes in migrating granule cells. Histograms showing the reduction of the frequency of spontaneous Ca^{2+} spikes in the somata of migrating cerebellar granule cells by ethanol (0–200 mM). Bar is S.D.
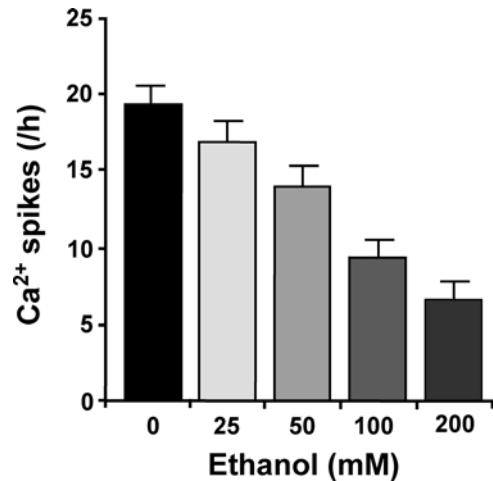
lowers the frequency of spontaneous Ca^{2+} spikes in the granule cell somata in a dose-dependent manner (Kumada et al. 2006). For example, the average number of spontaneous Ca^{2+} spikes in the granule cells was reduced to 88% (25 mM ethanol), 73% (50 mM ethanol), 48% (100 mM ethanol), and 35% (200 mM ethanol) of the control after administration of ethanol (Fig. 182.4). These results suggest that one of the cellular mechanisms underlying ethanol action on neuronal migration is the alteration of Ca^{2+} signaling.

182.7 Enhancing Ca^{2+} Signaling Reverses Alcohol Action on Granule Cell Migration

If ethanol slows granule cell migration by inhibiting Ca^{2+} signaling, enhancing Ca^{2+} release from internal Ca^{2+} stores or Ca^{2+} influxes across the plasma membrane may reduce the effect of ethanol on granule cell migration. To test this possibility, (1) caffeine, which increases internal Ca^{2+} release through the ryanodine receptors, (2) *N*-methyl-*D*-aspartate (NMDA) and (3) nicotine, which both induce Ca^{2+} influxes through the NMDA type glutamate receptors and the nicotinic acetylcholine receptors, are applied with ethanol. Intoxicating levels of ethanol have been reported to alter the activity of these receptors (Narahashi et al. 1999; Kumada et al., 2006). In the absence of ethanol, the addition of nicotine or caffeine to the culture medium does not appreciably change the speed of granule cell migration, whereas addition of NMDA significantly increases the speed of migration (Fig. 182.5). Interestingly, when caffeine or NMDA is added to the culture medium with ethanol, the effects of ethanol on the speed of granule cell migration are noticeably reduced at all dose levels (25–100 mM) (Fig. 182.5). In contrast, when nicotine is added to the culture medium with low doses (25 and 50 mM) of ethanol, nicotine has little effect on the rate of migration (Fig. 182.5). In the presence of a high dose (100 mM) of ethanol, the application of nicotine significantly amplifies the effects of ethanol on granule cell migration (Fig. 182.5). These results suggest that ethanol affects the migration of granule cells by altering multiple and distinct components of Ca^{2+} signaling (Kumada et al. 2006). Furthermore, these results demonstrate that the action of ethanol may be ameliorated by controlling Ca^{2+} signaling.
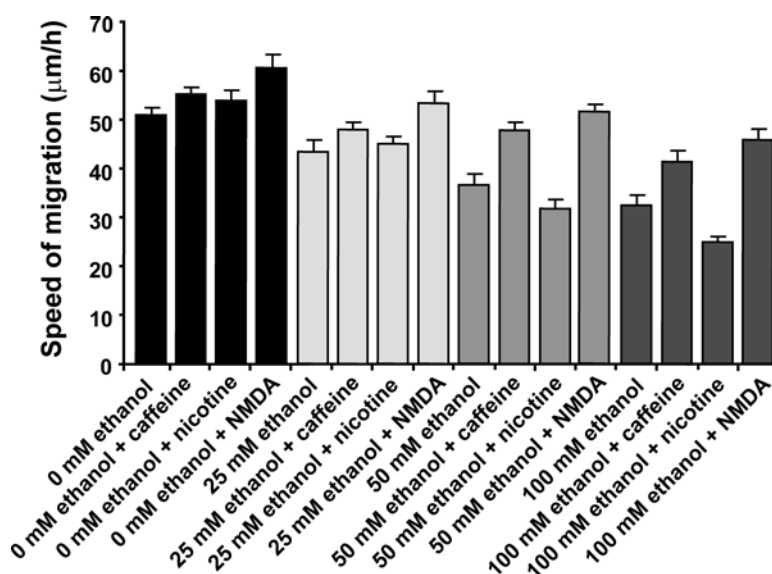
Fig. 182.5 Alterations of the Ca^{2+} signaling change the effect of ethanol on granule cell migration. An application of caffeine (1 mM), nicotine (1 μM), and NMDA (30 μM) alters the effects of four different doses (0, 25, 50, and 100 mM) of ethanol on the speed of granule cell migration. Bar is S.D.

182.8 cAMP Signaling Reciprocally Affects Alcohol Action on Granule Cell Migration

Ca^{2+} signaling pathways interact with numerous other signaling systems (Berridge et al. 2003). Among them, cyclic nucleotide pathways, such as those involving cyclic AMP (cAMP) or cyclic GMP (cGMP), are of particular interest, because alterations of these systems affect the motility of various types of cells (Howe et al. 2005; Veltman et al. 2005). Accordingly, the use of the cAMP enzyme immunoassay reveals that intraperitoneal injection of ethanol (5 g/kg body weight) into P10 mice increases cAMP levels but decreases cGMP levels in the cerebellum 1 h after injection (Kumada et al. 2006), suggesting that cAMP and cGMP signaling also play a role in the effects of ethanol on granule cell migration. To test the role of cyclic nucleotide signaling, first, cAMP signaling pathways are stimulated or inhibited. In the absence of ethanol, the stimulation of adenylyl cyclase (AC) with forskolin, which is upstream of cAMP signaling, markedly reduces the speed of granule cell movement; however, the inhibition of protein kinase A (PKA) with PKI, which is downstream of cAMP signaling, markedly increases the speed (Fig. 182.6). Similarly, without ethanol, application of a competitive cAMP agonist, Sp-cAMPS, reduces the speed of granule cell migration, whereas a competitive cAMP antagonist, Rp-cAMPS, increases the speed (Fig. 182.6). These results demonstrate that without ethanol, the stimulation of cAMP signaling slows down granule cell migration, whereas the inhibition of cAMP signaling accelerates migration. Importantly, the inhibition of PKA activity with PKI significantly reduces the effects of 25–50 mM ethanol on the speed of granule cell migration, but fails to change the action of 100 mM ethanol on the migration (Fig. 182.6). Application of Rp-cAMPS completely reverses the effects of 25–100 mM ethanol on the speed of granule cell migration (Fig. 182.6). Moreover, the inhibition of the activity of AC with 9CP-Ade significantly reduces the effects of 100 mM ethanol (Fig. 182.6). In contrast, the stimulation of AC activity with forskolin significantly enhances the effects of 25 mM ethanol on the speed of granule cell migration (Fig. 182.6). These results demonstrate that alcohol action on granule cell migration is highly sensitive
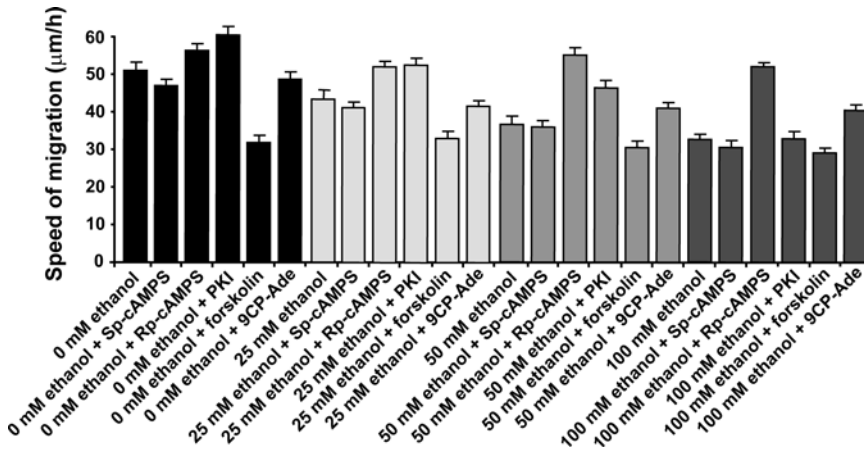
Fig. 182.6 cAMP signaling plays a key role in the ethanol-induced inhibition of granule cell migration. Altering cAMP signaling with Sp-cAMPS (20 μM), Rp-cAMPS (100 μM), PKI (5 μM), forskolin (30 μM), or 9CP-Ade (30 μM) changes the action of four different doses (0, 25, 50, and 100 mM) of ethanol on the speed of granule cell migration

to changes in the activity of cAMP signaling pathways: stimulating cAMP signaling amplifies alcohol action on granule cell migration, whereas inhibiting cAMP signaling reduces action (Kumada et al. 2006). Because the application of ethanol increases cAMP levels, ethanol may slow granule cell migration by stimulating cAMP signaling pathways.

182.9 Stimulation of cGMP Signaling Pathways Reduces Alcohol Action on Granule Cell Migration

In the case of the cGMP signaling pathway, without ethanol, stimulating cGMP signaling with a cGMP analogue, Br-cGMP, slightly increases the speed of granule cell movement, whereas inhibiting cGMP signaling with cGMP antagonist, Rp-8-pCPT-cGMPS, slightly decreases the speed (Fig. 182.7). Furthermore, inhibiting guanylyl cyclase with ODQ does not affect the speed of granule cell migration (Fig. 182.7). Interestingly, when the cGMP signaling pathway is stimulated with Br-cGMP, the effects of ethanol on granule cell migration are markedly reduced at all dose levels (25–100 mM) (Fig. 182.7). In contrast, inhibiting the cGMP signaling pathway with Rp-8-pCPT-cGMPS or ODQ does not change ethanol action on the speed of granule cell migration (Fig. 182.7). Cumulatively, these results demonstrate that cGMP signaling is also targeted by ethanol action in granule cell migration (Kumada et al. 2006). Application of ethanol may slow granule cell migration by reducing the activity of cGMP signaling pathways.

182.10 Alterations of Hydrolysis of cAMP and/or cGMP by PDE Modify Alcohol Action on Granule Cell Migration

If alcohol affects granule cell migration by altering the cAMP and cGMP signaling pathways, one mechanism controlling alcohol action might be the degradation of these cyclic nucleotides. Indeed, the alterations of the activity of cyclic nucleotide phosphodiesterases (PDE), which catalyze the
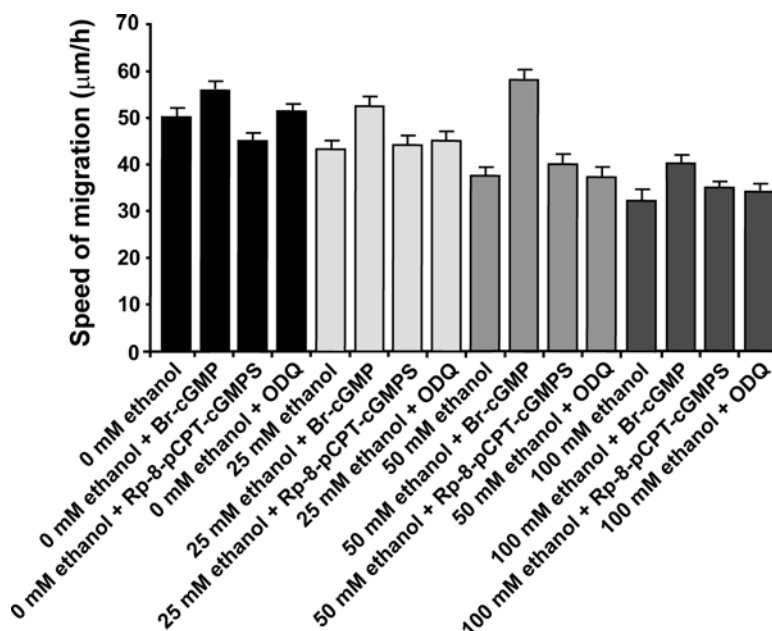
Fig. 182.7 Stimulation of cGMP signaling reduces the effects of ethanol on granule cell migration. Altering cGMP signaling with Br-cGMP (100 μM), Rp-8-pCPT-cGMPS (5 μM), or ODQ (1.5 μM) changes the action of four different doses (0, 25, 50, and 100 mM) of ethanol on the speed of granule cell migration

hydrolysis of cAMP and/or cGMP, change alcohol action on granule cell migration (Kumada et al. 2006). For example, application of EHNA, a PDE2 inhibitor that blocks the cGMP-dependent cleavage of cAMP and cGMP, significantly reduces ethanol action on granule cell migration (Kumada et al. 2006). In contrast, 8-MM-IBMX, a PDE1 inhibitor that blocks the Ca^{2+}/calmodulin-dependent cleavage of cAMP and cGMP, does not significantly change the effects of ethanol on granule cell migration (Kumada et al. 2006). These results indicate that alcohol may affect granule cell migration by altering the amplitude and duration of cyclic nucleotide signals by modifying the activity of a specific PDE family.

182.11 Ca^{2+} Spike-Dependent and Spike-Independent Mechanisms Underlying the Reversal of Alcohol Action on Granule Cell Migration

Changes in the frequency of Ca^{2+} transients positively correlate with changes in the speed of granule cell migration (Komuro and Rakic 1996; Kumada and Komuro 2004). Do caffeine, NMDA, cAMP antagonists, and cGMP agonists reduce alcohol action on granule cell migration by increasing the frequency of Ca^{2+} spikes? The use of a Ca^{2+} indicator dye reveals that without ethanol, the application of NMDA significantly increases the frequency of Ca^{2+} spikes in migrating granule cells, whereas caffeine does not affect the frequency (Fig. 182.8). Importantly, application of NMDA or caffeine markedly reduces the effects of ethanol on the frequency of Ca^{2+} spikes in granule cells (Fig. 182.8). In the case of cAMP signaling pathways, without ethanol, the stimulation of AC activity with forskolin significantly reduces the frequency of Ca^{2+} transients, while the inhibition of cAMP signaling
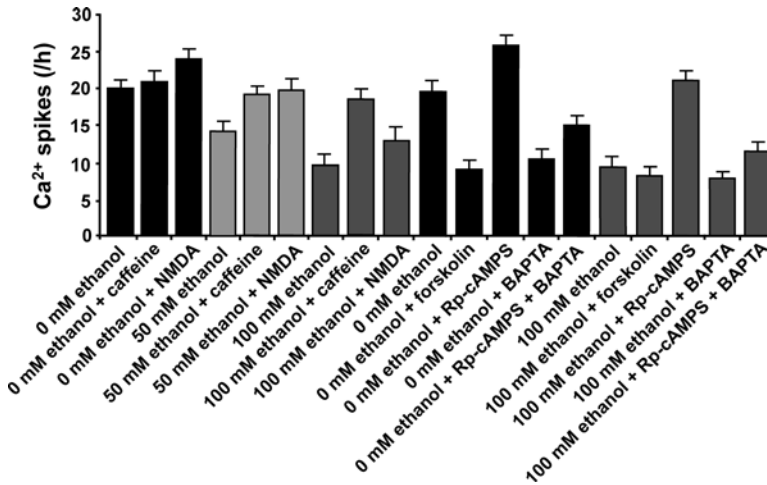
Fig. 182.8 Effects of caffeine, NMDA, forskolin and Rp-cAMPS on the ethanol-induced reduction of the frequency of Ca^{2+} spikes in the granule cell somata. Effects of caffeine (1 mM), NMDA (30 μM), forskolin (30 μM), Rp-cAMPS (100 μM), BAPTA-AM (10 μM), and Rp-cAMPS (100 μM)+BAPTA-AM (10 μM) on the frequency of spontaneous Ca^{2+} spikes in the granule cell somata in the presence and absence of ethanol (0, 50, and 100 mM)

with Rp-cAMPS significantly increases the frequency (Fig. 182.8). It is also noteworthy that the application of Rp-cAMPS completely eliminates the effects of ethanol on the frequency of Ca^{2+} transients (Fig. 182.8). Such effects of Rp-cAMPS on the frequency of Ca^{2+} transients are significantly reduced by a coadministration of an intracellular Ca^{2+} chelator, BAPTA-AM (Fig. 182.8b). In contrast, neither stimulating cGMP signaling with Br-cGMP nor inhibiting the activity of PDE2 with EHNA changes the effects of ethanol on the frequency of Ca^{2+} transients (Kumada et al. 2006). These results indicate that Ca^{2+} signaling and cAMP signaling may reverse alcohol action on granule cell migration by increasing the frequency of Ca^{2+} transients in their somata, whereas cGMP signaling and cyclic nucleotide phosphodiesterases may reduce alcohol action on migration without altering Ca^{2+} transients (Kumada et al. 2006).

182.12   Multiple Downstream Targets Are Involved in Reversing Alcohol Action on Granule Cell Migration

What downstream effectors are involved in the reversal of alcohol action on granule cell migration by altering Ca^{2+}, cAMP, or cGMP signaling? Although these signals interact with large varieties of downstream targets, protein kinase C (PKC), Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII), calcineurin, protein phosphatase 1 (PP1), Rho GTPase, mitogen-activated protein kinase (MAPK), and phosphoinositide 3-kinase (PI_3K) are potential targets. This is because these molecules are involved in controlling the motility of various types of cells. The use of pharmacological tools reveals that the reversal of alcohol action on granule cell migration by controlling the Ca^{2+} and cAMP/cGMP signaling pathways requires the activities of multiple but distinctive downstream effectors. For example, (1) caffeine needs the activities of CaMKII, calcineurin, PP1, Rho GTPase, MAPK and PI_3K; (2) NMDA needs the activities of PKC, CaMKII, calcineurin, PP1, MAPK and PI_3K; (3) Rp-cAMP needs the activities of PKC, CaMKII, calcineurin, PP1, Rho GTPase and PI_3K; (4) Br-cGMP needs the activities of PP1, Rho GTPase, MAPK and PI_3K (Kumada et al. 2006).

182.13 Alcohol Action on Granule Cell Migration In Vivo Is Reversed by Caffeine, Rp-cAMPS and Br-cGMP

The effects of alcohol on granule cell migration in vitro are significantly reduced by controlling the Ca^{2+}, cAMP and cGMP signaling pathways (Kumada et al. 2006). Could controlling the Ca^{2+}, cAMP and cGMP signaling pathways also reduce the effects of alcohol on granule cell migration in vivo? A single intraperitoneal injection of ethanol (5 g/kg body weight) into P10 mice raises blood ethanol levels to approximately 80 mM (equivalent to blood ethanol level <400 mg/dL) within 1 h after injection (Kumada et al. 2006), and decreases both the average distance of BrdU-labeled granule cells from the EGL-ML border and the number of BrdU-labeled granule cells in the ML, PCL, and IGL (Fig. 182.9a and b). These results demonstrate that a single injection of ethanol prevents granule cells from entering the ML and slows radial migration in the ML, PCL, and IGL (Kumada et al. 2006).

Most importantly, the injections of caffeine (2 mg/kg body weight), Rp-cAMPS (0.4 mg/kg body weight) or Br-cGMP (0.4 mg/kg body weight) into the subarachnoid space between the skull and the surface of the P10 mouse cerebellum with a single intraperitoneal injection of ethanol (5 g/kg body weight) completely reverses the effects of ethanol on granule cell migration in vivo (Fig. 182.9a and b). In contrast, the administration of NMDA (more than 0.01 mg/kg body weight) into the subarachnoid space between the skull and the surface of the cerebellum does not reduce the effect of ethanol on granule cell migration in vivo (Fig. 182.9 a and b), and often causes the death of injected pups, possibly from neurotoxic effects of high doses of NMDA. These results demonstrate that the effects of alcohol on granule cell migration in vivo can be reduced by controlling the Ca^{2+}, cAMP and cGMP signaling pathways (Kumada et al. 2006).
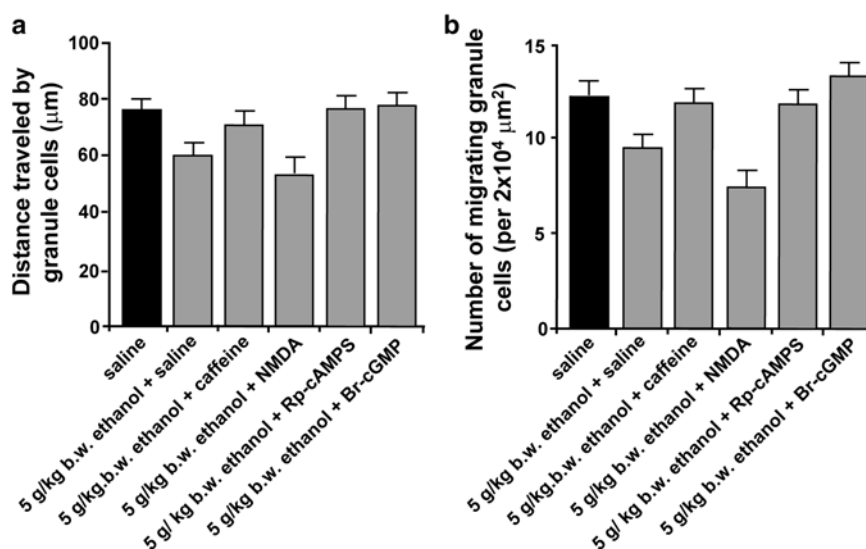
Fig. 182.9 Effects of ethanol on granule cell migration in vivo are reversed by an administration of caffeine, Rp-cAMPS and Br-cGMP. (**a** and **b**) The effects of the injection of 5 μl of saline, caffeine (2 mg/kg body weight), NMDA (0.01 mg/kg body weight), Rp-cAMPS (0.4 mg/kg body weight), and Br-cGMP (0.4 mg/kg body weight) into the subarachnoid space between the skull and the surface of the cerebellum of P10 mice on the ethanol (5 g/kg body weight)-induced changes in (**a**) the distance of the BrdU-labeled granule cells from the EGL-ML borders and (**b**) the number of BrdU-labeled cells in the ML, PCL, and IGL. Bar is S.D. P9 mice were injected intraperitoneally with 5-bromo-2'-deoxy-uridine (BrdU, 50 mg/kg body weight). One day after BrdU injection (at P10), mice were injected with saline, caffeine, NMDA, Rp-cAMPS, or Br-cGMP with or without ethanol injection (5 g/kg body weight, 25%, v/v mixed in saline). Two days after BrdU injection (at P11), mice are euthanized. The distribution of BrdU-labeled granule cells in the ML, PCL, and IGL was examined

182.14 Applications to Other Areas of Health and Disease

Recent studies reveal that Ca^{2+} signaling and cyclic nucleotide signaling are the central targets of alcohol action in neuronal cell migration. These results suggest two new directions of research regarding how diets, including alcohol, affect the development of brain, especially the migration of immature neurons. One direction is to determine what kinds of food worsen or ameliorate the effect of alcohol on neuronal cell migration in the developing brain. For example, drinking coffee or tea may reduce the effects of alcohol on neuronal cell migration because caffeine reduces the effect of alcohol on granule cell migration. Having foods or drinks which stimulate the Ca^{2+} and cGMP signaling pathways or inhibit the cAMP signaling pathways in immature neurons may ameliorate the effect of alcohol on neuronal cell migration, leading to the normal development of the fetal brain.

The other direction is to determine the potential risk of foods and drinks in influencing the migration of immature neurons. For example, foods which contain chemicals that inhibit Ca^{2+} release from intracellular Ca^{2+} stores of immature neurons may inhibit the migration of immature neurons. Likewise, foods which contain chemicals that stimulate the cAMP signaling pathways, such as AC or PKA, may slow down neuronal cell migration, leading to ectopic neurons in the brain.

In conclusion, elucidating the mechanisms underlying the alcohol-induced abnormal migration of immature neurons helps us to determine whether and how diets play a role in establishing neuronal cytoarchitecture and function in the developing brain by controlling neuronal cell migration.

182.15 Key Points of Cellular Mechanisms Underlying the Alcohol-Induced Inhibition of Neuronal Cell Migration

1. Recent studies suggest the involvement of the Ca^{2+}-PKC, cAMP-PKA, and cGMP-PKG signaling pathways in the alcohol-induced impairment of granule cell migration (Kumada et al. 2006, 2007; Jiang et al. 2008). These three signaling pathways interact with each other (schematically shown in Fig. 182.10). For example, the activity of adenylate cyclase 7 (AC7) is modified by PKC, and alcohol potentiates AC7 activity by altering the activity of PKCδ. The stimulation of PKA and PKG enhances the activity of voltage-dependent N-type and L-type Ca^{2+} channels, which in turn affects the Ca^{2+} signaling pathway. The activation of cAMP signaling pathways alters internal Ca^{2+} release through PKA-mediated phosphorylation of inositol 1,4,5-triphosphate receptors and ryanodine receptors. Moreover, the activity of PKA regulates NMDA receptor activity through an interaction with A-kinase anchoring protein 79. Therefore, it may be worth examining whether and how the interactions between the cAMP-PKA, Ca^{2+}-PKC, and cGMP-PKG signaling pathways play roles in controlling alcohol action on granule cell migration.
2. Alcohol also directly and indirectly induces alterations in the activity of other signaling molecules (such as Rho GTPase, MAPK/ERK). There is a functional link between the activity of Rho GTPase and the activities of Ca^{2+}- and PKA signaling. The changes in intracellular Ca^{2+} levels regulate Rho GTPase activity in various types of cells, although how the changes in Ca^{2+} levels modulate Rho GTPase activity is essentially unclear. Furthermore, cAMP/PKA is involved in controlling cell migration and cytoskeletal organization via activation of Rho GTPase. Interestingly, alcohol decreases the activity of MAPK/Erk in immature neurons. The reduction of MAPK/Erk activity may be involved in the alcohol-induced impairment of granule cell migration. This is because the reduction of phosphorylated Erk1 and Erk2 by inhibition of mitogen-activated protein kinase inhibits neurite outgrowth in cerebellar granule cells. Moreover, PKC and PKA alter the phosphorylation of Erk. Whether alcohol impairs granule cell migration via altering the activity of Rho GTPase and/or MAPK/Erk remains to be examined.
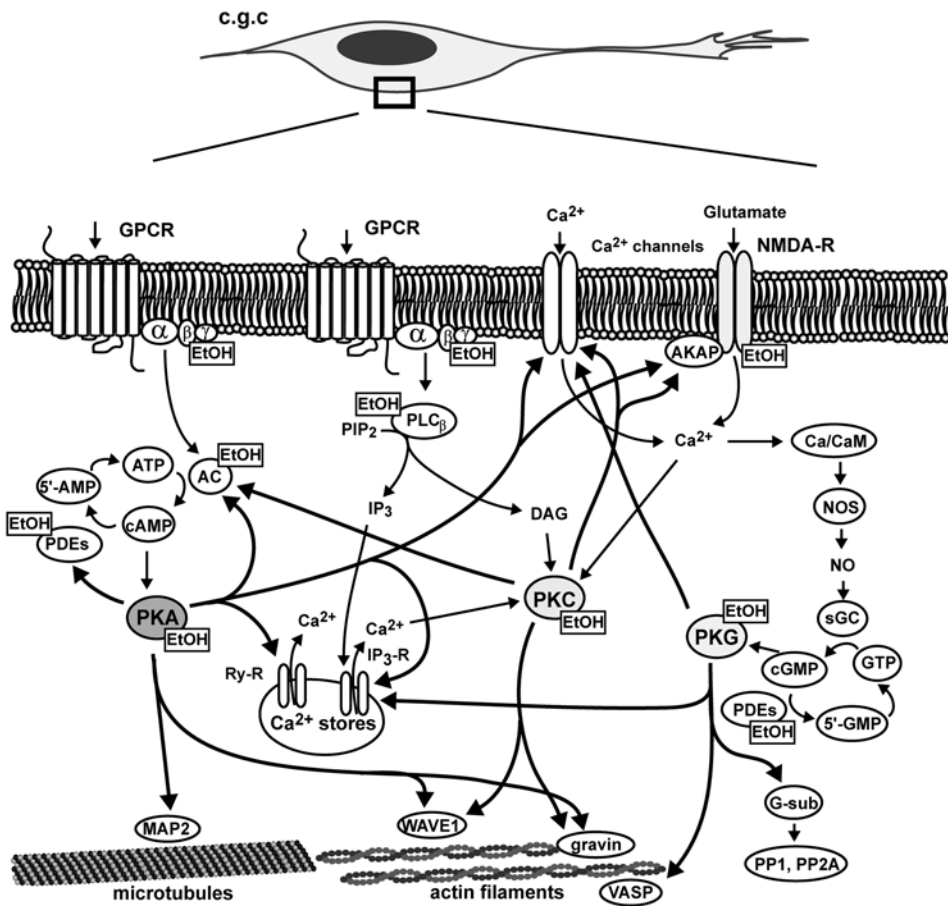
Fig. 182.10 Schematic drawing showing how ethanol affects the cAMP-PKA, Ca^{2+}-PKC, and cGMP-PKG signaling pathway in migrating granule cells. Abbreviation: *c.g.c.* cerebellar granule cells, *GPCR* G-protein coupled receptors, *NOS* nitric oxide synthase, *NO* nitric oxide, *sGC* soluble guanylyl cyclase

Summary Points

- Alcohol exposure inhibits the migration of cerebellar granule cells in vitro as well as in vivo.
- Alcohol exposure inhibits Ca^{2+} spikes in cerebellar granule cells.
- Alcohol exposure reduces intracellular cGMP levels of cerebellar granule cells but increases cAMP levels.
- Ca^{2+} signaling and cyclic nucleotide signaling are the central targets of alcohol action in neuronal cell migration. For example, stimulating Ca^{2+} and cGMP signaling or inhibiting cAMP signaling completely reverses the action of alcohol on cerebellar granule cell migration in vitro as well as in vivo.
- Aberrant migration of immature neurons in the fetal brain caused by maternal alcohol consumption may be corrected by controlling the activity of Ca^{2+} signaling and cyclic nucleotide signaling pathways.

Definitions and Explanations

Fetal alcohol syndrome: Fetal alcohol syndrome refers to a wide range of neuronal and extraneuronal anomalies that occurs in infants born to chronically alcoholic women.

Neuronal cell migration: In the developing brain, immature neurons migrate from their birthplace to their final destination. This active movement of immature neurons is essential for the formation of neuronal cytoarchitecture and proper differentiation. Excitatory neurons and inhibitory neurons originate from different regions of the brain, and exhibit different modes of migration.

Cerebellar granule cells: Cerebellar granule cells are glutamatergic excitatory interneurons, and the most abundant type of neurons in the mammalian brain. They receive synaptic input from the mossy fibers and Golgi cell axons, and send synaptic output to Purkinje cells, stellate cells, basket cells and Golgi cells.

Ca^{2+} spikes: Ca^{2+} spikes are transient increases of the intracellular Ca^{2+} levels of cells. The average frequency of Ca^{2+} spikes of migrating granule cells are 10–20 per hour. Alterations of frequency of Ca^{2+} spikes affect the speed of granule cell migration.

Speed of migration: Speed of migration is calculated by the total distance traveled by granule cells divided by the period of observation during the entire time-lapse session.

Key Facts of Neurological Features of Fetal Alcohol Syndrome (FAS)

1. FAS is one of the most common causes of mental retardation worldwide.
2. Microcephaly is present in nearly all cases of FAS.
3. Delayed neurologic development is in approximately 90% of cases of FAS.
4. Defects of speech and language development are evident in FAS.
5. The severity of the mental deficiency in FAS correlates most closely with the severity of the dysmorphic features. In one series, infants with the most severe dysmorphic manifestations of FAS had a mean IQ of 55, those with moderate manifestations had a mean IQ of 68, and those with mild manifestations had a mean IQ of 82.
6. Hypoplasias of the corpus callosum, the optic nerve and the cerebellum as well as hydrocephalus and abnormalities of the corticospinal tracts are common in FAS.

References

Bauer-Moffet C, Altman J. Expl Neurol. 1975;48:378–82.

Berridge MJ, Bootman MD, Roderick HL. Nat Rev Mol Cell Biol. 2003;4:517–29.

Borges S, Lewis PD. Brain Res. 1983;271:388–91.

Clarren SK, Smith DW. N Engl J Med. 1978;298:1063–7.

Clarren SK, Alvord EC, Sumi SM. J Pediatr. 1978;92:64–7.

Clarren SK, Astley SJ, Bowden DM, Lai H, Milam AH, Rudeen PK, Shoemaker WJ. Alcohol Clin Exp Res. 1990;14:674–83.

Coffin JM, Baroody S, Schneider K, O'Neill J. Cortex. 2005;41:389–98.

Committee on Substance Abuse. 1993;91:1004–6.

Coulter CL, Leech RW, Schaefer GB, Scheithauer BW, Brumback RA. Arch Neurol. 1993;50:771–5.

Dikranian K, Qin YQ, Labruyere J, Nemmers B, Olney JW. Dev Brain Res. 2005;155:1–13.

Goodlett CR, Horn KH, Zhou FC. Exp Biol Med. 2005;230:394–406.

Guerri C. Neurotoxicol Res. 2002;4:327–35.

Howe AK, Baldor LC, Hogan BP. Proc Natl Acad Sci USA. 2005;102:14320–5.

Jiang Y, Kumada T, Cameron DB, Komuro H. Dev Neurosci. 2008;30:7–23.

Jones DG. Prog Neurobiol. 1988;31:171–97.

Jones KL, Smith DW. Lancet. 1973;2:999–1001.

Komuro H, Kumada T. Cell Calcium 2005;37:387–93.

Komuro H, Rakic P. 1992;257:806–9.

Komuro H, Rakic P. Science. 1993;260:95–7.

Komuro H, Rakic P. J Neurosci. 1995;15:1110–20.

Komuro H, Rakic P. Neuron. 1996;17:275–85.

Komuro H, Rakic P. J Neurosci. 1998a;18:1478–90.

Komuro H, Rakic P. J Neurobiol. 1998b;37:110–30.

Komuro H, Yacubova E. Cell Mol Life Sci. 2003;60:1084–98.

Komuro H, Yacubova E, Yacubova E, Rakic P. J Neurosci. 2001;21:527–40.

Kornguth SE, Rutledge JJ, Sunderland E, Siegel F, Carlson I, Smollens J, Juhl U, Young B. Brain Res. 1979; 177:347–60.

Kotkoskie LA, Norton S. Alcohol Clin Exp Res. 1988;12:831–6.

Kumada T, Komuro H. Proc Natl Acad Sci USA. 2004;101:8479–84.

Kumada T, Lakshmana ML, Komuro H. J Neurosci. 2006;26:742–56.

Kumada T, Jiang Y, Cameron DB, Komuro H. J Neurosci Res. 2007;85:465–70.

Kumada T, Jiang Y, Kawanami A, Cameron DB, Komuro H. Dev Biol. 2009;326:237–49.

Lemoine P, Harousseau H, Borteyru JP, Menuet JC. Ther Drug Monit. 2003;25:132–6.

Manzardo AM, Penick EC, Knop J, Nickel EJ, Hall S, Jensen P, Gabrielli WF Jr. Alcohol Clin Exp Res. 2005;29:353–7.

Marcus JC. Neuropediatrics. 1987;18:158–60.

Miller MW. Science. 1986;233:1308–11.

Miller MW. Alcohol Clin Exp Res. 1993;17:304–14.

Narahashi T, Aistrup GL, Marszalec, Nagata K. Neurochem Int. 1999;35:131–41.

Peiffer J, Majewski F, Fischbach H, Bierich JR, Volk B. J Neurol Sci. 1979;41:125–37.

Peoples RW, Li C, Weight FF. Annu Rev Pharmacol Toxicol. 1996;36:185–201.

Riley EP, McGee CL. Exp Biol Med. 2005;230:357–65.

Sakata-Haga H, Sawada K, Hisano S, Fukui Y. Acta Neuropathol. 2001;102:36–40.

Shetty AK, Phillips DE. J Comp Neurol. 1992;321:19–32.

Siegenthaler JA, Miller MW. 2004;14:791–802.

Sokol RJ, Delaney-Black V, Nordstrom B. JAMA. 2003;290:2996–9.

Veltman DM, Roelofs J, Engel R, Visser AJ, Van Haastert PJ. Mol Biol Cell. 2005;16:976–83.

Walter HJ, Messing RO. Neurochem Int. 1999;35:95–101.

West JR, Chen WJ, Pantazis NJ. Metab Brain Dis. 1994;9:291–322.

Wisniewski K, Damabska M, Sher JH, Qazi Q. Neuropediatrics. 1983;14:197–205.

Yacubova E, Komuro H. J Neurosci. 2002;22:5966–81.

Yacubova E, Komuro H. Cell Biochem Biophys. 2003;37:213–34.

Chapter 183
Folate and the Effects of Prenatal Alcohol on the Brain

Yajun Xu and Jie Zhao

Abbreviations

BDNF	Brain-derived neurotrophic factor
BRFSS	Behavioral Risk Factor Surveillance System
CNS	Central nervous system
DNA	Deoxyribonucleic acid
dUMP	Deoxidized uridine monophosphate
dTMP	Deoxidized thymidine monophosphate
FAD	Flavine adenine dinucleotide
MS	Methionine synthetase
MTHF	Methyltetrahydrofolate
MTHFR	Methylenetetrahydrofolate reductase
RBC	Red blood cell
RNI	Recommended nutrient intake
RNA	Ribonucleic acid
SAH	S-adenosyl homocysteine
SAM	S-adenosyl methionine
THF	Tetrahydrofolate
TS	Thymidylate synthetase
UNG	Uracil DNA glycosylase
VB_{12}	Vitamin B_{12}

183.1 Introduction

Alcohol consumption during pregnancy can cause a wide array of disorders in the fetal brain, from subtle changes in intelligence to profound mental retardation (Sharpe et al. 2004). These effects can be manifested as severe damage in learning capabilities or impaired adaptation abilities for their environments. Prenatal alcohol exposure has become one of the leading causes of mental retardation in the Western world (Green 2007). On the severe end of the disorder spectrum is fetal alcohol syndrome

Y. Xu (✉)
Department of Nutrition and Food Hygiene, School of Public Health, Peking University
Health Science Center, No.38 Xue Yuan Road, Hai Dian District, Beijing 100191, China
e-mail: xuyajun@bjmu.edu.cn

(Sharpe et al. 2004), affecting from 1 to 7 per 1,000 live-born infants (Niccols 2007). The impairments in this syndrome are irreversible, therefore most people with fetal alcohol syndrome are not able to live independently (Sharpe et al. 2004), which causes a heavy load for their families and society.

Much effort has been made to prevent fetal alcohol syndrome, especially in western countries. In addition to avoiding drinking, other measures have also proved effective, such as folate supplementation. In this review, we focus on the impairment effects of prenatal alcohol exposure on the fetal brain and the protective effects of folate.

183.2 Prenatal Alcohol on Fetal Brain Development

183.2.1 Prenatal Alcohol Exposure

Alcohol is popular with people and there is no exception with women at the ages of childbearing. Recent data from the 2002 Behavioral Risk Factor Surveillance System (BRFSS) showed that more than half of women of childbearing age reported drinking alcohol, including an estimated 12.4% who reported binge drinking, which can be interpreted as no less than five drinks in the past month on any occasion (Centers for Disease Control and Prevention 2004). Alcohol is easily absorbed by stomach and intestines and quickly reaches the tissues through the blood circulation. The alcohol that mothers intake can transit the placenta into the fetus, which gives the infants exposure to alcohol before they are born. This is called prenatal alcohol exposure. Alcohol is a toxic agent which can cause oxidative stress on many embryonic tissues, especially the central nervous system (CNS), and is therefore a potent teratogen.

Although many studies have associated maternal alcohol consumption with birth defects, no definitive level of ingestion has been established as the threshold level beyond which congenital anomalies will result. Moreover, the perceived safety level of alcohol consumption during pregnancy has been lowered continuously as further studies have been conducted. Complete abstinence during pregnancy is recommended, because alcohol consumption in each trimester has been associated with abnormalities, and the lowest innocuous dose of alcohol is still not known.

183.2.2 Brain Malformation and Dysfunctions Caused by Prenatal Alcohol Exposure

The brain is one of the most susceptible organs to prenatal alcohol exposure. Fetuses exposed to alcohol during development can be born as children with a wide array of brain disorders, from subtle changes in intelligence to profound mental retardation (Sharpe et al. 2004), which can be understood as severe damage in learning capabilities or impaired adaptation abilities for their environments. Prenatal alcohol exposure has been previously reported to result in behavioral and cognitive deficits that continue into adulthood. These deficits are often manifested by poor performance on higher-order cognitive motor tasks, difficulties in maintaining postural balance, slower reaction times, and deficits in fine motor performance. The most severe disorder is called fetal alcohol syndrome, which is the sum of conditions that result from prenatal alcohol exposure, including microcephaly (defined as reduced brain weight relative to body weight), brain malformation and the impairment of behavior, intelligence, and cognition.

The mechanisms of brain damage induced by prenatal alcohol exposure are still not so clear. There are many hypotheses regarding this, such as alterations of neurotransmitters and receptors, brain-derived neurotrophic factor (BDNF), CNS cells and expressions of cell factors. In our researches, we found that the maturation of mitochondria in embryonic brain was affected by prenatal alcohol exposure (Xu et al. 2005a), and also that the expression of some of the mitochondrial protein was changed (Xu et al. 2005b), implying that drinking during pregnancy could further affect the oxidative phosphorylation function of mitochondrion, resulting in the lack of energy in fetal cerebral cells and finally the retardation of fetal cerebral development. As the fetal mice we selected were all without apparent brain malformations, our results suggested that the development of inner tissues may be disturbed even when the fetus seemed normal when born, and this is consistent with the clinical condition of children with fetal alcohol syndrome, most of whom have no defects in appearance, but have impairment of behavior when they are grown up.

183.3 Folate and Its Role in Human Health

183.3.1 Folate and Folic Acid

Folate is a water-soluble B-vitamin, also known as Vitamin B_9. Folate gets its name from the Latin word "folium" for leaf. In 1931, a researcher named Lucy Wills demonstrated that anemia in pregnancy could be corrected by using a yeast extract. Folate was identified as the corrective substance in yeast extract in the late 1930s, and was extracted from spinach leaves in 1941.

The name "folic acid" is widely acknowledged today, so what's the difference between folate and folic acid? Folate is the natural form of this vitamin existing in food; however folic acid is the man-made form of folate, which is also known as synthetic folic acid and often found in supplements and added to fortified foods. In January 1998, the US Food and Drug Administration introduced mandatory fortification of cereal-grain products with folic acid at a concentration of 140 µg/100 g (Food and Drug Administration 1996). In the UK, the Department of Health proposed fortification of flour with folic acid at 240 µg/100 g flour (Wright et al. 2001).

In fact, the bioavailability of folic acid is higher than that of folate; therefore, the dietary folate equivalent system was established: 1 µg dietary folate equivalent is defined as 1 µg of dietary folate, or 0.6 µg of folic acid supplement. This is reduced to 0.5 µg of folic acid if the supplement is taken on an empty stomach.

183.3.2 Physiological Functions of Folate

Folate is vital in the transferring of single carbon units in our bodies. It is reduced into tetrahydrofolate (THF) in intestinal mucous cells through twice reduction with the help of dihydrofolate reductase before entering the blood. THF is the active form of folate in our body, which can be transformed into methyltetrahydrofolate (MTHF), the carrier of single carbon units.

The metabolism of many substances important for life, including nucleic acid synthesis, amino acid metabolism and protein synthesis, can be affected in this way. Let us take two of the most important and well-accepted conversions, for example. One is that folate acts as a cofactor for enzymes that are essential in deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) synthesis by
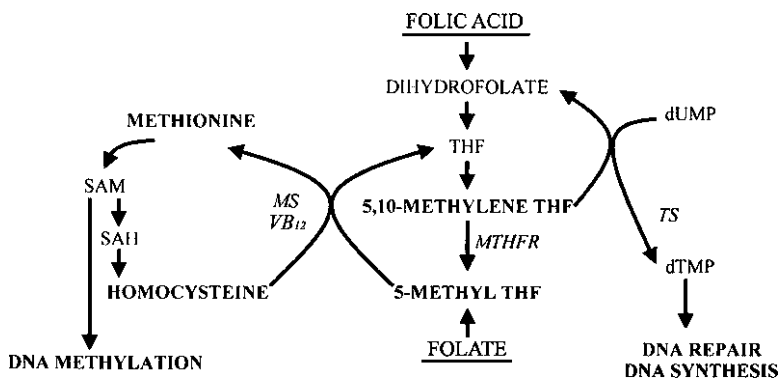
Fig. 183.1 Key functions of folate in human body. The *left part* of the figure illustrates the processes of methionine synthesis and SAM-mediated methylations including DNA methylation, from which we can see that the synthesis of methionine depends on the methyl radical transfer mediated by 5-methyl-THF. The *right part* of the figure demonstrates the process of thymidylate synthesis which is related to DNA repair and synthesis and 5,10-methylene-THF is vital in the process. *dUMP* deoxidized uridine monophosphate, *dTMP* deoxidized thymidine monophosphate

providing single carbon units for the de novo synthesis of nucleotide bases. The other is that folate is required in the transfer of methyl groups in the amino acid methylation cycle, an essential step in the recycling of homocysteine back to methionine (Fig. 183.1). It is notable that the conversion of homocysteine into methiomine with the help of 5-methyl-THF which provides the methyl radical is the only way to make use of 5-methyl-THF in humans.

As the metabolic process of folate is easily saturated, large amounts of unreduced folate exist in the blood and urine when too much folate is ingested. THF, especially 5-methyl-THF, is the main form of existence in the blood. It reaches the liver through the portal circulation and turns into polyglutamate folate to store in the liver. When needed, polyglutamate folate in storage can be released into the bloodstream and decomposed into monoglutamate folate. This binds with the plasma protein and reaches the target tissues that need it for use.

183.3.3 Homocysteine

Homocysteine is derived from *S*-adenosyl homocysteine (SAH) that is formed after *S*-adenosyl methionine (SAM) has donated a methyl group to be used in many methylation reactions (including that of DNA). Homocysteine is then remethylated to methionine by methionine synthetase (MS), which requires Vitamin B_{12} (VB_{12}) as a cofactor, and 5-methyltetrahydrofolate (5-methyl-THF) as substrate (Fig. 183.2). 5-methyl-THF is formed by the action of the flavine adenine dinucleotide (FAD)-dependent enzyme 5,10-methylenetetrahydrofolate reductase (MTHFR). MTHFR is at a crucial metabolic point, directing 5,10-methylenetetrahydrofolate (5,10-methylene-THF) to homocysteine remethylation instead of toward the enzyme thymidylate synthetase (TS) and the creation of thymidylate for DNA de novo synthesis or repair.

Homocysteine cannot turn into methionine if folate is deficient and so the homocysteine concentration in the body rises. Therefore, homocysteinemia can occur and disorders associated with homocysteine excess will be caused. Additionally, Vitamin B_{12} acts as the coenzyme in the reaction mentioned above and folate cannot fully play its role without it.
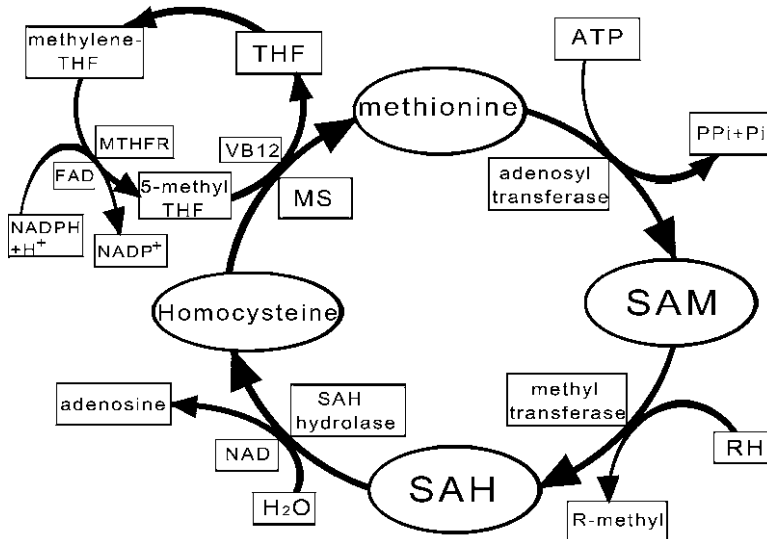
Fig. 183.2 Folate and methionine cycle. *MS* represents methionine synthetase. *RH* in the figure refers to biochemicals that can receive methyl group from SAM. For example, RH can be glycine and it changes to methyl-glycine after getting the methyl group from SAM which is denoted as R-methyl in the figure. The transformation of THF into methylene-THF is catalyzed by methylene-THF reductase which is not shown in the figure because of the lack of space. *VB₁₂* Vitamin B$_{12}$, *MTHFR* methylenetetrahydrofolate reductase

183.3.4 Absorption of Folate and Factors Affecting Its Concentration in the Body

In humans, folate is mainly stored in the liver, which is assumed to contain 50% of the normal total body folate content of 5–20 mg. Folate undergoes substantial enterohepatic recirculation, that is, much of the folate which undergoes biliary excretion is reabsorbed by the small intestine (Weir et al. 1985). However, the efficiency of this reabsorption may be influenced by dietary composition if digestion of foods happens to be occurring concurrently.

Naturally occurring dietary folate has a reduced pteridine ring and a polyglutamate polypeptide that must be hydrolyzed to a monoglutamate form before being absorbed by the intestinal cell. Fully oxidized folic acid is a synthetic form of folate and is found only in food that has been fortified with it. Folic acid is absorbed to a greater degree than the naturally occurring food folate (Johnson 2007). Intracellular folate concentrations are saturable and independent of excess exogenous folate supply and the threshold for intracellular folate accumulations is limited by the folate-binding capacity of the cell (Suh et al. 2001).

The absorption of folic acid can be influenced by a series of factors. For example, chronic alcoholism is often associated with impaired folate status. Intestinal malabsorption is one of the reasons for ethanol-induced folate deficiency. In addition, the use of oral contraceptive agents has been associated with low serum and red blood cell (RBC) folate levels in women 20–44 years of age. The use of anticonvulsant drugs, such as primidone and carbamazepine, also has an impact on tissue folate concentrations in rats (Suh et al. 2001).

183.3.5 Genetic Aspects of Folate Metabolism

As mentioned above, the enzyme MTHFR has received much attention in recent years because a thermolabile enzyme variant inherited as an autosomal recessive trait, later identified as a 677 C→T mutation resulting in an alanine to valine substitution, was found associated with increased plasma homocysteine levels and possible increased risk of cardiovascular disease. The MTHFR enzyme is involved directly in VB_{12}-dependent remethylation of homocysteine to methionine in which it provides the 5-methyl-THF necessary for this methylation. It is a crucial enzyme as it can direct the folate pool towards homocysteine remethylation at the expense of DNA and RNA biosynthesis. MTHFR is also flavin-adenine dinucleotide, a co-enzyme of VB_2 (riboflavin), dependent. The prevalence of the MTHFR 677 C→T variant, which results in an enzyme activity of about 50% of the normal value, and has distinctive thermolability under specific conditions of heat inactivation (Kang et al. 1991), is related to ethnicity: the frequency of homozygosity for the T allele (abnormal TT genotype) is relatively high throughout the world, around 10–15% in the UK, 20–30% in some Italian populations but only a few percent in Afro Americans (Schneider et al. 1998).

183.3.6 The Role of Folate in Reproduction and Development

Folate is necessary for fertility in both men and women. In men, it contributes to spermatogenesis. In women, it contributes to oocyte maturation, implantation and placenta formation. It is most important for women who may become pregnant since it is necessary for the production and maintenance of new cells, especially important during periods of rapid cell division and growth such as the embryonic stage. It has been shown that some kinds of birth defects are closely related to folate deficiency (Czeizel and Dudas 1992; Bailey et al. 2003), such as neural tube defects, congenital heart diseases, cleft lip, palate, etc. (Czeizel and Dudas 1992; Bailey et al. 2003;Cogswell et al. 2003). Among these, the relationship between folate deficiency and neural tube defects was first defined. Neural tube defects are usually separated into two main categories: (1) malformations of the spine (meningomyelocele or spina bifida) and (2) abnormalities of the skull and brain (anencephaly, acrania, and encephalocele). In spina bifida, the fetal spinal column does not close completely during the first month of pregnancy. There is usually nerve damage that causes at least some paralysis of the legs. In anencephaly, much of the brain does not develop. Babies with anencephaly are either stillborn or die shortly after birth. Investigations around the world have indicated that periconceptional supplementation with folic acid is able to decrease the rates of neural tube defects. As a result of this supplementation, a 19% reduction of neural tube defects prevalence occurred (Honein et al. 2001).

Another birth malformation associated with folate is Down's syndrome, which is the most common genetic cause of human mental retardation, with an incidence of approximately 1 in 600–1,000 live births (Zintzaras 2007). Down's syndrome has been linked with the abnormal metabolism of homocysteine, which is led by variants in a critical folate metabolizing enzyme. A thermolabile variant of MTHFR has been described in which a cytosine-to-thymine nucleotide (C677T) occurs, causing relatively reduced enzyme activity.

183.3.7 Folate Deficiency–Related Mental Diseases

Serum levels fall within days when intake is diminished, and as body stores are relatively low, folic acid deficiency can develop within 1–6 months, dependent upon nutritional status and the rate of utilization (Paul et al. 2004).

Folate deficiency and resultant increased homocysteine levels have been linked experimentally and epidemiologically with neurodegenerative conditions like stroke and dementia. Moreover, folate deficiency has been implicated in the pathogenesis of psychiatric disorders, most notably depression (Kronenberg et al. 2008). However, Balk et al. (2006) reported that deficiencies in Vitamins B_1 or folate generally cause neurological dysfunction, and supplementation with B_6, B_{12}, or folate may improve neurocognitive function in animal studies, but their effects are unclear in human studies. Overall, studies do not support an association between B vitamin status and age-related neurocognitive disorders (Balk et al. 2006) but the causal relationship between folic acid deficiency and neural tube defects is widely accepted and that is why mandatory folic acid supplementation is enforced in some countries.

183.3.7.1 Cognitive Impairments

Researchers have shown that low blood folate and raised homocysteine concentrations are associated with poor cognitive function. Folic acid supplementation is beneficial in improving cognitive function (D'Anci and Rosenberg 2004; Das 2008). However, Ellinson et al. (2004) pointed out that the present evidence did not support a correlation between serum VB_{12} or folate and cognitive impairment in people aged over 60 years and there is little evidence to justify treating cognitive impairment with VB_{12} or folate supplementation.

183.3.7.2 Schizophrenia

Psychiatric disorders are common among the elderly. The overall prevalence of depression in the USA is approximately 17% for women and 10% for men, and is increased more than twofold in individuals over the age of 65 (Mattson et al. 2002). The hypothesis that folic acid plays a role in the predisposition toward schizophrenia is biologically plausible, as folate levels have been shown to be involved in neurodevelopmental processes (Picker and Coyle 2005). Folate deficiency and subsequent elevated homocysteine levels increased the risk of schizophrenia, whereas risk was not increased in individuals with low folate levels, but normal homocysteine levels, indicating that the association between folate deficiency and schizophrenia may be caused by the alteration of homocysteine level induced by folate deficiency (Mattson et al. 2002). However, some researchers pointed out that folate deficiency has been associated with schizophrenia in affected patients independent of other factors such as homocysteine. But at the fetal stage, folate deficiency appears to exert its teratogenic effect primarily through elevating plasma homocysteine (Picker and Coyle 2005). Although the mechanism is still unclear and more research is needed to support the results mentioned above; the potential role of maternal folate deficiency and hyperhomocystinemia in the genesis of schizophrenia would extend the range of their known teratogenic effects and folate supplementation may benefit many psychiatric patients (Mattson et al. 2002).

183.3.7.3 Depression

Folate deficiency has been implicated in the pathogenesis of psychiatric disorders, most notably depression (Kronenberg et al. 2008). There is now substantial evidence of a common decrease in serum/red blood cell folate, serum VB_{12} and an increase in plasma homocysteine in patients with depression (Coppen and Bolander-Gouaille 2005). Deficits of both folate and VB_{12} are associated with a greater risk of depression during adulthood (Black 2008). Some studies have confirmed the

link between folate deficiency and depression and have provided evidence for a mechanism involving homocysteinemia and altered methylation reactions (Mattson et al. 2002). Furthermore, the MTHFR C677T polymorphism that impairs the homocysteine metabolism is shown to be overrepresented among depressive patients, which strengthens the association (Coppen and Bolander-Gouaille 2005).

However, another study showed that serum and red blood cell folate levels were associated with depression in younger individuals, but the relationship was less clear in older people (D'Anci and Rosenberg 2004).

A large literature has documented a role for folate in modifying the symptoms of depression (Mattson et al. 2002; Morris 2002). Among depressed patients, higher folate status has been linked to shorter and less frequent, depressive episodes as well as a better antidepressant response, while folate deficiencies may lead to poorer antidepressant treatment outcomes (Mischoulon and Raab 2007). Although it is unclear at present whether low folate status causes depression, antidepressant trials have demonstrated the benefits of higher folate status or folate supplementation relative to decreasing symptoms in depressed patients undergoing antidepressant therapy (Morris 2002).Therefore, it is suggested that oral doses of both folic acid (800 μg daily) and VB_{12} (1 mg daily) should be tried to improve treatment outcomes in depression (Coppen and Bolander-Gouaille 2005)

183.3.8 Possible Mechanism of Folic Acid on Mental Diseases

Black (2008) summed up that disruptions to myelination and inflammatory processes were the two possible mechanisms that associated folic acid or VB_{12} deficiency with abnormal behavior and development in infants. In the meantime, variants of several genes of folate-related metabolic pathways have been found to be significantly associated with the risk of neural tube defects in many studies (De Marco et al. 2006). Kronenberg et al. (2008) showed that whereas folate deficiency alone did not confer a clearly despair-like phenotype, folate-deficient mice lacking uracil DNA glycosylase (UNG) demonstrated significantly increased immobile time and reduced latency to float, indicating that impaired uracil repair was involved in neurodegeneration and neuropsychiatric dysfunction induced by experimental folate deficiency (Table 183.1).

Table 183.1 Key facts of folate and/or folic acid

1. Folate is a water-soluble B-vitamin. It is the natural form of this vitamin existing in food. Folic acid is the man-made form of folate and often found in supplements and added to fortified foods.

2. The bioavailability of folic acid is higher than that of folate; therefore, a dietary folate equivalent system was established.

3. The metabolisms of many processes important for life, including nucleic acid synthesis, amino acid metabolism and protein synthesis, can be affected by folate.

4. Folate is necessary for fertility in both men and women. In men, it contributes to spermatogenesis. In women, it contributes to oocyte maturation, implantation and placenta formation.

5. The absorption of folate/folic acid can be influenced by a series of factors, such as chronic alcoholism.

6. Maternal folate deficiency is related to fetal birth defects, especially neural tube defects.

7. Folate deficiency and resultant increased homocysteine levels have been linked with the pathogenesis of psychiatric disorders such as depression, and neurodegenerative conditions like stroke and dementia.

This table lists the key facts of folate/folic acid including the difference between folate and folic acid, roles of folate and/or folic acid in human metabolism, reproduction and development, and metal disorders related to folate/folic acid deficiency

183.4 Folic Acid Supplementation on Prenatal Alcohol Exposure Impairments

183.4.1 Folic Acid and Prenatal Alcohol Exposure

Investigations (Muldoon and McMartin 1994; Halsted et al. 2002) have indicated that alcohol exposure impairs folate absorption by inhibiting the expression of reduced folate carrier and decreasing the hepatic uptake and renal conservation of circulating folate, resulting in decreased serum folate levels. One of our studies (Xu et al. 2006a) has also shown that alcohol exposure during pregnancy caused a significant increase of maternal serum homocysteine, which might be responsible for brain malformations related to prenatal-alcohol-exposure, and folic acid supplementation during the organogenesis period showed protective effects against prenatal alcohol exposure. Our study (Xu et al. 2008) also indicated that folic acid supplementation could reverse the expression of alcohol-altered proteins related to energy production (some of which were mitochondria origin), signaling pathways and protein translation in the fetal brain, which were all important for embryonic development. This might explain the probable pathway through which folic acid functioned against alcohol's teratogenic action on fetal brain. Another study (Wang et al. 2009) demonstrated a suppression of ethanol-induced teratogenesis by folic acid supplementation, accompanied by a down-regulation of miR-10a expression and miR-10a has been found to be significantly up-regulated in the fetal mouse brain after prenatal ethanol exposure in this study.

As we mentioned above, folic acid plays an important part in the amino acid methylation cycle, an essential step in the recycling of homocysteine back to methionine as well as DNA and RNA synthesis because of its role in the transfer of single carbon units. The requirements of nucleic acid and protein synthesis are at their peak during the stages of embryogenesis and rapid fetal growth, so the demand for folic acid increases during pregnancy. However, alcohol ingestion inhibits folic acid absorption and oxidizes the pteridine ring of folic acid which may lead to folic acid deficiency (Suh et al. 2001).When folic acid deficiency reaches a certain degree, inhibition of the methylation cycle might impair the synthesis and function of specific proteins. This may contribute to the decreased expression of some proteins including the mitochondrial proteins found in our research (Xu et al. 2008). However, when enough folic acid is supplemented, the organic nucleic acid and protein synthesis can return to physiologic levels, therefore the malformation and dysfunction caused by alcohol can be reversed. In addition, folic acid may also play a role in the regulation of gene expression to change the expressions of enzymes or other proteins vital in brain development, which are altered by prenatal alcohol exposure (Wang et al. 2009). Also, folic acid deficiency can induce the increased level of homocysteine which can also be the cause of damage. Animal experiments showed that concurrent folic acid administration prevented homocysteine effects, possibly by its antioxidant and DNA stability maintenance properties (Matté et al. 2009) (Fig. 183.3).

183.4.2 Combined Effect of Folic Acid and VB_{12} on Prenatal Alcohol Exposure

An interesting phenomenon found in our studies (Xu et al. 2006a, b) was that folic acid and VB_{12} together could protect mouse embryos against ethanol-induced development toxicity better than folic acid alone at relatively low concentrations, both in vitro and in vivo. Since folic acid and VB_{12} are metabolically interdependent (see Fig. 183.1), additional supplementation of VB_{12} may enhance
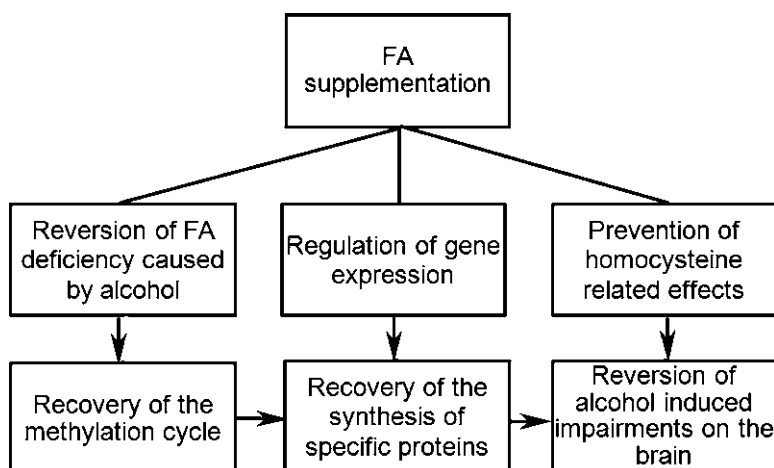
Fig. 183.3 Possible mechanisms of the antagonism of folic acid supplementation against prenatal alcohol exposure induced impairments. Three possible mechanisms of the antagonism of folic acid supplementation against prenatal alcohol exposure induced impairments which are mentioned in the text are illustrated in the figure. However, the exact mechanisms are not so clear at present

the utilization and biologic effects of folic acid. As a result, the embryonic DNA, RNA and protein synthesis might be enhanced, which could better make up the losses caused by ethanol toxicity. Also, the process of DNA methylation might be enhanced, which could suppress the expression of mutated genes caused by ethanol exposure, thereby decreasing the incidence of malformations.

183.5 The Recommended Intake of Folate and Food Resources

183.5.1 The Recommended Intake of Folate

Since the discovery of the link between insufficient folate and neural tube defects, governments and health organizations worldwide have made recommendations concerning folic acid supplementation for women intending to become pregnant. The recommended nutrient intake (RNI) for men and women from the age of 14 years to over 70 years is 400 µg dietary folate equivalent, which is equal to 400 µg of folate in natural foods or about 240 µg of folic acid in fortified foods (Johnson 2007). For women planning to conceive or those already pregnant and lactating mothers, the RNI is 600 and 500 µg dietary folate equivalent, respectively (Table 183.2). There has been some concern about the interaction between VB_{12} and folic acid. Folic acid supplements can correct the anemia associated with VB_{12} deficiency. Unfortunately, folic acid will not correct changes in the nervous system that result from VB_{12} deficiency. Permanent nerve damage could theoretically occur if VB_{12} deficiency is not treated. Therefore, intake of supplemental folic acid should not exceed 1,000 micrograms (1,000 µg or 1 mg) for adults aged 19 years and older, and 800 µg for pregnant and lactating women less than 18 years of age per day to prevent folic acid from masking symptoms of VB_{12} deficiency.

However, women who have had one pregnancy affected by a birth defect of the brain or spine are recommended to take 4,000 µg (4.0 mg) of folic acid each day at least 1 month before getting pregnant and during the first few months of being pregnant (Table 183.2). This is ten times the amount of

Table 183.2 Recommended intake of folate for different subjects

Subjects	RNI (µg dietary folate equivalent)
People from 14 to over 70 years old	400
Women planning to conceive or already pregnant	600
Lactating mothers	500
Women who had one pregnancy affected by a birth defect of the brain or spine	4,000 micrograms of folic acid each day at least 1 month before getting pregnant and during the first few months of being pregnant

Dietary folate equivalent is defined as 1 µg of dietary folate, or 0.6 µg of folic acid supplement. Folic acid listed in the last row refers to folic acid supplements

Table 183.3 Folate content in common food (µg/100 g)

Food	Folate content
Liver (pig)	236.4
Liver (chicken)	80.0
Spinach	347.0
Red amaranth	330.6
Tomato	132.1
Lettuce	49.6
Badish	22.5
Bean curd	66.1
Dried bean curd	57.9
Citrus	52.9
Banana	29.7
Strawberry	33.3
Peanut	104.9
Rice	32.7
Flour	24.8

This table lists some foods commonly available in different countries or areas. There is usually a slight difference in folate content in the listed food because the values can be influenced by food varieties, growing areas, seasons, measuring methods and so on

RNI for the general population. Studies have shown that the risk of neural tube defects is significantly reduced when supplemental folic acid is consumed in addition to a healthy diet prior to and during the first month following conception (Honein et al. 2001; Picker and Coyle 2005).

183.5.2 Food Resources of Folate

Unlike most bacteria and yeast, mammals cannot synthesize folate in vivo, and therefore require folate in the diet (Suh et al. 2001). Luckily, folate exists widely in foods from plants and animals. It is richly present in green leafy vegetables such as spinach, turnip greens, lettuces, dried beans and peas, citrus fruits, fortified cereal products, sunflower seeds, and certain other fruits and vegetables. Liver and liver products also contain high amounts of folate, as does baker's yeast (Table 183.3).

183.5.3 Folate Loss in Storage and Cooking Process

Folate is easily broken down by heat, light, and acid; therefore, it can be lost from foods during storage, preparation, or cooking. Long storage time at high temperatures, boiling the vegetables, washing vegetables after slicing, immersion in water for a long time and heating the leftover dishes repeatedly can all cause great loss of folate in vegetables.

The following will help preserve folate in foods as much as possible:

- Store vegetables and fruits in cool temperatures or in a refrigerator
- Wash vegetables before slicing them
- Cook with high heat for only a short time
- Steam or boil vegetables in a minimal amount of water
- Do not heat leftover dishes repeatedly
- Serve fruits and vegetables raw whenever possible

Of course, the best way to preserve folate in vegetables is to take them raw, but the problem of food hygiene arises at the same time. Folate-fortified foods, such as bread and flour, may meet the needs of both nutrition and food hygiene. Taking folate supplements according to biological need is also an option.

Interestingly, there are some ways to enrich the folate content of some kinds of foods, especially staple foods, which have been adopted in many countries. Studies indicate that the process of fermentation with yeast can somehow increase the total folate content in bread to more than that in the original flour (Osseyi et al. 2001; Kariluoto et al. 2004). Gujska and Majewska (2005) found that for both wheat and rye bread products, there was a 12% and 21% decrease of added folic acid from flour to bread stage, respectively, but there were almost no changes in the total endogenous folate content. This has confirmed some conclusions obtained by earlier studies that folate is produced during the leaving of dough with baker's yeast.

183.6 Supplementation with Folic Acid: Arguments Continue

Supplementation of pregnant human mothers with folate significantly decreases the incidence of developmental defects, including neural tube defects, conotruncal heart defects and cleft lip/palate (Picker and Coyle 2005). The results of Das (2008) suggested that a combination of eicosapentaenoic acid, docosahexenoic acid, arachidonic acid, and folic acid could be of significant benefit in dementia, depression, Alzheimer's disease, and impaired cognitive functions.

One big problem is whether or not we should use folic acid-fortified foods. In the USA and Canada, after folic acid fortification, the estimated total intake is approximately 800 μg/day for those taking multivitamins containing folic acid and this number may be an underestimation (Kim 2007). Although the toxicity of high folate levels in the body is unclear, there are many concerns about it. For one thing, folic acid supplementation and fortification may promote the progression of already existing undiagnosed preneoplastic and neoplastic lesions (Kim 2007). For another, high levels of folic acid may exacerbate the neurological consequences of a VB_{12} deficiency (D'Anci and Rosenberg 2004).

Besides the problem of supplementation amounts, when and how to supplement are also the focus of research. Some researchers (Morris 2002) presented that the greatest effects of folate supplementation occur in those with the lowest folate concentrations and the highest homocysteine levels. The current recommendation is to take extra folate, not just food fortification, through the first trimester of pregnancy, but this recommendation is seriously inadequate if folate and homocysteine are involved in disrupting neurodevelopment during the second trimester (Picker and Coyle 2005).

It has been reported that it may be more effective to supplement with methyltetrahydrofolate, which is the active form of folate and more readily absorbed, for the prevention and treatment of both depression and dementia (Mischoulon and Raab 2007).

To sum this up, the evidence to support supplementation with folic acid is not clear and some scientists are cautious on the subject (Morris 2002). There are still arguments on whether or not to supplement with folic acid during pregnancy or in elderly people, as well as how and when to do it to be beneficial. As a result, more research regarding this is needed.

183.7 Prevention of Prenatal-Alcohol-Exposure-related Abnormalities

Since prevention is of the greatest importance in our lives, current medical guidelines recommend that no alcohol should be consumed over the period of conception and throughout pregnancy (Tough et al. 2006). A study on prenatal alcohol exposure (Abate et al. 2008) also demonstrated that there was no so-called safe dose of alcohol ingestion. Low to moderate levels of prenatal ethanol exposure do not generate evident morphologic or neurobehavioral alterations in the offspring, but they exert a significant impact upon later ethanol-seeking and intake behaviors.

Since there is no safe dose, is there a safe period for drinking alcohol during the pregnancy? The answer is no to either. Although it has been found that prenatal alcohol exposure causes damage to the development of the brain at specific times in both animal studies and epidemiological results, agreement on the precise critical exposure time has not been agreed upon by scientists. The results of a birth cohort study (Sun et al. 2009) have also indicated that the association between prenatal ethanol exposure and the occurrence of some types of seizures reflecting underlying brain dysfunction is only observed from the 11th to the 16th week of gestation. Another review (Guerri et al. 2009) has shown that alcohol affects the embryonic stage of gastrulation and the ontogenetic stages of brain development that occurs in humans from the 7th to the 20th week of gestation. In conclusion, the most sensible behavior is to be far away from alcohol for the whole duration of a pregnancy.

There are still problems concerning alcohol intake in pregnancy. For example, the majority of women reduce alcohol consumption when they realize they are pregnant, but this recognition may not occur until well into the first trimester, potentially impacting embryonic development (Tough et al. 2006). There are also data revealing that a large proportion of women are not changing their drinking behaviors when pregnant, including the average amount of alcohol consumed per occasion while trying to conceive, thus putting their developing child at risk for alcohol exposure during the early stages of embryonic development (Tough et al. 2006).Taking all the problems above into consideration, we can see that the prevention of impairments that prenatal alcohol exposure causes is easier said than done and more attention and efforts are needed to do this.

183.8 Applications to Other Areas of Health and Disease

Supplementation with folic acid may reverse some of the effects of ethanol toxicity on the brain, which has been illustrated in detail above. In fact, the benefits of folic acid supplementation are much broader than that. Folate deficiency in adults can increase the risk of coronary artery disease, stroke, several types of cancers, and possibly Alzheimer's and Parkinson's diseases (Mattson et al. 2002). Folate supplementation may be of benefit for the treatment of these diseases but consensus regarding this has not been reached.

183.8.1 Cancers

Animal models of carcinogenesis have suggested that folate deficiency facilitates cancer formation, according to the results of case-control studies (Mattson et al. 2002). Folate may be helpful for the prevention of breast and cervical cancers. The occurrence of neoplastic processes, such as acute lymphoblastic leukemia in children is also likely to be associated with folate supplementation, but it remains to be confirmed (Eichholzer et al. 2006). Although folate appears to be preventive in the development of new cancers in persons without preexisting premalignant lesions, folic acid supplementation and fortification may promote the progression of already existing, undiagnosed preneoplastic and neoplastic lesions (Cornel et al. 2005; Kim 2007). However, the present research is not conclusive; hence, whether or not folic acid promotes the progression of cancer is still not clear. Long-term follow-up studies are warranted to determine the effect of folic acid on the incidence of cancer and on DNA methylation and other epigenetic regulatory mechanisms (Cornel et al. 2005).

183.8.2 Cardiovascular Disease and Stroke

Folate deficiency may induce increased levels of homocysteine. The association between hyper-homocysteine and atherosclerotic cardiovascular disease has been found in populations with different genetic backgrounds and lifestyles. Possible links between homocysteine metabolism and stroke have been examined and animal studies support a cause–effect relationship between elevated homocysteine levels, vascular pathology and stroke (Mattson et al. 2002). 5-methyltetrahydrofolic acid (5-MTHF), when given intra-arterially, not only improved flow-mediated dilatation without altering plasma homocysteine concentrations but also abolished homocysteine-induced increases in intracellular superoxide generation, thus is beneficial for cardiovascular diseases (Das 2003; Eichholzer et al. 2006).

183.8.3 Multiple Births

The results of research have shown an increase in twinning rates associated with the use of multivitamin supplements containing folic acid. Positive associations may in part be explained by residual confounding of in-vitro fertilization and ovarian stimulation, or by the effect of other vitamins in the multivitamins consumed (Eichholzer et al. 2006). Although the available evidence is not conclusive, a large study from China, which included many young mothers and where the use of ovarian stimulation is not common, did not show an increased risk of twinning after periconceptional folic acid use (Cornel et al. 2005).

183.8.4 Type 2 Diabetes

Studies showed that homocysteine levels are also associated with exacerbation of type 2 diabetes, rheumatoid arthritis and some other vascular events (Mattson et al. 2002). In addition, it is likely that elevated homocysteine levels, which can be induced by folate deficiency, contribute to the various organic pathologies in alcoholics, including liver disease, and cognitive and motor dysfunction (Mattson et al. 2002) (Fig. 183.4).

Fig. 183.4 Applications of folate to other diseases. Although the association between folate and the diseases listed here remains to be confirmed, it provides new insights into the studies of mechanisms and the treatment of these diseases
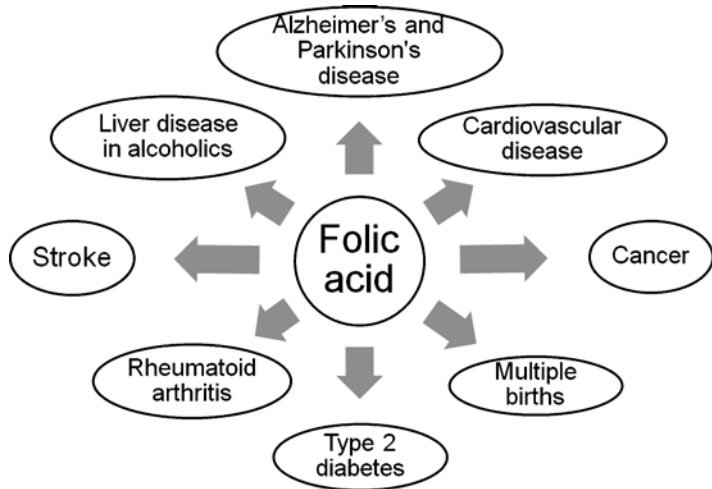
Summary Points

- Alcohol consumption during pregnancy, which is also termed as prenatal alcohol exposure, can cause a wide array of disorders in the fetal brain, from subtle changes in intelligence to profound mental retardation. The mechanisms of prenatal alcohol exposure induced brain damage are still not clear.
- Folate is a water-soluble B-vitamin, which is the natural form of this vitamin existing in food. Folic acid is the man-made form of folate, which is also known as synthetic folic acid and is often found in supplements or added to fortified foods.
- Chronic alcoholism is associated with impaired folate status and excess ethanol intake is often associated with folate deficiency. Folic acid administration during pregnancy shows protective effects against prenatal alcohol exposure induced brain malformation or mental disorders.
- Folate/Folic acid is vital in the transferring of single carbon units in our body, which is important for the metabolism of many substances, including nucleic acid synthesis, amino acid metabolism and protein synthesis. Since folic acid and VB_{12} are metabolically interdependent, additional supplementation of VB_{12} may enhance the utilization and biologic effects of folic acid.
- A dietary folate equivalent system is identified since the bioavailability of folic acid is higher than that of folate. The recommended nutrient intake (RNI) for men and women from the age of 14 years to over 70 years is 400 µg dietary folate equivalent.
- Foods that are rich in folate content are green leafy vegetables, dried beans and peas, citrus fruits, fortified cereal products, sunflower seeds and certain other fruits and vegetables. Liver and liver products also contain high amounts of folate, as does baker's yeast.
- Folate is easily inactivated by heat, light and acid, therefore can be lost from foods during storage, preparation or cooking. However the process of fermentation with yeast can somehow increase total folate content in breads to levels greater than the original flour.

Definitions and Explanations

Fetal alcohol syndrome: the sum of conditions that result from fetal alcohol exposure, including brain malformations and the impairment of behavior, intelligence, cognition, etc.

Mental retardation: severe damage in learning capabilities or adaptation abilities for environments.

Neural tube defects: serious birth defects of brain and/or spine due to the failure of the neural tube to close completely during fetal development, induced by folic acid deficiency, resulting in anencephaly and spina bifida.

Prenatal alcohol exposure: the behavior of drinking during pregnancy inducing alcohol exposure of children before they are born.

Recommended nutrient intake: This value is a goal for individuals; it is the daily dietary intake level that is sufficient to meet the nutritional requirements of 97–98% of all healthy individuals in a population.

Tetrahydrofolate: the active form of folate in the body. Folic acid that we intake is first transformed into tetrahydrofolate before becoming active in the body. A cycle exists between tetrahydrofolate and methyl-tetrahydrofolate, which is the provider of one-carbon units.

References

Abate P, Pueta M, Spear NE, Molina JC. Exp Biol Med (Maywood). 2008;233:139–54.

Bailey LB, Rampersaud GC, Kauwell GP. J Nutr. 2003;133:1961S–8S.

Balk E, Chung M, Raman G, Tatsioni A, Chew P, Ip S, DeVine D, Lau J. Evid Rep Technol Assess. 2006;134:1–161.

Black MM. Food Nutr Bull. 2008;29(2 Suppl):S126–31.

Centers for Disease Control and Prevention (CDC). MMWR Morb Mortal Wkly Rep. 2004;53:1178–81.

Cogswell ME, Weisberg P, Spong C. J Nutr. 2003;133 (5 Suppl. 2):1722S–31S.

Cornel MC, de Smit DJ, de Jong van den Berg LT. Reprod Toxicol. 2005;20:411–5.

Coppen A, Bolander-Gouaille C. J Psychopharmacol. 2005;19:59–65.

Czeizel AE, Dudas I. N Engl J Med. 1992;327:1832–5.

D'Anci KE, Rosenberg IH. Curr Opin Clin Nutr Metab Care. 2004;7:659–64.

Das UN. Nutrition. 2003;19:686–92.

Das UN. Prostaglandins Leukot Essent Fatty Acids. 2008;78:11–19.

De Marco P, Merello E, Mascelli S, Capra V. Neurogenetics. 2006;7:201–21.

Eichholzer M, Tönz O, Zimmermann R. Lancet. 2006;367:1352–61.

Ellinson M, Thomas J, Patterson A. J Hum Nutr Diet. 2004;17:3713–83.

Food and Drug Administration. Federal Register. 1996;61:8781–97.

Green JH. J Sch Health. 2007;77:103–8.

Guerri C, Bazinet A, Riley EP. Alcohol Alcohol. 2009;44:108–14.

Gujska E, Majewska K. Plant Foods Hum Nutr. 2005;60:37–42.

Halsted CH, Villanueva JA, Devlin AM, Chandler CJ. J Nutr. 2002;132 (8 Suppl.):2367S–72S.

Honein MA, Paulozzi LJ, Mathews TJ, Erickson JD, Wong L. JAMA. 2001;285:2981–6.

Johnson MA. Nutr Rev. 2007;65:451–8.

Kang SS, Wong PW, Susmano A, Sora J, Norusis M, Ruggie N. Am J Hum Genet. 1991;48:536–45.

Kariluoto S, Vahteristo L, Salovaara H, Katina K, Liukkonen KH, Piironen V. Cereal Chem. 2004;81:134–9.

Kim YI. Nutr Rev. 2007;65:504–11.

Kronenberg G, Harms C, Sobol RW, Cardozo-Pelaez F, Linhart H, Winter B, Balkaya M, Gertz K, Gay SB, Cox D, Eckart S, Ahmadi M, Juckel G, Kempermann G, Hellweg R, Sohr R, Hörtnagl H, Wilson SH, Jaenisch R, Endres M. J Neurosci. 2008;28:7219–30.

Matté C, Mackedanz V, Stefanello FM, Scherer EB, Andreazza AC, Zanotto C, Moro AM, Garcia SC, Goncalves CA, Erdtmann B, Salvador M, Wyse AT. Neurochem Int. 2009;54:7–13.

Mattson MP, Kruman II, Duan W. Ageing Res Rev. 2002;1:95–111.

Mischoulon D, Raab MF. J Clin Psychiatry. 2007;10:28–33.

Morris MS. Nutr Clin Care. 2002;5:124–32.

Muldoon RT, McMartin KE. Ethanol Clin Exp Res. 1994;18:333–9.

Niccols A. Brain Cogn. 2007;65:135–42.

Osseyi EO, Wehling RL, Albrecht JA. Cereal Chem. 2001;78:375–8.

Paul RT, McDonnell AP, Kelly CB. Hum Psychopharmacol. 2004;19:477–88.

Picker JD, Coyle JT. Harv Rev Psychiatry. 2005;13:197–205.

Schneider JA, Rees DC, Liu Y-T, Clegg JB. Am J Hum Genet. 1998;62:1258–60.

Sharpe TT, Alexander M, Hutcherson J, Floyd RL, Brimacombe M, Levine R, Mengel M, Stuber M. J Women Health (Larchmt). 2004;13:133–9.

Suh JR, Herbig AK, Stover PJ. Annu Rev Nutr. 2001;21:255–82.

Sun Y, Strandberg-Larsen K, Vestergaard M, Christensen J, Nybo Andersen AM, Gronbaek M, Olsen J. Am J Epidemiol. 2009;169:313–22.

Tough S, Tofflemire K, Clarke M, Newburn-Cook C. Clin Med Res. 2006;4:97–105.

Wang LL, Zhang Z, Li Q, Yang R, Pei X, Xu Y, Wang J, Zhou SF, Li Y. Hum Reprod. 2009;24:562–79.

Weir DG, McGing PG, Scott JM. Biochem Pharmacol. 1985;34:1–7.

Wright AJA, Finglas PM, Southon S. Trends Food Sci. 2001;12:313–21.

Xu Y, Liu P, Li Y. Wei Sheng Yan Jiu. 2005a;34:61–3.

Xu Y, Zhang G, Li Y. Beijing Da Xue Xue Bao. 2005b;37:346–50.

Xu Y, Li L, Zhang Z, Li Y. Toxicol Lett. 2006a;167:167–72.

Xu Y, Li Y, Tang Y, Wang J, Shen X, Long Z, Zheng X. Reprod Toxicol. 2006b;22:56–61.

Xu Y, Tang Y, Li Y. Brit J Nutr. 2008;99:455–61.

Zintzaras E. J Hum Genet. 2007;52:943–53.

Chapter 184
Decreased Appetite for Food in Alcoholism

Anna Kokavec

Abbreviations

ADX	Adrenalectomy/Adrenalectomized
ARC	Arcuate nuclei located in the hypothalamus
DHEAS	Dehydroepiandrosterone sulphate
GABA	γ-aminobutyric acid
GABA$_A$	γ-aminobutyric acid receptor/chloride ionophore
HPA	Hypothalamic-pituitary-adrenal axis
K$^+$	Potassium ion
mRNA	Messenger ribonucleic acid
Na$^+$	Sodium ion
NMDA	*N*-methyl-D-aspartate
NPY	Neuropeptide Y
PVN	Paraventricular nuclei located in the hypothalamus

184.1 Introduction

Alcohol consumption can induce the development of nutritional disorders as alcohol ingestion often replaces food intake (Orozco and De Castro 1991). While alcohol contains a large number of calories, these calories are classed as 'empty' calories because alcohol contains little nutritional value (Pirola and Lieber 1972). Alcoholic beverages may account for up to 50% of the total calorie intake in chronic alcoholics, which over time can lead to the development of a severely malnourished state (Lieber 1991). The nutritional content of alcoholic beverages is presented in Table 184.1.

Assessment of the behavioural effects of alcohol on appetite has often included some investigation of meal size (e.g. Strbak et al. 1998) and meal composition (e.g., Colditz et al. 1991). It appears that while short-term alcohol intake has little effect on meal size (Poppitt et al. 1996), long-term alcohol consumption can decrease the total amount of food consumed when food is freely available

A. Kokavec (✉)
School of Psychological Science, La Trobe University, Bendigo, Australia, 3552
e-mail: A.Kokavec@latrobe.edu.au

Table 184.1 Nutritional breakdown of alcoholic beverages[a]

	Light beer (285 ml)	Regular beer (285 ml)	Red wine (120 ml)	White wine (120 ml)	Spirits (30 ml)
Calories	47	105	80	75	66
Kilojoules	195	440	335	315	275
Carbohydrate (g)	6	8	0	1.5	0
Protein (g)	.8	.8	0	0	0
Fat (g)	0	0	0	0	0
Cholesterol (g)	0	0	0	0	0
Sodium (mg)	43	43	12	12	0
Potassium (mg)	42	42	Unknown	Unknown	0
Calcium (mg)	28.5	28.5	12	12	0
Iron (mg)	0	0	.4	.4	0

[a] Figures shown may vary between manufacturers

This table lists the nutritional breakdown of the most common commercially available alcoholic beverages. The nutritional content of the common alcoholic beverages is not the same. Spirits and white wine contain virtually no nutritional benefit to the individual, while on the other hand beer not only contains carbohydrate but also a large amount of salts

(Strbak et al. 1998). Further assessment of meal composition has highlighted that moderate–heavy alcohol drinkers when compared to controls consume significantly less food containing carbohydrate (Colditz et al. 1991), and more food containing fat and protein (Herbeth et al. 1988), and fat and salt (Caton et al. 2004).

The aim of this chapter is to explore the importance of this very specific alcohol effect (i.e. decrease in appetite for carbohydrate). In the next few sections evidence from a number of human studies conducted in our laboratory will be provided in order to highlight that a decreased appetite for carbohydrate may be a physiological *consequence* of alcohol consumption.

184.2 Alcohol as an Energy Source

184.2.1 Alcohol Pharmacology

Alcohol contains a high number of calories, but how the body uses energy from these calories is very complex. Animal studies have shown that alcohol lacks some characteristics of a nutrient in that alcohol does not promote optimum growth (Guthrie et al. 1990). Similarly, human data has confirmed that when alcohol is substituted for other food stuffs (e.g. carbohydrates) on a calorie-by-calorie basis, alcoholic individuals lose rather than gain weight (Colditz et al. 1991).

Alcohol is the end product of sugar metabolism formed from pyruvate in yeast and other microorganisms. The conversion of glucose to alcohol is an anaerobic process termed *alcoholic fermentation* and the sequence of reactions involved in the conversion of glucose to alcohol begins with the conversion of glucose into pyruvate. Pyruvate is then decarboxylated in a reaction catalyzed by pyruvate decarboxylase to form acetaldehyde, which in turn is reduced to alcohol by reduced nicotinamide adenine dinucleotide in a reaction catalyzed by alcohol dehydrogenase. When alcohol enters the body, alcohol dehydrogenase, with oxidized nicotinamide adenine dinucleotide acting as cofactor, converts alcohol to acetaldehyde and nicotinamide adenine dinucleotide in the liver. As the initial reduction of pyruvate to acetaldehyde is a nonreversible step, acetaldehyde rather than being converted back to pyruvate, is converted to acetate by aldehyde dehydrogenase, primarily in the mitochondria, before final oxidization into carbon dioxide and water (Berg et al. 2007).

184.2.2 Is Alcohol a Food?

In the past, we have drawn attention to the fact that alcohol may not be a food for the human body (for review see Kokavec and Crowe 2002). The known human energy systems are not able to utilize alcohol as an energy source because pyruvate cannot be produced from alcohol. In contrast, plants and anaerobic organisms are able to utilize the stored energy in alcohol via activation of the glyoxylate cycle, a gluconeogenic pathway responsible for the conversion of fat into carbohydrate. The human citric acid cycle and glyoxylate cycles at first appear similar. However, a major difference between the two energy pathways is that the glyoxylate cycle omits the steps in the citric acid cycle, which require activation of thiamine-dependent enzymes (Berg et al. 2007).

When alcohol enters the body, the ability of cells to maintain the store of thiamine is severely compromised (Zimatkin and Zimatkina 1996). Furthermore, extended periods of alcohol consumption can cause thiamine deficiency (Martin et al. 1985), even in well-nourished individuals (Rathanaswami and Sundaresan 1991). Thus, given that thiamine is required for the biosynthesis of insulin and alcohol can promote thiamine deficiency (Rathanaswami and Sundaresan 1991; Zimatkin and Zimatkina 1996), an alcohol-induced decrease in insulin may occur when alcohol is consumed alone after food (Kokavec and Crowe 2003).

The glyoxylate cycle may have a role in intermediary metabolism in the human liver. The key enzymes associated with the glyoxylate cycle can become active in the human liver after 3–4 days' fasting (Masters 1997), allowing lipid to be converted into carbohydrate. Thus, under conditions where activation of the glyoxylate pathway occurs, a decreased appetite for carbohydrate would also be expected.

184.2.3 Effect of Alcohol on Appetite for Carbohydrate

Investigations have shown that appetite for carbohydrate is hormonally regulated and largely dependent on the efficient performance of cortisol, a steroid under the control of the hypothalamic-pituitary-adrenal (HPA) axis, and insulin a pancreatic peptide hormone. Moreover, the effects of cortisol and insulin may be mediated through the regulation of hypothalamic neuropeptide Y (NPY), a 36-amino sequence pancreatic polypeptide, synthesis and release (Strack et al. 1995). A low–moderate level of cortisol stimulates appetite (Cohn et al. 1955) by promoting NPY release (Dean and White 1990), which in turn promotes insulin release (Rebuffe-Scrive et al. 1992) in order to stop feeding (Woods and Porte 1975).

NPY-induced feeding behaviour in the PVN appears to specifically increase carbohydrate intake (Stanley and Leibowitz 1984), and a lack of glucocorticoids by inhibiting NPY release in the PVN notably decreases carbohydrate intake (Tempel and Leibowitz 1989). Cortisol can increase the transcription rate of NPY mRNA (Dean and White 1990) and a sufficient release of cortisol may be necessary for NPY-stimulated insulin release (Wisialowski et al. 2000). NPY is synthesized by neurons in the hypothalamic arcuate nucleus (ARC) and while these neuronal axons can project to a number of areas (O'Donohue et al. 1985), projections to the paraventricular nuclei (PVN) have been strongly associated with stimulation of feeding (Muroya et al. 1999).

Fasting promotes an elevation in glucocorticoids and NPY gene expression (Hanson et al. 1997). In contrast, the level of insulin in nondiabetic individuals is reduced. Insulin acts locally to inhibit NPY gene expression in the ARC (Schwartz et al. 1992a) and a decrease in food intake is observed with insulin and adrenalectomy (ADX) due to a reduction in ARC NPY mRNA levels (White et al. 1990). The insulin-mediated inhibition of NPY gene expression in the ARC may be mediated through

GABAergic systems (Sato et al. 2005). There is co-localization of NPY and GABA in various brain areas (Deller and Leranth 1990) and NPY can inhibit potassium-stimulated glutamate release (Wang 2005). Alternatively, NPY protein and mRNA levels are increased by glutamatergic stimulation (Kim et al. 2000).

184.2.4 Effect of Alcohol on Receptor Systems

NPY-induced feeding in the hypothalamus may be dependent on activation of *N*-methyl-D-aspartate (NMDA) glutamate receptors (Lee and Stanley 2005). In the absence of glutamate excitation, NPY in the ARC has little influence on hypothalamic neuronal activity but instead has a modulatory role by either reducing glutamate release at presynaptic terminals or modulating the postsynaptic response to glutamate (Belousov and van den Pol 1997).

Chronic ethanol exposure can produce a significant reduction in NPY protein levels (Roy and Pandey 2002), and suppress NPY gene expression in the ARC (Kinoshita et al. 2000). Thus, these findings provide support for the behavioural data claiming that alcohol may alter appetite for carbohydrate. Moreover, this is also consistent with the accepted view that acute alcohol administration impairs functioning of excitatory NMDA glutamate receptors (Lustig et al. 1992) and potentiates the function of inhibitory $GABA_A$ receptors (Givens and Breese 1990). The key features of appetite behaviour in alcoholism are summarized in Table 184.2.

In the next few sections, we investigate the effect of commercially available alcohol on hormonal factors thought to be associated with appetite regulation in order to determine whether commercially available alcohol products promote a decrease in carbohydrate intake.

184.2.5 White Wine Before Food

In the brain, steroid hormones such as cortisol and dehydroepiandrosterone sulphate (DHEAS) act as modulators of synaptic events and salivary steroids can provide some indication of the level of cortisol and DHEAS in CSF (Guazzo et al. 1996). Cortisol may alter the binding of γ-aminobutyric acid (GABA) to inhibitory $GABA_A$ receptors in a biphasic fashion, with potentiation of GABA occurring at nanomolar levels and a reduction occurring at micromolar ones (Majewska et al. 1985). Alternatively, DHEAS modulates the action of cortisol (Guazzo et al. 1996), by acting as a GABA antagonist at the $GABA_A$ receptor (Demirgoren et al. 1991), in order to potentiate the function of excitatory NMDA glutamate receptors (Baulieu 1996). The key features of salivary cortisol is summarized in Table 184.3.

Table 184.2 Key features of feeding behaviour in long-term chronic alcoholics

1. Alcohol consumption usually replaces food intake
2. The alcoholic individual is often blamed for their highly irregular feeding behavior
3. Alcoholics usually consume less food when food is freely available
4. Alcohol can at times account for 50% of daily calories in long-term chronic alcoholics
5. Alcohol contains few nutrients and malnutrition is commonly associated with alcoholism
6. There is a preference for foods containing salt and protein during alcohol consumption
7. A decreased appetite for carbohydrate has been noted in long-term chronic alcoholics while consuming alcohol
8. Alcohol can alter biochemical processes associated with the regulation of appetite for carbohydrate

This table lists the key findings associated with impaired appetite for food in alcoholism. A decreased appetite for carbohydrate is one of the main factors associated with alcohol consumption

Table 184.3 Key features of salivary cortisol

1. Plasma-free cortisol is the most reliable measure of adrenal activity as plasma total cortisol values may be affected by the alteration of its carrier protein, corticosteroid-binding-globulin

2. It is not unusual in psychoneuroendocrinology for cortisol to be assessed in saliva

3. Amount of cortisol in saliva is highly correlated with the level of plasma free cortisol

4. Amount of cortisol in saliva has been found to be highly correlated with the level of cortisol in cerebrospinal fluid (i.e. in the brain)

5. Cortisol concentration in saliva is not dependent on saliva flow rate

6. No dilution effects have been observed. Thus, readings are highly accurate

7. As cortisol is released in response to stress, salivary measure of cortisol may offer a more accurate noninvasive measure of adrenal activity

Cortisol is the body's major stress hormone and stress associated with the blood taking procedure can falsely increase cortisol values making blood taking results at times difficult to interpret. Saliva sampling offers a convenient, noninvasive, and more reliable method for assessment of adrenal hormones

Fig. 184.1 Effect of white wine on salivary cortisol and salivary DHEAS before a meal. Mean salivary cortisol and salivary DHEAS before food (0 g), during ingestion of white wine containing 40 g alcohol (13–40 g), and after food. The level of cortisol and DHEAS data was measured in eight nondiabetic males aged 18–22 years across a 180-min period. Error bars have been included to show the average deviation from the Mean at each 45-min assessment point. The results showed a significant decrease in cortisol and DHEAS over time when white wine is consumed. The consumption of food promoted some recovery in cortisol but the level of DHEAS continued to decrease

The consumption of white wine significantly decreases salivary cortisol and DHEAS when consumed alone under fasting conditions (Kokavec et al. 2009). The cortisol-DHEAS relationship when white wine is consumed prior to food is shown in Fig. 184.1. While an absence of cortisol in CNS could indicate that glucose transport and glutamate uptake is promoted in astrocytes (Virgin et al. 1991) the significant reduction in DHEAS highlights that NMDA receptor activity is not promoted. Moreover, as NPY protein and mRNA levels in the ARC are increased by glutamatergic stimulation (Kim et al. 2000) the steroid data could support previous claims that an alcohol-induced reduction in NPY mRNA in ARC (Kinoshita et al. 2000) and NPY in PVN (Roy and Pandey 2002) occurs.

During fasting, insulin is usually reduced in order to promote feeding, and insulin administration during fasting may prevent the fasting-induced increase in NPY in PVN and NPY mRNA in ARC (Schwartz et al. 1992a). White wine prior to food does not increase plasma insulin (Kokavec and
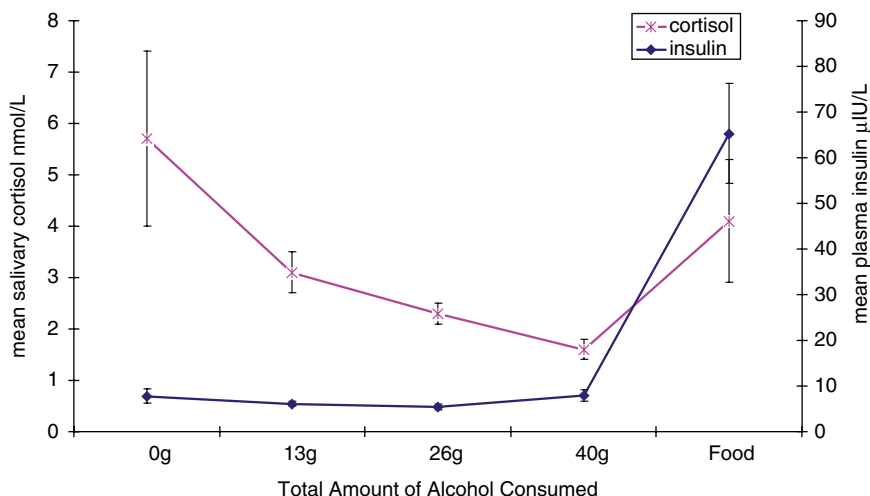
Fig. 184.2 Effect of white wine on plasma insulin and salivary cortisol prior to a meal. Mean plasma insulin and salivary cortisol before food (0 g), during ingestion of white wine (13–40 g alcohol) and after food is presented. The level of insulin and cortisol was measured in eight nondiabetic males across a 180-min period. Error bars have been included to show the average deviation from the mean at each 45-min assessment point. The results showed no change in insulin when white wine is consumed prior to food. However, the consumption of food promoted a significant and abnormally large increase in insulin immediately

Crowe 2006) and ketone production is maintained (Kokavec 2000). Taken together, this would suggest that white wine prior to food does not promote an elevation in plasma glucose and raises the possibility that an increase in NPY mRNA in ARC could occur under these conditions.

184.2.6 Effect of Alcohol-induced Dehydration

The expression of NPY in the ARC is influenced by both feeding and hydration factors. Moreover, a combination of ADX and chronic osmotic stimulation can increase NPY mRNA expression in neurons of the ARC (Larsen et al. 1993). Similarly, a combination of ADX and fasting can increase NPY gene expression in the medial basal hypothalamus (Hanson et al. 1997) and an increase in ARC NPY mRNA has also been observed in food (Johnstone et al. 2005) and calorie (Shimokawa et al. 2003) restricted animals.

Chronic osmotic stimulation can deactivate the HPA axis (Jessop et al. 1990) and alcohol may promote the development of a dehydration condition (Linkola et al. 1979). Similarly, we noted a significant alcohol-induced reduction in urinary Na^+ and K^+ excretion and reduced urine flow when white wine is consumed prior to food (Kokavec 2000). However, when we compared the level of urinary K^+ and urinary Na^+ in our study with urinary electrolyte data collected after several days fasting in non-obese individuals (Elia et al. 1984), we were surprised to find that the electrolyte data was very similar after 40 g alcohol despite participants being only mildly fasted prior to alcohol consumption.

Consuming white wine prior to food, despite promoting a significant reduction in steroid hormones (Kokavec and Crowe 2001a), may, therefore, increase NPY mRNA in the ARC (for review see Kokavec and Crowe 2001b), due to impaired salt and water balance. Although, inactivation of NMDA

receptors could prevent NPY in the ARC from influencing hypothalamic neuronal activity and instead may reduce glutamate release at presynaptic terminals and/or promote glutamate resistance. Therefore, the DHEAS and insulin data together may suggest modulation of NPY in PVN due to glutamate resistance (Belousov and van den Pol 1997). Similarly, a lack of glucocorticoids will also notably decrease carbohydrate intake (Tempel and Leibowitz 1989). Thus, the hormonal data suggests that ingesting white wine prior to a meal could reduce appetite for carbohydrate. The cortisol-insulin interaction when white wine is consumed alone before a meal is presented in Fig. 184.2.

184.2.7 Food After White Wine

The consumption of food after white wine can significantly reduce DHEAS and promote an increase in salivary cortisol concentration (Kokavec and Crowe 2001a). Laboratory investigations have demonstrated that ethanol administration prior to ingestion of a glucose load (McMonagle and Felig 1975) can potentiate the glucose stimulating properties of insulin and promote a rapid release of insulin (O'Keefe and Marks 1977). Similarly, we observed a significant elevation in plasma insulin when food was consumed after a moderate amount of white wine had already been ingested (Kokavec 2000).

The rapid release of insulin that was noted when food is consumed after white wine (Kokavec 2000) could reduce NPY gene transcription in ARC (Schwartz et al. 1992a). Furthermore, the significantly reduced level of DHEAS that was observed when food is consumed after white wine (Kokavec and Crowe 2001a) could promote a cascade of events commencing with increased GABA uptake at the GABA$_A$ receptor and then may involve inhibition of NPY in the ARC on hypothalamic neuronal activity, reduced glutamate release, and promotion of glutamate resistance (Belousov and van den Pol 1997). Therefore, the DHEAS, insulin and cortisol data could be highlighting that an NPY deficient state develops when food is consumed after white wine. Thus, when white wine is consumed prior to food appetite for carbohydrate could be inhibited when food is finally presented, which would encourage less food to be consumed.

184.2.8 White Wine After Food

A meal high in carbohydrate will usually promote a sudden increase in plasma glucose, which then stimulates insulin release by the β-cells in the pancreas. Circulating insulin levels in nondiabetic individuals usually rise with feeding (Schwartz et al. 1992a) and the level of plasma insulin remains elevated until the plasma glucose level begins to drop, which often can take several hours (Berg et al. 2007). In contrast, during fasting, insulin secretion is markedly reduced (Schwartz et al. 1992b) and cortisol is elevated in order to reduce glucose utilization and transport, and promote gluconeogenesis. While the relationship between cortisol and insulin is usually antagonistic elevations in cortisol and insulin can occur simultaneously in response to food intake. The role of cortisol in this instance is to modulate the effects of insulin on glucose utilization in order to ensure that energy stores are replenished (Goldstein et al. 1993).

The effect of white wine on steroid hormones may be dependent on the prior nutritional status of the individual. Consuming white wine alone after a meal can promote a significant elevation in DHEAS together with a significant decrease in cortisol (Kokavec and Crowe 2001a), plasma insulin (Kokavec and Crowe 2003), urinary K$^+$ excretion (Kokavec 2000) and a trend for a lowering of
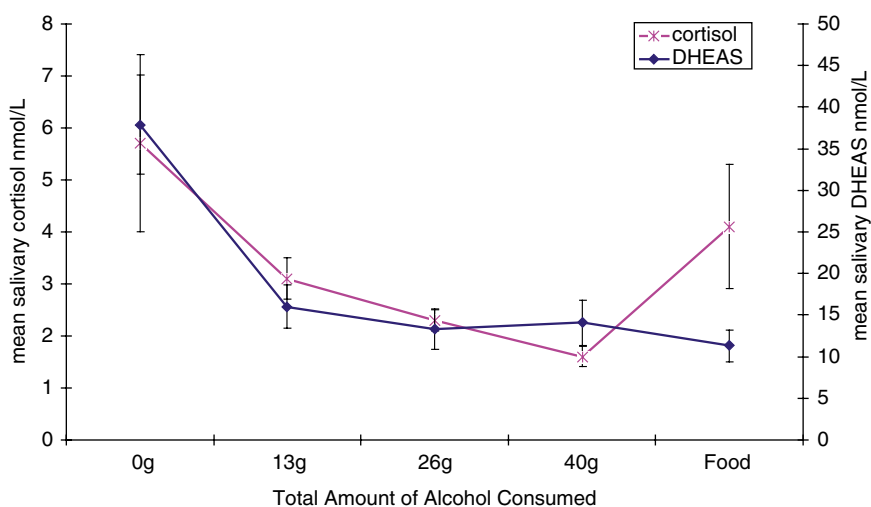
Fig. 184.3 Effect of white wine on salivary cortisol and salivary DHEAS after a meal. Mean salivary cortisol and salivary DHEAS before food (pre-food), after food, and during ingestion of white wine containing 40 g alcohol (13–40 g) in a group of eight nondiabetic males aged 18–22 years across a 180-min period. Error bars have been included to show the average deviation from the mean for the group at each 45-min assessment point. The results showed a significant decrease in cortisol and significant increase in DHEAS as soon as white wine was consumed alone after the meal
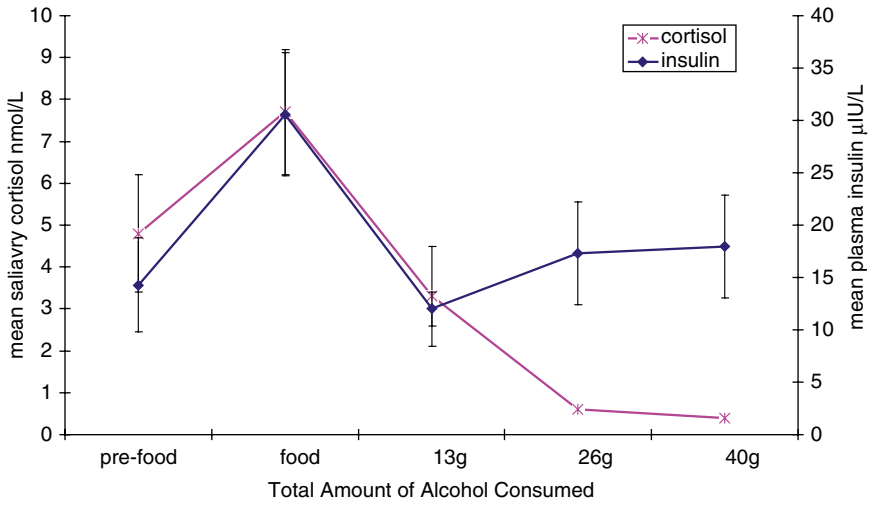
Fig. 184.4 Effect of white wine on salivary cortisol and plasma insulin after a meal. Mean salivary cortisol and plasma insulin before food (pre-food), after food, and during ingestion of white wine containing 40 g alcohol (13–40 g) in a group of eight nondiabetic males aged 18–22 years across a 180-min period. Error bars have been included to show the average deviation from the mean for the group at each 45-min assessment point. The results showed a significant decrease in insulin as soon as white wine is consumed. The level of insulin was similar to that observed prior to food intake despite individuals having consumed a high carbohydrate meal

plasma glucose (Kokavec and Crowe 2003). The cortisol-DHEAS and cortisol-insulin relationship is shown in Figs. 184.3 and 184.4, respectively. Our findings are consistent with rodent studies where it has been shown that ethanol treatment following glucose administration can promote a marked inhibition of glucose-induced insulin secretion (Tiengo et al. 1981). Therefore, this together could highlight that white wine may alter glucose utilization and metabolism.

The alcohol-induced elevation in DHEAS by inhibiting GABA uptake at the $GABA_A$ receptor could promote an increase in NPY mRNA in ARC and NPY level in PVN via potentiation of NMDA receptors (Kim et al. 2000). Moreover, a significant decrease in insulin (Kokavec and Crowe 2003) adds further support for an alcohol-induced increase in NPY mRNA in ARC. However, a significant alcohol-induced decrease in cortisol was also observed (Kokavec and Crowe 2001b), which could modulate the transcription of NPY in ARC (Dean and White 1990) and reduce the level of NPY in PVN (Sato et al. 2005).

184.2.9 Is All Alcohol the Same?

The effect of alcohol on the HPA axis may be dependent on the type of alcoholic beverage consumed. In the past, we have assessed a number of commercially available alcoholic beverages and found that the consumption of red wine and white wine under similar experimental conditions does not necessarily produce the same effect on the HPA axis. The effect of alcohol on the HPA axis may be dependent on not only the prior nutritional status of the individual but also the nutritional content of the alcoholic product being tested.

While most alcoholic beverages contain varying amounts of histamine (Lonvaud-Funel 2001), red wine is unique in that it contains a higher level of histamine when compared to other alcoholic products (Wantke et al. 1994) and (unlike other alcoholic beverages) can also promote histamine release (Intorre et al. 1996). Therefore, given that histamine can promote ACTH release (Knigge et al. 1988), the precursor for steroidgenesis (Endoh et al. 1996), it would not be unreasonable to assume that red wine may also influence the HPA axis differently than other alcoholic beverages.

184.2.10 Red Wine Prior to Food

When we assessed the effect of red wine on the HPA axis prior to food intake, it became clear that the amount of red wine being ingested was a very important factor. We observed that consumption of red wine can promote a significant decrease in salivary cortisol and salivary DHEAS. In contrast, ingestion of 2–3 standard units of red wine (20–30 g alcohol) can promote a trend for an increase in salivary DHEAS, but salivary cortisol remains lowered. After ingestion of four standard units of red wine (40 g alcohol), the concentration of salivary cortisol remains lowered and DHEAS continues to increase slightly (Fig. 184.5) (Kokavec et al. 2009).

Thus, the red wine data suggests that activation of $GABA_A$ receptors is promoted when red wine is consumed prior to food (Demirgoren et al. 1991). Alternatively, ingestion of 2–3 standard units of red wine (20–30 g alcohol) may promote the activation of NMDA receptors due to the inhibition of GABA. Following ingestion of four standard units of red wine (40 g alcohol), activation of NMDA receptors may continue to be promoted and NPY mRNA in ARC and NPY release in PVN may increase (Kim et al. 2000). We also noted a significant decrease in insulin when red wine is consumed prior to food, which further suggests that an alcohol-induced increase in NPY mRNA occurs in ARC. Therefore, the red wine data could suggest caution when consuming red wine prior to food with more than three standard units of red wine (>30 g alcohol) prior to food possibly decreasing carbohydrate intake. The cortisol-insulin interaction when red wine is consumed prior to a meal is presented in Fig. 184.6.
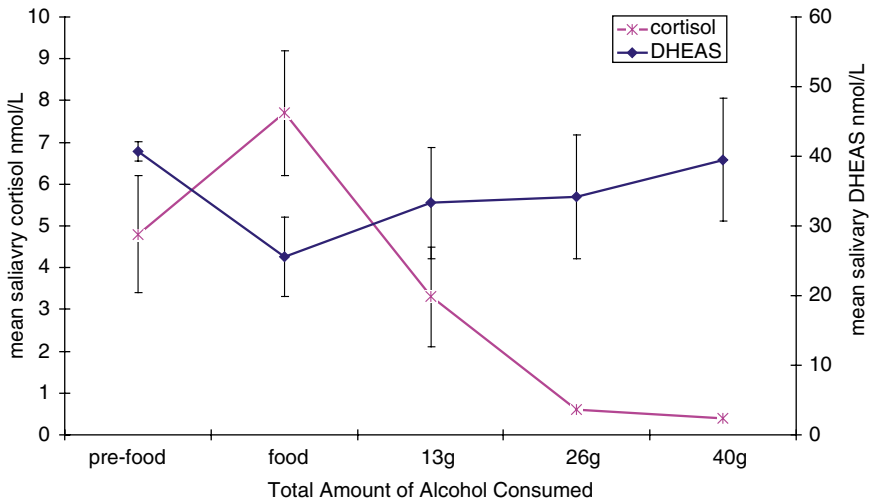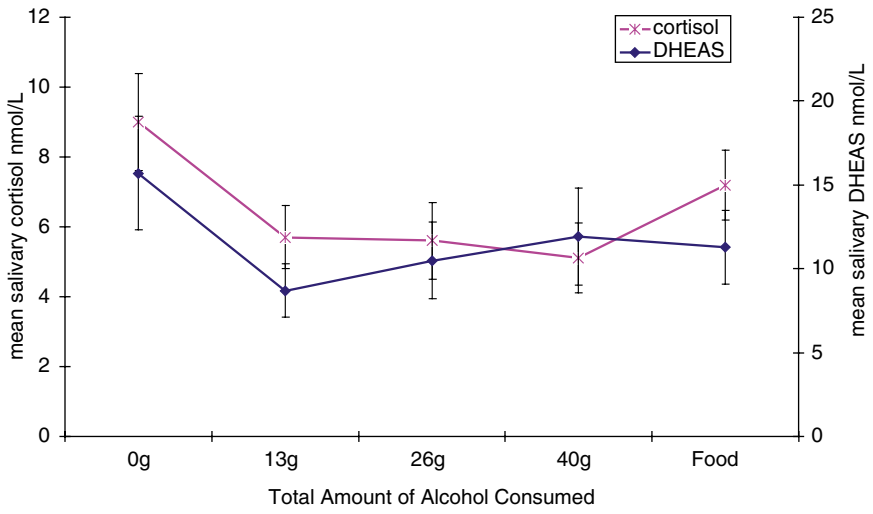
Fig. 184.5 Effect of red wine on salivary cortisol and salivary DHEAS before a meal. Mean salivary cortisol and salivary DHEAS before food (0 g), during ingestion of red wine containing 40 g alcohol (13–40 g), and after food in a group of eight nondiabetic males aged 18–22 years across a 180-min period. Error bars have been included to show the average deviation from the mean for the group at each 45-min assessment point. The results showed a significant decrease in cortisol and significant increase in DHEAS over time as more red wine is consumed
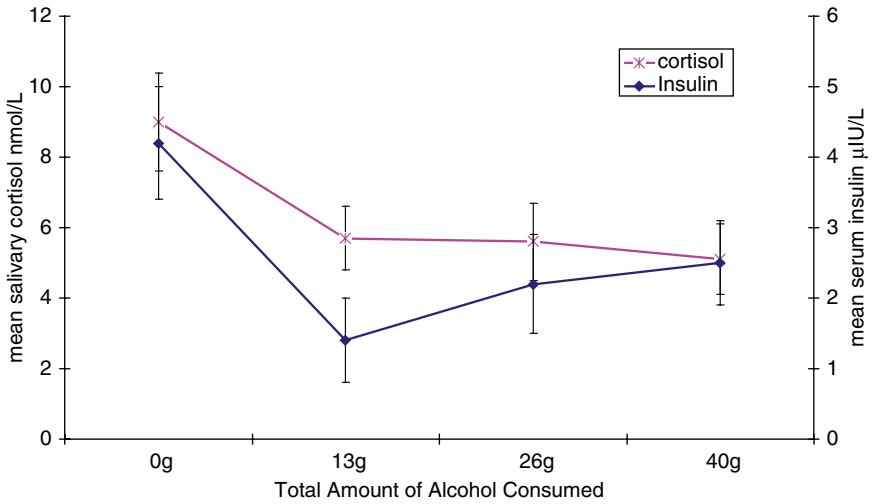
Fig. 184.6 Effect of red wine on salivary cortisol and plasma insulin before a meal. Mean salivary cortisol ($n = 8$) and plasma insulin ($n = 8$) was assessed before food (0 g) and during ingestion of red wine containing 40 g alcohol (13–40 g) on two separate occasions. A total of 16 nondiabetic males aged 18–22 years participated in one of the two 180-min testing sessions. Error bars have been included to show the average deviation of scores from the mean at each 45-min assessment point. The results showed a significant decrease in cortisol and insulin when red wine is consumed prior to food

184.2.11 Beer Before Food

Consuming beer, a product containing alcohol, various minerals, and approximately 8 g carbohydrate prior to food can promote a significant elevation in the level of fasting salivary DHEAS after only one standard unit of regular beer (i.e. 10 g alcohol) is ingested. Cortisol is significantly lowered and an increase in cortisol is only observed after 40 g alcohol is consumed. The consumption of three standard units of regular beer (30 g alcohol) can promote a further decrease in salivary cortisol with the level of DHEAS also being shown to become lowered. However, consumption of 40 g alcohol in the form of beer can promote an elevation in cortisol and no change in salivary DHEAS (Fig. 184.7). We compared the effects of light beer (2.3% alcohol per 100 ml) and heavy beer (4.9% alcohol per 100 ml) and found there to be no significant alcohol-induced differences in salivary cortisol or salivary DHEAS when trials were compared across time. Therefore, the effect of beer on salivary cortisol and salivary DHEAS was found to be the same regardless of alcohol content (Kokavec et al. 2009).

Simultaneous administration of ethanol and glucose can decrease the insulin response (Singh et al. 1980). Alternatively, consuming alcohol with carbohydrate (Marks 1978) can elevate insulin (O'Keefe and Marks 1977). An antagonistic relationship is known to exist between insulin and DHEAS, and it may be that when beer is consumed, the carbohydrate content of beer exerts some influence on the level of fasting insulin. An absence of ketone bodies was noted after 30 g alcohol, which could suggest that sufficient energy is available to meet the needs of the system.

Therefore, the steroid data when combined with early insulin findings could suggest that consuming alcohol with carbohydrate may decrease NPY gene expression in ARC, which could promote NPY deficiency by subsequently reducing NPY in PVN (Schwartz et al. 1992a). An elevation in insulin could reduce appetite for carbohydrate (Tempel and Leibowitz 1989) and NPY deficiency may promote alcohol consumption. Therefore, consuming alcohol with sufficient carbohydrate to alter insulin should probably not be promoted.
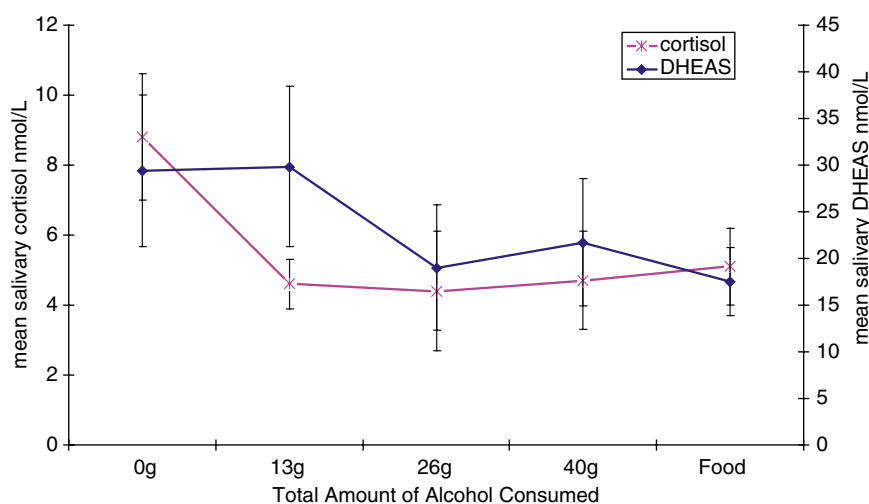
Fig. 184.7 Effect of beer on salivary cortisol and salivary DHEAS before a meal. Mean salivary cortisol and salivary DHEAS before food (0 g), during ingestion of high-alcohol beer containing 40 g alcohol (13–40 g) and after food in a group of eight nondiabetic males aged 18–22 years across a 180-min period. Error bars show the average deviation from the mean for the group at each 45-min assessment point. The results showed a significant decrease in cortisol and a significant but highly variable increase in DHEAS

184.3 Summary

Alcohol may not be a fuel for the human body. The known energy pathways cannot utilize alcohol as an energy source and it is unlikely that humans can convert the calories contained in alcohol to fuel using the usual energy pathways. The biochemical evidence presented above confirms that an alcohol-induced alteration in appetite for carbohydrate may occur when a range of commercially available alcohol products are ingested. Moreover, consuming alcohol prior to food can decrease the amount of food consumed when food is finally presented. Therefore, consuming commercially available alcohol alone before or after a meal should probably not be encouraged.

The material presented in this chapter is by no means extensive and has merely focussed on some of the more established biochemical aspects of carbohydrate intake regulation. There are several other biochemical factors associated with food intake (e.g. cholecystokinin, leptin, ghrelin) that have not been mentioned, and probably many more factors that remain to be discovered. However, this serves as a good starting point to perhaps make us start to question why alcoholics prefer to consume alcohol rather than food. It is possible that a consequence of alcohol consumption under certain conditions may be to promote an alteration in the way the body processes energy such that carbohydrate intake is discouraged and a malnourished state is encouraged.

184.4 Application to Other Areas of Health and Disease

Malnutrition is a common finding in the alcoholic population and the alcoholic individual is often blamed for his or her irregular feeding behaviour. While long-term alcohol abuse has been linked to a number of serious health conditions, steatosis or fatty liver is the primary cause of illness and death in alcoholics. The material presented here provides an explanation as to why the liver is often damaged in alcoholics, by suggesting that a consequence of alcohol consumption may be a reduced appetite for carbohydrate due to an alteration in energy metabolism. This information will be invaluable to a large number of health professionals and researchers who are working toward improving the health status of alcoholics.

Summary Points

- Alcohol consumption often replaces food intake in alcoholics.
- Alcohol is a high caloric substance but whether humans can generate any energy from alcohol is unknown.
- Alcohol can promote dehydration and may promote the development of a malnourished state.
- The known human energy systems are not able to utilize alcohol as an energy source.
- Alcohol may promote thiamine deficiency even in well-nourished individuals.
- Alcohol, if consumed alone, may alter appetite for carbohydrate regardless of whether alcohol is consumed before or after a meal.
- Consuming alcohol alone before a meal could result in less food being consumed when food finally becomes available.

Key Terms

Alcoholic fermentation: Series of chemical reactions involved in the conversion of glucose to alcohol.

Cortisol: A steroid hormone. The body's major glucocorticoid, synthesized and released by the hypothalamic–pituitary–adrenal axis.

Dehydroepiandrosterone sulphate: A steroid hormone. The body's major androgen synthesized and released by the hypothalamic-pituitary-adrenal axis.

Glyoxylate cycle: gluconeogenic pathway that allows fat to be converted to carbohydrate.

Hypothalamic–pituitary–adrenal axis: Hormonal pathway responsible for the synthesis and release of steroid hormones.

Insulin: Pancreatic peptide hormone that allows glucose to gain entry into cells located outside of the brain.

Neuropeptide Y: 36-amino sequence pancreatic polypeptide, which when released increases appetite for carbohydrate.

References

Baulieu E. J Clin Endocrin Metab. 1996;81:3147–51.

Belousov AB, van den Pol AN. J Physiol. 1997;499:747–61.

Berg JM, Tymoczko JL, Stryer L. Biochemistry. New York: WH Freeman and Company; 2007.

Caton SJ, Ball M, Ahern A, Hetherington MM. Physiol Behav. 2004;81:51–8.

Cohn C, Shrago E, Joseph D. Am J Physiol. 1955;180:503–7.

Colditz GA, Giovannucci E, Rimm EB, Stampfer MJ, Rosner B, Speizer FE, Gordis E, Willett WC. Am J Clin Nutr. 1991;54:49–55.

Dean RG, White BD. Neurosci Lett. 1990;114:339–44.

Deller T, Leranth C. J Comp Neurol. 1990;300:433–47.

Demirgoren S, Majewska MD, Spivak CE. Neuroscience. 1991;45:127–35.

Elia M, Crozier CB, Neale G. Clin Chim Acta. 1984;139:37–45.

Endoh A, Kristiansen SB, Casson PR, Buster JE, Hornsby PJ. J Clin Endocrinol Metab. 1996;81:3558–65.

Givens BS, Breese GR. J Pharmacol Exp Ther. 1990;2:528–38.

Goldstein, RE, Wasserman DH, McGuinness OP, Lacy DB, Cherrington AD, Abumrad NN. Am J Physiol. 1993;264:E119–27.

Guazzo EP, Kirkpatrick PJ, Goodyer IM, Shiers HM, Herbert J. J Clin Endocrinol Metab. 1996;81:3951–60.

Guthrie GD, Myers KJ, Gesser EJ, White GW, Koehl JR. Alcohol Clin Exp Res. 1990;14:17–22.

Hanson ES, Levin N, Dallman MF. Endocrinology. 1997;138:1041–7.

Herbeth B, Didelot-Barthelemy L, Lemoine A, Le Devehat C. J Stud Alcohol. 1988;49:268–72.

Intorre L, Bertini S, Luchetti E, Mengozzi G, Grema F, Soldani G. Alcohol. 1996;13:547–51.

Jessop DS, Chowdrey HS, Lightman SL. Brain Res. 1990;523:1–4.

Johnstone LE, Srisawat R, Kumarnsit E, Leng G. Stress. 2005;8:59–67.

Kim S, Kwon G, Shin S, Choe B. Neurochem Int. 2000;36:19–26.

Kinoshita H, Jessop DS, Finn DP, Coventry TL, Roberts DJ, Ameno K, Ijiri I, Harbuz MS. Neuroreport. 2000;11:3517–9.

Knigge U, Alsbjorn B, Thuesen B, Siemssen O, Christiansen PM. Eur J Clin Pharmacol. 1988;33:613–7.

Kokavec A. Effect of moderate white wine consumption on the hypothalamic-pituitary-adrenal axis in the absence and presence of adequate nutrition in young healthy males. Australia: La Trobe University Doctoral Dissertation; 2000.

Kokavec A, Crowe SF. Pharmacol Biochem Behav. 2001a;70:243–50.

Kokavec A, Crowe SF. Med Hyp. 2001b;57:667–72.

Kokavec A, Crowe SF. Med Hyp. 2002;58:411–5.

Kokavec A, Crowe SF. Alcohol Clin Exp Res. 2003;27:1718–23.

Kokavec A, Crowe SF. Ann Nutr Metab. 2006;50:407–12.

Kokavec A, Lindner AJ, Ryan JE, Crowe SF. Pharmacol Biochem Behav. 2009;93:170–6.

Larsen PJ, Mikkelsen JD, Jessop DS, Lightman SL, Chowdrey HS. J Neurosci. 1993;13:1138–47.

Lee SW, Stanley BG. Brain Res. 2005;1063:1–8.

Lieber CS. J Am Coll Nutr. 1991;10:601–32.

Linkola J, Fyhrquist F, Ylikahri R. Acta Physiol Scand. 1979;106:75–82.

Lonvaud-Funel A. FEMS Microbiol Lett. 2001;199:9–13.

Lustig HS, Chan J, Greenberg DA. Neurosci Lett. 1992;135:259–61.

Majewska MD, Bisserbe JC, Eskay RE. Brain Res. 1985;339:178–82.

Marks V. Clint Endocrinol Metab. 1978;7:333–49.

Martin PR, Majchrowicz E, Tamborska E, Marietta C, Mukherjee AB, Eckardt MJ. Science. 1985;227:1365–8.

Masters C. Mol Cell Biochem. 1997;166:159–68.

McMonagle J, Felig P. Metabolism. 1975;24:625–32.

Muroya S, Yada T, Shioda S, Takigawa M. Neurosci Lett. 1999;264:113–6.

O'Donohue TL, Chronwall BM, Pruss RM, Mezey E, Kiss JZ, Eiden LE, Massari VJ, Tessel RE, Pickel VM, DiMaggio DA, Hotchkiss AJ, Crowley WR, Zukowska-Grojec Z. Peptides. 1985;6:755–68.

O'Keefe SJ, Marks V. Lancet. 1977;1:1286–8.

Orozco S, De Castro JM. Pharmacol Biochem Behav. 1991;40:867–73.

Poppitt SD, Eckhardt JW, McGonagle J, Murgatroyd PR, Prentice AM. Physiol Behav. 1996;60:1063–70.

Pirola RC, Lieber CS. Pharmacology. 1972;7:185–96.

Rathanaswami P, Sundaresan R. Biochem Int. 1991;24:1057–62.

Rebuffe-Scrive M, Walsh UA, McEwen B, Rodin J. Physiol Behav. 1992;52:583–90.

Roy A, Pandey SC. Alcohol Clin Exp Res. 2002;26:796–803.

Sato I, Arima H, Ozaki N, Watanabe M, Goto M, Hayashi M, Banno R, Nagasaki H, Oiso Y. J Neurosci. 2005;25:8657–64.

Schwartz MW, Sipols AJ, Marks JL, Sanacora G, White JD, Scheurink A, Kahn SE, Baskin DG, Woods SC, Figlewicz DP, Porte D. Endocrinology. 1992a;130:3608–16.

Schwartz MW, Figlewicz DP, Baskin DG, Woods SC, Porte D. Endocr Rev. 1992b;13:387–414.

Shimokawa I, Fukuyama T, Yanagihara-Outa K, Tomita M, Komatsu T, Higamai Y, Tuchiya T, Chiba T, Yamaza Y. Neurobiol Aging. 2003;24:117–23.

Singh SP, Patel DG, Snyder AK. Acta Endocrinol. 1980;93:61–6.

Stanley BG, Leibowitz SF. Life Sci. 1984;35:2635–42.

Strack AM, Sebastian RJ, Schwartz MW, Dallman MF. Am J Physiol. 1995;268:R142–9.

Strbak V, Benicky J, Macho L, Jezova D, Nikodemova M. Metabolism. 1998;47:1269–73.

Tempel DL, Leibowitz SF. Brain Res Bull. 1989;23:553–60.

Tiengo A, Valerio A, Molinari M, Meneghel A, Lapolla A. Diabetes. 1981;30:705–9.

Virgin CE, Ha TPT, Packan DR, Tombaugh GC, Yang SH, Horner HC, Sapolsky RM. J Neurochem. 1991;57:1422–8.

Wang SJ. Neuroscience. 2005;134:987–1000.

Wantke F, Gotz M, Jarisch R. Allergy Proc. 1994;15:27–32.

White BD, Dean RG, Martin RJ. Brain Res Bull. 1990;25:711–5.

Wisialowski T, Parker R, Preston E, Sainsbury A, Kraegen E, Herzog H, Cooney G. J Clint Invest. 2000;105:1253–9.

Woods SC, Porte DJr. Diabetes. 1975;24:905–9.

Zimatkin SM, Zimatkina TI. Alcohol Alcohol. 1996;31:421–7.

Chapter 185
Gender Aspects in the Comorbidity of Eating Disorders and Alcohol Use Disorders

Tahany M. Gadalla

185.1 Introduction

Both eating disorders and alcohol use disorders are prevalent in men and women. However, while eating disorders are more prevalent in women, alcohol use disorders are more prevalent in men. Comparisons between clinical attributes of eating disorders, such as age of onset, frequency of various symptoms or duration of illness in men and women revealed no significant gender differences (Barry et al. 2002; Woodside 2002). Similar to women with eating disorders (Gruber et al. 2001), men with eating disorders were found to have an exaggerated perception of their body fat compared to controls (Mangweth et al. 2004). Barry and colleagues (2002) found no differences between men and women with binge eating disorders on measures of eating-related features such as eating concerns, shape, or weight concerns. These authors also found that women with a binge eating disorder experienced significantly greater body image dissatisfaction and drive for thinness compared to men with the same disorder (Barry et al. 2002).

Gender differences in risk factors for eating disorders and body dissatisfaction, such as self-esteem, perfectionism, and mass-media, have been suggested (Elgin and Pritchard 2006). Specifically, self-esteem, perfectionism, and mass-media were related to disordered eating behavior in women, whereas only perfectionism and mass-media were related to disordered eating behavior in men. Additionally, self-esteem and mass-media were related to body image dissatisfaction in women, whereas perfectionism and mass media were related to body image dissatisfaction in men (Elgin and Pritchard 2006). Lower socio-economic status and single marital status have been indicated as risk factors for eating disorders in both genders. For example, Lindblad and colleagues (2006) found a higher proportion of single parent families and families in need of child welfare among families of male patients with anorexia nervosa compared to the general population.

Gender differences in eating attitudes and behaviors toward food among individuals with eating disorders have also been suggested. Weltzin and colleagues (2005) found that men were less likely than women to engage in typical compensatory behaviors such as vomiting and more likely to engage in activities such as excessive exercise to control their body weight. They also found that men were more likely than women to binge rather than restrict food intake. Conversely, a small-scale study of substance abuse patients in a treatment setting revealed that men and women reported similar levels of engagement in binge eating and compensatory behaviors. However, the women displayed higher

T.M. Gadalla (✉)
Factor-Inwentash Faculty of Social Work/University of Toronto,
246 Bloor Street West, Toronto, Ontario, Canada, M5S 1V4
e-mail: tahany.gadalla@utoronto.ca

disturbed attitudes about body weight and shape compared to men (Jackson and Grilo 2002). More recently, research conducted by Gadalla (2009) examined gender differences in dieting behaviors in a nationally representative sample of Canadians with disordered eating behavior. The author found that men with disordered eating adopted less oral control and dietary restraint, were less preoccupied with body shape, and showed less desire for thinness compared to women. Furthermore, the research findings revealed no gender difference in engaging in compensatory behaviors such as vomiting.

Empirical research has also found a link between commitment to physical exercise and disordered eating attitudes and behaviors, particularly in men. Regimented physical exercise has been viewed as a predictor, risk factor and/or symptom of eating disorders (Asci et al. 2006; Woodside et al. 2004). However, research which has examined disordered eating behaviors in a community sample of men and women did not reveal gender differences in either level or intensity of physical exercise (Gadalla 2009). The temporal sequence of exercise and disordered eating behaviors, as well as the gender difference, if any, in the strength of their association have yet to be determined.

185.2 Comorbidity of Eating Disorders and Alcohol Use Disorders

During the past 20 years, the comorbidity of eating disorders and substance use disorders has emerged as a significant health issue. The American Psychological Association (2005) and the National Center on Addiction and Substance Use at Columbia University (2001) have identified the study of this comorbidity as an important research agenda. Three factors have contributed to the importance and the urgency of this issue: (1) The documented high co-occurrence rates of the two types of disorders (e.g., Corcos et al. 2001; Dansky et al. 2000; Gadalla and Piran 2007a; Krahn et al. 2005; Piran and Gadalla 2006; Piran and Robinson 2006). (2) The significant association between these comorbid disorders and medical, psychological, and social morbidity (e.g., Krahn et al. 2005; Wiederman and Pryor 1996). (3) The complicated treatment challenges associated with these comorbid disorders (Corcos et al. 2001; Dansky et al. 2000; Sinha and O'Malley 2000).

185.2.1 Research Based on Female Samples

An association between disordered eating and alcohol use disorders has been observed in samples of women drawn from treatment seeking patients, in addition to high school, college, and community populations. Clinical samples of women with eating disorders were found to have a high rate of alcohol use disorders (Wiederman and Pryor 1996). The prevalence of alcohol use disorders has been reported to be as high as 30–50% in treatment seeking samples of women with bulimia nervosa (Dansky et al. 2000). Similarly, women with alcohol use disorders have been found to have a high rate of disordered eating patterns (e.g., Grilo et al. 1995; Sinha and O'Malley 2000). In a follow-up study in which women diagnosed with either anorexia nervosa or bulimia nervosa were assessed every 6–12 months for a period of 8.6 years, and a substantial number developed alcohol-related problems during the course of the study (Franko et al. 2005).

Moreover, an association between disordered eating and alcohol consumption was also found in multiple samples drawn from high school and university students (e.g., Field et al. 2002; Neumark-Sztrainer et al. 1998). For example, when Adams and Araas (2006) examined the co-occurrence of bulimia nervosa with binge eating behaviors and high-risk alcohol behavior in a national sample of female college students, they found that students who reported purging tended to report heavier

alcohol use than those who did not. Furthermore, students who purged and drank alcohol reported more negative consequences than the non-purgers.

Few studies have examined the association between eating disorders and alcohol use disorders in nationally representative samples. Among them, Dansky and colleagues (2000) found a higher rate of alcohol dependence among women with bulimia nervosa compared with women without bulimia nervosa or with binge eating disorder. No such differences were found in the rates of alcohol abuse. In a community sample of Canadian women, 41.8% of those with a diagnosis of bulimia nervosa and 27.3% of those with sub-clinical symptoms of bulimia nervosa had drinking problems compared to 20.9% of the controls (Garfinkel et al. 1995). In a more recent study of a nationally representative sample of Canadian women, Piran and Gadalla (2006) reported significant associations between disordered eating behavior and measures of alcohol dependence and alcohol interference for women in all age groups.

185.2.2 Research Based on Male Samples

Eating disorders are much more common among women than men and have long been assumed to be found exclusively in women. Consequently, few studies have focused on eating disorders in men and even fewer have examined the association of eating disorders with alcohol use disorders in men. Most research on eating disorders in men has been based on case studies and small clinical samples without the use of appropriate control groups (Woodside et al. 2001). Men have been reported to comprise between 5% and 10% of eating disordered individuals in clinical settings (Woodside 2002) with significantly more gay and bisexual men suffering from these disorders compared to heterosexual men (Feldman and Meyer 2007). However, there is evidence to suggest that more men in the general population have eating disorders (Woodside et al. 2001) and that eating disorders in men are underdiagnosed and undertreated (Weltzin et al. 2005; Woodside et al. 2004).

A study which evaluated the relationship between alcohol dependence and eating disorders found that the lifetime rates of bulimia nervosa were found to be higher than expected in both men and women (Schuckit et al. 1996). Other findings from a small scale study of substance abuse patients in a treatment setting revealed that men and women reported similar levels of engagement in binge eating and compensatory behaviors; however, the women had higher disturbed attitudes about body weight and shape (Jackson and Grilo 2002). In a study of male patients treated for eating disorders, 37% were found to fulfill DSM-IV criteria for substance abuse (Carlat et al. 1997).

185.2.3 Research Comprised of Male and Female Samples

Gadalla and Piran (2007a) examined the above association using a nationally representative sample of 20,211 women and 16,773 men. In this study, respondents who reported being concerned about their weight during the 12 months prior to the interview, were administered the Eating Troubles module, EAT-26 developed by Garner et al. (1982). The measure used for alcohol dependence was based on the Composite International Diagnostic Interview, developed by Kessler et al. (1998). The level of alcohol interference indicated whether alcohol use interfered with the individual's normal routine, occupational/academic functioning, social activities, or relationships. The prevalence rate of disordered eating behavior for men was found to be 0.5% and that of alcohol interference 2.2% (Table 185.1). If these conditions were independent, the probability that they co-occur by chance

Table 185.1 Measures of alcohol consumption and body weight concerns in Canadian men and women, 2002 (From Gadalla and Piran 2007b. With permission)

	Men	Women
	$n = 16,773$	$n = 20,211$
Strong fear of being overweight – 12 months	7.7%	18.5%[***]
Strong fear of being overweight – lifetime	15.2%	32.3%[***]
Eating attitude test score >20	0.5%	2.8%[***]
Alcohol dependence – 12 months	3.9%	1.3%[***]
Alcohol interference – 12 months	2.2%	0.7%[***]

[***]$p < 0.0005$. The [***] indicate statistically significant difference between men and women using chi-square test

This table includes percentages of survey participants who reported having strong fear of being overweight in the 12 months prior to the interview, in their lifetime, those who scored > 20 on the EAT instrument, participants who were identified as alcohol dependent and participants whose drinking interfered with their daily activities.

Table 185.2 Rates of alcohol use in Canadian men and women in association with disordered eating behaviors (EAT-26 score ≤ 20 vs >20) (From Gadalla and Piran 2007b. With permission)

	EAT-26	Men	Women
Alcohol dependence – past 12 months	Score ≤ 20	3.8%[*]	1.3%[***]
	Score > 20	8.3%	3.8%
Alcohol interference – past 12 months	Score ≤ 20	2.2%[***]	0.6%[***]
	Score > 20	9.1%	3.0%
Sample size	Score ≤ 20	16,685	19,638
	Score > 20	88	573

This table shows the percentages of survey participants who scored > 20 versus ≤ 20 on the EAT instrument by within those who were identified as alcohol dependent

Significance levels refer to the associations between measures of alcohol use and disordered eating behavior within gender using chi-square test

[*]$p < 0.05$, [***]$p < 0.0005$

Data presented in the table indicate a strong association between disordered eating behavior and each of alcohol dependence and interference in women. For men, disordered eating behavior was strongly associated with alcohol interference and moderately associated with alcohol dependence

alone would be 0.012% (0.5% × 2.2%). However, the observed probability of the co-occurrence of eating disorders and alcohol interference was 0.048%, four times the chance probability, indicating an association between the two conditions. Similarly, the observed probability of co-occurrence of these two conditions for women was 0.085%, which was 4.4 times the probability of occurring by chance alone. All measures of alcohol use were consistently higher for women with disordered eating behavior, which was not the case for men (Table 185.2). While disordered eating behavior in women was strongly associated with alcohol dependence and alcohol interference, disordered eating behavior in men was strongly associated with alcohol interference and marginally associated with alcohol dependence.

By contrast, some studies did not find an association between eating disorders and alcohol use disorders (e.g., Dunn et al. 2002; Matthews 2004; Stock et al. 2002; Welch and Fairburn 1996). Dunn and colleagues (2002) noted that their nonclinical sample of college students who met the criteria for bulimia nervosa did not drink significantly more alcohol than non-eating disordered students. Furthermore, Stock and colleagues (2002) reported that female adolescents with restrictive eating disorders drank significantly less alcohol than matched controls. Additionally, Welch and Fairburn (1996) compared alcohol consumption in three groups of women recruited from the community,

women with bulimia nervosa, controls with other psychiatric disorders, and controls without such disorders. The authors found no difference in current alcohol consumption between bulimia nervosa cases and either control group. More recently, Matthews (2004) found no evidence of a concurrent relationship between eating disorders and alcohol use disorders in college students.

185.2.4 Review Studies

Holderness and colleagues (1994) reviewed 51 studies on eating disorders and substance use and abuse that were published between 1977 and 1991. In 24 of the studies reviewed, the percentage of individuals with bulimia nervosa who reported alcohol abuse and/or dependence ranged between 2.9% and 48.6% with a median of 22.9%. These authors also noted that among eight studies that included women with both bulimia nervosa and anorexia nervosa, the rates of alcohol abuse and/or dependence ranged between 12% and 39% with a median of 26%. More recently, Gadalla and Piran (2007b) conducted a meta-analysis of 41 studies on the co-occurrence of eating disorders and alcohol use disorders in women that were published between 1985 and 2006. Over one third of studies reviewed (15 studies) recruited their participants from the community, approximately one third (14 studies) recruited participants from educational institutions, and 29% (12 studies) recruited their participants from clinical settings (Table 185.3). The type of participants recruited for the comparison group in clinical studies also varied, with four studies recruiting controls from the community and three studies recruiting controls from general psychiatric current or previous patients. As would be expected, criteria used for eating disorder assessments were significantly associated with the type of sample used. Clinical measures were used mostly with clinical samples and behavioral measures with student samples (Fisher's exact test = 16.17, p-value = 0.001). Only four out of the 41 studies in the meta-analysis reported negative associations between eating disorders and alcohol use disorders. Two of the studies reported a negative relationship between anorexia nervosa and alcohol use disorders, with effect sizes of -0.85 and -0.49, while the remaining two studies reported negative relationships between bulimia nervosa or bulimic behavior and alcohol use disorders, with effect sizes of -0.07 and -0.92. As shown in Table 185.4, the mean effect size of overall eating disorders was 0.38 (se = 0.07) and was significantly different from zero ($p < 0.001$). A significant mean effect size was found for the relationship between alcohol use disorders and each eating disorder pattern except for anorexia nervosa. Based on Cohen's (1988) categorization of an effect size of 0.2 as small, 0.5 as moderate and 0.8 as large, the average effect size found in this meta analysis ranged from small to moderate and was largest for bulimia nervosa/bulimic behavior and alcohol use disorders.

Table 185.3 Types of samples and eating disorders assessment criteria used in the reviewed articles (From Gadalla and Piran 2007b. With permission)

Assessment of eating disorders	Type of sample			Total
	Clinical	Community	Students	
Clinical	10 (83.3%)	8 (53.3%)	1 (7.1%)	19
Psychometric	1 (8.3%)	2 (13.3%)	5 (35.7%)	8
Behavioral	1 (8.3%)	5 (33.3%)	8 (57.1%)	14
Total	12	15	14	41

This table includes a count of the number of studies used in the meta-analysis by type of sample participants and the criteria used to assess eating disorders

Fisher's exact test was used to test the association of type of participants and criteria used to assess eating disorders. Fisher's test = 16.17, p-value = 0.001, i.e. there was a significant association between the two characteristics

Table 185.4 Means, standard errors and homogeneity indices of effect size of the relationship between eating disorders and alcohol use disorders in women, by type of eating disorder (From Gadalla and Piran 2007b. With permission)

Type of eating disorder	Number of studies	Homogeneity index, Q	Between-study variability, I^2	Mean of ES (st error)
Any eating disorder	41	160.94***	75.15	0.38 (0.07)***
Bulimia nervosa/Bulimic behavior	29	132.13***	78.81	0.46 (0.10)***
Anorexia nervosa	8	22.59**	69.01	0.09 (0.14)
Purging	6	13.51*	62.98	0.41 (0.12)**
Restriction/dietary restraint	6	1.06	0.00	0.13 (0.03)***
Binge eating disorder	5	1.04	0.00	0.39 (0.14)**
Eating disorders not otherwise specified	9	12.09	33.82	0.41 (0.12)***

For articles that reported more than one measure of alcohol use disorders or eating disorders, effect sizes were derived for all measures and their mean calculated such that only one effect size per study per pattern of eating disorder was used. The overall mean (and its standard error) of all studies per type of eating disorder is shown in the above table

Mean effect sizes were transformed to z-values to test whether they were significantly different from zero. Except for anorexia nervosa, the mean effects for all types of disordered eating were significantly different from zero
* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$
The Q statistic measures the homogeneity of effect sizes across studies. Higher values of Q indicate lack of homogeneity among study results
The I^2 index is an estimate of the percentage of total variability in effect sizes that is due to between-studies variability rather than sampling errors within studies. The table shows significant heterogeneity among studies in the relationships between AUD and each of any ED, BN/bulimic behavior, AN, and purging reported by different studies. On the other hand, the relationship between AUD and each of binge eating disorder and dietary restraint were the most consistent with minimal heterogeneity across studies

The authors also noted that the co-occurrence rates of different patterns of disordered eating with alcohol use disorders were generally weakest and most divergent when participants were recruited from clinical settings and strongest and most homogeneous when participants were recruited from student populations.

185.3 Proposed Mechanisms of the Relationships Between Eating Disorders and Alcohol Use Disorders

While high rates of comorbidity of eating disorders and alcohol use disorders have been well documented and observed in samples drawn from clinical settings, educational institutions and the community, the nature of this relationship is still unclear. Several hypotheses have been proposed, each with supportive as well as contradictory research findings.

185.3.1 The Addictive Personality Hypothesis

The addictive personality hypothesis is based on the belief that certain individuals are predisposed to become addicted to one or more substances (Brisman and Siegel 1984). Supporters of this hypothesis stress the clinical and behavioral similarities between eating disorders, especially bulimia nervosa and binge eating, and alcohol use disorders. Two suppositions are at the heart of this hypothesis: (1) eating disorders can be characterized as an addiction and (2) individuals who are vulnerable to these two addictions share certain personality traits that can be used to identify them. Neither assumption is universally accepted (Wolfe and Maisto 2000).

It has been suggested that both bulimia nervosa and alcohol use disorders involve similar brain systems and share elements of preoccupation, loss of control (Gold et al. 2003), impulsivity (Fichter et al. 1994; Wiederman and Pryor 1996), and compulsivity (e.g., Franko et al. 2005). For example, bulimic women have been described as having symptoms of impulse control, which may explain the elevated alcohol use in this population (e.g., Fichter et al. 1994; Wiederman and Pryor 1996). It is not clear, however, whether binge eating carries other addiction criteria, such as physical dependence and tolerance. Research by Keel et al. (2001) found that purging in the absence of binging in normal-weight individuals may be related more to substance use than previously believed. Findings presented by Franko and colleagues (2005) found alcohol use to be more closely related to purging than binging and concluded that both vomiting and alcohol use represent a compulsive dimension of psychopathology.

Research studies documenting higher prevalence of borderline personality disorders in individuals with both eating disorders and substance use disorders compared with individuals with eating disorders alone (e.g., Grilo et al. 1995) provide supporting evidence to the addictive personality hypothesis. However, with the overlap between diagnostic criteria for borderline personality disorder and those for bulimia nervosa and substance abuse, these high prevalence rates could be the result of the diagnostic instruments utilized (Wolfe and Maisto 2000).

185.3.2 The Developmental Hypothesis

Vulnerability to adolescent stressors has also been used to explain the observed high co-occurrence of eating disorders and alcohol use disorders. Some researchers have emphasized the role of dysregulation in the co-occurrence of disordered eating patterns and substance use (e.g., Stewart et al. 2000). This view proposes that regulatory challenges may be expressed through engagement in different disordered eating and drug consumption behaviors. For example, some adolescents may engage in experimenting in drugs as well as disordered eating behavior to conform to social and culture pressures (Wolfe and Maisto 2000).

Several studies have reported associations between the use of problem weight loss methods, such as diet pills and vomiting and alcohol use in adolescents (e.g., French et al. 1997; Neumark-Sztainer et al. 1998; Keel et al. 1998). For example, French and colleagues (1997) found alcohol use to predict purging and binge eating among white adolescent females but not black females. In another study of adolescent boys, Keel and colleagues (1998) did not find a difference in alcohol use between boys with disordered eating and those without disordered eating. More recently, alcohol use was found to predict the use of laxatives and vomiting in white females and black males in a large sample of middle school students (Garry et al. 2003). Garry and colleagues (2003) also found that female students consistently reported use of all weight loss methods more frequently than male students. The dysregulation hypothesis could be evaluated further by examining associations between disordered eating behavior and other forms of behavioral dysregulation, such as risky sexual behavior, in addition to drinking behavior (Stewart et al. 2000).

185.3.3 The Family History Hypothesis

A familial relationship has been suggested as a contributor to the observed high co-occurrence rates of eating disorders and alcohol use disorders. This hypothesis is based on evidence of genetic links to both types of disorders. However, the mechanisms underlying this hypothesis have not been adequately described (Wolfe and Maisto 2000) and the findings of a number of studies have disputed it.

Research evidence in support of a common genetic predisposition to both eating disorders and alcohol use disorders include higher rates of eating disorders in adult children of alcoholics (e.g., Jonas and Gold 1988) and high rates of family history of alcohol abuse in bulimic patients (Bulik 1987). On the other hand, no relationship was found between parental alcohol use disorders and eating disorder symptomatology (Mintz et al. 1995), nor between prevalence of eating disorders and having an alcohol-dependent relative (Meyer 1997; Schuckit et al. 1996). Finally, in a large scale female twin study, Kendler and colleagues (1995) found the genetic factors for alcohol use disorders to be unrelated to the genetic factors of alcohol use disorders.

185.3.4 The Food Deprivation Hypothesis

Dietary restraint has been suggested as a mediating mechanism in explaining the relationship between body weight and shape preoccupation and adverse patterns of alcohol drinking, especially patterns of binge drinking (Stewart et al. 2000). Dietary restraint may result in intake disinhibition leading to both eating and drinking binges. Similarly, alcohol drinking restraint, motivated by the need to avoid high caloric intake, may also result in drinking binges (Stewart et al. 2000).

Stewart and colleagues (2000) found dietary restraint to be strongly associated with measures of binge drinking, quantity of alcohol consumed and excessive drinking in female university undergraduates. The authors concluded that chronic dieting was related to heavy drinking patterns. Kleiner and colleagues (2004) examined the relationship between body mass index and alcohol use in a sample of weight management female patients and found obese patients to have lower rates of alcohol use than women in the general population. Additionally, as body mass index increased, alcohol consumption decreased and it was found that body mass index increased during supervised abstinence. The authors concluded that overeating may compete with alcohol for brain reward sites and result in reduced alcohol intake and dependence rates and that alcohol may replace existing food reward pathways.

However, some controversial evidence counters the argument for the food deprivation hypothesis. Research by Bulik and Brinded (1993) reported that bulimics and controls failed to increase their alcohol consumption following a 19-h food deprivation period. It is not known, however, whether a longer food deprivation period would result in an increase in alcohol consumption.

185.3.5 The Negative Affective Hypothesis

Negative feelings and emotional instability have also been offered as explanations of the relationship between eating and substance use disorders, including alcohol (Benjamin and Wulfert 2005). This hypothesis stipulates that some individuals use both food and alcohol to self medicate when they feel distressed or anxious.

In a longitudinal study of patients with anorexia nervosa or bulimia nervosa, poor psychosocial functioning and a history of substance use were found to predict prospective onset of alcohol use disorders (Franko et al. 2005). Franko and colleagues (2005) also found depression to predict alcohol use disorders in women with anorexia nervosa. Additionally, in a sample of female relatives of alcoholics, women with lifetime bulimia nervosa and alcohol dependence were more likely than women with either disorder alone to have major depression (Duncan et al. 2006).

In a community-based study of correlates of binge eating disorders in men and women (Grucza et al. 2007), the authors reported a significantly higher prevalence of depression and probable alcohol

use disorder in persons with binge eating disorder compared with those without binge eating disorders. Further, in a nationally representative sample of Canadians, having disordered eating behavior was associated with significantly higher odds of major depression for both genders (Gadalla and Piran, 2009). Gadalla and Piran (2009) found that the initially significant association between disordered eating behavior and alcohol dependence became nonsignificant when depression was controlled for, while the significant association between disordered eating behavior and alcohol interference was reduced when depression was controlled for. Based on the findings of the later study, the authors suggested that depression may fully mediate the relationship between eating disorders and alcohol dependence and partially mediate their relationship with alcohol interference for both men and women.

It should be mentioned, however, that both behavioral and affective dysregulation can be related to life experiences, such as trauma (van der Kolk et al. 1996), as well as to inborn temperamental tendencies (Martin et al. 2000). Indeed trauma has been found to explain the observed relationship between binge eating and alcohol abuse (Dansky et al. 2000).

185.4   Discussion and Recommendations

Although research has generally reported high rates of co-occurrence between eating disorders and alcohol use disorders, there is great variability in the reported co-occurrence rates across studies. Methodological differences among studies make it difficult to compare findings across them. For example, studies investigating the comorbidity of eating disorders and alcohol use disorders have recruited participants from heterogeneous settings, such as, schools, clinics, and communities with large variability in the size of samples. Another factor that contributes to the variability in the reported rates is the use of a variety of instruments to measure eating disorders and a wide range of criteria to assess alcohol use disorders. Alcohol consumption is a complex behavior and measures of total number of drinks consumed may not yield the same pattern of association with eating disorders as measures of binge drinking or other measures that take into account adverse consequences to drinkers' lives (Stewart et al. 2000). In addition, women on average have lower body weight relative to men, a fact which should be taken into account when comparing patterns of alcohol consumption (Matthews 2004). Another factor that complicates the comparison of findings across studies is the use of different reference times for the diagnosis of both disorders which ranged from point-prevalence rates to lifetime occurrences. Only when researchers use common criteria for assessing both eating disorders and alcohol use disorders can meaningful comparisons between studies be made. Many studies collapse all eating disorders into one category and likewise for drug and alcohol abuse. This practice adds to the difficulty of making general inferences about the comorbidity of these disorders.

In addition, since clinical based studies are affected by sampling biases, researchers have repeatedly highlighted the role of population-based studies in assessing the extent and nature of comorbidity (Dansky et al. 2000; Welch and Fairburn 1996) as well as the importance of selecting appropriate controls in clinical studies. Clinical-based studies are affected by sampling biases especially when studying patients with multiple problems since comorbidity itself may influence individuals to seek treatment (Welch and Fairburn 1996). Moreover, these patients do not represent the entire range of symptoms present in the population.

Researchers are encouraged to continue to explore the mechanisms that could mediate this consistent pattern of co-occurrence of eating and alcohol use disorders, beyond specific mechanisms related to dietary restraint and body shape preoccupation that may lead both men and women to engage in disruptive alcohol binges. Well-designed empirical research regarding the etiological

relationship between eating disorders and alcohol use disorders is lacking (Wolfe and Maisto 2000). Most studies, to date, have used cross-sectional data, which precludes any definitive conclusions regarding the temporal sequence. Longitudinal, controlled studies are needed in order to establish the temporal sequence of the occurrence of eating disorders, alcohol use disorders, depression, anxiety, and family history of substance dependence.

Very few studies have focused on eating disorders in men and even fewer have attempted to compare men with and without eating disorders or men with eating disorders versus women with eating disorders. Evidence exists to suggest that eating disorders in men are underdiagnosed and undertreated (Weltzin et al. 2005; Woodside et al. 2004). Men may not seek treatment due to their experience of less severe symptoms or because they may not consider themselves at risk for eating disorders (Woodside et al. 2004). Other barriers to seeking treatment may include cultural biases and lack of treatment settings that are dedicated for men with eating disorders (Weltzin et al. 2005). Consequently, very little is known about eating disorders in men and its relationship with other forms of psychopathology. However, with the increasing pressure on men to be fit and to look muscular, there is supportive evidence that suggests body dissatisfaction and eating disorders in men are increasing (O'Dea and Abraham 2002). More research efforts should be directed to the study of all aspects of eating disorders in men.

185.5 Applications to Other Areas of Health and Disease

The focus of this chapter has been the comorbidity of eating disorders and alcohol use disorders. However, the empirical observations and discussion of underlying mechanisms presented here can be easily extended to the comorbidity of eating disorders and drug use disorders. Elevated rates of co-occurrence of eating disorders and drug abuse have been reported by many researchers (e.g., Carlat et al. 1997; Jackson and Grilo 2002; Piran and Robinson 2006; Welch and Fairburn 1996; Wiederman and Pryor 1996). Findings of these studies suggest that, in contrast with the consistent pattern regarding the association of eating disorders and alcohol use disorders in women and men, the findings regarding illicit drug use are markedly different between genders. For example, Gadalla and Piran (2007a) found disordered eating behavior to be associated with current illicit drug use and lifetime use of cocaine/crack, amphetamines (speed), MDMA (ecstasy) and hallucinogens, PCP, or LSD, and cannabis in a community sample of women, whereas in men, disordered eating behavior was only associated with amphetamine use. Most studies, however, tended to examine the associations between eating disorders and a restricted range of substance classes (Piran and Robinson 2006) or combine all substances in one group. Some substances may be used as appetite suppressants for the purpose of weight loss (Nappo et al. 2002) and others used for their stimulant and euphoric effects (Feldman et al. 1997). Thus, it is important that future studies examine the relationship between eating disorder patterns and each class of substances separately.

Summary Points

- Empirical research provides evidence of high comorbidity between alcohol use and all disordered eating patterns, except anorexia nervosa. This comorbidity was observed for both genders and is highest with binge eating and bulimic behavior.
- More research is needed to determine the temporal sequence of the occurrence of eating disorders and alcohol use disorders and to explain the mechanisms underlying their co-occurrence.

- Emerging research indicates that disordered eating in men is a growing concern. However, few studies included male participants and even fewer examined gender differences.
- Future research is encouraged to use longitudinal data collected from population-based samples.
- The importance of using appropriate control groups in clinical studies is highlighted.

Definitions and Explanations of Key Terms

Anorexia nervosa: Anorexia nervosa is a psychiatric diagnosis that describes an eating disorder characterized by low body weight and body image distortion with an obsessive fear of gaining weight.

Bulimia nervosa: Bulimia nervosa is an eating disorder characterized by recurrent binge eating, followed by compensatory behaviors, such as self-induced vomiting and the use of laxatives, enemas, and diuretics.

Purging: Purging refers to the act of using self-induced vomiting and the use of laxatives, enemas, or diuretics to get rid of ingested food.

Binge eating disorder: Binge eating consists of episodes of uncontrollable overeating, during which a person rapidly consumes a large amount of food.

Dietary restraint: Dietary restraint refers to behaviors that are intended to limit food intake, in an effort to manage weight. Such attitudes may include cutting food into small pieces, obsession with counting calories, etc.

Eating disorders not otherwise specified: Eating disorder not otherwise specified is described in the DSM-IV-TR as a "category [of] disorders of eating that do not meet the criteria for any specific eating disorder".

Alcohol dependence: Alcohol dependence describes the use of alcohol despite significant detrimental consequences. For a person to meet criteria for Alcohol Dependence, the person must meet three of a total of seven possible DSM-IV criteria within a 12 month period. The criteria include tolerance and withdrawal, losing control of drinking, a progression of addiction, and continuing to drink despite being aware that it is causing or psychological or physiological problem(s).

Alcohol interference: Alcohol interference refers to the interference of drinking alcohol with the person's work, study, social relationships, etc.

Key Points

- Empirical research provides evidence of high comorbidity between alcohol use and all disordered eating patterns, except anorexia nervosa. This comorbidity was observed for both genders and is highest with binge eating and bulimic behavior.
- Several hypotheses have been proposed to explain the mediating mechanisms between the two psychopathologies. By and large, these hypotheses have not been empirically tested. In addition, the temporal sequence of the occurrence of eating disorders and alcohol use disorders is not yet determined.
- Although there is evidence to suggest that disordered eating in men is a growing concern, few studies included male participants and even fewer examined gender differences.

References

Adams TB, Araas TE. Int J Eat Disord. 2006;39:240–4.

American Psychological Association Research agenda for psychosocial and behavioral factors in women's health: Health behaviours.. Recommendations from the Advisory Committee of the Psychosocial and Behavioral Factors in Women's Health: Creating an Agenda for the 21st Century Conference. 2005. http://www.apa.org/pi/wpo/behavior.html#alcohol. Accessed 15 May, 2005.

Asci FH, Tuzun M, Koca C. Eat Behav. 2006;7:362–7.

Barry DT, Grilo CM, Masheb RM. Int J Eat Disord. 2002;31:63–70.

Benjamin L, Wulfert E. Eat Behav. 2005;6:197–209.

Brisman J, Siegel M. J Subst Abuse Treat. 1984;1:113–8.

Bulik CM. Am J Psychiatry. 1987;144:1604.

Bulik CM, Brinded EC. Addiction. 1993;88:1545–51.

Carlat DJ, Camargo CA, Herzog DB. Am J Psychiatry. 1997;154:1127–32.

Cohen J. Statistical power analysis for the behavioral sciences. 2nd ed. Hillsdale: Lawrence Earlbaum Associates; 1988.

Corcos M, Nezelof S, Speranza M, Topa S, Girardon N, Guilbaud O, Taïeb O, Bizouard P, Halfon O, Venisse JL, Perez-Diaz F, Flament M, Jeammet Ph. Eat Behav. 2001;2:27–38.

Dansky BS, Brewerton TD, Kilpatrick DG. Int J Eat Disord. 2000;27:180–90.

Duncan AE, Neuman RJ, Kramer JR, Kuperman S, Hesselbrock VM, Bucholz KK. Drug Alcohol Depend. 2006;84:122–32.

Dunn EC, Larimer ME, Neighbors C. Int J Eat Disord. 2002;32:171–8.

Elgin J, Pritchard M. Eat Weight Disord EWD. 2006;11:e96–101.

Feldman RS, Meyer JS, Quenzer LF. Principles of neuropsychopharmacology. Massachusetts: Sinauer Associates, Inc. 1997.

Feldman MB, Meyer IH. Int J Eat Disord. 2007;40:218–26.

Fichter MM, Quadflieg N, Rief W. Psychol Med. 1994;24:591–604.

Field AE, Austin SB, Frazier AL, Gillman MW, Camargo CA, Jr Colditz GA. J Am Acad Child Adolesc Psych. 2002;41:846–53.

Franko DL, Dorer DJ, Jackson S, Manzo MP, Herzog DB. Int J Eat Disord. 2005;38:200–7.

French SA, Story M, Neumark-Sztainer D, Downes B, Resnick M, Blum R. Int J Eat Disord. 1997;22:315–22.

Gadalla TM. Int J Mens Health. 2009;8(1):72–81.

Gadalla TM, Piran.N. J Ment Health, 2009;18(6):486–94.

Gadalla TM, Piran N. Eat Disord. 2007a;15:189–203.

Gadalla TM, Piran N. Arch Womens Ment Health. 2007b;10:133–40.

Garfinkel PE, Lin E, Goering P, Spegg C, Goldbloom DS, Kennedy S, Kaplan AS, Woodside DB. Am J Psychiatry. 1995;152:1052–8.

Garner DM, Olmsted MP, Bohr Y, Garfinkel PE. Psychol Med. 1982;12:871–8.

Garry JP, Morrissey SL, Whetstone LM. Int J Eat Disord. 2003;33:55–63.

Gold MS, Frost-Pineda K, Jacobs WS. Psychiatr Ann. 2003;33:117–22.

Grilo CM, Levy KN, Becker DF, Edell WS, McGlashan TH. Addict Behav. 1995;20:255–60.

Gruber AJ, Pope HG, Borowiecki JJ, Cohane G. J Clin Psychol. 2001;62:609–11.

Grucza RA, Przybeck TR, Cloninger CR. Compr Psychol. 2007;48:124–31.

Holderness C, Brooks-Gunn J, Warren M. Int J Eat Disord. 1994;16:1–34.

Jackson TD, Grilo CM. Eat Weight Disord. 2002;7:276–83.

Jonas JM, Gold MS. Psychiatry Res. 1988;24(2):195–99.

Keel PK, Mayer SA, Harnden-Fischer JH. Int J Eat Disord. 2001;29:294–301.

Keel PK, Klump KL, Leon GR, Fulkerson JA. Int J Eat Disord. 1998;23:125–32.

Kendler KS, Walters EE, Neale MC, Kessler RC, Heath A, Eaves LJ. Arch Gen Psychiatry. 1995;52:374–83.

Kessler RC, Andrews G, Mroczek D, Ustun B, Wittchen H. Int J Methods Psychiatr Res. 1998;7:171–85.

Kleiner KD, Gold MS, Frost-Pineda K, Lenz-Brunsman B, Perri MG, Jacobs WS. J Addict Dis. 2004;232:105–18.

Krahn DD, Kurth CL, Gomberg E, Drewnowski A. Eat Behav. 2005;6:43–52.

Lindblad F, Lindberg L, Hjern A. Int J Eat Disord. 2006;39:662–6.

Mangweth B, Hausmann A, Walch T, Hotter A, Rupp CI, Biebl W, Hudson JI, Pope HG. Int J Eat Disord. 2004;35:102–8.

Martin GC, Wertheim EH, Prior M, Smart D, Sanson A, Oberklaid F. Int J Eat Disord. 2000;27:150–62.

Matthews CR. J Addict Dis. 2004;23:67–80.

Meyer DF. J Clin Psychol. 1997;53:107–16.

Mintz LB, Kashubek S Tracy LS. J Couns Psychol. 1995;42:65–70.

Nappo SA, Tabach R, Noto AR, Galduroz J.C. & Carlini E.A. Eating Behaviors. 2002;3:153–65.

National Center on Addiction and Substance Use at Columbia University. Food for Thought: Substance Abuse and Eating Disorders Conference. 2001;25(6). http://www.casacolumbia.org/absolutenm/templates/article.asp?articleid= 296&zoneid=40. Accessed June 25, 2005.

Neumark-Sztrainer D, Story M, Dixon LB, Murray DM. Am J Public Health. 1998;88:952–5.

O'Dea JA, Abraham S. J Am Coll Health. 2002;50:273–8.

Piran N, Gadalla TM. Addict. 2006;102:105–13.

Piran N, Robinson S. Women Health. 2006;44:1–20.

Schuckit MA, Tipp JE, Anthenelli RM, Bucholz KK, Hesselbrock VM, Nurnberger JI, Jr. Am J Psychiatry. 1996;153:74–82.

Sinha R, O'Malley SS. Alcohol Clin Exp Res. 2000;24:1312–9.

Stock SL, Goldberg E, Corbett S, Katzman DK. J Adolesc Health. 2002;31:176–82.

Stewart SH, Angelopoulos M, Baker JM, Boland FJ. Psychol Addict Behav. 2000;14:77–82.

van der Kolk BA, McFarlane AC, Weisaeth L. Traumatic stress: the effects of overwhelming experience on mind, body, and society. New York: Guilford Press; 1996.

Welch SL, Fairburn CG. Br J Psychiatry. 1996;169:451–8.

Weltzin TE, Weisensel N, Franczyk D, Burnett K, Klitz C, Bean P. J Mens Health Gend. 2005;2:186–93.

Wiederman, MW, Pryor T. Int J Eat Disord. 1996;20:163–8.

Wolfe WL, Maisto SA. Clin Psychol Rev. 2000;20:617–31.

Woodside DB. Healthy Weight J. 2002;16(4):52–5.

Woodside DB, Bulik CM, Thornton L, Klump KL, Tozzi F, Ficher MM, Halmi KA, Kaplan AS, Strober M, Delvin B, Bacanu SA et al. J Psychosom Res. 2004;57:273–8.

Woodside DB, Garfinkel PE, Lin E, Goering P, Kaplan AS, Goldbloom DS, Kennedy SH. Am J Psychiatry. 2001;158:570–4.

Chapter 186
The Great Disinhibitor: Alcohol, Food Cues, and Eating Behavior

Wilhelm Hofmann, Georg Förster, Wolfgang Stroebe, and Reinout W. Wiers

Abbreviation

BAC   Blood alcohol concentration

186.1 The Great Disinhibitor: Alcohol, Food Cues, and Eating Behavior

Lay theories of the association of alcohol and overweight focus mainly on beer-drinking men, who are believed to be at risk of developing beer bellies, defined as "a man's fat stomach, caused by too excessive consumption of beer" (*Oxford American Dictionary*, 2nd ed., 2005, p. 146). If one inferred from this that female beer-drinkers or wine drinkers of both genders were not at risk of gaining weight from excessive alcohol consumption, one would be wrong. The active ingredient in beer which is responsible for weight gain (or any other problem) is alcohol (ethanol) and beer shares this ingredient with all other alcoholic beverages. Thus, there can be wine bellies as well as beer bellies and while women are likely to store their weight in other places, both genders are equally at risk of weight gain.

In this chapter, we focus on two different ways by which alcohol can facilitate weight gain. First, alcohol does have a direct effect on caloric intake through the calories contained in alcohol. With 7 kilocalories per gram (kcal/g), alcohol has the second highest calorie content of any macronutrient, and people rarely compensate by eating less for the extra calories they take in by drinking beer or wine with their meals. Second, alcohol impairs people's ability to regulate or control their food intake. We will present a model illustrating the various influences by which alcohol can disrupt the self-regulation of eating by boosting the impulsive processing of tempting food cues in the environment and by disrupting executive control in the short and long run. Furthermore, we will discuss the modulating role of alcohol expectancies, possible spiraling patterns with respect to the interplay of alcohol and eating, and applications to other health domains.

W. Hofmann (✉)
University of Chicago, Booth School of Business, 5807 South Woodlawn Avenue,
Chicago, IL 60615
e-mail: wilhelm.hofmann@chicagobooth.edu

186.2 The Direct Route: Alcohol as Non-compensated Caloric Intake

Drinking two glasses of dry white wine (200 mL) adds 150 kcal to one's meal. This might not seem much, but the daily excess of 150 kcal would result in a weight gain of 3.5 kilogram per year (Stroebe 2008). To work off an extra 150 kcal, an adult weighing 70 kg would have to walk for 37 min or jog for 18 min. Ironically, many people seem to reverse this logic and drink a lot of alcohol and/or high caloric "energy drinks" after a sporting event. Adding alcohol to a meal would not pose a risk of weight gain, if people stayed within their daily calorie limit by proportionally reducing their calorie intake from food. However, people do not (or only very imperfectly) compensate for the additional caloric burden contained in high-caloric beverages of all sort, including alcohol (Mattes 2006; Yeomans et al. 2003). One cognitive explanation for this regulatory failure is that even individuals who closely monitor their calorie intake often do not take account of the caloric content of beverages to the same degree that they monitor the caloric content of food. Hence, they do not adjust their self-regulatory standards appropriately. A second more physiological explanation is that beverages, due to their low viscosity, are far less satiating than solid foods (Hulshof et al. 1993). Taken together, alcohol's direct influence on caloric intake is typically ignored and this effect alone can pose a serious threat to a person's weight goals.

186.3 The Indirect Route: Undermining Self-regulation

As Herman and Polivy (2004) point out, viewing eating behavior as simply regulated by bodily hunger and satiety signals is a great oversimplification. Eating behavior, at least in modern societies, is to a large extent also influenced by social norms (e.g., adherence to mealtimes, the presence of other people), the food environment (e.g., the presence of tempting food cues), and, most centrally to the present purpose, by internalized self-regulatory goals people harbor with regard to their food intake. Such self-regulatory goals are often related to matters of appearance (e.g., "I want to keep a slim figure because thin is attractive") or health ("I want to avoid eating too high-cholesterol food"). However, most psychological theories of eating regulation assume that people differ in the extent to which they regulate their weight by cognitively controlling their calorie intake. For example, Schachter's (1971) Externality Theory postulated that in contrast to normal weight individuals, who regulate their eating in response to internal cues of hunger or satiation, these cues are irrelevant to eating by obese. Their eating is triggered by external food-relevant cues such as the palatability of food or external cues in the environment, which signaled palatable food (e.g., sight or smell of food; salience of food cues).

Schachter's theory was later integrated by Herman and Polivy (1984) into their "Boundary Model of Eating," which has dominated eating research for decades. Herman and Polivy (1984) introduced the individual difference variable of "Restrained Eating" and developed the "Restraint Scale" to place people on this dimension. People vary on a continuum from unrestrained to restrained eating. At the unrestrained eating end of the continuum are normal eaters, individuals who have no weight problems and regulate their calorie intake in response to internal cues. At the restrained endpoint are restrained eaters (i.e., chronic dieters), who continuously monitor their calorie intake, trying to keep it below some regulatory standard or "diet boundary" which defines the maximum amount of calories they allow themselves to consume. As the cognitive control of calorie intake requires more cognitive resources than the automatic regulation in response to internal hunger and satiety cues, regulation can easily be disrupted by external factors, which reduce the individual's ability or motivation

to control their calorie intake. It is these restrained eaters whose eating control is likely to be deregulated by alcohol consumption.

Both externality theory and boundary model agree on the basic assumption that (a) weight is homeostatically regulated through bodily signals of hunger and satiety and that (b) for various reasons this homeostatic regulation malfunctions in individuals with weight problems or in restrained eaters. Although there can be no question that food intake and body weight are homeostatically controlled, the importance of this type of regulation for the development of overweight and obesity has increasingly been questioned (e.g., Lowe and Butryn 2007; Pinel et al. 2000). For example, Pinel and colleagues (2000) argued that people living in food-replete environments rarely experience energy deficits, but eat because of the pleasure that can be derived from food. Lowe and Butryn (2007) even suggested a distinction between *homeostatic* hunger, due to the prolonged absence of energy intake, and *hedonic* hunger, which is strongly influence by the availability and palatability of food.

Stroebe and colleagues (e.g., Stroebe 2008; Stroebe et al. 2008) incorporated the idea of hedonic eating into a goal conflict model of eating, which assumes that eating regulation of restrained eaters is dominated by a conflict between two incompatible goals, namely, the goal of maintaining or reducing their weight and the goal of enjoying palatable food. These individuals try to shield their weight control goal by suppressing thoughts about palatable food. Unfortunately (at least from the point of eating control), most of us live in food-rich environments, where palatable food is widely available and where we are surrounded by cues signaling palatable food. Such cues are likely to prime the eating enjoyment goal and to increase its cognitive accessibility. Once the goal of eating enjoyment is instigated by such palatable food cues, the goal of eating control will be inhibited, leading the individual to overeat.

The idea that eating involves relatively "primitive" hedonic influences as well as opposing higher-order processes of self-regulatory goal pursuit can also be derived from dual-process or dual-system conceptions of the mind (e.g., Hofmann et al. 2009; Strack and Deutsch 2004; Wiers et al. 2010). Specifically, these models generally assume an impulsive, association-based route to behavior determination whereby stimuli in the environment can automatically and effortlessly trigger motivational states such as cravings and desires and corresponding behavioral approach tendencies that have proven useful in the past to satisfy these cravings and desires. In contrast, long-term goal pursuit involves a series of coordinated higher-order processes of reasoning, behavioral decision making and behavior regulation (for more details, see Strack and Deutsch 2004). Importantly, the latter type of processing is typically more effortful in nature, and hence more easily disrupted than impulsive processing.

Thus, according to both the goal conflict and the dual-systems framework, the eating regulation of restrained eaters is dominated by a conflict between the reflective process of maintaining and shielding the weight control goal in the service of long-term goal pursuit and the more impulsive process that capture the hedonic short-term consequences of yielding to the temptation at hand. Whether one or the other side of this conflict wins, depends on the relative strength with which regulatory and impulsive influences impinge on final behavior determination. Figure 186.1 illustrates the competing influence of impulsive and reflective processing on caloric intake. In the following sections of this chapter, we will introduce the basic elements of the model and finally discuss the ways by which alcohol may modulate the effects of impulsive and reflective processing on eating behavior.

Focusing on reflective processes, Baumeister and Heatherton (1996) have identified three necessary factors for successful self-regulation: standards, self-monitoring, and the execution of control. First, self-regulatory goal standards have to be mentally represented in an accessible and consistent state during self-regulation (see Fig. 186.1). Active maintenance and shielding of self-regulatory goals from interference appears to build on working memory resources (e.g., Hofmann et al. 2008). Self-monitoring, in turn, pertains to the updated comparison of ongoing behavior with one's standards, similar to the "test" phase in feedback-loop models of self-regulation (e.g., Carver and Scheier 1981).
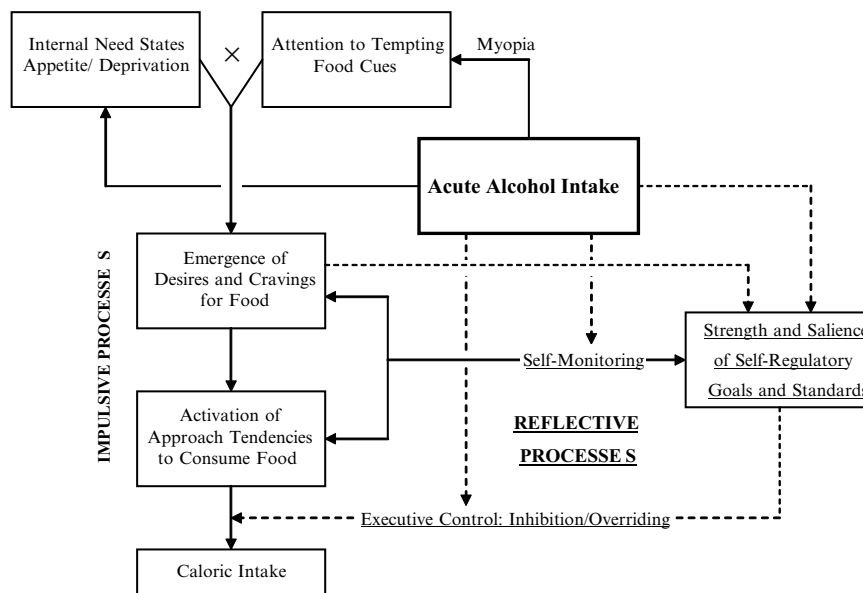
Fig. 186.1 A framework summarizing the key issues for possible acute alcohol effects on eating behavior as discussed in the present chapter. *Straight lines* indicate positive (facilitating) pathways. *Dotted lines* indicate negative (inhibitory) pathways. The framework holds that alcohol increases hunger and attention to salient food cues, thereby increasing the strength of cravings and desires for food. At the same time, alcohol appears to hamper reflective processing (underlined) in the service of self-regulatory goals. The figure does not show the direct link between alcohol consumption and caloric intake, indicating that alcohol in itself is a source of caloric intake that is typically not compensated for (see text)

In case discrepancies between standards and ongoing mental events are detected, an operative phase of executive control has to be set in motion if self-regulation is to be successful. Most forms of executive control can be described as either (a) the inhibition of a prepotent response (e.g., stopping an impulse to put a spoonful of mousse o chocolat into one's mouth) or (b) the overriding of a prepotent response, that is, substituting the undesired behavioral tendency with an alternative behavior (e.g., eating some healthy celery sticks instead). Self-regulation can go awry with regard to all three factors: First, people may fail to keep a clear representation of their self-regulatory goal in working memory in the first place. Second, even with intact goal-representations, they may fail to notice discrepancies between their standards and their actual thoughts or behavior. And third, even with goal representation and self-monitoring intact, people may lack sufficient self-regulatory resources (Baumeister and Heatherton 1996) or fail to recruit available resources (Muraven and Slessareva 2003) in the service of self-regulatory goal pursuit.[1]

As outlined in more detail elsewhere (Hofmann et al. 2009; Hofmann et al. 2008a), situational and dispositional boundary conditions may strongly influence people's self-regulatory success. Research on the self-regulation of eating has accumulated knowledge about conditions that disrupt the normal self-control of eating, especially for people who generally have high standards to restrain their caloric food intake (restrained eaters). Violation of dietary standards (Herman and Mack 1975)

---

[1]Note that we sketch self-regulation here as a resourceful, intentional, and conscious process of goal-pursuit. It is possible, however, that self-regulation can become habitual and automatized via repeated training (e.g., Fishbach and Shah 2006). Even though not in the focus of this chapter, such automatic forms of self-regulation may be far less susceptible to alcohol's detrimental influences on self-regulatory success described below. Common violations of self-regulatory standards suggest, however, that many individuals have not sufficiently transformed self-regulatory strategies into fully automatized routines.

temporary depletion of self-regulatory resources (Vohs and Heatherton 2000), cognitive load (Ward and Mann 2000), or tempting food stimuli (Fedoroff et al. 1997; Stroebe et al. 2008) have all been demonstrated as disinhibiting factors. As will be discussed in the next section, acute alcohol consumption is a very powerful situational disinhibitor, which appears to have a detrimental impact with regard to all the three factors of successful self-regulation identified above.

The present tug-of-war metaphor implies that the outcome of a self-regulatory conflict should not only hinge on the quality of self-regulatory goal pursuit, but also on the power of the temptation at hand. In the present framework we argue that the power of the temptation is jointly determined by the motivational need state of the organism (i.e., appetite) and the presence and features of food cues in the environment (see Fig. 186.1).[2] Exposure to palatable food stimuli triggers hedonic thoughts about the palatability of this food in restrained but not normal eaters (Papies et al. 2007) and the attention of restrained eaters becomes glued to those food stimuli (Papies et al. 2008). The hedonic quality associated with the food cue can then lead to the intrusion of cravings and desires into consciousness (Kavanagh et al. 2005). Such cravings and desires occupy attentional and working memory resources and therefore directly compete with the representation of self-regulatory goals and standards in working memory (see Fig. 186.1).

Once in the center of attention, the suppression of cravings and desires becomes difficult and can produce ironic effects such that the very thought that is supposed to be suppressed becomes even more strongly activated (Boon et al. 2002). In addition, cravings and desires are assumed to trigger the very behavioral schemas in memory that have proven to be useful in the past to fulfill the need (e.g., Strack and Deutsch 2004). Hence, tempting food cues in the environment may lead to the activation of behavioral tendencies to approach and consume the tempting object at hand (see Fig. 186.1). Whether these impulsive behavioral tendencies are enacted or not depends on whether sufficient executive control capacity can be mustered in order to inhibit or override the impulsive action tendencies.

One straightforward implication of the described role of food cues is that, all else being equal, more vivid and attractive food cues should lead to stronger desires and hence to more disinhibited behavior. For instance, work on delay of gratification suggests that resistance to temptation is more difficult when the tempting object is literally present than when it is not visible (Mischel et al. 1996). More direct evidence for this conjecture stems form a series of studies by Fedoroff, Polivy, and Herman (Fedoroff et al. 1997). Participants in the experimental group were exposed over an extended period to the sight and smell of highly attractive food. When given access to palatable food afterward, restrained eaters more likely show increased disinhibited eating.

Thus far, we have outlined a self-regulation framework that tries to understand and specify how impulsive, stimulus-triggered and reflective, goal-dependent forces clash in determining eating behavior. In the following section, we will illuminate potential mechanisms by which alcohol may affect the outcome of this struggle.

186.3.1   Alcohol's Acute Effects on Impulsive Processing Appetite and Attentional Myopia to Food Cues

There is reason to believe that alcohol may have a facilitating influence on the impulsive processing of tempting food stimuli. Specifically, alcohol may promote the strength of food cravings and desires by bolstering appetite and by enhancing attention to salient food cues (see Fig. 186.1). Indeed, one

---

[2] Because one focus of the present chapter is on external influences provided by present food cues, a second possibility not discussed further is that strong need states can also trigger from memory visual images of temptations that are not currently present, leading to similar cravings and desires as those emanating from present cues (for more details, see Kavanagh et al. 2005).

of alcohol's psychoactive effects appears to consist in a general stimulating effect on appetite (Westerterp-Platenga and Verwegen 1999). This effect is supported both by research in animals and humans although the exact physiological mechanisms by which alcohol exerts this effect are not perfectly well understood (for a review, see Yeomans et al. 2003). Accordingly, it has been found both in experimental and field studies in humans that alcohol – at least above a certain threshold – increases subjective ratings of hunger (e.g., Caton et al. 2004). As a consequence, craving and desires for tempting food cues in the environment should increase and overeating (and drinking) should become more likely.

A second acute effect by which alcohol may boost impulsive processing is attentional myopia (see Table 186.1 for key features). Originally proposed by Steele and Josephs (1990), the attentional myopia model holds that alcohol narrows the focus of attention and thoughts to the most salient stimuli in the environment. As a consequence, behavior will be disproportionally influenced by these salient cues rather to the exclusion of more distal cues. If salient cues favor the emergence of desires and cravings (e.g., rich food cues in one's environment), more disinhibited eating behavior is expected. In the food-rich environments people often find themselves in or even create themselves, this is arguably often the case. However, if the salient cues attended to favor self-controlled behavior (e.g., a dieting plan pinned on one's kitchen wall), alcohol myopia theory would even predict more self-regulated behavior.

The predictions of the attentional myopia model for alcohol consumption have been confirmed in other domains of self-regulation such as sexual risk taking (e.g., MacDonald et al. 2000). Mann and Ward (2004) applied the attentional myopia model in a study on food consumption in chronic dieters employing cognitive load (rather than alcohol) as a method to manipulate attentional capacity. Supporting the model, dieters in the low attentional capacity condition showed relatively more disinhibited eating behavior when available cues (i.e., a milkshake) promoted consumption than dieters in the high attentional capacity condition. Conversely, dieters in the low attentional capacity condition showed more restrained behavior when high-fat food contents and dieting were made salient prior to testing the milkshake as compared to the high attentional capacity group (Mann and Ward 2004). Additional measures of thought content supported the idea that attentional load induced more hedonic thoughts in the milkshake-salient condition and more dieting-related thoughts in the diet-salient condition whereas participants in the no load condition exhibited a broader range of thoughts.

In sum, alcohol's acute effects on the stimulation of appetite as well as on the narrowing of the perceptive field to the most salient cues – often consummatory in nature – may jointly contribute to an increased intrusion of food desires and cravings into consciousness. These in turn may compete with self-regulatory goals in working memory for scarce representational resources (see the negative link between cravings and self-regulatory goals in Fig. 186.1) and lead to an activation of consumption-oriented behavioral action schemas. If not held in check properly by executive control functions, overeating will become more likely.

Table 186.1 Key features of alcohol myopia

1. Alcohol myopia (Steele and Josephs 1990) refers to the tendency of alcohol to focus an individual's attention on proximal, highly salient stimuli or events in the environment to the disadvantage of more distant stimuli or events (hence the reference to myopia which is shortsightedness)

2. As a consequence, tempting stimuli (such as highly palatable food) in the environment may have a disproportionally strong influence on thought and emotion, leading to stronger cravings and desires and, ultimately, more impulsive behavior

3. However, to the degree that cues signaling control (rather than temptations) are salient, alcohol may even foster control (e.g., MacDonald et al. 2000; Mann and Ward 2004)

186.3.2   Alcohol's Acute Effects on Reflective Processing: Goal Standards, Self-Monitoring, and Executive Control

Next to alcohol's boosting influence on impulsive processes in eating (and indirect influences on the representation of self-regulatory goal standards), alcohol also appears to directly hamper reflective processing in a multitude of ways (Hull and Slone 2004). In our framework, we will focus on three main factors: representation of goal-standards, self-monitoring, and executive control capacity.

First, alcohol may impair the processes necessary to retrieve self-regulatory goal-standards into working memory and then in an active state necessary for conscious goal-pursuit. These two processes may together lead to weaker and less consistent representations of self-regulatory standards under alcohol intoxication (Baumeister et al. 1994). Some evidence indicates that alcohol, at least in higher doses, may hinder recall from long-term memory (Nelson et al. 1986). Hence, alcohol may hinder people from retrieving the very self-regulatory plans and intentions they had formed earlier. For instance, otherwise strongly represented intentions to diet may become temporarily suppressed. Also, it has been argued that successful self-regulation requires the maintenance of self-regulatory goals in working memory (Hofmann et al. 2008). Some research indicates that alcohol interferes with the maintenance function of working memory (Saults et al. 2007). Hence, self-regulatory goals may fade out of consciousness more easily under alcohol and cannot serve as well as comparison standards for self-monitoring and for mentally simulating the long-term consequences of one's conduct.

Second, there is strong evidence that alcohol negatively affects self-awareness (e.g., Hull and Bond 1986). Hence, intoxicated people may lose the ability to successfully attend to and monitor their behavior. With self-monitoring gone awry, discrepancies between the implications of an impulse to consume tempting food at hand and relevant goal standards to diet may simply go unnoticed.

Third and perhaps most central from a self-regulatory perspective, alcohol may seriously reduce people's capacity to inhibit or override prepotent impulses directed at the consumption of tempting food. That is, even though intoxicated persons may still be aware of existing conflicts between their impulses and their self-regulatory goals to some degree, they may nevertheless lack the cognitive resources for the kind of control – behavioral inhibition – that is necessary in order to stop impulsive action tendencies from becoming transformed into action or in order to resolve a conflict between two incompatible response tendencies (e.g., to eat chocolate versus celery sticks) in favor of one. This hypothesis is in line with a range of experimental studies demonstrating reduced inhibitory control after alcohol intake (e.g., Fillmore and Vogel-Sprott 1999). Most of these studies have employed the stop-signal paradigm (Logan et al. 1984) to examine the effects of alcohol on behavioral control. In a typical setup of such a task, participants have to react with quick, accurate choice responses to go-signal trials (e.g., categorizing letters via keypress). On a fraction of trials, however, a stop-signal (e.g., a brief auditory tone) accompanies a typical go-trial. In these trials, subjects are required to inhibit (i.e., suppress) the typical go-response. Inhibitory control is measured by the ability of the individual to inhibit prepotent go-responses at varying delay times with which the stop signal appears (with longer delays rendering inhibition of the go-response more difficult).

Using such a paradigm, Fillmore and Vogel-Sprott (1999) demonstrated that a moderate dose of alcohol resulting in an average BAC (blood alcohol concentration) of 73 mg/100 mL reduced the drinker's ability to inhibit behavior in response to stop-signals as compared to a placebo control group, whereas responses to go-signals were left unaffected. In other words, response inhibition seems to be much more vulnerable to the physiological effects of alcohol than response execution. Subsequent studies have shown that this effect depends on the presence of conflict between two competing action tendencies (Fillmore and Vogel-Sprott 2000). The above effect occurs when rewards are given both for acting (go-response) and for inhibition (stop-response) but disappears

when either one response is rewarded but the other is not. Taken together, these studies indicate (a) that alcohol's effects on response inhibition may be most decisive in mental tug-of-war situations in which an approach-avoidance conflict exists and (b) that alcohol is likely to tip the scales in favor of the approach reaction in such cases.

The cognitive capacities (representing standards, self-monitoring, inhibition) discussed in this section can all be subsumed among other functions under the umbrella term of executive cognitive functioning. A large body of neuropsychological data indicates that the neural substrate of executive cognitive functioning is provided by the prefrontal cortex, particularly its dorsolateral region (e.g., Giancola 2000). Hence, alcohol's acute effects on a whole range of executive cognitive functioning abilities may be explained by its detrimental effects on this brain region in particular. In fact, alcohol seems to predominantly affect the glucose metabolism in the prefrontal cortex as corroborated by neuroimaging research (e.g., Volkow et al. 1995). The prefrontal cortex is the central part of a system of neural networks that are assumed to be involved in working memory functions and in the top-down control (i.e., inhibition and overriding) of subcortical structures such as the amygdala, insulae, mesolimbic cortex and the striatum (Bechara 2005), which provide the neuroanatomical basis for stimulus-triggered affective states and impulsive action tendencies. Hence, the observation that alcohol leads to less inhibited behavior accords well with the notion that it selectively impairs the very structure that is "in a logical neuroanatomical position to intercept and inhibit these lower brain impulses" (Giancola 2000, p. 585).

186.3.3 Supporting Empirical Evidence

Taken together, the present framework predicts that alcohol may boost the strength of impulses (via food cravings and the activation of impulsive action tendencies) while at the same time reducing the capacity for reflective processing. In other words, alcohol should lead to an increased influence of impulsive processing and to a reduced influence of self-regulatory goal standards on eating behavior. These predictions were directly tested in a study by Hofmann and Friese (2008). At the beginning of the study, female participants completed a number of screening questionnaires including a measure of dietary restraint standards (Stunkard and Messick 1985) to assess individual differences in self-regulatory goal standards. We also assessed individual differences in impulsive affective reactions toward candy with a version of the Implicit Association Test (Greenwald et al. 1998). This task measures how quickly participants associate a given object (M&M's candies in this case) with positive versus negative affect (for more details, see Hofmann and Friese 2008). High scores on the measure indicate more positive automatic affective reactions toward the food and hence can be taken as an indicator of impulsive processing. After the assessment phase, participants engaged in two different product tests. In the first product test, they consumed a drink that either consisted of orange juice with vodka (alcohol condition) or solely orange juice (control condition). An intermediate filler task gave the alcohol dose time to unfold its impact before participants tasted and rated candy in a second product test. A first finding was that participants in the alcohol condition on average consumed significantly more candy than participants in the control condition (Hofmann and Friese 2008). More importantly, however, we also investigated the degree to which candy consumption could be predicted by impulsive influences (i.e., automatic affect) versus reflective influences (i.e., dietary restraint standards) depending on whether participants had consumed alcohol or not. As expected, candy consumption was reliably predicted by automatic affect for participants in the alcohol condition as indicated by the positive slope between automatic affect and candy consumption in Fig. 186.2 (left panel). However, candy consumption was not predicted by automatic affect in the control condition (Fig. 186.2, left panel).
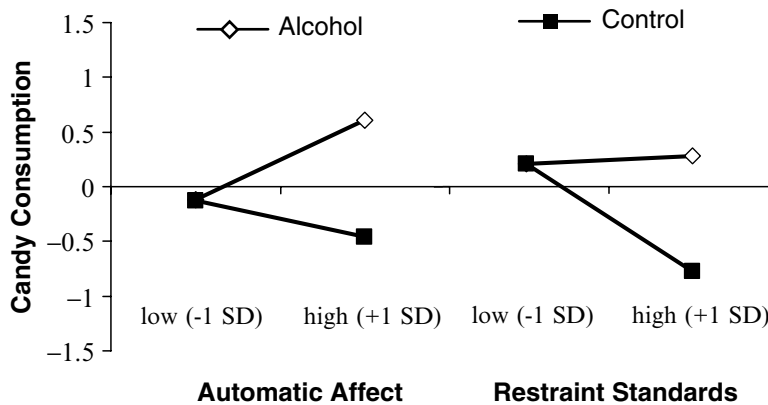
Fig. 186.2 Candy consumption as a function of alcohol consumption, automatic affect toward candies, and dietary restraint standards. The y-axis represents z-transformed candy (m&m's) intake during an unobtrusive taste and rate task with higher numbers indicating more candy consumption. Automatic affect toward the candy was assessed with an Implicit Association Test (Greenwald et al. 1998) as a measure of hedonic, impulsive reactions toward the candy. Restraint standards with regard to eating were assessed with a self-report scale. As can be seen from the two graphs, the relationship between automatic affect and candy consumption was stronger (as indicated by the steeper regression slope) for participants who had consumed alcohol before the taste and rate task (such that participants with high automatic affective reactions consumed most candy). In contrast, the expected negative relationship between restraint standards and candy consumption was more pronounced in sober participants (such that participants with high restraint standards consumed least candy) (Adapted from Hofmann and Friese 2008. With permission)

Conversely, dietary restraint standards were quite ineffective in participants who had consumed alcohol as indicated by the flat line in the right panel of Fig. 186.2. Dietary restraint, however, regulated candy consumption effectively for sober participants as indicated by the negative slope in Fig. 186.2 (right panel). Viewed in combination, these results yield strong evidence for the hypothesis that alcohol consumption fosters the influence of impulses on eating behavior while at the same time reducing the behavioral impact of self-regulatory goal standards as a controlling influence.

Similar findings on the relative impact of impulsive versus reflective influences on consummatory behavior has been obtained in a number of studies using other moderators such as cognitive load (Friese et al. 2008), ego depletion (Hofmann et al. 2007), or individual differences in working memory capacity (Hofmann et al. 2008; Thush et al. 2008). The strong convergence across the alcohol-related findings and the other moderators raises the question whether there may be a common element among these moderators that is responsible for producing functionally equivalent results. We think that the underlying connecting element may lie in the impairment of two central executive cognitive functions involved in impulse control: working memory capacity and inhibitory control (Giancola 2000; Hull and Slone 2004). Without support from these executive functions, bringing behavior in line with self-regulatory goals becomes more difficult. As reflective processing wanes, impulsive processes gain weight in determining the final outcome of a self-regulatory conflict.

186.3.4 Physiological Versus Alcohol Expectancy Effects

We have argued that alcohol impairs self-regulation by boosting impulsive influences and interfering with reflective processing. One remaining issue is whether all of these effects are purely due to the physiological effects of alcohol, or whether at least parts of these effects are the result of cognitive

Table 186.2 Key features of alcohol expectancies

1. Alcohol expectancies refer to people's beliefs about the effects of alcohol on thought, feeling, and action
2. Alcohol expectancies can be positive or negative
3. Typical positive alcohol expectancies comprise the beliefs that alcohol improves mood, reduces tension, increases sociability, and boosts self-esteem and assertiveness (e.g., Hull and Slone 2004)
4. Typical negative alcohol expectancies encompass the beliefs that alcohol decreases self-control, impairs intellectual performance, increases aggressiveness, and, at least in higher doses, creates unpleasant feelings of nausea.
5. It is generally assumed that positive alcohol expectancies increase the likelihood of alcohol consumption whereas negative expectancies decrease it.
6. Next to influencing alcohol consumption, alcohol expectancies have also been shown to mediate the effects of consuming alcohol. Thus, like a self-fulfilling prophecy, individuals may tend to behave in accordance with their alcohol expectations. Interestingly, it seems already sufficient for some of these effects to occur that individuals *believe* that they have consumed alcohol regardless of whether their actual drink really contained alcohol or not (Hull and Bond 1986).

mechanisms. More specifically, it has been argued that alcohol effects may be modulated by alcohol expectancies (see Table 186.2 for key features). Alcohol expectancies refer to the cognitive expectations people hold with regard to the consequences of alcohol consumption. A first assumption in the alcohol literature is that alcohol expectancies will influence the degree of alcohol *consumption* in a given situation of interest (Hull and Slone 2004). That is, people who harbor certain positive alcohol expectancies (e.g., "Alcohol makes me more relaxed when I am stressed") will consume more alcohol if they are in a situation where these expectations are relevant (e.g., having to deliver a stressful speech) than people who do not hold these expectancies or people who hold negative expectancies (e.g., "Alcohol will make me lose my concentration"). Applied to the relationship between alcohol and eating, the degree of alcohol consumption in the presence of eating may be influenced by the type of expectancies people hold. For instance, dieters holding the negative expectancy that alcohol will impair their self-regulation should be more cautious in consuming alcohol than dieters who do not hold that expectation and these kinds of negative expectancies may aid the self-regulation of eating as far as the consumption of alcohol is concerned. On the other hand, some individuals may primarily harbor positive alcohol expectancies and these may then have detrimental effects on dietary control. For instance, individuals may believe that alcohol helps them to deal with negative affect such as the frustration of having to refrain from so many tasty foods they would otherwise like to eat or feelings of guilt upon violation of dietary schedules. As discussed in more detail below, such positive expectancies may stimulate alcohol consumption in the presence of tempting food cues and ultimately lead to violations of standards and even to patterns of spiraling distress (Baumeister et al. 1994).

A second assumption concerning the role of alcohol expectancies is that alcohol expectancies can modulate the very *effects* of alcohol on behavior (Hull and Slone 2004). These expectancy effects may even be independent of the pharmacological effects of alcohol. That is, individuals may behave in accordance with their expectations whenever they believe that they have consumed alcohol, regardless of whether they actually received an alcoholic drink or a placebo (Hull and Bond 1986). For instance, it is plausible that individuals who expect alcohol to disinhibit their behavior in turn act more disinhibited than individuals who do not hold these expectations, all else being equal. This is because alcohol expectations may bias ongoing information processing systematically such that the expected behavioral outcome becomes more likely. Whether physiological and expectancy effects are additive or whether they interact is still an issue of ongoing debate (Hull and Bond 1986). There is, however, some indication that alcohol's physiological effects on the impairment of control tend to be stronger among those expecting detrimental effects on control (Fillmore et al. 1998), although negative expectancies may also sometimes lead to increased efforts at compensating the expected

impairments (Fillmore and Blackburn 2002). Possibly, whether such negative expectancies lead to decreased versus increased efforts at self-regulation following alcohol consumption may depend on how strongly people are motivated to summon an extra amount of willpower to counteract the expected effects. If control motivation is low, negative alcohol expectancies may lead to a pattern of acquiescence (Baumeister and Heatherton 1996) by which people actively give in to the temptation at hand (in the sense of the what-the-hell effect). If control motivation is high, however, negative expectancies may trigger increased efforts at self-regulation, similar to compensatory effects obtained with regard to other risk-situations such as ego depletion (Muraven and Slessareva 2003). Interestingly then, whereas negative alcohol expectancies about alcohol's disinhibiting influence may help people to resist consuming alcohol in the first place, once people are led to consume alcohol (though a lapse of self-control or social pressure) the same expectancies may be hard to counteract and amplify the physiological effect.

186.4 Alcohol's Long-term Effects on Executive Functioning

Next to alcohol's acute effects, there is mounting evidence that chronic alcohol consumption may have negative long-term effects on self-regulatory capacity (Volkow et al. 2004; Wiers et al. 2007). Specifically, chronic alcohol use may lead to frontal lobe dysfunctions as indicated by neurophysiological studies documenting decreased frontal lobe glucose utilization and blood flow in alcoholism (for a review, see Moselhy et al. 2001). These neuropathological changes may underlie the performance deficits in alcoholics as compared to nonalcoholics on a large range of executive cognitive functioning (Moselhy et al. 2001). Alcohol's long-term deleterious effects may be particularly consequential during adolescence, a sensitive period of brain maturation that is fraught with both opportunities as well as risks for the development of self-regulatory capacities (Steinberg 2005). In other words, chronic alcohol use during adolescence may slow down or even disrupt the development of the very functions needed for adult self-regulatory competencies. Early alcohol use and its negative effects on self-regulatory ability may be one reason underlying the co-occurrence of alcohol abuse and eating disorders, characterized by impulsive eating such as bulimia nervosa, binge eating disorder, and obesity (e.g., Grilo et al. 2002).

186.5 The Dynamic Interplay of Alcohol Consumption and Eating: Patterns of Snowballing

Thus far, we have examined the impact of alcohol as a predictor/moderator on eating behavior as an outcome in a linear fashion. As typical for the psychology of self-regulation, reality is often more complex. Specifically, adopting a feedback-loop perspective on self-regulation (Carver and Scheier 1981), self-regulatory outcomes may often serve as inputs for new self-regulatory loops and so forth. In this section, we want to specifically highlight one such dynamical pattern that may help to explain why the combination of alcohol use and eating behavior may sometimes "snowball," leading to a vicious circle of self-regulatory failure (Baumeister et al. 1994). An example of a potential snowballing pattern is illustrated in Fig. 186.3. As outlined above, acute alcohol intoxication may lead to disinhibited eating by boosting cravings and desires with regard to tempting food as well as by weakening resistance to these urges (Hofmann and Friese 2008). Failure to meet one's dietary standards may in turn trigger emotional distress (especially feelings of guilt or remorse) as soon as the person
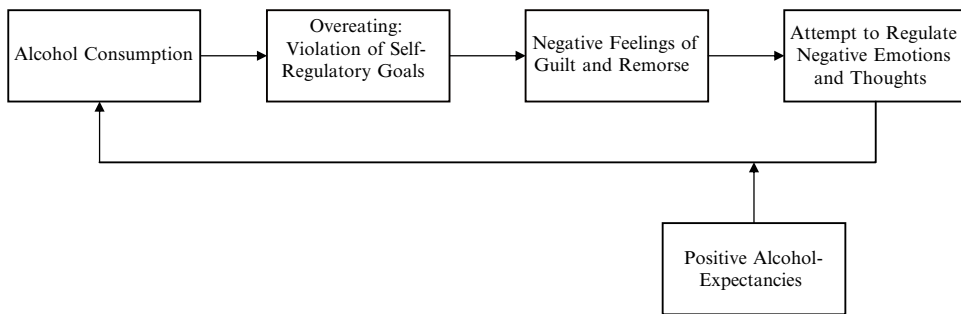
Fig. 186.3 A vicious cycle of alcohol consumption and overeating. The figure illustrates a possible "snow-balling" pattern of self-regulatory failure whereby alcohol consumption is both a cause of overeating (i.e., alcohol leading to disinhibited eating) as well as a consequence of overeating (i.e., alcohol as a means to cope with negative emotions due to overeating)

starts to self-monitor and reflect upon these failures. These negative emotional states, coupled with positive alcohol expectancies about its soothing effects, may lead the person into a new drinking episode in an attempt to cope with the negative feelings and thoughts (Baumeister et al. 1994), whereby the whole cycle may start all over again. Although clearly speculative, such dysfunctional patterns of misregulation may underlie the development of pathological forms of eating and account in part for the above-mentioned comorbidity between alcohol abuse and eating disorders. Once alcohol use enters the scene of eating disorders, it may be best understood as an integral part (i.e., both cause and effect) in an often vicious cycle of self-regulatory failure.

186.6 Conclusion: Alcohol and Eating

As this chapter has shown, alcohol can be considered a great threat to the self-regulation of eating behavior. What makes alcohol a particularly dangerous threat is the fact that, as we have tried to show, alcohol is akin to an enemy that uses several different weapons at once. To recapitulate, these include the direct caloric impact of alcohol as a beverage not typically compensated for, boosting effects on impulsive processing which may lead to increased craving for tempting food, and detrimental effects on the self-regulatory mechanisms involved in inhibiting and overriding prepotent but unwanted action impulses (see also summary points). Even though the attack is a broad one, all of these direct and multiple indirect effects ultimately appear to converge toward the same target: enhanced caloric intake. Alcohol thus really seems to earn the title chosen for the present chapter. However, at least two qualifications need to be emphasized. First, alcohol's effects seem to emerge mainly if there is a cognitive conflict in the first place (Fillmore and Vogel-Sprott 2000). Only if the hedonic, short-term prospects clash with highly valued long-term goals such as weight control or health concerns is alcohol likely to enter the ring as a decisive force. For this reason, restrained eaters are particularly at risk to experience alcohol's negative consequences on self-regulatory goal pursuit. Second, these effects may be modulated by alcohol expectancies such that people who expect alcohol to have a disinhibiting effect on their eating behavior may have a good reason for abstaining from alcohol consumption, but, once alcohol is consumed may be at special risk for what-the-hell types of effects (unless an extra surplus of willpower is summoned to counteract these expectancy effects).

186.7 Application to Other Areas of Health

The present framework can also be applied to other areas dealing with the self-regulation of health behavior (Hofmann, Friese et al. 2008; Wiers et al. in press). Most centrally, alcohol may act as a disinhibiting influence on other appetitive domains such as sexual behavior and drinking itself by boosting impulsive processes and impairing reflective processing. In other domains of health behavior where impulsive influences may be less salient (e.g., the use of sunscreen, for instance), alcohol may still impact reflective processing and lead to more careless behavior because people may fail to represent and act in accordance with their long-term health goals and standards. However, to the degree that attention can be directed toward salient cues signaling control (Mann and Ward 2004) or to the degree that self-regulatory behavior can be delegated to more automatic and habitual routines, the great disinhibitor may loose some of its disruptive power on the self-regulation of human behavior.

Summary Points

- Eating in humans can be regarded as self-regulatory behavior by which individuals often strive to attain certain self-regulatory goals such as weight control or healthy food intake
- Eating as self-regulation typically involves a fragile conflict between self-regulatory goals and impulsive, appetitive influences on eating behavior the latter of which are driven by the interplay of internal need states and external food cues in the environment
- The outcome of such self-regulatory conflicts can be strongly influenced by situational boundary conditions such as alcohol consumption.
- Alcohol has multiple short-term effects on eating behavior. These comprise direct and indirect effects.
- Direct short-term effects are given by the caloric load of alcohol itself are typically not compensated for.
- Indirect short-term effects involve (a) an increase in appetite and (b) detrimental short-term effects on self-regulation as given by a weaker representation of goal standards, reduced self-monitoring, and reduced executive control.
- These effects have a physiological basis but are also modulated by alcohol expectancy effects.
- Alcohol also has long-term effects on cognitive functioning which may further undermine the self-control of eating behavior. These chronic effects may partly account for the observed comorbidity between alcohol abuse and impulsive eating disorders.
- Alcohol use may be an integral part of dysfunctional self-regulatory loops whereby alcohol promotes overeating and overeating in turn promotes alcohol consumption. Such "snowballing" patterns may be a second factor accounting for the comorbidity between alcohol abuse and eating disorders.

Definition of Key Terms

Self-regulation: An individual's attempt to behave in accordance with his or her self-regulatory goal standards (e.g., dietary standards).
Self-monitoring: A comparison of actual behavior with one's self-regulatory goal standards. Discrepancies between the two indicate that further self-regulation is necessary.

> **Behavioral inhibition:** Higher-order mental control process by which a prepotent action tendency is stopped.
>
> **Alcohol myopia:** Narrowing of attention to most salient cues in the stimulus environment due to alcohol consumption.
>
> **Alcohol expectancies:** People's beliefs about the positive or negative effects of alcohol on thought, feeling, and action.

References

Baumeister RF, Heatherton TF. Psycho Inq. 1996;7:1–15.

Baumeister RF, Heatherton TF, Tice DM. Losing control: how and why people fail at self-regulation. San Diego: Academic Press; 1994.

Bechara A. Nat Neurosci. 2005;8:1458–63.

Boon B, Stroebe W, Shut H, Ijntema R. Brit J Health Psych. 2002;7:1–10.

Carver CS, Scheier MF. Attention and self-regulation: a control-theory approach to human behavior. New York: Springer; 1981.

Caton SJ, Ball M, Ahern A, Hetherington MM. Physiol Behav. 2004;81:51–8.

Fedoroff IC, Polivy J, Herman CP. Appetite. 1997;28:33–47.

Fillmore MT, Blackburn J. J Stud Alcohol. 2002;63:237–46.

Fillmore MT, Carscadden J, Vogel-Sprott M. J Stud Alcohol. 1998;59:174–9.

Fillmore MT, Vogel-Sprott M. Exp Clin Psychopharm. 1999;7:49–55.

Fillmore MT, Vogel-Sprott M. J Stud Alcohol. 2000;61:239–46.

Fishbach A, Shah JY. J Pers Soc Psychol. 2006;90:820–32.

Friese M, Hofmann W, Wänke M. Br J Soc Psychol. 2008;47:397–419.

Giancola PR. Exp Clin Psychopharm. 2000;8:576–97.

Greenwald AG, McGhee DE, Schwartz JLK. J Pers Soc Psychol. 1998;74:1464–80.

Grilo CM, Sinha R, O'Malley SS. Alcohol Res Health. 2002;26:151–60.

Herman CP, Mack D. J Pers. 1975;43:647–60.

Herman CP, Polivy J. A boundary model for the regulation of eating. In JA Stunkard, E Stellar, editors. Eating and its disorders. New York: Raven Press; 1984. p. 141–156.

Herman CP, Polivy J. The self-regulation of eating. In RF Baumeister, KD Vohs, editors. The handbook of self-regulation: research, theory, and applications. New York: Guilford; 2004. p. 492–508.

Hofmann W, Friese M. J Abnorm Psychol. 2008;117:420–7.

Hofmann W, Friese M, Strack F. Pers Psychol Sci. 2009;4:162–76.

Hofmann W, Friese M, Wiers RW. Health Psychol Rev. 2008a;2:111–37.

Hofmann W, Gschwendner T, Friese M, Wiers RW, Schmitt M. J Pers Soc Psychol. 2008;95:962–77.

Hofmann W, Rauch W, Gawronski B. J Exp Soc Psychol. 2007;43:497–504.

Hull JG, Bond CF. Psychol Bull. 1986;99:347–60.

Hull JG, Slone LB. Alcohol and self-regulation. In RF Baumeister, KD Vohs, editors. The handbook of self-regulation: research, theory, and applications. New York: Guilford; 2004. p. 466–491.

Hulshof T, de Graaf C, Weststrate JA. Appetite. 1993;21:273–86.

Kavanagh DJ, Andrade J, May J. Psychol Rev. 2005;112:446–67.

Logan GD, Cowan WB, Davis KA. J Exp Psychol Hum Percept Perform. 1984;10:276–91.

Lowe MR, Butryn ML. Physiol Behav. 2007;91:432–9.

MacDonald TK, Fong GT, Zanna MP, Martineau AM. J Pers Soc Psychol. 2000;78:605–19.

Mann T, Ward A. J Abnorm Psychol. 2004;113:90–8.

Mattes RD. Physiol Behav. 2006;89:66–70.

Mischel W, Cantor N, Feldman S. Principles of self-regulation: The nature of will-power and self-control. In ET Higgins, AW Kruglanski, editors. Social psychology: handbook of basic principles. New York: Guilford Press; 1996. p. 329–360.

Moselhy HF, Georgiou G, Kahn A. Alcohol Alcohol. 2001;36:357–68.

Muraven M, Slessareva E. Pers Soc Psychol B. 2003;29:894–906.

Nelson TO, McSpadden M, Fromme K, Marlatt GA. J Exp Psychol Gen. 1986;115:247–54.

Papies E, Stroebe W, Aarts H. J Exp Soc Psychol. 2007;43:810–7.

Papies EK, Stroebe W, Aarts H. J Exp Soc Psychol. 2008;44:1283–92.

Pinel JPJ, Assanand S, Lehman DR. Am Psychol. 2000;55:1105–16.

Saults JS, Cowan N, Sher KJ, Moreno MV. Exp Clin Psychopharm. 2007;15:576–87.

Schachter S. Emotion, obesity, and crime. New York: Academic; 1971.

Steele CM, Josephs RA. Am Psychol. 1990;45:921–33.

Steinberg L. Trends Cogn Sci. 2005;9:69–74.

Strack F, Deutsch R. Pers Soc Psychol Rev. 2004;8:220–47.

Stroebe W. Dieting, overweight and obesity: self-regulation in a food-rich environment. Washington, DC: American Psychological Association; 2008.

Stroebe W, Mensink W, Aarts H, Schut H, Kruglanski A. J Exp Soc Psychol. 2008;44:26–36.

Stunkard AJ, Messick S. J Psychosom Res. 1985;29:71–83.

Thush C, Wiers RW, Ames SL, Grenard JL, Sussman S, Stacy AW. Drug Alcohol Depend. 2008;94:116–24.

Vohs KD, Heatherton TF. Psychol Sci. 2000;11:249–54.

Volkow N, Wang G, Doria JJ. Alcohol Health Res World. 1995;19:296–9.

Volkow ND, Fowler JS, Wang GJ. Neuropharmacology. 200447 Suppl 1:3–13.

Ward A, Mann T. J Pers Soc Psychol. 2000;78:753–63.

Westerterp-Platenga MS, Verwegen C. Am J Clin Nutr. 1999;69:205–12.

Wiers RW, Bartholow BD, van den Wildenberg E, Thush C, Engels RCME, Sher KJ, et al. Pharmacol Biochem Be. 2007;86:263–83.

Wiers RW, Houben K, Roefs A, De Jong P, Hofmann W, Stacy AW. Implicit cognition in health psychology: Why common sense goes out of the window. In B Gawronski, BK Payne, editors. Handbook of implicit social cognition. New York: Guilford Press; 2010;463–488.

Yeomans MR, Caton S, Hetherington MM. Curr Opin Clin Nutr Metab Care. 2003;6:639–44.

Chapter 187
Brain Atrophy in Alcoholics

E. González-Reimers and F. Santolaria-Fernández

Abbreviations

AMPA	Alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
BMI	Body mass index
cAMP	Cyclic adenosine monophosphate
CREB	cAMP responsive element binding-protein
CT	Computerized tomography
DNA	Desoxiribonucleic acid
DEXA	Dual-energy x-ray absorptiometry
EEG	Electroencephalogram
GABA	Gamma-amino-butyric acid
HT	Hydroxytryptamine
MDA	Malondialdehyde
MRI	Magnetic resonance
NF-κB	Nuclear factor kappa B
NADP	Nicotinamide adenine dinucleotide phosphate
NADH	Reduced nicotinamide adenine dinucleotide
NMDA	N-methyl-D-aspartate
TNF	Tumor necrosis factor

187.1 Introduction

Ethanol exerts deleterious effects on the brain, both acutely and chronically. Acute alcohol intake affects brain function in a dose-dependent manner, so that at lower doses of ethanol induces euphoria and altered mood, in greater amounts it impairs speech and motor function, whereas higher doses affect respiratory and cardiovascular functions and may result in death. These risks are also present in binge drinkers; in addition, these alcoholics also develop organic brain damage and cognitive dysfunction. In fact, with time, chronic alcohol consumption leads to dependence and frank addiction,

E. González-Reimers (✉)
Servicio de Medicina Interna, Hospital Universitario de Canarias,
Ofra s/n 38320, La Laguna, Tenerife, Canary Islands, Spain
e-mail: egonrey@ull.es

whereas progressive cognitive dysfunction and brain atrophy also ensue, even with moderate amounts of ethanol consumption. Although not the only neurological alteration suffered by the chronic alcoholic patient, brain atrophy is frequently observed; it often affects relatively young people, and severely impairs mood, memory, judgement and other cognitive skills, so that it constitutes a major challenge for patients, physicians and society. This chapter focuses on some of the factors involved in the pathogenesis of brain atrophy, especially those related with altered nutrition in the wide sense of the term.

187.2 The Clinical Problem

Drinking patterns differ across countries and also within countries, according to age, sex, social class and lifestyle. In rural areas, excessive drinkers, mainly consumers of wine, develop cirrhosis after many years of regular consumption. At the other end of the spectrum, socially ostracised, homeless, undernourished alcoholics, usually living in an urban environment, are more prone to develop vitamin deficiency and Wernicke–Korsakoff syndrome. Another group of drinkers is constituted by binge drinkers, more frequently found among young people living in urban areas; sometimes binge periods coexist with heavy smoking and consumption of illicit drugs. Therefore, the neurocognitive alterations usually found in alcoholics are heavily influenced by lifestyle, drinking pattern, and coexistence of liver disease and/or other neurotoxic factors, making it difficult to discern if the observed effects are due to ethanol itself, to liver dysfunction, coexisting malnutrition, or depend more heavily on the effects of other drugs, such as tobacco or illicit drugs. In addition, different educational levels – roughly associated with drinking patterns – and previous behavioural disorders, which in many alcoholics act as contributing factors to alcohol dependence, complicate the scenario. It has been reported that more than 80% of those adolescents with alcohol abuse or dependence also showed another psychopathology (Thatcher and Clark 2005). Moreover, genetic predisposition, and the ability of ethanol to modulate the activity of at least 58 genes involved in neuronal activities (38 down-regulated, 15 up-regulated, 5 up-/down-regulated), potentially subjected to polymorphism (Wang et al. 2009), further complicates our understanding and knowledge of the mechanisms, which underlie brain alterations in alcoholics (Table 187.1).

Central nervous system affectation in chronic alcoholics includes brain atrophy, with variable degrees of cognitive dysfunction; the Wernicke–Korsakoff syndrome, related to thiamine deficiency, and cerebellar cortical degeneration, leading to dysmetria and ataxia, but also playing a role in cognitive impairment. Although pellagroid dermatitis is sometimes observed in malnourished alcoholics, ataxia and dementia due to vitamin B3 deficiency is uncommon. Other syndromes, such as Marchiafava–Bignami syndrome, or acute pontine myelinolysis, are less frequently encountered, but should be considered in the clinical evaluation of alcoholic patients with impaired mood and/or judgement, obtundation, stupor or frank coma, with or without variable symptoms related to cerebellar dysfunction. In addition, alcoholics show reduced cerebral blood flow (Christie et al. 2008), and are at increased risk of stroke and cerebral trauma. Furthermore, neurological effects of acute ethanol intoxication and of ethanol withdrawal, and the less frequently described ethanol- and tobacco-related amblyopia, complete the clinical syndromes derived from affectation of the central nervous system in the alcoholics. Thus, the spectrum of ethanol-induced brain alterations is wide, and the underlying mechanisms are incompletely understood, especially taking into account that the pathogenesis of central nervous system dysfunction may differ according to the nature and intensity of exposure, i.e., acute alcohol intoxication, chronic alcohol consumption and binge-drinking. Other factors, such as malnutrition or liver failure or, possibly, even the type of alcoholic beverage, may

Table 187.1 Key points of brain atrophy

Anatomoclinical forms of chronic brain damage	Brain cortical and subcortical atrophy
	Cerebellar degeneration
	Toxic amblyopia
	Pellagra
	Wernicke–Korsakoff encephalopathy
	Marchiafava–Bignami disease
	Central pontine myelinolysis
	Increased prevalence of stroke and cerebral trauma
Clinical features of brain atrophy	May vary from subtle alterations (Impaired verbal problem solving, abstracting abilities, visual–spatial performance, verbal memory and the ability to adapt problem-solving strategies to changing requirements) to frank dementia
	Mostly reversible with prolonged ethanol withdrawal
Underlying anatomic lesions	Neuronal death
	White matter alterations (demyelination and axonal death)
Proposed mechanisms	Direct effect of ethanol
	Cytokine (especially TNF-α) mediated neuroinflammation.
	Oxidative damage (disbalance between antioxidants and prooxidants)
	Thiamine deficiency
	Protein deficiency and malnutrition
	Excitotoxicity
	Coexisting liver disease

contribute. Importantly, the risk of dementia is increased in binge-drinkers (Jarvenpaa et al. 2005), as well as the risk of developing chronic alcoholism.

In any case, brain dysfunction is frequently observed in alcoholics admitted to general care services due to organic problems. Despite some discrepancies regarding its true prevalence, cognitive dysfunction, at least in its mildest forms, has been documented in more than 50% of alcoholic patients. Although verbal reasoning and verbal learning skills are relatively preserved, verbal problem solving, abstracting abilities, visual–spatial performance, verbal memory and the ability to adapt problem-solving strategies to changing requirements become more or less severely impaired. In a study of 100 alcoholics who had been sober for at least 21 days before inclusion in the analysis, cognitive efficiency (assessed by a battery of tests including perceptual motor skills, visuospatial processing, learning and verbal and non-verbal problem solving) was significantly impaired compared with 80 controls (Nixon et al. 1995). In that study, alcoholics also showed more depression, anxiety and symptoms related to childhood behavioural disorders, attention deficit disorders and conduct disorders, than controls, but the cognitive impairment could not be attributed to the coexisting behavioural dysfunction. Thus, although some conditions during childhood, such as conduct disorders, stress, anxiety and depression, or attention-deficit/hyperactivity disorders may predispose to ethanol abuse in later years, cognitive impairment takes place without the necessity of any other predisposing situation. Classically, cognitive impairment was attributed to frontal lobe lesions and their associated connections with other cortical and subcortical regions, but in recent years it has been shown that alcohol-mediated brain damage affects many other parts of the central nervous system, including hippocampus, corpus callosum (alterations in attention and executive functions have been related to subtle alterations in corpus callosum, Pfefferbaum et al. 2006), and pathways connecting the cerebellum and other parts of the central nervous system, such as cerebellothalamocortical and cerebelloponto cerebellar pathways.

187.3 Neuropathology

Ethanol provokes generalized brain shrinkage (Fig. 187.1), largely due to loss of cerebral white matter, but also to a reduction in the cortical grey matter, especially observable with magnetic resonance (MRI) or computerized tomography (CT).

Regarding white matter, the maximum atrophy has been observed in the prefrontal white matter (Kril et al. 1997), corpus callosum (Pfefferbaum et al. 2006) and cerebellum (Fitzpatrick et al. 2008). In general, the degree of brain atrophy has been related with the intensity of ethanol consumption. Ding et al. (2004) observed a relation between the amount of ethanol ingested and the area of the fluid-filled spaces in the brain. Harper showed an increase in the pericerebral space in men drinking more than eight drinks per day (Harper 2009). In the study by Kubota et al. (2001) of 1,432 non-alcoholic individuals, moderate alcohol consumption (less than 50 g/day) did not seem to affect brain volume; however, in the Framingham study Paul et al. (2008) did find a relation between any amount of ethanol consumption and brain atrophy. White matter regions in the frontal lobe were those mostly affected in alcoholics, especially among patients with Wernicke's encephalopathy, but also showing a relation with ethanol intake, estimated as maximum daily ethanol consumption (Kril et al. 1997). In a study on 43 alcoholics we found a significant ($p = 0.007$) relationship between the duration of alcohol intake and the bifrontal index, suggesting a relationship between ventricular dilatation and ethanol consumption (Fig. 187.2). Also, a relation was found between cortical atrophy assessed by CT and duration of ethanol consumption (rho = 0.37, $p = 0.014$). However, no relation was found between the total life-long amount consumed (expressed as kilogram ethanol/kilogram body weight) and the presence of brain atrophy.

Changes in white matter probably include both alterations in myelination and axonal integrity (Harper 2009), and it is possible that a synergist effect between ethanol consumption and thiamine deficiency also exists. These changes are reversible, at least in part, after ethanol withdrawal. Therefore, in alcoholic brain damage, there may be two components, one reversible and one permanent. In the latter, neuronal death would provoke axonal degeneration and white matter shrinkage, whereas structural alterations of myelin would be reversible after alcohol abstinence. Bartsch et al. (2007), in a study of 15 patients who completed abstinence, showed a significant brain volumetric gain, whereas no changes were observed among 10 controls. Changes in abstinent alcoholics were more marked in the superior vermis, perimesencephalic infratentorial and supratentorial periventricular borders, and
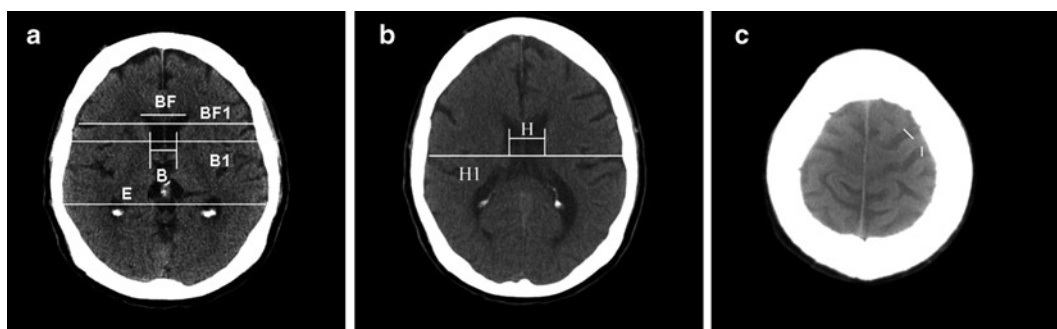
Fig. 187.1 Computerized tomography (CT) of the brain, showing some parameters relevant for calculation of indices of brain atrophy and/or ventricular dilatation. **a–c** CT of the brain, showing the diverse parameters utilised in this study. *Panel A*: BF/BF1= bifrontal index; B/B1= bicaudate index; BF/E=Evans index. B+ BF=Huckmann's digit. *Panel B*: H/H1=Cella media index. *Panel C*: Cortical atrophy is defined as the sum of the width of the four widest sulci at the two highest scanning levels, two of which are shown in the figure

Fig. 187.2 Relationship
between ethanol intake and
bifrontal index. Relationship
between ethanol intake and
bifrontal index, showing that
the longer the duration of
ethanol intake, the more
intense the ventricular
dilatation

Relationship between bifrontal index
and duration of ethanol consumption

r=0.40; p=0.007
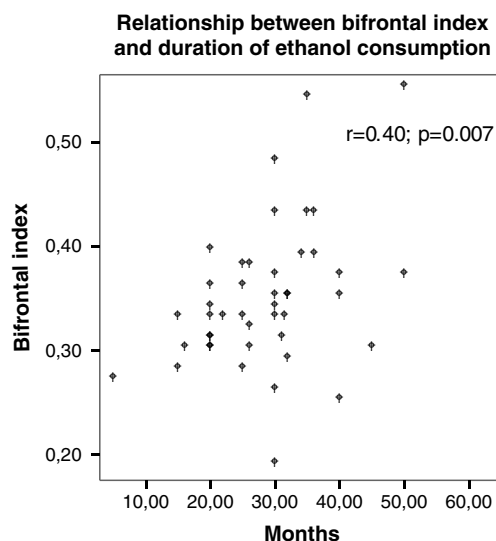
frontomesial and frontoorbital edges, and are not explainable only on the basis of simple rehydratation. These changes were accompanied by regain in cerebral choline, suggesting recovery from white matter damage potentially consistent with astrocyte regrowth and remyelination. Also, an increase in frontomesial N-acetylaspartate was observed. Cerebellar choline was significantly related with brain volume recovery, and frontomesial N-acetyl aspartate increase showed a significant correlation with improvement in attention and concentration, although not with other neuropsychological tests (auditory verbal learning test, standard progressive matrices, vocabulary test). In another study also performed with MRI and an automated three-dimensional method (boundary shift integral), the most rapid volume recovery was observed among those with the greatest baseline brain shrinkage and drinking severity. The study was performed with 18 alcoholics, and, in the first month of abstinence, tissue gain was apparent around the third, fourth and lateral ventricles, cerebellum, pons, hippocampi and the boundaries of frontal, parietal and superior temporal lobes. This study also showed a rapid reversal of volume gain to baseline levels even with consumption of relatively small amounts of ethanol (five drinks per day during 9 days) in reincident patients (Gazdzinski et al. 2005). These data strongly support the direct effect of ethanol on brain alterations and stresses the benefits of ethanol withdrawal, confirming early reports, which showed that even short-term (1 month) abstinence increases cortical grey matter volume, whereas long-term abstinence (1 year) leads to shrinkage of the enlarged ventricles. Working memory, visual spatial abilities and motor abilities also improve (Crews and Nixon 2009).

Frontal cortical grey matter is also affected, with neuronal loss and dendritic shrinkage, which are reversible after abstinence (Harper 2009). Indeed, as early as 2 days after intragastric administration of large amounts of ethanol to rats, neuronal death is already observed in several areas of the brain, accompanied by reduced hippocampal neurogenesis. Changes are more pronounced in adolescent rats and in those genetically predisposed (Crews and Nixon 2009). Detailed autopsy studies have revealed that neuronal loss was found in the superior frontal association cortex, while no loss was observed in the motor cortex. Loss of neurons was also observed in the hypothalamus, affecting the supraoptic and paraventricular nuclei, especially among those who consumed more than 100 g ethanol/day (Harding et al. 1996). Together with increased neuronal death, it is possible that ethanol also inhibits neuronal regeneration, reducing the survival of progenitor neuronal cells and also blunting the maturation and growth of the dendritic arbor of these cells (Crews and Nixon 2009).

Cerebellum alterations are also widespread among the alcoholics, especially among heavy drinkers during 10 or more years (Andersen 2004). Prevalence studies of cerebellar degeneration among alcoholics yield variable results depending upon the criteria employed (autopsy, radiological (MRI/CT scan) or clinical data), but may be estimated to be around 25–30%. In a series of 36 alcoholics with brain atrophy attended at our hospitalization unit, cerebellar atrophy affected 33% (García-Valdecasas-Campelo et al. 2007). Cerebellar affectation is characterized by shrinkage of the anterior superior cerebellar vermis and loss of Purkinje cells in the vermis and lateral lobes of cerebellum. These alterations cause ataxia and instability. Although some data suggest that ethanol alone does not cause cerebellar damage but only when coexisting with thiamine deficiency, experimental evidence does support that ethanol treatment and withdrawal reduces the number of Purkinje cells (Andersen 2004). In addition, white matter atrophy, particularly affecting the vermis, has also been described in chronic alcoholics. Cerebellar alterations in alcoholics may not only affect motor functions, but may also be related to cognitive and emotional disturbances – the so-called cerebellar cognitive affective syndrome (Fitzpatrick et al. 2008). These manifestations depend on the disruption of the cerebellocerebral circuitry, which connects the cerebellum and cerebral associative and paralimbic areas. The disruption of this circuitry provokes deficits in executive functioning and visuospatial skills, language alterations and disturbed personality and affective behaviour, all of which may add to the alterations due to direct frontal lobe affectation observed in the alcoholics. Cerebellar atrophy may also recover with abstinence (Cardenas et al. 2007).

187.4 Pathogenesis

187.4.1 Inflammation and Oxidative Damage

Detailed studies using a binge drinker rat model suggest that neuronal death occurs during ethanol intoxication, and not during withdrawal periods (Crews and Nixon 2009). Ethanol-induced brain damage may be related to oxidative stress derived from proinflammatory enzymes activated during ethanol intoxication. Inflammation not only causes neuronal death, but also inhibits regeneration. Transcription factors, such as cyclic adenosine monophosphate (cAMP) responsive element binding-protein (CREB), regulate the transcription of pro-survival factors, protecting neurons from excito-toxicity and apoptosis (Mantamadiotis et al. 2002).On the other hand, nuclear factor kappa B (NF-κB) is involved in proinflammatory and immune responses, is activated by cytokines, oxidative stress and glutamate, and promotes transcription of genes involved in the synthesis of proinflammatory cytokines such as tumor necrosis factor (TNF)-α. Ethanol has been associated with an increase in DNA binding to NFkB and a decrease in DNA binding to CREB, at least in hippocampal entorhinal cortex slice cultures (Zou and Crews 2005). By this way it is possible to explain the increase of reduced nicotinamide adenine dinucleotide phosphate oxidase (NADPH-oxidase) and other enzymes involved in the production of reactive oxygen species and the increase of oxidative damage mediated by ethanol. In this regard, there is the possibility that oxidative damage mediate brain atrophy (Nordmann 1994). In addition, several studies point out that flavanoids and other antioxidants exert protective effects in patients with Alzheimer's disease and there are even some reports suggesting that ingestion of wine in moderate amounts may protect against dementia, an effect that could be related to antioxidants present in wine.

Neuroinflammation may be related to neuronal degeneration. Microglial and asctrocyte responses to various brain insults include release of highly toxic products, such as reactive oxygen species, nitric

oxide, excitatory amino acids, cytokines and complement components, which cause neurodegeneration. Increased proinflammatory cytokines and chemokines expression suggest the presence of a brain proinflammatory status in several models of chronic brain damage. Experimental data have shown that an acute ethanol load cause lipid peroxidation in several areas of the brain (Uysal et al. 1989). Several studies suggest that antioxidants protect the brain from binge ethanol-induced damage and also tend to reverse ethanol-induced inhibition of neurogenesis (Crews et al. 2006). All these data, together with the well-known effect of TNF-α enhancing oxidative stress, strongly suggest a major role of this cytokine in neurodegeneration. Indeed, it is possible that part of increased lipid peroxidation is mediated by pro-inflammatory cytokines (Crews et al. 2006). In alcoholic subjects and experimental animals, increased intestinal permeability leads to a continuous exposure of Kupffer cells to intestinal antigens; these cells become activated and secrete pro-inflammatory cytokines, TNF-α being the most abundant of these. Increased TNF-α enters the brain; there, its increase lasts longer than in other tissues and exerts neurotoxic effects, including demyelination and neurodegeneration. The different behaviour of TNF-α after alcohol exposure, with rapid decrease in liver and serum, but persistence in brain, could be important in binge drinkers, with progressive neurodegeneration (Crews et al. 2006). TNF-α potentiates glutamate excitoxity, linked to excessive glutamate activation of N-methyl-D-aspartate (NMDA) receptor, since it reduces glial glutamate transporter activity and thus may also play a role in neurodegeneration (Zou and Crews 2005). Increased glutamate is related to an increase in the desire to consume ethanol. Therefore, increased TNF-α would be not only related to brain damage, but also to alcohol dependence. In accordance with these statements, in a study on 34 alcoholics we found significant relationships between TNF-α values (in percentiles) and several indices of cortical atrophy, such as bifrontal index, Evan's index and Huckmann's digit (Fig. 187.3).

In acutely intoxicated rats (5 g/kg ethanol, intraperitoneally), raised liver and brain malondialdehyde (MDA) levels were observed, reaching maximum differences with respect to controls 4 h after ethanol injection (Uysal et al. 1989), a result which lends support to the hypothesis of oxidative damage as a major pathogenic mechanism in ethanol-related brain damage. However, rats subjected to chronic ethanol ingestion (5 g/kg in saline for 6 weeks, although details on how rats ingested ethanol and the amount consumed are not provided) did not show changes in brain MDA or glutathione, despite an increase in both liver MDA and glutathione levels.
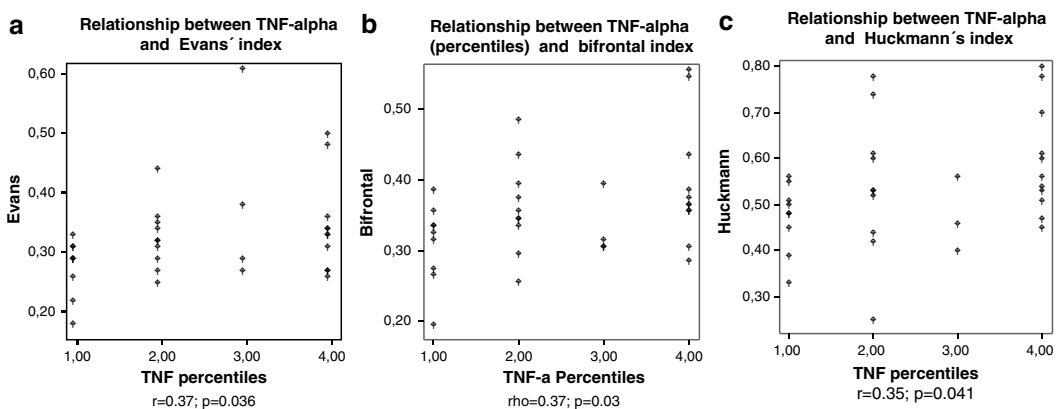
Fig. 187.3 Relationships between ventricular dilatation and Tumor necrosis factor (TNF)-alpha. Relationship between TNF-alpha (in percentiles) and several parameters related with ventricular dilatation (a = Evans' index; b = bifrontal index; c = Huckmann's digit). In the three panels it is evident that more intense degrees of ventricular dilatation are observed among those patients with higher TNF-alpha percentiles

187.4.2 Trace Elements

In close relation with oxidative damage, some trace elements could play a role in brain atrophy of alcoholics. Theoretically, some of them, such as zinc, copper, manganese and selenium, are involved in the antioxidant systems, so that their deficiency could explain some of the alterations observed. Chronic alcoholics show low serum zinc and selenium levels, and some controversy exists regarding copper. However, the relation of changes in trace elements with brain damage has been scarcely explored. There are several studies dealing with the relation between brain atrophy and copper levels. Squitti et al. (2002) found a relation between serum copper and brain atrophy in patients with Alzheimer's disease, so that levels over 1.02 mg/dl discriminated individuals with Alzheimer's disease from controls, with a sensitivity of 60% and a specificity of 95%. Toxicity of copper was probably related to the induction of peroxidation, but treatment with d-penicilamine, despite showing a lowering effect on lipid peroxidation, did not alter cognitive decline. On the other hand, in patients with Wilson disease, midbrain atrophy shows a correlation with neurological symptoms, both in probable relation with copper toxicity (Strecker et al. 2006). We also analysed the relationship between serum copper and brain atrophy, but our (preliminary) results do not support the existence of a relationship between copper and brain atrophy in alcoholics.

Increased iron has been related with early edema and, later, brain atrophy, after intracerebral bleeding, a process which can be reversed by deferoxamine. Indeed, after bleeding, once haemoglobin is degraded, iron concentration increases severalfold (Hua et al. 2007), and is capable of causing edema and brain damage by oxidative stress. Maschke et al. (2005) failed to find any relation between vermal atrophy and dentate iron concentrations – assessed by MRI – in alcoholics, but in a study of 29 alcoholics we found that serum ferritin is significantly higher among those with cerebellar atrophy (Fig. 187.4). No differences, however, were observed with serum iron. Thus, ferritin being an acute phase reactant, the possibility exists that the difference is more in relation with inflammation than with a direct effect of iron storage.

In Alzheimer's disease, as well as in alcoholic brain damage, controversy also exists regarding the role of zinc (Menzano and Carlen 1994). Low zinc may be involved in neuronal apoptosis, and in an increase in NMDA-gated neurotoxicity (Peters et al. 1987). It is hypothesized that low zinc levels may

Fig. 187.4 Relationship between serum ferritin and cerebellar atrophy. Relationship between serum ferritin and cerebellar atrophy. Patients (12) with cerebellar atrophy (1, *left bar*) showed higher ferritin levels (in ng/ml) than those (17 patients) without cerebellar atrophy (2, *right bar*)
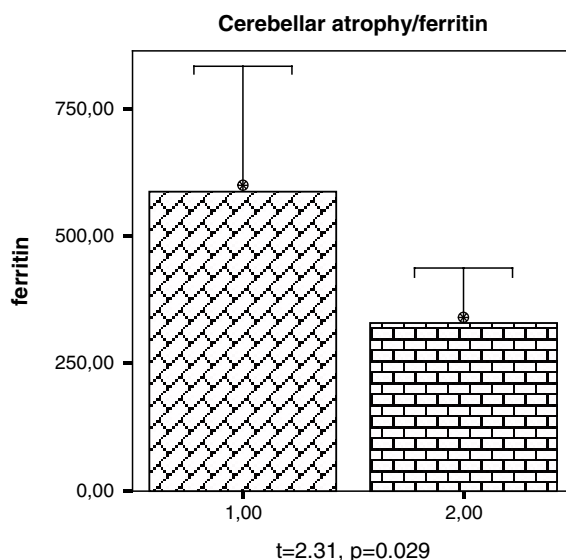
Fig. 187.5 Relationship between serum zinc and Evans'index. *Direct* relationship between serum zinc and Evans'index. Although the number of cases is small, this result does not support a role of low zinc in brain atrophy

Relationship between serum zinc and Evan´s index

rho=0.64; p=0.002
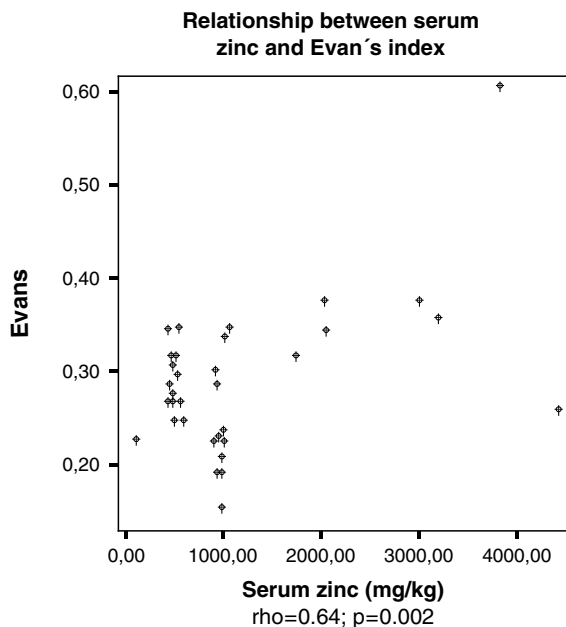
account for chronic alcoholic brain damage as well as alcohol withdrawal seizures, and a possible link between low zinc levels and hypercortisolism, as well as between hypercortisolism and brain dysfunction has been postulated (Menzano and Carlen 1994). However, this link is still merely hypothetical, and some results are inconsistent. For instance, we found a direct relationship between Evan's index and serum zinc (Fig. 187.5), a result that directly contrasts with the hypothesis linking brain atrophy to low zinc levels. We also failed to find any relation between cortisol levels and brain atrophy.

Selenium is another important element in the antioxidant system, since it is a cofactor of the glutathione-peroxidase system. It has been also shown that selenium is a necessary cofactor for normal brain development. Moreover, selenium depletion is associated with decreased activity of selenium-dependent enzymes and enhanced neuronal loss in animal models (Schweizer et al. 2004). Although low serum selenium levels have been repeatedly reported in alcoholics, the role of selenium deficiency in alcohol-related brain atrophy is largely speculative and results are not consistent. For instance, in a study of 21 alcoholics, serum selenium was directly related with bifrontal index (i.e., the more selenium, the more intense atrophy, Fig. 187.6), a result which does not support any role of low selenium on brain atrophy.

187.4.3 Vitamins

Deficiency of several vitamins, such as ascorbic acid, vitamin A, and vitamin E (due to antioxidant capabilities); cyanocobalamin, vitamin B6 and folic acid (by their relation with hyperhomocystein-aemia), and thiamine (as an etiologic factor of the Wernicke–Korsakoff encephalopathy) may be involved in the pathogenesis of brain atrophy in alcoholics.

As the above-mentioned trace elements, vitamin E may also protect against lipid peroxidation. Chronic ethanol feeding results in increased vitamin E demand by the liver (Nordmann 1994). Although the role of vitamin E in the central nervous system is uncertain, it has been shown that

Fig. 187.6 Relationship
between serum selenium and
bifrontal index. *Direct*
relationship between serum
selenium and bifrontal index

**Relationship between serum
selenium and bifrontal index**

rho = 0.44; p = 0.048
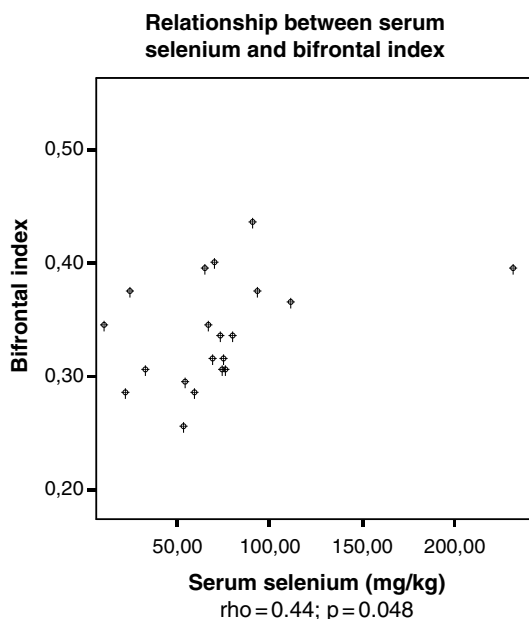
vitamin E supplementation may decrease ethanol-induced lipid peroxidation in rat cerebellum (Nordmann 1994).

A condition that must be considered in the study of brain disturbance in alcoholics is the Wernicke–Korsakoff syndrome, due to thiamine deficiency, which may also appear in nonalcoholics with protracted vomiting and/or different degrees of malnutrition. Typically, the clinical picture improves with thiamine supplementation. However, in many alcoholics – reaching as much as 80% of those affected by Wernicke's encephalopathy – Korsakoff psychosis ensues (Fitzpatrick et al. 2008). This is characterized by anterograde amnesia, cognitive impairment and confabulation, reduced affect, visuospatial alteration and also altered problem-solving capacity. Mammilary bodies and the dorsomedial nucleus of the thalamus are well-described anatomic targets of this entity, although others also describe neuronal loss in the anterior thalamic nuclei (Harding et al. 2000). In alcoholics, thiamine deficiency may result from inadequate intake, impaired absorption, reduced liver storage, and decreased transformation of thiamine in its active form. Thiamine deficiency may act synergistically with ethanol in the pathophysiology of cognitive impairment in alcoholics (Sechi and Serra 2007). Several mechanisms may be involved, such as reduction of thiamine-dependent enzyme activity, alteration of mitochondrial function and impaired oxidative metabolism, all leading to neuronal death. Decreased transketolase, alpha-ketoglutarate dehydrogenase and pyruvate dehydrogenase are observed in autopsy samples of cerebellar vermis of alcoholic patients with Wernicke–Korsakoff. Although a genetic predisposition has been sought for Wernicke–Korsakoff enecephalopathy, results are not conclusive (Guerrini et al. 2009).

On the other hand, many alcoholics with thiamine deficiency show brain atrophy, but the degree of atrophy is similar to that of patients with normal thiamine levels. As in alcoholics without any superimposed disease, atrophy of corpus callosum is also observed in relation with Wernicke's encephalopathy, but only in those cases related to ethanol abuse (Lee et al. 2005). Therefore, probably, there is a synergistic effect of thiamin deficiency and ethanol intake on brain alterations, at least regarding white matter shrinkage. In addition, several observations support a role of thiamine deficiency in cerebellar shrinkage, although the precise mechanism remains elusive. In this sense, the supplementation of staple foods like bread (and, eventually, beverages such as beer) with thiamine is a recommended practice (Harper 2009).

Brain atrophy has been put in relation with hiperhomocysteinaemia, especially at the hippocampus, in a study of 52 alcoholics who showed high levels of homocysteine (reaching 27 μmol/l in female alcoholics), low levels of folate and B6, but normal B12 levels (Bleich et al. 2003). This result is consistent with observations performed on otherwise healthy elderly subjects and in cases of dementia. Possibly, oxidative damage is the underlying mechanism, although low vitamin B12 levels are associated with brain atrophy (Vogiatzoglou et al. 2008) and more rapid cognitive decline. However, the precise pathogenic mechanisms, as well as the role of vitamin B12 in brain atrophy of alcoholics are largely unknown.

187.4.4 Nutritional Status: Protein–Calorie Malnutrition and Obesity

Protein–calorie malnutrition is a well-recognized alteration in alcoholics: indeed, not only muscle wasting, but frank malnutrition is a widespread finding in several studies dealing with alcohol-related pathologies. Although commonly associated to other nutritional deficiencies, several studies performed in growing children and individuals with eating disorders (Nogal et al. 2008) have described alterations in the myelinization process, ventricular dilatation and increased width of cortical sulci with cerebral atrophy in protein calorie malnutrition. In addition, prolonged malnutrition frequently precedes cerebellar alterations. In a study of 36 chronic alcoholics not affected by Wernicke–Korsakoff encephalopathy and 12 patients with Wernicke's encephalopathy it was found that malnutrition was associated with a sixfold increase in the risk of cerebellar atrophy. Cerebellar atrophy was present in 10 out of 12 undernourished alcoholics not affected by Wernicke's encephalopathy, but also in 11 out of 24 well-nourished alcoholic patients (Nicolas et al. 2000). These results also suggest that factors other than malnutrition are involved in cerebellar shrinkage in alcoholics. Indeed, ethanol consumption was also directly related to cerebellar shrinkage using stepwise regression analysis, in accordance with a previous study of the same group, performed on 40 well-nourished alcoholics, who showed a greater degree of brain shrinkage with age than controls, accompanied by functional derangement. Both morphological and functional alterations were correlated with the lifetime amount of ethanol consumed (Nicolas et al. 1997).

However, in 42 non-selected alcoholics, several nutritional parameters, especially those related to muscular assessment, such as brachial perimeter and handgrip strength, were also related to brain atrophy (Fig. 187.7a–c). Moreover, total lean mass was lower among alcoholics with frontal atrophy (not quantified, but assessed by a neuroradiologist), as well as trunk lean mass and limb lean mass. Interestingly, no relation was found between body mass index (BMI) and brain atrophy, or between fat parameters and brain atrophy. In this regard, obesity may also lead to brain atrophy and altered cognitive function. In a cross-sectional study on 114 individuals aged 40–66 years, brain atrophy was independently related both with age ($\beta = -0.39$) and BMI ($\beta = -0.22$; Ward et al. 2005). The association between increased BMI, brain atrophy and deranged cognitive performance has been confirmed in further studies, even in healthy adults, although the possibility exists than brain atrophy in these individuals is related to other risk factors, such as hyperhomocysteinaemia, dyslipemia, hypertension or diabetes.

Malnutrition in alcoholics has many causes, but, undoubtedly, poor nutritional intake is an important one (Santolaria et al. 2000). Irregular feeding is frequently observed in heavy alcoholics who have lost familial and wider social links. Classifying a series of patients in three groups according to eating habits, we found that cortical atrophy, estimated by measuring the width of cortical sulci, was more intense among those with poor eating habits (Fig. 187.8). Although it is likely that those with poor nutritional intake not only had protein calorie malnutrition, but also vitamin and micronutrient deficiency, this result stresses the importance of adequate nutrition in the alcoholic population at risk of brain atrophy (García-Valdecasas-Campelo et al. 2007).
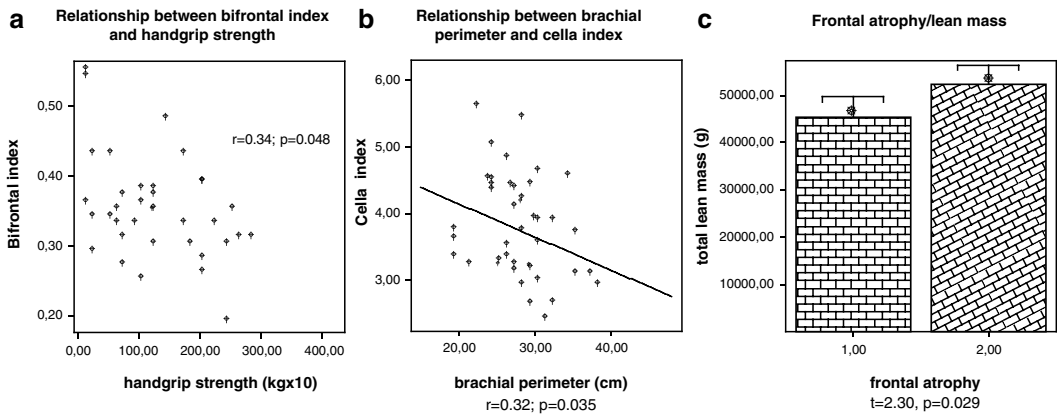
Fig. 187.7 Relationships between nutritional parameters and brain atrophy. Relationships between nutritional parameters and brain atrophy (*panel a* = relationship between handgrip strength and bifrontal index; *panel b* = relationship between cella index and brachial perimeter; *panel c* = relationship between the presence (1) or not (2) of frontal atrophy assessed by a neuroradiologist and total lean mass (assessed by dual energy x-ray absorptiometry)

Fig. 187.8 Relationship between eating habits and cortical atrophy. Relationship between eating habits and cortical atrophy in 35 patients, who reported normal food consumption (*left bar*, *n* = 11), irregular meals (*central bar*, *n* = 20) or very irregular eating habits (*right bar*, *n* = 4), consuming only snacks or sandwiches, always with large amounts of ethanol
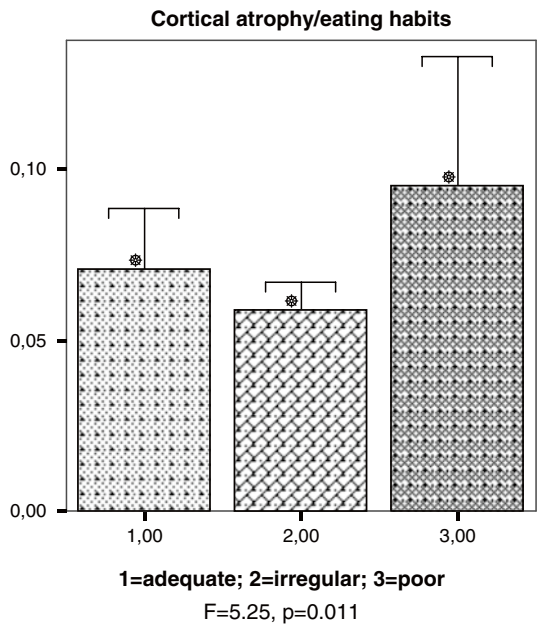
187.4.5 Liver Disease

Impaired liver function may also be associated with brain atrophy. In a classic neuropathological study on autopsies of 25 alcoholics and 44 controls, Harper and Krill (1985) found that the pericerebral space was 8.3% ± 3.3% in controls, but 16.2% ± 4.4% in alcoholics with liver disease, even greater than in alcoholics with Wernicke's encephalopathy. Amodio et al. (2003) found that several indices of brain atrophy were altered in 68 alcoholics, some of them of non-alcoholic etiology; indeed, atrophy was independent of alcoholic etiology, but was related only to age and to psychometric

Fig. 187.9 Relationships
between ventricular dilatation
and liver cirrhosis. Cirrhotics
(*left bar*, 17 cases) show less
ventricular dilatation than
non-cirrhotics (*right bar*,
30 cases). This result speak
against a possible relation
between liver failure and
brain atrophy
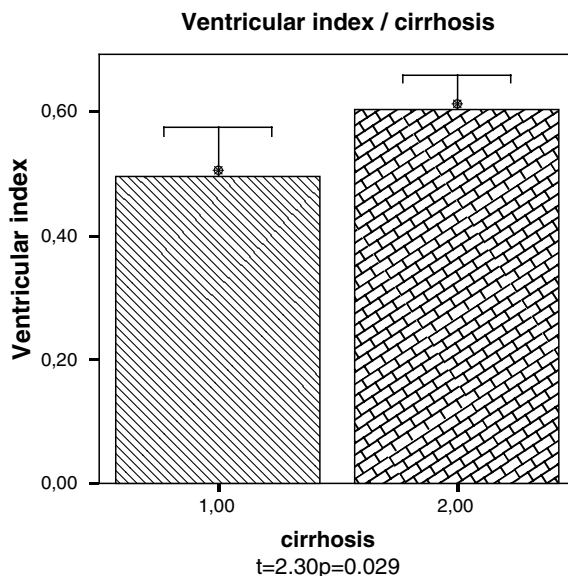
impairment and EEG changes, confirming previous studies. In this regard, Bernthal et al. (1987), studying 49 non-alcoholic cirrhotics, found that some of them showed brain atrophy, but others had brain edema, and that these changes were related to altered psychometric tests; Tarter et al. (1986) found a significant inverse relationship between serum albumin and bifrontal index (r = −0.32, $p <$ 0.05), and serum albumin and third ventricle (r = −0.30, $p < 0.05$) in 42 patients affected by nonalcoholic chronic liver diseases. Although high ammonia has been hypothesized to play a role in these alterations, no relation was found between brain atrophy indices and blood ammonia. It is possible that other factors, such as nutritional status, vitamin deficiency, or oxidative damage, may also account for these results. In this regard, in 17 alcoholic cirrhotics and 30 non-cirrhotic alcoholics (all heavy drinkers), we found that non-cirrhotic alcoholics showed more dilated ventricles than cirrhotics (Fig. 187.9) despite similar age. Moreover, a direct relationship was observed between cella index and bilirubin (r = 0.39, $p = 0.008$), and an inverse one between cella index and prothrombin activity (r = −0.32, $p = 0.03$), suggesting again that ventricular dilatation is more intense among those with preserved liver function, so that, in our experience, liver dysfunction is not related to brain atrophy.

187.4.6 Biochemical Changes and Altered Neurotransmission

It is hypothesized that alcohol-induced brain damage is attributable to two main mechanisms. The first is direct neurotoxicity mediated by ethanol, possibly by disturbances in the excitatory neurotransmission system. In addition, as commented before, thiamine deficiency may play an additive role, and this would be the second mechanim. There are marked differences in the alterations observed in neurotransmitter systems in binge drinkers and in chronic alcoholics (Ward et al. 2009). Glutamate, an excitatory neurotransmitter involved in learning and its modulation of consolidation and recall, is found to be raised in the nucleus accumbens in a binge-drinking experimental model in rats, but not in chronic alcoholics during alcohol consumption. Moreover, the amount of released glutamate depends on rat strain. Meléndez et al. (2005) showed an increase in extracellular glutamate in the nucleus accumbens, which was related to decreased uptake 24 h after a seven-day period

of intraperitoneal administration of 1 g /kg ethanol. Glutamate acts by binding to several receptors, including NMDA, alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and metabotropic glutamate receptor. It seems that in chronic alcohol exposure NMDA receptors are inhibited. However, as early as 3–5 h after detoxification there are changes in NMDA receptor sensitivity and an increase in glutamate release, which may be related to behavioural disturbances and alcohol craving (Ward et al. 2009).

Dopamine is involved in the mesolimbic reward pathway, and ethanol ingestion increases dopaminergic transmission and the firing rate of dopaminergic neurons. Chronic alcoholics need larger amounts of ethanol to evoke dopamine release to maintain the pleasurable effects of ethanol intake. These mechanisms are dramatically altered during ethanol withdrawal, leading to dysphoria and malaise. In addition, activation of D1 dopamine receptors, through phosphorilation of intermediate elements of the intracellular signal cascade, may affect glutamate activation of NMDA receptor, overriding the alcohol-induced inhibition of NMDA. Importantly, excessive activation of NMDA receptors is a major cause of neuronal cell death (Ward et al. 2009), probably by oxidative damage.

Ethanol modulates serotonin release in various areas of the central nervous system, especially through receptor 5HT-3, with different effects if exposure is acute or chronic. Serotonin release is involved in several aspects of alcohol-seeking, alcohol addiction and alcohol intoxication (Rodd et al. 2007), since it affects mood and cognitive performance. Serotonin levels depend on the levels of its precursor tryptophan, which competes with other large neutral amino acids for transport into the brain. For this reason, mental performance may be related to the ratio tryptophan/large neutral amino acids, which decreases after ethanol consumption. However, the possible effects of the altered metabolism of serotonin on brain shrinkage and neuronal death, as well as those of γ-aminobutyric acid (GABA), the main inhibitory neurotransmitter, also modulated by ethanol, are not known.

The opioid system is also influenced by ethanol. In a binge-drinking model in newborn rats (2.5 g/kg ethanol by nasogastric tube during days 2–6 of life) increased apoptosis of beta endorphin-secreting neurons (Sarkar et al. 2007) was observed, via activation of transforming growth factor beta-1 linked apoptotic signalling.

It is possible that neurotransmitters are also involved in the recovery of brain damage after abstinence. Alcohol withdrawal may lead to regeneration of the atrophic brain, with a nearly total functional recovery after prolonged abstinence. This is associated with ultrastructural changes including growth of both white and grey matter. As early as one day after stopping a binge-drinking period, proliferating microglia is observed in cortical and non-cortical brain regions (Crews and Nixon 2009). This first burst of cell proliferation is followed by the identification of immature neurons, peaking around 14 days of abstinence, located in certain areas, such as dentate gyrus. Although precise mechanisms are unknown, it is possible that glutamate-activated trophic NMDA receptors lead to increased CREB transcription, resulting in cell growth.

187.5 Conclusions

In summary, brain atrophy is a well-described entity in the alcoholic population, which may severely impair cognitive functions. Ethanol itself may cause brain atrophy through several mechanisms involving both accelerated neuronal death and blunted regeneration; probably, the principal mediator of these alterations is ethanol-induced neuroinflammation, which leads to cytokine activation and oxidative damage. Undoubtedly, coexisting alteration in vitamins, hormones micronutrients, as well as poor nutritional status, may all contribute to diffuse brain damage. It is also likely that thiamine deficiency, common in the alcoholics, also plays a synergistic role. Finally, some data, obtained by

other authors, also suggest a role of ethanol-associated liver disease on brain damage. In any case, our knowledge about this entity is still fragmentary and incomplete, and considerable research is needed for the efficient control of this complication.

187.6 Applications to Other Areas of Health and Disease

The abuse of ethanol, either in the form of excessive chronic consumption, or as binge drinking, is widespread, especially among adolescents and young adults. Even with appropriate nourishment, both forms of alcoholism may cause neurocognitive impairment and organic brain damage. Therefore, this problem is of paramount importance for the entire society, since it confers a risk of dementia to a significant proportion of young people, in addition to the many other disturbances caused by ethanol excess. Since withdrawal is associated with a marked improvement of neurocognitive damage, urgent social measures to limit excessive ethanol consumption are needed, especially directed at young people.

Equally important for the entire society is the Wernicke–Korsakoff syndrome, due to thiamine deficiency. Supplementation of basic foods, such as bread, or even alcoholic beverages, such as beer, with thiamine is a safe practice, already implemented in several countries.

Brain alterations in alcoholics also constitute another example of the rapidly expanding field of cytokine-related organ damage. This is linked to oxidative damage, and considerable research is still needed to precisely define the mechanisms involved, the potential therapeutic role of antioxidants, and the relation between altered cytokine release and neurotransmitter modulation and excitotoxicity.

The bulk of evidence indicate that severe protein deficiency may alter maturation and central nervous system function. As commented before, some alcoholics with intense addiction usually suffer loss of social and family links, and, literally forget about eating, a fact which strongly contributes to impaired nutrition. Brain atrophy in alcoholics is related with protein undernutrition. It is important to deepen our knowledge about the mechanism connecting cognitive impairment and protein deficiency, since this may help a wide proportion of people threatened by hunger in the developing world.

Summary Points

- Chronic brain damage associated to excessive ethanol consumption include cortical and subcortical atrophy, cerebellar degeneration, toxic amblyopia, pellagra, Wernicke–Korsakoff encephalopathy, Marchiafava–Bignami disease, central pontine myelinolysis and increased prevalence of stroke and cerebral trauma.
- Clinical features of brain atrophy may vary from subtle alterations (impaired verbal problem solving, abstracting abilities, visual-spatial performance, verbal memory, and the ability to adapt problem-solving strategies to changing requirements) to frank dementia. They are mostly reversible with prolonged ethanol withdrawal.
- Underlying anatomic lesions include neuronal death and white matter alterations (demyelination and axonal death)
- Pathogenesis of brain atrophy is complex and partially understood, but several mechanisms undoubtedly play a role, including: direct effect of ethanol metabolism, cytokine (especially TNF-α)-mediated neuroinflammation, oxidative damage (disbalance between antioxidants and prooxidants), thiamine deficiency, protein deficiency, excitotoxicity, and, perhaps, hyperammoniaemia related to coexisting liver disease.
- Recovery may be achieved with prolonged ethanol withdrawal and adequate nutrition

Definitions and Explanations

Wernicke–Korsakoff encephalopathy: Common complication observed in alcoholics, related to thiamine deficiency. Lethargy, disorientation and stupor may be accompanied by ophthalmoplegia and ataxia. Organic symptoms may improve with thiamine supplementation, but in some cases, confabulation, hallucinations, anterograde amnesia and intellectual impairment may ensue (Korsakoff's dementia).

Central pontine myelinolysis: Uncommon, usually fatal, complication of alcoholics, of unknown pathogenesis, characterized by demyelination and necrosis of pons and other areas of the brain leading to spastic quadriplegia, pseudobulbar palsy, and coma. Lesions and clinical picture are similar to those observed after rapid correction of profound hyponatremia.

Marchiafava–Bignami disease: An uncommon disorder which affects corpus callosum, leading to demyelination and necrosis. Initially described in Italian consumers of red wine, it also affects people worldwide, including malnourished nonalcoholics. There are three clinical forms (acute, subacute and chronic). Clinical picture ranges from convulsions and coma to mild dementia and progressive neurological deterioration.

Tobacco- and Alcohol-related amblyopia: Scotomas (blind spots) and decreased visual acuity within the central portion of the visual field, which affects undernourished alcoholic smokers, presumably caused by alcohol-mediated optic neuropathy, possibly associated with deficiency of thiamine and other micronutrients. It improves with proper diet, but may lead to permanent loss of vision if untreated.

Proinflammatory Cytokines: Molecules with pleiotropic effects, mainly involved in the inflammatory response, produced by many cells but especially by macrophages and cells involved in the immune response. Macrophages and immune cells secrete cytokines usually in response to antigens, and they generally act as signaling molecules, inducing synthesis and/or secretion of other inflammatory mediators.

Oxidative damage: Alteration of different molecules (especially DNA, lipids) of the cells by reaction with highly reactive compounds, mainly related to oxygen metabolism, including superoxide anion, hydroxyl anion, and hydrogen peroxide (powerful triggers of cytokine secretion). DNA alterations disrupt cellular metabolism and may be carcinogenic, and membrane lipid peroxidation causes cell death.

Antioxidants: Substances and/or enzymatic pathways that transform highly reactive oxidant species into less dangerous ones. Clinically important antioxidant systems which become altered in the alcoholic include glutathione peroxidase, superoxide dismutase and catalase. Several vitamins (A, C, E), and micronutrients also exert antioxidant activity.

Excitotoxicity: Mechanism of neuronal cell death, due to intense and prolonged activation of excitatory neurotransmitter (glutamate) receptors which generate increased influx of cations such as calcium and sodium, which in turn alter intracellular homeostasis and enzymatic pathways, ultimately leading to oxidative damage and cell death.

Tolerance: It is said that a subject is tolerant to alcohol when he needs progressively larger doses to achieve the same effects Tolerance leads to **physical dependence**, which is a state in which the patient needs ethanol to feel well, so that negative physical symptoms of withdrawal result from abrupt discontinuation or dosage reduction. Physical dependence is different from **addiction**, which refers only to the compulsive psychological necessity to consume a certain drug.

Dopamine neurotransmitter: Neurotransmitters are substances released into the synaptic cleft during neuronal stimulation. Dopamine acts in the mesolimbic system and plays a role in ethanol reward. During chronic consumption larger amounts of alcohol are required to evoke dopamine response (Tolerance), whereas in abstinence, rapid fall in dopamine release causes dysphoria (dependence).

References

Amodio P, Pellegrini A, Amista P, Luise S, Del Piccolo F, Mapelli D, Montagnese S, Musto C, Valenti P, Gatta A. Metab Brain Dis. 2003;28:63–78.

Andersen BB. Brain Res. 2004;1007:10–18.

Bartsch AJ, Homola G, Biller A, Smith SM, Weijers HG, Wiesbeck GA, Jenkinson M, De Stefano N, Solymosi L, Bendszus M. Brain. 2007;130:36–47.

Bernthal P, Hays A, Tarter RE, Van Thiel DH, Lecky J, Hegedus A. Hepatology. 1987;7:107–14.

Bleich S, Bandelow B, Javaheripour K, Müller A, Degner D, Wilhelm J, Havemann-Reinecke U, Sperliong W, Rüther E, Kornhuber J. Neurosci Lett. 2003;335:179–82.

Cardenas VA, Studholme C, Gazdzinski S, Durazzo TC, Meyerhoff DJ. Neuroimage. 2007;34:879–87.

Christie IC, Price J, Edwards L, Muldoon M, Meltzer CC, Jenningd JR. Alcohol. 2008;42:269–75.

Crews FT, Nixon K. Alcohol Alcohol. 2009;44:115–27.

Crews FT, Bechara R, Brown LA, Guidot DM, Mandrecker P, Oak S, Qin L, Szabo G, Wheeler M, Zou J. Alcohol Clin Exp Res. 2006;30:720–30.

Ding J, Eigenbrodt ML, Mosley TH, Hutchinson RG, Folsom AR, Harris TB, Nieto FJ. Stroke. 2004;35:16–21.

Fitzpatrick LE, Jackson M., Crowe SF. Neurosci Behav Rev. 2008;32:466–85.

Gazdzinski S, Durazzo TC, Meyerhoff D. Drug Alcohol Depend. 2005;78:263–73.

García-Valdecasas-Campelo E, González-Reimers E, Santolaria-Fernández F, de la Vega-Prieto MJ, Milena-Abril A, Sánchez-Pérez MJ, Martínez-Riera A, Rodríguez-Rodríguez E. Alcohol Alcohol. 2007;42:533–8.

Guerrini I, Thomson AD, Gurling HM. Alcohol Alcohol. 2009;44:166–70.

Harding A, Halliday G, Ng JLF, Harper CG, Kril JJ. Neuroscience. 1996;72:699–708.

Harding A, Halliday G, Caine D, Kril J. Brain. 2000;123:141–54.

Harper C. Alcohol Alcohol. 2009;44:136–40.

Harper C, Kril J. J Neurol Neurosurg Psych. 1985;48:211–7.

Hua Y, Keep RF, Hoff JT, Xi G. Stroke. 2007;38:759–76.

Jarvenpaa T, Rinne JO, Koskenvuo M, Räihä I, Kaprio J. Epidemiology. 2005;16:766–71.

Kril JJ, Halliday GM, Svoboda MD, Cartwright H. Neuroscience. 1997;79:983–98.

Kubota M, Nakazaki S, Hirai S, Saeki N, Yamaura A, Kusaka T. J Neurol Neurosurg Psych. 2001;71:104–6.

Lee ST, Jung YM, Na DL, Park SH, Kim M. J Neuroimaging. 2005;15:367–72.

Mantamadiotis T, Lemberger T, Bleckmann SC, Kern H, Kretz O, Martín Villalba A., Tronche F, Kellendonk C, Gau D, Kapfhammer J, Otto C, Schmid W, Schütz G. Nature Gen. 2002;31:47–54.

Maschke M, Weber J, Bonnet U, Dimitrova A, Böhrenkamper J, Sturm S, Müller BW, Gastpar M, Diener HC, Forsting M, Timmann D. J Neurol. 2005;252:704–11.

Meléndez RI, Hicks MP, Cagle SS, Kalivas PW. Alcohol Clin Exp Res. 2005;29:326–33.

Menzano E, Carlen LP. Alcohol Clin Exp Res. 1994;18:895–901.

Nicolas JM, Estruch R, Salamero M, Orteu N, Fernández-Sola J, Sacanella E, Urbano-Marquez A. Ann Neurol. 1997;41:590–8.

Nicolas JM, Fernández-Sola J, Robert J, Antúnez E, Cofán M, Cardenal C, Sacanella E, Estruch R, Urbano-Marquez A. QJM. 2000;93:449–56.

Nixon SJ, Tivis R, Parsons OA. Alcohol Clin Exp Res. 1995;19:577–81.

Nogal P, Pniewska-Siark B, Lewinski A. Neuro Endocrinol Lett. 2008;29:879–83.

Nordmann R. Alcohol Alcohol. 1994;29:513–22.

Paul CA, Au R, Fredman L, Massaro JM, Seshadri S, Decarli C, Wolf PA. Arch Neurol. 2008;65:1363–7.

Peters S, Koh J, Choi DW. Science. 1987;236:589–93.

Pfefferbaum A, Adalsteinsson E, Sullivan EV. Aging. 2006;27:994–1009.

Rodd ZA, Gryszowka VE, Toalston JE, Oster SM, Ji D, Bell RL, McBride WJ. J Pharmacol Exp Ther. 2007;321: 1003–12.

Santolaria F, González-Reimers E, Pérez-Manzano JL, Milena A, Gómez-Rodríguez MA, González-Díaz A, de la Vega MJ, Martínez-Riera A. Alcohol. 2000;22:47–157.

Sarkar DK, Kuhn P, Marano J, Chen C, Boyadijeva N. Endocrinology. 2007;148:2828–34.

Schweizer U, Bräuer AU, Köhrle J, Nitsch R, Savaskan NE. Brain Res Rev. 2004;45:164–78.

Sechi G, Serra A. Lancet Neurol. 2007;6:442–55.

Squitti R, Lupoi D, Pasqualetti P, Dal Forno G, Vernieri F, Chiovenda P, Rossi L, Cortesi M, Cassetta E, Rossini PM. Neurology. 2002;59:1153–61.

Strecker K, Schneider JP, Barthel H, Herrmann W, Wegner F, Wagner A, Schwarz J, Sabri O, Zimmer C. J Neurol. 2006;253:1024–9.

Tarter RE, Hays A, Sandford SS, Van Thiel DH. Lancet 1986;II:893–5.

Thatcher DL, Clark DB. In: Preedy VR, Watson RR, editors. Comprehensive handbook of alcohol related pathology. Amsterdam: Elsevier; 2005. pp. 181–93.

Uysal M, Kutalp G, Odzemirler G, Aykac G. Drug Alcohol Depend. 1989;23:227–30.

Vogiatzoglou A, Refsum H, Johnston C, Smith SM, Bradley KM, de Jager C, Budge MM, Smith AD. Neurology. 2008;71:826–32.

Wang LL, Li Y, Zhou SF. Toxicol Lett. 2009;187:99–114.

Ward MA, Carlsson CM, Trivedi MA, Sager MA, Johnson SC. BMC Neurology. 2005;5:23 (doi.10.186/1471-2377-5-23).

Ward RJ, Lamelland F, de Witte P. Alcohol Alcohol. 2009;44:128–35.

Zou JY, Crews FT. Brain Res. 2009;1034:11–24.

Chapter 188
Alcohol Consumption in Predementia and Dementia Syndromes

Francesco Panza, Vincenza Frisardi, Patrick G. Kehoe, Cristiano Capurso, Alessia D'Introno, Anna M. Colacicco, Gianluigi Vendemiale, Antonio Capurso, and Vincenzo Solfrizzi

Abbreviations

AD	Alzheimer's disease
APOE	Apolipoprotein E
ARCD	Age-related cognitive decline
βA	Amyloid beta
CAD	Coronary artery disease
CASI	Cognitive abilities screening instrument
CVD	Cerebrovascular disease
MCI	Mild cognitive impairment
MUFA	Monounsaturated fatty acids
PUFA	Polyunsaturated fatty acids
SFA	Saturated fatty acids
VaD	Vascular dementia
WML	White matter lesions

188.1 Introduction

188.1.1 Current Epidemiology of Dementia and Predementia Syndromes

Since population aging has become a worldwide phenomenon, the burden of age-related neurode-generative diseases, particularly dementia, is expected to increase dramatically in both developed and developing nations. The deterministic boundaries of perceived normal cognitive aging are not clearly defined while the clinical categorisation of predementia and dementia syndromes remain, at present, a work in progress. Dementia is a syndrome defined by impairments in memory and other cognitive functions that are severe enough to cause significantly reduced performance from a previous level of social and occupational functioning. Dementia is estimated to affect approximately 6% of the people aged 65 years and older, with the prevalence increasing exponentially with age, rising

F. Panza (✉)
Department of Geriatrics, Center for Aging Brain, Memory Unit,
University of Bari, Policlinico, Piazza Giulio Cesare, 11, 70124 Bari, Italy
e-mail: geriat.dot@geriatria.uniba.it

Table 188.1 Key features of dementia syndromes

1. Dementia is a syndrome definite by impairments in memory and other cognitive functions that are severe enough to cause significant decline from a previous level of social and occupational functioning
2. AD is the most common dementia and primary neurodegenerative disorder in the elderly, gradually leading to a complete psychological and physical dependency and finally to death within 1–2 decades
3. The diagnosis of AD is essentially a clinical one, and it is based on a typical clinical picture and findings, with a set of clinical criteria often used in research
4. Cognitive function declines over time, and the diagnosis of AD can be considered when the patient has impairments in memory and at least in one other cognitive function (executive dysfunction, agnosia, aphasia, apraxia), severe enough to cause impairment in social or occupational functioning
5. In advanced AD, common symptoms include also confusion, behavioural and gait disturbances, and the patients are increasingly dependent on others in activities of daily living
6. Another common form of dementia is VaD, its clinical presentation varies greatly depending on the causes and location of cerebral damage
7. Large-vessel disease leads commonly to multiple cortical infarcts and a multifocal cortical dementia syndrome
8. Small-vessel disease, usually resulting from hypertension and diabetes, causes periventricular white matter ischemia and lacunar strokes characterized clinically by subcortical dementia with frontal lobe deficits, executive dysfunction, slow information processing, impaired memory, inattention, depressive mood changes, slowing of motor function, Parkinsonian features, small-step gait, urinary disturbances and pseudobulbar palsy
9. The characteristic neuropsychological profile of VaD is believed to include frequently early impairment of attention and executive control function, with slowing of motor performance and information processing, while episodic memory is relatively spared compared to that in AD

This table lists the key facts of dementia syndromes including clinical pictures and criteria of Alzheimer's disease (AD) and vascular dementia (VaD), the most common dementia syndromes

to between 40% and 70% at the age of 95 years and above (Qiu et al. 2007). In Westernised countries, the most common forms of dementia are Alzheimer's disease (AD) and vascular dementia (VaD), with respective frequencies of 70% and 15% of all dementias (Whitehouse et al. 1997) (Table 188.1). Therefore, AD is the most common dementia and primary neurodegenerative disorder in the elderly that gradually leads to a complete psychological and physical dependency on others and finally to death within 1–2 decades. In the present chapter, we will use the term "predementia syndrome" to identify all conditions with age-related (non-pathological) deficits in cognitive function reported in the literature, including a mild stage of cognitive impairment based on a model of normality and the presence of pathological conditions considered predictive or early stages of dementia (Panza et al. 2005) (Table 188.2). Such predementia syndromes have been defined for AD and VaD, but have not yet been operationalized for other specific forms of dementia. Therefore, the term "predementia syndromes" includes different conditions and among these predementia syndromes, mild cognitive impairment (MCI) is, at present, the most widely used term to indicate nondemented aged persons with no significant disability and a mild memory or cognitive impairment that cannot be explained by any recognisable medical or psychiatric condition (Petersen et al. 1999; Winblad et al. 2004) (Table 188.2).

There is now ample evidence that MCI is often a pathology-based condition with a high rate of progression to AD (Petersen et al. 1999). Therefore, MCI has been classed as the predementia syndrome for AD (Panza et al. 2005). Recently, a number of subtypes of MCI have been proposed, intended to reflect the heterogeneity of different types of dementia (Table 188.2). In fact, the recent subclassification of MCI according to its cognitive features (including dysexecutive MCI and amnestic-MCI (aMCI) or aMCI and non-amnestic MCI (naMCI); single or multiple domain aMCI or naMCI) and clinical presentation (MCI with parkinsonism or cerebrovascular disease), or likely aetiology (MCI-AD, vascular MCI, or MCI-Lewy Body Disease) all represent an attempt to exert some control over this heterogeneity (Panza et al. 2010). Recently, a critical review was undertaken

Table 188.2   Key features of predementia syndromes

1. The term "predementia syndromes" identifies all conditions with age-related deficits in cognitive function reported in the literature, including a mild stage of cognitive impairment based on a normality model and pathological conditions considered predictive or early stages of dementia

2. Among predementia syndromes, MCI is, at present, the most widely used term to indicate non-demented aged persons with a mild memory or cognitive impairment that cannot be accounted for any recognized medical or psychiatric condition

3. The general criteria for MCI include (a) memory complaint, (b) objective memory disorder, (c) absence of other cognitive disorders or repercussions on daily life, (d) normal general cognitive function, (e) absence of dementia

4. MCI definitions can be broadly classified as amnestic (aMCI) and nonamnestic (naMCI)

5. There is now ample evidence that MCI is often a pathology-based condition with a high rate of progression to AD, and aMCI, with a central role for memory disorder and with relative preservation of other cognitive domains, was identified as the predementia syndrome for AD

6. aMCI can be subdivided into a single-domain subtype with a pronounced memory deficit or a multiple-domain subtype that includes memory impairment along with some impairment in other cognitive domains such as language, executive function, and visuospatial skills

7. The other major MCI subtype is naMCI, which similarly can be subdivided into single and multiple domain subtypes

This table lists the key facts of predementia syndromes including diagnostic criteria and clinical classification of mild cognitive impairment (MCI), the most common predementia syndrome

to try to define a new consensus on MCI, and a modification of Petersen's original criteria (Petersen et al. 1999) was proposed during the conference in Montreal (Winblad et al. 2004). Subsequently, the European Consortium on Alzheimer's Disease (EADC) (http://eadc.alzheimer-europe.org/introduction.html) working group on MCI proposed a novel diagnostic procedure with different stages, combining neuropsychological evaluation and family interview to detect MCI at the earliest possible stage (Portet et al. 2006).

The clinical presentation of VaD varies greatly depending on the causes and location of cerebral damage (Roman 2002). Large-vessel disease leads commonly to multiple cortical infarcts and a multifocal cortical dementia syndrome, whereas small-vessel disease, usually resulting from hypertension and diabetes, causes periventricular white matter ischemia and lacunar strokes characterized clinically by subcortical dementia with frontal lobe deficits, executive dysfunction, slow information processing, impaired memory, inattention, depressive mood changes, slowing of motor function, Parkinsonian features, small-step gait, urinary disturbances, and pseudobulbar palsy (Roman and Royall 1999). Recently, the term vascular cognitive disorder (VCD) has been proposed by Sachdev (Sachdev 1999) and it would become the global diagnostic category for cognitive impairment of vascular origin (Roman et al. 2004). VCD would include the group of syndromes and diseases characterized by cognitive impairment resulting from a cerebrovascular etiology. The main categories of VCD are vascular cognitive impairment (VCI) [i.e., vascular cognitive impairment no dementia (vascular CIND), and vascular MCI], VaD, and mixed AD plus cerebrovascular disease (CVD) previously termed "mixed dementia" (Sachdev 1999; Roman et al. 2004). Dementia is defined as executive control deficit producing loss of function for instrumental activities of daily living, while mixed AD plus CVD is defined as preexisting AD worsened by stroke (equivalent to prestroke dementia). Finally, VCI is a term referred to all forms of mild to severe cognitive impairment associated with CVD, including vascular CIND and vascular MCI, e.g., predementia syndromes with a presumed primary vascular basis. VCI is considered a premonitory phase of VaD, although VCI not always proceeds to VaD (Sachdev 1999; Roman et al. 2004). The characteristic neuropsychological profile of VCI is believed to include frequently early impairment of attention and executive control function, with slowing of motor performance and information processing, while episodic memory is relatively spared compared to that in AD (Erkinjuntti et al. 2000) (Table 188.1).

188.1.2 Lifestyle Changes and Prevention of Dementia and Predementia Syndromes

At present, there is no curative treatment for dementia and AD, nor is there a therapeutical approach to prevent the conversion of MCI to dementia. In previous years, extensive research has increased our knowledge of the aetiology of AD, other dementing disorders, and predementia syndromes, and several hypotheses have emerged from both laboratory and epidemiological research. Epidemiological evidence in particular supported the hypothesis that modifiable vascular and lifestyle-related factors are associated with the development of dementia and predementia syndromes in later life, opening new potential avenues for the prevention of these diseases (Panza et al. 2009a).

Given the lack of effective pharmacotherapies to treat dementia, lifestyle changes may offer alternative or supplementary treatment options for predementia syndromes, i.e., MCI or age-related cognitive decline (ARCD). Evidence from population-based longitudinal epidemiologic studies suggests that moderate exercise and physical activity are associated with a lower risk of dementia (Panza et al. 2009a). Among lifestyle- and vascular-related factors, the impact of diet, Mediterranean diet in particular, has also been the subject of recent interest (Panza et al. 2009a) while regular moderate consumption of alcohol (≤24 g/day) have been reported to prevent coronary artery disease (CAD) and to reduce the risk of ischaemic and haemorrhagic stroke (Panza et al. 2009a).

There is also much evidence existing and emerging, from population-based longitudinal cohort studies predominantly but also from some case-control studies, which suggest that alcohol consumption, particularly red wine within limits and/or of certain types, decreases risk of cognitive impairment or decline, predementia, and dementia syndromes. This is despite chronic alcohol abuse causing progressive neurodegenerative disease (Panza et al. 2009a) (Table 188.3). However, some of the variability in these studies may be due to cross-sectional designs used, restrictions by age or sex, or incomplete ascertainment (Panza et al. 2009a). It is especially important to examine data for men and women separately when alcohol consumption is a predictor variable, because gender-based consumption levels

Table 188.3 Key features of alcohol

1. An alcohol is any organic compound in which a hydroxyl group (–OH) is bound to a carbon atom of an alkyl or substituted alkyl group
2. Generally, the word alcohol refers to ethanol, the type of alcohol found in alcoholic beverages
3. Ethanol is a colourless, volatile liquid with a mild odour, which can be obtained by the fermentation of sugars
4. Ethanol in alcoholic beverages has been consumed by humans since prehistoric times for a variety of hygienic, dietary, medicinal, religious, and recreational reasons
5. The short-term effects of alcohol on the human body can take several forms. Alcohol, specifically ethanol, is a potent CNS depressant, with a range of side effects. The consumption of large doses of ethanol causes drunkenness (intoxication), which may lead to a hangover as its effects wear off. The amount and circumstances of consumption play a large part in determining the extent of intoxication
6. The long-term effects of alcohol in excessive quantities are capable of damaging nearly every organ and system in the body. Regularly consumption of alcohol is correlated with an increased risk of developing alcoholism, cardiovascular disease, malabsorption, chronic pancreatitis, alcoholic liver disease, and cancer. Damage to the CNS and peripheral nervous system can occur from sustained alcohol consumption
7. Research has found a correlation between light to moderate consumption of alcohol, one to two alcoholic beverages per day, and reduced risk of heart disease as well as other health benefits, including reduction in all-cause mortality and decreasing risk of dementia, including AD. However, at present, due to poor study design and methodology, the literature is inconclusive on whether moderate alcohol consumptions increases the risk of dementia or decreases it

This table lists the key features of alcohol including definition, short- and long-term health effects, and current research findings on the health effects of light to moderate consumption of alcohol

CNS central nervous system, *AD* Alzheimer's disease

are very different. In virtually every study which included both sexes, women consumed alcohol less frequently and in smaller amounts than men. Moreover, education, smoking, or the widely recognized AD genetic risk factor apolipoprotein E (*APOE*) ε4 allele often modified the association between alcohol drinking and cognitive impairment or decline. Indeed reported association between less years of education and predementia and dementia syndromes is supported by the majority of studies, although few studies have investigated lifestyle factors as a possible covariant with education (Panza et al. 2009a). Socioeconomic and educational factors, which contribute to drinking behaviour in different populations and countries, might influence the strength of association of alcohol and cognitive impairment or decline. Furthermore, the *APOE* ε4 allele, which has variable prevalence in different geographic locations (Panza et al. 1999) could be a possible effect modifier for the associations between alcohol/vascular risk factors and dementia syndromes (Panza et al. 2009a).

An alternative growing body of evidence suggests that chronic cigarette smoking is associated with abnormalities in brain morphology, cerebral blood flow, increased oxidative stress, and with increased risk of stroke, and these factors could confound and counteract possible cognitive benefits afforded by low to moderate alcohol consumption among smokers (Panza et al. 2009a). However, smoking and alcohol use are related; there are more heavy drinkers who smoke, which may produce a possible multiplicative risk effect for cognitive impairment or decline. Of note, drinking inversely correlates with increased age while risk for cognitive impairment occurs most often at extremely old age long after the peak drinking years of youth (Panza et al. 2009a). It is possible that over time, possibly influenced by cognitive decline, alcohol consumption will change, and therefore long-term follow-up studies are needed to clarify the outcomes of these changes. Furthermore, aspects of when and how drinking is measured and how these measurements relate to when and how cognitive decline is measured are important sources of variability that need to be borne in mind in these studies.

In this chapter, we have summarized the findings of the studies of alcohol consumption in cognitive impairment or decline, predementia, and dementia syndromes. We have reviewed clinical and epidemiological studies from the international literature, including both cross-sectional and longitudinal studies that involved subjects aged 60 years and above and where description of the diagnostic criteria for predementia or dementia syndromes has been attempted. Special attention was paid to the possible mechanisms behind reported associations of alcohol drinking with cognitive impairment or decline, predementia, and dementia syndromes.

188.2 Alcohol Consumption and Cognitive Functions in Older Age

188.2.1 Regular Alcohol Consumption and Cognitive Functions in Older Age

Several studies have assessed regular alcohol consumption and cognitive function among older adults, but with inconsistent results (Goodwin et al. 1987; Herbert et al. 1993; Christian et al 1995; Hendrie et al. 1996; Launer et al. 1996; Dent et al. 1997; Dufouil et al. 1997; Broe et al. 1998; Edelstein et al. 1998; Elias et al. 1999; Carmelli et al. 1999; Elwood et al. 1999; Leibovici et al. 1999; Dufouil et al. 2000; Cervilla et al. 2000a,b; Galanis et al. 2000; Bond et al. 2001, 2005; Zuccalà et al. 2001; Schinka et al. 2002; Verhaegen et al. 2003; Zhou et al. 2003; Stampfer et al. 2005; Lindeman et al. 2005; Ganguli et al. 2005; Reid et al. 2006; Ngandu et al. 2007; McGuire et al. 2007) (Tables 188.4 and 188.5). Early studies involving relatively small samples of young to middle-aged male social drinkers supported the notion that drinking at any level was associated with poorer performance on cognitive tests (Panza et al. 2009a). However, other studies corroborated these results

Table 188.4 Principal cross-sectional studies on the relationship between alcohol consumption and cognitive impairment in older subjects

References	Setting and study design	Subjects	Methods	Results and conclusions
Cross-sectional studies				
Goodwin et al. (1987)	Cross-sectional, population-based	270 men and women aged 65–89 years	Cognitive abilities assessed with a 30-item mental status questionnaire, abstract thinking measured with the HCT, and WMS. Emotional status measured by a 92-item self-rating checklist, and social interaction evaluated with a revised form of the Interview Schedule for Social Interaction. Alcohol consumption assessed during a 3-day period and questionnaires about present and past alcohol intake	Present or past alcohol intake was not associated with decreased cognitive, psychological, or social status
Hendrie et al. (1996)	Cross-sectional, population-based	2,040 participants aged 65 and older from a community-dwelling sample of black Americans	Community Screening Interview for Dementia, delayed recall of the EBMT, and ADL.; evaluation of alcohol consumption	Also after potential confounders were included, there was a small but significant dose effect of drinking for the drinkers, with subjects in the heaviest drinking category scoring poorest in cognitive tests and daily functioning. The scores of abstainers were worse than those of subjects in the lightest drinking category
Dufouil et al. (1997)	Cross-sectional, population-based	574 men and 815 women, aged 59–71 years	MMSE, TMT-B, WAIS -Revised, BVRT, Benton Facial Recognition Test, Paced Auditory Serial Addition Test, Auditory Verbal Learning Test, RPM, Word Fluency Test, and Finger Tapping Test; evaluation of alcohol intake and smoking habits	In men, no significant relation between alcohol consumption and cognitive scores was found. In contrast, among women, with a range of daily alcohol consumption between zero and approximately four drinks, an overall positive linear association between cognitive scores and alcohol consumption was found, also after adjustment for age, income, education, and depressive symptomatology
Carmelli et al. (1997)	Cross-sectional, population-based	589 male participants aged 59–69 years	MMSE, DSST, and BVRT. Evaluation of alcohol intake, smoking habits, and APOE genotyping	After adjustment for age, education and CVD, smoking was significantly associated with poor cognitive function in current smokers compared with never smokers, whereas light drinking (one or fewer drinks per day) showed a protective effect compared with abstainers. Stratification by APOE ε4 indicated that the protective effect of light drinking was stronger and the harmful effect of smoking was weaker among APOE ε4 carriers than among noncarriers

Elwood et al. (1999)	Cross-sectional, population-based	1,870 men aged 55–69 years	CAMCOG and MMSE, AH4 evaluating verbal and mathematical reasoning, and CRT. Evaluation of alcohol intake and smoking habits.	Light and moderate drinking showed no association with cognitive functions. Cigarette smoking showed no association, but there is evidence that the more able smokers quitted and become ex-smokers
Bond et al. (2001)	Cross-sectional and longitudinal, population-based (8 years)	1,836 participants aged 65 and older	CASI, CRT, and NART. Evaluation of alcohol intake and cigarette smoking habits	Lower cognitive test scores were observed for men who were either abstainers or in the heavy drinking group. For women, a linear relationship between alcohol consumption and cognitive performance was seen on two of the four measures of cognitive functioning, suggesting a possible positive relationship between light to moderate drinking and cognitive performance
Zuccalà et al. (2001)	Cross-sectional, multicenter pharmacoepidemiology survey	15,807 hospitalized patients, mean age 70.9 years	Hodkinson Abbreviated Mental Test score, and evaluation of alcohol intake	Adjusting for potential confounders, alcohol consumption was associated with decreased probability of cognitive impairment, a daily alcohol consumption of less than 40 g for women and 80 g or less for men might be associated with a decreased probability of cognitive impairment
Schinka et al. (2002)	Cross-sectional, population-based	395 participants aged 60–84 years	Neuropsychological battery that provided measures of general cognitive ability, executive function, memory, evaluation of alcohol intake and cigarette smoking habits	No evidence for a beneficial J-curve or threshold effect for drinking was found, but did not reveal any detrimental effect. No detrimental effect of smoking was found in any analysis; nor was there any evidence of an interaction between alcohol and cigarette use on any cognitive measure
Zhou et al. (2003)	Cross-sectional, population-based	3,012 participants aged 60 years old and older	MMSE and ADL, evaluation of alcohol intake, and smoking habits	Alcohol drinking was associated with cognitive impairment, and in all people who drink every day, there was a significantly increased risk of cognitive impairment. Smoking was also related to cognitive impairment, and current smoking was associated with a significantly increased risk of cognitive impairment
Lindeman et al. (2005)	Cross-sectional, population-based	883 participants aged 65 years old and older	MMSE, WAIS - Revised, Digits Forward, Fuld Object-Memory Evaluation, CDT, and two Color TMT; evaluation of alcohol intake	Older participants who ingested alcohol had significantly better test scores than did the abstainers on seven of nine cognitive function tests after adjusting for differences in sex, ethnicity, age, and years of education

(continued)

Table 188.4 (continued)

References	Setting and study design	Subjects	Methods	Results and conclusions
Cross-sectional studies				
Reid et al. (2006)	Cross-sectional, population-based	760 men aged 65–89 years	TMT-B, DSST, FAS Test, and Hopkins Verbal Learning test, and evaluation of alcohol use	Current light to moderate drinking (i.e., 7 or fewer drinks per week), as compared to never and former drinkers, and the number of years drinking at this level are both associated with better cognitive performance in older males

This table lists the principal findings of cross-sectional clinical and epidemiological studies on the relationship between alcohol consumption and cognitive impairment in older subjects, including setting, study design, and cognitive assessment used

HCT Halstead Category Test, *WMS* Wechsler Memory Scale, *EBMT* East Boston Memory Test, *ADL* Activities of Daily Living, *MMSE* Mini-mental State Examination, *TMT* Trail Making Test, *WAIS* Wechsler Adult Intelligence Scale, *BVRT* Benton Visual Retention Test, *RPM* Raven Progressive Matrices, *DSST* Digit Symbol Substitution Test, *APOE* Apolipoprotein E, *CAMCOG* Cambridge Cognitive Examination, *CRT* Choice Reaction Time, *CASI* Cognitive Abilities Screening Instrument, *NART* National Adult Reading Test, *CVD* Cerebrovascular Disease, *CDT* Clock Drawing Test

Table 188.5 Principal longitudinal studies on the relationship between alcohol consumption and cognitive decline in older subjects

References	Setting and study design	Subjects	Methods	Results and conclusions
Longitudinal studies				
Herbert et al. (1993)	Longitudinal, population-based (3 years)	1,201 subjects aged 65 years and older	Structured performance tests of immediate memory, digit span (from WAIS), and orientation; diagnosis of AD; evaluation of alcohol intake and smoking habits	Change in only one of the 3 cognitive tests (digit span) was significantly associated with one alcohol category (15 ml per day), and no dose-response relation was observed
Christian et al. (1995)	Retrospective cohort and co-twin-control study	4,739 twins born between 1917 and 1927	Two self-reported drinking histories (1970s and 1980s) and a telephone mental status interview (1990 and 1991)	No evidence was found to indicate an association between moderate long-term alcohol intake and lower cognitive scores in aging individuals. There was a suggestion of a small protective effect of past moderate alcohol intake on cognitive function with aging
Launer et al. (1996)	Cross-sectional and longitudinal, population-based (3 years)	489 men aged 69–89 years	MMSE, evaluation of alcohol intake and smoking habits	After adjustment for age, education, and smoking status, men with CVD/diabetes and low-to-moderate alcohol intake had a significantly lower risk for poor cognitive function than abstainers. Alcohol intake was not associated with cognitive decline
Dent et al. (1997)	Longitudinal, random sample of veterans of the second world war (9 years)	209 men, mean age: 64.3 years	WAIS, WMS, BVRT, RPM, Rey Auditory Verbal Learning Test, Controlled Oral Word Association Test, Boston Naming Test, NART, CRT, and HCT evaluation of alcohol intake and noncontrast computed tomography	Persistent lifelong consumption of alcohol and the level of intake seemed not to have any impact on cognitive performance among men in old age
Broe et al. (1998)	Longitudinal, population-based (3 years)	327 subjects, aged 75 years and older	MMSE, Reid Memory Test, tests of verbal fluency, subsets of the Boston Naming Test and similarities; CDT; and copied drawings of a cube, coils, and interlocking infinity loops; diagnosis of dementia and AD; evaluation of physical exercise, alcohol and smoking use	There were few significant associations between health habits and cognitive performance and these were not found consistently across cognitive measures

(continued)

Table 188.5 (continued)

References	Setting and study design	Subjects	Methods	Results and conclusions
Longitudinal studies				
Edelstein et al. (1998)	Longitudinal, population-based (13–18 years)	511 men and women aged 40–80 years	MMSE, TMT-B, Category Fluency, BFSRT, and BVRT, evaluation of alcohol intake and smoking habits	Moderate alcohol consumption and cigarette smoking patterns, reported 13–18 years and 3–7 years previously were weakly and inconsistently associated with subsequent cognitive function
Elias et al. (1999)	Cross-sectional and longitudinal, population-based (24 years)	1,786 subjects, aged 55–88 years	Eight cognitive tests of verbal memory, learning, visual organization and memory, attention, abstract reasoning, and concept formation; evaluation of weekly alcohol intake	Women who drank moderately (2–4 drinks/day) showed superior performance in many cognitive domains relative to abstainers. For men, superior performance was found within the range of 4–8 drinks/day, although fewer significant relations were observed. These results were confirmed by prospective analyses of 24-year drinking history
Leibovici et al. (1999)	Longitudinal, population-based (3 years)	833 subjects over 60 years	A computerized neuropsychometric examination assessed attention, primary and secondary memory, implicit memory, visuospatial ability, and language. Diagnosis of AD and evaluation of alcohol and tobacco consumption were also performed	Wine consumption was associated with an increased risk of decline over time in attention and in secondary memory. Smoking was associated with a decreased risk for decline over time in attentional and visuospatial functioning. No clear combined effect of smoking and drinking was found, even though smoking was found to increase the risk of decline in language performance when adjusted on wine consumption
Dufouil et al. (2000)	Longitudinal, population-based (4 years)	1,389 subjects, aged 59–71 years	MMSE, evaluation of alcohol consumption, APOE genotyping, and smoking habits	Alcohol consumption was associated with a decreased risk of cognitive decline in individuals without the APOE ε4 allele, whereas moderate drinking increased the risk of decline in APOE ε4 allele carriers. Also, lifetime smoking was a risk factor for cognitive decline in individuals without the APOE ε4 allele. The data also suggested a slight protective effect of smoking in APOE ε4 allele carriers
Cervilla et al. (2000a)	Longitudinal, population-based (1 year)	889 subjects, aged 65 or older	Cognitive impairment assessed at baseline and 1 year later using the organic brain syndrome (OBS) cognitive impairment scale from the short CARE structured assessment, evaluation of alcohol intake and smoking habits	No association between alcohol consumption and onset of cognitive impairment was found. Persistent cigarette smoking into late-life increased the risk for cognitive impairment

Cervilla et al. (2000b)	Longitudinal, population-based (9–12 years)	1,083 subjects, aged 65–74 years	MMSE, evaluation of alcohol intake and smoking habits	Older subjects who were abstinent before the age of 60 had poorer cognitive outcome than did those who drank mildly or moderately
Galanis et al. (2000)	Longitudinal, population-based (18 years)	3,556 men of Japanese ancestry, aged 71–93 years	CASI, and evaluation of alcohol intake	Positive association between a history of moderate alcohol consumption and cognitive performance in the elderly, as men who had consumed up to one drink a day during middle age were later found to have significantly better cognitive test results than nondrinkers
Verhaegen et al. (2003)	Cross-sectional and longitudinal, population-based (4 years)	516 subjects aged 70 years and older	Cognitive by unit-weighted consisted of four intellectual abilities (perceptual speed, episodic memory, fluency, and knowledge), each assessed by composites of two tests, evaluation of alcohol consumption and smoking behaviour	Cross-sectionally, better cognitive performances have been observed with higher levels of alcohol drinking, while alcohol was not associated with 4-year declines in cognition
Stampfer et al. (2005)	Cross-sectional and longitudinal, population-based (2 years)	12,480 subjects aged 70–81 years	Telephone Interview for Cognitive Status, EBMT, TICS 10-word list, a test of verbal fluency, and the digit span backward test. Evaluation of alcohol consumption and APOE genotype	After multivariate adjustment, moderate drinkers had better mean cognitive scores than nondrinkers. For cognitive decline, on test of general cognition, the relative risk of a substantial decline in performance over a 2-year period was 0.85 among moderate drinkers, as compared with nondrinkers. There were no significant differences in risks according to the beverage and no interaction with the APOE genotype
Bond et al. (2005)	Cross-sectional and longitudinal, population-based (8 years)	1,836 participants aged 65 and older	CASI, evaluation of alcohol intake and cigarette smoking habits	Alcohol consumers had higher scores (less cognitive decline) on cognition, measured by the CASI over an 8-year follow-up period, than abstainers. There were no significant gender differences in the absolute scores on CASI, and the rate of change over time did not vary
Ganguli et al. (2005)	Longitudinal, population-based (7 years)	1,681 individuals aged 65 years or older	Neuropsychological test panel of the CERAD, and among these tests: MMSE and TMT. Evaluation of alcohol intake and smoking habits	This cohort showed a consistent pattern of better baseline scores and lesser decline over time in individuals who consumed alcohol minimally or moderately, compared to those who reported no drinking at baseline

(continued)

Table 188.5 (continued)

References	Setting and study design	Subjects	Methods	Results and conclusions
Longitudinal studies				
Ngandu et al. (2007)	Longitudinal, population-based (21 years)	1,341 participants aged 65–79 years	MMSE, and neuropsychological tests evaluating episodic memory, semantic memory, psychomotor speed, executive function, prospective memory, and subjective memory. Evaluation of alcohol intake, smoking habits, and APOE genotyping	The nondrinkers both at midlife and later had a poorer cognitive performance than drinkers, especially in the domains related to fluid intelligence, i.e., executive function, psychomotor speed, as well as episodic memory, whereas the other cognitive functions showed little association with alcohol drinking. No interactions between APOE ε4 and alcohol or sex and alcohol were found.
McGuire et al. (2007)	Cross-sectional, population-based	2,716 subjects, aged 70 years and older	Adapted Telephone Interview for Cognitive Status, and evaluation of alcohol intake	For older adults with a level of cognitive functioning within normal ranges, moderate amounts of alcohol, an average of one drink or less daily, was protective for women, but not men

This table lists the principal findings of longitudinal clinical and epidemiological studies on the relationship between alcohol consumption and cognitive impairment in older subjects, including setting, study design, and cognitive assessment used. *WAIS* Wechsler Adult Intelligence Scale, *AD* Alzheimer's disease, *MMSE* Mini-Mental State Examination, *WMS* Wechsler Memory Scale, *BVRT* Benton Visual Retention Test, *RPM* Raven Progressive Matrices, *CRT* Choice Reaction Time, *HCT* Halstead Category Test, *CDT* Clock Drawing Test, *BFSRT* Buschke-Fuld Selective Reminding Test, *APOE* Apolipoprotein E, *CASI* Cognitive Abilities Screening Instrument, *CERAD* Consortium to Establish a Registry for Alzheimer Disease, *TMT* Trail Making Test, *EBMT* East Boston Memory Test

for a subsample of women whose drinking patterns were similar to their male counterparts (Panza et al. 2009a). Subsequent research with male and female college students and elderly men led to the conclusion that no significant negative relation exists between social drinking and level of cognitive functioning, although elevated alcohol consumption among young female social drinkers were related to better performance on many cognitive tests (Panza et al. 2009a).

More recent studies involving older subjects have indicated that a U- or J-shaped curve may best describe the relation between the level of alcohol consumption and cognitive performance (Goodwin et al. 1987; Christian et al. 1995; Hendrie et al. 1996; Launer et al. 1996). In general, light to moderate drinkers of alcohol performed at a higher cognitive level than either abstainers or heavy drinkers (Goodwin et al. 1987; Hendrie et al. 1996), although there were some notable exceptions (Goodwin et al. 1987; Launer et al. 1996). One study in particular, that involved older African American adults found that consumption of up to 5–6 g of alcohol per day (1/2 drinks) was correlated with better cognitive performance than abstainers (Hendrie et al. 1996). On the other hand, in one report, statistical adjustment for age, income, education, and gender rendered the findings non-significant (Goodwin et al. 1987). In another study, the protective effects of moderate alcohol consumption (odds ratio OR (95% confidence interval (CI)) = 0.3 (0.2–0.7) for less than one drink and 0.2 (0.1–0.4) for 1–2 drinks per day) were limited only to those participants who exhibited clinical conditions associated with atherosclerosis (Launer et al. 1996). However, as discussed above, significant variability in different countries on the level of alcohol content in drinks as well as in the criteria used in different articles to define terms such as light, moderate, and heavy drinking make the interpretation of findings difficult (Panza et al. 2009a).

Lower levels of alcohol intake have proportionally greater effects in the elderly, due to their reduced lean body mass and lower percentage of body weight made up of water. In fact, in several cross-sectional studies, moderate drinking, from up to 1 drink per day (up to 14 g of alcohol) to 4 drinks per day (52 g of alcohol), as compared with nondrinking has been associated with a better performance in many cognitive domains (Elias et al. 1999; Carmelli et al. 1999; Bond et al. 2001, 2003). In fact, in the Framingham Heart Study, the association between alcohol consumption and cognitive performance was analyzed separately for men and women, since the researchers anticipated a different gender-based alcohol-cognition relationship (Elias et al. 1999). Test performance of moderate male drinkers (>2 and <4 drinks per day) were significantly better than abstainers on logical memory delayed recall, whereas heavy (>4 and <8 drinks per day) drinkers performed better on logical memory delayed recall, attention and concentration (AC) composite score, and total composite score. Female drinkers showed superior performance compared to abstainers on more cognitive tests than male drinkers. Light female drinkers (1–2 drinks per day) performed better on logical memory delayed recall, on the learning and memory (LM) composite and the total composite, whereas moderate female drinkers scored significantly better than abstainers on delayed memory, word fluency, similarities, and the AC, LM, and total composite (Elias et al. 1999). Moreover, the Kame project, a study that used data from 1,836 cognitively intact elderly Japanese American men and women aged 65 and older, found that up to 26 g of alcohol per day for women was associated with higher Cognitive Abilities Screening Instrument (CASI) scores (Bond et al. 2001). In a recent cross-cultural comparison of Japanese and non-Hispanic White American older adults, the Kame project found that current consumption of alcohol (13–26 g of alcohol, 1–2 drinks per day), compared to abstinence or past alcohol consumption, was more strongly associated with higher CASI scores for women than men (Bond et al. 2003).

Furthermore, in cross-sectional studies, both better (Dufouil et al. 2000; Schinka et al. 2002; Lindeman et al. 2005; Reid et al. 2006) and poorer (Yoshitake et al. 1995) cognitive performances in association with higher levels of alcohol drinking have been observed (Table 188.4). In particular, the issue of sex differences in the relation of alcohol consumption and cognitive performance was

addressed by Dufouil and colleagues (2000) using data from the Epidemiology of Vascular Aging (EVA) study. This study included 574 men and 815 women, aged 59–71 years. No association between drinking and cognition was found for the male participants; while for the female participants, moderate alcohol consumption was associated with better performance on seven of the cognitive tests and an overall composite score (Dufouil et al. 2000). In fact, the OR for higher cognitive performance (i.e., the top 10% of the distribution of summary scores from the neuropsychological battery) was 2.5 (95% CI = 1.1–5.7) for women who usually consumed 2 or more drinks per day in comparison with nondrinkers. At the same time, some studies have found no associations between alcohol drinking and several cognitive functions (Elwood et al. 1999, Schinka et al. 2002). Elwood and colleagues did not find any significant association between alcohol consumption and cognitive function amongst 1,870 men aged 55–69 years from the Caerphilly Study, though ex-drinkers had markedly lower test scores than either current drinkers or men who had never drunk alcohol (Elwood et al, 1999).

The studies that have assessed changes in cognition prospectively have had contradictory results (Herbert et al. 1993; Christian et al. 1995; Launer et al. 1996; Dent et al. 1997; Broe et al. 1998; Leibovici et al. 1999; Dufouil et al. 2000; Cervilla et al. 2000a,b; Galanis et al. 2000; Verhaegen et al. 2003; Stampfer et al. 2005; Bond et al. 2004, 2005; Ganguli et al. 2005; Ngandu et al. 2007; McGuire et al. 2007) (Table 188.5). Drinkers in general have been proposed to have a greater decrease in global cognitive function (Dufouil et al. 2000) and attention (Leibovici et al. 1999) as compared with nondrinkers, but moderate drinkers (about one drink or less than 15 ml of alcohol per day) to have less decline in general cognition (relative risk (95% CI) = 0.77 (0.67–0.88)) (Stampfer et al. 2005) or psychomotor speed (Herbert et al. 1993) than nondrinkers. Further, some studies showed no association at all (Launer et al. 1996; Broe et al. 1998; Cervilla et al. 2000a,b; Verhaegen et al. 2003). However, in the Gospel Oak project, there was a non-significant association in the direction of a protective effect against onset of cognitive impairment for moderate drinkers (1–30 units per week, with 1 unit equivalent to a glass of wine or a single measure of spirits) compared with nondrinkers and heavy drinkers (30 units and over per week) (Cervilla et al. 2000a). Amongst longitudinal studies, Launer and colleagues showed in the Zutphen Elderly Study that men with cardiovascular disease or diabetes and light to moderate alcohol intake had a significantly lower risk of poor cognitive function compared to abstainers obtaining effects of large magnitude (OR (95% CI) = 0.3 (0.2–0.7) for less than one drink and 0.2 (0.1–0.4) for 1–2 drinks per day), but alcohol intake was not associated with cognitive decline in a 3-year follow-up (Launer et al. 1996). Finally, in a representative elderly cohort over an average follow-up of 7 years, a pattern of light to moderate drinking (from drinking once a month or less to drinking daily and weekly), compared to not drinking, was associated with lesser average decline in cognitive domains over the same period. In particular, the seemingly beneficial effects of alcohol intake against cognitive decline appeared concentrated in the areas of executive functions (OR (95% CI) = 0.20 (0.05–0.85) for light drinking and 0.05 (0.01–0.45) for moderate drinking), and general mental status (OR (95% CI) = 0.30 (0.14–0.65) for light drinking and 0.08 (0.02–0.28) for moderate drinking) (Ganguli et al. 2005). The results of this study were also consistent with those of the EVA Study, which found that alcohol intake was associated with a lower risk of cognitive deterioration among subjects without an *APOE* ε4 allele, but a higher risk in *APOE* ε4 carriers. In fact, compared with nondrinkers, non-ε4 carriers who reported drinking 2 drinks or more per day had a 50% decreased risk of cognitive deterioration (Dufouil et al. 2000).

The associations between current cognitive performance and alcohol drinking 5–24 years earlier have also been studied, with conflicting results. The global cognitive function may be poorer amongst both alcoholics and past drinkers as compared with nondrinkers or moderate drinkers (Christian et al. 1995) whilst being better among moderate drinkers and poorer among heavy drinkers as compared with nondrinkers (Galanis et al. 2000). Furthermore, although there were some gender

differences in observed associations, data from 1,469 relatively well-educated, noninstitutionalized subjects from Rancho Bernardo, California offered no compelling evidence that social drinking caused or prevented impaired cognitive function 13–18 years later (Edelstein et al. 1998). The large number of comparisons and inconsistent results suggest that the few statistically significant findings may be false positives. In the Framingham Heart Study, the mean levels of alcohol consumption over 24 years prior to neuropsychological testing in relation to cognitive performance was examined (Elias et al. 1999). For men, increasing alcohol consumption was associated with better performance only for logical memory delayed recall. For women, however, all measures, with the exception of similarities, were associated with better performance as consumption level increased (Elias et al. 1999). Moreover, in the cognitive sub-study of the Medical Research Council (MRC) Treatment Trial of Hypertension in Older Adults, involving a cohort of 1,083 older subjects that was followed-up for 9–12 years, those who were abstinent before the age of 60 had poorer cognitive outcomes than did those who drank lowly or moderately (Cervilla et al. 2000b). More recently, the Cardiovascular Risk Factors Aging and Dementia (CAIDE) Study investigated the relationship between midlife alcohol drinking and late-life cognitive functions (average follow-up period of 21 years) as well as between late-life alcohol drinking and late-life cognitive functions (Ngandu et al. 2007). In the CAIDE Study, at both midlife and late life examinations, the nondrinkers had a poorer cognitive performance than drinkers, especially in the domains related to fluid intelligence, i.e., executive function, psychomotor speed, as well as episodic memory, whereas the other cognitive functions showed little association. The late-life frequent drinkers had a better performance than the infrequent drinkers in episodic and prospective memory, whereas the midlife frequent and infrequent drinkers did not differ from each other in any of the cognitive domains. Further, no interactions between *APOE* ε4 allele and alcohol or sex and alcohol were found (Ngandu et al. 2007). On the other hand, in other longitudinal studies, a significant association between alcohol drinking and several cognitive measures has been proposed especially among women (Elias et al. 1999; McGuire et al. 2007). Smoking or *APOE* ε4 allele often modified the association between alcohol drinking and cognitive functions. However, studies on the interaction between smoking and alcohol consumption have yielded inconclusive results (Leibovici et al. 1999; Schinka et al. 2002; Ngandu et al. 2007). The role of alcohol in cognition might be modified by the presence of the *APOE* ε4 allele (Carmelli et al. 1999; Dufouil et al. 2000), but the patterns of interaction suggested have seen different results (Stampfer et al. 2005; Ngandu et al. 2007). Some studies investigating the effect of different types of alcohol on the cognitive function found no beverage-specific differences (Christian et al. 1995; Stampfer et al. 2005; Ngandu et al. 2007).

188.3   Alcohol Consumption, MCI, and Dementia

Alcohol consumption is also one of the possible determinants of clinical dementia (Hebert et al. 1992; Yoshitake et al. 1995; Broe et al. 1998; Orgogozo et al. 1997; Lemeshow et al. 1998; Kivipelto et al. 2001; Ruitenberg et al. 2002; Lindsay et al. 2002; Huang et al. 2002; Truelsen et al. 2002; Mukamal et al. 2003; Luchsinger et al. 2004; Larrieu et al. 2004; Järvenpää et al. 2005; Simons et al. 2006; Deng et al. 2006; Mehlig et al. 2008; Fujishima and Kiyohara 2002; McCallum et al. 2007; Leibovici et al. 2002) (Table 188.6). Epidemiological studies have recently reported an association between wine consumption and the incidence of AD. Red wine in particular was investigated in the Personnes Agees QUID (PAQUID) study, in which the relative risk for dementia and AD among 318 subjects who drank three or four glasses of wine each day in comparison with 971 total abstainers were 0.21 and 0.25, respectively. Among the 922 older subjects who drank no more than one or two

Table 188.6 Principal studies on the relationships among alcohol consumption and dementia, vascular dementia, Alzheimer's disease, and mild cognitive impairment

References	Setting and study design	Subjects	Methods	Results and conclusions
Hébert et al. (1993)	Longitudinal, population-based (3 years)	1,201 subjects aged 65 years and older	Structured performance tests of immediate memory, digit span (from WAIS), and orientation; diagnosis of AD; evaluation of alcohol intake and smoking habits	After adjustment for age, sex, and education, the estimated OR of AD was 0.7 (95% CI 0.3–1.4) for ever smokers compared with never smokers. For 40 pack-years of smoking, the OR of AD was 0.8 (95% CI 0.6–1.1). Consumption of 30 ml of alcohol per day was associated with an OR of 1.1 (95% CI 0.8–1.5). These findings suggested that recent mild-to-moderate consumption of alcohol is not substantially related to incidence of AD and that smoking does not increase risk of the disease
Yoshitake et al. (1995)	Longitudinal, population-based (7 years)	828 subjects aged 65 and older	Diagnosis of dementia, AD, and VaD; evaluation of alcohol consumption	Multivariate analysis showed that age, systolic blood pressure, drinking habits, and prior stroke episodes were significant independent precursors of VaD
Orgogozo et al. (1997)	Longitudinal, population-based (3 years)	3,777 subjects aged 65 and older	Diagnosis of dementia and AD; evaluation of alcohol intake	In the 318 moderate drinkers, as compared to the 971 nondrinkers, and after adjusting for possible confounders, the OR were respectively 0.19 for incident dementia and 0.28 for AD. Among the 922 mild drinkers respect to the abstainers the relative risk for AD was reduced significantly
Broe et al. (1998)	Longitudinal, population-based (3 years)	327 subjects, aged 75 years and older	MMSE, Reid memory test, tests of verbal fluency, subsets of the Boston naming test and similarities; CDT, and copied drawings of a cube, coils, and interlocking infinity loops; diagnosis of dementia and AD; evaluation of physical exercise, alcohol and smoking use	No associations were found with dementia or AD
Leibovici et al. (1999)	Longitudinal, population-based (3 years)	833 subjects over 60 years	A computerized neuropsychometric examination assessed attention, primary and secondary memory, implicit memory, visuospatial ability, and language. Diagnosis of AD and evaluation of alcohol and tobacco consumption were also performed	While moderate wine consumption was found to be associated with a fourfold diminishing of the risk of AD, this effect was found to disappear when institutionalization was taken into account. No protective effect for AD was found for smoking

Study	Design	Sample	Outcomes	Results
Kivipelto et al. (2001)	Longitudinal, population-based (3 years)	3,777 subjects aged 65 years and older	Diagnosis of dementia and AD; evaluation of alcohol intake	In the 318 moderate drinkers, as compared to the 971 nondrinkers, and after adjusting for possible confounders, the odds ratios were respectively 0.19 for incident dementia and 0.28 for AD. Among the 922 mild drinkers respect to the abstainers, the relative risk for AD was reduced significantly
DeCarli et al. (2001)	Cross-sectional and longitudinal, population-based (25 years)	369 individual twins, aged 67–81 years	Diagnosis of MCI, evaluation of alcohol intake, and APOE genotyping	Alcohol consumption was slightly protective against the risk of MCI, in the fourth examination of this cohort
Ruitenberg et al. (2002)	Longitudinal, population-based study (6 years)	5,395 subjects aged 55 years and older	Diagnosis of AD, VaD, or other dementia; evaluation of alcohol intake, and APOE genotyping	Light to moderate drinking (1–3 drinks per day) was significantly associated with a lower risk of any dementia and VaD. No evidence that the relation between alcohol and dementia varied by type of alcoholic beverage was found
Lindsay et al. (2002)	Longitudinal, population-based study (5 years)	6,434 subjects, aged 65 years and older	Diagnosis of incident AD, evaluation of alcohol intake, smoking habits, and APOE genotyping	APOE ε4 allele was associated with increased risks of incident AD, while regular wine consumption was associated with reduced risks. Smoking was not related to the risk of AD
Huang et al. (2002)	Longitudinal, population-based study (6 years)	402 subjects, aged 75 years and older	Diagnosis of incident dementia and AD and alcohol drinking	Light to moderate alcohol consumption was associated with a decreased incidence of dementia and AD
Truelsen et al. (2002)	Nested case-control of a longitudinal, population-based study (15 years)	83 demented patients and 1,626 nondemented subjects as controls, aged 65 years and older	MMSE and diagnosis of dementia, and alcohol intake assessed 15 years before	Average weekly total alcohol intake had no significant effect on risk of dementia. Monthly and weekly intake of wine was significantly associated with a lower risk of dementia. For beer and spirits, only a monthly intake of beer was significantly associated with an increased risk of dementia. The effect of alcohol on risk of dementia did not differ between men and women
Mukamal et al. (2003)	Nested case-control of a longitudinal, population-based study (6 years)	373 cases with incident dementia and 373 controls	Diagnosis of incident dementia (AD and VaD), average alcohol consumption, and magnetic resonance imaging findings	Compared with abstention, consumption of 1–6 drinks weekly is associated with a lower risk of incident dementia among older adults. A trend toward greater odds of dementia associated with heavier alcohol consumption was most apparent among men and participants with an APOE ε4 allele, with similar relationships of alcohol use with AD and VaD

(continued)

Table 188.6 (continued)

References	Setting and study design	Subjects	Methods	Results and conclusions
Luchsinger et al. (2004)	Longitudinal, population-based study (4 years)	908 subjects aged 65 years and older	Diagnosis of incident dementia (AD and dementia associated with stroke) and alcohol intake	After adjusting for age, sex, APOE ε4 status, education, and other alcoholic beverages, only intake of up to three daily servings of wine was associated with a lower risk of AD. Stratified analyses by the APOE-epsilon 4 allele revealed that the association between wine consumption and lower risk of AD was confined to subjects without the APOE ε4 allele
Larrieu et al. (2004)	Longitudinal, population-based study (8 years)	2,950 subjects, aged 65 years and older	Diagnosis of incident dementia and AD, and wine consumption	Even after adjustment on age, sex and education, moderate drinkers had a decreased RR of developing a dementia in the subsequent 8 years compared to nondrinkers with a RR of 0.56. Results on AD were quite similar, with a RR of 0.53 among moderate drinkers
Anttila et al. (2004)	Longitudinal, population-based study (23 years)	1,464 men and women aged 65–79 years	Diagnosis of incident dementia and MCI, and subjects classified as those who never drank alcohol, those who drank "infrequently" (less than once a month), and those who drank "frequently" (several times a month)	Alcohol drinking in middle age showed a U shaped relation with risk of MCI in old age. Only the carriers of APOE ε4 had an increased risk of dementia with increasing alcohol consumption
Espeland et al. (2005)	Longitudinal, population-based study (4.2 years)	4,451 community-dwelling women aged 65–79 years	Diagnosis of incident MCI and dementia, and annual modified MMSE. Subjects classified as abstainers, <1 drink/day, and >1 drink/day	Moderate alcohol intake was associated with an approximately 50% reduced risk of combined probable dementia and/or MCI. Significant decline in global cognition was less common among women who reported alcohol intake at baseline, also after adjustment for both demographic/social and clinical factors
Järvenpää et al. (2005)	Longitudinal, population-based study (25 years)	554 twins, aged 65 years or older at the time of dementia assessment	Diagnosis of incident dementia, evaluation of alcohol consumption, and binge drinking (i.e., alcohol exceeding the amount of 5 bottles of beer or a bottle of wine on 1 occasion at least once per month)	Midlife reports of binge drinking or passing out as a result of excessive alcohol intake at least twice during the previous year were risk factors for dementia later in life
Simons et al. (2006)	Longitudinal, population-based study (16 years)	2,805 subjects, aged 60 years and older	Diagnosis of incident dementia, and evaluation of alcohol intake	Moderate alcohol intake seemed to offer substantial protection against the onset of dementia

	Study design (duration)	Sample	Diagnosis/assessment	Findings
Deng et al. (2006)	Longitudinal, population-based study (2 years)	3,286 subjects, aged 60 years and older	Diagnosis of incident dementia, AD, and VaD and evaluation of alcohol intake	Light to moderate drinkers had a lower risk of dementia than nondrinkers, but a non-significant increased risk was observed in heavy drinkers
Solfrizzi et al. (2007)	Longitudinal, population-based study (3.5 years)	1,445 men and women aged 65–84 years	Diagnosis of incident MCI and progression from MCI to dementia; subjects classified as abstainers, 0–1 drink/day, 1–2 drink/day, and >2 drinks/day	In patients with MCI up to 1 drink/day of alcohol or wine may decrease the rate of progression to dementia. No significant associations were found between any levels of drinking and the incidence of MCI in noncognitively impaired individuals vs. abstainers
Mehlig et al. (2008)	Longitudinal, population-based study (34 years)	1,462 women aged 38–60 years	Diagnosis of dementia; evaluation of alcohol intake and smoking habits	Wine was protective for dementia, and the association was strongest among women who consumed wine only. In contrast, consumption of spirits at baseline was associated with slightly increased risk of dementia

This table lists the principal findings of longitudinal clinical and epidemiological studies on the relationships among alcohol consumption and dementia, VaD, AD, and MCI, including setting, study design, and cognitive assessment used

WAIS Wechsler Adult Intelligence Scale, *AD* Alzheimer's Disease, *OR* Odds Ratio, *95% CI:* 95% Confidence Interval, *MMSE* Mini-Mental State Examination, *CDT* Clock Drawing Test, *VaD* Vascular Dementia, *MCI* Mild Cognitive Impairment, *APOE* Apolipoprotein E, *RR* Relative Risk

glasses of wine each day compared to the abstainers the relative risk for AD was reduced significantly (0.55) (Orgogozo et al. 1997). This protective effect remained significant after further post hoc analyses were conducted (Lemeshow et al. 1998). Furthermore, these cross-sectional findings were confirmed in the subsequent 8-year follow-up of the PAQUID study, where among 2,950 initially nondemented subjects, moderate drinkers had a decreased relative risk of developing dementia (relative risk = 0.56) compared to nondrinkers (Lemeshow et al. 1998).

These results were consistent with the findings from some cohort studies (Ruitenberg et al. 2002; Lindsay et al. 2002; Huang et al. 2002; Deng et al. 2006, 98–100, 107), but not others (Hebert et al. 1992; Yoshitake et al. 1995; Broe et al. 1998; Fujishima and Kiyohara 2002; Kivipelto et al. 2001). The relationship between alcohol consumption and risk of dementia (AD, VaD, or other dementia) was also examined in the Rotterdam Study. The findings of this study, with an average follow-up of 6 years, suggested that light to moderate alcohol consumption (1–3 drinks per day) is associated with a reduced risk of dementia in individuals aged 55 years or older (hazard ratio (HR) (95% confidence interval) (CI) = 0.58 (0.38–0.90)); this effect seems to be unchanged by the source of alcohol (Ruitenberg et al. 2002). No association was found in women, whereas a lower risk was found for men drinking 1–3 drinks per day (HR (95% CI) = 0.58 (0.40–0.74)). A modification effect was found when the *APOE* ε4 allele was taken into consideration; the risk was lower among drinkers with an *APOE* ε4 allele, whereas it was less clear for drinkers without the *APOE* ε4 allele (Ruitenberg et al. 2002). This topic was also investigated in the Kungsholmen Project, a community-based dementia-free cohort (n = 402) followed for almost 6 years. Light to moderate alcohol consumption (as defined by them to be 1–21 drinks per week in men, 1–14 drinks per week in women) was associated with a decreased incidence of dementia (relative risk (95% CI) = 0.5 (0.3–0.7)) and AD (relative risk (RR) (95% CI) = 0.5 (0.3–0.7)) (Huang et al. 2002). In the Canadian Study of Health and Aging (CSHA), on 4,615 cognitively normal older subjects reassessed 5 years later, wine consumption (at least weekly consumption) was associated among other factors with a reduced risk of AD (OR (95% CI) = 0.49 (0.28–0.88)) (Lindsay et al. 2002). Finally, in China, light to moderate drinkers (1–21 drinks per week in men, 1–14 drinks per week in women) had a lower risk of dementia (OR (95% CI) = 0.52 (0.32–0.85)) than nondrinkers, but non-significant evidence towards elevated risk in heavy drinkers (OR (95% CI) = 1.45 (0.43–4.89)). A greater reduction of risk was observed for men (OR = 0.37) than for women (OR = 0.76) (Deng et al. 2006). Moreover, the effect of light to moderate drinking seemed most prominent for AD (OR (95% CI) = 0.63 (0.55–0.72)) than for VaD (OR (95% CI) = 0.31 (0.19–0.51)) or other dementia (OR (95% CI) = 0.45 (0.12–1.69)) (Deng et al. 2006).

In a nested case–control study on 373 cases with incident dementia and 373 controls who were selected from 5,888 adults aged 65 years and older, and participated in the CHS, the adjusted OR for dementia among whose weekly alcohol consumption was less than 1 drink was 0.65, compared with abstention; was 0.46 and 0.69 compared with 1–6 drinks and with 7–13 drinks, respectively, and was 1.22 when compared with 14 or more drinks (Mukamal et al. 2003). A trend toward greater odds for dementia associated with heavier alcohol consumption was most apparent among men and participants bearing an *APOE* ε4 allele, with similar relationships of alcohol use with AD and VaD (Mukamal et al. 2003). In the Copenhagen City Heart Study which rated alcohol consumption in a different manner to many other studies, the risk of developing dementia was significantly lower among monthly wine drinkers (HR (95% CI) = 0.43 (0.23–0.82)), in weekly wine drinkers (HR (95% CI) = 0.33 (0.23–0.82)) and, but not significantly, in daily drinkers. An increased risk for beer and for spirits was found in monthly, weekly, and daily drinkers, but not significantly. No difference was found between men and women. No association was found between any number of drinks (less than 1, 1–7, 8–14, 15–21, 22, or more) of alcohol consumed per week and the risk of dementia (Truelsen et al. 2002). The findings from the CHS were consistent with the PAQUID Study (Orgogozo et al. 1997) and the Rotterdam Study (Ruitenberg et al. 2002), but suggested a higher risk of dementia

with consumption greater than 2 drinks per day. Surprisingly, the Rotterdam Study found that the lower risk of dementia associated with alcohol use was more consistent among individuals with an *APOE* ε4 allele (Ruitenberg et al. 2002), but no significant interaction was detected. In the Washington Heights Inwood-Columbia Aging Project, with 908 subjects aged 65 years and older, the number of drinks per week was collected at baseline and subjects were classified as nondrinkers, light drinkers (less than 1 drink per month to 6 drinks a week), moderate drinkers (1–3 drinks a day), and heavy drinkers (more than 3 drinks a day). The light and moderate drinking categories were combined because of the low number of moderate drinkers. A significantly lower risk of AD was found in light to moderate wine drinkers in elderly individuals without the *APOE* ε4 allele (HR = 0.44, p = 0.004). No modification effect by sex was found (Luchsinger et al. 2004).

Some other population-based, prospective studies, with longer follow-up periods studied the effects of different patterns of alcohol intake on dementia (Järvenpää et al. 2005; Simons et al. 2006; Mehlig et al. 2008). In fact, in the Finnish Twin Cohort Study with a follow-up period of 25 years, reports of midlife binge drinking (i.e., alcohol exceeding the amount of five bottles of beer or a bottle of wine on one occasion at least once per month) or losing consciousness due to excessive alcohol intake at least twice during the previous year were risk factors for dementia later in life (RR (95% CI) = 3.2 (1.2–8.6)) (Järvenpää et al. 2005). A longitudinal cohort study conducted in Dubbo (Australia) on 2,805 subjects aged 60 years and older, initially free of cognitive impairment and followed for 16 years, confirmed as a modest intake of alcohol seemed to offer substantial protection against the onset of dementia, showing larger effect for 15–28 units per week (HR (95% CI); 0.40 (0.21–0.79) (Simons et al. 2006; McCallum et al. 2007). Finally, in the Prospective Population Study of Women in Goteborg, Sweden, in a 34-year follow-up, wine was protective for dementia (current drinking vs former or never drinking) (HR (95% CI) = 0.6 (0.4–0.8)), and the association was strongest among women who consumed wine only (HR (95% CI) = 0.3 (0.1–0.8)). In contrast, consumption of spirits at baseline was associated with slightly increased risk of dementia (HR (95% CI) = 1.5 (1.0–2.2)) (Mehlig et al. 2008).

For predementia syndromes, in a group of 369 nondemented, community-dwelling older men who participated in the National Heart, Lung, and Blood Institute (NHLBI) Twin Study, alcohol consumption was found to be slightly protective (relative risk (95% CI) = 0.93 (0.88–0.99)), but if individuals with CVD were excluded from the analysis this association disappeared (DeCarli et al. 2001). Recently, the impact of alcohol consumption on the incidence of MCI was evaluated in 1,445 cognitively normal individuals and on its progression to dementia in 121 patients with MCI, aged 65–84 years, participating in the Italian Longitudinal Study on Aging (ILSA), a large, population-based, prospective study with a sample of 5,632 subjects 65–84 years old with a 3.5-year follow-up. Patients with MCI who consumed up to 1 drink per day of alcohol had a reduction in the rate of progression to dementia in comparison with patients with MCI who never consumed alcohol (HR (95% CI) = 0.15 (0.03–0.78)). Overall, patients with MCI who consumed less than 1 drink per day of wine compared to nondrinkers had a decrease in the rate of progression to dementia of about 85% (HR (95% CI) = 0.15 (0.03–0.77)). Moderate intake of alcohol deriving from wine, in drinks controlled for the intake of alcohol deriving from other sources across a number of levels, was also associated with a significantly lower rate of progression to dementia. No significant associations were found between any levels of drinking and the incidence of MCI in non-cognitively impaired individuals versus abstainers (Solfrizzi et al. 2007) (Fig. 188.1).

To the best of our knowledge, only two other studies have examined the effect of alcohol consumption on risk for the incidence of MCI (Anttila et al. 2004; Espeland et al. 2005). After an average follow-up of 23 years, nondrinkers (OR (95% CI) = 2.15 (1.01–4.59)) and frequent drinkers (OR (95% CI) = 2.57 (1.19–5.52)) were both more than twice as likely to have MCI in old age as occasional drinkers (Anttila et al. 2004). However, the *APOE* genotype seemed to modify the relationship, such
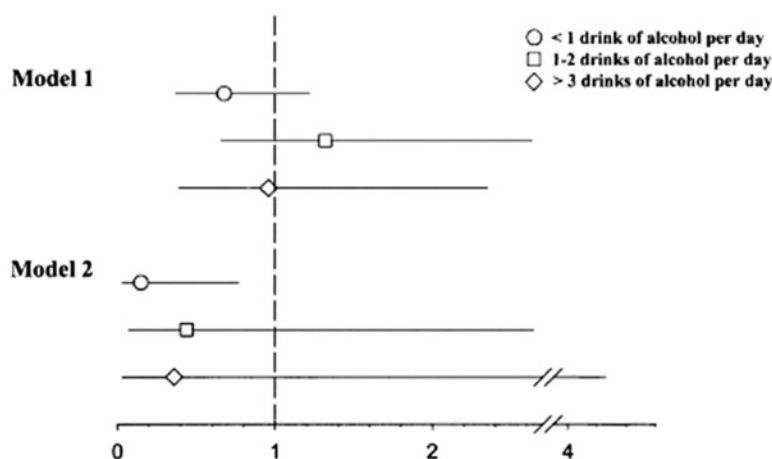
Fig. 188.1 Multivariate hazard ratios of incident mild cognitive impairment (MCI) among noncognitively impaired subjects and progression to dementia among patients with MCI. The Italian Longitudinal Study on Aging (ILSA). This figure shows the multivariate hazard ratios of incident MCI among noncognitively impaired subjects (Model 1) and progression to dementia among patients with MCI (Model 2) who drank <1 alcoholic drinks/day (circle with solid line) or one to two alcoholic drinks/day (square with solid line) or >2 alcoholic drinks/day (rhomb with solid line) versus abstainers (from Solfrizzi et al. Neurology. 2007;68:1790–89, with permission)

that the risk of old age dementia increased with increasing midlife alcohol consumption only among carriers of the *APOE* ε4 allele (Anttila et al. 2004). In the ILSA sample, we failed to confirm these findings, but we note that the alcohol consumption reported was a midlife determination (Solfrizzi et al. 2007). Probably, a follow-up period longer than 3.5 years would have revealed that moderate alcohol consumption might influence the incidence of MCI. On the other hand, our findings are consistent with those obtained in the Women's Health Initiative Memory Study with a 4.2 year-follow-up, which found that moderate alcohol intake (≥1 drink per day) was associated with an approximately 50% reduced risk of combined probable dementia and MCI (OR (95% CI) = 0.4 (0.28–0.99)) (Espeland et al. 2005). However, after adjusting for demographic and socioeconomic factors and baseline Modified Mini Mental State Examination (3MSE), the significance disappeared (Espeland et al. 2005). Currently, ours is the first study in which alcohol consumption was associated with the rate of progression of MCI to dementia, in fact, up to 1 drink/day of alcohol or wine may decrease the rate of progression to dementia in patients with MCI (Solfrizzi et al. 2007).

Very recently, a systematic review with meta-analysis was carried out to investigate any relationship between incident cognitive decline or dementia in the elderly and alcohol consumption between 1995 and March 2006 that only included data on subjects aged ≥65 from longitudinal studies (Peters et al. 2008). The quality of the studies included in this meta-analysis was assessed using standard criteria that measured key factors including appropriate design, recruitment, analysis, and provision of suitable information relating to key aspects of the study (Peters et al. 2008). Outcomes measured were very variably defined ranging from dementia alone or as well as various subtypes (mainly AD and VaD) or of subtypes of dementia (AD and VaD) alone or in combination (Peters et al. 2008). Eleven studies assessed cognitive decline or predementia syndromes (Peters et al. 2008). Studies with inadequate definition of the outcomes of interest were also excluded. Meta-analyses suggested that, at least in epidemiological studies, light to moderate alcohol use was associated with a 38% reduced risk of unspecified incident dementia (Fig. 188.2). Also in the studies included in this meta-analysis, there was no close agreement as to what might be considered an "appropriate" level of

Summary meta-analysis plot [random effects]

HR (1-7 standard drinks/week)[37]	0.70 (0.52, 0.93)
HR (8-14 standard drinks/week)[37]	0.65 (0.45, 0.96)
HR (15-28 standard drinks/week)[37]	0.40 (0.18, 0.79)
OR (frequent drinkers vs infrequent drinkers)[48]	1.44 (0.66, 3.15)
RR (women 1-14/men 1-21 units/week)[43]	0.50 (0.30, 0.70)
RR (250-500ml/day)[35]	0.56 (0.36, 0.92)
HR (1-3 drinks/day)[42]	0.58 (0.38, 0.90)
RR (<=250ml/day)[29]	0.81 (0.50, 1.30)
RR (250-500ml/day)[29]	0.19 (0.05, 0.66)
RR (>=500ml/day)[29]	0.31 (0.04, 2.42)
RR (Wine monthly consumption)[44]	0.43 (0.23, 0.82)
RR (Wine weekly consumption)[44]	0.33 (0.13, 0.86)
RR (Wine daily consumption)[44]	1.12 (0.43, 2.92)
HR (<1 drink/day)[30]	0.28 (0.08, 0.99)
HR (>1 drink/day)[30]	0.76 (0.41, 1.40)
OR (Women <1 drink/week)[25]	0.52 (0.30, 0.90)
OR (Women 1-6 drinks/week)[25]	0.57 (0.28, 1.17)
OR (Women 7-13 drinks/week)[25]	0.23 (0.09, 0.61)
OR (Women >=14 drinks/week)[25]	0.39 (0.14, 1.10)
OR (Men <1 drink/week)[25]	0.82 (0.38, 1.78)
OR (Men 1-6 drinks/week)[25]	0.36 (0.17, 0.77)
OR (Men 7-13 drinks/week)[25]	1.42 (0.58, 3.48)
OR (Men >=14 drinks/week)[25]	2.40 (0.86, 6.64)
OR (Light <=3 drinks/week)[46]	1.00 (0.50, 2.00)
OR (Moderate women 3-7/men 3-14 drinks/week)[46]	0.80 (0.30, 2.30)
OR (Heavy women>1/men>2 tdrinks/day)[46]	2.40 (0.70, 8.70)
combined	0.63 (0.53, 0.75)

0.01   0.1 0.2   0.5   1   2   5   10
* ratio (95% confidence interval)

Alcohol associated   Alcohol associated
with decreased risk   with increased risk

Fig. 188.2 Dementia and alcohol consumption. Forest plot generated using a random effects model in order to allow graphical representations of the findings of various studies with dementia as an outcome (from Peters et al. Age Ageing. 2008;37:505–12, with permission)

alcohol consumption particularly since the classification of light to moderate drinking varied widely. Possible benefit against dementia was shown for a variety of definitions including more than 1 drink per day, for weekly or monthly wine consumption; for 250–500 ml (usually wine); for more than 3 drinks per day and from 1 to 28 units per week (Peters et al. 2008). For effects on AD risk, light to moderate alcohol was associated with a significantly reduced risk of 32%, defining optimal amounts as weekly consumption of wine, 1–6 or more than 2 drinks per week, or more than 3 drinks/250–500 ml per day (usually wine), or where studied by gender, 1–3 per day in males (Peters et al. 2008). Although the point estimates were also in a similar direction for VaD and cognitive decline (0.82 and 0.89, respectively), the results were not statistically significant (Peters et al. 2008) (Fig. 188.3). With regard to effects on cognitive function, results for what could be considered "optimal" or non-deleterious consumption were mixed regarding the amount consumed per month or per day, in subjects with cardiovascular disease or diabetes where results ranged from 1–2 drinks per week, while for VaD patients 1–3 drinks per day in males appeared to be beneficial (Peters et al. 2008). Finally, another very recent meta-analysis included 15 prospective studies (follow-ups ranged from 2 to 8 years), with samples including 14,646 participants evaluated for AD, 10,225 participants evaluated

Summary meta-analysis plot [random effects]

OR (3-4 glasses/day) AD[32]	10.70 (2.00, 56.00)
OR (Wine-weekly) AD[38]	0.49 (0.28, 0.88)
OR (Beer-weekly) AD [38]	0.84 (0.51, 1.41)
OR (Spirits-weekly) AD[38]	0.78 (0.22, 1.19)
RR (1-21units/wk(m)1-14u/wk(f)AD[43]	0.40 (0.20, 0.60)
RR (250-500ml/day) AD[235]	0.53 (0.30, 0.95)
RR (<=250ml/day) AD[29]	0.55 (0.31, 0.99)
RR (250-500ml/day) AD[29]	0.28 (0.08, 0.99)
RR (>=500ml/day) AD[29]	0.48 (0.06, 3.92)
OR (Women 7-13 drinks/week) AD[25]	0.27 (0.10, 0.72)
OR (Men 1-6 drinks/week) AD[25]	0.36 (0.17, 0.80)
RR (Wine 1-21 drinks/week) AD[31]	0.69 (0.45, 1.09)
OR (Alcohol consumed) AD[45]	0.63 (0.35, 1.14)
combined	0.57 (0.44, 0.74)

ratio (95% confidence interval)

Alcohol associated with decreased risk   Alcohol associated with increased risk
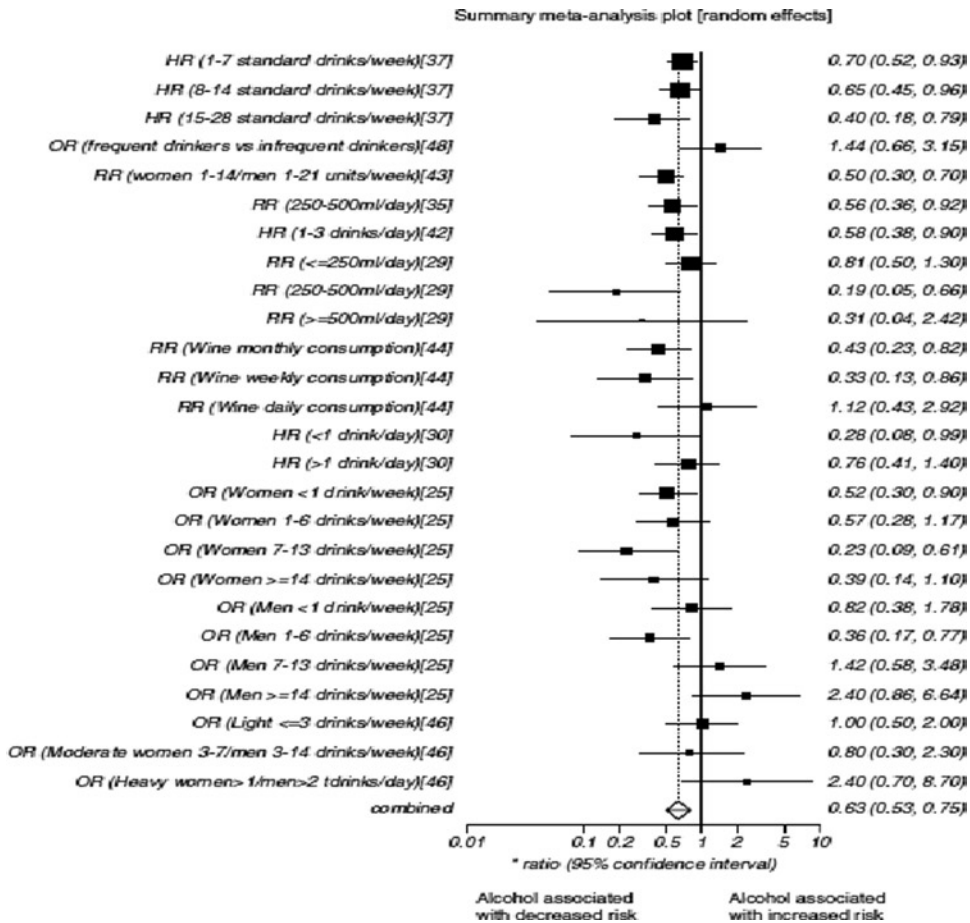
Fig. 188.3 Alzheimer's disease (AD) and alcohol consumption. Forest plot generated using a random effects model in order to allow graphical representations of the findings of various studies with AD as an outcome (from Peters et al. Age Ageing. 2008;37:505–12, with permission)

for VaD, and 11,875 followed for any type of dementia (Anstey et al. 2009). This meta-analysis indicated that light to moderate alcohol intake was associated with a 25–28% reduction in risk of AD, VaD, and any dementia compared with alcohol abstinence in older adults. Heavy drinking was not associated with increased risk of dementia in the present study (Anstey et al. 2009).

188.4 Alcohol and Cognitive Disorders: Possible Mechanisms

The mechanism by which light alcohol intake could be protective against cognitive decline impairment or decline in older age or against predementia and dementia syndromes is, at present, unclear (Fig. 188.4). The association between alcohol drinking and cognitive function could have different explanations in relation to cognitive domains explored. White matter lesions (WMLs), for example, would play a neuropathological role, given that alcohol drinking influenced measures of psychomotor speed, episodic memory, and executive function (Panza et al. 2009a). In fact, alcohol drinking has been associated with fewer brain infarcts and was shown to have a U-shape relationship with the prevalence of WMLs (Panza et al. 2009a). Furthermore, WMLs and infarcts, in turn, may reflect a vascular mechanism responsible for the observed association between alcohol and cognitive functions (Panza et al. 2009a). Different mechanisms may underlie the observed adverse effects of heavy
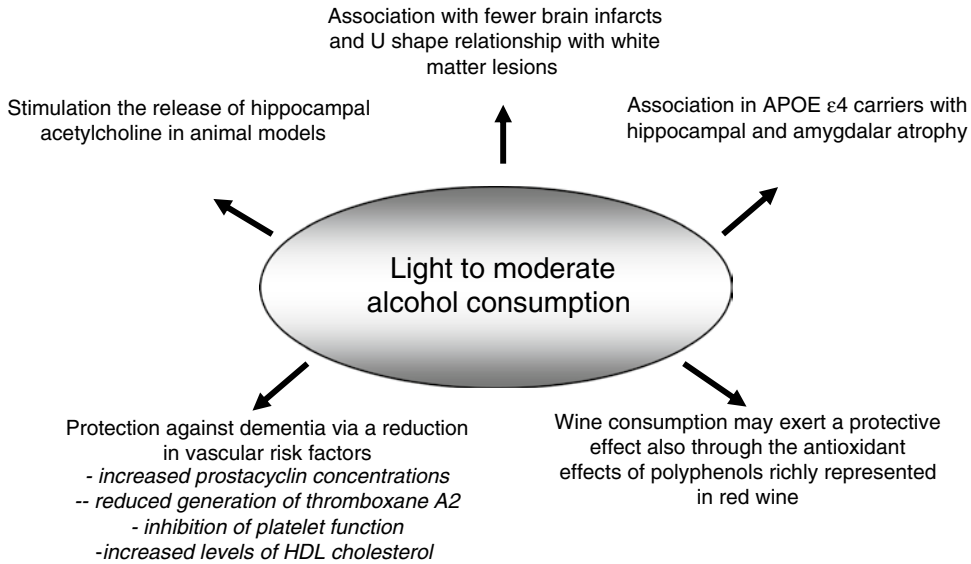
Fig. 188.4 Synopsis of the mechanism by which light to moderate alcohol intake could be protective against cognitive impairment or decline in older age or against predementia and dementia syndromes. This figure lists various possible mechanisms of light to moderate alcohol consumption linked to their neuroprotective properties against cognitive decline including modulation of cerebrovascular disease (e.g., white matter lesions), stimulation of the release of hippocampal acetylcholine in animal models, association with hippocampal and amygdalar atrophy, reduction in vascular risk factors or through the antioxidant effects of polyphenols richly represented in red wine

drinking and the potential beneficial effects of light to moderate drinking, and may also partly explain why deficits are reported in certain functions (e.g., delayed recall), whereas benefits are seen in others (e.g., learning) (Panza et al. 2009a). Indeed, higher doses of alcohol may affect cognitive functioning through increased release of acetylcholine from the hippocampus (Fadda and Rossetti 1998), which is an important neurotransmitter in memory and attention (Panza et al. 2009a). In contrast, evidence from animal studies indicated that low doses of alcohol may stimulate the release of hippocampal acetylcholine (Stancampiano et al. 2004). Finally, moderate alcohol consumption was associated with lower rates of cardiovascular disease and reduced cardiovascular risk factors (Naimi et al. 2005), which may serve to protect brain vasculature and prevent subclinical strokes, resulting in better preservation of cognitive performance (Panza et al. 2009a).

Alcohol consumption might protect from unspecified dementia by effects on the cerebral vasculature, supporting the observation that light to moderate alcohol intake might be protective against ischemic stroke (Palomaki and Kaste 1993). Moreover, light to moderate alcohol use is associated with a lower prevalence of MRI-defined WMLs and subclinical infarcts (den Heijer et al. 2004), although MRI abnormalities, HDL cholesterol levels, and fibrinogen levels only marginally influenced the association of alcohol consumption and dementia in the CHS (Panza et al. 2009a). The suggested protection against CVD resulting from light to moderate alcohol consumption may explain the perceived protection alcohol offers against VaD. In the Rotterdam study, the protective effect of alcohol consumption was found mainly for VaD, and the authors suggested that moderate alcohol intake might protect against dementia via a reduction in vascular risk factors (Panza et al. 2009a). In fact, moderate doses of alcohol may alter blood clotting mechanisms though increase of prostacyclin concentrations and reduction of thromboxane A2 generation and thus may inhibit platelet function (Panza et al. 2009a). Moderate alcohol consumption may also contribute to increased plasma levels of endogenous tissue-type plasminogen activator (tPA), a serine protease that regulates intravascular

fibrinolysis, and fibrinolytic activity while decreasing plasma fibrinogen levels (Panza et al. 2009a). It is also known that alcohol is associated with increased levels of HDL cholesterol, its subfractions HDL2 and HDL3, and its associated apolipoproteins A-I and A-II (Panza et al. 2009a). The association with HDL cholesterol is deemed to account for up to a half of the reduction in coronary events associated with moderate alcohol consumption (Panza et al. 2009a).

While the aforementioned factors could affect the risk of unspecified dementia and, probably, of VaD, other experimental and clinical findings may partly explain the suggested protection against AD provided by light to moderate alcohol consumption. Small amounts of alcohol have been reported to be associated with a lower prevalence of vascular brain findings and, in *APOE* ε4 carriers, with hippocampal and amygdalar atrophy, as assessed by MRI (den Heijer et al. 2004). Experimental studies found that ethanol initially increases hippocampal acetylcholine release, which could conceivably improve memory performance (Panza et al. 2009a).

Processes that originate, modulate, or precipitate the deposition of amyloid beta (βA) in the brain, such as oxidative stress, rather than vascular processes, may better explain the development of AD, and the vascular effects of the alcohol in alcoholic beverages may not be enough to explain the protective effects of the moderate intake of alcohol from dementia. The previously mentioned contribution of alcohol to increased plasma levels of endogenous tPA (Panza et al. 2009a) could promote Aβ removal since tPA is responsible for the formation of plasmin which is suggested to be an Aβ degrading enzyme (Miners et al. 2008). Wine consumption may exert a protective effect, either through alcohol intake itself, or through the antioxidant effects of polyphenols richly represented in red wine, or through both (Panza et al. 2009a). Although there have been some effects associated with alcohol-free red wine (Panza et al. 2009a), the constituents of red wine also have potentially beneficial vascular effects (139, 140) including, enhanced endothelial nitric oxide release (141), and reduced atherosclerosis in *APOE*-deficient mice (Waddington et al. 2004; Panza et al. 2009a). Red wine polyphenols are a complex mixture of flavonoids (mainly anthocyanins and flavan-3-ols) and non-flavonoids (such as resveratrol and gallic acid). Flavan-3-ols are the most abundant, with oligomeric and polymeric procyanidins (condensed tannins) often representing 25–50% of the total phenolic constituents (Waterhouse 2002). A recent study identified procyanidins as the principal vasoactive polyphenols in red wine and showed that they are present at higher concentrations in wines from areas of Southwestern France and Sardinia, where traditional production methods ensure that these compounds are efficiently extracted during vinification (Corder et al. 2006). Given the link between VaD, vascular risk, and the increasing body of evidence suggesting that AD may be influenced by vascular factors (Panza et al. 2009a), it may be concluded that the vascular protection associated to wine consumption decreases the risk of incident dementia/AD. In fact, in the 5-year follow-up PAQUID cohort, a significant inverse association between flavonoid intake and the risk of dementia was found (Commenges et al. 2000). It has been also suggested that the antioxidant properties of the flavonoids in wine may help prevent the oxidative damage implicated in dementia. Furthermore, oxidative stress is also likely to develop in the brain, contributing to neuronal death by various mechanisms such as formation of βA peptide, DNA damage, and abnormal tau protein (Panza et al. 2009a). The presence in wine of non-alcoholic components, such as particular antioxidants, could explain a differential effect of wine on dementia since liquor which does not seem to have as strong an effect has been shown to have less antioxidant activity than wine (Panza et al. 2009a). Nonetheless, in some studies on the neuroprotective role of moderate alcohol consumption, the most typically consumed alcohol types were beer and spirits (Panza et al. 2009a).

It is also possible that moderate lifestyles in general, which obviously vary according to different cultural environments, protect from cognitive impairment. Thus, it may not be the direct effect of alcohol or specific substances in alcoholic drinks that provide the protection, but moderate alcohol drinking may be an indicator of a complex set of favourable social and lifestyle factors. A protective

effect of alcohol on cognitive function in moderate drinkers may reflect a relatively poor health status among abstainers or because cognitive status influences alcohol consumption and overall health status (Panza et al. 2009a). The Mediterranean diet may serve as an interesting model for further studies of the association between alcohol and cognitive functioning, given the suggested role of many components of this diet (monounsaturated fatty acids (MUFA), polyunsaturated fatty acids (PUFA), and red wine) (Panza et al. 2009a) in different degrees of cognitive impairment. Indeed, the typical dietary pattern of Mediterranean diet is characterized by high intake of vegetables, fruits and nuts, legumes, cereals, fish, and MUFA with relatively low intake of meat, and dairy products, and moderate consumption of alcohol. Recently, in a community-based study involving 2,258 nondemented individuals in New York, adherence to a traditional Mediterranean diet was associated with a significant reduction in risk for AD (Scarmeas et al. 2006). However, in this study, the median daily intake of MUFA to saturated fatty acids (SFA) ratio for individual food categories by Mediterranean diet score tertiles was <1 and in overall about 2.5 times lower than the same value calculated from other studies on Mediterranean diet. This is notable given that a high MUFA to SFA ratio is one of the most important characteristics of the Mediterranean dietary pattern. Moreover, given the suggested role of different components of Mediterranean diet, it could be possible that alcohol influences the metabolism of PUFA and that this interaction could explain the role of both alcohol and PUFA in dementia and AD. Alcohol is a potent modulator of fatty acid metabolism and is known to influence the fatty acid profiles of different organs (Panza et al. 2009a). In animal studies, chronic alcohol exposure has been shown to decrease long-chain PUFA concentrations, especially docosahexaenoic acid and arachidonic acid in liver and brain tissues, depending on dosage and length of alcohol exposure (Panza et al. 2009a). In this context, the suggested neuroprotective role of light to moderate alcohol consumption may be a marker for a more complex dietary pattern or group of metabolic interactions. Further studies with dietary patterns more similar to the original Mediterranean model are needed to help dissect and confirm the aspects that contribute to the protective role offered by this diet against cognitive decline and dementia.

188.5 Applications to Other Areas of Health and Disease

As discussed, the beneficial effects of regular consumption of moderate levels of alcohol (≤24 g/day) have been demonstrated in the prevention of CAD and consistently show associations with reduced risk of ischemic and hemorrhagic stroke (Panza et al. 2009a). The definition of moderate drinking is very variable (ranging from 5 to 60 g of alcohol per day) depending on the study population and the assessment tools used (Panza et al. 2009a). The definition of moderate drinking used in the 2005 USDA Dietary Guidelines suggests consumption to be no more than 1 drink per day for women and no more than 2 drinks per day for men (U.S. Department of Health and Human Services and U.S. Department of Agriculture 2005). Heavy drinking is considered consuming an average of at least 2 drinks per day for men and at least 1 drink per day for women (U.S. Department of Health and Human Services and U.S. Department of Agriculture 2005). For light drinking, there is no standard definition but is presumably less than moderate drinking. Binge drinking is a pattern of alcohol consumption that achieves blood alcohol concentration to ≥0.08%; usually corresponds to >4 drinks on a single occasion for men or >3 drinks for women within 2 h (Panza et al. 2009a). However, definitions are not standardized in the literature and are not agreed on by all researchers (Panza et al. 2009a). In the United States, a standard alcoholic drink is more specifically defined as 12 ounces of regular beer, five ounces of wine, 1.5 ounces of 80 proof distilled spirits or liquor (gin, rum, vodka, whiskey), 17.74 ml of alcohol or 14 g of alcohol (Panza et al. 2009a). Thus, at the extreme, 2 drinks a day would be up to approximately 30 g of alcohol.

In particular, for cardiovascular conditions, reduction in both incidence of clinical CAD and severity of angiographically documented CAD has been documented with moderate alcohol drinking (Panza et al. 2009a). The benefit was consistently shown with various types of alcoholic drinks and drinking patterns (Panza et al. 2009a). Until large, prospective, randomized trials are available, which may be very difficult to undertake in practical terms, the preponderance of data that suggest that consumption of 1–2 drinks in men and 1 in women will be beneficial to the cardiovascular system (Panza et al. 2009a). Furthermore, heavy drinking is associated with increased hemorrhagic stroke risk, and there is some consensus about this relation in relevant reports (Klatsky 2005). The antithrombotic actions of alcohol might also result in increased hemorrhagic stroke risk at moderate drinking levels, but reports differ about whether lighter drinking increases hemorrhagic stroke risk or is unrelated (Panza et al. 2009a). The alcohol–hemorrhagic stroke relation seems similar for subarachnoid and intracerebral hemorrhage (Klatsky 2005). Reports are less concordant about alcohol–ischemic stroke interactions, but several analyses suggest a U-shaped or J-shaped distributions when the amount of drinking is plotted against ischemic stroke risk (Klatsky 2005). A meta-analysis performed on 35 studies on this topic revealed that heavy alcohol consumption increases the relative risk of stroke while light to moderate alcohol consumption may be protective against total and ischemic stroke (Reynolds et al. 2003). Nonetheless, the Cardiovascular Health Study (CHS) confirmed that association of alcohol use and risk of ischemic stroke was a U-shaped distribution, with modestly lower risk among consumers of 1–6 drinks per week, but even moderate alcohol intake may be associated with an increased risk of ischemic stroke among *APOE* ε4-carrier older adults (Mukamal et al. 2005a). Finally, in the Health Professionals Follow-up Study, a prospective analysis of more than 38,000 men who were free of known cardiovascular disease, alcohol consumption appeared to be associated with a higher risk for ischemic stroke among those who consumed more than 2 drinks per day (Mukamal et al. 2005b). However, alcohol was apparently not associated with risk at lower levels of intake. A pattern of intake characterized by moderate use 3–4 days per week appeared to be associated with the lowest risk. Red wine consumption was inversely associated with ischemic stroke risk, an association that was significantly different from the comparable associations of other beverages. These findings may also offer support for stroke reduction where to gain cardiovascular benefits people should avoid consuming more than 2 drinks daily (Mukamal et al. 2005b).

Regular, moderate wine consumption is often associated with reduced morbidity and mortality from and to a variety of chronic diseases in which inflammation is a root cause (Walzem 2008). Wine comes in a wide variety of styles that contain different ethanol and polyphenol contents. Controversy remains as to whether the alcohol or polyphenols contribute more to the health benefits of regular moderate wine consumption. The overall effect of wine consumption on health depends upon the total amounts consumed, the style and possibly the pattern of consumption (Walzem 2008). The apparent effect of wine consumption may be modified by other aspects of diet, for example, those consuming various levels of alcohol may also consume differential volumes of fruit, vegetable, and whole grain, and as such phytochemical intake and benefit may vary, particularly if wine may serve as a primary dietary source of phytochemical (Walzem 2008).

188.6 Conclusions

Drugs currently used in the symptomatic treatment of cognitive impairment and dementia unfortunately have a very limited therapeutic value, particularly on the management of psychiatric and behavioural symptoms. This is a constant reminder of the necessity to seek new therapeutic options to slow down the progression of predementia and dementia syndromes.

In the past few years, vascular and lifestyle-related factors for predementia and dementia syndromes have been an area of intensive research. At present, cumulative evidence has suggested that vascular risk factors may be important in the development of MCI, dementia, and AD (Panza et al. 2009a). Light to moderate alcohol drinking has been proposed as a protective factor against MCI and dementia in several longitudinal studies, but contrasting findings also exist and deriving overall conclusions from these studies has many limitations. Many of these studies were limited to cross-sectional design, restriction by age or sex, or incomplete ascertainment. Moreover, outcomes measured, the range of beverages that are available, drinking patterns and how they are categorised as well as follow-up periods studied and possible interactions with other lifestyle-related (i.e., smoking) or genetic-related (i.e., *APOE* genotype) factors are all sources of great variability. Indeed, the body of evidence examined in this chapter and the recent meta-analyses cited (Peters et al. 2008; Anstey et al. 2009) of all research published within the last 10 years suggested that light to moderate alcohol use may be associated with a reduced risk of unspecified incident dementia and AD, while for VaD, cognitive decline, and predementia syndromes the current evidence is only suggestive of a protective effect. Thus, at present, the most commonly used outcome measures for these kinds of studies appear to be unspecified dementia and AD, where prevalence and diagnostic classifications make the studies more practical compared with the small number of studies reporting VaD and other subtypes of cognitive decline. These are more difficult to classify, which is often further complicated by the relatively high vascular factor contribution to AD cases. On the other hand, the cardiovascular mechanisms that related to the suggested protective effects of alcohol may have an even greater effect on VaD (Table 188.7).

For the different types of beverages that exist, several studies have suggested that light to moderate wine consumption may be protective against dementia and cognitive decline but not total alcohol intake, beer, or spirits, although this is not conclusive (Panza et al. 2009a). In this context, it would be desirable to differentiate types of wine (e.g., red, white, rosé), but this information is not currently available. The failure to detect differences between types of beverages in some studies might be a consequence of differential gender interactions, although these analyses were adjusted for gender. Other issues are that some geographical regions typically consume specific types of alcoholic beverage (e.g., beer and spirits in Northern Europe), although observed associations and benefits offered by specific types of beverages were inconclusive. In general, wine-only drinkers may tend to consume wine less often than those who also drink other kinds of alcohol. In this way, wine-only drinkers could be viewed as the ones who consume the moderate quantities of ethanol beneficial for health, while the others may consume larger quantities; negative consequences of ethanol may outweigh the positive effects of healthy ingredients. Of course, measurement of alcohol consumption

Table 188.7 Key points of clinical and epidemiological studies on the relationships among alcohol consumption and dementia and predementia syndromes

A. Among lifestyle-related factors, low to moderate alcohol drinking has been proposed as a protective factor against the development of age-related changes of cognitive function, predementia syndromes, and cognitive decline of degenerative (Alzheimer's disease, AD) or vascular origin (vascular dementia, VaD) in several longitudinal studies, but contrasting findings also exist

B. Light to moderate alcohol use may be associated with a reduced risk of unspecified incident dementia and AD, while for VaD, cognitive decline, and predementia syndromes the current evidence is only suggestive of a protective effect

C. Epidemiological evidence suggested that the protective effects of alcohol are more likely with wine consumption and the absence of an apolipoprotein E (APOE) e4 allele. At present, there is no indication that light to moderate alcohol drinking would be harmful to cognition and dementia, and it is not possible to define a specific beneficial level of alcohol intake

This table lists the principal features of clinical and epidemiological studies on the relationships among alcohol consumption and dementia (AD and VaD) and predementia syndromes

must consider both volume consumed and the alcohol content of drinks, which is very variable in everyday living and in previous research, and this will remain an important consideration in considering previous research and planning future studies.

Whether the present divergent findings can be explained by the drinking patterns has not been extensively investigated, and studies with long follow-up periods are few (Panza et al. 2009a). It is possible that over time, and perhaps in association with cognitive decline, alcohol consumption patterns will change, and, therefore, long-term follow-up studies are needed to clarify the issue. Furthermore, with respect to the measurement of alcohol intake, in addition to the volume and alcohol content issue mentioned, the amount of detail collected on patterns of consumption varies widely in some studies which often range from data on recent consumption to some assessing historial patterns of consumption or lifetime abstinence/change in consumption. This may be particularly pertinent in the elderly as people may reduce consumption as they age, although not all studies agree with this (Panza et al. 2009a), however, it also contains hazards associated with recall bias. It may be that the prevalence of binge drinking has only increased recently, especially for women, but it is surprising that so few studies assessed this in their participants (Panza et al. 2009a). Therefore, the impact of alcohol drinking on cognitive functions might be somewhat different at different time points in individual's lives. Nonetheless, the current balance of evidence suggests that alcohol consumption in old age substantially agrees with that of midlife consumption in relation to cognitive decline (Panza et al. 2009a). At present, there is no evidence indicating whether starting to drink at a later age would be beneficial against predementia or dementia syndromes.

Furthermore, smoking may be a significant confounder of alcohol effects and thus both may not only individually affect dementia and cognitive decline, but each may also modify the effects of the other. In fact, there were several studies focused on alcohol and cognitive impairment or decline, in which there was no evidence of an interaction between alcohol and smoking on cognitive measures, with a few notable exceptions (Panza et al. 2009a). The overall findings from three Canadian data sets suggested that smoking may reduce the risk of dementia among drinkers (Tyas et al. 2000) while another recent study reported that these interactions were significant only for wine and smoking, suggesting that ingredients other than ethanol in wine may be protective against the adverse effects of smoking or of course it could suggest that there is higher consumption of wine amongst smokers compared with nonsmokers (Mehlig et al. 2008). Further analysis of this interaction, particularly in longitudinal studies and within genetic risk groups, is needed to determine whether this interaction can be replicated.

Finally, genetic susceptibility seems to modify the effect of alcohol on risk of dementia and predementia syndromes, with some, but not all studies suggesting that the *APOE* ε4 carrier status acting as a possible effect modifier for these associations (Panza et al. 2009a). Nonetheless, the protective effects of light to moderate alcohol consumption against dementia and cognitive decline are more likely in the absence of an *APOE* ε4 allele (Panza et al. 2009a). The effect of the *APOE* ε4 allele on dementia is suggested to attenuate with increasing age, which might partly explain the conflicting results concerning effect modification in studies on elderly cohorts (65 years and older) (Panza et al. 2009a). Very recently, in the CAIDE study, after an average follow-up of 21 years, there was a statistically significant multiplicative (*p*-values: infrequent drinking = 0.04, frequent drinking = 0.03) and additive interaction (infrequent drinking: relative excess risk from interaction (RERI) = 1.97, $p < 0.001$, frequent drinking: RERI = 2.95, $p < 0.001$) between the *APOE* ε4 carrier status and alcohol drinking for dementia risk (Kivipelto et al. 2008). One possible explanation could be that people with the ε4 allele have less effective neural repair mechanisms (Panza et al. 2009a), and thus they would be more susceptible to the deleterious effects of alcohol. It is also possible that it is a particular drinking pattern (i.e., binge drinking) which together with *APOE* ε4 carrier status forms a hazardous combination in some populations (Panza et al. 2009a). However, what has yet to be investigated as a possible additional variable is whether any additional genetic variants, such as genes encoding enzymes involved in alcohol metabolism, may also be involved.

Ultimately, since intervention studies are unlikely to be performed in this area, perhaps the most useful evidence comes from overview of epidemiological studies which still have a number of limitations. At present, there doesn't appear to indication that light to moderate alcohol drinking would be harmful to cognition and dementia. However, it is not possible to define a specific beneficial level of alcohol intake in relation to what might be beneficial to cognitive function and dementia. Acknowledging the well-known harmful effects related to heavy consumption of alcohol and the lack of long-term follow-up studies or randomized controlled trials, it would be premature to recommend whether some alcohol consumption, even to abstainers would be helpful in preventing cognitive decline or predementia syndromes or even delaying the onset of dementia. Possibly, at present, in moderate to heavy alcohol drinkers, experiencing memory difficulty, or with suggested diagnoses of MCI or early AD, among management options, given the challenge in achieving total abstinence, allowing some light to moderate drinking (rather than encouraging which may convey confusing health messages), provided there are no other contraindications to suggest otherwise may at the very least not contribute significant additional harm (Panza et al. 2009a).

Summary Points

- An increasing body of epidemiological evidence suggests that light to moderate alcohol consumption could offer some benefit for some health outcomes including cognitive function and heart disease.
- In particular, light to moderate alcohol drinking has been proposed, although not universally, as a protective factor against the development of age-related changes of cognitive function including predementia syndromes, and cognitive decline of degenerative (Alzheimer's disease, AD) or vascular origin (vascular dementia, VaD) in several longitudinal studies.
- Different outcome measures, types of beverages, measurement of drinking patterns, or follow-up periods, or possible interactions with other lifestyle-related (e.g., smoking) or genetic factors (e.g., *APOE* or other genes) are current sources of great variability where there need to be efforts to refine.
- Light to moderate alcohol consumption may be associated with a reduced risk of unspecified incident dementia and AD, while it may also be a benefit for less studied VaD, cognitive decline, and predementia syndromes.
- Reported protective effects from alcohol consumption seem to be most likely attributed to the consumption of wine and in people not having *APOE* e4 alleles. However, at present, there is no indication whether light to moderate alcohol drinking would be harmful to cognition and dementia, and it is not possible to define a specific beneficial level of alcohol intake.

Key Terms and Definitions

Alcohol: Any organic compound where a hydroxyl group (−OH) is bound to a carbon atom of an alkyl or substituted alkyl group. Generally, the word alcohol refers to ethanol, the type of alcohol found in alcoholic beverages. Ethanol is a colourless, volatile liquid with a mild odour which can be obtained by the fermentation of sugars.
Dementia: It is a syndrome defined by impairments in memory and other cognitive functions that are severe enough to cause significant impairment and decline from a previous level of social and occupational functioning.

Predementia syndrome: This term identifies all conditions with age-related deficits in cognitive function, including a mild stage of cognitive impairment based on a model of normality or also due to pathological conditions considered predictive or early stages of dementia.

Mild cognitive impairment (MCI): It is a clinical label that includes non-demented aged persons with memory impairment that is more pronounced than what would be expected normal for that age but not severe enough as to cause significant disability.

Age-related cognitive decline (ARCD): It is defined as an objectively identified decline in cognitive functioning consequent to the aging process that is within normal limits given the person's age, not as pronounced as for MCI, but for which there are no defined diagnostic criteria, and scant usage in epidemiological studies.

References

Anstey KJ, Mack HA, Cherbuin N. Am J Geriatr Psychiatry. 2009;17:542–55.

Anttila T, Helkala EL, Viitanen M, Kåreholt I, Fratiglioni L, Winblad B, Soininen H, Tuomilehto J, Nissinen A, Kivipelto M. B.M.J. 2004;329:539.

Bond GE, Burr R, McCurry SM, Graves AB, Larson EB. Int Psychogeriatr. 2001;13:207–23.

Bond GE, Burr R., Rice MM, McCurry SM, Graves AB, Teri L, Bowen JD, McCormick WC, Larson EB. J Aging Health. 2003;15:371–90.

Bond GE, Burr R, McCurry SM, Rice MM, Borenstein AR, Kukull WA, Teri L, Bowen JD, McCormick WC, Larson EB. J Aging Health. 2004;16:615–40.

Bond GE, Burr R, McCurry SM, Rice MM, Borenstein AR, Larson EB. Int Psychogeriatr. 2005;17:653–68.

Broe GA, Creasey H, Jorm AF, Bennett HP, Casey B, Waite LM, Grayson DA, Cullen J. Aust N. Z. J. Public Health. 1998;22:621–3.

Carmelli D, Swan GE, Reed T, Schellenberg GD, Christian JC. Neuroepidemiology. 1999;18:125–33.

Cervilla JA, Prince M, Mann A. J Neurol Neurosurg Psychiatry. 2000a;68:622–6.

Cervilla JA, Prince M, Joels S, Lovestone S, Mann A. Long-term predictors of cognitive outcome in a cohort of older people with hypertension. Br J Psychiatry. 2000b;177:66–71.

Commenges D, Scotet V, Renaud S, Jacqmin-Gadda H, Barberger-Gateau P, Dartigues J-F. Eur J Epidemiol. 2000;16:357–63.

Corder R, Mullen W, Khan NQ, Marks SC, Wood EG, Carrier MJ, Crozier A. Nature. 2006;444:566.

Christian JC, Reed T, Carmelli D, Page WF, Norton JA Jr, Breitner JC. J Stud Alcohol. 1995;56:414–6.

DeCarli C, Miller BL, Swan GE, Reed T, Wolf PA, Carmelli D. Arch Neurol. 2001;58:643–7.

Deng J, Zhou DH, Li J, Wang YJ, Gao C, Chen M. Clin Neurol Neurosurg. 2006;108:378–83.

Dent OF, Sulway MR, Broe GA, Creasey H, Kos SC, Jorm AF, Tennant C, Fairley MJ. B.M.J. 1997;314:l655–7.

den Heijer T, Vermeer SE, van Dijk EJ, Prins ND, Koudstaal PJ, van Duijn CM, Hofman A, Breteler MM. Am J Clin Nutr. 2004;80:992–7.

Dufouil C, Ducimetière P, Alperovitch A. Am J Epidemiol. 1997;146:405–12.

Dufouil C, Tzourio C, Brayne C, Berr C, Amouyel P, Alperovitch A. Epidemiology. 2000;11:280–4.

Edelstein SL, Kritz-Silverstein D, Barrett-Connor E. J Women's Health. 1998;7:1271–81.

Elias PK, Elias MF, D'Agostino RB, Silbershatz H, Wolf PA. Am J Epidemiol. 1999;150:580–9.

Elwood PC, Gallacher JE, Hopkinson CA, Pickering J, Rabbitt P, Stollery B, Brayne C, Huppert FA, Bayer A. J Epidemiol Community Health. 1999;53:9–14.

Erkinjuntti T, Inzitari D, Pantoni L, Wallin A, Scheltens P, Rockwood K, Desmond DW. Ann N. Y. Acad Sci. 903: 262–272.

Espeland MA, Gu L, Masaki KH, Langer RD, Coker LH, Stefanick ML, Ockene J, Rapp SR. Am J Epidemiol. 2005;161:228–38.

Fadda F, Rossetti ZL. Prog Neurobiol. 1998;56:385–431.

Fujishima M, Kiyohara Y. Ann N. Y. Acad Sci. 2002;977:1–8.

Galanis DJ, Joseph C, Masaki KH, Petrovich H, Ross GW, White L. Am J Public Health. 2000;90:1254–9.

Ganguli M, Vander Bilt J, Saxton JA, Shen C, Dodge HH. Neurology. 2005;65:1210–7.

Goodwin JS, Sanchez CJ, Thomas P, Hunt C, Garry PJ, Goodwin JM. Am J Public Health. 1987;77:173–7.

Hebert LE, Scherr PA, Beckett LA, Funkenstein HH, Albert MS, Chown MJ, Evans DA. Am J Epidemiol. 1992;135:347–55.

Herbert LE, Scherr PA, Beckett LA, Albert MS, Rosner B, Taylor JO, Evans DA. Am J Epidemiol. 1993;137:881–91.

Hendrie HC, Gao S, Hall KS, Hui SL, Unverzagt FW. J Am Geriatr Soc. 1996;44:1158–65.

Huang W, Qiu C, Winblad B, Fratiglioni L. J Clin Epidemiol. 2002;55:959–64.

Järvenpää T, Rinne JO, Koskenvuo M, Räihä I, Kaprio J. Epidemiology. 2005;16:766–71.

Klatsky AL. Stroke. 2005;36:1835–6.

Kivipelto M, Helkala EL, Hänninen T, Laakso MP, Hallikainen M, Alhainen K, Soininen H, Tuomilehto J, Nissinen A. B.M.J. 2001;322:1447–51.

Kivipelto M, Rovio S, Ngandu T, Kåreholt I, Eskelinen M, Winblad B, Hachinski V, Cedazo-Minguez A, Soininen H, Tuomilehto J, Nissinen A. J Cell Mol Med. 2008;12:2762–71.

Larrieu S, Letenneur L, Helmer C, Dartigues JF, Barberger-Gateau P. J Nutr Health Aging. 2004;8:150–4.

Launer LJ, Feskens EJ, Kalmijn S, Kromhout D. Am J Epidemiol. 1996;143:219–27.

Leibovici D, Ritchie K, Ledesert B, Touchon J. Int J Epidemiol. 1999;28:77–81.

Lemeshow S, Letenneur L, Dartigues JF, Lafont S, Orgogozo JM, Commenges D. Am J Epidemiol. 1998;148:298–306.

Lindeman RD, Wayne SJ, Baumgartner RN, Garry PJ. J Gerontol A Biol Sci Med Sci. 2005;60:1065–70.

Lindsay J, Laurin D, Verreault R, Hébert R, Helliwell B, Hill GB, McDowell I. Am J Epidemiol. 2002;156:445–53.

Luchsinger JA, Tang MX, Siddiqui M, Shea S, Mayeux R. J Am Geriatr Soc. 2004;52:540–6.

McCallum J, Simons LA, Simons J, Friedlander Y. Ann N. Y. Acad Sci. 2007;1114:121–9.

McGuire LC, Ajani UA, Ford ES. Ann Epidemiol. 2007;17:93–9.

Mehlig K, Skoog I, Guo X, Schütze M, Gustafson D, Waern M, Ostling S, Björkelund C, Lissner L. Am J Epidemiol. 2008;167:684–91.

Miners JS, Baig S, Palmer J, Palmer LE, Kehoe PG, Love S. Brain Pathol. 2008;18:240–52.

Mukamal KJ, Kuller LH, Fitzpatrick AL, Longstreth WT Jr, Mittleman MA, Siscovick DS. J.A.M.A. 2003;289:1405–13.

Mukamal KJ, Chung H, Jenny NS, Kuller LH, Longstreth WT Jr, Mittleman MA, Burke GL, Cushman M, Beauchamp NJ Jr, Siscovick DS. Stroke. 2005a;36:1830–4.

Mukamal KJ, Ascherio A, Mittleman MA, Conigrave KM, Camargo CA Jr, Kawachi I, Stampfer MJ, Willett WC, Rimm EB. Ann Intern Med. 2005b;142:11–19.

Naimi TS, Brown DW, Brewer RD, Giles WH, Mensah G, Serdula MK, Mokdad AH, Hungerford DW, Lando J, Naimi S, Stroup DF. Am J Prev Med. 2005;28:369–73.

Ngandu T, Helkala EL, Soininen H, Winblad B, Tuomilehto J, Nissinen A, Kivipelto M. Dement Geriatr Cogn Disord. 2007;23:140–9.

Orgogozo JM, Dartigues JF, Lafont S, Letenneur L, Commenges D, Salamon R, Renaud S, Breteler MB. (Paris) 1997;153:185–92.

Palomaki H, Kaste M. Stroke. 1993;24:1828–32.

Panza F, Solfrizzi V, Torres F, Mastroianni F, Del Parigi A, Colacicco AM, Basile AM, Capurso C, Noya R, Capurso A. Neurosci Lett. 1999;277:53–6.

Panza F, D'Introno A, Colacicco AM, Capurso C, Del Parigi A, Caselli RJ, Pilotto A, Argentieri G, Scapicchio PL, Scafato E, Capurso A, Solfrizzi V. Am J Geriatr Psychiatry. 2005;13:633–44.

Panza F, Capurso C, D'Introno A, Colacicco AM, Frisardi V, Lorusso M, Santamato A, Seripa D, Pilotto A, Scafato E, Vendemiale G, Capurso A, Solfrizzi V. J Alzheimers Dis. 2009a;17:7–31.

Panza F, Capurso C, Solfrizzi V. J.A.M.A. 2009b;299:2853–4.

Panza F, Frisardi V, Capurso C, D'Introno A, Colacicco AM, Imbimbo BP, Santamato A, Vendemiale G, Seripa D, Pilotto A, Capurso A, Solfrizzi V. Am J Geriatr Psychiatry. 2010;18:98–116.

Peters R, Peters J, Warner J, Beckett N, Bulpitt C. Age Ageing. 2008;37:505–12.

Petersen RC, Smith GE, Waring SC, Ivnik RJ, Tangalos EG, Kokmen E. Arch Neurol. 1999;56:303–8.

Portet F, Ousset PJ, Visser PJ, Frisoni GB, Nobili F, Scheltens P, Vellas B, Touchon J; MCI Working Group of the European Consortium on Alzheimer's Disease (EADC). J Neurol Neurosurg Psychiatry. 2006;77:714–8.

Qiu C, De Ronchi D, Fratiglioni L. Curr Opin Psychiatry. 2007;20:380–5.

Reid MC, Van Ness PH, Hawkins KA, Towle V, Concato J, Guo Z. J Geriatr Psychiatry Neurol. 2006;19:98–105.

Reynolds K, Lewis LB, Nolen JD, Kinney GL, Sathya B, He J. J.A.M.A. 2003;289:579–88.

Roman GC. Acta Neurol Scand. 2002;Suppl. 178:6–9.

Roman GC, Royall DR. Alzheimer Dis Assoc Disord. 1999;13 (Suppl. 3):S69–80.

Román GC, Sachdev P, Royall DR, Bullock RA, Orgogozo JM, López-Pousa S, Arizaga R, Wallin A. J Neurol Sci. 2004;226:81–7.

Ruitenberg A, van Swieten JC, Witteman JC, Mehta KM, van Duijn CM, Hofman A, Breteler MM. Lancet. 2002;359:281–6.

Sachdev P. Int J Geriatr Psychiatry. 1999;14:402–3.

Scarmeas N, Stern Y, Tang MX, Mayeux R, Luchsinger JA. Ann Neurol. 2006;59:912–21.

Schinka JA, Vanderploeg RD, Rogish M, Graves AB, Mortimer JA, Ordoric PI. J Int Neuropsychol Soc. 2002;8:811–8.

Simons LA, Simons J, McCallum J, Friedlander Y. Med J Aust. 2006;184:68–70.

Solfrizzi V, D'Introno A, Colacicco AM, Capurso C, Del Parigi A, Baldassarre G, Scapicchio P, Scafato E, Amodio M, Capurso A, Panza F, Italian Longitudinal Study on Aging Working Group. Neurology. 2007;68:1790–89.

Stampfer MJ, Kang JH, Chen J, Cherry R, Grodstein F. N Engl J Med. 2005;352:245–53.

Stancampiano R, Carta M, Cocco S, Curreli R, Rossetti ZL, Fadda F. Brain Res. 2004;997:128–32.

Tyas SL, Koval JJ, Pederson LL. Stat Med. 2000;19:1685–96.

Truelsen T, Thudium D, Grønbæk M. Neurology. 2002;59: 1313–9.

U.S. Department of Health and Human Services and U.S. Department of Agriculture. Dietary guidelines for Americans, 6th ed. Washington, DC: U.S. Government Printing Office; 2005.

Verhaegen P, Borchelt M, Smith J. Health Psychol. 2003;22:559–69.

Waddington E, Puddey IB, Croft KD. Am J Clin Nutr. 2004;79:54–61.

Walzem RL. Inflammopharmacology. 2008;16:265–71.

Waterhouse AL. Ann N. Y. Acad Sci. 2002;957:21–36.

Whitehouse PJ, Sciulli CG, Mason RM. Psychopharmacol Bull. 1997;33:129–33.

Winblad B, Palmer K, Kivipelto M, Jelic V, Fratiglioni L, Wahlund LO, Nordberg A, Bäckman L, Albert M, Almkvist O, Arai H, Basun H, Blennow K, de Leon M, DeCarli C, Erkinjuntti T, Giacobini E, Graff C, Hardy J, Jack C, Jorm A, Ritchie K, van Duijn C, Visser P, Petersen RC. J Intern Med. 2004;256:240–6.

Yoshitake T, Kiyohara Y, Kato I, Ohmura T, Iwamoto H, Nakayama K, Ohmori S, Nomiyama K, Kawano H, Ueda K, Sueishi K, Tsuneyoshi M, Fujishima M. Neurology. 1995;45:1161–8.

Zuccalà G, Onder G, Pedone C, Cesari M, Landi F, Bernabei R, Cocchi A; Gruppo Italiano di Farmacoepidemiologia nell'Anziano Investigators. Alcohol Clin Exp Res. 2001;25:1743–8.

Zhou H, Deng J, Li J, Wang Y, Zhang M, He H. Age Ageing. 2003;32:205–10.

Chapter 189
Sweet Preference and Mood: Implications for the Risk of Alcoholism

Alexei B. Kampov-Polevoy

Abbreviations

SD   Sweet disliking
SL   Sweet liking
GABA   γ-Aminobutyric acid
FH+   Positive family history of alcoholism
FH–   Negative family history of alcoholism
PMS   Premenstrual syndrome

189.1 Introduction

We all like sweets from the moment we are born. Mother Nature designed us this way because sweet taste is an indicator of highly caloric carbohydrate foods that are necessary for us to survive at early age. Mother's milk is very sweet, if anyone remembers. We perceive sweet taste as calming, soothing, and comforting. Reaction to the sweet taste is our basic pleasure, the yardstick by which we measure all our positive experiences. That is why even in our language the word "sweet" is synonymous with anything good. We call our loved ones *sweethearts* and *sweeties*, our favorite music is *sweet music*, and, even in business, we are trying to make *sweet deals* with our partners.

Our response to the sweet taste is closely associated with our overall ability to experience all natural pleasures. Therefore, any changes in our hedonic response to sweets may reflect changes in functional activity of the brain reward system. For example, preference for stronger sweet taste and craving for sweets was consistently reported in individuals suffering from anxiety, depression, and dysphoria. Furthermore, our knowledge of the soothing effect associated with eating sweet foods that we acquired in infancy can provide us a serious disservice in our adult life: some of us continue to use sweet foods as a tranquilizer which, in some cases, leads to the development of binge eating behavior and obesity.

The key role in regulation of our pleasurable response to sweet taste is played by endogenous opioid peptides (e.g., endorphins and enkephalins) that have similar physiological effects to exogenous opiate drugs such as morphine and heroine. These endogenous peptides as well as their multiple

---

A.B. Kampov-Polevoy (✉)
Department of Psychiatry, University of North Carolina at Chapel Hill,
237 Medical School Wing B, Campus Box 7160, Chapel Hill, NC 27599-7160
e-mail: kampov@med.unc.edu

receptor subtypes (e.g., μ, β, κ) are found in various networks throughout the brain, but particularly within the regions involved in emotional regulation, responses to pain and stress, endocrine regulation, and food intake.

Despite the importance of sweet taste and its association with emotional health, the literature about this subject is scarce. In this chapter I will attempt to systematize the existing knowledge regarding physiological mechanisms underpinning hedonic response to sweets and the links between distortions of sweet taste and various psychiatric conditions with an emphasis on alcoholism.

189.2 Hedonic Response to Sweet Taste

The gustatory system is primarily devoted to a quality check of food, while simultaneously detecting nutrients and avoiding toxic substances. Sweet is one of the five primary taste qualities (along with bitter, sour, salty, and umami). Sweet-tasting foods and beverages are highly preferred by plant-eating animals including humans, presumably because sweetness reflects the presence of caloric sugars.

Liking sweet tastes is strongly influenced by inborn (innate) factors and positive hedonic (pleasurable) responses to sweet taste can be detected in human infants during the first minutes after birth (Steiner et al. 2001). Hedonic response to sweet taste is believed to be a stable heritable trait that reflects qualitative differences in taste perception rather than more cognitive reactions based on associations between the taste and attitudes toward, or social acceptability of, liking sweet foods (Looy and Weingarten 1991). The role of genetic factors in perception of sweet taste and preference for sweet foods can be illustrated by the results of a recent study of 473 twin pairs, which showed that approximately half of the variation in liking for sweet solution and liking and use-frequency of sweet foods (49–53%) was explained by genetic factors, whereas the rest of the variation was due to the environmental factors unique to each twin individual (Keskitalo et al. 2007).

189.2.1 Sweet-liking/Sweet-disliking Phenotypes

It is important to note that although all humans have an innate preference for the sweet taste, the magnitude of hedonic response to sweet taste as well as avidity to consume sweet foods significantly varies across individuals. Such differences may be noted in infancy (Steiner et al. 2001) and persist as children become young adults (Desor and Beauchamp 1987). Two major stable patterns of hedonic response to sweet taste have been described in the literature (Thompson et al. 1976). With Type I response (often referred to as *sweet disliking*), subjects prefer progressively higher concentrations of sucrose solution up to the middle range of concentration, followed by a breakpoint after which preference declines with increased concentration. The Type II response (also referred to as *sweet liking*) is characterized by continuous increase with eventual leveling off in liking of progressively more concentrated sucrose solutions (Fig. 189.1). Similar patterns have been described in animals as well (Sinclair et al. 1992), which may indicate that these patterns can be a characteristic of all mammals.

189.2.2 Factors Influencing Hedonic Response to Sweet Taste

Although perception of sweet taste appears to be a fairly stable trait, there are some factors that are known to be associated with variability of hedonic response to the sweet taste.
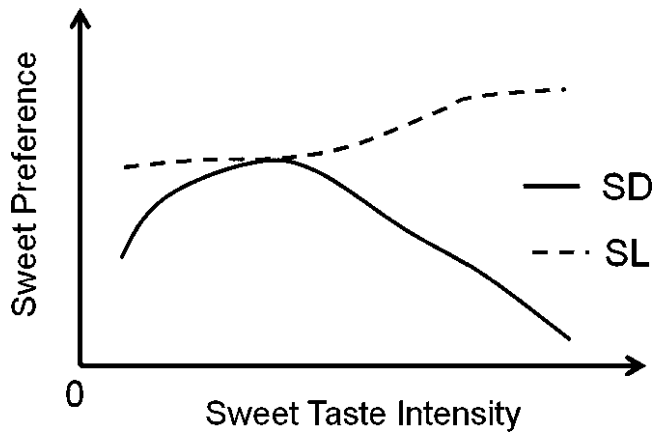
Fig. 189.1 Types of hedonic response to sweet taste in animals and humans. Although both animals and humans have an innate preference for sweet-tasting substances, the magnitude of hedonic response to sweet taste as well as avidity to consume sweet foods significantly varies across individuals. Two major stable patterns of hedonic response to sweet taste have been described in the literature. With Type I response (often referred to as *sweet disliking*, *SD*), subjects prefer progressively higher concentrations of sucrose solution up to the middle range of concentration, followed by a breakpoint after which preference declines with increased concentration. The Type II response (also referred to as *sweet liking*, *SL*) is characterized by continuous increase with eventual leveling off in liking of progressively more concentrated sucrose solutions. These two patterns of hedonic response to sweet taste are believed to be associated with activity of the brain opiate system that to a large extent is regulated by genetic factors. Sweet liking is believed to be associated with suppression of the opioidergic transmission in the brain

Ethnic background: Ethnic origins have been shown to have an impact on the hedonic response to sweet taste. For example, Americans of African descent were shown to prefer stronger sweet taste than Americans of European descent (Bacon et al. 1994).

Age: The degree of preferred sweetness also may vary with age. Children tend to prefer sweeter solutions compared to adults (De Graaf and Zandstra 1999). Younger people also consume more sugar than do older people (Drewnowski 1997).

Gender-related factors: Sex differences may also influence hedonic response to sweet taste, with women being more sensitive to the mood-altering effect associated with eating sweet-tasting foods and reporting stronger cravings for sweet-tasting foods (Kampov-Polevoy et al. 2006). It is of interest that the sex differences in hedonic response to and craving for sweets can be seen only in adult individuals, while no such difference was noted in infants (Beauchamp and Moran 1982). These findings may indicate that sex hormones may play a significant role in the development of sweet preferences as was initially suggested by Wade and Zucker (1969). The other indications that sex hormones can modulate a perception of and craving for the sweet taste come from studies that showed a fluctuation of sweet cravings and consumption of sweet foods (but not other types of foods) throughout the menstrual cycle (Bowen and Grunberg 1990).

In summary, a pleasurable response to the sweet taste is an innate reaction and the level of positive emotional response to sweet taste, as well as consumption of sweets, are influenced to a large degree by genetic factors. There are two major patterns of the hedonic response to sweet taste – sweet disliking and sweet liking. Of the factors identified to date that influence hedonic response to sweet taste, gender seems the most influential with women being more sensitive to mood-altering effect of sweet-tasting foods and more likely to crave and eat sweets in response to emotional stress.

189.3 189.3 Physiological Mechanisms Underpinning Hedonic Response to Sweet Taste

The mechanisms regulating hedonic response to sweet taste are complex, and detailed discussions of these complexities are beyond the scope of this chapter. Here, a brief overview of the two major categories of mechanisms of response to sweet taste is presented: the peripheral mechanisms, responsible for the perception of sweet taste, and the central mechanisms, responsible for emotional response for sweets.

189.3.1 Peripheral Mechanisms/Role of the Taste Receptors

The initial event of perception of sweet taste occurs in taste receptor cells, which are clustered in the taste buds in taste papillae on the tongue surface. The perception of sweetness intensity is related to the number of papillae that varies widely among people. These variations may be due to alleles in genes that develop and maintain sensory cells. To date, three sweet-taste receptors have been identified in both mice and humans, which are regulated by polymorphisms of sweet-receptor genes (*TAS1R1, TAS1R2, TAS1R*3). Polymorphisms of these genes have a large effect on the intake of sweet-tasting substances in both animals and humans (Liao and Schultz 2003).

189.3.2 Central Mechanisms/Role of the Brain Reward System

Hedonic responses to sweet taste may be modulated not only by peripheral mechanisms, but also by the brain reward system that regulates perception of all naturally occurring pleasures. This system was first described by Olds and Milner (1954) who observed that when electrodes were placed in certain areas of the brain, rats would actively self-stimulate these areas often to the exclusion of other activities including eating. The brain reward system is located in the mesolimbic part of the brain and involves complex interrelationships of at least four important neurochemical pathways (i.e., serotonergic, opioidergic, GABAergic, and dopaminergic), with a pleasurable response associated with increased dopamine accumulation in the nucleus accumbens. Without the normal functionality of the brain reward system, an individual will experience a so called reward-deficiency syndrome that includes hypohedonia (diminished ability to experience pleasure) and inability to cope with stress. Individuals with the reward-deficiency syndrome are likely to seek substances and/or behaviors that will overcome this hypohedonic state by activating the brain reward system. These substances and behaviors include alcohol, opiates, psychostimulants, nicotine, carbohydrates, cannabinoids, gambling, sex, and indulgence in any excessive pleasure or thrill-seeking behaviors, such as video gaming, etc. (for review, see Comings and Blum 2000).

Sweet-tasting substances (both caloric and noncaloric sweeteners) stimulate sweet-taste receptors on the surface of the tongue, which, in turn, results in activation of the μ-opioid receptors on GABA interneurons (projection neurons that interact with dopamine neurons) in the ventral tegmental area, to cause a disinhibition of dopamine cell firing in the nucleus accumbens that is subjectively perceived as pleasure (Lemon et al. 2004). Microdialysis studies show a robust rise in extracellular accumbens dopamine levels following exposure to sweet tastes. Recently, Pecina and Berridge (2005) have shown that the perception of pleasantness of sweet taste in rats is strongly influenced by

μ-opioid receptor activation in a single cubic millimeter site localized in the rostrodorsal quarter of the medial shell of the nucleus accumbens, an observation indicating very tight neuroanatomical localization of the hedonic response to sweet taste. According to DiChiara and North (1992), opioid pathways in the brain reward system are associated with feelings of satiety, sedation, rest, and "bliss." In this regard, it is important to note that sweet preference and hedonic response to sweet taste seem to be associated with activity of the brain opioid pathways. Animal studies showed that stimulation of these pathways with morphine shifts the sweet preference/aversion curve left toward preference for weaker sweet taste (Calcagnetti and Reid 1983), while its blockade shifts sweet preference toward more concentrated sweet solutions (Leventhal et al. 1995). Therefore, the sweet-liking phenotype, described earlier in this chapter may be associated with inhibition of the opioidergic pathways in the brain reward system and can be a potential marker of the reward-deficiency syndrome.

Knowledge of physiological mechanisms underpinning hedonic response to sweet taste leads to several hypotheses that may have important practical implications:

1. Considering that eating of sweet-tasting foods is associated with stimulation of the opioidergic pathways in the brain, one would expect that consumption of sweets will exert an effect similar to those of opiate agonists (e.g., morphine) – produce a positive affective state, reduce emotional stress, and cause analgesia. On the other hand, chronic consumption of sweet-tasting foods may lead to the development of elements of physical dependence such as increased consumption of sweets, loss of control over eating sweets, as well as development of symptoms similar to symptoms of opiate withdrawal when consumption of sweet-tasting foods is discontinued.
2. Considering the ability of sweet-tasting foods to produce positive emotional states and reduce emotional stress, one would also expect that people will eat sweets to self-medicate the negative mood states such as anxiety, fatigue, and/or depression.
3. Considering that preference for stronger sweet taste (sweet liking) is associated with blockade of opioidergic pathways that play an important role in regulation of the activity of the brain reward system, it is logical to hypothesize that the sweet-liking phenotype may serve as a marker for the reward-deficiency syndrome. If this hypothesis is correct, we would expect the sweet-liking phenotype to be associated with the negative affect and with the inclination to self-medicate this affective state with sweet-tasting foods, alcohol, and drugs of addiction.

The following sections seek support for the above-mentioned hypotheses in the available literature.

189.4 Effects of Ingestion of Sweet Foods

The effects of ingestion of sweet tasting food are summarized in Table 189.1.

Table 189.1 Effects associated with eating of sweet-tasting foods

Effects of acute intake	Effects of chronic intake
Feeling of well-being, sedation, and relaxation Reduction of emotional stress and alleviation of negative mood states	Development of symptoms that are similar to symptoms of physical dependence: 1. Enhanced intake of sweet-tasting foods 2. Abrupt discontinuation of eating sweets after a period of daily intake of sweet-tasting foods may lead to symptoms similar to symptoms of opiate withdrawal
Analgesia	Development of tolerance to analgesic effect of opiate drugs

189.4.1 Effect of Acute Ingestion of Sweet-Tasting Substances

189.4.1.1 Effect of Sweet Taste on Mood

As stated earlier, positive emotional reactions to sweet taste can be detected in humans within the first few minutes after birth. Intraoral sucrose administration has been shown to induce rapid and sustained calming effects in crying newborns (for review, see Bhattachrjee and Mathur 2005). Similar mood-altering effects of sweet-tasting foods have been noted in adults as well. For example, eating of sweet food improves an experimentally induced negative mood state in healthy adults (Macht and Mueller 2007), with the effect being more pronounced in women than in men. Furthermore, college students reported that the magnitude of their craving for sweet carbohydrate foods correlates with the severity of the negative mood states such as anxiety, fatigue, and/or depression (Christensen and Pettijohn 2001). Therefore, positive mood effects of sweet-tasting foods may contribute to the habit of eating sweets as a coping mechanism against stress.

189.4.1.2 Effect of Sweet Taste on Perception of Pain

There is a large body of evidence indicating that consumption of sweet-tasting foods may produce significant analgesia in both animals and humans. For example, acute exposure to sweet (e.g., sucrose) solutions was shown to produce analgesia sufficient to conduct minor surgical procedures in human infants. A similar effect was demonstrated in prepubertal children as well as in adult females but not in adult males. The brain opioidergic pathways seem to play an important role in sweet-induced analgesia because such analgesia may be reversed by the opiate antagonist naloxone (for review, see Bhattachrjee and Mathur 2005).

189.4.2 Effect of Chronic Ingestion of Sweet-tasting Foods: Do We Become Dependent on Sweetness?

Although acute consumption of sweet foods may cause marked opiate-mediated analgesia, chronic exposure to sweets attenuates morphine-induced analgesia, which indicates the development of tolerance to opiates. Furthermore, animal studies demonstrate that chronic exposure to sweet-tasting foods may lead to the development of symptoms similar to those seen in individuals with substance dependence. For example, rats maintained on a diet of chronic intermittent access to a sucrose solution and chow tend to increase their sugar intake (Avena et al. 2006) and show behavioral and neurochemical changes similar, albeit smaller in magnitude, to rats dependent on opiates (Rada et al. 2005; Colantuoni et al. 2002).

There is emerging evidence showing that chronic exposure to sweet foods may cause long-term changes in preference for and consumption of sweet foods in humans, at least in children. For example, infants fed with sugar solutions prefer stronger sweet taste and like sweet foods later in life more than children who have not been fed with sweet water as infants (Beauchamp and Moran 1982). Children who were routinely fed sugar water during infancy preferred significantly higher levels of sucrose when compared to those who were rarely or minimally exposed (Pepino and Mennella 2005). In adults, immediate but short-lived reduction in sweet preference can be noticed after ingestion of the sweet solution (Cabanac and Duclaux 1970). However, this effect was noted only in individuals with sweet-disliking phenotype but not in sweet-liking individuals (Looy et al. 1992; Looy and Weingarten 1992).

189.4.3 Acute Effect of Noncaloric Sweeteners

It is important to emphasize that the effects sweet foods have on the brain reward system are associated with the oral stimulations of sweet-taste receptors rather than with the chemical composition or caloric value of ingested food. This hypothesis is supported by the elegant animal experiments using a sham-feeding procedure, when the food, after being eaten, did not enter the stomach but rather was removed from the gastrointestinal tract, thus eliminating any postabsorptive effect of consumed foods (Hajnal et al. 2004). This study provided a clear indication that concentration-dependent increase in dopamine levels in the rat nucleus accumbens depends on the taste but not on the composition of the studied foods. These findings may also explain why the noncaloric sweetener saccharine increases beta-endorphin levels in rat cerebrospinal fluid and plasma of the same magnitude as natural sugars (Yamamoto et al. 2000).

In summary, oral sucrose administration has been shown to produce positive emotional responses, to alleviate negative mood states, and to produce marked analgesia. These phenomena have been reported in both animals and humans, with women being more sensitive to these effects than men. Such effects are more likely to be associated with the sweet taste than with the chemical composition or caloric value of ingested food. Chronic consumption of sweet-tasting substances may lead to a condition similar to physical dependence to opiates with symptoms including elevated sugar consumption, increased tolerance to morphine, and signs of opiate withdrawal.

189.5 Sweet Taste and Mood Disorders

The literature provides consistent evidence showing that negative mood states are associated with the preference for stronger sweet taste, craving for sweet foods, and excessive consumption of sweet-tasting foods. For example, a study of healthy children shows significant correlation between sweet preference and depressive symptoms (Mennella et al. 2008). It is also believed that some people use sweet-tasting foods to self-medicate their negative emotional state.

Healthy individuals: In the study of healthy college students, Christensen and Pettijohn (2001) have shown that 90% of females and 55% of males identified themselves as cravers for sweet carbohydrate foods. In this sample, the magnitude of carbohydrate cravings significantly correlated with the experience of negative mood states such as anxiety, fatigue, and/or depression.

Patients with depression: In a clinical population, depressed individuals were shown to have a greater craving for and consumption of sweet carbohydrate foods than non-depressed controls (Christensen and Somers 1996; Wurtman 1988). Furthermore, the magnitude of the preference for sweet foods in depressed patients positively correlated with the level of depression (Fernstrom et al. 1987).

The association between depressed mood and sweet craving/consumption is most evident in patients with seasonal affective disorder, a condition characterized by recurrent depressive episodes that typically begin to appear in the fall and remit in the spring. These patients report strong cravings for sweet foods that are consistently associated with the depressive episodes (Rosenthal et al. 1984). Moreover, patients with seasonal affective disorder report that indulging in their craving significantly reduces negative mood (Leibenluft et al. 1993).

Patients with premenstrual syndrome (PMS): The other illustration of a link between negative affect and craving for sweets is PMS. It is commonly known that food cravings and mood tend to fluctuate throughout the menstrual cycle. In comparison to other phases of the menstrual cycle, during the luteal phase (10 days preceding menses), women report increased craving and consumption of sweet carbohydrate foods, which can double in comparison with postmenstrual period (Bowen

and Grunberg 1990). This phenomenon is especially pronounced in women with PMS when the depressed mood positively correlates with craving for sweet foods (Both-Orthman et al. 1988). Women also reported an improvement in mood following consumption of the carbohydrate-rich meal (Wurtman et al. 1989).

In summary, sweet preference and craving for sweet-tasting foods positively correlates with severity of the negative mood states (e.g., anxiety, depression) in both healthy individuals and patients with clinical depression. Consumption of sweets alleviates negative mood states and can be used for self-medication.

189.6 Hedonic Response to Sweet Taste and Excessive Alcohol Intake

189.6.1 Animal Studies

189.6.1.1 Association Between Consumption of Sweet-tasting Solutions and Alcohol Intake

During the last three decades, evidence indicating a close positive association between hedonic response to sweet taste, avidity to consume sweet-tasting foods, and excessive alcohol intake in both animals and humans has accumulated. The first evidence connecting consumption of sweets with alcohol intake came from animal studies. In 1978, Ramirez and Sprott reported that C57BL mice, known for their high voluntary alcohol intake, consume much larger quantities of saccharin solution than do DBA/2J mice that are known for their relatively low alcohol intake. A similar association (*correlation coefficient* = 0.7) between voluntary consumption of a 0.1% saccharin solution and subsequent voluntary consumption of 15% alcohol solution was demonstrated in randomly bred Wistar rats (for review, see Kampov-Polevoy et al. 1999).

Later studies showed that association between consumption of sweet solutions and alcohol intake may have a genetic origin. For example, Belknap et al. (1993) showed a high genetic correlation (*correlation coefficient* = 0.77) between saccharin and alcohol intake in 15 inbred mouse strains. A similar correlation between sucrose consumption and alcohol intake can be seen in the F2 generation of crosses between alcohol-preferring C57BL/6ByJ and alcohol-avoiding 129/J strains of mice. Further analysis showed that intakes of sucrose and ethanol are influenced by a few genes and that the "genetically determined component of these correlations was stronger than the component related to environmental factors" (Bachmanov et al. 1996). Similar results have been demonstrated in rats genetically selected for their high/low alcohol intake (Overstreet et al. 1997).

189.6.1.2 Saccharin-induced Polydipsia and Excessive Alcohol Intake

One of the interesting characteristics of intake of sweetened solutions by alcohol-preferring rats is their tendency to consume these solutions far beyond the limit of normal daily fluid intake. This tendency was initially reported in randomly bred rats (Kampov-Polevoy et al. 1990), when it was noted that, although all studied rats had a high preference for 0.1% saccharin solution, some of them (40%) consumed saccharin solution on average 32% over the limit of their normal daily fluid intake, a condition we described as saccharin-induced polydipsia. Subsequently, these polydipsic rats consumed almost 10 times as much alcohol during the first week of an alcohol/water choice experiment as rats that consumed saccharin solution within the limits of their normal daily fluid intake.
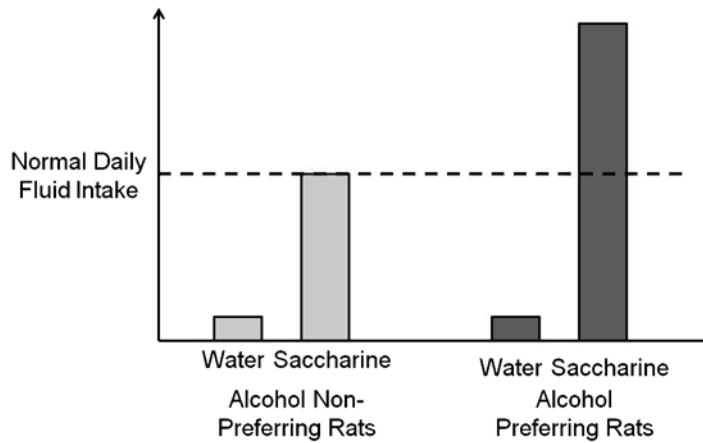
Fig. 189.2 Association between consumption of sweet-tasting substances and alcohol intake in rats. The figure illustrates the results of the study of consumption of sweet 0.1% saccharine solution in a free choice with water by rats genetically selected for excessive voluntary alcohol consumption and rats genetically selected to reject alcohol. The diagram shows that both strains of rats have similar high preference for saccharine solution that exceeds 90%. However, alcohol-nonpreferring rats, that are known to be sweet dislikers, consume sweet solution within the limits of normal daily fluid intake, when alcohol preferring rats who are known to be sweet likers, may double and in some cases quadruple their DFI when sweet solution is available. These findings are consistent with the results of clinical studies showing that sweet-liking individuals have an elevated risk to both alcohol-use disorders and bulimia nervosa that manifests itself by loss of control over food intake. Furthermore, comorbidity between substance-use disorders and bulimia is reported to be as high as 50%

Saccharine-induced polydipsia is especially apparent in rats genetically selected for alcohol preference. For example, high alcohol drinking rats exhibited a 370% increase in daily fluid intake when 0.1% saccharin solution was available along with water, whereas low-alcohol-drinking animals consumed saccharin within their normal daily fluid intake (Overstreet et al. 1997) (Fig. 189.2). Saccharin-induced polydipsia was shown to be a reliable predictor of subsequent alcohol intake, with a correlation coefficient of up to 0.9 between these two variables in P rats (Kampov-Polevoy et al. 1995), which makes this trait one of the best predictors of alcohol intake in rodents.

The dramatic increase in daily fluid intake in the presence of saccharin exhibited by alcohol-preferring rats may be an animal analogue of the clinical phenomenon known as *loss of control*. In the clinical situation, loss of control refers to the behavior in which a rewarding substance is taken in larger amounts or over longer periods of time than is intended. Interestingly, the link between loss of control over the consumption of sweets and the excessive alcohol intake was noted in humans as well. For example, overall comorbidity between eating disorders (e.g., bulimia nervosa that manifests itself by loss of control over food intake in general and sweet foods in particular) and alcohol abuse/dependence was reported to be as high as 50% (Dansky et al. 2000).

189.6.1.3 Preference for the Strong Sweet Taste and Alcohol Intake

In 1992, Sinclair et al. reported that rats with a genetically determined predisposition to high alcohol consumption preferred more concentrated sweet solutions compared to alcohol-avoiding rats. In this study, alcohol-preferring rats, as well as alcohol-nonpreferring rats, were tested by being given a free choice between tap water and an ascending series of saccharin concentrations, starting at 2 mg/L and doubling the concentration every day until a final level of 4096 mg/L was reached.

This experiment showed that, when rats were exposed to up to the 64 mg/L saccharin solution, their preference for it was generally the same in all animal groups. However, when exposed to more concentrated saccharin solutions, alcohol-nonpreferring rats generally had a lower preference ratio, compared to alcohol-preferring rats. The relevance of these findings to human alcoholism was later tested by evaluating the sweet preferences of alcoholics and nonalcoholic control subjects, as described in the following section.

189.6.2 Human Studies

189.6.2.1 Association Between the Sweet-liking Phenotype and Alcohol Intake

There is growing evidence linking the sweet-liking phenotype (preference for stronger sweet taste) and genetic risk for alcoholism. Our own study of healthy college students (Kampov-Polevoy et al. 2003a) indicates that sweet liking is more prevalent in children of alcoholic parents who are known to have four to nine times greater risk of becoming an alcoholic than children of nonalcoholic parents. Similar findings have been reported in the samples of alcoholics, addicts, and control (non-addicted) subjects (Kampov-Polevoy et al. 2003b). Thus, these and similar studies support the hypothesis that the sweet-liking phenotype is associated with the genetic risk of alcoholism.

However, unlike animal studies, in humans, the sweet-liking phenotype by itself seems to be insufficient to predict a diagnosis of alcohol dependence in clinical samples. As can be seen in the
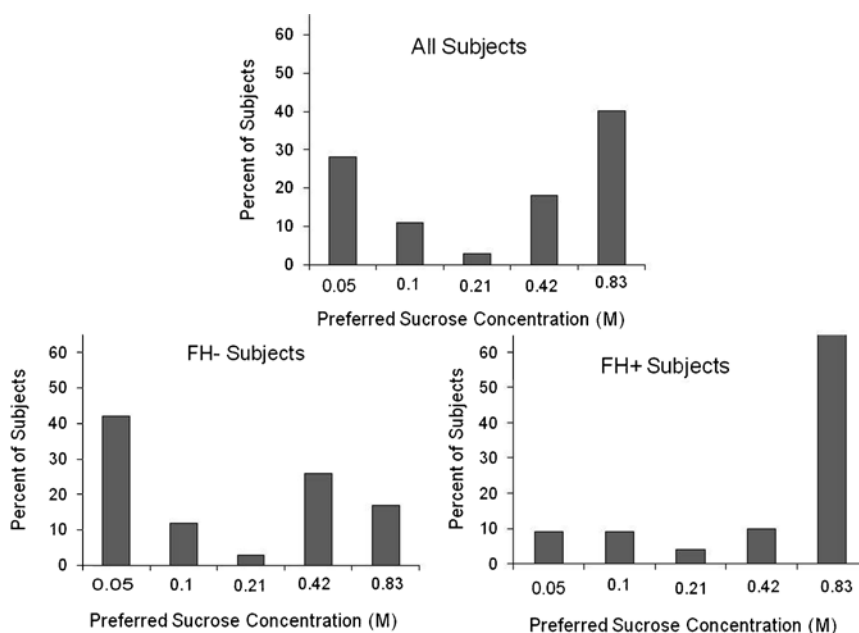
Fig. 189.3 Preference for five sucrose concentrations in male alcoholics with (FH +) and without (FH-) family history of alcoholism. This diagram presents a distribution of preferred sugar solutions in the sample of male patients with alcohol dependence ($n = 48$). The diagram shows approximately equal representation of sweet likers (patients preferring highest offered [0.83 M] sugar solution) and sweet dislikers (patients preferring lower sucrose solutions) in the sample. Sweet liking seems to be associated with the genetic risk of alcoholism and, therefore, is more prevalent among the children of alcoholic parents ($n = 20$) than among children of nonalcoholics ($n = 28$). Therefore, the sweet-liking phenotype may be considered as a potential marker for the familial form of alcoholism

Fig. 189.3, in a sample of alcoholic patients there is a similar representation of sweet-liking and sweet-disliking individuals, which indicates that sweet-liking status is linked not to diagnosis of alcoholism but to genetic risk for this disease evaluated on the basis of family history.

So now, the question is whether the sweet-liking phenotype has any practical value for prediction of the actual risk for having alcohol-use disorders in any given individual. The studies conducted during the last decade show that such prediction can be made if sweet liking is combined with another factor – personality trait called novelty seeking. Novelty seeking has been consistently associated with deviance proneness, disregard of social norms as well as with early onset of alcohol drinking and excessive alcohol drinking (Finn et al. 2000). In their recent report, Grucza et al. (2006) demonstrated that novelty seeking modulates the level of the alcoholism risk in high-risk families with high novelty seeking magnifying this risk and low novelty seeking acting as a protective factor. On the other hand, in the low-risk families, there was no effect of novelty seeking on the prevalence of alcohol-use disorders. These findings are consistent with our own data indicating that, in clinical populations, the estimated odds of being an alcoholic, on average, increase by 11% as NS score increases by 1 point in sweet-liking but not in sweet-disliking subjects (Kampov-Polevoy et al. 2004) (Fig. 189.4). Combination of preferred sucrose concentration and novelty-seeking score was shown to predict alcoholic vs. nonalcoholic group status at 65% sensitivity and 94% specificity, with correct classification in 85% of subjects (Kampov-Polevoy et al. 1998). Our most recent study (unpublished data) of 158 healthy college students demonstrated that individuals with a sweet-liking phenotype and high novelty seeking had a 27-fold increase in likelihood for having alcohol-related problems compared to sweet-disliking individuals with low novelty seeking.

In summary, there is growing evidence showing the hedonic response to sweet taste and the avidity to consume sweet-tasting foods is closely associated with the level of alcohol consumption in both animals and humans. This phenomenon, which, to a large extent, is based on genetic mechanisms,
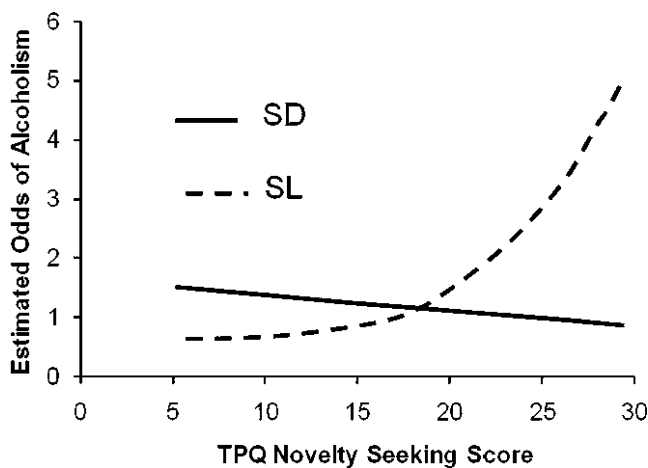
Fig. 189.4 Interaction between sweet-liking/sweet-disliking phenotypes and novelty seeking in prediction of alcoholic status of an individual. Both the sweet-liking and high novelty-seeking phenotypes are frequent findings in patients with alcohol-use disorders. However, neither of these traits separately can accurately predict an individual's risk for alcoholism. Sweet liking is associated with elevated sensitivity to the rewarding effect of alcohol and family history of alcoholism, but sweet liking alone has not been linked to excessive drinking. On the other hand, novelty seeking was shown to be closely associated with early onset of drinking, frequency and severity of drinking episodes, and disregard of societal norms. The diagram illustrates interaction of two independent factors, novelty seeking and sweet-liking phenotype, in the prediction of the alcoholism risk. One can see a dramatic increase of the risk of being an alcoholic in sweet likers with high novelty-seeking scores. At the same time in sweet-disliking individuals who are less sensitive to the rewarding effect of alcohol, excessive alcohol drinking associated with high novelty seeking does not lead to the development of alcohol-use disorders

was first described in laboratory animals where consumption of sweet saccharin solution can be considered as the most accurate predictor of the voluntary alcohol consumption of any given animal. In humans, the relation between response to sweet taste and alcohol intake is more complex. While genetic risk of alcoholism estimated on the basis of family history of alcoholism was shown to be associated with hedonic response to sweet taste, sweet response by itself is not sufficient to predict the risk of alcohol-related problems. Such prediction can only be made using a combination of hedonic response to sweet taste that reflects activity of the brain reward system and novelty seeking – a personality trait that is consistently associated with deviance proneness and excessive drinking.

189.7 Application to Other Areas of Health and Disease

As discussed above, the pleasure associated with consumption of sweet-tasting foods is one of our fundamental pleasures. Stimulation of the sweet-taste receptors in the oral cavity leads to the release of β-endorphins in the brain that have an effect similar to those of opiate agonists, such as morphine, that cause analgesia as well as feelings of well-being, sedation, and "bliss." Individuals with hypofunction of the brain opiate system have a diminished ability to experience pleasure, including pleasure associated with eating sweets. That leads to the preference for stronger sweet taste (i.e., sweet liking), which may be considered to be a marker of the activity of the brain opiate system.

The link between hypofunction of the brain opiate system, diminished ability to experience pleasure, and perception of sweet taste may explain the positive association between distortions of the sweet taste and negative mood states such as depression and anxiety that has been noted in both clinical populations and healthy individuals. Considering that a mentioned dysfunction of the brain opiate system may at least partially be determined by genetic mechanisms (for review see Gianoulakis 2004), testing hedonic response to the sweet taste may be an important instrument for evaluation of genetic predisposition to these disorders although further investigations are needed.

Furthermore, individuals with the hypofunction of the brain opiate system and reward-deficiency syndrome are likely to seek substances and/or behaviors that will overcome this hypohedonic state by activating the brain reward system. The most natural choice in this situation is the one we all learned in infancy – when in distress, we need to eat something sweet. At first it was sweet mother's milk or sugar water that calmed the baby down. Later in life, a candy served the same purpose. Eating sweets leads to the instant release of β-endorphins in the brain that has an effect of the internal tranquilizer. As adults, women, who are more sensitive to the mood-altering effect of sweets (Kampov-Polevoy et al. 2006), are more likely to eat sweets to cope with negative emotions and stress, which may explain a higher prevalence of bulimia nervosa noted in women compared to men (Antczak and Brininger 2008). It should be also mentioned that women diagnosed with bulimia nervosa are likely to be sweet likers (Franko et al. 1994), which may indicate that sweet-liking status and the associated dysfunction of the brain opiate system may predispose women to this disorder.

On the other hand, men, who are less sensitive to the positive mood-altering effect of sweets, may choose alcohol to cope with negative emotional states. This behavior is more likely to be observed in sweet-liking men who are more sensitive to the rewarding effect of alcohol. Furthermore, combination of sweet liking, indicative of sensitivity to the positive emotional effect of alcohol, with high novelty seeking that facilitates drinking behavior and disregard of societal norms, produces high risk for developing alcohol-related problems and alcohol-use disorders.

A conceptual model that illustrates a link between hedonic response to sweet taste, affective disorders, alcohol-use disorders, and bulimia are presented in Fig. 189.5.
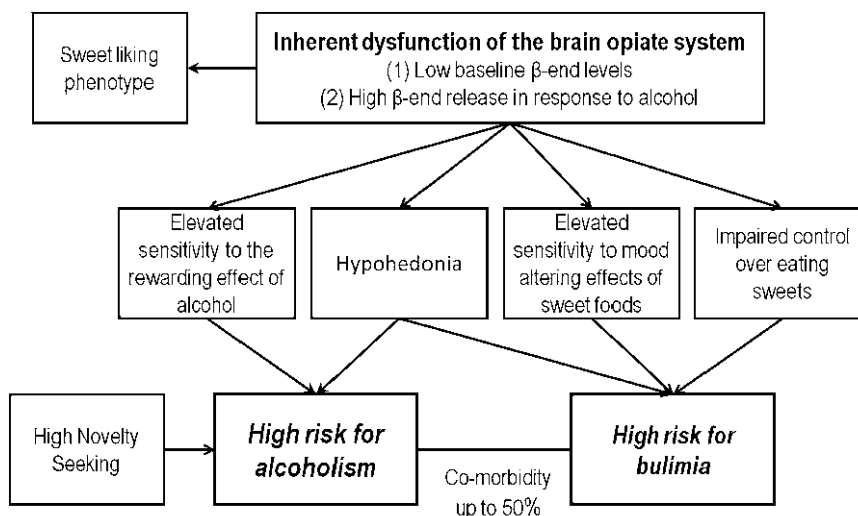
Fig. 189.5 The following diagram may help to conceptualize material presented in this chapter. The brain opioidergic pathways play an important role in mediation of hedonic responses to sweet taste. Inhibition of these pathways caused by either genetic factors (e.g., in children of alcoholics) or by opioid receptor blockers (e.g., naloxone) shifts the preference toward stronger sweet taste. Therefore, preference for stronger sweet taste (sweet liking) may be an indicator of the dysfunction of the brain opioidergic pathways. These pathways play an important role in functioning of the brain reward system and their inhibition may lead to diminished ability to experience pleasures and elevated sensitivity to rewarding effects of sweet-tasting foods and alcohol. As a result, sweet-liking individuals, both animals and humans, are prone to use and abuse sweet foods and alcohol to self-medicate their negative emotional state and to cope with emotional stress. Sweet-liking women seem to be more sensitive to mood-altering effects of sweet foods and use these foods for coping with negative affect. This elevated sensitivity in combination with impaired control over eating sweets may explain higher prevalence of bulimia nervosa in women compared to men. Sweet-liking men, who are less sensitive to the mood-altering effect of sweet-tasting foods, are more likely to use alcohol for self-medication of negative affect. High novelty seeking that facilitates frequent episodes of excessive drinking significantly increases the risk of alcohol-use disorders in sweet-liking men. The high comorbidity between alcohol-use disorders and bulimia nervosa also supports the hypothesis that these disorders may have similar mechanisms

Summary

- A pleasurable response to sweet taste is an innate reaction. The level of positive emotional response to sweet taste, as well as consumption of sweets, is influenced to a large degree by genetic factors.
- There are two major patterns of the hedonic response to sweet taste – sweet disliking and sweet liking.
- Oral sucrose administration produces positive emotional responses, alleviates negative mood states, and produces marked analgesia in both animals and humans, with women being more sensitive to these effects than men. Such effects are more likely to be associated with sweet taste than with chemical composition or caloric value of ingested food.
- Chronic consumption of sweet-tasting substances may lead to a condition similar to physical dependence to opiates with symptoms including elevated sugar consumption, increased tolerance to morphine, and signs of opiate withdrawal when access to sweets is discontinued.
- Sweet preference and craving for sweet-tasting foods positively correlates with severity of the negative mood states (e.g., anxiety, depression) in both healthy individuals and patients with clinical

depression. Consumption of sweets leads to alleviation of the negative mood states and can be used for self-medication.

- Hedonic response to sweet taste and the avidity to consume sweet-tasting foods are closely associated with the level of alcohol consumption in both animals and humans. In animal experiments, consumption of sweet saccharin solution can be considered as the most accurate predictor of the voluntary alcohol consumption of any given animal.
- In humans, the association between response to the sweet taste and alcohol intake is more complex than in animals. While the genetic risk of alcoholism estimated on the basis of family history of alcoholism was shown to be linked with hedonic response to sweet taste, sweet response by itself is not sufficient to predict the risk of alcohol-related problems. Such prediction can be made only using a combination of hedonic response to sweet taste that reflects activity of the brain reward system and novelty seeking – a personality trait that is consistently associated with excessive drinking.

It is important to keep in mind that:

- Sweet likers are more sensitive to mood-altering and analgesic effects of sweets than sweet dislikers.
- Women are more sensitive to these effects than men.
- Children are more sensitive to these effects than adults.

Terminology List

Sweet disliking: Describes a pattern of sweet preference that is characterized by continuous increase, with eventual leveling off in liking of progressively more concentrated sweet solutions.

Sweet liking: Describes a pattern of sweet preference that is characterized by preference to progressively higher concentrations of sucrose solution up to the middle range of concentration, followed by a breakpoint after which preference declines with increased concentration.

GABA: γ-Aminobutyric acid is the main inhibitory neurotransmitter in the mammalian central nervous system.

Polydipsia: Excessive or abnormal fluid consumption.

Hypohedonia: Diminished ability to experience pleasure.

References

Antczak AJ, Brininger TL. (2008) Eat Disord. 2008;16:363–377.
Avena NM, Rada P, Moise N, Hoebel BG. (2006) Neuroscience. 139:813–820.
Bachmanov AA, Reed DR, Tordoff MG, Price RA, Beauchamp GK. (1996) Behav Genet. 26:563–573.
Bacon A, Miles J, Schiffman SS. Physiol Behav. 1994;55:603–606.
Beauchamp GK, Moran M. (1982). Appetite. 3:139–152.
Belknap JK, Crabbe JC, Young ER. (1993) Psychopharmacology. 112:503–510.
Bhattachrjee M, Mathur R. (2005) J Physiol Pharmacol. 49:383–394.
Both-Orthman B, Rubinow DR, Hoban MC, Malley J, Grover GN. (1988) Am J Psychiatry. 145:628–631.
Bowen D, Grunberg N. (1990) Physiol Behav. 47:287–291.
Calcagnetti D, Reid L. (1983) Pharmacol Biochem Behav. 18:567–569.
Colantuoni CRP, McCarthy J, Patten C, Avena NM, Chadeayne A, Hoebel BG. (2002) Obes Res. 10:478–488.
Comings DE, Blum K. (2000) Prog Brain Res. 126:325–341. Review.
Christensen L, Pettijohn L. (2001) Appetite. 36:137–145.
Christensen L, Somers S. (1996) Int J Eat Disord. 20:105–109.

Dansky BS, Brewerton TD, Kilpatrick DG. (2000) Int J Eat Disord. 27:180–190.

De Graaf C, Zandstra EH. (1999) Physiol Behav. 67:513–520.

Desor JA, Beauchamp GK. (1987) Physiol Behav. 39:639–641.

DiChiara G, North RA. (1992) Trends Pharmacol Sci. 13:185–193.

Drewnowski A. (1997) Annu Rev Nutr. 17:237–253. Review.

Cabanac M, Duclaux R. (1970) Science. 1970;168:496–497.

Fernstrom MH, Krowinski RL, Kupfer DJ. (1987) Biol Psychiatry. 22:529–539.

Finn PR, Sharkansky EJ, Brands KM, Turcotte N. (2000) J Abnorm Psychol. 109:122–133.

Franko DL, Wolfe BE, Jimerson DC. (1994) Physiol Behav. 56:969–973

Gianoulakis C. (2004) Curr Top Med Chem. 4:39–50. Review.

Grucza RA, Robert Cloninger C, Bucholz KK, Constantino JN, Schuckit MI, Dick DM, Bierut LJ. (2006) Alcohol Clin Exp Res. 30:1176–1183.

Hajnal A, Smith GP, Norgren R. (2004) Am J Physiol Regul Integr Comp Physiol. 286:R31–37.

Kampov-Polevoy AB, Kasheffskaya OP, Sinclair JD. (1990) Alcohol. 1990;7:83–85.

Kampov-Polevoy AB, Overstreet DH, Rezvani AH, Janowsky DS. (1995) Pharmacol Biochem Behav. 57:791–795.

Kampov-Polevoy AB, Garbutt JC, Janowsky DS. (1999) Alcohol Alcohol. 34:386–95.

Kampov-Polevoy AB, Alterman A, et al. (2006) Eat Behav. 7:181–187.

Kampov-Polevoy AB, Eick C, Boland G, Khalitov E, Crews FT. (2004) Alcohol Clin Exp Res. 28:1291–1298.

Kampov-Polevoy AB, Garbutt JC, Janowsky DS (1998) Alcohol Clin Exp Res. 22:610–614.

Kampov-Polevoy AB, Garbutt JC, (2003a) Alcohol Clin Exp Res. 27:1743–1749.

Kampov-Polevoy AB, Ziedonis D, (2003b) Alcohol Clin Exp Res. 27:1929–1936.

Keskitalo K, Tuorila H, Spector TD, Cherkas LF, Knaapila A, Silventoinen K, Perola M. (2007) Am J Clin Nutr. 86:1663–1669.

Leibenluft E, Fiero PL, Bartko JJ, Moul DE, Rosenthal NE. (1993) Am J Psychiatry. 150:294–301.

Lemon CH, Brasser SM, Smith DV. (2004) J Neurophysiol. 92:536–544.

Leventhal L, Kirkham T, (1995) Brain Res. 685:205–210.

Liao J, Schultz P. (2003) Mamm Genome. 14:291–301.

Looy H, Callaghan S, Weingarten HP. (1992) Physiol Behav. 52:219–225.

Looy H, Weingarten H. (1991) Chem Senses. 16:123–130.

Looy H, Weingarten HP. (1992) Physiol Behav. 52:75–82.

Macht M, Mueller J. (2007) Appetite. 49:667–674.

Mennella JA, Pepino MY, Yourshow LM, Lehman SM (2008) Int Alcohol Clin Exp Res. 32:239A, Abstract 916.

Olds J, Milner P. (1954) J Comp Physiol Psychol. 47:419–427.

Overstreet DH, Halikas JA, Seredenin SB, Kampov-Polevoy AB, Viglinskaya IV, Kashevskaya O, Badishtov BA, Knapp DJ, Mormede P, Kiianmaa K, Li T.-K., Rezvani A. (1997) Alcohol Clin Exp Res. 21:840–8.

Pecina S, Berridge KC. (2005) J Neurosci. 25:11777–11786.

Pepino MY, Mennella JA. (2005) Chem Senses. 30 Suppl 1:i319–20.

Rada P, Avena NM, et al. (2005) Neuroscience. 134:737–744.

Rosenthal NE, Sack DA, (1984) Arch Gen Psychiatry. 41:72–80.

Sinclair JD, Kampov-Polevoy A, Stewart R, Li TK. (1992) Alcohol. 9:155–160.

Steiner J, Glaser D, Hawilo ME, Berridge KC. (2001) Neurosci Biobehav Rev. 25:53–74.

Thompson D, Moskowitz H, Campbell RG. (1976) J Appl Physiol. 41:77–83.

Wade GN, Zucker I. (1969). J Comp Physiol Psychol. 69:291–300.

Wurtman JJ. (1988) J Clin Psychiatry. 49 Suppl:37–39.

Wurtman RJ, O'Rourke D, Wurtman JJ. (1989) Ann N Y Acad Sci. 575:75–82; discussion 82–5.

Yamamoto T, Sako N. (2000) Physiol Behav. 69:345–350.

Chapter 190
Anxiety and Self Medication with Alcohol

Carmen C. Moran and Anthony J. Saliba

Abbreviations

GAD   Generalised anxiety disorder
PANAS   Positive affect negative affect schedule

190.1 Introduction

People drink alcohol for many reasons and in many contexts. The reasons for drinking can be categorised in several ways, including physiological and familial perspectives, and can be influenced by various factors, including social pressure and marketing of the product. Estimates of drinkers in the population are extremely variable, in one study alone ranging from 92% to 6%, but the variation included differences across countries, gender, and other sample characteristics (Gmel et al. 2006). The variability associated with estimates may be at least somewhat related to the difficulty in defining a 'drinker'; is someone who consumes a few glasses per year at social functions such as weddings to be included for instance? In many countries over half the population are drinkers, at least some of the time (Breslow and Graubard 2008; Gmel et al. 2006). In a US-wide study of over 20,000 drinkers, 26% of men and 20% of women admitted to drinking daily (Breslow and Graubard 2008).

Early research sought to establish a relationship between alcohol consumption and the reduction of negative emotions. However, not all drinking is problematic nor related to psychopathology. There is a vast literature on problem drinking, addiction, and the threats to well-being that overconsumption poses for the drinker and for others. Several journals are dedicated to this problem. This chapter does not review that literature; rather, this chapter examines the research on drinking motives, which focuses on nonclinical samples and reasons for drinking potentially independent of alcohol addiction or dependence. The presumption behind this approach is that 'drinking motives are the most proximate factor that precedes alcohol use' (Kuntsche et al. 2007, p. 76). Such information can, in turn, help inform health providers about circumstances when nonclinical aspects of alcohol consumption may or may not be problematic, such as moderate consumption to self-manage sub-clinical levels of anxiety.

A.J. Saliba (✉)
National Wine and Grape Industry Centre, Charles Sturt University,
Locked Bag 588, Wagga Wagga, NSW, 2678, Australia
e-mail: asaliba@csu.edu.au

190.2 Anxiety

One of the major factors that affects drinking motives is anxiety. While there is concern about giving too much emphasis to mood reduction as a prime reason for drinking (Hussong et al. 2008; Wilson et al. 1989), current research shows that anxiety level is an important influence when included with other variables in research on consumption. Table 190.1 presents the key features of anxiety and its relationship to drinking motives.

Anxiety has many lay and formal definitions. Even in the research literature it is not consistently defined or measured. In part this is due to the different ways people experience anxiety and in part due to the different words used to describe the feelings associated with anxiety. Various terms are used apparently interchangeably with anxiety, including some that are associated with specific disorders, such as 'phobia' and 'panic', with passing states, such as 'apprehensiveness' and 'fear', or with longer term emotional states such as 'angst'. In some cases anxiety is seen as part of a temperamental disposition, in others as a reaction to events. In the latter case, the term anxiety may be used in the same way as 'stress'.

Symptoms of anxiety vary across individuals, but there are some commonly reported ones: high levels of apprehension and worry, restlessness, muscle tension, and sometimes other physical symptoms such as accelerated heart rate and difficulty getting to sleep (Andrews et al. 2003; Menzies and Moran 1994). When symptoms become excessive, prolonged, and very distressing, they may result in a clinical diagnosis such as generalised anxiety disorder (GAD). When accompanied by specific beliefs, fears, or behavioural avoidance, then the conditions of agoraphobia or social phobia may be diagnosed. There are many other anxiety disorders with some overlap in symptomatology and diagnostic criteria (American Psychiatric Association 1994; Andrews and Slade 2002). The prevalence of anxiety and anxiety disorders is high, especially when compared with mood and behavioural disorders (e.g., see Fig. 190.1). Despite the variety of anxiety and related disorders, a common picture of anxiety is one of worry, tension, and internal physical discomfort, with an overarching negative emotional state.

The precise nature of anxiety is important in the study of motives for drinking. It is generally accepted that anxiety is accompanied by negative affect but unlike depressive states, anxiety is not associated with an absence of positive affect. Thus, an anxious person may have a range of emotions,

Table 190.1 Key features of anxiety

1. Anxiety is an unpleasant subjective *state*, which can also be related to a personality *trait*, that is, be part of an enduring characteristic of a person
2. Anxiety can be characterised by cognitive, emotional, physiological, and behavioural symptoms. People vary in the extent to which they experience anxiety in these domains
3. Anxiety is related to reactions associated with the fight-or-flight (and freeze) response. Current research examines anxiety reactions across numerous biopsychosocial systems
4. Anxiety is sometimes differentiated from fear, with fear having a more objective cause than anxiety. That is, fear is considered to be about a threat that most people would recognise. Anxiety is more subjective.
5. Estimates on the prevalence of anxiety is difficult, because people can use different terms to explain the feelings associated with anxiety, such as 'stressed', 'fearful', 'jittery'. Anxiety can also be passing. Surveys usually focus on the prevalence of anxiety disorders
6. Anxiety *disorders* are characterised by *very* high levels of anxiety, usually prolonged, and accompanied by varying physical and behavioural patterns depending on the disorder. For example, these patterns can include avoidance, compulsive repetitive behaviours, and hyperactivity, which in turn relate to disorders such as phobia, obsessive–compulsive disorder, and post-stress disorders
7. Survey estimates put the 12 month prevalence of anxiety *disorders* at 14% (Australian Bureau of Statistics 2008). This means that within a 1-year period, 14 people in 100 reported having anxiety disorder

This table lists the key features of anxiety, and the basic distinction between the feelings of being anxious and an anxiety disorder

Fig. 190.1 Prevalence of anxiety, affective, and substance use disorders in Australia. Prevalence data show the percentage of people affected by anxiety, affective (mood) and substance use disorders in a 12-month period. These data were collected as part of large nationwide survey on health (Data from Australian Bureau of Statistics 2008. With permission)
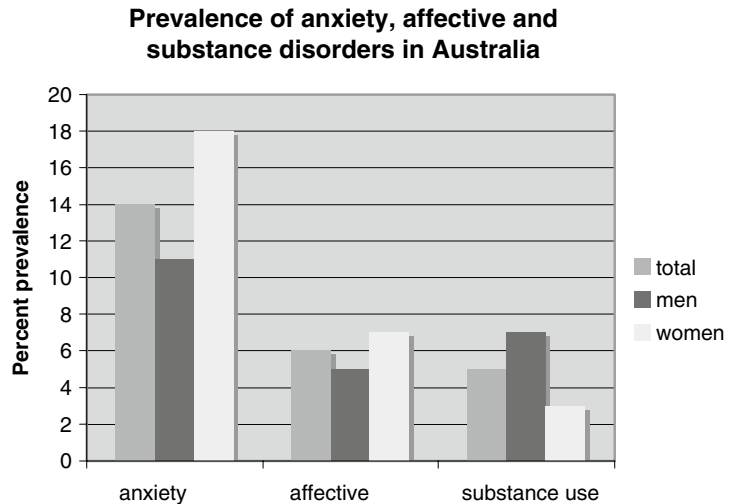
both positive and negative, and alcohol consumption may vary depending on the prevailing emotional state, that is, whether it is positive or negative. Consumption will also vary according to whether an individual has a tendency to use alcohol to cope. In recent times *individual differences in anxiety* and *using alcohol to cope* have been researched using one of two main frameworks: (a) the Self Medication Model and (b) the Drinking Motives Model. The Self-Medication Model focuses mainly on negative affective states, whereas the Drinking Motives Model considers the reasons for drinking in terms of both positive and negative effects.

190.3 Self-medication Model

The Self-medication model (also known as the Self-Medication Hypothesis) relates to the consumption of alcohol in order to deal with negative emotions that cannot be addressed in other ways or through other resources (Khantzian 2003). The Self-Medication Model overlaps somewhat with the Drinking Motives Model described below. However, research using the Self-Medication Model is more focused on clinical disorders and is less likely to look at positive emotions as a reason for drinking.

Individuals high in arousability have been shown to exhibit higher levels of anxiety (Hicks et al. 1992). Self medication with alcohol may be more frequent in those who are physiologically reactive under stress. Using 'normal' college students, Colder examined reasons for drinking, alcohol use, concurrent or recent stressors and physiological reactivity in an experimental context (Colder 2001). The coping motive (as a measure of self-medication) was related to stressful life events and to emotional reactivity measured physiologically through respiration bellows, electrocardiograph, and skin conductance. In this study, the coping motive was not related to trait[1] negative affect (measured with PANAS items such as 'scared' and 'distressed'). These results suggest that the construct *drinking to cope* is more likely to be associated with being physiologically sensitive to stress. It could be proposed that those whose physiological reactions are less elevated by stressful events are less likely to regard drinking as a way of coping with their reactions, and thus less likely to use alcohol for self-medication.

---

[1] According to trait theory in Psychology, traits are relatively stable over time and although differ amongst individuals, are not influenced by external factors nearly as much as are 'states'.

Much of the work on the Self-Medication Model looks at depression rather than anxiety. For example, Suh et al. (2008) report that the tendency to self medicate with alcohol was associated with lower depression scores. The low depression scores were not a consequence of drinking at the time of measurement. Because the low depression was also associated with high repression scores, Suh suggested that participants were denying their depression (i.e., they were repressing their depression). It is not clear from other aspects of the results whether this was in fact the case. Indeed, it is possible that the self-medication worked, at least in terms of the target symptoms.

Because self-medication research overlaps with that of the drinking motives research, further relevant research is discussed below under the motives model, and occasionally the terms coping motive and self-medication are used interchangeably.

190.4 The Drinking Motives Model

In the Drinking Motives Model three motives are frequently discussed: the enhancement motive, the social motive, and the coping motive (Cooper et al. 1992). Enhancement motives are measured by items such as 'because it [drinking alcohol] makes you feel good'. Social motives are measured by items such as 'it makes social gatherings more enjoyable'. Coping motives are measured by items such as 'to forget your worries'. A fourth motive, the conformity motive, is sometimes included.

The relationship between drinking motives and type of affect is summarised in Fig. 190.2. The underlying assumption is that people can drink to increase positive affect or drink to reduce negative affect. The focus of the motive may be internal or external. The internal–positive affect combination provides the *enhancement* motive, which is drinking to feel good about oneself. Increasing positive affect can also be external in focus, such as drinking to enjoy a party more, and this is the *social* motive. Decreasing negative affect can be internal in focus, and this is captured in the *coping* motive and the desire to be rid of anxiety and other negative feelings. Finally decreasing negative affect can be external in focus and this relates to the *conformity* motive and the desire to reduce isolation and rejection.

Benefit gained:

	Internally	Externally
Increase positive affect	*Enhancement motive*	*Social motive*
Decrease negative affect	*Coping motive*	*Conformity motive*

Direction of Change

Fig. 190.2 Representation of the Drinking Motives Model. The Drinking Motives Model as represented in this figure is adapted by the authors from Cooper's motives questionnaire (Cooper et al. ; Cooper 1994), which in turn has been examined in other research. This figure shows how the motives for drinking are differentially focussed on either increasing or decreasing negative affect (or feelings) and on gains that are internal or external

190.5 Drinking Motives and Consumption Patterns: Initial Results

In early research, each of the three main drinking motives was associated with alcohol consumption frequency, but in different ways. The coping motive was associated with more frequent drinking and potential abuse and dysfunction, whereas the enhancement motive was associated with frequent and heavy drinking but not alcohol abuse. The social motive was mainly associated with increased drinking in social situations (Cooper et al. 1992). In a later study on adolescent drinking and overuse, a conformity motive was added to the questionnaire to capture issues related to adolescent peer pressure to drink (Cooper 1994). The results resembled those of the 1992 study in that the coping motive was associated with high use and 'drinking problems', whereas the enhancement motive was associated with high frequency and quantity but not 'drinking problems'. The social and conformity motives were not strong predictors of quantity consumed or problem drinking, but subsequent research has examined social motives as they relate to social anxiety and extended information on this aspect of drinking. This research is discussed under the heading of social anxiety below.

190.6 Anxiety and the Coping Motive

The coping motive is especially relevant in the context of anxiety and can be defined as drinking to cope with emotional discomfort or distress, in other words to deal with anxiety. The coping motive is usually hypothesised to be the best predictor (within the motives model) of problem drinking. While taste is a strong motive for drinking alcohol, in data from our ongoing research we note that drinking to reduce anxiety is also very frequently reported as a reason for drinking, for different types of alcohol beverages (see Fig. 190.3). High anxiety on its own, however, is not a predictor of
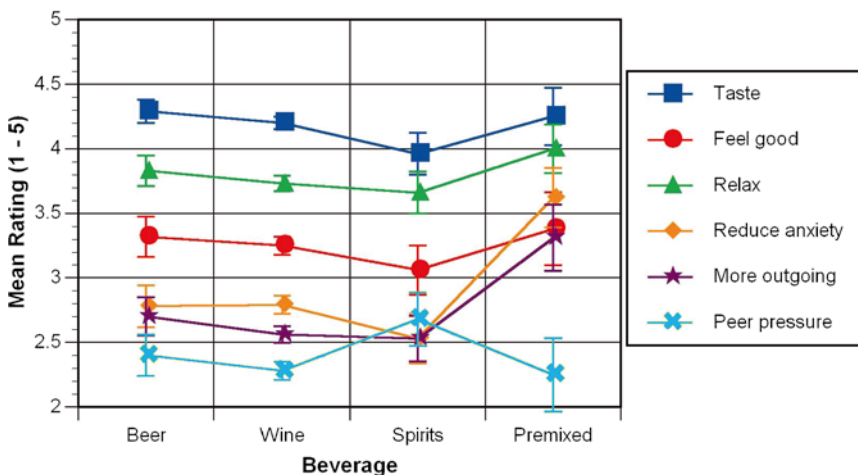
Fig. 190.3 Motives for drinking by type of beverage. In terms of the Drinking Motives Model discussed in this chapter, 'feeling good' parallels enhancement motive, 'more outgoing' parallels the social motive, 'reducing anxiety' parallels the coping motive, and 'peer pressure' parallels the conformity motive. In this data, 'taste' is the most strongly cited reason for drinking alcohol, but other motives are also salient, particularly the desire to relax, which could be related to the other motives, for example to the coping, enhancement and social motives. The patterns of motives are relatively consistent across different beverage types, except for the premixed drinks (Data are authors' own)

increased alcohol consumption. Research has shown that motives and drinking behaviours interact with type of mood or emotional state.

In order to evaluate this claim, it is necessary to differentiate between coping motives for alleviating depressed mood and those for alleviating anxious mood, rather than just looking at drinking 'to feel better'. Participants high on anxiety coping motives are more likely to drink when anxious, whereas those high on depression coping motives are more likely to drink when depressed (Grant et al. 2009). This pattern suggests that high anxiety alone is not responsible for increased alcohol consumption, but does predict an increase in consumption for those already with a tendency to drink to cope with anxiety. Thus, 'anxiety-drinkers' do not necessarily drink when depressed, but do when anxious. Other people high in anxiety do not drink to cope, and thus do not necessarily increase their drinking when anxious. In a similar vein, Martens et al. reported that individuals high in negative affect (measured on the PANAS, which includes items such as afraid, nervous) and coping drinking motives were at greater risk for alcohol-related problems (Martens et al. 2008)

Personality interacts with both anxiety and having a high coping motive. Individuals drinking because of a coping motive are also higher on measures of neuroticism and anxiety sensitivity (perceiving anxiety symptoms as highly aversive; Goldstein and Flett 2009). High generalised anxiety is more likely to be associated with the coping motive when mediated by a high expectation that alcohol reduces anxiety. These variables, high anxiety, coping motive, and high expectancy have been shown to combine to predict high consumption. Goldsmith and colleagues sampled undergraduate students, and those who formed a hazardous drinking subgroup that were more likely to have positive expectations about alcohol's beneficial effects on tension and worry (Goldsmith et al. 2009). The coping motive is defined as drinking in order to reduce anxiety; research supports the pattern that those high on coping motive are also likely to be higher on anxiety, perceive anxiety symptoms as more aversive, and be more likely to expect alcohol to relieve their anxiety.

190.7 Social Anxiety and the Coping Motive

Social anxiety tends to be related more to the coping motive than the social motive for drinking. Social anxiety refers to anxiety that occurs in social situations, usually where a person feels they are being evaluated. It can be related to specific situations, such as parties or public speaking, or it may be more generalised. It could be expected that the social motive would be especially relevant to this group. The general rubric of social anxiety is different to the personality trait of introversion (the two are sometimes considered one and the same); however, individuals with social anxiety are often higher in introversion (Janowsky et al. 2000). The current authors have several unpublished datasets that suggest a link between introversion and alcohol consumption, presumably driven by a coping motive – allowing them to overcome the anxiety associated with tasks they find difficult under normal circumstances yet are expected to do as part of modern-day life.

Drinking is also mediated by *self-image*, a construct which includes assessing one's self-worth according to others' approval (Moeller and Crocker 2009). Being highly concerned with self-image, however, also generates high levels of anxiety. Self-image factors may indirectly determine drinking levels when those who score high on self-image goals see high alcohol use as an *expected* behaviour within their peer group and their high anxiety about self image then makes them more likely to drink to reduce that anxiety. Self-image goals have been shown to be associated with both coping motives and with higher heavy episodic drinking in University undergraduates (Moeller and Crocker 2009). Moeller and Crocker did not measure social motives, as they were particularly interested in drinking to cope with anxiety.

The impact of others' opinions on one's behaviour does not always indicate problems of self-image or anxiety, as other people sometimes provide useful information about social norms (the descriptive social norm, as distinct from the injunctive social norm). Lee and colleagues found that when combined with a high social motive for drinking, friends' approval (the injunctive norm) could lead to risky drinking in social situations (Lee et al. 2007). They did not measure anxiety and its relationship to need for approval.

Social anxiety is an inconsistent predictor of drinking in the absence of other mediating variables and has been related to both increased and decreased consumption (Ham and Hope 2005; Ham et al. 2005). Lewis et al. (2008) offer a complex mediation model that suggests this may be the case because social anxiety is not directly related to alcohol problems, except when socially anxious subjects are also high on the coping or conformity motives. High socially anxious subjects have been shown to have both higher consumption in social situations and greater expectancies that the alcohol will reduce their social anxiety (Tran et al. 2004). On the other hand, socially anxious subjects did not differ from others when drinking in positive affect situations (Tran et al. 2004). Social anxiety, therefore, relates more strongly to the coping motive, that is, reducing anxiety, than to the social motive which is more about increasing enjoyment.

Nevertheless, social motives have been reported as more relevant predictors of alcohol misuse than coping motives in some social contexts, for example in a sample of younger adolescents aged 13–16 (Bradiza et al. 1999). Misuse in this context was assessed by a mix of frequency and amount consumed, which is suggestive of frequent binge drinking. Frequent binge drinking, although intermittent and thus 'passing', can be associated with other behaviours that have more enduring negative consequences (e.g., as a result of inappropriate sexual activity and drink-driving).

Some researchers combine motives, for example, the desire to feel good in social situations is interpreted as a coping motive as well as a social motive. Some questionnaires may specifically address this, such as *The Alcohol Expectancies for Social Evaluative Situations Scale* (Bruch 1992), which measures coping motives in terms of social motives. Socially anxious people have an attentional bias to social threat that may prompt increased consumption to cope with that threat. That is, self-medication with alcohol may be also prompted by perceptual factors in social contexts (Carrigan et al. 2004). Generalising this to the treatment of problem drinking, therapists need to consider not just social anxiety levels but perceptual factors operating in social contexts.

190.8 In Vivo Research

Most of the work on drinking motives is done in the context of the three or four motives proposed by Cooper and relies on survey methodologies. As an alternative to the survey method, Swendsen and colleagues asked participants to respond to questions generated on a handheld computer three times a day across 30 days (Swendsen et al. 2000). The questions assessed current mood: active, peppy, happy, relaxed, quiet, bored, sad, or nervous. The participants also entered information on their drinking either as they drank or just prior to drinking. Information from the Beck Depression Inventory, State-Trait Anxiety Inventory and demographic questions were also collected. Although the study was framed in terms of the Self-Medication Model, the results resemble those framed in the coping model framework because they addressed interactions between positive and negative affective states and drinking. Nervousness was the only negative state to be associated with increased alcohol consumption. Being happy was associated with increased alcohol consumption as well, which supports the drinking model's assumption that drinking is not always motivated by a need to manage negative affect.

Swendsen's study suggests using alcohol to cope worked because it was associated with a subsequent reduction in anxiety. As already noted in other research, in this study the effect was more marked for those higher in anxiety than depression: People high on anxiety were more 'rewarded' by drinking than those high on depression. People seem to be well aware of this differential effect themselves and are more likely to drink to cope when anxious but not when depressed (Hussong et al. 2005). Whether such rewards are beneficial or harmful to the individual over time will depend on other factors including the presence of specific anxiety disorders and comorbidity factors (Robinson et al. 2009). The physiological and behavioural consequences of alcohol consumption are also important considerations.

190.9 Measurement of Alcohol Intake

Within research using the survey method, consumption is most often measured in terms of self-reported frequency, such as number of days per month, and quantity, such as number of drinks in a sitting. The amount of alcohol is not always clearly specified in terms of standard measures of alcohol or 'standard drinks'. Survey participants often estimate the amount in terms of number of drinks. Consumption may be reported as separate constructs of frequency, quantity, and problem-related drinking behaviours, but treated as a global measure such as 'increased consumption' or 'problem drinking'. Self-reported drinking may be influenced by socially desirable response patterns; these can be powerful enough in some individuals to cause an underestimation of consumption by as much as 33% (Davis et al. 2010). It is not possible to make a simple linear adjustment to responses since individual differences impact on response bias in a complex way.

Differences in patterns of drinking may be more informative than individual analyses on frequency, quantity and problems. For example, low frequency but high consumption is indicative of binge drinking, which may then be associated with problems as a result of drinking. O'Connor and Colder (2005) demonstrated five classifications of alcohol usage patterns in a sample of college students, which they then differentially related to the personality variables 'sensitivity to reward' and 'sensitivity to punishment'. Sensitivity to reward was a significant predictor of the usage patterns of binge drinking and problem drinking. Behavioural problems were more associated with binge drinking for female subjects. That is, if they engaged in binge drinking they were more likely to have subsequent problems, which include social consequences. Relating the personality variables to the Drinking Motives Model, O'Connor and Colder found that sensitivity to reward was significantly correlated with all drinking motives, whereas sensitivity to punishment was more strongly correlated to the coping motive and the conformity motive. Thus sensitivity to reward was associated with binge and problematic drinking, and furthermore, the relationship was mediated by the coping, social and enhancement motives for drinking but not the conformity motive. This study suggests that consumption is related more to a desire to feel better in oneself, rather than appear better to others.

190.10 Anxiety Disorders and Alcohol Consumption

The relationship between alcohol use and anxiety is bi-directional: people drink when anxious (self-medication, high coping motive) but drinking can lead to higher anxiety and in some cases generalised anxiety or panic disorder (Brady et al. 2007). With other anxiety disorders, especially social phobia and agoraphobia, the symptoms cause the person to self-medicate with alcohol which may or may not prove problematic over time (Brady et al. 2007; Kushner et al. 1990; Page and Andrews

1996). Alcohol increases anxiety in some disorders, but decreases it in others. In cases where there is one broad diagnosis such as agoraphobia, self-medication for anxiety levels may depend on other comorbidity factors such as panic attacks. As Brady and colleagues point out, unravelling the relationship is complicated by co-existing diagnoses and alcohol reactions (Brady et al. 2007). From a health perspective, the individual's anxiety as well as any problematic drinking would need to be addressed in terms of bi-directional effects. The literature shows a long history of self-medication with alcohol (thus supporting the relevance of the coping motive) although other terms were used in the very early literature. Conger (1956) for example, who highlighted the impact of the anxiolytic properties of alcohol, framed alcohol use in the context of learning theory rather than a motives model.

The moderate consumption of alcohol to control subclinical levels of anxiety *may* be an acceptable practice (though further research is required). What is clearer is that alcohol consumption to control *clinical* levels of anxiety that remain otherwise untreated is unwise.

190.11 Gender Differences

Gender is a potentially important individual difference in coping with alcohol because of the way alcohol is differentially used and metabolised by males and females. However, it is not possible to provide a consistent picture of gender differences in the context of drinking motives. Whereas there are some known patterns of gender differences in alcohol consumption, for example, males drink more, on average (Gmel et al. 2006), the results as they relate to anxiety, self-medication, and the coping motive are not clear. In specific anxiety disorders, such as agoraphobia or social phobia, there is a long-held clinical impression that males are more likely to self-medicate with alcohol (Moran and Andrews 1985). On the other hand, women report higher levels of arousability and are more likely to present with anxiety disorders (Saliba et al. 1998).

Whereas there is a demonstrated relationship between high alcohol consumption and anxiety reduction for males, alcohol may increase anxiety in women in social contexts (Wilson et al. 1989). However, when Wilson and colleagues tested a female sample they found alcohol elevated mood, but the effect was found in the placebo group as well suggesting a strong expectancy effect operating in their study. They did not report on alcohol use outside the laboratory setting other than to state that preexisting expectations about alcohol were not related to their results (Wilson et al. 1989). In our dataset ($N = 1,229$) we have found some small but statistically significant gender differences. This information is presented in Table 190.2, which shows that men score higher on items related to social and enhancement motives. Of special relevance to this chapter, we found no significant gender differences for drinking to cope with anxiety.

Men utilise health services much less frequently than women, are less likely to arrange regular check-ups and are also less likely to have symptoms checked for fear of wasting the health professional's time (Australian Institute for Health and Welfare 2001; O'Brien et al. 2005). Unsurprisingly therefore, the incidence of a range of diseases is higher in males than females (Saliba 2008). Although speculative, it may be that males are more in need of self-medication practices due to an unwillingness to seek help.

Using an adolescent sample, Hussong and colleagues were unable to find any consistent patterns of self-medication with alcohol and variables such as mood and conduct problems, and decided that the gender differences did not deserve further examination in their results (Hussong et al. 2008). This seems to be the pattern in several studies, where the differences are not sufficiently consistent, if they exist at all, to be able to draw broad conclusions. A whole of modelling approach, where multivariate analyses incorporates the influence of age, situation, personality, arousability and other variables, as well as gender, is required to determine the influence of gender on self-medication with alcohol.

Table 190.2 Motives for drinking alcohol by gender

| Motives[a] | Means (s.e.m.)[b] | | p |
	Female	Male	
Enhancement (makes me feel good)	3.19 (.048)	3.34 (.056)	.036
Social (makes me more outgoing)	2.49 (.046)	2.69 (.055)	.004
Coping (reduces my level of anxiety)	2.83 (.049)	2.80 (.056)	.681
Conformity (most of my friends drink it)	2.36 (.051)	2.47 (.059)	.129

[a]Motives are based on 'reasons for drinking' rather than the Cooper (1992) scale referred to in text

[b]Standard error of the mean

Gender differences are inconsistent in the literature on drinking motives. In our large Australian sample ($N = 1,229$) men scored significantly higher on a five-point scale for social and enhancement motives than women (albeit with small differences) but there were no significant gender differences for drinking to cope with anxiety or conforming to friends' behaviour (Data are the authors' own)

In the motives and self-medication literature, therefore, there is no *consistent* evidence that males are more likely to score higher on self-medication or on the coping motive, or show a differential relationship between motive and consumption when compared with females. This lack of consistent gender difference may relate to the age group of several samples, the nonclinical nature of the samples used, or changes to gender differences in drinking behaviours in recent years.

190.12 Other Factors Related to Anxiety, Motives and Self-medication

One of the major limitations in the motives and self-medication literature is the reliance on either student or clinical samples. While the importance of problem drinking in these groups is unequivocal, there is also a need for information on the everyday drinker who is older and not presenting at clinics, and the extent to which drinking to alleviate 'everyday' anxiety poses a health risk. In addition, there is little or no emphasis on the type of beverage consumed. For example, there is no information in this body of research on motives for drinking wine and whether the effects differ from those for drinking spirits. Our currently unpublished data suggest there are differences across beverages, particularly with consumers of mixed drinks (see Fig. 190.3). In light of this and recent research demonstrating a health benefit for wine, over and above alcohol (Lindberg and Ezra 2008), it would seem to be important to examine motives for drinking across individual beverages.

The recent media discussion on the putative health benefits of wine has added to the list of possible motives for drinking that are not covered in the 'Drinking Motives Model'. The literature is sparse on information about how many people believe wine is healthy. Figure 190.4 offers some data in this regard, showing that approximately 26% believe wine to be healthy, with the remainder undecided or disagreeing. Saliba and Moran (2010) found that those who perceive wine as healthy consume more frequently in terms of daily patterns, without consuming more volume of wine across time (see Fig. 190.5). There is also some initial evidence in this data to support the idea that those who drink wine to reduce anxiety are also more likely to believe it is healthy for them ($r = .237, p < .0001$).

Fig. 190.4 Percentage of people who consider wine to be healthy. Over 26% of a large Australian telephone survey (*N* = 1229) agree or strongly agree that wine is healthy A large proportion did not agree. The question did not ask whether wine was unhealthy, so disagreement does not indicate a belief that wine is specifically unhealthy (Data are authors' own)
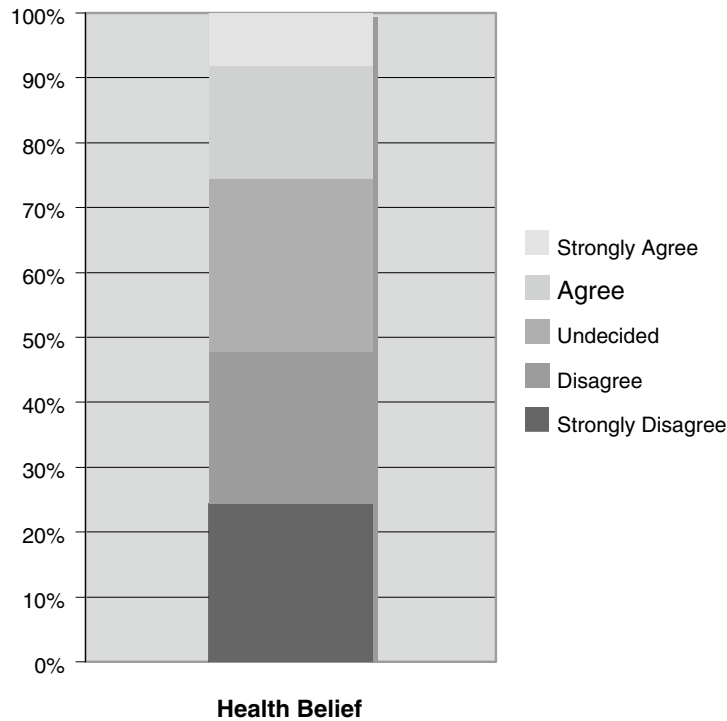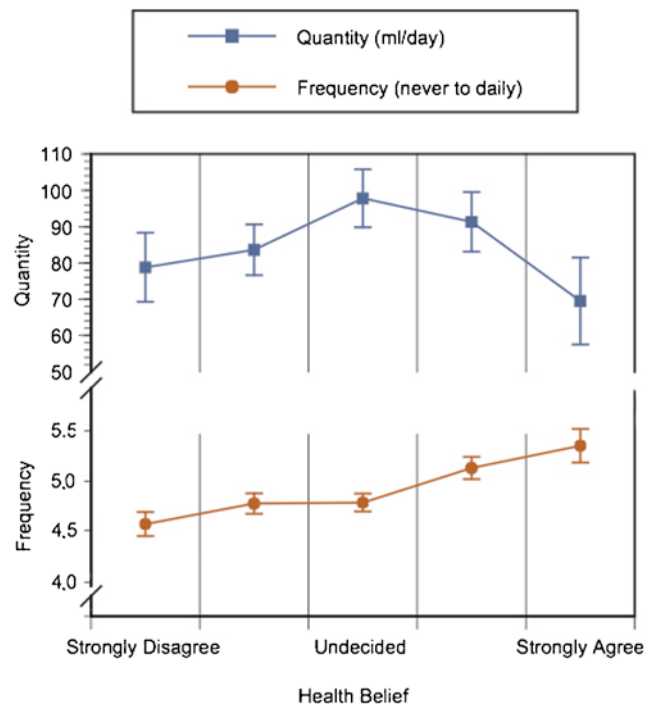

Fig. 190.5 Frequency and Volume of Consumption by level of belief that wine is healthy. This figure shows that those who strongly agree that wine is healthy drink more frequently (*bottom line*) but tend to drink the same or less overall (*top line*). Thus a belief that wine is healthy does not appear to predispose to overuse (Data are authors' own)

This effect is more evident in older adults. In light of the widespread information about the putative health affordance of wine, it is timely to extend the research on drinking motives to include other information on beliefs and motives for drinking specific types of alcohol.

190.13 Applications to Other Areas of Health and Disease

In Western counties, large percentages of people drink alcohol at least some of the time and anxiety reduction can be a proximal motive for drinking. For the health provider, the challenge is to determine when this is problematic. The coping motive framework helps predict when well-being or health is threatened rather than enhanced, but a multivariate approach is needed, for example incorporating personality and situational variables. Research suggests that the coping motive is likely to be associated with higher consumption and potential problematic drinking, in high anxious individuals. The social motive is more likely to be associated with binge-drinking, which may be age related, but there are no clear predictions for longer term problems due to drinking per se, although there can be major negative consequences as a result of alcohol-induced risk behaviours. The enhancement motive has been shown to have inconsistent relationships with level of alcohol use. These patterns can vary depending on samples. In most cases, current work is based on adolescent or young college students.

The motives model has application to other areas of consumption and well-being. It provides a useful pathway to consider the broader set of variables that impinge on consumption and over-consumption of food, alcohol, and other drugs. The motives model is now being applied to marijuana use (Lee et al. 2009; Zvolensky et al. 2009). There is a clear need to reduce smoking, and psychological therapies examine patients' motives for smoking across a broad biopsychosocial perspective (Lujic et al. 2005). Using the motives framework can provide additional information on reasons for smoking, without being in competition with well-established theoretical perspectives (Piko et al. 2007). However, as the motives model suggests, behaviour is not driven only by a desire to reduce negative affect, whether anxiety or depression, but is also driven by a desire to increase positive affect. Personality traits and situational factors influence the import of particular motives. As a result, health and disease behaviours can be driven by motives as outlined in the motives model above, but a multivariate approach will be most fruitful in understating the drivers of healthy and unhealthy behaviours.

Summary Points

- Large proportions of people drink alcohol and some drink often. Not all alcohol consumption is problematic. A broad base of information on motives for drinking contributes to the differentiation between problem and nonproblem drinking.
- Anxiety is a commonly cited reason for drinking, with an underlying assumption that alcohol will help alleviate anxiety symptoms.
- The relationship between anxiety and alcohol consumption can be researched using either the Self-Medication Model or the Drinking Motives Model. The Self-Medication Model focuses mainly on negative affective states, whereas the Drinking Motives Model considers the reasons for drinking in terms of both positive and negative affect.
- The Self-Medication Model treats consumption of alcohol as a means to deal with negative emotions that cannot be addressed in other ways or through other resources (Khantzian 2003).

- In the Drinking Motives Model three to four motives are frequently discussed: the enhancement motive, the social motive, the coping motive and the conformity motive (Cooper et al. 1992; Cooper 1994). The enhancement motive is measured by items such as 'because it [drinking alcohol] makes you feel good'. The social motive is measured by items such as 'it makes social gatherings more enjoyable'. The coping motive is measured by items such as 'to forget your worries'. The conformity motive is measured by a desire to fit in with others expectations.
- The coping motive is the best predictor (within the motives model) of problem drinking. Research suggests that the coping motive is likely to be associated with higher consumption and potential problematic drinking, in high anxious individuals. High anxiety on its own, however, is not a predictor of increased alcohol consumption. Motives and drinking behaviours interact with type of mood or emotional state, as well as expectations about the effects of alcohol.
- Social anxiety refers to anxiety that occurs in social situations, usually where a person feels they are being evaluated. Social anxiety is associated with an increase in the coping motive rather than the social motive for drinking.
- The social motive is more likely to be situationally determined and associated with binge drinking, which may be age related. The enhancement motive has been shown to have inconsistent relationships with level of alcohol use. The conformity motive is not a strong predictor in general circumstances. These patterns can vary depending on samples.
- The relationship between alcohol use and anxiety is bi-directional: people drink when anxious (self-medication, high coping motive) but drinking can lead to higher anxiety and in some cases can be associated with the onset of an anxiety disorder.
- Clinical interventions for problem drinking cannot target anxiety alone because the state itself does not predict problem drinking; rather incorporating a motives model with knowledge of anxiety level provides a better predictor.
- The recent media discussion on the putative health benefits of wine has added to the list of possible motives for drinking that are not covered in the Drinking Motives Model. Other motives may also be relevant to drinking behaviours.
- The motives model has application to other areas of consumption and well-being. It provides a useful pathway to consider the broader set of variables that impinge on consumption and overconsumption of food, alcohol and drugs.

Definitions and Explanations of Key Terms

Anxiety: A state characterised by high levels of apprehension and worry, restlessness, muscle tension, and sometimes other physical symptoms such as accelerated heart rate and difficulty getting to sleep. When it becomes chronic or is associated with extreme distress or behavioural problems it becomes an anxiety disorder.

Social anxiety: Anxiety that occurs in social situations, usually where a person feels they are being evaluated.

Positive affect: A pleasant emotional state or feeling, characterised by positive labels such as happiness, calm, or a sense of well-being.

Negative affect: An unpleasant emotional state or feeling, characterised by negative labels such as anxiety, depression, or distress.

Self-medication: Ingestion of substances based on experience rather than formal professional advice, in order to achieve a beneficial effect, usually a change in sense of well-being.

The Drinking Motives Model: Model to explain drinking based on special goals related to management of positive and negative affect.

References

American Psychiatric Association. Diagnostic and statistical manual of mental health disorders. 4th ed. Washington: APA; 1994.

Andrews G, Slade T. Psychopathology. 2002;35:100–6.

Andrews JG, Creamer M, Crino R, Hunt C, Lampe L, Page A. The treatment of anxiety disorders. 2nd ed. New York: Cambridge University Press; 2003.

Australian Bureau of Statistics (ABS). National survey of mental health and wellbeing: summary of results, 2007 (cat. no. 4326.0). Canberra: ABS; 2008.

Australian Institute for Health and Welfare. Australian health trends 2001. Canberra Australia: Australian Institute of Health and Welfare; 2001.

Bradiza CM, Reifman A, Barnes GM. J Stud Alcohol. 1999;60:491–9.

Brady KT, Tolliver BK, Verduin ML. Am J Psychiat. 2007;164:217–21.

Breslow RA, Graubard BI. Alcohol Clin Exp Res. 2008;32:513–21.

Bruch M. J Res Pers. 1992;26:137–49.

Carrigan MH, Drobes DJ, Randall CL. Psychol Addict Behav. 2004;18:374–80.

Colder CR. Psych Addict Behav. 2001;15:237–45.

Conger JJ. QJ Stud Alcohol. 1956;17:296–305.

Cooper ML, Russell M, Skinner JB, Windle M. Psychol Assessment. 1992;4:123–32.

Cooper ML. Psychol Assessment. 1994;6:117–28.

Davis CG, Thake J, Vilhena N. Addict Behav. 2010;35:302–11.

Gmel G, Graham K, Kuendig H, Kuntsche S. Addiction. 2006;101:16–30.

Goldsmith AA, Tran GQ, Smith JP, Howe SR. Addict Behav. 2009;34:505–13.

Goldstein AL, Flett GL. Behav Modif. 2009;33:182–98.

Grant VV, Stewart SH, Mohr CD. Psych Addict Behav. 2009;23:226–37.

Ham LS, Hope DA. Addict Behav. 2005;30:127–50.

Ham LS, Carrigan MH, Moak DH, Randall CL. J Psychopathol Behav. 2005;27:115–21.

Hicks RA, Conti PA, Nellis T. Percept Motor Skill. 1992;74:659–62.

Hussong AM, Gould LF, Hersh MA. J Stud Alcohol Drugs. 2008;69:296–307.

Hussong AM, Galloway CA, Feagans LA. J Stud Alcohol. 2005;66:344–53.

Janowsky DS, Morter S, Tancer M. Depress Anxiety. 2000;11:121–5.

Khantzian EJ. Prim Psychiat. 2003;10:47–54.

Kuntsche E, Knibbe R, Engels, R, Gmel G. J Stud Alcohol Drugs. 2007;68:76–85.

Kushner MG, Sher KJ, Beitman BD. Am J Psychiat. 1990;147:685–95.

Lee CM, Geisner IM, Lewis MA, Neighbors C, Larimer ME. J Stud Alcohol Drugs. 2007;68:714–21.

Lee CM, Neighbors C, Hendershot CS, Grossbard JR. J Stud Alcohol Drugs. 2009;70:279–87.

Lewis MA, Hove C, Whiteside U, Lee CM, Kirkeby BS, Oster-Aaland L, Neighbors C, Larimer ME. Psych Addict Behav. 2008;22:58–67.

Lindberg ML, Ezra AA. Clin Cardiol. 2008;31:347–51.

Lujic C, Reuter M, Netter P. Eur Psychol. 2005;10:1–24.

Martens MP, Neighbors C, Lewis MA, Lee CM, Oster-Aaland L, Larimr ME. J Stud Alcohol Drugs. 2008;69:412–9.

Menzies RG, Moran CC. The nature and treatment of anxiety. Sydney: Anxiety Disorders Clinic University of Sydney; 1994.

Moeller S, Crocker C. Psych Addict Behav. 2009;23:334–40.

Moran CC, Andrews G. Brit J Psychiat. 1985;146:262–7.

O'Brien RK, Hunt K, Hart G. Soc Sci Med. 2005;61:503–16.

O'Connor RM, Colder CR. Psych Addict Behav. 2005;19:10–20.

Page AC, Andrews G. Aust NZ J Psychiat. 1996;30:410–4.

Piko BF, Wills TA, Walker C. Addict Behav. 2007;32:2087–98.

Robinson J, Jitender S, Cox BJ, Bolton J. J Anxiety Disord. 2009;23:38–45.

Saliba AJ (2008). Impact of rurality on optical health: review of the literature and relevant Australian Bureau of Statistics data. Rural and Remote Health, 8 (online), 1056. http://www.rrh.org.au

Saliba AJ, Henderson RD, Deane FP, Mahar D. J Gen Psychol. 1998;125:263–9.

Saliba AJ, Moran CC. Food Quality and Preference. 2010;21(7):692–96.

Suh JJ, Ruffins S, Robins EC, Albanese MJ, Khantzian EJ. Psychoanal Psychol. 2008;25:518–32.

Swendsen JD, Tennen H, Carney MA, Affleck G, Willard A, Hromi A. J Abnorm Psychol. 2000;109:198–204.

Tran GQ, Anthenelli RM, Smith JP, Corcoran KJ, Rofey DL. J Stud Alcohol. 2004;65:715–24.

Wilson GT, Brick J, Adler J, Cocco K, Breslin C. J Stud Alcohol. 1989;50:226–35.

Zvolensky MJ, Marshall EC, Johnson K, Hogan J. Exp Clin. 2009;17:31–42.

Part XXXIII
Quality of Life

Chapter 191
Developmental Aspects of Health Related Quality of Life (HRQL) in Food Related Chronic Disease: The Example of Food Allergy

Audrey DunnGalvin and Jonathan O'B. Hourihane

Abbreviations

HRQL	Health Related Quality of Life
FAQLQ	Food Allergy Quality of Life Questionnaire
PF	Parent Form
FAIM	Food Allergy Independent Measure
OIT	Oral Immunotherapy

191.1 Introduction

In recent decades our understanding of human health has changed. In the 1970s, older biomedical definitions of health, based on 'an absence of disease', were justly criticized as reductionist and limited in scope and clinical researchers began defining health as a dynamic, multifactor, biopsychosocial phenomenon that influences physical, psychological and social functioning (Engle 1977). Recognition of the importance of these influences on health and disease is consistent with evolving conceptions of mind and body and represents a significant change in medicine and the life sciences. Recent developments include the idea that emotional processes such as stress moderate activity in nearly all systems of the body and can directly influence the pathophysiology of disease. Discovery of these and other relationships between behaviour and health has changed the way health and disease are understood. The biopsychosocial perspective has also changed how health and disease are measured. It is now recognised that it is essential to include outcome measures that reflect the patient perspective for evidence-based decision making in clinical practice. Outcomes research has been key in altering the culture of clinical practice and health care research by changing how we assess the end results of health-care services, including clinical and therapeutic interventions, evaluation and health policy. Further, the promotion of evidence-based practice has increased the demand for outcome data. Health related quality of life measures provide a powerful means of measuring outcomes, enabling service providers in the clinical field to audit 'outcome' information for particular populations, thereby altering and improving resources and programmes, and prioritizing needs.

A. DunnGalvin (✉)
Clinical Investigations Unit, Department of Paediatrics and Child Health, Cork University Hospital, University College Cork (UCC), Wilton, Cork, Ireland
e-mail: a.dunngalvin@ucc.ie

Health Related Quality of Life (HRQL) is a multidimensional construct, which evaluates physical, psychological and social components that may be impacted by a disease or medical condition, from the patient perspective. There are two major types of HRQL instruments, generic and disease-specific. Generic HRQL instruments are not specific to any particular disease and are therefore useful for comparing HRQL across different conditions, whereas disease-specific questionnaires focus on issues pertinent to one disease. However, generic instruments are necessarily more 'general' and therefore less sensitive to the particular problems associated with a particular condition. Disease-specific HRQL questionnaires which provide an in-depth picture of the day to day concerns of patients are an increasingly important outcome measure particularly in the context of chronic diseases. They are also able to capture small changes in HRQL that may occur as a result of clinical or therapeutic treatment.

However, there are important questions that must be answered before HRQL measures can reach their full potential in research, practice and policy. These questions include: what are the correlates of HRQL (e.g. anxiety, compliance, risk perception, coping behaviours) and how may they impact on perception of health and health reporting? Which variables are causally related to HRQL status, and which variables are the effects of HRQL status?

Since HRQL depends on the subjective perception of a disease, what are the underlying neurobiological mechanisms, and are these unidirectional or bidirectional?

Such questions have relevance for the interpretation and usefulness of HRQL measures in clinical practice (e.g. treatment choices for certain patient groups and individual patients), health policy (e.g. the allocation of health-care funds), the development of psycho-educational interventions (the precise targeting of information) and research (the causal direction of factors related to HRQL). We know that physiological measures often correlate poorly with functional capacity and well-being (Guyatt 1985) and patients with the same clinical criteria often have dramatically different responses, which depend on the subjective perception of disease impact. Such perception may be impacted by gender, for example, resulting in different health-reporting rates between sexes (DunnGalvin et al. 2006, 2008).

Some researchers in the field have attempted to develop causal pathway models to explain the direction of factors related to health related quality of life. Wilson and Cleary (1995) proposed that there is an unidirectional relationship between several kinds of outcomes, for example, biological and physiologic phenomena give rise to symptoms (and treatment side effects), which in turn have effects on functioning domains (such as physical, social and role functioning). The constellation of these effects leads to general health perceptions and, ultimately, an individual's concept of his/her overall HRQL. All of the above are also influenced by innate characteristics and environmental factors. Ferrans et al. (2005) modified the Wilson and Cleary model to make it simpler and have added more complete explanations for the components of the model. Sousa and Kwok (2005) used structural equation modelling to examine the relationship between the components of the original model. They conclude that the model fits the data (derived from patients with HIV) reasonably well but suggested that links be added between symptoms and general health perceptions and symptoms and HRQOL. The correlations for these links, however, were modest to low.

The previous models briefly allude to the possibility that the flow of the model may not be strictly unidirectional but do not provide data on this important consideration. If the flow is bidirectional for some of the components, this has profound implications in terms of interpretation and application of HRQL results. Furthermore the models have been developed from adult patients, and developmental considerations have not been taken into account (DunnGalvin et al. 2009a–d).

The evolution of the biopsychosocial perspective on health and health related quality of life has also coincided with a growing recognition of the multidimensionality and complexity of causation, including how environmental, social, psychological and biological systems interact to influence

health and developmental outcomes. Thelen and Smith (1994:127) suggest that 'the boundaries between what is innate and what is acquired become so blurred as to be at the very least uninteresting compared to the powerful questions of developmental process'.

A developmental trajectory or pathway may be understood as a lifelong process of developmental integration that involves complex interactions between biological and environmental factors that influence the phenotypic expression of physiology, psychology and behaviour (Halfon and Hochstein 2002). They may also delineate critical or sensitive transition points in development when physiological or environmental variables associated with a particular disease may have a relatively greater impact and/or interact with already existing normative demands and changes in socialization (Halfon and Hochstein 2002). Because children are rapidly changing and developing in response to these biopsychosocial influences, the developmental process plays an important role in shaping and determining their health and health related quality of life.

Research on the perception of health related quality of life – and its impact in terms of behaviour – may be particularly relevant in the context of chronic disease in childhood, as children not only have to meet their age-related developmental tasks, but they also have to manage their disease, which leads to a heightened risk of maladaptation (DunnGalvin et al. 2009a–d). A chronic condition may affect and/or interact with already existing normative demands and changes in socialization (Schmidt. 2003). Thus, although most children follow normative developmental pathways and encounter predictable transition points, disease-specific pathways may be embedded within these trajectories and influence the phenotypic expression of physiology, psychology and behaviour (Halfon and Hochstein 2002). Adaptational processes of children and adolescents with chronic conditions are of utmost importance because of their long-term consequences. Children with any chronic condition have twice the risk of developing mental health disorders of healthy children, even without an accompanying physical disability (Schmidt 2003).

In this chapter we review literature on the impact of food allergy on HRQL of children, teens and their parents. Biological hypersensitivity to environmental stimuli is a central feature of food allergy entailing a need for constant vigilance about, and avoidance of, certain foods (Table 191.1).

We begin with a brief overview of prevalence, mechanisms and clinical symptoms of food allergy. We then examine literature on the impact of food allergy on the perceived health related quality of life of children, teens and parents. Next, we present research on developmental differences in perception of the impact of food allergy and the behaviours or coping strategies children evolve in order to deal with this impact. We then draw on selected neurobiological literature in allergic diseases, in addition to some of the key psychobiological theories in current work on threat perception in health, to argue for a broader understanding of HRQL. This review also aims to provide a scientific basis for

Table 191.1 Key facts of food allergies

- *A food allergy* is an adverse immune response to a food protein and the food protein triggering the allergic response is termed a food *allergen*.
- Food allergy is distinct from other adverse responses to food, such as food intolerance, pharmacologic reactions and toxin-mediated reactions.
- Six to eight percent of children under the age of three, and nearly 4% of adults, have food allergies and prevalence is rising.
- Food allergies cause roughly 30,000 emergency room visits and 100–200 deaths per year in the USA.
- The most common food allergies in adults are shellfish, peanuts, tree nuts, fish and eggs, and the most common food allergies in children are milk, eggs, peanuts and tree nuts.
- Treatment consists of avoidance diets, in which the allergic person avoids all forms of the food to which they are allergic. For people who are very sensitive, this may include touching or inhaling the problematic food.
- Those diagnosed with a food allergy may carry an autoinjector of epinephrine such as an EpiPen or Twinject.

the development of appropriate models linking symptoms, functioning, development, underlying physiological mechanisms and HRQOL.

191.2 Prevalence, Mechanisms and Clinical Manifestations of Food Allergy

Atopy may be defined as a genetically and environmentally determined predisposition to clinically expressed disorders, including allergic rhinitis, atopic dermatitis or eczema, food allergy and allergic asthma, regulated through immune phenomena in which many cells (i.e. mast cells, eosinophils and T-lymphoctytes) and associated cytokines, chemokines and neuropeptides play a role.

Food allergy is growing in prevalence, and increasing rates of diagnosis means that many more parents and children must learn to live and cope with food allergy. Food allergy affects approximately 6–8% of young children and 3–4% of young adults in the UK, USA and Europe (Sampson 2005).

Allergy, particularly to peanuts, is the most common cause of anaphylaxis outside hospital yet there are other common food causes such as shellfish, fish, milk, soy, wheat and eggs (Sampson 2005). These foods may not only cause fatal or near-fatal reactions, but also tend to induce persistent sensitivity in most patients, in contrast to other foods such as milk, eggs and soybeans, which are frequently associated with milder reactions and are usually outgrown.

The life-threatening nature of anaphylaxis makes prevention the cornerstone of therapy (Hourihane et al. 1998a). Avoidance of the responsible food allergen and emergency management in the form of injectable epinephrine (Epipen or Anapen), in case food allergen is accidentally ingested, is the only reliable therapy offered to those living with food allergy. Anticipatory guidance measures form the cornerstone of advice, including reading food ingredient labels, concern for cross-contamination, vigilance in a variety of social activities and immediate access to the Epipen. However, avoidance is complicated by the fact that peanuts, nuts and soy can be found in many foods (e.g. breads, muffins, pastries, biscuits, cereals, soups, ice creams, seasoning, sauces) and in different forms as an emulsifier or thickening agent.

Food allergy occurs when the body's immune system mounts an exaggerated response against the offending food, which acts as an allergen. It is a type of hypersensitivity reaction. It can be either:

- A type I, IgE-mediated reaction: this is the usual cause of food allergy. After initial sensitisation, the release of mediators such as histamine are triggered each time a person is exposed to the food. It is these mediators that cause symptoms.
- A delayed, type IV-mediated reaction: these reactions are mediated mainly by T-cells. They typically affect the gastrointestinal tract or skin, for example, exacerbation of eczema in children after milk ingestion.

The European Academy of Allergy and Clinical Immunology has proposed a revised nomenclature for allergic and related reactions (Johansson et al. 2004). According to this proposal, adverse reactions to food should be termed 'food hypersensitivity'. The term food allergy should be used when immunological mechanisms have been demonstrated, and includes both IgE- and non-IgE-mediated reactions. All other reactions, which have sometimes been referred to as 'food intolerance', should be termed non-allergic food hypersensitivity (Fig. 191.1).

In an IgE-mediated reaction, symptoms involving the oropharynx and gastrointestinal tract may occur within minutes of ingesting a food allergen. Itching and swelling of the lips, tongue and soft palate as well as nausea, abdominal pain, vomiting and diarrhoea have all been demonstrated secondary to food allergy (Sicherer 2002). Anaphylaxis refers to a sudden, severe, potentially fatal, systemic allergic reaction that can involve skin, respiratory tract, gastrointestinal tract and cardiovascular system. The most dangerous symptoms include breathing difficulties and a drop in blood
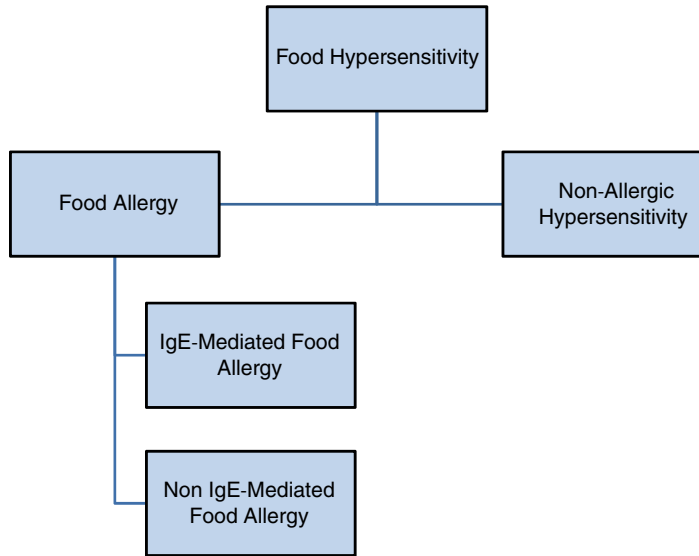
Fig. 191.1 Nomenclature proposed by the European Academy of Allergology and Clinical Immunology. Flow chart with terms describing adverse reactions to foods (Adapted from Johansson et al. 2004)

pressure, or shock, which are potentially fatal. Symptoms of anaphylaxis may develop within seconds or a few hours after ingestion of a food allergen, with the vast majority of reactions developing in the first hour. Symptoms can include swelling (especially lips, tongue or throat), difficulty in breathing, abdominal cramps, vomiting, diarrhoea, circulatory collapse, coma and death. Typical allergy medications such as antihistamines work too slowly and cannot reverse the effects of chemical mediators. Adrenaline or epinephrine, therefore is the treatment of choice and must be administered by injection promptly (Hourihane 1998b; Sicherer 2002).

A growing number of families must live and cope with food allergy on a day-to-day basis, however, the socio-emotional impact of food allergy on children and families has been little researched until recently (DeBlok 2009; DunnGalvin et al. 2007, 2008). The majority of research in food allergy has been bio-medical in orientation, focusing on issues such as the molecular structure of allergens, or methods of diagnosis. In the last 5 years, there has been a growing interest in the development of questionnaires to measure the impact of food allergy on health related quality of life (DeBlok et al. 2007). These studies have provided an insight into the everyday burden of living with food allergy.

191.3 The Impact of Food Allergy on Health Related Quality of Life (HRQL)

Early studies used generic HRQL questionnaires, in particular the Child Health Questionnaire (Landgraf et al. 1999) to investigate the impact of food allergy on perceived health related quality of life (DunnGalvin et al. 2008, 2010).

191.3.1 Research Using Generic HRQL Measures

The first study on HRQL was carried out by Primeau and colleagues (2000), who studied a sample of 301 patients and evaluated the quality of life and family relations of children and adults with

peanut allergy, and compared the results to that of children and adults with rheumatological disease (CRD). It was shown that the parents with food allergic children had difficulties in many areas. Remarkably, the authors found that families with peanut allergic children experience significantly more disruption in their familial and social interactions/activities than families with a child with CRD and suggested that this may be due to the constant risk of sudden death in the peanut allergy group leading to greater parent restriction of activities. There was also evidence that the educational and emotional support needs of families with food allergy are not being met (Sicherer 2002). The authors found that the effect of manufacturers labelling their product with 'May contain traces of nut' gave rise to parents' frustration and limited food choices. In addition, parents have the responsibility of ensuring their children do not ingest peanuts or food containing traces of peanuts which may be difficult in the context of modern food preparative techniques.

Sicherer et al. (2001) measured parental perception of physical and psychological functioning of families living with food allergy. The authors randomly selected 400 members of the food and anaphylaxis network, with families of children age 5–18 years old and had 253 responses. Results indicated that peanut allergy impacted significantly on general health, parental distress and family activities. Those with two or more food allergies scored significantly lower, depending on how many foods they were avoiding. There was also evidence to suggest that the educational and emotional support needs of these families are not being met.

Bollinger et al. (2006), in a survey of 87 parents in the USA, found that over half had made significant changes to their social activities to accommodate their child's food allergy, avoiding birthday parties, soccer games and school field trips. Forty-one percent of the parents surveyed said their child's allergy had a significant impact on their own stress levels. The authors conclude that studies are needed about how stress and avoiding activities might affect the psychological and social development of children with food allergies.

Avery et al. (2003) assessed the effect of peanut allergy on the quality of life in children aged 7–12 years and contrasted this with experiences of children with insulin-dependant diabetes mellitus (IDDM). Their results indicated that children with IDDM have similar problems as children with peanut allergy. These include food choices, social restriction, issues relating to school, the carrying and use of a syringe and the chronic nature of the condition. Results showed that children with peanut allergy had poorer quality of life and are more anxious concerning accidental ingestion of peanut than children with diabetes are of having a hypoglycaemic reaction. Gender differences have also been noted (Marklund et al. 2004), with girls reporting lower HRQL.

191.3.2 HRQL Research Using Disease-Specific Measures

The first validated HRQL food allergy specific measure, the Food Allergy Quality of Life–Parental Burden (FAQL-PB) questionnaire (Cohen et al. 2004) measures the parental burden associated with having a child with food allergy. Scores in the food-allergic cohort were significantly lower for general health perception, parental distress and worry, and interruptions and limitations in usual family activities, than in healthy controls. Scales were also lower in subjects with multiple food allergies.

More recently, several measures have been developed to assess quality of life in children and teens, under the aegis of EuroPrevall, an EU project which aims to improve quality of life for parents, children, teenagers and adults with food allergy (DeBlok et al. 2007; DunnGalvin et al. 2008, 2010). EuroPrevall is a multidisciplinary integrated project (IP) involving 17 European member-states. Of the 63 partners, there are 15 clinical organisations and six small–medium sized enterprises (SMEs) as well as the leading allergy research organisations in Europe. Since the project began in 2005, new partners have also joined from New Zealand, Australia, Russia, India, Ghana and China. Three food

allergy specific questionnaires have been developed and published under the auspices of EuroPrevall (DunnGalvin 2008, 2010; Flokstra DeBlok et al. 2008, 2009a, b). These are Food Allergy Quality of Life Questionnaire – Parent Form (parent-administered for children aged 0–12 years), and the Food Allergy Quality of Life Questionnaire – Child/Teen/Adult Form (self-administered for children and teens aged 8–17 years and adults aged 18 +)

The FAQLQ-PF, -CTF and AF were developed and validated in five stages: (1) item generation using focus groups with children, teens, and parents' expert opinion and literature review; (2) item reduction, using clinical impact and factor analysis; (3) the evaluation of internal and test-retest reliability and construct validity; (4) cross-cultural and content validity examined by administering the questionnaire in a US sample (FAQLQ-PF, only); and (5) longitudinal validity examined by administering the questionnaire over three time points pre/post food challenge.

Key Points of the Food Allergy Quality of Life Questionnaire: Parent Form (FAQLQ-PF)

Developed using gold standard quantitative and qualitative methodology
Three age groups:

- 0–3 years – 14 items
- 4–6 years – 26 items 1 Form
- 7–12 years – 30 items

Three subscale scores (*emotional impact; food anxiety; social and dietary limitations*) calculated as the mean of each scale. The total score is calculated as the mean of the three subscales.
Supplementary sections:

- clinical child variables
- parental concern for their child's emotional and physical health
- stress levels experienced by parents and family
- impact on child and family activities
- expectation of outcome following accidental ingestion of allergen
- satisfaction with clinical therapy, intervention, information, etc.

Very high reliability and validity (cross-sectional, cross-cultural, longitudinal).
Validated in seven languages, to date.

The development and validation studies found a severe impact of food allergy on HRQL in relation to psychosocial aspects of children's and teen's everyday lives. For example, in the initial focus groups put in place to generate items for the FAQLQ-PF, parents suggested that the anxiety associated with the risk of a potential reaction has more profound effects on emotional and social aspects of a child's everyday life, than clinical reactivity induced by food intake. The importance of a subscale assessing this aspect of anxiety was subsequently confirmed using clinical impact and factor analytic methodologies (DunnGalvin et al. 2008–2010). Children were also found to be 'generally anxious', that is, the anxiety associated with food often 'generalised' to non-food situations (DunnGalvin & Hourihane, 2009,a,b,c). In addition, multivariate analysis showed an interaction between sex and age group for impact of general emotional impact on HRQL scale, in effect, parents of boys reported higher mean total scores up to the age of 6 years; parents of girls reported higher mean scores in the 6–12 years age group, particularly in the subscales 'general emotional impact' and 'food anxiety'; whereas boys had higher scores in the 'social and dietary limitations' subscale at all ages. Example of items associated with each subscale may be seen in Table 191.2.

Table 191.2 Examples of items and content in the three subscales of the *Food Allergy Quality of Life Questionnaire – Parent Form* (FAQLQ-PF) (Reprinted from DunnGalvin et al. 2008)

Emotional Impact: Items concern psychological phenomena such as feeling different from other children, frustration, control and generalised anxiety stemming from food allergy: *My child feels different from other children because of food allergy.*

Food Anxiety: Items concern anxiety relating to food: *My child is afraid to try new foods because of food allergy.*

Social and Dietary Limitations: Items concern everyday dietary and social restrictions: *My child's ability to take part in pre-school events involving food (class parties, treats, lunchtime) is limited by food allergy.*

Three factors (emotional impact, food anxiety, social and dietary limitations) emerged following exploratory and confirmatory factor analysis in the development and validation of the Food Allergy Quality of Life Questionnaire – Parent Form (FAQLQ-PF)

Fig. 191.2 Flowchart showing study design and FAQLQ-PF scores at three time points (baseline, 2 months, 6 months) for children aged 0–12 years undergoing diagnostic food challenges. Although significant differences were found between positive and negative groups on all subscales and total score at 6 months (F (2,59) = 6.221, $p < 0.003$), HRQL improved significantly post challenge time points (all $p < .05$) for *both* positive and negative groups. Higher scores indicate greater impact of food allergy on HRQL (Reprinted from Hourihane and DunnGalvin 2009)

We evaluated longitudinal validity by administering the FAQLQ-PF to parents of children 0–12 years before the child underwent a clinically indicated food challenge, and at 2 months and 6 months post food challenge (DunnGalvin et al. 2010; Hourihane et al. 2009). In total, 82 children underwent a challenge (42 positive, 40 negative). Although significant differences were found between positive and negative groups on all subscales and total score at 6 months (F (2,59) = 6.221, $p < 0.003$), interestingly we found that HRQL improved significantly post challenge time points (all $p < .05$) for *both* positive and negative groups (Fig. 191.2). A possible explanation for improvement in the 'positive' groups (long suspected but never documented) concerns the impact of uncertainty on perception of HRQL. This also suggests that a food challenge (open or double blind) may be valuable, not only as an essential diagnostic tool, but as a therapeutic one. In effect, by providing a sense of certainty, a food challenge may have a positive impact on HRQL, irrespective of outcome. Other published research on uncertainty in chronic disease strengthens this argument (e.g. Mullins et al. 2007).

Table 191.3 Odds ratios for likelihood of volunteering to take part in IT study calculated according to level of expectation of adverse outcomes following accidental ingestion by their child (FAIM): 1 = Group B, consent to immunotherapy (DunnGalvin et al. in press)

FAIM: Expectation of Adverse Outcomes (1)	Odds Ratio (95% CI)	*p*-Value
Adjusted Effects[a]		
What chance do you think your child has of accidentally ingesting the food to which they are allergic? (>3.5)	3.421 (1.811–6.267)	.03
What chance do you think your child has of having a severe reaction if food is accidentally ingested? (>3.5)	3.945 (1.965–5.105)	.001
What chance do you think your child has of dying from their food allergy following ingestion in the future? (>3.5)	4.263 (2.351–7.613)	.005
What chance do you think your child has of effectively treating them or receiving effective treatment from others (including Epipen administration) if they accidentally ingest a food to which they are allergic? (>3.5)	3.267 (1.905–5.344)	.01
FAIM total score (>3.5)	6.753 (3.451–9.728)	.002

[a]Adjusted for age, sex, experience of anaphylaxis, experienced symptoms, socio-economic variables

Parents who perceive that their child is at high risk of dying from food allergy are more likely to enrol their child in an investigational trial in which the child will be given peanut immunotherapy (OR 6.75; CI 3.45–9.73). This perceived level of threat may be an important factor motivating parents to consent to their children taking part in investigational therapies in a 'controlled' environment

A recent study (DunnGalvin et al. 2009d) examined specific psychological factors, related to HRQL, that may impact on parents' decisions to take part in clinical studies. Parents of food allergic children were offered investigational oral immunotherapy (OIT) in the regular outpatient clinic. Forty parents (Group A) declined, and 25 parents (Group B) agreed to take part. Both groups completed the Food Allergy Quality of Life – Parent Form (FAQLQ-PF).

Our results show that parents who perceive that their child is at high risk of dying from food allergy (Table 191.3) are more likely to enrol their child in an investigational trial in which the child will be given peanut immunotherapy (OR 6.75; CI 3.45–9.73). This is in spite of the fact that the experimental therapy is intensive and has attendant adverse risks including induction of anaphylaxis, compared to the routine clinical practice. The association was independent of the severity of symptoms, experience of anaphylaxis and perception of the impact of food allergy on HRQL. Socio-economic status was not a significant factor.

These findings may be explained, in part, by parental concern to avoid potentially life-threatening consequences of accidental ingestion in the often 'uncontrolled' environment of their child's everyday life. This perceived level of threat may be an important factor motivating parents to consent to their children taking part in investigational therapies in a 'controlled' environment, even though this involves a protocol in which reactions are more likely than if not in the trial. These findings concur with Zupanic et al. (1997), who found that determinants of parental authorisation for involvement of newborn infants in clinical trials included perceptions of risk and benefit to the child.

191.4 Living and Coping with the Impact of Food Allergy

The way in which children and adolescents perceive and cope with chronic health conditions is considered as an increasingly important predictor of health and psychological well-being in clinical and psychosocial research (Schmidt et al. 2003). In medical and health psychology, efforts have increasingly been made to assess coping of children and adolescents with chronic conditions. Coping has

not only been shown to be related to patient HRQL, but mediates health behaviour as well as health-care utilisation (Feeney 2000).

Although quantitative studies provide consistent, replicable results that can be compared across populations, there are also inherent complexities in studying the experience of living with a disease in the dynamic, interactional process within the family. Life transitions provide a naturalistic research opportunity to investigate adaptability to stress and the link to health outcomes and health related quality of life.

Thus, there is an increasing recognition of the need to qualitatively explore patients' experiences, of what it is like to live with a chronic condition in order to better understand the decisions people make about coping and managing their condition. The personal meaning of having a particular disease 'is strongly related to the patient's self-care and to the degree of psychological and social adaptation to the disease' (Kyngas and Hentinen 1995:734) and compliance with medical direction is thus determined in part by the person's individual perception of the condition and its management.

A recent study (DunnGalvin et al. 2008, 2009) represented a first attempt to provide an integrated developmental framework to explain the onset, development and maintenance of food allergy related cognitions, emotions and behaviour. Sixty-two children/teenagers aged 6–15 years took part in 15 age appropriate focus groups, 52% of whom were female. Parents were also interviewed. All children were physician diagnosed with IgE-mediated food allergy and had been issued with an anapen/epipen. Through qualitative enquiry, a framework for evaluating children with food allergy was developed. Developmentally appropriate techniques such as vignettes (where children could comment on characters in the third person) and activity books were designed to stimulate discussion, maintain interest and minimize threat to the child's self-esteem.

Analyses of the data encompassed precipitating events (stressful events in children's lives caused by food allergy related factors), psychological impact (cognitive appraisal and emotional effects) and behavioural consequences or coping strategies. Open coding (the first step in analysis) in qualitative grounded theory (Charmaz 2000) may be seen as a descriptive 'still' of all the meaning in the data. For example, children discussed growing up and living with food allergy, about feeling different, about low awareness in their social worlds, about their fears and uncertainties in relation to experiencing an allergic reaction, food safety and socialising in many different contexts (eating out, going to the cinema, being with friends, meeting new people). The transcript data was organised into multiple codes and then into categories. Axial coding (the next step in analysis) links codes with distinct

Fig. 191.3 Flowchart showing analytic method in grounded theory. Open coding in grounded theory attempts to fracture the data in order to extract as much information as possible. The transcript data was organised into multiple codes and then into categories. Axial coding links codes with distinct categories structure (experi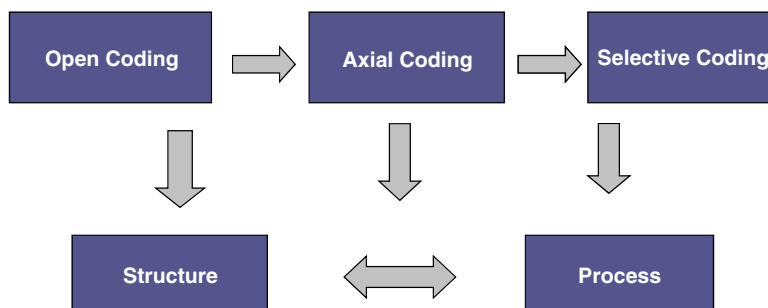ence) with process (what happens as a result) while, at the same time, attempting to retain as much meaningful information as possible. Selective coding results in a theoretical model (DunnGalvin and Hourihane 2009)
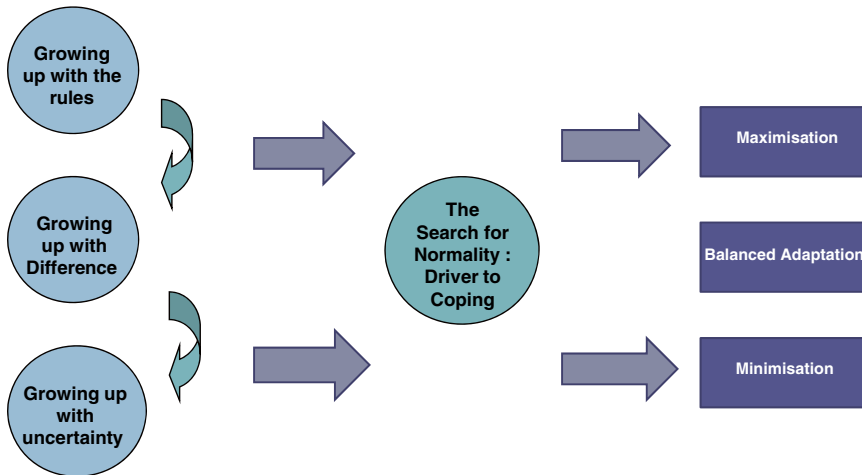
Fig. 191.4 The basic model of structure and process: experience and behaviour. The experience of living with food allergy, 'living with the rules', 'living with difference' and 'living with uncertainty' leads children to cope by means of minimisation, maximisation and balanced adaptation, in the search for normality (DunnGalvin and Hourihane 2009)

categories to form a substantive theory of action, while, at the same time, attempting to faithfully represent the dynamic interrelationships of the children's experience. The analytic method is illustrated in Fig. 191.3.

Our findings indicated that experience and coping in food allergy is more than simply a strategy, it is a cumulative history of interactive processes (age, gender and disease specific) that are embedded in a child's developmental organization.

We can conceptualise food allergy as a central 'lens' in children's lives through which they interpret experiences. When children and teens are confronted with a stressful event, such as a birthday party, a novel situation, an allergic reaction or making new friends, the way in which they appraise the event and its attendant emotional impact are viewed through this lens. The basic model is illustrated in Fig. 191.4.

How this lens is constructed and its psychological impact (uncertainty, anxiety, confusion, difference) on individual children is modified by age, gender, context, prior experience, attitudes of parents, attitudes of peers and levels of general awareness. In most children under the age of 8 years, there is a certainty of parental and adult knowledge and a consequent sense of control of events relating to food allergy. However, an important transition point occurs when children learn or feel that parents (and therefore children themselves) cannot conclusively prevent an allergic reaction, after which we see a change in cognitions, emotions and behaviour, and coping strategies become more differentiated.

191.5 Living with Uncertainty Is a Central Theme in the Experience of Food Allergy

To provide an example, *living with uncertainty* (DunnGalvin et al. 2008a, b; 2009a–d) is an important concept that affects children's sense of control, beliefs about risk, level of vigilance and confidence in safety. Young children have an illusory perception of control because of parent protection. However, we see the roots of uncertainty in even very young children who are aware of parent anxiety and speak about

the possibility of a reaction occurring at any time, 'because you never know what might happen'. However, always being aware and alert to the possibility of danger is a heavy burden for children in their everyday lives. Becky (age 10) explains 'because food is always around it is hard to forget about it' and Matt (age 11) says '…I can't just eat something like my friends … or be with people without thinking about what they are eating'. Being constantly vigilant also affects children's enjoyment of social events 'well … it means you can never relax at a party and just enjoy it' (Kevin, age 11).

Anxiety appears to be particularly strong in children aged 9–12 years. Even when carefully following the rules, children often cannot pinpoint why a reaction occurred. Older children and teens emphasise the uncertainty of living with food allergy and the consequent feeling of a loss of control: 'sometimes you can't find the cause [of a reaction] … it just happens, you know … not knowing makes you worried and unsure of yourself … what can you do' (Fran, age 15); 'people have died … and sometimes they don't even know why … even toothpaste has been blamed' (Patrick, age 14). Low general awareness also contributes to uncertainty. Adolescents have a full understanding and realisation of uncertainty in their everyday lives. For example, Grace (age 13) captured the feelings of many teens when she describes why she feels anxious: 'when I get up in the morning I can't be sure I won't have a reaction that day'.

A growing awareness of uncertainty impinges on children's beliefs and subsequent coping strategies. Although being vigilant allows children to feel some form of control over uncertainty, this is undermined because of low understanding and awareness in restaurants, shops, activity camps, schools, peers, etc., in the general population and difficulties in the interpretation of labels on foods. Although their roots may be discerned in children in the youngest age group, by adolescence, children's coping strategies become more defined, in some cases more rigid, and an expanding social world gives further impetus to the search for normality. *Normality* has multiple meanings depending on the particular developmental trajectory of the child in question. The search for normality becomes clearer when we turn to the coping strategies children use to manage food allergy. For some, normality may mean assurance that they are safe at all times and are accepted and understood by particular friends, for others it
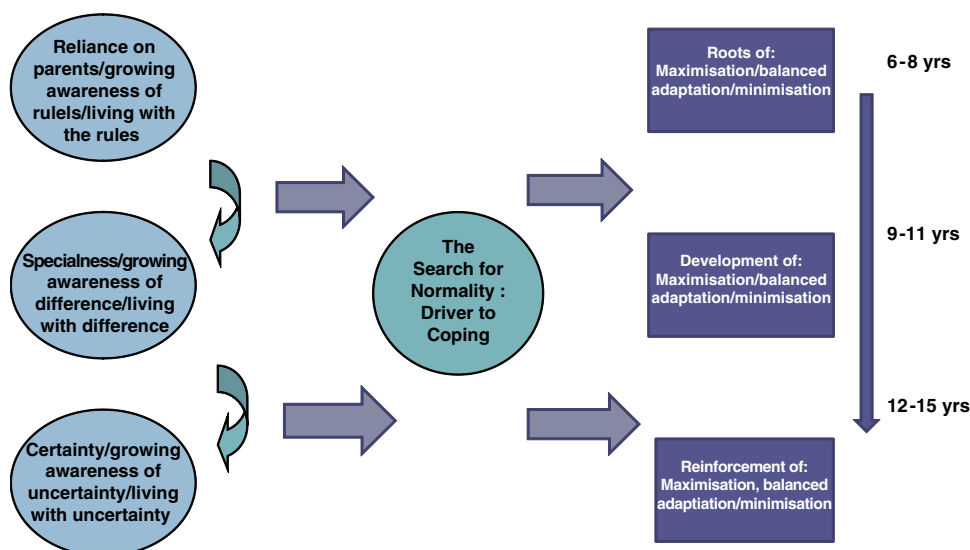

Fig. 191.5 The developmental pathway model. Following axial coding, developmental differences were examined based on the Fig. 191.4 above, in order to describe a conceptual theory of the studied phenomenon: growing up, living and coping with food allergy (DunnGalvin et al. 2009)

means being able to interact freely and being accepted as normal 'in the real world', and for some it means finding a balance between the two. The developmental model is shown in Fig. 191.5.

Coping strategies were found to lie on a maximisation/avoidance to minimisation/risk continuum. They may be emotion focused or problem focused, often they are both. Some are actions, interactions or cognitions. Their defining quality is that they are used in clusters by particular children. *Maximisation* involves placing food allergy at the centre of your life, *minimisation* involves rejecting food allergy as an important part of your life and *balanced adaptation* involves balancing safety with integration. Emotional, cognitive and behavioural strategies are associated with each of these axial categories.

Anxious children tended to use avoidant strategies to cope with living with food allergy. Many clinicians assume that these strategies are necessary and adaptive, if they are proportionate. However, we found that high levels of anxiety, vigilance and generalised avoidance of situations and people not directly related to food consumption are associated with maladaptive avoidant strategies. A surprising finding was that anxious children and teens are not necessarily those who experience the most or recent reactions. For example, many of the children who described themselves as anxious or worried about food allergy could not remember ever having had a serious reaction.

Minimising strategies are also maladaptive in that children who use them also engage in risky behaviour, such as deliberately eating an allergic food. Children are told by clinicians and parents that being allergic to a certain food means that they can never have 'even a taste' of that allergen, any food containing the allergen or any food that may have come into contact with the allergen. Because of the difficulty for clinicians and scientists in determining risk thresholds, children must live by this rule. There were, however, important developmental differences. For example, it was noticeable that younger children described deliberately eating an allergic food in their homes or when parents were present at a social occasion, out of curiosity to experience what peers can eat without difficulties. By 'eating just a little bit' and seeing how they react, children in the middle age group appear to be trying to determine their own risk thresholds: 'you'd have a small bit now and then and see what happens' (Johnny, age 11). It may also be a way for children to exert control over uncertain conditions. Older children, and particularly teens, appeared deliberately eating an allergic food as a means of coping in a social situation in order to cope with feelings of difference. This risk behaviour developmental process is illustrated in Fig. 191.6.

Parents and children share many of the same broad-based experiences, concerns and anxieties, and use many of the same coping strategies as emerged from focus groups with children and teens. Parents struggle with how to support children's independence while controlling their own anxiety and genuine fears of increased risk. Parents respond to conditions in individual ways in a search for normality by maximization, minimization and balanced adaptation, clusters of coping strategies that were also found in children.

Our findings of high levels of anxiety in a food allergic sample of children and parents are supported by epidemiological research. In child/adolescent populations with allergic diseases in general, up to one third may meet criteria for co-morbid anxiety disorders (Bender Berz et al. 2005). In adult populations with asthma, the estimated rate of panic disorder ranges from 6.5% to 24% (Katon 2004). Studies have also documented associations between anxiety disorders and allergy (Kovalenko et al. 2001). Patients attending allergy clinics reported higher levels of depression compared to the general population. A birth cohort study in Finland (Timonen 2003) revealed that at epidemiological levels, skin prick test positive females exhibited up to a 1.8-fold greater risk of developing lifetime depression when compared with skin prick test negative subjects. In addition, the corresponding risk increased up to 2.7-fold among females, who had a positive skin prick test together with self-reported allergic symptoms. Maternal atopy alone almost doubled the risk of lifetime depression in female probands when compared with families in which no maternal atopy existed. In contrast, parental atopy did not predict any type of depression in male probands.
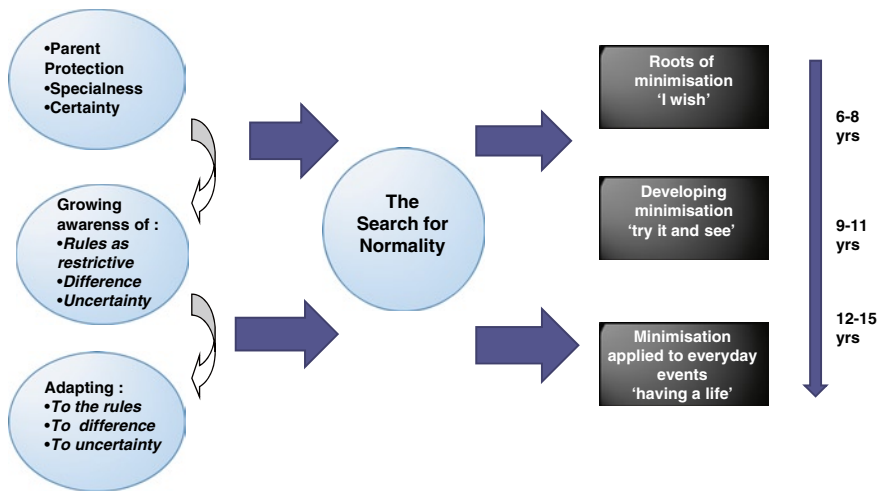
Fig. 191.6 The developmental pathway model applied to the evolution of risk behaviour. Because they were diagnosed when infants, young children feel that they are 'the same' as other children, and parents help them to feel normal and protected in their everyday lives. They therefore have an illusory perception of control and certainty. As children become more aware of the rules as restrictive, together with a growing awareness of difference and uncertainty, the search for normality becomes stronger and children evolve strategies in order to cope. Although their roots may be discerned in children in the youngest age group, by adolescence, children coping strategies become more defined, and in some cases more rigid, and an expanding social world gives further impetus to the search for normality (DunnGalvin and Hourihane 2009)

191.6 Underlying Mechanisms Related to Perception of HRQL: Physiological and Psychological Responsiveness

Research (animal and human) shows how the environment (including the prenatal environment) can change our anatomy, brain and central nervous system. Neuroendocrine sensitisation effects following exposure to maternal stress during the first year of life have been reported in 4.5-year-olds (e.g. Essex et al. 2002). A recent study undertaken in a sample of 10-year-old children from the Avon Longitudinal Study of Parents and Children (ALSPAC) has demonstrated for the first time a significant link between prenatal anxiety, particularly in late pregnancy, and individual differences in salivary cortisol (O'Connor et al. 2003). A relatively small study has also identified a link between maternal anxiety and salivary cortisol in children at 5 years of age. Children whose mothers exhibited higher levels of morning cortisol during pregnancy, and more fear of bearing a disabled child, showed higher levels of salivary cortisol (Gutteling et al. 2005). The same group showed similar associations in another sample of children at 4–6 years of age (Gutteling et al. 2004). Clearly, further studies are required to fully understand the relationship between PS/anxiety during pregnancy and HPA function in human children and adults.

Neuroendocrine changes have also been associated with social adaptation in pre-school children (Gunnar et al. 2003). In understanding childhood influences on health and health perception, this neuroendocrine window provides an opportunity to examine these person-environment responses. Assessing cortisol activity in response to starting pre-school, Gunnar and colleagues emphasise that it is neuroendocrine *adaptability* that is important rather than simply the level of response. Providing evidence for the context-specific HPA activation during childhood experiences, it appears that it is the repeated triggering of the stress response rather than neuroendocrine activation itself which may be problematic for shy children, as they perceive threat to a greater number of everyday events (Watamura et al. 2004).

For most children who become allergic or asthmatic, the polarization of their immune system into an atopic phenotype probably occurs during early childhood. The establishment of the Th1/Th2 balance during early childhood and the final tuning at the important middle childhood years (Sampson 2005) implies that children may be especially vulnerable to environmental and lifestyle stressors affecting this balance. This period coincides with the transition point discussed earlier, when children begin to experience uncertainty. Chronic diseases that are characterised by dysregulation of inflammation, such as food allergy, are particularly susceptible to modulation by stress and emotion.

Prenatal, perinatal and early life events (e.g. stress in mothers) appear to be crucial in programming the infant's immune system, independent of genetic susceptibility. Maternal genetics related to oxidative stress genes may influence the child's atopic risk beginning in utero. Sustained cortisol secretion can affect Th1/Th2 differentiation both in the foetus and in the newborn infant, and is able to increase susceptibility to allergic diseases (von Hertzen 2002). Wright and colleagues (2004a) found that higher caregiver stress in the first 6 months after birth was associated with increases in the children's allergen-specific proliferative response (a marker of the allergic immune response), higher total IgE levels and increased production of TNF-α and reduced IFN-γ in a birth cohort of children predisposed to allergic disease. This risk is thought to be mediated by the effects of stress on neuro-immunoregulation, which in turn modulates hypersensitivity responses. A dysfunctional neuroendo-crine-immune interface associated with abnormalities of the 'systemic anti-inflammatory feedback' and/or 'hyperactivity' of the local pro-inflammatory factors may play a role in the pathogenesis of atopic/allergic diseases and later co-morbid anxiety disorders.

Chronic stress may induce a state of hyporesponsiveness of the HPA axis, whereby cortisol secretion is attenuated leading to increased secretion of inflammatory cytokines typically counter-regulated by cortisol. While the ability to activate an increase in cortisol in response to some stimuli in early life may be adaptive, prolonged exposure to stress may change the cortisol response if examined at a later developmental stage (Wright et al. 2004b).

Sex differences have also been noted. Different patterns of cytokine responses between males and females have been suggested as contributing in part to gender-specific differences in the self-reporting rates and perception of HRQL in food allergy, discussed earlier. We already know that components of stress and the stress response differ between men and women. The tend-and-befriend response, mediated by oxytocin and endogenous opioids, may be more applicable to women than the fight-or-flight response, which was based largely on studies of men. Even within the flight-or-flight response pattern there are sex-based differences. The HPA axis interacts with the reproductive function, such as menstruation. Further, the *nature* of stressors may also influence sex differences in immune reactivity to stress (Kang et al. 1997) involving a complex interaction between biology and environment. For example, there are gender differences in the *types* of stressors to which an individual is likely to be exposed. The complexity of these sex- and gender-based interactions may explain the more adverse effects of food allergy on female over male general emotional well-being, discussed earlier.

As discussed, a number of studies have examined the impact that the activity of the stress system may have on immune activation and symptoms in humans. A state of stress-induced HPA hyporesponsiveness has also been demonstrated in research participants with chronic inflammatory disorders. Wamboldt et al. (2003) found an attenuated cortisol response among adolescents with positive skin test reactivity to an allergic disease compared with those with skin test positivity alone or nonatopic individuals. It appears that chronic stress may induce a state of hyporesponsiveness of the HPA axis, whereby cortisol secretion is attenuated leading to increased secretion of inflammatory cytokines typically counter-regulated by cortisol.

Some studies have considered whether immune activation and the *experience* of having an atopic disease, particularly during childhood, influence the responsiveness of the HPA axis. The extant literature indicates that both physiological and psychological stressors activate similar neural circuitry, acting as two different routes to a bidirectional communication network between the brain

and the immune system (Maier and Watkins 1998). During an immune response, the brain and the immune system communicate with each other in order to maintain homeostasis. Two major pathways, the HPA-axis and the SNS are involved in this bidirectional interaction (Elenkov et al. 2000). Consistent with this model, neural circuitry underlying stress and emotions can regulate inflammation (Black 2002) and peripheral inflammatory mediators can influence mood and cognitive function (Wichers and Maes 2003).

The advent of cognitive neuroscience and functional neuroimaging has brought unprecedented new opportunities to study the neurobiology of these processes. Rosencrantz and colleagues (2005) examined the neural circuitry underlying the interaction between emotion and asthma symptom exacerbation, using fMRI during antigen challenge to examine regional brain activation in adults with mild allergic asthma. They demonstrated an association between activity in the anterior cingulated cortex (ACC) and insula to asthma-relevant emotional stimuli (e.g. wheeze) compared with valence-neutral stimuli and markers of inflammation in participants exposed to an antigen. The activation accounted for > 40% of the variance in peripheral markers. These brain regions may be hyperresponsive to disease-specific emotional and afferent physiological signals, which may contribute to the dysregulation of peripheral processes, such as inflammation (McAfoose and Baune 2009). The authors suggest that reciprocal modulation may occur between peripheral factors regulating inflammation and central neural circuitry underlying emotion and stress reactivity.

This is an area of research which has the potential to provide answers to questions relating to the complex interaction between physiology and psychology in the developmental pathways of allergic diseases in males and females (DunnGalvin et al. 2006), and may have preventative and therapeutic implications in terms of both immune and anxiety disorders (DunnGalvin et al. 2009c).

191.7 Cognitive Emotional Sensitisation

The theory of *cognitive emotional sensitisation* (Brosschot 2002) may further elucidate explanatory mechanisms for findings in the biopsychosocial impact of food allergy. This theory is based on the notion of *cognitive bias*, one of the best-documented cognitive phenomena in experimental psychopathology.

The simplest form of plasticity in nervous systems is that repeated stimulation may lead to habituation (decreased response) or sensitization (increased response). Sensitization has been widely observed across the phylogenetic scale, and may be present at multiple levels in the organism: at the cellular, psychological and interpersonal level (see Brosschot 2002). Generally, sensitisation is caused by an increased efficiency in the synapse due to repeated use, in particular following irregular and extreme stimulation. It constitutes a feed-forward mechanism, helping the individual to react more efficiently in situations with increased probability of harm (Ursin and Eriksen 2001; Overmier 2002). Brosschot (2002) used the metaphor of an unfolding scanner or antenna, directing its dish towards the source of potentially threatening information and amplifying it. The level of background arousal is very important: high levels of arousal result in the stimulus repetition inducing sensitization, even though repetition of that same stimulus under conditions of low arousal would lead to habituation (see Overmier 2002).

Cognitive emotional sensitisation is therefore a higher form of sensitisation, involving cognitive bias. Much research has shown that anxious persons have a cognitive processing priority for information that is related to their fears. The emotional Stroop results show that this multilevel sensitization could develop for many different types of concern-related information. For example, in relation to pain, Crombez (1998) emphasises two important determinants that pertain to our findings: *novel* pain produces a large disruption in a primary task, as does the temporal *unpredictability* of an aversive

noxious stimulus. In an attempt to find an explanation for the lack of consistency across some attentional bias studies, Crombez also emphasizes the importance of anxiety in the manifestation of cognitive bias, and suggests analysing more precisely what *type* of information is *really* threatening for what *type* of patient, whether, as discussed earlier, this is a threat to safety or to self-concept.

Emotional arousal tends to bring to awareness of one's predominant cognitive bias and potentially triggers one's most salient behavioural programmes. Anxiety in itself, unrelated to relevant health threat, may activate neural networks in children with food allergy because these networks are easily activated by *any* stimulus that induces limbic activity (Ursin 2001). Thus, children need not have actually, or recently, experienced an allergic reaction in order to feel anxious. The type of threat, in addition to emotional arousal, is also very important; for example, if a child perceives that revealing that he/she is food allergic will have an impact on his/her ability to fit in with peers, this may result in risky behaviour rather than avoidant behaviour.

Finally, each time anxiety is felt and the networks are triggered, arousal probably helps to further strengthen the associations in this network. Emotional arousal at the time of experiencing a stimulus (internal as well as interaction with environment) is thought to be critical in influencing memory strength for this stimulus and therefore consolidation of the strong fear network and its sensitization (Brosschot 2002). The amygdala modulates the establishment of memory traces in other brain regions (e.g. the hippocampus; see McCaugh 2004). Although much research attributes a specialised role for harm avoidance to the amygdala circuits (see review LeDoux and Phelps 2000), and for reward processing to the nucleus accumbens (DiChiara et al. 2004), these structures support a number of additional functions, such as associative learning and attention filtering which cut across both appetitive and aversive processing. Associative learning is affected by the way in which feedback is processed, that is, the representation of the value of the outcome that becomes linked through learning to the stimuli options (Ernst et al. 2003). The learning itself may be fully developed by middle to late childhood and behaviour expressed as highly trained (and probably neurally pre-activated), easily triggered behavioural patterns or, at the neural level, sensitized motor programs, coupled to the corresponding highly activated cognitive (and emotional) network (Brosschot 2002; Ursin and Eriksen 2001).Finally, increasing coordination and integration of the mostly physiological regulatory systems (e.g. information processing) over the course of development means that by the time children reach their teens, self-perception, emotional reactions and cognitive appraisal mechanisms have become relatively stable and consistent. Therefore, perception of HRQL and attendant behaviours may develop and depend on many factors, such as the amount and type of subjective threat, parental risk perception, peer and general attitudes to the disease, social environment, sex, age of development and culture (including gender).

191.8 Applications to Other Areas of Health and Disease

In this chapter, using food allergy as an example, we reviewed relevant literature to argue for a broader evaluation of HRQL in order to provide a framework for the construction of appropriate models linking symptoms, functioning, development, underlying physiological mechanisms and HRQOL in chronic disease involving food in children.

The research presented here implies that studies in health related quality of life that take account of biobehavioural developmental subsystems are likely to be more informative than those restricted to physiological or psychological domains alone. Developing functional systems interact, react with and program one another. For example, early life origins research has delineated mechanisms linking psychological stress, personality and emotion to neuro-immunoregulation as well as

increased risk of atopy. Furthermore, it appears that immune activation and the *experience* of having an allergic disease, particularly during childhood, influences the responsiveness of the HPA axis.

The implications of this developing field of research are enormous with applications extending to include the effect of social experience on learning and on health outcomes. Social and physiological adaptation is required in order to cope with transitional life experiences, whether these are due to early maternal separation in the form of childcare, starting school, the experience of competition or a particular disease.

A chronic condition may affect and/or interact with normative developmental pathways and risk of maladaptive outcomes may follow transition points that are particular to a specific disease. Disease-specific pathways may be embedded within developmental trajectories and predict phenotypic expression of physiology, psychology and behaviour. A simple illustration of this dual pathway is shown in Fig. 191.7.

Findings may also be applicable to other chronic diseases involving diet such as diabetes and celiac. Diabetes, like food allergy, is a 'hidden' disease, largely unsymptomatic but characterised by sudden and unpredictable symptomatic events. In a series of focus groups with children aged 6–12 with diabetes (submitted), we found many of the same transition points (e.g. balancing safety with the need to 'belong'); however, there were also differences. In addition to a growing awareness of 'uncertainty' in
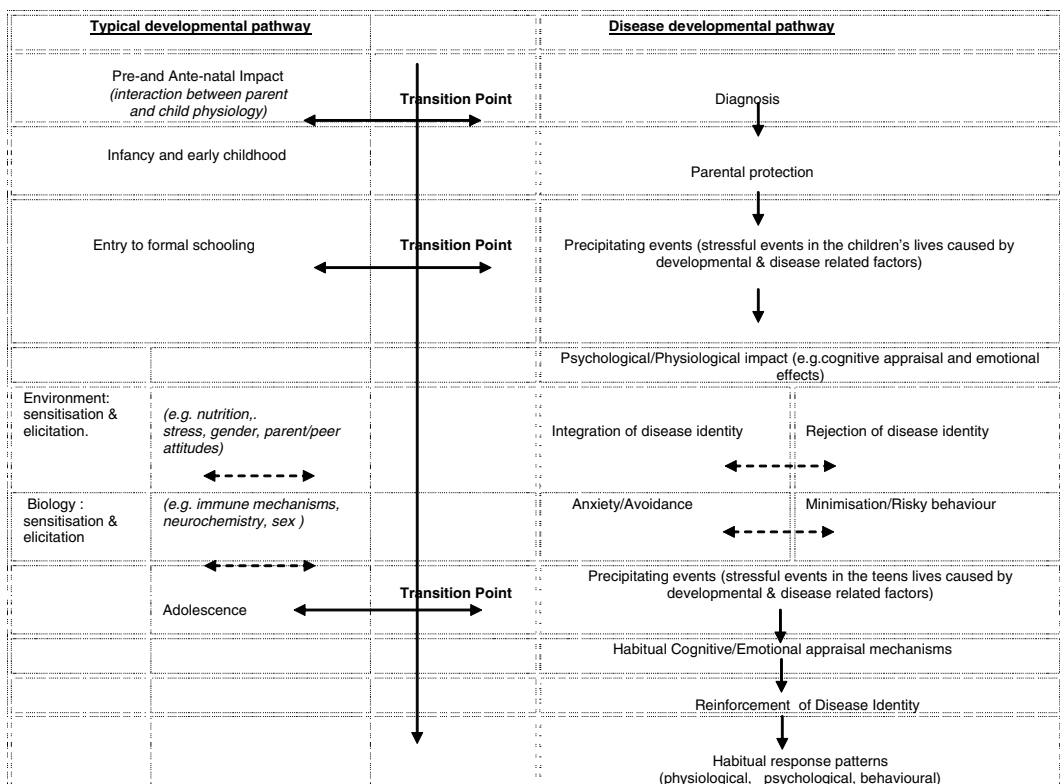
Fig. 191.7 Developmental framework model illustrating the integration of food allergy-specific pathway within the normal trajectory. A chronic condition may affect and/or interact with normative developmental pathways and risk of maladaptive outcomes may follow transition points that are particular to a specific disease. Disease-specific pathways may be embedded within developmental trajectories and predict phenotypic expression of physiology, psychology and behaviour (Dunn Galvin and Hourihane in press)

managing diabetes, there was a growing awareness of 'embarrassment' and a public attitude of 'blame' toward the diabetic adolescent. This awareness resulted in concealment and risky behaviour in some cases. Research in diabetes shows that adolescence, when responsibility for self-care is largely transferred from parent to child, is consistently associated with a decline in metabolic control (e.g. Hoey et al. 1999). While the decline is partly attributed to physiological changes the main cause is a substantial decline in levels of self-care (e.g. Morris et al. 1997). Anxiety and depression associated with uncertainty has also been noted in childhood diabetes (Mullins et al. 2007). Further, the need to address uncertainty in the context of its differing gender impact may also be discerned from research into other 'hidden' diseases. Austin et al. (2000), in a 4-year study on adjustment in epilepsy, found that girls evolved more behaviour problems from pre- to post-adolescence. In addition, they found that children were very worried about the possibility and unpredictable nature of seizures.

191.9 Conclusion

An integrated developmental perspective provides a powerful place to illuminate our understanding of individual differences in the expression and impact of chronic diseases. For example, research into the behavioural significance of the different trajectories of biopsychosocial maturation can aid in the development of psychoneurobiological models that may ultimately predict health-related quality of life outcomes.

A HRQL research infrastructure that has sufficient scope (both breadth and depth) will still fail in its goal if the knowledge is not linked across levels and domains. Four elements are essential to success in integration. The first is the development of a coherent conceptual framework within which the connections make sense. The second involves a cross-disciplinary research project in order to address key issues of linkage between developmental processes and outcomes at different levels. The third element relates to the need for innovative quantitative and qualitative methodologies which can be used to tease out the relative contribution of biopsychosocial factors to HRQL. The last relates to the need for longitudinal birth cohort studies.

A broader understanding of HRQL will ultimately lead to the promotion of earlier, more effective preventive strategies and interventions focused on maximizing optimal health development and quality of life.

Summary Points

- Outcomes research has been key in altering the culture of clinical practice and health care research by changing how we assess the end results of health care services.
- Health Related Quality of Life (HRQL) is a multi-dimensional construct, which evaluates physical, psychological, and social components, from the patient perspective.
- There are important questions that must be answered before HRQL measures can reach their full potential in research, practice and policy.
- Disease- specific pathways may be embedded within normal developmental trajectories and predict phenotypic expression of physiology, psychology and behaviour.
- The immune system in concert with psychological factors, such as stress, may play a role in the development of abnormal immune and allergic responses. In turn, immune activation and the experience of having an atopic disease, particularly during childhood, may influence the responsiveness of the HPA axis.

- Appropriate pathway models must be developed to incorporate broader aspects linked to HRQL and to incorporate developmental biopsychosocial trajectories.
- An integrated developmental perspective may promote increased understanding of individual differences in the expression and impact of many chronic diseases, with applications extending to include the effect of social experience on learning and on health outcomes.
- A broader understanding of HRQL may lead to the promotion of earlier, more effective preventive strategies and interventions focused on maximizing optimal health development and quality of life.

Key Terms

Health related quality of life: A multidimensional construct, which evaluates physical, psychological and social components that may be impacted by a disease or medical condition, from the patient perspective.

Reliability: The consistency of a measurement, or the degree to which an instrument measures the same way each time it is used under the same condition with the same subjects.

Validity: There are several forms of validity, but in essence, validity refers to the ability of a measure to capture the construct of interest (e.g. health related quality of life) in a meaningful and effective manner.

Developmental trajectory: A lifelong process of developmental integration that involves complex interactions between biological and environmental factors that influence the phenotypic expression of physiology, psychology and behaviour.

Sensitive transition point: Period in development when physiological or environmental variables associated with a particular disease may have a relatively greater impact and/or interact with already existing normative demands and changes in socialization.

Coping/adaptation: How individuals mobilize, guide, manage, energise and direct behaviour, emotion or orientation, or how they fail to do so, under stressful conditions, such those associated with a chronic disease.

Sensitisation/cognitive emotional sensitisation: Sensitisation is caused by an increased efficiency in the synapse due to repeated use, in particular following irregular and extreme stimulation. Cognitive emotional sensitisation is a higher form of sensitisation, involving cognitive bias.

References

Austin JK, Dunn DW, Huster GA. Childhood epilepsy and asthma: changes in behavior problems related to gender and change in condition severity. Epilepsia. 2000;41:615–23.

Avery NJ, King RM, Knight S, Hourihane JOB. Assessment of quality of life in children with peanut allergy. Pediatr Allergy Immunol. 2003;14:378–82.

Black PH. Brain Behav Immun. 2002;16:622–53.

Brosschot JF. Cognitive–emotional sensitization and somatic health complaints. Scand J Psychol. 2002;43 (2):113–21.

Bollinger ME, Dahlquist LM, Mudd K, Sonntag C, Dillinger L, McKenna K. The impact of food allergy on the daily activities of children and their families. Ann Allergy Asthma Immunol. 2006;96:415–21

Charmaz K. Grounded theory: objectivist and constructivist methods. In Denzin N, Lincoln Y, editors. Handbook of qualitative research. 2nd edn. Thousand Oaks: Sage; 2000. p. 509–535.

Cohen BL, Noone NS, Munoz-Furlong A, et al. Parental burden in food allergy. Journal of Allergy Clin Immunol. 2004;114 5:1159–63.

DiChiara G, Bassareo V, Fenu S, DeLuca MA, Spina L, Cadoni C, Acquas E, Carboni E, Valentini V, Lecca D. Dopamine and drug addiction: the nucleus accumbens shellconnection. Neuropharmacology. 2004;47:227–41.

DunnGalvin A, Hourihane J O'B, Frewer L, Knibb RC, Oude Elberink JNG, Klinge, I. Incorporating a gender dimension in food allergy research: a review. Allergy. 2006;61:1336–43.

DunnGalvin A, de Blok BMJ. Dubois A, Hourihane JO'B. Development and Validation of the Food Allergy Quality of Life – Parent Administered Questionnaire (FAQLQ-PF) for food allergic children aged 0-12 years. Clinical and Experimental Allergy. 2008;38:977–86.

DunnGalvin A, Dubois AEJ, Hourihane J. Child vs maternal perception of HRQoL in food allergy: developmental trajectories and evolution of risk behaviour. Allergy. 2007;62 (Suppl. 83):70–166.

DunnGalvin A, Roberts S, Hourihane JO'B. Causal pathway analysis of mothers' responses to government advice on peanut avoidance. Oxford Journal of Public Health. 2008a;30(1):114–5.

DunnGalvin A, Gaffney A, Hourihane JO'B. Developmental pathways in food allergy: a new theoretical model. Allergy. 2009a;64:560–8.

DunnGalvin A, Hourihane JO'B. Self-assessment of reaction thresholds in food allergy: a new theory of risk taking which changes over time. J Allergy Clin Immunol. 2009b;123:S142.

DunnGalvin A, Hourihane JO'B. Developmental trajectories in allergic diseases: A review. Advances in Food and Nutrition Research, Elsevier Inc. 2009c. Volume 56 (pp. 65–102).

DunnGalvin A, Burks WJ, Dubois AEJ, Chang WC, Hourihane JO'B. Profiling Families Enrolled in Food Allergy Immunotherapy Studies DunnGalvin A, Chang WC, Laubach S, Steele PH, Dubois AEJ, Wesley Burks AW, Hourihane JO'B, Pediatrics 2009d;124:e503–e509.

DunnGalvin A, Cullinane C, Daly D, Flokstra-de Blok BMJDubois AEJ, Hourihane JO'B..Longitudinal validity and responsiveness of the Food Allergy Quality of Life Questionnaire – Parent Form (FAQLQ-PF) in children 0-12 years following positive and negative food challenges. Clin Exp Allergy. 2010;40(3):476–85

DunnGalvin A, Hourihane JO'B. (submitted) A Chronic Disease Impacts Directly on Child's Normal Trajectory of Psychological Development in Both a Generic and Disease-Specific Manner: Similarities and Differences in Food Allergy and Diabetes.

Elenkov IJ, Wilder RL, Chrousos GP, Vizi ES. The sympathetic nerve – an integrative interface between two supersystems: The brain and the immune system. Pharmacol Rev. 2000;52:595–638.

Engle G. The need for a new medical model: a challenge for biomedicine. Science 1977;197:129–96.

Feeney JA. Implications of attachment style for patterns of health and illness. Child Care Health Dev. 2000;26: 277–88.

Ferrans CE, Zerwic JJ, Wilbur JE, Larson JL. Conceptual model of health related quality of life. J Nursing Scholarship. 2005;27:336–42.

Flokstra-de Blok BMJ, DunnGalvin A, Vlieg-Boersta BJ, Oude Elberink JNG, Duiverman EJ, Hourihane JO, Dubois AEJ. Development and validation of a self-administered Food Allergy Quality of Life Questionnaire for children. Clin Exp Allergy. 2009;39:127–37.

Flokstra-de Blok BMJ, DunnGalvin A, Vlieg-Boersta BJ, Oude Elberink JNG, Duiverman EJ, Hourihane JO, Dubois AEJ. Development and validation of the self-administered Food Allergy Quality of Life Questionnaire for adolescents. J Allergy Clin Immunol. 2008;122:139–44.

Flokstra-de Blok BMJ, van der Meulen GN, DunnGalvin A, Vlieg-Boersta BJ, Oude Elberink JNG, Duiverman EJ, Hourihane JO, Dubois AEJ. Development and validation of the first disease-specific quality of life questionnaire for adults; The Food Allergy Quality of Life Questionnaire-Adult Form (FAQLQ-AF). Allergy 2009;64(8):1209–17.

Gutteling BM, de Weerth C, Buitelaar JK Maternal prenatal stress and 4–6 year old children's salivary cortisol concentrations pre- and post-vaccination. Stress. 2004;7:257–60.

Gutteling BM, de Weerth C, Buitelaar JK. Prenatal stress and children's cortisol reaction to the first day of school. Psychoneuroendocrinology. 2005;30:541–9.

Gunnar M, Sebanc A, Tout K, Donzella MA, van Dulman M. Temperament, peer relationships, and cortisol activity in preschoolers. Dev Psychbiol. 2003;43:346–68.

Halfon N, Hochstein M. Life course health development: An integrated framework for developing health, policy and research. In: Milbank Q.80:433–79; 2002.

Hoey, H, Mortensen, H, McGee, H, & Fitzgerald, M, for the Hvidore Study Group. Is metabolic control related to quality of life? A study of 2103 children and adolescents with IDDM from 17 countries. Diab Res Clin Pract. 1999;44 (Suppl):S3.

Hourihane JO, Roberts SA, Warner JO. Resolution of peanut allergy: case-control study BMJ. 25 Apr 1998a;316 (7140):1271–5.

Hourihane JO. Prevalence and severity of food allergy – need for control. Allergy. 1998b;53 (46 Suppl):84–8.

Hourihane JOB, Flokstra-de Blok BMJ, Dubois AEJ, Kahlon R, Dunn Galvin A. Food challenge has a rapidly established and persistent positive effect on quality of life of children 0–12 years irrespective of the clinical outcome of the challenge. J Allergy Clin Immunol. 2009;123:S143.

Johansson SGO, Bieber T, Dahl R. Revised nomenclature for allergy for global use: report of the Nomenclature Review Committee of the World Allergy Organisation. J Allergy Clin Immunol. 2004;5:832–6.

Katon W. Clinical and health services relationships between major depression, depressive symptoms, and general medical illness. Biol Psychiatry. 2004;54:216–26.

Kang DH, Coe CL, McCarthy DO, Ershler WB. Immune responses to final exams in healthy and asthmatic adolescents. Nurs Res. 1997;46:12–9.

Kovalenko PA, Hoven CW, Wu P, Wicks J, Mandell DJ, Tiet Q. Association between allergy and anxiety disorders in youth. Aust New Zealand J Psychiatry. 2001;35: 815–21.

Kyngas H, Hentinen M. Meaning attached to compliance with self-care, and conditions for compliance among young diabetics. J Adv Nursing. 1995;21:729–36.

LeDoux JE, Phelps EA. Emotional networks in the brain. In Lewis, M, Haviland J, editors. Handbook of emotions. New York: Guilford Press; 2000. pp. 134–145.

Maier SF, Watkins LR. Stressor controllability, anxiety, and serotonin. Cognit Ther Res 1998;22:595–613.

Marklund B, Ahlstead, Nordstrom G. Health-related quality of life among adolescents with allergy-like conditions – with emphasis on food hypersensitivity. Health and Quality of Life Outcomes 2004;2:65–9.

McAfoose J, Baune BT. Evidence for a cytokine model of cognitive function. Neurosci Biobehav Rev. 2009;33:355–66.

McCaugh JL. The amygdala modulates the consolidation of memories of emotionally arousing experiences. Annu Rev Neurosci. 2004;27:1–28.

Mullins LL, Wolfe-Christensen C, Hoff Pai AL, Carpentier MY, Gillaspy S, Cheek J, Page M. The relationship of parental overprotection, perceived child vulnerability, and parenting stress to uncertainty in youth with chronic illness. J Paediatric Psychol 2007;32:973–82

Morris AD, Boyle DI, McMahon AD, Greene SA, MacDonald TM, Newton RW. Adherence to insulin treatment, glycaemic control and ketoacidosis in insulin-dependent diabetes mellitus. The DARTS/MEMO Collaboration. Diabetes Audit and Research in Tayside Scotland. Medicines Monitoring Unit. Lancet. 1997;350:1505–10.

O'Connor TG, Heron J, Golding J, Glover V, the ALSPAC study team. maternal antenatal anxiety and behavioural/emotional problems in children: a test of a programming hypothesis. J Child Psychol Psychiat 2003;44:1025–36.

Overmier JB. Sensitization, conditioning, and learning: can they help us understand somatization and disability? Scand J Psychol. 2002;43 (2):105–12.

Primeau MN, Kagan R, Joseph L, Lim H, Dufresne C, Duffy C, Prhcal D, Clarke A. The psychological burden of peanut allergy as perceived by adults with peanut allergy and the parents of peanut-allergic children. Clin Exp Allergy. 2000;30:113.

Rosenkranz MA, Busse WW, Johnstone T, Swenson CA, Crisalfi GM, Jackson MM et al. Neural circuitry underlying the interaction between emotion and asthma symptom exacerbation. Proc Natl Acad Sci. 2005;102:13319–24.

Sampson HA. Food allergies. In M Feldman et al., editors. Sleisenger and Fordtran's gastrointestinal and liver disease. 8th ed., vol. 1. Philadelphia: Saunders; 2005. pp. 427–439.

Schmidt S. Coping with chronic disease from the perspective of children and adolescents – a conceptual framework and its implications for participation. Child Care Health Dev. 2003;29 1: 63–75.

Sicherer SH. Food allergy. Lancet. 2002;360:701–10.

Timonen M, Jokelainen J, Hakko H, Silvennoinen-Kassinen S, Meyer-Rochow VB, Herva A Räsänen P .Atopy and depression: results from the Northern Finland 1966 Birth Cohort Study.Mol Psychiatry. 2003;8(8):738–44.

Ursin H, Eriksen HR. Sensitization, subjective health complaints, and sustained arousal. In: Sorg B, Bell I, editors. The role of neural plasticity in chemical intolerance. Ann N Y Acad Science 933:119–29; 2001.

von Hertzen LC. Maternal stress and T-cell differentiation of the developing immune system: possible implications for the development of asthma and atopy. J Allergy Clin Immunol. 2002;109 (6):923–8.

Wamboldt MZ, Laudenslager M, Wamboldt FS, et al. Adolescents with atopic disorders have an attenuated cortisol response to laboratory stress. J Allergy Clin Immunol. 2003;111:509–14.

Watamura SE, Donzella B, Kertes DA, Gunnar MR. Developmental changes in baseline cortisol activity in early childhood: relations with napping and effortful control. Dev Psychobiol. 2004;45:125–133.

Wilson IB, Cleary PD. Linking clinical variables with health-related quality of life. A conceptual model of patient outcomes. JAMA. 1995;273:59–65.

Wright RJ, Finn P, Contreras JP, Cohen S, Wright RO, Staudenmayer J, et al. Chronic caregiver stress and IgE expression, allergen-induced proliferation, and cytokine profiles in a birth cohort predisposed to atopy. J Allergy Clin Immunol. 2004a;113 (6):1051–7.

Wright RJ, Cohen RT, Cohen S. The impact of stress on the development and expression of atopy. Curr Opin Allergy Clin Immunol 2004b;5:23–9.

Zupanic JAF, Gillie P, Streiner DL, Watts JL, Schmidt B. Determinants of parental authorisation for involvement of newborn infants in clinical trials. Pediatrics. 1997;99:213–6.

Chapter 192
Nutrition and Quality of Life in Older People

Salah Gariballa

Abbreviations

BMI   Body mass index
BMR   Basal Metabolic Rate
CCK   Cholecystokinin
DHSS   Department of Health and Social Security
EAR   Estimated Average Daily Requirements
FAO   Food and Agriculture Organisation
HRQol   Health-related quality of life
PEU   Protein-Energy Undernutrition
RDA   Recommended dietary allowances
tHcy   Total plasma homocysteine
WHO   World Health Organisation

192.1 Introduction

The number of older people is growing rapidly worldwide and looks set to continue to increase further in the future. For example by 2025, one-tenth of the world's population will be aged 65 or older and Asia will see the proportion of its elderly population almost double, from about 6% in 2000 to 10% in 2025. In absolute terms, this represents a stark increase in just 25 years from about 216 millions to about 480 million older people. This has created a need for additional knowledge of age-related changes relevant to nutrition, which has importance in the treatment and prevention of disease, and in maintaining good health and quality of life (QoL) in an ageing population. It is well recognized that with advancing age, there is a high incidence of chronic diseases, and evidence points to the importance of nutrition in the development, susceptibility and outcome of these diseases. There is no doubt that good nutrition contributes to the health and well-being of elderly people and to their ability to recover from illness (Fig. 192.1).

S. Gariballa (✉)
Department of Internal Medicine, Faculty of Medicine and Health Sciences,
UAE University, Al-Ain, United Arab Emirates
e-mail: s.gariballa@uaeu.ac.ae

Trends in Aging, by World Region

Population Ages 65 and Older
Percent
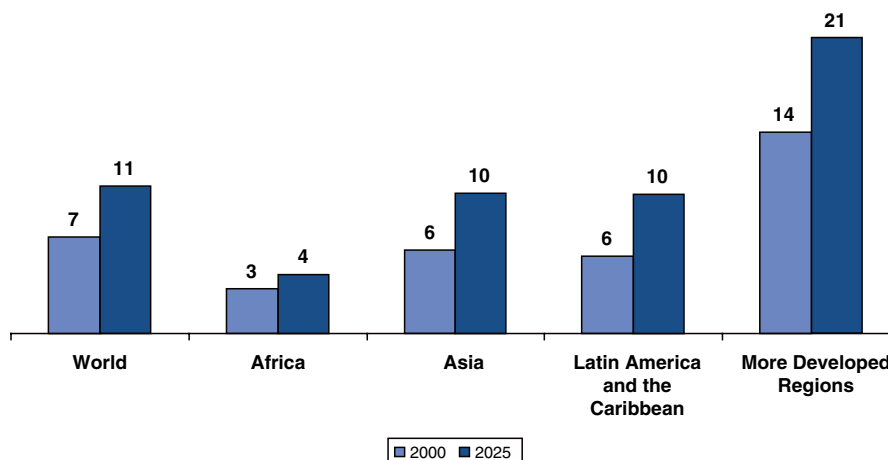
Source: United Nations, *World Population Prospects: The 2004 Revision* (medium scenario), 2005.

© 2006 Population Reference Bureau

Fig. 192.1 Trends in aging by world region (www.prb.org/presentations/j_trends-aging)

192.2 Age-Related Physiological and Pathological Changes Relevant to Nutrition

Ageing in man may be accompanied by changes, which may impair the search for food and its subsequent intake, but such changes are complex and difficult to document. Anorexia and weight loss are common and important clinical problems in the elderly; and the causes are multifactorial. There is a growing recognition that age-related physiological anorexia may predispose to protein-energy undernutrition (PEU), in the elderly particularly in the presence of other 'pathological' factors associated with ageing; such as social, psychological, physical and medical factors, the majority of which are responsive to treatment.

192.2.1 Physiological Changes

192.2.1.1 Hormonal Changes

The potential mechanisms of physiological anorexia of ageing are however, poorly understood but they are the focus of recent research. Current evidence suggests that a combination of reduced sensory perception within the gastrointestinal tract, a decline in opioid modulation of feeding, particularly in older women, and an increase in the satiating effects of Cholecystokinin (CCK) contribute to this anorexia. For example, CCK, the best characterized of the gastrointestinal hormones is known

to play a role in the control of food intake. There is evidence that sensitivity to the satiating effects of CCK increases with age. The combination of increased circulating CCK concentrations and enhanced sensitivity to the satiating effects of CCK in older people suggests that CCK may be a significant contributor to the anorexia of ageing.

With age, the time taken for the emptying of the stomach after large volumes of food is altered, this affects satiation. This may explain why older adults feel a greater satiating effect after an average meal compared to younger ones. Other hormones (leptin), neurotransmitters (opioids & nitric oxide) and protein (cytokines) may also have a role to play in anorexia and weight loss of ageing.

192.2.1.2 Gastrointestinal Tract

Objective changes in smell and taste have been observed, which may directly decrease food intake or alter the type of foods, which are selected. With ageing, there may be a progressive loss in a number of taste buds per papilla on the tongue. The remaining taste buds, which detect primarily bitter or sour tastes, show a relative increase with ageing. In addition, the ability to identify foods while blindfolded decreases with advancing age. This is a common perceived problem among elderly individuals who complain of loss of both taste and smell. Impaired appetite is often associated with reduction in taste and smell, which occur in up to 50% of elderly people. Taste thresholds are higher among institutionalized than in healthy elderly men and the use of drugs, particularly antihypertensive medication, appears to be a contributing factor. There are some documented gastrointestinal changes in the elderly, which could affect their food intake. For example changes in peristaltic activity of the oesophagus, which may result in delay of oesophageal emptying. Absorption of some nutrients, in particular vitamin B_{12} may be impaired because of mild ageing-related achlorhyria, but the evidence here is incomplete. Some researchers have reported widespread nutritional deficiencies associated with bacterial contamination of the small bowel. Others have reported a significant improvement in nutritional status in elderly patients after treatment of bacterial contamination with antibiotics. Stronger evidence point to no association between bacterial colonization of the bowel and nutritional status. The most likely interpretation of these apparently conflicting reports is that bacterial contamination of an anatomically normal small bowel in the elderly is the result rather than the cause of malnutrition. The mechanisms through which malnutrition might cause bacterial growth are not fully understood but there is evidence that the activity of several enzyme systems involved in bactericidal processes may be reduced in malnutrition.

192.2.1.3 Body Mass and Composition

Changes in body composition seen with ageing includes a decrease in lean body mass and an increase in body fat. Decreased physical activity accounts for the increased body fat and this may lead to decreased energy or calorie intake with ageing. These changes in body composition including those in fat distribution may be associated with changes in various physiological functions that affect metabolism, nutrient intake, physical activity and risk for chronic disease.

192.2.1.4 Energy Requirement

To date, the scientific evidence about energy requirement in the elderly is often incomplete and highly variable. The reasons for this include: paucity and variability of data on energy intake and

requirements; and most important of all, diversity of physical activity patterns in the elderly population. In a series of studies, elderly subjects from the USA consumed on average more energy than subjects in European studies, however the USA trials included less people compared to the European studies. The DHSS longitudinal study, which examined energy intake in 365 elderly people in 1967/1968 and 5 years later found that the average energy intake had fallen from 2,235 to 2,151 kcal per day for men and from 1,711 to 1,636 kcal per day for women. A similar trend for energy intakes to fall with age over 5 years was observed in a study of 269 elderly people in Gothenberg, Sweden.

192.2.2 Energy Expenditure

192.2.2.1 Basal Metabolic Rate (BMR)

BMR reflects the energy requirements for maintenance of the intracellular environment and the mechanical processes such as respiration and cardiac function that sustain the body at rest. It usually accounts for between 60% and 75% of total energy expenditure. The FAO/WHO/UNU Expert Consultation (1985), used equations to predict BMR. These equations may be less appropriate for the elderly populations, especially older men because of small numbers in the study, since more data have been collected which allowed a more precise estimate of current energy requirement in the elderly. BMR increases with body size, particularly with lean body mass and this explains why it is higher in men than women; and 10–20% less in old people because of reduced muscle mass and increased fat mass with ageing.

192.2.2.2 Physical Activity

In most working populations, physical activity accounts for 10–35% of total energy expenditure. The energy expenditure of different activities depend on the amount of work being carried out, the weight of the individual and the efficiency with which that work is carried out. In general, ageing is associated with a reduction in efficiency, which may make standard tasks like walking expend up to 20% more energy in older people. This reduced efficiency may be one reason why older individuals slow down. It may be contributing to negative energy balance, weight loss and undernutrition in some settings.

192.2.2.3 Thermogenesis

The term Thermogenesis encompasses a wide variety of phenomena which include energy expenditure and heat generation associated with feeding, body temperature maintenance and thermogenic response to various specific stimuli such as smoking, caffeine, and drugs. thermogenesis has also been postulated to play a part in the regulation of body weight. This field of research is complex in humans, and the theory is derived mainly from animal models. In the elderly, resting circulating catecholamine concentrations are elevated, and the responsiveness to catecholamines may decline with age, as is the case in experimental animals. Thermic response to meal ingestion in human appears to be influenced by age, physical activity and body composition. It is possible that the fall in the capacity for thermogenesis with age may explain the increased risk of hypothermia in the elderly. However, in most cases of hypothermia there is a precipitating physical cause such as stroke, which may or may not have a direct effect on thermogenesis.

192.2.2.4 Protein Requirement

There is almost a consensus regarding the current recommendation for protein intake of free living healthy elderly, which is between 0.75–0.8 g/kg. Total protein contained in lean body mass falls with age and protein synthesis, turnover, and breakdown all decrease with advancing age. Based on series of studies and literature review in 1980, Munro and Young stated that progressive loss of protein is a major feature of ageing throughout adult life. This appears to affect some tissues, notably muscle, more than others. There is no direct evidence to suggest that this erosion of tissue protein is due to lack of adequate amounts of protein in the average diet. Ill health, trauma, sepsis and immobilization may upset the equilibrium between protein synthesis and degradation. A group of researchers studied the dietary protein requirements of elderly men and women aged 56–80 years using short-term nitrogen balance techniques and calculations recommended by the 1985 Joint FAO/WHO/UNU Expert consultation. They have also recalculated nitrogen-balance data from three previous protein requirement studies in elderly people. From the current and retrospective data they reported that a safe protein intake for elderly adults would be 1.0–1.25 g/kg/day.

192.2.2.5 Vitamins

Because of low food intake and increased incidence of physical diseases, which may interfere with intake, absorption, metabolism and utilization, vitamin deficiency is more likely in the elderly compared to the young. Intake of most vitamins is reduced in smokers and alcoholics are more likely to suffer from folate and thiamine deficiency. Up to 50% of elderly in the surveyed populations ingests vitamin supplements even though there is no documented benefit from this practise when the diet is adequate. Some studies showed that multivitamin supplement on elderly patients produced significant clinical benefits. However, most other studies, which examined vitamin supplementation often, showed no consistent statistically significant difference between supplement and placebo administration. Two large surveys of vitamin status in elderly people within the past 12 years have improved knowledge of this subject: The Boston Nutritional Status Survey and the Survey in Europe on Nutrition and the Elderly. Current evidence including the SENECA and the Boston surveys on vitamin requirements of elderly people with reference to the National Research Council recommended dietary allowances (RDA) is that "there are data to indicate that the 1989 RDAs are too low for the elderly population (i.e., ≥51 years) for riboflavin, vitamin B_6, vitamin D and vitamin B_{12} – at least for certain groups of elderly people. The present RDAs for elderly people appear to be appropriate for thiamin, vitamin C and folate, but are probably too high for vitamin A. There are not enough data to make judgement on the appropriateness of the RDAs, or safe and adequate intakes for elderly people for vitamin K, niacin, biotin and pantothenic acid".

192.2.2.6 B-group Vitamins and Homocysteine

B vitamins including folate and vitamins B_2, B_6, and B_{12}, are major determinants of homocysteine metabolism and plasma tHcy concentration and hyperhomocysteinaemia is associated with cardiovascular, mental and bone health. The National Diet and Nutrition Survey of older people in the UK reported low biochemical status of one or more micronutrients in 40% of the older population, including B vitamins. Although several case-control and prospective cohort studies showed associations between modest elevation of plasma total homocysteine and cardiovascular disease, including stroke, only recently that sufficient evidence has mounted to suggest that the association is independent

and may be dose related. Several observations suggest that homocysteine have a role in the development of vascular diseases. For example, homocysteine may promote the oxidation of low-density lipoprotein cholesterol, vascular smooth muscle cell proliferation, platelet and coagulation factors activation and endothelial dysfunction. The prevalence of hyperhomocysteinaemia in the general population is between 5% and 10%. However, rates may be as high as 30% to 40% in the elderly population. Homocysteine may therefore, represent an important and potentially modifiable risk factor for cardiovascular diseases in the elderly. Causes of moderate hyperhomocysteinaemia which are all more common in the elderly include nutritional deficiencies of folic and B-group vitamins (B_{12}, B_6 and B_2), renal impairment, hypothyroidism, malignancies (acute lymphoblastic leukaemia, carcinoma of the breast, ovary and pancreas), medications/toxins (folate antagonists such as methotrexate, phenytoin, carbamazepine and vitamin B6 antagonists such as theophylline, azarabine, oestrogen-containing oral contraceptives, cigarette smoking), severe psoriasis, genetic defects in homocysteine metabolism and ageing per se. In a prospective study of 2,127 men and 2,639 women aged 65–67 years in 1992–1993 from Hordaland County, Norway, 162 men and 97 women died during a median 4.1 years of follow-up. The association between mortality and plasma total homocysteine (tHcy), distributed by quintiles with use of those with a concentration < 9.0 μmol/L as the referent group, was highly significant for both nonvascular and cardiovascular causes of death. An increase in tHcy of 5 μmol/L was associated with a 49% increase in all-cause mortality, a 50% increase in cardiovascular mortality, a 26% increase in cancer mortality and a 104% increase in noncancer, noncardiovascular mortality. Thus, plasma tHcy was a strong predictor of both cardiovascular and noncardiovascular mortality. A number of recently completed randomized trials on B vitamin homocysteine lowering and risk of stroke do not provide clear evidence of any beneficial effect, although in one trial fewer patients assigned to active treatment than to placebo had a stroke. There are many ongoing prospective, controlled intervention trials using folate, vitamin B_{12} and vitamin B_6 as homocysteine-lowering agents, the results of which (plus future metanalyses) may provide important information as to whether these vitamins can be protective against cardiovascular diseases including stroke. However, even if homocysteine-lowering therapies prove to be effective it still does not clear up whether the beneficial effect can be ascribed to a reduction in homocysteine or to an independent effect of the B-vitamins themselves.

A recent cross-sectional study from Scotland in the UK tested the association between cognitive performance and plasma vitamin B_{12}, folate and homocysteine in community-dwelling elderly. The authors used several cognitive tests in 2 cohorts, one aged 63 years and the other aged 78 years. They reported that concentrations of folate and B_{12} were positively associated with cognitive ability after controlling for childhood IQ. Cognitive function was inversely related to plasma homocysteine concentrations. A new hypothesis of the link between high levels of homocysteine and depressed mood is emerging. A plausible explanation for the association is that high homocysteine levels cause cerebrovascular disease and neurotransmitter deficiency, which cause depression of mood. Interventional studies would be needed to test this hypothesis.

192.2.2.7 Antioxidants

There are many theories on the ageing process. One important theory is that accumulation of oxygen-free radicals over the years leads to cumulative damage to cellular structure and function and consequently physical changes of ageing. Since then, there has been much interest in the role of antioxidants on the ageing processes.

There are several reasons why consumption of fruit and vegetables merits special attention. Besides contributing to non-starch polysaccharides, they are rich sources of vitamins and minerals

such as carotene, vitamins A, E, C and potassium. Several of these micronutrients have antioxidant properties and they may have a role in protecting against oxidative free radicals, which may be involved in the mechanism of atherosclerotic injury and ageing. Evidence is also accumulating to show that free radical damage may be important in other diseases such Parkinson's disease, Alzheimer's disease, chronic inflammatory disease and cancer and that some of diseases (cardiovascular and cancer) may be prevented or delayed to some extent by dietary changes such as reduction in fat intake and increased consumption of fruits, grains and vegetables.

192.2.2.8 Trace Elements

Knowledge of the exact role and dietary requirements for some of the following minerals (Cobalt, Copper, Chromium, Flouride, Iodine, Manganese, Molybdenum and Selenium) is incomplete for three reasons: they have only recently been found to be essential; dietary deficiencies of many are unknown; and the utilization of one may be affected by the amount of other elements present. However, for some there are recommended dietary intakes, which may be adequate and safe, but their optimum intakes are unknown.

192.3 Pathological Changes

192.3.1 Medical and Social Factors

Risk factors for undernutrition amongst elderly people in the community includes: isolation with an inability to go out shopping, loss of spouse, depression and bereavement, decreased mobility, dementia, anorexia due to disease especially cancer, medications, poor dentition, alcoholism and most important of all acute illness. In institutions, lack of supervision and assistance at mealtimes may be an important factor resulting in poor food intake (Table 192.1).

   Because old people are disproportionately isolated, on low income or disabled, socio-economic factors and disease are likely to have more influence on their nutritional status than age alone.

Table 192.1 Factors associated with poor nutritional status in older people in community and home care settings

Poor eye sight and hearing problems
Joint problems and hand tremors
Isolation
Inability to go out shopping and poor income
Depression and bereavement
Poor cognitive and physical functioning
Nausea, and vomiting
Poor appetite
Anorexia due to disease especially cancer, medications
Poor dentition and chewing problems
Acute illness
In institutions,
lack of supervision and assistance at mealtimes may be an important factor resulting in poor food intake

192.3.2 Cognitive Function

Cognitive decline and dementia are common in old age. For example, one in five of hospitalized older people has cognitive impairment at any one time, whereas dementia affects one in 20 people over the age of 65 and one in five over the age of 80. The central nervous system requires constant supply of glucose, and adequate brain function and maintenance depends on almost all essential nutrients. For example, B-group vitamins (folate and vitamin B_6 and B_{12}) deficiency or congenital defects in the enzymes associated with these pathways has been found to be associated with severe impairment of brain function. Although severe deficiencies and congenital defects are rare, milder subclinical vitamin deficiencies are not uncommon in the elderly. Many recent experimental and epidemiological studies have shown associations between loss of cognitive function or dementia and inadequate B-group vitamin status in older people. A recent study has found graded association between elevated plasma homocysteine, an indicator of inadequate B-group vitamins and cognitive impairment in healthy elderly community dwellers. A recent Cochrane review examined the effects of folic acid supplementation, with or without vitamin B_{12}, on elderly healthy or demented people, in preventing cognitive impairment or retarding its progress. The small number of studies which have been reviewed provide no consistent evidence either way that folic acid, with or without vitamin B_{12}, has a beneficial effect on cognitive function of unselected healthy or cognitively impaired older people. In a preliminary study, folic acid was associated with improvement in the response of people with Alzheimer's disease to cholinesterase inhibitors. In another, long-term use appeared to improve the cognitive function of healthy older people with high homocysteine levels. More studies are needed on this important issue. A growing body of evidence also supports the notion that oxidation and inflammation are part of the mechanisms responsible for cognitive decline and progression to dementia in older people. Recent research found that the use of vitamin E supplements, but not vitamin C supplements, may be related to modest cognitive benefits in older women. Supplementation with Vitamin E has also been found to lead to significant delay in the progression of dementia.

Macronutrients such as carbohydrates may have a role on cognitive function. A study of 11 men and 11 women aged 61–79 years consumed either 300-ml drink containing 774 KJ as pure protein, carbohydrate, or fat or a nonenergy placebo on four separate mornings after an overnight fast. Energy intake from protein, carbohydrate, or fat was found to enhance memory independently of elevations in blood glucose.

The extent of the relationship between inadequate nutrients status and loss of cognitive function in older people remains unclear. Advances in the understanding of this complex relationship may depend on the outcome of longitudinal prospective nutritional intervention studies starting prior to the onset of neurocognitive decline.

192.3.3 Depression and Well-being

The relationship between nutrition and older people psychiatry has received little attention. Recent research on the role of micronutrients in psychiatric disorders in older adults has revealed that low folic acid/vitamin B12 has been found to be associated with depression in older persons. For example, the Rotterdam study has reported a relationship between hyperhomocyteinaemia, vitamin B12 and folate deficiency and depressive disorders. Quality of life has also recently become a clinically relevant outcome measure when evaluating new treatment strategies in patient's population, particularly an older one. Studies have shown a close relationship between undernutrition and poor quality of life in some populations such as institutionalized older people and cancer patients. A study
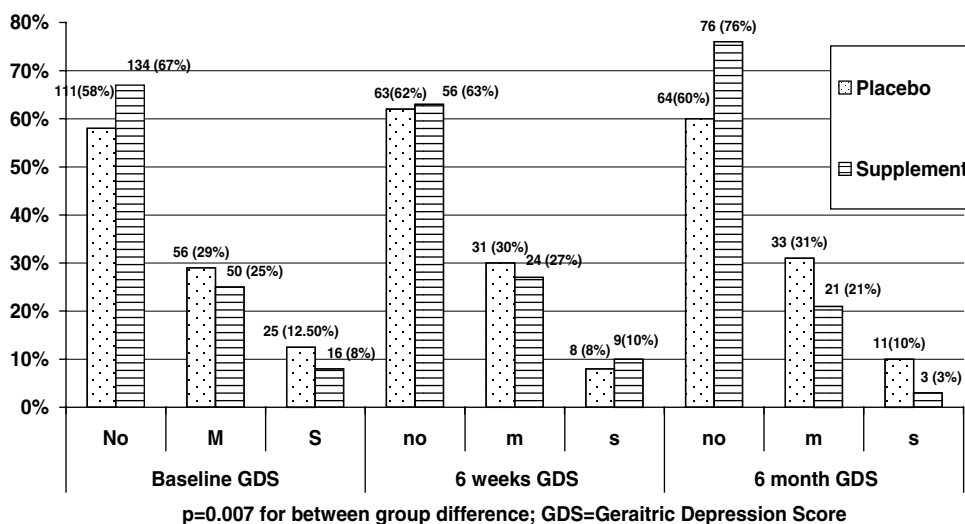
Fig. 192.2 The effect of supplements on the number (%) of patients with no depression (No), mild depression (M), and severe depression (S), over 6 months compared to placebo

published recently has shown that oral nutritional supplementation of hospitalized acutely ill older patients led to a statistically significant benefit on depressive symptoms. Improvement in depressive symptoms also coincided with increase in red-cell folate and plasma vitamin B12 concentrations (Fig. 192.2). There is also some evidence, which suggests that a low intake of fish and/or n-3 PUFA is associated with depressed mood. Recently completed randomized controlled intervention trials found no effect of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) supplementati on mental well-being in the general older population studied.

192.4 Nutritional Status and Quality of Life in Older People

With advancing age both undernutrition and chronic diseases become more common [1]. There is evidence linking protein-energy undernutrition or its markers with clinical outcomes in acute and non-acute care settings. Poor nutrition leads to ill health and ill health to poor nutrition, so identifying priorities for managements still remain a challenge. A recent review of the literature on nutrition and older people psychiatry reported that although this issue has received little attention, there has been recent research on the role of micronutrients in psychiatric disorders in older adults. Studies have also shown a close relationship between undernutrition and poor quality of life in some populations such as institutionalized older people and cancer patients. Quality of life is a subjective multidimensional measure reflecting functional status, emotional and social well-being as well as general health. It has recently become a clinically relevant outcome measure when evaluating new treatment strategies in patient's population particularly older ones (Table 192.2).

Studies on assessment of the efficacy of nutritional support on older patient's outcomes hitherto have been limited to open ones. A metaanalysis of trials of protein and energy supplementation in older people reported that data were limited by the poor quality of most included trials. Future trials should have sufficient power, proper concealed allocation and blinding of treatment and should focus on outcome measures of relevance to patients such as improvement in function and quality of life.

Table 192.2 Key features of quality of life

- Health is defined by a state of complete physical, mental and social well-being and not only absence of disease
- Health-related quality of life scores often attempt to measure the psychological, physical and social effects of an illness and it is response to treatment
- Quality of life is therefore a subjective multidimensional measure reflecting functional status, emotional and social well-being as well as general health
- Quality of life has recently become a clinically relevant outcome measure when evaluating newtreatment strategies in patient's population particularly older ones

Despite growing evidence that nutritional support improves outcome in older people, there is however lack of good-quality data of the effects of nutritional support on quality of life measures in older people.

192.4.1 Assessment of Quality of Life

Health is defined by a state of complete physical, mental and social well-being and not only absence of disease. Health-related quality of life scores often attempt to measure the psychological, physical and social effects of an illness and it is response to treatment. This latter point is important because in this day and age, efficacy of treatment is not only judged on safety and ability to improve clinical outcomes but also on acceptability to patients and cost-effectiveness. Outcome measures which encompass quality of life measure such as the SF 36 are therefore very important especially in older people (Table 192.3). A large number of generic and disease-specific quality of life measures have been developed and some have been validated mainly for cancer in palliative care.

192.4.2 Undernutrition and Quality of Life

A prospective study of 579 randomly selected home-living older people has found that lower self-perceived health had the highest power to predict risk of malnutrition, with increased number of depression symptoms and higher age as second and third predictors.

A very recent systematic review examined the relationship between health-related quality of life and nutritional status of the patient. The authors reviewed studies that relate health-related quality of life to nutritional status and examined the tools (questionnaires) that they were to use to investigate this relationship. A critical review of published studies was carried out via an investigation of the following databases: MEDLINE (via PubMed), EMBASE, The Cochrane Library, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Institute for Scientific Information (ISI) Web of Science, Latin American and Caribbean Health Sciences Literature (LILACS), Spanish Health Sciences Bibliographic Index (IBECS). The search was carried out from the earliest date possible until July 2007.The medical subject heading terms used were 'quality of life', 'nutritional status' and 'questionnaires'. The articles had to contain at least one questionnaire that evaluated quality of life. Twenty-eight documents fulfilling the inclusion criteria were accepted, although none of them used a specific questionnaire to evaluate HRQoL related to nutritional status. However, some of them used a combination of generic questionnaires with the intention of evaluating the same. Only three studies selectively addressed the relationship between nutritional status and quality of life, this evaluation being performed not by means of specific questionnaires but by statistical analysis of data obtained via validated

Table 192.3 Key features of SF-36 quality of life assessment questionnaire

- The SF36 is a validated Quality of life Medical Outcomes Study 36-items General Health Survey questionnaire
- The questionnaire consists of 36 questions forming 8 multi-item scale including physical functioning, role limitations- physical, role limitation- emotional, bodily pain, general health, vitality, social functioning and mental health
- The SF 36 validity is now well established and it has been used in several large studies
- The SF 36 has been adapted for use with older adults
- The questionnaire is measured on a 0 to 100 (good health) scale, self-administered with help provided when needed and takes about 10 minutes to complete

questionnaires. The first study by Eriksson et al. investigated measurements of nutritional status and health-related quality of life. The author's objective was to relate a well-established questionnaire of nutritional status (MNA) to a likewise well-established questionnaire of health-related quality of life (SF-36) in community dwelling, free-living and, healthy 70–75-year-old persons. Before an interview, the MNA and SF-36 questionnaires were filled in by 128 participants from a sample of 262 subjects. Their results showed that the MNA worked well as a measurement in this sample. Many MNA aspects correlated with the SF-36 scales. The correlations between MNA total score and the eight SF-36 scales varied from.27 to.62. This correlation was partly due to the fact that MNA has questions of health but also to the fact that there is an empirical relation between nutrition and health. The authors concluded by saying "The MNA measurement is applicable to a healthy, free-living elderly population and parts of the MNA can be interpreted as measurements of health-related quality of life. Low values of SF-36 could also be used as predictors of risk of malnutrition, although further studies are required to confirm this result". The second study was a cross-sectional survey to determine the independent association of nutritional risk with HR-QOL in frail older adults. Data were collected by interviewer-administered questionnaire. Nutritional risk was measured by SCREEN (Seniors in the Community: Risk Evaluation for Eating and Nutrition) and HR-QOL by perceived health status and report of number of days in the past month where physical or mental health was not good, or where activities were limited. Frail ($n = 367$) seniors were recruited from 23 community service providers. A wide variety of covariates were also measured. Multivariate modelling based on a conceptual model was used to identify factors associated with HR-QOL. The results showed that nutritional risk appears to be a significant and important factor associated with HR-QOL. Other significant covariates were: falls, social supports, social activity, health behaviours, pain and medication use. Nutritional risk as measured by SCREEN appears to be a significant covariate in explaining differences in HRQOL among frail older adults. Further work should determine if nutritional risk predicts changes in HR-QOL over time. The third study evaluated the scored Patient-generated Subjective Global Assessment (PG-SGA) tool as an outcome measure in clinical nutrition practise and determine its association with quality of life (QoL). This was a prospective 4-week study assessing the nutritional status and QoL of ambulatory sixty cancer patients aged 24–85 years receiving radiation therapy to the head, neck, rectal or abdominal area. Outcome measures were scored PG-SGA questionnaire, subjective global assessment (SGA), QoL (EORTC QLQ-C30 version 3). According to SGA, 65.0% (39) of subjects were found to be well-nourished, 28.3% (17) moderately or suspected of being malnourished and 6.7% (4) severely malnourished. PG-SGA score and global QoL were correlated ($r = -0.66$, $P < 0.001$) at baseline. There was a decrease in nutritional status according to PG-SGA score and SGA; and a decrease in global QoL after 4 weeks of radiotherapy. There was a linear trend for change in PG-SGA score and change in global QoL between those patients who improved (5%) maintained (56.7%) or deteriorated (33.3%) in nutritional status according to SGA. There was a correlation between change in PG-SGA score and change in QoL after 4 weeks of radiotherapy. Regression analysis determined that 26% of the variation of change in QoL was explained by change in PG-SGA.

192.4.3   Effects of Nutritional Support on Quality of Life

Poor nutrition may lead to ill health and ill health to poor nutrition. For example, many studies have found that lower self-perceived heath/quality of life and/or symptoms of depression increased risk of malnutrition and that malnutrition leads to poor quality of life and increased depression symptoms. So identifying priorities for management remains a challenge. Prior to coming into hospital elderly people in the community are more likely however, to have premorbid decrease in energy or calorie intake, less lean body mass and impaired immune response, which may be associated with poor nutritional. Their nutritional status is likely to deteriorate further as the result of the catabolism associated with the acute illness. This is compounded further by the demands of the sometimes-prolonged period of rehabilitation. Nutritional depletion during rehabilitation, however, may be more serious than during acute illness, since rehabilitation periods may extend over weeks and months, and weight loss, although less marked than in the early catabolic phase may be greater overall. In 1971, a study compared nutrient intakes of long stay, acutely ill and rehabilitation patients, and showed that energy and protein intakes were lowest in the latter group. A clinical review by Caro and colleagues on the effects of nutritional intervention on quality in adult oncology patients reported that nutritional intervention should be integrated into oncology care because it increases tolerance and response to treatment, decrease complications and improve quality of life by controlling symptoms such as nausea, vomiting, pain. Quality of life has also been found to be related to nutritional status in dialysis patients. Providing individualized nutritional counselling improves many components of quality of life, compared with standard nutritional care, in the stage prior to dialysis treatment. A recent randomized placebo-controlled study has reported that nutritional supplementation of older people during acute illness and convalescence/rehabilitation period significantly improves quality of life. The improvements in quality of life indices was accompanied by significant improvements in biomarkers of nutritional status in the supplement group, which were evident at 6 weeks and sustained at 6 months (Table 192.4 and Fig. 192.3). Improvement of micronutrients status such as vitamin B12 and red-cell folate would be the most plausible explanation for the improvement in well-being of our study population. Although there are well-known changes in micronutrients status in old age that significantly correlate with adverse physical outcomes such as cardiovascular, disease, cerebrovascular disease, impaired immune function and bone health all contributing to the development of frailty less is known of a relationship between B12, folate and quality of life. There is however evidence of a strong link between B12/folate status and depression in older adults.

The lack of statistically significant differences in anthropometeric measures between the supplement and placebo group could be due to the short time frame of the supplementation and to inherent difficulties in measuring these nutritional indices in ageing patients. This is especially true for studies in the elderly, being affected by age-related changes, disability, illness and injury. Another plausible explanation for our results would be that mild subclinical nutritional deficiencies, which are known to be common even in relatively healthy persons, which otherwise would have gone unnoticed in our supplement group, have been corrected, hence the clinical benefit. This trial has demonstrated that nutritional supplementation of hospitalized older people does lead to a clinically important benefit.

In conclusion, the number of older people is growing rapidly worldwide and looks set to continue to increase further in the future act on quality of life for older people. This has created a need for additional knowledge of age-related changes relevant to nutrition which has importance in the treatment and prevention of diseases and in maintaining good health and quality of life in an ageing population. Evidence is emerging of a link between undernutrition and poor quality of life in older people and that improvement in nutrition status leads to improvement in quality of life but there is an urgent need for more research in this field. The prospect of the effects of improved nutritional status of older people quality of life could have an important and a substantial health and economic impact.

Table 192.4 Effect of supplements on quality of life (SF-36 domains) compared to placebo

	Group	N	Mean Baseline	(SD)	Mean 6 months	(SD)	Difference at 6 months	Treatment effect (95% CI)	P-value
SF-36 Physical Function	Placebo	107	34.7	(30.5)	32.5	(27.3)	6.6	7.0 (0.5 to 13.6)	0.035
	Supplements	95	33.5	(29.0)	39.1	(30.5)			
SF-36 Role Physical	Placebo	106	17.7	(32.2)	28.8	(37.1)	10.3	10.2 (0.1 to 20.2)	0.047
	Supplements	94	17.3	(33.4)	39.1	(38.7)			
SF-36 Bodily Pain	Placebo	107	41.4	(29.7)	55.1	(28.9)	2.5	1.9 (−5.7 to 9.5)	0.619
	Supplements	95	42.0	(31.4)	57.7	(30.2)			
SF-36 General health	Placebo	106	46.3	(22.2)	49.4	(23.0)	1.3	−0.1 (5.4 to 5.1)	0.956
	Supplements	96	48.5	(22.4)	50.7	(23.3)			
SF-36 Vitality	Placebo	106	39.6	(23.3)	42.3	(21.4)	8.1	4.7 (−0.7 to 10.1)	0.088
	Supplements	95	45.8	(24.7)	50.4	(24.3)			
SF-36 Social Function	Placebo	107	51.0	(32.0)	58.7	(30.0)	7.4	7.8 (0 to 15.5)	0.050
	Supplements	95	48.5	(33.5)	66.1	(29.9)			
SF-36 Role Emotional	Placebo	105	42.9	(45.0)	52.1	(44.3)	5.2	5.0 (−6.3 to 16.2)	0.384
	Supplements	96	43.1	(45.6)	57.3	(42.9)			
SF-36 Mental Health	Placebo	105	65.1	(21.3)	66.9	(21.8)	5.7	3.3 (−1.5 to 8.1)	0.181
	Supplements	95	69.4	(19.3)	72.6	(18.4)			
Barthel	Placebo	119	16.5	(4.4)	18.6	(2.6)	−0.4	−0.3 (−0.8 to 0.3)	0.369
	Supplements	106	16.3	(4.6)	18.2	(3.1)			

Treatment effect: difference in quality of life scores at 6 months, after adjustment for baseline quality of life scores, age, and gender
Outcomes are based on patients who completed both the baseline and 6-month assessments
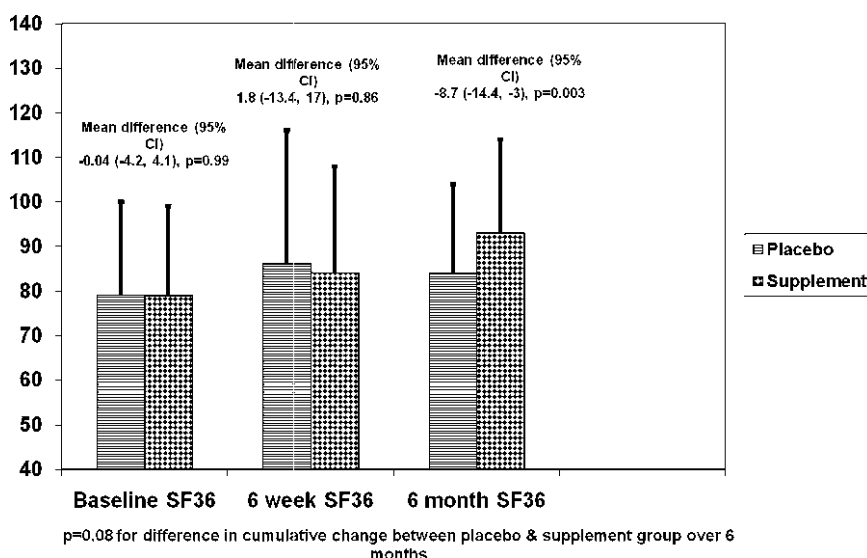
Fig. 192.3 Overall SF-36 scores of placebo and supplement group over 6 months mean (SD)

192.5 Application to Other Areas of Health and Disease

Undernutrition can adversely affect physical, psychological and behavioural function and this can have major social and economic implications. Evidence is emerging of a link between undernutrition and poor quality of life in older people and that improvement in nutrition status leads to improvement in quality of life. Older people should therefore be advised to eat a balanced diet containing a variety of nutrient-dense foods; more fruits, vegetables and grains; foods containing adequate amounts of calcium and vitamin D. Widespread implementation of this strategy could have a substantial economic impact and improve mental health for older people.

Summary Points

- Many societies worldwide have experienced a considerable increase in the number of elderly people.
- Ageing, disease, life style, and environmental factors account for many of the changes observed in older people.
- There is a growing recognition that age-related physiological changes may predispose to protein-energy undernutrition, in the elderly particularly in the presence of other 'pathological' factors associated with ageing; such as social, psychological, physical, and medical factors, the majority of which are responsive to treatment.
- This has created a need for additional knowledge of age-related changes relevant to nutrition, which has importance in the treatment and prevention of diseases and in maintaining good health and quality of life in an ageing population.
- Evidence is emerging of a link between undernutrition and poor quality of life in older people and that improvement in nutrition status leads to improvement in quality of life but there is an urgent need for more research in this field.

Key Points of Diet, Nutrition and Quality of Life in Older People

1. A healthy older person's dietary patterns and the food eaten are not likely to be that much different from what is known about those of younger age.
2. The majority of 'pathological' factors associated with ageing; such as social, psychological, physical and medical factors, which may predispose to undernutrition, are responsive to treatment.
3. New evidence is emerging of a link between undernutrition and poor quality of life in older people and that improvement in nutrition status leads to improvement in quality of life.
4. Future research should focus on the role of adequate nutrition and active life in prevention and treatment of disease and improving quality of life in the ageing population.
5. Older people should be advised to eat a balanced diet containing a variety of nutrient-dense foods; more fruits, vegetables and grains; foods containing adequate amounts of calcium and vitamin D and this may need to be monitored in certain individuals.

References

Bhat RS, Chiu E, Jeste DV. Curr Opin Psychiatry. 2005;18:609–14.
Campbell KL, Ash S, Bauer JD. Clin Nutr. 2008;27:537–44.
Eriksson BG, Dey DK, Hessler RM, Steen G, Steen B. Nutr Health Aging. 2005;9:212–20.
Gariballa S, Forster S. Clin Nutr. 2007;26:545–51.
Gariballa S, Forster S. J Am Geriatr Soc. 2007;55:2030–4.
Gariballa SE, Sinclair AJ. Ageing & the elderly. In Geissler C, Powers H, editors. International textbook of human nutrition, 11th ed. New York: Elsevier Science; 16; 2005. p. 321–336.
Gariballa SE, Sinclair AJ. Br J Nutr. 1998;80:7–23.
Johansson Y, Bachrach-Lindström M, Carstensen J, Ek AC. J Clin Nurs. 2009;18:1354–64.
Isenring E, Bauer J, Capra S. Eur J Clin Nutr. 2003;57:305–9.
Keller HH. J Nutr Health Aging. 2004;8:245–52.
MacIntosh CG, Morley JE, Horowitz M, Chapman IM. Nutrition. 2000;16:983–95.
Milne AC, Potter J, Avenell A. Cochrane Library. 2002; issue 3, Oxford.
United Nations, World Population Prospects: The 2004 Revision (medium scenario) 2005. www.prb.org/presentations/j_trends-aging
Wanden-Berghe C, Sanz-Valero J, Escribà-Agüir V, Castelló-Botia I, Guardiola-Wanden-Berghe R. Red de malnutrición en iberoamérica – ciencia y tecnología para desarrollo (Red MeI – CYTED. Br J Nutr. 2009;101:950–60.

Chapter 193
Biopsychosocial, Behavioural Aspects and Quality of Life with Home Enteral Nutrition

Agostino Paccagnella, Alessandra Mauri, Gessica Schiavo

Abbreviations

AN   Artificial nutrition
EN   Enteral nutrition
HEN   Home enteral nutrition
HRQoL   Health-related quality of life
PN   Parenteral nutrition
QoL   Quality of life
WHO   World Health Organization

193.1 Introduction

Many diseases that are curable from a medical standpoint cannot be healed by medicine as yet. This channels patients presenting such disorders into a condition that is defined as chronic. A chronic disease is characterised by the need to manage it in the long term to undergo complex, long-term, therapeutic interventions from the onset of complications subsequent to the treatment itself. Chronicity is almost always accompanied by a worsened health condition, following the progress of the basic disease. The ability to diagnose a disease or a condition of deficiency (e.g. malnutrition) is considered a positive factor – from a biomedical viewpoint – as it enables to plan a series of interventions focused on managing the physical health of the subject. When an acute disease is diagnosed, the process is scheduled, medical treatments are decided in advance and healing can be achieved during a certain time interval. This encourages patient compliance. The acute disease alters the life of the subject for a defined period of time. Moreover, social, physical changes and alterations in the framework and habits of the patient are limited in time and can therefore often be managed. The situation concerning the diagnosis and treatment of chronic diseases from which the patient will not heal is quite different. The consequences of the chronic disease influence all aspects of the life of a subject, affecting him psychologically, socially and contextually. Disease characteristics can change in time, producing several types of complications, new symptoms and new therapeutic needs. In this case, the biomedical approach alone for scheduling and evaluating interventions will not suffice

A. Paccagnella (✉)
Nutrition, Metabolism and Diabetes Unit, Ospedale Ca' Foncello, 31100 Treviso, Italy
e-mail: apaccagnella@ulss.tv.it

anymore because the aspects involved are many. The needs, feelings and expectations of both the patient and his relatives become key factors in treatment, which entails taking care of the whole patient and not only of his body. A typical example of treatment, combined with a chronic disease is HEN, which is administered to subjects who cannot be fed by mouth due to an underlying disease and who are sent home on artificial nutrition (AN) after a certain period of hospital treatment. The possibility of sending home patients with chronic diseases that prevent food intake by mouth has basically changed home health care. It has changed the economic conditions of health-care institutions, and also raised ethical issues on the risk of therapeutic obstinacy. Home care is highly beneficial for those who were either not receiving appropriate treatment or were forced to stay long in hospital. HEN has become a therapeutic option that considerably lengthens the life of patients who were previously doomed to malnutrition, in some cases even significantly postponing the time of death. But this very outcome and its clinical (patients whose basal disease deteriorates slowly and progressively), ethical (should therapy be terminated? when?) and social implications have an impact on the patient as a whole (Buchman 2005). Taking for granted that therapeutic results and actions must be evaluated with the appropriate clinical, anthropometric, blood-chemical monitoring systems and equipment to provide the patient with the best physical conditions possible given the basal disease, it would be naive to theorise that only physiological parameters are indicators of the state of well-being of a patient undergoing HEN, since this treatment becomes part of the life of the patient in various moments of the day, and for very long periods, if not forever. Hence the idea of shifting focus from a biochemical or biomedical model, which considers the illness from a purely objective standpoint, to a model that can deal with the patient in all his facets, considering his broader biopsychosocial framework. This chapter describes the reference theoretical framework, treatment characteristics and impact on both subjects and their lives of a transition to artificial nutrition from oral feeding. It defines quality of life and health-related 'quality of life' (QoL), evaluating the importance of measuring the 'health-related quality of life'' (HRQoL) in patients who are sent home on enteral artificial nutrition. The chapter briefly describes standardised tools that are most used according to literature for the evaluation of HRQoL and the possible problems found in measuring this parameter.

AN comprises artificial parenteral nutrition (PN) and artificial enteral nutrition (EN). PN consists in using venous catheters to administer nutrients directly into the bloodstream through a peripheral or central venous access. EN allows nutrients to be administered directly into the gastrointestinal system with special probes that are inserted either through the nose or stomies created through the abdominal wall.

This chapter will specifically enlarge on EN by analysing aspects of the impact of treatment in the daily life of subjects.

193.2 The Theoretical Framework: A Biopsychosocial Approach

The World Health Organization (WHO) has long invited medicine to adopt a new approach to the evaluation and management of chronic diseases (WHO 1986). According to this theory, the correct approach and management of a chronic disease demands a biopsychosocial approach that centres treatment on the patient and his relatives who become the lead actors in the management of the disease. In medical literature, the 'biochemical model' (that evaluates the objective alterations of the patient) is increasingly integrated into the holistic model that can consider the viewpoint of the patient (e.g. how he experiences his disease and subsequent treatment and effects on daily life) (Aspinwall and Staudinger 2003). This approach shifts focus from the disease 'of the body' to the

disease 'of the patient' who is deemed a person with an inner world of his own and lives in a specific physical and social framework. Adopting this overall standpoint, the therapeutic intervention is managed along with the patient who becomes the active protagonist of his decisions, and even the idea of wellness is considered from a subjective viewpoint, conversely to the directive and prescriptive intervention of the biomedical approach. The 'biopsychosocial' model combines the medical and psychosocial models of health to implement an intervention that issues from a 'reasonable dialogue' with the subject under treatment and his relatives. Focus is not on the disease anymore but on health, which is deemed as an attempt to create new balances to reach physical, psychological and subjective wellness, starting from the sociocultural framework the individual belongs to.

Even treatment-based relations change in this context. While in the acute patient, especially at the time of diagnosis, the biomedical approach defines the operator as the competent person who, in a directive and prescriptive framework, is entrusted with the most appropriate decisions required to define the disease, in chronic patients treatment-based relations develop over a prolonged period of dialogue with the patient, assuming therapeutic features in a broad sense. The health care operator and the user are the two key actors of the relationship. The operator is trained on diagnostic, prognostic, treatment and prevention techniques, but only the user has direct experience of the disease, of the social framework in which he lives and of his values and preferences. The operator must know where the patient lives, his attitude towards health and treatment and his expectations to directly establish relations with the patient and work on the treatment. This is implemented in a new perspective in which the organic disease and subjective experience of the user concerning the disease have the same importance.

193.3 Eating and Feeding

Sharing food is an essential factor in social relations and friendship. The intake of food, the food-related attitude and the act of eating itself have complex and varied features that continuously intersect the biological framework with the affective and social life of the individual. Therefore, the type of food shared, meal characteristics and rate of occurrence are very strong indicators and components of affective bonds. They are directly related with the construction and reproduction of emotional relations, converging to form a basic element in the life of a subject. In various societies food is a way of establishing bonds, managing power and defining roles. Several messages that do not merely stop at the level of nutritional function but can be inserted into the complex and circular biopsychosocial interpretative model move through the symbology of food that is prepared, offered and accepted. When a disease makes it impossible for a patient to eat again, causing him to resort to tube feeding it is easy to imagine the deep lifestyle changes subsequent to the diagnosis of a chronic disease and the intervention of AN as treatment and prevention of malnutrition.

This chapter defines the concept of the intrinsic artificiality of EN, considering the attitude of the patient towards the mode of administration and not towards the type of 'food' used, which can be natural like home-made blended foods, or an industrial item that is produced and packaged in a totally artificial framework. According to this definition, home-made blended foods infused through a nasogastric tube possess the therapeutic traits of artificiality, while an artificial substance taken by mouth (e.g. an industrial product for patients with Crohn's disease) is, by the same definition, a natural food that has no therapeutic valency. As a matter of fact, the person who 'eats by mouth' can manage food both in a specific (e.g. choose the food from a menu) and social sense (e.g. organise a dinner to close a business), as he can share it with others in the most diverse frameworks. This can paradoxically occur with an industrial product for oral use that is administered to a patient who

presents a specific disease, which requires him to take special oral food. He can, however, sit down at table, experience lunch as a social moment and on some occasions even let another person taste the artificial food. Conversely, the need to infuse either blended or industrial food through a tube, which deprives the patient of the sense of taste and smell, modifies the feeling of satiety and, especially, refrains the patient from attending social food-sharing moments – if only for the embarrassment of having to expose the terminal part of the PEG to others – expresses in itself the concept of artificiality of enteral nutrition.

Therefore, this chapter will hereinafter designate as 'eating' everything that is taken by mouth and has implicit repercussions on the affective, social, cultural and biological framework. It will designate that which is commonly and historically called 'food' and which envisages the act of eating. AN and, especially, EN (including HEN), instead, designate all calories and macro- and micronutrients that are infused through a tube to ensure nourishment to the body, but which deprive the person of the psychosocial implications of "eaten food". Hence, AN envisages important clinical monitoring, requires informed consent to position the tubes, the continuous use of nutripumps to infuse food, specific result indicators and blood chemistry monitoring.

These concepts make it easy to understand that artificial nutrition is an example of therapeutic intervention in which the integrated and holistic dimension that creates wellness is damaged, and subjective balances are modified.

EN shifted to the domestic framework (HEN) requires specialist health-care skills (e.g. evaluation of the need, choice of nutritional mixture and route of administration), presupposes continuous contact with health-care operators and the acquisition of some specific management skills on the part of both the patient and his family (caregivers). The therapeutic intervention that modifies 'eating' and turns it into 'nutrition' (namely EN) does not necessarily prevent the patient from performing routine daily tasks. Some patients go on working and travelling. But to maintain their normal productive activities through HEN, it certainly generates new biological, emotional and relational variables.

Moreover, the social and affective characteristics of food are not the only factors that must be considered in the transition from eating to AN, as there are other forms of change associated with sensory deprivations such as, for instance, the loss of the taste and smell of food, altered body image (e.g. stepping into the swimming pool with the PEG) or interference in certain frameworks of life of the subject (e.g. sexuality). The life characteristics of these subjects, their emotional and psychosocial difficulties, the physical and practical obstacles they face in carrying out their tasks, the complications and the reactions of relatives are all factors that must be considered and evaluated in planning home-based interventions and treatment.

A special subgroup of patients is the one formed by subjects in a permanent vegetative condition that was mainly caused by cerebrovascular accidents or degenerative diseases, such as Parkinson's syndrome or Alzheimer's disease. In such subjects (who were defined as 'non-competent'), the concept of quality of life evaluation necessarily shifts to the relational and environmental framework, such as the impact of treatment and home care, on their caregivers (Hebert et al. 2007), and the situation is evaluated by operators on the basis of clinical scales (Fayers and Machin 2001).

193.4 Biomedical Aspects of Enteral Nutrition

As already mentioned, enteral nutrition entails introducing either industry-produced nutrients (calories, macro- and micronutrients) or processed foods (e.g. blended foods and chopped foods) with the assistance of a 'tube' (nasogastric tube, NGT; percutaneous gastrostomy, PEG; surgical jejunostomy, SJ; nasojejunal tube, NJT; percutaneous jejunostomy, PEJ; surgical gastrostomy SGS). It therefore either improves or maintains an adequate nutritional condition by treating or preventing malnutrition

and its complications in single organs and systems, influencing the risk of complications and altering the risk of death for patients (NICE 2005; Lochs et al. 2006; Bankhead 2007).

HEN is a set of organisational modes for EN administration at home when the clinical condition of the patient is stable, and his social and family framework can guarantee the safety and efficacy of treatment outside the hospital on a home care regime.

HEN has the same indications as EN administered in the hospital but it allows treatment to be administered at home, thus avoiding long stays in hospital and reintegrating the patient into his family, social and, at times, work-related framework (Lochs et al. 2006; Bankhead 2007).

193.4.1 Epidemiology

Epidemiological studies on enteral nutrition at home are still few due to the few registers or databases appointed to collect such data. This data estimates a progressive increase in HEN with a growth trend of over 20% in the past. A multicentre, retrospective study promoted by the European Society of Parenteral and Enteral Nutrition to evaluate indications and practice of HEN in 23 centres in eight European countries in 1998 highlighted an incidence of 163 cases/10^6 inhabitants/year (range: 62–457 cases/10^6 inhabitants/year). The paper reported that the main indication for HEN was the presence of dysphagia (84.6%), and the main diseases associated with the request were neurological (49.1%) and neoplastic (head and neck region: 26.5%) (Hebuterne et al. 2003). Despite this important rise in HEN, its incidence and prevalence is extremely varied and diversified, and depends on the clinical condition and organisation of the reference territory (Jones et al. 2007; Paccagnella et al. 2008).

Compared with the epidemiological data of HEN, the method was applied to patients hospitalised as *nursing home residents (NHRs)* in few cases. A recent survey carried out in the USA found that about 34% of the 1.4 million NHRs require some assistance to eat (Centers for Medicare and Medicaid Services 2005). It is currently estimated that about 2–34% of NHRs are nourished by tube feeding (Mitchell et al. 2003).

Our data on NHRs who underwent enteral nutrition (period: 2000–2005) revealed that 6.6% of all subjects were fed by means of tubes, with an incidence of 223.4 cases/10^6 inhabitants/year and a prevalence of 279.4 cases/10^6 inhabitants (Morello et al. 2009). If the study considers the entire population of patients aged >65 years who undergoes HEN (including 664 subjects at home in the period 2001–2006) (Fig. 193.1), a mean incidence of 269.9 cases/10^6 inhabitants/year can be noticed, with a prevalence of 313.5 cases/10^6 inhabitants. If the prevalence study is based on patient age in
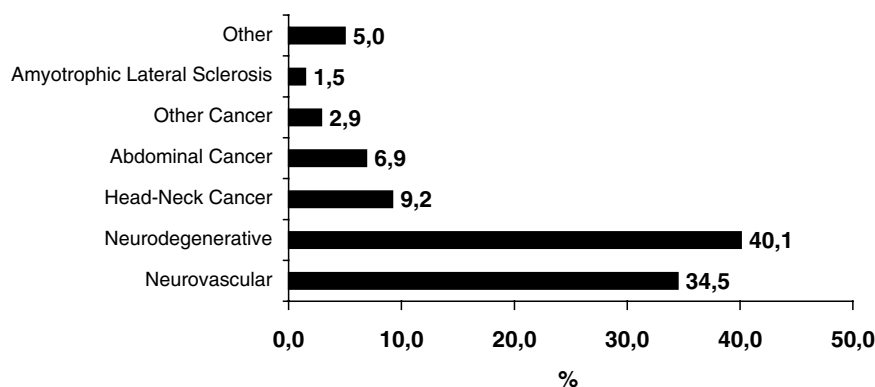

Fig. 193.1 Incidence of diseases leading to HEN (664 subjects > 65 year at home)

this sample group, there would be 95.8 cases/10^6 inhabitants for patients aged 66–75 years, 151.3 for those aged 75–85, 116.0 for those aged 86–95 and 17.7 for patients aged >95 years.

193.4.2 Medical Indications for Treatment

National and international guidelines agree that EN is the first choice method in all conditions, which recommend AN as they have adequate anatomofunctional gastrointestinal integrity. This is based on the fact that EN is more physiological, is worsened by fewer complications (especially infections), costs less and can be managed with greater ease. The transit of nutrients along the intestine safeguards its trophism, either conserving or restoring the integrity of the absorbing surface.

Table 193.1 specifies when a patient should undergo EN. EN (just as HEN) must basically either prevent or reduce the risk of malnutrition (or undernutrition) that can act synergically with the basic disease, increasing the risk of complications and of the decease of patients. Table 193.2 reports the physical and psychosocial consequences of hyponutrition. Contraindications to EN are intestinal occlusion or subocclusion, chronic intestinal ischaemia, high flow jejunal or ileal fistulae, untreat-

Table 193.1 Indications for EN (Amended by the National Institute for Health and Clinical Excellence, NICE 2005)

EN should be considered for patients when
• The patient has eaten very small amounts for the last 5 days or more, or
• The patient is very unlikely to eat more than very small amounts for the next 5 days or more (whatever current BMI or history or weight loss), or
• The patient has a BMI <18.5 kg/m² (ref. range: 20–25 kg/m²), or
• The patient has unintentionally lost >10% body weight within the previous 3–6 months, or
• The patient has a BMI <20 kg/m² and unintentionally lost >5% within the previous 3–6 months, or
• The patient has poor absorptive capacity, is catabolic and/or has high nutrient losses and/or has a condition that increases their nutritional needs (i.e. hypermobility)

This table specifies when a patient should undergo EN
The criterion, amended by NICE 2005, includes reduction of food intake, fasting, weight loss, low BMI, alteration of absorptive capacity and condition of increasing nutritional needs

Table 193.2 Same physical and psychosocial effects of undernutrition in chronic patients (Amended by the National Institute for Health and Clinical Excellence, NICE 2005)

Adverse effect	Consequence
Impaired immune responses	Risk of infections
Impaired wound healing	Surgical wound dehiscence, development of post-surgical fistulae, anastomotic failures, risk of wound infections and ununited fractures
Reduced muscle and respiratory muscle strength, and fatigue	Inactivity, inability to work, poor self-care; abnormal muscle (or neuromuscular) function; poor cough pressure, risk of chest infections; difficulty weaning malnourished patients from ventilators
Inactivity	Predisposition for pressure sores and thromboembolism especially in bed-bound patients
Water and electrolyte disorders	Cardiac arrhythmias, muscle pain, increased vulnerability to refeeding syndrome, and iatrogenic sodium and water overload
Vitamin deficiencies	Specific vitamin deficiency states (e.g. Wernike–Korsakoff syndrome), osteoporosis
Impaired thermoregulation	Hypothermia and falls, especially in the elderly
Impaired psychosocial function	Apathy, depression, self-neglect, hypochondriasis lack of self-esteem, poor body image, lack of interest in food, deterioration in social interactions

Undernutrition causes *many consequences for human organs and systems with many physical and psychosocial adverse consequences*

able vomiting, paralytic ileum and/or intense diarrhoea and severe alterations in intestinal function subsequent to enteropathies or deficiencies in the absorbing surface (DiBaise and Scolapio 2007).

The same indications reported in Table 193.2 apply to the home-based patient who undergoes HEN. However, this requires concurrent suitable clinical and environmental conditions, a patient with a stable clinical condition, the possibility of managing the basic disease at home, suitability of the house to ensure correct management and the presence, in patients who are not self sufficient, of a caregiver or of nursing care at home. Lastly, as discussed below, since HEN interferes considerably in the life of the patient and his family, it requires the informed consent of the patient and a correct evaluation of the economic and psychological cost for the patient and his relatives, considering the prognosis of the basic disease and/or the results that can really be obtained with HEN.

193.4.3 Enteral Feeding Routes of Access

Once HEN is recommended, the clinical condition of the patient has been evaluated, the anatomy and functionality of the digestive system and envisaged duration of treatment have been defined and the ideal access route for tube feeding of nutrient mixtures must be established.

Many types of enteral feeding tubes can be used to deliver nutrition to the stomach or upper gastroenteric tract. In practice, enteral feeding tubes can be divided into two main categories: (a) those positioned through the nose (nasogastric, nasoduodenal and nasojejunal tubes), which are generally recommended for EN that is scheduled for at most 30 days; (b) those requiring minor surgery (percutaneous endoscopic gastrostomy, PEG; percutaneous endoscpic jejunostomy, PEJ), which are recommended for EN >30 days (Bankhead 2007). An epidemiological study conducted in Europe estimated that 813 on 1,3972003 patients undergoing HEN (58.2%) wore a PEG, 410 (29.3%) an NGT, 76 (5.4%) underwent surgical jejunostomy and 3.4% other means of access (Hebuterne et al.).

In our experience, PEG and SNG were the main access routes chosen by patients undergoing HEN either at home or in a nursing home, but the NGT is used more than the PEG (Paccagnella et al. 2008; Morello et al. 2009). Figure 193.2 reports the incidence of use for the main types of enteral feeding tubes in 664 patients aged >65 years treated by our unit in the period 2001–2006.
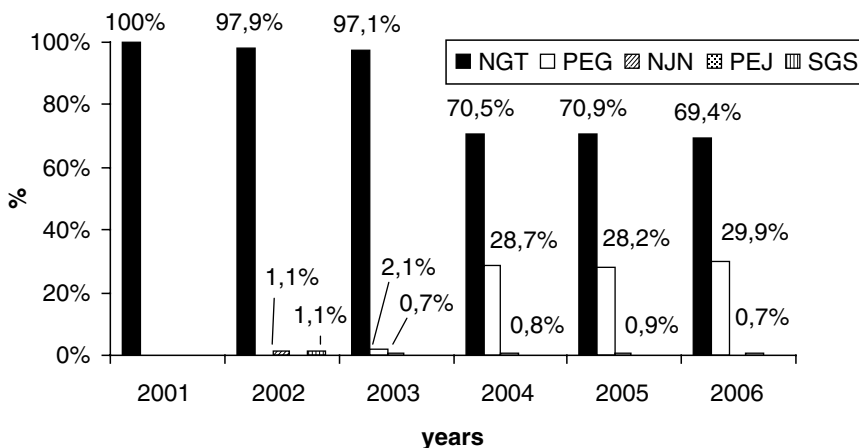

Fig. 193.2 Enteral access device from 2001 to 2006 (664 subjects > 65 year at home). *NGT* nasogastric tube, *PEG* percutaneous gastrostomy, *SJ* surgical jejunostomy, *NJT* nasojejunal tube, *PEJ* percutaneous jejunostomy, *SGS* surgical gastrostomy

In some clinical situations as, for instance, tumours in the head and neck region under chemoradiotherapy, PEG is to be preferred to NGT to enhance patient mobility because it is less visible and has a lower impact on the quality of life (Arends et al. 2006). Placing of the PEG for prophylactic purposes prior to the implementation of radiochemotherapy treatment proved effective, in these cases, in reducing the risk of malnutrition (Cady 2007). However, in our experience, similar results have been obtained with the NGT as long as the patient follows a treatment and monitoring track that is monitored by specialists and is proposed on the first medical examination of the patient (Paccagnella et al. 2009).

193.4.4 Complications of HEN

The progress of placement techniques and improvements in management have achieved success percentages of 90–95% and 95–98%, respectively, for SNG and PEG. But management of these medical aids is not free of complications (Iyer and Crawley 2007). Data published in literature reports several mechanical complications related to SNG and PEG placement, such as mechanical traumas (haemorrhages, perforations) and inhalation of food into airways (1.8%). Migration (16–41%) or dislocation of the tube and mechanical malfunction such as kinking, cracking and breaking are more common and can occur in 6–20% of cases. A frequent complication is an occluded tube (20%) (Iyer and Crawley 2007).

Placement of a PEG can cause endoscopic complications such as bleeding (0.02–0.06%), oesophageal perforation (0.008–0.04%) and inhalation (0.3–1.0%). Unintentional dislocations can occur in 1.6–0.4% of cases, and a clogged PEG tube is often reported (45%). A serious but not common complication is the buried bumper syndrome (1.5–1.9%). Gastrocolocutaneous fistula, small bowel, liver and splanchnic injury occur rarely (Schrag et al. 2007).

A retrospective study conducted on a cohort of 55 patients wearing a PEG highlighted that the most common complications recorded during a period of 25.9 months were granulation tissue (67%), broken or leaky tube (56%), leakage around the tube site (6%) and stomal infection requiring antibiotics (45%) (Crosby and Duerksen 2005). Infections at the site of the stomy are a frequent complication, whose incidence varies from 5% to 30% and can be reduced by antibiotic prophylaxis. Necrotising fasciitis is rare (Iyer and Crawley 2007).

EN often causes gastrointestinal complications, such as nausea (10–20%), diarrhoea (30%), abdominal distension and pain, constipation, gastroesophageal reflux and vomiting. Mechanical and gastrointestinal complications can be associated with metabolic complications, such as the refeeding syndrome (RS), alterations in the electrolyte and water balance and hypo/hyperglycaemias (DiBaise and Scolapio 2007).

A very rare complication described in literature in patients wearing a PEG is tumour implantation or metastasis at the site of stomy (Iyer and Crawley 2007). Risk factors that increase mortality in patients subject to PEG placement after the age of 75 have been defined in recent years. Urinary infections and past episodes of pneumonia (ab ingestis) have recently been associated with diabetes mellitus, chronic obstructive bronchopneumopathy and low blood levels of albumin.

193.4.5 Enteral Formulas

Enteral tube feeding formulas are designated by the US Food and Drug Administration (FDA) as medical foods: 'a food which is formulated to be consumed or administered enterally under the

Table 193.3 Main types of formulas for EN

	Polymeric	Elemental or semi-elemental
Proteins	Whole or hydrolysed proteins	L-aminoacids, tripeptides
Carbohydrates	Maltodextrins, polysaccharides, oligosaccharides	oligosaccharides (<10 glucose molecules)
Lipids	LCT, or LCT + MCT	MCT + LCT (50:50)
Osmolarity	Iso-osmolar	Hyperosmolar
Lactose, gluten	Present at times	Always absent
Fibre	Present at times	Always absent
Palatability	Acceptable	Poor
Costs	Contents	High

Enteral formulas can be divided into two categories: polymeric or elemental and semi-elemental formulas. These formulas are different in proteins, carbohydrates, lipids, osmolarity, presence of lactose and gluten, fibre, palatability and costs

supervision of a physician and which is intended for the specific dietary management of a disease or condition for which distinctive nutritional requirements, based on recognized scientific principles, are established by medical evaluation' (Bankhead et al. 2009).

Enteral formulas are industrially prepared mixtures that fully meet the need for macronutrients (i.e. proteins, lipids and carbohydrates), micronutrients (i.e. vitamins, mineral salts and trace elements) and water in patients who cannot meet daily requirements via oral intake but possess a functional digestive system (DiBaise and Scolapio 2007; Chen and Peterson 2009). They usually contain 1.0 Kcal/ml, but there is a higher calorie version containing 1.5 or 2 Kcal/ml. In our experience, in over 65 subjects, the mean infused calories is 23.3 ± 6.0.

Enteral formulas can be divided into two categories: polymeric or elemental and semi-elemental formulas (Chen and Peterson 2009) (Table 193.3). Polymeric formulas can be hypocaloric, normocaloric, hyperproteic, hypoproteic, energising, fibre-enriched, age-specific (e.g. paediatric), with a high content of soluble fibre and FOS, with natural blended foods, enriched with immunomodulating agents. There are also disease-specific formulas (e.g. for diabetics and for patients with respiratory failure). Enteral tube feeds can be administrated continuously with a nutripump, or discontinuously (boluses). As already mentioned, the PEG and tubes can be used to administer mixtures, water and drugs (Magnuson et al. 2005).

193.4.6 Outcome

Several studies have been undertaken to examine the effect of enteral nutrition. A review of literature reported a 1-month mortality rate of 8–41%, a 1-year mortality rate of 40–65% after feeding tube placement and a median survival rate that was well under a year. The largest study, comprising 81,105 patients, reported mortality rates of 23.9%, 63% and 81.3% at 1 month, 1 year and 3 years, respectively, among medicare beneficiaries who were discharged after gastrostomy placement.

Our data conducted on 482 nursing home residents who were administered EN during the period 2001–2005 reported an overall survival rate of 85.3% at 1 month, 50% at 1 year and 36% at 3 years. Median survival exceeded 13 months (Morello et al. 2009). Outcome and life expectancy with HEN depend on the condition of the patient and the medical situation.

Schneider et al. (2001) proved that age is an independent factor, which influences mortality. The chances of being alive at 1 year were 88% in children, 47% in adults (16–70 years) and 30% in older patients (>70 years). 5.5 per cent patients in the population analysed remained dependent on HEN, 32.6% resumed full oral nutrition, 20.2% died during the first month on HEN and 35% died after

more than 1 month on HEN (219 ± 257 days). This poor outcome was also influenced by the severity and nature of the underlying disease. In the USA, 59% of cancer patients and 48% with neurological swallowing disorders died 1 year after commencing HEN (Hebuterne and Schneider 2005).

193.5 Psychosocial Aspects of Home Enteral Nutrition

193.5.1 Evaluating Quality of Life and Health-Related Quality of Life

Aspects related to the cost of treatment, complications, mortality and prognosis cannot be considered as the only indicators to evaluate the efficacy of a treatment. Chronic patients should achieve psychological wellness that is commonly defined as 'quality of life' (QoL). In this sense QoL can be deemed as the modern operative term that defines the concept of 'happiness'. When QoL is mentioned without further specifications, it will embrace all factors that contribute towards it, but direct actions on the quality of life – even to improve it – must refer to a series of 'indicators'.

The wellness study, namely QoL evaluation, can also be applied to a condition of imbalance and discomfort to explore the daily impact of a disease or treatment on the life of everybody, on relations, mood and self-awareness. Health is deemed as the subjective, overall well-being of the patient, making room for his daily experiences and subjective viewpoint. During a disease, especially a chronic condition, reference is made to a concept that is more wide ranging than quality of life, namely health-related quality of life (HRQoL). It is 'the subjective assessment of the impact of disease and treatment across physical, psychological, social and somatic domains of functioning and wellbeing' (Reviky et al. 2000). In our case, for instance, the impact of HEN on subjects presenting a chronic disease and on their caregivers must be evaluated. In these special conditions, an individual develops a personal evaluation of what good quality of life is on the basis of his physical conditions, and depending on his personality profile, mode of coping and attitude towards health. HRQoL can be distinguished from QoL in that it concerns itself primarily with those factors that fall under the purview of health-care providers and health-care systems.

193.5.2 Measuring HRQoL

The HRQoL evaluation has several therapeutic goals and advantages, and implies the use of measurement scales and statistical correlations that embrace several domains. The most widespread compound measurements are HRQoL profiles generated by self-administered scales, which can be used to measure cross-sectional differences in quality of life between patients at a point in time (discriminative instruments) or longitudinal HRQoL changes in the same patient during a period of time (evaluative instruments). Both discriminative and evaluative instruments must be validated. There are two basic approaches to quality-of-life measurement available, namely generic instruments that provide a summary of well-being and HRQoL, and specific instruments that focus on problems associated with single disease conditions, patient groups, functional areas, or specific treatments applied. Approaches are not mutually exclusive. Of the many questionnaires available, the SF-36 (Ware et al. 1993) and Psychological Wellbeing Questionnaire (Ryff and Keyes 1995) stand out for the considerable availability of data on their validity and reliability. Especially, the SF-36 questionnaire is short and easy to complete is validated in many countries, and is therefore often used for comparative

studies of data. Other self-administered scales, like the Satisfaction profile (SAT-P; Majani and Callegari 1998), have a 'user-friendly' structure and only require brief administration and scoring times. It has an analogical, non-verbal response and is ideal for administration to both the elderly and subjects with writing problems.

The use of standardised instruments saves time and efforts required to perfect new custom-made instruments. There are no specific scales to evaluate the impact of HEN on HRQoL. Loeser et al. (2003) constructed an 'ad hoc' scale created by crossing a specific PEG impact evaluation module in conjunction with the QLQ-C30 scale for evaluations carried out during their study. But this scale has not been validated as yet. However, it confirms the need for specific instruments for subjects treated with home enteral nutrition.

193.5.3 Non-Standardised and/or Qualitative Instruments: Semistructured Interviews and Subjective Evaluation scales

Authors are increasingly integrating these standardised scales with semistructured interviews (for qualitative evaluations) or non-standardised scales to extend the information collected. Semistructured interviews were, for instance, used to analyse the impact on QoL in patients wearing PEGs (Brotherton et al. 2006). Other cases required a list of the advantages and disadvantages perceived during HEN treatment (Paccagnella et al. 2007) or scales to evaluate subjective tolerance to nutritional techniques (Roberge et al. 2000). Aspects of environmental impact have also been evaluated, since the therapy is a treatment that must be administered in the home of the patient. In our recent paper (Paccagnella et al. 2007) we used the Environmental Impact Exam (EIE), a questionnaire that was specially designed to study the perception of the living environment in patients and relatives during the illness, on their return home.

193.5.4 Why Measure the Quality of Life in HEN

The concepts of QoL and of HRQoL are central in the contemporary bioethical debate. Several controversies are in progress in medical and bioethical literature concerning placement of feeding tubes in patients presenting chronic diseases. These controversies centre on the decision concerning therapy, and also on the subjects involved in the same decisions, on ethical and legal aspects and on the role of various members of the multidisciplinary team in appropriately defining the characteristics of patients who need treatment with feeding tubes. The organisation that HEN requires can be naturally modulated or evaluated in response to the insurance and/or financial system provided by the country that envisaged it. Some questions should be asked in this framework. Is there a way of offering patients a quality intervention that can reduce risks associated with HEN? Is it possible to find a model that marries the culture of medicine with the current patient-centred approach? Which parameters, irrespective of the clinic, could show appropriate relations between the efficacy of the intervention, its cost and the well-being of the single patient?

Feeding tubes are unattractive and low-profile 'button' type tubes are the choice for gastric or jejunal feeding in some, especially the young. For feeding, low-profile tubes require brand-specific adapters or extension tubes that can wear out over time; hence, patients will need a supply of these. Regular gastric tubes may occasionally be too long and cumbersome, interfering with activity,

clothing, and moving. AN-related changes are many, and the subject must be actively involved in preparing his return to his life and home. The therapeutic nutrition programme can be adequate for hospital treatment, but it must be adapted and specially designed for the patient when he is sent home to ensure integration – as far as possible – with the characteristics and conditions of his life and work (see Box 193.1). The use of syringes, pumps and other medical aids must be discussed and evaluated with the patient to suit his preferences (for instance, many patients who use the pump prefer night feeding). All these aspects lead to evaluate, along with the patient, the impact of treatment on his quality of life in order to implement all improvements required.

Box 193.1

Two Stories of Hen

Mrs. Piera is 75 years. She cannot eat due to a tumour in the larynx that caused her to undergo several laryngectomies with subsequent progressive dysphagia. Every morning Mrs. Piera goes out to buy bread and the newspaper. She is autonomous and keeps her house and self in order. She regularly meets her friends and often plays with her grandchildren. She infuses nutrients and water into her PEG four times a day. For Mrs. Piera, HEN is a byword for autonomy and an acceptable quality of life. She has a positive attitude towards the PEG.

Carlo is 45 years. He suffers from a significant gastroparesis with chronic abdominal pain. He has undergone multiple surgeries for duodenal ulcers and obstructions. He is unmarried and lives alone. He has only one PEG through which he is slowly infused a nutrient and water almost the whole day. He must do the same at night. His abdominal pains often force him to stay in bed and prevent him from working for days, from going out, from meeting friends or a woman to form a family. His attitude towards HEN is ambivalent.

193.6 HEN and Its Impact on HRQoL

As already mentioned, HRQoL measures the combination between clinical, objective and measurable data, and subjective evaluations. Several studies (Terrel et al. 2004; Brotherton et al. 2006; Paccagnella et al. 2007; Bozzetti 2008) report the significant impact on QoL that, especially, surfaces concerning psychological and emotional factors associated with the inability to eat, taste and share food with others, the subsequent exclusion from family and social life, the inability to share the non-nutritional aspects of food with the social functions that eating food with others implies. Such inconvenience must certainly be associated with the specific characteristics of the treatment, which removes all eating-related factors and requires acceptance of treatment centred solely on feeding, something patients consider as one of the major disadvantages of the treatment. First difficulties arising from PEG feeding include symptoms such as vomiting, diarrhoea, infection of the PEG site and leakage that are reported as problems impacting on QoL by patients who wear a PEG (Table 193.4). Patients also report several psychosocial inconveniences. In fact, if on the one hand they are relieved of the pressure to consume an oral diet, and appreciate recovery of physical wellbeing and are less concerned over the risks related to their health (e.g. they are less stressed by problems related to dysphagia or risks related to malnutrition), on the other hand they are disturbed by several psychosocial effects related to PEG that have an impact on their QoL (Table 193.5). Three review articles evaluate the latest studies in the field of HRQoL and HEN (Brotherton and Judd 2007; Bozzetti 2008; Sampson et al. 2009) concluding that clearly tube feeding has an impact

Table 193.4 Symptoms associated with enteral feeding subjectively perceived as impacting on QoL (Roberge et al. 2000)

Low-impact symptoms	Intermediate-impact symptoms	High-impact symptoms
Nausea	Pain	Fatigue
Vomiting	Dyspnoea	
Constipation	Insomnia	
Diarrhoea	Appetite	

Enteral feeding can cause symptoms of different kind that can be differently tolerated. This table indicates the main symptoms experienced by patient and the degree of impact as subjectively experienced divided by low-, intermediate- and high-impact symptoms

Table 193.5 Psychosocial symptoms, subjectively perceived, as PEG-related problems impacting on QoL (Bannermann et al. 2000; Roberge et al. 2000; Verhoef and Van Rosendaal 2001; Malone 2002; Gee et al. 2005; Brotherton et al. 2006; Paccagnella et al. 2007; Rogers et al. 2007)

Problems with sleep

Difficulty in finding a place to feed

Missing being able to eat and drink

Problems in social occasions when food is shared

Perception of negative attitudes of others towards feeding them

Feeling a burden to family members

Poor body image

Fear about feeding tubes

Sensory deprivation

Grief

Anger

Depression

Frustration

Limitations concerning social life and travel

Interference with family life

Interference with intimate relationships

Interference with social activities

Interference with hobbies

Discomfort experienced while dressing and washing and restricted choice of clothing

In the table are summarized the main inconvenience perceived by patients wearing a PEG. Data are collected with quantitative and qualitative measures and describe all the daily discomforts expressed by patient in managing artificial nutrition

on the patient's quality of life. But these reviews underscore a varied and heterogeneous picture of the HRQoL impact of HEN. The differences depend on several factors, such as variable factors related with the underlying primary diagnoses, access routes, and measuring instruments that produce results that are not always consistent and comparable. Underlying diseases significantly, but not exclusively, include acute (e.g. stroke and head injury) and degenerative (e.g. dementia, Parkinson's disease and lateral sclerosis) neurological disorders. However, subjects undergoing PEG also count patients with cancer in the head, neck or oesophagus, and patients with cystic fibrosis. Hence, literature describes a very heterogeneous population – in terms of basic diagnosis – of subjects undergoing HEN. Even access routes can be of various types. In the studies mentioned, most patients were fed via PEG, but some studies recruited patients with NGT or NJT. All these differences are an obstacle to defining a coordinated, comparable picture of results, and we can only describe some common emerging themes. But not all results were consistent. In fact, some studies back the theory that HEN is deemed to help maintain QoL although it may be at a reduced level, especially when it is measured in time (Klose et al. 2003) and found PEG subjectively perceived as

useful in maintaining QoL over time, especially in the younger subjects (Weaver et al. 1993). This study found an interesting discrepancy between evaluations made by family members concerning the benefit of the procedure for the patient, and their refusal of applying the procedure to themselves if they were in the same situation. Even subjective opinions of patients on the impact of HEN present some ambivalences that reveal both perception of the utility (or inevitability?) of treatment ('I cannot do without it'), and an evaluation of its cost in terms of changes brought in their daily lives. Such ambivalences also surfaced in the assessment of other physical features and of the impact of the treatment and, especially, of inconveniences related to the use of stomies and tubes on the physical image. An interesting point surfaces from a longitudinal study, whose authors report that, though most subjects and caregivers have no second thoughts over the decision to have a PEG, this does not necessarily indicate better QoL (Verhoef and Van Rosendaal 2001). In the study conducted by Sampson et al. (2009) that analysed the impact of HEN in subjects presenting dementia, the authors concluded that despite the very large number of patients receiving this intervention, there was insufficient evidence to suggest that enteral tube feeding was beneficial in patients with advanced dementia in influencing survival, quality of life, prevention of bed sores, nutritional and functional condition and behavioural and psychiatric symptoms.

All reviews of latest contributions to relations between HEN and HRQoL lead to disappointing conclusions. In short, the data reveals that patients acknowledge the life-saving function of the therapeutic intervention of HEN, but they also declare that tube feeding finally came to dominate their lives and was associated with an appreciable burden of treatment (Jordan et al. 2006). We think that this depends on several factors, especially the fact that eating does not only involve the intake of food, but is associated with complex factors – as mentioned – the lack of which causes psychosocial deprivation in the life of subjects. This is added to the emotional impact (anticipatory grief) generated by basic diseases.

193.6.1 Problems and Limits of the Evaluation of HRQoL

Considering the discussion so far, it is hard to evaluate the effect of HEN on the QoL of a subject without taking into account the emotional impact of the basic disease, which is often chronic and has a fatal prognosis. Another problem that should be considered when analysing the aforementioned reports concerns the use of different measurements and scales, which makes it rather difficult to conduct a comparative study. Even the problem of access routes that are neither consistent nor identical in terms of management in these studies is not negligible. Different tubes can produce different reactions both in terms of symptoms and of emotional experience related to the tolerance of treatment and the image of self. Moreover, the number of subjects enrolled in many studies is less than the representative sample. Again, despite the hope of evaluating the progress of the long-term impact on QoL, longitudinal studies have struggled with loss of patient numbers at the time of follow-up data collection. A recent review (Marin Caro et al. 2007) centred on nutritional intervention and QoL in adult oncology patients found that no study is reported to prospectively investigate the effects of EN on QoL.

193.6.2 Caregivers

The term caregiver indicates the person who attends to either disabled or sick people, namely professional caregivers and family caregivers are those who look after a person in need. The difference between the two roles concerns their theoretical and practical background, but above all it relates to their motivational features. The professional caregiver's motivation is occupational, whereas a family

caregiver is in a position he or she has not freely chosen, and which constitutes an additional role arising from the illness of a loved one. Therefore, family caregivers have to cope with the challenge of a role they were not prepared to take on. Taking care of a sick family member requires a strong commitment that can change in time. Since care recipients are mainly attended to by family caregivers, irrespective of the presence of an external support, focus must be on them, also because the sick person's overall well-being highly depends on the psychophysical status of the family member who is taking care of him. The term 'burden' indicates the overall impact of caring responsibilities on the caregiver, who might feel demoralised, isolated and trapped in the role. Therefore, while assessing care needs, it is also essential to consider the demands of informal caregivers and anything else that might support them in this delicate community care task, both in 'material' and 'moral' terms.

193.6.3 The Viewpoint of Caregivers

Some studies analysed the effect on the subjective well-being of caregivers in managing HEN in various chronic patient types. The scope of these studies was to evaluate the impact of home care that significantly involved caregivers. Caregivers manage all treatment prescribed for non-competent subjects; hence, the importance of evaluating the impact of home care on them and of assessing whether social support, such as help from a family member, hospital assistance and professional help, could have some effect in reducing the caregiver's burden. Although caregivers are constantly under a lot of stress, there seems to be a strong link between the physical and cognitive disabilities of the patient and the extent of his daily needs, and the well-being of caregivers (Douglas et al. 2005). Studies compared HRQoL in patients and their caregivers. SAT-P test results reveal that the group of caregivers does not differ from the group of patients concerning perceived satisfaction in QoL. In particular, the scores of males fall within the normal range in the considered functions, while females – the majority of caregivers – seem to suffer a greater perceived cost in the management of patients. Perceived satisfaction on sleep-eating-leisure functions and at physical and psychological levels are below the average, when compared to the control group. Caregivers underlined different advantage and disadvantage concerned HEN (Table 193.6) even if management services are always deemed adequate and competent and all caregivers have been pleased by the service received (Silver and Wellman 2002; Brotherton et al. 2006; Paccagnella et al. 2007).

Although more attention has been paid to the viewpoint of caregivers, and there is greater awareness of the risk of the burden of managing a chronically ill person at home, less attention is paid to understanding the kind of support required to reduce the stress of caregivers. When the location of therapy is shifted from the hospital to the home of patients, the assessment of the impact of managing therapy should take into account all facilitating features that can be activated.

193.6.4 Health-Care Operators

There are no specific comparative studies on the viewpoint of health-care operators and those of patients or caregivers. Evaluations are often based either on clinical data or on instruments such as, for instance, the Karnofky index that does not cover all areas of autonomy and quality of life evaluation of the subject. The important factor in evaluating the quality of life of the patient after the therapeutic intervention concerns the need to train operators to make a biopsychosocial evaluation of subjects in order to provide an intervention designed to suit both the effects on the body of the person and on the person as a whole.

Table 193.6 Main disadvantages and advantages of HEN pointed out by caregivers (Brothertorn et al. 2006; Paccagnella et al. 2007)

Main disadvantages	Main advantages
Seeing the missing sensory aspects of nutrition in the patient	Improved physical conditions
Problems in physical/sexual relations between adults	General comfort/practicality of HEN
Problems due to emotional relations between the patient and his caregiver	Hope in the patient's survival
Remarks on the limited freedom of the caregiver himself	Feel less anxious or fearful of complications of eating by mouth
Lack of autonomy of the patient	To have the relative back home
Technical difficulties associated with HEN management	
QoL of patients considered boring due to the loss of pleasure generated by food and the act of eating	
Lack of quality of life	
Problems caused by reduced patient mobility	
Strong commitment to treatment management, which diminishes their own autonomy	

In the table are listed the main advantages and disadvantages pointed out by caregivers of HEN patients as subjectively perceived. To each subject was asked to point out the main disadvantages and the advantages, as they perceived it, in managing the home enteral nutrition of their relative. Results are then categorised into main classes of disadvantages and advantages by different judges. It is a qualitative method to evaluate the impact of home enteral nutrition at home and to have more information about quality of life of caregivers. In the table are pointed out main results

193.7 The Link Between HEN, QoL and ethics

Hebuterne (2005) presents us with questions on HEN that force us to consider its use: Is it well tolerated by the patient? Does it improve the clinical condition of the patient or does it only maintain it unchanged? Does it improve the quality of life of the patient or does it leave it unaltered? Does it improve the outcome of the patient and his survival? These questions make room for many considerations, and do not make it easy to formulate univocal answers. National and international scientific societies have long wondered about the ethical aspects of artificial nutrition.

To date, it is a matter for discussion whether AN must be deemed as a medical act or a compulsory caregiving intervention. In 2005,2005 the case of Terry Schiavo fuelled an international debate. The patient was in a permanent vegetative condition, and died after suspension of PEG-based HEN. The suspension, which was authorised by judiciary authorities on request of the husband, supported the former wish of the patient (Charatan). Even our clinical experience counts several cases of patients in whom the decision to commence HEN raised more than a few questions and doubts (Box 193.2).

It is interesting to notice that a study conducted in the early 1990s by Solomon et al. (1993) and based on interviews with 1,146 doctors and nurses, found that while the feasibility of using a ventilator or any other end of life support was questioned, there was extensive consent in not discontinuing nutrition and hydration. On the other hand further studies (Callahan et al. 1999) report that home care with HEN is not preceded by appropriate information for the patient or his relatives, and that relatives and other care givers request doctors to especially use the PEG (Table 193.7).

Over the past 20 years, the debate has been enriched by extensive literature, and every scientific society specialised in these features of home care enlarge on the ethical aspect of HEN in their guidelines. Basically, all agree on the advisability of suspending HEN when it becomes 'futile treatment'. Unfortunately, the concept of 'futile treatment' lacks a consistent definition, though some of them consider it as either ineffective or incapable of achieving a desired goal or result, despite heroic efforts (Andrews and Geppert 2007). On the other hand, it is very hard to establish 'if' and 'when'

Box 193.2

The case of Paola

Mrs. Paola, aged 70 years was diagnosed with left parietal meningioma: a benign tumour for which she underwent surgery. At 74, she underwent surgery again for a recurrence. The next year, following a left sylvian infarction she became completely hemiparetic and aphasic. During the next months she became totally dependent on the care of her relatives. At 77, she developed a third recurrence of the tumour that the neurosurgeons of her city deem inoperable. Therefore, the relatives decided that Paola should undergo surgery again in the neurosurgery department of another country. During the postoperative phase a complication forced Paola to undergo further resection surgery of the tumour. At that point Paola was totally unconscious, bed-bound and fed with an NG tube. When she returned to her city, a neurologist wrote: 'The patient is drowsy. She opens her eyes only under intensive stimulation. Pain stimuli evoke movement in the left lower limb. She does not answer verbally, nor can she understand when spoken to.' The picture is compatible with a permanent vegetative condition. At the age of 78 a PEG was positioned for HEN, as requested by her relatives.

One year elapsed from the placement of the PEG to her death. The survival of Paola was influenced by the HEN, but did this prolong her life or her agony?

Photo: Paola at the time of PEG placement.

Table 193.7 Key features of home enteral nutrition

1. HEN is a set of organisational modes for EN administration at home and has the same indications as PN.
2. HEN is administered to subjects who cannot be fed by mouth due to an underlying disease and who are sent home on artificial nutrition (AN) after a certain period of hospital treatment.
3. HEN must basically either prevent or reduce the risk of malnutrition (or undernutrition) that can act synergically with the basic disease, increasing the risk of complications and of patient decease.
4. Enteral feeding tubes can be divided into two main categories: (a) those positioned through the nose (nasogastric, nasoduodenal and nasojejunal tubes), recommended for at most 30 days; (b) those requiring minor surgery (percutaneous endoscopic gastrostomy, PEG; percutaneous endoscopic jejunostomy, PEJ), which are recommended for EN > 30 days.
5. Enteral tube feeding formulas are divided into two categories: polymeric or elemental and semi-elemental are industrially prepared mixtures that fully meet the need for macro- and micronutrients and water in patients who cannot meet daily requirements via oral intake but possess a functional digestive system.
6. SNG and PEG placement causes several mechanical complications such as mechanical traumas (haemorrhages, perforations) and inhalation of food into airways.
7. Literature reported a 1-month mortality rate of 8–41%, a 1year mortality rate of 40–65% after feeding tube placement, and a median survival rate that was well under a year.

HEN should be implemented, depending on the HRQoL evaluation of a patient. This seems absolutely unacceptable when the patient lacks self-awareness. A paradox that we experience daily, and which is already documented in the USA (Hoefler 2000), is that many people are inclined to make their relatives (e.g. elderly parents and children in a permanent vegetative condition) undergo HEN even when some cases risk the administration of futile treatment, but the same people usually say that they would not like to undergo HEN or other forms of hydration, when they are questioned about what they would choose for themselves.

The fact remains that in most European countries, in America and in Asia, AN (to which HEN belongs) is not deemed as a basic duty of care – such as 'eating', considering the theories explained so far – but as a 'medical treatment', whose implementation always requires the consent of the patient or of his relatives (NICE 2005), and which can be discontinued on the basis of clinical reasons or administered for a palliative purpose, depending on the clinical condition of the patient.

193.8 Future Developments

Many quality of life measurements that are widely used are limited in their ability to record the quality of life of individual patients. These limitations depend on the structure and content of the measurements, how they were developed and their weighting systems. Some of these problems can be overcome by using individualised measurements, but these have their own problems which need further attention. A compromise could lie in using recently developed standardised measurements that are sufficiently wide ranging to include most facets of life that are important to any patient, but which also use direct weighting systems. This should lead to an individualised assessment of patient quality of life. The extent to which such measurements mirror the quality of life of an individual requires further assessment, and the clinical utility and interpretability of these measures must also be established.

Concluding, the themes that surfaced from the studies analysed assuredly require further study, but they provide important descriptions of the psychological and social life of the patient, clarifying the key factors that must be considered by all operators in clinical practice.

193.9 Applications to Other Areas of Health and Disease

The recent biopsychosocial approach promoted by the World Health Organization wants us to consider the person from a 'global' perspective, taking into account the physiological, psychological and social implications of any treatment administered. In special conditions as chronic treatment as HEN (Home Enteral Nutrition) an individual develops a personal evaluation of what good quality of life is on the basis of his physical conditions, and depending on his personality profile, mode of coping, and attitude towards health. For chronic diseases patients should achieve psychological wellness that is commonly defined as quality of life" (QoL) or health-related quality of life (HRQoL). Therefore, all chronic diseases that need a prolonged treatment such as artificial nutrition should be evaluated on health-related quality of life. It is important to choose measures that are diffusely shared to be able to compare results of different studies and to make a follow-up of the evaluation whenever possible.

Using measures of health-related quality of life studies represents a new promising field to improve the impact of the therapy in chronic patients and to understand the different subjective outcomes.

Summary Points

- In the chapter we point out the difference between eating and feeding and we designate as 'eating' everything that is taken by mouth and has implicit repercussions on the affective, social, cultural and biological framework. It designates that which is commonly and historically called 'food' and which envisages the act of eating.
- Enteral nutrition is an example of therapeutic intervention (feeding) in which the integrated and holistic dimension that creates wellness is damaged, and subjective balances are modified. AN designates all calories and macro- and micronutrients that are infused through a tube to ensure nourishment to the body, but which deprive the person of the psychosocial implications of 'eaten food'.
- Patients undergoing home enteral nutrition should achieve psychological wellness that is commonly defined as 'quality of life' (QoL). In these cases of chronic condition, reference is made to a concept that is more wide ranging than quality of life, namely health-related quality of life (HRQoL).
- The data reveals that patients acknowledge the life-saving function of the therapeutic intervention of home enteral nutrition, but they also declare that tube feeding finally came to dominate their lives and was associated with an appreciable burden of treatment.
- To date, it is a matter for discussion whether artificial nutrition must be deemed as a medical act or a compulsory caregiver intervention.

Key Terms

Biopsychosocial approach: An approach promoted by the World Health Organization that centres treatment on the patient and his relatives who become the lead actors in the management of the disease. This approach shifts focus from the disease 'of the body' to the disease 'of the patient' who is deemed a person with an inner world of his own and lives in a specific physical and social framework.

Quality of life quality of life (QoL): is used in health care to refer to an individual's emotional, social and physical well-being, including their ability to function in the ordinary tasks of living.

Health-related quality of life: The wellness study can also be applied to a condition of imbalance and discomfort to explore the daily impact of a disease or treatment on the life of everybody. HRQoL refers to patient outcome measures that extend beyond traditional measures of mortality and morbidity to include such dimensions as physiology, function, social activity, cognition, emotion, sleep and rest, energy and vitality, health perception and general life satisfaction.

Home enteral nutrition: AN comprises artificial parenteral nutrition (PN) and artificial enteral nutrition (EN). EN allows nutrients to be administered directly into the gastrointestinal system with special probes that are inserted either through the nose or stomies created through the abdominal wall. Home enteral nutrition is when the treatment is moved to the home of the patients and it is often administered by a caregiver.

Caregivers: The term caregiver indicates the person who attends to either disabled or sick people, namely professional caregivers and family caregivers are those who look after a person in need.

References

Andrews MR, Geppert CMA. In: DeLegge MH, Mattox T, Mueller C, Worthington P, editors. The A.S.P.E.N. nutrition support core curriculum: a case-based approach-the adult patients. Silver Spring: ASPEN; 2007. p. 740–60.

Arends J, Bodoky G, Bozzeti F, Fearon K, Muscaritoli M, Selga G, Van Bokhorst-de van der Schueren MA, von Meyenfeldt M, DGEM (German Society for Nutritional Medicine), Zurcher G, Fietkau R, Aulbert E, Frick B,

Holm M, Kneba M, Mestrom HJ, Zander A; ESPEN (European Society for Parenteral and Enteral Nutrition). Clin Nutr. 2006;25: 245–59.

Aspinwall L, Staudinger U. A psychology of human strengths. Washington: American Psychological Association; 2003.

Bankhead R, Fang, JC. In: DeLegge MH, Mattox T, Mueller C, Worthington P, editors. The A.S.P.E.N. nutrition support core curriculum: a case-based approach-the adult patients. Silver Spring: ASPEN; 2007. p. 233–45.

Bankhead R, Boullata J, Brantley S, Corkins M, Guenter P, Krenitsky J, Lyman B, Metheny NA, Mueller C, Robbins S, Wessel J; A.S.P.E.N. Board of Directors. J Parenter Enteral Nutr. 2009;33:122–66.

Bannerman E, Pendlebury J, Phillips F, Ghosh S. Eur J Gastroenterol Hepatol. 2000;12:1101–109.

Bozzetti F. Curr Opin Clin Nutr Metab Care. 2008;11:661–5.

Brotherton A, Abbott J, Aggett P. J Hum Nutr Diet. 2006;19:355–67.

Brothertorn AM, Judd PA. J Hum Nutr Diet. 2007;20: 513–22.

Buchman, AL. In: Lochs H, Thomas DR, editors. Home care enteral feeding. Nestlé Nutrition Workshop Series Clinical & Performance Program, Vol 10. Basel: Karger; 2005. p. 143–66.

Cady J. Clin J Oncol Nurs. 2007;11:875–80.

Callahan CM, Haag KM, Buchanan NN, Nisi R. J Am Geriatr Soc. 1999;47:1105–109.

Centers for Medicare and Medicaid Services. MDS active resident information report: third quarter, physical functioning and structural problems eating ADL support. Baltimore: Centers for Medicare and Medicaid Services; 2005.

Charatan F. BMJ. 2005;330:1467.

Chen Y, Peterson SJ. Nutr Clin Pract. 2009;24:344–55.

Crosby J, Duerksen D. Dig Dis Sci. 2005;50: 1712–17.

DiBaise JK, Scolapio JS. Gastroenterol Clin North Am. 2007;36:123–44.

Douglas SL, Daly BJ, Kelley CG, O'Toole E, Montenegro H. Chest. 2005;128:3925–36.

Fayers PM, Machin D. Quality of life. Assessment, analysis and interpretation. Chichester: Wiley; 2001.

Gee L, Abbott J, Hart A, Conway SP, Etherington C, Webb AK. J Cyst Fibros. 2005;4:59–66.

Hebert RS, Arnold RM, Schulz R. J Pain Symptom Manage. 2007;34:539–46.

Hebuterne X, Bozzetti F, Moreno Villares JM, Pertkiewicz M, Shaffer J, Staun M, Thul P, Van Gossum A; ESPEN-Home Artificial Nutrition Working Group. Clin Nutr. 2003;22:261–6.

Hebuterne, X, Schneider, SM. In: Lochs H, Thomas DR, editors. Home care enteral feeding. Nestlé Nutrition Workshop Series Clinical & Performance Program, Vol 10. Basel: Karger AG; 2005. p. 89–102.

Hoefler JM. Death Stud. 2000;24:233–54.

Iyer KR, Crawley TC. Gastrointest Endosc Clin N Am. 2007;17:717–29.

Jones B, Holden C, Stratton R, Micklewright A, Dalzell M. Annual BANS report 2007. Artificial nutrition support in UK 2000–2006. A report by the British Artificial Nutrition Survey (BANS), a committee of BAPEN (The British Association for Parenteral and Enteral Nutrition); 2007.

Jordan S, Philpin S, Warring J, Cheung WJ, Williams J. J Adv Nurs. 2006;56:270–81.

Klose J, Heldwein W, Rafferzeder M, Sernetz F, Gross M, Loeschke K. Dig Dis Sci. 2003;48:2057–63.

Lochs H, Dejong C, Hammarqvist F, Hebuterne X, Leon-Sanz M, Schütz T, Van Gemert W, Van Gossum A, Valentini L, DGEM (German Society for Nutritional Medicine), Lübke H, Bischoff S, Engelmann N, Thul P; ESPEN (European Society for Parenteral and Enteral Nutrition). Clin Nutr. 2006;25:260–74.

Loeser C, von Herz U, Küchler T, Rzehak P, Müller MJ. Nutrition. 2003;19:605–11.

Magnuson BL, Clifford TM, Hoskins LA, Bernard AC. Nutr Clin Pract. 2005; 20:618–24.

Majani G, Callegari S. Test SAT-P. Soddisfazione Soggettiva e Qualità della Vita. Trento: Centro Studi Erickson; 1998.

Malone M. J Parenter Enteral Nutr. 2002;26:164–8.

Marin Caro MM, Laviano A, Pichard C. Clin Nutr. 2007;26:289–301.

Mitchell SL, Teno JM, Roy J, Kabumoto G, Mor V. JAMA. 2003;290:73–80.

Morello M, Marcon ML, Pizzolato D, Baruffi C, Giometto M, Favaro V, Rebuffi S, Cenerelli P, Calabrò M, Spinella N, Tessarin M, Paccagnella A. Nutr Clin Pract. 2009;24:635–41.

National Institute for Health and Clinical Excellence (NICE). Nutrition support in adults: oral supplements, enteral tube feeding and parenteral feeding. London: Second draft for consultation; 2005.

Paccagnella A, Mauri A, Berto R, Falchero S, Baruffi C, Marcon ML, Faronato PP, Dal Ben G, Foscolo G. Minerva Med. 2007;98:5–17.

Paccagnella A, Baruffi C, Pizzolato D, Favaro V, Marcon ML, Morello M, Semenzin M, Rebuffi S, Fossa E, Baronato P, Spinella N, Tessarin M, Foscolo G. Clin Nutr. 2008;27:378–85.

Revicki DA, Osoba D, Fairclough D, Barofsky I, Berzon R, Leidy NK, Rothman M. Qual Life Res. 2000;9:887–900.

Ryff CD, Keyes CL. J Pers Soc Psychol. 1995;69:719–27.

Roberge C, Tran M, Massoud C, Poirée B, Duval N, Damecour E, Frout D, Malvy D, Joly F, Lebailly P, Henry-Amar M. Br J Cancer. 2000;82:263–9.

Rogers SN, Thomson R, O'Toole P, Lowe D. Oral Oncol. 2007;43: 499–507.

Sampson EL, Candy B, Jones L. Enteral tube feeding for older people with advanced dementia review. Cochrane Database Syst Rev. 2. 2009; Art.No.:CD007209. DOI:10.1002/14651858.CD007209.pub2.

Schneider SM, Raina C, Pugliese P, Pouget I, Rampal P, Hebuterne X. J Parenter Enteral Nutr. 2001;25:203–9.

Schrag SP, Sharma R, Jaik NP, Seamon MJ, Lukaszczyk JJ, Martin ND, Hoey BA, Stawicki SP. J Gastrointestin Liver Dis. 2007;16:407–18.

Silver HJ, Wellman NS. J Am Diet Assoc. 2002;102:831–6.

Solomon MZ, O'Donnell L, Jennings B, Guilfoy V, Wolf SM, Nolan K, Jackson R, Koch-Weser D, Donnelley S. Am J Public Health. 1993;83:14–23.

Terrell JE, Ronis DL, Fowler KE, Bradford CR, Chepeha DB, Prince ME, Teknos TN, Wolf GT, Duffy SA. Arch Otolaryngol Head Neck Surg. 2004;130:401–8.

Verhoef MJ, Van Rosendaal GM. J Clin Gastroenterol. 2001. 32:49–53.

Ware JE, Snow KK, Kosinski M, Gandek B. SF-36 health survey: manual and interpretation guide. Boston: The Health Institute; 1993.

Weaver J.P., Odell P, Nelson C Arch. Fam. Med. 1993;2:953–56.

World Health Organization (WHO). Ottawa charter for health promotion: an international conference on health promotion, the move towards a new public health. Geneva: World Health Organization; 1986.

Chapter 194
Quality of Life, Diet, and Behavior in Cancer

Brenda Larson and Aminah Jatoi

Abbreviations

CACS	Cancer-related anorexia cachexia syndrome
TNF-alpha	Tumor necrosis factor alpha
IL-1	Interleukin 1
IL-6	Interleukin 6
IFN-gamma	Interferon gamma

194.1 Introduction

Anorexia and weight loss are common in patients with cancer and carry a tremendous impact on the social and psychosocial aspects of cancer care. Studies in patients with advanced disease have suggested that as many as 80% of patients experience anorexia, or loss of appetite, and as many as 82% experience weight loss (Poole and Froggatt 2002). This symptom and sign have major psychosocial ramifications for patients.

194.2 Impact of Anorexia and Weight Loss

Anorexia and weight loss have ramifications relevant to patients' prognosis and quality of life. Dewys and others conducted the first major study to support the prognostic significance of weight loss in cancer patients. Focusing upon 3041 patients treated on 12 Eastern Cooperative Oncology Group protocols, these investigators observed that weight loss of >5% of baseline weight prior to the start of cancer treatment predicted a shortened survival (Table 194.1). Patients with such weight loss also manifested lower response rates to chemotherapy. Weight loss tended to correlate with performance status (Dewys et al. 1980). Along these same lines, a study in which a questionnaire was administered to 1115 patients with advanced cancer, showed that a patient's own assessment of his or her nutritional status, including their own opinion of their appetite and food intake, carried prognostic

A. Jatoi (✉)

Department of Oncology, Mayo Clinic, 200 First Street SW, Rochester, Minnesota, USA
e-mail: jatoi.aminah@mayo.edu

Table 194.1 Weight loss is associated with major differences in survival in cancer patients (Adapted from Dewys et al. 1980)

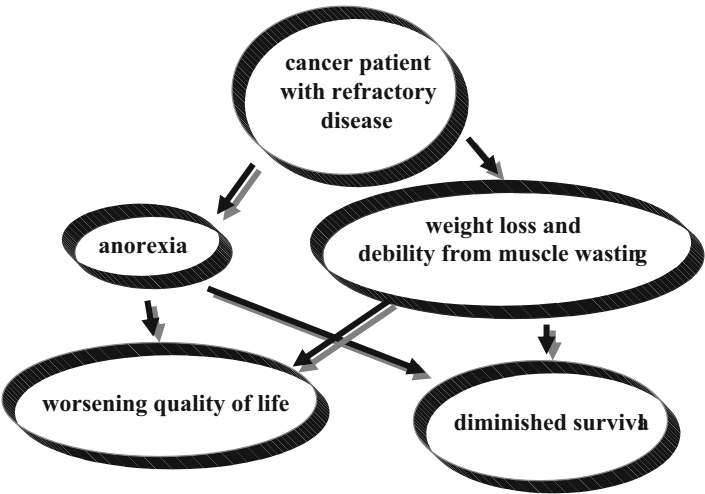| Weight loss and early death			
Median survival (weeks)			
Cancer	No weight loss	Weight loss	*P*-value
Lung, small cell	34	27	<0.05
Lung, non-small cell	20	14	<0.01
Breast	70	45	<0.01
Colon	43	21	<0.01
Prostate	46	24	<0.05

Fig. 194.1 Anorexia and weight loss in cancer patients are closely linked to survival and quality of life

significance (Loprinzi et al. 1994). Thus, for the patient, the patient's family, and for the team of health care providers, loss of appetite and loss of weight predict a shortened survival.

This latter point is an important one. Indeed, cancer patients and their families find this sign and symptom distressing. Patients typically rank loss of appetite within their top ten most bothersome symptoms (Walsh et al. 2000). Anorexia is often intimately related to other frequently bothersome symptoms including weakness, fatigue, depression, and anxiety. Furthermore, many health care providers underestimate how distressing anorexia and weight loss are to patients and families (Tanghe et al. 1998) (Fig. 194.1).

A number of observations suggest that weight loss leads not only to physical decline, but can also lead to deterioration of emotional, psychological, and social quality of life. A recent observational study by Reid et al. highlights some of the issues with which patients struggle as a result of anorexia and weight loss. In interviews with 15 cachetic cancer patients and their caregivers, certain themes emerged. One of these was the "visuality of cachexia." Patients expressed concern about what they described as a "wasted" appearance. This issue led some to withdraw and lessen their social interactions due to embarrassment about their appearance or the desire to avoid the unwanted attention. Some also relayed that the change in their appearance led to a loss of self-identity. A second theme was that many patients recognized their cachexia as a manifestation of their declining health. Of interest, patients were more likely to recognize that the weight loss was related to the cancer while family members were more likely to ascribe it to altered taste and felt that it could be reversed by feeding. Patients and families also expressed frustration that their health care providers did not do more

to try to ameliorate these symptoms. Some viewed this as a lack of concern or a lack of complete competence. A third theme was "conflict over food." Caregivers tended to be more concerned about their loved one's weight loss and tended to focus on food as a way of restoring health. Many patients felt pressure to eat in order to satisfy their caregivers and avoid conflict (Reid et al. 2009).

Who is more concerned about the foregoing: the patient or the family? In a survey of 199 cancer patients receiving home care, Hopkinson found that when asked about their level of concern, 34% expressed concern about weight loss and 44% expressed concern about decreased intake. However, if a family member assisted the patient with the survey, the "patient" was more likely to report concern about both weight loss (59%) and decreased intake (53%) (Hopkinson et al. 2006) – an observation that suggests that family members may be contending with more heightened concerns than the patient. Providing the same message, a smaller study of women caring for their partners with advanced cancer again found that the patient's anorexia and weight loss was more of a concern for the caregiver (Strasser et al. 2007). It is clear from many of these observations that eating is deeply woven into our social culture. Some have suggested that female caregivers struggle more with the anorexia of their loved ones as they view food preparation as part of their role and a necessary part of nurturing (Holden 1991). There is also concern that the caregiver may consider a patient's rejection of food as a personal rejection of the love and attention that he/she provides by means of the preparation and serving of the food (Reid et al. 2009).

In Holden's survey of advanced cancer patients with cachexia, caregivers again reported weight loss to be of greater concern than patients. Some of these caregivers expressed concern that weight loss would be the direct cause of death and would occur if oral intake did not improve. The patients themselves were more likely to express concern about pain, dyspnea, weakness, and fear of death (Holden 1991). In their respective series, both Holden and Strasser identify that tension can arise when the patient and caregiver are at different points in acceptance (Holden 1991; Strasser et al. 2007). Other studies of advanced cancer patients have also found that too much encouragement by the family or caregiver to eat can create tension (McClement et al. 2003). In the Holden study, 64% of patients expressed appreciation of their caregiver's efforts to offer food while 28% reported that their caregiver pushed too hard, and such efforts evolved into anger and conflict. She also found that both patients and caregivers grieved over the loss of mealtimes as an opportunity for social interaction (Holden 1991).

Many who have studied the psychosocial ramifications of anorexia and weight loss have suggested that perhaps, if patients and families had a better understanding of why the anorexia and weight loss existed, it would be easier to cope and accept.

194.3 Pathophysiology of Cancer-associated Anorexia/Cachexia

Thus, there is a clear need to spend time with cancer patients and their families and to explain that loss of appetite and loss of weight is "not their fault." In fact, the complex pathophysiology of this sign and symptom should allow patients and their families to shift their focus away from blaming each other with a more apt focus on healing.

It is clear that a number of causes of anorexia and weight loss are a direct result of the cancer or its treatment. Mechanical problems created by the tumor may lead to dysphagia, obstruction, malabsorption, or other related problems. These issues are particularly relevant to patients with head and neck cancer or malignancies of the gastrointestinal tract. Certain treatments, such as chemotherapy and radiation can exacerbate these symptoms, causing mucositis or constriction of the esophagus or other bowel-related symptoms such as nausea, vomiting, diarrhea, or constipation. Similarly, surgery can also exacerbate such mechanical problems, also resulting in dysphagia, other obstructive symptoms, or
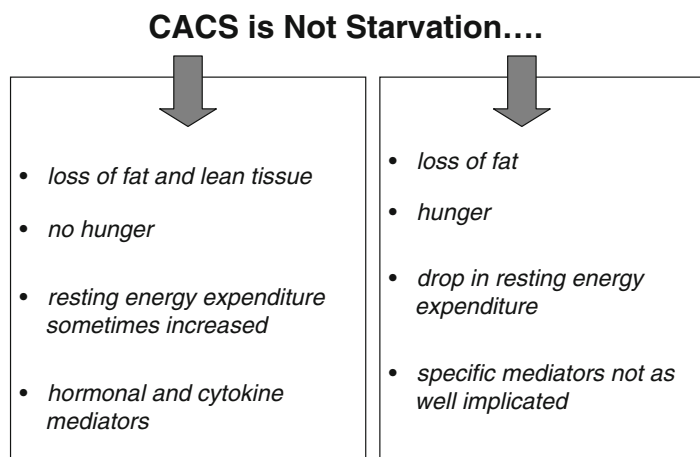
CACS is Not Starvation….

- *loss of fat and lean tissue*

- *no hunger*

- *resting energy expenditure sometimes increased*

- *hormonal and cytokine mediators*

- *loss of fat*

- *hunger*

- *drop in resting energy expenditure*

- *specific mediators not as well implicated*

Fig. 194.2 There are major physiologic differences between cancer-associated anorexia and starvation

short-bowel symptoms. For many patients, appetite will also be affected by an altered sense of taste, dry mouth, or mucositis that frequently occur as treatment side effects. Other symptoms that are common in cancer patients including pain, fatigue, and depression may contribute to poor appetite and weight loss as well. For these reasons, many cancer patients do eat less and studies have demonstrated that cancer patients who are suffering weight loss do in fact consume fewer calories (Bruera et al. 1984).

Despite these, many secondary causes of anorexia and weight loss, multiple studies suggest that the problem is more complex and driven by a disordered pathophysiology which is commonly termed the "cancer-related anorexia cachexia syndrome." The cancer-related anorexia cachexia syndrome (CACS) is felt to result from the interplay between the tumor and the host (Baracos 2000), and most commonly, it is defined among patients with incurable or treatment-refractory malignancies. In contrast to classical starvation, the CACS represents a metabolic derangement which results from more than a decline in caloric intake (Fig. 194.2).

194.4 Altered Resting Energy Expenditure

A cogent example of how CACS differs from starvation is found in assessments of resting energy expenditure (REE). It appears that many cancer patients suffer from a hypermetabolic state, whereas in starvation, metabolism slows. In one study, 66 patients with lung cancer were compared to 33 matched healthy controls. The patients with lung cancer were found to have increased REE and when adjusted for fat-free mass, those with small-cell lung cancer had a more profound increase in REE then those with non-small-cell lung cancer or healthy controls (Staal-van den Brekel et al. 1997).

194.5 Changes in Nutrient Metabolism

Altered carbohydrate metabolism is thought to be part of the cancer-related anorexia cachexia syndrome as well. Many solid tumors produce excess lactate that must be converted to glucose through the liver's Cori cycle. Glucose turnover via the Cori cycle is increased in cachetic cancer patients in comparison to healthy controls (Tisdale 2000). This gluconeogenesis pathway makes inefficient use

of ATP (Inui 2002). Cancer patients with weight loss have been noted to have a 40% increase in hepatic glucose production in contrast to the reduced hepatic production observed in persons with anorexia nervosa (Tayek 1992).

The loss of fat that occurs in many cancer patients does not come as a surprise. The abnormalities of lipid metabolism observed in cancer patients include increased lipid catabolism, decreased lipolysis, and decreased activity of lipoprotein lipase an enzyme that clears triglycerides from the plasma (Inui 2002). There is evidence of further dysregulation in that cancer patients will continue to oxidize fatty acids even in the presence of glucose (Tisdale 2001).

The abnormalities of protein metabolism are perhaps the most striking feature of the cancer-related anorexia cachexia syndrome. In the CACS, there is a profound loss of lean body mass in contrast to the weight loss of classic starvation where the body uses fat to spare muscle tissue. Skeletal muscle biopsies in cachetic cancer patients have shown both decreased protein synthesis and increased protein degradation (Lundholm et al. 1976). Other studies have shown that many of these cancer patients have increased synthesis of secretory, or acute-phase reactants, by the liver (Emery et al. 1984). These observations have led to speculation that perhaps the demand for amino acids to fuel the increased synthesis of acute phase proteins is met by the increased breakdown of skeletal muscle (Inui 2002). Other investigators have suggested that perhaps part of the muscle breakdown in cancer patients may be secondary to a marked decrease in activity levels as it is well known that severe deconditioning leads to sarcopenia (Skipworth et al. 2007). In all likelihood, a combination of both occurs. Further mechanisms leading to abnormal protein metabolism have not been fully elucidated, but multiple mediators have been suggested (Baracos 2000).

194.6 Cytokine Mediators

Cytokines are hormone-like proteins that are produced by a variety of immune cells and play a major role in immune function. Over time, it has been observed that many of the metabolic derangements present in cancer patients are similar to those seen in persons with infection. Since this observation, cytokines have been studied extensively in an attempt to clarify their role in CACS. The cytokines that have been best studied in cancer-associated cachexia include TNF-alpha, IL-1, IL-6, and IFN-gamma. Studies have shown that the cachexia seen in cancer can be reproduced by administration of cytokines to animals. These animals manifest increased rates of protein degradation, decreased protein synthesis, and decreased amino acid uptake, which lead to a decrease in skeletal muscle protein mass (Argiles and Lopez-Soriano 1999). There is also direct stimulation of adipocyte lipolysis through inhibition of lipoprotein lipase (Tisdale 2008). Further studies have shown that these metabolic derangements can be counteracted by administration of monoclonal antibodies that neutralize cytokine activity (Matthys and Billiau 1997).

194.7 Hormonal Mediators

Hormonal mediators including leptin, neuropeptide Y, and the melanocortin pathway have also been named as possible contributors, but further study is needed. Leptin is a hormone secreted by adipose tissue to regulate weight. In healthy individuals, weight loss leads to decreased leptin levels as part of an adaptive response to starvation. Within the brain, decreased leptin levels increase signals to eat and suppress energy expenditure by the body (Inui 2002). In a mouse model, administration of certain cytokines resulted in an increase in serum leptin levels (Sarraf et al. 1997). Neuropeptide Y is a potent orexigenic hormone. In a study of tumor-bearing rats, there was impaired release of this
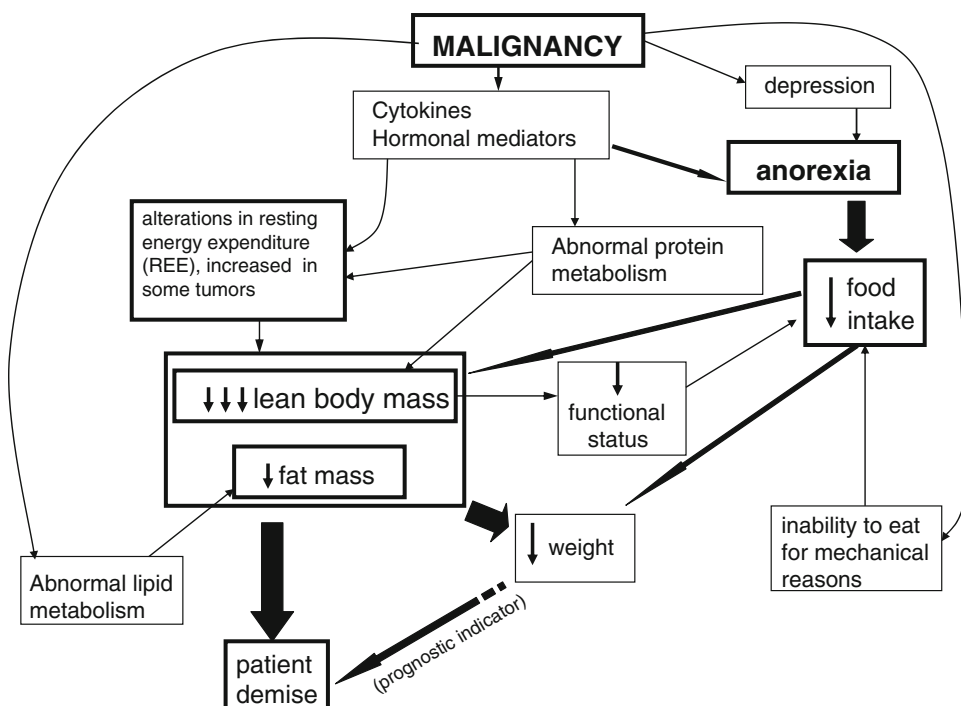
Fig. 194.3 Pathophysiology of CACS. Advanced malignancy leads to anorexia, weight loss, and patient demise through several interrelated pathways

hormone within the periventricular nucleus (McCarthy et al. 1993). The melanocortin system is a principle regulator of body weight and maladaption of this signaling system has been described in some anorectic states. In one study, rats that were anorectic from prostate cancer increased their food intake and gained weight after receiving a melanocortin receptor antagonist (Wisse et al. 2001). In another study, mice that lacked a melanocortin receptor were resistant to sarcoma-induced anorexia and weight loss despite tumor progression (Marks et al. 2001) (Fig. 194.3).

194.8 Treatment

Multiple studies have focused on remedies for CACS, which have included behavioral interventions, pharmacologic agents, and caloric supplementation. These authors strongly believe that in treating CACS, no one intervention can reverse all aspects of this syndrome and thoughtful one-on-one interactions between the patient and the health care provider are of the utmost importance in helping patients cope.

194.9 Dietary Counseling

A few studies have evaluated the role of dietary counseling in patients with cancer and weight loss. Ovesen et al. looked at 105 cancer patients who were receiving chemotherapy. Half these patients were randomized to receive regular dietary counseling by a trained dietician during the first 5 months of treatment. Patients who underwent dietary counseling did in fact eat more. However, the counseled patients did not increase their weight, live longer, or manifest an improvement in quality of life

(Ovesen et al. 1993). A subsequent meta-analysis by Halfdanarson et al. reviewed five trials of dietary counseling that involved a standardized quality of life measurement. A variety of cancer patients were involved in these trials including patients receiving treatment with both palliative and curative intent as well as patients receiving chemotherapy, radiation therapy, or surgery. Three of these individual trials reported a benefit in quality of life for the patients receiving dietary counseling while two did not. When these five trials were viewed in aggregate, there was only a trend toward benefit in improved quality of life. The authors concluded that there may be certain patients who benefit from such counseling and that the trend toward improved quality of life provides justification for further study (Halfdanarson et al. 2008).

194.10 Treating the Underlying Problem

The National Comprehensive Cancer Network guidelines recommend that the first step in treating cancer-associated anorexia is to diagnose and treat all possible causes of secondary anorexia. As previously described the CACS is complex and multifaceted. It therefore behooves us to manage mechanical problems as feasible, aggressively palliate nausea and vomiting, and consider a trial of metaclopromide, when appropriate, to aid bowel motility. Palliation of pain, diarrhea, and constipation are also important. Depression can certainly affect appetite and should be treated. Some anecdotal reports suggest that mirtazapine or an atypical anti-psychotic agent can lead to weight gain independent of its antidepressant effects. Good symptom palliation is an important aspect of cancer care and may also lead to improved appetite, weight, quality of life, and psychosocial welfare.

Effective treatment of the underlying malignancy can lead to marked improvement in symptoms including anorexia and weight loss. This phenomenon is well recognized by oncologists. Geels et al. evaluated 300 breast cancer patients who reported symptoms and completed quality of life questionnaires. Thirty eight percent of these women reported anorexia during the pretreatment questionnaire and 91.7% of patients who experienced a complete or partial response to treatment reported improvement in their anorexia. Of all the symptoms reported, anorexia was the most likely to improve. (Geels et al. 2000). Unfortunately, the vast majority of patients with metastatic cancer eventually find themselves contending with disease that has become refractory to antineoplastic therapy.

194.11 Pharmacologic Treatment

Multiple agents have been studied for their ability to treat CACS. These have shown varying degrees of success and further agents are being evaluated. To date, corticosteroids and progestational agents have provided the best results.

194.12 Corticosteroids

The landmark study evaluating the role of corticosteroids was that of Moertel and others published in 1974. These investigators randomized 116 patients with advanced gastrointestinal cancer, poor dietary intake, and a life expectancy of less than 2 months to treatment with dexamethasone at either 0.75 mg or 1.5 mg four times a day versus placebo. After 2 weeks, more than half the patients treated with dexamethasone reported increased appetite and greater than a quarter reported increased strength. There was no survival benefit seen in any one group (Moertel et al. 1974). This was followed by three further placebo-controlled studies that showed improvement in appetite in patients with

advanced cancer treated with corticosteroids. Of note, none of these studies reported benefit in terms of weight gain (Loprinzi et al. 1999). One of these studies did report improved quality of life for women with terminal cancer receiving methylprednisolone (Popiela et al. 1989).

The mechanism of action resulting in improved appetite is not known but may involve an effect on inflammation. Many speculate that the benefits patients experience with short courses of corticosteroids may be related to more than just improved appetite as these agents are used for palliation of many other symptoms common in advanced cancer patients including nausea, fatigue, and depression (Shih and Jackson 2007).

Unfortunately, longer-term use of corticosteroids can lead to bothersome side effects including myopathy, ulcers, increased infections, decreased bone mineral density with resultant increased fracture risk, fluid retention, cushingoid features, and adrenal insufficiency.

194.13 Megesterol Acetate

Megesterol acetate is a progestational agent that was noted to cause increased appetite and resultant weight gain in women with breast cancer taking it as anti-neoplastic therapy.

The first large randomized trial evaluating megesterol acetate in patients with CACS was performed by Loprinzi et al. in which 133 patients were randomized to either megesterol acetate or placebo. Sixteen percent of the patients in the megesterol acetate group gained more than 15 pounds versus only 2% (n = 1) in the control group. When evaluating the average rate of weight loss, it was less in the megesterol acetate group at 1.2 pounds per month versus 2.4 pounds per month in the control group (Loprinzi et al. 1990). A later study by this same group showed that the weight gained was primarily due to an increase in adipose tissue and a small amount of fluid gain rather than an increase in lean body mass (Loprinzi et al. 1993b). A subsequent dose finding study suggested that 800 mg daily gave the best benefit to side effect response. The authors suggested that given the potential side effects, starting at a lower dose and increasing as needed would be appropriate (Loprinzi et al. 1993a).

Whether this benefit of weight gain leads to larger benefits in terms of overall survival or quality of life is less clear. A study of megesterol acetate versus placebo in 243 patients receiving chemotherapy for small-cell lung cancer evaluated participant's toxicity, treatment response, survival and quality of life. The megesterol acetate group had less nausea and more weight gain but, also had an inferior response to treatment and showed a trend toward inferior survival. There was no change in quality of life scores over time in either group (Rowland et al. 1996). These results show that despite increases in weight and improvements in appetite, megesterol acetate does not appear to improve survival.

Megesterol acetate has been approved by the US Food and Drug Administration for anorexia and weight loss in persons with AIDS and approved for cancer cachexia in most European countries. It is commonly used for this indication in the USA.

194.14 Megesterol Acetate Versus Corticosteroids

A study comparing megesterol acetate to corticosteroids was performed by Loprinzi et al. in 496 patients with cancer-associated weight loss. Patients were randomized to megesterol acetate 800 mg daily versus Dexamethasone 0.75 mg four times daily versus the anabolic steroid Fluoxymesterone, which was found to be ineffective. Dexamethasone and megesterol acetate had similar efficacy in terms of appetite improvement reported in 60–70% of participants completing questionnaires. There was a trend toward increased weight in the megesterol acetate group as compared to the others. Dexamethasone had more toxicity in terms of peptic ulcers, myopathy, and cushingoid changes. Thirty six percent of
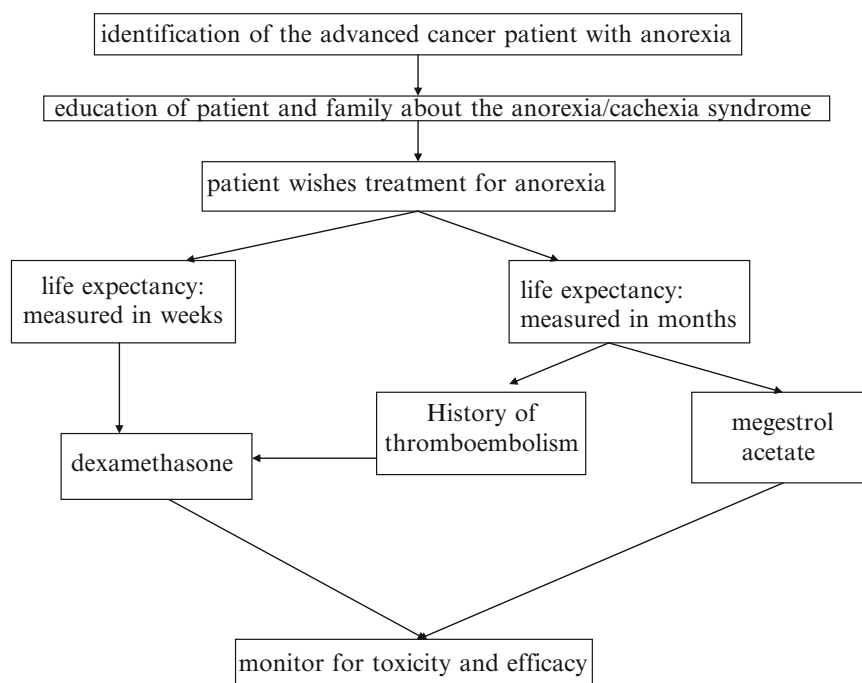
Fig. 194.4 Choosing an appetite stimulant. Guidelines for choosing an appetite stimulant in the appropriate patient

participants receiving Dexamethasone discontinued treatment due to these effects. There was a higher incidence of thromboembolism (5%) in the megesterol acetate group versus 1% in the Dexamethasone group. Twenty five percent of participants in the megesterol acetate group discontinued therapy. There was no significant survival difference between the study arms and no effect on quality of life scores (Loprinzi et al. 1999). This study and its report of side effects have led to the consensus that dexamethasone is the preferred agent in patients with a poor prognosis and short life expectancy. These patients tend to benefit from steroids in terms of increased energy, appetite, and overall well-being over the short term and often do not live long enough to experience the longer-term side effects. Megesterol acetate, on the other hand, is better tolerated over a longer time duration and also shows a trend toward improved weight gain. This agent is contraindicated in persons with a history of thromboembolism (Fig. 194.4).

194.15 Agents Requiring More Investigation

Melatonin is a pineal hormone involved in neuroendocrine regulation and may have anti-TNF activity as well. Some have also suggested that it has "oncostatic" effects (Lissoni et al. 1997). An initial study by Lissoni et al. evaluated supportive care versus supportive care plus melatonin 20 mg nightly in 100 patients with metastatic solid tumors. He found no difference in food intake between the two groups, but less weight loss in the melatonin group. TNF levels were higher in the supportive care alone group (Lissoni et al. 1996).

Thalidomide is a second immunomodulatory agent that has been evaluated in CACS as well as in AIDS-associated cachexia. This drug has been shown to decrease production of TNF in both in vitro and in vivo models (Bruera et al. 1999). In a study of 50 patients with advanced pancreatic cancer and weight loss, thalidomide 200 mg daily was shown to attenuate weight loss and the loss of lean body mass as compared to placebo (Gordon et al. 2005).

Androgens are known for their potential to increase muscle and lean body mass in healthy individuals. Oxandrolone has been found to be beneficial in maintaining weight in patients with catabolic conditions including HIV-associated muscle wasting, burns, trauma, and chronic obstructive pulmonary disease (Orr and Fiatarone 2004). A study comparing Nandrolone to placebo in patients with HIV-associated weight loss resulted in increased lean body mass and improvement in perceived overall health (Storer et al. 2005). None of these agents have been well tested in persons with cancer and further studies are needed to evaluate the longer-term safety and efficacy.

Other agents that may hold promise and are in the early stages of testing include ghrelin, carnitine, and anti-myostatin agents. Anecdotal reports or an understanding of the pathophysiology of cancer-associated cachexia have led to the testing of multiple agents including cannabinoids, fish oils, and anti-TNF agents, none of which have shown benefit in randomized trials.

194.16　Decision to Use an Appetite Stimulant

There is hope that one of these agents will emerge and show a strong benefit for patients with CACS. At the current time, our ability to manage this symptom complex remains limited. Patients and families frequently ask about appetite stimulants and for some patients these agents may be appropriate. We would recommend that the following criteria are met before prescribing an agent: 1) All secondary causes of anorexia and weight loss have been addressed. 2) Patients have been counseled about the side effects and relative benefits of these agents. 3) It is also important to understand the motivation that the patient has for requesting an appetite stimulant and ensure that they not chastise themselves for their inability to eat normally and maintain their weight. For some patients, an in-depth discussion that anorexia and weight loss are not their fault, provides considerable relief (Fig. 194.5).
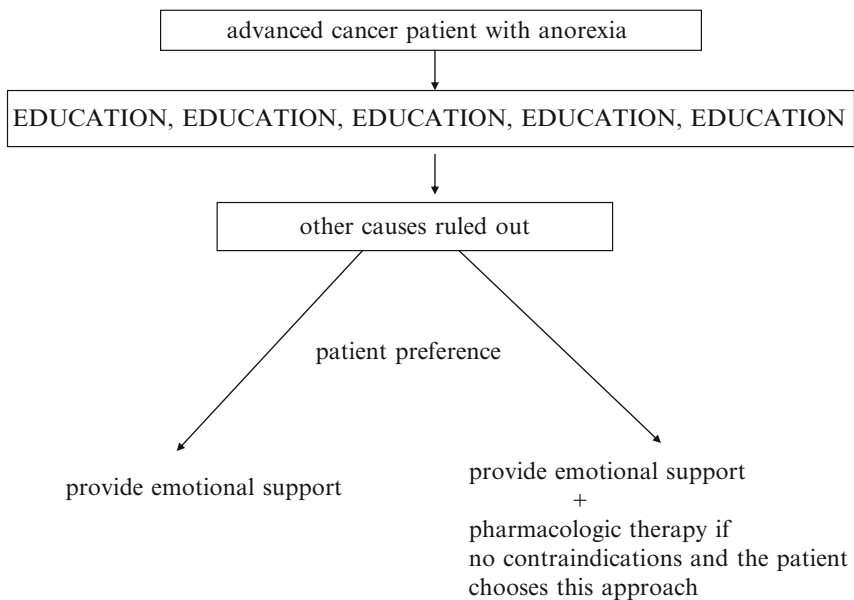

Fig. 194.5 Approach to the patient with advanced cancer and anorexia. This figure highlights the importance of patient education and treating reversible causes of anorexia and weight loss prior to prescribing an appetite stimulant. The choice to use such an agent should be left to the patient, but all patients require emotional support from their health care providers

194.17 Parenteral Nutrition

Patients and families may ask about parenteral nutrition. North American and European registry data from the 1990s indicate that 40% of the nearly 6000 patients receiving home parenteral nutrition were cancer patients. The most common malignancies were gastrointestinal and gynecologic as these often lead to the most common indications for use including bowel obstruction, fistula, or short bowel syndrome (Mackenzie and Gramlich 2008). Studies over the years have shown that this intervention is beneficial only in select circumstances.

A meta-analysis performed by Klein et al. in 1986 was one of the first major studies to lend insight to this question. Their meta-analysis looked at 28 smaller prospective trials of parenteral nutrition in cancer patients. The studies included patients treated with surgery, chemotherapy, radiation therapy, and a single study of no therapy. A pooled analysis of the surgical trials showed a significant decrease in major surgical complications and in hospital mortality which was 50% less than that of the group not receiving such nutritional support. Pooled analyses of patients treated with chemotherapy revealed a nonsignificant decrease in survival and worse response to treatment in the group receiving parenteral nutrition as compared to controls. In patients receiving radiation therapy, there was no benefit in either the parenteral nutrition or control groups in tolerance of treatment or survival. The study group was left to conclude that parenteral nutrition may have a role in surgical patients, particularly those with gastrointestinal malignancies, but probably should not be used routinely in nonsurgical cancer patients (Klein et al. 1986). Further studies have come to similar conclusions about the benefits of parenteral nutrition in select surgical patients with gastrointestinal malignancies. A later meta-analysis by McGeer et al. examined the role of parenteral nutrition in patients receiving chemotherapy. They again found no benefit in favor of nutritional support, but did find that it lead to higher rates of infectious complications (McGeer et al. 1990).

Further studies have examined the role of parenteral nutrition in patients with advanced cancer. Torelli et al. looked at 26 patients with limited life expectancy due to advanced cancer. These patients were receiving parenteral nutrition as an adjunct to medical therapy or as a supportive care maneuver. They found that parenteral nutrition had no bearing on outcome and did not improve the quality of life for the majority of patients who received it (Torelli et al. 1999). Hoda et al. published the Mayo Clinic series of 52 patients with incurable malignancies sent home on parenteral nutrition from 1975–1999. The most common reasons for parenteral nutrition were obstruction, short bowel syndrome, malabsorption, and fistula. Only two patients in this series received parenteral nutrition for anorexia. The median time to death was 5 months after starting parenteral nutrition but, sixteen patients lived for longer than a year. This study suggests that parenteral nutrition may be appropriate for certain very select cancer patients but that it is extremely difficult to predict who these patients might be (Hoda et al. 2005).

An observational study by Orrevall et al. interviewed patients with advanced cancer, and their caregivers, who were receiving parenteral nutrition due to anorexia. In their series, it was out of desperation over poor appetite and weight loss that caused many to turn to parenteral nutrition. This led to decreased conflict over food and gave family members a sense of relief. It also led to improvement in patients' weight, energy, level of activity, and quality of life. These investigators also noted that much of the positive effect that patients and families experienced was due to the support provided by the advanced home care teams that were involved with administering the parenteral nutrition (Orrevall et al. 2004, 2005).

These studies have led many, including these authors, to conclude that parenteral nutrition should not be routinely offered but can be considered only for very select patients. These may include perioperative patients with gastrointestinal malignancies and patients with mechanical problems where starvation is likely to be the cause of death before the tumor-related death occurs. It is also important

Key Features of CACS

Manifestations
- Anorexia
- Weight loss
- Shortened survival
- Weakness and fatigue
- Decreased quality of life
- Anxiety for patients/families
- Strain on relationships

Causes
- Decreased caloric intake
- Cancer and/or its treatment
- Increased resting energy expenditure
- Abnormal nutrient metabolism
- Cytokines and hormonal mediators

Coping Strategies
- Dietary counseling
- Appetite stimulants
- EDUCATION
- Showing empathy
- Refocus on nurturing
- Psychosocial support

Fig. 194.6 Key features of CACS. Summary of key features of cancer-associated anorexia cachexia syndrome and mechanisms for coping

to again point out that cancer-associated anorexia can be a multifaceted problem and unlikely to be remedied by providing caloric support alone. The reason that these select patients may benefit suggests that their weight loss is not completely due to the CACS. Orrevall's small study does raise an interesting question about the benefit of parenteral nutrition for patients with anorexia and also drives home an important point about how patients benefit from further support by health care providers (Fig. 194.6).

194.18 Helping Patients Cope with CACS

As we have previously described, there is no simple solution for this complex problem. For this reason, perhaps, the efforts of health care providers should be focused on how to best help patients and their caregivers to cope.

An observational study by Hopkinson and Corner evaluated 232 patients with advanced cancer receiving home care and examined their responses to CACS. These investigators found that responses ranged from acceptance to self-action. Patients expressed the view that they should be "good patients" in that they should be trying to eat and should also eat certain healthy foods. Some patients took supplements and tried special diets in attempts to be proactive and remain in control. The nurses working with these patients frequently felt that they had little to offer. Some nurses avoided discussing diet because they did not want to bring up a topic that generated anxiety. Other nurses spent time on re-focusing patients towards feeling comfortable with either eating or not eating based upon what was enjoyable to them and not feeling anxious or guilty about the choice (Hopkinson and Corner 2006).

A further observational study by McClement et al. evaluated the response of family members to the anorexia of their loves ones' with advanced cancer. Some caregivers chose a mentality of "fighting back" while others chose a path of "letting nature take its course." She found that, although the families who embraced the mentality of "fighting back" had good intentions, their loved one often became angry or upset by the pressure to eat. The families comfortable with letting nature take its

course would focus their efforts on other nurturing activities or just being present. Many of these patients expressed appreciation for their care and lack of coercion to eat (McClement et al. 2003).

What becomes clear from all of these observational studies is that patients and their families need more then just high-tech interventions (and perhaps they do not need these at all), they need psychosocial support. Orrevall et al. learned that patients receiving HPN benefited greatly from the health care providers who rendered this service, perhaps as much or even more than they did from the nutrition itself (Orrevall et al. 2005).

After conducting interviews with patients and families with advanced cancer, both Holden and Reid stress the importance of education (Holden 1991; Reid et al. 2009). Patients and families should be told that anorexia and weight loss are a part of the process of advanced cancer and something over which they likely have little control. If successful, this will take some pressure off patients and their caregivers so that the latter may refocus on other ways to nurture. Above all, patients and caregivers must have the ongoing support of their health care providers to help find the best way for each patient to contend with anorexia and weight loss in order to maintain the best quality of life possible.

Summary Points

- Anorexia and weight loss are common in patients with cancer.
- CACS has ramifications directly relevant to prognosis and quality of life.
- CACS is a multifactorial process due to altered pathophysiology and secondary processes.
- It is important to treat the underlying malignancy and all secondary causes of anorexia and weight loss as best able.
- Consider pharmacologic, behavioral, or nutritional interventions for select patients.
- Ultimately, it is important to support patients and caregivers in efforts to cope by providing education and reassurance.

Key Terms

Anorexia: The symptom of poor appetite.
Cachexia: Non-volitional loss of weight, and body mass often associated with weakness and fatigue.
Performance status: A rating that attempts to quantify the general well-being of a patient with cancer in order to judge their ability to tolerate treatment.
Quality of life: A person's overall sense of well-being and contentment.
Pathophysiology: The changes in normal bodily functions secondary to disease.
Cytokines: Hormone-like proteins that are produced by a variety of immune cells and play a critical role in cellular communication.
Palliative: Treatment undertaken with the intent of controlling symptoms rather than the disease process.
Corticosteroids: Steroid hormones that are produced in the adrenal gland or synthetically and are involved in several cellular processes. Also used as an appetite stimulant or to palliate a variety of other symptoms.
Megesterol acetate: A progestational agents that can be administered as anti-neoplastic therapy or as an appetite stimulant.
Parenteral nutrition: Intravenous feeding.

References

Argiles JM, Lopez-Soriano FJ. Med Res Rev. 1999;19:223–48.

Baracos VE. Nutrition. 2000;16:1015–8.

Bruera E, Carraro S, Roca E, Cedaro L, Chacon R. Cancer Treat Rep. 1984;68:873–6.

Bruera E, Neumann CM, Pituskin E, Calder K, Ball G, Hanson J. Ann Oncol. 1999;10:857–9.

Dewys WD, Begg C, Lavin PT, Band PR, Bennett JM, Bertino, JR, Cohen MH, Douglass HO, Engstrom PF, Ezdinli EZ, Horton J, Johnson GJ, Moertel CG, Oken MM, Perlia C, Rosenbaum C, Silverstein MN, Skeel RT, Sponzo RW, Tormey DC. Am J Med. 1980;69:491–7.

Emery PW, Edwards RHT, Rennie MJ, Souhami RL, Halliday D. Br Med J. 1984;289:584–6.

Geels P, Eisenhauer E, Bezjak A, Zee B, Day A. J Clin Oncol. 2000;18:2395–405.

Gordon JN, Trebble TM, Ellis RD, Duncan HD, Johns T, Goggin PM. Gut. 2005;54:540–5.

Halfdanarson TR, Thordardottir EO, West CP, Jatoi A. J Support Oncol. 2008;6:234–7.

Hoda D, Jatoi A, Burnes J, Loprinzi C, Kelly D. Cancer. 2005;103:863–8.

Holden CM. Hospice J. 1991;7:73–83.

Hopkinson J, Corner J. J Pain Symptom Manage. 2006;31:293–305.

Hopkinson JB, Wright DNM, McDonald JW, Corner JL. J Pain Symptom Manage. 2006;32:322–31.

Inui A. CA Cancer J Clin. 2002;52:72–91.

Klein S, Simes J, Blackburn GL. Cancer. 1986;58:1378–86.

Lissoni P, Paolorossi F, Tancini G, Barni S, Ardizzoia A, Brivio F, Zubelewicz B, Chatikhine V. Eur J Cancer. 1996;32A:1340–3.

Lissoni P, Paolorossi F, Ardizzoia A, Barni S, Chilelli M, Mancuso M, Tancini G, Conti A, Maestroni GJ. J Pineal Res. 1997;23:15–9.

Loprinzi CL, Ellison NM, Schaid DJ, Krook JE, Athmann LM, Dose AM, Mailiard JA, Johnson PS, Ebbert LP, Geeraerts LH. J Natl Cancer Inst. 1990;82:1127–32.

Loprinzi CL, Michalak JC, Schaid DJ, Mailiard JA, Athmann LM, Goldberg RM, Tschetter LK, Hatfield AK, Morton RF. 1993a;11:762–7.

Loprinzi CL, Schaid DJ, Dose AM, Burnham NL, Jensen MD. J Clin Oncol. 1993b;11:152–4.

Loprinzi CL, Laurie JA, Wieand HS, Krook JE, Novotny PJ, Kugler JW, Bartel J, Law M, Bateman M, Klatt NE, Dose AM, Etzell PS, Nelimark RA, Mailliard JA, Moertel CG. J Clin Oncol. 1994;12:601–7.

Loprinzi Cl, Kugler JW, Sloan JA, Mailiard JA, Krook JE, Wilwerding MB, Rowland KM, Camoriano JK, Novotny PJ, Christensen BJ. J Clin Oncol. 1999;17:3299–306.

Lundholm K, Bylund AC, Holm J, Schersten T. Eur J Cancer. 1976;12:465–73.

Mackenzie ML, Gramlich L. Appl Physiol Nutr Metab. 2008;33:1–11.

Marks DL, Ling N, Cone RD. Cancer Res. 2001;61:1432–8.

Matthys P, Billiau A. Nutrition. 1997;13:763–70.

McClement SE, Degner LF, Harlos MS. J Palliat Med. 2003;6:737–49.

McCarthy HD, McKibbin PE, Perkins AV, Linton EA, Williams G. Am J Physiol. 1993;264:E638–43.

McGeer AJ, Detsky AS, O'Rourke K. Nutrition. 1990;6:233–40.

Moertel CG, Schutt AJ, Reitemeier RJ, Hahn RG. Cancer. 1974;33:1607–9.

Orr R, Fiatarone Singh M. Drugs. 2004;64:725–50.

Orrevall Y, Tishelman C, Herrington MK, Permert J. Clin Nutr. 2004;23:1280–7.

Orrevall Y, Tishelman C, Permert J. Clin Nutr. 2005;24:961–70.

Ovesen L, Allingstrup L, Hannibal J, Mortensen EL, Hansen OP. J Clin Oncol. 1993;11:2043–9.

Poole K, Froggatt K. Palliat Med. 2002;16:499–506.

Popiela T, Lucchi R, Giongo F. Eur J Cancer Clin Oncol. 1989;25:1823–9.

Reid J, McKenna H, Fitzsimons D, McCance T. Int J Nurs Stud. 2009;46:606–16.

Rowland KM, Loprinzo CL, Shaw EG, Maksymiuk AW, Kuross SA, Jung SH, Kugler JW, Tschetter LK, Ghosh C, Schaefer PL, Owen D, Washburn JH, Webb TA, Mailiard JA, Jett JR. J Clin Oncol. 1996;14:135–41.

Sarraf P, Frederich RC, Turner EM, Ma G, Jaskowiak NT, Rivet DJ, Flier JS, Lowell BB, Fraker DL, Alexander HR. J Exp Med. 1997;185:171–5.

Shih A, Jackson KC. J Pain Palliat Care Pharmacother. 2007;21:69–76.

Skipworth RJE, Stewart GD, Dejong CHC, Preston T, Fearon KCH. Clin Nutr. 2007;26:667–76.

Staal-van den Brekel AJ, Schols AM, Dentener MA, ten Velde GP, Buurman WA, Woulters EF. Thorax. 1997;52:338–41.

Strasser F, Binswanger J, Cerny T. Palliat Med. 2007;21:129–37.

Storer TW, Woodhouse LJ, Sattler F, Singh AB, Schroeder ET, Beck K, Padero M, Mac P, Yarasheski KE, Geurts P, Willemsen A, Harms MK, Bhasin. J Clin Endrocrinol Metab. 2005;90:4474–82.

Tanghe A, Evers G, Paridaens R. Eur J Oncol Nurs. 1998;2:14–26.
Tayek JA. J Am Coll Nutr. 1992;11:445.
Tisdale MJ. Nutrition. 2000;16:1013–4.
Tisdale MJ. Nutrition. 2001;17:438–42.
Tisdale MJ. Curr Opin Support Palliat Care. 2008;2:256–61.
Torelli GF, Campos AC, Meguid MM. Nutrition. 1999;15:665–7.
Walsh D, Donnelly S, Rybicki L. Suppor Care Cancer. 2000;8:175–9.
Wisse BE, Frayo RS, Schwartz MW, Cummings DE. Endocrinology. 2001;142:3292–301.

Chapter 195
Quality of Life Assessment in Prader–Willi Syndrome

Pietro Caliandro, Graziano Grugni, Domenica Taruscio, Yllka Kodra, and Luca Padua

Abbreviations

BE	Behavior emotional
BP	Bodily pain
CH	Change health
CHQ-PF50	Child Health Questionnaire-Parent Form 50
FA	Family activity
FC	Family cohesion
GBE	Global behavior emotional
GGH	Global general health
GH	General health
MCS	Mental Composite Score
MH	Mental health
MMS	Mini-Mental State
PCS	Physical Composite Score
PE	Parental emotional
PF	Physical functioning
PHS	Physical Score
PSS	Psychosocial Score
PT	Parental time
PWS	Prader–Willi syndrome
QoL	Quality of life
RE	Role – emotional
REB	Role – emotional behavior
RP	Role – physical
SE	Self-esteem
SF	Social functioning
SF-36	Short Form-36
VT	Vitality

P. Caliandro (✉)
Institute of Neurology, Largo F. Vito 1, 00168, Roma, Italy
and
Fondazione Pro Iuventute Don Carlo Gnocchi, Roma, Italy
e-mail: p.caliandro@rm.unicatt.it

195.1 Introduction

Prader–Willi syndrome (PWS) is a neurogenetic disorder, characterized by neonatal hypotonia, mental and motor development retardation, hypogonadism, hyperphagia, morbid obesity, and dysmorphic facial features starting in late infancy or adolescence (Holm et al. 1993). Table 195.1 summarizes the most typical clinical aspects of PWS. The incidence of PWS is estimated to be 1:26,676 and the population prevalence is 1:76,574 (Vogels et al. 2004). The syndrome is caused by the delation of a specific gene in the paternally inherited chromosome 15q11q13 (Goldstone 2004).

Prader–Willi syndrome patients present a complex clinical picture and a consequent increased morbidity and mortality (Butler et al. 2002; Schrander-Stumpel et al. 2004; Thomson et al. 2006). In order to provide good assistance, an early diagnosis and a multidisciplinary approach to the disease are fundamental (Eiholzer and Whitman 2004). The multidisciplinary team involved in the care of Prader–Willi syndrome patients and their families should include several medical and nonmedical professional figures such as child psychiatrists, pediatric endocrinologists, clinical geneticists, orthopedic specialists, educational psychologists, and social workers. But all these professional figures should know what the patient wants and what kind of relationship there is between the traditional clinical outcome measures and the patient's perspective. Over the last 2 decades, clinical researchers emphasized the need for a thorough evaluation of patient's QoL in order to study the impact of chronic illnesses and their treatments on the patient's life (Guyatt et al. 1993).

The need for standardized measures of such items stimulated an extensive and rigorous process, allowing the development of validated patient-oriented instruments (Ware et al. 1994). This new approach may be very useful in the chronic and genetic syndromes involving the physical, emotional, psychological, cognitive, and social aspects of patients' life.

195.2 Concepts on QoL Assessment

QoL of PWS patients has been assessed using validated patient-oriented tools (Caliandro et al. 2007): (1) the Short Form-36 (SF-36) (Apolone et al. 1997) and (2) the Child Health Questionnaire-Parent Form 50 (CHQ-PF50) (Ruperto et al. 2001), according to the patient's age. CHQ-PF50 was used to evaluate patients from 6 to 14 years old, while SF-36 was used in patients older than 14. SF-36 consists of 36 questions covering the general health status of patients (Ware et al. 1994). This questionnaire

Table 195.1 Key features of Prader–Willi syndrome

- Prader–Willi syndrome is a complex syndrome caused by the delation of a specific gene in the paternally inherited chromosome 15q11q13
- The clinical picture is very complex and it needs a multidisciplinary approach
- Neonatal and infantile central hypotonia with poor suck gradually improves with age
- Feeding problems are typical in infancy with the need for special feeding techniques and poor weight gain
- Excessive or rapid weight gain on weight-for-length chart is common after 12 months but before 6 years of age; central obesity occurs in the absence of intervention
- Facial features are distinctive – dolichocephaly in infants, narrow face/bifrontal diameter, almond-shaped eyes, small-appearing mouth with thin upper lip, downturned corners of mouth (three or more required)
- Hypogonadism presents features depending on age
- Global developmental delay before age 6; mild to moderate mental retardation or learning problems in older children
- Hyperphagia/food foraging/obsession with food

provides eight specific categories of physical and emotional scores: Physical Functioning (PF), Role – Physical (RP), Bodily Pain (BP), General Health (GH), Vitality (VT), Social Functioning (SF), Role Emotional (RE), and Mental Health (MH), summarized in two main scores: Physical Composite Score (PCS) and Mental Composite Score (MCS). Very low scores for PCS indicate severe physical dysfunction, distressful bodily pain, frequent tiredness, and an unfavorable evaluation of health status. Very low scores for MCS indicate frequent psychological distress, and severe social and role disability due to emotional problems.

The Child Health Questionnaire (CHQ-PF50) is a generic QoL tool that measures child's physical, emotional, and social well-being with or without disability above the age of 5 years, and it consists of domains representing the most essential components of a child's QoL (Landgraf et al. 1996). The CHQ-PF50 is a parent-completed questionnaire. CHQ-PF50 consists of 50 items covering the general health status of patients with the aim to assess the effects of intervention being a quick and easy QoL measure used in conjunction with other more functionally based outcome measures. CHQ-PF50 provides 15 specific categories of physical and emotional scores (4 specific categories regarding patient's parents: Parental Time (PT), Parental Emotional (PE), Family Activity (FA), Family Cohesion (FC) and others concerning children: Physical Functioning (PF), Role – Physical (RP), Bodily Pain (BP), Global General Health (GGH), General Health (GH), Change Health (CH), Role – Emotional Behavior (REB), Behavior – Emotional (BE), Mental Health (MH), Global Behavior – Emotional (GBE), Self-esteem (SE) summarized into two main scores: Physical Score (PHS) and Psychosocial Score (PSS). Very low scores for PHS indicate severe physical dysfunction, distressful bodily pain, frequent tiredness, and unfavorable evaluation of the health status. Very low scores for PSS indicate frequent psychological distress and severe social and role disability due to emotional problems. Higher CHQ-PF50 scores (0–100) indicate better health.

One of the main differences between the SF-36 and the CHQ-PF50 is that the SF-36 is a patient-oriented questionnaire, while the CHQ-PF50 is a parent-completed questionnaire. Therefore SF-36 is useful only in patients with a good Mini-Mental State (MMS) (with a score higher than 24), and who are able to fill in the questionnaire. The CHQ-PF50, instead, is useful also in patients with an important cognitive impairment because it is a parental form questionnaire and therefore parents are requested to evaluate the QoL of their children.

Both questionnaires must be administered in accordance with standardized methodologies (Padua et al. 1998; Andresen et al. 2000), before any contact with physicians. More details on QoL assessment are available in the Table 195.2.

Table 195.2 Key features of quality of life (QoL) assessment

- The evaluation of patient's quality of life (QoL) is useful to study the impact of chronic illnesses and their treatments on the patient's life
- Different kind of questionnaire assessing QoL are available
- Generic questionnaires assess the general aspects of QoL. The most used tools are the Short Form-36 item questionnaire (SF-36) and the Child Health Questionnaire-Parent Form 50 (CHQ-PF50). The SF-36 is used in adults and the CHQ-PF50 is subjects from 6 to 14 years old
- Disease-specific questionnaires are ones which assess the impact of specific features of a single pathology on QoL. An example is the Boston Carpal Tunnel Questionnaire (BCTQ) specific for carpal tunnel syndrome or the Myasthenia Gravis Questionnaire (MGQ) specific for myasthenia gravis
- Region- or site-specific questionnaires are based on the concept of a single functional unit, such as the upper extremity. The questionnaire Disability of the Arm, Shoulder and Hand (DASH) scores assess the ability of the upper limb
- The QoL questionnaires must be chosen according to the pathology we want to study
- The most useful choice is the association of a generic questionnaire with a disease or site specific questionnaire (when available)

195.2.1 QoL of PWS Patients According to SF-36 and CHQ-PF50 Scores

Both in patients older and younger than 14 years, the physical and mental aspects of QoL are involved when compared with the healthy Italian subjects. In patients older than 14 years old, only the sub-score "Vitality" shows any statistical difference. On the other hand, in patients who were 14 years old or younger, "Bodily Pain" and "Family Cohesion" did not show statistically significant differences when compared with the same scores of the Italian norms. Tables 195.3 and 193.4 report the mean value and, in parenthesis, the standard deviation of the SF-36 and CHQ-PF50 scores. Those data are obtained from a sample of 29 patients (Caliandro et al. 2007). Twenty patients, older than 14 years (mean age 26.45 years; range 15–35; SD 7.54, 13 females and 7 males), were evaluated by SF-36, 9 patients who were 14 years old or younger (mean age 11.67 years; range 5–14; SD 3.00, 4 females and 5 males) were evaluated by the CHQ-PF50.

195.2.2 Correlation Between SF-36 Scores and Clinical Features

The impairment of QoL is mainly influenced by specific clinical aspects. The main score PCS and the sub-score PF are negatively related with the weight at the moment of the observation (respectively p: 0.02, Spearman −0.56 and p: 0.03, Spearman −0.49); as the weight is higher the physical function is more impaired (Figs. 195.1 and 195.2). The sub-score PF is also negatively related with the height (p: 0.02, Spearman –0.53).

GH is positively related to the weight at birth (p: 0.003, Spearman 0.76); as the birth weight is higher, the general health is better.

The main score MCS and the sub-score RE are positively related to birth weight (respectively p: 0.047, Spearman 0.58 and p: 0.02, Spearman 0.64); the mental aspects of QoL are less impaired in patients with a higher birth weight (Fig. 195.3). VT is positively related to the age of patients (p: 0.03, Spearman 0.48).

MH and MCS are lower in patients with characteristic facial features (respectively p: 0.003 and p: 0.003) (Fig. 195.4). MH is also lower in patients with narrow hands with straight ulnar border (p: 0.005) and in patients with osteoporosis (p: 0.02). SF is lower in patients with hypopigmentation (p: 0.048). VT is lower in patients with speech articulation defects (p: 0.01). SF and BP are lower in patients with unusual skill jigsaw puzzles (respectively p: 0.02 and p: 0.007).

195.2.3 Correlation Between CHQ-PF50 Scores and Clinical Features

Comparing CHQ-PF50 and clinical picture, FA and PHS are lower in patients with characteristic facial features (respectively p: 0.04 and p: 0.04) and in patients with decreased fetal movement or infantile

Table 195.3 SF-36 scores in PWS patients

PF	RF	BP	GH	VT	SF	RE	MH
means	means	means	means	means	means	means	means
(SD)	(SD)	(SD)	(SD)	(SD)	(SD)	(SD)	(SD)
67.37	62.94	63.25	57.4	66.15	70.25	51.83	60.9
(26.19)	(39.12)	(33.71)	(18.27)	(23.47)	(30.06)	(41.63)	(21.44)

Table 195.4 CHQ-PF50 scores in PWS patients

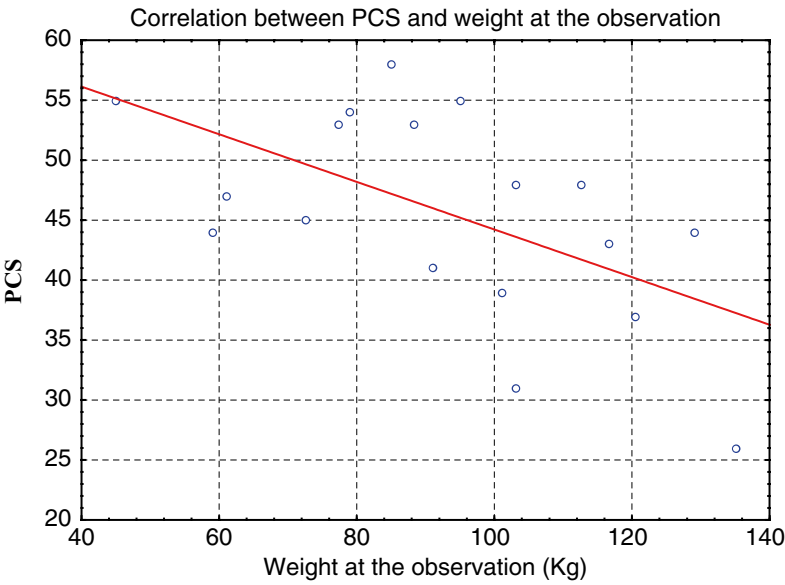| GGH	PF	REB	RP	BP	BE	GBE	MH	SE	GH	CH	PE	PT	FA	FC	PHS	PSS
means	means	means	means	means	means	means	means	means	means	means	means	means	means	means	means	means
(SD)	(SD)	(SD)	(SD)	(SD)	(SD)	(SD)	(SD)	(SD)	(SD)	(SD)	(SD)	(SD)	(SD)	(SD)	(SD)	(SD)
62.2	66.4	62.3	77.8	82.2	49.7	51.3	58.9	65.3	66.7	3.9	54.61	77.8	72.3	71.7	45.3	37.4
(29.1)	(34.1)	(34.7)	(32.3)	(21.7)	(22.5)	(35.6)	(25.6)	(15.9)	(15.5)	(1.3)	(25.7)	(27.8)	(33.9)	(35.3)	(12.1)	(10.6)

Fig. 195.1 Correlation between Physical Composite Score (PCS) and weight The Figure 1 shows that general physical dysfunction is more evident in patients with a higher weight
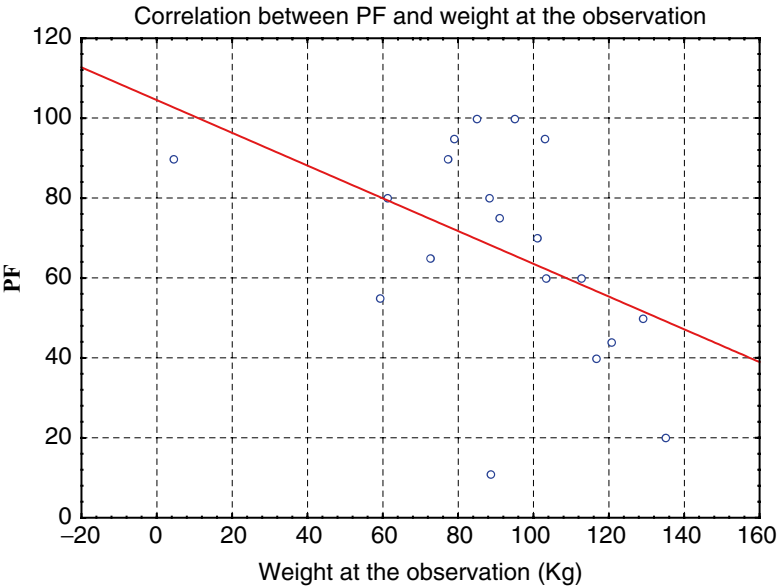
Fig. 195.2 Correlation between the sub-score physical functioning (PF) and weight

lethargy (respectively p: 0.045 and p: 0.045); MH and FC are lower in patients with thick viscous saliva with crusting at corners of the mouth (respectively p: 0.02 and p: 0.02); GH is higher in patients with high pain threshold (p: 0.04); SE is lower in patients with altered temperature sensitivity (p: 0.02) in patients without scoliosis (p: 0.02) and in patients with higher MMS score (p: 0.03 Spearman –0.7).

MMS score is higher in patients with altered temperature sensitivity (p: 0.02) and in patients without scoliosis. Any other statistically significant difference is revealed.
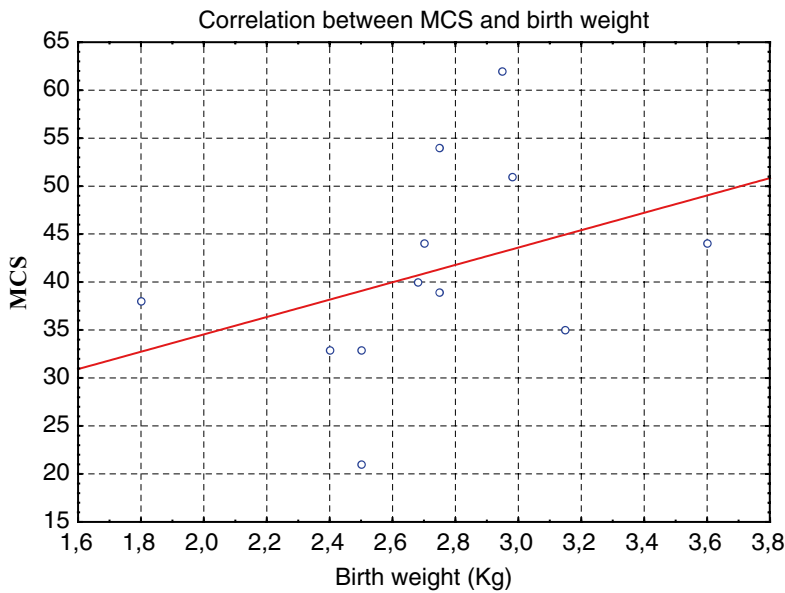
Fig. 195.3 Correlation between Mental Composite Score (MCS) and birth weight

Fig. 195.4 Mental health (MH) sub-score in patients with and without characteristic facial features
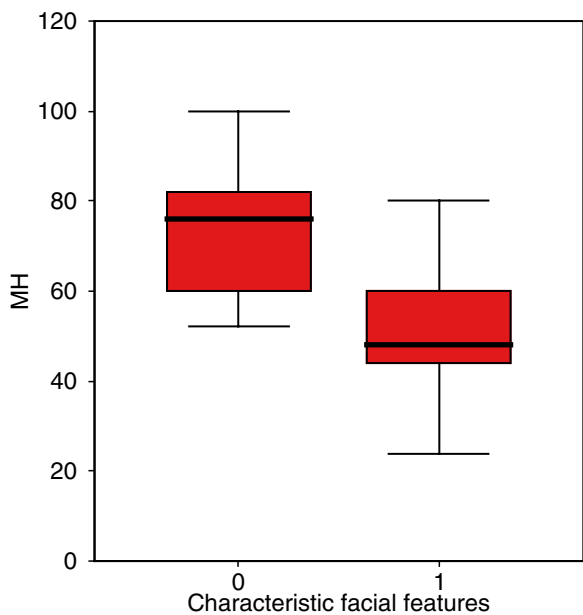
195.3 Conclusion

Prader–Willi syndrome (PWS) is a genetic disorder characterized by extreme obesity accompanied by other, multisystem clinical manifestations encompassing both physical and behavioral/cognitive abnormalities (Holm et al. 1993). A lot of studies focused on the correlations between the phenotypic

aspects and the genetic findings (D'Angelo et al. 2006; Dennis et al. 2006) and on the relationship between phenotype and the risk of cardiac and respiratory problems, fractures, leg ulceration, sleep disorders, and scoliosis (Butler et al. 2002). The multidimensional problems of patients with PWS cannot be treated with a single intervention and benefit from a team approach to optimize outcomes. In this contest, patient's perception about his pathology is important in solving everyday problems and improving patient's QoL.

In the sample of patients older than 14 years, QoL is intensely impaired both in the mental and physical aspects. About the correlation between the QoL assessment and clinical findings in patients older than 14 years, the physical aspects of QoL are mainly influenced by weight; the higher the weight, the worst is QoL regarding the physical aspects. Unexpectedly, a more severe obesity does not cause more impairment of QoL due to emotional aspects. On the other hand, mental aspects are negatively and mainly influenced by the presence of characteristic facial features and positively influenced by the birth weight; the higher the weight at birth, the lower is the impairment of QoL due to mental aspects. A possible explanation is that patients with a higher birth weight have less probability to develop those phenotypic characteristics which mainly cause an involvement of mental aspects of QoL. Indeed, comparing patients with and without characteristic facial features, the second ones, which have a more important involvement of mental aspects of QoL, have a higher birth weight. However, we are not able to explain if the birth weight influences the development of some pathognomonic phenotypic aspects and related emotional problems or if the birth weight is a phenotypic aspect which is influenced, as the facial phenotype, by genetic factors or by mother's alimentation.

Also in patients who were 14 years old or younger, QoL is impaired in both physical and mental aspects. In these patients, BP and Family Cohesion (FC) have no significant differences when compared to the same scores of the Italian norms. In other words, PWS patients do not experience limitations due to pain. As expected, also QoL of parents' is impaired. Indeed, a PWS patient influences parents' time, emotional life and everyday activities (the sub-scores Parental Time – PT, Parental Emotional – PE and Family Activity – FA are impaired), but FC is not influenced.

It is interesting to observe that the sub-score BP is impaired in patients older than 14 years and not impaired in patients younger than 14 years. A possible explanation might be that the CHQ-PF50 questionnaire is filled by parents and they might have some difficulties in evaluating an extremely personal sensation like pain.

In patients younger than 14 years, the physical aspects of QoL are mainly influenced by the presence of decreased fetal movement/infantile lethargy and the presence of characteristic facial features. It is interesting to note that patients with a high MMS have a low self-esteem; they have more knowledge of their body and their pathology and, therefore, need more psychological aids.

195.4 Applications to Other Areas of Health and Disease

The evaluation of Quality of Life (QoL) may be very useful in the chronic and genetic syndromes involving the physical, emotional, psychological, cognitive, and social aspects of patients' life in order to study the impact of chronic illnesses and their treatments on the patient's life. The assessment of QoL is particularly important in diseases with a multi system impairment. The multidimensional problems of patients cannot be treated with a single intervention and benefit from a team approach to optimise outcomes. In this contest, patient's perception about his/her pathology is important in solving every day problems and improving patient's QoL.

Summary Points

- Prader-Willi syndrome (PWS) is a genetic disorder characterized by extreme obesity accompanied by other, multisystem clinical manifestations encompassing both physical and behavioral/cognitive abnormalities.
- In PWS patients older than 14 years, QoL is intensely impaired both in the mental and physical aspects.
- In PWS patients older than 14 years, physical aspects of QoL are mainly influenced by weight; the higher is the weight the worst is QoL regarding the physical aspects. Unexpectedly, a more severe obesity does not cause a more impairment of QoL due to emotional aspects.
- In PWS patients older than 14 years, mental aspects are negatively and mainly influenced by the presence of characteristic facial features and positively influenced by the birth weight; the higher is the weight at birth the lower the impairment of QoL due to mental aspects.
- In patients younger than 14 years the physical aspects of QoL are mainly influenced by the presence of decreased fetal movement/infantile lethargy and the presence of characteristic facial features.
- Patients younger than 14 years and with a high MMS have a low self esteem; they have more knowledge of their body and their pathology and therefore, they need more psychological aids.

Key Terms

- **Short Form-36 (SF-36):** A questionnaire to assess general aspects of quality of life in adult subjects.
- **Child Health Questionnaire-Parent Form 50 (CHQ-PF50):** A questionnaire to assess general aspects of quality of life in children younger than fourteen years old.
- **Mini Mental State (MMS):** A test to evaluate the cognitive ability of subjects.
- **Physical Composite Score (PCS) and Mental Composite Score (MCS):** The two main scores of the SF-36 questionnaire. Very low scores for PCS indicate severe physical dysfunction, distressful bodily pain, frequent tiredness and an unfavourable evaluation of health status. Very low scores for MCS indicate frequent psychological distress, and severe social and role disability due to emotional problems.
- **Physical Score (PHS) and Psychosocial Score (PSS):** The two main scores of the CHQ-PF50 questionnaire. Very low scores for PHS indicate severe physical dysfunction, distressful bodily pain, frequent tiredness and unfavourable evaluation of the health status. Very low scores for PSS indicate frequent psychological distress, and severe social and role disability due to emotional problems.

References

Andresen EM, Lollar DJ, Meyers AR. Arch Phys Med Rehabil. 2000;81:S1–4.
Apolone G, Mosconi P, Ware JE. Questionario sullo stato di salute SF-36. Milano: Guerini e associate; 1997.
Butler JV, Whittington JE, Holland AJ, Boer H, Clarke D, Webb T. Dev Med Child Neurol. 2002;44:248–55.

Caliandro P, Grugni G, Padua L, Kodra Y, Tonali P, Gargantini, L, Ragusa L, Crinò A and Taruscio D. J Paediatr Child Health. 2007;43:826–30.

D'Angelo CS, Da Paz JA, Kim CA, Bertola DR, Castro CI, Varela MC, Koiffmann CP. Eur J Med Genet. 2006;49:451–60.

Dennis NR, Veltman MW, Thompson R, Craig E, Bolton PF, Thomas NS. Am J Med Genet. 2006;140:434–41.

Eiholzer U, Whitman BY. J Pediatr Endocrinol Metab. 2004;17:1153–75.

Goldstone A. Trends Endocrinol Metab. 2004;15:12–20.

Guyatt GH, Feeny DH, Patrick DL. Ann Intern Med. 1993;118:622–29.

Holm VA, Cassidy SB, Butler MG, Hanchett JM, Greenswag LR, Whitman BY, Greenberg F. Pediatrics. 1993;91:398–402.

Landgraf JM, Abetz L, Ware JE. The CHQ User's Manual. Boston: The Health Institute, New England Medical Center; 1996.

Padua R, Romanini E, Zanoli G. L'analisi dei risultati nella patologia dell'apparato locomotore: Outcome research e questionari di autovalutazione. Milan: Guerini Editore; 1998.

Ruperto N, Ravelli A, Pistorio A, Malattia C, Viola S, Cavuto S for the Paediatric Rheumatology International Trials Organisation (PRINTO). Clin Exp Rheumatol. 2001;19:S91–5.

Schrander-Stumpel CT, Curfs LM, Sastrowijoto P, Cassidy SB, Schrander JJ, Fryns JP. Am J Med Genet A. 2004;124:333–8.

Thomson AK, Glasson EJ, Bittles AH. J Intellect Disabil Res. 2006;50:69–78.

Vogels A, Van Den Ende J, Keymolen K, Mortier G, Devriendt K, Legius E, Fryns JP. Eur J Hum Genet. 2004;12:238–40.

Ware JE, Kosinski M, Keller SK. SF-36 Physical and Mental Health Summary Scales: A user's manual. Boston: New England Medical Centre; 1994.

Chapter 196
Dysphagia, Behavior, and Quality of Life

D. A. de Luis, Mick P. Fleming, and Colin R. Martin

Abbreviations

NGT   Nasogastric tube
PEG   Percutaneous endoscopic gastrostomy
QOL   Quality of life
TPT   Transpiloric tube

196.1 Introduction

Oropharyngeal dysphagia results in high mortality, morbidity, and economic costs. Epidemiological data are scant estimates of the prevalence of dysphagia among individuals older than 50 years, and range from 15% to 22% (Lindgren and Janzon 1991). Within health-care institutions, it is estimated that 15% of patients in short-term care hospitals and up to 60–70% of nursing home occupants have feeding difficulties (Groher and Bukatman 1996).

196.2 Etiology and Epidemiology

The prevalence of dysphagia in certain pathologies has been reviewed, with the following incidences: rheumatic disease (rheumatoid arthritis 28%; polymyositis 12–54%), neurological disease (Huntington's disease 95%), multiple sclerosis (frequency varies depending on the location of the lesion, 48–100%), cerebral palsy (27%), stroke (20–100%), Parkinson's disease (50%), and in the general population (20%) (Kuhlemeir 1994).

The prevalence of dysphagia is usually more frequent in neuromuscular disease, tumor or surgery involving the head, neck, and upper limbs (Martin 1991). It is typical for brain pathologies (affected) to affect the oral phase of swallowing, while the esophageal phase is affected by local disease (Table 196.1).

D.A. de Luis (✉)
Institute of Endocrinology and Nutrition, Medicine School and
Unit of Investigation, Hospital Rio Hortega. Hospital Clinico,
University of Valladolid, Valladolid, Spain
e-mail: dadluis@yahoo.es

Table 196.1 The relationship between dysphagia caused by specific diseases and the three phases of deglutition

Phase of deglutition	Dysphagia
Esophagus phase	Head and neck tumors, cervical injuries
Pharynx phase	Stroke, multiple sclerosis (multiple), cerebral palsy, amyotrophic lateral sclerosis
Oral phase	Neuromuscular diseases that affect motility or sensibility of muscles related with deglutition

This table shows the affects of dysphagia caused by other named specific diseases on the three phases of deglutition

Neurological disease is the leading cause that must be considered in a patient with dysphagia. Stroke is probably the most frequent cause of dysphagia, affecting the oral phase of deglutition and presenting with aspiration pneumonia as a major complication (Kidd et al. 1995). In patients with acute cerebrovascular injury, bilateral involvement is typically present in dysphagia, it affects mainly the oral apraxia deglutition, where the patient has forgotten how to swallow but retains physical ability to swallow. Dysphagia can be overcome during the course of a spontaneous recovery of the neurological condition; for others it is important to be prepared to undertake deglutition rehabilitation and all appropriate measures to prevent aspiration.

Patients with multiple sclerosis show an alteration in the myelin alterations that trigger the neurological problems in this disease, and the deglutition problems, too. Symptoms of dysphagia and frequency may vary depending on the location of the lesion; these patients are in advanced forms (subsidiary gastrostomy) of supplemented intake (Buchholz 1987). Neurodegenerative diseases such as Parkinson's disease with a dysphagic course are also a frequent cause of aspiration pneumonia (Kirshner 1989). We can also include in this group of neurodegenerative diseases disorders such as Alzheimer's dementia and Huntington's disease.

The motor neuron pathologies are a group of diseases in which there are is decreased numbers of neurons that govern the motor activity in different muscle groups. The most common type is amyotrophic lateral sclerosis, where there are a considerable number of motor neurons in the brain and spinal cord. In patients afflicted with this entity, dysphagia often presents as one of the first symptoms, usually in the first 4–5 months (Negus 1994).

Other diseases affecting the nervous system may also present with clinical dysphagia as a symptom of the worsening of the clinical course of the disease. In infections such as poliomyelitis, residual damage may present as dysphagia of pharyngeal phase. Myotonic dystrophy produces facial and pharyngeal muscle weakness, resulting in a secondary dysphagia. Also in dystonia and dyskinesia (involuntary movements and contractions), if there is involvement of the facial, oral, or lingual palatopharyngeal muscles, then there are problems with swallowing. Closed head injuries and brain tumors can affect neurons that influence the oropharyngeal motility, introducing additional problem such as swallowing disorders.

In addition to the above-mentioned diseases and conditions, it must be remembered that certain drugs affect the mechanism of swallowing through various mechanisms. Thus, there are drugs that lower the pressure of the lower esophageal sphincter (alpha-blockers, anticholinergics, barbiturates, beta-adrenergic, dopamine channel blockers, calcium, nitrates, alcohol, and caffeine), while another group of drugs increases the pressure of this sphincter (antacids, alpha-adrenergic agonists, beta-adrenergic antagonists, cholinergic agonists, and prokinetics). Other drugs may worsen swallowing by altering the level of consciousness (alcohol, antiepileptics, antidepressants, antihistamines, antitussives, antipsychotics, antiemetics, and steroids). Finally, there are drugs that can cause dysphagia secondary to the production of esophagitis (quinidine, aspirin, nonsteroidal anti-inflammatory drugs, vitamin C). The correct evaluation of a patient with dysphagia, therefore, requires not only a neurological history, together with the use of imaging techniques, but also must take into account not only any but all medications being taken by the patient.

196.3 Diagnosis of Dysphagia

In many cases the clinical signs of dysphagia are very obvious, as shown in Table 196.2, with evident symptoms, while at other times the signs are less evident and manifest as indirect symptoms (Table 196.3). In certain situations, it can be difficult to achieve a reliable diagnosis of this entity.

One technique to make a more objective diagnosis of an impairment of the swallowing is video-fluoroscopy with barium (Levis and Kidder 1996). This procedure uses small volumes of high-density barium mixed with food of different consistencies to provide radiographic evidence of oral and pharyngeal swallowing. This technique is not only useful to note the diagnosis of impaired swallowing, but also in planning the therapeutic strategies for these patients. If the patient's diagnosis requires an evaluation of the role of the vocal cords, the technique of choice is endoscopy (Perlman and Van Daele 1993), as this technique allows an excellent assessment of the dynamics and paralysis of the pyriform sinus and valleculae, and also the presence of a delayed onset of the pharyngeal stage.

Another technique used is the determination of pressures obtained by pharyngeal manometry; however this technique is used in research protocols and not in clinical practice (Castell 1993; Klahn and Perlman 1999).

There are times in everyday clinical practice when there are no available techniques for the study of dysphagia; thus the presence of symptoms may be used to both directly and indirectly support the diagnosis in combination with certain techniques of physical examination. The examination of the V nerve is made using a tongue depressor and a small sharp instrument slipped in the facial surface. The VII nerve examination is performed by having the patient smile. The IX nerve exam is conducted by having the patient say "AH," which requires elevation of the palate, it also (uses the reflection of) enables a check of the vomiting reflex by touching the back wall of pharynx with a swab. The vagus and IX nerves were examined by having the patient protrude his or her tongue; tongue lateralization indicates injury of these nerves. It is also necessary to explore the cough reflex and the cognitive level for a full study of the patient's situation; all of these examinations and assessments of the mechanism of deglutition in patients with suspected dysphagia have proven useful in the management of the problem (Odderson et al. 1995).

Table 196.2 Relationship between the clinical symptoms of dysphagia and the three phases of deglutition

Phase of deglutition	Symptoms
Esophagus phase	Vomiting, regurgitation, reflux
Pharynx phase	Stagnant and motionless liquid and solid intake (a lot of) deglutition effort with various food, pain with deglutition, aspiration of food
Oral phase	(Bad) poor control of tongue, reduction in the closed lips, facial muscle weakness, failure to drink from a cup

This table integrates a list of the clinical symptoms of dysphagia with the three phases of deglutition

Table 196.3 A list of the indirect clinical affects on the person of dysphagia

Refusing to eat
Aversion to food
Repeated episodes of pneumonia
Weight loss
Anorexia
Malnutrition
Dehydration

This table provides a list of the indirect clinical affects that are secondary to dysphagia

196.4 Therapeutic Approach to the Problem

Once the patient has been diagnosed with dysphagia, the patient must be nourished in a safe manner, while putting in place different strategies to address the therapeutic swallowing disorders. Treatment of these patients requires a multidisciplinary approach involving radiologists, gastroenterologists, dieticians, nurses, social workers, and a nutritionist to lead the group.

The first priority is to conduct a proper nutritional assessment of the patient to decide the right route of access, so that in patients unable to ingest a minimum of 50% of their caloric and protein requirements by mouth, nutrition should be given by enteral nasogastric tube (NGT) (Fig. 196.1), transpyloric tube (TPT) (Fig. 196.2), percutaneous endoscopic gastrostomy (PEG) (Fig. 196.3), or parenteral access. Usually the NGT tube is used, but if the enteral route is to be used for more than 3 weeks, PEG is indicated (Fertl et al. 1998; Annoni et al. 1998).

Fig. 196.1 Fine bore tube used for enteral feeding. Picture of a fine bore tube used for enteral gastric tube feeding, the most frequent enteral access for enteral nutrition
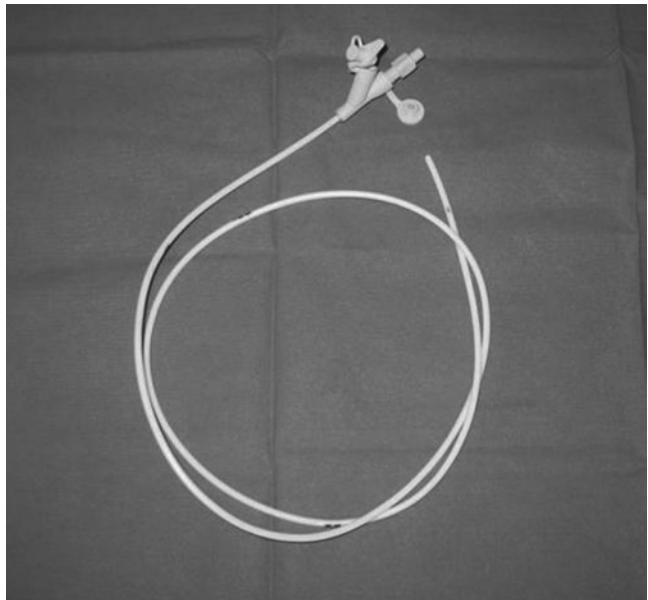
Fig. 196.2 Transpyloric tube for enteral feeding to the duodenum. Picture of a transpyloric tube which delivers enteral feeds to the duodenum for increase nutrient absorption. Indicated for use in patients with a high risk of aspiration
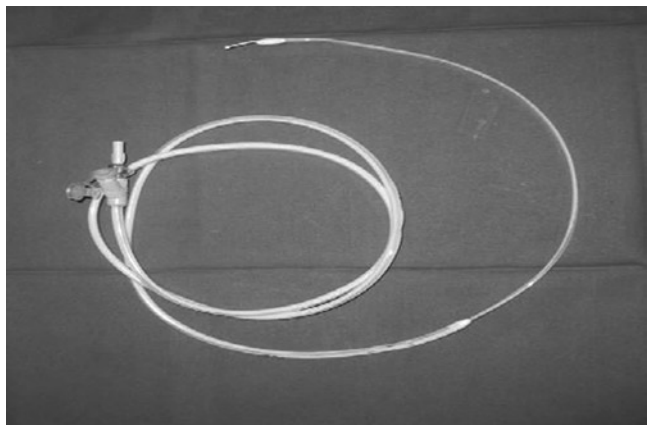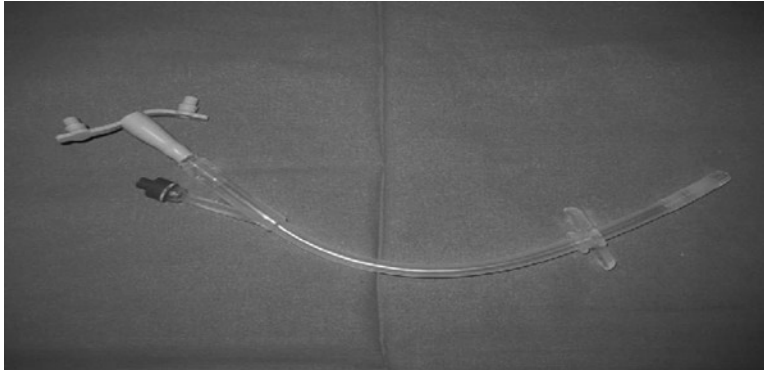
Fig. 196.3 Percutaneous endoscopic gastrostomy tube (PEG tube). Picture of Percutaneous Endoscopic Gastrostomy tube (PEG tube), indicate for use in patients requiring more than 3 weeks of enteral nutrition
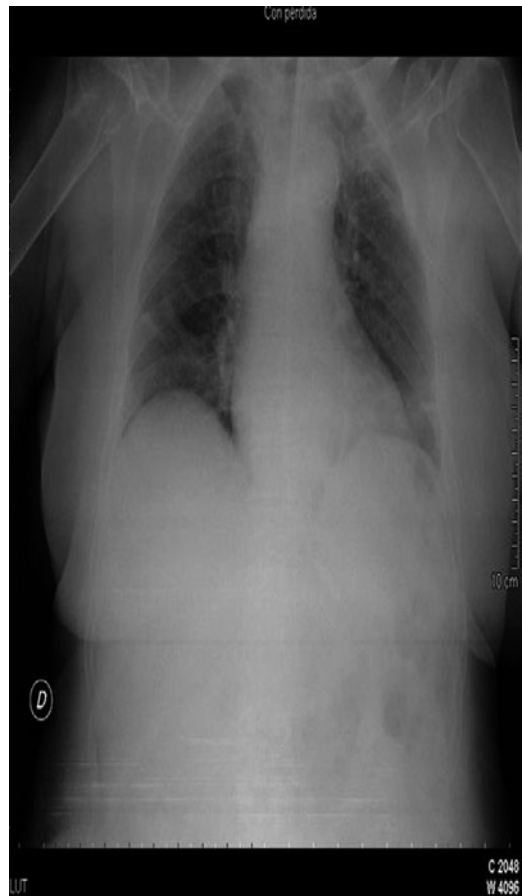
Fig. 196.4 X-ray of chest with gastric tube feeding in situ. Copy of x-ray of chest with gastric feeding tube in situ. Correct position to ensure tube is in the stomach to prevent aspiration should be confirmed by x-ray prior to commencement of feeding

Radiographic (control to assess the right situation of this device must be realized) assessment is often needed (Fig. 196.4). Enteral nutrition has proven its usefulness in a highly prevalent group of patients with dysphagia, such as patients with stroke. It is reported that there was a decrease in mortality at 3 months of using a polymeric formula during 4 weeks after a stroke,

10% versus 30% in the supplemented group (Duncan et al. 1996; Mitchell et al. 1997; Nyswonger and Helmchen 1992).

Patients with oral nutrition intake problems must make an oral nutrition effort in successive stages by changing the texture of food. It should be noted that according to different international guidelines for patients with dysphagia, these patients should receive diets with modification of the texture in a phased way. This means starting with a first phase, in which thick purees are administered, and they are not allowed liquids, including water; a second phase, in which they are allowed some fruit drinks, but not water; a third stage, which includes the previous purees, e.g., eggs, cooked fish, and vegetables; and a fourth phase, which allows any fluid intake and solid food except food which is granular (e.g., corn and rice); the fifth phase is intended to be a return to a normal diet. Taking into account the difference in consistency of food in these stages, the utility of these products is clearly shown to fulfill a function that is not only nutritious, but also to assist in swallowing by changes in the texture of the dish (Hunter 1996).

Therefore, it is assumed that supplementing the diet of these patients with oral lyophilized products will help to achieve better nutrition and therefore a decrease in hospital stay and complications. Sometimes it is impossible to achieve the proper texture of foods in each phase for a given patient, so various companies have marketed nutritional products that have come to form part of a new concept known as "basic food," which adapts and makes changes in food texture and nutrition in an effort to achieve optimal quality of life in patients with these specific nutritional requirements. These new products include first courses, main courses, and desserts; in some of these cases, the products have been lyophilized from natural sources, while retaining their nutritional characteristics with regard to micronutrients (de Luis and Aller 2003). Our group has performed several investigations with these products so as to assess the reconstitution with water (de Luis et al. 2002), along with acceptability to the patient (in terms of different characteristics such as smell, taste, color, and especially texture). In another work, we have compared a group of patients on a soft diet versus a conventional lyophilized diet, and the latter obtained higher scores in all assessed characteristics, especially in terms of excellent texture (de Luis et al. 2001; de Luis et al. 2006a).

196.5 Implications on Quality of Life

Quality of life may be defined as a patient's appraisal of, and satisfaction with, his or her current level of functioning compared with what is perceived to be possible. Evidence regarding the quality of life provides patients with a comprehensible measure of the functional consequences that result from the complex interaction between disease and treatment. Quality of life is impaired in patients with dysphagia and nutrition problems (Fig. 196.5). In some studies, low body mass index, indicating protein caloric malnutrition, was found to negatively influence quality of life in older adults (Crogan and Pasvogel 2003).

Our group has completed a study exploring the influence of nutritional status and oral dietary intake on quality of life in elderly patients with dysphagia (de Luis et al. 2006a). Quality of life (QoF) was assessed using the well-validated SF-36 questionnaire (Brazier et al. 1992). The SF-36 QOL questionnaire is a self-administered questionnaire containing 36 items which takes about 5 min to complete. It measures health on eight multidimensional measures, covering functional status, well-being, and overall health (Table 196.4).

The SF-36 health status questionnaire showed a score of 96.3 ± 9.9 points in our patients with dysphagia (de Luis et al. 2006b). Correlation analysis showed a positive correlation among (the next) certain parameters and the SF-36 score (carbohydrate intake, $r = 0.51$; $p < 0.05$), (protein intake, $r = 0.4$; $p < 0.05$), and (caloric intake, $r = 0.5$; $p < 0.05$). Anthropometric and biochemical parameters did not have any correlation with the SF-36 score. In the multivariate analysis with a dependent variable (SF-36 score), only carbohydrate intake remained in the model adjusted for body mass index, albumin,
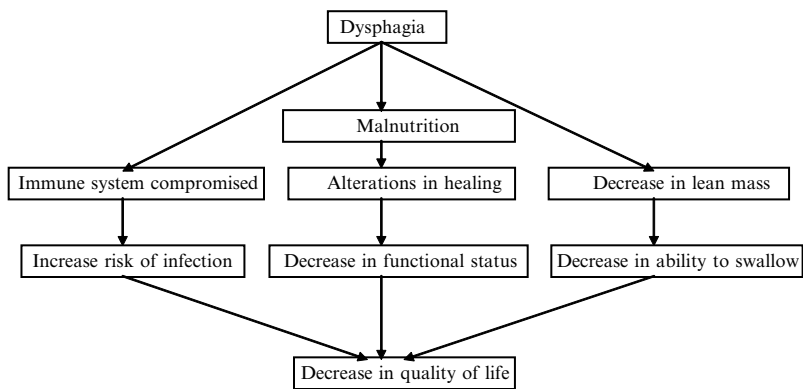
Fig. 196.5 The clinical symptoms and wider affects of dysphagia and their relationship to changes in quality of life. Diagram showing the clinical symptoms and wider secondary affects of dysphagia and their relationship with changes in quality of life

Table 196.4 A list of the key features of the SF-36 quality of life measure

Reference of the manual for the SF36, SF36v2, and SF12	Ware, J.E., Snow, K.K., Kosinski, M., Gandek, B. (1993). *SF-36® Health Survey Manual and Interpretation Guide*. Boston, MA: The Health Institute, New England Medical Center
	Ware, J.E., Kosinski, M., Dewey, J.E. (2000). *How to Score Version Two of the SF-36 Health Survey*. Lincoln, RI: QualityMetric, Incorporated
	Ware, J.E., Kosinski, M., Keller, S.D. (1995). SF-12®: *How to Score the SF-12®Physical and Mental Health Summary Scales. Second Edition* edition. Boston, MA: The Health Institute, New England Medical Center
Items	36
Domains measured	Physical functioning, role limitation due to physical problems, bodily pain, general health, vitality, social functioning, role limitation due to emotional and mental health problems
Mode of administation	Self-administered
Properties	Designed from the Medical Outcomes Short Form Health Survey. Validated for measuring the health status of people over 14 years of age in terms of their physical and mental health functioning it is provides a subjective measurement of eight of the most common health related concepts which allows useful comparisons of these key health concepts across client groups. It is considered to be a general measure and as such does not focus on specific conditions but has been succesfully validated in a variety of physical and mental health conditions
	An updated version of the SF-36 (the SF36v2) was produced in 1996 this version adopted a five-level response format for respondents
	Abbreviated 12-item SF-12 version is also available

This table provides a list of the key features and pieces of information about the SF36 quality of life measure for those unfamiliar with its use

age, and sex, with an increase of 0.1 (CI 95%: 0.01–0.191) SF-36 point with each 1 g of carbohydrate intake. Our patients with dysphagia had normal weight and body mass index accompanied by a moderate depletion in serum proteins. QOL was related to dietary intake, and was unrelated to anthropometric or biochemical parameters.

Dietary intake in our patients showed low intake of certain vitamins and minerals as well as total energy. However, a proper distribution of macronutrients was observed. Carbohydrate, caloric, and protein intake patterns were positively correlated with quality of life as defined by the SF-36 score. QOL is clearly an important consideration in clinical outcome. In previous studies, no benefit in

quality of life by the administration of oral dietary supplements to patients was detected (Keele et al. 1997). However, Beattie et al. (2000; Isering et al. 2004) reported a benefit on QOL in malnourished patients with oral supplementation.

This study demonstrated a positive correlation among the energy and protein and carbohydrate intake patterns with quality of life. This association does not indicate a direct relationship, but a good nutritional status is likely to improve the quality of life. We recommend further studies, particularly cross-sectional and intervention trials are required in this area. This study is the first to show a correlation between quality of life and carbohydrate intake in a multivariate model. A cross-sectional study (Demark-Wahnefried et al. 2004) reported that the consumption of a diet rich in fruits and vegetables was associated with higher levels of physical functioning and quality of life among older cancer patients.

Ponzer et al. (1999) reported that half of the elderly women with hip fractures displayed signs of protein-energy malnutrition and this was associated with a low quality of life. No relation was detected between anthropometric and biochemical parameters and quality of life in our population. However, in the study of Crogan and Pasvogel (2003), low BMI, indicating protein-caloric malnutrition, was found to negatively influence the quality of life in nursing home patients. Further studies are needed in this topic area to elucidate these interesting relationships.

196.6 Applications to Other Areas of Health and Interest

This area of health care has considerable implications for other health specialists (Fig. 196.6), for example:

1. Radiologists, to help with the diagnosis of these types of patients with the newly emerging techniques such as videofluroscopy with barium.
2. Gastroenterologists who need to pursue enteral access to enteral nutrition (transpyloric tubes or percutaneous endoscopic gastrostomy).
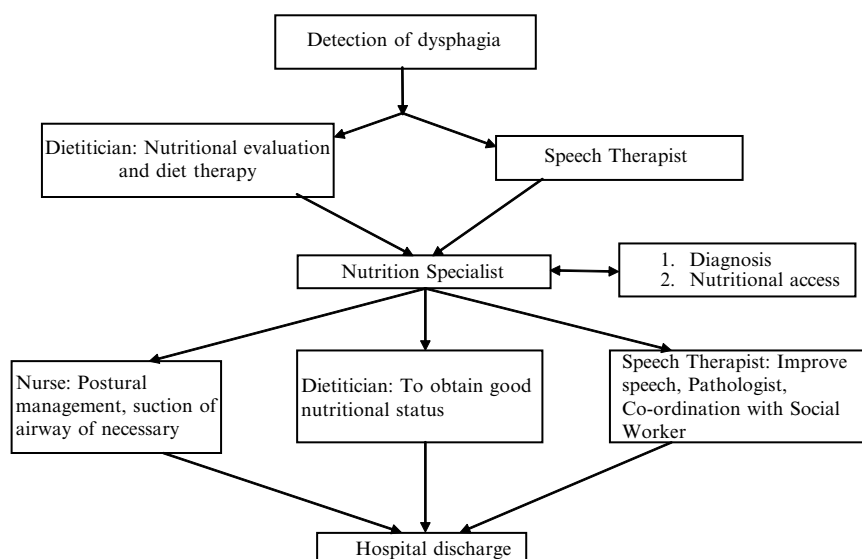

Fig. 196.6 The specialists and their role in the treatment of the person with dysphagia. Diagram showing the different specialists working within dyspaghia treatment and their role in the diagnosis and treatment of the person with dysphagia

3. Dieticians, for assessing the right dietary intake and to improve the different phases of oral diet.
4. Social workers, to improve the quality of life after hospital discharge.
5. Speech specialists, to improve language recovery after neck surgery.

Summary Points

- Dysphagia is a nutritional problem of first order in a negligible proportion of patients; treatment requires a multidisciplinary approach in which a nutrition specialist plays an important role.
- There are new diagnostic techniques (videoflouroscopy with barium) that are necessary (for knowing balancing exploration) examination with conventional clinical techniques that will enable us to make a better diagnosis of the patient.
- It is also necessary to take into account lyophilized nutritional products that can improve the recovery of these patients.
- Some studies have demonstrated that the quality of life in this type of patients is related to dietary intake, and could be improved with nutritional supplementation.

Definition of Key Terms

Aspiration pneumonia: A type of lung inflammation resulting from the aspiration of food, liquid, or gastric contents into the upper respiratory tract.

Apraxia: A group of cognitive disorders characterized by the inability to perform previously learned skills that cannot be attributed to deficits of motor or sensory function. The two major subtypes of this condition are ideomotor (see apraxia, ideomotor) and ideational apraxia, which refers to loss of the ability to mentally formulate the processes involved with performing an action. For example, dressing apraxia may result from an inability to mentally formulate the act of placing clothes on the body. Apraxias are generally associated with lesions of the dominant parietal lobe and supramarginal gyrus.

Dysphagia: Difficulty in swallowing which may result from neuromuscular disorder or mechanical obstruction. Dysphagia is classified into two distinct types: oropharyngeal dysphagia due to malfunction of the pharynx and upper esophageal sphincter; and esophageal dysphagia due to malfunction of the esophagus.

Enteral nutrition: Nutritional support given via the alimentary canal or any route connected to the gastrointestinal system (i.e., the enteral route). This includes oral feeding, sip feeding, and tube feeding using nasogastric, gastrostomy, and jejunostomy tubes.

Gastrostomy: Creation of an artificial external opening into the stomach for nutritional support or gastrointestinal compression.

Quality of life: A generic concept reflecting concern with the modification and enhancement of life attributes, e.g., the physical, political, moral, and social environment; the overall condition of a human life.

References

Annoni JM, Vuagnat H, Frischknecht R, Uebelhart D. Disabil Rehabil. 1998;20:308–14.
Beattie A, Prach AT, Baxter JP, Pennington CR. Gut. 2000;46:813–18.
Brazier JE, Harper R, Jones NMB. BMJ. 1992;305:160–2.

Buchholz D. Dysphagia. 1997;1:152–4.

Castell DO. Dysphagia. 1993;8:337–8.

Crogan NL, Pasvogel A. J Gerontol A Biol Sci Med Sci. 2003; 58:159–64.

de Luis DA, Aller R. Rev Clin. 2003; 203:384–5.

de Luis DA, Aller R, Cabezas G, Rojo S, Cuellar L, Terroba C, Izaola O. Actividad Dietética. 2001; 13:16–20.

de Luis DA, Aller R, Izaola O, Cabezas G, Rojo S, Cuellar L, Terroba M. Nutr Hosp. 2002; 27; 240–4.

de Luis DA, Izaola O, Mateos M, Aller R, Terroba C, Cuellar L. Medicina Clin Barc. 2006a; 127:374–5.

de Luis DA, Izaola O, Mateos ML, Cuellar L, Terroba MC, Aller R. Nutrition. 2006b; 22:584.

Demark-Wahnefried W, Clipp EC, Morey MC, Pieper CF, Sloane R, Snyder DC. Int J Behav Nutr Phys Act. 2004; 29:16.

Duncan HD, Walters E, Silk DB. BMJ. 1996; 312:973–4.

Fertl E, Steinhoff N, Schofl R, Potzi R, Doppelhauer A, Muller C, Auff E. Eur Neurol. 1998;40:27–30.

Groher ME, Bukatman R. Dysphagia. 1996;1:3–6.

Hunter AMB. NCP. 1996;11:157–69.

Isering EA, Capra S, Bauer JD. Br J Cancer. 2004;91:447–52.

Keele AM, Bray M, Emery P. Gut. 1997;40:393–9.

Kidd D, Lawson J, Nesbitt R, MacMahon J. Q J Med. 1995;88:409–13.

Kirshner HS. Dysphagia. 1989;3:184–8.

Klahn M, Perlman A. Dysphagia. 1999;14:131–8.

Kuhlemeir KV. Dysphagia. 1994;9:209–17.

Levis MM, Kidder JA. Chicago, IL: American Dietetic Association; pp. 1–13. 1996.

Lindgren S, Janzon L. Dysphagia. 1991;6:187–92.

Martin AW. Dysphagia. 1991;6:129–34.

Mitchell SL, Kiely DK, Lipsitz LA. Arch Intern Med. 1997;122:1149–53.

Negus E. B J of Nursing. 1994;3:263–9.

Norton B, Homer-Ward M, Donnelly MT, Long RG, Holmes GK. BMJ. 1996;312:13–16.

Nyswonger GD, Helmchen RH. J Neurosci Nurs. 1992;24:220–3.

Odderson IR, Keaton JC, McKenna BS. Arch Phys Med Rehabil. 1995;99:1130–33.

Perlman AL, Van Daele AJ. J Med Speech Lang Pathol. 1993;11:223–32.

Ponzer S, Tidermark J, Brismar K, Soderqvist A. Clin Nutr. 1999;18:241–6.

Chapter 197
Bariatric Surgery and Health-Related Quality of Life

Raed Tayyem, Abdulmajid Ali, John Atkinson, and Colin R. Martin

Abbreviations

BMI	Body mass index
DVT	Deep venous thrombosis
EQ-5D	EuroQoL
HDL	High-density lipoprotein
LDL	Low-density lipoprotein
PE	Pulmonary embolism
SF-36	The Short-Form (36) Health Survey
WHO	World Health Organisation

197.1 Introduction

The body mass index (BMI) is calculated by dividing weight in kilograms, by height in meters squared, using the following equation: BMI = weight (kg)/height^2 (metres^2). The ideal BMI of an adult is 20 to 24.9. Individuals with BMI of 25–29.9 are considered overweight. Obesity is defined as a chronic condition associated with a BMI of 30 or more, and results in increased morbidity and mortality (Table 197.1). The World Health Organization (WHO) classifies obesity into three categories (Table 197.2; Ellison and Ellison 2008).

Obesity epidemic has reached alarming levels in the world. In the United States, two thirds of adults are overweight, one third are obese (Pohl et al. 2006), and approximately 5% of the population are morbidly obese (DeMaria 2007). Obesity and associated medical conditions cost the health system in the United States a staggering US$100 billion per year (Ellison and Ellison 2008), which is roughly equal to 10% of the medical expenditure (Livingston and Fink 2003). The socioeconomic impact of the obesity epidemic is similar to that from poverty, smoking, or alcohol abuse (Peter et al. 2005).

According to the Foresight Report in 2007, the United Kingdom has the fastest increase in the disease in Europe, with prevalence rates comparable to the United States. Three quarters of the

C.R. Martin (✉)
School of Health, Nursing and Midwifery, University of the West of Scotland,
Ayr Campus, Beech Grove, Ayr, KA8 0SR, UK
e-mail: colin.martin@uws.ac.uk

Table 197.1 Key features of obesity

1.	Obesity is a complex multifactorial chronic disease in which several factors interplay in poorly understood mechanism, resulting in physical, social, and psychological impairments.
2.	Genetic, hormonal, psychological, social, and behavioral factors such as dietary habits and physical inactivity are the major players in the development of obesity.
3.	Obesity carries significant risks to the health, leading to physical comorbidities (e.g., diabetes mellitus), psychological comorbidities (e.g., depression), and social impairments (e.g., social isolation).
4.	The prevalence of obesity in the world has been steadily rising.
5.	Treating obesity and obesity comorbidities is expensive. In the USA alone, obesity costs the health system US$100 billion per year.
6.	Nonsurgical approach of behavioral modification interventions and pharmacotherapy will fail in 90% of obese patient within 5 years. Bariatric surgery provides the only effective and sustainable approach to treat morbid obesity.
7.	Obesity has a major impact on quality of life that has the potential to improve with treatment.

This table lists the key facts of obesity including the basic concept of obesity, mechanisms of developing obesity, health risks of obesity, cost of obesity, treatment of obesity and quality of life in obesity

Table 197.2 WHO classification of obesity

Class	Description	BMI (kg/m^2)
Class one	Mild obesity	30–34.9
Class two	Severe obesity	35–39.9
Class three	Morbid obesity	≥40

This table lists WHO classes of obesity

population are overweight, and one quarter are obese. Obesity costs the UK economy UK£7 billion and the NHS UK£2 billion per year. It is expected that obesity will cost the UK economy UK£45 billion and the NHS UK£6.5 billion in 2050 (Butland et al. 2007).

197.2 Etiology

Obesity is a complex multifactorial disease in which genetic, psychological, social, and behavioral factors such as dietary habits and physical inactivity interact in a poorly understood mechanism (Pohl et al. 2006). Other factors currently under investigation, which may be responsible for obesity and obesity comorbidities, include chronic inflammatory state, gut hormones modulation, and calcium and vitamin D interactions (Major et al. 2008).

The familial tendency of obesity, high concordance for obesity in identical twins and the increased risk of obesity in certain ethnic groups may indicate a genetic predisposition for obesity (Pohl et al. 2006). Obesity genes have been isolated, which may explain why the nonsurgical treatment of obesity will not provide significant and sustainable weight loss for more than a year (Balsiger et al. 1997; McTigue et al. 2003).

Binge eating is rapid consumption of a large amount of food. Grazing is eating smaller amounts of food continuously throughout the day. Chronic low-grade anxiety may manifest as grazing, meanwhile binge eating may result from more intense emotions such as anger (Glinski et al. 2001). Behavioral studies revealed three eating patterns in obese patients: sweet eaters (consumption of food high in calories such as fat and sugar), volume eaters (consumption of large portions), and sedentary lifestyle (lack of exercise and physical activity).

197.3 Obesity Comorbidities

In morbidly obese patients, the prevalence of diabetes mellitus, hypertension, high cholesterol, arthritis, and poor general health is higher compared to normal weight individuals (Table 197.3; Gould et al. 2006). An overweight person, with a BMI of over 25, will have higher risk of diabetes mellitus compared to those with a BMI of less than 25 (Colquitt et al. 2005). It is estimated that in obese patient, for every 1 kg increase in weight, the risk of diabetes increases by 4.5% (Wolf and Colditz 1998). The risk of metabolic syndrome consisting of insulin resistance, hypertension, and hyperlipidemia is higher in an overweight population, leading to increased risk of heart disease and stroke (Pohl et al. 2006). The lifelong risk of hypertension will double as the BMI increases from 25 to 35 (Presutti et al. 2004). Obesity is associated with increased risk of a number of malignancies including breast, colon, prostate, endometrial, kidney, and gallbladder (Colquitt et al. 2005; Pohl et al. 2006).

Obesity is associated with increased risk of death (Fig. 197.1; Calle et al. 2003). Obesity results in more than 400,000 deaths in the United States each year (DeMaria 2007), which is second only to

Table 197.3 Obesity-related comorbidities

Metabolic: Type 2 diabetes mellitus, hyperlipidemia, metabolic syndrome
Cardiovascular: Hypertension, coronary artery disease, peripheral vascular disease
Respiratory: Sleep apnea, asthma
Neurological: Stroke
Hematological: DVT, PE
Gastrointestinal: Fatty liver, cirrhosis, gallbladder disease, gastroesophageal reflux disease (GORD)
Musculoskeletal: Osteoarthritis, low back pain, disc disease
Dermatological: Dermatitis
Increased risk of cancer and cancer related deaths
Gynecological: Dysmenorrhea
Obstetrics: Preeclampsia
Infertility
Poor health related quality of life
Psychological: Depression, anxiety

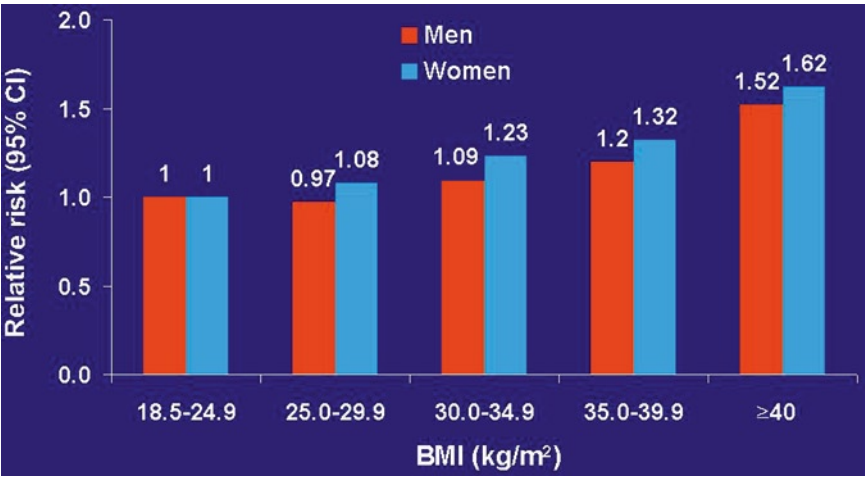This table lists some of the commonly encountered obesity comorbidities

Fig. 197.1 Relationship between BMI and mortality. The diagram shows positive linear relationship between BMI and mortality

smoking as a cause of death (Presutti et al. 2004). It is predicted that obesity is likely to overtake smoking as the leading cause of death (Mokdad et al. 2004; Gould et al. 2006). Morbidly obese patients may suffer from a 22% reduction in their life expectancy, which is equivalent to the loss of approximately 12 years of life (Buchwald et al. 2004).

197.4 Bariatric Surgery

Modest weight reduction has been shown to have beneficial effect on the cardiovascular system, cholesterol level, and blood sugar (Table 197.4; Colquitt et al. 2005). Clinical trials showed that behavioral changes result in 4% of weight loss compared to 8% with pharmacotherapy (Matarasso et al. 2007; Wee 2009), and 90% of obese patient treated nonsurgically will relapse within 5 years (Salem et al. 2005). Bariatric surgery has been shown to be more effective than the nonsurgical approach, and weight reduction is sustainable beyond 1 year (McTigue et al. 2003). Bariatric surgery also led to resolution or improvement of obesity comorbidities in a substantial majority of patients and produced a significant reduction in mortality (Table 197.5; Buchwald et al. 2004; Sjostrom et al. 2004, 2007; Gould et al. 2004; DeMaria 2007; Ashrafian et al. 2008).

Table 197.4 The effects of 10 kg weight loss

10 mmHg reduction in systemic blood pressure
20 mmHg reduction in diastolic blood pressure
91% reduction in angina symptoms
33% increase in exercise tolerance
10% reduction in cholesterol
15% reduction in LDL
30% reduction in triglycerides
8% increase in HDL
30–50% reduction in fasting blood sugar
15% reduction in glycosylated hemoglobin (Hb A_{1c})
50% reduction in the risk of developing diabetes
20% reduction in mortality
30% reduction in diabetes-related deaths
40% reduction in obesity-related cancer deaths

This table demonstrates the effects of 10 kg weight reduction on the cardiovascular system, cholesterol level, blood sugar and mortality

Table 197.5 Outcome of bariatric surgery

The measured outcome	Percentage (%)
Excess weight loss	61.2
Diabetes mellitus resolved	76.8
Diabetes mellitus resolved or improved	86.0
Metabolic syndrome resolved	80.0
Hypertension resolved	61.7
Hypertension resolved or improved	78.5
Hypercholesterolemia improved	70.0
Obstructive sleep apnea resolved	83.6
Obstructive sleep apnea resolved or improved	85.7
GORD resolved or improved	87.5
Mortality reduction	31.6–53

This table demonstrates bariatric surgery outcome in terms of resolution or improvement of obesity comorbidities

Bariatric surgery has been traditionally classified according to the mechanism of action into restrictive (e.g., gastric balloon, gastric band, sleeve gastrectomy, vertical banded gastroplasty), malabsorptive (e.g., biliopancreatic diversion – Scopinaro procedure, duodenal switch) or restrictive–malabsorptive (e.g., gastric bypass; Fig. 197.2; Buchwald 2002; Gould et al. 2006). Many of these procedures can be performed laparoscopically, safely and effectively (Nguyen et al. 2005). National guidelines recommend bariatric surgery for individuals who have a BMI of 40 or more, or a BMI of 35 or more and suffer from obesity comorbidity. Other requirements for surgery include failure of the medical management and the ability to understand the consequences and risks of surgery (Brolin 2002; Presutti et al. 2004; Colquitt et al. 2005; Anon. 2006; DeMaria 2007).

Bariatric surgery is contraindicated in patients suffering from active substance abuse, and uncontrolled major psychiatric disorder (Brolin 2002; Presutti et al. 2004). Extremes of age are not a contraindication to bariatric surgery (Peter et al. 2005; Treadwell et al. 2008). Complications specific to bariatric surgery may arise early in the postoperative period or later, months or years after the operation (Table 197.6; Buchwald et al. 2004; Presutti et al. 2004; Colquitt et al. 2005; Gould et al. 2006; DeMaria 2007; Ellison and Ellison 2008).
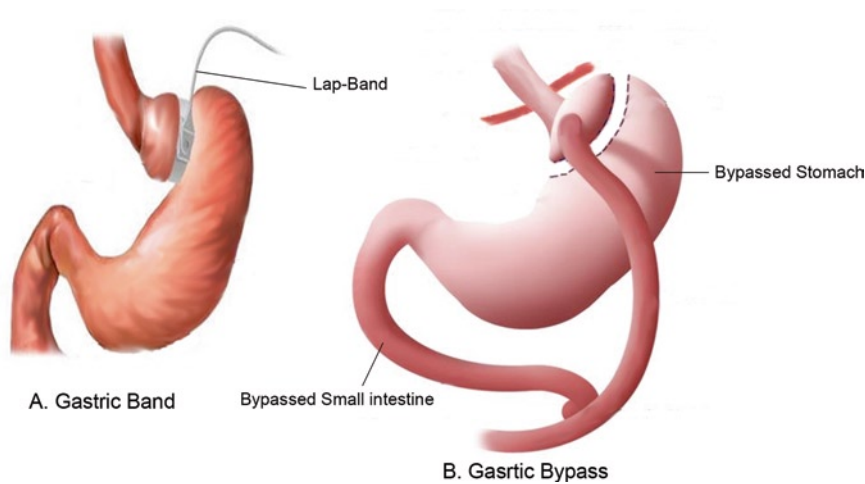
Fig. 197.2 Demonstration of gastric band and gastric bypass. Demonstration of the commonly used bariatric procedures: (**a**) Gastric band and (**b**) gastric bypass

Table 197.6 Complications recorded following different bariatric procedures

Complications (bariatric procedure)	Percentage (%)
Band slippage (Lap-band)	13.7
Wound infection (Gastric bypass)	3–6
Incisional hernia (Gastric bypass)	0.5–8.6
Bowel obstruction (Gastric bypass)	2
Anastomotic leak (Gastric bypass)	1
Operative mortality for purely restrictive procedure	0.1
Operative mortality for gastric bypass	0.2–0.5
Operative mortality for biliopancreatic diversion	1.1

This table lists some of the commonly seen complications following bariatric surgery

197.4.1 Overview of Health-Related Quality of Life in Bariatric Surgery

Health is defined by the World Health Organization (WHO) as a state of complete physical, psychological, and social well-being. Therefore, quality of life assessment should measure the functioning and well-being of the physical, mental, and social aspects of one's life (Mathus-Vliegen and de Wit 2007). Obesity has the potential to adversely affect the quality of life. Accordingly, attention needs to be placed to understand the health issues from the patient perspective; to be able to evaluate the patients' subjective experience of symptoms and their impact on quality of life. The results of studies in which patients' experiences and perspectives have been evaluated will help the clinicians to better understand that obesity and bariatric surgery outcomes are important to the patient. Consequently, resources can be directed toward treatments most valued by patients (Reaney et al. 2008).

197.4.2 Quality of Life Versus Health-Related Quality of Life

There is no universally accepted definition (Foster 2006; Costanza et al. 2008) or measurement (Costanza et al. 2008) of quality of life. One simple definition of quality of life is emotional, social, and physical well-being; spiritual satisfaction; and ability to function in the ordinary tasks of living (Livingston and Fink 2003; Fallowfield 2009). Quality of life is subjective, multidimensional, and dynamic. The subjectivity of quality of life arises from the fact that each person rates his or her own quality of life from a unique self-perspective, based on his or her own feelings, experiences, and priorities. Each person's assessment of their own quality of life will change over time, depending on their priorities, experiences, and circumstances in a given time, which explains the dynamic property of quality of life (Reaney et al. 2008). The multidimensional aspect subdivides into health-related and non-health- or environment-based domains (Table 197.7). The domains measured by health-related quality of life have the potential to improve with treatment. On the contrary, the domains of non-health quality of life, which can adversely affect health, are unlikely to improve with the appropriate medical care (Spilker and Revicki 1999).

Health-related quality of life consists of health status and health perception. Health status measures the degree of well-being or illness by measuring the functional impairment, symptoms, and occasionally objective measurement of the signs. Health perception reflects the patients' perception of their condition or treatment and its effects. It is the more difficult of the two components to measure, as it relies on patients' subjective assessment. A health-related quality of life instrument should produce meaningful data by displaying satisfactory psychometric criteria such as validity, reliability, specificity, sensitivity, and responsiveness to change. Validity is the extent to which the items in an instrument assess all relevant aspects of targeted concepts. Content validity is a fundamental concept of the instrument's validity, as there is no point saying that an instrument has excellent reliability and sensitivity if it does not measure what it is supposed to measure (Reaney et al. 2008).

Table 197.7 Examples of the domains measured in both types of quality of life

Health-related quality of life	Nonhealth-related quality of life
Functional status e.g. the ability to dress	Environment, e.g., quality of water
Mental health (psychological) and emotional well-being, e.g., depression	Personal resources, e.g., capacity to form friendships
Social engagement and occupational ability, e.g., engagement in activities	
Physical state and symptom state, e.g., pain	

This table shows examples of the different domains or aspects of life measured in health related quality of life and non health related quality of life

197.4.3 Applications to Other Areas of Health and Disease

Bariatric surgeons often make implicit subjective judgments on patients' quality of life; however, few of them will use explicit objective assessment of the quality of life by using health-related quality of life instruments. In addition, when health-related quality of life has been recorded as secondary endpoint of clinical trials, results have rarely modified the overall interpretation of the trial (Contopoulos-Ioannidis et al. 2009).

Obesity carries detrimental effects on the quality of life through physical, psychological, and social impairments (Fig. 197.3). Potential domains of health-related quality of life that might be adversely affected by obesity are illustrated in a proposed conceptual framework (Fig. 197.4).

197.4.4 Health-Related Quality of Life Instruments Used in Bariatric Research

It is important to differentiate between generic health-related quality of life instrument and condition-specific instrument. For example, obesity-specific instrument measures the impact of obesity and weight loss on the individual's health-related quality of life. In bariatric surgery, objective measurement of weight loss has been the standard common practice; nevertheless, subjective assessment of health related quality of life has been less standardized.

A systematic literature review examined instruments used to assess health-related quality of life in bariatric patients, and analyzed their suitability with reference to a proposed conceptual framework.

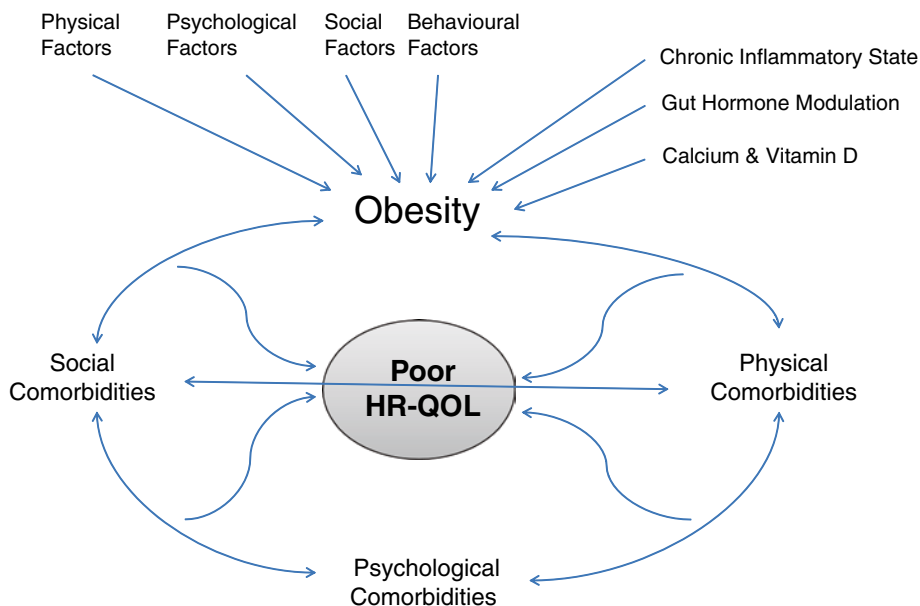**Fig. 197.3** Relationship between obesity, obesity comorbidities, and quality of life. The graphical model illustrates a proposed relationship between obesity and the physical, psychological and social comorbidities. The demonstrated vicious cycle clearly carries detrimental effects on the health related quality of life. The various etiologic factors contributing to the development of obesity are also shown in this model
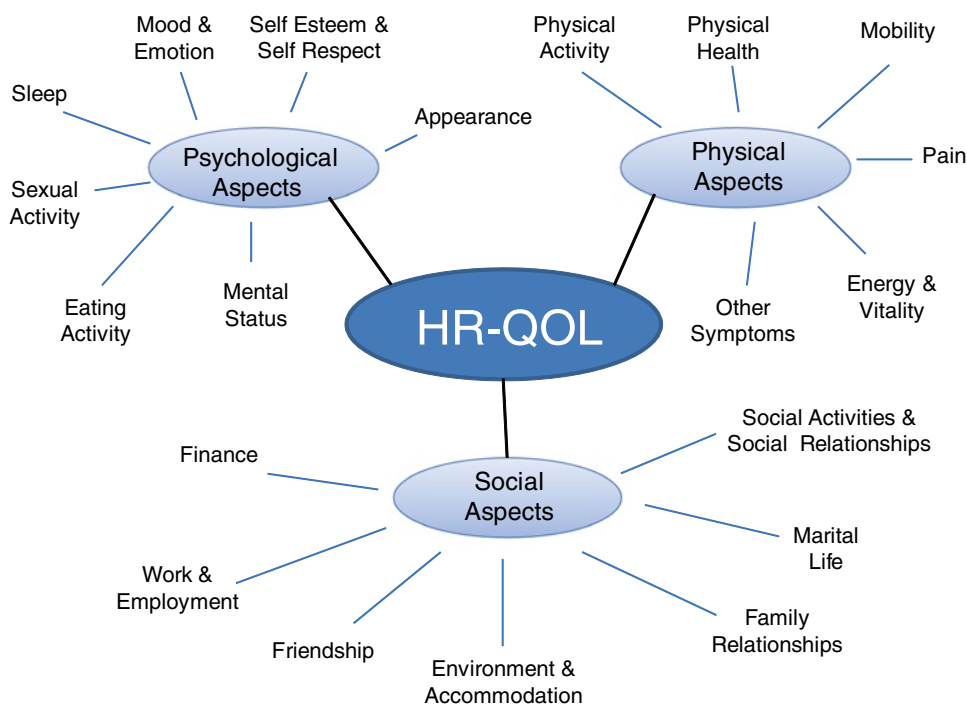
Fig. 197.4 A proposed conceptual framework of domains of bariatric-specific quality of life. A proposed conceptual framework demonstrates the potential domains or aspects of health related quality of life that might be adversely affected by obesity, obesity comorbidities and bariatric surgery

The framework identifies 20 fundamental domains of health-related quality of life pertinent to bariatric patients, which are almost equally distributed among the three main aspects of the framework; namely: the physical aspects (six domains), the psychological aspects (seven domains), and the social aspects (seven domains) (Fig. 197.4). The framework provides better insight into the problems of obesity, and equally important, a window to explore the patient experience after the operation; whether that experience was as good as anticipated (e.g., weight loss or resolution of the comorbidities) or bad (e.g., complications).

Generic health-related quality of life instruments contain many irrelevant items and overlook significant pieces of information. Obesity-specific instruments, on the other hand, do not include all the relevant domains important to the bariatric patient (Table 197.8). Therefore, the currently available instruments, whether generic or obesity-specific, will underestimate the full impact of obesity and bariatric surgery on health-related quality of life. This fact has been acknowledged by bariatric researchers, as they administered more than one health-related quality of life instrument in their studies, which is time-consuming, will increase the number of irrelevant items, and still will not pick up all the important domains (Reaney et al. 2008).

197.4.5 Generic Health-Related Quality of Life Instruments

There are hundreds of health-related quality of life instruments and patient-reported outcome instruments; however, the most commonly used instruments in bariatric surgery are SF-36 and EQ-5D.

Table 197.8 The domains of the commonly used health-related quality of life instrument in bariatric surgery

Aspect of life		Generic instrument					Obesity-specific instrument						
		SF-36	EQ-5D	NHP	WHOQL	MANSA	BAROS	IWQOL	OSQOL	HRQL	OWLQOL	OAS-SF	SOS
Physical	Physical health	P	P		P	P		P	P	P	P	P	
	Physical activity	P	P		P		P	P		P	P	P	P
	Energy/vitality	P			P				P		P		
	Mobility		P	P				P					
	Pain	P	P	P									
	Other symptoms										P		
Psychological	Mental state	P	P			P			P	P	P	P	
	Mood/emotion	P		P							P	P	
	Sleep			P	P								
	Sexual function					P	P	P			P	P	P
	Eating status						P	P		P	P	P	
	Self esteem						P	P		P	P	P	
	Appearance			P						P	P	P	P
Social	Social activity	P		P	P		P	P	P	P		P	P
	Marital life				P								
	Family relationships	P			P	P							
	Environment/ accommodation				P	P							
	Friendship	P			P								
	Work				P	P	P	P		P			
	Finance				P	P							

This table compares commonly used health related quality of life in bariatric surgery against the domains in the proposed conceptual framework. The table clearly shows that these instruments are lacking important domains as informed by the framework

The Short Form (36) Health Survey (SF-36) is one of the most commonly used generic health-related quality of life instruments, which has been used literally in thousands of studies (Livingston and Fink 2003). Health economics use it as a variable in the quality-adjusted life year (QALYs) calculation to determine the cost-effectiveness of a health treatment. SF-36 instrument consists of 36 validated items distributed among eight scaled domains of vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning, and mental health (Anon. 2009).

EuroQoL (EQ-5D) is a commonly used, validated, short, generic health survey instrument, composed of five items including mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. It provides a single index value that can be used in clinical and economical evaluation of health care (Anon. 1990). World Health Organization Quality Of Life (WHOQOL 100) assesses generic health-related quality of life over a 2-week recall period. It includes 100 items which have been reduced to 26 validated items in WHOQOL-BREF instrument, covering four domains of physical health, mental health, social relationships, and environment (Anon. 1998).

197.4.6 Obesity-Specific Quality of Life Instruments

To evaluate health-related quality of life of a specific condition or disease, the use of condition specific instrument is preferable to a generic instrument, because it will provide better psychometric properties, namely, content validity. In addition, the attribution factor is better in condition-specific instrument. This concept can be explained by the following example: When using generic instruments, obese patients will rate their general health, sleep, social activity, etc. without direct reference to obesity, which will make the rating susceptible to external influence from other conditions or factors. However, the use of obesity-specific instruments will filter out external influences as it will only rate the impact of obesity (Reaney et al. 2008).

Despite the increased recognition of the advantages of condition-specific instruments and the limitations of generic instruments, relatively few obesity-specific and bariatric-specific instruments have been developed and are ready for use. Moreover, their use in bariatric surgery has not become a frequent practice. Bariatric Analysis and Reporting Outcome System (BAROS) evaluates the results of bariatric surgery by analyzing three domains: weight loss, changes in comorbidities, and health-related quality of life. The quality of life instrument used in BAROS is the validated quick six-item questionnaire (Moorehead et al. 2003).

Impact of Weight on Quality of Life (IWQOL) has 74 items developed at Duke University to measure eight domains of health, social interpersonal interaction, work, mobility, self-esteem, sexual life, daily living activities, and comfort with food (Kolotkin et al. 1995; Mathus-Vliegen and de Wit 2007). There are some concerns regarding its reliability and validity (Livingston and Fink 2003). The IWQOL has been reduced to 31-item psychometrically sound and clinically sensitive instrument (Kolotkin et al. 2001). Obesity-Specific Quality of Life (OSQOL) is a validated 11-item instrument covering four domains of physical state, vitality, and desire to do things; relations with other people; and psychological state (Le Pen et al. 1998; Mathus-Vliegen and de Wit 2007).

Health-related Quality of Life (HRQL) is a validated 55-item instrument looking at five domains of general well-being, health distress, and depression, self-esteem with three major levels of functioning (self-regard, physical appearance, and work productivity), physical and social activities (Mathus-Vliegen et al. 2004; Mathus-Vliegen and de Wit 2007). Unfortunately, this lengthy, time-consuming instrument is unreliable when administered serially on patients with stable weighs (Livingston and Fink 2003). Obesity and Weight Loss Quality of Life Instrument (OWLQOL) and Weight-Related

Symptom Measure (WRSM) has two parts: part one records the patient's feelings about their weight, including 17 items, and part two records 20 items about weight-related symptoms and how much they bother the patient (Niero et al. 2002). Both have been shown to display good internal consistency, test–retest reliability, and convergent validity (Mathus-Vliegen and de Wit 2007).

Obesity Adjustment Survey is an instrument with a huge collection of 95 items from the Mental Health Inventory, the Sickness Impact Profile, and the Eating Inventory, which was condensed into a shorter 20-item survey (Butler et al. 1999; Livingston and Fink 2003). Obesity Adjustment Survey Short Form (OAS-SF) is a sensitive and valid measure of obesity, though it is limited, as it only measures psychological distress aspect of health-related quality of life (Butler et al. 1999; Livingston and Fink 2003; Mathus-Vliegen and de Wit 2007). The Bariatric Quality of Life Index (BQL) is a 30-item measure of well-being in bariatric surgery patients, which is a validated instrument ready for clinical use (Weiner et al. 2005). Obesity-Related Well-Being Scale (ORWELL 97) questionnaire is a simple, valid (Mathus-Vliegen and de Wit 2007), and reliable measure of obesity health-related quality of life, which can be used in current clinical practice. It consists of measuring two subscales: ORWELL 97–1, which is related to psychological status and social adjustment, and ORWELL 97–2, which is related to physical symptoms and impairment (Mannucci et al. 1999).

197.5 Conclusion

Various aspects of the morbidly obese patients' life can be adversely affected, though much remains to be understood to be able to measure it scientifically and accurately. Most of the bariatric literature either did not report the quality of life outcome, or the quality of life outcome has not been given the appropriate weight and importance. Numerous generic and obesity-specific instruments have been developed and used on bariatric patients over the years; nevertheless, none of them proved to be without limitations. In particular, the content validity of the used instruments, which is a vital element when it comes to deciding the type of instrument to be used, has been below the standards. Obese patients need to be given the opportunity to decide the severity of impairment on their quality of life, based on their own experience and criteria. Only then the full impact of morbid obesity and bariatric surgery can be assessed. A proposed conceptual framework detailing all the pertinent domains can be used to develop a new bariatric-specific instrument. Such an instrument will display excellent content validity and cover all the potential aspects that might be impacted by morbid obesity and bariatric surgery.

Summary Points

- *Obesity* is a complex and poorly understood multifactorial chronic condition associated with a BMI of 30 or more, and results in increased morbidity and mortality. The World Health Organization classifies obesity into severe obesity with BMI of 35–39.9 and morbid obesity with BMI of 40 or more.
- *Obesity* carries significant risks to the live of affected individual including physical, psychological, and social *comorbidities.* Higher BMI carries higher risks to health, to the extent that an almost linear relationship exists between the BMI and mortality.
- *Prevalence of obesity* in the world is on the rise, with no signs of slowing. The numbers are expected to double every 5–10 years if no active measures are instituted immediately. Obesity costs the health system in the United States a staggering $100 billion per year.

- *Nonsurgical approach* to induce weight loss in obesity, consisting of behavioral modification interventions (diet, physical exercise, and lifestyle change) and pharmacotherapy, will fail in 90% of patients within 5 years. *Bariatric surgery* provides the only effective and sustainable approach to treat morbid obesity and reverse its adverse effects.
- Bariatric procedures may be restrictive (e.g., gastric balloon, gastric band, sleeve gastrectomy, vertical banded gastroplasty), malabsorptive (e.g., biliopancreatic diversion – Scopinaro procedure, duodenal switch), or restrictive–malabsorptive (e.g., gastric bypass).
- There is no universally accepted definition or measurement of *quality of life.* However, it can be looked at as a subjective, multidimensional, and dynamic measurement of an individual's emotional, social, and physical well-being; spiritual satisfaction; and ability to function in the ordinary tasks of living.
- Quality of life and *health-related quality of life* have been wrongly used synonymously. Health-related quality of life measures specific aspects or domains of quality of life that have the potential to improve with treatment. It is consists of health status and health perception.
- Health-related quality of life instrument should produce meaningful data by displaying satisfactory *psychometric criteria* such as validity, reliability, specificity, sensitivity, and responsiveness to change. *Content validity* is a fundamental concept of an instrument's validity.
- Health-related quality of life instruments are either *generic or condition-specific*. When evaluating health-related quality of life of a particular condition, the use of condition specific instrument is more appropriate because it displays better content validity.

Definitions of Key Terms

Body Mass Index (BMI): is measured by dividing weight in kilograms, by height in meters squared. Ideal BMI of an adult is 20 to 24.9. Individuals with BMI of 25–29.9 are considered overweight and BMI of 30 or more are considered obese.
Obesity: is a chronic condition associated with a BMI of 30 or more and results in increased morbidity and mortality. Obesity can be further classified according the BMI into severe obesity and morbid obesity.
Obesity comorbidity: is condition either caused or aggravated by obesity. It includes physical, psychological, and social comorbidities.
Bariatric surgery: is conducted on the stomach or the intestine to help severely obese and morbidly obese patients to lose weight. The word "bariatric" originated from the Greek root *baro*, which means weight, as in barometer; and suffix *iatrics* which means treatment, as in pediatrics.
Health: is a state of complete physical, psychological, and social well-being.
Quality of life: is a descriptive term that refers to an individual's emotional, social, and physical well-being; spiritual satisfaction; and their ability to function in the ordinary tasks of living.
Health-related quality of life: relates to aspects or domains of quality of life that have the potential to improve with treatment.
Content validity: is the extent to which an instrument measures the intended content area.
Obesity-specific instrument: is an instrument that measures the impact of obesity and weight loss on the individual's health-related quality of life.
Bariatric-specific instrument: measures the impact of obesity, weight loss, and bariatric surgery on health-related quality of life of the severely obese and morbidly obese patients.

References

Anon. Health Policy. 1990;16:199–208.

Anon. Psychol Med. 1998;28:551–8.

Anon. Online. Date of access 15 October 2006: http://www.nice.org.uk/nicemedia/pdf/CG43NICEGuideline.pdf

Anon. Online. Date of access 17 October 2009: http://www.qualitymetric.com/WhatWeDo/GenericHealthSurveys/SF36v2HealthSurvey/tabid/185/Default.aspx

Ashrafian H, le Roux CW, Darzi A, Athanasiou T. Circulation. 2008;118:2091–102.

Balsiger BM, Luque de LE, Sarr MG. Mayo Clin Proc. 1997;72:551–7.

Brolin RE. JAMA. 2002;288:2793–6.

Buchwald H. J Am Coll Surg. 2002;194:367–75.

Buchwald H, Avidor Y, Braunwald E, Jensen MD, Pories W, Fahrbach K, Schoelles K. JAMA. 2004;292:1724–37.

Butland B, Jebb S, Kopelman P, McPherson K, Thomas S, Mardell J, Parry V. (2007) Online. Date of access 17 October 2009: http://www.foresight.gov.uk/Obesity/17.pdf

Butler GS, Vallis TM, Perey B, Veldhuyzen van Zanten SJ, MacDonald AS, Konok G. Int J Obes Relat Metab Disord. 1999;23:505–11.

Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ. N Engl J Med. 2003;348:1625–38.

Colquitt J, Clegg A, Loveman E, Royle P, Sidhu MK. Cochrane Database Syst Rev. 2002;CD003641.

Contopoulos-Ioannidis DG, Karvouni A, Kouri I, Ioannidis JP. BMJ. 2009;338:a3006.

Costanza R, Fisher B, Ali S, Beer C, Bond L, Boumans R, Danigelis NL, Dickinson J, Elliott C, Farley J, Gayer DE, Glenn LM, Hudspeth TR, Mahoney DF, McCahill L, McIntosh B, Reed B, Rizvi SAT, Rizzo DM, Simpatico T, Snapp R. S. A. P. I. E N. S 2008;1:17–21.

DeMaria EJ. N Engl J Med. 2007;356:2176–83.

Ellison SR, Ellison SD J Emerg Med. 2008;34:21–32.

Fallowfield L. (2009) Online. Date of access 15 October 2009: http://www.medicine.ox.ac.uk/bandolier/painres/download/whatis/WhatisQOL.pdf

Foster JH. Clin Eff Nurs. 2002;9:295–301.

Glinski J, Wetzler S, Goodman E. Obes Surg. 2001;11:581–8.

Gould JC, Garren MJ, Starling JR. J Gastrointest Surg. 2004;8:983–7.

Gould JC, Garren MJ, Gutowski KA. Clin Obstet Gynecol. 2006;49:375–88.

Kolotkin RL, Crosby RD, Kosloski KD, Williams GR. Obes Res. 2001;9:102–11.

Kolotkin RL, Head S, Hamilton M, Tse CK. Obes Res. 1995;3:49–56.

Le Pen C, Levy E, Loos F, Banzet MN, Basdevant A. J Epidemiol Community Health. 1998;52:445–50.

Livingston EH, Fink AS. Arch Surg. 2003;138:383–8.

Major GC, Chaput JP, Ledoux M, St-Pierre S, Anderson GH, Zemel MB, Tremblay A. Obes Rev. 2008;9:428–45.

Mannucci E, Ricca V, Barciulli E, Di BM, Travaglini R, Cabras PL, Rotella CM. Addict Behav. 1999;24:345–57.

Matarasso A, Roslin MS, Kurian M. Plast Reconstr Surg. 2007;119:1357–62.

Mathus-Vliegen EM, de Wit LT. Br J Surg. 2007;94:457–65.

Mathus-Vliegen EM, de WS, de Wit LT. Surgery. 2004;135:489–97.

McTigue KM, Harris R, Hemphill B, Lux L, Sutton S, Bunton AJ, Lohr KN. Ann Intern Med. 2003;139:933–49.

Mokdad AH, Marks JS, Stroup DF, Gerberding JL. JAMA. 2004;291:1238–45.

Moorehead MK, Ardelt-Gattinger E, Lechner H, Oria HE. Obes Surg. 2003;13:684–92.

Nguyen NT, Wilson SE, Wolfe BM. J Am Coll Surg. 2005;200:621–9.

Niero M, Martin M, Finger T, Lucas R, Mear I, Wild D, Glauda L, Patrick DL. Clin Ther. 2002;24:690–700.

Peter S, Craft R, Tiede J, Swain J. Arch Surg. 2005;140:165–8.

Pohl JF, Stephen M, Wilson DP. South Med J. 2006;99:833–44.

Presutti RJ, Gorman RS, Swain JM. Mayo Clin Proc. 2004;79:1158–66.

Reaney M, Martin C, Speight J. Patient. 2008;1:151–63.

Salem L, Jensen CC, Flum DR. J Am Coll Surg. 2005;200:270–8.

Sjostrom L, Lindroos AK, Peltonen M, Torgerson J, Bouchard C, Carlsson B, Dahlgren S, Larsson B, Narbro K, Sjostrom CD, Sullivan M, Wedel H. N Engl J Med. 2004;351:2683–93.

Sjostrom L, Narbro K, Sjostrom CD, Karason K, Larsson B, Wedel H, Lystig T, Sullivan M, Bouchard C, Carlsson B, Bengtsson C, Dahlgren S, Gummesson A, Jacobson P, Karlsson J, Lindroos AK, Lonroth H, Naslund I, Olbers T, Stenlof K, Torgerson J, Agren G, Carlsson LM. N Engl J Med. 2007;357:741–52.

Spilker, B, Revicki, D.A. In: Spilker B, editor. Quality of life and pharmacoeconomics in clinical trials. Philadelphia: Lippincott-Raven; 1999. pp. 25–32.

Treadwell JR, Sun F, Schoelles K (2008) Ann Surg. 2008;248:763–76.

Wee CC. JAMA. 2009;302:1097–104.

Weiner S, Sauerland S, Fein M, Blanco R, Pomhoff I, Weiner RA. Obes Surg. 2005;15:538–45.

Wolf AM, Colditz GA. Obes Res. 1998;6:97–106.

Chapter 198
The Impact of Dietary Restrictions on Quality of Life in Kidney Disease

Cheryl Glover, Pauline Banks, Amanda Carson, Mick P. Fleming, and Colin R. Martin

Abbreviations

CAPD   Continuous ambulatory peritoneal dialysis
CKD   Chronic kidney disease
ESRD   End-stage renal disease
GFR   Glomerular filtration rate
HRQoL   Health-related quality of life
KDQOL   Kidney Disease Quality of Life Questionnaire
NICE   National Institute for Clinical Excellence
QALY   Quality-adjusted life year
QoL   Quality of life
RRT   Renal replacement therapy

198.1 Introduction

The key facts concerning chronic kidney disease are summarized in Table 198.1.

198.2 Chronic Kidney Disease (CKD)

A person has chronic kidney disease (CKD) if they have kidney damage or a glomerular filtration rate (GFR) of less than 60 for 3 months or more; GFR being a measure of kidney function (National Kidney Foundation 2002). CKD can be divided into five stages (see Table 198.2). These stages are classified according to evidence of kidney damage and level of kidney function, measured by GFR. Stage 5 of CKD is also called end-stage renal disease (ESRD) and it is at this stage that renal replacement therapy is required to sustain life (National Collaborating Centre for Chronic Conditions 2008).

C.R. Martin (✉)
School of Health, Nursing and Midwifery, University of the West of Scotland,
Ayr Campus, Beech Grove, Ayr, KA8 0SR, UK
e-mail: colin.martin@uws.ac.uk

Table 198.1 Key facts of chronic kidney disease

1. The primary function of the kidney is to maintain a stable interior milieu by the selective retention and elimination of water, electrolytes and other solutes.
2. If kidney function is lost, the patients enter a stage of ESRD.
3. ESRD is incompatible with life unless kidney function is replaced by dialysis treatment or kidney transplantation
4. Hemodialysis is the default therapy for patients in ESRD.
5. Peritoneal dialysis is the other major treatment used in ESRD.
6. Transplant provides the best long-term outcome.
7. A rigorous treatment regime must be followed in terms of all three of the Renal Replacement Therapies.

This table lists the key facts of Chronic Kidney Disease including the function of the kidney, which patients need renal replacement therapy and the types of therapy available
ESRD end-stage renal disease

Table 198.2 Stages of chronic kidney disease (Modified from the National Kidney Foundation (USA) Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines, 2002)

	Description	GFR
1	Kidney damage with normal or increased GFR	≥90
2	Kidney damage with mild decrease in GFR	60–89
3	Moderate decrease in GFR	30–59
4	Severe reduction in GFR	15–29
5	Kidney failure or end-stage renal disease	<15

The stages of kidney disease as determined by glomular filtration rate (GFR)

198.3 End-Stage Renal Disease (ESRD)

There are currently over 45,000 people receiving some form of Renal Replacement Therapy (RRT) in the United Kingdom (Farrington et al. 2008). This number is expected to increase, as it has done in the past few decades (Cross Party Group on Renal Disease 2005). This increase is being caused by advances in health care which have helped to improve survival rates in the ESRD population. It is also due to the rise in diabetes, which is one of the causes of renal failure. These factors also coincide with the growth of an aging general population; the incidence of renal failure increasing with age (Cross Party Group on Renal Disease 2005).

There are three choices for RRT available to those with ESRD: conservative care, dialysis (hemodialysis or peritoneal), and kidney transplant.

Conservative or palliative care is considered in cases where dialysis may not prolong life. Such patients that may choose to opt for symptom control without dialysis include those that suffer from extensive comorbidities or the very elderly (Levy et al. 2006).

Transplant provides the best long-term outcome for patients with ESRD. However, the shortage of organs, unsuitability for transplant, and organ rejection can mean that many patients spend a number of years on dialysis.

The two modes of dialysis are very different. For a summary see Table 198.3.

In addition to the actual dialysis process, dialysis patients are also required to take any medications that are required and also adhere to fluid and dietary restrictions.

Patients of any chronic disease face challenges from the disease itself, from side effects, and other restrictions imposed by treatment regimes. Therefore, the aims of management extend beyond the strictly medical aspects of treatment (Cross Party Group on Renal Disease 2005). In the past 2

Table 198.3 Types of dialysis currently available

	Hemodialysis	Continuous ambulatory peritoneal dialysis (CAPD)	Automated peritoneal dialysis (APD)
Method	Blood is transferred from the body into a machine which filters out waste products and passes this filtered blood back into the body	Uses the body's own filtration. A catheter is inserted into the patients peritoneum into which dialysis fluid is infused. Dialysis and filtration occur across the peritoneal capillaries. Fluid is in place for 4–6 h, removed, and then replaced for the process to begin again	Same process as CAPD; however APD involved the use of a machine to fill and drain the abdomen, usually while the patient is asleep. For some an exchange must also be carried out during the day
Frequency	Usually 3 sessions of approximately 4 h/week	3 to 5 times a day. The exchange process takes 30–40 min	Every 24 h, overnight
Location	For most in a hospital although can be performed at home	At home by the patient or a carer	At home by the patient or a carer

The main types of dialysis that are currently available. Irrespective of the most appropriate type of dialysis modality chosen, each form of dialysis incurs a significant burden to the patient

decades, there has been a shift in medicine to the aim of providing more holistic care. In light of this, the issue of patient quality of life (QOL) is becoming increasingly important, with QOL now an essential outcome in clinical studies.

198.4 Quality of Life (QOL) and Health-Related QOL (HRQOL)

Quality of life is a well-known and well-used phrase, but there have been many definitions put forward for the term and there is no consensus on the exact meaning. Bowling (2005) suggests that "in general terms quality can be described as a grade of goodness" (p.7). Quality of life has been studied in relation to many different aspects of life, including objective terms such as income, subjective terms such as happiness and well-being, and in collective terms such as equality (Phillips 2006). The definition that seems to encompass all these aspects has been given by the World Health Organization Quality of Life Group (WHOQOL), which state that QOL is an

> individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, values and concerns…[it includes]…physical health, psychological state, level of independence, social relations, personal beliefs and their relationship to salient features of the environment. (WHOQOL 1995).

Health-Related Quality of Life (HRQOL) narrows down the focus to those aspects of life affected by health. HRQOL may be studied for many different reasons, including the comparison of the effectiveness of different treatments, the cost-effectiveness of treatments in terms of Quality-Adjusted Life Years (QALYs) and in order to provide a more holistic view of the patient to enable treatment regimes to be tailored to individual needs.

198.5 The Impact of End Stage Renal Disease (ESRD) on QOL

Advances in technology have meant that people with renal disease can survive for longer. With the increase in survival rates, combined with the growing number of people with renal disease, quality of life has become increasingly important in this population.

Identifications of predictors of HRQOL could make it possible to intervene in some way with the aim of increasing the HRQOL in people with renal disease, while HRQOL is an important outcome in itself, higher quality of life is also associated with lower hospital utilization and mortality in this patient group (Bass et al. 1999).

The areas of life suggested to have an impact on HRQOL in ESRD are numerous and broad:

- Freedom/control/independence (Bass et al. 1999; Juergensen et al. 2006)
- Social relationships (Juergensen et al. 2006) including family relationships (Bass et al. 1999; Wuerth et al. 2007)
- Anxiety (Bass et al. 1999)
- Role (Bass et al. 1999; Juergensen et al. 2006) including work (Juergensen et al. 2006)
- Energy (Bass et al. 1999)
- Body image (Juergensen et al. 2006)
- Sexual relations (Juergensen et al. 2006; Bass et al. 1999)
- Mental attitude/mood (Bass et al. 1999)
- Sleep (Wuerth et al. 2007; National Collaborating Center for Chronic Conditions 2008)
- Cognitive function (Klahr et al. 1983)
- Finances (Pedrini et al. 1996; National Collaborating Center for Chronic Conditions 2008; Fouque 2009)
- Recreation and exercise (Ash et al. 2006)
- Relationships with medical staff (Middleton et al. 1999)
- Patient education (Burge et al. 1979)
- Physical symptoms (Hays et al. 1994; Fernstrom et al. 1996)
- Physical function (Ware and Sherbourne 1992; Bass et al. 1999)
- Pain (Kaplan De-Nour and Czaczkes 1972; Banks, in prep)

Additional QoL burdens specifically for dialysis include:

- General dialysis issues (Henkel 2006)
- Dietary restrictions (Vlaminck et al. 2001)
- Scheduling of dialysis sessions and time restrictions

Based on our review of the literature, we have drafted a conceptual framework of the aspects of life that are impacted by ESRD (Fig. 198.1).
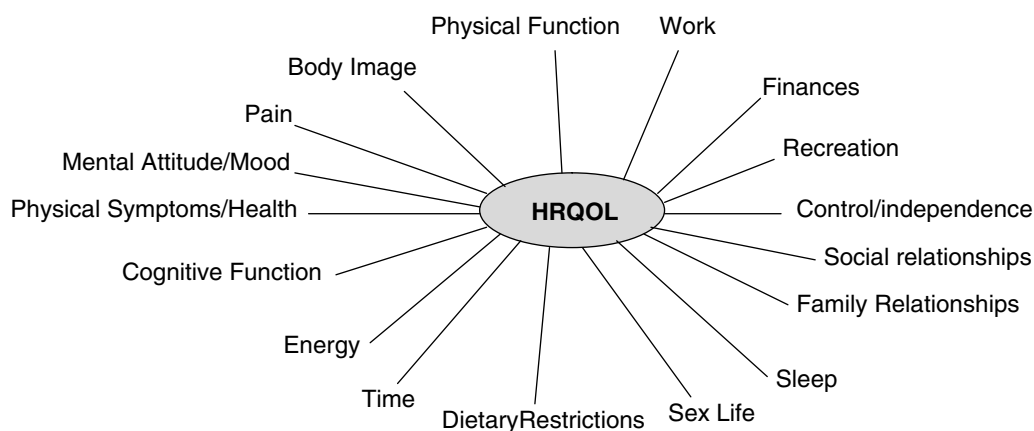

Fig. 198.1 Framework of health-related quality of life measurement in ESRD. The impact of ESRD on HRQoL is multi-factorial and represents an interactive complex process between many domains of patient experience

198.6 The Necessity of Dietary and Fluid Restrictions

According to the National Institute for Clinical Excellence (NICE 2010),

> diet … is one of the cornerstones in the treatment of CKD [Chronic Kidney Disease]. (p. 95)

A major role of the kidneys is to excrete waste products. In CKD, the ability of the kidneys to perform this function is reduced and therefore dietary restrictions are required to compensate (to a certain extent) for this.

The comorbidities and complications involved in CKD and ESRD are such that each individual is truly individual, and dietary restrictions must be tailored to individual needs. Dietary restrictions and modifications depend on the stage and nature of the kidney disease and must coincide with any existing dietary restrictions such as those for diabetes.

The relationship between diet and kidney disease is multifaceted; diet is important in treating CKD on its own and in order to prevent other conditions, however kidney disease itself has an effect on appetite and the numerous dietary restrictions can affect quality of life.

198.6.1 Restrictions

Protein has been recognized as having a negative effect on renal disease for over a century now and there have been numerous studies on the effects of a low protein diet on both diabetic and nondiabetic renal patients. A meta-analysis of these studies concluded that protein restriction slows the progression of renal disease and death in both of these groups. A recent Cochrane Review on nondiabetic patients found that a protein-restricted diet in patients with chronic kidney disease reduced the occurrence of death by 32%, compared with higher or unrestricted protein intake.

Conversely, patients once on dialysis are now recommended to consume a diet rich in protein, especially those on peritoneal dialysis because proteins in the body can be passed out through the dialysis fluid. As the dialysis fluid contains dextrose, peritoneal patients are also recommended to reduce their intake of food that is high in fat in order to prevent weight gain.

Patients are also recommended to restrict foods containing sodium, phosphorous, and potassium (in the case of hemodialysis). The reduction of sodium in the diet is recommended to keep blood pressure down and also to reduce sodium-induced thirst as fluid restrictions are also necessary. High levels of phosphorous can cause osteoporosis and high levels of potassium can cause an arrhythmia.

Patients on hemodialysis are greatly restricted on the amount of fluids that they consume. This is because healthy kidneys work continuously to remove excess fluid but the hemodialysis machine only has a limited time to attempt to remove 2–3 days worth of excess fluid. As well as liquids, patients are restricted in their intake of food that has a high fluid content such as soup and certain fruit. Excess fluid can cause breathing difficulties, high blood pressure, and heart disease. Patients using peritoneal dialysis are also restricted in their fluid intake but not to the same extent as those on hemodialysis. See Table 198.4 for a summary of dietary restrictions in both hemodialysis and peritoneal dialysis.

Inadequate intake and loss through dialysis, and of course the insufficiency of the kidneys to perform their usual functions, lead to vitamin deficiencies among dialysis patients and care must be taken to ensure patients receive enough vitamins through their diet or supplements.

Restricted diets can be unpalatable and time-consuming to prepare and so impair a person's quality of life and for these reasons NICE recommends solid reasoning for such restrictions.

For a more comprehensive explanation and rationale of nutritional guidelines and how to apply them to individual cases in renal disease, see Ash et al. (2006) or Fouque et al. (2007).

Table 198.4 Restrictions associated with different types of dialysis

Hemodialysis	Peritoneal Dialysis
↓ Fluid intake greatly	↓ Fluid intake
↑ Protein	↑ Protein
↓ Sodium	↓ Sodium
↓ Phosphorous	↓ Phosphorous
↓ Potassium	No potassium restrictions
No specific fat restrictions	↓ Fat

Restrictions associated with different types of dialysis. Irrespective of the dialysis modality undetaken by the patient, fluid and dietary restrictions represent a significant burden to the quality of life of the individual

198.6.1.1 The Effects of Kidney Disease on Appetite and Malnutrition

Patients with chronic kidney disease often suffer from reduced appetite, which becomes more apparent as the disease progresses. This reduction in appetite may be caused partly by a loss in taste sensitivity which has been demonstrated both in CAPD patients and hemodialysis patients. A study by (Fernstrom 1996) replicated these effects but found that this reduced taste sensitivity could also be seen in predialysis patients when compared to controls.

Reduced appetite contributes to malnutrition, which is common in CKD. It should be noted that malnutrition can also be caused by a very low protein diet which, although shown to reduce death in renal disease, when linked to malnutrition can have very negative effects. Indeed, malnutrition is associated with increased mortality among dialysis patients. In a large study of over 3,500 people, caregiver assessment of undernourishment and low Body Mass Index (BMI) were found to be independent predictors of mortality; with BMI remaining a significant predictor 5 years from initial measurement. The effects of malnutrition further emphasize the importance of diet in this group of patients.

Maintaining the correct balanced diet for the individual with kidney disease may be of benefit to their medical health but the restrictions and modifications on diet can affect their day-to-day quality of life (Fig. 198.2).

198.6.1.2 The Effects of Dietary and Fluid Restrictions on Quality of Life in Renal Patients

Dialysis patients can lose freedom and control in many aspects of their lives, not least in that of their diets. The effects of dietary and fluid restrictions on QOL in the renal population has been recognized so much so that the most commonly used renal specific measure of QOL, the Kidney Disease Quality of Life Questionnaire (KDQOL) includes questions on these areas.

A large study of hemodialysis patients showed that indicators used for measuring nutritional status such as appetite and energy intake are strongly associated with health-related quality of life as measured by the SF-36. These effects exist even after controlling for comorbidities and dialysis dose.

The evidence of the effects of dietary restrictions on QOL comes primarily, however, from qualitative studies using focus groups and interviews. In one such focus group study, which had the aim of identifying concerns about dialysis, both patients and health-care providers identified dietary restrictions as an issue that affected quality of life. In this study, there were more comments on dietary restrictions than social relationships, anxiety, energy and sleep among others, showing the importance of dietary restrictions on the lives of the patients. One patient commented, "I would love to get back to eatin' what I want."

And a health-care provider commented that "It's not an easy diet by any means … it affects life's little pleasures."
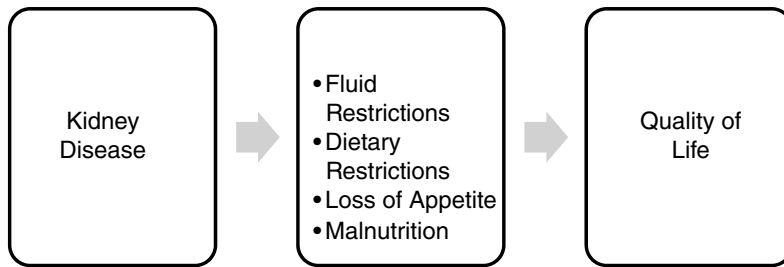
Fig. 198.2 How kidney disease affects quality of life as a function of dietary factors. Kidney disease affects quality of life in many ways however a key treatment impact on the experience of quality of life concerns the dietary and fluid restrictions which are a necessary part of the regimen

An earlier study by Kaplan de-Nour stated that diet is a constant source of frustration to patients, with the fluid restriction being especially difficult. In this study, patients reported trying to keep occupied all day in order to avoid drinking.

The dietary restrictions do not just affect the patient with renal disease, but also those around them. In a study by Banks, one carer for a renal patient kept returning to the issue of food (interestingly her husband, who was the renal patient did not mention it at all):

> I found it really hard knowing everything changes, everything about a person changes … their eating habits have to change … and learning, learning about food and the amount a lot because he can only take a 1,000 ml a day learning to adjust to everything what that entails …we were given a list of foods to avoid but I wish I'd had somebody to guide me along, lots of little paths you know not just one big one but lots of little paths. [In the hospital]… I was taking him in fruit everyday and his potassium went … really high and it's learning all those things that you don't associate that you think is okay. I found all that a hard lesson to learn and I'm still learning … and sometimes find it hard.

This same carer talked about diet and fluid restrictions in terms of,

> Lots of all those silly little things that you don't think of … that are so important, that play such a big part in our lives.

The same carer commented on how hard the fluid restrictions were on her husband:

> …sometimes he gets cross and because he can't drink I don't mean alcohol drink I mean he said yesterday I could've stuck my head under the tap and never stopped drinking…. I could've drunk gallons today you know gallons I just didn't want to stop and he finds that hard.

Fluid and dietary restrictions do not just affect the pleasurable sensations of taste and the quenching of thirst, but are also important in social situations. And, the importance of social support in kidney disease and quality of life is well known. The impact of dietary or fluid restrictions on the quantity or quality of social contact has not yet been investigated. The social implications, and also the effects on family, of fluid restrictions are commented on by a renal patient here:

> speaking/counselling is so very important so that there is somebody who your partner apart from me can actually talk to about what it means in their life how the changes will be how the fact that when you have a fluid restriction what that means for the whole family it's not just you it means that they don't go to the pub, every time you go out to your friends house the first thing people say to you – do you want a cup of tea/do you want a drink…. Because I think it's like an alcoholic oh have one drink it'll be alright have one drink, so you have that going on or they give you a mug of coffee like enormous and I mean I don't have the will power to go well I'll just have 2 sips and sit it to one side. So it's educating your family so that they know that you have to be involved with weenie tea cups. You know and just so that you know what a fluid restriction means it's not just drinking it's everything.

Dietary restrictions affect the lives of those with renal disease in such an all-encompassing way. In this same study by Banks this is demonstrated by a renal community nurse repeatedly highlighting

Fig. 198.3 Areas of life experience affected by dietary and fluid restrictions. Life experience is significantly affected by dietary and fluid restrictions which are a necessary and important part of a comprehensive and inclusive treatment package for patients with kidney disease
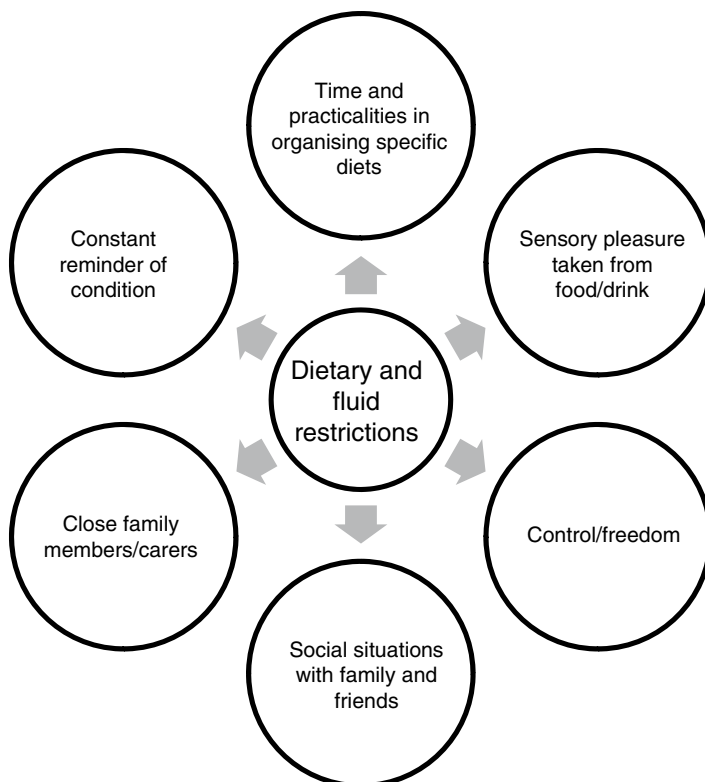
that fluid and dietary restrictions was one of the common issues that people brought up to her and asked her questions about.

> I think they always worry, is the diet right, should they be eating this, should they be drinking that?

Figure 198.3 summarizes a number of the key areas of life experience that the dietary and fluid restrictions in ESRD can impact on.

It has been suggested that the issue of dietary restrictions may be more important in elderly renal patients, where quality of (remaining) life may be more important. This article highlighted the practice in a nursing home of educating residents about the consequences of diet on their renal disease, and then honoring the resulting dietary decisions made by the residents.

It could be suggested that the preoccupation with dietary and fluid restrictions, as well as indicating the impact they have on quality of life, could also indicate a desire to regain some form of control over a disease that takes away so much control from the lives of the patient and their family. So it seems that dietary and fluid restrictions might impact on quality of life both directly and indirectly.

198.6.1.3 Noncompliance with Dietary and Fluid Restrictions

Noncompliance rates for dietary and fluid restrictions in ESRD vary across studies, but on the whole are considered high. A study of over 500 patients, using a specially designed instrument to measure adherence to diet and fluid restrictions, found 72% of hemodialysis patients reported mild to very severe non-adherence with fluid guidelines and 81% reported mild to very severe non-adherence with diet guidelines. More research is needed to identify reason for noncompliance. The recognition

of the effects of dietary and fluid restrictions on quality of life is very important and there are things that can be done to minimize these effects. In one particular study, individualized nutritional counseling actually improved quality of life in predialysis patients compared to standard nutrition care.

198.7 Conclusions

The quality of life issues in ESRD are wide ranging and include issues on appetite and dietary restrictions. The list of dietary restrictions and nutritional advice for this group is long and highly individualized, depending, among many other things, on dialysis modality and existing comorbidities. These restrictions greatly affect patient quality of life and also to an extent the lives of close family members. This should be considered when providing nutritional advice to those people that live with ESRD – patients and carers. As the interest in quality of life grows in the area of ESRD, the impact of dietary and fluid restrictions need to be recognized for their importance and for the significant effects that they have.

Summary Points

- Quality of life issues in ESRD are broad and complex, and include issues on appetite and dietary restrictions as part of the treatment battery.
- Dietary restrictions and nutritional advice for this group is extensive and highly individualized.
- Dietary restrictions and nutritional advice for this group is dependent on dialysis modality and existing comorbidities.
- Dietary restrictions greatly affect patient quality of life.
- Quality of life must be considered when providing nutritional advice to those people that live with ESRD, including not just patients but also their carers and significant others.
- Interest in quality of life is developing in the area of ESRD as is the relationship of psychosocial variables to dietary and fluid restrictions.

Definitions of Key Terms

Continuous Ambulatory Peritoneal Dialysis: is a form of dialysis that takes place inside the abdomen using the peritoneum via a process of osmosis to remove metabolic toxins. A catheter is surgically implanted to facilitate the process.
Chronic Kidney Disease: is a term that refers to the gradual and usually permanent deterioration in normal renal functioning.
End-stage Renal Disease: is the end point of chronic renal disease where the kidneys fail to function at a level to support the essential body functions.
Glomerular Filtration: is considered to be the best test for measuring the functioning of the kidneys. It is an estimate of how much blood passes through the glomeruli over a specified period of time, usually 1 min.
Health-Related Quality of Life: is a multidimensional, subjective, and (preferably) self-administered health construct.

Quality of Life: is a measure of how much a person enjoys a range of normal life activities and possibilities. It can be seen as a feeling of satisfaction with life and/or a feeling of general well-being of a person.

Renal Replacement Therapy: is a treatment used when the kidneys are unable to function adequately. The specific procedures can include dialysis either Hemodialysis or peritoneal and continuous hemofiltration.

Quality-adjusted Life Year: is a measurement that considers both the quality of life and the length of a person's life. It is used as a measure of disease burden for health economists to evaluate the value for money of a treatment.

References

Acchiardo SR, Moore LW, Latour PA. Kidney Int Suppl. 1983;16:S199–203.

Ash S, Campbell K, MacLaughlin H, McCoy E, Chan M, Anderson K, Corke K, Dumont R, Lloyd LMA, Montgomery-Johnson R, Tasker T, Thrift P, Trotter B. Nutr Diet. 2006;63:S35–45.

Banks P. Unpublished data from a study used to inform the development of a training programme for the NHS. In preparation.

Bass EB, Jenckes MW, Fink NE, Cagney KA, Wu AW, Sadler JH, Meyer KB, Levey A, Powe NR. Med Decis Making. 1999;19:287–95.

Bowling A. Measuring health: a review of quality of life measurement scales. Maidenhead: Open University Press; 2005.

Burge JC, Park HS, Whitlock CP, Schemmel RA. Kidney Int. 1979;15:49–53.

Campbell KL, Ash S, Bauer JD. Clin Nutr. 2008;27:537–44.

Cross Party Group on Renal Disease. Renal disease in Scotland: a strategy for future management. Edinburg: The Scottish Parliament; 2005.

Cukor D, Cohen SD, Peterson RA, Kimmel PL. J Am Soc Nephrol. 2007;18:3042–55.

Dwyer JT, Larive B, Leung J, Rocco M, Burrowes JD, Chumlea WC, Frydrych A, Kusek JW, Uhlin, L. J Renal Nutr. 2002;12:213–23.

Farrington AH, Casula A, Ansell D, and Feehally, J. UK Renal Registry 11th Annual Report. Bristol: UK Renal Registry; 2008.

Fernstrom A, Hylander B, Rossner S. Clin Nephrol. 1996;45:169–74.

Fouque D LM. Cochrane Database of Systematic Reviews 2009 Contract No.: 0.1002/14651858.CD001892; 2009.

Fouque D, Vennegoor M, Ter Wee P, Warnner C, Basci A, Canaud B, Haage P, Konner K, Kooman J, Martin-Malo A, Pedrini L, Pizzarelli F, Tattersall J, Tordoir, J, Vanholder R. Nephrol Dial Transpl. 2007;22:45–87.

Garg AX, Blake PG, Clark WF, Clase CM, Haynes RB, Moist LM. Kidney Int. 2001;60:1867–74.

Hays RD, Kallich JD, Mapes DL, Coons SJ, Carter WB. Qual Life Res. 1994;3:329–38.

Henkel G. Caring Ages. 2006;7:10.

Juergensen E, Wuerth D, Finkelstein SH, Juergensen PH, Bekui A, Finkelstein FO. Clin J Am Soc Nephrol. 2006;1:1191–6.

Kaplan De-Nour A, Czaczkes JW. Psychosom Med. 1972;34:333–44.

Klahr S, Buerkert J, Purkerson ML. Kidney Int. 1983;24:579–87.

Leavey SF, Strawderman RL, Jones CA, Port FK, Held PJ. Am J Kidney Dis. 1998;31:997–1006.

Levy J, Pusey C, Singh A. Fast facts: renal disorders. Oxford: Health Press; 2006.

Mapes DL, Lopes AA, Satayathum S, McCullough KP, Goodkin DA, Locatelli F, Fukuhara S, Young EW, Kurokawa K, Saito A, Bommer J, Wolfe RA, Held PJ, Port FK. Kidney Int. 2003;64:339–49.

Middleton RA, Allman-Farinelli MA. J Nutr. 1999;129:122–5.

National Kidney Foundation. Am J Kidney Dis. 2002;39:S1–266.

National Collaborating Centre for Chronic Conditions. Chronic kidney disease: national clinical guideline for early identification and management in adults in primary and secondary care. London: Royal College of Physicians; 2008.

National Institute for Health and Clinical Excellence (NICE) 2010. Chronic Kidney Disease: national clinical guideline for early identification and management in adults in primary and secondary care. http://www.nice.org.uk/nicemedia/live/12069/42116.pdf accessed 12.10.10.

Pedrini MT, Levey AS, Lau J, Chalmers TC, Wang PH. Ann Intern Med. 1996;124:627–32.

Phillips D. Quality of life: concept, policy and practice. London: Routledge; 2006.

Pifer TB, McCullough KP, Port FK, Goodkin DA, Maroni BJ, Held PJ, Young EW. Kidney Int. 2002;62:2238–45.

Vlaminck H, Maes B, Jacobs A, Reyntjens S, Evers G. J Clin Nurs. 2001;10:707–14.

Ware JE, Sherbourne CD. Med Care. 1992;30:473–83.

Weisbord SD. Adv Chronic Kidney D. 2007;14:319–27.

WHOQOL. Soc Sci Med. 1995;41:1403–9.

Wu AW, Fink NE, Cagney KA, Meyer KB, Jenckes MW, Bass EB, Rubin HR, Sadler JH, Powe NR. Am J Kidney Dis. 2001;37:11–21.

Wuerth D, Finkelstein SH, Finkelstein FO. Adv Chronic Kidney D. 2007;14:353–7.

Chapter 199
Huntington's Disease: Quality of Life and Diet

Glenn R. Marland and Colin R. Martin

Abbreviations

BMI	Body Mass Index
CAG	Cytosine, adenine, and guanine
DVLA	Driver Vehicle Licensing Authority
EHDI	European Huntington's Disease Initiative
HD	Huntington's disease
HDA	Huntington's disease Association
HDQoL-C	Huntington's disease Quality of Life Battery for Carers
PEG	Percutaneous endoscopic gastrostomy feeding
QoL	Quality of life

199.1 Introduction

Huntington's disease (HD), an incurable disorder of the central nervous system, is distinct in being a mental illness of identified genetic etiology. It is caused by a single defective autosomal dominant gene (Harper 1996). Transmission through a dominant gene means only one HD gene is needed, each child having a 50% risk, in contrast to transmission from a recessive gene when two genes are required, one from each parent. As the gene is autosomal, both genders are equally at risk (Fig. 199.1). The gene has been identified since 1993, and has a 100% expression rate (Meiser and Dunn 2000), meaning that those having the gene that live long enough will develop HD (The Huntington's Disease Collaborative Research Group 1993); there are no unaffected carriers as occurs in conditions transmitted through recessive genes. If the gene is not passed on, then the disease will not be inherited and that individual's children are not at risk. New gene mutations are very rare and are anyway not confined to those with HD in the family. An accurate predictive test has also been available since 1993. Symptom onset is usually between the ages of 35 and 55, but it can occur at any age including infanthood; juvenile onset is defined as any age below 10 (Quarrell 1999).

G.R. Marland (✉)
School of Health, Nursing and Midwifery, University of the West of Scotland,
Dumfries Campus, Dudgeon House, Bankend Road, Dumfries, DG1 4ZN, UK
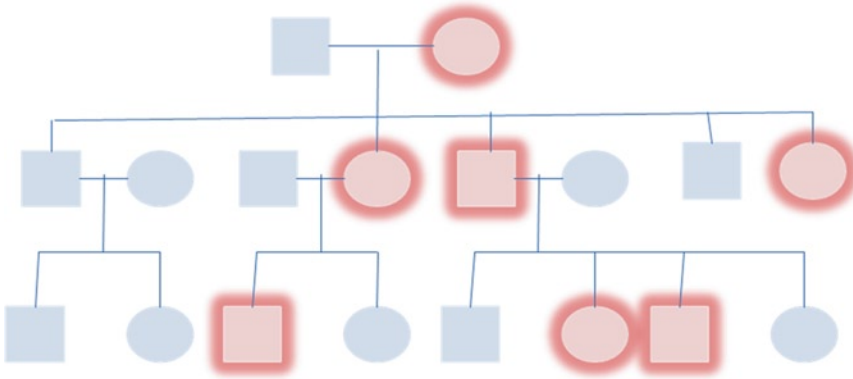e-mail: glenn.marland@uws.ac.uk

Fig. 199.1 Genetic transmission of Huntington's disease. Inheritance pattern of Huntington's disease. This figure shows the transmission of the Huntington's disease gene and represents a 50% probability. Squares represent males and circles represent females. Shapes with a glow represent inheritance of the Huntington's disease gene

Research is still to delineate the molecular pathogenesis, although it is known that the disease is linked to an expansion of polyglutamine in the novel protein Huntingtin (Zhang et al. 2005). All genes produce proteins, and the particular protein product of the HD gene is known as Huntingtin (The Huntington's Disease Collaborative Research Group 1993). Huntingtin is normally associated with healthy functioning of the nervous system, but the mutated variant present in HD is linked to damage and ultimately destruction of neuronal tissue (Bentley 1999). This damage occurs particularly in the basal ganglia and cerebral cortex, and leads to the subsequent physical and psychological changes (HDA fact sheet 1 2008), so destructive to Quality of Life (QoL). The gene is located on the short arm of chromosome 4 and is known as IT15. It is composed of three DNA bases cytosine, adenine, and guanine often abbreviated to CAG. The building block of the protein coded as CAG is called glutamine, hence "polyglutamine" or too many CAG repeats is associated with HD (Quarrell 1999). Although there are CAG repeats in healthy individuals, repeats of 36 or more are linked to HD. The higher the number of CAG repeats, the more there is likely to be an earlier onset of the condition, and this is more likely to occur when the disease is inherited from the father (Kirkwood et al. 2001). The predictive test cannot ascertain the age when the symptoms will manifest; a neurologist can only make a clinical judgment. There are also a number of approaches to testing for HD (Fig. 199.2). HD has an inexorable progression being chronic and neurodegenerative in nature. It has motor, cognitive, and psychiatric symptoms (The Huntington's Disease Collaborative Research Group 1993), but medical curative treatment is fruitless (Raphael et al. 2004); death occurring 15–30 years after symptom onset (Hart and Semple 1990).

Worldwide prevalence has been estimated to be 10 in every 100,000 people (Quarrell 1999), but this means that 1 in every 1,000 is affected by HD as a family member or friend, so the effects on QoL are pervasive. Also because of its genetic transmission, clusters occur in particular regions, for example, Tasmania (Quarrell 1999) and the west of Scotland (McGill 2003). The historical tendency in Britain to export those regarded as deviant to the colonies contributed to this clustering effect in the new world. George Huntington, an American GP in Long Island, observed involuntary dance-like (choreiform) movements in some of his patients. He also noticed that for some the condition seemed to be inherited. It is unclear who first observed this tendency as both his father and grandfather were GPs before him in the same locality and he was taken out on home visits by his father (Quarrell 1999). The symptoms of HD have also been noted in texts from the middle ages (Kolb and Whishaw 1995). The identification of this distinct disease was credited to George Huntington, however, through his

Fig. 199.2 Testing
approaches for Huntington's
disease. This figure shows the
three alternative approaches
to diagnosis of Huntington's
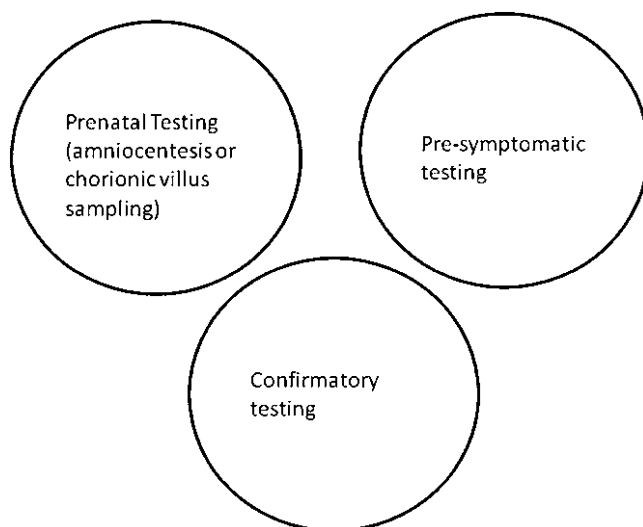disease gene. The three
approaches are mutually
exclusive

Fig. 199.3 Interventions for
Huntington's disease.
Interventions available
following a confirmed
diagnosis of Huntington's
disease. Dietary factors are a
crucial domain in the
therapeutic armamentarium
and should be integrated into
a comprehensive care
package that includes
psychosocial and spiritual
support and physical exercise.
The three approaches are
interdependent
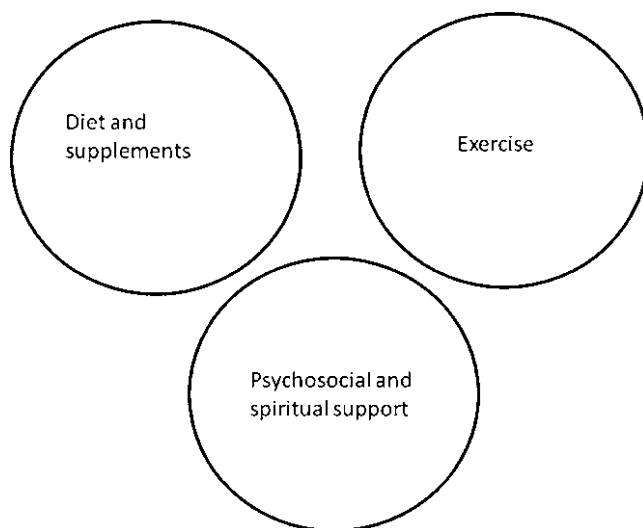
publication "On Chorea" in 1872 in the Philadelphia-based *Medical and Surgical Reporter*. Most of this paper was devoted to chorea caused by infection, which was common at the time; only on the last page did he describe the hereditary form (Quarrell 1999).

HD is complex and multifaceted, severely and diversely impacting on QoL throughout its course. As its effects are diverse, it is convenient to consider these in early, middle, and late stages, although they are idiosyncratic affecting each individual, family, and carers differently. The late or palliative stage can have a long duration, and there is a compelling argument that quality of life could be enhanced by applying similar palliative approaches common in conditions such as cancer (Travers and Partington 2004). Although the need to maintain adequate diet throughout these stages is a clinical imperative, the specific nutritional requirements are unclear (Rae et al. 2009). A characteristic of HD is unintended weight loss, but the cause is unknown (Aziz et al. 2008), however diet and dietary supplements represent a key component of a comprehensive treatment package for HD (Fig. 199.3).

It is likely, however, to be multifactorial and related to decreased calorific intake from dysphagia, increased energy expenditure due to the physical activity associated with almost constant involuntary movement (Pratley et al. 2000; Gaba et al. 2005) and an underlying hypermetabolic state (Aziz et al. 2008). User–carer groups play an increasingly important role in raising awareness and pressing for a cure. The famous American folksinger Wood Guthrie had HD; his second wife Marjorie formed the Committee to Combat Huntington's disease in 1967, the year of Woody's death (Quarrell 1999). Due to the work of Mauveen Jones, whose father had HD, a similar organization 'Combat' developed in the UK, although it has now changed its name to the Huntington's Disease Association (Quarrell 1999).

199.2 Quality of Life and Diet

Tsuang and Vandermey (1980, p. 100) give a particularly vivid summary representing the devastation that HD wreaks on QoL. "A crueler disease than Huntington's could hardly have been devised by a committee of devils." The notion of stages in HD has been used (Quarrell 1999; Hoffman 1999; Kirkwood et al. 2001) as an illustrative guide. Presentation in each individual, however, is idiosyncratic and not everyone experiences all symptoms. Rating scales, for example, the Unified Huntington's Disease Rating Scale (Huntington's Study Group 1996) can help in the assessment process. The stages of Huntington's disease are shown in Table 199.1.

Table 199.1 Stages of Huntington's disease

Stages of HD	
Early stage	Initial onset of symptoms that are usually psychiatric in nature, family members may report that the affected person has changed in personality and this may involve sexual promiscuity. Lack of concentration, memory lapses and depression can occur even years before the onset of motor symptoms. Psychosis can also be a precursor. Death is unusual, except by suicide. The person becomes increasingly irritable with themselves and others. Weight loss is apparent and persists throughout the course of the disease. Chorea (Greek for dance)-form involuntary movements start to occur and may precede or follow psychiatric symptoms; they usually cease when the person is sleeping. Bradykinesia (slowness of voluntary movement) is evident and can be detected diagnostically when observing the person flicking their eyes from side to side rapidly as possible. Handwriting becomes difficult and eventually illegible. The gait is characteristic with wide legs and staggering ungainly movement. Speech starts to be affected both in rhythm and rate and may become slurred. As the disease shades into the middle stage, it is unlikely that employment will be maintained.
Middle stage	Motor symptoms are now in the ascendency with marked involuntary movements and clumsiness, and there is increasing dependence on help with activities of daily living. Involuntary movements affect large muscle groups of limbs face and trunk. Speech may be incoherent or the person may become mute. Swallowing becomes increasingly difficult and may cause choking. There is a triad of movement difficulties: chorea, bradykinesia and dystonia. Dystonia manifests as abnormally slow and prolonged contractions of muscles. Sleep is restless. Loss of drive and volition may be mistaken for laziness. Epilepsy is particularly associated with juvenile HD. Some people become progressively rigid and do not experience the usual degree of involuntary movements also most characteristic in juvenile onset.
Late stage	Dependence on others in daily living. Voluntary movement is possible only with extreme effort. Dystonia and rigidity increase in magnitude. Weight loss is marked. Incontinence of both feces and urine is common. Secondary conditions such as bronchial pneumonia are often the cause of death.

This table summarizes the key stages in the progression of Huntington's disease. The symptom profile is broad and idiosyncratic but follows an inevitable trajectory toward extreme incapacitation and, ultimately, death

199.2.1 Early Stage

On the face of it, genetic testing seems desirable and takes the form of a blood test usually in the UK in a regional genetics service. Genetic testing, however, has proved to be a mixed blessing, having an array of affects on QoL. The provision of counselling and support in preparation for and post testing is associated with QoL. Mariscal et al.'s (2009) Spanish prospective multicenter study with 18 participants showed that those who accepted the predictive test had a trend of decreased scores on QoL and no difference in scores of anxiety and depression compared to those who rejected the test (hospital depression and Euro QoL scales were used). For those who know they are at risk, QoL can be undermined, even when presymptomatic, because of the inevitable worry and tendency to interpret every accident or clumsy action as a sign of disease onset.

Even the early stage of HD is characterized by loss and declining QoL. It is known that genetic discrimination is associated with inheritable diseases and Bombard et al. (2009) have demonstrated that in relation to HD, the earlier the gene is identified, the sooner the discrimination begins. Their self-report survey with a study sample of 233 at risk, but currently asymptomatic individuals (response rate of 80%) evidenced that this discrimination was in family, social, and insurance domains. Muto and Nakai's (2009) ongoing qualitative study in Japan suggests that the stigma of HD is also strongly internalized by those at risk. So far, only 18 participants have been recruited, but they report a tendency to put off visiting hospital even when they experience subtle physical changes; they procrastinate about diagnostic testing. If employment is lost, then help may be required as to benefit entitlement and voluntary agencies may provide this.

The ability to drive will also be lost as the disease progresses. In the UK, the law is that the Driver and Vehicle Licensing Authority (DVLA) must be informed when a medical condition affects ones fitness to drive (Quarrell 1999) and this must be relevant or prospective disability (HDA, Fact sheet 13 2008). The onus of responsibility is on the individual that if presymptomatic they are not obliged to contact the DVLA, but must do so at onset of symptoms (HDA, Fact sheet 13 2008). The difficulty each individual faces is deciding when this stage has been reached, despite the denial process inevitable when disease progression outpaces psychological adjustment.

Although the cause of unintended weight loss is unknown, Aziz et al. (2008) postulate that it is related to a hypermetabolic state and that other signs and symptoms in the early stage are unlikely to contribute. Their evidence comes from following up 379 participants from the European Huntington's Disease Initiative (EHDI) and they found that higher CAG repeat number scores were associated with a faster decrease in body mass index (BMI). Two studies (Pratley et al. 2000; Gaba et al. 2005) examining energy expenditure and physical activity using indirect calorimetry over a 24 h span found that compared to controls total energy expenditure was 11–14% higher in subjects with early- to mid-stage HD, and this at the time was attributed to increased physical activity during waking hours. Weight loss leads to a general weakening and decrease in feelings of wellness and therefore of QoL (Nance and Sanders 1996). It is of clinical significance that this occurs despite adequate or even increased calorific intake (Morales et al. 1989; Van der Burg et al. 2008), and that it begins to manifest in gene carriers who are presymptomatic (Mochel et al. 2007).

Although the need for an adequate calorific intake, usually of around 5,000 calories daily, throughout the course of the condition is a clinical imperative, clear guidelines on the number and components of calories required is not available to clinicians and further research is indicated (Rae et al. 2009). The HDA (Fact Sheet 5 2008), however, does make useful recommendations based on practical experience in their published fact sheets. They recommend, for example, drinking 1 pint of full cream milk each day as a source of protein and adding 2 ounces of skimmed milk powder to add calories. It is a common and often early sign of neurodegenerative conditions such as HD to experience olfactory impairment (Hawkes 2006). The loss of the sense of smell diminishes QoL, and even early in the

disease process diminishes the enjoyment of food. Being underweight impacts on QoL and increases the risk of infection, muscle wasting, and lethargy (HDA Fact Sheet 5 2008). Recurrent thoughts of suicide are common and these are often acted upon.

199.2.2 Middle Stage

Although the early stage of HD is associated with sexual promiscuity, it has long been observed clinically that sexual dysfunctions and infertility are frequent (Fedoroff et al. 1994) as the condition progresses. It is also known that the severity of the condition is correlated to declining plasma testosterone levels (Markianos et al. 2005). HD poses a challenge to the entire multidisciplinary team, but the assessment and caring role of nurses is particularly needed as the disease progresses and has been described as pivotal (Kent 2004). Sometimes diagnosis is not made until this stage (Quarrell 1999). Although medicines such as neuroleptics and antidepressants are often prescribed, as always in terms of QoL, there is a cost to pay in side effects. Particular care must be taken with neuroleptics as some side effects such as rigidity and slowness of movement may be mistaken for symptoms. There is a constant need to maintain a safe environment and this should be adapted to promote safety in anticipation rather than reacting to incidents, although known trigger factors of behavioral problems should be avoided. Speech therapy is invaluable in reviewing swallowing difficulties on an ongoing basis. Preventive strategies for choking should be devised as should the management of choking episodes so that all hospital staff or carers are confident in working within an agreed care plan. This should include but go beyond proficiency in the Heimlich maneuver. Again the HDA fact sheets give very useful practical advice. Dietician input is also essential both to help ensure a high-calorific diet and also on the type and preparation of food to ameliorate swallowing problems. Although weight loss is integral to the disease process, it will be exacerbated by insufficient diet. Although people with HD are not innately more susceptible to dental abnormalities, they tend to have more dental problems (HDA Fact Sheet 8 2008). Involuntary movements, inability to coordinate opening the mouth, apathy, and low mood are just some of the contributory factors to this issue. The causes of potentially poor dietary intake are several and diverse (Table 199.2).

199.2.3 Late Stage

This stage is often characterized by total reliance on others for all activities of daily living. Care is likely to be provided in residential services, but may still be provided at home with 24 h care by family

Table 199.2 Common causes of poor diet

Common causes of inadequate diet	
Physical	The fine dexterity necessary to prepare food will diminish and eventually be completely lost. The ability to chew and swallow food is compromised as is the hand and eye coordination necessary to eat unaided. Often there is difficulty in taking an appropriate portion of food, which can be chewed successfully. Poor dental health.
Psychological	The mean age of onset of HD is 42, an age associated with independence, maturity, and productivity; it is psychologically hard to accept the dependence symbolized by being fed by others. Low mood and depression, often associated with HD, may diminish appetite and enjoyment of food.
Social	The embarrassment of eating in front of other people may lead to the avoidance of meal times.

This table summarizes the key physical, psychological, and social causal factors of poor diet and nutritional status in Huntington's disease

Table 199.3   Behavioral changes associated with Huntington's disease

Behavioral change
• Emotions liability
• Reduced empathy
• Aggression
• Excitement
• Depression
• Apathy
• Challenging and antisocial behavior
• Anger

This table summarizes the key behavioral changes associated with Huntington's disease. There is no typical behavioral profile, and the patient may experience any combination of these behavioral changes within a dynamic, changing context

and Social Care and District Nursing services. Aubeeluck et al. (2009) investigated the impact of HD on the QoL of family carers. The QoL of 45 family carers was measured using the HDQoL-C (Aubeeluck and Buchanan 2007). This validated tool invites carers to independently reflect on their lives in the last 2 months. The results showed a significant difference between self-reported QoL of current main carers in comparison to those who no longer maintained main carer roles. Full-time carers also reported a significantly lower QoL than part-time carers. The qualitative data suggested that carers often and increasingly neglected their own needs as the disease progressed. Although QoL can only be perceived by the individual, it is hard to imagine that for the person with HD this is anything but invariably low. There has been a call in the literature for palliative services and approaches to be applied to neurodegenerative conditions (McLeod 2001; Oneschuck 2001) including HD (Travers and Partington 2004).

By this stage, difficulties with eating and drinking are magnified and compounded. It is essential to allow time for chewing and swallowing. Inadequate hydration is likely to result in a myriad of effects such as urinary tract infection, constipation, disorientation, and reduced skin integrity. There is an increasing risk, however, of aspiration as well as of choking. Eventually PEG feeding may be necessary. HD predisposes to pressure sores because of incontinence, involuntary and constant movement, weight loss, and the potential for inadequate hydration adds to this toxic formulae. Specially adapted chairs are available that help to prevent accidents caused by involuntary movement and which can help to prevent pressure being confined to specific body areas (Quarrell 1999). Although global dementia is often attributed to the late stages, clinically it has been observed that awareness of environment and ability to understand are preserved much more than in other conditions bracketed under the label of dementia and therefore stimulation, for example, watching favorite TV programs, is required to maintain QoL. Behavioral changes in the patients with HD are broad and complex, and the main changes associated with psychological health are shown in Table 199.3.

199.3   Conclusion

HD profoundly impacts QoL for the individuals and their family and carers. There are a constellation of symptoms. Although these present idiosyncratically as they arise because of damage in the basal ganglia and the cerebral cortex, the ability to control voluntary movement and also limit movements that are involuntary are common. Emotional changes and psychiatric symptoms are

almost invariably part of the syndrome. Personality can seem to change even before the onset of these symptoms and weight loss can also occur at this time probably as part of a hypermetabolic state. HD presents challenges to the full multidisciplinary and multiagency teams throughout its course in early, middle, and late stages not least being the need to maintain adequate calorific intake.

Summary Points

- HD is incurable, and death occurs around 20 years after onset of symptoms, so QoL is affected for a long period for the individual, carers, family, and friends.
- HD is transmitted by a single autosomal dominant gene with a 100% expression rate a predictive test has been available since 1993.
- HD is a chronic degenerative condition with an array of motor, cognitive, and psychiatric symptoms that are best illustrated in early, middle, and late stages.
- Loss of life and social skills combine with stigma to contribute to the feelings of hopelessness and isolation making the risk of suicide high.
- The cause of the unintended weight loss is likely to be multifactorial and related to decreased calorific intake from dysphagia, increased energy expenditure due to the physical activity associated with almost constant involuntary movement, and an underlying hypermetabolic state.
- Dietary considerations are intrinsic to any consideration of QoL; although weight loss is part of the disease process attention to calorific intake is essential, the HDA provide invaluable advice.

Definitions of Key Terms

Huntington's disease: is an incurable, autosomal, dominant, inherited, degenerative condition of the central nervous system. It has psychiatric, motor, and cognitive symptoms, with mean age of onset of 42, but can affect people of any age, including infants and octogenarians.

The Huntington's Disease Association: is a voluntary group committed to promoting awareness of the condition and pressing for a cure. It was established initially in the USA but has inspired similar organizations throughout the world.

Body Mass Index: is a statistical measurement that compares an individual's height and weight. It is defined mathematically as a person's body weight divided by the square of their height and remains the most widely used tool to calculate weight problems within a population sometimes for insurance purposes. A BMI of 18.5 to 25 is regarded as optimal and below 18.5 indicates the person is underweight as is commonly the case in HD.

Percutaneous endoscopic gastrostomy: feeding is when nutrition is given through a tube which passes into the stomach through the abdominal wall. This means that nutrition can be provided despite swallowing or chewing difficulties. This is sometimes required in the later stages of Huntington's disease.

Quality of life: is a term used to denote the general well-being of an individual or a society. It has both subjective and objective aspects and these can be expressed in a quality-of-life index.

References

Aubeeluck A, Buchanan H. The Huntington's disease quality of life battery for carers: reliability and validity. Clin Genet. 2007;71(5):434–45.

Aubeeluck A, Wilson E, Seymour J, Taylor R. Clin Genet. 2009;76(Suppl. 1):95–101.

Aziz N, Van der Burg J, Landwehrmeyer J, Brundin P, Stijnen T. Weight loss in Huntington disease increases with higher CAG repeat number. Neurol. 2008;71:1506–13.

Bombard Y, Palin J, Veenstra G, Friedman J, Creighton S, Currie L, Paulsen J, Bottorff J, Hayden M. Clin. Genet. 2009;76 (Suppl. 1):95–101.

Bonelli RM, Wenning GK, Kapfhammer HP, Huntington's disease: present treatments and future therapeutic modalities. Int Clin Psycgopharmacol. 2004;19(2): 51–62.

Bentley P. Dementia demystified. Nurs Times. 1999;95(45):47–9.

Fedoroff, J, Peyser, C, Franz M, Folstein S. Sexual disorders in Huntington's disease. J Neuropsychiatr Clin Neurosci. 1994;6:147–53.

Gaba A, Zhang K, Marder K, et al. Energy balance in early-stage Huntington disease. Am J Clin Nutr; 2005;81:1335–41.

Harper P, editor. Huntington's disease: major problems in neurology, 2nd edition. London: Saunders; 1996.

Hart S, Semple J, editors. Neuropsychology and the dementias. London: Taylor and Francis; 1990.

Hawkes C. Olfaction in neurodegenerative disorder. In: Hummel T, Welge-Lüssen A, editors. Taste and smell, an update. Basel: Karger; 2006.

Hoffman N. Understanding the neuropsychiatric symptoms of Huntington's disease. J Neurosci Nurs. 1999;31(5):309–13.

Huntington's Study Group. Unified Huntington's Disease Rating Scale: reliability and consistency. Mov Disord. 1996;11(2):136–42.

Kent A. Huntington's disease. Nurs Standard. 2004;18(32):45–51.

Kirkwood S, et al. Progression of symptoms in the early and middle stages of Huntington's disease. Arch Neurol. 2001;58(2):273–8.

Kolb B, Whishaw I. Fundamentals of human neuropsychology, 4th edition. New York: WH Freeman; 1995.

Markianos M, Panas M, Kalfakis N, Vassilopoulos D. Plasma testosterone in male patients with Huntington's disease: relations to severity of illness and dementia. Ann Neurol. 2005;57:520–5.

Morales M, Estevez J, Suarez H, Villalobos R, Chacin D, Bonilla E. Nutritional evaluation of Huntington disease patients. Am J Clin Nutr. 1989;50:145–50.

Van der Burg J, Bacos K, Wood I, et al. Increased metabolism in the R6/2 mouse model of Huntington's disease. Neurobiol Dis. 2008;29:41–51.

Mochel F, Charles P, Seguin F, et al. Early energy deficit in Huntington disease: identification of a plasma biomarker traceable during disease progression. PLoS ONE 2007;2:e647.

McGill M. Scottish Huntington's Association Annual Report 2002–2003. SHA: Elderslie; 2003.

McLeod A. Multiple sclerosis and palliative medicine. Progr Palliative Care. 2001;9(5):196–8.

Meiser B, Dunn S. Psychological impact of genetic testing for Huntington's disease: an update of the literature. J Neurol Neurosurg Psychiatr 2000;69 5 574–8.

Nance M, Sanders G. Characteristics of individuals with Huntington disease in long-term care. Mov Disord. 1996;11:542–8.

Oneschuck D. Progressive multifocal leucoencepholopathy and sporadic Creutzfeld-Jacob disease: a review and palliative management in a hospice setting. Progr Palliative Care. 2001;9(5):202–05.

Pratley R, Salbe A, Ravussin E, Caviness J. Higher sedentary energy expenditure in patients with Huntington's disease. Ann Neurol. 2000;47:64–70.

Quarrell O. Huntington's disease: the facts. Oxford: Oxford University Press; 1999.

Rae D, Simpson S, Campos L. On behalf of the EHDN Standards of Care Dieticians Working Group Department of Clinical Genetics, Grampian University Hospital Trust, Aberdeen, Scotland, UK. Clin Genet. 2009;76(Suppl. 1): 85–94.

Raphael M, Bonelli A, Gregor K, Wenning B, Hans P, Kapfhammer A. Int J Clin Psychopharmacol. 2004;19:51–62.

The Huntington's Disease Collaborative Research Group. A novel gene containing a trinucleotide repeat that is expanded and unstable on Huntington's disease chromosomes. Cell. 1993;72:971–83.

The Huntington's Disease Association, Fact Sheet 1. General information about Huntington's disease and the Huntington's disease Association; 2008. www.hda.org.uk. Accessed Dec 18, 2009.

The Huntington's Disease Association, Fact Sheet 5. Huntington's disease and diet; 2008. www.hda.org.uk. Accessed Dec 18, 2009.

The Huntington's Disease Association, Fact Sheet 8. The importance of dental care; 2008. www.hda.org.uk. Accessed Dec 18, 2009.

The Huntington's Disease Association, Fact Sheet 13. Huntington's disease and driving; 2008. www.hda.org.uk. Accessed Dec 18, 2009.

Travers E, Partington D. The Scottish Huntington's Association Palliative Care Education Project. Scottish Nurse. 2004;9:30–1.

Tsuang M, Vandermey R. Genes and the mind: inheritance of mental illness. Oxford: Oxford University Press; 1980.

Zhang RY, Li L, Zhang L, Wang H, Yei CF. Effects of Shenwu capsule on the behavior and neurotrophic factors in the rats with mimic Huntington's disease. J Beijing Univ TCM. 2003;26:34–8.

Part XXXIV
Body Image

Chapter 200
Personal Values, Vanity, Physical Health, and Perceived Body Image Influences in Food-Purchasing and Consumption Decisions

Barry O'Mahony and John Hall

Abbreviations

LOV List of values (a list or scale of questions developed by Kahle (1983) to identify the influence of personal values on behavior)
CSPI The Center for Science in the Public Interest

200.1 Introduction

Although food is a vital part of the chemical process of life, the manner in which people choose the foods that they eat is subject to a wide variety of external and internal influences, ranging from socio-cultural conditioning to the effects of the media (Pyke, 1970; Chang, 1977; Visser, 1992; Keane and Willetts,1994; Getley, 1995). While weight, health, diet, and exercise receive constant media and governmental attention, very little is known about why consumers choose one food over another or about the influence of body image in the food consumption process (Rozin, 2000). Consequently, there is a need for an empirically based understanding of the factors that influence food purchasing and consumption behavior. In this chapter, we examine the influence of body image, vanity, and personal values in the food-purchasing and consumption decisions of young women in the age range of 18–30 years. We then discuss the results of an empirical investigation that unearthed a number of healthy and unhealthy consumption practices that young women engaged in as a means to achieve their perceived body image ideals.

200.2 Body Image, Vanity, and Personal Values

Body image is described by Thompson (1993) as personal perceptions of the way our bodies appear, which we form in our minds. Body image is therefore psychological in nature, involving perception, imagination, emotions, and physical sensations (Lightstone, 1999). As a result, it is sensitive to changes in mood, environment, and physical experience and is heavily influenced by self-esteem.

B. O'Mahony (✉)
School of Hospitality, Tourism and Marketing, Victoria University, Melbourne City, Vic 8001, Australia
e-mail: Barry.OMahony@vu.edu.au

While Thompson (1997) acknowledges the impact of psychological processes in the formation of perceived body image, he asserts that the media plays a significant role in the formation of peoples' perceptions of what is acceptable. Noting a trend in popular women's magazines toward increasing slenderness of models as well as an increase in articles and advertisements addressing dietary issues, he concludes that this has provided women with the ideal body image goal. Moreover, Thompson (1997) asserts that the media is one of the most powerful and effective communicators of the thin ideal due to the popularity of television, movies, and magazines. This ideal has, in turn, been proposed as a modulating force in the amount and type of food that is consumed (Rozin, 1996; Thompson, 1997).

Netemeyer et al. (1995) also recognize the importance of psychological processes in the development and marketing of products and services. Their work concentrates on vanity, which they describe as a fixation, and this fixation can involve both physical appearance and the achievement of personal goals. Their research shows that physical appearance has a marked influence on consumer behavior, and that this can lead to both positive and negative consumption behavior.

Netemeyer et al. (1995) assert that marketing practitioners are aware of the importance of both physical and achievement vanity, and this is reflected in advertising themes that highlight product ownership as a status symbol or measure of achievement (Table 200.1).

In addition to media, advertising, and vanity, perceived body image is influenced by our reflection in the mirror, feedback from others, sociocultural values, self-talk, and mental pictures (Goward, 1993). Rokeach (1968) explains that values are enduring and that they guide our actions and judgments in specific situations. Personal values in the consumption process lead the consumer beyond immediate goals to end states of existence.

Vinson et al. (1977) assert that values are responsible for the selection and maintenance of the ends or goals toward which individuals strive. In the context of this chapter, Getley (1995) asserts that people will make choices about food depending on their values. For example, if they value nutritional gain from food, they will make particular choices, which will reflect this value. Moreover, Rokeach (1968) reports that various combinations of values significantly differentiate individuals. Personal values, therefore, have a major influence on people's lifestyle, interests, outlook, and consumption priorities (Table 200.2).

Although studies have identified a number of variables that may influence food consumption decisions including culture (Chang 1977; Flandrin and Hyman, 1984; Bourdieu, 1986; Mennell, 1985; Visser, 1986), taste (Douglas, 1978; Marshall, 1995; Wright et al., 2001), social status (Bourdieu,1986; Rozin, 1996), health and nutrition (Anderson et al., 1995; Stockley, 1991, Mikela, 2000), food trends (Goody, 1982; Mennell, 1985; Marshall, 1995; Sassen, 1998), marketing (Hall et al., 2001), convenience (Sassen, 1998, Mikela, 2000), religion (Sherrat, 1995; Rozin, 1996; O'Mahony, 2004) and gender (Thompson, 1993; Raats et al, 1995). In a recent comprehensive

Table 200.1 Key features of vanity

Netemeyer et al. (1995) assert that vanity comprises the following four trait aspects:
- An excessive concern for physical appearance.
- A positive (and perhaps inflated) view of one's physical appearance.
- An excessive concern for personal achievements.
- A positive (and perhaps inflated) view of one's personal achievements.

Using this framework Netemeyer et al. (1995) have conducted a raft of studies in order to develop and validate a series of scaled questions specifically designed to measure each of these element of vanity. The resulting "Vanity Scale" is a useful and valuable research tool for the conduct of quantitative studies.

This table provides an explanation of the vanity scale and the construct which it comprises. The scale has been used in a variety of previous quantitative studies and thus the variables have been validated. It is an accepted research instrument within the discipline of marketing and consumer behavior

Table 200.2   Key features of personal values

Personal values have a direct impact on purchasing and consumption decisions. This means that people will make choices about food purchasing and consumption that fit with their personal values. For example, if they and are concerned for their physical well-being, they will make purchasing and consumption decisions that reflect this value. Rokeach (1968) was among the first to report that various combinations of values differentiate individual preferences. His work, produced the Rokeach Value Survey, an instrument used to measure values which comprises 18 instrumental values and 18 terminal values. More recently, however, Rokeach's scales has been modified into a smaller set of nine, person oriented, terminal values. The reduced list relates more directly to a person's daily life roles and situations and is known as the List of Values or LOV scale. This scale has subsequently been validated across a variety of consumer studies and these studies have confirmed that values have a major impact on purchasing and consumption decisions. Examples include Beatty et al. (1985); Kahle (1986); Muller (1989); Kamakura et al. (1991); Kamakura and Novak (1992); Blamey and Braithwaite (1997); Jago (1998), and Hall et al. (2001)

This table explains the key features of personal values and discusses the origins of the value-oriented scales. The table describes how early work in this area has resulted in a reduced list of values (the LOV scale) specifically designed for consumer behavior research. The table also provides references for a number of previous studies where the scale has been used in consumer research

investigation, O'Mahony and Hall (2007) combined these variables with the vanity scale of Netemeyer et al. (1995) and Kahle's (1983) List of Values (LOV) scale in a mixed methods study that explored issues such as dieting, food avoidance, and other strategies that are invoked by young women in order to maintain or improve their physical appearance.

200.3 Review of Procedures

For the qualitative phase of their study, O'Mahony and Hall (2007) selected a non-probability, convenience sample of 50 female respondents in the age group of 18–30 years. They then conducted interviews using a semi-structured interview schedule, where respondents were asked a series of questions about their food consumption, dietary and food avoidance habits. This research phase yielded some interesting results in its own right; however, one of the strengths of the research was that the insights that were uncovered helped to explain the results of their follow-up quantitative survey, which utilized a questionnaire that incorporated both the vanity and LOV scales.

This study involved 500 female respondents who were recruited via a non-probability snowball or referral sampling method. Respondents were asked to rate each question, from one anchored as not important at all, to seven anchored as extremely important.

Overall, 488 valid questionnaires were obtained from 243 respondents between the ages of 18 and 24 years and 245 between the ages of 25 and 30 years. As can be seen in the figures below, a good representation of demographic characteristics was achieved (see Figs. 200.1, 200.2, and 200.3).

200.4 Summary of Analyses

O'Mahony and Hall (2007) conducted an exploratory factor analysis, and confirmed the appropriateness of this procedure for their data, using the Kaiser–Meyer–Olkin measure of sampling adequacy as well as Bartlett's test of sphericity. The resulting factor analysis uncovered eight factors; however, the most dominant factor related to physical appearance and body shape (see Table 200.3).
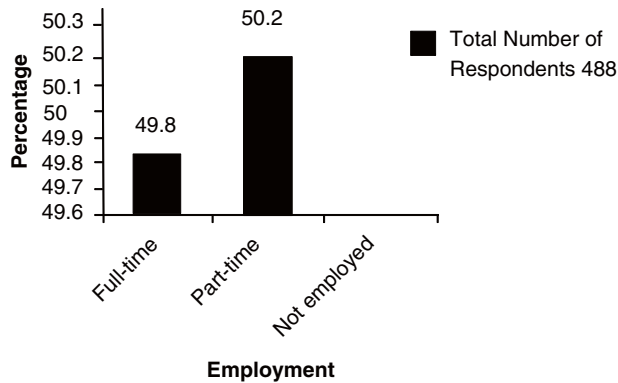
Fig. 200.1 It shows the age range of respondents. Of the sample of 488 respondents, 49.8% (or 243 respondents) were in the age range of 18–24 years, while 50.2% (or 245 respondents) were in the age range of 25–30 years
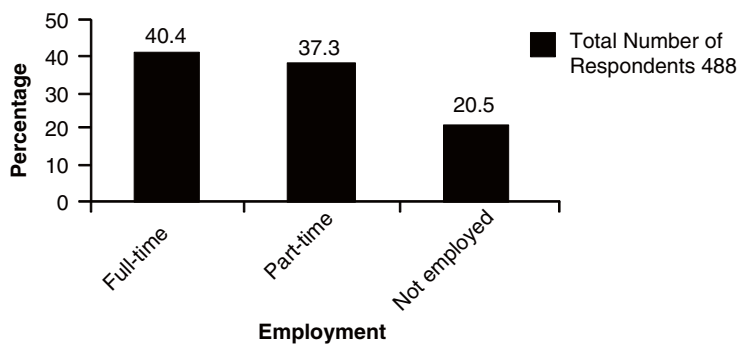
Fig. 200.2 The figure shows respondents' employment status. The sample was divided into three employment categories. These were full-time employed, part-time employed, or not employed. As can be seen, nearly 80% of respondents were employed and 37.3% of those employed were employed on a part-time basis
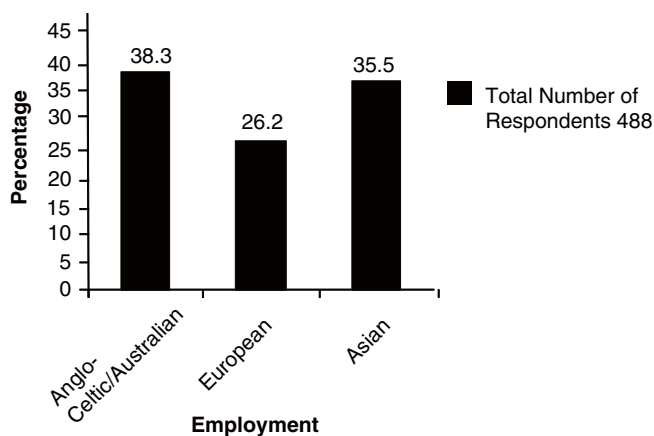
Fig. 200.3 It provides a summary of respondents' cultural background. Respondents were categorized as Anglo-Celtic/Australian, European, or Asian; however, cultural background was not found to be influential in purchasing or consumption decisions

Table 200.3 The factors of influence

Factor	Total	% of variance	Cumulative (%)
Appearance	8.527	24.367	24.363
Time	3.597	10.277	34.640
Marketing	2.915	8.328	42.968
Price	2.256	6.447	49.415
Food qualities	1.893	5.409	54.824
Cultural	1.690	4.828	59.652
Environmental	1.407	4.006	63.658
Filling food	1.075	4.006	67.664

This table presents the results of the factor analysis, which provided eight factors with eigen values greater than 1 and accounted for an acceptable 66.7% of variance. The most dominant factor in this analysis related to physical appearance and body shape

Table 200.4 List of values and vanity

Variable	Security	Belonging	Fun	Warm relationships	Accomplishment	Well-respected	Vanity
Improve physical appearance	X	X		X		X	X
Help lose weight	X			X		X	X
Effect on body shape	X	X	X		X	X	X
Avoid high fat		X	X		X	X	X
Effect on physical shape			X			X	X
Maintain physical shape	X	X	X			X	X
Diet when had wrong foods						X	X
Fear of weight gain	X					X	X
Exercise to compensate for wrong foods		X				X	
Calorie conscious							X
Avoid high carbohydrates	X	X				X	X
Think about health benefits		X	X		X	X	X
Low in cholesterol	X	X					X

This table shows the results of the analysis of variance and identifies significant differences between the two categories of the top box analysis associated with the variables physical appearance factor and items from the list of values and vanity scales

X identifies significant differences observed at the .05 level using ANOVA

Cronbach's alpha was used to assess the internal reliability of this factor and a most acceptable score of .867 was achieved, showing that the physical appearance factor and the variables that it comprises were important considerations for young women and that these variables could be connected with either the consumption or avoidance of particular food products. O'Mahony and Hall (2007) further found that the influence of physical concerns, operationalized in the vanity scale and values, through the LOV scale, were also linked to body image (Table 200.4).

Not surprisingly, the study found that those that were strongly influenced by vanity scored highly on the variables related to the physical appearance and body shape factor. These variables included improvement in physical appearance, weight shedding, effect on body shape, avoidance of high fat, effect on physical shape, maintenance of physical shape, diet on consumption of wrong foods, fear

of weight gain, calorie consciousness, avoidance of high carbohydrates, and consumption of foods low in cholesterol.

It was also found that there was a connection between the variables that make up the LOV scale and physical appearance. These findings are of interest because the values of security, belonging, fun and enjoyment, warm relationships, accomplishment, and respect were linked with physical appearance and body shape. Moreover, the findings were evident regardless of age, employment status, culture, or religious background. The qualitative phase of the research provides further insights into a more complete understanding of these findings. One respondent explained, for example, that appearance was her primary concern when purchasing or consuming food. She explained that she got lazy at times, but did try to eat healthy foods. Although she valued self-image and tried to restrict her food intake to achieve her image goals, she often broke out and consumed foods that she believed were not healthy.

Others linked the value of fun and enjoyment with their purchasing and consumption behavior, stating that they sought enjoyment from eating and that for them mealtimes had to be a pleasurable experience. They expressed the view that they did not want to eat the same foods but sought variety in their consumption. An important component of the enjoyment of mealtimes was sharing the experience with family and friends. As a result, they sought food that was interesting and could enhance the shared experience. Thus, the value of warm relationships was associated with the sharing of meals as well as the content of those meals.

The value of accomplishment also featured in the qualitative study. Respondents linked physical appearance with accomplishment, self-fulfillment, and achievement of goals. This finding links with what Netemeyer et al. (1995) refer to as achievement vanity in that respondents felt that physical appearance may have an impact on goal achievement.

The link between physical appearance, body shape, and the value of being respected was also explained. Respondents described this as a need to look attractive. Respondents also felt that portraying a healthy image and having a good figure was important in order to be well respected.

The views of these young women in relation to what was required to improve physical appearance were also of interest. For example, all respondents felt that there was a negative link between body shape and junk food, while fruit and vegetables were considered healthy. Cutting out fat and junk food was the main strategy employed by these respondents in order to achieve body image ideals and this strategy included avoidance of favorite foods. Some respondents cut meat from their diet as a means to achieving body image goals; however, they were concerned about a lack of iron and other nutrients. Others confided that they skipped entire meals to try to maintain body shape, often eating only during the day, with no evening meals or dinner. Others categorized creamy sauces as bad food and suggested that these should be replaced with tomato-based sauces. In addition to the perceived effect of healthy eating on body shape, respondents asserted that eating healthy food made one feel better about oneself, highlighting a link between consumption and self-confidence. One respondent explained that if one looked good, it gave one confidence, adding that if she started to gain weight, she lost confidence and did not feel good about herself.

Respondents also felt that most healthy foods did not fill you up and explained that they often felt unsatisfied after eating. When this occurred, the temptation was to grab a packet of chips or some other unhealthy snack alternative, especially in outdoor situations where there was a perceived lack of control over the food supply. This led to high levels of guilt for most respondents and, as a result, exercising to compensate for eating the wrong foods was prevalent. The main catalyst for guilt leading to strenuous, compensatory exercise was chocolate, and this was closely followed by snack foods. In some cases, an already punishing gym schedule was increased, depending on the perceived level of unhealthy consumption that had been engaged in.

200.5 Summary of Implications

The O'Mahony and Hall (2007) study highlights the links between perceived body image and food-purchasing behavior, showing that personal values, vanity, physical health, and physical shape are indeed major factors of influence in the purchasing and consumption decisions of 18–30-year-old women. It also confirms that respondents engage in healthy and unhealthy consumption practices in order to achieve their perceived body image ideals. Consuming food that was low in fat and exercising were perceived to be healthy practices, while unhealthy practices included dieting and the avoidance of entire meals.

The link between fear of weight gain and personal values was an important finding. When unhealthy foods were consumed, respondents were racked with guilt, and they felt concerned that if their physical appearance was not in line with their body image ideal, they would lose their sense of security, sense of belonging, and respect. Thus, peer pressure was a significant motivator in the quest for an ideal body image. For this reason, many respondents punished themselves by engaging in activities designed to counteract what they perceived to be unhealthy consumption. This included abstaining from favorite foods, avoiding carbohydrates, and exercising to compensate for eating what they perceived to be the wrong foods.

For these young women, therefore, body image is indeed a psychological state, and food-purchasing and consumption decisions are connected to both their physical and psychological well-being. Their perceptions of what are good and bad foods are linked, however, with their understanding of the effect that these foods will have on physical shape and not on nutritional value. This could mean that many young women of childbearing age are not getting the nutrition that is needed to remain healthy. Although significant, it is possible that this group is not fully aware of the link between nutrition and physical health. Stockley (1991) maintains, for example, that the terms in which dietary advice is presented are not easily understood. This is supported by more recent work by Kozup et al. (2003), who found that consumers had difficulty in interpreting food labels, and the Center for Science in the Public Interest (CSPI, 1997) published concerns about a general lack of knowledge about the fat content of meals among the public and among nutritionists.

Body image is a dynamic concept, however, and can be shaped by the media. Koval (1986) notes, for example, that the ideal body shape has changed dramatically over the last 100 years passing though stages such as the rounded hips portrayed in works of art, to the full figure portrayed by actors such as Marilyn Monroe in the 1960s to the more recent extremely thin portrayal of women in the media. As a result, there is a need for continual research into this dynamic concept and it is suggested that future research involving women of different age groups would provide further valuable insights into this phenomenon.

200.6 Application to Other Areas of Health and Disease

Effective treatment of illnesses that result from food consumption behavior relies on a full understanding of the factors that influence food-purchasing and consumption decisions. Exploring the links between perceived body image and food-purchasing behavior can assist in this understanding. The study profiled in this chapter shows that personal values, vanity, physical health, and perceived body image were major factors of influence in the purchasing and consumption decisions of 18–30-year-old women. It was also identified that respondents to these studies engaged in healthy and unhealthy consumption practices in order to achieve their perceived body image ideals. There are opportunities to extend this research to gain a more comprehensive understanding of the influence

of perceived body image on purchasing and consumption decisions on women in different age groups and to extend the research to men. The finding that body image can take precedence over nutrition in consumption decisions is also of relevance.

Summary Points

- Body image is a psychological process.
- Perceptions of body image are inextricably linked with personal values.
- Vanity effects perception of body image.
- Physical appearance is most important to those respondents that value belonging, warm relationships, respect, and security.
- Respondents engaged in strategies to achieve or maintain body shape.
- Respondents experience guilt when they have consumed what are perceived to be the wrong foods.
- Respondents punish themselves by avoiding food, skipping meals, dieting, and exercising.

Definitions of Key Terms

Body image: Refers to personal perceptions of the way our bodies appear, which we form in our minds.

Vanity: Refers to a fixation that can involve both physical appearance and the achievement of personal goals.

Personal values: Enduring, inherent values that guide our actions and judgment in specific situations. In the consumption process, personal values lead the consumer beyond immediate goals to end states of existence.

Mixed methods: Mixed method studies involve both qualitative and quantitative data collection methods studies. In general, a qualitative phase is used to collect data on an unexplored topic and the results are used to conduct a more comprehensive quantitative study.

Non-probability sampling: Non-probability sampling is a sampling technique that does not involve random selection but rather selects respondents on the basis of what they can contribute to the research. In most cases, a purposive sample is obtained by selecting respondents with specific characteristics (e.g., age and gender) to provide insights into a particular phenomenon.

References

Anderson A, Millburn K, Lean M. In: Marshall D, editors. Food choice and the consumer. London: Blackie Academic & Professional; 1995. pp. 105–29.

Beatty SE, Kahle L, Homer P, Misra S. J Psychol Marketing. 1985;2:181–200.

Blamey RK, Braithwaite VA. J Sustain Tourism. 1997;5:29–45.

Bourdieu P. Distinction: a social critique of the judgement of taste. London: Routledge and Kegan Paul; 1986.

Center for Science in the Public Interest. A diners guide to health and nutrition claims on restaurant menus. Washington DC: Center for Science in the Public Interest; 1997.

Chang KC, editor. Food in Chinese culture: anthropological and historical perspectives. New York: Yale University Press; 1977.

Douglas M. The Annual Report of the Russell Sage Foundation (1977–1978). New York: Russell Sage; 1978.

Flandrin JL, Hyman P. Food foodways. 1984;Sample issue:1–32.

Getley A. VCE human development, 2nd edn. Melbourne: Macmillan; 1995.

Goody J. Cooking cuisine and class: a study in comparative sociology. Cambridge: Cambridge University Press; 1982.

Goward P. Body image and eating awareness. Melbourne: The Victorian Health Promotion Foundation; 1993.

Hall J, Lockshin L, O'Mahony GB. Int J Wine Market. 2001;13:36–53.

Jago L. The analysis of values in major events. Unpublished doctoral thesis. Melbourne: Victoria University; 1998.

Kahle LR. Social values and social change: adoption to life in America. New York: Warner; 1983.

Kahle LR. J Market. 1986;50: 37–47.

Kamakura W, Wagner A, Mazzon, JA. J Consumer Res. 1991;18:208–18.

Kamakura WA, Novak TP. J Consumer Res. 1992;19:119–32.

Keane A, Willetts A. Nutrition Food Sci. 1994;94:5–17.

Koval, R. Eating your heart out: food, shape and the body industry. Australia: Penguin; 1986.

Kozup JC, Creyer EH, Burton S. J Market. 2003;67:19–34.

Lightstone J. Improving; 1999. www.ualberta.ca.

Marshall D. Food choice and the consumer. London: Chapman & Hall; 1995.

Mikela J. In: Meiselman HL, editors. Dimensions of the meal: the science, culture, business, and art of eating. Gaithersburg: Aspen; 2000; pp. 7–18.

Mennell S. All manners of food. London: Blackwell; 1985.

Muller TE. J Int Consumer Market. 1989;1:57–79.

Netemeyer RG, Burton S, Lichtenstein DR. J Consumer Res. 1995;21: 612–26.

O'Mahony GB, Hall JA. J Hospitality Tourism Manage. 2007;13:57–69.

O'Mahony GB. J Hospitality Tourism Manage. 2004;1:19–27.

Pyke M. Food science and technology. London: John Murray; 1970.

Raats M, Daillant-Spinnler B, Deliza R, MacFie H. In Marshall D, editor. Food choice and the consumer. London: Blackie Academic & Professional; 1995. pp. 239–62.

Rokeach M. Beliefs attitudes and values. San Francisco: Jossey Bass; 1968.

Rozin P. In: Meiselman HL and MacFie HJ, editors. Food choice, acceptance and consumption. London: Blackie Academic & Professional; 1996. pp. 83–104.

Rozin P. Psychol Today. 2000;33:48–56.

Sassen S. Globalisation and its discontents: essays on the new mobility of people and money. New York: The New Press; 1998.

Sherratt A. Drugs in History and Anthropology, Eds. J. Goodman, P. Lovejoy and A. Sherratt, Routledge, London 1995.

Stockley L. The Food Network, London 1991.

Thompson SB. Eating disorders: a guide for health professionals. London: Chapman & Hall; 1990.

Thompson JK. Body image, eating disclosure, and obesity. Washington, DC: American Psychological Association; 1997.

Vinson DE, Scott JE, Lamont LM. J Market. 1977;41:44–50.

Visser M. Much depends on dinner. Toronto: McClelland & Stewart; 1986.

Visser M. The rituals of dinner: the origins, evolution, eccentricities, and meaning of table manners. New York: Penguin Books; 1992.

Wright LT, Nancarrow C, Kwok PM. Br Food J. 2001;103:348–57.

Chapter 201
Factors Influencing Body Image During Adolescence

Rheanna N. Ata, Ariz Rojas, Alison Bryant Ludden, and J. Kevin Thompson

Abbreviations

BMI   Body mass index
SEM   Structural equation modeling
SES   Socioeconomic status

201.1 Introduction

Over the years, research has implicated a number of developmental (e.g., pubertal timing), psychological (e.g., self-esteem), and sociocultural (e.g., culturally-defined and transmitted messages regarding attractiveness) factors in the development and maintenance of body image disturbance and related issues in adolescents. In this chapter, we will focus exclusively on sociocultural factors that affect adolescent body image, using the Tripartite Influence Model of body image and eating disturbance as our conceptual framework. We will begin by providing some background information on body image and body image disturbance, and offer an explanation as to why adolescents may be particularly vulnerable to the latter. Then, we will explicate the role of the media in transmitting messages to adolescents regarding culturally defined and encouraged images of attractiveness that suggest that females have thin bodies and males have lean, muscular bodies. Next, we will discuss the direct and indirect influences of parents and peers, including appearance-related teasing and criticism and modeling of eating- and weight-related behaviors, which may serve to reinforce media-transmitted messages. Finally, we will highlight the role of cultural factors such as acculturation and the connection between body image disturbance and other areas of health.

201.2 Body Image and Body Image Disturbance

Defining body image is so "tricky" that Thompson et al. (1999) pointed out the existence of 16 different terms used interchangeably by researchers and clinicians (Table 201.1). The common consensus, however, is that body image is a complex, multidimensional construct (Thompson et al. 1999)

R.N. Ata (✉)
Department of Psychology, University of South Florida,
4202 E. Fowler Avenue, PCD 4118G, Tampa, FL 33620-8200
e-mail: rata@mail.usf.edu

Table 201.1 Terms used interchangeably with "body image"

Weight satisfaction	Body dysphoria
Size perception accuracy	Body dysmorphia
Body satisfaction	Body schema
Appearance satisfaction	Body percept
Appearance evaluation	Body distortion
Appearance orientation	Body image
Body esteem	Body image disturbance
Body concern	Body image disorder

This table lists the 16 terms commonly used interchangeably with "body image". For definitions of these terms refer to: Thompson et al. (1999)

that relates to how an individual feels about and perceives his/her body. Body image is believed to play a vital role in determining one's quality of life (Cash 1994) and is influenced by physiology, psychological factors, and society (Rierdan and Koff 1997). Body image disturbance has been measured by examining cognitive components, such as negative attitudes about the body or unrealistic expectations for appearance; behavioral components, such as avoiding perceived body scrutiny from others (e.g., avoiding being seen in a bathing suit); and perceptual components where body size perceptions are evaluated (Thompson et al. 1999).

201.3 Adolescence as a Period of Increased Vulnerability

Although body image disturbance and eating disorders can theoretically develop in any individual, they tend to be most prevalent among adolescents (Table 201.2). While puberty strictly refers to the period during which adolescents gain reproductive capability, it encompasses all physical changes experienced by adolescents (Steinberg 2005). One important physical change associated with puberty is the change in body composition. While body fat increases in both sexes during puberty, the increase for girls is faster and much more obvious (Steinberg 2005). Thus, even when they are within a healthy weight-range, adolescent girls may become overly concerned with their weight and appearance.

Changes in body composition lead to changes in appearance and self-image, which can lead to changes in behavior (Steinberg 2005). Whether the biological changes brought about by puberty cause the individual to look more attractive or more awkward, changes in appearance may lead to changes in the way others view and react to the adolescent. Unfortunately, the impact of this attention may cause the adolescent to become confused and self-conscious in his/her new body. While boys move from a "culturally undesirable state" during puberty to a culturally encouraged one – from being short and thin to tall and muscular – girls undergoing puberty lose the thinness associated with prepubescent adolescence (Steinberg 2005). This is a great loss, given the emphasis the society in which we live places on physical attractiveness in the form of a thin figure.

The physical changes associated with puberty are not the only changes responsible for the increased susceptibility of adolescents to body-related concerns. Due to cognitive changes associated with puberty, adolescents' thinking becomes less grounded in fact and more highly based on deductive reasoning (e.g., Wiseman et al. 2005). Thus, if adolescents perceive something to be a desired behavior or image, they may deduce that their acceptance by others depends on whether they are able to imitate the desired behavior or image. Adolescents' belief that everyone is watching and judging them stems from their newfound ability to think about thinking, or engage in metacognition.

Table 201.2 Key features of adolescence

1. Puberty is marked not only by changes in:
    (a) Body composition
    (b) Primary and secondary sex characteristics
    (c) Circulatory, endocrine, respiratory, and other systems within the body; but also by increased awareness among adolescents of how their own bodies look in comparison with their peers' bodies
2. Cognitively, adolescents are able to reason at a higher level, able to take account of multiple perspectives as they make decisions; however, they may be hindered in their decision-making by:
    (a) Continuing development of the frontal cortex of the brain and an overactivation of the limbic system, which may be associated with heightened emotions (Steinberg 2008)
    (b) A tendency toward egocentrism, which is associated with heightened self-consciousness and a feeling that one is unique or special (Steinberg 2008).
3. As a result of physical maturation, increasing social pressures, and emerging personal values and decision-making abilities, adolescents are faced with new developmental tasks (Havighurst 1952) that relate to social interactions such as:
    (a) Forming relationships with peers of both sexes
    (b) Appreciating one's body
    (c) Achieving emotional independence
    (d) Understanding one's social role as a man or woman
    (e) Engaging in socially responsible behavior
4. However, "storm and stress" is more likely to be heightened during adolescence as compared to childhood or adulthood (Arnett 1999); it is characterized by:
    (a) Conflicts with parents
    (b) Mood disruptions
    (c) High rates of risk behaviors

This table provides a brief description of the physical, cognitive, and social/behavioral changes associated with adolescence

According to Elkind (1967), this ability not only leads to increased introspection and self-consciousness, but also to self-absorption or adolescent egocentrism. Elkind defines adolescent egocentrism as the inability to discriminate between one's own cognitions and concerns and those of others. Adolescents falsely believe that their behavior and appearance are the focus of everyone else's attention (Elkind 1967) and, thus, may feel the need to look a certain way in order to be accepted and judged positively by those around them.

201.4 An Overview of the Tripartite Model

Sociocultural theories of body image disturbance "examine the influence of common or culture-wide social ideals, expectations, and experiences on the etiology and maintenance of body image disturbance" (Heinberg 1996, p. 32). Although the majority of sociocultural influence research has focused on the impact of the media, it is important to note that messages portrayed therein are not the sole contributors to body image disturbance and disordered eating among adolescents. All adolescents are exposed to the media, but not all develop poor body image and/or disordered eating patterns. Individual differences may be accounted for by more proximal influences. Messages portrayed by the media become particularly problematic when they are reinforced by more immediate sociocultural agents such as parents (Dunkley et al. 2001) or peers.

Recent work in our lab has focused on testing a theoretical model that includes a variety of sociocultural factors. Our model, the Tripartite Influence Model (Table 201.3), asserts that three formative influences (family, peers, media) lead to the development of body dissatisfaction and eating disturbances

Table 201.3 Key features of the Tripartite Model

1. Media, parental, and peer influences can lead to the development of body dissatisfaction and eating disturbances directly, and also indirectly, through internalization and comparison.
2. Internalization of appearance ideals and comparison to others (especially upward comparisons to those who are more attractive, thinner, etc.) can lead to increased body dissatisfaction.
3. Body dissatisfaction is associated with increased disordered eating behaviors (i.e., restriction and bulimia). It is also related to psychological distress and more severe forms of psychopathology.

This table describes the key features of the Tripartite Model and how, according to this model, influences such as those exerted by the media, parents, and peers can lead to increased body dissatisfaction among adolescents
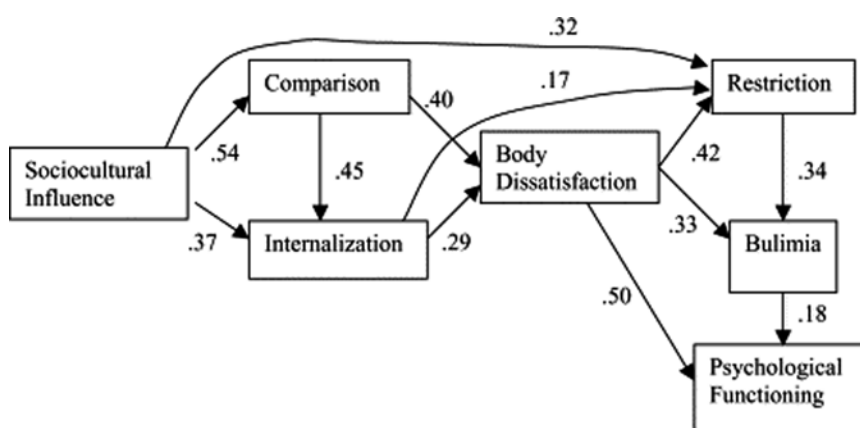

Fig. 201.1 The Tripartite Influence Model of body image and eating disturbance: Final SEM model with standardized path coefficients (Reprinted from Keery et al. 2004. Copyright (2004), with permission from Elsevier). *SEM* structural equation modeling

directly, and also indirectly, through two mediational mechanisms (appearance comparison, internalization of appearance ideals) (Thompson et al. 1999). Appearance comparison refers to a tendency to compare one's own appearance to others – typically, the comparison is an upward comparison (i.e., to someone who is more attractive, thinner, etc.) and, therefore, is likely to lead to a decrease in appearance satisfaction. Internalization refers to a process whereby one has endorsed or brought into a message or view, to the point that it becomes part of their belief system. In terms of the internalization of appearance ideals, this means that someone believes that it is important to try to look like the ideal images promoted via the media.

We have conducted a series of studies with adults and adolescents using structural equation modeling (SEM) to test the directionality of the hypothesized relationships in the Tripartite Model (van den Berg et al. 2002; Keery et al. 2004; Shroff and Thompson 2006a). Figures 201.1 and 201.2 illustrate the findings from Keery et al. (2004) and Shroff and Thompson's (2006a) studies with two large samples of adolescent girls. In both cases, the data indicate that the formative influences have both a direct and mediated effect (through comparison and internalization) on body image and eating disturbance.

In the sections that follow, we provide a more detailed account of the research on the three formative influences that compose the Tripartite Model (media, parents, peers). These factors are actually multidimensional, involving many different social and interpersonal influences on an adolescent's body image.
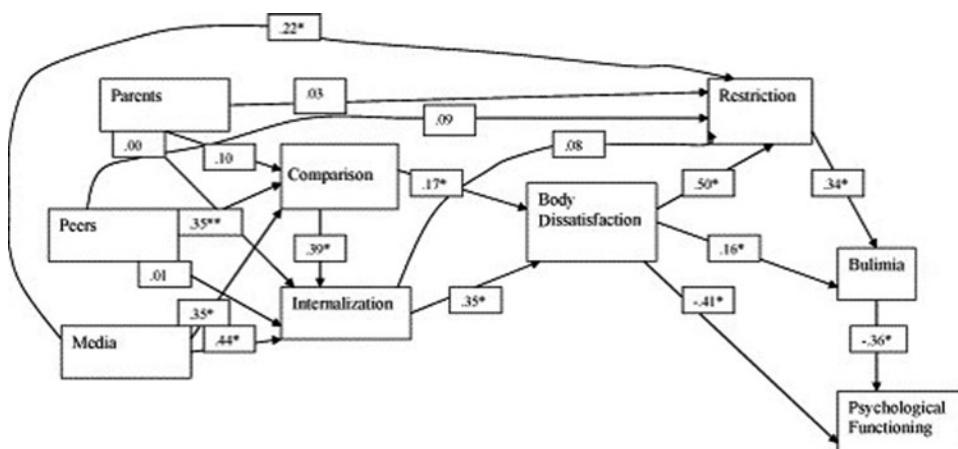
Fig. 201.2 The Tripartite Influence Model of body image and eating disturbance: Final SEM model. (Reprinted from Shroff and Thompson 2006a. Copyright (2006), with permission from Elsevier) *SEM* structural equation modeling

201.5 Media Influences

Over the last 20 years, a great deal of empirical work has documented the negative effects of media exposure to unrealistically thin images on body image dissatisfaction and eating disturbances (Thompson et al. 1999; Thompson and Smolak 2001; Smolak and Thompson 2009). Media exposure may consist of a variety of sources, including print media (e.g., magazines), TV, movies, and internet. In this section, we briefly review some of the large-scale studies to illustrate descriptively some of the effects then turn our attention to the recent work consisting of prospective investigations.

Young girls are often exposed to magazines that contain unrealistic images of thinness and attractiveness, along with messages that it is important for them to focus on appearance (Cusumano and Thompson 1997). In fact, surveys suggest that perhaps 50% of elementary school girls read teen magazines weekly (Thompson and Smolak 2001).

A large-scale study by Field et al. (1999) examined over 6,900 adolescent girls (aged 9–15) and found that frequency of reading of women's fashion magazines was associated with the intensity of their weight concerns. Grigg et al. (1996) surveyed over 800 Australian adolescent girls and found that 87% wanted to look like the media-promoted slender ideal.

Young girls and boys are also exposed to images and messages regarding the importance of appearance through television and movies. A relatively new form of media, the internet, provides another route for exposure. Although there is no research to date on the internet with young individuals, research with college students indicates that young women often seek out sites (pro-anorexia and pro-eating disorder) that contain information that glamorizes thinness (Harper et al. 2008) and this exposure is correlated significantly with body dissatisfaction.

In perhaps the most comprehensive prospective study to date, Field et al. (1999) conducted follow-up studies at 1 and 7 years with her original sample (Field et al. 2001, 2008). These researchers found that a key predictor of the onset of weight concerns at 1 year was wanting to look like media figures. At 7 years, attempting to look like these media images and dieting predicted the onset of binge-eating. Dohnt and Tiggemann (2006) evaluated very young girls (5–8) prospectively, finding that the viewing of appearance-oriented TV, but not magazines, predicted a decrease in body image satisfaction 1 year later.

Research on the effects of media on body image has largely been focused on adults (see Thompson 2009) and this work has clearly documented the negative effects on body image, via correlational, experimental, and prospective analyses (see Levine and Murnen 2009). This type of conclusion cannot currently be made based on the rather limited work with adolescents (see above); however, the emerging evidence is suggestive of a strong influence on body image. The findings noted earlier with the Tripartite Model (Keery et al. 2004; Shroff and Thompson 2006a) and the recent prospective studies (Dohnt and Tiggemann 2006; Field et al. 2008) are encouraging developments in this area of research that require replication and extension.

One of the limitations of work in this area is that many studies use a single measure of media. In actuality, there are many different dimensions of media influence, including: exposure to images (or messages), gathering information from media sources, feeling pressure from media, and internalizing media influences. In our work, we have conceptualized media as multidimensional and developed scales to capture multiple components through our Sociocultural Attitudes Towards Appearance Questionnaire (Thompson et al. 2004). A multidimensional assessment model of media influence should be considered by researchers for future work in the area of media and adolescent body image.

201.6 Parental Influences

Although youth tend to turn away from their parents and toward their peers for advice and guidance during adolescence, research suggests that "parental relationships retain their relevance and remain a powerful predictor of adolescent body dissatisfaction" (Bearman et al. 2006, p. 238). Parental behavior may influence adolescents' body image and weight-related behaviors either directly (e.g., appearance-related commentary and teasing, encouragement to diet) or indirectly (e.g., modeling of weight-related behaviors, parent–adolescent relationship). In the following sections, we review the research on the various direct and indirect ways that parents may affect adolescents' body image (Table 201.4).

201.6.1 Appearance-related Feedback and Commentary

In an attempt to determine the origins of appearance-related feedback and commentary received by adolescents, McCabe et al. (2003) conducted a series of in-depth interviews with 40 adolescent boys

Table 201.4 Examples of parental influences on adolescents' body image

Direct influences
Appearance-related teasing and criticism
Pressures to modify appearance (e.g., encouragement to lose weight)
Indirect influences
Social support/connectedness
Parent body mass index (BMI)
Parent body image
Parent–adolescent relationship
Modeling of disordered eating and appearance concerns

This table lists potential parental influences on adolescents' body image. The influences have been divided into those that are directly related to adolescents' weight and/or appearance and those that are believed to exert a more indirect effect

and 40 adolescent girls. They found that when parents make comments about their children's bodies, they tend to focus on the overall appearance of their daughters' versus the functionality of their sons' bodies. Most maternal comments were considered by their daughters and sons to be positive, encouraging, and supportive. While the majority of girls also reported receiving messages from their fathers in regards to their bodies, very few boys reported having received such messages. When messages from fathers were received, they were also categorized as primarily positive and supportive.

When negative messages were received by girls, they tended to interpret them as being supportive (mothers) or downplayed their seriousness (fathers; McCabe et al. 2003). Overall, girls reported a higher number of negative messages (73 total) than boys (13 total), which led the researchers to conclude that boys may be protected from such messages. Another possible explanation is that boys may be less attuned to such messages and, therefore, less likely to detect them than girls (McCabe et al. 2003). In fact, when adolescent boys were asked to describe the extent to which they felt their parents, siblings, friends, and the media influenced their feelings about their bodies, the majority of the boys claimed that none played an important role in determining their body image (Ricciardelli et al. 2000). A minority of the boys reported that their mothers (25%) and fathers (25%) exerted some influence on their feelings about their body shape and size. Messages about muscles from fathers have been related to boys' body image and satisfaction with body parts; messages from mothers about shape have been found to predict the latter (Stanford and McCabe 2005).

General feedback from mothers and fathers on the size and shape of their children's bodies has been found to predict body image satisfaction in their daughters and sons, respectively (McCabe and Ricciardelli 2003). These results provide some evidence for the gender-linked transmission model, which posits that fathers exert greater influence on sons and mothers exert greater influence on daughters (Wertheim et al. 1999). Earlier research that suggests that increased paternal commentary is associated with increased weight dissatisfaction among adolescent girls (Keel et al. 1997), and more recent research that suggests that maternal commentary is associated with increased weight and body dissatisfaction among adolescent boys (Vincent and McCabe 2000; Stanford and McCabe 2005), are inconsistent with this model.

201.6.2 Teasing and Criticism

Appearance-related teasing is another direct influence that can have adverse effects on adolescent body image. According to a retrospective study, 72% of female college students indicated that they had experienced appearance-related teasing or criticism during childhood or adolescence (Cash 1995). Participants further indicated that these experiences were moderately (29%) or more (42%) upsetting and that they occurred over an average period of approximately 6 years. Given the average length of time to which females were subject to these events, and the fact that facial features and weight (i.e., heaviness) were the primary targets, it is not surprising that 71% of participants reported that their current perceptions and feelings about their bodies were at least partially affected by their experiences of teasing.

In terms of offenders, some of the worst teasers tend to be family members. In one study, 23% of adolescent girls reported having at least one parent who teased them about their appearance (Keery et al. 2005). Results are mixed, however, when it comes to the frequency of teasing by mothers versus fathers. Retrospective accounts by female college students suggest that mothers not only tease more than fathers, but are also more likely to be deemed the worst of teasers (Cash 1995). Research conducted with adolescent females, however, indicates that fathers tease more than mothers and that modeling of such behaviors by fathers is associated with increased teasing by siblings (Keery et al. 2005).

Whether the teaser is the mother, father, or a sibling, girls who report teasing by family members score higher on measures on body dissatisfaction, social comparison, internalization of the sociocultural ideal of thinness, depression, and disordered eating. They also tend to report lower levels of self-esteem (Keery et al. 2005). It is important to note, however, that the "appraised severity of these interpersonal experiences – their perceived frequency, longevity, and emotional impact at the time" appears to be more influential in predicting body image than the mere presence or absence of teasing (Cash 1995, p. 127). Although less research has been conducted on the effects of teasing on boys, teasing by fathers and mothers about weight does not seem to predict adolescent boys' body image (Schwartz et al. 1999).

201.6.3 Modeling of Weight-related Behaviors

One particularly relevant form of weight-related behavior that parents model for their adolescents is dieting. While parent dieting did not predict increases in body dissatisfaction in early- or middle-adolescent girls or boys over a 5-year period (Paxton et al. 2006), such parental behavior has been associated with more behavioral indicators of body and weight concern. For instance, girls who report maternal dieting are more likely to have engaged in both healthy and unhealthy behaviors to control their weight than girls who do not report maternal dieting, even after controlling for body mass index (BMI), race, grade, and socioeconomic status (SES; Vincent and McCabe 2000; Keery et al. 2006). In a smaller sample of adolescent girls from New Zealand, maternal dieting did not influence daughters' dieting behaviors; however, girls who reported paternal dieting were more likely to have engaged in extreme weight control behaviors (i.e., skipping meals, crash dieting; Dixon et al. 1996).

201.6.4 Pressures to Modify Appearance

Parental modeling of dieting does not seem to be as important in predicting adolescent body- and weight-related attitudes and behaviors as encouragement to diet (Wertheim et al. 1999, 2002). Although most parents report that they never encourage their daughters to lose weight (mother 61%, father 58%), about a quarter of parents admit that they encourage their daughters to lose weight either sometimes (mother 14%, father 16%) or often (mother 11%, father 9%; Wertheim et al. 1999). While the aforementioned study focused exclusively on adolescent girls, more recent research suggests that sons and daughters are equally likely to be recipients of parental encouragement to diet (Wertheim et al. 2002).

Not surprisingly, encouragement to diet is highly correlated between mothers and fathers, indicating that parents are relaying similar messages and values to their adolescents about the importance of attaining the thin-ideal (Wertheim et al. 1999). Maternal encouragement, body-related compliments, dieting, and criticism, however, add unique predictive ability to models predicting adolescent girls' eating behaviors – even after controlling for the same paternal variables. Furthermore, daughters' reports of maternal encouragement to lose weight predict daughters' eating behaviors above and beyond paternal reports of the same variables. These results suggest that while both parents play a role in reinforcing societal messages of attractiveness, mothers tend to exert greater influence on their daughters than fathers and – perhaps more importantly – daughters' perceptions of encouragement are more important than the actual presence or absence of encouragement (Wertheim et al. 1999).

More recent research further supports the role of mothers as the primary agents of their children's socialization. In two studies of Australian adolescents, perceived pressure from mother (Ricciardelli and McCabe 2001) and parent encouragement to lose weight (Ricciardelli and McCabe 2003) predicted body dissatisfaction in boys and girls. In contrast, pressure from father to lose weight was only predictive of body dissatisfaction in boys (Ricciardelli and McCabe 2001). Perceived pressure from family to lose weight was also associated with body image and eating attitudes and behaviors in a US sample of adolescents (Ata et al. 2007), but was not found to be predictive of body dissatisfaction among older adolescents prospectively (Presnell et al. 2004).

201.6.5 Parent–adolescent Relationship

Adolescents' perceptions of their relationships with their parents have been associated with their dieting attitudes and behaviors and body image both concurrently and longitudinally. Short-term (i.e., 1-year follow-up) longitudinal research with early-adolescent girls indicates that parental relationships that are lower in warmth and higher in conflict are associated with less healthy dieting and a more negative body image, while more positive parental relationships are associated with a more positive body image (Archibald et al. 1999). A more recent study, that followed adolescents over a period of 3 years, found that decreases in mothers' intimacy and increases in mother–daughter conflict were related to increased weight concerns among girls across the course of adolescence (May et al. 2006). Similarly, girls, but not boys, who report greater parent–child connectedness (i.e., extent to which they perceive love from and closeness to their parents) and acceptance by their mothers and fathers appear to be less dissatisfied with their bodies concurrently (Barker and Galambos 2003) and over a period of 5 years (Boutelle et al. 2009). While the mother–son relationship does not appear to affect boys' weight concerns, conflict with fathers has been associated with increased weight concerns in adolescent boys and girls (May et al. 2006). The more prominent connection between parent–adolescent relationships and girls', as compared to boys', body concerns may be due to the relatively greater importance emotional support (especially from mothers) and connectedness play in the development of female adolescents (Geuzaine et al. 2000).

201.6.6 Concluding Points

Although the research is not entirely consistent in terms of whether mothers or fathers play the most salient role, it is clear that parents can affect adolescent body image. The mechanisms by which parents may exert influence can be either direct or indirect. Regardless of whether parents are reinforcing societal messages via modeling or teasing, it is important to keep in mind that "young people's *perceptions* of parents' weight-related attitudes and behaviors may be more relevant to adolescent body dissatisfaction, weight concerns, and weight control behaviors than parents *actual* attitudes and behavior" (Keery et al. 2006, p. 106).

201.7 Friend/Peer Influences

During adolescence, both males and females become more peer-oriented, as reliance on friends for support and approval increases significantly. With this increased intimacy comes the sharing of thoughts and behaviors among friends. Close friends are likely to be similar both in terms of their

body image and their eating behaviors during adolescence (Paxton et al. 1999; Hutchinson and Rapee 2007). Cliques may be a key place where adolescents generate their own body image perceptions. Adolescents are in a social context where it is easy to compare themselves to peers in relation to their eating behaviors and the way that they talk and think about their own bodies. Not only do peers have an influence on adolescents' body perceptions in these direct ways, but also the peer social context can indirectly influence body perceptions and attitudes. For example, concerns about attracting romantic partners, finding friends, or participating in sports with peers may engender an orientation to one's body or appearance. Friends influence adolescents' body image by eliciting appearance-related cognitions through direct means by causing social comparisons, engaging in appearance-related conversations, modeling eating behaviors, and through teasing, and also through indirect means by engaging with adolescents in a social context where they may become more aware of their appearance. In the following sections, we outline the various direct and indirect ways that peers affect adolescents' attitudes about their appearance and their bodies.

201.7.1 Social Comparisons

Even what we have called the direct effects of social comparisons with peers can vary in how directly peers influence one another. Friends may make comparisons for adolescents (i.e., "I think those jeans look much better on her than on you") or adolescents may observe their peers and make the comparisons themselves (i.e., "I wish that I could wear those skinny jeans that my friend has"). We will discuss the direct comparisons made by others below under the section on teasing and criticism. These influences are not unrelated, however. When adolescent girls report that they are teased by their friends about their appearance, that their friends are preoccupied with weight and dieting, that they often have conversations about appearance with their friends, and that they see their friends as key influences on their ideas about weight loss and the perfect body, they are more likely to compare their own appearance to the appearance of others (Shroff and Thompson 2006b). In fact, Shroff and Thompson (2006b) found that higher levels of social comparisons help to explain the links between peer influence (i.e., peer teasing, preoccupation, conversations) and adolescent girls' body dissatisfaction. When adolescent girls individually report making more social comparisons, their body image concerns are higher; in addition, when friendship groups are characterized by having higher levels of social comparisons, friends in the group are more likely to be dissatisfied with their bodies (Paxton et al. 1999).

201.7.2 Appearance-related Conversations

Focus group research with early adolescent girls indicates that "fat talk," namely discussion about body shape inadequacy that often includes the "I'm so fat" statement, is common discourse and helps to bond girls together (Nichter 2000, p. 46). Adolescents may actually feel pressure from peers to engage in this fat talk; however, whether they actually engage in the conversation is related to adolescents' perceptions of their own bodies and their actual weight because they may not want to bring attention to their bodies when they are overweight or underweight (Nichter 2000). Fat talk is not the only type of appearance-related conversation among peer groups; and it is important to acknowledge that boys also have appearance-related conversations with friends (Jones et al. 2004). Adolescent boys who talk with friends about how their bodies look in clothes and what they would like their bodies to look like are more likely to internalize media ideals about muscularity, which is associated with greater

body image dissatisfaction (Jones et al. 2004). Adolescent girls who are more likely to talk with their peers about how they look generally – in terms of such topics as clothes and make-up or looking their best – in addition to body shape, are more likely to report low body-esteem, internalization of media messages about thinness, and body dissatisfaction (Jones et al. 2004; Clark and Tiggemann 2007). Clark and Tiggemann's (2007) cross-sectional research on early adolescent girls from Australia suggests that appearance schemas mediate this relationship between peer conversations and body dissatisfaction. They found that appearance-related conversations with peers enhance the salience of appearance in terms of self schemas and in terms of what adolescents spend their time thinking about, which then increases their body dissatisfaction (Clark and Tiggemann 2007). Their longitudinal research indicates that adolescents who engage in more appearance-related conversations with peers are also more likely to internalize appearance ideals and have more appearance-related self schemas 1 year later (Clark and Tiggemann 2008). Talking with friends about what to wear or about how one looks may prime adolescents to internalize negative messages and transfer cognitions about appearance to their understandings of self – these conversations may continue to have effects over time.

201.7.3 Teasing, Criticism, and Pressures to Modify Appearance

When adolescents share comments with peers about appearance, these experiences can be particularly damaging to adolescents' body image when they receive criticism or are teased about their appearance. Both boys and girls who report that they are teased by same-sex and opposite-sex peers – either about the size, shape, or build of their bodies, or specifically about their weight for girls or muscularity for boys – are more likely to report increased internalization of media ideals and body image dissatisfaction (Jones et al. 2004). This research suggests that teasing from family and peers reinforces the societal value of appearance and emphasizes desirable physical attributes (Jones et al. 2004). As previously mentioned, retrospective research by Cash (1995) involving female college students suggests that it is the frequency, longevity, and emotional impact of the teasing that is associated with adolescents' feelings about their bodies. Notably, male adolescents perceive appearance-related pressure and teasing at levels that are similar to or higher than females (Jones and Crawford 2006), and appearance-related criticism by peers is significantly positively related to boys', as well as girls', body dissatisfaction (Jones et al. 2004). Research on boys from middle and high schools in China revealed that adolescents who perceive more sociocultural pressures from peers, parents, or the media related to appearance and more appearance-related teasing were more likely to report concerns about being fat (Jackson and Chen 2008). Perceptions of the evaluations of others may be just as important as actual criticism in terms of the effects on adolescents' body image, as this perceived evaluation may influence body image by increasing the feelings of pressure perceived by adolescents to modify their appearance (Ata et al. 2007). For both boys and girls, feeling pressures from peers and family to either lose weight or gain muscle is associated with a greater discrepancy between their actual body size and shape and their ideal body size and shape (i.e., what they'd like their bodies to look like; Ata et al. 2007).

201.7.4 Modeling of Eating Behaviors

Along with having conversations about food and being exposed to appearance-related criticism, the peer group is likely to be the place where disordered eating is modeled, particularly among girls. In friendship cliques of girls characterized by high levels of dieting and extreme weight loss behaviors, as well as heightened concerns and conversations about weight and dieting, social comparisons, and

pressures from peers to be thin, members of the clique, on average, have more body image concerns and more disordered eating (Paxton et al. 1999; Hutchinson and Rapee 2007). Girls' own levels of dieting and extreme weight-loss behaviors can be predicted from their friends' self-reports of their eating behaviors (Hutchinson and Rapee 2007).

201.7.5 Indirect Effects of Peer Social Contexts

The social context of peers may also be an environment where, indirectly, adolescents may become more attuned to how they appear in front of others. For adolescents, simply wanting to be accepted by peers and to fit in may be associated with a desire to change their appearance. Lower peer acceptance, perceived social support, and friendship intimacy are associated with poor body image among adolescent females (Gerner and Wilson 2005). In contrast, having social support from friends and acceptance may help adolescents rise above sociocultural pressures and feel more positively about their bodies by fostering resilience (Stice et al. 2002; Ata et al. 2007).

Social situations, like romantic relationships or engaging in sports, may bring appearance concerns to the forefront. Girls who are romantically involved with boys have poorer body image than those who are not romantically involved (Compian et al. 2004). When adolescent girls perceive that being thin will positively impact their friendships with boys (e.g., popular boys will like them more; they will be more popular among boys and gain more recognition among male friends), they are more likely to have body image concerns and experience body dissatisfaction (Gerner and Wilson 2005).

For boys, the social context that is particularly likely to bring about body dissatisfaction is sports. Adolescent boys who express body dissatisfaction or a desire to modify their bodies are more likely to do so in the context of their experiences participating in a particular sport (Ricciardelli et al. 2006). It may be that boys perceive that it is more socially acceptable to express these concerns in relation to sports, as opposed to other situations such as romantic relationships.

201.7.6 Concluding Points

As seen in Table 201.5 and in the previous sections, peers may influence adolescents' body image in both direct and more indirect ways. Based on the research summarized above, it is clear that adolescents

Table 201.5 Examples of peer influences on adolescents' body image

Direct influences of peers through interactions and modeling
Social comparisons
Appearance-related conversations
Appearance-related teasing and criticism
Pressures to modify appearance
Modeling of disordered eating and appearance concerns
Indirect influences of peer social contexts
Social support
Romantic relationships
Sports

This table lists potential peer influences on adolescents' body image. The influences have been divided into those that are believed to exert a direct effect through interactions between adolescents and their peers and peer-modeling, and those such as social contexts, which are believed to exert a more indirect effect

care very much about how they think their peers view them, and there is a strong link between adolescents' perceptions of their peers' appraisals and how adolescents feel about their own bodies. Worrying about fitting in with peers in general, seeking relationships with same-sex and opposite-sex peers, and participating in different activities with peers may also bring about appearance-related concerns; however, social support and close friendships may serve to help adolescents cope with pressures and to feel better about their bodies.

201.8   Cultural Factors

Historically, researchers have focused on body image concerns in predominately White/Caucasian US samples with growing interest in the presentation differences among males and females. Yet, little research has focused on the racial and ethnic differences of body image in both males and females (Grabe and Shibley Hyde 2006) and there is growing awareness regarding the impact that social and cultural variables have on body dissatisfaction and disordered eating (Crago and Shisslak 2003). Earlier studies suggested that body image dissatisfaction was highest among White females; however, more recent findings have suggested that the incidence of disordered eating and body image concerns among cultural groups may vary according to age and acculturation status (Roberts et al. 2006) whereas others suggest that differences are minimal in adolescence (Shaw et al. 2004). Adolescence is a time when youth are particularly susceptible to the influence of culture, as many seek clarification of ethnic identity and attempt to align with culturally-dictated appearance norms. In the following sections, we review the literature regarding cultural factors influencing body image during adolescence (Table 201.6). Moreover, the influence of acculturation and acculturative stress in the context of body image dissatisfaction will be highlighted.

201.8.1   Cultural Factors by Race/Ethnicity

The majority of the literature comparing body image dissatisfaction among different race/ethnic groups has focused on Black–White differences in females. When compared to White adolescents, African-American adolescents report significantly lower awareness of appearance-related dominant societal standards and significantly lower internalization of those standards (Abrams and Cook Stormer 2002). A recent meta-analysis revealed that Black females demonstrated greater body image

Table 201.6   Examples of cultural factors influencing adolescents' body image

Racial/ethnic background

Caregiver educational attainment (socioeconomic status)

Acculturation (parental and adolescent)

Acculturative stress

Body mass index (BMI)

Peer group composition

Culturally-oriented television viewing

This table lists cultural factors that may influence adolescents' body image. Some of these factors are directly related to the adolescent (e.g., adolescent acculturation), while others exert indirect influences via the adolescent's parent(s)/caregiver(s) (e.g., socioeconomic status)

satisfaction (global and weight related) than White females across all effect sizes (Roberts et al. 2006). Moreover, studies have found greatest racial differences occurring during the early 20's (Roberts et al. 2002; Grabe and Shibley Hyde 2006), suggesting that later adolescence/young adulthood is a time of significant social comparison and interpretation or consolidation of ethnic norms. One explanation for the differences may lie in the cultural socialization of Blacks versus Whites. Whereas Black adolescents are more likely to describe the ideal woman in terms of personality traits (e.g., strong), White adolescents describe physical traits (e.g., hair and height) as preferable (Parker et al. 1995). Similarly, Black males tend to report a preference for a medium to larger frame and more satisfaction with and pride in their bodies than White males. However, Black adolescents may be more likely to engage in extreme weight loss and muscle gain strategies (Ricciardelli et al. 2007) and binge eating (Johnson et al. 2002) than White males.

Research investigating Hispanic adolescent females' body image is inconsistent; however, meta-analytic findings indicate that there are no differences between Hispanic and White females on measures of body dissatisfaction, with Hispanic females reporting higher body dissatisfaction than Black females (Grabe and Shibley Hyde 2006). Research on inpatient samples indentifies different findings. In comparison to Caucasian adolescent females, Hispanic and African-American females are less likely to report body image dissatisfaction and dietary restraint (White and Grilo 2005). Similar findings were reported by Barry and Grilo (2002), who found that Caucasian females displayed greater body disapproval and body image disturbance than Hispanic and African-American adolescents. Reports of body image in Hispanic adolescent males do not appear to differ from those of White males. Hispanic boys are more likely to participate in both normative and extreme weight loss strategies, binge eat, and engage in weight/muscle gain behaviors to a greater frequency than White males (Ricciardelli et al. 2007).

The general pattern of findings related to Asian adolescent females suggests that they maintain similar body image concerns as White females (Grabe and Shibley Hyde 2006). Research on Asian adolescent males is inconsistent and scarce, but implies no differences when compared to White males on measures of body image and weight loss. Asian males report binge eating and desire for weight gain more than White adolescent males (Ricciardelli et al. 2007).

A discussion regarding the impact of culture on body image is not complete without mentioning the intertwined effects of SES. While cultural upbringing influences subsequent internalized appearance-related norms, SES affects the extent to which these norms are reinforced and maintained. For example, Black and White adolescent females whose caregivers have higher educational attainment (college or greater) are more likely to report greater awareness of societal standards than girls with caregivers reporting lower educational attainment (high school or less; Abrams and Cook Stormer 2002).

Overall, research investigating racial and ethnic differences in body image is limited and future research is warranted. The existing literature suggests that Black and Hispanic females demonstrate greater body image satisfaction, less awareness, less internalization, but greater binge eating than White and Asian-American females. Less is known regarding males' attitudes and perceptions, but the findings to date are suggestive of similar weight-related concerns, increased muscularity, and binge eating in ethnic populations to a greater extent than White males.

201.8.2 Acculturation

At its most basic level, individual acculturation is defined as the resulting process when an individual from a different cultural background interacts with members of a receiving culture (e.g., mainstream). Following repeated interactions, the individual exhibits subsequent changes in beliefs, values,

and/or practices. While the process of acculturation is behavioral, there are psychological challenges and outcomes that result from the act of becoming acculturated. When there is some difficulty in the process, acculturative stress occurs, with major incompatibilities contributing to psychopathology (Berry 1997). Both cultural and psychological variables work to impact the level of acculturative stress.

The bulk of the literature examining the relationship between acculturation and body image has focused almost exclusively on Hispanic youth. Adolescents experiencing acculturative stress rate themselves as less physically attractive than White youth (Hawley et al. 2007). Hispanic youth who are at risk for being overweight or are overweight report greater body dissatisfaction than normal weight youth, with greater discrepancies occurring in male samples (Ayala et al. 2007). One reason for body image concerns in youth may be related to the US desire for thinness, which is less common in Hispanic cultures that value full-figured bodies. More acculturated youth have been found to prefer thinner figures than less acculturated youth, with females showing a stronger preference than males (Olvera et al. 2005). Hispanic adolescents who report greater agreement with socially prescribed norms of beauty and thinness are more likely to exhibit disordered eating and compensatory behaviors (Ayala et al. 2007). Patterns of body dissatisfaction also differ by gender. When compared with more acculturated males, Hispanic males who are less acculturated are more dissatisfied with their looks, perhaps due to the devaluation of the Hispanic appearance and internalization of the White thin ideal (Nieri et al. 2005). Finally, patterns in body image satisfaction are also influenced by the level of parental acculturation. As parents acculturate to the dominant culture, they are more likely to be influenced by media and societal norms regarding weight. For example, Olvera and colleagues (2005) found that mothers who were more acculturated preferred and rated thinner body types as more attractive than less acculturated mothers. As a result, girls of more acculturated mothers were more likely to select a thinner body type as the representative ideal. Thus, parent and adolescent acculturation and acculturative stress serve to influence body image satisfaction in Hispanic youth. More research is necessary to determine the impact of acculturative factors in other ethnic groups.

Aspects of acculturative stress may also be related to peer relationships and the media. As noted in the previous sections, peers and the media can have a significant influence on appearance-related concerns in adolescence. Along that line, peer group composition has been implicated in moderating the effects of race/ethnicity on body image perceptions. When adolescent females maintain a group of mixed racial/ethnic friends, they are more likely to report higher internalization of societal standards than those with less diverse friends. Moreover, African-American girls with mixed friends report higher awareness and internalization of appearance-related norms than African-American females without mixed friends, with similar trends occurring for Hispanic females (Abrams and Cook Stormer 2002). Thus, it is important to recognize that peer relationships work to magnify acculturative stress and body image dissatisfaction.

Additionally, it is well documented that mainstream television viewing is associated consistently with decreased body image in adolescents. Schooler (2008) found that when Hispanic girls viewed Black-oriented television frequently, they were more likely to report greater body image satisfaction. Therefore, when media features ideals that are supportive of cultural norms, body image concerns decrease.

201.8.3 Concluding Points

Cultural and acculturative factors influence the incidence of disordered eating and body image perceptions among ethnic youth. Adolescence is regarded as a time where culture may be incompatible

with societal norms. In turn, supportive networks are necessary in order to negate the message of thin as ideal.

201.9 Applications to Other Areas of Health

Research has clearly linked adolescents' body image, specifically body dissatisfaction, with a myriad of negative outcomes, including psychological distress and more severe forms of psychopathology. More specifically, body image has been linked to depression, negative affect, low self-esteem, eating disorders, and body dysmorphic disorder (Stice and Bearman 2001; McCabe and Ricciardelli 2003; Steinberg et al. 2004). Body image disturbance has also been associated with risky sexual behaviors (Gillen et al. 2006) and substance use (Palmqvist and Santavirta 2006).

201.10 Future Research

A wide variety of social and interpersonal influences have been shown to have an impact on adolescents' body image. The bulk of research has targeted three formative influences: media, peers, and parents. We reviewed a wide range of studies that evaluated one or more of these factors and the relationship with body image. There is a great deal of support for all three influences; however, many future research avenues remain open. For instance, although a few studies have evaluated the unique contribution of each of the three influences within one study (e.g., Keery et al. 2005; Shroff and Thompson 2006a), much more work needs to be done in this regard with younger samples, boys, different ethnicities, and cross-culturally. Additionally, few studies use a wide range of indices of sociocultural influence, limiting the ability to discern which particular aspect of media, peer, or parental influence is uniquely associated with body image disturbance. Finally, we need much more prospective and experimental work; to date, the great majority of work has been of a correlational nature.

Summary Points

- Body image issues can develop at any point throughout the lifespan, but are most common during adolescence.
- Sociocultural theories of body image disturbance examine the influence of factors such as parents, peers, and the media.
- Peer and parent influences on adolescent body image can be either direct (e.g., appearance-related teasing) or indirect (e.g., via social context).
- The media contribute to adolescent body image by transmitting messages regarding culturally-defined ideals of attractiveness.
- Existing research on racial and ethnic differences in body image suggests that Black and Hispanic females demonstrate greater body image satisfaction and binge eating than White and Asian-American females.
- Body image disturbance has been linked to eating disorders, depression, negative affect, low self-esteem, risky sexual behavior, and substance use.

Definitions

Acculturation: Behavioral processes whereby one adapts to a new culture; can lead to subsequent changes in beliefs, values, and/or practices.

Acculturative stress: Psychological tension that may be experienced as a result of difficulties encountered during acculturation.

Adolescence: Developmental period typically considered to range from age 13–17.

Appearance comparison: Comparing of one's appearance to the appearance of another in order to derive information about the former.

Body mass index: One of the most commonly used measures of overweight and obesity, calculated by dividing a person's weight (in kilograms) by their height (in meters squared).

Body image: Broad concept including feelings, thoughts, and perceptions about one's body.

Body dissatisfaction: The affective component of body image.

Body image disturbance: Poor body image characterized by negative feelings about one's body or appearance.

Body dysmorphic disorder: Psychological disorder characterized by obsession with a perceived flaw in one's appearance.

Internalization: Incorporation of socially transmitted messages into one's self-concept.

Socioeconomic status: Relative social standing based on factors including education and income.

References

Abrams LS, Cook Stormer C. J Youth Adolesc. 2002;31:443–50.

Archibald AB, Graber JA, Brooks-Gunn J. J Res Adolesc. 1999;9:395–415.

Arnett JJ. Am Psychol. 1999;54:317–26.

Ata RN, Ludden AB, Lally MM. J Youth Adolesc. 2007;36:1024–37.

Ayala GX, Mickens L, Galindo P, Elder JP. Ethn Health. 2007;12:21–41.

Barker ET, Galambos NL. J Early Adolesc. 2003;23:141–65.

Barry DT, Grilo CM. Int J Eat Disord. 2002;32:335–43.

Bearman SK, Presnell K, Martinez E, Stice E. J Youth Adolesc. 2006;35:229–41.

Berry JW. Appl Psychol Int Rev. 1997;46:5–34.

Boutelle K, Eisenberg ME, Gregory ML, Neumark-Sztainer D. J Psychosom Res. 2009;66:309–16.

Cash TF. In: Cash TF, Pruzinsky T, editors. Body image: a handbook of theory, research, and clinical practice. New York: The Guilford Press; 1994, p. 269–276.

Cash TF. Soc Behav Pers. 1995;23:123–9.

Clark L, Tiggemann M. J Clin Child Adolesc. 2007;36:76–86.

Clark L, Tiggemann M. Dev Psychol. 2008;44:1124–34.

Compian LL, Gowen LK, Hayward C. J Res Adolesc. 2004;14:23–47.

Crago M, Shisslak CM. Eat Disord. 2003;11:289–304.

Cusumano DL, Thompson JK. Sex Roles. 1997;37:701–21.

Dixon R, Adair V, O'Connor S. J Adolesc Health. 1996;19:303–7.

Dohnt H, Tiggemann M. Dev Psychol. 2006;42:929–36.

Dunkley TL, Wertheim EH, Paxton SJ. Adolescence. 2001;36:265–78.

Elkind D. Child Dev. 1967;38:1025–34.

Field AE, Camargo CA, Jr, Barr Taylor CB, Berkey CS, Frazier L, Gillman MW, Colditz GA. J Am Academy Child & Adolesc Psychiatr. 1999;38:754–60.

Field AE, Camargo CA, Jr, Barr Taylor C, Berkey CS, Roberts SB, Colditz GA. Pediatr. 2001;107:54–60.

Field AE, Javaras KM, Anea P, Kitos N, Camargo CA, Jr, Taylor CB, Laird NM. Arch Pediatr Adolesc Med. 2008;162:574–9.

Gerner B, Wilson PH. Int J Eat Disord. 2005;37:313–20.

Geuzaine C, Debry M, Liesens V. J Youth Adolesc. 2000;29:79–91.

Gillen MM, Lefkowitz ES, Shearer CL. J Youth Adolesc. 2006;35:243–55.

Grabe S, Shibley Hyde J. Psychol Bull. 2006;132:622–40.

Grigg M, Bowman J, Redman S. Prev Med. 1996;25:748–56.

Harper K, Sperry S, Thompson JK. Int J Eat Disord. 2008;41:92–5.

Havighurst RJ. Developmental tasks of adolescence. In: Developmental tasks and education. New York: David McKay Co.; 1952. Chapter 5, p. 33–71.

Hawley SR, Chavez DV, St Romain T. Hispan J Behav Sci. 2007;29:283–99.

Heinberg LJ. In: Thompson JK, editor. Body image, eating disorders, and obesity: An integrative guide for assessment and treatment. Washington, DC: American Psychological Association; 1996. p. 27–47.

Hutchinson DM, Rapee RM. Behav Res Ther. 2007;45:1557–77.

Jackson T, Chen H. J Adolesc Res. 2008;23:154–71.

Johnson WG, Rohan KJ, Kirk AA. Eat Behav. 2002;3:179–89.

Jones DC, Crawford JK. J Youth Adolesc. 2006;35:257–69.

Jones DC, Vigfusdottir TH, Lee Y. J Adolesc Res. 2004;19:323–39.

Keel PK, Heatherton TF, Harnden JL, Hornig CD. J Treat Prevent. 1997;5:216–28.

Keery H, Boutelle K, van den Berg P, Thompson JK. J Adolesc Health. 2005;37:120–7.

Keery H, Eisenberg ME, Boutelle K, Neumark-Sztainer D, Story M. J Psychosom Res. 2006;61:105–11.

Keery H, van den Berg P, Thompson JK. Body Image. 2004;1:237–51.

Levine M, Murnen SK. J Soc Clin Psychol. 2009;28:9–42.

May AL, Kim J, McHale SM, Crouter AC. Int J Eat Disord. 2006;39:729–40.

McCabe MP, Ricciardelli LA. Health Psychol. 2003a;22:39–46.

McCabe MP, Ricciardelli LA, Ridge D. Sex Roles. 2003b;55:409–19.

Nichter M. Fat talk: what girls and their parents say about dieting. Cambridge: Harvard University Press; 2000.

Nieri T, Kulis S, Keith VM, Hurdle D. Am J Drug Alcohol Abuse. 2005;31:617–39.

Olvera N, Suminski R, Power TG. Obesity Res. 2005;13:1970–9.

Palmqvist N, Santavirta N. J Youth Adolesc. 2006;35:203–17.

Parker S, Nichter M, Nichter M, Vuckovic N, Sims C, Ritenbaugh C. Hum Organ. 1995;54:103–14.

Paxton SJ, Eisenberg ME, Neumark-Sztainer D. Dev Psychol. 2006;42:888–99.

Paxton SJ, Schutz HK, Wertheim EH, Muir SL. J Abnorm Psychol. 1999;108:255–66.

Presnell K, Bearman SK, Stice E. Int J Eat Disord. 2004;36:389–401.

Ricciardelli LA, McCabe MP. Sex Roles. 2001;44:189–207.

Ricciardelli LA, McCabe MP. Psychol Sch. 2003;40:209–24.

Ricciardelli LA, McCabe MP, Banfield S. J Psychosom Res. 2000;49:189–97.

Ricciardelli LA, McCabe MP, Ridge D. J Health Psychol. 2006;11:577–87.

Ricciardelli LA, McCabe MP, Williams RJ, Thompson JK. Clin Psychol Rev. 2007;27:582–606.

Rierdan J, Koff E. Adolescence. 1997;32:615–24.

Roberts A, Cash TF, Feingold A, Johnson BT. J Consult Clin Psych. 2002;74:1121–31.

Roberts A, Cash TF, Feingold A, Johnson BT. J Consult Clin Psych. 2006;74:1121–31.

Schooler D. J Adolesc Res. 2008;23:132–53.

Schwartz DJ, Phares V, Tantleff-Dunn S, Thompson JK. Int J Eat Disord. 1999;25:339–43.

Shaw H, Ramirez L, Trost A, Randall P, Stice E. Psychol of Addictive Beh. 2004;18:12–18.

Shroff H, Thompson JK. J Health Psychol. 2006b;11:533–51.

Shroff H, Thompson JK. Body Image. 2006a;3:17–23.

Smolak L, Thompson JK, editors. Body image, eating disorders, and obesity in youth: Assessment, treatment and prevention. 2nd ed. Washington, DC: American Psychological Association; 2009.

Stanford JN, McCabe MP. Body Image. 2005;2:105–13.

Steinberg AR, Phares V, Thompson JK. J Youth Adolesc. 2004;33:421–9.

Steinberg L. Adolescence. 7th ed. Boston: McGraw Hill; 2005.

Steinberg L. Dev Rev. 2008;28:78–106.

Stice E, Bearman SK. Dev Psychol. 2001;37:597–607.

Stice E, Presnell K, Spangler D. Health Psychol. 2002;21:131–8.

Thompson JK. J Soc Clin Psychol. 2009;28:127–32.

Thompson JK, Heinberg LJ, Altabe M, Tantleff-Dunn S. Exacting beauty: theory, assessment, and treatment of body image disturbance. Washington, DC: American Psychological Association; 1999.

Thompson JK, Smolak L, editors. Body image, eating disorders, and obesity in youth: assessment, treatment and prevention. Washington, DC: American Psychological Association; 2001.

Thompson JK, van den Berg P, Roehrig M, Guarda A, Heinberg LJ. Int J Eat Disord. 2004;35:293–304.

van den Berg P, Thompson JK, Brandon K, Coovert M. J Psychosom Res. 2002;53:1007–20.

Vincent M, McCabe MP. J Youth Adolesc. 2000;29:205–20.

Wertheim EH, Martin G, Prior M, Sanson A, Smart D. Eat Disord. 2002;10:321–34.

Wertheim EH, Mee V, Paxton SJ. Sex Roles. 1999;41:169–87.

White MA, Grilo CM. Int J Eat Disord. 2005;38:78–84.

Wiseman C, Sunday S, Becker A. Child Adolesc Psychiatr Clin N Am. 2005;14:453–71.

Chapter 202
Body Image and Eating Disorders Among Immigrants

Nan M. Sussman and Nhan Truong

Abbreviations

APA   American Psychiatric Association
ED   Eating disorders

202.1 Introduction

Eating disorders are generally defined as a disturbance in the perception of body shape resulting in restrictive or binge eating/purging patterns (Mintz and O'Halloran 2000). Extant literature had conceptualized eating disorders as culture-bound syndromes (Prince 1985), manifested in two disorders described in the DSM-IV: anorexia nervosa and bulimia. Anorexia is defined as a disorder in which the individual is resistant to maintaining a minimally normal weight, has an intense fear of gaining weight, and has infrequent menstrual periods (American Psychiatric Association 1994); bulimia is defined as a disorder in which the individual has recurrent episodes of excessive binge eating, a strong sense of lack of control, and recurrent compensatory behaviors (e.g. use of laxatives, enemas, vomiting, excessive exercise (APA 1994)). In the extreme, both syndromes can lead to death by starvation. Moreover, these eating disturbances have been understood as specific to Western culture as, in general, women in cultures removed from Western media exposure (Akiba 1998) or economic development and modernization (Lee and Lee 2000) had higher body esteem and lower fat concerns. Significant levels of disordered eating have been found in the USA, Britain, Canada, and Australia with lower prevalence in Western Europe and rare occurrences in Africa and Latin America.

202.2 Cultural Differences in Body Ideal

Culture, it appears, influences both attitude toward body shape in general, evaluation of one's own body, and eating behaviors. While body shape, size, and weight are essential elements of physical attractiveness for many cultures, each differs in their preferences. Kenyans (Furnham and Alibhai 1983)

N.M. Sussman (✉)
Department of Psychology, College of Staten Island, City University of New York,
Staten Island, New York
e-mail: nan.sussman@csi.cuny.edu

and Ugandans (Furnham and Baguma 1994), for example, rated larger female figures more favorably than did British women, who found female anorexic figures appealing. Similarly, Cogan, Bhalla, Sefa-Dedeh, and Rothblum (1996) found that women from Ghana were more likely to rate larger body sizes as ideal compared to US students. Caribbean women of African descent maintained this preference with studies finding obesity associated with satisfaction, wealth, and happiness (Simeon et al. 2003). Little normative data exists about Central and South American women in their home country although there is speculation that the body ideal is shorter and rounder than the US ideal. Mexican-Americans, for example, are heavier than their White nonHispanic counterparts, and children who were overweight had a stronger affiliation to Mexican culture (Ayala et al. 2007).

In traditional Chinese culture, heavy women were evaluated positively (Nasser 1988) and some contemporary Chinese women view plumpness as a component of the ideal female body shape (Chen and Swalm 1998). Current studies of Hong Kong Chinese adolescent females find, in comparison with American adolescents, similar body dissatisfaction but lower drive for thinness, and among college-aged Chinese women, lower body dissatisfaction and drive for thinness (Leung et al. 2004). Chinese women also consistently score lower on self-esteem scales which may be attributed in part to the self-effacing nature of Chinese values (Bond and Cheung 1983). Scant research has investigated normative body image among Eastern European women. However, in a comparison of the link between slimness and sexual attractiveness of women rated by Finnish and Russian men, researchers found the slim ideal was held by the Finnish but not the Russians (Haavio-Mannila and Purhonen 2001).

Some studies have also examined the role of ethnicity within a single country in shaping body preferences. Results indicate that, within the US, Asians and Whites prefer the thin body ideal and Hispanics and African-Americans tend to prefer a larger body size (Molloy and Herzberger 1998). Black women tend to be less preoccupied with dieting and weight loss and less negative about their body image than White and Latin American women (Cash and Henry 1995; Miller et al. 2000). Also, African-American women perceived themselves to be more sexually attractive, have higher self-esteem, and higher body esteem than the other ethnic groups (Miller et al. 2000).

There is support among many studies correlating poor body satisfaction with increased risk or prevalence of eating disorders. In the USA, thinness is a core body ideal and is highly valued (Garner et al. 1980). Unfortunately, this ideal is often unattainable and results in negative evaluations of one's body. Two concepts which have been developed to assess the subjective self-perception of the body, commonly referred to as body image, are body esteem, an overall evaluation of one's body, and satisfaction with individual parts of the body. General self-esteem is also associated with both body image and eating disorder risks (Mintz and Betz 1988).

202.3 Body Image and Eating Disorders

The majority of American women tend to overestimate their body size, and thus view their bodies in self-deprecating ways (Lewis and Donaghue 1999) which results in general dissatisfaction with their bodies (Cash and Henry 1995) and poor self-esteem (Matz et al. 2002). America's obsession with thinness combined with body dissatisfaction, which has consistently been demonstrated to be a risk factor in eating disorders (Altabe and Thompson 1992), has resulted in negative physical health consequences for an estimated seven million (predominantly white) females in the USA who are afflicted with eating disorders (EDs) (Eating Disorder Statistics 2003) and many more who are at risk for disordered eating. Among White US women, EDs were correlated with low body esteem (Striegel-Moore et al. 1993) and low self-esteem (Joiner and Kashubeck 1996) among other factors. It is estimated that 1.15 million people in the UK have an eating disorder.

This link between body dissatisfaction, low body or self-esteem, and disordered eating is not found uniformly in other countries or among immigrant samples. Chinese (Pan 2000) and Japanese (Mukai et al. 1998) women had lower body esteem than US women but not greater rates of eating disorders and Doan (2001) found that self-esteem and eating disorder symptomology were unrelated among East Asian-Americans. Among Indian female adolescents, decreased appetite and excessive weight loss is found but not accompanied by body image disturbances or fear of becoming fat (Khandelwal and Saxena 1990). Additionally, Afro-Caribbean British women, compared to Caucasian British, were less likely to have feelings of depression or anxiety related to disordered eating attitudes (Dolan et al. 1990). However, among Chinese-Australian women, eating pathology was associated with lower levels of satisfaction with the body. In summary, culture shapes its citizens' preferences for body shape and size, evaluation of body against a cultural norm (body image), and the association between body attitudes and eating behaviors. Therefore, in this chapter, the literature will be reviewed by world region.

202.4 Immigration and Cultural Transitions

Rapid cultural changes in the world, coinciding with the expanded influence of Western culture and increased immigration, have shifted our current thinking and understanding of eating disorders from culture-bound to culture-transition syndromes (see Table 202.1). Transitions may take place within a culture as Western values and attitudes have permeated domestic perspectives of body image. For example, Khandelwal and Saxena (1990) indicate that India is increasingly influenced by Western values and may result in anorexia being more prevalent. Transitions also take place within an individual's psychological attitudes, values, and behaviors as one migrates from home country to host country. Among the new values and norms to which immigrants are exposed are those pertaining to the culturally ideal body type and standards of physical attractiveness. Thus, one question posed by researchers is "What is the effect of immigration and its consequences for body image and the risks for eating disorders?"

Table 202.1   Key facts about immigration

1. In 2005, world immigration totaled 190,633,564
2. Of the top ten countries that were recipients of migrants, eight were Western economically developed countries (USA, Russia, Germany, France, Canada, UK, Spain, Australia).
3. Regions of origin of immigrants:

To	From	Percent of total immigration to host country (%)
USA	Mexico	30
	East and Southeast Asia	18
	Central America	8
France	North Africa	47
Canada	East and South Asia	12
UK	South Asia	15
Spain	South America	18
Australia	Asia	7
Germany	Europe	50

This table provides recent demographic statistics on immigrant country of origin and country of destination

Table 202.2 Definitions and explanations

1. **Acculturation:** Although the concept is complex, we refer to the adoption of thoughts, attitudes, values, and behaviors of the host culture. Acculturation has been measured employing single variables such as length of residence in the host country, and multi-item scales of language use.
2. **Body image:** Body image refers to an evaluation of one's body (positive or negative) that involves feelings about his/her body in relation to the body ideal. Some concepts employed to measure body image include body parts dissatisfaction/satisfaction, body dissatisfaction/satisfaction and body esteem.
3. **Eating disorder:** Eating disorder in this chapter has referred to the clinical syndromes anorexia nervosa and bulimia, as well as risk for the development of eating disorders, maladaptive eating attitudes and behaviors, and eating pathology.
4. **Immigrant:** Immigrant refers to individuals who moved from their country of birth and settled in the host country. We distinguished between individuals who migrated to the host country, referred to as "immigrants" or "first generation immigrants" and individuals who were born in the host country but had immigrant parents, referred to as "second generation immigrants".
5. **Host country:** The country to which the immigrant migrated and settled. This term is in contrast to the home country, the country to which the immigrant was born.

This table lists five terms and their definitions that are used often in the chapter. The definitions will improve the understanding of the research discussed in the text of the chapter

Immigrants undergo a process of cultural transition in which their attitudes, beliefs, values, and behaviors change as they adapt to their new home country. This adaptation process is referred to as acculturation (see Table 202.2), although recent conceptualizations suggest a more complex and nuanced intersection of maintenance of attitudes from the country of origin and adaptation of attitudes from the new home country (Trimble 2003). Growing attention has been paid to the role of multi-directional acculturation on the mental and physical health of immigrants living in the USA, Australia, and Britain. A second research question asks "Will the process of immigration uniformly influence all migrants or will the level of individual acculturation to the host country affect body attitudes and eating behaviors?" Speculation is that both individual level and cultural level variables modify the effect of immigration on body image and eating disorders.

Findings from the past literature are equivocal. Immigration to a Western country has been identified as a possible risk factor in eating disorders (Geller and Thomas 1999) as has been the increased acculturation level. The latter has been found among Hispanic-American girls (Gowen et al. 1999) and other acculturated ethnic minority women (Cachelin et al. 2000; Chamorro and Flores-Ortiz 2000).

Other studies find no link between acculturation and eating disorders among Asian- and Chinese-American women (Haudek et al. 1999; Pan 2000). Among East Asian immigrants, acculturation did not predict desire to be thinner, feelings of guilt after eating, or fear of being overweight (Barry and Garner 2001). Huang (2001) found that only Asian-American women, who more strongly identified with White American culture, were more likely to engage in compensatory weight loss behavior but not binge eating. Among African-Americans, evidence demonstrates that they are less likely to internalize the thin ideal than Asian or White Americans (Shaw et al. 2004).

These inconsistencies may be explained by examining residential patterns of immigrants. Urban dwellers who are surrounded by ethnic peers and thus less influenced by the dominant culture's body standards may be buffered against body dissatisfaction and risks for eating disorders. In two studies, Caribbean-Americans (Sussman et al. 2007) and Mexican-Americans (Fisher et al. 1994) who lived in ethnic urban enclaves revealed lower anxiety, higher self-esteem, and a few ED symptoms than those peers living in suburban or more integrated neighborhoods.

This chapter, in addition to reviewing the literature by world region of the immigrant, will also report the effects of acculturation. It should be noted that measures of acculturation vary dramatically among studies: some include a unitary measure while others are multi-dimensional; some use self-report assessments and others are archival. These variations make direct comparisons and syntheses troublesome.

202.4.1 Immigrants from Asia

Very few studies have examined body image and eating disordered attitudes and behaviors of non-clinical Asian sample populations within their own countries. Kayano et al. (2008) examined eating attitudes and body dissatisfaction among Filipino, Omani, Japanese, Indian, and Euro-American adolescents. Not surprisingly, both male and female European youth indicated the greatest desire to be thin compared to the other groups. However, Filipino males and females and Indian females indicated greater maladaptive eating attitudes than their European counterparts. Among Filipinos, non-hunger related motivational eating patterns have been shown as a result of "demographic changes, economic development, and nutritional transitions" (p. 23). These motivations include the environment, such as being surrounded by delicious foods, eating socially, particularly among family and friends, and emotional eating due to loneliness, depression, and anxiety. Eating disordered behavioral patterns among Indians may be due to belief aspects of their Hindu religion, which include vegetarianism. Perhaps the greater their beliefs in Hinduism, the more likely they are to follow a strict vegetarian diet which in turn leads to higher disordered eating attitudes. Among the female Japanese adolescents, maladaptive dieting and a desire to be thin occurred when there was an increase in body mass index (BMI). Among the Filipino, Indian, and Japanese Asian groups, the Japanese adolescents appeared to have the healthiest eating attitudes and behaviors overall. This may be due to the relatively low BMI in Japanese female adolescents, and therefore they were satisfied with their bodies and felt no need to diet or be thin.

202.4.1.1 Body Image and Eating Disorders

Studies on Asian immigrants have generally shown that migrating to Western countries such as the USA and European countries has led to lowered body image and greater risk for eating disorders. Waller and Matoba (1999) examined the relationship between emotional eating and disordered eating among Japanese women who were born and currently reside in their home country, Japanese women who have lived in the UK for at least 9 months and currently reside in the UK, and British women living in the UK. Japanese women living in the UK showed a relationship between emotional eating and bulimic attitudes, similar to the patterns found in the British women. However, this association was not found in the Japanese women in Japan. In another study comparing Chinese women from Hong Kong and Chinese women from mainland China (Lee and Lee 2000), Chinese women from Hong Kong adopted the Western beauty ideal, were slimmer, had greater body dissatisfaction, and greater eating disorder behaviors. In another study by Mujtaba and Furnham (2001), British Asian immigrant females from Pakistan reported higher levels of risk for developing eating disorders compared to Pakistani females in Pakistan. In Choudry and Mumford's (1992) study, Pakistani immigrants living in the UK showed a higher prevalence of bulimia than Pakistanis residing in their home country. Thus, for Asian women moving to the West, immigration itself appears to be a risk factor for EDs.

202.4.1.2 Acculturation Effects

A closer examination of the process of immigration has shown that more acculturated Chinese immigrants to Western culture report lower body satisfaction and lower eating disorders. Among immigrant Chinese-Americans born in Taiwan, China, and Hong Kong, participants who were less Chinese (more acculturated) on the Chinese Orientation subscale showed lower body satisfaction

(Cheng 2001). In another study of Chinese undergraduate students who were primarily born in Hong Kong (10% were US born) and lived in the USA, females who were bicultural or mostly American (high acculturation) on the Suinn-Lew Acculturation Scale reported significantly greater bodily perfectionism and higher eating disorder scores than females who were very or mostly Asian (low acculturation) and males (Davis and Katzman 1999).

Some researchers have examined underlying psychological mechanisms through which acculturation plays a role in body image and eating disordered attitudes and behaviors. Humphry and Ricciardelli (2004) found that in their sample of primarily Asian-Australian immigrants who were born in China, Hong Kong, Malaysia, and Singapore (7% were Australian-born), women who had a weak Chinese identity (high acculturation) on the Ethnic Identity Scale did not differ from those with a strong Chinese identity (low acculturation) on eating disorder attitudes. It was only when high acculturated Chinese-Australian females perceived more pressure to lose weight from their father or best friends that they showed greater eating disorder attitudes than their low acculturated counterparts. In the same study, women who reported a high Chinese identity and higher parental care showed higher levels of eating disorders. In another study on Chinese immigrants living in New Zealand, two aspects of acculturation, values toward other groups and interpersonal distrust, mediated the relationship between positive or healthy appraisal of perfectionism and eating disorders (Chan and Owens 2006). Here, a positive appraisal of perfectionism appears to serve as a buffer between adopting the values, attitudes, and behaviors of the host culture and the development of eating disorders.

Other studies have indicated that acculturation does not play a role in the body image and eating disorders. In a study on East Asian immigrants by Barry and Garner (2001), acculturation was not related to wanting to be thin, guilt from eating, afraid of being overweight, and worrying about having fat on the body. In another study (Pan 2000), among Chinese-American women acculturation did not correlate with body image attitudes, eating attitudes, and eating behaviors. In Soh et al.'s (2007) study of Northern European and East Asian women with and without eating disorders, acculturation was not related to eating concerns among East Asian Australians and Singaporean Chinese women. Based on the National Latino and Asian American Study, acculturation – defined as US born versus immigrant, number of parents born in the USA and length of residence in the USA – did not predict eating disorders within the past 12 months (Nicdao et al. 2007). In two studies employing the Suinn-Lew Asian Self-Identity Acculturation Scale (SL-ASIA), one on South Asian-American women who were predominantly Indian (89%) and second generation (79%) (Iyer and Haslam 2003), and the other on Korean immigrant women to the USA (18%) and second generation Korean-American women (82%) (Jackson et al. 2006), acculturation was not related to risk for developing eating disorders. Iyer and Haslam (2003) also found that the SL-ASIA was not associated with body image disturbance in their sample of South Asian-American women.

Researchers have examined other variables that may contribute to body image and eating disorders among this ethnic population. For Asian women, not only do societal pressures to be thin play a role in eating disordered behaviors, but also intrafamilial relations and conflicts. In Humphry and Ricciardelli's (2004) sample of predominantly Asian-Australian immigrants, parental bonding and physical appearance also predicted eating disorder attitudes, such that Chinese-Australian women who reported high parental overprotection and less satisfaction with their physical appearance tended to show higher eating disorder attitudes.

Among British Asian females who were predominantly Muslim second generation immigrants from India- and Pakistan-born parents (Furnham and Husain 1999), conflicts with parents over socializing – going out and choice of friends – correlated with higher risk for eating disorders. Similarly, in a study of British Asian female immigrants from Pakistan and Pakistani females in Pakistan, greater conflict with parents and greater overprotection from parents were associated with higher risk for developing eating disorders (Mujtaba and Furnham 2001). British Asian immigrants had greater conflict with parents, greater overprotection from parents, and higher risk for developing eating disorders

than their Pakistani counterparts. In a study of South Asian US immigrant women (31%) and American born South Asian women (69%), three aspects of teasing, overall appearance, weight and shape, and ethnicity were related to body dissatisfaction and eating disorders (Reddy and Crowther 2007).

The current paradigm around eating disordered behavior and attitudes is understood to be culture transition rather than culture-bound. In many countries, Western cultural values and ideas around the thin body ideal have influenced their culture's body image ideal. Interestingly, unique symptoms associated with eating disorders have been evidenced in India (Khandelwal and Saxena 1990). Here, anorexia and bulimia are less prevalent than in countries where thinness and body image is emphasized. Whereas anorexia is generally found to be correlated with negative body image, this is not the case among this population. Rather, hysterical symptoms have been found to correlate with anorexia. This may be a result of poor socioeconomic conditions, where poverty and famine are among the main concerns in the everyday lives of these people.

202.4.2 Immigrants from Central and South America

The USA is the largest recipient of immigrants from Central and South America and these residents, collectively referred to as Hispanics, are the largest immigrant group in the USA; Mexican-Americans form the majority. Attempts to estimate the frequency of ED among this population has resulted in conflicting figures: One study indicates that 4.3% of Mexican-American women suffer from Bulimia, similar to Caucasian Americans (Lester and Petrie 1998) while another study concludes that Hispanic have more severe binge eating compared to White and Black Americans (Fitzgibbon et al. 1998). Among Mexican-American women, the relationship between body esteem/satisfaction, acculturation, and eating disorders is also inconsistent. One study found no effect of acculturation on body esteem (Schwartz et al. 1998); one found no effect of body satisfaction on bulimia symptomology (Lester and Petrie 1995); and two others found that body dissatisfaction was positively related to anorexia and bulimia (Joiner and Kashubeck 1996; Straeter 2002). More consistent were the results examining the association between acculturation to the USA and ED: Three studies found that acculturation did not predict ED (Joiner and Kashubeck 1996; Kuba and Harris 2001; Lester and Petrie 1995) while Chamorro and Flores-Ortiz (2000) report that more acculturated women had more disordered eating. However, each of these studies used different measures of acculturation (one used a US Eurocentric scale and two others used generation as a proxy for acculturation – second generation women, presumed to be more acculturated, compared to first generation) which weakens comparisons.

Puerto Rican immigrants in New York and Cuban immigrants in Florida form two other large groups who have been investigated. In a qualitative study of 12 women from both ethnic groups, those who immigrated at a young age and were assumed to be more acculturated to US culture were more dissatisfied with their bodies (Smith 2001). In another study, among Cuban-American women, body dissatisfaction was linked to ED but acculturation was not (Rodriguez-Hanley 2004).

202.4.3 Immigrants from Russia and Eastern Europe

In Eastern Europe, the thin body ideal is not emphasized as it is in Western countries and thus striving for extreme thinness and accompanying eating disorders are less frequent. Few studies have examined the role of acculturation on body image and eating disorders among Eastern European immigrants. Some studies have found that the more acculturated to Western body ideals Eastern European immigrants became, the more negative was their body image and the higher their eating disordered attitudes and

behaviors. Greenberg, Cwikel, and Mirsky (2007) examined risk for developing eating disorders in both male and female native Israeli and immigrant European college students living in Israel. The majority of the immigrants came from the former Soviet Union (93%), mostly Russia and Ukraine. The immigrants were separated into two groups, veteran immigrants with a length of residence in Israel of approximately 9.5–12.5 years, and new immigrants with a length of residence of about 1.5–2.5 years. In general, the native Israeli and veteran immigrants indicated a higher prevalence for eating disorder attitudes. Veteran female immigrants showed a higher risk for developing eating disorders than the new female immigrants. Differences in female immigrant groups were found to be the greatest with bulimia. This suggests that Russian and Ukrainian female immigrants who live in Israel for a longer length of time are more likely to adopt the thin ideal and standards of a Westernized culture and are therefore more at risk for developing eating disorders than those who recently immigrated to Israel. The researchers suggest that the lack of prevalence for eating disordered attitudes among the new immigrants may be because they are less likely to have served in the Israeli Defense Forces, the Israeli army, which would expose them to maladaptive eating behaviors and attitudes. Also among the veteran immigrants, prolonged exposure to Western media may have influenced their eating attitudes and behaviors.

Bulik (1987) presented two case studies of Eastern European women who were new immigrants to the USA with their families. Before both women immigrated to the USA they were not preoccupied with the desire to be thin. However, within 2 years after living in the USA, they developed eating disorders, one with bulimia and the other with anorexia nervosa. Both women left their country during their adolescence and adapted to American culture quickly. Adopting a sense of independence from the family conflicted with the traditional family values of their own culture. This led to feelings of guilt. Also, these two women played conflicting family roles, the loyal child and the parent. Since their parents decided to immigrate to the USA, both women had no choice in leaving their home country. As obedient children, they followed their family's decisions. When they moved to the USA, they became translators for the family since they were the most fluent in English. As a result, they felt like they were the parent in the family as well. Feeling conflicted with their family roles and guilt over wanting independence, both women felt a sense of emptiness. Moreover, they felt like they did not fit in with American society and a lack of acceptance when they first moved to the USA. Through the media and interactions with peers, they learned that being thin was a way to gain social status, approval, and acceptance. They began to base their self worth on the slenderness of their body and their control of food intake.

Pavlova, Uher, and Papevoza (2008) interviewed six young Czech female sojourners to the USA and echoed similar experiences of isolation in their host country as one of the trajectories through which they either developed eating disorders or worsened their eating disorder symptoms.

In contrast to the previous studies described, one study found that acculturation plays a role in body image among Eastern European immigrants, but less so in eating disordered attitudes. Sussman, Truong, and Lim (2007) found that Eastern-European immigrant women who identified less with their birth country (more acculturated) indicated lower body esteem and were less satisfied with their body parts. US born European women exhibited higher risk for eating disorders than the Eastern-European immigrant women, but the difference was not significant.

202.4.4 Immigrants from Europe

The flow of immigrants from Europe to other regions of the world is light. During the 1990s, there was a significant migration from Ireland to UK, Canada, and the USA. However, this group was not included in any studies of body image and ED. Geller (2005) found that in their sample of second-generation Greek and Italian women living in Canada, greater internalization of the Western

thin ideal was predictive of higher risk for eating disorders. Greater conflicts with their family and higher levels of perfectionism also led to higher risk for eating disorders. Although not directly related to eating disorders, higher body mass index was related to more extreme weight loss behaviors.

Since the creation of the European Union and the loosening of immigration policies, there has been considerable immigration within Europe although few studies have examined these populations. For example, Germany has been the destination country of more than 7 million immigrants, about 50% from Europe, but none of these immigrant groups have been investigated regarding eating disorders. In one of the few studies investigating trans-European movements, Kirchengast and Schober (2006) found that migrant children from Turkey and the former Yugoslavia to Vienna and Austria were found to have a higher prevalence of being overweight and obese.

202.4.5 Immigrants from the Middle East

There is little normative information about the body image and ED risks or behaviors among women in Middle-Eastern countries. In one of the few studies, Abdollahi and Mann (2001) found that in their sample of Iranian women living in Iran and in the USA, exposure to Western media, length of residence in the USA, and language use were not associated with disordered eating symptoms and body image issues. The researchers suggest that the lack of differences in body image and eating disorder symptoms between the two groups may be due to the high Westernization of Iran prior to the Islamic revolution in 1978, which is evident in the familiarity with Western culture among the participants' parents. Also, the Iranian population in Los Angeles is large, and this may serve as a buffer against the effects of exposure to Western body image ideals.

Other factors that influence body image and eating disorders among Middle-Eastern immigrants include independence, control, sexuality, religion, and familial and individual personality factors. Timimi (1995) describes the process by which adolescent Arab female immigrants develop eating disorders: their yearning for independence and seeking pleasure in the self conflicts with their family traditions and expectations, as well as their Muslim religion and identity. These conflicts lead to feelings of guilt and depression, and therefore they may seek solace in food constraints as a way to purify the Muslim self. These maladaptive eating behaviors then result in the development of anorexia nervosa.

202.4.6 Immigrants from the Caribbean and Africa

In the Caribbean and Africa, the body ideal tends to deviate substantially from the Western thinness ideal. One Caribbean woman described the body image ideal in her home country, "A women can almost never be too fat. Even if I had weighed 80 kg, men would have found me more attractive than if I were thin." (Willemsen and Hoek 2006, p. 353). In a study of South Asian, African, and mixed adolescents living in Trinidad, a greater percentage of overweight African adolescents were satisfied with their body size than the South Asian and mixed overweight adolescents (Simeon et al. 2003). Similarly, in a study on cross cultural differences in body image perceptions among Kenyan Asian immigrant females living in Britain, Kenyan British females, and British females, the Kenyan Asian immigrant group perceived the larger female body shapes more positively and the thin female body shape more negatively than the other groups (Furnham and Alibhai 1983). This difference in beauty ideal may stem from the poor socioeconomic conditions of these developing countries, whereby overweight and normal body size signify wealth and having a healthy body (Simeon et al. 2003).

Very few studies have investigated the effects of immigration on body image and eating disorders among this population. Willemsen and Hoek (2006) presented a rare case study of a Caribbean Antillean woman who immigrated to the Netherlands and subsequently developed anorexia nervosa through adopting the thin beauty ideal there, primarily through television. Other case studies of Caribbean and African women with eating disorders describe their struggles with separation from their parents, as well as family and sexual conflicts (Geller and Thomas 1999).

In general, however, Caribbean and African female immigrants tend to display a lower prevalence of eating disorders and greater body satisfaction than Westerners. In Sussman, Truong, and Lim's study (2007), Caribbean immigrant women were more satisfied with their body parts than Eastern-European immigrant women (see Fig. 202.1). Moreover, Caribbean immigrant women had the lowest
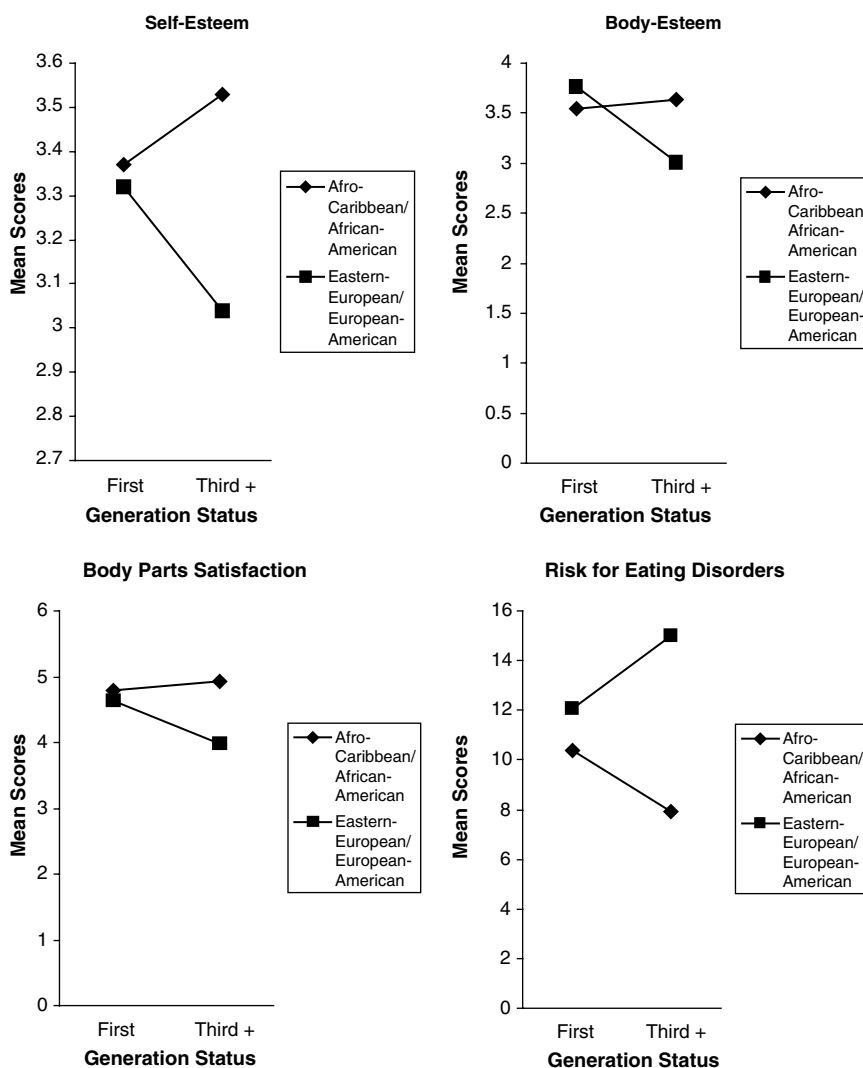

Fig. 202.1 Ethnicity moderating effects of acculturation (Sussman et al. 2007). This figure shows the moderating effects of country of origin for immigrants to the USA. As Caribbean immigrant women became more acculturated to the USA (first generation compared to third + generations), they had higher self-esteem, body esteem, and body parts satisfaction, and lower risk for eating disorders. However, as Russian immigrant women became more acculturated to the USA, they had lower self-esteem, body esteem, and body parts satisfaction, and were at higher risk for eating disorders

risk for eating disorders compared to Eastern European and Chinese immigrant women. This may in part be due to the fact that the Caribbean immigrant women resided in neighborhoods that were primarily Caribbean immigrants. Therefore isolating themselves away from the Western thinness ideal may have served as a buffer against developing a negative body image. In another study of first generation immigrant Jamaican-American women and US born African-American women, both groups did not differ in body satisfaction and both displayed similar body ideals (Williams 2007). However, the Jamaican-American immigrant women displayed a higher drive toward thinness. The higher drive to be thin among the immigrant group may in part have resulted from their experiences of acculturative stress, which was found to be related to concerns over one's body image.

202.5 Summary

The effects of immigration to Western countries on body image, risks for ED, or ED symptomology vary by cultural group. Among Asian immigrants, lower body esteem was often associated with greater risks for ED while for Central and South American immigrants, the correlation was equivo-cal. Immigration does not appear to negatively affect the body satisfaction of Caribbean or African immigrant women (see Table 202.3).

The level of acculturation to the host country was predicted by many researchers to be positively associated with ED or risks for the syndromes – the higher the acculturation, the higher the risk for the disease. This variable too was modified by home cultural group. The experience of Asian immi-grants generally supported the prediction whereby the more acculturated women had disordered eating or higher risks for ED. The data from Central and South American women were inconsistent although predominantly demonstrated no relationship between the level of acculturation and ED. Caribbean immigrants had the lowest incidence of ED in part because they acculturated the least. It

---

Table 202.3   Key points of eating disorders among immigrants

1. Eating disorders such as anorexia and bulimia had been found primarily among women in Western countries. In extreme forms, these diseases result in death. These syndromes were based on an idealized body type of extreme thinness which was perceived as attractive. The majority of the nonwestern world did not hold extreme thinness as an ideal female form.

2. World wide immigration has grown in the last two decades primarily from the developing countries to the West. One question posed by mental health and other health professionals was what would be the effect of immigration to the West on women's attitudes toward their bodies, risks for and prevalence of eating disorders. In general terms, research finding indicate that there is not a uniform effect of immigration. Women from Africa and the Caribbean do not appear to be negatively affected by immigration while Asian immigrants to the West tend to have lowered body image and greater risks for eating disorders.

3. Immigration's effect on body dissatisfaction and eating disorders can be modified by the extent to which the immigrant has acculturated or adapted to the host country. The more they live in integrated neighborhoods, have adopted attitudes of the host country toward body ideals and the attractiveness of thinness, the more likely they will be dissatisfied with their bodies and engage in disordered eating. Russian immigrants were found to be affected by acculturation level to the West either with body dissatisfaction or eating disorders. However, other studies examining Asian and Central and South American immigrants found that acculturation levels did not affect disordered eating. So high acculturation to the host country does not necessarily result in poor mental and physical health. Other factors also shown to affect their mental health include family conflicts and parental overprotection.

This table explains the general factors that influence the development of body dissatisfaction and eating disorders among women in Western countries. Since there are hundreds of thousands of women from other regions of the world immigrating to the West, many studies have examined whether these women are at risk for negative attitudes toward their bodies and for eating disorders

Table 202.4 Summary points

- Eating disorder symptoms include dissatisfaction with one's body which results in near-starvation eating behaviors or bingeing/purging patterns. Extreme forms can result in death.
- Until recently, eating disorders were found almost exclusively in Western countries due primarily to the emphasis of extreme thinness as a standard of beauty.
- Ideal body sizes, features, and standards of beauty vary from culture to culture.
- As a culture becomes more exposed to Western media and the thinness ideal, eating disorders begin to appear primarily among young women.
- Much research has focused on how immigration to the West affects women's body ideals, dissatisfaction with their bodies, risks for eating disorders and prevalence of the syndrome.
- Another research question focused on how the level of adjustment to the host country (acculturation) affects body dissatisfaction and eating disorders.
- Results indicate that the culture of the immigrant influences how the immigrant reacts, Russian and Asian immigrants are the most dissatisfied with their bodies and the more they have adapted to values and attitudes in the West, the more likely that they will suffer from eating disorders.
- Caribbean and African immigrants, despite having body ideals that are very different from those in the West, are the most satisfied with their bodies and least likely to suffer from eating disorders.
- Health and mental health professionals should be aware of culture and acculturation and their affect on eating disorders when interviewing or treating an immigrant patient.

This table summarizes each of the major points in the chapter in the order that they are presented. These points also summarize the major research findings regarding immigration and body image and risk or prevalence of eating disorders

Table 202.5 Suggestions for future research

1. More studies need to test "pure" first generation immigrant samples on acculturation and other sociocultural factors that affect body image and eating disorders.
2. Further investigate sociocultural factors that influence body image and eating disorders among immigrants in countries that have been little researched, such as in Central and South America, the Middle East, and Caribbean and Africa.
3. More studies need to conduct cross-cultural comparisons on body image and eating disorder pathologies between individuals of a specific ethnicity residing in their native home country and a second group of individuals of the same ethnicity who immigrate to a Western host country.
4. Conduct studies on body image and eating disorders among immigrants across several countries employing the same acculturation measures.
5. Conduct studies that employ more powerful methodologies, such as longitudinal studies that examine influence of acculturation and other sociocultural factors on body image and eating disorders among immigrants across different time points.

This table provides suggestion for future research studies by including a larger number of countries and limiting weaknesses in current methodologies

is speculated that living in separate ethnic enclaves buffered them from the dominant culture's body ideal that differed from the normative ones in Africa or the Caribbean (see Table 202.4).

Ironically, for many of the immigrant women, the less acculturated they were, the healthier they were, at least with regard to body image and eating habits. However, we caution drawing many generalizations from the data. Lack of standardization of assessment instruments, inconsistent operational definitions of variables, and methodological weaknesses hamper the ability to integrate the growing literature on this topic. Increased care must be taken to improve the validity and comparability of the research. See Table 202.5 for suggestions for future research directions.

202.6 Applications to Other Areas of Health and Disease

While admitting to the limitations of the research, we suggest that physicians and mental health specialists pay attention to the cultural background, immigration status, level of acculturation, and familial relationships when conducting intake interviews. As discussed in this chapter, some countries such as in Eastern Europe are not as concerned with the slim body ideal as in Western countries, and in the Caribbean and Africa the body ideal deviates substantially from the Western ideal. Cross cultural comparison studies between a group of individuals from a specific ethnicity residing in their native home country and another group of individuals from the same ethnicity who immigrated to a Western host country have shown significant differences in their body image and eating disordered pathology. Some studies have shown that the level of acculturation plays a role in body image and eating disorders, such that the more the immigrant adopts the attitudes, thinking, values, and behaviors of the Western host country, the more they will be at risk for developing eating disorders. Finally family conflicts, specifically with the parents, have been found to contribute to body image concerns and eating disorders.

Also, we have to be aware that the EDs may be presented differently in different countries and may be triggered by different variables than those shown in the USA, UK, and other Western countries where EDs have been prevalent. Case studies in India have shown that eating disorders manifest in different and unique symptoms from those in Western countries.

References

Abdollahi P, Mann T. Int J Eat Disord. 2001;30:259–68
Akiba D. J Soc Psychol. 1998;138:539–40.
Altabe M, Thompson JK. Int J Eat Disord. 1992;11:397–402.
American Psychiatric Association (APA). DSM-IV. Washington, DC: American Psychiatric Press; 1994.
Ayala GX, Mickens J, Galindo P, Elder J. Ethnic Heal. 2007;12:21–41.
Barry DT, Garner DM. Eat Weight Disord. 2001;6:90–8.
Bond MH, Cheung TS. J Cross-Cult Psychol. 1983;14:153–71.
Bulik CM. Int J Eat Disord. 1987;6:133–41.
Cachelin FM, Veisel C, Barzegarnazari E, Striegel-Moore RH. Psychol Women Quart. 2000;24:244–53.
Cash TF, Henry PE. Sex Roles. 1995;33:19–28.
Chamorro R, Flores-Ortiz Y. Int J Eat Disord. 2000;28:125–9.
Chan CKY, Owens RG. Psychol Heal. 2006;21:49–63.
Chen W, Swalm RL. Percept Motor Skills. 1998;87:395–403.
Cheng C-Y. Dissert Abst Int. 2001;61:7A.
Choudry IY, Mumford DB. Int J Eat Disord. 1992;11:243–51.
Cogan JC, Bhalla SK, Sefa-Dedeh A, Rothblum ED. J Cross-Cult Psychol. 1996;27:98–113.
Davis C, Katzman MA. Int J Eat Disord. 1999;25:65–70.
Doan LM. Dissert Abst Int. 2001;62:544B.
Dolan B, Lacey JH, Evans C. Br J Psychiatry. 1990;157:523–8.
Eating Disorder Statistics. Data File. 2003. http://womensissues.about.com.
Fisher M, Pastors D, Schneider M, Peeler C, Neopolitan B. Int J Eat Disord. 1994;16:67–74.
Fitzgibbon HL, Spring B, Avellone ME, Blackman LR, Pingitore R, Stolley M. Int J Eat Disord. 1998;24:43–52.
Furnham A, Baguma P. Int J Eat Disord. 1994;15:81–9.
Furnham A, Alibhai N. Psychol Med. 1983;13:829–37.
Furnham A, Husain K. Soc Psychiatry Psychiatr Epidemol. 1999;34:498–505.
Garner DM, Garfinkel PE, Schwartz D, Thompson M. Psychol Rep. 1980;47:483–91.

Geller G. Dissert Absts Int. 2005;56:7b.

Geller G, Thomas CD. Eat Disord J Treat Prevent. 1999;7:279–97.

Gowen LK, Hayward C, Killen JD, Robinson TN, Taylor CB. J Res Adolesc. 1999;9:67–83.

Greenberg L, Cwikel J, Mirsky J. Int J Eat Disord. 2007;40:51–8.

Haavio-Mannila E, Purhonen S. J Sex Res. 2001;38:102–11.

Haudek C, Rorty M, Henker B. Int J Eat Disord. 1999;25:425–33.

Huang LL. Dissert Abstr Int. 2001;62:1083B.

Humphry TA, Ricciardelli LA. Int J Eat Disord. 2004;35:579–88.

Iyer DS, Haslam N. Int J Eat Disord. 2003;34:142–7.

Jackson SC, Keel PK, Lee YH. Int J Eat Disord. 2006;39:498–502.

Joiner GW, Kashubeck S. Psychol Women Quart. 1996;20:419–35.

Kayano M, Yoshiuchi K, Al-Adawi S, Viernes N, Dorvlo ASS, Kumano H, Kuboki T, Akabayashi A. Psych Clin Neurosci. 2008;62:17–25.

Khandelwal SK, Saxena S. Br J Psychiatry. 1990;157:784.

Kirchengast S, Schober E. J Biosoc Sci. 2006;38:695–705

Kuba SA, Harris DJ. Heal Care Women Int. 2001;22:281–98.

Lee S, Lee AM. Int J Eat Disord. 2000;27:317–27.

Lester R, Petrie TA. J Multicult Counsel Develop. 1998;26:157–65.

Lester R, Petrie TA. J Counsel Psychol. 1995;42:199–203.

Lewis V, Donaghue N. Percept Motor Skills. 1999;89:165–71.

Leung F, Wang J, Tang CW-Y. J Psychosom Res. 2004;57:59–66.

Matz PE, Foster GD, Faith MS, Wadden TA. J Consult Clin Psychol. 2002;70:1040–4.

Miller KL, Gleaves DH, Hirsch TG, Green BA, Snow AC, Corbett CC. Int J Eat Disord. 2000;27:310–6.

Mintz LB, Betz NE. J Counsel Psychol. 1988;35:463–71.

Mintz LB, O'Halloran MS. J Pers Assess. 2000;74:489–504.

Molloy BL, Herzberger SD. Sex Roles. 1998;38:631–43.

Mujtaba T, Furnham A. Int J Soc Psychiatry. 2001;47:24–35.

Mukai T, Kambara A, Sasaki Y. Sex Roles. 1998;39:751–63.

Nasser M. J Psychosom Res. 1988;32:573–7.

Nicdao EG, Hong S, Takeuchi DT. Int J Eat Disord. 2007;40:22–6.

Pan AS. Dissert Abstr Int. 2000;61:544B.

Pavlova B, Uher R, Papezova H. Eur Eat Disord Rev. 2008;16:207–14.

Prince R. Soc Sci Med. 1985;21:197–203.

Reddy SD, Crowther JH. Cult Div Ethnic Minor Psychol. 2007;13:45–53.

Rodriguez-Hanley A. Dissert Abstr Int. 2004;65:2110B.

Schwartz MA, Vazquez LA, Vazquez EG, McNeil K. Differences in body image satisfaction: impact of gender and culture. Poster at the 106th Am. Psychol. Assoc. Conference. 1998, August.

Shaw H, Ramirez L, Trost A, Randall P, Stice E. Psychol Addict Behav. 2004;18:12–8.

Simeon DT, Rattan RD, Panchoo K, Kungeesingh KV, Ali AC, Abdool PS. Eur J Clin Nutr. 2003;57:157–62.

Smith AL. Dissert Abstr Int. 2001;62:1600B.

Soh NL-W, Touyz S, Dobbins TA, Surgenor LJ, Clarke S, Kohn MR, Lee EL, Leow V, Rieger E, Ung KEK, Walter G. Aust N Z J Psychiatry. 2007;41:536–45.

Straeter SV. Dissert Abstr Int. 2002;63:4388B.

Striegel-Moore RH, Silberstein LR, Rodin J. J Abnorm Psychol. 1993;102:297–303.

Sussman NM, Truong N, Lim J. Int J Intercult Relat. 2007;31:29–49.

Timimi SB. Psychotherapy. 1995;32:141–9.

Trimble JE. In: Chun KM, Organista PB, Marin G, editors. Acculturation: advances in theory, measurement, and applied research. Washington, DC: American Psychological Association; 2003. p. 3–13.

Waller G, Matoba M. Int J Eat Disord. 1999;26:333–40.

Willemsen EMC, Hoek HW. Int J Eat Disord. 2006;39:353–5.

Williams KN. Dissert Abstr Int. 2007;68:5A.

Part XXXV
The Young and Adolescents

Chapter 203
"My Body Is My Template": Why Do People Suffering from Anorexia Nervosa See Their Bodies Differently?

Naresh Mondraty and Perminder Sachdev

Abbreviations

ACC	Anterior cingulate cortex
AN	Anorexia nervosa
BN	Bulimia nervosa
BIID	Body integrity identity disorder
EBA	Extrastriate body area
FBA	Fusiform body area
fMRI	Functional magnetic resonance imaging
IPL	Inferior parietal lobule
MPFC	Medial prefrontal cortex
SPL	Superior parietal lobule
TPJ	Temporo-parietal junction

203.1 Introduction

In Western societies, feminine beauty has become synonymous with thinness. It is therefore unsurprising that the desire to lose weight and be thin becomes manifest in the preadolescence years and reaches a pathological crescendo in a few unlucky young women (Sachdev 2009). Paradoxically, "feeling fat" is a very common experience among women in general, not only among those who diet but also among women who do not concern themselves unduly with weight issues (Striegel-Moore et al. 1986; Cooper et al. 2007). This has contributed to misconceptions that anorexia nervosa (AN) falls within this normal experience and is a choice made by the sufferer.

In AN, a sufferer does not see her skeletal body as it really is. When asked about her body, she does not just *think* she is fat, but also *sees* and *feels* herself as fat. This disturbance of self-evaluation often focuses around the abdomen, buttocks, and thighs. Though the self body image is grossly distorted, this erroneous perception does not extend to judging the figures of other people (Cash and Deagle 1997). The "experiencing of fatness" and "fear of fatness," paired with low body weight, is pathognomonic of *true* AN. The focus of the discussion in this chapter is on this group. There is a

N. Mondraty (✉)
Wesley Eating Disorders Centre, Wesley Hospital, 85 Milton Street, Ashfield, Sydney NSW, 2131 Australia
e-mail: naresh.mondraty@wesleymission.org.au

subgroup of patients without this body size distortion, no less unwell, who are considered as atypical presentations (Ramaciotti et al. 2002).

The sufferer in true AN is plagued with extreme thoughts, urges, and emotions that are congruent with the perceptual distortion; the accompanying behaviors and explanatory rationalizations are equally bizarre. Patients will often restrict their intake to a few hundred calories a day, exercise for several hours or purge food, losing a significant percentage of body weight over a few months. The fear of fatness and the perceptual distortion are not alleviated by weight loss and can increase as weight continues to fall.

The conscious tactile-kinesthestic (felt) awareness of one's own body is referred to as *body schema*. This definition was developed in the early twentieth century as neurological conditions were being described in which patients experienced their bodies as having markedly changed (Head 1918). *Body image* can be envisaged as a conscious dynamic multifaceted construct of the body with physical, perceptual, visceral, emotional, and cognitive dimensions. There is no single entity as "The Body Image" (Fisher 1990). Body image subsumes this definition of body schema.

Hilde Bruch was one of the first to develop the idea of body image disturbance in AN by including the perceptual accuracy of the body size, accuracy of recognizing visceral stimuli, and the emotional reaction to the body (Bruch 1973). Most importantly, she conceived that body image was in constant interaction with biological, psychic, and social forces. Bruch herself states, "the expression body image is so widely used in psychiatric evaluation that it surprising how vague the concept is." There are arguably two components to the body image distortion in AN: a perceptual disturbance. Congenitally blind children have distorted body images (Kinsbourne and Lempert 1980) but very few develop AN (McFarlane 1989). This may reflect the extent social forces, via the visual media, play in the internalization of body ideals. Body image is constructed through societal values and vice versa.

There are arguably two components to the body image distortion in AN: a perceptual disturbance by which individuals overestimate their body size or distort its shape, and a cognitive dissatisfaction with one's body size or appearance (Rosen 1990). However, even the latter attitudinal component involves emotional, cognitive, and visceral elements.

The difference between body schema and body image can easily be illustrated by the neuropsychiatric disorder – Body Integrity Identity Disorder (BIID; Brang et al. 2008). It is characterized by an intense desire for amputation of a specific healthy limb. This disowning begins in childhood and there is a stable precise line where amputation is desired. The limb is "missing" in the body schema. Over time, intense negative emotions toward the limb develop and the person develops a negative body image, leading some to mutilate the disowned limb. In cases where amputation has been carried out, the subject is often satisfied and comfortable in their new body. Ultimately one needs to accept that body image is a theoretical construct and refer specifically to facets within it. The perceptual error in true AN is a *disturbance in size awareness* and in the sufferer leads to *body size distortion.* Bruch appropriately placed "disturbance in size awareness" within the body image constellation as she recognized that the degree of disturbance is influenced by parallel disturbances in the visceral, emotional, and cognitive dimensions.

Some body schema disturbances can be accounted for purely by neurobiological explanations. The disturbance in body size awareness can be explained plausibly only by adding psycho-social factors to a neurobiological hypothesis. A significant biological contribution to AN is suggested by the stereotyped constellation of symptoms, the substantial heritability, and the small percentage (0.3–1.5%) of women in the general population who go on to develop the illness (Kaye 2008). The convergence of emerging neuropsychiatric research with psychosocial data allows development for explanatory models for the disturbance in body size awareness.

203.2 Psychological Studies

Research into body image distortion in AN has explored the attitudinal and perceptual components separately. There is a variety of rating scales to measure attitudes to one's body. Schematic figural scales such as the Body Image Assessment (Williamson et al. 1989) require the subject to select from a range of figures or silhouettes, the best fit for their perceived and ideal size. The discrepancy between the perceived and ideal is recorded as the measure of dissatisfaction. Questionnaires such as the Body Shape Questionnaire (Cooper et al. 1987) assess body dissatisfaction caused by feelings of being fat.

Studies trying to quantify the perceptual disturbance have used variants of video distortion, mirrors, calipers, and lens on whole bodies (Skrzypek et al. 2001). An extensive meta-analysis of body image disturbance concluded that attitudinal body dissatisfaction measures produced substantially larger effect sizes than perceptual size estimation inaccuracy (Cash and Deagle 1997). Some perceptual studies have shown that a subgroup of AN sufferers does overestimate the size of their bodies but overall the results have been inconsistent. A study of 100 women with AN, using video distortion on a life-size screen, showed only 20% clearly overestimated their size (Probst et al. 1998). AN patients do not show disturbances in other perceptual tasks. There is no evidence of any difference in appraisal of neutral object size or in estimation of the body forms of other women (Cash and Deagle 1997). One can conclude that AN women do not have a physiological disturbance in their visual perception. The findings support the hypothesis that body size awareness is an integration of perceptual, emotional, cognitive, and visceral components combined with self-mentation.

203.3 Prodrome to Body Size Distortion in AN

There is evidence of a disturbance in size awareness in girls prior to developing AN. People who develop AN report feeling fat even when they were regarded as healthy children (Bruch 1973). A body image develops that is associated with negative self-evaluation, particularly in terms of a lack of attractiveness (Cooper et al. 2007). Prospective studies have shown that healthy girls with the highest body dissatisfaction, perceived fatness, and weight concerns are most likely to develop eating disorders (Killen et al. 1996).

AN usually occurs between ages 15 and 19 in postpubertal women (Herpertz-Dahlmann 2009). As a normal physiological response to puberty, there is an increase in appetite, accompanied by a growth spurt and fat deposition in the breasts, hips, thighs, and subcutaneous tissue (Tanner 1990). Body weight on average increases by 40%, with a substantial deposition of fat tissue, in girls between age 11 and 13 (Tanner and Whitehouse 1977). This is a time of massive role change as among other factors the young woman's body becomes sexualized in a social sense. Paradoxically while her appetite is increasing and her body is becoming feminized, she has internalized the societal view that slimness is highly prized. As such, dieting is a common behavior in this age group (Keel et al. 2007). Longitudinal studies of the healthy population suggest that weight and shape concerns develop through childhood and become common by late adolescence in girls (Marchi and Cohen 1990).

The small percentage of young women who are at greatest risk of developing true AN seem to have a disturbed body image prepubertally. Both perceptual and attitudinal aspects of body image may be exacerbated due to psychiatric (e.g., mood and anxiety disorders), psychological (e.g., trauma), and social reasons (e.g., conflict at home and school). The decision to diet is made as actual body size and appetite increase, and body image worsens for a number of psycho-social reasons.

These women have the cognitive style (Roberts et al. 2007) to be successful dieters/restricters and lose several kilograms of weight over a short period of time. The "distorted size awareness" is clinically detectable after this weight loss. There may be a differential vulnerability in brain tissue to the effects of starvation, nutritional deficiencies, and hormonal disruption.

203.4 Body Image Processing in Healthy Women

The following discussion will focus on body image processing in healthy women. This allows for later development of explanatory models of abnormal body image processing in AN. When a young woman evaluates her *own* body (see Fig. 203.1a) a fronto-parietal network is activated. This network involves coactivated regions processing body schema and body ownership. The converging evidence from lesion and neuroimaging studies points to the parietal lobe as the storehouse of body templates (Wolpert et al. 1998), with all incoming body-related sensory stimuli referenced against it. In contrast to the somatotopic maps in the anterior parietal cortex (Penfield and Rasmussen 1950), it is hard to characterize precise body-related functions in the posterior parietal cortex. This region of the cortex is highly differentiated with defined subareas (Nickel and Seitz 2005). The anterior part of the superior parietal lobule (SPL) receives somatosensory information while the posterior part receives visual information. The supramarginal gyrus integrates somato-sensory information with visual information (Rizzolati et al. 1998). It is likely that parallel processes occur locally in neuronal clusters and are integrated supramodally. The right hemisphere seems to play a stronger role in body-related processes and holistic aspects of vision (Springer and Deutsch 1998).

Combining these poly-sensory body templates into the *embodied self* requires coactivation of a right fronto-parietal network. (Keenan and Gorman 2007; Hodzic et al. 2009). The right middle frontal lobe is activated for self-referencing but is also involved in executive functions such as attention (Macrae et al. 2004; Sachdev et al. 2008; Hodzic et al. 2009). The right frontal area is considered part of a network dedicated to the representation of self (Sugiura et al. 2006). The prefrontal cortex
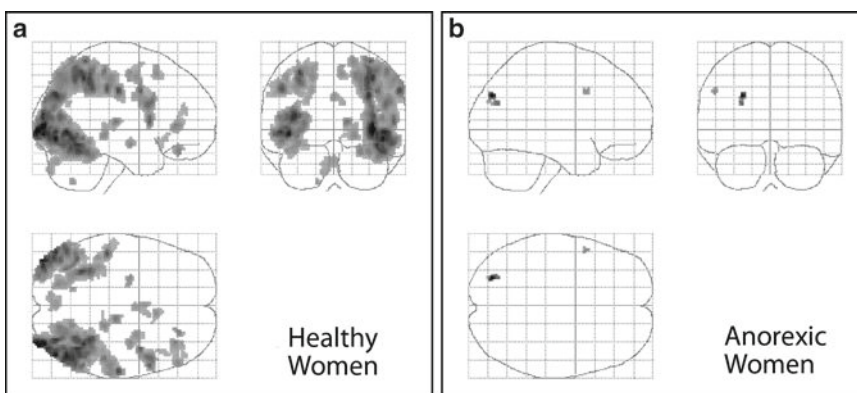

Fig. 203.1 Processing of own body. (**a**) When a young woman evaluates her *own* body widely distributed regions of the brain are coactivated. The network includes areas in the parietal, frontal, and occipital lobes and processes body schema and body ownership. The parietal lobe supramodally integrates polysensory information and acts as a storehouse of body templates. (**b**) The processing of *self* by anorexic women is quite discrepant. Whereas a widely distributed network is activated in healthy women, far fewer regions are activated in AN women, as if the brain was inhibiting the level of processing. In addition, there is decreased activation in the insula, the prefrontal cortex, and precuneus compared with healthy controls
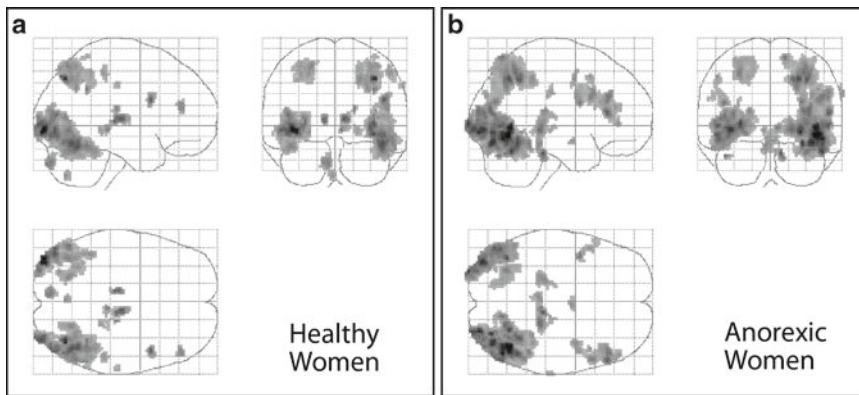
Fig. 203.2 Processing of nonself body. (**a**) In healthy women the brain utilizes some of the same neural resources including the extrastriate body area (EBA) and the fusiform body area (FBA). Processing self and nonself, in particular the parietal and occipital lobes. The human body seems to be the preferred stimuli for a number of regions in the extrastriate visual cortex

serves as a mental space (working memory) where body schema, emotions, and attitudes can be manipulated (LeDoux 1996).Within the parietal lobe, three regions, the right inferior parietal lobule (IPL), the right tempo-parietal junction (TPJ), and the precuneus are implicated in creating this sense of agency (Blanke et al. 2005; Uddin et al. 2006; Tsakiris et al. 2008; Legrand and Ruby 2009).

The concept of body image includes emotional and attitudinal components. The regions of interest include the insula, cingulate gyrus, amygdala (emotional system), and the hippocampus (internalized attitudes to the body). During self body processing, the insula is activated in healthy women (Sachdev et al. 2008). The insula has a unique contribution to make to body image as it acts as an integrating centre (Craig 2009). It is involved in interoceptive perception including pain, hunger, satiety, and information from the viscera. It is reciprocally connected with the parietal lobe via the somatosensory cortex and the IPL. Somatoparaphrenia can occur from insula damage (Vallar and Ronchi 2009) suggesting that body processing is shared with the parietal lobe. The metarepresentation of subjective feelings is contained in the anterior insula. It is linked with the anterior cingulate cortex (ACC) which serves as the motor representation of emotion (Craig 2009). These connections make the insula well-placed to integrate body interoceptive, body schema, and emotional information.

The act of observing *another's* body has little functionally in common with self-processing. Parsimoniously, the brain utilizes some of the same neural resources, in particular the occipital lobes and IPL (see Fig. 203.2a). This is consistent with the IPL's higher integrative function in the association cortex. The human body seems to be the preferred stimuli for a number of regions in the extrastriate visual cortex (Peelen and Downing 2007). Though they both respond to whole and body parts, the extrastriate body area (EBA) preferentially responds to body parts and the fusiform body area (FBA) to whole bodies suggesting different functions. There is an absence of insula activation (Sachdev et al. 2008). This supports the role of the insula in self rather than nonself processing.

203.5 Body Image Processing in AN

Women with AN seem to process the bodies of *other* women in the same way that healthy women do (see Fig. 203.2b). There is activation of the visual cortex, the extrastriate visual areas, the posterior parietal cortex, and the frontal lobes. This is important as it shows that there is no fundamental
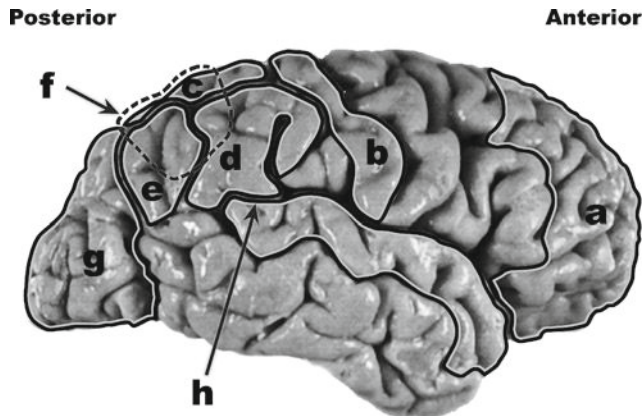
Fig. 203.3 Cortical areas involved in self body evaluation. Self body evaluation activates widely distributed areas in the cortex. The anterior parietal lobe (postcentral gyrus, (**b**) contains various somatotopic maps concerned with localization and shape of the body surface and posture within the body. The role of the posterior parietal cortex in body-related functions is less well understood. The anterior part of the superior parietal lobule (**c**) receives somatosensory information while the posterior part receives visual information from the occipital lobe (**g**). The inferior parietal lobule is divided into the supramarginal gyrus (**d**) and angular gyrus (**e**). The supramarginal gyrus integrates somatosensory information with visual information. The *embodied self* requires coactivation of a right fronto-parietal network. Within the parietal lobe, three regions – the right inferior parietal lobule (**d, e**), the right tempo-parietal junction (**h**), and the precuneus (**f**) – are implicated in creating the sense of agency. The right frontal area is considered to be part of a network dedicated to the representation of self, and the prefrontal cortex (**a**) serves as a mental space, where body schema, emotions, and attitudes can be manipulated

disturbance in the functional neuronal architecture in the anorexic brain in relation to body image processing. When healthy women look at other women, there was a reduced signal in the medial prefrontal cortex (MPFC) whereas there was increased activation in this region in anorexic women. Activation of the MPFC may be related to the metacognitive process of mentalizing about oneself (Johnson et al. 2002). Neuroimaging results suggest that the MPFC is being engaged by AN patients because they compare themselves intensely with other women's bodies, which reflects the clinical experience (Sachdev et al. 2008).

However, the processing of *self* by AN patients is quite discrepant (see Fig. 203.1b). Whereas a widely distributed fronto-parietal network is activated in healthy women, far fewer regions are activated in AN women, as if the brain was inhibiting the level of processing. In addition, there is decreased activation in the insula, the prefrontal cortex, and precuneus compared with healthy controls (Fig. 203.3).

203.6 Explanatory Models for Body Image Disturbance in AN

The following models are neurobiological accounts for body image disturbance and body size disturbance. Using available evidence they focus on various regions of potential dysfunction that are *not* mutually exclusive. Rarely, AN is mimicked by brain lesions in the cortical and subcortical regions (Uher and Treasure 2005). These lesions have been in the frontal and parietal lobes and have presented with typical AN psychopathology. This does suggest that body image relies on a widespread network which can be disturbed with damage to connecting white matter tracts or directly to neuronal correlates. The explanatory models are not irreconcilable with psychosocial formulations.

203.6.1 Parietal Lobe Dysfunction and Distorted Templates

The *existence* of multiple body schema templates is supported by diverse clinical presentations following damage to the right parietal lobe (Berlucchi and Aglioti 1997). Multiple supernumerary phantom limbs and somatoparaphrenia can develop together or separately following damage to the right SPL (Vallar and Ronchi 2009). A bizarre clinical picture arises in which the person delusionally attributes ownership of their paralyzed arm to someone else and claims the phantom arm as real. A number of case studies have described the existence of "articulated" phantom limbs in subjects who suffer from congenital absence of limbs (Funk et al. 2005). In a study using plasticine modeling, congenitally blind children did internalize a representation of their bodies but compared with that of sighted children, it was impoverished and systematically distorted (Kinsbourne and Lempert 1980). These examples suggest that there are preformed templates in the right parietal lobe that are malleable and can be distorted.

There is some evidence that body size awareness is a template. Disturbances in size awareness in obesity vary depending on the age of onset. People who become obese as adults have a more realistic awareness of body size than those who suffer lifelong obesity (Bruch 1973). Exaggerated size perception occurs in healthy children, adolescent girls, and adults (Killen et al. 1996; Cooper et al. 2007). Bruch (1973) refers to adults with exaggerated interpretations of curved flesh as "thin fat people." Hypometabolism in parietal regions has been found in resting studies (Delvenne et al. 1997) and in body processing in AN (Uher et al. 2005). Structural studies do suggest that temporal and parietal regions are vulnerable to persisting damage (Castro-Fornieles et al. 2009). It is possible that small functional neuronal clusters in the posterior parietal lobe (right SPL, right IPL, and precuneus) operate in parallel, and in conjunction with the insula and medial frontal cortex, give the conscious experience of body schema and body size.

The small percentage of young women at greatest risk of developing AN have some degree of size distortion. The prodromal templates may be distorted due to genetic or other biological forces. The young women internalize the socio-cultural bias against fatness, and develop strong body dissatisfaction. The speed and extent of weight loss in the still developing brain seems to "lock in" the distortion by affecting vulnerable region(s) via starvation, nutritional deficiencies, and hormonal disruption. The distorted body size cannot be updated by real-time information. Neither the fear of fatness nor the experience of fatness is alleviated by weight loss and can persist after weight recovery. This suggests that the distorted template is not a function of low weight.

There are numerous examples including somatoparaphrenia, supernumerary phantom limbs, and BIID that show that the human brain has the capacity to use bizarre rationalizations to fit its templates regardless of contradictory data. The word phantom is used in various body schema disturbances. Experientially, the young woman is trapped in a fat phantom body, with varying degrees of insight to her predicament. Despite objective facts such as weights or reliable contrary evidence from trusted friends and family, the young woman will trust her phantom body.

203.6.2 Insula Hypofunction and Body Integration

There are certain factors that make the insula a region of interest, in particular its links with other brain regions. The insula integrates interoceptive, body-related, and self-related information. The insula has been recognized as a key region involved in the representation of the body schema (Bonda et al. 1995), with its ability to integrate information from multiple sensory modalities (Schneider et al. 1993). Somatoparaphrenia can occur from insula damage suggesting that body processing is shared with the parietal lobe. Resting studies in AN have found hypometabolism in the insula
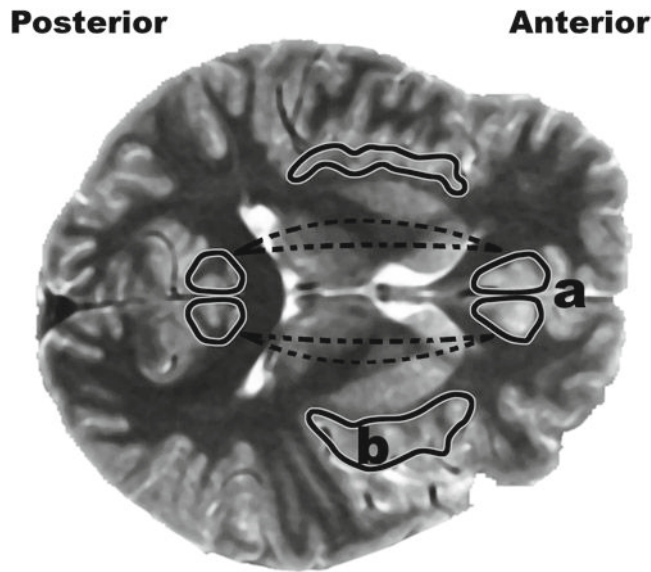
Fig. 203.4 Insula hypofunction and body integration. The concept of body image includes emotional and attitudinal components. The regions of interest include the insula (**b**), cingulate gyrus (**a**), and the amygdala comprising the emotional system and the hippocampus for the internalized attitudes to the body. The insula lies within the Sylvian fissure and has a unique contribution to make to body image as it acts as a limbic integrating centre. It is involved in interoceptive perception which encompasses bodily sensations including pain, hunger, satiety, and information from the viscera. It is reciprocally connected with the parietal lobe via the somatosensory cortex and the inferior parietal lobule. The metarepresentation of subjective feelings is contained in the anterior insula. It is linked with the anterior cingulate cortex which serves as the motor representation of emotion. These connections make the insula well placed to integrate body introceptive, body schema, and emotional information. Insula hypofunction in anorexia nervosa may compromise the efficient integration of information resulting in body size distortion and disturbed hunger/satiety signals

(Kojima et al. 2005). In AN there is decreased activation of the insula in self body processing (Sachdev et al. 2008). The dysfunction potentially arises from recursive interplay between distorted hunger/satiety signals (Muller et al. 2008) and distorted body sensory signals. If due to hypofunction the insula is not able to integrate information efficiently and/or is receiving inaccurate information, disturbance in body size awareness may result (Fig. 203.4).

203.6.3 Amygdala-Hippocampal Hyperfunction

The amygdala plays a role in modulating body image. There are several transient factors that negatively affect the perceptual and attitudinal body image components in healthy women, including imagining of different social situations (Haimovitz et al. 1993), recent food intake (Vocks et al. 2007), and induction of negative mood states (Plies and Florin 1992). In anorexic women, recent food intake causes increased distortion of size estimation (Crisp and Kalucy 1974). The amygdala plays a dynamic role in body image by assigning affective significance to every changing external and internal sensory event. A functional magnetic resonance imaging (fMRI) study in which AN subjects viewed images of high-calorie or low-calorie food showed increased activation in the left hemisphere of insula, anterior cingulate gyrus, and amygdala-hippocampal region (Ellison et al. 1998; Uher et al. 2004) which make up the fear network. In anorectic patients, confrontation with

their own distorted body shape was associated with activation of the right amygdala (Seeger et al. 2002).

Resting studies showed increased perfusion (Takano et al. 2001), and structural studies showed persisting atrophy to the amygdala-hippocampal complex (Giordano et al. 2001).

This is suggestive of high anxiety and stress-induced damage (Harrison and Critchley 2007). The development of phobias is likely to develop during the dieting phase and evolve with the disease. Clinically one observes a generalizing of fears with a decreasing range and amount of foods consumed, people with whom food is consumed, and places where food is consumed. The amygdala has a specific role in enhancing memory consolidation. A receptor stimulated by adrenaline, the alpha-2B receptor, acts to consolidate memories. Individuals with one of two variants of this receptor have better emotional memories (De Quervain et al. 2007). A similar mechanism could arguably make AN brains vulnerable to the sensitization of high calorie food (Sachdev 2009).

The widespread inhibition seen in self-processing in AN (Sachdev et al. 2008) may be mediated via the amygdala. Subcortical input to the cortex is weak but feedback is massive (Logothetsis 2008). Specialized sensory information travels from the thalamus via a quick pathway to the amygdala and a slower pathway to the cortex (LeDoux 1996). The amygdala projects to the cortex including the insula (Shelley and Trimble 2004) and visual cortex (Chen et al. 2009). Feedback from the cortex to subcortical structures may modulate the quality of sensory information it receives early in an emotional episode.

203.6.4 Left–Right Hemispheric Imbalance

The role of the right hemisphere in body-related processes seems relatively stronger than the left hemisphere (Springer and Deutsch 1998). It has been suggested that the left hemisphere stores prototypes more effectively and anorexic women store an inappropriately fatter body image. In a divided visual field experiment, anorexic women judged themselves equal to fat distortions of their own body, more quickly when the stimuli was presented to the left hemisphere (Smeets and Kosslyn 2001). Lesions in the fronto-parietal regions that have mimicked AN have had a right hemispheric preponderance.

Anosognosia (unawareness of illness) of the emaciated state often occurs in AN. It is often masked by the opposite assertion of being fat but sometimes the person just claims to be of normal weight. Anosognosia usually occurs in a right hemispheric stroke and when confined to the right parietal lobe the unawareness tends to be confined to body image. A possible explanation for this phenomenon is that with a right–left hemispheric imbalance, the dominant left hemisphere compensates by creating a false mental schema (Ramachandran and Rogers-Ramachandran 1996). One can speculate that in AN, a distorted body template in the left parietal lobe falsely dominates the hypofunctioning right parietal lobe/template.

203.7 Prognostic Implications and Treatment

Body image disturbance causes significant distress, persists even following otherwise successful treatment (Windauer et al. 1993), and is a reliable predictor of relapse (Rosen 1990). The large number of studies concerning the assessment of negative body image in AN stands in contrast to the few attempts to influence the way these patients actually experience their bodies. Although treatment

programs specifically targeting body image concerns have been developed, no randomized controlled trials for adolescent and adult eating disorders exist (Herpertz-Dahlmann and Salbach-Andrae 2009). Cognitive techniques are used to identify and modify negative body-related thoughts. Treatment approaches that address the disturbance in body size awareness directly aim to correct the distortion by providing corrective feedback. Components include body exposure and desensitization using full-length "mirror confrontation" with the aim of developing a more objective or realistic view of their shape. Small pilot studies using mirror confrontation have shown improvement in body dissatisfaction and body avoidance in AN (Key et al. 2002; Vocks et al. 2007). Body image therapy is often a component of AN treatment and requires research into its efficacy.

203.8 Applications to Other Areas of Health and Disease

The treatment of AN requires a unified team including dieticians, nurses, psychologists, psychiatrists, and physicians. The most difficult aspect of treating a person with AN is engagement in the therapeutic process. This is in no small part due to the fear caused by body size distortion. Nutritional, psychological, and nursing care can be informed by this, in particular in understanding why sometimes patients seem to sabotage treatment.

Inclusion of strategies that are psycho-educative and mindfulness-based allows acceptance of some degree of body distortion while the patient, family, and treating team work together toward recovery. Demonstrating a biological basis to AN may help in decreasing stigma within the community and families.

Body size distortion seems to be present across eating disorders including bulimia nervosa (BN), binge eating disorder and obesity. People of a healthy weight with BN may perceive themselves as fat and people who are obese may underestimate their size (Bruch 1973). As with AN, treatment interventions need to increase the patient's awareness of their size distortion, with the aim of normalizing the eating behavior.

203.9 Conclusions

AN is a window into the new neuroscience in which the psychological and neurobiological interweave like vaporous threads. It illustrates how the environment can act on the brain to produce changes which in turn influence the environment the individual creates (Sachdev 2009). In this sense, it can serve to take the blame away from patients and their families, who are all victims of the brain's distortion. It helps explain why AN sufferers are so trapped by the illness. In effect, the young woman is being asked by others to put on weight, while her own brain is telling her the one thing she dreads, that "she is already fat."

While acknowledging psychological and social factors, one must accept that in true AN women distort their body size. Various explanatory models for disturbance in body size awareness have been outlined. The unifying theme is that there is discrepancy between the body size perception and its internal template representation. This causes distress and phobic avoidance of an ever-increasing list of factors associated with weight gain. There is a breakdown in self-awareness that leads the anorexic woman to vehemently deny her low weight, which is congruent with her experience, albeit irrational, of the judgment of those around her.

Summary Points

- Some body schema disturbances can be accounted for purely by neurobiological explanations. The disturbance in body size awareness can be explained plausibly only by including psycho-social factors in an extension of the neurobiological hypothesis.
- There is evidence of body size distortion and body image disturbance in some healthy girls and young women prior to developing AN. As actual body size increases around puberty, and changes occur in body shape, dissatisfaction with body image occurs for a number of psycho-social reasons, and young women often resort to weight-reducing diets.
- The "distorted size awareness" is clinically detectable after rapid and substantial weight loss. There is a spectrum of insight into the emaciated state, ranging from open acknowledgment to total denial.
- Brain imaging shows that women with AN seem to process the bodies of *other* women in the same way that healthy women do, indicating that there is no disturbance in the functional capacity of the perceptual part of the brain.
- Brain activity is quite discrepant when an anorexic woman processes her *own* body, with decreased activation in fronto-parietal network, in particular the insula, the prefrontal cortex, and precuneus.
- Body image and body size disturbance causes significant distress during illness and recovery, persists even after weight restoration, and is a predictor for relapse.
- Though a number of treatments for body image disturbance have been described, no controlled trials have yet been carried out into their effectiveness.

Definitions

Body schema: The conscious tactile-kinesthestic (felt) awareness of one's own body.

Body dissatisfaction: Negative emotions and cognitions toward one's body size or appearance.

Body size distortion: Distortion in size awareness which is modulated by cognitive style, emotional state, and introceptive awareness.

Body image: A theoretical dynamic construct of the body with physical, perceptual, visceral, emotional, and cognitive dimensions. It subsumes the definitions of body schema, body dissatisfaction, and body size distortion. It is a product of biological, psychological, and socio-cultural forces.

Anosognosia (from Greek, "a" without, "nosos" disease and "gnosis" knowledge): A broad term which could be used for denial of any type of neurological deficit. The unawareness in anosognosics persists despite logical arguments and the demonstration of contradictory evidence. There is a spectrum of insight into body size distortion in AN with a proportion of patients unaware of their emaciated state.

Somatoparaphrenia: The person disowns the paralyzed left limb, finds it repugnant, may try to dispose it, and rationalizes its presence in incongruous ways. It is often brought about by extensive right-sided lesions or localized to the R superior parietal lobule or more rarely insular damage. The delusion disappears after some weeks though the paralysis remains.

> **Key Point**
>
> **AN Without Body Size Disturbance**
>
> It is worth noting that there is a subgroup of AN *without* disturbance in body size awareness.
>
> These women, as equally unwell as *true* anorexics, do not report a significant drive for thinness or a morbid fear of becoming fat. They acknowledge their emaciation and seem to restrict food to avoid somatic symptoms and anxiety. Prevalence within AN overall varies but has been reported in up to 20% of the AN population (Ramaciotti et al. 2002). Lasegue (1873) originally described "vague sensations of fullness, of pain occurring postprandium or at the beginning of the meal." Tourette (1895) labeled his group "Anorexia Gastrique" as they seemed to suffer a phobic anxiety about gastric pain. The visceral and emotional symptoms are present in all anorexic patients but in this atypical group, they dominate the clinical picture. The groups may represent opposite ends of the spectrum of body size distortion with a mixture in between. One could hypothesize that there may be differences in the underlying neural disturbance between the two extremes.
>
> Subjective awareness of emotional state is based on the neural representation of the physiological state. This function is carried out by the anterior insula cortex (Craig 2009). The right anterior insula showed the greatest activity in those who were most viscerally aware (Critchley et al. 2000). The sensitivity to interoceptive information is increased by lean body composition (Rouse et al. 1988). Anxiety and anxiety disorders are prevalent in women who develop eating disorders (Raney et al. 2008). The atypical group may initially restrict food as a result of visceral sensations and distressing emotions, and eventually develop a phobic avoidance.
>
> Bruch (1978) acknowledged the existence of earlier descriptions but wrote, "yet I call it a new disease because it is only in the last 15 years to 20 years that AN is occurring at an increasingly rapid rate." The atypical group may have been the predominant presentation over 100 years ago. The cultural bias toward thinness which has resulted in the "normative discontent" (Rodin et al. 1985) that healthy women feel about their bodies may have *negatively selected* for the true anorexic and explains the increased prevalence of AN.

References

Berlucchi G, Aglioti S. Trends Neurosci. 1997;20:560–4.

Blanke O, Mohr C, Michel C, Pascual-Leone A, Brugger P, Seeck M, Landis T, Thut G. J Neurosci. 2005;25:550–7.

Bonda E, Petrides M, Frey S, Evans A. Proc Natl Acad Sci USA. 1995;92:11180–4.

Brang D, McGeoch PD, Ramachandran VS. NeuroReport. 2008;19:1305–6.

Bruch H. Eating disorders, obesity, anorexia nervosa and the person within. Great Britain: Routledge and Kegan Paul; 1973.

Bruch H. The golden cage. Somerset: Open Books; 1978.

Cash TF, Deagle EA. Int J Eat Disord. 1997;22:107–25.

Castro-Fornieles J, Bargallo N, Lazaro L, Andres S, Falcon C, Plana M, Junque C. J Psychiatr Res. 2009;43:331–40.

Chen Y, Zhu B, Shou T. J Neulet. 2009;453:126–30.

Cooper M, Deepak K, Grocutt E, Bailey E. Eur Eat Disord Rev. 2007;15:366–72.

Cooper P, Taylor Z, Cooper M, Fairburn C. Int J Eat Disord. 1987;6:485–94.

Craig AD. Nat Rev. 2009;10:59–70.

Critchley HD, Elliot R, Mathias CJ, Dolan RJ. J Neurosci. 2000;20:3033–40.

Crisp AH, Kalucy RS. Br J Med Psych. 1974;47:349–61.

Delvenne V, Goldman S, De MV. Psychiatry Res. 1997;74:83–92.

De Quervain DJF, Kolassa IT, Ertl V, Onyut PL, Neuner F, Elbert T, Papassotiropoulos A. Nat Neurosci. 2007;10:1137–9.

Ellison Z, Foong J, Howard R, Bullmore E, Williams S, Treasure J. Lancet. 1998;352:1192.

Fisher S. In: Cash TF, Pruzinsky T, editors. Body images: development, deviance and change. New York: The Guildford Press; 1990. p. 3–20.

Funk M, Shiffrar M, Brugger P. Exp Brain Res. 2005;164:341–6.

Giordano GD, Renzetti P, Parodi RC, Foppani L, Zandrino F, Giordano G, Sardenelli F. J Endocrinol Invest. 2001;24:510–4.

Haimovitz D, Lansky LM, O'Reilly P. Int. J. Eat Disord. 1993;13:77–84.

Harrison N, Critchley H. Br J Psychiatry. 2007;191:192–4.

Head H. Brain. 1918;41:57–253.

Herpertz-Dahlmann B. Child Adolesc Psychiatr Clin N Am. 2009;18:31–47.

Herpertz-Dahlmann B, Salbach-Andrae H. Child Adolesc Psychiatr Clin N Am. 2009;18:131–45.

Hodzic A, Muckli L, Singer W, Stirn A. Hum Brain Mapp. 2009;30:951–62.

Johnson S, Baxter L, Wilder L, Pipe J, Heiserman J, Prigatano G. Brain. 2002;125:1808–14.

Kaye W. Physiol Behav. 2008;94:121–35.

Keenan J, Gorman J. Cortex. 2007;43:1074–82.

Key A, George CL, Beattie D, Stammers K, Lacey H, Waller G. Int J Eat Disord. 2002;31:185–90.

Killen JD, Taylor CB, Hayward C, Haydel KF, Wilson DM, Hammer L, Kraemer H, Blair-Greiner A, Strachowski D. J Consult Clin Psychol. 1996;64:936–40.

Kinsbourne M, Lempert H. J Gen Psych. 1980;102:33–7.

Kojima S, Nagai N, Nakabeppu Y, Muranaga T, Deguchi D, Nakajo M, Masuda A, Naruo T. Psychiatry Res. 2005;140:251–8.

Lasegue C. Med Times Gazette. 1873;2:367–9.

LeDoux J. The emotional brain. New York: Touchstone; 1996.

Legrand D, Ruby P. Physiol Rev. 2009;116:252–82.

Logothetsis N. Nature. 2008;453:869–78.

Marchi M, Cohen P. J Am Acad Child Adolesc Psychiatry. 1990;29:112–7.

Macrae C, Moran J, Heatherton T, Banfield J, Kelley W. Cereb Cortex. 2004;14:647–54.

McFarlane AC. Can J Psychiatry. 1989;34:431–3.

Muller T, Focker M, Holtkamp K, Herpertz-Dahlmann B, Hebebrand J. Child Adolesc Psychiatr Clin N Am. 2008;18:117–29.

Nickel J, Seitz R. Anat Embryol. 2005;210:463–72.

Peelen MV, Downing PE. Nature. 2007;8:636–48.

Penfield W, Rasmussen T. The cerebral cortex of man: a clinical study of localization of function. New York: MacMillan; 1950.

Plies K, Florin I. Psychol Health. 1992;7:235–42.

Probst M, Vandereycken W, Van Coppenolle H, Pieters G. J Psychosom Res. 1998;44:451–6.

Ramachandran VS, Rogers-Ramachandran D. Nature. 1996;382:501.

Ramaciotti CE, Dell'Osso L, Paoli RA, Ciapparelli A, Coli E, Kaplan AS, Garfinkel P. Int J Eat Disord. 2002;32:206–12.

Raney TJ, Thornton LM., Berrettini W, Brandt H, Crawford S, Fichter MM, Halmi KA., Johnson C, Kaplan AS, LaVia M, Mitchell J, Rotondo A, Strober M, Woodside DB, Kaye WH, Bulik CM. Int J Eat Disord. 2008;41:326–32.

Rizzolati G, Luppino G, Matelli M. Electroencephalogr Clin Neurophysiol. 1998;106:283–96.

Roberts ME, Tchanturia K, Stahl D, Southgate L, Treasure J. Psychol Med. 2007;37:1075–84.

Rodin J, Silberstein LR, Striegel-Moore RH. In: Sonderegger R, editor. Nebraska symposium on motivation. Lincoln: University of Nebraska; 1985. p. 267–307.

Rosen J. In: Cash TF, Pruzinsky T, editors. Body images: development, deviance and change. New York: The Guildford Press; 1990. p. 190–214.

Rouse C, Jones G, Jones K. Psychophysiology. 1988;25:400–7.

Sachdev P. The yipping tiger and other tales from the neuropsychiatric clinic. Sydney: New South Press; 2009.

Sachdev P, Mondraty N, Wei W, Gulliford K. Neuropsychologia. 2008;46:2161–8.

Schneider R, Friedman D, Mishkin M. Brain Res. 1993;621:116–20.

Shelley B, Trimble M. World J Biol Psychiatry. 2004;5:176–200.

Seeger G, Braus D, Ruf M, Goldberger U, Schmidt M. Neurosci Lett. 2002;326:25–8.

Skrzypek S, Wehneier PM, Remschmidt H. Eur Child Adolesc Psychiatry. 2001;10:215–21.

Smeets MAM, Kosslyn SM. Int J Eat Disord. 2001;29:409–16.

Springer S, Deutsch G. Left brain, right brain. San Francisco: W.H Freeman; 1998.

Striegel-Moore R, McAvay G, Rodin J. Int J Eat Disord. 1986;5:935–47.

Sugiura M, Sassa Y, Jeong H, Miura N, Akitsuki Y, Horie K, Sato S, Kawashima R. Neuroimage. 2006;24:143–9.

Takano A, Shiga T, Kitagawa N, Noyama T, Katoh C, Tsukamoto E, Tamaki N. Psychiatry Res. 2001;107:45–50.

Tanner JM, Whitehouse RH. Acta Med Auxologica. 1977;9:29.

Tanner JM. Acta Paediatr Scand. 1990;79:963–5.

Tourette G. Traite clinique et therapeutique de l'hysterie. Paris: Nourit et Co; 1895.

Tsakiris M, Constantini M, Haggard P. Neuropsychologia. 2008;46:3014–8.

Uddin LQ, Molner-Szakacs I, Zaidel E, Iacoboni M. Soc Cogn Affect Neurosci. 2006;1:65–71.

Uher R, Murphy T, Brammer MJ. Am J Psychiatry. 2004;161:1238–46.

Uher R, Murphy T, Friedrich H, Dalgleish T, Brammer MJ, Giampieto V, Phillips ML, Andrew CM, Ng VW, William SCR, Campbell IC, Treasure J. Biol Psychiatry. 2005;58:990–7.

Uher R, Treasure J. J Neurol Neurosurg Psychiatry. 2005;76:852–7.

Vallar G, Ronchi R. Exp Brain Res. 2009;192:533–51.

Vocks S, Legenbauer T, Heil A. Appetite. 2007;49:467–75.

Williamson DA, Davis CJ, Bennett SM, Goreczny AJ, Gleaves DH. Behav Assess. 1989;11:433–46.

Windauer U, Lennerts W, Talbot P, Touyz SW, Beumont PJV. Br J Psychiatry. 1993;163:195–200.

Wolpert DM, Goodbody SJ, Husain M. Nat Neurosci. 1998;1:529–32.

Chapter 204
Motor Learning Approaches for Improving Negative Eating-related Behaviors and Swallowing and Feeding Skills in Children

Justine Joan Sheppard

Abbreviations

DST   Dynamic systems theory
NICU   Neonatal intensive care unit
SLP   Speech-language pathologist

204.1 Introduction

Infants and young children experience a complex of sensations, movements, and interactive behaviors during eating and swallowing. These early experiences support the development of eating and swallowing skills and shape the child's behaviors for participation in eating situations. Both acquisition of eating skills and associated motivations for eating and eating-related behaviors are often affected when events occur during the development of eating skills that disrupt this process. The risk for the disruption of eating motivation and behaviors is intensified if the child has a co-occurring physiological or psychological disorder (Chatoor 2009b; Cooper-Brown et al. 2008; Lefton-Greif and Arvedson 2007; Sullivan 2008). Food refusal and disruptive mealtime behaviors may be exacerbated as the child struggles to avoid eating challenges that require skills that have not yet developed sufficiently to meet the demands (McKirdy et al. 2008; Sheppard 2008).

Although the prevalence of this profile of co-occurring delay in acquisition of developmental skills for eating and motivational and behavioral difficulties associated with eating is not known, the interaction is suggested by the high prevalence of feeding disorder in children with developmental delays, 33–80%, as compared with that in typically developing children, 25–45% (Burklow et al. 1998; Linscheid 2006). Clinical experience in both diagnosis and treatment of children with swallowing and feeding disorder support the contention that consideration of this association between skills and behaviors is central to resolving both problems and achieving the desired outcomes of mature skills and appropriate eating behaviors (Sheppard 1994, 2008). The purpose of this chapter is to consider the strategies derived from research on acquisition of skilled movement behaviors that may be useful for their treatment.

J.J. Sheppard (✉)
Department of Biobehavioral Sciences, Teachers College, Columbia University,
525 W. 120th Street, New York, NY 10027
e-mail: jjs74@columbia.edu

204.2 Developmental Acquisition of Mature Motor Skills for Swallowing and Eating

Typically, children acquire the generally recognized sequence of "milestone" eating skills from birth to 2 years. These include competencies for sucking, transition from nipple to spoon feeding, biting and chewing foods from soft to firm, from single pieces to multiple pieces, complex consistencies, drinking from cup and straw and independent feeding with hands and a progression of utensils culminating in mature function (Delaney and Arvedson 2008; Carruth and Skinner 2002). Underlying these milestone skills are subskills and related neuro-motor competences that support the advancing skills and the child's nutritional need to consume increasing amounts of food within a conventional meal time period. The underlying competencies include: (a) changes in the biomechanics of the oral-pharyngeal phase of swallowing from a suck-swallow to the mature pattern for bolus manipulation and propulsion, (b) ability to swallow larger boluses, (c) ability to swallow more viscous boluses, and (d) ability to tolerate and manage increasing coarseness in food texture and increasing variety of food tastes (McKirdy et al. 2008; Sheppard 1994). Furthermore, these skills and subskills are dependent on parallel development in the collaborative functions, breath control, body postural control, and use of shoulder, arm, and hand (Carruth and Skinner 2002).

Inherent in this developmental process is learning to identify and integrate experiential information associated with eating and swallowing that includes contact sensation for touch, pressure, temperature, and taste; distance sensations for smell, vision, and hearing; proprioceptive information for position and movement of joints and muscles, body position in space, respiration, hunger, thirst, and the condition of the gut (Table 204.1)(Hadders-Algra 2000b; Sheppard 2008).

There is a level of physiological maturity that determines the earliest age at which the child can engage in learning each of these skills (Sheppard 1994; Sheppard and Mysak 1984); however, the age at which children achieve functional competency varies with the individual care-giving practices for introduction of utensils and food types, for seating during eating, for presenting opportunities for advancing eating skills and independence, and for supporting the child in mastering these skills. The typical period for acquisition of these milestones coincides with a period of brain plasticity that facilitates learning of the skills and the co-occurring, motivational, and behavioral dynamics (Johnson 2004; Kolb et al. 2004). For example, specific intervals within this period of brain plasticity have been found to be significant for chewing skills and taste tolerances. Six months of age has been noted to be the critical and sensitive period for beginning acquisition of chewing skills, with aversive responses to texture and difficulty in acquiring chewing skills occurring when chewable foods are introduced after age 10 months (Illingworth and Lister 1964; Johnson 2004). Differential awareness and preference for tastes have been noted to emerge from birth through 2 years of age (Menella and Beauchamp 1998) with experience-dependent effects found in the first six months (Gerrish and Menella 2001).

204.3 Acquisition of Motivation and Pragmatics for Eating

Maturation of eating skills and the emotional underpinnings for the pragmatics of eating develop in tandem. The pragmatics of eating refers to its social components, the context-dependent behaviors for eating, and the relationships between the involved parties. Homeostasis, attachment, separation, and individuation, evolving as physiological and emotional capabilities, are expressed in the

Table 204.1 The developmental progression of eating skills and subskills culminating in mature swallowing and feeding function

Milestone eating skill	Swallowing and feeding subskills	Related postural and manipulative subskills
Sucking	• Suck–swallow–breathe coordination for nipple feeding • Expression–suction balance needed for a specific nipple system • Oral grasp and containment of nipple and fluid • Ability to expel nipple from mouth • Generalization of sucking skills/performance to different nipples, feeding partners, and independence	• Alerting, orienting head and mouth toward food and opening mouth • Semi-reclining postural alignment and stabilization • Holding hands on breast/bottle during sucking • Strength and stamina for task
Transition feeding from nipple to spoon	• Adjustment of oral initiation of the reflexive swallow and pharyngeal phase swallowing dynamics to accommodate changing oral and pharyngeal anatomy • Swallow–breathe coordinations for larger and more viscous boluses • Removing food from spoon, containing and transferring into place for swallowing • Ability to expel food	
Spoon feeding variety of foods that do not require mastication	• Transition of swallow dynamics from suck–swallow to propulsion swallow • Sensory tolerances for variety of food tastes and textural coarseness • Ability to contain and process coarser and more viscous food and transfer into place for swallowing • Tongue propulsion forces for more viscous and larger boluses	• Transition from semi-reclining to upright postural alignment and stabilization • Increasing participation in feeding with upper body movement toward approaching bolus
Biting	• Alignment of mandible and maxilla for severing • Crushing force onset and offset for biting • Ability to contain and expel pieces	• Independence strategies – holding food in hand while controlling oral participation (beginning finger-feeding)
Chewing	• Mouth opening timing, size and shape adjustments for bolus characteristics, and techniques of the feeder • Ability to contain, collect, and transport for mastication and expelling • Ability to coordinate mandible, tongue, and cheek movements for mastication • Ability to control cyclical crushing force onset and offset • Judgment of swallow-ready consistency • Tongue propulsion dynamics for progression of increasing levels of chewing difficulty • Tongue propulsion forces for more viscous and larger boluses	• Independence strategies – self-feeding with fingers

(continued)

Table 204.1 (continued)

Milestone eating skill	Swallowing and feeding subskills	Related postural and manipulative subskills
Drinking from cup and straw	• Lip and cheek coordination for maintaining mouth on cup or straw • Ability to sip • Sequential sip-swallow • Ability to contain and control a low viscosity/low cohesiveness bolus • Ability to initiate time of swallow for the faster moving liquid bolus	• Head–neck postural alignment and control for cup/straw drinking • Independence strategies – holding cup or straw in hand while controlling oral participation
Independence	• Coordinating /controlling skilled, simultaneous hand–mouth functions • Pacing size of bolus • Pacing rate of food intake • Alternating foods and food and liquid • Maintaining acceptable, age-appropriate neatness	• Upper body and upper extremity control • Maintaining utensils and food on tray/table

The motor capabilities in developmental swallowing and feeding skills are expressed in milestones. Embedded in these milestones are the underlying swallowing and feeding subskills, the related postural and manipulative capabilities, and stamina for performance and completion of the meal

Table 204.2 The pragmatics for swallowing and eating activities

Pragmatic categories in eating	Examples
Tolerance for variation in eating activities	• Eating environments • Eating partners • Food tastes and viscosities • Postural alignments and seating
Psychosocial skills	• Separation and emerging independence • Regulation of feeding routines • Compliance to guiding adult • Dyad reciprocity
Attending	• Transition to and from other activities • Maintaining attention • Alternating attention
Self-reliance	• Tolerating trial and error learning • Persisting at task following error

The pragmatics of eating emerges as a developmental sequence resulting from the psychosocial interaction between the child and their social environment

interactive pragmatics of eating. Eating is a setting in which the infant and young child are seen to practice these emerging psychosocial skills. Strategies for dyadic reciprocity; for communicating hunger, satiety, and preferences; and for asserting independence are worked out by infant and caregiver in the arena of their daily eating experiences (Chatoor 2009a; Davies et al. 2006; Satter 1990). These behaviors are expressed in the natural environment as an integral part of swallowing and eating function (Table 204.2).

The child's motivation for eating and the pragmatics for expressing eating preferences result from the accumulated intrinsic (organic) and extrinsic (environmental and interpersonal) experiences that are associated with eating and the resulting conditioned expectations for positive and negative outcomes. Conditioned aversions and affinities associated with eating tend to be relatively resistant to

change over time. General observation of typical populations suggests that preferences (and aversions) for food, eating partners, and eating routines tend to be long lasting.

204.4 Abnormal Diet-related Eating Skills and Behaviors

It is useful to conceptualize pediatric swallowing and feeding disorders as consisting of a complex interaction of developmental, psychosocial, and organic features that cut across etiologies. These features have been considered in classification systems. Manikam and Perman (2000) postulated the categories of medical, nutritional, behavioral, psychological, and environmental as etiologies for pediatric swallowing and feeding disorder. They found these etiologies to occur in clusters, rarely as independent causes. Burklow et al. (1998) segmented the medical etiology into structural, neurological, cardio-respiratory, and metabolic categories with the additional, "behavioral issues." In their study most children presented with more than one category of disorder, with 85% coded as having behavioral problems as part of the cluster. Other comorbidities have been reported. Digestive function problems, including esophageal reflux, and frequent middle ear infections, have high prevalence in children seen for early feeding intervention (Fluehr et al. 2004; Sullivan et al. 2000). Prematurity and associated neonatal intensive care unit (NICU) experience, vision and hearing impairments, and speech-language pathology (SLP) diagnoses, including speech and language disorders and delays and familial issues have been seen to cluster with the need for swallowing and feeding intervention (Fluehr et al. 2004). The high prevalence of behavioral problems across classifications and etiologies suggest that behavioral problems may occur as both a primary problem, associated with psychological and neuropsychiatric etiologies, and a secondary problem, occurring in children with primary anatomical, neurological, medical, and developmental etiologies.

Udall (2007) conceptualized functional categories of pediatric swallowing and feeding problems as developmental, gut motility, behavioral problems, and neurological impairment. The developmental category included skill sets (subskills and milestone skills) needed for advancing from nipple feeding, through the various developmental levels of function leading to mature, independent, nutritionally satisfactory, swallowing, and feeding behaviors. Although the developmental sequences and age expectations for eating skills and subskills in typically developing children and the characteristics of delayed development have been well documented (see Delaney and Arvedson 2008, for a recent review), information is sparse on the prevalence of delayed development of skills in the various etiologies or diagnostic categories of swallowing and feeding disorder.

Delayed development of eating skills and subskills may occur as a primary disorder in children with cognitive impairment and neuro-motor disorders, such as cerebral palsy and apraxia. Additionally, the delay may be secondary to those medical or behavioral disorders that interfere with the child's access to the sensory and motor experiences necessary for advancing skills Whether the failure to develop skills is seen as a primary or secondary disorder, symptom-specific intervention is needed to support acquisition of mature swallowing and eating skills and behaviors and to develop optimum quality of performance (Hadders-Algra 2000b; Manikam and Perman 2000; Sheppard 2008).

204.5 Treatment Approaches

Given the complexity of pediatric swallowing and feeding disorder, a multifactorial approach is indicated that assures that medical problems have been stabilized or resolved, the caregiver is included in the process, informed, and supported appropriately, the child's swallowing capabilities are determined

to be adequate for the demands of the program, the therapeutic tasks are within the child's physiological capabilities with respect to oral, pharyngeal, esophageal, and gastrointestinal function and the child's nutritional status is not compromised (McKirdy et al. 2008; Schauster and Dwyer 1996). In general, research has focused on strategies to improve medical, behavioral, and movement disorder (Manikam and Perman 2000), in some instances combining a variety of interventions (McKirdy et al. 2008; Williams et al. 2007) and in some instances exploring effectiveness of an individual strategy or category of strategies (Gisel 1996; Pizzo et al. 2009; Pinnington and Hegarty 2000).

The question of whether it is more effective to treat the behavioral and movement aspects of swallowing and feeding disorder separately or in a combined program was addressed in a study of school-aged children who exhibited both negative behaviors and impaired skills (Bailey and Angell 2005). In this study, the combined program resulted in greater improvement in both mealtime behaviors and skills than did the same strategy sets implemented separately.

204.6 Treating the Developmental Motor and Behavioral Disorder

Dynamic Systems Theory (DST) has provided the foundation for strategies to treat developmental motor disorders (Thelen 1995). The theory posits development as resulting from the interactions of body biomechanics, brain structures, psychosocial characteristics and specific environmental stimulation, support, and structure. Rather than consider motor development as an unfolding of a predetermined sequence of skill as had earlier theories (Hadders-Algra 2000a), DST posited an interaction between nature and nurture that suggested that trial and error learning and behavior were integral to the process. Hadders-Algra (2000b) further postulated that structured sensory and motor experiences form neuronal networks that support the child's learning for advancing developmental skills and improving their efficiency.

The motor sciences literature provides research-based guidance for optimizing the learning environment. This evidence base can be used to advantage to advance eating skills and prevent or remediate negative mealtime behaviors. The strategies have been found to be effective for transitioning school-aged children from tube to oral feeding. These children exhibited food refusal and negative eating behaviors that, heretofore, had prevented their developing the skills needed for a successful transition and subsequent maturation of eating skills and behaviors (McKirdy et al. 2008). The program consisted of five steps to address the differential training needs at the early, intermediate, and advanced stages of motor skill learning. The first three steps supported the early learning stage during which behaviors were brought under control of a guiding adult in instructional noneating and eating-related tasks. The fourth step supported early and intermediate stage learning during which eating skills were trained in individualized sequences that were configured for the child's physiological and developmental capabilities. The fifth step supported the advanced stage in which the skill levels were advanced to enable eating with new eating partners and in new environments. The five steps were repeated, as needed, as transitions were made from one training objective to the next.

204.7 Motor Learning Strategies

Motor learning strategies are appropriate for selecting appropriate practice tasks, developing and improving the child's eating behaviors, and structuring the child's practice opportunities (Tables 204.3 and 204.4).

Table 204.3 Developmental attention skills and examples of parallel developmental eating activities

Developmental levels of attention	Examples of eating activities
Focused attention to a simple continuous target	Sucking from a nipple
Sustained attention to repetitive targets	Dependent eating of sequence of spoonfuls of a single food; self-feeding sequence of bites
Selective attention	Maintaining eating in a distracting environment
Divided attention	Eating while attending to instructions for guiding the activity
Alternating attention	Alternating eating and drinking; alternating eating and use of signing or speech to communicate

Attention skills emerge as an embedded hierarchy with performance at each subsequent level dependent on the level of mastery of the previous levels. Ability to attend is a skill that is differentiated from motivation to perform which is a behavior

204.7.1 Improving Behaviors for Eating

Considerations in motor learning for improving behaviors are attention to task, tolerance for the task conditions, and acquiring and maintaining motivation to comply with the instructions of the guiding adult (Schmidt and Wrisberg 2004; Danielson 2002; Sheppard 2008). These are precursors for successful training and are established, reestablished, and advanced as the program objectives and related tasks are advanced.

Attention to task has been conceptualized in a developmental, five-level hierarchy that includes sustained attention, selective attention, divided attention, and alternating attention (Sohlberg and Mateer 1989). Development of attending skills occur in parallel with eating behaviors and have been observed to be precursors for participation in eating tasks (McKirdy et al. 2008). See Table 204.3 for examples of categories of attention demands and examples of associated eating tasks. Building skills for attention to task occurs in the early motor learning stage for each skill and sub-skill and is a limiting factor in the rate of the progression of skills leading to mature swallowing and eating function.

Tolerance of the experiential information is established in the early learning stage, as well (Hadders-Algra 2000b; McKirdy et al. 2008; Sheppard 1994, 2008). It is seen as the capability of the child to maintain a calm and alert state as unfamiliar experiences are introduced. Negative behavior, such as decompensation and avoidance, occur when the tolerance level is exceeded by the duration, complexity, or intensity of the experiential information. In order to engage in eating tasks, adequate tolerances are required for sitting in a chair, smells, tastes and textures of food, utensils, social closeness of the guiding adult, the eating environment and, for self-feeding including food and utensils on the high chair tray or table in front of the child, and holding food or utensil in hand while processing food in mouth (Sheppard 1994, 2008).

Motivation to comply with the instructions of the guiding adult is an instructional strategy that supports learning in tasks that are not intrinsically motivating. In some children, eating is a motivation in itself (Satter 1990). Deficient motivation for engaging in eating is seen as a maintaining factor for pediatric swallowing and feeding disorders. Thus, compliance to the guiding adult substitutes for motivation to eat as a means for maintaining instructional control (McKirdy et al. 2008). Positive reinforcement (Kerwin 1999), and escape extinction (Hoch et al. 2001) have been found to be effective strategies for maintaining motivation at early, intermediate, and advanced stages of mastery. Extrinsic feedback regarding number of trials remaining before completion of task (see next) has been found to be useful, as well, in establishing and maintaining motivation to comply with the guiding adult (McKirdy et al. 2008; Schmidt and Wrisberg 2004).

Table 204.4 Approaches and strategies used in motor learning that are applicable to pediatric swallowing and feeding disorder

Motor learning focus	Motor learning approach/strategy	Desired outcome
Attention to task	Exercises to develop sustained focus on task that is adequate for task demands	Reduction of negative behaviors and increase in neutral and positive behaviors in eating and drinking tasks
Tolerance for experiential information	Regulating selection and complexity of sensory information in order to maintain a quiet alert state in response to the sensory experience associated with the set up, performance, and conclusion of the eating/drinking task	
Motivation to comply with the guiding adult	Exercises to develop and improve child's ability to follow the instructive guidance of an adult mediator promptly and with optimum effort	
Task specificity	Exercises using the target task with respect to its sensory conditions, motor components, and expected outcome	Achieving optimum efficiency, accuracy and retention in acquisition, and maintenance of eating and drinking skills and subskills, and acquisition and retention of appropriate neutral or positive mealtime behaviors
Variability in developmental sequence	Flexible selection of program objectives with respect to expected, normal developmental sequences in order to accommodate individual competencies, skills, and preferences	
Implicit learning	Using behavior modification strategies, including cuing and positive reinforcement, in natural task structures and environments	
Transfer of learning	Exercises that support advancing skills for performing in all appropriate natural environments	
Rehearsal	Exercises that violate the functional integrity of the target task with the aim of reducing practice errors and negative behaviors	
Maximizing practice opportunities	Providing for maximum number of daily task repetitions in practice and daily routines	
Blocked and random practice routines	Organizing task sequences for repetition of a single task (blocked sequence) or for random sequencing of two or more tasks	
Extrinsic feedback	Information provided to the child regarding number of task repetitions remaining, adequacy of their task performance, and adequacy of their compliance to the guiding adult	

The evidence base in motor learning provides criteria for selecting practice strategies that will optimize the improvement of behaviors and the learning of skills at early, intermediate, and advanced stages of skill acquisition

204.7.2 Selecting Appropriate Practice Tasks

Task selection is a relevant issue from initiation of treatment to resolution of the swallowing and feeding disorder at each transition toward advancing the child to mature behaviors and skills. Approaches to be considered in selecting tasks are specificity of learning, variability in developmental sequences, implicit learning, and transfer of learning (McKirdy et al. 2008; Sheppard 2008).

Task specificity refers to practicing of the target skill at the beginning, intermediate, and advanced stages of learning. In this strategy, aspects of the sensory information and demands of the task may be simplified or emphasized to facilitate learning. Task specificity has received considerable attention in the ongoing debate on the usefulness of nonfeeding oral motor exercise in treating pediatric swallowing and feeding problems (Bailey and Angell 2005; Clark 2003; Gisel 2008; Manikam and Perman 2000; McKirdy et al. 2008; Williams et al. 2007; Wilson et al. 2008). Evidence from studies of learning for a variety of gross and fine motor tasks indicates that the fastest learning, expressed in number of task repetitions or number of sessions, and the best retention of skill result from practice experiences that most closely approximate the natural environment, the sensory information, and the movement coordinations of the target task (Schmidt and Wrisberg 2004; Sheppard 2005; Thelen 1995). Furthermore, studies of developmental movement characteristics and sequences that compare eating with other oral movement behaviors have demonstrated substantial differences between oral skills in both sensory information and motor demands (Wilson et al. 2008). The lack of equivalency between oral skills has been used to further support specificity of training as a preferred intervention strategy.

Variability in developmental motor sequences has been demonstrated in the normal acquisition of developmental skills. Atypical progressions and patterns of movement have been observed in studies of walking and swallowing tongue postures in young children to result in normal, mature function (Largo et al. 1993; Schwab et al. 1986). Although following developmental sequences for independence in eating, food types and skills may be appropriate in some instances, treatment decisions that were appropriate for the individual child but violated developmental guidelines have resulted in successful behavioral and skill outcomes in making the transition from tube to oral feeding (McKirdy et al. 2008; Williams et al. 2007).

Implicit learning refers to gains in skill resulting from experiences with the target task without directing attention to the training or the change. In this training procedure, naturally occurring tasks are modified to regulate task difficulty. Cuing and reinforcement are used to support the desired changes. Implicit training has been found to result in more effective performance, better retention, and better ability to attend to additional environmental demands as compared with explicit learning conditions (Schmidt and Wrisberg 2004). The benefits of implicit training have been demonstrated in children with special needs as well (Vinter and Detable 2003).

Transfer of learning refers to changes in practice environments and/or training partners, as part of the intervention plan, with the objective of improving skills and behaviors sufficiently for performance in all appropriate natural environments. This may include classroom, community, and home settings with their respective changes in eating partners. The rate of progress is optimized by prompt initiation of the transfer from therapeutic to natural environment at intermediate and advanced learning stages for each skill and subskill (McKirdy et al. 2008).

204.7.3 Practice Strategies

Motor learning approaches to consider when structuring practice sessions are rehearsal strategies, maximizing practice, blocked versus random practice, and providing extrinsic feedback (McKirdy et al. 2008; Sheppard 2008).

Rehearsal refers to practice exercises in which the functional integrity of the target task is disrupted or the task is nonfunctional. Several types of rehearsal strategies have been used in swallowing and feeding programs. Fractionalization of the task refers to practice of parts of a task separately, e.g., biting off and swallowing chewable pieces of food without chewing. Simulations refer to practicing

an alternative to the target task, which may appear to be similar, e.g., using a "chewy tube" (a ridged, flexible, plastic tube) to practice chewing. Simplification refers to disrupting the natural task with the aim of reducing difficulty, e.g., slowing the rate. Segmentation refers to practice of one part of a complex task before adding the next part and practicing the two parts together, e.g., working on acceptance before introducing self-feeding (Chatoor 2009b; Fischer and Silverman 2007; Gisel 1996; Hoch et al. 2001; Linscheid 2006; Pizzo et al. 2009; Williams et al. 2007). The effect of the rehearsal strategies on rate of learning and retention differ depending on the stage of learning and the nature of the task. Some benefit has been found for the use of simulation, fractionalization, and segmentation during the early learning stage. Simplification results in better outcomes than other rehearsal strategies for interactive task sequences as are found in eating and swallowing (Schmidt and Wrisberg 2004).

Maximizing practice opportunities has been found to be the single most important factor related to outcomes for quality of performance and retention of skill (Schmidt and Lee 1999). During the early stage of learning, practice requires more assistance and reinforcement. During the intermediate and later stages of learning, the learner may be more independent. However, in all stages practice should be maximized for improvement and retention of skill (Schmidt and Wrisberg 2004). The benefits of intensive practice for improving swallowing and feeding have been well documented (Bailey and Angell 2005; Cooper-Brown et al. 2008; Gisel 1996; Kerwin 1999; McKirdy et al. 2008; Pizzo et al. 2009; Schmidt and Wrisberg 2004; Sheppard 2005; Williams et al. 2007).

"*Blocked*" *and* "*random*" *practice* refer to the sequencing of trials during practice sessions. In blocked practice there are drill-like repetitions of a single task, e.g., taking bites of cracker until it is finished. In random practice a set of related tasks is performed in random order, e.g., interspersing drinks between bites of cracker. Here again, results differ based on stage of learning. Blocked practice is more effective at the early learning stage as fewer errors may occur. However, random practice results in better retention for intermediate and advanced stages overall (Schmidt and Wrisberg 2004).

Extrinsic feedback refers to information provided to the child before, during, and following practice trials regarding number of trials or amount of time before the practice session is completed, the adequacy of performance, and the adequacy of compliance to the guiding adult. Extrinsic feedback has been found to improve motivation and correction of error. Effects differ depending on the stage of learning, timing of feedback, and the feedback schedule. Overall positive feedback is more effective for supporting learning than is negative feedback. Stronger benefits accrue from feedback during early learning. More frequent feedback yields best results during early learning, while intermittent feedback is more effective during intermediate and advanced stages. Feedback that is provided immediately after a trial is completed increases the likelihood that, under the same stimulus conditions, the action will be repeated (Schmidt and Wrisberg 2004).

204.8 Applications to Other Areas of Health and Disease

Motor learning approaches provide useful evidence-based models for addressing a variety of developmental issues in which behavioral and developmental motor disorders co-occur. Motor learning strategies may be incorporated into therapeutic programs for swallowing-based activities, such as taking oral medications, saliva control, and oral hygiene, in addition to eating and drinking. Furthermore, it may be useful to consider these strategies in habilitation of other developmental motor disorders.

Conceptualization of the differential between acquisition of motor skills and co-occurring behaviors during the critical and sensitive periods and at later ages is helpful for formulating appropriate and effective programs for infants and older children. It is noteworthy that in typically developing children learning of motor skills and their supporting behaviors occur more rapidly

during critical and sensitive periods, that is, learning requires fewer task repetitions and informal training strategies are sufficient to maintain motivation and achieve satisfactory outcomes. In the older child, however, more task repetitions and carefully selected "coaching" strategies are needed to support learning of skills and associated behaviors to achieve the desired outcomes.

Motor learning strategies that are most likely to have broader applications in treatment of pediatric behavioral and nutritional disorders that do not involve neuromotor problems, such as cerebral palsy or apraxia, are implicit learning and the related concept of task specificity. In this regard, optimum learning with respect to rate, retention, and achievement of competency, involves practice of the target task and training within the natural environments.

204.9 Discussion

Intervention for swallowing and feeding disorders in children is a complex process that involves management or resolution of contributing causes, supporting caregivers as they develop their skill sets for participating in the interventions, and habilitation of the child's deficiencies in motivation, behaviors related to eating and the skills, subskills, and underlying competency needed by the child to eat and drink all appropriate foods in all appropriate environments. Key features of this discussion address: (a) consideration of co-occurring abnormalities in behaviors and skills as a unified disorder, (b) the importance of developing tolerable practice routines using the target task, and (3) consideration that a typically developing child acquires these skills and behaviors in three years as an indication of their complexity and the expected duration of the treatment program. See Table 204.5 for key considerations in motor learning approaches for managing eating-related behaviors and co-occurring swallowing and feeding disorders.

Table 204.5 Key considerations in motor learning approaches for managing eating-related behaviors and co-occurring swallowing and feeding disorders

- Motor learning approaches address the continuous process of skill acquisition from emergence through to achievement of mature form and function. In this context, eating is seen as a complex set of motor skills that are related to each other by their common link to nutrition, hydration, and psychosocial participation. Eating-related behaviors are considered to be an integral part of eating function. Optimum efficiency and effectiveness for treatment of problematic skills and behaviors is achieved when intervention addresses this duality as a unified disorder.
- Underlying sensory–motor competencies that support the development of the skill set of mature swallowing and eating skills and behaviors are developed most efficiently within the functional task environment. These underlying competencies are:
    Body postural control,
    Strength, stamina, and precision of movement of oral and pharyngeal structures and upper extremities in eating,
    Praxic competencies for organizing the appropriate motor response to meet the demands of the particular food, utensil, and eating environment,
    Mature attending behaviors, and the abilities to appreciate and integrate the complex environmental and experiential information for generating appropriate responses.
- In typically developing children, this process spans the first two to three years of life. Expectations for habilitation in children presenting with disordered swallowing and feeding should be considered in light of the complexity of the process, the duration of acquisition in the typical population, and the added burden for the child learning these skills and behaviors at ages when brain plasticity is no longer optimum for this learning.

Motor learning approaches view acquisition of complex movement functions, such as swallowing and eating as an interdependent process that includes motivation, behavioral control, attention, and sensory and motor competencies. The goal in a motor learning approach is to optimize outcomes over all these interdependent factors

Summary of Key Points

- Delayed or deficient developmental skills and behavioral problems co-occur as primary and secondary issues in pediatric swallowing and eating disorders.
- Both problems may occur during or after the critical and sensitive periods for acquisition of swallowing and eating skills; however, when they are present after the critical and sensitive period they tend to be more resistant to treatment.
- An integrated treatment program that addresses both behaviors and skills has been found to be most effective.
- Motor learning approaches provide models for integrated programs that address both issues. These approaches are appropriate for infants and children.
- These approaches have been successful in habilitating milder disorders, such as acceptance of restricted variety of foods, as well as more severe disorders, such as refusal to transition from tube to oral feeding.
- The evidence base in the motor sciences supports the notion that better outcomes result from interventions that involve practice of functional tasks as they occur typically in the natural environment.
- Motor learning approaches provide specific strategies for behavioral control, task selection, and practice routines that are applicable to swallowing and feeding disorders.
- The desired outcomes for a feeding and swallowing program are:
- Resolution of behavioral issues related to eating as they occur in natural eating environments. These include disruptive mealtime behaviors, food refusal, and abnormally restrictive food preferences.
- Acquisition of age-appropriate skills for independent eating and drinking of all food types.
- Generalization of these behaviors and skills to all appropriate natural environments.

Definitions and Explanations of Key Terms

Attention to task: It is a component of eating behavior that refers to the maintenance of the level of attention that is required for adequate, task performance.

Blocked practice: Describes use of drill-like, repetitive task sequences in a practice session

Complex consistencies: Are solid foods consisting of an aggregate of pieces with varying composition in each bite. This bolus type presents high level of demand for swallowing and feeding skills.

Conditioned aversions: Are negative associations with swallowing and feeding that predispose to negative eating behaviors

Extrinsic feedback: Refers to information provided to the child regarding adequacy of performance and amount of time or trials remaining in the practice session

Homeostasis, attachment, and individuation: Are three stages of emotional/behavioral development in infancy and early childhood.

Implicit learning: Refers to maintenance or improvement in behaviors and skills that results from interventions in the natural task environment that do not disrupt the integrity of the task or draw attention to the learning.

Intrinsic feedback: Refers to experiential information generated by performance of the eating task and its physiological consequences.

Motivation for compliance: Refers to the willingness or desire to conform to the guidance of a leader or authority figure, usually associated with a perceived incentive

> **Motor learning approaches:** Refers to a situation-based model for training skilled movement behaviors that incorporate concepts and strategies for optimizing learning of skills and supporting behaviors.
>
> **Negative eating behaviors:** Refer to a variety of behavioral scenarios, including food/meal refusal, verbal and physical aggressions and fleeing, associated with meal and snack situations, and of sufficient severity or persistence to interfere with nutrition, hydration, or acquisition of swallowing and feeding skills.
>
> **Random practice:** Describes use of randomly sequenced practice of skill components in complex tasks
>
> **Rehearsal:** It is a training strategy in which the natural task that is the target of training is modified or a similar task is substituted as a means for facilitating learning
>
> **Task specificity:** Refers to the differences in experiential information, movement skills, and behaviors between traits and knowledge as significant considerations for training
>
> **Tolerance of the sensory array:** Refers to the ability to maintain a calm and alert state while experiencing the sensory aggregate during practice.

References

Bailey RL, Angell ME. Educ Train Dev Disabil. 2005;40:80–96.

Burklow KA, Phelps AN, Schultz JR, Mc Connell K, Rudolph C. J Gastroint Nutr. 1998;27:143–7.

Carruth BR, Skinner JD. J Am Coll Nutr. 2002;21:88–96.

Chatoor I. Diagnosis and treatment of feeding disorders in infants, toddlers, and young children, Washington, DC: Zero to Three; 2009a.

Chatoor I. Zero to Three. 2009b;29:44–9.

Clark HM. Am J Speech Lang Pathol. 2003;12:400–15.

Cooper-Brown L, Copeland S, Dailey S, Downey D, Petersen MC, Stimson C, Van Dyke DC. Dev Disabil Res Rev. 2008;14:147–57.

Danielson C. Enhancing student achievement: a framework for school improvement. Alexandria: Association for Supervision and Curriculum Development; 2002.

Davies WH, Satter E, Berlin KS, Sato AF, Silverman AH, Fischer EA, Arvedson JC, Rudolph CD. J Fam Psychol. 2006;20:409–17.

Delaney AL, Arvedson JC. Dev Disabil Res Rev. 2008;14:105–17.

Fischer EA, Silverman AH. Semin Speech Lang. 2007;28:223–31.

Fluehr R, Cress C, Spilker A. Poster presentation, ASHA Conference, November 2004, Philadelphia, PA.

Gerrish CJ, Menella JA. Am J Clin Nutr. 2001;73:1080–5.

Gisel E. Dysphagia. 1996;11:48–58.

Gisel E. Dev Disabil Res Rev. 2008;14:165–73.

Hadders-Algra M. Dev Med Child Neurol. 2000a;42:566–72.

Hadders-Algra M. Dev Med Child Neurol. 2000b;42:707–15.

Hoch TA, Babbitt RL, Farrar-Schneider D, Berkowitz M, Owens JC, Knight TL, Snyder AM, Rizol LM, Wise DT. Educ Treat Child. 2001;24:76–98.

Illingworth RS, Lister J. J Pediatrics. 1964;65:839–48.

Johnson MH. Bremer G, Fogel A, editors. In: Blackwell handbook of infant development. Malden: Blackwell Publishing; 2004.

Kerwin ME. J Pediatric Psychol. 1999;3:193–214.

Kolb B, Gibb R, Robinson TE. In: Lerner J, Alberts AE, editors. Current directions in developmental psychology. Upper Saddle River: Pearson/Prentice Hall; 2004.

Largo RH, Kunda S, Thun-Hohenstein L. In: Kalverboer AF, Hopkins B, Geuze R, editors. Motor development in early and later childhood: Longitudinal approaches. Cambridge: Cambridge University Press; 1993.

Lefton-Greif MA, Arvedson JC. Semin Speech Lang. 2007;28:161–5.

Linscheid TR. Behav Modif. 2006;30:6–23.

Manikam R, Perman JA. J Clin Gastroenterol. 2000;30:34–46.

McKirdy L, Sheppard JJ, Osborne M, Payne P. Lang Speech Hear Serv Sch. 2008;39:249–60.

Menella JA, Beauchamp GK. Pediatric Asthma Allergy Immunol. 1998;12:161–4.

Pinnington L, Hegarty J. Dysphagia. 2000;15:213–23.

Pizzo B, Williams KE, Paul C, Riegel K. Behav Intervent. 2009;24:195–203.

Satter E. J Pediatrics. 1990;117:S181–9.

Schauster H, Dwyer J. Perspect Pract. 1996;96:277–81.

Schmidt RA, Lee TD. Motor control and learning, a behavioral emphasis. 3rd ed. Champaign: Human Kinetics; 1999.

Schmidt RA, Wrisberg CA. Motor learning and performance, a problem-based approach. 3rd ed. Champaigne: Human Kinetics; 2004.

Schwab L, Nieman CW, Gisel E. Am J Occuptional Ther. 1986;40:180–5.

Sheppard JJ. In: Rosenthal SR, Sheppard JJ, Lotze M, editors. Dysphagia and the child with developmental disabilities, medical, clinical and family interventions. San Diego: Singular Publishing Group; 1994. p. 37–76.

Sheppard JJ. Perspect Swallowing Swallowing Disord. 2005;14:6–10.

Sheppard JJ. Lang Speech Hear Serv Sch. 2008;39:227–36.

Sheppard JJ, Mysak ED. Child Dev. 1984;55:831–43.

Sohlberg MM, Mateer C. Introduction to cognitive rehabilitation: theory and practice. New York: Guilford Press; 1989.

Sullivan PB. Dev Disabil Res Rev. 2008;14:128–36.

Sullivan PB, Lambert B, Rose M, Ford-Adams M, Johnson A, Griffiths P. Dev Med Child Neurol. 2000;42:674–80.

Thelen E. Am Psychol. 1995;50:79–95.

Udall JN. Curr Probl Pediatric Adolesc Health Care. 2007;37:374–99.

Vinter A, Detable C. Am J Mental Retard. 2003;108:94–107.

Williams KE, Riegel K, Gibbons B, Field DG. J Dev Phys Disabil. 2007;19:227–35.

Wilson EM, Green JR, Yunusova YY, Moore CA. Semin Speech Lang. 2008;29:257–66.

Chapter 205
The Young and Adolescents: Initiating Change in Children's Eating Behavior

Tom Baranowski, Teresia O'Connor, and Janice Baranowski

Abbreviations

IRM   Item response modeling
BMI   Body mass index

205.1 Introduction

Changing dietary behavior can be important for health concerns (e.g., to manage diabetes, prevent obesity, treat food allergies), or just appearance (e.g., more slender self presentation). Behavior change programs may use interpersonal methods (e.g., a physician, health educator, dietitian, or behavior therapist), electronic self-management (e.g., websites designed for self-monitoring diet and setting goals to change), or even videogames (Baranowski et al. 2003a). Whatever the target behavior or the medium, the behavior change principles and procedures are the same.

Dietary behavior change programs for children have generally had weak effects (Ammerman et al. 2002). When more substantial changes have occurred (Epstein et al. 2001), it appears likely to have been due to the self-selected (e.g., responses to media advertisements) and thereby more highly motivated nature of the sample, who would likely have benefitted from any of a variety of types of programs offered. Furthermore, when changes have occurred, they have usually been detected immediately after the program, but not over longer time intervals (Thompson et al. 2009). Thus, a distinction has arisen between factors in the initiation and in the maintenance of change. Little is known about how to maintain changes once initiated (Fuglestad et al. 2008), especially among children. Thus, this chapter focuses on initiating dietary change, and uses the mediating variable model (Fig. 205.1) as a framework for understanding how interventions should work. The basic model is expanded to guide research on more realistic interventions. In each case, more research is needed to provide a firmer scientific foundation for what has been essentially an intuitive and ad hoc process.

T. Baranowski (✉)
Children's Nutrition Research Center, Department of Pediatrics, Baylor College of Medicine,
1100 Bates Street, Houston TX 77030, USA
e-mail: tbaranow@bcm.edu;

Fig. 205.1 The simple
mediating variable model as an
organizing framework
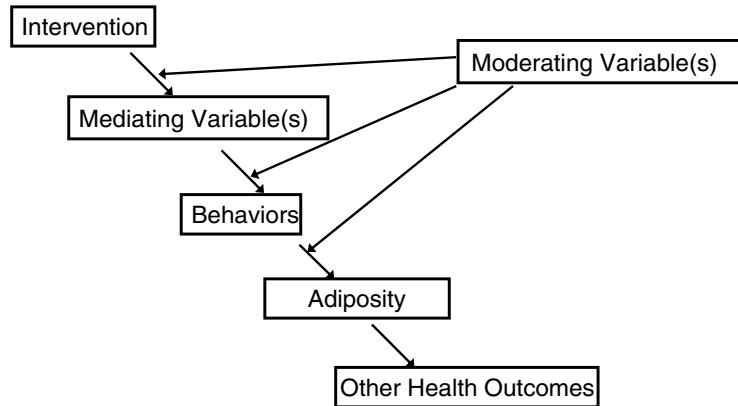
205.2 Simple Mediating Variable Model for Initiating Dietary Behavior Change

The mediating variable model started as a tool to analyze what variables accounted for relationships (Baron and Kenny 1986), and thereby provide the "science" for program evaluation. A model targeting childhood obesity and its sequelae can be found in Fig. 205.1. This is the simplest presentation of this model with only one intervention component and one mediating variable.

The mechanisms of action of the mediating variable model start with the implementation of a program. The implemented intervention impacts mediating variables, i.e., influences on the targeted behaviors. Changes in mediating variables change behavior. Changes in behavior change adiposity. Moreover, changes in adiposity influence downstream phenomena (e.g., metabolic syndrome, food allergies, social attractiveness/acceptance, etc.). Thus, behavior change programs are really mediating variable change programs. Variables can also moderate the relationships in the mediating variable model, i.e., differentially allow or enable the intervention to have its effects. For example, some interventions have worked with girls, but not boys; hence, gender would be a moderating variable (Gortmaker et al. 1999). Most attention has been paid to demographic variables as moderating variables, but mediating variables could also be moderators, e.g., an intervention has an effect only among those with high preference for a food at baseline (e.g., Latif et al. in press).

Assumptions of the mediating variable model include that targeted behaviors are strongly and causally related to the health outcome of interest. If not causally related, changes in the behavior will not effect changes in the physiological processes. If not strongly related, then even extensive change in the behavior may effect only small changes in the physiological processes. Using the same reasoning, the targeted mediating variables must be causally and strongly related to the behavior. Intervention procedures must be selected and implemented that can change the mediating variables enough to change the behaviors enough to have the desired impacts on the physiological processes. Interventions must also be thoroughly implemented. If interventions are not thoroughly implemented with high fidelity to the original design, whatever effects are detected will have come more by chance than by design. The relationships from intervention implementation to physiological change are multiplicative which means the effects of even strong relationships early in the chain of events can be minimized by weak links anywhere along the chain. To be able to study these relationships, measures with high levels of validity and reliability are necessary both because low reliability minimizes the ability to detect true strong relationships (Traub 1994), and low validity indicates we would not really know if our interventions are working as theoretically specified.

The ideal intervention would be based on highly predictive theory with substantial formative research to adapt the theoretical constructs to local circumstances, and thereby maximize the likelihood of its effectiveness. The ideal evaluation would use a randomized clinical trial as the design (often a group randomized design when working with groups of children, e.g., in school (Baranowski and Cerin 2008; Donner and Klar 1996), and measure relevant aspects of the environment as moderating variables (Baranowski and Cerin 2008), relevant psychosocial and environmental mediators, the targeted behaviors, and aspects of program delivery (dose, fidelity, reach; Baranowski and Jago 2005) at least before and after the intervention, and at crucial other times.

205.3   Where to Find Mediating Variables

Knowledge used to be considered the primary, if not only, mediating variable (Contento et al. 1995). Termed a theory of enlightened self-interest (Baranowski et al. 2003b), investigators thought that participants would do the behaviors that were in their self-interest, and interventions primarily needed to effectively convey that knowledge. An early literature review of hundreds of published dietary change studies, however, demonstrated that knowledge by itself was not an effective mediator of dietary behavior change interventions (Contento et al. 1995). Thus, some knowledge is a necessary, but not a sufficient, component of a dietary change intervention.

Since then, mediating variables have usually been selected from theory-based cross-sectional studies (Baranowski et al. 1998). A limitation of this source is the inability to assess causality. For example, although self-efficacy has been shown to be related to behavior in a broad variety of cross-sectional studies, one longitudinal study found that behavior predicted later self-efficacy, but not the reverse (Nigg 2001). Another longitudinal study exploded cross-sectional findings by showing that maternal restrictive food parenting practices followed the onset of obesity, but did not precede it (Rhee et al. 2009), thereby minimizing the concern about restrictive parenting causing obesity. The best source of mediating variables would be studies testing what variables mediated dietary change outcomes. Fortunately, there are accumulating studies of what variables mediate dietary change interventions in children (Cerin et al. 2009). Using variables identified from this source should ensure that the variables meet the assumption of causality and that procedures are available to manipulate them. A review of the literature testing mediation in dietary behavior change revealed that the only variable detected as a mediator in multiple studies (thereby minimizing chance findings) was outcome expectancies, i.e., variation in the belief of good or not so good outcomes from engaging in the targeted behavior (a motivational variable; Cerin et al. 2009). This suggests that interventions must carefully identify a targeted population's beliefs about what will happen from engaging in a dietary behavior and then design messages or activities that persuade people that their likely experience of positive outcomes will increase and of negative outcomes will decrease. There is a growing literature on tailored messages (i.e., messages individualized to the beliefs of each participant) which is very promising (de Vries et al. 2008), but little research has been done with tailoring persuasive messages with children.

The literature review on mediating variables (Cerin et al. 2009) also revealed that in some cases an intervention exacerbated a mediator that minimized behavior change (i.e., increased a mediator that was negatively correlated with the behavior), called a suppressor effect. For example, at the end of one intervention, participants perceived more barriers, rather than less. This suggests that additional research, done in a more systematic fashion, is needed to design interventions that have desired effects on mediating variables (Baranowski et al. 2009).
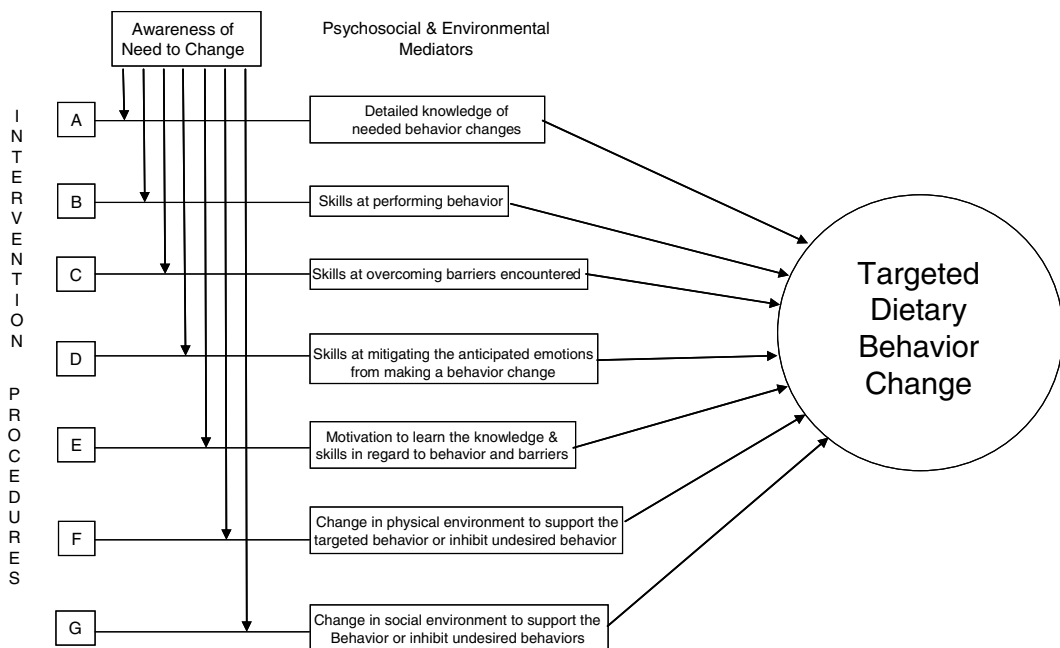
Fig. 205.2 Mediating variables for initiating child dietary behavior change

205.4 More Complex Mediating Variable Model

Behavior change is likely a function of more than one mediating variable. Based on the existing research and logic, initiating dietary change likely requires someone to (a) be aware of the need to change; (b) know precisely what changes are needed in their usual routines; (c) develop skills to do them in ways likely to be successful (Brug 2008); (d) anticipate problems or barriers to doing these behaviors and become skilled at overcoming them (Lesley 2007); (e) be sufficiently motivated to initiate these changes at levels necessary to have the desired effects and to resist temptations not to change (Brug 2008); (f) be prepared to mitigate the emotions (e.g., anxiety, frustration, depression, deprivation) likely to occur when changing their behavior (Bagozzi et al. 1998); and (g) organize their environment (both physical and social, at home and other frequented locations) to support the new behaviors, and minimize distractions or temptations not to do the behaviors (Jago et al. 2007). We believe these are the mediating variables needed to initiate changes in a child's dietary behaviors. Thus, an effective intervention would need to have at least seven components (A–G in Fig. 205.2), each targeted at a different mediating variable to successfully initiate a desired behavior change. If one of these variables is already high in a child or their home, then no further changes in that variable may be necessary. How best to induce changes in these variables has received scant attention and therefore requires extensive further research.

205.5 A Two-Mediator Model: Intervening with Parents to Influence Children

The person responsible for a child's behavior change varies across childhood. In the earlier ages, the parent or guardian is the primary person responsible because the young child can at best reject food, but not select foods to be eaten. Later in childhood, e.g., adolescence, the child often becomes
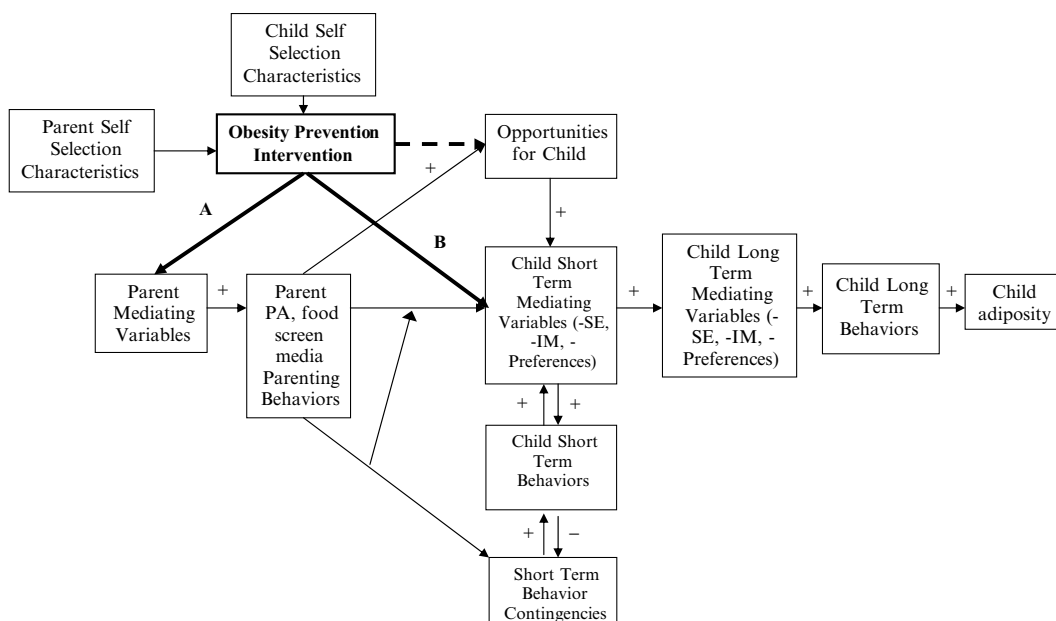
Fig. 205.3 Multiple mediation model of effects from obesity prevention intervention with parents to child obesigenic behaviors and adiposity

progressively more responsible. This, however, will vary by family, parenting style (Hughes et al. 2005), and the parent's willingness to transfer control. There will be many pathways of change in responsibility from early childhood to late adolescence, and into the adult years. At the point of a major social role change at the end of high school (entrance to the "adult" years), there were remarkable shifts in behavior, likely reflecting shifts at the start of the adult years in who was responsible for behavior change (Baranowski et al. 1997).

Thus, in the earliest years, parents are necessarily the target for a child's nutrition intervention (Ells et al. 2005). However, little attention has been paid to how best involve parents in behavior change interventions. A review of interventions with family components (O'Connor et al. 2009) identified five primary methods by which programs had involved parents: (1) newsletters/homework sent home; (2) fun nights or organized events for families to attend; (3) telephone contact with parents; (4) organized activities for family; and (5) family counseling or parent training. Overall, there was a lack of high quality studies from which to draw systematic conclusions. Despite the poor evidence base, sending printed material home (the method used by the majority of studies reviewed) was not sufficient to effect change. Family counseling/parent training and telephone calls were identified as warranting closer evaluation with well-designed fully powered studies (O'Connor et al. 2010). Intervening with an adult (e.g., the parent) to influence the child introduces more variables and longer chains of effects from intervention to child outcomes. Figure 205.3 presents a more complex and perhaps more realistic, mediating variable model that incorporates mediators of parents' behavioral change to influence children's behavior.

205.6 Why Might It Be Important to Involve Parents?

Parents are an important influence on children's health beliefs and behaviors. While personal child factors have been associated with youth's dietary behaviors (Neumark-Sztainer et al. 2003), parental factors and behaviors have also emerged as important correlates of children's

behaviors. Parental intake (Pearson et al. 2009), parental role modeling (Pearson et al. 2009), availability and accessibility of foods in the home (Pearson et al. 2009) (likely under parental control), parental education and parental rules (Pearson et al. 2009) were important determinants in children's dietary behaviors. Parental influences may also persist beyond adolescence providing support for targeting parental factors to achieve some maintenance of children's lifetime dietary changes.

Parents may influence their children's dietary behaviors both indirectly and directly. Indirectly, they are one of the key determinants of the home environment (e.g., availability and accessibility of foods (Jago et al. 2007)), which in turn influences the child's behavior. Parents also establish an emotional climate in the home through their parenting style (Darling and Steinberg 1993), which has consistently been associated with a wide range of youth behaviors and may facilitate or inhibit parent–child interactions. The most common method to describe general parenting style involves two dimensions of parenting: nurturance and demandingness (Baumrind 2005). Nurturance is the warmth, support, and open communication provided by a parent to a child to promote self-regulation and independence in the child. Demandingness is the expectations, rules, monitoring, and conformation provided by a parent to a child to promote integration into society. By crossing these dimensions, four quadrants or typologies of parenting style emerge: authoritative (high nurturance, high demandingness); authoritarian (low nurturance, high demandingness); permissive (high nurturance, low demandingness); and uninvolved (low nurturance, low responsiveness) (Maccoby et al. 1983). An authoritative parenting style predicted lower risk for overweight in children (Rhee et al. 2006) and increased fruit consumption in adolescents (Kremers et al. 2003). Based on the general parenting style dimensions and typologies, a measure of parental attitudes and behaviors intended to socialize children around feeding was developed (Hughes et al. 2005). Indulgent feeding style was associated with higher child weight status (Hughes et al. 2008).

Directly, parents influence children's dietary behaviors by their food-related parenting practices. Parenting practices are the context-specific behaviors parents use to influence child behavior (Darling and Steinberg 1993). Examples of parenting practices include establishing and reinforcing rules, monitoring, contingency management (if–then statements), praising, and providing choices. Within the feeding context, restrictive parenting practices were consistently associated with greater consumption of less healthy foods and greater weight status (Faith et al. 2004). Conversely, parents who (1) enhanced availability and accessibility of fruit and vegetables, (2) used teachable moments (e.g., use mealtimes to teach about healthy eating), and (3) avoided firm discipline around eating, had children with greater fruit and vegetable consumption than parents who tended to use all parenting practices indiscriminately or had higher use of firm discipline practices (O'Connor et al. 2009). Parenting practices that are context-specific and goal-directed may be easier to change than parenting styles. Therefore, research needs to expand and define effective parenting practices that can be promoted to encourage healthful eating among children.

In order to create effective dietary change interventions that include procedures targeting parents to achieve behavior change in children, there needs to be a better understanding of the variables mediating intervention effects on parents and thereby could be targeted to effect change. Very little research has explored parental mediating variables that potentially affect their food parenting practices. General parental attitudes about obesity were associated with use of restrictive feeding practices with their children, after controlling for covariates including parent and child body mass index (Musher-Eizenman et al. 2007). It is likely that other mediating variables such as parental self-efficacy, intrinsic motivation, subjective norms, and perceived control also affect parental use of effective parenting practices. All these, and potentially others, need to be explored and scales need to be developed and validated for each (Baranowski et al. 2004).

205.7 Measurement

To be able to evaluate intervention programs targeted directly at children, or targeted at parents to influence children, better measures are needed. A simulation study demonstrated that validity coefficients need to be at 0.90 or higher to minimize classification error (De Moor et al. 2003). Since reliability coefficients place limits on validity coefficients, reliability needs to be at this level or higher, as well. Most current measures, however, do not even come close to these levels (Baranowski et al. 2004).

New psychometric methods, called Item Response Modeling (IRM), have become available to enhance our understanding of optimal approaches to measurement and how to improve them (Wilson et al. 2006). IRM fits a latent variable to items which facilitates the comparison of respondents and items along the same latent variable, and thereby permits tests of whether different groups use the same scale in different ways (Baranowski et al. 2006), and whether an intervention affects the meaning of items in a scale (Baranowski et al. 2006). These are among a variety of uses not formerly possible. Application of IRM methods to measures that have been demonstrated to have adequate psychometric characteristics using classical test theory methods revealed severe limitations in the distribution of items along the distribution of participants. This suggests that the existing scale had limited content validity in assessing the full range of beliefs (Watson et al. 2006). Attempting to expand the range of items using theoretically prescribed procedures was not effective (Baranowski et al. 2010). Alternatively, briefer instruments can be developed by eliminating items revealed to be redundant at points along the latent variable, thereby reducing respondent burden (Table 205.1) (Jago et al. 2009).

205.8 Conclusions

We are still in relatively early stages of understanding how to design interventions effective in initiating child dietary behavior change. The mediating variable model is useful in advancing this agenda because it integrates more basic behavioral research with intervention research. Intervention research would benefit from a clearer understanding of the influences of dietary behaviors on health outcomes (Bachman et al. 2006) and the influences on dietary behaviors (Baranowski 2006). Intervention research should progress through a series of formative studies that first indentify the behaviors influencing the health outcomes in a targeted population, next identify the primary causal and stronger influences (mediators) on the targeted behaviors, and finally identify the intervention procedures most likely to effect substantial change in the target mediators (Baranowski et al. 2009). When major

Table 205.1 Key features of item response modeling (IRM)

1. An increasingly used advanced psychometric procedure that fits a latent variable to items in a questionnaire.
2. IRM compares the distribution of the respondents with the distribution of the items, thereby permitting an analysis of the distributional content validity of the items.
3. IRM estimates a latent variable that is not sample-specific: this permits comparison of whether different groups respond to the same item at the same location (called differential item functioning).
4. IRM offers the promise of reducing response burden by eliminating items that are redundant at a particular point on the variable, while maintaining high validity.

This table lists the key features of IRM

interventions have been mounted, thorough mediating variable analyses need to be conducted to elucidate effective mediating variables for use in ensuing trials. Much work remains to be done to elucidate effective ways to change children's dietary behaviors.

205.9 Applications to Other Areas of Health and Disease

Behavior change has been challenging across a broad variety of behaviors and in many demographic groups. Most behavior change programs have emphasized increasing knowledge, which has not been working. The advantage of the mediating variable model is that it integrates the behavior theory literature of influences on behavior with the intervention literature. All these areas of behavior change intervention would benefit from adopting the mediating variable model perspective, both as a conceptual tool to design more effective interventions and as an analytic tool to assess if the intervention worked as designed.

Summary Points

- Dietary behavior change programs have generally not been working.
- New models are needed to understand how programs work, to guide future development.
- The mediating variable model provides a perspective that integrates basic behavioral research with intervention research.
- Mediating variables must be selected from the basic literature on variables shown to be causally and substantially influencing the targeted behaviors.
- The existing literature is weak on identifying variables that causally and substantially influence behaviors.
- One problem is that the designs need to be longitudinal.
- The interventions must include procedures to effectively manipulate the selected mediators.
- The existing literature is weak on identifying these procedures, too.
- Another problem is the low validity and reliability of measures of both the behaviors and the mediators.
- More models are needed to identify pathways of effects that can guide the design of ensuing interventions.

Definitions

Dietary behavior: What a person does when selecting and eating food.
Mediating variable: A variable demonstrated to be on the causal pathway between an intervention and a change in a behavior.
Mediating variable model: The model used to test mediating relationships and to guide the development of interventions.
Moderating variable: A variable for which one category or end of a dimension facilitates behavior change more so that the other category end of a dimension.
Intervention procedures: Activities demonstrated to induce changes in mediating variables.
Theory of enlightened self-interest: Posits that people will change their behavior in response to new knowledge about their behavior, especially the outcomes of their behavior.

Nurturance: Warmth, support, and open communication provided by a parent to a child to promote self-regulation and independence in the child.

Demandingness: Expectations, rules, monitoring, and confrontation provided by a parent to a child to promote integration into society.

Parenting style: Parent attitudes and behaviors that influence the emotional climate that parents create in a home to socialize their children.

Parenting practices: Behaviors used by parents to influence their child in a specific context.

Psychometric methods: Methods to analyze the validity and reliability of measures.

Item response modeling: A psychometric technique that fits a latent variable to items, which permits a variety of innovative tests.

Classical test theory: The traditional psychometric methods.

Outcome expectancy: The set of beliefs about the outcomes (good or bad) from doing a behavior.

References

Ammerman A, Lindquist C, Lohr K, Hersey J. Prev Med. 2002;35:25–41.

Bachman CM, Baranowski T, Nicklas TA. Nutr Rev. 2006;64:153–74.

Bagozzi RP, Baumgartner H, Pieters R. Cogn Emotion. 1998;12:1–26.

Baranowski T, Cullen K, Basen-Engquist K, Wetter D, Martineau D, Prokhorov A, Cummings S, Chorley J, Hergenroeder A, Beech B. Prev Med. 1997;26:694–703.

Baranowski T, Anderson C, Carmack C. Am J Prev Med. 1998;15:266–97.

Baranowski T, Baranowski J, Cullen KW, Marsh T, Islam N, Zakeri I, Honess-Morreale L, DeMoor C. Am J Prev Med. 2003a;24:52–61.

Baranowski T, Cullen KW, Nicklas T, Thompson D, Baranowski J. Obes Res. 2003b;11 (Suppl):23S–43S.

Baranowski T, Jago R. Exerc Sport Sci Rev. 2005;33:163–8.

Baranowski T. J Am Diet Assoc. 2006;106:808–11.

Baranowski T, Allen DD, Masse LC, Wilson M. Health Educ Res. 2006;21 (Suppl. 1):i98–109.

Baranowski T, Cerin E. Int J Pediatr Obes. 2008;3:194–5.

Baranowski T, Cerin E, Baranowski J. Int J Behav Nutr Phys Act. 2009;6:6.

Baranowski T, Watson KB, Bachman C, Baranowski JC, Cullen KW, Thompson D, Siega-Riz AM. Int J Behav Nutr Phys Act. 2010;29:7–25.

Baranowski T, Klesges LM, Cullen KW, Himes J. Prev Med. 2004;38:S1–13.

Baron RM, Kenny DA. J Pers Soc Psychol. 1986;51:1173–82.

Baumrind D. New Dir Child Adolesc Dev. 2005;108:61–9.

Brug J. Fam Pract. 2008;25 (Suppl. 1):i50–5.

Cerin E, Barnett A, Baranowski T. J Nutr Educ Behav. 2009;41:309–18.

Contento I, Balch GI, Bronner YL, Lytle L, Maloney SK, Olson CM, Swadener SS. J Nutr Educ. 1995;27:277–418.

Darling N, Steinberg L. Psychol Bull. 1993;113:487–96.

De Moor C, Baranowski T, Cullen KW, Nicklas T. Public Health Nutr. 2003;6:393–9.

de Vries H, Kremers SP, Smeets T, Brug J, Eijmael K. Am J Health Promo. 2008;22:417–25.

Donner A, Klar N. J Clin Epidemiol. 1996;49:435–9.

Ells LJ, Campbell K, Lidstone J, Kelly S, Lang R, Summerbell C. Best Pract Res Clin Endocrinol Metab. 2005;19:441–54.

Epstein L, Gordy CC, Raynor HA, Beddome M, Kilanowski CK, Paluch R. Obes Res. 2001;9:171–8.

Faith MS, Scanlon KS, Birch LL, Francis LA, Sherry B. Obes Res. 2004;12:1711–22.

Fuglestad PT, Rothman AJ, Jeffery RW. Health Psychol. 2008;27:S260–70.

Gortmaker SL, Peterson K, Wiecha J, Sobol AM, Dixit S, Fox MK, Laird N. Arch Pediatr Adolesc Med. 1999;153:409–18.

Hughes SO, Power TG, Orlet Fisher J, Mueller S, Nicklas TA. Appetite. 2005;44:83–92.

Hughes SO, Shewchuk RM, Baskin ML, Nicklas TA, Qu H. J Dev Behav Pediatr. 2008;29:403–10.

Jago R, Baranowski T, Baranowski JC. Pub Health Nutr. 2007;10(7):681–9.

Jago R, Baranowski T, Watson K, Bachman C, Baranowski JC, Thompson D, Hernandez AE, Venditti E, Blackshear T, Moe E. Int J Behav Nutr Phys Act. 2009;6:20.

Kremers SP, Brug J, de Vries H, Engels RC. Appetite. 2003;41:43–50.

Latif H, Watson K, Nguyen N, Thompson D, Baranowski J, Jago R, Cullen KW, Baranowski T. Health education & Behavior, in press.

Lesley ML. Patient Educ Couns. 2007;65:137–46.

Maccoby E, Martin J. In Mussen PH, editor. Handbook of child psychology. New York: Wiley; 1983. p. 1–101.

Musher-Eizenman DR, Holub SC, Hauser JC, Young KM. Obesity (Silver Spring). 2007;15:2095–102.

Neumark-Sztainer D, Wall M, Perry C, Story M. Prev Med. 2003;37:198–208.

Nigg CR. Ann Behav Med. 2001;23:11–20.

O'Connor T, Jago R, Baranowski T. Am J Prev Med. 2009;37:141–9.

O'Connor TM, Hughes SO, Watson KB, Baranowski T, Nicklas JA, Fisher Jo, Beltran A, Baranowski JC, Qu H, Shewchuk RM. Pub Health Nutr. 2010;13:91–101.

Pearson N, Biddle SJ, Gorely T. Public Health Nutr. 2009;12:267–83.

Rhee KE, Lumeng JC, Appugliese DP, Kaciroti N, Bradley RH. Pediatrics. 2006;117:2047–54.

Rhee KE, Coleman SM, Appugliese DP, Kaciroti NA, Corwyn RF, Davidson NS, Bradley RH, Lumeng JC. Obesity (Silver Spring). 2009;17:1724–9.

Thompson D, Baranowski T, Cullen K, Baranowski J, Watson K, Jago R. Prev Med. 2009;49:518–26.

Traub RE. Thousand Oaks, CA: Sage; 1994.

Watson K, Baranowski T, Thompson D, Jago R, Baranowski J, Klesges LM. Health Educ Res. 2006;21 (Suppl. 1):i85–97.

Wilson M, Allen DD, Li JC. Health Educ Res. 2006;21 (Suppl. 1):i4–18.

Chapter 206
Eating Disorders and Behavioral Aspects of School-Based Prevention Programs

Riccardo Dalle Grave, Lucia Camporese, and Elettra Pasqualoni

Abbreviation

BMI   Body mass index

206.1 Introduction

Eating disorders are one of the most common health problems afflicting female adolescents and young women in Western countries (Lewinsohn et al. 1993). They are characterized by disturbance of eating behaviors and/or weight-control behaviors associated with a specific core psychopathology (i.e., the overvaluation of shape and weight and their control) (Fairburn and Harrison 2003). Either the behavior disturbances or the associated specific core psychopathology are important causes of physical and psychosocial morbidity (Fairburn and Harrison 2003), with an increased risk of death (Agras 2001). Only a subgroup of individuals with eating disorders receive treatment (Newman et al. 1996), and often after many years of illness when their disorder has already become chronic (Herzog et al. 1992). Complete remission has been described in 40% of patients who complete evidence-based treatments (Fairburn et al. 2009), and some need to be admitted to intensive and costly inpatient treatments (Dalle Grave et al. 2008).

The above facts stimulated considerable efforts in developing prevention programs, particularly in schools, because eating disorder typically starts during school age and schools often provide access to adolescents at risk (Dalle Grave 2003). School-based eating disorder programs have been described and evaluated by controlled studies in several Western countries (e.g., Canada, the USA, Norway, Switzerland, the Netherlands, the UK, Italy, Australia, Croatia, and Israel) (Dalle Grave 2003), and a large body of knowledge is available about their effectiveness and limits.

The aims of this chapter are: (1) to review the efficacy of school-based eating disorder prevention programs; (2) to suggest some implications for stakeholders in the health-care sector; and (3) to suggest some strategies to improve the future eating disorder prevention.

R. Dalle Grave (✉)

Department of Eating and Weight Disorder, Villa Garda Hospital, Via Montebaldo 89,
I-37016 Garda (VR), Italy
e-mail: rdalleg@tin.it

206.2 Eating Disorder Prevention Programs: A Few Definitions

Eating disorders prevention programs can be classified into three broad-categories: *universal*, *selective*, and *indicated*. Universal programs are directed at "all" consenting individuals in a given population, such as a given grade level in a school, and aim at reducing risk and promoting protective factors. Selective and indicated interventions target specific subgroups for intervention. Selective interventions target those who are at elevated risk based on group-level characteristics that are not directly related to etiology. Because eating disorders are complex diseases derived by the interaction of genetic and environmental risk factors (Striegel-Moore and Bulik 2007), a selective prevention might focus on asymptomatic children with first-degree affected relatives or with some risk factor supported by multiple independent prospective studies (e.g., elevated perceived pressure to be thin, internalization of the thin-ideal standard of female beauty, obesity, body dissatisfaction, and negative affect) (Shaw et al. 2009). Finally, an indicated intervention involves targeting individuals who either have signs of the disorder (e.g., dieting with an overvaluation of shape and weight and their control) but are in an early stage of a progressive disorder. In practice, this distinction is difficult to maintain. Many universal programs for eating disorder prevention, for example, are focused only on girls and women – and female sex is considered the most powerful potential risk factor for eating disorders. In addition, some selective intervention easily may include individuals with unhealthy weight-loss behaviors – and unhealthy weight-loss behaviors could be both a risk factor and an early sign of an eating disorder.

206.3 The Two Generations of School-Based Eating Disorder Prevention Programs

Two main generations of universal school-based eating disorder prevention programs have been described (Dalle Grave 2003).

The first generation adopted a didactic approach that supplied information with on nutrition, body image, and the nature of eating disorders. The didactic approach produced an improvement in knowledge of eating disorders, but were ineffective in changing dysfunctional attitudes (e.g., the overvaluation of shape and weight and their control) and unhealthy behaviors (e.g., dietary restraint to change or control shape and body weight) (Dalle Grave 2003).

The second-generation programs introduced an interactive and experientially educational approach and other innovative strategies designed to change dysfunctional attitudes and unhealthy behaviors and to target well-established risk factors underlying eating disorder psychopathology. Examples include dissonance-based approach (Shaw and Stice 2008), cognitive restructuring techniques to challenge dysfunctional attitudes about shape, weight, and their control (Dalle Grave et al. 2001; Stewart et al. 2001), messages on video to dissuade against dieting (Paxton et al. 2002), active techniques to foster a change in eating habits, including self-monitoring (Stewart et al. 2001), prevention videotape on dieting and body image (Withers et al. 2002), strategies to improve body image by building general self-esteem (O'Dea and Abraham 2000), and Internet-based multimedia prevention programs based on psychoeducational self-help materials (Winzelberg et al. 1998; Celio et al. 2000).

206.4 Effects of School-Based Eating Disorder Prevention Programs

In the last 10 years, several universal and selective school-based eating disorder prevention programs have been evaluated by randomized control studies and the efficacy of these studies has been analyzed by some systematic reviews (Dalle Grave 2003; Stice and Shaw 2004; Stice et al. 2007; Yager and O'Dea 2008).

The three key findings of a recent meta-analysis are (Stice et al. 2007): (1) 51% of the prevention programs examined produced significant reductions in at least one established risk factor of eating disorder psychopathology; (2) 29% of the prevention programs resulted in significant reductions in eating disorder psychopathology, and (3) some prevention programs reduced eating disorder psychopathology and prevented its increase: an increase that was reported by control groups. These outcomes are encouraging, considering that first-generation prevention interventions were not effective at reducing eating disorder psychopathology and or eating disorder risk factors (Shaw et al. 2009).

Some aspects of school-based prevention programs examined by the reviews appeared to be related to positive program outcomes (Dalle Grave 2003; Stice and Shaw 2004; Stice et al. 2007; Yager and O'Dea 2008).

1. *Selective prevention programs generally tend to obtain more positive results than universal programs.* Most universal programs achieved their knowledge acquisition goals, but only some produced positive effects on dysfunctional attitudes and none a persistent change of unhealthy behaviors. Most of the selective programs, on the contrary, produced positive effects both on dysfunctional attitudes and dysfunctional unhealthy behaviors. Positive effects on high-risk subjects were also observed in some universal programs, but not in all the studies (Becker et al. 2008). Two main reasons could explain the poorer results observed in the universal programs with respect to targeted programs (Dalle Grave 2003): (1) the level of dysfunctional attitudes and unhealthy behaviors in unselected samples may be so low that it is difficult to detect any significant intervention effect; (2) the unselected sample may not be sufficiently motivated to fully engage in the prevention program.

2. *Didactic interventions produced fewer positive effects than interactive interventions.* Most didactic interventions produced changes in knowledge acquisition but very few induced changes in dysfunctional attitudes and unhealthy behaviors. This observation adds further evidence to the conclusions by prevention researchers in other areas that psychoeducational didactic interventions are less effective than interventions that actively engage students and teach new skills (Dalle Grave 2003).

3. *Programs that focused on older participants (older than 15 years) produced stronger prevention effects on dysfunctional attitudes and unhealthy behaviors.* One possible explanation of this observation is that few students are engaging in unhealthy weight-control behaviors or evidencing significant eating disorder psychopathology at a younger age (11–12 years). It is therefore very difficult to achieve statistically significant decreases in dysfunctional attitudes and unhealthy behaviors. The efficacy of prevention programs in young students should be evaluated following them through their high school years to determine the long-term effects of program participation (Dalle Grave 2003). Another possibility is that younger subjects without eating, shape, and weight concerns may not be sufficiently motivated to fully engage in the prevention program. Finally, interventions may be more effective in older adolescents because they are delivered during the peak-risk period when eating disorder psychopathology emerges (Shaw et al. 2009).

4. *Prevention programs delivered by trained professionals are more effective than those delivered by endogenous providers (e.g., teachers, and counselors).* Two main reasons may explain this finding (Shaw et al. 2009). First, endogenous providers have competing demands (e.g., teaching) that obstruct the maintenance of fidelity to the program. Second, endogenous providers often receive less training on the program compared with trained professionals.

5. *Some contents of the intervention seem to produce better outcome.* The number of procedures and techniques used in the programs varied considerably as did overlap between programs with positive and negative outcomes. These make it difficult to conclude whether the specific contents of the prevention programs have positive effects on dysfunctional attitudes and unhealthy behaviors. Dissonance-induction interventions seem to produce larger effects for thin-ideal internalization, body dissatisfaction, dieting, and negative affect, and eating disorder psychopathology than programs without this content (Stice et al. 2007). Positive results have been obtained with programs

focused on: body acceptance, health education activities that build self-esteem, healthy weight-control behaviors, critical analysis of the thin ideal, and the use of computers and the Internet as a delivery medium (Stice et al. 2007; Yager and O'Dea 2008). On the contrary, interventions with a psychoeducational focus and with sociocultural content and a stress and coping focus had limited effects (Stice et al. 2007, Shaw et al. 2009). These data indicate that the prevention of eating disorder psychopathology can be obtained by several and different procedures and strategies and probably also by some nonspecific factors not evaluated by the studies. Table 206.1 reports a summary of the most promising school-based prevention programs evaluated by the research.

206.5 Implications for Stakeholders in the Health-Care Sector

Three main practical implications for stakeholders in the health-care sector can be suggested from results obtained by school-based eating disorder prevention programs.

1. There is no statistical evidence that school-based prevention programs for eating disorders have harmful effects (Pratt and Woolfenden 2002; Dalle Grave 2003). To date, the results obtained by these programs can reassure parents, teachers, and other stakeholders that these interventions have no general harmful effects on student attitudes and behaviors.
2. The encouraging results from selective prevention programs for high-risk individuals might stimulate stakeholders in the health-care sector to promote selective interactive prevention programs for middle to late adolescent subjects with high risks for eating disorders. The programs should preferably be delivered by professional interventionists and should address eating disorder risk factors and promote healthy weight-control behaviors. Since targeted programs have the intrinsic potential to produce stigmatization in participants, future research is needed to develop models and strategies to avoid this undesirable effect. Some recent technology-based efforts (CD-roms, Internet-based homework, guided chat rooms) may help to solve these problems.
3. The poor results obtained by universal eating disorder prevention programs in early adolescents as evaluated in controlled trials suggest that for the moment it is not advisable to spend money for indiscriminate universal eating disorder prevention. However, since some clinical cases derive from low-risk groups, research on universal prevention should continue and the school remains an important place where this type of study is possible. Since universal programs are generally ineffective in improving unhealthy behaviors, in designing a universal prevention program it is mandatory to place more emphasis on behavioral changes by including a stronger link between knowledge and attitudes and behaviors (Steiner-Adair et al. 2002).

Table 206.2 reports some suggestions for stakeholders in the health-care sector to optimize the implementation and evaluation of school-based eating disorder prevention programs (Dalle Grave 2003).

206.6 Strategies to Improve the Future Eating Disorder Prevention

The poor outcome of universal eating disorder prevention programs may largely be attributed to our limited knowledge of eating disorder risk factors and by the insufficient efficacy of the methods used to manipulate the identified potential risk factors (see Table 206.3). However, the encouraging results obtained by the second-generation programs suggest that research has the potential to improve the outcome from eating disorder prevention intervention.

Table 206.1   Promising school-based eating disorder prevention programs

Program	Description
The body project (Shaw and Stice 2008)	The program is based on social psychological principle of cognitive dissonance. The theory postulates that encouraging girls and women to take an active position against the culturally mandated thin ideal, they will experience cognitive dissonance with a shifting of their belief systems toward an antithin-ideal stance. The intervention (3- and 4- session versions) reduced the risk for future onset of both eating disorder symptoms and obesity and mental health-care use at 1-year follow-up (Stice et al., 2006). Through a 3-year follow-up experimental group showed significantly greater decreases in thin-ideal internalization, body dissatisfaction, negative affect, eating disorder symptoms, and psychosocial impairment and lower risk for eating pathology than controls. Most importantly, the intervention reduced in the experimental group the risk for onset of threshold and subthreshold anorexia nervosa, bulimia nervosa, and binge-eating disorder compared with controls (6% vs. 15%) (Stice et al. 2008)
Healthy weight intervention (Stice et al. 2006)	The program was originally designed as a control group in a study testing the dissonance program. It is a brief 4-session intervention that teaches participants how to achieve and maintain a healthy weight by making small, gradual changes in diet and exercise. The intervention reduced the future onset of both eating disorder symptoms and obesity and result in improved psychosocial functioning and reduced mental health-care use at 1-year follow-up (Stice et al. 2006). The intervention also reduced the onset of eating disorders at 3-year follow-up (Stice et al. 2008)
Girl talk (McVey et al. 2004)	Girl Talk is a brief (6-sessions) interactive intervention focused on promoting critical media use, body acceptance, healthy weight-control behaviors, and stress management skills using a peer-support group. The intervention administered by public health nurses in a school, led to increases in weight-related esteem and decreases in dieting at post-test and 3-month follow-up among middle schools girls compared with the control group (McVey et al. 2003a). A subsequent evaluation of the intervention in other schools, however, did not replicate these positive findings (McVey et al. 2003b)
Student bodies (Winzelberg et al. 2000)	Student Bodies is an 8-week computer-administered program based on cognitive–behavioral body-dissatisfaction interventions that provides information on eating disorders, healthy weight-control behaviors, and nutrition. It also includes e-mail support interchange. The program showed produced a significant reduction of body dissatisfaction (Low et al. 2006), and positive outcome have been replicated by others (Taylor et al. 2006)
Weigh to eat (Neumark-Sztainer et al. 1995)	Weight to eat is a psychoeducational intervention that incorporates social–cognitive principles for behavior change. It is aimed to improve knowledge, attitudes, behaviors related to nutrition and weight control, body and self-image, and promoting greater self-efficacy in approaching social pressures regarding excessive eating and dieting. An effectiveness trial that evaluates the 10-session intervention administered by a health educator found that it produced significant improvements in knowledge, healthy weight-control behaviors, dieting, and binge eating at 6-month follow-up, although only the effects for binge eating remained significant at the 2-year follow-up
AIDAP eating disorder prevention program (Dalle Grave and De Luca 1999)	The AIDAP program is based on a broad cognitive–behavioral conceptualization of eating disorders and it was designed to prevent the development of eating disorders by reducing the prevalence of dietary restraint and the level of concern on shape and body weight in participants. It uses an interactive and not didactic educational approach with the inclusion, as in cognitive–behavioral therapy, of cognitive restructuring, homework, role-play, and practical activities and group discussions. The 6-session program, evaluated in Italy by a controlled study, produced in the experimental group an increase in knowledge, and a decrease in some attitudes maintained at 12-month follow-up (Dalle Grave et al. 2001). An evaluation of the program in a sample of young students confirmed its efficacy in reducing eating disorder attitudes and dieting behavior (Pokrajac-Bulian et al. 2006)

Table 206.2 Suggestions for stakeholders in the health-care sector to optimize the implementation and evaluation of school-based eating disorder prevention programs (Dalle Grave 2003).

1. The program must be easily inserted in the context of the school with lessons no longer than 50 min
2. Providers should be extensively trained before beginning the interventions
3. The program should be written in a manual to facilitate intervention fidelity and dissemination
4. Fidelity should be cheeked by a supervisor who evaluates several recorded prevention sessions
5. In order to eliminate possible contamination effects, it is advisable to use a control group in a separate site
6. The administration of the program should be across a wide spectrum of people with the involvement of parents, teachers, and school administrators
7. Booster sessions should be routinely planned to reinforce the maintenance of the positive effect of the intervention
8. Programs should select quantitative and qualitative outcome measures for evaluating potential negative effects
9. Short- (6 months) and long-term (1 or more years) follow-up assessments should be routinely conducted in prevention research

Table 206.3 Some of the potential risk factors for anorexia nervosa and bulimia nervosa (Dalle Grave 2003; Fairburn and Harrison 2003; Striegel-Moore and Bulik 2007)[a]

General factors
- Female
- Adolescence and early adulthood
- Living in a Western society

Individual-specific factors
- Family history
  - Eating disorders
  - Depression
  - Alcoholism (bulimia nervosa)
  - Obesity (bulimia nervosa)
- Premorbid experiences
  - Neonatal complications
  - Adverse parenting (especially low contact, high expectations, parental discord)
  - Sexual abuse
  - Family dieting
  - Critical comments about eating, shape, or weight from family and others
  - Occupational and recreational pressure to be slim
  - Media exposure to images of thin people
- Premorbid characteristics
  - Low self-esteem
  - Anxiety and anxiety disorders
  - Obesity (risk factor for bulimia nervosa)

[a]Risk factors are defined as "antecedent condition associated with an increase in the likelihood or adverse, deleterious, or undesirable outcomes" (Kazdin et al. 1997)

206.6.1 Enhancing Reliance on Risk-Factor Research When Designing New Prevention Programs

Most of the school-based prevention programs have been designed without being guided by modern research on risk factors (e.g., retrospective case–control studies and prospective cohort studies). Even though few eating disorder risk factors are yet known with confidence, it is advisable that future prevention programs are designed targeting empirically established risk factors.

It is also important to develop new instruments for detecting high-risk individuals based on the last findings derived by risk-factor research.

206.6.2 Improving the Design of the Eating Disorder Prevention Trials

Most of the eating disorder programs are affected by a number of methodological limitations. Many studies did not include a control group, and therefore they are unable to distinguish intervention effects from the effects of passing time. Several prevention trials did not use randomization to assign participants to condition and only a few used a placebo control condition. In many cases, sample sizes and follow-up were inadequate and did not reach meaningful conclusions. Many studies do not calculate effect sizes, making it difficult to interpret the real effects of the intervention. Most of the studies used outcome measures based on self-report assessment questionnaires. Such instruments tend to overestimate psychopathology and are not the ideal way of assessing eating disorder features. Furthermore, outcome measures evaluated only changes in certain dysfunctional attitudes and unhealthy behaviors and not the real effect on the prevalence and the incidence of eating disorders. These and other methodological limitations should be overcome by the future research studies.

206.6.3 Importing Strategies from the Treatment of Eating Disorders

The prevention programs could improve with the inclusion of some useful strategies adopted by the self-help with books. The self-help intervention produced positive outcome in the treatment of bulimia nervosa and binge-eating disorder (Loeb et al. 2000; Dalle Grave 1997). Self-help books may be used either by subjects on their own (pure self-help) or with guidance from therapists (guided self-help). The contents of some self-help books (Fairburn 1995; Dalle Grave 1998) are derived from cognitive–behavioral therapy of bulimia nervosa, the most effective therapy evaluated by controlled trials (Wilson and Shafran 2005). Self-help with manuals uses some effective strategies to increase motivation to change, to decrease dietary restraint, and to reduce the overvaluation of shape, weight, and eating control. Positive effects would be likely including these strategies taken from the self-help manual approach in future selective and indicated programs.

206.6.4 Integrating Eating Disorder and Obesity Prevention Programs

There are several reasons for integrating eating disorder and obesity prevention (Neumark-Sztainer 2003; Haines and Neumark-Sztainer 2006; Dalle Grave 2003). First, eating disorders and obesity often co-occur. Case–control studies found that obesity is a potential risk factor for bulimia nervosa (Fairburn et al. 1997) and binge-eating disorders (Fairburn et al. 1998) and binge-eating disorder is very common among persons with obesity (de Zwaan 2001). Second, one intervention is obviously cheaper than two, an important issue to consider in a period of global financial crisis. Third, the elimination of some conflicting information on diet, physical activity, and body image, and their potential iatrogenic effects coming from interventions delivered separately (e.g., some preventive obesity strategies, such as monitoring food intake, might promote excessive concern over eating control, and vice versa strategies aimed at eliminating any form of cognitive restraint may favor overeating and the onset of overweight) (Dalle Grave 2003).

An integrated approach, including both strategies to prevent obesity following a healthy lifestyle and to prevent eating disorder accepting the genetic diversity of human body, is a challenge to be tested in the next generation of prevention trials. However, to develop effective prevention interventions, the identification of risk factors shared between obesity and eating disorder is essential. Some preliminary data indicate that dieting, media use, body image dissatisfaction, and weight-related teasing may be relevant both for the development of eating disorder and obesity (Haines and Neumark-Sztainer 2006).

Support to the integration of the two fields comes from the data of one study indicating that a school-based obesity prevention program aimed to promote healthful nutrition and physical activity produced a significant greater reduction in experimental group of new onset disordered weight-control behaviors (self-induced vomiting or use of laxatives or diet pills to control weight) than in control group (Austin et al. 2007).

206.6.5 Creating an Environment with Lower Risk

Sociocultural factors seem to play a key role in the development of eating disorders. Support for these statements come from four lines of evidence (Striegel-Moore et al. 2007): (1) the preponderance of female cases of eating disorders; (2) the increasing incidence of eating disorders associated with the decreasing ideal body weight size for women; (3) the higher incidence and prevalence of eating disorders in cultures that value female thinness; and (4) the significant relationship between thin-ideal internalization and future disordered eating.

It is very improbable that simple and brief school-based prevention programs will be able to produce a real reduction in the incidence and prevalence of eating disorder without a strong action aimed to change some sociocultural risk factors. The shift from a prevention model based on personal responsibility toward a public health prevention model has been also advocated for obesity (Brownell and Horgen 2004). Public health organizations are responsible for ensuring the safety of the public and environmental changes (Brownell and Horgen 2004), including the body size of the fashion models portrayed in the media, the control of the advertising of the diet industry, the availability of the dresses for all the size, the fight against the stigma associated with obesity of, and the availability of healthy food. An example of the combination of education with public health intervention that produced positive changes in the population is the antismoking campaign combined with high tobacco taxes.

Efforts to change some potential environment eating disorder risk factors have been implemented in Spain, France, and Italy. In Italy, for example, where fashion is no doubt an important part of its culture and society, the "National Manifest of Self-regulation in Italian Fashion against Anorexia" has been published which was recommended, as versus obliged, to be adopted by the fashion designers. The key recommendations include: (1) to disseminate an healthy Mediterranean beauty model; (2) to protect the fashion models' health not allowing those with a diagnosis of clinical eating disorder (evaluated by a M.D. using current diagnostic criteria, including Body Mass Index (BMI)) to participate at fashion shows; (3) to ban the models under the age of 16 from the fashion shows; (4) to stimulate the fashion industry to include in their collection dresses of all the sizes; (5) to adopt the internal regulation of the fashion industries to adopt specific measures to ensure the respect of the manifest principles. In addition, the "Tavolo Moda e Salute" (tr. Fashion and Health Table) has been recently opened by the Milan mayor. The aim of this initiative, which sees the participation of eating disorder scientific societies, fashion designers, and political authorities, is to develop for the next Milano Expo 2015 concrete social–cultural actions to prevent eating disorder.

Although no data are available on the impact of public health initiatives, these initial efforts open a new era in the prevention of eating disorder, which have the potential to address with success the sociocultural risk factors of eating disorders.

206.7 Conclusions

School-based eating disorder prevention is still in its infancy. Recently, however, promising results have been achieved in identifying potential risk factors and small, but significant, progress has been made in developing and evaluating innovative interventions. Results obtained by the school-based controlled trials must reassure parents, teachers, and stakeholders in the health-care sector that school-based eating disorder prevention programs do not have harmful effects on student attitudes and behavior. Selective prevention programs have obtained promising results, and positive effects have been obtained using an interactive format, dissonance approach, and by focusing on participants in middle to late adolescence. Universal prevention expectations have unfortunately been disappointed, especially with children and young adolescents. The combination of school-based prevention program with public health strategies aimed at creating an environment with lower risk seem essential to achieve a real reduction in the incidence of eating disorders.

206.8 Applications to Other Areas of Health and Disease

Randomized experimental trials on eating disorder prevention programs could help to isolate the role of risks factor on eating disorder psychopathology, and could help to improve the identification of risk factors shared between obesity and eating disorder.

Summary Points

- The first-generation programs using didactic approach were ineffective in changing dysfunctional attitudes and unhealthy behaviors.
- The new generation programs, adopting an interactive educational approach and other innovative strategies (e.g., dissonance-based approach, healthy weight-control behaviors, cognitive restructuring techniques, strategies to improve body image by building general self-esteem, and strategies using Internet and other modern technology), obtained significant reductions of some established risk factor for eating disorder, and a significant reduction of eating disorder psychopathology.
- Good results have been obtained by selective prevention programs, using an interactive format, dissonance approach, and by focusing on participants in middle to late adolescence.
- Potential strategies to improve the future eating disorder prevention include:
  - Enhancing reliance on risk-factor research when designing new prevention programs
  - Improving the design of the eating disorder prevention trials
  - Importing strategies from the treatment of eating disorders
  - Integrating eating disorder and obesity prevention programs
  - Creating an environment with lower risk

Definitions and Explanations

Universal prevention: Programs targeting "all consenting individuals in a given population".
Selective prevention: Programs targeting to those who are at elevated risk to develop the disorder.
Indicated prevention: Programs targeting individuals who either have signs of the disorder but are in an early stage of a progressive disorder.

Key Points

- Selective prevention programs generally tend to obtain more positive results than universal programs.
- Didactic interventions produced fewer positive effects than interactive interventions.
- Programs that focused on older participants (older than 15 years) produced stronger prevention effects on dysfunctional attitudes and unhealthy behaviors.
- Prevention programs delivered by trained professionals are more effective than those delivered by endogenous providers (e.g., teachers and counselors).
- Some contents of the intervention produced better results (e.g. dissonance-induction interventions, body acceptance, health education activities that build self-esteem, healthy weight-control behaviors, critical analysis of the thin ideal, the use of computers and the Internet as a delivery medium).

References

Agras WS. Psychiatr Clin North Am. 2001;24:371–9.

Austin SB, Kim J, Wiecha J, Troped PJ, Feldman HA, Peterson KE. Arch Pediatr Adolesc Med. 2007;161:865–9.

Becker CB, Bull S, Schaumberg K, Cauble A, Franco A. J Consult Clin Psychol. 2008;76:347–54.

Brownell KD, Horgen KB. New York: Contemporary Books; 2004.

Celio AA, Winzelberg AJ, Wilfley DE, Eppstein-herald D, Springer EA, Dev P, Taylor CB. J Consult Clin Psychol. 2000;68:650–7.

Dalle Grave R. Eat Weight Disord. 1997;2:169–72.

Dalle Grave R. Verona: Positive Press; 1998.

Dalle Grave R. Dis Manag Health Outcomes. 2003;11:579–93.

Dalle Grave R, De Luca L. Verona: Positive; 1999.

Dalle Grave R, De Luca L, Campello G. Eat Dis. 2001;9:327–37.

Dalle Grave R, Bohn K, Hawker D, Fairburn CG. New York: Guilford; 2008.

de Zwaan M. Int J Obes Relat Metab Disord. 2001;25(Suppl. 1):S51–5.

Fairburn CG. New York: Guilford; 1995.

Fairburn CG, Harrison PJ. Lancet. 2003;361:407–16.

Fairburn CG, Welch SL, Doll HA, Davies BA, O'Connor ME. Arch Gen Psychiatry. 1997;54:509–17.

Fairburn CG, Doll HA, Welch SL, Hay PJ, Davies BA, O'Connor ME. Archives of General Psychiatry. 1998;55:425–32.

Fairburn CG, Cooper Z, Doll HA, O'Connor ME, Bohn K, Hawker DM, Wales JA, Palmer RL. Am J Psychiatry. 2009;166:311–9.

Haines J, Neumark-Sztainer D. Health Educ Res. 2006;21:770–82.

Herzog WGR, Vandereycken W. In: Herzog W, Deter H, Vandereycken W, editors. The course of eating disorders. Berlin: Springer; 1992.

Kazdin AE, Kraemer HC, Kessler RC, Kupfer DJ, Offord DR. Clin Psychol Rev. 1997;17:375–406.

Lewinsohn PM, Hops H, Roberts RE, Seeley JR, Andrews JA. J Abnorm Psychol. 1993;102:133–44.

Loeb KL, Wilson GT, Gilbert JS, Labouvie E. Behav Res Ther. 2000;38:259–72.

Low KG, Charanasomboon S, Lesser J, Reinhalter K, Martin R, Jones H, Winzelberg A, Abascal L, Taylor CB. Eat Disord. 2006;14:17–30.

McVey GL, Lieberman M, Voorberg N, Wardrope D, Blackmore E. Eat Disord. 2003a;11:169–85.

McVey GL, Lieberman M, Voorberg N, Wardrope D, Blackmore E, Tweed S. Eat Disord. 2003b;11:187–95.

McVey GL, Davis R, Tweed S, Shaw BF. Int J Eat Disord. 2004;36:1–11.

Neumark-Sztainer D. Adolesc Med. 2003;14:159–73.

Neumark-Sztainer D. Butler R, Palti H. J Nutr Educ. 1995;27:24–30.

Newman DL, Moffitt TE, Caspi A, Magdol L, Silva PA, Stanton WR. J Consult Clin Psychol. 1996;64:552–62.

O'Dea JA, Abraham S. Int J Eat Disord. 2000;28:43–57.

Paxton SJ, Wertheim EH, Pilawski A, Durkin S, Holt T. Prev Med. 2002;35:474–91.

Pokrajac-Bulian A, Zivcic-Becirevic I, Calugi S, Dalle Grave R. Eat Weight Disord. 2006;11:171–8.

Pratt BM, Woolfenden SR. Cochrane Database Syst Rev. 2002:CD002891.

Shaw H, Stice E. In: Legcroy C, editor. Handbook of prevention and intervention programs for adolescent girls. Hoboken: Wiley; 2008.

Shaw H, Stice E, Becker CB. Child Adolesc Psychiatr Clin N Am. 2009;18:199–207.

Steiner-Adair C, Sjostrom L, Franko DL, Pai S, Tucker R, Becker AE, Herzog DB. Int J Eat Disord. 2002;32:401–11.

Stewart DA, Carter JC, Drinkwater J, Hainsworth J, Fairburn CG. Int J Eat Disord. 2001;29:107–18.

Stice E, Shaw H. Psychol Bull. 2004;130:206–27.

Stice E, Shaw H, Burton E, Wade E. J Consult Clin Psychol. 2006;74:263–75.

Stice E, Shaw H, Marti CN. Annu Rev Clin Psychol. 2007;3:207–31.

Stice E, Marti CN, Spoor S, Presnell K, Shaw H. J Consult Clin Psychol. 2008;76:329–40.

Striegel-Moore RH, Bulik CM. Am Psychol. 2007;62:181–98.

Striegel-Moore RH, Dohm FA, Kraemer HC, Schreiber GB, Taylor CB, Daniels SR. Int J Eat Disord. 2007;40:481–7.

Taylor CB, Bryson S, Luce KH, Cunning D, Doyle AC, Abascal LB, Rockwell R, Dev P, Winzelberg AJ, Wilfley DE. Arch Gen Psychiatry. 2006;63:881–8.

Wilson GT, Shafran R. Lancet. 2005;365:79–81.

Winzelberg AJ, Taylor CB, Sharpe T, Eldredge KL, Dev P, Constantinou PS. Int J Eat Disord. 1998;24:339–49.

Winzelberg AJ, Eppstein D, Eldredge KL, Wilfley D, Dasmahapatra R, Dev P, Taylor CB. J Consult Clin Psychol. 2000;68:346–50.

Withers GF, Twigg K, Wertheim EH, Paxton SJ. J Psychosom Res. 2002;53:1021–7.

Yager Z, O'Dea JA. Health Promot Int. 2008;23:173–89.

Chapter 207
Treating Obesity in Childhood: Behavioral Considerations

Fiona Davies and Louise A. Baur

Abbreviations

BMI   Body mass index weight/height^2 (kg/m^2)
RCT   Randomized–controlled trial

207.1 Introduction

The high prevalence of child and adolescent obesity in most developed, and many developing, countries highlights the need for effective treatment of affected individuals. This chapter provides a brief overview of the prevalence, causes, and consequences of child and adolescent, and then focuses on the behavioral approaches used in its management.

207.2 Obesity in Childhood and Adolescence: An Overview

207.2.1 Rising Prevalence of Obesity

Childhood obesity is a major public health problem facing most westernized, and many westernizing, communities (Lobstein et al. 2004). Over the past 2 decades, the pediatric obesity epidemic has spread throughout the world, with some countries in economic transition now having prevalence rates higher than those in the US. The worldwide prevalence of overweight (including obesity) in children and young people aged 5–17 years is approximately 10%, with that of obesity alone being 2–3%. However, certain regions and countries have particularly high rates of pediatric obesity. For ample, more than 30% of children and adolescents in the Americas, and approximately 20% of those in Europe, are overweight or obese, with lower prevalence rates being seen in sub-Saharan Africa and Asia, although prevalence rates are rising rapidly in those countries undergoing

L.A. Baur (✉)
Discipline of Paediatrics and Child Health, University of Sydney, Sydney, NSW 2006, Australia
and
Weight Management Services, The Children's Hospital at Westmead, Westmead, NSW 2145, Australia
e-mail: louiseb3@chw.edu.au

nutrition transition. Sociodemographic differences also occur, with overweight being high among the poorer children in developed countries, and the richer children in developing countries.

207.2.2 Complications

Not only is obesity increasingly common, but obese children and adolescents may suffer from a range of both immediate and future comorbidities, as shown in Table 207.1 (Lobstein et al. 2004). Because of the range of potential obesity-associated comorbidities, children and young people affected by obesity should have a formal medical assessment.

207.2.3 Etiology of Obesity: An Overview

What factors lead to the development of obesity? Put simply, obesity is a chronic disorder affecting energy imbalance, i.e. there is a disturbance in the balance between energy expenditure and energy intake. This energy imbalance arises as a consequence of a complex interaction between genetic, social, behavioral, and environmental factors.

Energy balance is influenced by a detailed set of physiological pathways, of which the hypothalamus acts as the central regulator of energy homeostasis and energy intake. Circulating peripherally derived factors, including satiety signals derived from the gastrointestinal system, as well as long-term signals of energy stores (leptin, insulin) and short-term hunger (ghrelin) modulate this system. The resultant energy regulation system protects against weight loss, but does not protect against weight gain (Spiegelman and Flier 2001). With increasing body fatness, the resultant increase in circulating leptin (the principal fat store size signal) has only a limited effect on reducing food intake, presumably due to cellular resistance to leptin signaling.

There is a strong familial association with obesity, with many studies showing that part of this association is through a shared genetic predisposition (Bouchard 2009). While genetic factors make

Table 207.1 Potential complications of obesity in childhood and adolescence

System	Health problems
Cardiovascular	Hypertension, adverse lipid profile (low HDL cholesterol, high triglycerides, high LDL cholesterol)
	Medium- and long-term: Increased risk of hypertension and adverse lipid profile in adulthood, increased risk of coronary artery disease in adulthood, left ventricular hypertrophy
Endocrine	Hyperinsulinemia, insulin resistance, impaired glucose tolerance, impaired fasting glucose, type 2 diabetes mellitus *Medium- and long-term*: Increased risk of type 2 diabetes mellitus and metabolic syndrome in adulthood
Hepatobiliary	Nonalcoholic fatty liver disease, gallstones
Neurological	Benign intracranial hypertension
Reproductive	Polycystic ovary syndrome, menstrual abnormalities
Orthopedic	Back pain, slipped femoral capital epiphyses, tibia vara, ankle sprains, flat feet
Psychosocial	Social isolation and discrimination, decreased self-esteem, body image disorder, bulimia
	Medium- and long-term: Poorer social and economic "success", bulimia
Respiratory	Obstructive sleep apnea, asthma, poor exercise tolerance
Skin	Acanthosis nigricans, striae, intertrigo

This table lists the range of potential obesity-associated complications in childhood and adolescence, by organ system. In some cases, medium- to long-term complications are listed, as well as the more immediate problems

Table 207.2 Summary of strength of evidence on factors that might promote or protect against weight gain and obesity (Adapted from World Health Organization 2003)

Evidence	Decreased risk	No relationship	Increased risk
Convincing	Regular physical activity		Sedentary lifestyles
	High dietary intake of NSP [a] (dietary fiber)		High intake of energy-dense micronutrient-poor foods
Probable	Home and school environments that support healthy food choices for children		Heavy marketing of energy-dense foods and fast-food outlets
	Breastfeeding		High intake of sugars – sweetened soft drinks and fruit juices
			Adverse socioeconomic conditions
Possible	Low glycemic index foods	Protein content of diet	Large portion sizes
			High proportion of food prepared outside the home (developed countries)
			"Rigid restraint/periodic disinhibition" eating patterns
Insufficient	Increasing eating frequency		Alcohol

This table shows the strength of evidence (i.e. insufficient, possible, probable, or convincing) on factors that might promote or protect against weight gain and obesity. The table is adapted from a World Health Organization (2003) publication in which these factors are considered in detail

[a]*NSP* nonstarch polysaccharides

a major contribution to an individual's susceptibility to the development of obesity, unless the "correct" environmental conditions exist, an individual's genetic predisposition for obesity may not be fully expressed. The increased prevalence of obesity in recent decades in genetically stable populations highlights the central role of recent important environmental trends in the development of the obesity epidemic. Table 207.2 summarizes the strength of the evidence for factors associated with promotion of, or protection against, the development of obesity in both adult and pediatric populations, as outlined in a World Health Organization report (World Health Organization 2003). The varied range of factors influencing both energy expenditure and intake emphasizes the obesogenic nature of the broader environment in westernized societies.

207.2.4 Overview of Management

Given the significance of child and adolescent obesity, in terms of both prevalence and complications, and the broader obesogenic environment in which individuals live, how can it be tackled? While primary prevention will be vital in curbing the epidemic, treatment of those children and adolescents who are currently obese is needed to improve both their immediate and long-term health outcomes. The broad principles of treatment should include the following elements (see Table 207.3):

- Assessment and treatment of any medical and psychosocial comorbidities
- Family involvement
- A developmentally appropriate approach (different approaches for adolescents and children)
- Long-term behavior change
- Long-term dietary change
- Increased physical activity
- Decreased sedentary behavior
- Consideration of the use of pharmacotherapy in adolescents

Table 207.3 Basic principles of management of obesity in childhood and adolescence

Assess and treat medical or psychosocial comorbidities

Family involvement

Developmentally appropriate approach

- *Preadolescent children: focus on parents*
- *Adolescents: consider separate sessions for the young person and parent(s)*

Long-term behavioral change

Long-term dietary change

- *Energy reduction*
- *Food choices that are lower in fat and have a lower glycemic index*
- *Reduction in high-sugar foods and drinks*
- *Water as the main beverage*
- *Avoidance of severe dietary restriction*
- *Appropriate portion sizes*
- *Modified eating patterns (regular meals, eat together as a family, avoid eating while watching the television)*

Increase in physical activity

- *Incidental activity*
- *Active transport options (e.g. walking, cycling, using public transport)*
- *Lifestyle activities*
- *Organized activities*
- *Improved access to recreation spaces and play equipment*

Decrease in sedentary behavior

- *Television, computer, play-station, and other small-screen recreation*
- *Alternatives to motorized transport*

Consideration of pharmacological therapy

- *Consider use of sibutramine or orlistat in moderately to severely obese adolescents, as an adjunct to lifestyle modification*
- *Metformin may be indicated in insulin-resistant adolescents*

This table lists the basic principles of management of obesity in childhood and adolescence. More details of long-term behavioral change are given in the rest of the chapter

The 2009 Cochrane Review on treatment of child and adolescent obesity included 64 randomized–controlled trials (RCTs) and provides some guidance as to the effectiveness of clinical interventions (Oude Luttikhuis et al. 2009). The review noted that there are limited quality data, making it difficult to recommend one treatment program over another. However, the review showed that combined behavioral lifestyle interventions, compared to standard care or self-help, can produce a significant and clinically meaningful reduction in overweight in children and adolescents in the short and long term. The review also highlighted that in obese adolescents consideration should be given to the use of either orlistat (a gastrointestinal lipase inhibitor) or sibutramine (a centrally acting appetite suppressant), as an adjunct to lifestyle interventions, although this approach needs to be carefully weighed up against the potential for adverse effects.

The rest of this chapter focuses on the evidence for, and practicalities of, behavioral change in the management of child and adolescent obesity.

207.3 Introduction to Behavioral Interventions

The behavioral research tradition has led to the widespread therapeutic use of behavioral modification techniques in a variety of settings, including education, parenting, and health. Behavioral therapies focus particularly on operant conditioning and the use of reinforcement to change the frequency of

Table 207.4 Matching behavioral techniques to behavioral antecedents and consequences

	Antecedents	Behavior	Consequences
Patient factors	Access to screens	Eating too much	Weight gain/loss
	Negative affect	Eating the wrong foods	Low self-esteem
	Parental feeding style	Too much screen time	Health problems
	Attitudes to food/activity	Low physical activity	Bullying
	Family/peer norms		Social isolation
	Sports facilities		
	Individual differences		
Behavioral techniques	Cognitive restructuring	Problem-solving	Behavioral contracting
	Preplanning	Self-monitoring	Reinforcement
	Goal setting	Parenting training	Shaping
	Stimulus control	Relapse prevention	
	Modeling		

This table lists patient factors, which may precede obesogenic behaviors (antecedents), examples of obesogenic behaviors, and their consequences. The table also describes behavioral techniques, which can be used to manage each of these areas

occurrence of a behavior. Operant conditioning relates to voluntary behavior, which is maintained by consequences. Behavioral therapies aim to change both the stimulus conditions and the consequences of behavior in a positive way. In obesity treatment, for example, this may mean reducing cues to eat (stimulus control), so that eating occurs less frequently and increasing positive reinforcement for exercise so that exercise behaviors happen more often. There is strong evidence that behavior modification, used correctly, is successful in changing the frequency of behavior in real-world settings.

Stemming from the behavioral tradition, cognitive–behavioral therapies incorporate the idea that thoughts and beliefs are also important drivers of behavior and that by introducing more helpful thinking patterns behavioral changes can be achieved more readily. The cognitive–behavioral therapies make three basic assumptions that – cognition affects behavior, cognition can be monitored and changed, and changes in cognition can lead to changes in behavior (Dobson and Dozois 2001). Cognitive–behavioral therapies combine behavioral and cognitive change techniques.

At its best, behavioral modification relies on a thorough behavioral assessment or functional analysis, which looks at the antecedents and consequences of behavior for each individual, with the aim of changing the behavioral contingencies driving the behavior. Similarly, cognitive–behavioral therapy is based on individualized case formulations, which link thoughts and beliefs to behavior and emotions. The match between the main behavioral change techniques and behavioral contingencies is provided in Table 207.4.

In obesity treatment, cognitive and behavior modification strategies are often manualized and taught to the parents of obese children, so that the parents may use them to help change their children's behavior and may also use them for themselves in a whole of family approach. Children, especially older children, are often taught the same strategies. The interventions discussed below can thus be targeted at children alone, at parents alone, at parents and children, or at the family as a whole. Behavioral and cognitive interventions are aimed at changing obesogenic behaviors and altering energy balance in a favorable direction. Without intervention, obesogenic behaviors and their associated weight gain track into adulthood, reinforcing the need for early intervention.

207.3.1 Overview of Behavioral Interventions in Obesity Treatment

The majority of RCTs in childhood and adolescent obesity treatment utilize predominantly behavioral modification techniques, with some trials including cognitive interventions or other approaches

such as parenting training. A review of the RCTs in the latest Cochrane Review (Oude Luttikhuis et al. 2009) shows that the most common techniques are self- or parental monitoring, stimulus control, goal setting or contracting, reinforcement, and contingency management. In particular, Epstein and colleagues have published a variety of studies on the treatment of pediatric obesity over the last 20 years, which have included many of these traditional behavioral modification techniques (e.g. Epstein et al. 1985, 2005). Other frequent techniques include modeling, preplanning, problem-solving, parenting training, and cognitive restructuring. Details of the various cognitive and behavioral treatment techniques are described in the next section.

Details of the exact components of treatment programs tend to be lacking in obesity treatment research; this may be partly due to the lack of a common language for behavioral change interventions, as suggested by Abraham and Michie (2008). It may also be due partly to the requirements of journals for brief articles (Baranowski et al. 2003). This has an impact on the ability of other researchers and practitioners to replicate the treatment programs. This is in contrast to the manualized approaches common in clinical psychology research, which allow for relatively precise replication in a clinical context. However, it is still possible to draw some broad conclusions about the interventions that should be considered in obesity treatment programs.

There is strong evidence that parental involvement in treatment of childhood obesity is important, and that behavioral change techniques need to be taught to parents so that they can change the home environment. For example, if parents change their own behavior so that there are few or no energy-dense foods at home, this is likely to have an impact on the child's weight as it reduces access to these foods. McLean et al. (2003), in a systematic review of 16 studies, found that targeting both children and parents for weight loss, training parents in behavior change, and teaching a greater number of behavior change techniques were all associated with greater weight loss.

207.4 Specific Behavioral Techniques in Obesity Treatment

207.4.1 Self-Monitoring

Self-monitoring is a core component of behavioral approaches, and is widely used in obesity treatment. Although many studies do not provide details of the self-monitoring requirements, those that do typically include recording food intake, physical activity and/or sedentary behavior, and weight (e.g. Epstein et al. 1995; Saelens et al. 2002; Johnston et al. 2008). Self-monitoring as a behavioral technique is often used in a more comprehensive form in other contexts, in which people record their behavior, along with its antecedents and consequences. It is assumed that this allows a greater awareness of both their behavior and how it is influenced by the environment, and therefore allows a greater capacity to change the behavior including changing the antecedents and consequences. It is often the first step in treatment. Some obesity researchers have described more comprehensive approaches to self-monitoring (e.g. Braet et al. 2004; Kalavainen et al. 2007) and a more comprehensive approach is suggested in many studies by the inclusion of stimulus control and contingency management techniques.

Self-monitoring has been associated with greater weight loss in both children and adolescents, including both low-income and minority groups with severe obesity. In addition, parental self-monitoring has been associated with greater self-monitoring among children and adolescents, as well as with greater weight loss (e.g. Kirschenbaum et al. 2005; Germann et al. 2006a). In the studies described above, self-monitoring involved parents and children writing down each day all food consumed (including calculating grams of fat and calories), the number of steps taken per day as

measured by a pedometer, and exercise done. It follows that helping clients to adhere to self-monitoring is a worthwhile component of behavioral interventions for obesity. Overall, the research suggests that a useful level of child and parental self-monitoring would include writing down daily food intake, physical activity and sedentary behavior. In addition, weight should be monitored at intervals (perhaps weekly). Ideally, writing down the triggers for eating or sedentary behavior, as well as their outcome would be useful – particularly where patients are having difficulty adhering to diet or activity recommendations.

207.4.2 Goal Setting, Behavioral Contracting, Reinforcement, and Contingency Management

Following on logically from self-monitoring, which identifies current behavior, are a number of techniques focused around changing current behaviors in the desired direction. Goal setting, behavioral contracting, reinforcement, and contingency management are related techniques, which are used in one form or another in most of obesity treatment studies (e.g. Epstein et al. 1995; Saelens et al. 2002; Johnston et al. 2008). Goal setting is the identification of desired behavior or outcomes and may refer to the setting of specific targets for weight loss, but may also refer to target behaviors such as food intake, active play, or limiting the time spent watching television. Reinforcement is the systematic use of rewards for desired behavior and goal achievement, while behavioral contracting specifies in advance the relationship between behavioral or outcome goals and rewards. Shaping uses reinforcement for gradual approximations to the goal behavior. This suggests that obesity treatment programs should specify behavioral and outcome goals, match suitable rewards for goal achievement, and specify these in a behavioral contract. Goals might include weight loss, dietary goals, decreased sedentary behavior (such as watching TV or using computer games), or time spent in active play. Depending on the age of the child, rewards could include praise, privileges, or nonfood treats such as outings or toys for active play. Younger children benefit from more frequent rewards, while older children may respond to longer term rewards.

207.4.3 Stimulus Control

Stimulus control in obesity treatment involves changing environmental factors, which trigger obesity-related behaviors. There has been considerable basic research on the environmental factors influencing food intake, such as variety, container size, and distraction (e.g. Kahn and Wansink 2004; Wansink and Cheney 2005; Remick et al. 2009). There has also been significant research on parental feeding styles and childhood obesity (e.g. Moens and Braet 2007; Rhee 2008). These studies provide a good starting point for stimulus control in obesity treatment. The aim of stimulus control is to decrease cues to eat unhealthy food by having it less accessible and decreasing reminders to eat, decreasing cues for sedentary behaviors such as watching television, and increasing cues for activity by making it part of the routine and increasing access to options for active play. Epstein et al. (1995) used strategies such as not keeping energy-dense foods at home, having exercise equipment such as bikes readily available, and turning the television to the wall. The nature of the cues for different behaviors may also vary between individuals, and between different families and homes. For example, if people regularly eat in front of the television, the television may itself become a cue (conditioned stimulus) for eating (Epstein et al. 1995). In this situation, decreasing access to the television may also help to decrease food intake. See Table 207.5 for an explanation of stimulus control.

Table 207.5 Key features of stimulus control

1. A stimulus is a cue or trigger for a particular behavior
2. By controlling the stimulus, it is possible to control the behavior
3. Stimulus control is a set of techniques for controlling stimulus conditions in an attempt to control specific behaviors
4. In obesity treatment, stimulus control techniques can be used by parents, and by children, to assist in managing obesogenic behaviors

This table explains the use of stimulus control in managing obesogenic behaviors

207.4.4 Preplanning and Problem-Solving

Preplanning and problem-solving are aimed at preventing future obesity-related behaviors and have been widely used in treatment studies (e.g. Epstein et al. 2000a). Preplanning is used to anticipate and prepare for high-risk situations for unhealthy behaviors such as parties or rainy weather. For example, if it is apparent that on holidays or outings family eating habits change to include more fried or energy-dense food, preplanning is aimed at identifying changes that could be made, such as preparing lunch at home or carrying a water bottle rather than buying soft drink. Problem-solving is aimed at solving identified problems to ensure a better result in the future and to help with maintenance of change; it can be used as part of preplanning.

207.4.5 Parenting Training

Parenting training has also been used in a number of studies, and is likely to be particularly suited to parents of younger children who have greater control over their child's behavior. Typically, parenting training covers a range of behavioral, and sometimes cognitive, modification techniques, which were traditionally used to address excessive disruptive behaviors in children. It also aims to increase positive, prosocial behaviors in both parents and children. Obesity-conducive behaviors in children (e.g. demanding large portions of unhealthy food) or resistance to healthy behaviors (e.g. refusing to go for a walk with a parent) can be conceptualized as disruptive behaviors; it therefore seems logical to include parenting training in childhood obesity treatment programs. Parenting training allows parents to be targeted as the primary means of behavior change in the child both through their own authority and by acting as role models (e.g. Golan et al. 1998, 2006). Ideally, parenting training equips parents to set limits on unhealthy behavior, while maintaining a high level of support and encouragement for their child. Another important area in which parents can influence their children is through their own behavior. This is known as modeling, and requires the parents to "do what they say," by maintaining their own healthy habits (e.g. Epstein et al. 1985).

207.4.6 Cognitive Restructuring

Cognitive restructuring has been used in number of studies to address unhelpful beliefs, which may prevent behavior change or help to maintain unhealthy habits (e.g. Duffy and Spence 1993). Generally, cognitive restructuring could be used to change the antecedents of behavior, but may also be used to change the consequences of behavior by influencing how people respond to success or

failure in behavioral or outcome change. Ideally, this would be preceded by a cognitive–behavioral assessment and self-monitoring to identify the unhelpful beliefs or thoughts, which influence the likelihood of obesity-related behavior. Parental beliefs such as "he deserves a treat" and "it's not fair I have to make my child do this" can be particularly powerful barriers to behavior change, and ultimately weight loss.

207.4.7 Relapse Prevention

Relapse prevention is the structured preparation for maintenance of behavior change, and has been used in some obesity treatment studies (e.g. Kalavainen 2007). Relapse prevention usually involves identification of the warning signs for slipping back into old behaviors, strategies for addressing this if it occurs, a description of what behaviors need to be maintained, and strategies for maintaining new habits. For example, a warning sign might be failing to be active for several days in a row, or an increase in snacking. The relapse prevention plan would then identify what to do to return to activity or decrease snacking. Relapse prevention plans may include any of the techniques already discussed. For example, ongoing self-monitoring may be part of the plan.

207.5 Review of the Evidence Base for Behavioral Techniques in Obesity Treatment

The literature shows that, when used in combination, behavioral modification techniques are successful in changing obesogenic behaviors and aiding weight loss (Oude Luttikhuis et al. 2009). However, we do not know precisely which techniques should be used, when in treatment they should be introduced, and which aspects of behavior change (e.g. diet, activity, sedentary behavior, parenting) are best suited to which techniques. Nor do we know which individuals and families would respond best to different approaches.

207.5.1 Psychological Models of Obesity

The development of validated psychological models of obesity and weight gain, which integrate eating behaviors, sedentary behaviors, and physical activity, would aid progress in the field by helping clinicians to make better treatment decisions. While a number of health behavior change models exist, and have been applied in obesity research, much more remains to be done to understand the moderating and mediating variables which may contribute to behavior change, and thus intervention outcome (Baranowski et al. 2003).

Some of the models that have received attention include Behavioral Learning Theory, Social Cognitive Theory, the Health Belief Model, the Theory of Reasoned Action or Theory of Planned Behavior, the Transtheoretical Model, and ecological models (Baranowski et al. 2003). Behavioral economics is a recent approach that has been used in obesity treatment (e.g. Epstein et al. 2005). However, much of the available research using these models focuses on one behavior (e.g. decreasing sedentary behavior) at a time, and does not integrate environmental and biological factors, which

may also influence behavior change (Baranowski et al. 2003). The role of emotions in obesity have also been somewhat overlooked (Baranowski et al. 2003), although recently the links between negative emotional states and binge eating are starting to receive some attention (e.g. Stice 2002), as are the links with bullying (e.g. Suisman et al. 2008).

207.5.2 Treatment Planning

Much of the research base consists of multicomponent treatment programs, and consequently it is difficult to know which parts of the intervention are the active ingredients (Braet et al. 2004). Some studies published by Epstein and colleagues investigate one additional component at a time, but these are additions to an existing multicomponent treatment program (e.g. Epstein et al. 2000a, b). For example, Epstein et al. (2000b) investigated whether it was better to target a decrease in sedentary behaviors or an increase in active behaviors at two levels of intensity of intervention (low and high). They found similar results for both levels of intensity and for either target behavior – all four conditions were effective in reducing overweight as can be seen in Fig. 207.1.
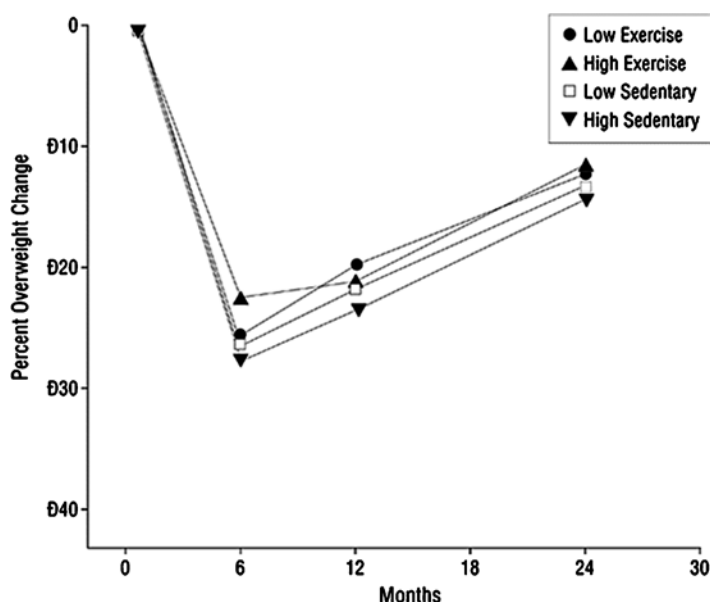

Fig. 207.1 Change in percent overweight from baseline for obese children receiving low or high exercise or sedentary behavior interventions. Results from a study performed by Epstein et al. (2000b) in 8–12-year-old children who, at baseline, were 20–100% overweight. All participants received a 6-month program (20 sessions; involving both child and parent) and were randomized to one of four experimental groups: (**a**) high sedentary (20 h/week decrease in targeted sedentary behavior; n = 22 at baseline); (**b**) low sedentary (10 h/week decrease in targeted sedentary behavior; n = 23); (**c**) high exercise (32.2 km [20 miles]/week increase in physical activity; n = 23); or (**d**) low exercise (16.1 km [10 miles]/week increase in physical activity; n = 22). Change in percent overweight from baseline is shown for experimental group at 6 (end of program), 12, and 24 months. Changes from baseline were significant at 6, 12, and 24 months (*P* < 0.001) (Reprinted from Epstein et al. 2000b, with permission. Copyright © (2000) American Medical Association. All rights reserved)

As mentioned earlier, there are also a variety of behavioral approaches to obesity treatment, and many aspects of treatment planning remain unclear, including methods, timing, intensity, and tailoring (Lobstein et al. 2004). Finally, despite the dominance of cognitive–behavioral therapy in mental health, the majority of the RCTs in the Cochrane Review (Oude Luttikhuis et al. 2009) utilize predominantly behavioral approaches, with cognitive techniques being used less often. Well-designed studies comparing behavioral to cognitive–behavioral therapy approaches may shed some light on the best approach.

The studies included in the Cochrane Review (Oude Luttikhuis et al. 2009) are focused on the active phase of treatment, rather than prevention or maintenance of weight loss. Just as we need to know how to apply behavioral interventions in treatment, we also need to know how to apply them in prevention and maintenance. It is important to draw a distinction between those factors which cause a problem (addressed by prevention programs), those that maintain a problem and/or predict treatment outcome (addressed by treatment programs), and those factors which predict maintenance of treatment outcomes (addressed by relapse prevention). For example, conscientiousness as a personality trait might improve treatment outcome by enhancing adherence to treatment but be unrelated to the causes of obesity, or negative emotional states might maintain obesity by triggering binge eating but not be a causal factor. Similarly, self-monitoring might assist in the treatment phase but not in prevention, or problem-solving might assist in the maintenance phase but not in the treatment phase. Given the difficulty of maintaining weight loss over time, an understanding of both the predictors of weight loss and the predictors of weight maintenance is critical to obesity treatment. While current programs are focused on weight loss and measure maintenance over time, it may be that different skills or strategies are required for the maintenance stage. In addition, prevention programs may need to target different variables to treatment programs.

207.5.3 Individual Differences in Treatment Response

It is the nature of clinical trials that there are exclusion criteria for participation, as this allows a purer test of treatment effects. Because of this, real-world implementation of programs used in clinical trials may not always obtain equivalent outcomes. An understanding of the effect of individual differences in family situation, culture, personality, or other circumstances such as physical or developmental problems is needed in order to adequately tailor interventions to different groups. The interaction between child and parent factors may also be important; for example, difficult child temperament and a parenting style low in behavioral control was found to be more common in obese children and adolescents compared to an equivalent nonobese sample (Zeller et al. 2008). In addition, the complications of obesity may in and of themselves affect treatment success. For example, social exclusion impairs self-regulatory capacity and the ability to resist eating unhealthy snack foods (e.g. Baumeister et al. 2005), and this may also apply to the effects of weight-related bullying in overweight children or adolescents. That is, an understanding of the effects of individual differences or circumstances on the effectiveness of treatment would aid clinicians in making the best choice of treatment options for their particular client group or for an individual child or family.

Thus, while we know that behavioral interventions are a vital contributor to treatment outcome in obesity, there is still a lot to be learnt. Theoretical developments such as models of obesity-related behavior in childhood are required, as is research on individual differences in treatment response, and basic research on the drivers of obesity-related behaviors. Finally, the development of a common

language and manualized approaches, which can be replicated in clinical settings would provide a worthwhile advance in obesity treatment.

207.6 The Challenges of Delivering Behavioral Therapy in Clinical Practice

As discussed previously, published research on obesity treatment, including the studies included in the Cochrane review, may not be representative of usual clinical practice due to the use of stringent exclusion criteria (Oude Luttikhuis et al. 2009). For example, typical exclusion criteria include psychiatric conditions in parent or child, learning disabilities, and extreme obesity. The cases seen in clinical practice may therefore be far more complex than the typical families seen in clinical trials and require a different approach. In the Weight Management Service at The Children's Hospital at Westmead in Sydney, it is common to see families with multiple psychosocial problems including mental disorders, learning disabilities, chronic illness or disability, poverty, and domestic violence. These families have multiple barriers to behavioral change and often have difficulty adhering to treatment recommendations or carrying out behavioral tasks such as self-monitoring, do not attend treatment reliably, or drop out early. This phenomenon is also common in the research literature, with reported rates of attrition in the Cochrane Review as high as 42% (Oude Luttikhuis et al. 2009).

Attrition appears to be an important factor affecting treatment outcome, with children who attend treatment reliably much more likely to achieve weight loss (e.g. Reinehr et al. 2009; Germann et al. 2006b). This may be due to a number of factors, including the increased treatment intensity which comes with regular attendance. For example, for parents to effectively use behavioral change techniques with their children, they need to attend treatment sessions in order to learn the techniques in the first place. A range of factors may be important in attrition. These fall into two broad categories – patient factors and treatment service factors. Potential patient factors include psychosocial barriers, a lack of effective parenting skills, problems with motivation, parental perceptions of their child's health, the child not wanting to attend, or barriers to adherence to treatment (e.g. Reinehr et al. 2009; Cote et al. 2004). Potential treatment service factors include the time commitment required to attend treatment, insufficient follow-up, perceived quality of care, insufficient tailoring, a lack of attention to child engagement in treatment, and less than optimal therapeutic relationships (e.g. Cote et al. 2004).

Research on the success of psychological therapies in general demonstrates that a range of factors contribute to treatment outcome (e.g. Asay and Lambert 1999). These include client factors (e.g. demographic factors, personality, and individual differences such as hope), therapist factors (e.g. skills or empathy), relationship factors (specifically, an effective working relationship between the health professional and their patient), and technique factors (i.e. the specific therapeutic approach used). The research described above suggests that this framework may also be applicable to obesity treatment programs, and may provide a framework for understanding problems with attrition or adherence to treatment.

In summary, in order for children to benefit from an obesity treatment program they and their parents need to attend reliably, complete the program of treatment, adhere to treatment recommendations, and change their behavior. Parental behavior change is likely to be particularly challenging and yet is central to treatment success. Adherence to the treatment program is likely to be especially challenging for families with multiple psychosocial barriers. Possible approaches include designing the service to cope with these barriers by the inclusion of specialist staff, excluding these types of

families from the treatment program until problems are resolved, or building comprehensive links with other types of social services to meet the needs of these families.

207.6.1 Other Challenges in Treating Child and Adolescent Obesity

The above overview of behavioral management of pediatric obesity provides an evidence base for a range of therapists as they seek to treat children and adolescents affected by obesity. However, there are several challenges in translating such evidence into everyday clinical practice. Following are some considerations.

207.6.2 Gaps in the Current Evidence Base

The 2009 Cochrane Review on treating child and adolescent obesity (Oude Luttikhuis et al. 2009) has highlighted a number of gaps in the research evidence, as summarized below:

- What interventions work best for:

  ○ Different levels of obesity severity, ages, and developmental stages?
  ○ Long-term maintenance of healthy weight following initial treatment of obesity?
  ○ Specific ethnicities, religious groups, or culturally diverse populations?

- What family characteristics promote weight outcome success?
- What is the role of self-esteem and the family's capacity to change behavior in effective treatment?
- What are the most cost- and resource-effective methods of treating pediatric obesity in different health-care settings?
- What is the role of bariatric surgery in the treatment of severely obese adolescents?
- What are the potential harms as well as benefits of different interventions?

207.6.3 Patients with Psychosocial Comorbidities, and Few Experienced Staff

Most of the studies looking at strategies for behavioral management of obesity in children and adolescents have typically been performed in white, middle-class, intact families where the degree of motivation for change is relatively high and where there are few, or no, associated psychosocial comorbidities (Oude Luttikhuis et al. 2009). But the reality of pediatric obesity, in western societies at least, is that it is more common in families from lower socioeconomic groups, with single parents and often a range of associated psychological or social problems (Lobstein et al. 2004). Likewise, many of the obesity behavioral management studies to date have taken place in tertiary-level units with highly skilled staff (Oude Luttikhuis et al. 2009). However, usual weight management services in many countries have a smaller complement of experienced staff and there may be little, or no, clinical psychologist input into the treating team. Thus, the current evidence base of behavioral management of obesity will need to be adapted to use with such clinical situations (see Table 207.6 for some suggestions). How do you provide services when patients have a range of psychiatric or social problems, and where the therapists are unlikely to include a social worker or clinical psychologist?

Table 207.6 Potential barriers to behavioral change in families attending obesity treatment programs

Barrier	Effect	Potential intervention strategy
Family in crisis (e.g. domestic violence)	At risk, and unable to focus on weight management	Crisis intervention
		Case management until the situation has stabilized
		Involvement of additional support services such as child protection
Poverty	Access to healthy food	Focus on low-cost food alternatives
	Access to activities and recreation space	Provision of low-cost physical activity alternatives
Culturally and linguistically diverse clients	Service may not be provided in their first language	Use of interpreters
	Cultural practices may not fit with standard advice on diet and activity	Culturally sensitive weight management advice
Learning disabilities or developmental disorders	Ability to benefit from education about diet and activity	Greater family involvement
		Intensive practical intervention
		Involvement of specialist support services
Mental disorders	Unable to attend treatment or focus on weight management	Involvement of mental health treatment and support services
	Poor motivation	Case management until the situation has stabilized
	At risk	
Physical health problems	May not be able to participate in physical activity due to functional limitations	Provide alternative options

This table lists the barriers to obesity treatment, their effect on treatment response, and some options for intervention

There is an urgent need for obesity management studies performed in such everyday, "real-life" clinical situations.

207.6.4 Providing a Weight Management Service in a Resource-Poor Environment

Despite the high prevalence of pediatric obesity, in many regions and countries there are relatively few resources to provide effective treatment of those who are affected by the problem. Thus, therapists may find themselves practicing in environments where they are relatively unsupported. Following are some practical suggestions for providing services in such a situation:

- Wherever possible, establish links with other weight management health professionals, for professional support, continuing education, and shared care.
- Consider shared care arrangements. For example, can the patient be comanaged by a family doctor, dietitian, and/or clinical psychologist?
- Explore the use of more time-efficient strategies such as group programs and at least some use of email and phone contacts with patients.
- Where possible, consider educating referring health professionals in some basic obesity management principles, so that they are better able to manage patients independently of more specialized intervention.
- Provide guidelines on the assessment and treatment of patients which can be used by a range of health professionals.

- Set realistic goals for treatment, rather than expecting to obtain the results found in well-funded research settings.
- Focus on sound implementation of core behavioral modification techniques. For example, introduce self-monitoring and practice it with the patient in session, check for understanding of why monitoring is important, and follow-up to ensure monitoring is being done.

207.6.5 Considerations in Establishing and Running a Pediatric Weight Management Service

Despite the increasing public recognition of the problem of obesity in many countries, the planning for effective treatment services, especially for children, has lagged behind. Following are some reflections on the elements found useful in establishing and running a pediatric weight management service.

207.6.5.1 Staffing

Effective staffing of a pediatric weight management service, whether a large multidisciplinary service, or a smaller one with fewer therapists, is vital. Because obesity management involves work that crosses traditional discipline boundaries, staff members should be flexible and willing to move outside usual professional "silos" of knowledge. They should have good teamwork skills, cultural competence, and a respectful attitude toward obese people. The latter is very important, as there are many examples of health professionals, including those working in obesity management, having negative and stigmatizing attitudes toward obesity and obese people (e.g. Schwartz et al. 2003). Importantly, staff should be child and youth friendly, and readily able to work with families.

In most cases, a multidisciplinary clinical team is required. Ideally, a larger service should include a senior nurse (often the "conductor of the orchestra"), and a pediatrician or adolescent physician, dietitian, clinical psychologist, social worker, and exercise professional. In practice, many services do not have the full complement of health professionals. In this case, we would recommend that professionals treating children or young people with obesity should liaise, as needed, with other health professionals who can provide complementary skills.

207.6.5.2 Physical Facilities

The clinic facility should be readily accessible by, and comfortable for, big people who may have problems with mobility. There should be access to the disabled and wide corridors and doorways, with chairs that are sturdy and can seat large people. Weight scales should allow sensitive measurement of very large people (e.g. 250+ kg) and, in the case of medical or nursing assessment, there should be large blood pressure cuffs. Mirrors should be minimized.

A range of strategies may help to destigmatize the experience of attending a weight management clinic for individual children and their families. For example, consider the name of the clinic – "Weight Management Clinic" may be less confronting than, say, "Obesity Clinic". Front desk staff should also be trained to make patients feel relaxed and at ease. An additional strategy in our clinical service is the use of a highly interactive video game (e.g. Eye-Toy™; Sony Computer Entertainment Inc.),

which is set up in part of the waiting room and which encourages high levels of safe physical activity within the confines of a clinic. Children can take turns to play games, or can play together.

207.6.5.3 Database and Service Audit

The weight management service should be supported by a database that can also allow audit and research studies to be undertaken. Measurements of height and weight should be entered onto an electronic database, and body mass index (BMI) calculated and plotted on an electronic BMI for age chart.

207.6.5.4 Health Professional Training

Ongoing health professional training of many levels of staff is required, from undergraduate level through to continuing postgraduate professional education, and for many types of clinician. Because obesity management is a relatively new discipline, there may not be appropriate continuing professional education services available, even in large tertiary-level institutions. Staff should therefore be encouraged to seek such training out, or to develop their own training opportunities, perhaps in liaison with their clinical service, the broader hospital or their professional body, as appropriate.

207.6.5.5 Liaison with Other Clinical Services

Coordination with clinical services that manage obesity-associated medical comorbidities is vital, and may include Psychiatry, Adolescent Medicine, Sleep Unit, Hepatology, Endocrinology, Dermatology, General Medicine, Gynecology, and Orthopedics. Shared protocols for assessment and management may need to be developed and key staff in the other services may require additional training regarding obesity. Families and young people with severe obesity may also have significant family dysfunction, psychiatric comorbidities, and/or parenting concerns; hence, the importance of effective links with Psychiatry, Social Work, and even Child Protection Services, and the need for obesity clinical staff to have a good understanding of the psychosocial aspects of pediatric medicine.

207.7 Applications to Other Areas of Health and Medicine

Obesity is associated with a range of other pediatric health issues, which may be the primary reason for presentation to health practitioners. These include complications of obesity, such as type 2 diabetes, obstructive sleep apnea, or fatty liver disease, as well as conditions or therapies for which obesity may be a complication, such as congenital neuromuscular disease or long-term steroid therapy. In most of these cases, clinicians should recognize that effective management of obesity is likely to be required. Importantly, patients or their families may not always recognize the need for weight management intervention, and hence clinicians should approach this issue in a sensitive manner. At the same time, ignoring "the elephant in the room" of obesity, may be potentially detrimental to the health of the child or adolescent. While treatment advice may need to be modified if, for example, patients have limitations to movement (e.g. spina bifida) or severe dietary restrictions

(e.g. significant food allergies), the broad principles of therapy, as outlined above, can be applied to all patients and their families.

Summary Points

1. Child and adolescent obesity is prevalent in many countries, and may be associated with a range of medical and psychosocial complications. Early intervention is critical as childhood obesity tracks into adulthood.
2. Effective management of pediatric obesity involves family involvement, a developmentally appropriate approach, long-term behavior change, long-term dietary change, increased physical activity, decreased sedentary behavior, and consideration of use of pharmacotherapy in adolescents.
3. Evidence suggests that behavioral modification techniques should be used in pediatric obesity treatment. Training in these techniques is recommended for all health professionals involved in obesity treatment, with the involvement of specialist staff wherever possible.
4. The most commonly used behavioral strategies in pediatric obesity trials include self- or parental monitoring, stimulus control, goal setting or contracting, reinforcement, contingency management, modeling, preplanning, problem-solving, parenting training, and cognitive restructuring. These strategies are aimed at changing obesogenic behaviors and altering energy balance.
5. In usual clinical practice, challenges may include appropriate management of families with multiple psychosocial barriers, and providing behavioral management where there is limited availability of a clinical psychologist.
6. A multidisciplinary weight management service should provide a welcoming and destigmatizing environment, easy physical access for large people, and staff with good teamwork skills and a respectful attitude toward obese people.

Key Terms in the Behavioral Treatment of Obesity

Behavioral contracting: Explicitly links goals to reinforcement in an agreement. That is, desired behaviors are specified in detail along with their specific reward. For example, a child may be allowed 15 min playing a computer game as a reward for an hour of active play.

Cognitive restructuring: Is a technique used in cognitive–behavioral therapies and refers to identifying and challenging unhelpful thoughts and generating more helpful alternatives. For example, a belief that emotional distress is best relieved by eating chocolate or another comfort food might be modified by an alternative belief that talking to a friend may be more helpful.

Goal setting: Involves setting clear behavioral targets. For example, a goal may be to eat a specified number of servings of vegetables per day, or to be active for a certain period each day.

Modeling: Is an approach stemming from social learning theory in which clinicians or parents demonstrate the types of behaviors that are required. An example would be parents changing their own eating or activity habits in the desired direction for the child.

Parenting training: Involves teaching parents skills in behavior management. In obesity research, this often refers to limit setting, with the aim of decreasing obesity-related behaviors. For example, by teaching a parent how to cope with a child who is constantly asking for food.

Preplanning: Is advance preparation for handling challenging situations such as parties or outings in order to assist compliance to diet and activity goals. For example, developing a strategy to decrease food intake at a buffet by using a smaller plate.

Problem-solving: Generally refers to a structured process involving several steps – identifying the problem, generating options, evaluating the options, choosing an option, planning, implementation, and monitoring. For example, problem-solving could be used to determine the best option for increasing incidental activity.

Randomized–controlled trial: An experimental design comparing at least one treatment group with a control group, and where participants are randomly assigned to group.

Reinforcement: In obesity treatment, this usually refers to positive reinforcement, which is providing praise, rewards, or attention for desired behaviors in order to increase their frequency. Reinforcement is about the consequences of behavior. For example, parent's praising their child for being physically active or eating their vegetables. It is related to goal setting and behavioral contracting.

Relapse prevention: Is a process of identifying the early warning signs for the re-emergence of problematic behaviors, and developing a plan and coping responses to deal with the signs of relapse.

Self-monitoring: Involves patients (or their parents) observing and recording their behavior and how it relates to their environment in a diary or other record. Ideally, the record should include the behavior as well as its antecedents and consequences. For example, noting that more snacking occurs in front of the television.

Shaping: Is the process of reinforcing gradual changes to behavior on the way to a goal. For example, praising a child for turning off the TV after a shorter viewing period than usual.

Stimulus control: Changing the environment to reduce cues for undesirable behavior, and increase cues for desired behaviors. That is, changing the antecedents of behaviors. For example, decreasing television time reduces exposure to ads for food and may decrease cues to snack.

References

Abraham C, Michie S. Health Psychol. 2008;27:379–87.

Asay TP, Lambert MJ. In: Hubble MA, Duncan BL, Miller SM, editors. The heart and soul of change: what works in therapy? Washington, DC: American Psychological Association; 1999. p. 33–56.

Baranowski T, Cullen KW, Nicklas T, Thompson D, Baranowski J. Obes Res. 2003;11(Suppl Oct):23S–43S.

Baumeister RF, DeWall CN, Ciarocco NJ, Twenge JM. J Personal Social Psychol. 2005;88:589–604.

Bouchard C. Am J Clin Nutr. 2009;89:1494S–501S.

Braet C, Tanghe A, Decaluwé V, Moens E, Rosseel Y. J Pediatr Psychol. 2004;29:519–29.

Cote MP, Byczkowski T, Kotagal U, Kirk S, Zeller M, Daniels S. Int J Qual Health Care. 2004;16:165–73.

Dobson KS, Dozois DJA. In: Dobson KS, editor. Handbook of cognitive-behavioral therapies. New York: Guilford; 2001. p. 3–39.

Duffy G, Spence SH. J Child Psychol Psychiatry. 1993;34:1043–50.

Epstein LH, Wing RR, Koeske R, Valoski A. Behav Ther. 1985;16:345–56.

Epstein LH, Valoski AM, Vara LS, McCurley J, Wisniewski L, Kalarchian MA, Klein KR, Shrager LR. Health Psychol. 1995;14:109–15.

Epstein LH, Paluch RA, Gordy, CC, Saelens BE, Ernst, MM. J Consult Clin Psych. 2000a;68:717–21.

Epstein LH, Paluch RA, Gordy CC, Dorn J. Arch Pediat Adol Med. 2000b;154:220–6.

Epstein LH, Roemmich JN, Stein, RI, Paluch, RA, Kilanowski CK. Ann Beh Med. 2005;30:201–9.

Germann JN, Kirschenbaum DS, Rich BH. J Pediatr Psychol. 2006a;32:111–21.

Germann JN, Kirschenbaum DS, Rich BH, O'Koon JC. J Adoles Health. 2006b;39:553–61.

Golan M, Fainaru M, Weizman A. Int J Obes. 1998;22:1217–24.

Golan M, Kaufman V, Shahar DR. Br J Nutr. 2006;95:1008–15.

Johnston CA, Tyler C, McFarlin BK, Poston WSC, Haddock K, Reeves R, Foreyt JP. Pediatrics 120: 2008;e1450–7.

Kahn BE, Wansink B. J Consum Res. 2004;30:519–33.

Kalavainen MP, Korppi MO, Nuutinen OM. Int J Obes. 2007;31:1500–8.

Kirschenbaum DS, Germann JN, Rich BH. Obes Res. 2005;13:1527–9.

Lobstein T, Baur L, Uauy R. Obes Rev. 2004;5(Suppl 1):4–104.

McLean N, Griffin S, Toney K, Hardeman W. Int J Obes. 2003;27:987–1005.

Moens E, Braet C. Behav Res Ther. 2007;45:1357–68.

Oude Luttikhuis H, Baur L, Jansen H, Shrewsbury VA, O'Malley C, Stolk RP, Summerbell CD. Cochrane Database Syst Rev. 2009; Issue 1. Art. No.: CD001872. doi:10.1002/14651858.CD001872.pub2.

Reinehr T, Widhalm K, l'Allemand D, Wiegand S, Wabitsch M, Holl RW. Obesity 2009;17:1196–9.

Remick AK, Polivy J, Pliner P. Psychol Bull. 2009;135:434–51.

Rhee K. Ann Am Acad Polit Sci. 2008;615:11–37.

Saelens BE, Sallis JF, Wilfley DE, Patrick K, Cella JA, Buchta R. Obes Res. 2002;10:22–32.

Schwartz MB, O'Neal Chambliss H, Brownell KD, Blair SN, Billington C. Obes Res. 2003;11:1033–9.

Spiegelman BM, Flier JS. Cell 2001;104:531–43.

Stice E. Psychol Bull. 2002;128:825–48.

Suisman JL, Slane JD, Burt A, Klump KL. Eating Behav. 2008;9:493–6.

Wansink B, Cheney MM. JAMA 2005;293:1727–8.

World Health Organization. Diet, nutrition and the prevention of chronic diseases: report of a joint WHO/FAO expert consultation. WHO technical report series: 916. Geneva: WHO; 2003.

Zeller MH, Boles RE, Reiter-Purtill J. Int J Obes. 2008;32:1474–80.

Part XXXVI
Adults and the Elderly

Chapter 208
The Potential of Internet-Based Programs for Eating Disorder Prevention in Students

Katajun Lindenberg, Markus Moessner, and Stephanie Bauer

Abbreviations

AN	Anorexia nervosa
AN_{TSI}	Anorexia nervosa total severity index (SEED)
BMI	Body mass index
BN	Bulimia nervosa
BN_{TSI}	Bulimia nervosa total severity index (SEED)
ED	Eating disorders
EDNOS	Eating disorders not otherwise specified
ICT	Information and communication technology
SEED	Short Evaluation of Eating Disorders (Bauer et al. 2005)
WCS	Weight Concern Scale (Killen et al. 1994)

208.1 Introduction

College is a time of numerous changes, including moving away from home and fending for oneself. Entering university is often combined with elevated stress levels and high pressure, due to increased responsibility and lifestyle rearrangements. Not surprisingly, the transition from high-school to college is known to be a vulnerable phase to develop mental disorders (Dyson and Renk 2006). Besides anxiety and depression, disturbed eating behavior is observed frequently in college students, especially in females (Delinsky and Wilson 2008).

Unaccustomed freedom in college life can lead to changes in eating patterns formerly set by family routine (Hesse-Biber and Marino 1996). Easy access to high-calorie cafeteria food, limited kitchen facilities, and small budgets for meals contribute to unhealthy college eating habits. A phenomenon called "freshman fifteen" (Holm-Denoma et al. 2008) is used to describe the average weight gain of 15 lbs by students in their first year of college. This may be caused by increased alcohol intake, consumption of fast food, lack of sleep and regular exercises, and late night meals (Delinsky and Wilson 2008).

The peak onset of eating disorders (ED) has been found to correlate with the time when adolescents leave home and start college (Striegel-Moore et al. 2003). Although full ED syndromes like anorexia

K. Lindenberg (✉)
Center for Psychotherapy Research, University Hospital Heidelberg, Bergheimer Straße 54,
69115 Heidelberg, Germany
e-mail: katajun.lindenberg@med.uni-heidelberg.de; lindenberg@psyres.de

nervosa (AN) and bulimia nervosa (BN) are quite rare and affect only two to four per cent of the population (Striegel-Moore et al. 2003; Hoek 2006), subthreshold ED are more prevalent and represent similar levels of functional impairment to full ED (Stice et al. 2009). In a representative study of more than 4000 college-age students, nearly half of the students (46%) reported that they were trying to lose weight (Lowry et al. 2000).

Disturbed eating can be caused by stress, negative events or adverse moods. As an example, binge eating has been found to be associated with negative affect. Furthermore, increased levels of stress and coping with pressure might also result in weight loss, when students try to maintain control over eating and skip meals (Fairburn et al. 2008). To avoid weight gain, a substantial proportion of female adolescents apply unhealthy weight regulation methods like excessive exercise, abuse of laxatives, diet pills, self-induced vomiting, or fasting (Grilo 2006).

It is estimated that almost half of the female college students display disturbed eating behaviors or try to lose weight. Hence, we consider ED prevention to be particularly indicated in this age cohort.

208.2 Eating Disorder Prevention Programs

Programs for prevention of ED have existed since the late 1980s (Fingeret et al. 2006), targeting mainly high-school and college-age students. Because some risk factors for ED are considered potentially modifiable (Stice 2002), most ED prevention concepts focus on reducing these factors (e.g., improving body image and promoting a healthy, well-balanced diet, and nutrition).

Results from a meta-analysis by Stice and Shaw (2004) showed that selective (in contrast to universal) programs, which were offered solely to high-risk individuals older than 15 years of age, were more effective than programs provided to unselected samples. It is assumed that high-risk individuals might be more motivated to engage actively in the prevention program because they experience higher distress. Interactive programs in contrast to didactic program formats were found to produce stronger effects. Further, programs containing several follow-up sessions resulted in higher intervention effects compared to brief, single-session programs.

Social psychology experiments show that inducing individuals to act in a manner that is contrary to their attitude (cognitive dissonance) reliably produces attitudinal change (Festinger 1957). Stice et al. (2008) used this principle of dissonance induction to reduce thin-ideal internalization as part of an ED prevention program for high-risk high-school and college students. The program was found to reduce risk for future threshold and subthreshold ED onset by 60% over a 3-year follow-up relative to assessment-only controls (Stice et al. 2008).

Over the past years, internet-based programs have shown promise in improving ED prevention approaches. For example, the program "Student Bodies" contains a cognitive–behavioral intervention in combination with moderated forum boards for college-age students. "Student Bodies" was found to reduce body image concerns at 12-months follow-up, and to reduce ED incidence in a subgroup of students with elevated body mass index (BMI) and compensatory behaviors (Taylor et al. 2006).

208.3 Challenges in ED Prevention

ED prevention is challenged in many ways. The main challenges are listed in the following section.

208.3.1 Target Group

Full-syndrome ED are rare in the general population, which underlines the need to develop prevention programs for specific target populations, in which the risk is elevated. However, targeting the right population is a complex issue, because empirical evidence on whether and when high-risk individuals develop ED is scarce.

Over the past decades, thinness has increasingly become a standard of female beauty. Many women and girls strive for the thin ideal advertised in the media, and dieting has become a part of their lifestyle. ED risk factor literature identifies dieting and restricting food as risk factors for developing an ED (Jacobi et al. 2004). The majority of dieters, however, do not develop full-syndrome ED. As mentioned above, the prevalence of ED is low, although almost half of all college-age students report trying to lose weight. Dieting can take many forms, from starvation to moderate calorie restriction to a preoccupation with the distinction of good and bad foods (French and Jeffery 1994). The discrepancy between an oversupply of food and the strive for thinness is ubiquitous in western societies, and maintaining a well-balanced diet can be helpful to avoid weight gain and prevent obesity. Many individuals are not aware of their disturbed behavior or deny having eating problems. However, the transition from healthy to at-risk dieting is smooth and difficult to identify.

Moreover, college-age students are a challenging target group. Compared to school-based programs, where the intervention can be integrated as part of the curriculum, it is difficult to motivate students in college to participate in a prevention program. College life is exciting and many students may not pay a lot of attention to mental and physical health or underestimate the consequences of their unhealthy lifestyle. Consequently, they do not necessarily feel the urge to engage in an ED prevention program.

208.3.2 Psychological Barriers to Seek Help

Seeking help is a big effort for many individuals suffering from ED. Only about half of all individuals affected by AN and BN take up ED treatment (Cachelin et al. 2006; Waller et al. 2009). Success rates for treatment of chronically ill cases are poor, whereas early intervention was found to be predictive for treatment success (Reas et al. 2000). Several reasons keep individuals from asking for help. Many report feelings of shame and fear of stigma or do not consider their level of impairment as being a serious psychological problem. Furthermore, individuals with ED symptoms often report that fear of disclosure from others kept them from undergoing treatment (Cachelin et al. 2006). Many individuals are unfamiliar with mental health services and consider seeing a therapist as a sign of weakness (Meyer 2001).

208.3.3 Timing of Prevention Efforts

The process of falling ill is relatively unknown. People develop ED symptoms at different points in their life. Because prevention comes too late for individuals who already show manifest ED symptoms, some authors argue that prevention should be offered as early as possible (e.g., Celio et al. 2000). However, it is questionable whether prevention programs targeting young age groups can ultimately lead to sustainable effects on preventing ED onset many years later. Thus, the challenge is to find the optimal timing for prevention and a time and cost efficient way to guarantee sustainability of the preventive effects.

Table 208.1 Key features of individualized prevention

1. Prevention in large, heterogeneous populations, in which different individuals might need different intensity of support, requires a specific strategy to balance benefits and burdens of the prevention effort.
2. Stepped care interventions contain modules of varying intensity. The main idea of stepped care is to try the lowest intensity first and to provide more intense (and more costly) interventions only to those individuals, who need more support.
3. Information and communication technologies enable time and cost efficient matching of intervention intensity to personal needs. Online screening procedures can assess risk categories and recommend the most appropriate level of support. Low-intensity modules can be administered completely automated. Administration of participants and longitudinal monitoring, that allows timely reactions to dysfunctional changes and referral to more intensive modules, become more feasible with technology-enhanced programs.

This table summarizes the key features of individualized prevention and highlights the potential of technology-enhanced programs to tailor interventions to individual needs

208.3.4 Overcoming the Challenges: Individualization of Support

Universal prevention programs targeting unselected samples do not appear appropriate for a rare disease, because only very few individuals are expected to fall ill. Therefore, targeted prevention seems more promising, although it is a challenge to identify the high-risk population. It is crucial to address these individuals in a low-intensive, anonymous way, to overcome psychological barriers to help-seeking. Symptom courses of high-risk individuals can then be observed over time in order to intervene promptly, when disturbed eating behavior shifts to ED pathology.

To address different needs of individuals at different times, innovative approaches suggest to individualize prevention programs and to offer modules of varying intensity (Bauer et al. 2009). Each participant can use the type and amount of support that he or she needs by matching support intensity to the individual level of impairment. Following the idea of stepped care, low-intense modules should be offered first, while more intensive (and more costly) modules should be reserved for those individuals only who need more support. The key features of individualized prevention are summarized in Table 208.1.

208.4 The Internet as an Opportunity for Health-Care Delivery

The technological developments in recent years offer many opportunities to improve health care. They enable the implementation of such above mentioned, individualized, stepped care interventions and have advantages for both providers and users.

208.4.1 Provider Perspective

Information and communication technologies (ICT) enable providers to offer online support and to tailor interventions to individual needs. The scope and geographical coverage of the internet allows large populations to be addressed at relatively low effort. In addition, computer-based data collection makes assessment of health-related parameters more time and cost efficient than traditional paper–pencil questionnaires. In particular, the administration of participants and longitudinal assessments (monitoring) becomes more feasible with technology-enhanced programs. The continuous monitoring of symptoms at short intervals (e.g., weekly) allows prompt reactions to dysfunctional changes and, if necessary, individualized adaptation of the intervention.

208.4.2   User Perspective

The number of users looking for help in the internet is increasing. Easy access and anonymity may play an important role. Interventions of low intensity offer the possibility to get information and exchange experience with other users or counselors in an anonymous way, e.g., via forums or chat rooms. Anonymity makes asking for help easier, particularly when feelings of shame and fear of stigma play a role. Affected individuals can get support from peers who find themselves in comparable situations ("peer support"), or from professional counselors. Low-intense and anonymous offers can bridge the gap between health care and everyday life and encourage users to seek professional treatment. In addition, internet offers can be accessed independently from time and place, which facilitates access to health care particularly in rural areas (Bauer and Kordy 2008).

In the area of prevention, broadly disseminated, easy access interventions are of special importance. One example will be introduced in the following.

208.5   Es[s]prit: An Internet-Based Program for ED

The internet-based program Es[s]prit was developed for the prevention and early intervention of ED in college-age students (Bauer et al. 2009). The program integrates different areas of mental health care from prevention up to early detection, early intervention, and regular face-to-face counseling and treatment, by offering different modules of varying intensity.

The main idea is to individually tailor the support, so that each Es[s]prit user can get the support that he or she needs. In contrast to standardized programs, Es[s]prit is flexible in terms of duration of the intervention and amount of support, i.e., it is up to the participants which modules they want to use to which extent and for how long.

The conceptualization of prevention in several stepped modules (stepped care) allows to adjust prevention intensity to individual needs. Low-intensive modules are mainly automated, so that large populations can be addressed at relatively low effort. The higher the module intensity, the more support costs are required. However, the proportion of the population, which might need this intensive way of support, is relatively small.

The development of symptoms during participation in Es[s]prit is expected to be highly heterogeneous. For some individuals, anonymous, low-intensity counseling, supportive monitoring, peer support, and psychoeducation may be sufficient to reduce symptoms. However, others may develop severe ED symptoms over time. These individuals can be identified by an automated alarm system and referred to the consultation chat (see below), where the anonymous contact can be used to motivate users to seek more intensive treatment, i.e., inpatient or outpatient treatment.

The most important tool enabling the individualization is ICT. All Es[s]prit components are internet-based and mainly automated. The symptom monitoring and feedback system, which also identifies deteriorations and indicates referral to more intensive modules, is organized by the data management system Web-Akquasi (Percevic et al. 2006).

208.5.1   Es[s]prit Modules

Es[s]prit contains five modules that are explained in the following section, ordered by increasing intensity (see also Fig. 208.1).
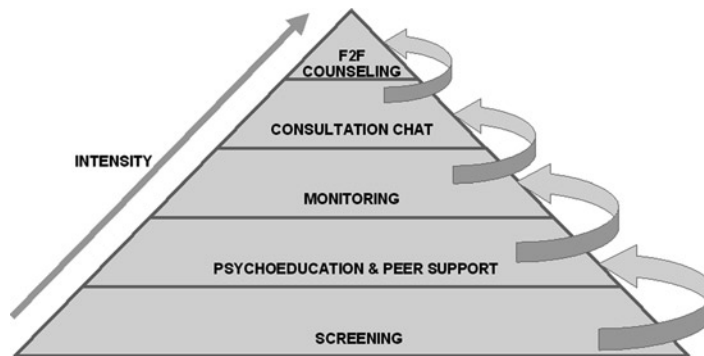
Fig. 208.1 Individually tailored stepped care: Five modules of increasing intensity for individualized prevention and early intervention of ED. This figure shows the five Es[s]prit modules in increasing intensity from bottom to top. According to the idea of stepped care, modules of lower intensity (screening, psychoeducation and peer support, supportive monitoring and feedback module) are completely automated. Only the higher intensive modules (consultation chat and face-to-face counseling) need personal resources, but the proportion of the population that needs this intensive way of support is relatively low

208.5.1.1 Screening

The online screening assesses the individual risk of developing an ED. The Weight Concern Scale (WCS) developed by Killen et al. (1994), a commonly used screening instrument (e.g., Taylor et al. 2006), serves as measure to identify high-risk individuals. Depending on the individual screening result, participants receive a feedback message, either inviting them for registration (to have access to some or all Es[s]prit components) or explaining the reason of exclusion.

Healthy individuals have access to the psychoeducative pages of Es[s]prit and are invited to register and participate in the moderated internet forum. While there is no need for healthy individuals to improve their eating attitudes and eating behavior, they can help to provide peer support and offer advice to other users (high-risk individuals). In addition, they are informed that they can repeat the screening in case they need further support in the future.

Individuals showing weight and shape concerns or slight ED symptoms are expected to bear a higher risk of developing an ED. Therefore, individuals scoring above the threshold of a WCS score of 40 and/or showing slight symptoms (i.e., mild bingeing, BMI < 18.5 or mild compensatory behavior) are invited to register for Es[s]prit with access to all components.

Individuals who report manifest ED symptoms (i.e., frequent bingeing or purging, BMI < 17.5) are excluded from registration and directly referred to a cooperating counseling center, because the offer of Es[s]prit as a prevention program would probably not be sufficient for these severely affected individuals. In case that these users do not want to seek face-to-face treatment, they are provided with internet addresses for online support.

At registration, participants must agree with the user conditions and can choose a pseudonym as username to communicate anonymously. Participants receive an email containing a link to activate their account before they can use Es[s]prit, to make sure that they can be contacted, if necessary.

208.5.1.2 Psychoeducation and Peer Support

The Es[s]prit website contains detailed information on ED in general, risk factors, first signs of an ED, and self-help strategies. All individuals can access the information pages illustrated by comprehensive

personal examples. The information material is provided with support of the German Federal Center for Health Education (Bundeszentrale für gesundheitliche Aufklärung (BZgA) 2007).

Furthermore, all registered users can share information and discuss different questions in a moderated internet forum. The forum posts are checked by the Es[s]prit administrator on a daily basis and inappropriate messages such as pro-anorectic or aggressive statements are deleted.

208.5.1.3 Supportive Monitoring and Feedback System

Es[s]prit contains a supportive monitoring and feedback module that assesses relevant factors and behaviors weekly via a brief online assessment and serves for both early detection of deteriorations and continuous support. The monitoring data are stored and organized by the data management software Web-Akquasi, which automatically schedules the weekly assessments and sends reminder emails containing a link that forwards the user to the respective assessment. Data entered by the user are directly evaluated with regard to current symptom status and symptom change compared to the previous assessment. Immediately after answering the questionnaire, participants receive an automated feedback message related to their symptom development, containing reinforcement of improvements, and advice on how to counteract negative developments.

The monitoring assesses four dimensions of risk: (1) body dissatisfaction, (2) overconcern with body weight and shape, (3) balanced nutrition and eating behavior, and (4) binges and compensatory behavior. Each dimension has a predefined functional and nonfunctional range resulting in two status categories (functional and nonfunctional, see Fig. 208.2), and four change categories over 2 weeks: continuously functional (f), continuously nonfunctional (n), improved from nonfunctional to functional (i), and deteriorated from functional to nonfunctional (d) (see Fig. 208.3). Given the four patterns of change on each of these four dimensions plus the two status categories, when no comparison is possible (in week 1), monitoring results can be classified in 16 categories ($2 \times 2 \times 2 \times 2$) for the first week and 256 categories from the second week onward ($4 \times 4 \times 4 \times 4$). The feedback algorithm was described in detail by Moessner et al. (2008). A total of about 3,000 feedback messages (10–15 per category in order to avoid repetitions) are stored in the Web-Akquasi database.
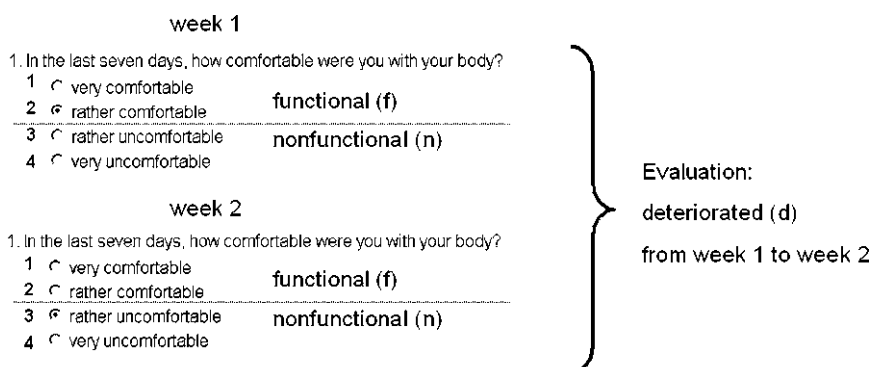

Fig. 208.2 Supportive monitoring and feedback system – Evaluation example: Assessing change from week 1 to week 2 on the example of the dimension "body dissatisfaction." This figure illustrates how the monitoring and feedback system assesses change over 2 weeks on the example of the dimension "body dissatisfaction": scores in the functional range in week 1 and in the nonfunctional range in week 2 are evaluated as deterioration

dimension	status week 1	status week 2	change
body dissatisfaction	nonfunctional	nonfunctional	n
over concern with body weight and shape	functional	nonfunctional	d
balanced nutrition and eating behavior	nonfunctional	functional	i
binges and compensatory behavior	functional	functional	f

n = nonfunctional, d = deteriorated, i = improved, f = functional

> **Feedback:**
> "Going through phases where you do not feel good about your body is absolutely normal. Keeping your body properly nourished by eating regular meals and snacks is the key to feeling positive about your body in the long run. You have done a great job with improving your eating!"

Fig. 208.3 Supportive monitoring and feedback system – Evaluation algorithm: Example feedback message according to symptom change on each of the four monitoring dimensions. This figure illustrates the evaluation algorithm. Given the four change categories (n, d, i, f) on each of the four dimensions, participants' monitoring courses over 2 weeks can be classified in $4 \times 4 \times 4 \times 4 = 256$ categories (see text for details). This example feedback message refers to scores in the nonfunctional range on "body dissatisfaction", deteriorations in "overconcern with body weight and shape", improvements in "balanced nutrition and eating behavior", and scores in the functional range in "binges and compensatory behavior"

In case of deteriorations, the feedback messages contain suggestions for alternative behaviors to interrupt the dysfunctional development. If indicated, the use of other support modules is recommended (i.e., forum, chat, or face-to-face counseling). An alarm system intervenes when predefined alarm criteria (i.e., low BMI, frequent binging or purging) are reported by a participant. An alert mail is automatically sent to the administrator, who in turn contacts the corresponding participant via email to motivate him/her to use the consultation chat. The chat can then be used to motivate the participant to seek face-to-face treatment, if necessary.

208.5.1.4 Consultation Chat

The anonymous consultation chat allows for an early, low-intensity intervention and is guided by a clinician. Chat sessions are provided in two different settings: Users can participate in group chat sessions, which are offered on a monthly basis for a duration of 90 min. Furthermore, participants can register for an individual 1-to-1 chat (30 min), if they want to discuss more private issues that they do not want to share with other users in the group setting. Prior to the individual chat, the online counselor can access all information available on impairment and symptom courses of this specific participant by using the Web-Akquasi software. The early, anonymous contact via chat can then be used to motivate severely impaired participants to seek treatment in one of the cooperating counseling centers and to refer them to the regular health-care system.

208.5.1.5 Face-to-Face Counseling

The cooperation with counseling centers is crucial to ensure that affected individuals get help without delay. Feelings of shame and fear prevent some of the affected individuals from undergoing treatment. Therefore, it is important to motivate severely impaired individuals to seek help. Once they are motivated, it is necessary to refer them to regular treatment early, because long waiting periods can have a negative influence on motivation (Schmidt et al. 2008).

208.5.2 Experiences with Es[s]prit

208.5.2.1 Screening

Es[s]prit has been offered to University of Heidelberg students since February 2007. The program does not exclude non-students; however, flyers and posters advertised it only at the University of Heidelberg. Until September 2009, $N = 1582$ completed the initial self-test on the web page (see Fig. 208.4). According to the screening results, Es[s]prit seems to attract many individuals who are already affected by severe ED symptoms or in treatment. From all users who completed the screening questionnaire, $N = 236$ (15%) were excluded because of current ED treatment and $N = 299$ (19%) because of too severe ED symptoms. In total, 48% of all screened users met the inclusion criteria for participation. One hundred and seventy (25%) out of 671 users, who were invited for participation because of high-risk according to the WCS score, registered for full participation in Es[s]prit. In addition, 13 out of 77 (17%) individuals, who were invited because of mild ED symptoms, registered for the program.

Healthy individuals who show neither weight and shape concerns nor ED symptoms are not invited for full participation. However, they can register for participating in the online forum, to get and provide peer support. Out of those $N = 299$ healthy individuals, $N = 9$ (3%) registered for the forum.

Internet-based modules facilitate the screening procedure in many ways. On the other hand, providers cannot control who registers for the program. $N = 8$ participants, who were excluded in previous screenings, registered for the program by repeating the screening several times and manipulating some scores (i.e., assumedly providing false information). As they signed up for the chat, however, they were told that the support they get by using Es[s]prit was not sufficient for their level of impairment.
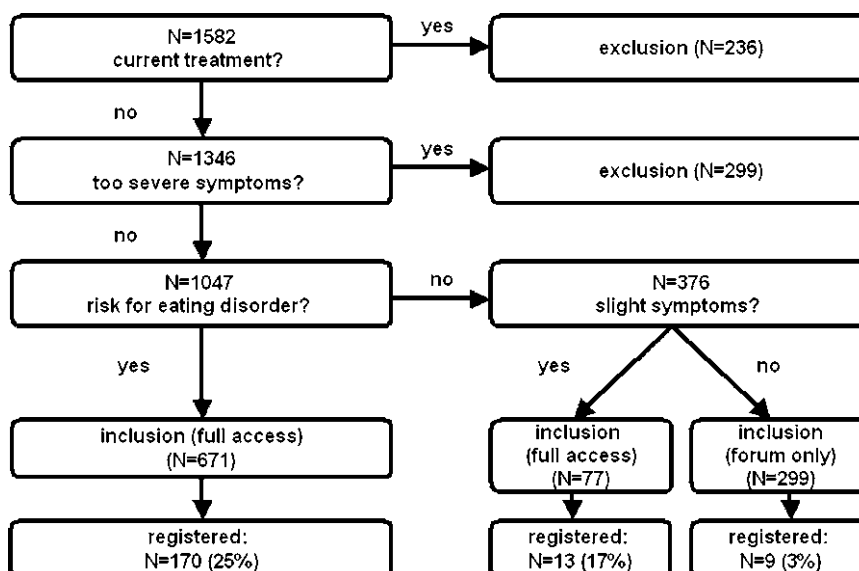

Fig. 208.4 Screening results. This figure illustrates the screening procedure. From a total of 1,582 participants, almost one-third have been excluded because of either current treatment or too severe symptoms ($N = 236$ and $N = 299$, respectively). Participants with neither risk nor slight symptoms were invited to the forum only, whereas at-risk participants or individuals who showed first symptoms were invited with full access to all components (see text for details)

In total, $N = 200$ participants registered for Es[s]prit; $N = 191$ of them had full access to all modules and $N = 9$ only access to the forum.

208.5.2.2 Participants

Participants were mainly females (88%) with a mean age of 27.8 years (SD = 10.3), whereas about 25% of all participants were older than 30 years of age. The mean BMI of Es[s]prit users was 23.6 (SD = 5.7), including a subgroup (25%) of overweight people (BMI > 25).

The sample of Es[s]prit users is characterized by high-risk with a mean WCS score of M = 65.5 (SD = 19.5) and a relatively high level of impairment, measured by total severity scores (TSI) from the Short Evaluation of Eating Disorders (SEED) for AN and BN (Bauer et al. 2005). The Anorexia nervosa total severity index (SEED) (AN_{TSI}) and Bulimia nervosa total severity index (SEED) (BN_{TSI}) scores are higher than in a healthy population (Es[s]prit users: M = 0.9, SD = 0.4 and M = 0.9, SD = 0.6, respectively; healthy controls: AN_{TSI} M = 0.5, SD = 0.3 and BN_{TSI} M = 0.2, SD = 0.3), but lower than those of a clinical sample (AN patients: AN_{TSI}: M = 1.9, SD = 0.5 and BN_{TSI}: M = 1.0, SD = 0.7; BN patients: AN_{TSI}: M = 0.9, SD = 0.5 and BN_{TSI}: M = 2.1, SD = 0.6).

208.5.2.3 Utilization of Modules

One hundred and twenty-seven out of 191 (71.7%) registered participants, who had full access to all Es[s]prit components, activated their account by clicking the link in the activation e-mail. The forum was used by 26 participants who posted 226 messages in total.

The monitoring was used in average 6.7 times per user (SD = 9.6) until deregistration, and 9.3 times (SD = 14.2) by those participants who were still using the program at the time of data analysis. The alarm system has sent alert mails for eight participants so far, who were contacted by the administrator and invited for the consultation chat. All of them replied after being contacted by the administrator. In total, $N = 11$ participants used the consultation chat at least once, and 8 out of those 11 indicated that finally they were prepared to seek face-to-face counseling or treatment. The actual health-care utilization cannot be assessed due to the anonymity of the program.

208.5.2.4 Acceptance and Satisfaction

Three months after registration and at deregistration, participants are asked to evaluate the program. Two thirds of the program evaluations were assessed at deregistration, therefore the results might be negatively biased (because early deregistration might be associated with poorer satisfaction). When we asked for the main reason for participation, 76% named the anonymity of the program (see Fig. 208.5). For 71.5% of the users, Es[s]prit was the first offer they ever used to get help concerning eating-related problems.

Overall, Es[s]prit was evaluated positively: 50% of the users rated the program as being either "very helpful" or "helpful", and 48% as "neutral"; 67% were altogether satisfied with the program, 60% would participate again, and 70% would recommend it to a friend, if they were worried about his/her eating behavior. More than 1/3 of all participants said that without Es[s]prit they would not have known whom to ask with regard to their ED-related questions. When participants were asked to evaluate the specific components, the majority of them rated the various modules as good concepts (see Fig. 208.6). About 30–60% of all participants experienced the different components as helpful.
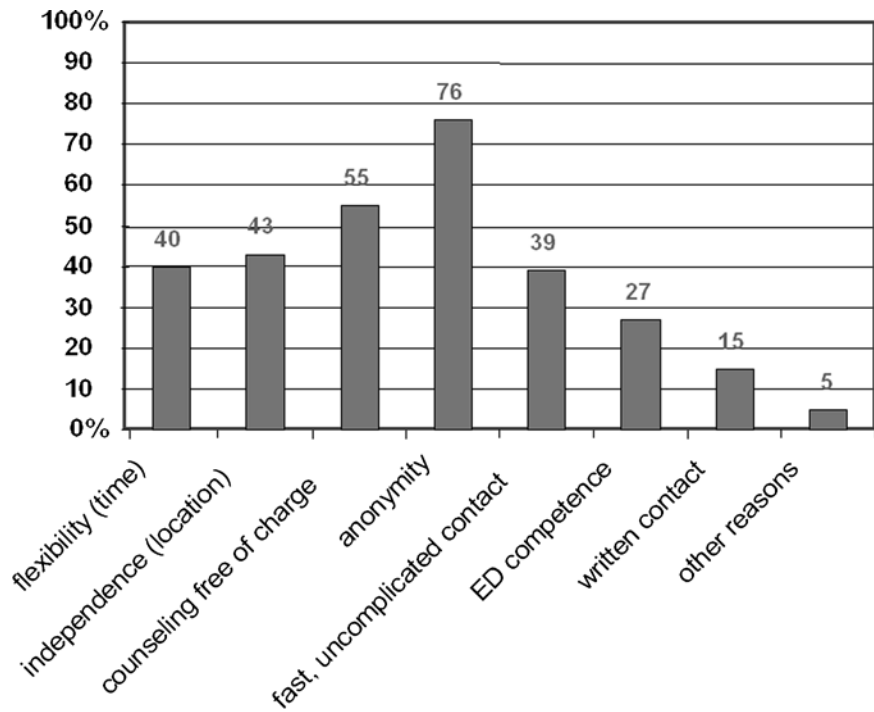
Fig. 208.5 Reasons for participation in Es[s]prit. The reasons for participation in Es[s]prit are shown in this figure as percentage of participants who named this specific aspect. Multiple responses were allowed
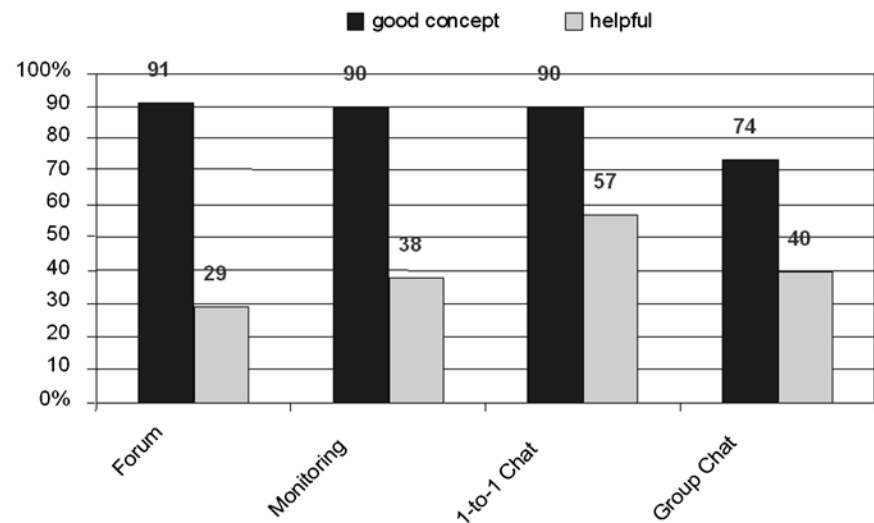

Fig. 208.6 Acceptance of Es[s]prit modules. Three months after registration and at deregistration participants were asked to evaluate the program. This figure shows the percentage of participants who rated the Es[s]prit modules as being good concepts (*black bars*) and personally helpful (*gray bars*). *Note*: participants are free to decide on whether and how intensive they want to use the specific modules

208.5.2.5 Feasibility

The program is running reliably and technically stable. Most of the components are automated, i.e., the screening, registration, weekly monitoring and feedback system, as well as the alarm system.

208.6 Conclusion

Es[s]prit offers a time and cost efficient way to address large populations with relatively low effort: For most participants, the low-intensity (and less costly) components, which are completely automated and do not need any personal resources, seem to be sufficient. Personal resources are needed to react in case of alert mails, to observe the forum activity and to provide chat sessions. This is in line with the idea of stepped care.

The forum is not used as frequently as expected. An explanation for that could be the huge offer of internet portals and self-help groups in social network platforms. The supportive monitoring and feedback system is used frequently by the participants and appears to be a good way to identify those who develop symptoms (early detection). Those participants, who were still in the program at the time of data analysis, have used the monitoring more frequently on average, which may indicate that they benefit more than individuals who decide to deregister early.

Overall, the subgroup of overweight individuals tends to benefit less from Es[s]prit. Some feedback messages related to dieting and restricting food are perceived as inadequate by overweight participants, who apply these behaviors as methods to avoid further weight gain, while according to the feedback system it is perceived as dysfunctional behavior. The conflicting recommendations for overweight and underweight individuals are a challenge in ED prevention and might be solved by approaches that promote healthy eating in general.

The chat proved to be a good way to communicate anonymously and motivate impaired participants to start a more intensive treatment.

By most of the participants, various modules were rated as good concepts in general, and as personally helpful by 30–60% of the users (depending on the specific module). Overall, Es[s]prit was found to be well accepted in a college-age sample, although there is still room for improvement. On the other hand, all modules are anonymous and mainly automated, which makes Es[s]prit feasible to address large populations at reasonable effort.

208.7 Applications to Other Areas of Health and Disease

Internet-based, individualized, stepped care prevention programs tailoring offer to individual needs such as Es[s]prit might be beneficial for many kinds of mental disorders. One advantage of internet-based offers lies in their potential to automate screening, reminder, feedback, and alarm functions. These advantages are essential for the prevention of mental disorders, because tailoring is the only way to help the few affected people without unnecessarily bothering the large group of healthy individuals. Prevention programs could further be implemented as combined programs by screening for risk for various disorders (e.g. depression, anxiety, addiction, and ED) and recommending the use of the most appropriate modules.

Similar to step-up care, i.e., offering modules of increasing intensity for health promotion and prevention, internet-based platforms may also be used as step-down interventions for maintenance treatment, aftercare, and relapse prevention.

Finally, such programs (especially the supportive monitoring and feedback component) appear promising for patients with multiple illness episodes or chronic conditions. Alarm systems may help to detect deteriorations early. This would allow timely referral to e.g., booster sessions or, if needed, more intensive treatment, which is ultimately expected to reduce suffering and increase the symptom-free time.

Summary Points

- Numerous changes and high-stress levels are assumed to make college students more vulnerable to develop mental disorders such as ED.
- Low-intensity, anonymous offers appear promising to address students at-risk of developing an ED.
- Individually tailored, stepped care programs can help to match the appropriate level of support to the diverse needs of individual users.
- Monitoring and alarm systems can identify deteriorations in symptom courses automatically and refer participants to more intensive support levels without delay.
- ICT enables the time and cost efficient implementation of a stepped care approach.

Key Terms

- **Targeted prevention:** In contrast to universal prevention, which targets unselected samples, targeted prevention addresses high-risk groups.
- **Individualized care:** In contrast to standardized programs, individualized care is flexible in duration and amount of support. Each individual is free to decide which of the interventions offered by the provider he/she wants to use depending on personal needs, preferences, and choices.
- **Stepped care:** Stepped care programs allocate intensity and therapeutic resources depending on participants' individual impairment and symptom course.
- **Monitoring:** Monitoring denotes the longitudinal observation of symptoms and behaviors. It is used to provide supportive feedback and identify deteriorations early.
- **Early intervention:** Early intervention refers to the timely provision of professional therapeutic support soon after the manifestation of ED symptoms. Early intervention is assumed to be associated with a more favorable treatment course of mental disorders.

References

Bauer S, Kordy K. E-mental-health. Heidelberg: Springer; 2008.
Bauer S, Winn S, Schmidt U, Kordy H. Eur Eat Disord Rev. 2005;13:191–200.
Bauer S, Moessner M, Wolf M, Haug S, Kordy H. Brit J Guid Couns. 2009;37:327–36.
Bundeszentrale für gesundheitliche Aufklärung (BZgA). Themenschwerpunkte: Prävention von ernährungsabhängigen Krankheiten. Retrieved 30 June, 2007, from http://www.bzga.de/
Cachelin FM, Striegel-Moore RH, Regan PC. Eur Eat Disord Rev. 2006;14:422–9.

Celio AA, Winzelberg AJ, Wilfley DE, Eppstein-Harald D, Springer, EA, Dev P, Taylor, CB. J Consult Clin Psych. 2000;68:650–7.

Delinsky SS, Wilson GT. Eating Behaviors. 2008;9:82–90.

Dyson R, Renk K. J Clin Psychol. 2006;62:1231–44.

Fairburn CG, Cooper Z, Shafran R, Bohn K, Hawker DM, Murphy R, Straebler S. In: Fairburn CG, editor. Cognitive behavior therapy and eating disorders. New York: Guilford; 2008. p. 136–46.

Festinger L. A theory of cognitive dissonance. Evanston: Row & Peterson; 1957.

Fingeret MC, Warren CS, Cepeda-Benito A, Gleaves DH. Eating Disorders: J Treat Prevent. 2006;14:191–213.

French SA, Jeffery RW. Health Psychol. 1994;13:195–212.

Grilo CM. Eating and weight disorders. New York: Psychology Press; 2006.

Hesse-Biber S, Marino M. J Psychol. 1996;125:199–216.

Hoek HW. Curr Opin Psychiatr. 2006;19:389–94.

Holm-Denoma JM, Joiner TE, Vohs KD, Heatherton TF. Health Psychol. 2008;27:3–9.

Jacobi C, Hayward C, de Zwaan M, Kraemer HC, Agras W. Psychol Bull. 2004;130:19–65.

Kann L, Kinchen SA, Williams BI, Ross JG, Lowry R, Grunbaum JA, Kolbe LJ. Youth risk behavior surveillance -United States, 1999. MMWR CDC Surveillance Summaries. 2000;49:1–96.

Killen JD, Taylor CB, Hayward C, Wilson DM, Haydel F, Hammer LD, Robinson TN, Litt I, Varady A, Kraemer H. Int J Eat Disorder. 1994;16:227–38.

Lowry R, Galuska DA, Fulton JE, Wechsler H, Kann L, Collins JL. Am J Prev Med. 2000;18:18–27.

Meyer DF. J College Stud Psychother. 2001;15:23–36.

Moessner M, Zimmer B, Wolf M, Bauer S. In: Bauer S, Kordy H, editors. E-mental-health. Heidelberg: Springer; 2008.

Percevic R, Gallas C, Arikan L, Moessner M, Kordy H. Psychotherapeut. 2006;51:395–7.

Reas DL, Williamson DA, Martin CK, Zucker NL. Int J Eat Disorder. 2000;27:428–34.

Schmidt U, Andiappan M, Grover M, Robinson S, Perkins S, Dugmore O, Landau S, Treasure J, Eisler I, Williams C. Brit J Psychiat. 2008;193:493–500.

Stice E. Psychol Bull. 2002;128:825–48.

Stice E, Shaw H. Psychol Bull. 2004;130:206–27.

Stice E, Marti CN, Spoor S, Presnell K, Shaw H. J Consult Clin Psych. 2008;76:329–40.

Stice E, Marti CN, Shaw H, Jaconis M. J Abnorm Psychol. 2009;118:587–97.

Striegel-Moore RH, Dohm FA, Kraemer H, Taylor CB, Daniels S, Crawford PB, Schreiber GB. Am J Psychiat. 2003;160:1326–31.

Taylor CB, Bryson S, Luce KH, Cunning D, Doyle AC, Abascal LB, Rockwell R, Dev P, Winzelberg AJ, Wilfley DE. Arch Gen Psychiat. 2006;63:881–8.

Waller G, Schmidt U, Treasure J, Murray K, Aleyna J, Emanuelli F, Crockett J, Yeomans M. Psychiatric Bull. 2009;33:26–9.

Chapter 209
Behavioral Interventions for Preventing and Treating Obesity in Adults

Manoj Sharma and Melinda J. Ickes

Abbreviations

ACSM	American College of Sports Medicine
ADA	American Dietetic Association
BMI	Body Mass Index
HEI	Healthy Eating Index
IOM	Institute of Medicine
PA	Physical Activity
RWJF	Robert Wood Johnson Foundation
USDA	US Department of Agriculture
USDHHS	US Department of Health and Human Services
WHO	World Health Organization

209.1 Introduction

Problems of overweight and obesity have reached epidemic proportions (Ogden et al. 2002). Globally, approximately 1.6 billion adults (age 15+) were classified as overweight and of those at least 400 million were obese (World Health Organization [WHO] 2005). The World Health Organization projects these statistics to increase; by 2015, approximately 2.3 billion adults will be overweight and more than 700 million will be obese all over the world. In the USA, obesity prevalence doubled among adults between 1980 and 2004. More than one-third of adults, or over 72 million people, were obese in 2005–2006. This included 33.3% among adult men and 33.2% among adult women (US Department of Health and Human Services [USDHHS] 2007). Adult obesity rates continued to rise in 37 states; rates rose for a second year in a row in 24 states, and for a third year in a row in 19 states. Mississippi had the highest rate at 31.7%, with Colorado at the lowest rate of 18.4% (Robert Wood Johnson Foundation [RWJF] 2008). Table 209.1 summarizes some key points related to obesity.

Multiple measures have been used to define overweight and obesity. Body Mass Index (BMI) has been one of the most widespread measures: BMI = Weight (kg)/[height (m)]^2 with overweight

M. Sharma (✉)
Health Promotion & Education, University of Cincinnati, Cincinnati, OH 45221-0068, USA
e-mail: manoj.sharma@uc.edu

Table 209.1 Key points related to obesity

- Globally, approximately 1.6 billion adults were classified as overweight and of those at least 400 million were obese.
- In the USA, it is estimated that approximately 300,000 deaths annually are attributed to obesity-related conditions.
- For a large majority of individuals, overweight and obesity result from excess calorie consumption and/or inadequate physical activity.
- The Surgeon General's *Call to Action to Prevent and Decrease Overweight and Obesity* identified the importance of individuals, families, communities, schools, worksites, organizations, government, and the media to work together to build solutions to prevent and control overweight and obesity in the USA.
- The prevention of weight gain and the maintenance of a healthy weight in people with a healthy weight or modest weight loss in overweight individuals is likely to be easier, less expensive, and potentially more effective than the treatment of obesity after it has fully developed.
- Successful weight management to improve overall health for adults requires a lifelong commitment to healthful lifestyle behaviors emphasizing sustainable and enjoyable eating practices and daily physical activity.

Table 209.2 Obesity measures

Measure	Criteria
Body mass index	Overweight: 25.0–29.9 kg/m^2
	Obesity: >30 kg/m^2
Waist circumference	Men: > 102 cm
	Women: > 88 cm
Waist-to-hip ratio	≥ 1.0
Neck circumference	Men: ≥ 37 cm
	Women: ≥ 34 cm

classified as a BMI of 25–29.9 kg/m^2 and obesity as a BMI over 30 kg/m^2 (USDHHS 2007). Additional obesity measures used in the literature include waist circumference, waist-to-hip ratio, and neck circumference. See Table 209.2 for a summary of these measures.

209.2 Consequences of Obesity

In the United States, it is estimated that approximately 300,000 deaths annually are attributed to obesity-related conditions. Obesity has been related to an increase in the risk of a variety of physical consequences including cardiovascular disease, high blood pressure, high cholesterol, type 2 diabetes, stroke, certain types of cancer, gallbladder disease, osteoarthritis, sleep apnea, and respiratory problems (USDHHS 2007). In fact, type 2 diabetes rates rose in 26 states; and in four states, more than 10% of adults now have type 2 diabetes (RWJF 2008).

Besides physical consequences, psychological factors, which have been related to those dealing with obesity, include depression and low self-esteem (USDHHS 2007). A widespread stereotype and negative attitude toward overweight and obese individuals has led to discrimination, as well as feelings of shame and guilt among these individuals (Cossrow et al. 2001). Only a few studies have been reported on the topic of overweight stigmatization, but common threads of prejudicial treatment and discrimination were apparent (Table 209.3).

Societal costs cannot be dismissed, as the economic burden of adult obesity not only affects the individual, but society as a whole. In the USA, the national health-care expenditures related to overweight and obesity in adults were estimated between $98 billion and $129 billion (Institute of Medicine [IOM] 2004), with about 9% of the national health-care budget spent on the direct costs of obesity and its consequent diseases. Medical costs associated with overweight and obesity involved

Table 209.3 Consequences of obesity

Types of consequences	
Physical	*Increased risk of developing*:
	• Cardiovascular disease
	• High blood pressure
	• High cholesterol
	• Type II diabetes
	• Stroke
	• Certain types of cancer
	• Gallbladder disease
	• Arthritis
	• Sleep disturbances
	• Asthma
Psychological	• Depression
	• Low self-esteem
	• Feelings of shame and guilt
	• Stigmatization
	• Discrimination
Societal	• Medical costs
	• Morbidity costs
	• Mortality costs

both direct and indirect costs (USDHHS 2007; Wolf 1998). According to Finkelstein et al. (2003), direct medical costs included preventive, diagnostic, and treatment services. In contrast, indirect costs were related to morbidity (income lost from decreased productivity, restricted activity, and absenteeism) and mortality costs (the value of future income lost by premature death).

209.3 Determinants of Obesity

Overweight and obesity are caused by numerous and complex factors. Body weight is shaped by a combination of genetic, metabolic, behavioral, environmental, cultural, and socioeconomic influences (USDHHS 2007; WHO 2005). Some of the determinants have been considered nonmodifiable, such as genetics, sex, age, and race. However, most of the population was more likely affected by the influences of surroundings, opportunities, or conditions predisposing individuals to obesity (Moreno et al. 2004).

For a large majority of individuals, overweight and obesity result from excess calorie consumption and/or inadequate physical activity (PA) (Office of the Surgeon General 2001). Very few Americans meet the majority of the Dietary Guidelines for Americans (US Department of Agriculture [USDA] and USDHHS 2005), with only 3% of all individuals meeting four of the five recommendations for the intake of grains, fruits, vegetables, dairy products, and meat. The quality of diets consumed was determined using the Healthy Eating Index-2005 (HEI-2005), a tool designed to measure diet quality in terms of compliance with the key, diet-related recommendations of the 2005 Dietary Guidelines for Americans. The HEI-2005 includes 12 components: total fruit; whole fruit; total vegetables; dark green and orange vegetables and legumes; total grains; whole grains; milk; meat and beans; oils; saturated fat; sodium; and calories from solid fats, alcoholic beverages, and added sugars. Component scores for the US population aged 2 and older were below the maximum possible score for every component, except for total grains and meat and beans; with the total

Table 209.4 Modifiable behaviors related to obesity treatment and prevention

Behaviors	
Physical activity	Participation in at least 60 min of moderate-to-vigorous physical activity (PA) per day
Sedentary behaviors	Limiting screen time (television, video game, and computer use) to less than 2 h/day
Fruit and vegetable consumption	Eating five or more servings of fruit and vegetables daily
Sweetened beverage consumption	Increasing water consumption in relation to the amount of sweetened beverages consumed

score reported as 57.5 out of a possible 100. Scores were particularly low for dark green and orange vegetables and legumes, whole grains, sodium, and calories from solid fats and added sugars. Additionally, nine out of ten Americans were unaware of the number of calories they consumed each day.

With regard to physical activity, less than one-third of adults engage in the recommended amount, and 40% of adults engage in no leisure-time PA (USDHHS 2000). According to the Physical Activity Guidelines released in 2008, all adults should avoid inactivity, with health benefits increasing as PA increases. The guidelines recommend at least the equivalent of 150 min/week of moderate-intensity aerobic PA for substantial health benefits and 300 min/week of moderate-intensity PA for more extensive health benefits (USDHHS 2008).

Sedentary behaviors, including television viewing, have also been associated with an increased risk of overweight and obesity. The BMI of those who watched more than 2 h of television per day was associated with overweight or obesity in both men and women. Also, watching more than 2 h of television per day was related to higher intakes of energy and macronutrients, which corresponded to an increased likelihood to be overweight (Bowman 2006). The 2-day mean television hours were 2.3 h (95% CI, 2.2–2.4 h) for normal weight adults, 2.6 h (95% CI, 2.5–2.7 h) for overweight adults, and 3.0 h (95% CI, 2.85–3.15 h) for obese adults.

Supported by the American Medical Association (Goutham 2008), four well-recognized behaviors have the capability of offsetting the development and treatment of obesity (See Table 209.4). These behaviors include participating in at least 60 min of moderate-to-vigorous PA per day; limiting screen time (television, video game, and computer use) to less than 2 h per day; increasing water consumption in relation to the amount of sweetened beverages consumed; and eating five or more servings of fruit and vegetables daily. Determinants of obesity considered modifiable, prevalent, and relatively easy to change should directly relate to the treatment and prevention of obesity in adults.

209.4 Call to Action

The Surgeon General's *Call to Action to Prevent and Decrease Overweight and Obesity* (2001) identified the importance of individuals, families, communities, schools, worksites, organizations, government, and the media to work together to build solutions to prevent and control overweight and obesity in the United States. Healthy People 2010 also recognized the importance of increasing the proportion of adults who were at a healthy weight and reducing the proportion of adults who were obese (USDHHS 2000). Interventions that modify factors for obesity can be for prevention or treatment. Interventions for prevention and treatment of obesity can be behavioral, pharmacological, surgical, or environmental.

209.5   Review of Obesity Treatment Interventions in Adults

Treatment interventions are implemented with overweight or obese individuals with a goal of weight loss. According to Wilson and McAlpine (2006), the following should be considered: does treatment cause weight loss? does weight loss improve outcomes? can weight loss be maintained? what are the health implications of failing to maintain a loss? and is treatment available? Most programs designed to promote weight-loss for individual adults have had limited long-term success for a majority of the participants (Tsai and Wadden 2005). Existing guidelines call for clinicians to promote sustained weight loss in their obese adult patients. The US Preventive Services Task Force (USPSTF 2003) guidelines suggest that high-intensity counseling coupled with behavioral interventions building skills, motivation, and support will produce sustainable weight loss. A summary of treatment interventions aimed at targeting adult obesity in the United States, with results published since 2000, can be found in Table 209.5.

A total of 19 treatment interventions were found, with approaches including structured meal plans, dietary adherence, supervised exercise classes, use of supplements, self-weighing, social support, internet-based tutorials, behavioral counseling, individualized plans, and feedback. Most of the interventions ($n = 11$) were not based on any explicit behavioral theory. The Transtheoretical Model was most widely used ($n = 4$), followed by social cognitive theory ($n = 2$). In terms of duration, interventions ranged from 9 to 52 weeks, with the longest intervention conducted over a 9-year period. Both group sessions and one-on-one counseling were utilized as a means to deliver the programs. In addition, two programs relied strictly on internet-based communication and two programs incorporated telephone-based coaching and counseling. A majority of the interventions reported on anthropometric measures such as body weight, waist circumference, percentage body fat, and HDL/LDL levels. Significant changes were found in all but two interventions. Caloric intake, PA levels, outcome expectations, physical functioning, vitality, mental health, and quality of life were also measured.

209.6   Review of Obesity Prevention Interventions in Adults

Preventive interventions are implemented with an unselected population that may be normal weight or obese with a goal of prevention of weight gain. The prevention of weight gain and the maintenance of a healthy weight in people with a healthy weight or modest weight loss in overweight individuals is likely to be easier, less expensive, and potentially more effective than the treatment of obesity after it has fully developed. Therefore, assessing and comparing programs for reducing the current prevalence of obesity is very important (Yates and Murphy 2006). Public health obesity prevention efforts have focused mainly on individual education and an emphasis on teaching behavioral skills (Schmitz and Jeffery 2000). Commonly suggested educationally modifiable public health strategies to combat obesity are promoting breastfeeding, limiting television viewing, increasing physical activity, increasing fruit and vegetable intake, controlling portion size, and limiting soft drink consumption (Gerberding and Marks 2004). A summary of prevention interventions aimed at adult obesity in the United States, with results published since 2000, can be found in Table 209.6.

Fewer prevention interventions were found ($n = 5$) compared to the treatment interventions mentioned above. The focus was more on lifestyle changes, with topics such as increasing PA and meeting dietary recommendations. Only one intervention was not based on any explicit behavioral theory, with cognitive–behavioral approach ($n = 2$), social marketing theory ($n = 1$), and social cognitive theory ($n = 1$) used as a framework for the others. In terms of duration, interventions ranged from 3 months to 5 years, with monthly follow-ups and continued individual/group sessions a part of a majority of

Table 209.5 Obesity treatment interventions in adults

Study/ Year	Theory	Intervention	Duration	Major findings
Metz et al. (2000)	No known behavioral theory	• Overweight and obese (BMI ≥ 25 and ≤ 42) individuals (*n* = 302) with hypertension/dyslipidemia or type 2 diabetes mellitus were randomly assigned to prepared meal plan or usual care diet (UCD) for 52 weeks • The prepared meal plan was formulated to provide recommended levels of sodium, fat, fiber and was fortified to meet 100% of recommended dietary allowance for 22 essential vitamins and minerals	52 weeks	• In the prepared meal plan group, the average weight loss from baseline was 6.9 ± 4.0, 7.8 ± 6.3 kg after 26 weeks, and 5.8 ± 6.8 kg after 52 weeks as compared to UCD group losing 2.3 ± 3.6 kg after 12 weeks, 2.4 ± 5.4 kg after 26 weeks, and 1.7 ± 6.5 kg after 52 weeks. The difference between two groups was significant (*p* < 0.001) • In both groups, both interventions improved blood pressure, total and low-density lipoproteins, cholesterol, glycosylated hemoglobin, and quality of life
Jakicic et al. (2002)	No known behavioral theory	• Three groups: (a) long bouts of exercise, (b) short bouts of exercise, (c) short bouts of exercise combined with home exercise equipment • Focused on modifying both eating (reducing fat intake to 20–30% of total calorie intake, which was between 1,200–1,500 kcal/day using structured meal plans) and exercise behaviors (maintain exercise to 200 min/week) • Group meetings were scheduled weekly for months 1–6, biweekly for months 7–12, and monthly for months 13–18	18 months	• The mean decrease in weight from baseline to 18 months was −7.8 ± 7.5 kg (*p* < 0.001) • The mean decrease in BMI from baseline to 18 months was −2.8 ± 2.7 kg/m² (*p* < 0.001) • The mean increase in PA from baseline to 18 months was 1,146 ± 1,300 kcal/week (*p* < 0.001) • The mean reduction in energy intake from baseline to 18 months was −498.1 ± 783.7 kcal/day (*p* < 0.001) • The mean reduction in fat intake from baseline to 18 months was −27.4 ± 38.4 g/day (*p* < 0.001)
Karanja et al. (2002) – Steps to Soulful Living	Social support	• 26 weekly group meetings & a weekly supervised exercise class (*n* = 66, African-American women) • Dietary goal was to reduce fat intake to 25% of total energy & exercise goal was to exercise 3–4 times a week for 30 min or more • Intervention had five key elements: (1) increasing identification between counselors and participants, (2) building social support, (3) providing information in a demonstration format, (4) involving family and community, (5) increasing program ownership	26 weeks	• Over the 26 weeks women lost a mean of 3.7 ± 5.1 kg or a mean loss of 3.3% of their body weight • 56% of the participants lost 2.4 kg (5 lb) or more • Participants who attended at least 75% of the group meetings lost a mean of 6.2 kg at 6 months and those who attended fewer meetings lost a mean of 0.9 kg

Study	Theory	Duration	Intervention	Results
Miller et al. (2002) Diet, Exercise, and Weight Loss Trial (DEW-IT)	No known behavioral theory	9 weeks	• Lifestyle intervention group ($n = 22$) and control group ($n = 23$) • Lifestyle group required DASH (Dietary Approach to Stop Hypertension) diet, reduced sodium, weight-loss goal of 10 or 1.25 lb/week for 8 weeks, and exercise for 30–45 min	• From baseline to follow-up BMI decreased by -1.9 kg/m² in life style group and was significant when compared to control group ($p < 0.0001$) • From baseline to follow-up weight decreased by -5.5 kg in life style group and was significant when compared to control group ($p < 0.0001$)
Tate et al. (2003)	No known behavioral theory	1 year	• One group ($n = 46$) received Internet-based tutorial on weight loss, a new tip and link each week, and directory of weight-loss resources • Second group ($n = 46$) in addition received behavioral e-counseling and interacted with counselors via e-mail about calorie and fat intake, and exercise energy expenditure	• Behavioral e-counseling group had greater reduction in weight (-4.4 vs. -2.0 kg, $p = 0.04$), body mass index (BMI) (-1.6 vs. -0.8 kg/m², $p = 0.03$, and waist circumference (-7.2 vs. -4.4 cm, $p = 0.05$) when compared to Internet group • Both groups reported significant reductions in caloric intake between 0 and 12 months ($p < 0.001$) • For both groups mean increase in exercise energy expenditure did not differ from 0 to 12 months ($p = 0.26$)
Mayer-Davis et al. (2004) – Pounds off with empowerment	Goal setting	12 months	• 3 interventions based on a goal of achieving 10% weight loss over 12 months: Intensive lifestyle intervention, reimbursable lifestyle intervention, and usual care • Intensive lifestyle intervention included group sessions led by nutritionists, written materials, encouragement and suggestions for PA at low-to-moderate intensity for sedentary people, dietary modifications, and self-monitoring tools • Reimbursable lifestyle intervention was condensed and included four 1-h sessions over 12 months and 3 group sessions and 1 individual session • Usual care included 1 individual session by a nutritionist	• Weight change at 6 months was significantly greater among intensive lifestyle participants compared with usual care participants (2.6 vs. 0.4 kg, $p < 0.01$) • At 12 months, greater proportion of intensive lifestyle participants had lost 2 kg or more than usual care participants (49% vs. 25%, $p < 0.05$) • No change in weight was observed between reimbursable lifestyle and usual care participants

(continued)

Table 209.5 (continued)

Study/ Year	Theory	Intervention	Duration	Major findings
Finch et al. (2005)	Outcome expectations theory	• Two groups: one group received positive- or optimistic-outcome expectations and second group received balanced-outcome expectations (both positive and negative) • 8 weekly, 1-h group sessions involving presentation by facilitator and a group discussion • First 4 sessions influenced expectations about losing weight • Second 4 sessions were designed to implement self-designed weight-loss plan	8 weeks, follow-up at 18 months	• No significant differences in weight change by treatment group were observed at 8 weeks, $F_{(3, 212)} = 0.70$, $p < 0.40$; 6 months, $F_{(3, 201)} = 0.01$, $p < 0.93$; or 18 months, $F_{(3, 181)} = 0.18$, $p < 0.67$ • Positive outcome expectations and satisfaction were found to be associated with weight loss
Kennedy et al. (2005)	No known behavioral theory	• Two treatment groups: Group intervention ($n = 20$) and individual intervention ($n = 20$) • Group intervention: nutrition education in six monthly group meetings using group discussion. • Individual intervention: 15 individualized meetings, record keeping, and basic dietary assessment using computer software	6 months	• Mean weight loss in all participants at 6 months was 3.3 kg (s.d. 3.5, $p < 0.05$). In group-based intervention, mean weight loss was 3.1 kg (s.d. 3.5, $p < 0.05$) while in individual intervention it was 3.4 kg (s.d. 3.5, $p < 0.05$) • Mean BMI decrease in all participants was 1.2 kg/m^2 (s.d. 1.3, $p < 0.05$). In group-based intervention, it was −1 (s.d. 1) while in individual intervention it was −1.3 (s.d. 1.3, $p < 0.05$)
Blissmer et al. (2006)	Transtheoretical model	• RCT in which all participants ($n = 144$) completed a 6-month clinical weight-loss program and were randomized into two 6-month extended care groups. The program focused on changing lifestyle rather than weight loss. The extended care group received two additional individualized TTM reports, via mail, at 9 and 12 months.	24 months	At 6 months, there were increases in the physical and mental composite measures as well as physical functioning, general health, vitality, and mental health subscales of the SF-36. Despite some weight regain, the improvements in the mental composite scale as well as the physical functioning, vitality, and mental health subscales were maintained at 24 months. There were no significant main effects or interactions by extended care treatment group or weight-loss group (whether or not they maintained 5% loss at 24 months)

Study	Theory	Description	Duration	Results
Howard et al. (2006) – Women's Health Initiative Dietary Modification Trial	No known behavioral theory	• Groups of 8–15 participants underwent a series of sessions to promote dietary and behavioral changes to reduce dietary fat to 20% and increase consumption to ≥ 5 fruits and vegetables in first 12 months, after that 4 per year • Additionally 3 individual interviews that used targeted messages and provided personalized feedback • The control group received diet-related education materials	9 years	• Women in the intervention group lost weight in the first year (mean of 2.2 kg, $p < 0.001$) and maintained lower weight than control women during an average 7.5 years of follow-up (difference, 1.9 kg, $p < 0.001$ at 1 year and 0.4 kg, $p = 0.01$ at 7.5 years) • Weight loss was greatest in women who reduced their percentage of energy from fat
Nelson et al. (2006) – HOLDSS	Transtheoretical model & social cognitive theory	• Patient-centered personal risk counseling based on stage of change. – Stage of change was assessed at each visit and intervention accordingly tailored. • Measurements at baseline, 6 weeks, 3 months, 6 months	6 months	• At 6 weeks, the mean body weight change from baseline was 2.7 lb as compared to 0.6 lb in control group ($p < 0.01$); at 3 months, the mean body weight change from baseline was 5.2 lb as compared to 1.3 lb in control group ($p < 0.001$); at 6 months, the mean body weight change from baseline was 5.6 lb as compared to 0.9 lb in control group ($p < 0.01$) • Changes in behavior and its antecedents not measured
Schneider et al. (2006)	No known behavioral theory	This study was designed to examine the effects of a 10,000 steps exercise prescription on sedentary, overweight/obese adults ($n = 56$), and to examine the effects of adherence on body composition and cardiovascular risk factors	36 weeks	38 participants (68%) wore pedometers daily for 36 weeks and were available for post-testing. Significant improvements were noted in mean values for walking volume, body weight, BMI, percentage body fat, fat mass, waist circumference, hip circumference, and high-density lipoprotein. The adherers had large improvements in body composition measures, whereas the nonadherers showed little or no change in these variables
Burke et al. (2007)	No known behavioral theory	The joint effects of personal preference of dietary treatment and a calorie-restricted, low-fat lacto-ovo-vegetarian diet compared with a standard calorie-restricted, low-fat omnivorous diet were examined. RCT ($n = 176$)	18 months	No significant interaction between preference and dietary treatment. The only effect observed for diet was a borderline significant decrease in LDL:HDL cholesterol for the LOV-D group ($p = 0.06$). Within the LOV-D groups, those who were 100% adherent had significant reductions in monounsaturated fat ($p = 0.02$) and total fat ($p = 0.05$) intakes at 18 months

(continued)

Table 209.5 (continued)

Study/ Year	Theory	Intervention	Duration	Major findings
Johnson et al. (2008)	Transtheoretical model	Overweight or obese adults were randomized to no-treatment control or home-based, stage-matched multiple-behavior interventions for up to three behaviors related to weight management at 0, 3, 6, and 9 months	24 months	Significant treatment effects were found for healthy eating, exercise, managing emotional distress, and untreated fruit and vegetable intake progressing to Action/Maintenance at 24 months. The groups differed on weight lost at 24 months. Covariation of behavior change was much more pronounced in the treatment group, where individuals progressing to Action/Maintenance for a single behavior were 2.5–5 times more likely to make progress on another behavior. The impact of the multiple-behavior intervention was more than three times that of single-behavior interventions
Carr et al. (2008) –ALED-I	Transtheoretical model & Social cognitive theory	Internet-delivered theory-based PA behavior change program intended to improve cardiometabolic disease risk factors in sedentary overweight adults. RCT with delayed-intent-to-treat control group	16 weeks	Both groups had similar baseline PA levels. ALED-I increased PA by an average of 1,384 steps/day ($p = 0.03$) compared to 816 steps/day ($p = 0.14$) for the control group. Waist circumference and Coronary Risk Ratio decreased in the ALED-I group and did not change in the control group.
Lutes et al. (2008) –ASPIRE	No known behavioral theory	The ASPIRE group ($n = 20$) was provided brief instruction about nutrition and PA and asked each week to choose and make one small, potentially permanent change in food choices and caloric intake and one small change in physical activity; a standard educationally-based treatment group ($n = 20$); a wait list control group ($n = 19$). Active treatment groups received identical resistance and aerobic training programs	4 months	Intention-to-treat analyses showed that participants in the ASPIRE group lost significantly more weight than the standard and control groups (−4.4 vs. −1.1 and +0.1 kg, respectively), and the greater initial weight loss in the ASPIRE group was sustained 3 months after active treatment (4.1 kg)
Tucker et al. (2008)	No known behavioral theory	Eleven 30-min telephone coaching sessions were spaced throughout the study; the initial conversation lasted 60–90 min. Supplement or placebo capsules were taken daily over the 17 weeks. RCT ($n = 60$ men, 60 women)	17 weeks	Subjects taking the supplement lost more 3.1 ± 3.7 kg of weight ($F = 4.1$, $p = 0.045$). Participants receiving coaching lost more: 3.2 ± 3.6 kg of weight ($F = 4.8$, $p = 0.032$). Subjects receiving both the supplement and coaching lost the most weight, implying an additive effect ($F = 2.9$, $p = 0.039$)

Goldfinger et al. (2008) –Project HEAL	Community based participatory research	1 year	Twenty-six overweight and obese African-American adults lost a mean of 4.4 pounds at 10 weeks, 8.4 lb at 22 weeks, and 9.8 lb at 1 year. Participants reported decreased fat consumption and sedentary hours, and improved health-related quality of life
Van Wormer et al. (2009) –Weigh By Day	No known behavioral theory	12 months	Self-weighing was a significant predictor of body weight over time. Participants lost about 1 extra pound for every 11 days they self-weighed during treatment. In addition, participants who self-weighed at least weekly were 11 times more likely to lose at least 5% of their pretreatment weight after 6 months. Improvements attenuated after 12 months

Project HEAL: Healthy Eating, Active Lifestyles, a peer-led weight-loss program, was developed through extensive collaboration with community members and experts in nutrition, exercise, and peer education

A prospective cohort design was utilized to examine 100 participants enrolled in a weight-loss trial that encouraged frequent, objectively measured self-weighing at home. The intervention consisted of a 6-month behavioral weight-loss program that employed telephone counseling, a written manual, and a home tele-monitoring scale

Table 209.6 Obesity prevention interventions in adults

Study/Year	Theory	Intervention	Duration	Major findings
Kuller et al. (2001) – Women's Healthy Lifestyle Project	Cognitive–behavioral approach	• Participants were randomly assigned into control group ($n = 275$) and lifestyle intervention group ($n = 260$) • Aimed at increasing leisure time physical activity, preventing weight gain, and preventing the increase of LDL cholesterol • Restrict dietary fat to 25% • Intensive group program during the first 6 months and follow-up individual/group sessions from 6 through 54 months	5 years	• In the lifestyle intervention group the weight change at 6 months was –10.7 lb ($p < 0.01$), at 18 months –6.7 lb ($p < 0.01$), at 30 months -4.7 lb ($p < 0.01$), at 42 months –2.2 lb ($p < 0.01$), and at 54 months –0.18 lb ($p < 0.01$) • Corresponding significant reductions were also found in waist circumference as compared to control group
Bachar et al. (2006) – Cherokee Choices	Social marketing theory	• Components: Worksite wellness for adults, church-based health promotion, and social marketing using TV documentary series, and TV advertisements • Worksite wellness program ($n = 86$) and church wellness program had healthy cooking demonstrations, classes on exercise techniques, and	3 years	• 88% completed the worksite wellness program and 56% met the goals • 70.9% lost weight (29.1% < 5 lb, 12.8% 5 to < 10 lb, 20.9% 10 to < 20 lb, 8.1% ≥ 20 lb) • In 86 participants, 0.85 kg/m^2 change in BMI between June 2002 and June 2005
Ash et al. (2006)	Cognitive–behavioral approach	A randomized–controlled trial ($n = 176$) of two intervention groups, a group-based cognitive–behavioral therapy lifestyle intervention, Fat Booters Incorporated – (FBI) and individual-ized dietetic treatment (IDT) and control group receiving an information booklet only (BO). The intervention groups involved weekly contact for 8 weeks with monthly follow-up to 6 months and further follow-up at 12 months, conducted in real practice setting	1 year	A statistically significant difference between groups was observed for weight change over time ($p < 0.05$). Change in weight for the FBI group was significantly greater than the BO group at 3 and 12 months ($p < 0.05$). Significant differences in self-efficacy were observed over time ($p < 0.02$), with both intervention groups having greater self-efficacy than the BO group

Study	Theory	Description	Duration	Results
Whitt-Glover et al. (2008)	Social cognitive theory	A faith-based PA intervention on daily walking and moderate- and vigorous-intensity PA ($n = 87$). Sedentary black adults participated in eight group sessions that included discussion of physical activity–related topics, an instructor-led PA session, and weekly incentives to promote physical activity. Walking was assessed weekly in steps per day by using a pedometer	3 months	After 12 weeks, moderate- and vigorous-intensity PA increased by 67 ± 78 and 44 ± 66 min/week, respectively ($p \leq 0.01$), and daily walking increased by $1,373 \pm 728$ steps per day ($p < 0.001$)
Eiben and Lissner (2006)–Health Hunters	No known behavioral theory	Women, 18–28 years old ($n = 40$), with at least one severely obese parent, were randomized to the intervention or control group of the "Health Hunters" program. During 1 year of follow-up, the intervention group received an individualized behavioral program focusing on food choice, physical activity, and other lifestyle factors	1 year	The intervention group displayed significant improvements in body weight, BMI, waist circumference, waist-to-hip ratio and self-reported physical activity. Changes in body composition, although not significant, suggested that the intervention tended to be associated with improved body composition

the interventions (*n* = 3). Programs were implemented in the community, worksites, and via faith-based settings. All five interventions achieved some sort of success, with significant reductions in weight, waist circumference, BMI, an increase in PA and daily walking, as well as self-efficacy.

209.7 Components Among Successful Interventions

The American Dietetic Association (ADA) takes the stance that successful weight management to improve overall health for adults requires a lifelong commitment to healthful lifestyle behaviors emphasizing sustainable and enjoyable eating practices and daily PA (ADA 2009). Components among successful interventions, both treatment and prevention, revolved around a similar mentality.

The use of theory was important in the design and measurement of the interventions. Particularly in the treatment interventions, very few mentioned the use of theory. In terms of measuring an individual's motivation to change, the Transtheoretical Model was widely used. Just as important, however, is adequately measuring and documenting changes in behavioral constructs of the theory chosen (Sharma 2006). As a whole, even the interventions that cited use of theory did not report on all behavioral constructs in relation to the desired behavior change.

Behavior modification strategies incorporated into successful interventions included: self-monitoring such as keeping food and exercise diaries; stress management coping strategies such as meditation and relaxation techniques; stimulus control in which individuals learn how to shop for healthy food and consciously avoid situations in which overeating occurs; problem-solving techniques; contingency management where individuals learn to reward behavior change and; building social support through friends and family to assist in motivation and reinforcement. Those interventions which centered on the individual and their goals resulted in better adherence (Ash et al. 2006), which has been related to greater outcome measures. Individualized stage-matched, multiple behavior interventions had significant effects on progression to action/maintenance for healthy eating, exercise, managing emotional distress, and weight among those most at risk (Johnson et al. 2008).

209.8 Recommendations for Enhancing Obesity Prevention and Treatment Interventions

After reviewing both treatment and prevention interventions related to obesity in adults, the interventions must target both PA and nutrition behaviors. Lifestyle interventions with a focus on incorporating favorable changes in eating and exercise behavior into daily routines appear to be more effective than those without this focus (Seo and Sa 2008). Changes including increased fruit and vegetable consumption, decreased fat intake, decreased consumption of sweetened beverages, adequate consumption of water, and restricting portion sizes are important aspects to dietary improvements (Barton and Whitehead 2008).

Encouraging adults to participate in PA must be integrated into any treatment or prevention intervention. For those trying to prevent significant weight gain, recommendations are for at least 150 min/week of moderate-intensity physical activity. Modest reduction in weight gain have been reported for the above recommendations; however, for those individuals who are overweight or obese, there is a greater weight loss and enhanced prevention of weight gain for levels of moderate-intensity PA of 250–300 min/week (American College of Sports Medicine [ACSM] 2009). Results from short-term interventions (≤6 months) have shown the enhanced magnitude of weight loss when

the intervention focuses on a combination of diet plus PA (Jakicic et al.); reported reductions in body weight of 11.4%, 8.4%, and 0.3% in males participating in 12 weeks of diet plus exercise, diet alone, or exercise alone, respectively.

There is need for all interventions to be based on behavioral theories. Use of behavioral theories helps aid the understanding of which components work and to what extent, helps in timing the interventions, and makes professional communication and comparison easier (Sharma 2006). Theories such as the Transtheoretical Model really helped to individualize the intervention, increasing the likelihood for success (Johnson et al. 2008; Seals 2007).

In terms of setting, more interventions should target community and worksite settings where early stages of obesity can be detected and programmatic efforts initiated in a timely manner. By targeting existing social networks, locating programs in places where individuals already gather, and utilizing community members who already have the trust of their members, interventions are more likely to be deep-rooted in the community – and therefore more successful (Goldfinger et al. 2008). Employee social networks may be leveraged through worksites to facilitate weight loss and maintenance (Benedict and Arterburn 2008). Churches may be an ideal setting for prevention efforts, particularly in African-American communities, because of their central role in spiritual guidance, communication, social support, and networking (Whitt-Glover et al. 2008). Interventions need to be targeted toward multiethnic and minority adults. Strategies recommended include incorporating individual sessions, family involvement, and problem-solving strategies into multicomponent programs that focus on lifestyle changes (Seo and Sa 2008).

In terms of the duration of the intervention, interventions that are at least 6-month long must be planned. Studies incorporating interventions with face-to-face contact with participants occurring more than once a month had greater success than those where contact occurred less than once per month (Benedict and Arterburn 2008). When possible, individualized, one-on-one counseling should be used as an educational approach (Johnson et al. 2008). Counseling delivered electronically and by phone proved to be effective if face-to-face interaction was not possible.

Beyond individual obesity treatment and prevention programs, public policy becomes a powerful means to effect change in order to alter population-level diet and PA behavior. Some of the most significant factors include the high cost of healthy foods, the location of grocery stores, access to safe places to exercise, and the availability of preventive health-care services (RWJF 2008). Such change can also be used to modify social norms, where the healthy choice becomes the accepted standard (McKinnon et al. 2009).

209.9 Applications to Other Areas of Health and Disease

Overweight and obesity have been related to such a myriad of physical consequences, most of which relate to increased morbidity and mortality (USDHHS 2007). We have already seen that being overweight and obese leads itself to a variety of diseases. In terms of both treatment and prevention, it seems that primary care providers are missing opportunities to help their patients (Boardley et al. 2007). There has been an increase in weight-related education with those clinics which have started to routinely record BMI. In addition, patients have reported the desire to receive information and help from their primary care physician, making this the ideal time to incorporate strategies to both treat and prevent adult obesity. Reasons most primary care providers do not talk to their patients about weight management and/or prevention include time constraints, not enough training, lack of financial incentive, and failure to believe that patients can be successful (Boardley et al. 2007). Providing education to physicians and related occupations would be beneficial in the targeting of the obesity issue.

209.10 Conclusion

Despite widespread acknowledgment that obesity is endangering the health of millions of Americans; the country is still failing to respond clearly or comprehensively. The diversity of both obesity treatment and prevention interventions which were found to be effective was promising, as it increased the likelihood of finding a suitable program which could be adapted to specific community needs. Nonetheless, programs must be developed around community needs, and be guided by those that have already been successful. As Doak et al. (2006) stated, "There is no need to reinvent the wheel" (p. 129). Building on successful interventions and relating them to specific community needs will increase the chance of success. Improving an individual's ability to sustain achieved weight loss and prevent weight gain remains a major challenge in the management of overweight and obesity (Lang and Froelicher 2006) and must also be considered in the implementation of future interventions.

The most effective obesity prevention and treatment requires collaboration among health-care providers, nurses, dietitians, psychologists, health educators, community leaders, and policy makers (Lang and Froelicher 2006). There is a need for continued research addressing strategies that focus on the underlying societal causes of obesity through action in sectors such as transport, environment, employment conditions, education, health and food policies, and social and economic policies (Lemmens et al. 2008). According to Dr. Risa Lavizzo-Mourey, President and CEO of the Robert Wood Johnson Foundation, "We must work together, governments, schools and communities, to improve nutrition and increase PA for all ages. We must ensure that strong policies are implemented and enforced in every state, not only to help reverse existing obesity rates, but to prevent obesity among our nation's children—and generations to come" (RWJF 2008).

Summary Points

- The diversity of both obesity treatment and prevention interventions that were found to be effective was promising.
- Programs must be developed around community needs, and guided by those that have already been successful.
- Interventions which centered on the individual and their goals resulted in better adherence.
- Effective obesity prevention and treatment programs focus on both increasing PA and modifying dietary behaviors.
- The most effective approach in obesity prevention and treatment requires collaboration.
- Public policy changes can be used to modify social norms, where the healthy choice becomes the accepted standard.

Key Terms

Overweight: BMI of 25–29.9 kg/m^2.
Obesity: BMI over 30 kg/m^2.
Direct medical costs: Costs related to preventive, diagnostic, and treatment services.
Morbidity costs: Income lost from decreased productivity, restricted activity, and absenteeism.
Mortality costs: The value of future income lost by premature death.
Treatment intervention: Implemented with overweight or obese individuals with a goal of weight loss.
Prevention intervention: Implemented with an unselected population that may be normal weight or obese with a goal of prevention of weight gain.

References

American College of Sports Medicine (ACSM). J Am Col Sport Med. 2009;11:459–71.

American Dietetic Association. J Am Diet Assoc. 2009;109:330–46.

Ash S, Reeves M, Bauer J, Dover T, Vivanti A, Leong C. Int J Obes. 2006;30:1557–64.

Bachar J, Lefler L, Reed L, McCoy T, Bailey R, Bell R. Prev Chronic Dis. 2006;3:A103.

Barton R, Whitehead K. J Hum Nutr Diet. 2008;21:373–406.

Benedict M, Arterburn D. Am J Health Promot. 2008;22:408–16.

Blissmer B, Riebe D, Dye G, Ruggiero L, Greene G, Caldwell M. Health Qual Life Outcomes. 2006;4:43–52.

Boardley D, Sherman C, Ambrosetti L, Lewis J. J Am Board Fam Med. 2007;20:252–7.

Bowman S. J Pub Health Res Prac Policy. 2006;3:1–11.

Burke L, Hudson A, Warziski M, Styn M, Music E, Elci O, Sereika M. Am J Clin Nutr. 2007;86:588–96.

Carr L, Bartee T, Dorozynski C, Broomfield J, Smith M, Smith D. Prev Med. 2008;46:431–8.

Cossrow N, Jeffrey R, McGuire M. J Nutr Ed. 2001;33:208–14.

Doak CM, Visscher T, Renders M, Seidell JC. Obes Rev. 2006;7:111–36.

Eiben G, Lissner L. Int J Obes. 2006;30:691–6.

Finch E, Linde J, Jeffery R, Rothman A, King C, Levy R. Health Psychol. 2005;24:608–16.

Finkelstein E, Fiebelkorn I, Wang G. Health Aff. 2003;3:219–26.

Gerberding J, Marks J. Am J Public Health. 2004;94:1478–9.

Goldfinger J, Arniella G, Wylie-Rosett, Horowitz C. J Health Care Poor Underserved. 2008;19:180–92.

Goutham R. Am Fam Physician. 2008;78:56–64.

Howard B, Manson J, Stefanick M, Beresford S, Frank G, Jones B. JAMA 2006;295:39–49.

Institute of Medicine. Preventing childhood obesity: health in the balance. Washington, DC: National Academy Press; 2004.

Jakicic J, Wing R, Winters-Hart C. Med Sci Sports Exerc. 2002;34:1653–9.

Johnson S, Paiva A, Cummins C, Johnson J, Dyment S, Wright J. Prev Med. 2008;46:238–46.

Karanja N, Stevens V, Hollis J, Kumanyika S. Ethn Dis. 2002;12:363–71.

Kennedy B, Paeratakul S, Champagne C, Ryan D, Harsha D, McGee B. Ethn Dis. 2005;15:373–8.

Kuller L, Simkin-Silverman L, Wing R, Meilahn E, Ives D. Circulation 2001;103:32–7.

Lang A, Froelicher E. Eur J Cardiovasc Nurs. 2006;5:102–14.

Lemmens V, Oenema A, Klepp K, Henriksen H, Brug J. Obes Rev. 2008;9:446–55.

Lutes L, Winett R, Barger S, Wojcik J, Herbert W, Nickols-Richardson S, Anderson E. Ann Behav Med. 2008;35:351–7.

Mayer-Davis E, D'Antonio A, Smith S, Kirkner G, Levin Martin S, Parra-Medina D. Am J Public Health. 2004;94:1736–42.

McKinnon R, Orleans T, Kumanyika S, Haire-Joshu D, Krebs-Smith S, Finkelstein A. Am J Prev Med. 2009;36:351–7.

Metz J, Stern J, Kris-Etherton P, Reusser M, Morris C, Hatton D. Arch Intern Med. 2000;160:2150–8.

Miller E, Erlinger T, Young D, Jehn M, Charleston J, Rhodes D. Hypertension 2002;40:612–8.

Moreno LA, Tomas C, Gonzalez-Gross M, Bueno G, Perez-Gonzalez JM, Bueno M. Int J Obes Relat Metab Disord. 2004;28:S16–20.

Nelson M, Robbins A, Thornton J. Mil Med. 2006;171:409–14.

Office of the Surgeon General. The Surgeon General's call to action to prevent and decrease overweight and obesity. Rockville: Office of the Surgeon General; 2001.

Ogden CL, Flegal KM, Carroll MD, Johnson CL. JAMA 2002;288:1728–32.

Robert Wood Johnson Foundation. F as in fat: how obesity policies are failing in America. 2008.

Schmitz M, Jeffery R. Med Clin North Am. 2000;84:491–512.

Schneider P, Bassett D, Thompson D, Pronk N, Bielak K. A J Health Promo. 2006;21:85–9.

Seals J. J Am Acad Nurse Pract. 2007;19:63–71.

Seo D, Sa J. Prev Med. 2008;47:573–82.

Sharma M. Obes Rev. 2006;7:261–9.

Tate D, Jackvony E, Wing R. JAMA 2003;289:1833–6.

Tsai A, Wadden A. Ann Intern Med. 2005;142:56–66.

Tucker L, Cook A, Nokes N, Adams T. Am J Health Promo. 2008;23:121–9.

US Department of Health and Human Services. Healthy people 2010. 2nd ed. Washington, DC: US Government Printing Office; 2000.

US Department of Health and Human Services. Overweight and obesity. US Department of Health and Human Services, Centers for Disease Control and Prevention; 2007.

US Department of Health and Human Services. Physical activity guidelines for Americans, 2008. Washington, DC: US Government Printing Office; 2008.

US Department of Health and Human Services & U.S. Department of Agriculture. Dietary guidelines for Americans, 2005. 6th ed. Washington, DC: US Government Printing Office; 2005.

US Preventive Services Task Force. Behavioral counseling in primary care to promote a healthy diet: recommendations and rationale. Rockville: Agency for Healthcare Research and Quality; 2003.

VanWormer J, Martinez A, Martinson B, Crain A, Benson G, Cosentino D, Pronk N. Am J Prev Med. 2009;36:70–3.

Whitt-Glover M, Hogan P, Lang W, Heil D. Prev Chronic Dis. 2008;5:1–9.

Wilson A, McAlpine D. Med Care Res Rev. 2006;63:570–98.

Wolf AM. Obes Res. 1998;6:2S.

World Health Organization. Obesity and overweight. 2005.

Yates J, Murphy C. Asia Pac J Clin Nutr. 2006;15:74–9.

Chapter 210
The Use of a Cognitive Behavioral Program for Diabetes and Cardiovascular Risk Reduction

Jeroen Lakerveld, Sandra D.M. Bot, and Giel Nijpels

Abbreviations

CBP   Cognitive behavior program
CVD   Cardiovascular diseases
MI   Motivational interviewing
PST   Problem-solving treatment
RCT   Randomized, controlled trial
T2DM   Type 2 diabetes mellitus
TPB   Theory of planned behavior
TTM   Transtheoretical model

210.1 Introduction

Overweight, reduced physical activity, smoking, and an unhealthy diet are lifestyle-dependent risk factors that are associated with cardiovascular diseases (CVD) and type 2 diabetes (T2DM) (Reaven 1995; Yusuf et al. 2004; Willi et al. 2007). Changing these risk factors has the potential to postpone or prevent the development of CVD and T2DM. Although prescribing risk-lowering drugs seems to be easier and more widely accepted by medical practitioners and patients, interventions that lower CVD and T2DM risk by improving lifestyle are likely to be safer and less expensive than drug therapy (Montori et al. 2007). Moreover, changing lifestyle behavior has been shown to be at least as effective as drug treatment in reducing the rate of progression to T2DM in people with impaired glucose tolerance (Knowler et al. 2002; Gillies et al. 2007). In addition to CVD and T2DM, changing an unhealthy lifestyle might also lower the risk of other diseases and ailments, and might have a positive influence on the lifestyle behavior of family members. That is, of course, if the lifestyle program leads to a structural behavioral change. Numerous lifestyle programs have been developed, and many of them use a cognitive behavioral approach to target the lifestyle of participants. Lifestyle interventions based on behavioral or cognitive–behavioral strategies have been reported to be more effective than health education or instruction alone (King et al. 1998;

J. Lakerveld (✉)
Department of General Practice and the EMGO Institute for Health and Care Research, VU University Medical Center, van der Boechorststraat 7, 1081 BT, Amsterdam, The Netherlands
e-mail: j.lakerveld@vumc.nl

Petrella and Lattanzio 2002; Wadden et al. 2004; Shaw et al. 2005). Cognitive–behavioral programs (CBPs) are interventions based on the principles underlying cognitive–behavioral therapy. The term cognitive–behavioral therapy is used in various ways to refer to behavior therapy, cognitive therapy, and therapy based on the pragmatic combination of principles of behavioral and cognitive theories (British Association of Behavioural and Cognitive Psychotherapies 2009). Because the word *therapy* can be interpreted as the attempted remediation of a health problem such as a disease or disorder, the word *program* is preferable in the context of prevention. Thus, CBPs can be seen as programs that share a theoretical basis in behavioristic learning and cognitive psychology, and that use instruments of change (methods, techniques) derived from these theories.

CBPs that are described in the literature vary in many ways. The programs differ with regard to setting, instruments of change, target population, theoretical background, time to follow-up, outcome measures, and effectiveness. Furthermore, they target different lifestyle behaviors, such as dietary behavior, smoking, physical activity, or a combination. By means of reviews that are published on this subject, an overview is given of lifestyle intervention programs with a cognitive behavioral approach to reduce the risk of CVD and T2DM in adults. Additionally, often used instruments of change and influential theoretical models are discussed. This qualitative "review of reviews" is intended to give an overall picture of the current knowledge, rather than an exhaustive summary of the relevant published literature.

210.2 Data Sources

In order to underpin our overview with available scientific evidence, the electronic databases MEDLINE and the Cochrane Database of Systematic Reviews were searched to identify reviews that focus specifically on randomized, controlled trials (RCTs) based on cognitive and behavioral intervention strategies. The search terms included *lifestyle intervention*, *prevention*, *cardiovascular diseases*, *diabetes*, *cognitive*, and *behavior*. Reviews were eligible for inclusion if they were lifestyle orientated and focused on diet, nutrition, increased physical activity, individually or in combination. Reviews with smoking as the main focus were not included. The reviews had to satisfy the inclusion criteria for RCTs listed in Table 210.1.

Table 210.1 Criteria for the inclusion of reviews for this chapter

Category	Criteria for inclusion
Time period	Publication date January 1965 to April 2009
Publication language	English
Study population	Human adults only
	Healthy or high-risk populations
Study design	Review including RCTs or studies with a quasi-experimental design
Intervention setting	Primary care
Intervention components	One or more of the following intervention types: individual counseling, support groups, classes, telephone or e-mail contact
Outcomes reported	Absolute or relative risk of CVD/ mortality or T2DM.
	Lifestyle behavior (physical activity, dietary behavior), weight, body-mass index

210.3 Effectiveness of Cognitive–Behavioral Programs

Reviews that evaluated the effectiveness of CBPs are summarized in Table 210.2 (dietary interventions), Table 210.3 (physical activity interventions) and Table 210.4 (a combination of dietary and physical activity interventions).

Interventions appear to be more successful in changing the lifestyle behavior of high-risk populations than that of general, healthy populations (Ebrahim and Davey 2000; Ammerman et al. 2002; Davies et al. 2004; Gillies et al. 2007; Fleming and Godwin 2008). Extensive programs that have a multiple risk factor approach and include long follow-up booster sessions tend to be effective in changing the risk of CVD and/or T2DM (King et al. 1998; Miller and Dunstan 2004; Gillies et al. 2007; Orozco et al. 2008). Furthermore, effective interventions included those that applied behavioral or cognitive–behavioral strategies (King et al. 1998; Shaw et al. 2005).

Interventions were found to vary widely in the range and type of techniques used, even when targeting the same behavior among similar participants. The theoretical underpinning of the various interventions is also very diverse, and is often not clearly described in reviews. On the other hand, many theoretical models underlying CBPs are more or less comparable, and contain elements that are similar to theoretical models such as the theory of planned behavior (TPB), the theory of self-regulation or the transtheoretical model (TTM).

Despite the popularity of the TTM, in recent years it has been the subject of increased criticism, leading to discouragement of further use of this theory (van Sluijs et al. 2004). The focus and key concepts of frequently used influential theoretical models are presented in Table 210.5.

Many programs that use cognitive behavioral approaches include one or more (elements) of the following instruments of change:

210.3.1 Risk Communication

Involving participants in decision-making concerning the management of their risk may improve their adherence to lifestyle programs. A barrier to the implementation of lifestyle changes is often misperception of the risk (van Steenkiste et al. 2004a, b). As a result, the participants are not encouraged and motivated to change their lifestyle. This concept is also incorporated in Leventhal's self-regulation model (Leventhal 1982). This theory assumes that the cognitions of a patient with regard to a personal health issue determine the attitude of the patient (see also Table 210.5). Risk communication aims to create awareness and to resolve a possible mismatch between the patient's actual risk and perceived risk. Examples of risk communication tools are: risk tables/user-friendly risk charts or providing a risk-adjusted age (Grover et al. 2007).

210.3.2 Motivational Interviewing

Motivational interviewing (MI) is a counseling method with which to elicit behavioral change by helping people to explore and resolve ambivalence in a respectful counseling atmosphere (Miller and Rollnick 2002). It is a well-known method of counseling. The therapeutic relationship is more like a partnership or companionship than a situation with expert/recipient roles. Motivation is an integral part of changing an individual's behavior and stimulating the adaptation to good healthy

Table 210.2 Reviews of cognitive behavioral programs based on dietary interventions for diabetes or cardiovascular risk reduction

Authors	Title	Included interventions	Results/conclusions
Ammerman et al. (2002)	The efficacy of behavioral interventions to modify dietary fat and fruit and vegetable intake: a review of the evidence	Behavioral dietary interventions in promoting dietary change related to chronic disease risk reduction	Interventions appeared to be more successful in positively changing dietary behavior among populations at risk of (or diagnosed with) disease than among general, healthy populations. The majority of the interventions reviewed resulted in meaningful improvements in dietary factor behaviors associated with the prevention of chronic disease, particularly among individuals at elevated disease risk. Small group interaction and goal-setting seem to be the most effective component of dietary interventions
Ashenden et al. (1997)	A systematic review of the effectiveness of promoting lifestyle change in general practice	Trials examining the effectiveness of dietary advice by several primary care health workers	The effectiveness of the trials included in this review was very mixed. No clear result can be given due to the heterogeneity of the trials. The individual results of the trials reported only small changes in behavior; no substantial changes. General practitioners should direct their efforts toward high-risk groups in which the potential for substantial change may be greater
Gillies et al. (2007)	Pharmacological and lifestyle interventions to prevent or delay type 2 diabetes in people with impaired glucose tolerance: systematic review and meta-analysis	RCTs that evaluated interventions to delay or prevent T2DM by means of dietary programs	Lifestyle interventions focusing on diet reduce the rate of progression to T2DM in people with impaired glucose tolerance. Lifestyle interventions seem to be at least as effective as drug treatment.
Nield L. et al. (Nield et al. 2008)	Dietary advice for the prevention of type 2 diabetes mellitus in adults	RCTs of 12 months or longer with dietary advice for the prevention of T2DM as intervention	Dietary advice appears to be effective in reducing the risk of T2DM compared to a control group over six years. However, there are no high-quality data on the efficacy of dietary intervention for the prevention of T2DM.
Pignone MP et al. (Pignone et al. 2003)	Counseling to promote a healthy diet in adults: a summary of the evidence for the U.S. Preventive Services Task Force	RCTs that examined the effectiveness of counseling in changing dietary behavior	Dietary counseling of patients by primary care providers produces modest changes in self-reported consumption of saturated fat, fruits and vegetables, and possibly dietary fiber. Interventions that are more intensive were more likely to produce important changes than brief interventions, but they may be more difficult to apply to typical primary care patients. Interventions using interactive health communications, including computer-generated telephone or mail messages, can also produce moderate dietary changes. Their effect on health outcomes is unclear.

Table 210.3 Reviews of cognitive behavioral programs based on physical activity interventions for diabetes or cardiovascular risk reduction

Authors	Title	Included interventions	Results/conclusions
Ashenden et al. (1997)	A systematic review of the effectiveness of promoting lifestyle change in general practice	Trials which assessed brief to intensive exercise advice	The effectiveness of the trials included in this review was very mixed. No clear result can be given due to the heterogeneity of trials. The individual results of the trials reported only small changes in behavior; no substantial changes
Eakin et al. (2000)	Review of primary care-based physical activity intervention studies: effectiveness and implications for practice and future research	Primary care-based physical activity interventions	Primary care-based physical activity counseling is moderately effective in the short term, although there is considerable variability across studies. Studies in which the interventions were tailored to participant characteristics and which offered written materials to patients produced stronger results
Eaton and Menard (1998)	A systematic review of physical activity promotion in primary care office settings	Physical activity promotion in primary care setting	There is limited evidence from well-designed trials that office-based physical activity promotion in primary care settings is efficacious in promoting changes in physical activity that could conceivably have lasting clinical benefits
Gillies et al. (2007)	Pharmacological and lifestyle interventions to prevent or delay type 2 diabetes in people with impaired glucose tolerance: systematic review and meta-analysis	RCTs that evaluated interventions to delay or prevent T2DM by means of dietary programs	Lifestyle interventions focusing on physical activity reduce the rate of progression to T2DM in people with impaired glucose tolerance even more than studies with interventions focusing on diet. Lifestyle interventions seem to be at least as effective as drug treatment
King et al. (1998)	Physical activity interventions targeting older adults. A critical review and recommendations	Physical activity interventions; community based	Effective interventions included those that employed behavioral or cognitive–behavioral strategies as opposed to health education or instruction alone. In addition, programs that also used either a supervised home-based format or a combination of group- and home-based formats typically reported comparable or better physical activity adherence relative to programs that used a class or group format only. Ongoing telephone supervision of the physical activity program was shown to be an effective alternative to face-to-face instruction, resulting in adherence rates over extended periods of time (i.e. up to 2 years)

Table 210.3 (continued)

Authors	Title	Included interventions	Results/conclusions
Orozco et al. (2008)	Exercise or exercise and diet for preventing type 2 diabetes mellitus (T2DM)	Exercise interventions of at least 6 months duration	No firm conclusion can be drawn about the effectiveness of exercise alone in preventing T2DM
Petrella and Lattanzio (2002)	Does counseling help patients get active?	Studies focusing on physicians promoting physical activity	Most studies found positive relationships between counseling and change in level of physical activity. No long-term effect of the interventions was established

habits. The five main guiding principles of MI are: express empathy, develop discrepancies, avoid argumentation, roll with resistance, and support self-efficacy (see also Table 210.6).

210.3.3 Problem-Solving Treatment

Problem-Solving Treatment (PST) is a brief, structured psychological intervention that can be defined as the self-directed cognitive–behavioral process by which a person attempts to identify or discover effective or adaptive solutions for specific problems encountered in everyday life (Mynors-Wallis 2005). PST aims to increase a person's ability to solve problems in a structured way and to increase the person's self-management. This is done in seven stages (see Table 210.7). The treatment involves an active collaboration between participant and therapist, with the participant taking an increasingly active role in planning the treatment and implementing activities between the treatment sessions. The therapist helps participants to gain a sense of mastery over their difficulties.

210.3.4 Booster Calls/Booster E-mails

Preventing or delaying a relapse to the "old" and unwanted lifestyle behavior is an important step in producing long-lasting behavioral change, and booster sessions can be an essential instrument. Telephone or e-mail booster sessions act as a reminder for the participants to reinforce what they have learned, e.g. during face-to face sessions, and to give them support and feedback. In this way, maintenance sessions might facilitate the consolidation of skills learned during earlier sessions, and thereby prolong their use even after the booster sessions have ended.

210.4 Authors' Conclusions

Research on the effectiveness of cognitive behavioral programs for CVD and T2DM risk reduction has increased, but the results of trials are not consistent. Systematically reviewing these trials is complicated, because there is much heterogeneity in the study design, the theoretical underpinning,

Table 210.4 Reviews of cognitive behavioral programs based on a combination of dietary and physical activity interventions for diabetes or cardiovascular risk reduction

Authors	Title	Included interventions	Results/conclusion
Ebrahim and Davey et al. (2000)	Multiple risk factor interventions for primary prevention of coronary heart disease	Studies using counseling education to modify more than one cardiovascular risk factor. At least 6 months follow-up	The pooled effects suggest multiple risk factor interventions have no effect on mortality. Changes in risk factors were relatively modest and in some cases may have been overestimated for methodological or statistical reasons
Gillies et al. (2007)	Pharmacological and lifestyle interventions to prevent or delay type 2 diabetes in people with impaired glucose tolerance: systematic review and meta-analysis	RCTs that evaluated interventions to delay or prevent T2DM with a focus on diet and exercise	Lifestyle interventions focusing on a combination of physical activity and diet reduce the rate of progression to T2DM in people with impaired glucose tolerance. Lifestyle interventions seem to be at least as effective as drug treatment
Goldstein et al. (2004)	Multiple behavioral risk factor interventions in primary care: summary of research evidence	Interventions addressing multiple behavioral risks	There is evidence for the efficacy of medium- to high-intensity dietary counseling by specially trained clinicians in high-risk patients. There is fair to good evidence for moderate, sustained weight loss in obese patients receiving high-intensity counseling, but insufficient evidence regarding weight-loss interventions in nonobese adults. Evidence for the efficacy of physical activity interventions is limited. There remain to be large gaps in our knowledge about the efficacy of interventions to address multiple behavioral risk factors in primary care.
Miller YD & Dunstan DW (Miller and Dunstan 2004)	The effectiveness of physical activity interventions for the treatment of overweight and obesity and type 2 diabetes	Studies focusing on increasing the level of physical activity or reducing sedentary behavior	Strategies that combine diet and physical activity are more effective than physical activity alone. Combined lifestyle strategies are most successful for maintained weight loss, although most programs are unsuccessful in producing long-term changes. There is little evidence of compliance to prescribed behavior changes. Limited evidence suggests that continued professional contact and self-help groups can help to sustain weight loss. Evidence suggests that interventions can lead to small but clinically meaningful improvements in glycemic control, even in the absence of weight loss.

(continued)

Table 210.4 (continued)

Authors	Title	Included interventions	Results/conclusion
Orozco et al. (2008)	Exercise or exercise and diet for preventing T2DM	RCTs with at least 6 months follow-up and with T2DM incidence as outcome measure	Interventions aimed at increasing exercise combined with diet are able to decrease the incidence of T2DM in high-risk groups
Shaw et al. (2005)	Psychological interventions for overweight or obesity	RCTs of psychological intervention versus a comparison intervention with weight change as outcome measure	People who are overweight or obese benefit from psychological interventions, particularly behavioral and cognitive–behavioral strategies, to enhance weight reduction. They are predominantly useful when combined with dietary and exercise strategies. The bulk of evidence supports the use of behavioral and cognitive–behavioral strategies in order to change the lifestyle behavior of participants

Table 210.5 The focus and key concepts of frequently used behavioral change theories

Theory/ model	Focus	Key concepts
Theory of planned behavior (Ajzen 1985)	Attitude toward behavioral change, the perceived pressure of important others, and perceived behavioral control. These are linked to the intention, which is directly linked to behavioral change. Perceived behavioral control also has a direct link with change	Attitude Subjective norms Perceived behavioral control Intention
Theory of self-regulation (Leventhal 1982)	An approach is for the participant to realize a personal health issue and understand the factors involved in that issue. The participant must decide upon an action plan for resolving the health issue. The patient will need to deliberately monitor the results in order to appraise the effects, checking for any necessary changes in the action plan	(Health) threat Representations of the threat Response
Transtheoretical model (Prochaska and DiClemente 2005)	Readiness to change or attempt to change a health behavior varies among individuals and within an individual over time. Relapse is a common occurrence and part of the normal process of change	Precontemplation Contemplation Preparation Action Maintenance
Protection motivation therapy (Rogers 1983)	According to this theory, there are two sources of information: (1) environmental (e.g. verbal persuasion, observational learning) and (2) intrapersonal (e.g. prior experience).This information elicits either an "'adaptive' coping response (i.e. the intention to improve one's health) or a 'maladaptive' coping response (e.g. avoidance, denial).	Threat appraisal Coping appraisal Protection motivation response
Social cognitive theory (*Bandura* 1986)	Behavior is explained by dynamic interaction among personal factors, environmental influences, and behavior.Each factor affects each of the others and determines behavioral change.	EnvironmentSituation Behavioral capability Expectations Expectancies Self-control Observational learning Reinforcements Self-efficacy Emotional coping responses Reciprocal determinism

the target population, and the content and delivery of the interventions. In order to be able to draw conclusions about the effect of CBPs on absolute CVD or T2DM risk, there is a need for studies with a longer time to follow-up. Overall, some concluding observations can be made: the effectiveness of CBPs is greater in participants who are at high risk than in participants with a lower risk. Furthermore, extensive programs with a multiple risk factor approach and long-term follow-up booster sessions appear to work best.

Examples of such studies are the Diabetes Prevention Program (Knowler et al. 2002), the Diabetes Prevention Study (Lindstrom et al. 2003), and the Da Qing Study (Pan et al. 1997). However, criticism that is often heard is that the interventions that work best are very labor-intensive. For instance, in one study 16 face-to-face sessions provided by case managers were needed to achieve the target weight reduction and exercise levels (Knowler et al. 2002).

Theory is the only foothold we have in the development of behavioral dietary and physical activity interventions, and the application of theory should improve the likelihood of effectiveness of the

Table 210.6 Key features of motivational interviewing (Miller 1983)

1. Express empathy
   (a) Acceptance and understanding facilitates change
   (b) Skillful reflective listening is fundamental
   (c) Ambivalence is normal
2. Develop discrepancies
   (a) Awareness of consequences is important
   (b) Engage in a discussion between present behavior and valued goals
   (c) Participant-driven rationale for change
3. Avoid argumentation
   (a) Arguments are counterproductive
   (b) Judging (why?) breeds defensiveness
   (c) Resistance is a signal to change therapeutic strategies
   (d) Labeling is unnecessary
4. Roll with resistance
   (a) New perceptions are invited but not imposed
   (b) The participant is a valuable resource for solutions
   (c) Collaboration is valued
   (d) Mutually negotiated solutions
5. Support self-efficacy
   (a) Hope is motivating
   (b) Participant is responsible for choosing and initiating
   (c) There is hope in the range of alternatives

Table 210.7 Key stages of problem-solving treatment (Mynors-Wallis 2005)

Problem-Solving Treatment consists of seven stages:
1. Explanation and rationale
2. Problem definition
3. Establishing SMART goals
4. Generating solutions
5. Selecting preferred solution
6. Implementing solution
7. Evaluation of progress

interventions (Brug et al. 2005). Theories stimulate researchers to consider which elements should be included in their intervention, and why. Such programs therefore need to be theory-driven. Behavioral change theories are conceptual models that can be used to chart the biological, cognitive, behavioral, psychosocial, and/or environmental determinants of changes in an individual's behavior. Theories also provide a good basis for evaluation of the intervention, not only in terms of "does it work", but also: "how does it work?" This is an important issue, because in this way it is possible to determine which elements are effective in the intervention, or, on the other hand of equal importance, why an intervention was ineffective (Michie and Abraham 2004).

Although many traditional theoretical models have been used as a framework for various interventions, they have only been able to explain the variance in actual behavioral change to a limited extent. More understanding of the determinants that precede behavioral change may result in the development of more integral models, which include, for instance habit strength. It is suggested that frequently performed behavior is often a matter of habit, which does not involve repeated decision making (Aarts et al. 1998). This has consequences for our view of models in which intentional determinants are used to predict behavior, e.g. as in the TPB. It is even suggested that traditional health education approaches may have limited value for strongly habitual health-related behaviors (de Bruijn et al. 2009).

Although they form a population that experiences the most problems due to an unhealthy lifestyle, people of lower socioeconomic class are less likely to participate in lifestyle interventional trials (Lakerveld et al. 2008a). Changing health behavior can only be effective if the program is tailored with the orientation and knowledge of the target population. For example, the more externally oriented locus of control of people of lower socioeconomic class implies that they less frequently believe that changing their behavior will have an effect on their health, which makes it more difficult for them to change their behavior. This might partly explain why they benefit less from lifestyle interventions than people in higher socioeconomic classes do. In addition, people of lower socioeconomic class often live in a deprived neighborhood, which in itself is a risk factor for unhealthy behavior, because of greater exposure to unfavorable physical and social factors. Measures can be taken to increase the number of participants in an intervention, such as making it convenient for them to join a program and reducing the barriers for participation. Locating the program in close proximity to the homes of the participants, or offering incentives, might be helpful in this respect. The challenge is to reach this subgroup, in order to eliminate health disparities among different segments of the population.

Generating a long-lasting change in lifestyle behavior in order to reduce the modifiable risk factors for CVD and T2DM is difficult and complicated, but not impossible. Although promising results of trials have been published, solid, theory-driven trials with a long follow-up period are still needed in order to make it possible to determine the effectiveness for cognitive behavioral programs on absolute CVD or T2DM risk reduction.

Currently, a start has been made by undertaking a comprehensive RCT to study the effectiveness of a CBP aimed at lifestyle changes in people who are at risk (Lakerveld et al. 2008b). The program addresses several components of the TPB and the theory of self-regulation, and makes use of the effective components and instruments of change that are described earlier. The specific focus is on motivation and self-management to achieve change in structural lifestyle behavior. The counseling methods that are used in the intervention are MI and PST. MI is used with the aim to reinforce the participant's attitude and behavioral intention (according to the TPB), and elicit, clarify, and resolve ambivalence associated with behavioral change (see also Tables 210.6 and 210.7). PST is then used to support the participant in finding ways to overcome this discrepancy, to strengthen the participant's perceived behavioral control, and to provide the tools to overcome barriers that hinder a structural change in lifestyle behavior. Nurse practitioners in the participating general practices provide these counseling sessions. The participants receive a maximum of six individual 30-min counseling sessions, followed by 3-monthly booster sessions by phone for a period of 1½ years. The primary outcome measures are the diabetes risk score and the cardiovascular risk score. The risk of developing diabetes will be assessed by means of a risk function, calculated according to data from the ARIC Study (Schmidt et al. 2005). Absolute cardiovascular risk will be assessed with a risk score, calculated according to the SCORE project (Conroy et al. 2003). Secondary outcome measurements include differences in lifestyle behavior (dietary behavior, physical activity behavior, and smoking behavior) and the cost-effectiveness and cost-utility of the CBP.

A process evaluation will be carried out to study the effective and ineffective elements of the intervention. This will provide information on aspects of the study that may increase or reduce the effectiveness of the program, and could be valuable for the further development of interventions that are (more) effective and feasible.

In our opinion, there are certain requirements that must be met by the participants in order to achieve successful behavioral change: first of all, they need to realize that they are at higher risk; second, they need to be willing to change; and third, they need to be able to change. To meet these requirements, specific "instruments of change" might be of use; e.g. risk communication, MI and/or PST, respectively.

210.5 Applications to Other Areas of Health and Diseases

Some instruments that are used in CPBs for CVD and T2DM risk reduction are derived from other health fields in which they are effectively applied. For instance, MI is used extensively for psychological diseases and the treatment of addiction to smoking and alcohol (Rubak et al. 2005).

PST (with the T standing for *therapy* instead of *treatment*, in this case) has been applied for a wide range of psychological disorders in many areas. For example, it has been found to be suitable for deliberate self-harm patients (in reducing rates of depression, hopelessness, and suicidal ideation after a suicide-attempt), for strengthening problem-solving abilities and assertiveness in mildly mentally retarded people, in palliative care, and in diabetes care.

Summary Points

- Lifestyle interventions based on behavioral or cognitive behavioral strategies are more effective than health education or instruction alone.
- Programs need to be theory-driven.
- The effectiveness of programs is greater in participants who are at high risk of developing CVD or T2DM than in participants with a lower risk.
- An approach combining diet and physical activity appears to be the most effective.
- Intensive and long-term involvement with the participants will more likely result in a structural behavioral change.
- Promising instruments of change are: risk communication, motivational interviewing, and problem-solving treatment.

Key Terms

Cognitive behavioral program: Aims to help participants or patients change the way of thinking, feeling, and behaving. It is used as a treatment for various mental health and physical problems, but also to change unwanted lifestyle behaviors such as smoking, physical inactivity, or an unhealthy diet.

Cardiovascular disease: Refers to the class of diseases that involve the heart or arterial blood vessels. Examples of cardiovascular diseases are cerebrovascular accident (stroke) and myocardial infarction (heart attack).

Type 2 diabetes mellitus: The most common form of diabetes. This chronic (lifelong) disease is marked by high levels of glucose in the blood. Family history and genetics play a large role. Low activity level, poor diet, and excess body weight (especially around the waist) increase the risk for type 2 diabetes.

Risk communication: An interactive process of exchanging information and opinions on health risks between participants or patients and caregivers.

Motivational Interviewing: Is a directive, client-centered counseling style for eliciting behavior change by helping clients to explore and resolve ambivalence.

Problem-solving treatment: A fairly short and simple treatment. It can be provided by a doctor or a trained nurse or counselor. Participants or patients are taught how to cope with problems and helps them to take small steps toward coping.

Key Features of Cognitive Behavioral Programs

- The term cognitive behavioral program is used in various ways to refer to programs based on behavior therapy, cognitive therapy, or a combination of these two.
- Cognitive behavioral therapy is traditionally used to treat depression, but nowadays its foundation is also employed in other areas, for instance in lifestyle behavioral change interventions.
- Habits (such as unwanted lifestyle behaviors) are acquired and can be unlearned using cognitive behavioral programs.
- Cognitive behavioral programs are based on the idea that thoughts, emotions, and behavior interact closely.
- Influencing the participant's concepts is a key element to influence emotions and behavior.
- The emphasis is on the behavior at present and in the future, rather than behavior in the past.
- cognitive behavioral program can be done individually or with a group of people.

References

Aarts H, Verplanken B, van Knippenberg A. Predicting behavior from actions in the past: repeated decision making or a matter of habit? J Appl Soc Psychol. 1998;28:1355–74.

Ajzen I. From intentions to action: a theory of planned behavior. In: Action-control: from cognition to behavior. New York: Springer; 1985. p. 11–39.

Ammerman AS, Lindquist CH, Lohr KN, Hersey J. The efficacy of behavioral interventions to modify dietary fat and fruit and vegetable intake: a review of the evidence. Prev Med. 2002;35:25–41.

Ashenden R, Silagy C, Weller D. A systematic review of the effectiveness of promoting lifestyle change in general practice. Family Practice. 1997;14:160–75.

Bandura A. Social foundations of thought and action. Englewood Cliffs: Prentice-Hall; 1986.

British Association of Behavioural and Cognitive Psychotherapies. What are cognitive and/or behavioural psychotherapies? 2009. http://www.babcp.com/silo/files/what-is-cbt.pdf

Brug J, Oenema A, Ferreira I. Theory, evidence and intervention mapping to improve behavior nutrition and physical activity interventions. Int J Behav Nutr Phys Act. 2005;2:2.

Conroy RM, Pyorala K, Fitzgerald AP, Sans S, Menotti A, De Backer G, De Bacquer D, Ducimetiere P, Jousilahti P, Keil U, Njolstad I, Oganov RG, Thomsen T, Tunstall-Pedoe H, Tverdal A, Wedel H, Whincup P, Wilhelmsen L, Graham IM. Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. Eur Heart J. 2003;24:987–1003.

Davies MJ, Tringham JR, Troughton J, Khunti KK. Prevention of Type 2 diabetes mellitus. A review of the evidence and its application in a UK setting. Diabet Med. 2004;21:403–14.

de Bruijn GJ, Kremers SP, Singh A, van den Putte B, van Mechelen W. Adult active transportation: adding habit strength to the theory of planned behavior. Am J Prev Med. 2009;36:189–94.

Eakin EG, Glasgow RE, Riley KM. Review of primary care-based physical activity intervention studies: effectiveness and implications for practice and future research. J Fam Pract. 2000;49:158–68.

Eaton CB, Menard LM. A systematic review of physical activity promotion in primary care office settings. Br J Sports Med. 1998;32:11–6.

Ebrahim S, Davey SG. Multiple risk factor interventions for primary prevention of coronary heart disease. Cochrane Database Syst Rev. 2000;4.

Fleming P, Godwin M. Lifestyle interventions in primary care: systematic review of randomized controlled trials. Can Fam Physician. 2008;54:1706–13.

Gillies CL, Abrams KR, Lambert PC, Cooper NJ, Sutton AJ, Hsu RT, Khunti K. Pharmacological and lifestyle interventions to prevent or delay type 2 diabetes in people with impaired glucose tolerance: systematic review and meta-analysis. BMJ 2007;334:299.

Goldstein MG, Whitlock EP, DePue J. Multiple behavioral risk factor interventions in primary care. Summary of research evidence. Am J Prev Med. 2004;27:61–79.

Grover SA, Lowensteyn I, Joseph L, Kaouache M, Marchand S, Coupal L, Boudreau G. Patient knowledge of coronary risk profile improves the effectiveness of dyslipidemia therapy: the CHECK-UP study: a randomized controlled trial. Arch Intern Med. 2007;167:2296–303.

King AC, Rejeski WJ, Buchner DM. Physical activity interventions targeting older adults - A critical review and recommendations. Am J Prevent Med. 1998;15:316–33.

Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, Nathan DM. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med. 2002;346:393–403.

Lakerveld J, Ijzelenberg W, van Tulder MW, Hellemans IM, Rauwerda JA, van Rossum AC, Seidell JC. Motives for (not) participating in a lifestyle intervention trial. BMC Med Res Methodol. 2008a;8:17.

Lakerveld J, Bot S, Chinapaw M, van Tulder M, van Oppen P, Dekker J, Nijpels G. Primary prevention of diabetes mellitus type 2 and cardiovascular diseases using a cognitive behavior program aimed at lifestyle changes in people at risk: design of a randomized controlled trial. BMC Endocr Disord. 2008b;8:6.

Leventhal HNDR. Self-regulation and the mechanisms for symptom appraisal. Symptoms, illness behavior, and help-seeking. New York: Prodist; 1982. p. 55–86.

Lindstrom J, Louheranta A, Mannelin M, Rastas M, Salminen V, Eriksson J, Uusitupa M, Tuomilehto J. The Finnish Diabetes Prevention Study (DPS): lifestyle intervention and 3-year results on diet and physical activity. Diabetes Care. 2003;26:3230–6.

Michie S, Abraham C. Interventions to change health behaviours: evidence-based or evidence-inspired? Psychol Health. 2004;19:29–49.

Miller WR, Rollnick S. Motivational Interviewing: preparing people for change. New York/London: Guilford; 2002.

Miller YD, Dunstan DW. The effectiveness of physical activity interventions for the treatment of overweight and obesity and type 2 diabetes. J Sci Med Sport. 2004;7:52–9.

Montori VM, Isley WL, Guyatt GH. Waking up from the DREAM of preventing diabetes with drugs. BMJ 2007;334:882–4.

Mynors-Wallis LM. Problem-solving treatment for anxiety and depression: a practical guide. Oxford: Oxford university press; 2005.

Nield L, Summerbell CD, Hooper L, Whittaker V, Moore H. Dietary advice for the prevention of type 2 diabetes mellitus in adults. Cochrane Database Syst Rev. 2008;CD005102.

Orozco LJ, Buchleitner AM, Gimenez-Perez G, Roque IF, Richter B, Mauricio D. Exercise or exercise and diet for preventing type 2 diabetes mellitus. Cochrane Database Syst Rev. 2008;CD003054.

Pan XR, Li GW, Hu YH, Wang JX, Yang WY, An ZX, Hu ZX, Lin J, Xiao JZ, Cao HB, Liu PA, Jiang XG, Jiang YY, Wang JP, Zheng H, Zhang H, Bennett PH, Howard BV. Effects of diet and exercise in preventing NIDDM in people with impaired glucose tolerance - The Da Qing IGT and diabetes study. Diabetes Care. 1997;20:537–44.

Petrella RJ, Lattanzio CN. Does counseling help patients get active? Systematic review of the literature. Can Fam Physician. 2002;48:72–80.

Pignone MP, Ammerman A, Fernandez L, Orleans CT, Pender N, Woolf S, Lohr KN, Sutton S. Counseling to promote a healthy diet in adults: a summary of the evidence for the U.S. Preventive Services Task Force. Am J Prevent Med. 2003;24:75–92.

Prochaska JO, DiClemente CC. The transtheoretical approach. In: Norcross JC, Goldfried MR, editors. Handbook of psychotherapy integration. New York: Oxford University Press; 2005. p. 147–71.

Reaven GM. Pathophysiology of insulin resistance in human disease. Physiol Rev. 1995;75:473–86.

Rogers RW. Cognitive and physiological processes in fear appeals and attitude change: a revised theory of protection motivation. In: Cacioppo JT, Petty RE, editors. Social psychophysiology: a sourcebook. London: Guilford; 1983.

Rubak S, Sandboek A, Lauritzen T, Christensen B. Motivational interviewing: a systematic review and meta-analysis. Br J Gen Pract. 2005;55:305–12.

Schmidt MI, Duncan BB, Bang H, Pankow JS, Ballantyne CM, Golden SH, Folsom AR, Chambless LE. Identifying individuals at high risk for diabetes - The Atherosclerosis risk in communities study. Diabetes Care. 2005;28:2013–8.

Shaw K, O'Rourke P, Del Mar C, Kenardy J (2005) Psychological interventions for overweight or obesity. Cochrane Database Syst Rev; 2005.

van Sluijs EMF, van Poppel MNM, van Mechelen W. Stage-based lifestyle interventions in primary care: are they effective? Am J Prevent Med. 2004;26:330–43.

van Steenkiste B, van der WT, Stoffers HE, Grol R. Barriers to implementing cardiovascular risk tables in routine general practice. Scand J Prim Health Care. 2004a;22:32–7.

van Steenkiste B, van der WT, Timmermans D, Vaes J, Stoffers J, Grol R. Patients' ideas, fears and expectations of their coronary risk: barriers for primary prevention. Patient Educ Couns. 2004b;55:301–7.

Wadden TA, Butryn ML, Byrne KJ. Efficacy of lifestyle modification for long-term weight control. Obes Res. 2004;12:151S–62S.

Willi C, Bodenmann P, Ghali WA, Faris PD, Cornuz J. Active smoking and the risk of type 2 diabetes: a systematic review and meta-analysis. JAMA 2007;298:2654–64.

Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F, McQueen M, Budaj A, Pais P, Varigos J, Lisheng L. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. Lancet 2004;364:937–52.

Chapter 211
Treatment of Diet-Related Disorders in Adult Diabetes

Ying-Xiao Li, Kai-Chun Cheng, Akihiro Asakawa, and Akio Inui

Abbreviations

5HT-4	5-HydroxyTryptamine Receptor 4
BMI	Body Mass Index
DCCT	Diabetes Control and Complications Trial
GERD	Gastroesophageal Reflux Disease
GI	Gastrointestinal
PI3K	Phosphatidylinositol 3-Kinase
TTG	Tissue Transglutaminase Test
WHO	World Health Organization

211.1 Introduction

The worldwide prevalence of diabetes is currently 150 million and is expected to increase to 300 million by the year 2025. The global obesity epidemic is contributing to a rapid increase in diabetes prevalence. People with diabetes are more likely to experience limitations in mobility, social role function, and activities of daily living. Given the growing disability burden of diabetes, a better understanding of ways to help people with diabetes sustain active, productive, and fulfilling lives is needed. The identification of modifiable factors associated with disability in diabetes may lead to methods for reducing the disability burden of this common chronic disease.

According to the most recent recommendations of worldwide nutrition studies, changes in dietary composition could play a significant role in improving insulin sensitivity and reducing the risk of diabetes and its complications. The brain senses and then responds to nutrient-related signals arising from changes in intracellular energy content or the availability or metabolism of substrates such as free fatty acids. Dietary changes may reduce the risk of diabetes.

A. Inui (✉)

Department of Psychosomatic Internal Medicine, Kagoshima University Graduate School of Medical and Dental Sciences 8-35-1 Sakuragaoka, Kagoshima 890-8520, Japan
e-mail: inui@m.kufm.kagoshima-u.ac.jp

211.2 Obesity in Diabetes

211.2.1 Overview

The incidence of obesity and type 2 diabetes is increasing throughout the world. A World Health Organization (WHO) consultation on obesity recently summarized prevalence data and found that the incidence was increasing not only in the Western world but also in all other regions. The association between obesity and the risk of developing type 2 diabetes has been repeatedly observed in both cross-sectional and prospective studies. In particular, central abdominal obesity is predictive of the development of type 2 diabetes (Lundgren et al. 1989; Ohlson et al.1985). Although there is a general agreement that obesity and type 2 diabetes can, to a certain extent, be explained by genetic factors, the rapid increase over the last few years indicates that the environment, rather than genetic make-up, is responsible for the increase (Campbell et al. 2001).

Body mass index (BMI) and body weight gain are strongly associated with diabetes risk (Colditz et al. 1995). A weight gain of 11–20 kg in 14 years of follow-up increased the age-adjusted relative diabetes risk 5.4-fold in female nurses who had normal weight (BMI, 22–25 kg/m^2) at age 18 years relative to nurses with normal weight at age 18 years who had no weight gain or a weight loss of more than 5 kg. In addition to overall obesity, body fat distribution, especially increased intra-abdominal fat, is a predictor of type 2 diabetes (Chan et al. 1994; Han et al. 1998). The BMI of middle-aged women was strongly correlated with the 3-year incidence rates of type 2 diabetes (Mishra et al. 2007), whereas annual weight changes during this period did not significantly predict the onset of type 2 diabetes (Mishra et al. 2007).

211.2.2 Glycemic Control and Weight Management in Diabetes

The results of large studies such as the Diabetes Control and Complications Trial (DCCT) (9) have demonstrated that glycemic control is an essential factor for improving clinical outcomes for people with diabetes. Intensive therapy strategies designed to lower blood glucose concentrations reduce microvascular complications such as retinopathy and nephropathy. Weight gain was significantly greater in the cohort of patients receiving intensive treatment with insulin or sulfonylureas relative to the cohort receiving dietary intervention and conventional treatment (Gottesman 2004). These results suggest that the health-care provider must strive to maintain a balance between achieving glycemic control and controlling weight when designing a treatment regimen (Fig. 211.1) for an individual patient. In obese people with type 2 diabetes, weight loss clearly improves hyperglycemia and lowers the risk of comorbidities such as hypertension and dyslipidemia (Wing et al. 1987). Dietary therapy can reduce fasting blood glucose levels in overweight type 2 diabetic patients, although the degree of improvement is influenced more by the restriction in caloric intake than by body weight (Wing et al. 1987). Moreover, caloric restriction has an important regulatory effect on metabolism that is independent of weight loss; reducing caloric intake often improves glycemic control more rapidly than weight loss (UKPDS 1990).

211.2.3 Dietary Composition

Appetite may be influenced by a variety of physiological, psychological, emotional, and cultural factors. It has long been established that a transient decline in blood glucose is recognized by the
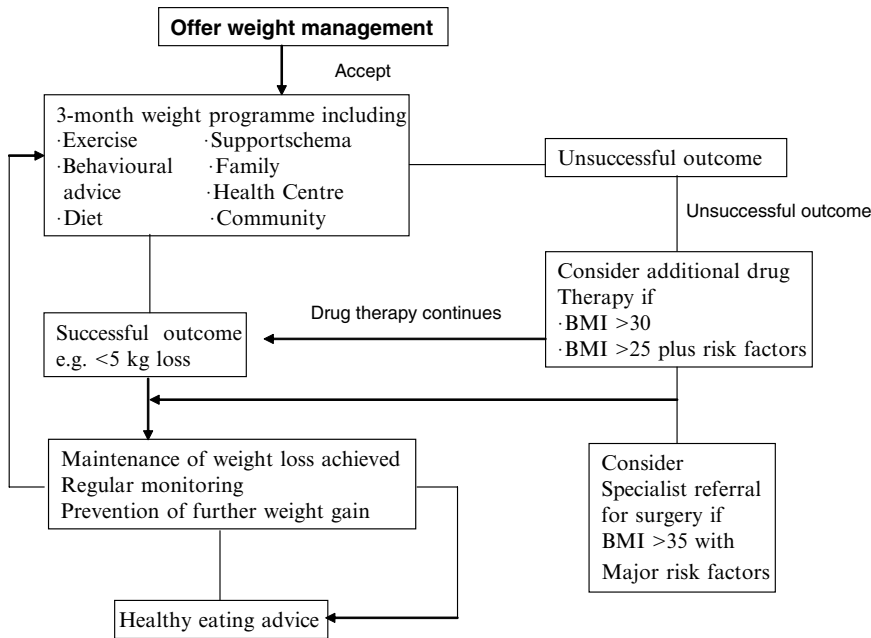
Fig. 211.1 Standard procedure for treating obesity in Type 2 diabetes. The standard procedure takes the Type 2 diabetes patients into account as well and constitutes a simple straightforward approach to successful long-term treatment of the obese Type 2 diabetes patients. To integrate the factors of diet, exercise, drug therapy, and environment, this procedure is a key to successful long-term treatment for obesity

central nervous system and influences hunger and meal-seeking behavior (Campfield et al. 2003). Blood glucose dynamics and diet are linked in a complex relationship, and strategies to regulate blood glucose levels must be designed depending on the diet.

Controversy still exists regarding whether lowering of dietary fat intake enhances weight loss by itself, rather than through energy restriction. Majority of the evidence shows that energy restriction is the overriding factor linked to weight loss in type 2 diabetes after the consumption of usual low-fat, high-carbohydrate diets (NIH 1998). While weight loss relates to energy deficit alone, the composition of the weight-reducing diet can, however, affect glycemia and lipid levels. Replacement of saturated fat with either monounsaturated fat or carbohydrates was shown to equally affect weight loss in obese diabetic subjects and positively affect lipid levels, supporting other evidence that energy content is the major determinant of weight loss (Gumbiner 1999); the replacement of saturated fats was achieved by advising the subjects to replace certain foods. The study questions the dogma that still governs dietary instruction in diabetes, and emphasizes the need to make dietary changes as simple as possible for diabetic patients already burdened with the procedures associated with managing diabetes (NIH 1998). As yet, no scientific evidence exists to show that greater or more sustained weight loss occurs in diabetes by such manipulations as the intake of foods with low glycemic index or raising the protein proportion in the diet, although there is some concern with regard to the possible adverse effects associated with the consumption of high-protein foods by diabetic subjects. Similarly, very-low-calorie diets result in more rapid weight loss initially, but the weight loss is not sustained in the long term (Heilbronn et al. 1999). Such low-calorie diets could predispose to greater binge-eating activity and are recommended in medical emergencies, and should be accompanied with careful monitoring of glucose levels and early reduction in medication (Garner et al. 1998).

To conclude, multiple components of a healthy diet, e.g., high fiber and low saturated fats, reduce diabetes risk and contribute to sustained weight loss; they should therefore be included in long-term

lifestyle interventions. Dietary composition plays a key role in diabetes prevention, primarily by sustaining long-term weight loss and secondarily by initiating weight loss and reducing the risk of diabetes.

211.2.4 Nutritional Education and Coping Skills Training in Diabetes

Prediabetic individuals or those with diabetes should receive individualized nutritional education, preferably provided by a registered dietitian familiar with diabetes nutritional education. Behavioral factors (including missing meals, alcohol intake, lack of exercise, and poor recognition of the need to self-treat) also contribute to hypoglycemia risk. These risk factors can be modified with patient education (Boyle et al. 2007).

Autonomy in daily treatment will enable patients to introduce behavioral adaptations in their daily life, thereby allowing them to control the disease throughout their life-span. Nutritional education would allow for a permanent, voluntary, and conscious change in habits and eating behaviors. Eating behavior appears to be a reflection of the individual's personality, with its strengths and weaknesses; rational beliefs; and family and personal history. Major barriers to weight loss that are often overlooked are psychological and behavioral factors. Many people eat in response to negative emotions. To save time, questionnaires can be sent out to the patient as a means of self-evaluation before their weight management appointment; the successful completion of the questionnaires can serve as an indicator of the patient's level of motivation and compliance. Psychological evaluation should include determining possible underlying depression. If the patient is found to be suffering from depression, this factor should be considered as part of the patient's weight management (Plodkowski et al. 2003).

The six key behaviors (strategies) that successful weight-loss maintainers use include (i) a low-calorie, low-fat diet; (ii) eating breakfast; (iii) consistent patterns of eating; (iv) high levels of physical activity; (v) regular self-monitoring of weight; and (vi) preventing weight regains from turning into big relapses (Wing et al. 2001). Diabetes requires a substantial degree of patient involvement for effective self-management. Although diabetes education has been the standard of care, it is clear that provision of knowledge alone does not change behavior. Coping skills training (Fig. 211.2) is a cognitive–behavioral intervention that focuses on improving competence and mastery by retraining
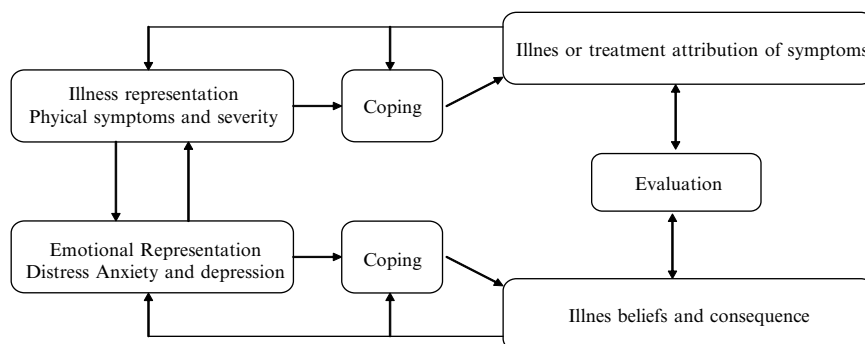

Fig. 211.2 A dynamic model of coping skills training in health and Illness. This model includes the treatment perceptions and the common-sense model of self-regulation behaviors. It reflects a dynamic interaction between the three stages (representation, coping, and appraisal) and parallel processing: cognitive and emotional processes may operate independently, although they generally interact

inappropriate or nonconstructive coping styles and patterns of behavior into more constructive behavior.

Cognitive–behavioral modification is comprised of three steps: (i) recognition of thoughts and feelings; (ii) problem solving; and (iii) guided self-dialogue. The first step is encouraging the individual to reflect on how they think and then respond to situations. The individual's thoughts are then assessed to determine whether the thoughts are based on fact or assumption. Once the thoughts are assessed, the next step is to solve the patient's social problem(s). The third step is teaching the individual to use his or her thoughts to guide the decision made in the previous step. A pen and paper should be used when teaching this skill. Group members can list their negative thoughts and then the member and the group can formulate alternate positive thoughts to counter the negative thoughts (Grey et al. 2004). However, further studies on the relationship between behavioral interventions using problem solving and glycemic and psychosocial outcomes in adults should be carried out. Coping skills training may still be an important methodology for health-care providers to use in assisting patients to control blood glucose levels and lose weight, in combination with nutritional education and exercise to decrease BMI, hypertension, or hyperlipidemia (Grey et al. 2004).

211.3 Gastrointestinal Complications in Diabetes

211.3.1 Overview

GI motility disturbances, including esophageal motor dysfunction, gastroparesis, intestinal enteropathy (which can cause diarrhea and constipation), are often found in a substantial number of patients with diabetes mellitus (Fig. 211.3). Cross-sectional epidemiological studies suggest that the prevalence of GI symptoms is increased in both type 1 and 2 diabetic subjects (Bytzer et al. 2001a). Some studies have noted that the incidence of GI motility disturbances is higher in female diabetic patients than in males (Bytzer et al. 2001b). Gastropathy may result in delayed emptying of solids and ingestible particles, rapid emptying of liquids, bezoar formation, malnutrition, and weight loss.

The causes of GI motility disturbances remain unclear. Autoimmune damage; metabolic insults that alter critical cellular pathways and essential trophic factor signaling, resulting in smooth muscle atrophy and neural apoptosis; and transdifferentiation (Horvath et al. 2006; Rayner et al. 2006) have been suggested as causes in the literature. Other potential etiologies of intestinal dysfunction in patients with diabetes include ischemia and hypoxia due to microvascular disease of the GI tract; mitochondrial dysfunction (Leinninger et al. 2006); the formation of irreversible, advanced glycation end products; and peroxynitrite-mediated endothelial and enteric neuron damage (Hoeldtke et al. 2002). In vitro studies also suggest that hyperglycemia can induce apoptosis of enteric neurons and impair phosphatidylinositol 3-kinase (PI3K) pathway activity. However, apoptosis can be prevented by glial cell-derived neurotrophic factors (Rayner et al. 2006; Leinninger et al. 2006).

Several issues should be considered while treating a patient with GI dysmotility, such as the patient's nutritional status, pain management, prokinetic therapy, symptom suppression, and the consideration of endoscopic or surgical management. Attention to nutritional status is of paramount importance in the management of these patients. Specific deficiencies should be identified and appropriate replacements instituted (Sellin et al. 2008).
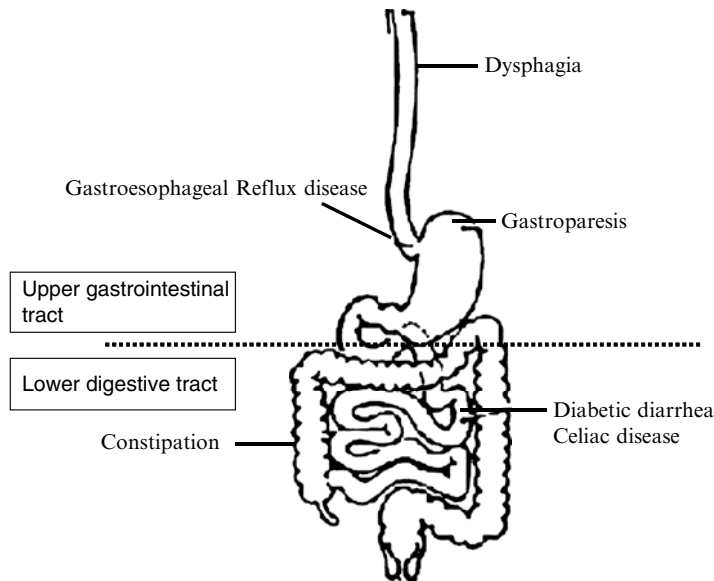
Fig. 211.3 Possible complications involved in gastrointestinal motility disorder. Diabetes can potentially affect any part of the gastrointestinal tract. The common gastrointestinal complications of diabetes include dysphagia, gastroesophageal reflux disease, gastroparesis, diarrhea, and constipation

211.3.2 Esophageal Complications and Treatment

Up to 50% of diabetic patients have esophageal abnormalities, including GI motility disturbances and/or acid reflux (Kinekawa et al. 2001). In a previous study, esophageal symptoms were found to be slightly more prevalent in patients with diabetes than in control subjects; however, they were proportionately less common than measured changes in motility (Talley 2003).

Esophageal complications of diabetes can be successfully treated. Gastroesophageal reflux disease (GERD) can be managed effectively with medicines that are conventionally used to reduce acid reflux. Antireflux surgery, however, is recommended only for patients with disease that is refractory to medical treatment. Patients with oral and esophageal candidiasis are treated effectively by improving glycemic control and administering oral antifungal agents, such as fluconazole. Symptomatic dysphagia, however, is more difficult to manage, particularly in the presence of advanced diabetic motor neuropathy. In these cases, early diagnosis of dysphagia is important, and glycemic control should be resorted to for treating this reversible condition (Sellin et al. 2008).

211.3.3 Diabetic Gastroparesis and Treatments

211.3.3.1 Symptoms and Diagnosis

Diabetic gastroparesis usually occurs during the onset of chronic diabetes; it is a frequent and sometimes troubling complication of the disease. Epigastric fullness, bloating, nausea, and vomiting may be indications of gastroparesis. These symptoms, although nonspecific, are caused by delayed gastric emptying (Lysy et al. 2006). Recurrent symptoms have a deleterious impact on nutrition and

limit the ability of oral hypoglycemic agents to control blood sugar. Recurrent episodes of hyperglycemia have been linked to delay gastric emptying (Lysy et al. 2006). The assumed pathogenesis of this link is that chronic hyperglycemia leads to neuropathic changes and dysfunctional innervations of the stomach and, therefore, to delayed gastric emptying and alteration of antroduodenal motility (Horowitz et al. 2005), which induces a sense of fullness.

Hyperglycemia can limit the efficacy of some prokinetic agents (Rayner et al. 2005). These findings were found to be statistically significant, but it is not clear whether they are clinically meaningful. Nevertheless, glycemic control remains the bedrock of therapy for diabetic gastroparesis. Hormonal changes might also be an important factor in diabetic gastroparesis.

A diagnosis of diabetic gastroparesis is usually made on the basis of the patient's medical history. Physical examination does not usually aid in diagnosis. Delayed emptying of a labeled solid material in the absence of any anatomic abnormalities is considered diagnostic for gastroparesis. Concomitant GI can be ruled out through endoscopy. The most useful diagnostic technique for gastroparesis is nuclear scintigraphy. Other techniques that have been used for diagnosing gastric emptying in previous studies include breath tests, the use of radiopaque markers, electrogastrograms, capsule endoscopy, and measurement of antroduodenal motility (Sellin et al. 2008).

211.3.3.2   Dietary Modification

Products of fat digestion are known to slow gastric emptying, while nondigestible solids may predispose to gastric bezoar formation. Therefore, small-volume, frequent meals, that are low in insoluble fiber and fat are generally recommended, despite a lack of evidence to support this approach (Rayner et al. 2005; Abell et al. 2006) Thorough chewing, remaining upright for 1–2 h postprandially, and supplementation with multivitamins have also been advocated. Increasing the proportion of energy provided as liquids rather than solids may be beneficial because delayed liquid emptying is rare. An elemental diet is limited by unpalatability (Kuo et al. 2007) but may be a short-term option, despite the lack of evidence to support its superiority over polymeric feeding. Total parenteral nutrition is expensive and impractical, and is associated with potentially serious complications, including sepsis.

Indications for nutritional supplementation include weight loss of ≥10% during a period of 3–6 months, inability to maintain recommended body weight, and severe symptoms requiring hospitalization or nonpharmacological intervention (e.g., nasogastric tube to relieve nausea and vomiting) (35,36 Rayner et al. 2005; Abell et al. 2006).

211.3.3.3   Therapeutic Options

Therapy depends on the severity of symptoms, the ability of patients to maintain adequate nutrition, and their responsiveness to therapy. The primary aim of therapy is to optimize glycemic control. Hyperglycemia induces the development of autonomic neuropathy; blood sugar control can be used as a possible approach to reverse abnormal motility. Beyond the critical factor of glycemic control, the treatment of diabetic gastroparesis is similar, in general, to that of regular gastroparesis. Therapies may involve diet modification, pharmacotherapy, and more invasive approaches to treat "gastric failure." A low-fat, low-residue diet accompanied by frequent small meals can minimize postprandial fullness. Avoidance of nutrients that delay gastric emptying (fat, fiber) may also improve gastroparesis (Abell et al. 2006).

Several therapeutic agents (Tables 211.1 and 211.2) are available to treat patients with diabetic gastropathy. These include prokinetic and antiemetic agents, as well as analgesics for pain management.

Table 211.1 Treatment options for gastroparesis disorder

Treatment	Mechanism	Adverse effects	Evidence comments
Metoclopramide (Reglan), 10 mg four times daily	Serotonin(5-HT3)receptor antagonist, central dopanine(102)receptor antagonist	Dystonic reactions, tardive dyskinesia extrapyramidal symptoms hyperprolactinemia	Symptoms improved in 25–62% of patients
	Normalize gastric slow-wave dysrhythmias by inhibiting gastric smooth muscle relaxation produced by dopamine		Physicians should discuss the risk of tardive dyskinesia with their patients and document this discussion in the medical records
Erythromycin 250 mg three times daily	Motilin receptor agonist Prokinetic effects via action on gastroduodenal motilin receptors	Nausca, vomiting abdominal pain: antibiotic resistants	Most studies are open-label design
Bethanechal (Urechaline) 25 mg four times daily	Nonspecific chalinergic muscarinic receptor agonist	Salivation : blurred vision : abdominal cramps and bladder spasm	Not a ture prokinetic agent
Batinlitmen laxin type A (Botox)	Inhibits acetylchaline release from synaptic vosicles in pylorus		Most studies are open-lable design
Surgery	Gastric decompression, partial gastrectomy with Roux-en-Y gastriojejunostomy		No well-designed studies for diabetic gastroparesis studies are nonrandomoized, unblendded, or care series
Gastric electric stimulation	Electric stimulation with high-energy, long-duration pulses	Possible infection, gastric erosion	No well-designed studies; more data are needed

This table lists the key facts of treatment options for gastroparesis. Treatments are listed in order from most to least likely to be used (Sellin et al. 2008). Therapeutic considerations depend on the severity of symptoms, the ability of the patient to maintain adequate nutrition and their responsiveness to therapy. Generally, more severe symptoms still require pharmacologic intervention

Table 211.2 Common used prokinetic drugs

Drug	Mechanism of action	Administration route	Dose(mg)	Adverse reactions
Erythromycin	Motilin agonist	IV, oral	50–250 (3-4 times per day)	Nausea, vomiting, abdominal pain, arrhythmia
Cisapride	5-HT4-receptor agonist: 5-HT3-receptor antagonist	Oral	10-20 (2-4 times per day)	Arrhythmia, abdominal pain, diarrhoea, headache
Metoclopramide	D2-receptor antagonist: 5-HT3-receptor antagonist; 5-HT4-receptor agonist	IV, SC, IM, oral	10	Dystomia, tardive dyskinesia, sedation, hyperprolactinaemia
Domperidone	D2-receptor antagonist	Oral	10–20 (2-4 times per day)	Hyperprolactinaemia, dry mouth, headache

This table lists the key facts of the most commonly used prokinetic agents include metoclopramide, domperidone, erythromycin and cisapride. The mainstay of pharmacological therapy of the gastroparesis is the use of prokinetic agents. The aim of therapy is to improve symptoms by accelerating gastric emptying, despite a poor correlation between the two (Kuo et al. 2007)

5-HT serotonin, *D* dopamine, *IM* intramuscular, *IV* intravenous, *SC* subcutaneous

The prokinetic effect is theoretically elicited through a coordinated set of pressure waves moving through the antrum, pylorus, and duodenum. However, there is little evidence of their efficacy in GI motor disorders; further, they are associated with a high prevalence of side effects outside of the GI tract. Both metoclopramide and domperidone are antagonists of dopamine receptors that may inhibit gastric emptying, although the dopamine receptor-mediated pathway in the brain stem may regulate nausea. Metoclopramide and domperidone exert their therapeutic effect by blocking these actions. Metoclopramide can also act as an agonist of 5-hydroxytryptamine receptor subtype 4 (5HT-4) to stimulate the cholinergic neural pathway in the stomach (Kuo et al. 2007). Metoclopramide is the most widely used drug for the treatment of diabetic gastroparesis because it brings about short-term improvements in both symptoms and gastric emptying rates. Patients are often treated with meto-clopramide for long-term management of diabetic gastroparesis, but its real efficacy has not been proven (Camilleri et al. 2007).

Erythromycin acts as a molecular mimic of motilin to stimulate motor activity, primarily in the upper GI tract. Erythromycin binds to the motilin receptor and initiates similar biologic effects. Erythromycin administered in low doses (50–100 mg) will effectively correct gastroparesis even in patients with refractory symptoms. Erythromycin administered intravenously and as an oral liquid suspension are more potent prokinetic agents than the tablet form (Abell et al. 2003). Cisapride and tegasorod are 5HT-4 agonists that induce the release of acetylcholine from myenteric cholinergic neurons along the GI tract. They are available in both tablet and suspension form (Lata et al. 2003).

There are also some innovative approaches to treat diabetic gastroparesis. An intrapyloric injection of botulinum toxin may decrease pylorospasms associated with gastroparesis and can improve symptoms (Jones 2002). Moreover, no serious adverse effects have been noted. Gastric electrical stimulation as a therapeutic modality for diabetic gastroparesis is an attractive concept that involves surgical intervention; however, the device sometimes has to be removed because of complications (Bromer et al. 2005). In individuals who are undernourished, enteral feeding can be an option. Nevertheless, surgery for treating gastroparesis should be resorted to as a last option; however, post-operative complications limit the efficacy of surgical intervention in the treatment of diabetic gastro-paresis (Abell et al. 2003).

In sum, complications can most often be resolved with simple approaches such as dietary modi-fication. As the severity of symptoms increases, a more aggressive approach must be considered if patients fail to respond to more conventional approaches. However, possible therapeutic options are limited and are not necessarily evidence based.

211.3.4 Intestinal Complications and Treatments

211.3.4.1 Diarrhea

Diarrhea is a more clinically relevant and troubling problem in patients with diabetes. There are at least two possible causes of diabetic diarrhea. The first is impaired adrenergic regulation of fluid and electrolyte transport secondary to decreased α2-adrenergic input. The second is slow intestinal transit and subsequent bacterial overgrowth. Nonetheless, multiple other etiologic factors must be considered in the clinical evaluation of diabetic diarrhea. Possible etiologies include rapid intestinal transit, bacterial overgrowth, medications (e.g., metformin, acarbose, or miglito), the use of artificial sweeteners, celiac disease, pancreatic insufficiency, or nondiabetic diarrhea.

It is commonly assumed that the rate of small bowel transit is reduced, leading to bacterial over-growth in patients with diabetes. However, rapid gastric emptying can also accompany decreased intestinal transit times. Individuals with diarrhea and associated autonomic neuropathy, primarily

diabetic, can have an extremely rapid orocecal transit time (<20 min) and a positive glucose or lactulose hydrogen breath test (Watkins et al. 2003). Differentiation of rapid-transit from slow-transit diarrhea is important. Antibiotic treatment is appropriate for slow-transit diarrhea with bacterial overgrowth, whereas rapid-transit diarrhea might be more effectively treated with more conventional antimotility drugs such as loperamide.

Therapeutic strategies should be specifically tailored to target the underlying pathophysiology, which include diet modification for patients with celiac disease or rotating antibiotics for those with bacterial overgrowth in the small bowel. If the specific cause of diarrhea cannot be identified, empiric therapy with basic antidiarrheal agents (e.g., loperamide) is a reasonable starting point. A trial of clonidine is an option for patients in whom it is well tolerated. Although there have been reports on the effectiveness of octreotide in patients with diabetic diarrhea (Camilleri et al. 2007), its use is often not required.

211.3.4.2 Celiac Disease

Between 3% and 8% of individuals with diabetes have celiac disease. Celiac disease is a genetic autoimmune disease in which an immune response is triggered by the consumption of foods containing gluten – wheat, rye, and barley. The disease is characterized by a range of symptoms that can include gas, bloating, diarrhea, weight loss, and other gastrointestinal problems. Most people who have celiac disease do not know they have it, and some are asymptomatic. The symptoms are diverse and nonspecific (Hill et al. 2005). The introduction of the tissue transglutaminase test (TTG) (Greenberg 2008) has simplified the diagnosis of celiac disease.

Celiac disease is treated entirely through dietary management, which consists of removal of gluten from the diet; such a gluten-free diet is a lifelong dietary requirement (Table 211.3). Further, temporary nutritional supplementation may be provided to patients suffering from clinical disorders related to celiac-induced nutritional deficiencies. Once a patient has been established on a gluten-free diet, most guidelines recommend annual TTGs to monitor continued intentional or unintentional gluten exposure. In addition, follow-up through dietary review is also considered helpful.

211.3.4.3 Constipation

Constipation and the use of laxatives are relatively common in patients with diabetes (Maleki et al. 2000). The prevalence of constipation is higher in women than in men and is more prevalent among patients with diabetes who are taking medications that promote constipation (e.g., Ca^{2+} channel

Table 211.3 Gluten-free foods

Foods of these types that are fresh (nonprocessed) and unseasoned are gluten free
Meat; fish; milk; juice, coffee; tea; cheese; fruit; vegetables; potatoes; rice; butter; cream; olive oil…
Processed foods that are usually gluten free
Popcorn, corn chips, potato chips; chili; yogurt; Asian soups with rice noodles; ice cream; many candies…
Foods that normally contain gluten can be purchased gluten free
Pasta; pizza; bread; crackers; cookies; cake mixes; soup mixes; soy sauce…

Treatment of celiac disease is entirely through dietary management, which consists of removal of all gluten from the diet. The gluten-free diet is a lifelong dietary requirement. This table lists the key facts if the sorts of gluten-free foods. Patients should be instructed to always check tables packaged foods to ensure that ingredients are gluten free

blockers) (Maleki et al. 2000). In this patient population, constipation most likely results from slow transit caused by smooth muscle myopathy, autonomic neuropathy, or neuroendocrine imbalances.

The radiopaque marker method, a noninvasive technique for measuring colonic stool transit frequency, provides information on segmental colonic transit time. Prolonged colon transit in diabetic patients, particularly in diabetics with constipation compared to those without constipation, may be due to a slow transit in the left and rectosigmoid colon. However, delayed transit is not a specific finding in diabetics, since idiopathic constipation is characterized by either exaggerated reservoir functions of the ascending and transverse colon or an impairment of the propulsive function in the descending colon (Darwazeh 1991).

There are no specific treatments for diabetes-associated constipation, although improved glycemic control may be beneficial (Maleki et al. 2000). In most cases, however, diabetic patients are treated the same way as those with idiopathic chronic constipation. In the absence of defecatory dysfunction, bulking agents, osmotic laxatives (e.g., polyethylene glycol 3,350 powder), and stimulant laxatives can be used. The new Cl-channel agonist, lubiprostone, might also be beneficial, as it has been shown to be effective in patients with chronic constipation (Ambizas et al. 2007).

211.4   Conclusions

- According to the most recent recommendations of worldwide nutrition studies, changes in dietary composition could play a significant role in improving insulin sensitivity and reducing the risk of diabetes and its complications.
- Multiple components of a healthy diet (e.g., high fiber and a low saturated fat intake) reduce diabetes risk and contribute to sustained weight loss.
- Coping skills training may be an important methodology for health-care providers to use in assisting diabetic patients to control blood glucose levels and lose weight, in combination with nutritional education and exercise to decrease BMI, hypertension, or hyperlipidemia.
- Strategies for weight loss include decreasing total energy intake, maintaining a balanced deficit diet, increasing physical activity, and adjusting energy balance to prevent weight regain.
- Gastrointestinal symptoms are common in patients with diabetes, but are also prevalent in the general population. Any part of the gastrointestinal tract can be affected, and presenting symptoms depend on the affected parts.
- Treatment should be directed at tighter glycemic control and reduction of symptoms, which can improve the clinical condition of many diabetic patients. However, in some patients, effective clinical management is problematic because no therapies are available to prevent or treat the underlying disease mechanisms (Camilleri et al. 2007).

Key Terms

Obesity: A condition that is characterized by excessive accumulation and storage of fat in the body and that in an adult is typically indicated by a body mass index of 30 or greater.
Gastroesophageal reflux disease: A highly variable chronic condition that is characterized by periodic episodes of gastroesophageal reflux usually accompanied by heartburn and that may result in histopathologic changes in the esophagus – abbreviation GERD.

Gumbiner B. Treating obesity in Type 2 diabetes: calories, composition and control. Diabetes Care. 1999;22:886–8.

Han TS, Feskens EJ, Lean ME, Seidell JC. Associations of body composition with type 2 diabetes mellitus. Diabet Med. 1998;15:129–35.

Heilbronn LK, Noakes M, Clifton PM. Effect of energy restriction, weight loss, and diet composition on plasma lipids and glucose in patients with type 2 diabetes. Diabetes Care. 1999;22:889–95.

Hill ID, Dirks MH, Liptak GS, Colletti RB, Fasano A, Guandalini S, Hoffenberg EJ, Horvath K, Murray JA, Pivor M, Seidman EG. Guideline for the diagnosis and treatment of celiac disease in children: recommendations of the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition. Pediatr Gastroenterol Nutr. 2005;40:1–19.

Hoeldtke RD, Bryner KD, McNeill DR, Hobbs GR, Riggs JE, Warehime SS, Christie I, Ganser G, Van Dyke K. Nitrosative stress, uric Acid, and peripheral nerve function in early type 1 diabetes. Diabetes. 2002;51:2817–25.

Horvath VJ, Vittal H, Lorincz A, Chen H, Almeida Porada G, Redelman D, Ordog T. Reduced stem cell factor links smooth myopathy and loss of interstitial cells of cajal in murine diabetic gastroparesis. Gastroenterology. 2006;130:759–70.

Horowitz M, Fraser RJ. Gastroparesis: diagnosis and management. Scand J Gastroenterol Suppl. 1995;213:7–16.

Jones MP. Access options for withdrawn motility-modifying agents. Am J Gastroenterol. 2002;97:2184–8.

Kinekawa F, Kubo F, Matsuda K, Fujita Y, Tomita T, Uchida Y, Nishioka M. Relationship between esophageal dysfunction and neuropathy in diabetic patients. Am J Gastroenterol. 2001;96:2026–32.

Kuo P, Rayner CK, Jones KL, Horowitz M. Pathophysiology and management of diabetic gastropathy: a guide for endocrinologists. Drugs. 2007;67:1671–87.

Lata PF, Pigarelli DL. Chronic metoclopramide therapy for diabetic gastroparesis. Ann Pharmacother. 2003;37:122–6.

Leininger GM, Edwards JL, Lipshaw MJ, Feldman EL. Mechanisms of disease: mitochondria as new therapeutic targets in diabetic neuropathy. Nat Clin Pract Neurol. 2006;2:620–8.

Leventhal H, Cameron L. Behavioural theories and the problem of compliance. Patient Educ Couns. 1987;10:117–38.

Lundgren H, Bengtsson C, Blohme G, Lapidus L, Sjo È stro Èm L. Adiposity and adipose tissue distribution in relation to incidence of diabetes in women: results from a prospective population study in Gothenburg, Sweden. Int J Obes. 1989;13:413–23.

Lysy J, Israeli E, Strauss Liviatan N, Goldin E. Relationship between hypoglycaemia and gastric emptying abnormalities in insulin-treated diabetic patients. Neurogastroenterol Motil. 2006;18:433–40.

Maleki D, Locke GR 3rd, Camilleri M, Zinsmeister AR, Yawn BP, Leibson C, Melton LJ 3rd. Gastrointestinal tract symptoms among persons with diabetes mellitus in the community. Arch Intern Med. 2000;160:2808–16.

Mishra GD, Carrigan G, Brown WJ, Barnett AG, Dobson AJ. Short-term weight change and the incidence of diabetes in midlife: Results from the Australian Longitudinal Study on Women's Health. Diabetes Care. 2007;30:1418–24.

National Institutes of Health, National Heart Lung and Blood Institute. Clinical guidelines for the identification, evaluation and treatment of overweight and obesity in adults: the evidence report. Bethesda: US Department of Health and Human Services, Public Health Service, NIH, NHLBI; 1998.

Ohlson LO, Larsson B, Sva È rdsudd K, Welin L, Eriksson H, Whilhelmsen L. The influence of body fat distribution on the incidence of diabetes mellitus: 13 5 years of follow-up of the participants in the study of men born in 1913. Diabetes. 1985;34:1055–8.

Plodkowski RA, St Jeor ST. Medical nutrition therapy for the treatment of obesity. Endocrinol Metab Clin North Am. 2003;32:935–65.

Report of a WHO consultation on obesity. Obesity: preventing and managing the global epidemic. Geneva. 3–5 June; 1997.

Rayner CK, Horowitz M. New management approaches for gastroparesis. Nat Clin Pract Gastroenterol Hepatol. 2005;2:454–62; quiz 493.

Rayner CK, Horowitz M. Gastrointestinal motility and glycemic control in diabetes: the chicken and the egg revisited. J Clin Invest. 2006;116:299–302.

Sellin JH, Chang EB. Therapy Insight: gastrointestinal complications of diabetes pathophysiology and management. Nat Clin Pract Gastroenterol Hepatol. 2008;5:162–71.

Shakil A, Church RJ, Rao SS. Gastrointestinal complications of diabetes. Am Fam Physician. 2008;77:1697–702.

Talley NJ. Diabetic gastropathy and prokinetics. Am J Gastroenterol. 2003;98:264–71.

UK Prospective Diabetes Study (UKPDS). Group. Response of fasting plasma glucose to diet therapy in newly presenting type II diabetic patients (UKPDS 7). Metabolism. 1990;39:905–12.

Watkins PJ, Buxton Thomas MS, Howard ER. Long-term outcome after gastrectomy for intractable diabetic gastroparesis. Diabet Med. 2003;20:58–63.

Wing RR, Hill JO. Successful weight loss maintenance. Annu Rev Nutr. 2001;21:323–41.

Part XXXVII
Other General or Specific Conditions

Chapter 212
The Impact of Health-Promoting Media-Literacy Education on Nutrition and Diet Behavior

Lynda Bergsma and Elizabeth Ferris

Abbreviations

BMI	Body Mass Index
EDI-2	Eating Disorders Inventory-2
EDI-BD	Eating Disorders Inventory-Body Dissatisfaction Scale
MAQ	Media Attitudes Questionnaire
PACS	Physical Appearance Comparison Scale
PANAS	Positive and Negative Affect Schedule
PASTAS-W	Physical Appearance State and Trait Anxiety Scale – Weight
Q-EDD	Questionnaire for Eating Disorder Diagnosis
RSES	Rosenberg Self-Esteem Scale
SATAQ	Sociocultural Attitudes Towards Appearance Questionnaire
SCT	Social Cognitive Theory
SLT	Social Learning Theory
SPPA	Self-Perception Profile for Adolescents
TPB	Theory of Planned Behavior
TRA	Theory of Reasoned Action

212.1 Introduction

Public health professionals increasingly recognize that the media have a significant influence on the behavior of young people with regard to nutrition, dieting, eating disorders, body image, overweight, and obesity. In their review of research on the media's influence on health, the Committee on Public Education of the American Academy of Pediatrics (2001) stated that research has shown primary negative health effects on body concept, self-image, nutrition, dieting, and obesity.

L. Bergsma (✉)
Mel & Enid Zuckerman College of Public Health, University of Arizona,
P.O. Box 245209, Tucson, Arizona 85724
e-mail: lbergsma@u.arizona.edu

Some researchers estimate that youth spend 33–50% of their waking hours with some form of mass media (Strasburger and Wilson 2002). Children and teens are spending an increasing amount of time using "new media" like computers, the Internet, and video games, without cutting back on the time they spend with "old" media like TV, print, and music. A recent study found that the total daily media exposure of young people increased from 7:29 to 8:33 h between 2000 and 2005, counting time as double when multitasking with two different forms of media (Kaiser Family Foundation 2005). The large amount of time youth spend with media makes it critical to address related health concerns.

Public health professionals have used many strategies to address the effects of media on health. Regulating media content, limiting children's media use, and social marketing are approaches that have been used traditionally, but media literacy education has emerged in the last 20 years as a promising alternative to the censorship of regulating "unhealthy" programming or limiting media use (Heins and Cho 2003). Media literacy has been defined as "the ability to access, analyze, evaluate, and create media in a variety of forms" (Thoman and Jolls 2005). Rather than trying to protect youth from potentially harmful messages, media literacy education to promote health involves them in a critical examination of media messages that influence their perceptions and practices. It is designed to give youth the critical thinking skills necessary to ameliorate the influence of these messages and make healthy choices (Bergsma and Carney 2008).

212.2 Theoretical Foundations

The theoretical foundations for health-promoting media literacy education derive from a combination of the Theory of Reasoned Action (TRA), in which a causal chain of beliefs, attitudes, and behavioral intentions drives *behavior* at the individual level, while Social Learning Theory (SLT) explains that people are learning at the interpersonal level not only from their own experiences, but by observing the actions of others and the benefits of those actions (Glanz and Rimer 2005).

At the interpersonal level, theories of health behavior assume that individuals exist within and are influenced by a social environment. The opinions, thoughts, behavior, advice, and support of the people surrounding an individual influence his or her knowledge, beliefs, attitudes, and behavior. The social environment of youth includes many influences, primary among which are family, friends, school, and the media. It is social learning that is examined in media effects research; for example, see "The Role of Media in Childhood Obesity" (Kaiser Family Foundation 2004) that reviews more than 40 studies on the role of media in the dramatically increasing rates of childhood obesity in the United States.

Social Cognitive Theory (SCT), which evolved from SLT, has been used successfully as the underlying theory for behavior change in areas ranging from dietary change (Baranowski et al. 1993) to pain control (Lorig et al. 1999). Integrating concepts and processes from cognitive, behaviorist, and emotional models of behavior change, it includes the constructs of reciprocal determinism, behavioral capability, expectations, self-efficacy, observational learning, and reinforcement.

212.2.1 Constructs of Health-Promoting Media Literacy Education

Social Cognitive Theory and the Theory of Planned Behavior (TPB), which evolved from the TRA, contain the same additional behavioral construct – that of self-efficacy or perceived locus of control – which falls within the category of individual empowerment. This empowerment construct is also clearly a component of media literacy education. Pioneer media literacy educator Elizabeth Thoman advocates a philosophy of empowerment through media literacy education, based on the work of Paulo Freire (1970, 1973). At the heart of this philosophy is an inquiry process developed into a

construct called the empowerment education spiral and consisting of four components – awareness, analysis, reflection, and action – all designed to enable people to fully comprehend and act upon the content, form, purpose, and effects of media messages (Thoman and Jolls 2005). From a public health perspective, Bergsma (2004) shows that the pedagogical links between health promotion and media literacy can be traced to Freire's empowerment education model.

In addition to *empowerment*, three other constructs must be included within a health-promoting media literacy education intervention to change beliefs, attitudes, intentions, and behaviors. In health promotion, it is generally accepted that knowledge is necessary but insufficient to change health behavior. Therefore, while media literacy education has a knowledge construct that provides information about such things as how and why different forms of media operate as they do, including the manipulating design of advertising, this knowledge alone will seldom result in behavior change, although health-promoting media literacy education research clearly shows that *knowledge about the media and the health issue* can change beliefs and attitudes (Bergsma and Carney 2008). Finally, media literacy education must help people develop the *habits of inquiry* and the *critical analysis and expression skills* that they need to be critical thinkers (National Association for Media Literacy Education 2007) about the health issue, and therefore better informed for making decisions about behavior change.

Health-promoting media literacy education to achieve behavior change addresses people at both the individual level and the intrapersonal level of social interaction with, and learning from, media messages of all kinds, including those from narrative contexts such as film and persuasive contexts such as advertising and promotion. Figure 212.1 posits an integrated individual and interpersonal model for achieving behavior change in which the four constructs of health-promoting media literacy education act as buffering influences between the media environment in which we live (outside the model) and the individual and interpersonal behavioral change constructs of the Theory of Planned
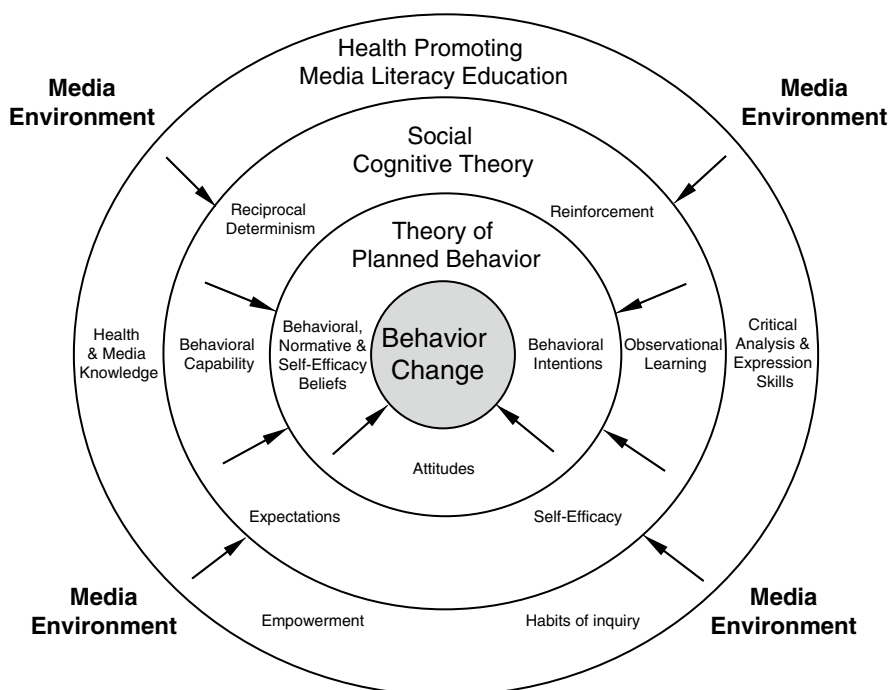

Fig. 212.1 Integrated individual and interpersonal health-promoting media-literacy education model. This figure presents an integrated model of behavior change that involves providing the health information and media literacy life skills necessary for living in a media-saturated environment that can undermine health lifestyle choices

Behavior and Social Cognitive Theory. It is important to note that within these theoretical contexts, people can be influenced both positively and negatively by media messages, resulting in behavior change that is healthy or unhealthy. Health-promoting media literacy education helps establish the media and health knowledge, critical analysis and expression skills, habits of inquiry, and individual empowerment that potentially will lead individuals to make healthy decisions for themselves. It is within this context that we next explore the research literature on the use of health-promoting media literacy education to address dietary-related public health concerns.

212.3 Review of the Literature

212.3.1 Study Selection

A total of 23 studies were reviewed for possible inclusion in this literature review, and five studies were ultimately selected. Studies were reviewed using the criteria established for a prior systematic review of the effectiveness of health-promoting media literacy education (Bergsma and Carney 2008) as follows:

- Studies were published in English from 1990 to December 2008.
- Studies were peer reviewed or dissertations and publicly available via a searchable index.
- Studies described the sample, study design, intervention, and evaluation measures.
- Studies included an experimental media literacy intervention that focused on improving nutrition or reducing eating disorders in youth.
- The media literacy intervention was longer than 25 min.
- Studies focused primarily on teaching critical media literacy skills, and the media literacy intervention was not a smaller part of a larger curriculum.

Six studies were excluded because they did not meet these primary selection criteria. From the remaining 17 studies, five studies were selected to explore here (Table 212.1) because they provided a representative sample of all of the studies examined, they demonstrated effectiveness or served as a foundational study for subsequent research, they were conducted over a 10-year period from 1998 to 2008, they focused on eating disorder prevention, they dealt with study populations of diverse ages, they utilized somewhat similar study designs but diverse intervention lengths ranging from 45 min to 9 h, and they took place in different settings including classroom, community, and laboratory (Table 212.2). They also taught a majority of the five media-literacy concepts (Table 212.3) and they utilized many of the same measurement tools (Table 212.4).

Table 212.1 Five studies selected for review

1. The effect of media analysis on attitudes and behaviors regarding body image among college students (Rabak-Wagener et al. 1998)
2. Primary prevention of disordered eating among preadolescent girls: Feasibility and short-term effect of a community-based intervention (Neumark-Sztainer et al. 2000)
3. Comparison of media-literacy programs to strengthen college women's resistance to media images (Irving and Berel 2001)
4. Media literacy as a prevention intervention for college women at low- or high-risk for eating disorders (Coughlin and Kalodner 2006)
5. The effectiveness of media literacy and eating disorder prevention in schools: A controlled evaluation with 9th grade girls (Dysart 2008)

This table presents the titles of the five studies reviewed in this chapter along with the citation for each study

Table 212.2 Key points for comparison of studies

Study author(s)	Rabak-Wagener et al. (1998)	Neumark-Sztainer et al. (2000)	Irving and Berel (2001)	Coughlin and Kalodner (2006)	Dysart (2008)
Focus	To investigate how a media literacy education intervention that focused on critiquing popular fashion advertisements and creating more inclusive fashion advertisements would affect beliefs and behaviors about individual body image	To promote body acceptance and prevent dieting behaviors among preadolescent girls via enhancement of media literacy and advocacy skills.	To compare the effectiveness of two distinct media literacy interventions at reducing body dissatisfaction and increasing skepticism about media messages that depict a thin ideal of beauty	To reduce eating disorder risk factors, particularly internalization of the thin body ideal and body dissatisfaction, and to determine the degree to which level of risk for an eating disorder (low or high) interacts with the effects of media literacy	To reduce primary eating disorder risk factors, including sociocultural attitudes toward appearance, self-perception, relevant eating disorder behaviors, body dissatisfaction, drive for thinness, bulimia behaviors, thin body ideal internalization, self-esteem, and anxiety about physical appearance.
Theoretical basis	Media advocacy reframing theory	None discussed	Cognitive model of emotional response and the message interpretation process model (Austin and Johnson (1997))	Sociocultural model of eating disorders and cognitive–behavioral theory	Social cognitive theory, cognitive dissonance theory, cognitive–behavioral theory, social comparison theory, Identity theories of psychosocial development, and feminist theories
Sample population (n)	105 female & male undergraduate students from healthful living classes at a medium-sized metropolitan university in the Midwest U.S., aged 18–23. Intervention = 44 women & 16 men Control = 31 women & 15 men	226 female fifth and sixth grade students from 24 Midwestern Girl Scout troops, average age 11. Intervention = 115 Control = 111	110 female college students from an introductory psychology classes at Washington State University, average age 19. Internally oriented intervention = 31 Externally oriented intervention = 27 Video-only intervention = 28 Control = 24	92 female undergraduate students in introductory women's studies courses at a rural university, average age 20. Intervention = 45 (26 low-risk & 19 high-risk) Control = 47 (31 low-risk & 16 high-risk)	62 female high-school students from a private school in North Carolina, aged 14–15. Intervention = 31 Control = 31
Research design	Pretest post-test design	Pretest, post-test, and 3-month retest design	Pretest post-test design with three experimental groups and a control group	Pretest delayed post-test (8 weeks) design	Pretest, post-test, and multiple retest (6 weeks and 6 months) design
Setting	In class	Community based	Lab/classroom small groups of 2–6	In class	In class, 3 small groups/condition
Length	6.5 h	9 h	45 min	3 h	5.3 h
Teacher	Researcher and instructor	Girl scout troop leader	Researcher	Researcher	Researcher

This table lists key points from the five studies reviewed in this chapter, including study author(s), study focus, theoretical basis for study, sample population of study, research design used in study, setting and length of study, and study intervention teacher

Table 212.3 Media literacy core concepts included in study interventions

Study author(s)	Media literacy concepts included[a]
Rabak-Wagener et al. (1998)	1,2,4,5
Neumark-Sztainer et al. (2000)	1,2,3,4
Irving and Berel (2001)	1,3,4
Coughlin and Kalodner (2006)	1,2,3,4
Dysart (2008)	1,2,3,4,5

This table shows which of the five core concepts of media literacy listed below were included in each of the studies reviewed

[a]Numbers refer to *Media Literacy Core Concepts* (Thoman and Jolls 2005) taught as follows:

1. *All media messages are constructed.* Intervention taught about how the media differs from reality, evaluating what is shown compared to real life experiences.

2. *Media messages are created using a creative language with its own rules.* Intervention taught about recognizing advertising/production techniques or creating/producing media messages.

3. *Different people experience the same message differently.* Intervention explored how media affects different people, what people can do to avoid negative effects of media, or that people can take action to change the media.

4. *Media have embedded values and points of view.* Intervention taught how to identify stereotypes, myths, biases, values, lifestyles, and/or points of view represented in or omitted from media messages.

5. *Most media messages are constructed to gain profit and/or power.* Intervention taught about the purpose of advertising or marketing strategies, skepticism toward advertising, or creating counteradvertising. (Bergsma and Carney 2008)

The five studies discussed in this literature review examine the impact of health-promoting media literacy education on nutrition and diet behavior among youth and adolescents. The studies focus specifically on media literacy interventions that seek to reduce a composite of eating disorder risk factors and assess changes in media-related knowledge, attitudes, and behaviors. The goal in developing media literacy interventions that teach young girls to think critically about media messages that promote thinness is to prevent body dissatisfaction and subsequent eating disorders (Berel et al. 1998; Levine and Smolak 2006).

Following is a close examination of each of the five health-promoting media literacy education intervention studies (Table 212.1), in order of the date of the study from oldest (1998) to most recent (2008), for the purpose of identifying what is known and what still needs to determined about the impact of health-promoting media literacy education on nutrition and diet behavior.

212.4 Study Details

212.4.1 First Study Title: The Effect of Media Analysis on Attitudes and Behaviors Regarding Body Image Among College Students (Rabak-Wagener et al. 1998)

The overall goal of this study was to determine how college students' beliefs and behaviors about their body image were affected by participating in media analysis, specifically analyzing and reframing fashion advertisements. The study is unique among the studies reviewed here in that the study population (n = 105) included both men and women between the ages of 18 and 23. The study utilized a pretest, post-test only design, with one intervention (44 women and 16 men) and one control group (31 women and 15 men).

Table 212.4 Measures utilized

Study author(s)	Rabak-Wagener, et al. (1998)	Neumark-Sztainer et al. (2000)	Irving and Berel (2001)	Coughlin and Kalodner (2006)	Dysart (2008)
Measures[a]	11-item survey to measure beliefs and behaviors regarding fashion advertising images	Dieting behaviors Perceived Weight status Knowledge about body changes during puberty Print media Habits Self-efficacy to affect weight-related social norms Perceived satisfaction Perceived affect Body satisfaction Scale – 6-item version (Slade et al. 1990) Sociocultural Attitudes Towards Appearance Questionnaire (SATAQ) (Heinberg et al. 1995)	Eating Disorder Inventory (EDI-2) (Garner 1991) Physical Appearance State and Trait Anxiety Scale (PASTAS) (Reed et al. 1991) Sociocultural Attitudes Towards Appearance Questionnaire SATAQ (Heinberg et al. 1995) Media Attitudes Questionnaire MAQ (Irving et al. 1998) Positive and Negative Affect Scale (PANAS) (Watson et al. 1988)	Questionnaire for Eating disorder diagnosis (Q-EDD) (Mintz et al. 1997) Eating Disorder Inventory EDI-2 (Garner 1991) Sociocultural Attitudes Toward Appearance Questionnaire SATAQ (Heinberg et al. 1995) Personal Appearance Comparison Scale PACS (Thompson et al. 1991)	Self-Perception Profile for Adolescents (SPPA) (Harter 1998) Eating Disorder Inventory (EDI-3) (Garner 2004) Sociocultural Attitudes Towards Appearance Questionnaire (SATAQ-3) (Thompson et al. 2004) Rosenberg Self-Esteem Scale (RSES) (Rosenberg 1965) Physical Appearance State and Trait Anxiety Scale (PASTAS) (Reed et al. 1991) Media Attitudes Questionnaire (MAQ) (Irving et al. 1998)

This table provides a comparison of the measures utilized in the studies reviewed, in order to determine which studies used the same measures and which used different measures. Note that several of the studies adapted the measures and did not use all items from every measurement tool

[a]Measures with no citation were developed specifically for the study

212.4.1.1 Intervention Design

The intervention took place in a college classroom over a total of 6.5 h and was delivered by the researcher and an undergraduate course instructor. The intervention group first watched the video *Slim Hopes* (Kilbourne 1995) and then discussed fashion industry norms and critically analyzed fashion advertisements. The intervention made an effort to include analysis of male and female fashion advertisements, though the video content was focused primarily on females. Finally, the intervention included a creative component in which the students reframed fashion advertisements.

212.4.1.2 Measures

The researchers developed an 11-item survey instrument to measure beliefs and behaviors pertaining to fashion advertising images. Using a 7-point Likert-type scale, study participants responded to behavior statements such as "I make decisions about dieting or exercise based more upon how I look than on my health status," and belief statements such as "Adult models in advertisements have an ideal body size and shape."

212.4.1.3 Results

At pretest, both the intervention and control group strongly agreed with the following behavior statement more than any other: "I make decisions about dieting or exercise based more upon how I look than on my health status." While the intervention group demonstrated significant changes in beliefs about body image when compared to the control group, there were no significant changes in behavior. When analyzing the data by gender, however, the study revealed that women in the intervention group did, in fact, show significant changes in both body image beliefs and behaviors, indicating that the study was more successful among women than men, and that behaviors are more difficult to change than beliefs.

212.4.2 Second Study Title: Primary Prevention of Disordered Eating among Preadolescent Girls: Feasibility and Short-Term Effect of a Community-Based Intervention (Neumark-Sztainer et al. 2000)

For this study the researchers designed and evaluated a community-based intervention, entitled *Free to Be Me*, to promote body acceptance and prevent unhealthy dieting behaviors among preadolescent girls via the enhancement of media literacy and advocacy skills (Neumark-Sztainer et al. 2000). The study included an intervention (n=115) and control group (n=111) of 226 fifth and sixth grade Girl Scout troop members, average age 11 years, and used a pretest, post-test, 3-month retest design.

212.4.2.1 Intervention Design

The intervention focused on the interaction between socioenvironmental, personal, and behavioral factors, following the Social Cognitive Theory concept of reciprocal determinism. The girls learned steps to combat the negative impact of media on their body image and self-esteem by comparing

body types of real women to those seen in magazines, analyzing magazines and television commercials for positive and negative media messages and imagery, and creating and performing commercials or skits with positive messages about body image and self-esteem. They were also encouraged to increase their sense of self-efficacy to combat weight-related social norms presented in the media. The intervention took place over six 90-min sessions and was conducted by Girl Scout troop leaders. The published study includes a detailed content outline of the intervention sessions.

212.4.2.2 Measures

Measures included dieting behaviors; body-related knowledge and attitudes; media-related knowledge, attitudes, and behaviors; and program satisfaction and perceived effect. Participants were asked about specific dieting behaviors over the past month such as if they were currently trying to lose weight, had started a diet, or tried to lose weight to look like girls on television. The study also measured unhealthy eating behaviors including taking laxatives, skipping meals, purging, using diet pills, and perceived binge eating.

To measure body-related knowledge and attitudes, participants reported their perceived weight status ("underweight," "somewhat underweight," "just the right weight," "somewhat overweight," or "overweight"). A 6-item version of the Body Satisfaction Scale (Slade et al. 1990) was used to produce a summary body satisfaction score concerning attitudes toward participants' height, weight, body shape, thighs, stomach, and face. True/false questions were used to assess knowledge of how one's body changes during puberty, while the Sociocultural Attitudes Towards Appearance Questionnaire (SATAQ) (Heinberg et al. 1995) measured acceptance of various body types.

Another item adapted from the SATAQ was used to measure internalization of the media's ideal body image, as well as participants' knowledge of the media's effect on their body image, food choices, and dieting behaviors. To study the print media choices of the participants, they were asked about their reading behaviors and intentions (read, plan to read, never read) regarding several magazines aimed at adolescent females, including *Girl's Life, American Girl, New Moon*, and *Seventeen. American Girl* and *New Moon* were considered more positive media choices than the other magazines, based on their lack of advertising and focus on promoting self-esteem as opposed to fashion. Self-efficacy to affect weight-related norms in the media and within one's peer group was assessed with a seven-item scale developed for this study that included statements such as: "I can do something about the types of advertisements shown on TV and in the magazines," and "If someone teased one of my friends about her body size, I would stand up for her and try to be supportive"(Neumark-Sztainer et al. 2000).

Other aspects the researchers took into account were program satisfaction overall, satisfaction with specific activities, and the participants' perceived effect on their attitudes and behaviors. Perceived effect was assessed with questions such as, "Do you think the program helped you to feel better about yourself?"

212.4.2.3 Results

At baseline, 30% of the participants indicated that they were trying to lose weight and perceived themselves to be overweight, but fewer girls reported they had tried to lose weight to look like girls on television or had used unhealthy dieting behaviors. Overall there were no statistically significant changes in dieting behavior, although the trend was in a positive direction. While at post-test 20% indicated they were trying to lose weight (less than at baseline), at follow-up that number increased to 25%, the same as reported by the control group. The intervention had a modest post-test impact on body-related knowledge and attitudes, but this also was not sustained at 3-month follow-up.

The intervention had significant impact on media-related behaviors. At post-test and follow-up, when compared to the control group, intervention participants reported a significant increase in self-efficacy to combat weight-related social norms and showed a significant decrease in internalization of the thin body ideal portrayed in the media. Intervention participants were also significantly less likely than those in the control group to have read *Seventeen* magazine at post-test and 3-month follow-up, opting instead for the more girl-friendly publication *New Moon.* A majority of the participants and Girl Scout troop leaders indicated overall satisfaction with the program.

212.4.3 Third Study Title: Comparison of Media-Literacy Programs to Strengthen College Women's Resistance to Media Images (Irving and Berel 2001)

This study examined whether two distinct and brief (45 min) media-literacy interventions could reduce negative body image in a sample of college women (n=110) and promote media skepticism about the realism, similarity, and desirability of media messages that depict a thin ideal of beauty. The study compared both an internally oriented intervention to address negative body image and internalization of the thin ideal (n=31) and an externally oriented intervention to address media skepticism (n=27). In addition to the two intervention groups, the pretest, post-test research design also included a video-only intervention (n=28) and control group (n=24). The average age of the study group was 19.

212.4.3.1 Intervention Design

Participants in the externally oriented intervention were encouraged to think critically about the media and challenge unhealthy messages at three levels: personal, interpersonal, and societal. First, they watched a 15-min abridged version of the *Slim Hopes* video (Kilbourne 1995) and then they participated in group discussion and learned to evaluate media by asking the "3 Rs" questions: (1) Is it real? (2) Is it right? and (3) How do I reinforce these messages in my own life? (Austin and Johnson 1997).

Participants in the internally oriented intervention also viewed the abridged version of *Slim Hopes* and participated in group discussion, but unlike the externally oriented intervention, this group went on to discuss how media exposure compounds negative body image and to learn about body image constructs, including perceptions, beliefs, attitudes, and behaviors. Participants also learned how to self-monitor their negative body image thoughts and take steps to ensure that media exposure does not increase them.

The video-only group watched the abridged *Slim Hopes* video and participated in a short discussion, for a total of 15 min. All intervention participants completed a pretest before the intervention and a post-session questionnaire immediately after the intervention, while women in the no-intervention control group completed the questionnaire only. At the end of all four conditions, the investigator distributed postcards from About-Face, a San Francisco-based media activism organization (www.about-face.org).

212.4.3.2 Measures

The study measured body dissatisfaction, media skepticism, intention to engage in media activism, and changes in affect as a result of the interventions. Body dissatisfaction was assessed with the Eating Disorders Inventory-Body Dissatisfaction (EDI-BD) scale (Garner 1991), and awareness and

thin ideal internalization were measured using the Sociocultural Attitudes Towards Appearances Questionnaire (SATAQ) (Heinberg et al. 1995). Anxiety about weight and physical appearance was assessed with the Physical Appearance State and Trait Anxiety Scale-Weight measure (PASTAS-W) (Reed et al. 1991).

Prior to study participation, participants completed the Media Attitudes Questionnaire (MAQ) (Irving et al. 1998), to assess media skepticism, and provided information on Body Mass Index (BMI). The 22-item MAQ includes six subscales that assess perceived realism of media images, perceived similarity to models portrayed in media, desirability of looking like models portrayed in media, identification with models portrayed in media, positive expectancies associated with being thin, and intentions to engage in dieting behavior. No pretest was performed regarding body image and internalization variables, and specific dieting behaviors were not measured in the study.

Intention to engage in media activism was assessed by providing participants, immediately after the post-test, with postcards to send to the media activism organization in order to receive free information, and tracking how many postcards were sent. Finally, changes in affect as a result of the various interventions were measured using the Positive and Negative Affect Schedule (PANAS) (Watson et al. 1988).

212.4.3.3 Results

The study concluded that all three interventions, externally oriented, internally oriented, and video-only, were successful in increasing skepticism about media images that depict a thin ideal of beauty and were "particularly effective at reducing participants' perceptions that media images depicting a thin standard of beauty are *realistic* and *similar* to participants themselves" (Irving and Berel 2001).

There were no differences between the intervention groups and control group on body image variables, socioculturally determined attitudes toward appearance, and affect. Although the internally oriented intervention was specifically aimed at reducing negative body image and internalization of the thin ideal, neither of these results was obtained. Specific results on the subscales of the MAQ were not reported in the published study, including results concerning intentions to engage in dieting behavior.

Finally, more participants (36%) in the video-only intervention sent a postcard requesting information from the media activism organization than those in the internally oriented intervention (19%), the externally oriented intervention (15%), and the control group (5%), indicating that the interventions had a differential impact on intentions to engage in media activism.

212.4.4 Fourth Study Title: Media Literacy as a Prevention Intervention for College Women at Low- or High-Risk for Eating Disorders (Coughlin and Kalodner 2006)

This study stands apart from others in that participants were screened for eating disorder risk at baseline so that results could be analyzed for low- and high-risk individuals. Ninety-two females participated, with 47 in the control group (mean age 19.6) divided into 31 low-risk and 16 high-risk, and 45 in the experimental group (mean age 20.2) divided into 26 low-risk and 19 high-risk. The study employed a pretest 1 week before the intervention and a delayed post-test 8 weeks after the intervention.

212.4.4.1 Intervention Design

The two-session, interactive, discussion-oriented intervention totaled 3 h in length. Entitled Acknowledging and Rejecting the Media's Influence on Eating and Body Image Disturbance (ARMED), it used cognitive behavioral activities to combat body dissatisfaction based on the knowledge that these strategies have improved body image in college women (Butters and Cash 1987; Grant and Cash 1995). The intervention group watched the complete *Slim Hopes* video (Kilbourne 1995), discussed the negative effects of the thin body ideal presented by the media, and learned cognitive behavioral strategies to combat these media messages.

212.4.4.2 Measures

The study measured cognitions, behaviors, and symptoms of eating disorders; awareness and internalization of thin body ideal; and the degree to which participants make social comparisons to their own appearance. Cognitions and eating disorder behaviors were measured using the self-reporting Questionnaire for Eating Disorder Diagnosis (Q-EDD) (Mintz et al. 1997). Participants at low-risk were asymptomatic of eating disorders, while those in the high-risk category included women who fell into the categories of "symptomatic" or "eating disordered."

Eating disorder symptoms were measured with the self-reporting Eating Disorders Inventory-2 (EDI-2) (Garner 1991), using the following four of the 11 subscales: body dissatisfaction, drive for thinness, perfectionism, and ineffectiveness. Awareness and internalization of societal standards were measured using two subscales of the SATAQ (Heinberg et al. 1995), while the Physical Appearance Comparisons Scale (PACS) was used to assess degree of social comparison (Thompson et al. 1999).

212.4.4.3 Results

Compared to high-risk participants in the control group, high-risk participants in the intervention group demonstrated significant reductions in body dissatisfaction, drive for thinness, internalization of societal standards of beauty, and feelings of ineffectiveness. High-risk participants did not show a significant reduction in perfectionism, physical appearance comparisons, or awareness of the thin body ideal. Both intervention and control group low-risk participants evidenced no change in any measured eating disorder risk factor.

Overall, the findings were promising in light of the fact that previous studies of media literacy interventions to address the primary eating disorder risk factors of body dissatisfaction and thin ideal internalization, such as Irving and Berel's 2001 study, did not yield encouraging results. The researchers attributed their success to their analysis of the results based on participant risk factor.

212.4.5 Fifth Study Title: The Effectiveness of Media Literacy and Eating Disorder Prevention in Schools: A Controlled Evaluation with Ninth Grade Girls (Dysart 2008)

This PhD dissertation evaluated an 8-week media literacy intervention aimed at reducing primary eating disorder risk factors in adolescent girls. The study population consisted of 62 high-school females at an all-girls private school, ages 14–15. The study employed a between groups, modified

pretest, post-test experimental design in which the control group participated in a substance abuse intervention for comparison.

212.4.5.1 Intervention Design

The eight intervention sessions were adapted from a variety of sources, including GO GIRLS!™ (Eating Disorders Awareness & Prevention 1998). This program had shown promise in reducing the thin ideal internalization in earlier studies, but the results were not significant, and the intervention showed no change in dieting behaviors (Levine and Smolak 2006). This study hypothesized that the intervention would reduce body dissatisfaction, bulimic behavior, internalization of societal standards of beauty, and weight anxiety.

The 40-min intervention sessions took place once a week over 8 weeks and focused on various topics, including but not limited to the following: how to analyze advertising messages for false motives, how advertisements affect body image, media stereotypes, advertising tactics, contradictory media messages aimed at different targets, and communicating knowledge to a younger female. Participants also watched a different Kilbourne video, *Killing Us Softly III: Advertising Images of Women* (Kilbourne 1999) and participated in a cognitive dissonance exercise by writing letters to younger students about reducing the impact of the thin body ideal.

212.4.5.2 Measures

This dissertation measured behaviors and risk factors of eating disorders, including self-perception, relevant eating disorder behaviors, body dissatisfaction, drive for thinness, bulimia behaviors, sociocultural attitudes toward appearance, thin body ideal internalization, self-esteem, and anxiety about physical appearance. Other media-related measures included assessing media as a source of information and media attitudes. Data were collected pre- and post-intervention at 2 days, 6 weeks, and 6 months following the final intervention session.

Self-perception was only measured pre-intervention with the Self-Perception Profile for Adolescents (SPPA) (Harter 1998), mainly to reinforce the assumption of group similarity achieved through random assignment. Post-intervention measures included the following:

- Eating disorder behaviors were assessed with an updated version of the Eating Disorder Inventory (EDI-3) (Garner 2004), which also includes The Eating Disorder Risk Composite of the following three subscales: drive for thinness, bulimia, and body dissatisfaction.
- The Sociocultural Attitudes Towards Appearance Questionnaire (SATAQ-3) (Thompson et al. 2004), an update revision of the SATAQ used in some of the studies above, was used to measure internalization of media and societal appearance ideals and viewing the media as an important source of information.
- Self-esteem was assessed using the Rosenberg Self-Esteem Scale (RSES) (Rosenberg 1965).
- Anxiety about physical appearance was assessed using the Physical Appearance State and Trait Anxiety Scale (PASTAS) (Reed et al. 1991).
- The Media Attitudes Questionnaire (MAQ) (Irving et al. 1998) was used to assess media realism and similarity.

212.4.5.3 Results

At all post-intervention data collection points, the intervention group reported significant reductions in internalization of the thin body ideal, in the influence of media as a source of information

on appearance, and in seeing oneself and others as similar to media ideals. Drive for thinness differences were significant initially, but did not maintain in subsequent follow-up. Body dissatisfaction differences approached significance at post-test and 6 months, but bulimia, weight-related anxiety, realism, and self-esteem results were not significant throughout the study. At follow-up, the intervention group reported the lowest degree of risk factors for eating disorders.

212.5 Analysis of the Studies

The five studies reviewed here utilized health-promoting media literacy interventions with varying degrees of success in their attempt to achieve changes in unhealthy dieting knowledge, attitudes, and behaviors, and eating disorder risk factors. These and other studies have employed health-promoting media literacy education interventions with a relatively broad range of children, adolescents, and young adults, (Bergsma and Carney 2008) utilizing many different theoretical bases, which implies that this relatively young field of research has not yet identified an ideal critical age group nor a best practice approach.

In addition, the complexity and prevalence of eating disorders moderates any one theory's ability to account for the heterogeneity of the disorders (Dysart 2008). While Social Cognitive Theory may be helpful to address sociocultural risk factors, individual behavioral change must also be addressed through the use of such theories as the Theory of Planned Behavior (Fig. 212.1). Social Cognitive Theory examines the media context surrounding young people, but the Theory of Planned Behavior individualizes that context. The model in Fig. 212.1, therefore, takes into account that media literacy education is, and must be, contextual.

Although most girls are repeatedly exposed to unrealistic societal body image ideals in the media, all girls do not struggle with eating issues. One of the interesting questions for public health is what are the protective factors that prevent some girls from buying into the media stereotypes of skinny women? We hypothesize that one of them is well-developed media literacy skills. In addition, recent research also suggests that an approach combining genetics and environment may provide promise for promoting healthy eating behaviors (Striegel-Moore and Bulik 2007).

212.5.1 Addressing Behavior Change

Research suggests that health-promoting media literacy education interventions may be more effective in preventing unhealthy behaviors than correcting them once they are established (Neumark-Sztainer et al. 2000). As a result, many health-promoting media literacy education interventions are designed to prevent a behavior as opposed to change a behavior. While most studies of health-promoting media literacy education interventions include some measure of attitudes and beliefs, measures of behavior are not as prevalent, and those studies that do address behavior change report mixed and sometimes incomplete results.

The *Free to Be Me* community-based intervention to prevent disordered eating among adolescent girls addressed dieting behavior change in Girl Scout troop members (Neumark-Sztainer et al. 2000), though no statistically significant behavior changes were present at the 3-month follow-up. In the study entitled "Effect of Media Analysis on Attitudes and Behaviors Regarding Body Image Among College Students," the researchers report a significant, positive behavior change among the women in the study with regard to the statement, "I make decisions about dieting or exercising based more upon

how I look than on my health status." Yet they do not provide an actual P value to support their claim of significance (Rabak-Wagener et al. 1998). They do provide measures of significance for women and men on the entire aggregate of five behavioral questions, which demonstrate that women showed significant, positive changes, as compared to the control group, while the men did not. The PhD dissertation study found no change in bulimic behaviors, though these were low at baseline and may have experienced a floor effect (Dysart 2008). In addition, these three studies did not use the same scales to measure behavior change, making it impossible to compare them in any meaningful way.

These examples support past research in health promotion and education, which demonstrates that it is more difficult to change behaviors than beliefs. In a recent systematic analysis of health-promoting media literacy education research studies, it was evident that the majority of outcomes involved knowledge and attitudes and revealed less about actually preventing or changing risky health behavior (Bergsma and Carney 2008). This means that more longitudinal studies are needed to measure more concrete behavioral outcomes such as changes in body mass index or changes in daily dietary regimen to include more fresh fruits and vegetables and less processed foods, for example.

No study reported any results of change in behavioral intention, even though the Theory of Planned Behavior clearly identifies it as an important precursor to behavior change. While the study comparing media-literacy programs to strengthen college women's resistance to media images (Irving and Berel 2001) and the dissertation study (Dysart 2008) used the Media Attitudes Questionnaire (MAQ), which includes two questions that relate to intention to engage in dieting behavior, the former study did not report any findings for these questions and the latter used a modified version of the MAQ that did not include them. Of the 22 items from the MAQ, the two statements related to behavioral intention are: (1) *I plan to go on a diet to lose weight in the next 6 months* and (2) *I want to lose some weight in the next 6 months* (Irving et al. 1998).

212.5.2 Reducing Eating Disorder Risk Factors

Although the studies on a whole may not have succeeded in achieving changes in behavior or behavioral intentions, there were some promising trends in the reduction of eating disorder risk factors, including internalization of the thin body ideal. The SATAQ scale, used in three of the studies, is a commonly used measure for evaluating thin ideal internalization and is, therefore, useful as a consistent benchmark in comparing the effectiveness of health-promoting media literacy education interventions on reducing the thin ideal internalization (Dysart 2008; Irving and Berel 2001; Coughlin and Kalodner 2006).

Reductions in body dissatisfaction were somewhat less prevalent. The dissertation intervention evidenced no significant outcomes in regard to body dissatisfaction, which the researcher suggested might be due to the "deeply imbedded media effects that may require dissonance provoking experiences to change" (Dysart 2008). The *Free to Be Me* community-based intervention with Girl Scouts reported modest changes in body knowledge and attitudes at post-test, but these did not remain at 3-month follow-up. This led the researchers to suggest that because young people are exposed to numerous and constant media messages about the sociocultural thin body ideal, it may not be realistic to expect substantial and long-term changes in body image attitudes from a brief intervention (Neumark-Sztainer et al. 2000). Yet this intervention was nine hours in length, the longest of all the interventions reviewed here.

The authors of the study that examined the 3-h *ARMED* media literacy intervention for college students at low and high risk for eating disorders suggested that the absence of any impact on body image variables may be explained by the difficulty in modifying attitudes toward media and self that

have, over time, become ingrained as a result of the comparison process. They concluded that changes in behavior "may require a longer, more comprehensive intervention program" than was provided in their study (Coughlin and Kalodner 2006). Overall, the longer interventions (Table 212.1) seemed to achieve more significant outcomes than the shorter interventions. A 2006 study of the impact of intervention length on intervention effects indicated that longer interventions may be more successful at reducing body dissatisfaction and thin body ideal internalization (Watson and Vaughn 2006). Clearly, length of intervention is still a major variable that needs study.

All of the studies taught a majority of the critical media literacy concepts, with the shortest intervention teaching only three of the five concepts (Table 212.2). This may also have made that intervention less effective since a recent systematic review of health-promoting media literacy education studies suggests that "effective interventions seem somewhat more likely than ineffective interventions to have taught all the core concepts" (Bergsma and Carney 2008).

212.5.3 Changing Media Attitudes and Behaviors

Media attitudes and behaviors were specifically addressed in four of the five interventions with a strong degree of success. At post-test and 3-month follow-up, the *Free to Be Me* intervention significantly increased the participants' self-efficacy to challenge social norms and significantly decreased internalization of the thin body ideal portrayed in the media. It also impacted the print media choices of the participants, as postintervention they opted for more girl-friendly magazines than those that focused on fashion (Neumark-Sztainer et al. 2000). In the media analysis intervention, college students participated in a critique of fashion advertisements and were then evaluated on changes in beliefs related to fashion images. At post-test, the intervention group showed significantly reduced beliefs with regard to such statements as: "Adult models in advertisements have an ideal body size and shape" (Rabak-Wagener et al. 1998). The interventions in the "Comparison of Media-Literacy Programs to Strengthen College Women's Resistance to Media Images" study significantly increased media skepticism (Irving and Berel 2001), and the dissertation intervention reduced the influence of media as a source of information about appearance (Dysart 2008). Unfortunately, in these studies and others like them, there has not been enough definitive research to show that changes in media attitudes and behaviors result in changes in health behaviors.

In some cases, the researchers utilized the same media literacy program materials. Jean Kilbourne's videos appeared in four out of the five studies; *Slim Hopes* was used in three interventions, while *Killing Us Softly III* was used in a fourth (Kilbourne 1995, 1999). In the study that specifically compared an externally oriented and an internally oriented intervention against a video-only intervention, with *Slim Hopes* remaining the common factor in each intervention, the researchers suggested that the video may have been the common factor in increasing media skepticism across the three interventions. Other studies did not specifically make any link to the inclusion of the Kilbourne videos and the intervention outcomes, positive or negative.

212.5.4 Study Populations

While men and boys are often overlooked in studies of eating disorders, statistics indicate that one third of young men experience body dissatisfaction (Corson and Andersen 2002). The "Effect of Media Analysis on Attitudes and Behaviors Regarding Body Image Among College Students"

(Rabak-Wagener et al. 1998) intervention was the only study that involved both men and women, and it demonstrated a stronger impact on the beliefs and behaviors of the female participants than those of the men. While the researchers made an effort to include fashion advertisements depicting both men and women in the intervention discussion and critique activities, the *Slim Hopes* video was aimed primarily at women and may not have appealed to the men (Rabak-Wagener et al. 1998). Although no other study made an effort to include men, the dissertation study suggested that the lack of young boys in the study population was a limitation to the results (Dysart 2008).

212.5.5 Pedagogical Approach

All of the five studies included in this chapter conclude that media literacy education has significant potential to promote healthy knowledge, attitudes, and behaviors with regard to body dissatisfaction and eating disorders, and it merits further study. Many questions remain, however, regarding which variables contribute more or less to the effectiveness of health-promoting media literacy education. One variable that is seldom examined is pedagogical approach. While the studies provide considerable information on *what* the intervention taught, they provide little, if any, information on *how* the intervention taught it. In other words, we know the content that was taught, but not the pedagogical approach that was used. For example, the *Free to be Me* community-based study provides a good content outline of the intervention sessions, but no information about pedagogical approach. Although the study reports that the Girl Scout troop leaders who took primary responsibility for teaching the program received a detailed leader handbook and three hours of training, and they were monitored for fidelity to the "protocol" by a registered dietician who provided the troop leader training, the "protocol" is only vaguely defined as the "implementation of all sessions as intended." Yet successful health-promoting media literacy education results not so much from *what* is taught as *how* it is taught (Bergsma and Carney 2008), as outlined in the *Core Principles of Media Literacy Education* (National Association for Media Literacy Education 2007). Media literacy education must be grounded in inquiry-based, process-oriented pedagogy. Unfortunately, whether the pedagogical approach used in the sample studies included in this chapter was one of inquiry or indoctrination is unclear, as it is in most such published studies. In order to greatly enhance the field of research on health-promoting media literacy education, future studies must provide more reliable information on the pedagogical approach used by the intervention and examine it as variable that may affect outcomes.

212.6 Applications

Media literacy education interventions have been used to promote health in numerous areas, including violence prevention, tobacco use prevention, alcohol abuse, nutrition and dieting behavior, body image, eating disorders (Bergsma and Carney 2008), sexual behavior (Pinkleton et al. 2008), drug abuse prevention (Doba and Doukoullos 2001), and prevention of marijuana use (DeKorne et al. 2002). Given this body of practice and research on the use and effectiveness of media literacy education to promote health, it is reasonable to assume that this approach to health promotion could be applied to numerous health issues among youth. Interestingly, however, there is little research on its use to promote physical activity. Yet certainly the media give many mixed messages about physical activity that require analysis on the part of both youth and adults in order for them to think critically

Fig. 212.2 Key questions to ask when analyzing media messages. This figure suggests key questions to ask when analyzing media messages, including questions to analyze audience, authorship, messages, meanings, representations, and reality (The table is part of the National Association for Media Literacy Education's *Core Principles of Media Literacy Education in the United States* – www.namle.net/core-principles. Used with permission)

about the numerous constructions of reality about physical fitness activities that the media portray, the values and points of view about physical fitness activities that are conveyed, and how different people might understand the messages differently. Another application would be to engender more critical thinking and behavior regarding safe driving practices among teenagers, despite the mixed messages they receive from the media. Health-promoting media literacy education could be used to empower youngsters to explore the key questions to ask when analyzing media messages (Fig. 212.2) developed by the National Association for Media Literacy Education. Although all the questions are important for critical analysis, a key question for health-related subjects is "What is left out of this message that might be important to know?" because media messages about health issues like tobacco, alcohol, sex, and violence often glamorize them and frequently portray them without consequences. For example, sex in the media is generally portrayed without the three Cs: no commitment, no condoms, and no consequences.

212.7 Summary

Based on everything we have studied and analyzed in this chapter, what do we know and what do we still need to know about the effectiveness of health-promoting media literacy education as it relates to issues of body dissatisfaction, nutrition, dieting behavior, and eating disorders?

The media present an ideal body type that is considerably thinner than the average female. Research demonstrates that exposure to this type of thinness-promoting media contributes to body dissatisfaction, dieting, and unhealthy behaviors. Body dissatisfaction is so pervasive in women that it is becoming a normative trend, and it is increasing for young men as well, highlighting the crucial need for interventions that address this risk factor. Addressing body dissatisfaction through health-promoting media literacy education interventions is imperative because body dissatisfaction is a key risk factor in the onset of disordered eating behaviors.

Numerous studies of the effects of a health-promoting media literacy education intervention on preventing body dissatisfaction, unhealthy dieting, and eating disorders have been conducted over the past 30 years with mixed results. They appear to be more successful in changing knowledge and attitudes than behaviors, a pattern that is consistent with much of the research in health promotion and education. Therefore, health-promoting media literacy interventions may be more effective at preventing the onset of the health problem than in changing behavior once it has become ingrained.

While the research on health-promoting media literacy education is promising, a great deal more study must be done to develop best practices in this field of endeavor.

- We must continue to develop and test theoretical foundations for health-promoting media literacy education, such as the Message Interpretation Process (Austin et al. 2000) and the Integrated Individual and Interpersonal Model of Health-Promoting Media Literacy Education proposed in this chapter (Fig. 212.1).
- Successful studies must be replicated.
- New studies should utilize at least some of the same measurement tools as past ones so that meaningful comparisons can be made.
- More tangible efforts should be made to measure actual behavior change resulting from the interventions or, at the least, changes in behavioral intention(s).
- Finally, because the pedagogical approach utilized in health-promoting media literacy education must be inquiry-based and grounded in critical thinking, not the more traditional health education approach of teacher bestowing knowledge upon pupil, research must pay significantly more attention to *how* the interventions are taught while continuing to examine *what* is taught.

Definitions and Explanations of Key Terms

∗**Media:** all electronic or digital means and print or artistic visuals used to transmit messages.

∗**Literacy:** the ability to encode and decode symbols and to synthesize and analyze messages.

∗**Media literacy:** the ability to encode and decode the symbols transmitted via media and the ability to synthesize, analyze, and produce mediated messages.

∗**Media education:** the study of media, including "hands on" experiences and media production.

∗**Media literacy education:** the educational field dedicated to teaching the skills associated with media literacy.

Health-promoting media literacy education: the education field dedicated to teaching the skills associated with media literacy that can also promote health.

Social Cognitive Theory: a three-way, dynamic, reciprocal theory in which personal factors, environmental influences, and behavior continually interact. A basic premise is that people learn not only through their own experiences, but also by observing the actions of others and the results of those actions.

Theory of Planned Behavior: human action is guided by three considerations: (1) beliefs about the likely consequences of the behavior, (2) beliefs about the normative expectations of others, and (3) beliefs about the presence of factors that may facilitate, or impede, the performance of the behavior.

Body dissatisfaction: discontent with the overall shape and size of one's body.

Thin ideal internalization: the acceptance or endorsement of societal messages about weight, thinness, and attractiveness, in contrast to general awareness of these messages.

*Definitions are produced with permission from the website of the National Association for Media Literacy Education WWW.NAME.net.

References

Austin E, Johnson K. J Health Commun. 1997;2:17–42.
Austin EW, Pinkleton BE, Fujioka Y. Pediatrics. 2000;105:343–9.
Baranowski T, Domel S, Gould R. J Nutr Educ. 1993;25:114–20.
Berel S, Irving L. J Prim Prev. 1998;18:415–30.
Bergsma LJ. Am Behav Sci. 2004;48:152–64.
Bergsma LJ, Carney ME. Health Educ Res. 2008;23:522–42.
Butters J, Cash T. J Consult Clin Psych. 1987;55:889–97.
Committee on Public Education American Academy of Pediatrics. Pediatrics. 2001;107:423–6.
Corson PW, Andersen AE. In: Cash TF, Pruzinsky T, editors. Body image: A handbook of theory, research and clinical practice. New York: Guilford Press; 2002. pp. 192–9.
Coughlin J, Kalodner C. Body Image. 2006;3:35–43.
DeKorne C, Bergsma LJ, Doba S. Anti-drug education with the New York Times: focus on Marijuana. New York, NY: The New York Times Newspapers in Education; 2002.
Doba S, Doukoullos ES. Media literacy for drug prevention: A unit for middle school educators. New York, NY: The New York Times Newspapers in Education; 2001.
Dysart M. The effectiveness of media literacy and eating disorder prevention in schools: A controlled evaluation with 9th grade girls. Raleigh, NC: North Carolina State University; 2008.
Eating Disorders Awareness & Prevention. GO GIRLS!™: Giving our girls inspiration and resources for lasting self-esteem. Seattle, WA: Eating Disorders Awareness and Prevention, Inc.; 1998.
Heins M, Cho C. Media literacy: An alternative to censorship. New York, NY: Free Expression Policy Project; 2003.
Freire P (1970) Pedagogy of the oppressed. New York, NY: The Continuum Publishing; 1970.
Freire P. Education for critical consciousness. New York, NY: The Continuum Publishing; 1973.
Garner D. Eating disorder inventory-2: professional manual. Odessa, FL: Psychological Assessment Resources; 1991.
Garner D. EDI-3: Eating disorder inventory professional manual. Lutz, FL: Psychological Assessment Resources; 2004.
Glanz K, Rimer BK. Theory at a glance: A guide for health promotion practice, 2nd ed. Washington, DC: National Cancer Institute; 2005.
Grant J, Cash T. Behav Ther. 1995;26:69–84.
Harter S. Manual: Self-perception profile for adolescents. Denver, CO: University of Denver; 1998.
Heinberg L, Thompson J, Stormer S. Int J Eat Disorder. 1995;17:81–9.
Irving L, DuPen J, Berel S. Eat Disorder. 1998;6:119–31.
Irving L, Berel S. Psycho Women Quart. 2001;3:35–43.
Kaiser Family Foundation. The role of media in childhood obesity. Menlo Park, CA: The Henry J. Kaiser Family Foundation; 2004.
Kaiser Family Foundation. Generation M: Media in the lives of 8–18 year-olds. Menlo Park, CA: The Henry J. Kaiser Family Foundation; 2005.
Kilbourne J. Slim hopes: Advertising and the obsession with thinness. Northampton, MA: Media Education Foundation; 1995.

Kilbourne J. Killing us softly III: Advertising images of women. Northampton, MA: Media Education Foundation; 1999.

Levine M, Smolak L. The prevention of eating problems and eating disorders. Mahwah, NJ: Lawrence Erlbaum; 2006.

Lorig K, Sobel D, Stewart A. Med Care. 1999;37:5–14.

Mintz L, O'Halloran M, Mulholland A, Schneider P. J Couns Psychol. 1997;44:63–79.

National Association for Media Literacy Education. Core principles of media literacy education in the United States. Cherry Hill, NJ; 2007.

Neumark-Sztainer D, Sherwood NE, Coller T, Hannan PJ. J Am Diet Assoc. 2000;100:1466–73.

Pinkleton BE, Austin EW, Cohen M, Chen Y, Fitzgerald E. Health Commun. 2008;23:462–72.

Rabak-Wagener J, Eickhoff-Shemek J, Kelly-Vance L. J Am Coll Health. 1998;47:29–35.

Reed D, Thompson J, Brannick M, Sacco W. J Anxiety Disord. 1991;5:323–32.

Rosenberg M. Society and the adolescent self-image. Princeton, NJ: Princeton University Press; 1965.

Slade P, Newton T, Brodie D, Kiemle G. Psychol Health. 1990;4:213–20.

Strasburger V, Wilson B. Children, adolescents, and the media. Thousand Oaks, CA: Sage; 2002.

Striegel-Moore R, Bulik C. Am Psychol. 2007;62:181–98.

Thoman E, Jolls T. Medialit kit—literacy for the 21st century: An overview and orientation guide to media literacy education. Los Angeles, CA: Center for Media Literacy; 2005.

Thompson J, Heinberg L, Tantleff S. Behav Therapist. 1991;14:174–80.

Thompson J, Heinberg L, Altabe M, Tanleff Dunn S. Exacting beauty: Theory, assessment, and treatment of body image disturbance. Washington, DC: American Psychological Association; 1999.

Thompson J, van den Berg P, Roehrig M, Guarda A, Heinberg L. Int J Eat Disorder. 2004;35:293–304.

Watson D, Clark L, Tellegen A. J Pers Soc Psychol. 1988;54:1063–70.

Watson R, Vaughn L. Eat Disord. 2006;14:385–400.

Chapter 213
Treatment of the Night Eating Syndrome

Albert J. Stunkard and Kelly C. Allison

Abbreviations

BED	Binge Eating Disorder
BMI	Body Mass Index
CBT	Cognitive Behavior Therapy
HDRS	Hamilton Depression Rating Scale
MDD	Major Depressive Disorder
NES	Night Eating Questionnaire
NES	Night Eating Syndrome
NESHI	Night Eating Symptom History and Inventory
NESS	Night Eating Symptom Scale
NREM	Non-Rapid Eye Movement Sleep
PMR	Progressive Muscle Relaxation
QLES-Q	Quality of Life, Enjoyment, and Satisfaction Questionnaire
SPECT	Single Photon Emission Computed Tomography
SRED	Sleep-Related Eating Disorder
SSRIs	Selective Serotonin Reuptake Inhibitors

213.1 Introduction

The Night Eating Syndrome (NES) is described and defined in the chapter by Lundgren in this book. It was described over 50 years ago as a disorder characterized by evening hyperphagia (eating 25% of the daily food intake after supper) and insomnia, all made worse by stress (Stunkard et al. 1955). Nocturnal ingestions (i.e., waking up from sleep to eat) were first reported by Birketvedt et al. (1999).

NES represents a delay in the circadian pattern of meal times. A consensus was recently reached on a set of diagnostic criteria (see Lundgren's chapter). The two core criteria of NES are evening

A.J. Stunkard (✉)
Center for Weight and Eating Disorders, Department of Psychiatry,
School of Medicine, University of Pennsylvania, 3535 Market Street,
Philadelphia, PA, 19104-3309, USA
e-mail: stunkard@mail.med.upenn.edu

hyperphagia and nocturnal ingestions (Allison et al. in press (a)). Awareness and recall of eating episodes distinguishes NES from Sleep-Related Eating Disorder (SRED) (Howell et al. 2009).

Obese persons with NES appear to be less successful at weight loss attempts than those without NES (Stunkard et al. 1955). Gluck et al. (2008) also reported that persons with NES lost less weight (4.4 kg) than those without NES (7.3 kg, $p = 0.003$).

An overlap between NES and Binge Eating Disorder (BED) occurs in 7–25% (Stunkard et al. 1996; Allison et al. 2005,2006, 2007). An important difference between the two disorders is that nocturnal ingestions in NES are not objectively large, approximately 300 calories per episode (Birketvedt et al. 1999). Persons with BED and NES share similar types of psychopathology in relation to their disordered eating, but BED patients have higher levels of psychopathology than do night eaters or control subjects (Allison et al. 2005).

213.2 Serotonin and NES

The most effective four studies for the treatment of NES used Selective Serotonin Reuptake Inhibitors (SSRIs) (Stunkard et al. 2009). The background for these studies was furnished by Single Photon Emission Computed Tomography (SPECT), using ^{123}I-ADAM, a radiopharmaceutical agent selective for the serotonin transporter (Newberg et al. 2005; Lundgren et al. 2009). The diagnosis of NES in this SPECT study was carefully established by a seven-day food and sleep record as well as a clinical interview using the NES History and Inventory (NESHI; unpublished clinical interview). The night eating of these patients was severe (an evening caloric intake of $42.2 \pm 12.3\%$ of total daily caloric intake) and 9.4 ± 3.9 nocturnal awakenings with ingestions per week (Table 213.1).

Lundgren shows that the serotonin binding capacity was greater in night eaters than among control subjects in the midbrain ($p < 0.001$) and temporal lobes ($p < 0.01$) (Lundgren et al. 2009) and at far greater rates than that of patients with Major Depressive Disorder (MDD) (Newberg et al. 2005; Lundgren et al. 2009).

The elevated levels of SERT return a large proportion of serotonin from the synapse to the cell body, leaving a deficit of serotonin at the synapse. This deficit delays the night eaters' circadian rhythms of food intake and several neuroendocrine functions. This serotonin deficit suggests that increased serotonergic activity may alleviate NES. This is precisely what the SSRIs do (Fig. 213.1).

NES has responded to SSRIs in all four studies in which they were used. The first study consisted of case reports of four night eaters who showed strong responses to the SSRIs, paroxetine and fluvoxamine (Miyaoka et al. 2003). Three more studies of night eaters, identified by the Night Eating Questionnaire (NEQ) (Allison et al. 2008) and NESHI were conducted by our group. The first of these three studies was a 12-week open-label trial of sertraline with 17 night eaters, which showed highly significant decreases in the core NES behaviors (O'Reardon et al. 2004). Five subjects who achieved complete remission lost 4.8 ± 2.6 kg while the 12 other subjects gained 0.6 ± 5.4 kg.

Table 213.1 Key features of the treatment of the NES

SPECT studies show that night eaters manifest increased reuptake of serotonin from the synapse.	This reuptake (into the cell body) depletes synaptic serotonin which is believed to be the mechanism of NES.
SSRIs block the reuptake of serotonin and restore serotonin levels at the synapse.	Four studies of SSRIs have been effective in NES.
NES is associated with disorders of eating, sleeping, and mood and dysfunctional cognitions.	Allison et al. developed CBT specifically for NES by combining cognitive treatments for each of these disorders.

Fig. 213.1 Greater SERT bnding in midbrain of night eaters. This figure shows the markedly elevated SERT uptake of 6 subjects with the Night Eating Syndrome (NES) and the lower uptakes of the patients with MDD and matched control subjects (Reproduced from Lundgren et al. 2009, by permission)
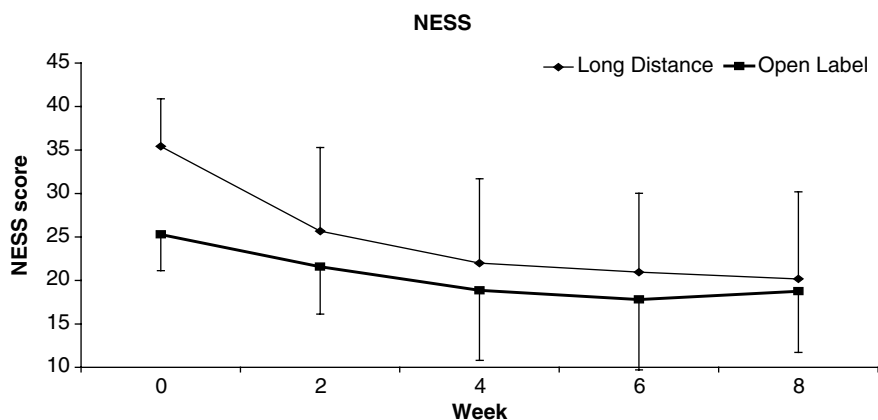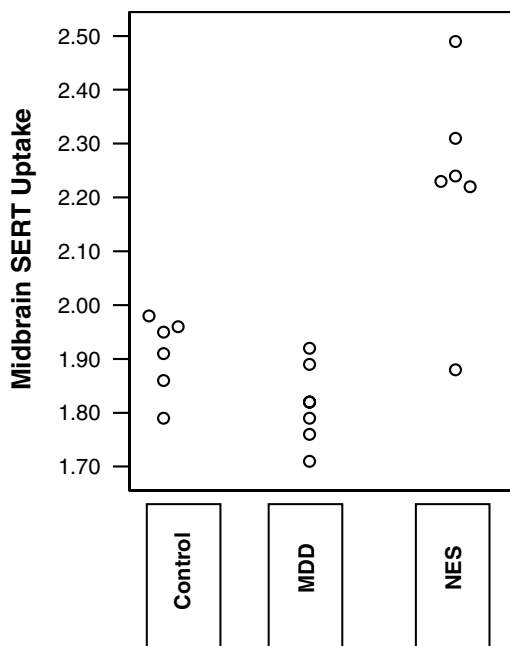
Fig. 213.2 Comparison of the NESS scores between two open label studies of sertraline. This figure shows changes in the NESS of two independent studies. One was a long-distance study and the other an open-label trial. Last Observation Carried Forward (LOCF) was used in both studies. The similarity between two different patient groups and different circumstances in treatment is striking (Reproduced from Stunkard et al. 2006, by permission)

The second of the three studies, also an open-label trial of sertraline, enrolled 50 night eaters who lived at a distance from our clinic (Stunkard et al. 2006). They received treatment from their own physicians in consultation with our research team. Patients achieved a 66% reduction in calories consumed after the evening meal, 70% reduction in nocturnal ingestions and, among overweight and obese subjects, a 2.2 kg weight loss. A comparison of the results of the two open-label studies is shown in Figs. 213.2, 213.3, and 213.4. There was a striking similarity in the outcome of these two trials of sertraline, performed with different patients and under very different circumstances.

Our third study was a double-blind, placebo-controlled trial of sertraline with 34 night eaters over a period of 8 weeks (O'Reardon et al. 2006). Dosing was flexible, starting at 50 mg/day and increased,
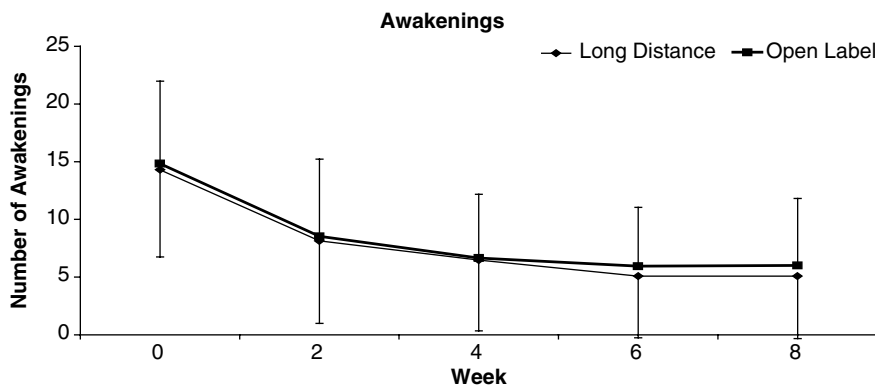
Fig. 213.3 Comparison of number of awakenings per week in two open label studies of sertraline. The significant decreases in number of awakenings per week were similar in both studies
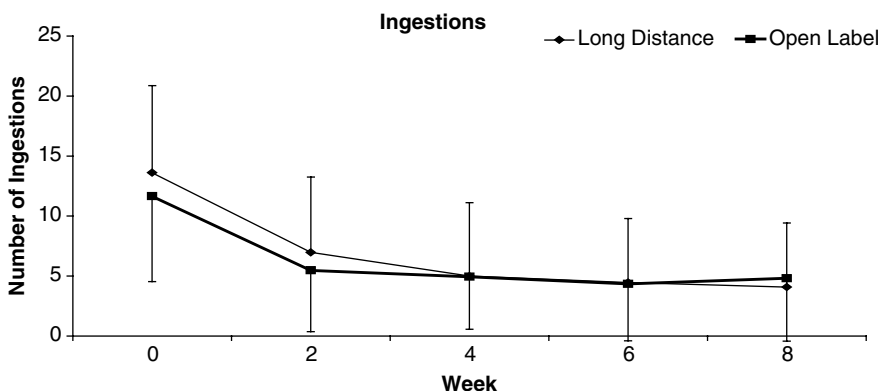
Fig. 213.4 Comparison of number of nocturnal ingestions per week between two open label studies of sertraline. The significant decreases in number of nocturnal ingestions per week were also similar in both studies

as needed, to 200 mg/day, with a final mean of 126.5 mg/day. Assessed with the Clinical Global Impression of Improvement Scale (Guy 1976), the "responder status" to sertraline (71%) was far greater than the 18% for placebo patients ($p < 0.002$). In addition, caloric intake after the evening meal fell by 68% compared to a 29% decrease in the placebo group ($p < 0.009$). The number of nocturnal ingestions of patients who received sertraline fell by 81% (from 8.3/week to 1.6/week). By contrast, nocturnal ingestions by placebo patients fell by only 14% (from 6.4/week to 5.5/week).

Overweight night eaters lost 2.9 ± 3.8 kg during the 8 weeks of sertraline, compared to 0.3 ± 2.7 kg among placebo subjects ($p = 0.06$ for the full model, and $p = 0.007$ for the main effect at week 8). This is the third time we have reported sertraline producing weight loss in obese persons, while no other studies have reported an independent effect of sertraline on weight loss. It suggests that the weight loss may be the result of restoration of serotonin at the synapse. Decreases in the primary outcome measures were, notably, not correlated with changes in depressed mood. Improvements in NES were evidently not a sole function of an antidepressant effect.

Figures 213.5, 213.6, and 213.7 show changes in three measures of the night eating syndrome in sertraline and placebo subjects in a randomized controlled trial.

Fig. 213.5 Change in caloric intake after supper across 8 weeks of treatment. Proportion of calories consumed after dinner fell from 47.3% to 14.8% in the sertraline group compared to a fall from 45% to 32% in the placebo group (Reproduced from O'Reardon et al. 2006, by permission)
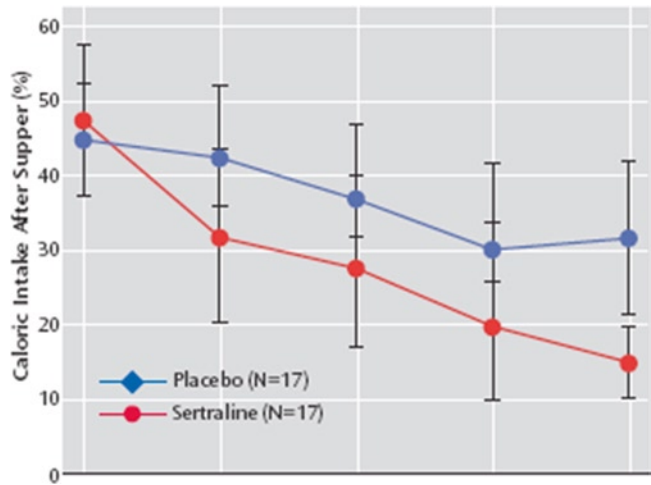
Fig. 213.6 Change in the number of awakenings per week across eight weeks of treatment. Number of awakenings per week fell from 8.8 per week to 2.3 per week in the sertraline group, as compared to 6.4 to 5.5 per week in the placebo group (Reproduced from O'Reardon et al. 2006, by permission)
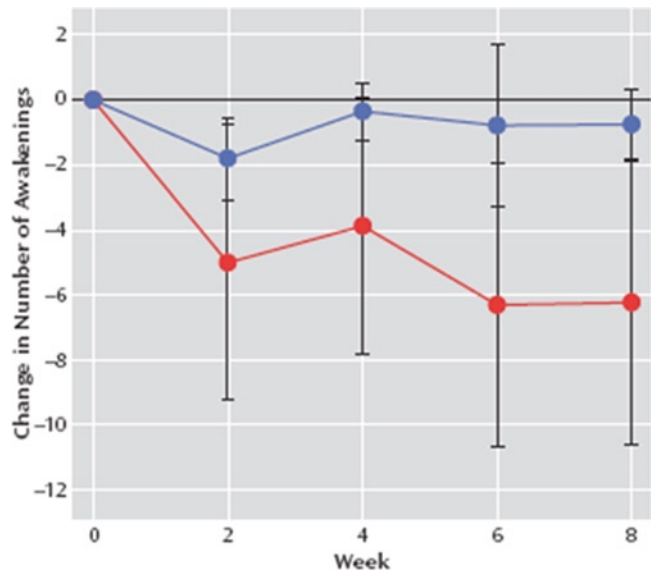
213.3 Topiramate

There have been case reports of the use of topiramate in treating NES, although they are more commonly reported among patients with SRED (Howell et al. 2009). O'Reardon et al. (2004) found that among a group of six sertraline nonresponders, topiramate produced significant reductions on the Night Eating Symptom Scale (NESS), percentage of calories consumed after dinner, and weight (-4.6 kg over 12 weeks, $p < 0.05$), accompanied by nonsignificant decreases in nocturnal awakenings and ingestions (personal communication with John O'Reardon, M.D., September, 2005).

Fig. 213.7 Weight loss across 8 weeks of treatment. Weight fell by 2.9 kg among the overweight subjects in the sertraline group as compared to a 0.3 kg drop among placebo participants (Reproduced from O'Reardon et al. 2006, by permission)
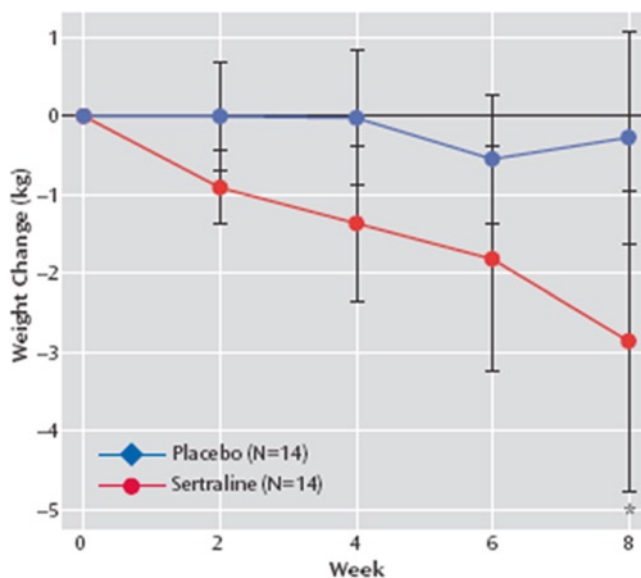
213.4 d-fenfluramine

The evidence of serotonergic dysfunction in NES, and its restoration of normal function with SSRIs indicate the importance of serotonin in the NES. This suggestion was strongly supported by a study of the treatment of seven night eaters with the serotonergic agent, d-fenfluramine (Spaggiari et al. 1994). The diagnosis of NES in these patients was established by careful clinical studies and polysomnographic recordings. All subjects were fully awake when they ate and remembered its occurrence, ruling out SRED (Schenck and Mahowald 1994). Their NES symptomatology was severe, with a mean of 3.4 eating-related awakenings per night and a duration of 7.4 years. Eating episodes occurred promptly upon waking from nonrapid eye movement sleep (NREM), within 30 s of waking in half of the episodes. The average duration of eating was 3.5 min, followed by a return of sleep. The mean number of calories ingested during the night was said to be 1,200 kcal.

Patients were treated with d-fenfluramine (15–30 mg/night) which produced a "dramatic improvement" in their NES. Night eating episodes fell by at least 50% and were associated with a greater than 70% decrease in total caloric intake. No patients showed any "substantial modification" in their daytime eating habits. One patient dropped out early because of "asthenia and drowsiness."

213.5 Phototherapy

The effect of SSRIs in restoring disordered circadian rhythms to normal raises the question of whether other measures might have the same effect. Foremost among measures to alter circadian rhythms is phototherapy. A reasonable basis for phototherapy of NES is its ability to shift circadian rhythms; a delay in these rhythms of night eaters is a key element of this disorder. It is, significantly, associated with attenuation of the usual nighttime elevation of melatonin and leptin (Birketvedt et al. 1999). The lowered level of leptin at night may well play a role in its failure to suppress night time eating. This rationale led the group of Friedman et al. (2002, 2004) to explore the treatment of NES with phototherapy.

They treated two night eaters with bright light therapy. One was a 51-year-old obese woman with a BMI of 51 and a Hamilton Depression Rating Scale (HDRS) score of 18. She had been treated for depression for 2 years with paroxetine at a dose of 40 mg/day when she reported a worsening in her symptoms (Friedman et al. 2002). The other night eater was a 46-year-old nonobese man with a BMI of 23, and an HDRS score of 16 who complained of fatigue and insomnia (Friedman et al. 2004).

Each patient was treated with bright light (10,000 lux) therapy for 14 consecutive morning sessions of 30 min each; the female patient continued on her dose of paroxetine. After 14 weeks neither patient any longer met criteria for NES, and their scores on the HDRS fell, for the female patient, from 18 to 7, and, for the male patient, from 16 to 4.

One month after the end of phototherapy, all of the female patient's night eating symptoms recurred. Strikingly this relapse did not extend to depression and her HDRS score remained low (6). The patient was again treated with the same bright light protocol for 12 sessions and her NES symptoms were once again "completely suppressed." No further information about her course has been reported.

A tantalizing report from Sweden describes the treatment of four female night eaters with phototherapy (Bylesjo et al. 2006). Treatment was of one hour duration administered some time between 7 and 9 A.M., at a dose of only 1,500 lux. It occurred daily for 10 days and then twice weekly for 4½ more weeks. Three of the patients lost weight from the beginning (from 1.5 to 2.4 kg) and the fourth one gained at first and then lost below her starting weight. Unfortunately, the NES status of the patients was not mentioned after discontinuation.

213.6 Psychotherapy

Efforts to assess psychotherapy for NES have been limited. Only one controlled trial has been reported. This is unfortunate since the effects of medication may not extend over the long term once it is discontinued.

The controlled trial was of 1 week's duration, involving 10 night eaters who practiced 20 min of Progressive Muscle Relaxation (PMR) each morning. Their outcomes were compared to those of a control group of 10 night eaters who sat quietly for 20 min (Pawlow et al. 2003). Immediately after the PMR session, there was a reduction in anxiety, stress, and levels of salivary cortisol. The presumption underlying this treatment was that anxiety is a determinant of NES. This presumption was supported by significant decreases in anxiety that were associated with decreases in evening appetite and increases in morning appetite.

Practicing these techniques for a week led to continuing reduction in stress and anxiety and comparable changes in eating behavior: lower hunger in the evening and greater hunger in the morning. There was a trend for decreased caloric intake in the evening and greater caloric intake in the morning.

213.7 Cognitive Behavioral Therapy

Cognitive Behavioral Therapy (CBT), developed by Beck et al. (1976), is a promising treatment for NES. CBT was pioneered for eating disorders by Fairburn for Bulimia Nervosa (Fairburn 1981) and BED (Fairburn et al. 1993).

Allison et al. (in press (b)) developed a CBT program specifically for NES. NES combines features of eating, sleeping, mood, and stress disorders, and Allison combined previous treatments for each of them. Laying the groundwork for therapeutic intervention, Allison et al. (2004) examined the

specific cognitions associated with eating by persons with NES. Patients were asked to record their thoughts before and after night eating episodes. Among the most common themes were: (1) food cravings (for specific foods), (2) anxiety and agitation ("I could work myself into a panic just thinking about having to go to bed without my snacks"), (3) distress about disruption of sleep, and (4) feeling compelled to eat (particularly to sleep) ("I won't be able to sleep if I don't get some food in my stomach.") These and other dysfunctional thoughts were identified with the use of the Nighttime Eating Assessment (Allison and Stunkard 2007) and were helpful in treatment.

Weight loss was also included as a goal of treatment for overweight and obese patients. To facilitate weight loss and to advance food intake to earlier in the day for all patients, food and sleep logs were kept by all patients. Caloric goals were recommended for overweight and obese participants at 1,200–1,500 kcals for women and 1,500–1,800 kcals for men. A registered dietician analyzed food records to facilitate adherence with these recommendations.

Three questionnaires were administered prior to each therapy session, as they had been in the medication trials: (1) the Night Eating Symptom Scale (NESS) (O'Reardon et al. 2004); (2) the Beck Depression Inventory (Beck 1996); and (3) the Quality of Life, Enjoyment, and Satisfaction Questionnaire (QLES-Q) (Endicott et al. 1993).

213.8 Pilot Treatment

Twenty-five subjects were recruited with the aid of the NESS (O'Reardon et al. 2004) for a pilot study of CBT (Allison et al, in press (b)). Fourteen subjects completed the trial; the remaining eleven dropped out, with most of these discontinuing before the third session. Significant reductions on four major outcome variables were noted using Mixed Model Regression Analysis to maximize data from all participants (Verbeke and Molenberghs 1997): (1) percent of calories consumed after dinner until awakening the following morning 29% (from 35.0% to 24.9%: $p < 0.0001$); (2) Number of awakenings, (from 13.5/week to 8.5/week; $p < 0.018$); (3) number of nocturnal ingestions fell by 70% (from 8.7/week to 2.6/week ($p < 0.0001$); and (4) the NESS fell from 28.7 to 16.3; $p < 0.0001$). In addition, weight fell by 3.1 ± 0.4 kg ($p < 0.0001$) (Allison et al, in press (b)).

The 14 completers, as expected, showed greater improvement in the two core criteria than the results for the entire sample of 25 patients: (1) caloric intake after dinner fell from 36% to 22% ($p < 0.05$) and (2) nocturnal ingestions from 5.6/week to 0.5/week ($p < 0.001$).

The attrition rate in this study was high, reflecting the frequent experience in CBT: persons may not have anticipated the effort involved in keeping records (of food intake, sleep, mood, etc.) and of making sustained behavioral changes. Also, there was a high lifetime comorbidity rate with other psychiatric disorders, including 48% for anxiety disorders, 36% for mood disorders, and 24% for BED. These comorbidities may have reduced patients' ability to improve to change their NES with this active therapy (Allison et al, in press (b)).

213.9 Current Statistics on the Treatment of NES

The NES is a disorder of moderate prevalence, readily diagnosed, and effectively treated. One might well expect that it should be widely and effectively treated. Such is not the case. A survey of 159 night eaters (Goncalves et al. 2009) found that only 27% believed that their physicians had ever heard of the NES and 41% of patients said that their physicians had not listened to their concerns.

213.10 Conclusions

NES is believed to be a disorder of moderate severity in the general population, but higher among obese persons. However, definitive prevalence study data is required. NES appears to result in a deficit of serotonin at the synapse which is remedied by SSRIs and possibly by psychotherapeutic measures. The disorder is not well-recognized by the medical profession and most patients go untreated. Current therapies deserve much wider distribution.

213.11 Applications to Other Areas of Health and Disease

The major problem with the NES is its limited recognition by the medical profession and others. The limited recognition of NES leads to inadequate treatment of treatable disorders and inappropriate treatment of others.

Prominent among specific problems posed by this limited recognition is insomnia, which is frequently encountered in the NES. This insomnia responds readily to standard treatments for NES, particularly the SSRIs. Attempts to treat the insomnia of NES with the usual hypnotics often produce a confusional state in which night eating may also occur. NES can be confused with BED, for which treatments may differ. While NES occurs periodically (nightly), BED does not occur periodically. Furthermore, the food intake of the binges of BED is far greater than the food consumed at night in NES.

Since insomnia, NES, and BED afflict a large number of persons, the distinctions in the diagnoses and consequent treatments are needed; a major information campaign is warranted. The limited recognition of NES is easily diagnosed and effectively treated. The disorder warrants a major information campaign.

Summary Points

- There are three types of treatment for the NES: pharmacotherapy, phototherapy, and psychotherapy.
- SSRIs are the most studied and probably most effective treatment for NES.
- Phototherapy with bright light in the morning has proven effective in controlling NES in a small number of patients.
- controlled trial of PMR produced a reduction in anxiety and evening appetite and an increase in morning appetite.
- pilot study of CBT of 25 night eaters produced a decrease in evening hyperphagia, number of awakenings, and nocturnal ingestions, and a weight decrease of 3.1 kg. The study had a high attrition rate.

Key Terms

Cognitive Behavior Therapy (CBT): psychotherapeutic approach that aims to solve problems concerning dysfunctional emotions, behaviors, and cognitions through a goal-oriented, systematic procedure

Selective Serotonin Reuptake Inhibitors (SSRIs): medications that, as the name indicates, selectively inhibit reuptake of serotonin from the synapse in the brain

Serotonin Transporter (SERT): a protein that moves serotonin from the synapse to the cell body

Single Photon Emission Computed Tomography (SPECT): method of measuring serotonin transporters in the brain by radiography of dye-assisted cells

Phototherapy: method of treatment for circadian disorders using exposure to daylight or to specific wavelengths of light

Progressive Muscle Relaxation (PMR): technique for reducing anxiety by alternately tensing and relaxing the muscles

References

Allison KC, Stunkard AJ, Thier SL. Overcoming the night eating syndrome: A step-by-step guide to breaking the cycle. Oakland, CA: New Harbinger; 2004.

Allison KC, Stunkard AJ. Self-help for night eating syndrome. In: Latner J, Wilson GT, editors. Self-help for obesity and binge eating. New York: Guilford Press; 2007, pp. 310–24.

Allison KC, Lundgren JD, O'Reardon JP, Martino NS, Sarwer DB, Wadden TA. Eat Behav. 2008;9:62–72.

Allison KC, Lundgren JD, O'Reardon JP, Geliebter A, Gluck ME, Vinai P, Mitchell JE, Schenck CH, Howell MJ, Crow SJ, Engel S, Latzer Y, Tzischinsky O, Mahowald MW, Stunkard AJ. Int J Eat Disord. In press (a).

Allison KC, Stunkard AJ. Treatment of night eating syndrome. In: Grilo CM, Mitchell JE, editors. Treatment of eating disorders. New York: Guilford. In press (b).

Allison KC, Lundgren JD, Moore RH, O'Reardon JP, Stunkard AJ. Am J Psychother. In press (c).

Beck AT. Manual for the beck depression inventory II San Antonio: Harcort Brace; 1996.

Beck AT, Rush AJ, Shaw BF, Emery G. Cognitive therapy of depression. New York: Guilford; 1976.

Birketvedt G, Florholmen J, Sundsfjord J, Osterud B, Dinges D, Bilker W, Stunkard AJ. JAMA. 1999;282: 657–663

Bylesjo EI, Boman K, Wetterberg L. J Eat Disorder. 2006;20:443–6.

Endicott J, Nee J, Harrison W, Blumenthal R. Psychopharm Bull. 2003;29:321–6.

Fairburn CG. Psychological Med. 1981;11:707–11.

Fairburn CG, Marcus MD, Wilson GT. Cognitive-behavioral therapy for binge eating and bulimia nervosa: a comprehensive treatment manual. In: Fairburn CG, Wilson GT, editors. Binge eating: nature, assessment, and treatment. New York: Guilford; 1993. pp. 361–404.

Friedman S, Even C, Dardennes R, Guelfi JD. Am J Psychiat. 2002;159:875–6.

Friedman S, Even C, Dardennes R, Guelfi JD. Light therapy, non-seasonal depression and night-eating syndrome. Canadian J Psychotherapy. 2004;49:790.

Gluck ME, Venti CA, Salbe AD, Krakoff J. Am J Clin Nutr. 2008;88:900–5.

Goel N, Stunkard AJ, Rogers NL, Van Dongen HPA, Allison KC, O'Reardon JP, Ahima RS, Cummings DE, Heo M, Dinges DF. J Biol Rhythms. 2009;24:85–94.

Goncalves MD, Moore RH, Stunkard AJ, Allison KC. Eur Eat Disorders Rev. 2009;17:184–90.

Guy W. ECDEU assessment manual for psychopharmacology. Washington, DC: US Department of Health, Education and Welfare Publication (ADM); 1976, pp. 76–338.

Howell MJ, Schenck CH, Crow SJ. Sleep Med Rev. 2009;13:23–4.

Lundgren JD, Amsterdam J, Newberg A, Allison KC, Wintering N, Stunkard A. Eat Weight Disord. 2009;14:45–50.

Miyaoka T, Yasukawa R, Tsubouchi K, Miura S, Shimizu Y, Sukegawa T, Maeda T, Mizuno S, Kameda A, Uegaki J, Inagaki T, Horiguchi J. Int Clin Psychopharmacol. 2003;18:175–7.

National Task Force on the Prevention and Treatment of Obesity. Dieting and the development of eating disorders in overweight and obese adults. Arch Int Med. 2000;160:2581–9.

NESHI, unpublished questionnaire, available from the authors.

Newberg AB, Amsterdam JD, Wintering N, Ploessl K, Swanson RL, Shults J, Alavi A. J Neucl Med. 2005;46:973–7.

O'Reardon JP, Stunkard AJ, Allison KC. Int J Eat Disord. 2004;35:16–26.

O'Reardon JP, Allison KC, Martino NS, Lundgren JD, Heo M, Stunkard AJ. Am J Psychiat. 2006;164:893–8.

Pawlow LA, O'Neil PM, Malcolm RJ. Int J Obes Rel Met Disord. 2003;27:970–8.

Schenck CH, Mahowald MW. Int J Eat Disord. 1994;15:343–56.

Spaggiari MC, Granella F, Parrino L, Marchesi C, Melli I, Terzano M. Sleep. 1994;17:339–44.

Striegel-Moore RH, Franko DL, Thompson D, Affenito S, Kraemer HC. Obes Res. 2006;14:139–47.

Stunkard AJ. The pain of obesity. Palo Alto, CA: Bull Publishing; 1976. pp. 41–63.

Stunkard AJ, Grace WJ, Wolff HG. Am J Med. 1995;19:78–86.

Stunkard AJ, Allison KC, Lundgren JD, Martino NS, Heo M, Etemad B, O'Reardon JP. J Clin Psychiat. 2006;67:1558–72.

Stunkard AJ, Allison KC, Lundrgren JD, O'Reardon JP. Obes Rev. 2009;10 (suppl 2): 69–77.

Verbeke G, Molenberghs G. Linear mixed models in practice: A SAS-oriented approach. New York: Springer; 1997. pp. 222–33.

Part XXXVIII
Selective Methods

Chapter 214
Psychological Assessment of Eating Disorders

Wayne A. Bowers and Alissa A. Haedt-Matt

Abbreviations

AN	Anorexia Nervosa
APA	American Psychiatric Association
BED	Binge Eating Disorder
BDI	Beck Depression Inventory
BN	Bulimia Nervosa
DSM	Diagnostic and Statistical Manual of Mental Disorders
EAT	Eating Attitudes Test
EDE	Eating Disorders Examination
EDE-Q	Eating Disorders Examination Questionnaire
EDI	Eating Disorders Inventory
EDNOS	Eating Disorder Not Otherwise Specified
HAMD	Hamilton Depression Scale
MMPI	Minnesota Multiphasic Personality Inventory

214.1 Introduction

Eating disorders, including anorexia nervosa (AN), bulimia nervosa (BN), binge eating disorder (BED), and eating disorders not otherwise specified (EDNOS), are complex and relatively uncommon disorders. The reported lifetime prevalence of AN and BN among women ranges from 0.3% to 3.7% and 1.0% to 4.2%, respectively. BED prevalence rates are 1–2.5%, while prevalence rates for EDNOS range from 1.3% to 30.1%. The *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV-TR; APA 2000) groups these disorders as they have common features in the context of separate or distinctive symptom clusters. However, a more parsimonious view has been generated that suggests looking at eating disorders as a whole based on common characteristics seen amongst all the eating disorders. This perspective, or Transdiagnostic model (Waller et al. 2007; Fairburn 2008), stresses common features associated with eating disorders (e.g., overvalued concerns about

W.A. Bowers (✉)

Department of Psychiatry, University of Iowa, 2916 John Pappajohn Pavilion,
Iowa City, IA 52242
e-mail: wayne-bowers@uiowa.edu

eating, weight, and shape) and proposes that those features better define the disorder and have more value when it comes to planning treatment. This model also suggests eating disorders share core psychopathology which helps maintain the disordered behavior. This includes concepts like clinical perfectionism, low self-esteem, an inability to cope appropriately with certain emotional states and interpersonal difficulties. The transdiagnostic model offers more utility when assessing these individuals from a psychological perspective.

Psychological assessment contributes vital quantitative and qualitative information concerning eating disorder symptomatology and general emotional and cognitive functioning. It can be extremely useful when assessing the level or intensity of the disorder and is of tremendous benefit when developing treatment strategies. Psychological testing for this population can be broadly divided into four areas: tests addressing eating disorder symptomatology, personality factors, general psychiatric symptomatology, and intellectual/neuropsychological functioning. For the purpose of this chapter, we will be focusing on eating disorder symptoms, personality factors, and general psychiatric features.

214.2 Tools for Assessing Disordered Eating

Assessment of eating disorder psychopathology can be accomplished by valid and reliable tests targeting this area Table 214.1. Brief, self-report measures such as the Eating Attitudes Test (EAT; Garner and Garfinkel 1979) and Eating Disorders Inventory (EDI; Garner 1991) identify specific aspects of the disorder including desire for thinness, binge/purge behavior, and restraint in eating. The EAT and the first three subscales of the EDI (drive for thinness, bulimic symptoms, and distortion of body image) are additionally useful for documenting change during treatment. A recent valuable assessment tool is the Eating Disorders Examination (EDE; Fairburn and Cooper 1993). This comprehensive, semi-structured interview is designed to assess broad clinical features of an eating disorder, especially attitudes and behaviors related to the illness over the preceding four weeks. Because the EAT, EDI, and EDE are valid, reliable, and easily administrated instruments, repeat administration of these tests can document severity of illness at admission as well as record improvements during treatment. They can also indicate areas of focus in treatment.

214.2.1 Eating Attitudes Test (EAT)

The EAT was designed as an objective self-report measure of the symptoms of an eating disorder in adults and older adolescents (Garner and Garfinkel 1979). The EAT-26 (Garner et al. 1982) is a 26-item scale, shortened from the original 40-item version. Items are rated on a 6-point Likert scale ranging from "never" to "always." The most symptomatic scores receive a score of 3, the next one a 2, and so on. At least three symptomatic responses receive a score of 0. The EAT-26 is often used as a screening tool for eating pathology, with a cut-point score of 20 or higher reflecting concern regarding eating attitudes. Although a score of 20 or higher does not necessarily indicate an individual has an eating disorder, it does indicate concerns regarding body weight, body shape, and eating. In addition to a total score, the EAT-26 yields three subscales: Dieting, Bulimia/Food, and Oral Control.

The EAT-26 has been found to differentiate AN, BN, and BED from controls and can differentiate AN and BN from BED. The test–retest reliability of this measure was high ($r = 0.89$) over a 4–5 week period (Banasiak et al. 2001). Cronbach's alpha for a sample of AN participants was 0.90, demonstrating high internal consistency (Hurley et al. 1990). While the EAT-26 cannot diagnose

Table 214.1 Measures of eating and related psychopathology

Name	Subscales	Format	Time to administer	Copyright
Disordered eating				
Eating Attitudes Test-26	• Dieting • Bulimia • Oral Control	26-item self-report questionnaire	5 min	David M. Garner and Paul E. Garfinkel (1979), David M. Garner et al. (1982)
Eating Disorder Inventory-3	*Eating disorder specific* • Drive for thinness • Bulimia • Body dissatisfaction *General psychological* • Low self-esteem • Personal alienation • Interpersonal insecurity • Interpersonal alienation • Interoceptive deficits • Emotional dysregulation • Perfectionism • Asceticism • Maturity fears *Composites* • Eating disorder risk • Ineffectiveness • Interpersonal problems • Affective problems • Overcontrol • General psychological Maladjustment	91-item self-report questionnaire	20 min	Psychological Assessment Resources, Inc.
Eating Disorders Examination	• Restraint • Eating concern • Shape concern • Weight concern • Behavioral frequencies	Semi-structured clinical interview (EDE)	45–60 min	EDE: Christopher G. Fairburn, Zafra Cooper, and Marianne O'Connor (2008)
		33-item self-report questionnaire (EDE-Q)	10 minutes	EDE-Q: Christopher G. Fairburn and Sarah Beglin (2008)
Personality				
Minnesota Multiphasic Personality Inventory-2	*Validity* • Lie • Infrequency • Correction *Clinical* • Hypochondriasis • Depression • Hysteria • Psychopathic deviate • Masculinity/femininity • Paranoia • Psychasthenia • Schizophrenia • Hypomania • Social introversion	567-item self-report questionnaire	60–90 min	University of Minnesota (2001) Test distributor: Pearson Assessments

Table 214.1 (continued)

Name	Subscales	Format	Time to administer	Copyright
NEO Personality Inventory-Revised	• Neuroticism • Extraversion • Openness to experience • Agreeableness • Conscientiousness	240-item self-report questionnaire	35–45 min	Psychological Assessment Resources, Inc.
Comorbid psychopathology				
Beck Depression Inventory-II	• Affective • Somatic	21-item self-report questionnaire	5 min	Pearson Assessments
Hamilton Depression Scale	–	17-item clinician rated interview	5–10 min	None

Summary of the content, format, administration time, and copyright information for each of the recommended measures of eating and related psychopathology

specific eating disorders it has been used extensively in research on eating disorders. The short nature of the measure and ease of administration lend its use to clinical populations and as a tool for repeated assessment of patients to track progress in treatment. The EAT-26 also has been shown to be a sensitive measure when assessing remission for individuals who have recovered from AN (Garner et al. 1982).

214.2.2 Eating Disorders Inventory (EDI)

The EDI (Garner 1991) is an easily administered self-report measure of psychological traits or constructs, shown to be clinically relevant in individuals with an eating disorder. The third version of the EDI (EDI-3; Garner 2004) provides normative information for females with eating disorders who range in age from 13 to 53 years. Normative protocols were collected in various outpatient and inpatient settings and these data are provided for the following DSM-IV-TR diagnostic groups: (a) AN-Restricting type; (b) AN-Binge-Eating/Purging type; (c) BN; and (d) EDNOS. It is a standardized measure yielding objective scores and profiles that are useful in case conceptualization and treatment planning for individuals who are diagnosed or may be diagnosed with an eating disorder. It can be completed in a relatively brief period and may be administered either individually or in a group setting.

The EDI-3 consists of 91 items organized into 12 primary scales, consisting of three eating-disorder-specific scales (Drive for Thinness, Bulimia, and Body Dissatisfaction) and nine general psychological scales (Low Self-Esteem, Personal Alienation, Interpersonal Insecurity, Interpersonal Alienation, Interoceptive Awareness, Emotional Dysregulation, Perfectionism, Asceticism, and Maturity Fears). The psychological scales are highly relevant to, but not specific to, individuals with an eating disorder. The EDI-3 also provides information regarding concepts that are consistent with psychological theories identified as relevant to development and maintenance of eating disorders.

The EDI-3 is a commonly used assessment instrument in the treatment outcome literature. Internal consistency reliability estimates are above 0.80 and test–retest coefficients range from 0.93 to 0.98. The Drive for Thinness, Bulimia, Body Dissatisfaction, and Interoceptive Awareness subscales of the EDI have demonstrated discriminant validity in distinguishing patients with eating disorders from psychiatric comparison groups (Garner 2004). While not appropriate for diagnosis, the EDI-3

is extremely useful as both a screening measure and a measure for tracking progress throughout treatment. It also is a valuable research tool for assessing areas of psychopathology, identifying meaningful patient subgroups, and assessing treatment outcome. Additionally, it can be helpful in defining areas for psychological intervention and the conceptualization and development of treatment plans.

214.2.3 Eating Disorders Examination (EDE)

The EDE (Fairburn and Cooper 1993) is a semi-structured clinical interview, considered to be the "gold standard" in eating disorder assessment. The EDE assesses frequency of disordered eating behaviors (binge eating, self-induced vomiting, laxative misuse, diuretic misuse, fasting, and excessive exercise) and specific eating disorder features on four subscales: Restraint, Eating Concern, Shape Concern, and Weight Concern. In addition to these subscales, the total EDE score can be used as an index of global eating disorder severity. Disordered eating attitudes and behaviors are assessed for the previous 28-day period using a seven-point scale (ranging from 0 to 6), with higher scores reflecting greater frequency (e.g., "On how many days over the past 28 days have you been consciously trying to restrict what you eat?") or severity (e.g., "Over the past 28 days, how important has your weight been in influencing how you feel, judge, think, or evaluate yourself as a person?").

The EDE has been used extensively in descriptive and treatment outcome research and is sensitive to change over time (Sysko et al. 2005). The EDE subscales have demonstrated good discriminant validity distinguishing between women with eating disorders and noneating disordered controls (Cooper et al. 1989; Fairburn and Cooper 1993), and reasonable concurrent validity with self-reports of vomiting, dietary restraint, and overeating (Rosen et al. 1990). Internal consistency of the EDE subscales has been reported to be 0.75–0.78 for Restraint, 0.68–0.78 for Eating Concern, 0.68–0.70 for Weight Concern, and 0.70–0.82 for Shape Concern (Cooper et al. 1989; Beumont et al. 1993). Further, studies using the EDE have documented high (kappa = 0.83–0.99) interrater reliability (Wilson and Smith 1989; Rosen et al. 1990) and test–retest reliability correlations of 0.70 or higher (Fairburn and Beglin 1994).

As a structured instrument, the EDE requires greater training of interviewers and more time to administer compared to the self-report assessments described above. However, the main advantage of the EDE is that it can be used to make diagnoses of DSM-IV eating disorders. Diagnostic items are assessed for the previous 3-month period to correspond to duration requirements in the DSM-IV. Thus, the EDE is ideal if the purpose of assessment is to generate reliable diagnoses.

The Eating Disorders Examination Questionnaire (EDE-Q; Fairburn and Beglin 1994) is a 33-item self-report version of the EDE interview. Like the EDE, the EDE-Q assesses the main behavioral and attitudinal features of eating disorders over a 28-day period, generating a total score and four subscale scores: Eating Concern, Shape Concern, Weight Concern, and Restraint. This scale also monitors methods of weight control including laxative and diuretic misuse, vomiting, and excessive exercising. Thus, the EDE-Q provides the same information as the EDE in a more easily administered self-report method. However, the EDE-Q should be used to screen for potential eating disorder cases and cannot be used to establish diagnoses.

The EDE-Q has been directly compared with the EDE in two published reports (Hurley et al. 1990; Rizvi et al. 2000), and has consistently performed well. In addition, Beglin and Fairburn (1994) found that the EDE-Q was better at case identification than the EAT-26, another commonly used eating disorder screening questionnaire. More recently, Luce and Crowther (1999) examined the internal consistency and test–retest reliability of the EDE-Q. In their analysis, Cronbach's alphas were used at two different time-periods to assess internal consistency. Alphas ranged from 0.78 and

0.81 for the eating concern subscale to 0.92 and 0.93 for the shape concern. Pearson correlations between time 1and time 2 for the subscales ranged from 0.81 to 0.94 and were all highly significant. These results further support the psychometric adequacy of this measure.

214.3 Tools for Assessing Personality

Awareness of state and trait aspects of personality can aid the psychotherapeutic process. Using assessment tools such as the NEO-PI-R (Costa and McCrae 1985) to assess these dimensional features and the Minnesota Multiphasic Personality Inventory-2 (MMPI-2; Butcher et al. 1989) to assess categorical features is a great asset for treatment and tracking progress. Assessment of personality functioning and the presence of Axis I comorbid disorders such as depression and anxiety disorders (Margolis et al. 1994) with paper and pencil inventories such as the MMPI-2 and/or NEO-PI help to identify patients with these vulnerabilities. Instruments that evaluate state personality features (MMPI-2) can alert health care providers to Axis II diagnoses and personality trait vulnerabilities. At the same time an awareness of personality traits (NEO-PI-R) can also aid the psychotherapeutic process while assessing important dimensional rather than categorical features.

214.3.1 Minnesota Multiphasic Personality Inventory (MMPI)

The MMPI is the most widely used and researched of all personality inventories (Butcher et al. 1989). There are more than 10,000 published articles, books, and chapters about this test. Reliability information on the MMPI-2 basic scales is good with correlation coefficients ranging from 0.67 to 0.92 for males and 0.58 to 0.91 for females. The second edition of the MMPI (MMPI-2; Butcher et al. 1989) is a broad-based paper and pencil questionnaire to assess major patterns of personality and broadly defined areas of psychopathology. It consists of 567 true or false questions that individuals answer based on how they are feeling on that day. The test is divided into two profiles. The validity scales consist of the lie (L), infrequency (F), and correction (K) scales. The L Scale includes common human faults that most people are willing to admit; thus, a person is likely to be exaggerating their virtues or claiming high moral standards if they do not admit to these faults. The F Scale includes pairs of items that ask similar questions to determine any inconsistencies where the clients have contradicted themselves in their responses. Finally, K Scale items are designed to reveal the clients' attempts at clinical defensiveness. Overall, the validity scales are useful in determining if the patient is presenting in an honest and forthright manner.

The clinical scales consist of 10 scales with 8 focusing on broad areas of psychopathology and 2 related to gender role beliefs and social comfort. Scale 1 (Hypochondriasis) is a psychologically based disorder manifested through physical symptoms and reflects a person's preoccupation with physical problems. Scale 2 (Depression) is designed to assess depressed mood or clinical depression. Scale 3 (Hysteria) deals with the client's specific physical complaints and denial of concern about the physical problems, and might detect an inability to deal effectively with life stresses. Scale 4 (Psychopathic Deviate) is intended to assess comfort with rules and regulations, hostility and/or anger, and a tendency to blame others for their problems. Scale 5 (Masculine–Feminine Interests) measures stereotypic masculine and feminine interests and addresses issues related to gender roles. Scale 6 (Paranoia) indicates defensiveness, suspiciousness, and wariness of other people's intentions or motives. Scale 7 (Psychasthenia) reflects feelings of anxiety, concern, obsessive ruminations, and

general maladjustment. Scale 8 (Schizophrenia) taps into feelings of alienation, differentness, confusion, bizarre sensations, isolation, and blatantly psychotic behavior. Scale 9 (Mania) suggests excessive energy, psychomotor acceleration, imperturbability, and scattered behavior. Finally, scale 10 (Social Introversion–Extraversion) measures social shyness, the preference for solitary pursuits, and lack of social assertiveness.

The results of the MMPI-2 are intended to develop inferences about the individual's unique behaviors and way of thinking. Test interpretation can help determine the severity of impairment, outlook on life, approaches to problem solving, typical mood states, likely diagnoses, and potential problems in treatment. The clinician is able to compare a respondent's choices to those of a large normative comparison group as well as to the results derived from earlier MMPI and MMPI-2 studies. The clinician forms inferences about the clients by analyzing their response patterns on the validity and clinical scales using published guidebooks to the MMPI-2. These texts are based on results obtained from over 10,000 MMPI/MMPI-2 research studies (Graham 1987).

Although the MMPI-2 may yield extensive information about the client, it is not a replacement for a clinical interview. The clinical interview helps the test administrator to develop conclusions that best apply to the client from the many hypotheses generated from test results. Furthermore, important aspects of the client's behaviors that were not reflected in the test results may emerge in an interview. For similar reasons, test results should not be interpreted until the clinician has obtained a biopsychosocial history from the client.

214.3.2 NEO-PI-R

The NEO-PI-R (Costa and McCrae 1992) is a 240-item questionnaire developed by factor analytic studies using adult volunteers aged 20–90 years. This test is designed to measure five major dimensions or domains of personality and some of the more important traits or facets that define each domain. Together, the 5 domain scales and 30 facet scores of the NEO-PI-R allow a comprehensive assessment of adult personality. There are five global domains: Neuroticism, Extraversion, Openness, Agreeableness, and Conscientiousness. The five global factors are measures of normal adult personality, and the ranges of very low, low, high, and very high reflect variation from the average or norm. Therefore, this scale represents traits that are present in all individuals to some degree; there is no "cutoff point" which separates those who have a trait from those who do not. Similarly, the ranges are conceptualized in terms of individual differences; high and low scores indicate neither health nor psychopathology, but the degree to which one presents each trait (McCrae and Costa 1990; Costa and McCrea 1992). Each of the five global domains is composed of six facets, which represent groups of intercorrelated traits. Grouping the five domains provides a comprehensive representation of an individual's emotional, interpersonal, experiential, attitudinal, and motivational styles (Costa and McCrea 1992). The NEO-PI-R has useful applications in counseling, clinical psychology, psychiatry, behavioral medicine and health psychology, vocational counseling and industrial/organizational psychology, and educational and personality research.

Neuroticism (N) indicates the range of emotional stability, even-temperedness, and adjustment versus the susceptibility to psychological distress and negative affect. High scores indicate that the presence of distress increases the likelihood that the individual will experience other negative states, including a vulnerability to irrational ideas, decreased impulse control, and a tendency to handle stressful situations poorly, whereas low scores indicate less possibility of maladjustment. Neuroticism taps into a general tendency to experience negative affect (fear, sadness, embarrassment, anger, guilt, or disgust) along with poor impulse control, and lower generalized coping ability. However, it is not

a measure of psychiatric pathology. A very high score on N can occur without significant diagnostic symptoms. Low scores on N reflect emotionally relaxed, calm, even-tempered individuals who can face upsetting situations without getting upset or rattled.

Extraversion (E) suggests the degree to which one is assertive, active, enjoys excitement and stimulation, and has a tendency to be upbeat, energetic, and optimistic. They tend to be cheerful, upbeat, are social, like people, and prefer large groups or gatherings. Individuals low on this dimension are reserved, serious, independent, even-paced, and prefer to be alone. Low scores on E may be seen as less friendly and may be sluggish in demeanor. These individuals may appear shy, but actually simply prefer to be alone or in small groups of well-known individuals. They are not exuberantly happy, but do not usually suffer from unhappiness or pessimism.

Openness (O) refers to one's openness to experience. Open individuals are curious about their intra- and interpersonal worlds and are willing to consider novel and unconventional ideas, experiences, and values. Their lives are experientially rich, and their thinking patterns would be considered intelligent, creative, and divergent. They experience both positive and negative emotions more keenly than do closed individuals. Those with low scores are likely to be conventional in their behavior and outlook, prefer familiar surroundings, and are closed or guarded in their emotional expression. Closed individuals are predictable and conservative in their approach to life and their outlook, and their emotional responses would be somewhat muted.

Agreeableness (A) is concerned with a person's preference between compassion and antagonism. Individuals high in A can be seen as soft-hearted, good-natured, trusting, and altruistic. These individuals tend to be helpful, responsive to others, and empathetic. Individuals low on this factor would be seen as cynical, abrasive, uncooperative, and irritable. They would also be described as vengeful, manipulative, and unfeeling.

Conscientiousness (C) is concerned with control of impulses and temptations and the ability to organize and follow through on tasks. Will to achieve is another way of understanding C. A high C is associated with academic and occupational success and achievement or may lead to compulsive behaviors or workaholic tendencies. These individuals are seen as scrupulous, punctual, and reliable. A high score reflects determined, strong-willed, and resolute behavior, while a low score on C implies less organization, a lower degree of drive and planning and less concern for adhering to standards. Spontaneous behavior lacking thought for the consequences is common for a low score. Low C's are not necessarily lacking in values or morals; however, they may be less exacting in applying them.

Each domain score is comprised of six characteristics, sometimes referred to as facets. If the evaluated person obtains a high score on a certain scale, there is a high probability that the person can be described as suggested above. The higher the score is, the more characteristic these descriptions are for the evaluated person. The same thing happens for low scores: the lower the score is the more characteristic are the typical descriptions for low scores. All dimensions of facets are bi-directional. In other words, a low score on any facet or domain means stronger tendencies toward the opposite character traits and behavioral tendencies.

214.4 Tools for Assessing Comorbid Psychopathology

Often, treatment of comorbid conditions presents as serious a challenge as the primary eating disorder. Affective disorders are the most common Axis I comorbid condition, present in 50–80% of eating disorders. Tests that evaluate depression include the Beck Depression Inventory (BDI; Beck 1961) and the Hamilton Depression Scale (HAMD; Hamilton 1960).

214.4.1 Beck Depression Inventory (BDI)

The BDI-Second Edition (BDI-II; Beck et al. 1996) is a 21-item self-report instrument intended to assess the existence and severity of symptoms of depression as listed in the DSM-IV-TR (APA 2000). Individual questions of the BDI assess mood, pessimism, sense of failure, self-dissatisfaction, guilt, indecisiveness, punishment, self-dislike, self-accusation, suicidal ideas, crying, irritability, social withdrawal, body image, work difficulties, insomnia, fatigue, appetite, weight loss, bodily preoccupation, and loss of libido. Items 1–13 assess symptoms that are psychological in nature, while items 14–21 assess more physical symptoms. Items have been changed to indicate increases or decreases in sleep and appetite, and items labeled body image, work difficulty, weight loss, and somatic preoccupation were replaced with items labeled agitation, concentration difficulty, and loss of energy. Many statements were reworded resulting in a substantial revision of the original BDI.

The BDI takes approximately 10 min to complete, although clients require a fifth–sixth grade reading level to adequately understand the questions (Groth-Marnat 1990). The BDI demonstrates high internal consistency, with alpha coefficients of 0.86 and 0.81 for psychiatric and non-psychiatric populations, respectively (Beck et al. 1988). Test–retest reliability for the BDI found that regardless of whether tests were reissued at 2 or 6 week intervals, scores on the inventory tended to reflect changes in the clinical depth of depression. Groth-Marnat (1990) reports that the revised BDI discriminates psychiatric from non-psychiatric patients and results in higher scores for patients with major depressive disorder compared to patients with dysthymic disorders. Cut score guidelines for the BDI-II are given with the recommendation that thresholds be adjusted based on the characteristics of the sample and the purpose for use of the BDI-II. Total scores between 5 and 9 are considered normal ups and downs; scores between 10 and 18 indicate mild to moderate depression; scores between 19 and 29 indicate moderate to severe depression; while scores between 30 and 63 suggest severe depression. Individuals who score below 4 may be engaging in possible denial of depression or faking good. Scores over 40 are significantly above even severely depressed persons and may suggest a possible exaggeration of depressive symptoms. The BDI is designed for use by trained professionals. While it should be administered by a knowledgeable mental health professional who is trained in its use and interpretation, it is often self-administered.

214.4.2 Hamilton Depression Scale (HAMD)

The HAMD (Williams 1989) is used to assess the severity of depressive symptoms present in both children and adults. The test measures the severity of depressive symptoms in individuals, often those who have already been diagnosed as having a depressive disorder. The 17-item version of the HAMD is more commonly used than the 21-item version. Examples of items for which interviewers must give ratings include overall depression, guilt, suicide, insomnia, problems related to work, psychomotor retardation, agitation, anxiety, gastrointestinal and other physical symptoms, loss of sex drive, hypochondriasis, loss of insight, and loss of weight. It is often used as an outcome measure of depression in evaluations of antidepressant psychotropic medications and is a standard measure of depression used in research of the effectiveness of depression therapies and treatments.

In the 17-item version, nine of the items are scored on a five-point scale, ranging from zero to four. A score of zero represents an absence of the depressive symptom being measured, a score of one indicates doubt concerning the presence of the symptom, a score of two indicates mild symptoms, a score of three indicates moderate symptoms, and a score of four represents the presence of severe symptoms. The remaining eight items are scored on a three-point scale, from zero to two, with zero representing absence of symptom, one indicating doubt that the symptom is present, and two representing

clear presence of symptoms. For the 17-item version, scores can range from 0 to 54. One formulation suggests that scores between 0 and 6 indicate a normal person with regard to depression, scores between 7 and 17 indicate mild depression, scores between 18 and 24 indicate moderate depression, and scores over 24 indicate severe depression.

The HAMD has demonstrated good interrater reliability (average correlation between two raters was.88; Bagby et al. 2004) and high internal consistency in longitudinal studies of patients with eating disorders (alpha ranged from 0.83 to 0.89; Williams 1989). A recent review examining the psychometric properties of this measure across multiple studies concluded that the measure had adequate internal reliability, convergent validity, and discriminant validity (Bagby et al. 2004). It can be administered prior to the start of medication and then again during follow-up visits, so that medication dosage can be changed in part based on the patient's test score. The HAMD is often used as the standard against which other measures of depression are validated.

Because the HAMD is an interviewer-administered and rated measure, there is some subjectivity when it comes to interpretation and scoring. Interviewer bias can impact the results so there is a need to have raters well trained in the use of this measure. As with the BDI, the HAMD is designed for use by trained professionals. While it should be administered by a knowledgeable mental health professional who is trained in its use and interpretation, it is often self-administered.

214.5 Applications to Other Areas of Health and Disease

Psychological assessment of individuals with an eating disorder creates information that can be utilized in treatment and for understanding these serious problems. However, there are other weight related problems for which psychological assessment may be useful. One area is weight management. Psychological assessment may identify an eating disorder that was not readily apparent. Also, assessment can suggest comorbid problems (e.g., depression or anxiety) that could interfere with an individual's attempt at weight loss. A second area is in the use of Bariatric Surgery. Most Bariatric Surgery programs involve psychological/psychiatric assessment prior to the initiation of surgery. Again, psychological assessment may reveal an unapparent eating disorder or co-morbid anxiety or depression that could influence the outcome of the surgery. More importantly, assessment also may reveal an individual's ability to maintain the suggested dietary habits after Bariatric Surgery.

Summary Points

- Eating disorders are complex and multifaceted problems.
- Psychological assessment can determine diagnosis or problem areas.
- Psychological assessment can contribute to effective treatment.
- Psychological assessment can potentially identify comorbid problems.
- Psychological assessment compliments history presented by the individual.

Definitions of Key Terms

Agreeableness: a person's preference between compassion and antagonism.
Asceticism: tendency to seek virtue through pursuit of spiritual needs.
Conscientiousness: concerned with control of impulses and temptations and the ability to organize and follow through on tasks.

Extraversion: the degree to which one is assertive, active, enjoys excitement and stimulation.

Interoceptive awareness: the understanding of internal awareness and bodily sensations.

Neuroticism: the range of emotional stability, even-temperedness, and adjustment.

Openness: one's openness to experience.

Perfectionism: a desire to be perfect and the belief that personal achievements need to be superior.

Restraint: restraint over eating.

Transdiagnostic model: an assumption that AN and BN are one disorder with a single cause.

References

American Psychiatric Association. Diagnostic and statistical manual of mental disorders, 4th ed. Washington, DC: American Psychiatric Association; 2000.

Bagby RM, Ryder AG, Schuller DR, Marshall MB. Am J Psychiat. 2004;161:2163–77.

Banasiak SJ, Wertheim EH, Koerner J, Voudouris NJ. Int J Eat Disorders. 2001;9:85–9.

Beck AT. Arch Gen Psychiat. 1961;4:561–71.

Beck AT, Steer RA, Garbin MG. Clin Psychol Rev. 1988;8:77–100.

Beck AT, Steer RA, Brown GK. Manual for the Beck depression inventory-II. San Antonio, TX: Psychological Corporation; 1996.

Beumont PJ, Kopec-Schrader EM, Talbot P, Touyz SW. Aust NZ J Psychiat. 1993;27:506–11.

Butcher JN et al. The Minnesota Multiphasic Personality Inventory-2 (MMPI-2): Manual for administration and scoring. Minneapolis, MN: University of Minnesota Press; 1989.

Cooper Z, Cooper PJ, Fairburn CG. Brit J Psychiat. 1989;154:807–12.

Costa PT, McCrae RR. The NEO personality inventory manual. Odessa, FL: Psychological Assessment Resources; 1985.

Costa PT, McCrae RR. NEO PI-R professional manual. Odessa, FL: Psychological Assessment Resources; 1992.

Fairburn CG. Cognitive-behavior therapy and eating disorders. New York, NY: Guilford Press; 2008.

Fairburn CG, Beglin SJ. Int J Eat Disorders. 1994;16:363–70.

Fairburn CG, Cooper Z. The eating disorder examination. In: Fairburn C, Wilson GT, editors. Binge eating: Nature, assessment and treatment, 12th ed. New York: Guilford Press; 1993. pp. 317–31.

Garner DM. Eating Disorders Inventory -2. Odessa, FL: Psychological Assessment Resources; 1991.

Garner DM. Eating Disorders Inventory 3: Professional manual. Odessa, FL: Psychological Assessment Resources; 2004.

Garner DM, Garfinkel PE. Psycholol Med. 1979;9:273–9.

Garner DM, Olmstead MP, Bohr Y, Garfinkel PE. Psychol Med: 1982;12:871–8.

Graham JR. The MMPI: A practical guide, 2nd ed. New York: Oxford Press; 1987.

Groth-Marnat G. The handbook of psychological assessment. 2nd ed. New York: John Wiley & Sons; 1990.

Hamilton M. J Neurol Neurosur Ps. 1960;23:56–62.

Hurley JB, Palmer RL, Stretch D. Int J Eat Disorders. 1990;9:419–24.

Luce KH, Crowther JH. Int J Eat Disorders. 1999;25:349–51.

Margolis R. Int J Eat Disorders. 1994;2:231–6.

McCrae RR, Costa PT. Personality in adulthood. New York: Guilford Press; 1990.

Rizvi SL, Peterson CB, Crow SJ, Stewart Agras W. Int J Eat Disorders. 2000;28:311–6.

Rosen JC, Vara L, Wendt S, Leitenberg H. Int J Eat Disorders. 1990;9:519–28.

Sysko R, Walsh BT, Fairburn CG. Int J Eat Disorders. 2005;37:100–6.

Waller G, Cordery H, Corstorphine E, Hinrichsen H, Lawson R, Mountford, V, Russell, K. Cognitive behavioral therapy for eating disorders: A comprehensive treatment guide. Cambridge, UK: Cambridge University Press; 2007.

Williams JBW. Arch Gen Psychiat. 1989;45:742–7.

Wilson GT, Smith D. Int J Eat Disorders. 1989;8:173–9.

Chapter 215
Behavioral Assessment of Pediatric Feeding Problems

Colleen Taylor Lukens

Abbreviations

BAMBI   Brief Autism Mealtime Behavior Inventory
BPFAS   Behavioral Pediatric Feeding Assessment Scale
CEBI   Children's Eating Behavior Inventory
DINE   Dyadic Interaction Nomenclature for Eating
GRSFS   Global Rating Scale for Feeding Situations
IFS   Infant Feeding Scale
MICS   Mealtime Interaction Coding System
MOS   Mealtime Observation Schedule
ORI-CEBI   Oregon Research Institute Child Eating Behavior Inventory
STEP   Screening Tool of Feeding Problems
T1DM   Type 1 diabetes mellitus

215.1 Pediatric Feeding Disorders

Feeding behavior in young children lies on a continuum from typical eating behavior, which allows caloric intake adequate for weight gain, linear growth, and satisfactory nutritional intake, to maladaptive eating behavior, which interferes with satisfactory nutritional intake such that weight gain, health, and development are compromised. Pediatric feeding disorders are indicated if a child's maladaptive eating behavior results in insufficient weight gain or significant nutritional deficits or if a child demonstrates severely disruptive behavior at mealtime. It has been reported that clinically significant feeding disorders occur in young children at a 25–45% incidence rate, and in up to 80% of children with developmental disabilities (Linscheid et al. 2003).

Pediatric feeding disorders can be conceptualized in a number of ways; however, the biopsychosocial model is an efficient one to account for both etiological factors and intervention strategies (Kedesdy and Budd 1998; Crist and Napier-Phillips 2001; Fischer and Silverman 2007). Biological

C.T. Lukens (✉)
Pediatric Feeding and Swallowing Center, The Children's Hospital of Philadelphia,
34th Street & Civic Center Boulevard, Philadelphia, PA 19104, USA
e-mail: lukens@email.chop.edu

Table 215.1 Key features of pediatric feeding disorders

1. Pediatric feeding disorders are indicated if a child demonstrates eating behavior that results in insufficient weight gain or significant nutritional deficits or if a child displays disruptive mealtime behavior that is distressing to caregivers.
2. Feeding disorders are observed in 25–45% of the general pediatric population.
3. Feeding disorders can manifest as food refusal, selective eating, and disruptive mealtime behavior.
4. Although they can originate with physiological conditions, feeding disorders are often maintained by environmental factors.
5. Support for a behavioral approach to assessment and intervention is well documented.

This table lists the key facts about pediatric feeding disorders

factors contributing to feeding problems include, among others, anatomical difficulties (e.g., delayed development of oral–motor skills, structural abnormalities in the oral cavity, dysphagia) and compromised medical status (e.g., respiratory disorders, gastrointestinal difficulties, neurological conditions). Psychological factors influencing feeding development include the developmental status of the child, the child's temperament, parental management of mealtime behaviors, and the quality of parent–child interactions. Finally, social factors such as family and socioeconomic variables can contribute to or maintain feeding difficulties. The biopsychosocial model concedes that these variables rarely exert their influence in isolation and allows for the interactive nature of these factors.

Consistent with this model, multidisciplinary intervention is often warranted in the treatment of pediatric feeding disorders. For example, medication management or surgical intervention can be implemented to manage gastrointestinal problems, or oral–motor practice can be introduced to advance mechanical skills. However, once these factors have been identified and ameliorated, challenging mealtime behaviors often persist (Table. 215.1). Although feeding problems may originate with a medical or developmental condition, maladaptive mealtime behaviors that were once a result of organic factors often fall under the control of environmental contingencies (Babbitt et al. 1994). This maintenance of maladaptive mealtime behaviors by environmental factors necessitates a behavioral approach to their assessment and treatment, and the effectiveness of the evaluation and treatment of pediatric feeding problems from a behavioral perspective has been well documented (Kedesdy and Budd 1998; Kerwin 1999; Linscheid 2006).

Behavioral intervention programs focus on manipulating antecedent situations and environmental contingencies with goals of modifying maladaptive mealtime behavior, which in most cases subsequently improves nutritional intake and promotes weight gain and linear growth. Behavioral intervention is indicated once medical and mechanical difficulties have been addressed, in order to minimize the adverse effects of physical discomfort or skill deficit. Other considerations for intervention include the feasibility of treatment, medical necessity, and caregiver receptiveness to intervention, and these factors are influenced by the nature and severity of the feeding problem (Kedesdy and Budd 1998). The information necessary for determining the appropriate course of intervention is gathered during interdisciplinary evaluation, which includes behavioral assessment.

Once intervention has been determined to be necessary and viable, treatment goals are established. Goals of behavioral intervention may include modifying nutrition-related behavior such as increasing the volume and variety of foods consumed or increasing caloric intake. Targets of treatment can be related to skill development as well and include advancing the texture of foods eaten and improving a child's willingness to feed himself or herself. Finally, the focus of intervention can be a child's challenging behavior at mealtime or parent–child interactions (e.g., decreasing disruptive mealtime behavior, decreasing caregiver stress at mealtimes, improving the quality of parent–child interactions at mealtimes) (Linscheid et al. 2003; Fischer and Silverman 2007). Just as necessary and

sufficient conditions for treatment are determined via behavioral assessment, treatment goals are formulated based on information gathered during behavioral evaluation.

215.2 Behavioral Assessment of Feeding Disorders

Behavioral assessment methods are utilized in both research and clinical practice in the evaluation of a variety of behavioral disorders. Behavioral assessment can be used for diagnostic and prognostic purposes; more specifically, it can be used to identify the nature or cause of particular problems or to predict future behavior. In addition, behavioral assessment can provide normative data for comparison purposes. Information necessary for the design of effective treatment programs can also be garnered via behavioral assessment. Finally, baseline and outcome data necessary for evaluating treatment efficacy can be obtained through behavioral assessment.

Fundamental tenets of the behavioral assessment of feeding disorders, based on those described by Mash and Terdal (1997), in regard to general behavioral difficulties, are listed in Table. 215.2. A variety of tools and methods have been designed to understand behaviors that are associated with poor nutritional intake (Crist et al. 1994). These evaluation methods allow the user to gather information regarding presenting concerns, contributing factors, and maintaining stimuli. More specifically, behavioral assessment is utilized to evaluate the relationship between mealtime behavior and environmental contingencies (Kedesdy and Budd 1998). Also, treatment goals are established on the basis of information gathered during behavioral assessment. The most common methods for evaluating mealtime behavior include caregiver interviews, observational coding systems, and standardized caregiver self-report measures.

215.2.1 Clinical Interview

The clinical interview is used universally in evaluating behavioral difficulties in young children and is among the most widely used assessment tools in clinical practice (Mash and Terdal 1997). In the behavioral assessment of pediatric feeding problems the clinical interview is utilized to garner information regarding the nature of a child's feeding difficulty, information about the child, information

Table. 215.2 Tenets of behavioral assessment

1. Behavioral assessment is based on the conceptualization of feeding problems as a class of behaviors that interfere with nutritional intake or cause significant caregiver distress and are maintained by environmental contingencies.
2. Key components of behavioral assessment include understanding child behavior, caregiver behavior, and caregiver–child interactions at mealtimes.
3. Behavioral assessment is used to examine behaviors that are directly of interest and considered for modification, rather than behaviors that are indicative of underlying causes of feeding problems.
4. Behavioral assessment may be enhanced by considering multi-method evaluation.
5. Behavioral assessment tools are most useful if they can be utilized as part of an ongoing assessment process rather than at a single time period.
6. Behavioral assessment has an empirical basis (i.e., using psychometrically sound instruments and procedures that are examined empirically).

This Table describes the fundamental tenets of behavioral evaluation as applied to the assessment of pediatric feeding disorders

about the primary feeder, and information regarding caregiver and child interactions, as well as other potential contributing and maintaining factors. It serves as a screening tool to guide further assessment and intervention. Such interviews are typically not standardized, but general models have been created by specialists in the field (Kedesdy and Budd 1998). Most often, the primary caregiver is the source of information gathered during a clinical interview.

215.2.2 Behavioral Observation

Direct observational methods involve the recording of behavior, following established coding systems, and include methods for evaluating the reliability of the information gathered (Mash and Terdal 1997). The advantages of direct observation are numerous, including direct access to behavior, objective evaluation of mealtime behavior, and methods for establishing the reliability of data collected. However, bias may still exist, including the reactivity of the individual being observed and the bias of the observer. Also, direct observational methods are often complex, costly, and time consuming.

Direct mealtime observations of feeding behavior are utilized to objectively evaluate the mealtime routine as well as specific caregiver and child behaviors, all of which may be targets for intervention. Such observations can be conducted and evaluated with or without structured coding systems. For example, specific mealtime behaviors can be identified and their frequency recorded during pre-established intervals (Fig. 215.1). Alternatively, mealtime behaviors can be coded utilizing a variety of standardized observational coding systems, including the Dyadic Interaction Nomenclature for Eating (DINE; Stark et al. 2000), the Mealtime Observation Schedule (MOS; Sanders et al. 1993), the Global Rating Scale for Feeding Situations (GRSFS; Stark et al. 1994), and the Mealtime Interaction Coding System (MICS; Hayden et al. 1998). These standardized measures require review of videotaped mealtimes in order to code the frequency of occurrence of a variety of caregiver and child mealtime behaviors. Two of these measures are described in detail below, and further information can be accessed by contacting the authors of each system.

In addition, functional analysis or functional assessment can be conducted to evaluate observed mealtime behavior. Functional assessment entails the identification of functional relationships between mealtime behavior, and environmental determinants and contingencies (Chung and Kang 2006). Functional analysis has been utilized in a number of studies evaluating mealtime behavior problems in young children and has led to the identification of the most common functions of challenging mealtime behaviors (Munk and Repp 1994; Girolami and Scotti 2001; Piazza et al. 2003). Such assessment has facilitated the development of effective behavioral intervention for the treatment of pediatric feeding disorders.

215.2.3 Caregiver Self-Report Measures

Standardized caregiver self-report measures are utilized to evaluate a caregiver's perception of mealtime behavior problems. Self-report measures are typically questionnaires that require caregivers to provide information regarding parenting practices, child behavior, or emotions related to mealtimes (Mash and Terdal 1997; Crist and Napier-Phillips 2001). Most commonly, caregiver report inventories identify specific mealtime behavioral difficulties encountered by caregivers and assess the frequency and severity of these behaviors.

Examples of caregiver report inventories include the Behavioral Pediatric Feeding Assessment Scale (BPFAS; Crist and Napier-Phillips 2001), the Children's Eating Behavior Inventory (CEBI;
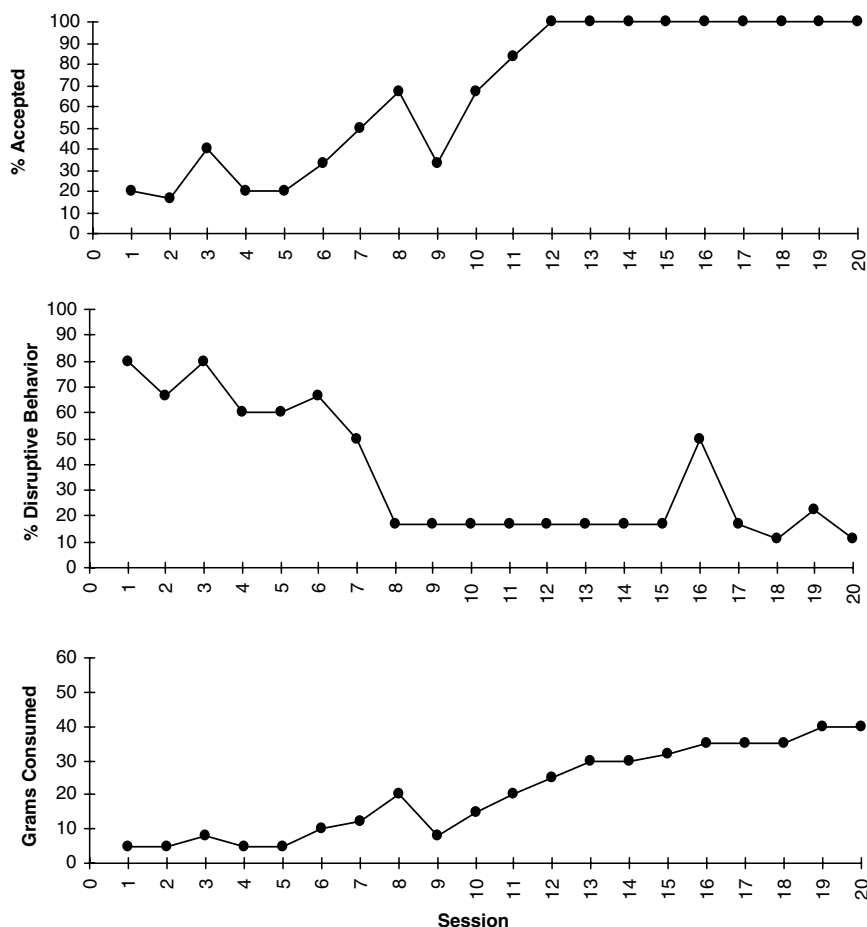
Fig. 215.1 Coding of mealtime behavior. This figure depicts the coding of mealtime behavior without the use of a standardized coding system. Mealtime behaviors of interest (e.g., percentage of offered bites consumed, percentage of intervals in which disruptive behavior is observed, and grams of food consumed) are identified and defined. The occurrence of these behaviors is then recorded according to pre-established intervals. Data is summarized and examined over the course of intervention

Archer et al. 1991), the Screening Tool of Feeding Problems (STEP; Matson and Kuhn 2001), the Infant Feeding Scale (IFS; Chatoor et al. 1997), the Brief Autism Mealtime Behavior Inventory (BAMBI; Lukens and Linscheid 2008), and the Oregon Research Institute Child Eating Behavior Inventory (ORI-CEBI; Lewinsohn et al. 2005), among others. Five of these measures are described below, and each is readily available by contacting the authors.

Caregiver report inventories are often preferable to functional assessment or behavioral observation due to their ease of use and efficient assessment of mealtime behaviors. Caregiver report inventories have been found to be comparable to direct behavioral observation. For example, data collected by Piazza-Waggoner and colleagues (2008) support the utility and validity of the BPFAS as compared to direct observation of mealtime behavior. However, when considering their use in research or clinical practice, it is imperative to consider the most common biases associated with self-report including social desirability, acquiescence, demand characteristics, faking, or lying. As well, it is important to consider the psychometric properties of such measures including reliability, validity, and normative data (Mash and Terdal 1997).

215.3 Behavioral Assessment Tools

215.3.1 Observational Coding Systems

215.3.1.1 Mealtime Observation Schedule (MOS)

The MOS (Sanders et al. 1993) is a direct observation measure of children's eating behavior and parental management of mealtime behavior. The MOS was derived from the Family Observation Schedule (FOS), which was predominantly used in the evaluation of parent–child interactions, for children presenting with oppositional behavior.

The psychometric properties of the MOS were examined in a 1993 study conducted by Sanders and colleagues. The authors revised the FOS by including items related to mealtime behavior problems demonstrated by young children in a series of pilot studies. A preliminary version of the measure with 30 items was examined for reliability. Item retention, deletion, and addition resulted in 17 categories of childhood mealtime behavior and 15 categories of parent behavior (Table 215.3). The MOS requires that users review videotaped meals and code the presence of parent and child behaviors during 10-s intervals over the course of a 20-min meal.

In the 1993 validation study, interrater reliability was determined to be adequate, with kappa coefficients ranging from .71 to .99 for the various parent behaviors assessed and from .50 to .99 for the child behaviors evaluated. In the evaluation of the validity of the measure, the authors examined correlations between in-home parent-reported assessment of mealtime behavior difficulties and observational measures of mealtime behavior as assessed by the MOS. The authors found that mealtime difficulty as reported by parents was significantly correlated with mealtime difficulties as assessed by the MOS.

Table 215.3 Behavior categories of the mealtime observation schedule

Child Behaviors	Parent Behaviors
Disruptive	*Aversive*
Noncompliance	Aversive contact
Complaint	Aversive prompt
Demands	Aversive specific instruction
Physical Negative	Aversive vague instruction
Oppositional	Aversive eating comment
Noninteractional	Aversive social attention
Refuses food	
Holds food	
Spits/vomits	
Leaves table	*Nonaversive*
Plays with food	Praise
	Contact
Appropriate	Prompt
Requests food	Specific instruction
Prepares food	Vague instruction
Bites	Eating comment
Chews	Social attention
Appropriate verbal	Presents food
Engaged in activity	Removes food

This table lists the parent and child mealtime behaviors that are recorded when utilizing the MOS. The occurrence of each behavior during 10-s intervals is recorded

The researchers utilized the MOS to examine the relationship between parental management strategies and the mealtime behavior of toddlers and preschool-age children. They compared these variables between children referred to a clinic for the treatment of feeding difficulties and children without identified feeding problems. The results of the study indicated that children with feeding difficulty demonstrated more disruptive mealtime behaviors as measured by the MOS than children without feeding difficulty, lending support to the validity of the MOS in the evaluation of childhood mealtime behavior problems. In addition, parents of children with feeding difficulty demonstrated higher levels of negative and coercive mealtime behavior management strategies than did parents of children without feeding difficulty.

Sanders and colleagues then used the MOS to examine the mealtime behavior of children with cystic fibrosis as compared to children referred for treatment of feeding difficulties and children with no identified feeding problems (Sanders et al. 1997). They found that children referred to a clinic for treatment of feeding problems demonstrated higher levels of disruptive behavior than children not referred, and children with cystic fibrosis did not differ from children referred for treatment of feeding difficulties, lending partial support to the hypothesis that children with cystic fibrosis demonstrate clinically significant levels of disruptive mealtime behavior. As well, mothers of children with cystic fibrosis demonstrated higher levels of aversive mealtime behavior and lower levels of positive attention than did mothers of children in the comparison groups.

The MOS shows promise as an objective rating scale for documenting observed mealtime behavior problems in young children as well as the mealtime behaviors of caregivers. The MOS has been demonstrated to be a reliable instrument and preliminary data suggests that the MOS can discriminate between children with significant feeding problems and those without. Replication of these findings and further validation are warranted to support its use in research and clinical work with children presenting with feeding problems.

215.3.1.2   Dyadic Interaction Nomenclature for Eating (DINE)

Similar to the MOS, the DINE (Stark et al. 2000) is a behavioral coding system used in the assessment of caregiver and child mealtime behaviors and interactions through direct observation. The DINE was created to examine the occurrence of mealtime behavior problems in children with cystic fibrosis as compared to children without cystic fibrosis in an objective manner (Stark et al. 2000). It was created on the basis of the literature describing children with feeding problems as well as general parenting. The DINE requires the user to carefully review mealtimes that are video recorded. Most behaviors on the DINE are coded as to their occurrence or nonoccurrence during 10-s intervals; however, the overall frequency of a few behaviors is recorded as well.

The DINE is comprised of three categories: parent behavior, child behavior, and child eating behavior (Table 215.4). The parent behavior category requires the coder to indicate the presence of direct commands, interrupted commands, coaxing, parent verbalizations, reinforcement provision, physical prompting, and feeding during mealtimes. The child behavior category designates the presence of noncompliance with direct commands, food refusal, complaints, requests for food, child verbalizations, and occurrences of the child leaving the table. Finally, the child's eating behaviors that are recorded include the number of bites of food eaten and sips of fluid taken. In the initial study, using the DINE, the authors found that although children with cystic fibrosis and their parents did not differ from children without cystic fibrosis in the rate of mealtime behavior difficulty, children with cystic fibrosis and their parents engaged in problematic mealtime behaviors more frequently. As well, parenting strategies utilized did not result in children with cystic fibrosis meeting specified dietary requirements.

Table 215.4 Coding categories in the dyadic interaction nomenclature for eating (Adapted by permission from Stark et al. 2000)

Parent behaviors	Child behaviors	Child eating
Direct commands	Away from table	Bites
Indirect commands	Child talk	Sips
Coax	Food refusal	
Feed	Requesting food	
Physical prompt	Noncompliance	
Reinforcement		
Parent talk		

This table includes the categories of parent and child behavior recorded when utilizing the DINE. Occurrence of parent and child behaviors during 10-s intervals is recorded, while overall frequency of child eating behaviors is recorded

The DINE has been used more recently to examine the mealtime behavior of infants, toddlers, and school-aged children with cystic fibrosis. For example, Powers and colleagues (2005) used the DINE to study the rate of mealtime behavior difficulties in infants and toddlers with cystic fibrosis as compared to children without cystic fibrosis. The authors found that although children with cystic fibrosis did not differ from a comparison group in the rate or frequency of mealtime behavior difficulties, parents of children with cystic fibrosis engaged in higher rates and a higher frequency of providing commands during mealtimes. The results suggested, as did those of Stark and colleagues in the original study, that mealtime behavior problems prevented children with cystic fibrosis from meeting nutritional needs. Similar results were found in a study examining mealtime behaviors of school-aged children with cystic fibrosis (Stark et al. 2005).

The DINE has also been utilized in research with children with type 1 diabetes mellitus (T1DM). Similarly, the authors found that children with T1DM did not differ from children without T1DM in the presence of mealtime behavior difficulties, contrary to what is often reported by parents during clinical interviews (Patton et al. 2004). The authors subsequently utilized the DINE to examine the relationship between mealtime behavior difficulties and glycemic control in children with T1DM (Patton et al. 2006a). They found that although children with T1DM and their parents engaged in mealtime behaviors and interactions that did not differ from children without T1DM, higher levels of mealtime behavior difficulties were significantly related to poorer glycemic control and dietary adherence.

The DINE is a mealtime coding system that has been effectively utilized to evaluate the mealtime behavior and parent–child interactions that occur around mealtimes (details on the coding system are available from the authors). It has been demonstrated to be a valid research tool, compared to psychometrically sound caregiver report measures of mealtime behavior difficulties and correlated with health outcomes in pediatric populations. The clinical utility of the DINE has not been reported, likely because of the complex nature of the scoring system, which requires review of video-recorded mealtimes and reliability ratings.

215.3.2 Standardized Caregiver Report Inventories

215.3.2.1 Behavioral Pediatric Feeding Assessment Scale (BPFAS)

The BPFAS is a caregiver-report instrument utilized to examine patterns of parent and child behavior around mealtimes (Crist and Napier-Phillips 2001). The authors originally created the measure to evaluate mealtime behavior problems commonly observed in young children with cystic fibrosis as

Table 215.5 Categories and sample items from the Behavioral Pediatrics Feeding Assessment Scale (Adapted by permission from Crist et al. (1994). For more information, please contact the author: William.Crist@iwk.nshealth.ca)

	Never	sometimes	always		Problem for you	
Child behavior						
My child eats fruits	1 2 3	4	5		Yes	No
My child comes readily to mealtime	1 2 3	4	5		Yes	No
My child tantrums at mealtime	1 2 3	4	5		Yes	No
My child has a poor appetite	1 2 3	4	5		Yes	No
Parent's feeling/strategies						
I get anxious when feeding my child	1 2 3	4	5		Yes	No
I use threats to get my child to eat	1 2 3	4	5		Yes	No
I feel confident my child gets enough to eat	1 2 3	4	5		Yes	No

This table includes sample items from the BPFAS. Items from both the child and parent sections of the measures are listed

compared to children with no health concerns (Crist et al. 1994). The measure was created using items from the few available rating scales of childhood-feeding difficulties in combination with original items designed specifically for the scale.

The result was a 35-item standardized caregiver report inventory, designed to obtain information on the mealtime behavior of children between the ages of 9 months and 8 years of age (Table 215.5). Twenty-five items are descriptions of childhood mealtime behaviors while the remaining ten items describe caregiver strategies for managing mealtime behavior problems. The measure requires a caregiver to indicate how often his or her child engages in a particular eating behavior or how often the caregiver uses a particular management strategy, using a five-point Likert scale ranging from "Never" to "Always." Items are phrased both positively and negatively, and some items are transformed such that higher scores represent more problematic mealtime behavior. Responses to the Likert-scale items are summed to create a total frequency score.

In addition, a total problem score provides information on the respondent's perception of a child's behavior as problematic. Caregivers are asked to indicate if they consider a particular child behavior or parental strategy to be a problem, indicating "Yes" or "No." The items considered to be problematic by caregivers are summed to create a total problem score.

The BPFAS demonstrates satisfactory psychometric properties, as indicated in two validation studies conducted by Crist and colleagues. In a 1994 study examining the mealtime behavior of children with cystic fibrosis as compared to children with no health problems, the authors reported reliability data for the BPFAS collected from a previous pilot study. They noted that evaluation of internal consistency using Cronbach's alpha indicated values of.88 for the full scale,.84 for the child section, and.74 for the parent section. Also, test–retest reliability over a 2-year interval revealed significant correlations, ranging from.82 to.85 for each of the subscales and the total score.

A second validation study was conducted by Crist and colleagues in 2001. Similar data on internal consistency was revealed (.76 for the full scale in a sample including both children referred for feeding problems and a normative sample). With regard to validity, the BPFAS was shown to discriminate between children referred to clinics for feeding problems and a normative sample. In their 2001 validation study, Crist and colleagues conducted a factor analysis on the 25 child-related items of the BPFAS. A five-factor structure was identified in each of three independent samples. The interpretable factors identified included picky eaters, toddler refusal – general, toddler refusal – textured foods, older children refusal – general, and stallers.

The picky eaters factor comprised items related to a child's willingness to try new foods. The toddler refusal – general factor included items describing disruptive mealtime behavior such as whining, tantrum behavior, and expelling food, whereas the toddler refusal – textured foods factor reflected

refusal behavior specific to chewable foods. The older children – general factor was composed of items unique to older children including delaying meals by talking, getting up from the table, and requesting alternative foods after a mealtime. The authors noted that the stallers factor was less well-defined than other factors; however, it included items such as letting food sit in the mouth, preference for drinking over eating, and not coming readily to the table.

The BPFAS has subsequently been used to evaluate the mealtime behavior of children with chronic illnesses in which feeding problems are prevalent. For example, the BPFAS has been frequently used with the population of children with cystic fibrosis. Crist and colleagues originally designed and validated the measure as part of a line of research examining the mealtime behavior problems of children with cystic fibrosis as compared to healthy children. In these aforementioned studies, the authors used the BPFAS and determined that parents of children with cystic fibrosis perceived their children's behavior as more problematic than a comparison group and that behavioral problems and caloric intake were negatively correlated (Crist et al. 1994). Given this research using the BPFAS with children with cystic fibrosis, the 2001 Consensus Committee on nutrition in children with cystic fibrosis recommended that the BPFAS be utilized in clinical assessment and intervention for children with cystic fibrosis (Borowitz et al. 2002).

Powers and colleagues have utilized the BPFAS in a series of studies assessing the mealtime behavior of infants and toddlers with cystic fibrosis. In a 2002 study, the researchers found that parents of infants and toddlers with cystic fibrosis indicated a higher occurrence of mealtime problems and a greater frequency of child-related behavior problems at mealtimes than did parents of children without significant health difficulties (Powers et al. 2002). Problems endorsed at the highest rate by the families of children with cystic fibrosis included willingness to try new foods, willingness to eat vegetables, poor appetite, and preference for fluids over solid food. In a similar study, the researchers found higher levels of mealtime behavior difficulties in infants and toddlers with cystic fibrosis as compared to children with no identified health difficulties on all four subscales of the BPFAS (Mitchell et al. 2004). In a 2003 intervention study, Powers evaluated the outcome of a behavioral intervention to increase caloric intake in toddlers with cystic fibrosis. The authors utilized the BPFAS at baseline to ensure that there were no significant differences between the comparison and treatment groups in parent-reported feeding difficulties prior to intervention (Powers et al. 2003).

More recently, the BPFAS has been used to assess the mealtime behavior of children with T1DM. Patton and colleagues (2006b) examined the utility of the BPFAS for assessment of mealtime behaviors in children with T1DM and utilized the BPFAS to delineate the patterns of mealtime behaviors common to children with T1DM. In examining the factor structure of the first 25 items of the BPFAS (Child Frequency items), the researchers found that the factors extracted mirrored the five factors identified by Crist and Napier-Phillips (2001). However, they noted two additional factors that are potentially unique to children with T1DM, including a dietary burden factor and a disruptive behavior factor. The dietary burden factor included items such as poor appetite, enjoys eating, and comes readily to the table. The disruptive behavior factor included items related to tantrum and crying behavior. As well, the authors noted that children with T1DM, similar to children with identified feeding disorders, demonstrated food refusal, picky eating, stalling, and difficulty advancing the texture of foods eaten.

The BPFAS has also been utilized to assess eating and mealtime behavior problems in children with autism. Martins et al. (2008) compared the eating behavior of children with autism to typically developing children and siblings using subsections of the BPFAS. The authors found that although statistically significant differences between the eating behavior of children with autism and typically developing children were noted, these differences were diminutive and not likely to be clinically relevant. Thus, the findings of this study provide a catalyst for ongoing research examining the clinical utility of measures such as the BPFAS.

The BPFAS has been used to evaluate the outcome of behavioral intervention for the treatment of pediatric feeding problems. For example, Byars and colleagues utilized the BPFAS to confirm the presence of a significant behavioral feeding problem prior to admission to a multicomponent behavioral intervention program, targeting decreased dependence on gastrostomy tube feedings (Byars et al. 2003). The authors found that at baseline, the group referred for behavioral intervention did not differ from the reference group described in the original Crist and Napier-Phillips(2001) study. This study suggests clinical implications for the BPFAS as a screening tool to determine the presence of significant mealtime behavioral problems warranting intervention.

In sum, the BPFAS is a tool useful in research and clinical practice. As a research tool, the BPFAS has been used to identify feeding problems associated with specific pediatric conditions, for example, cystic fibrosis and T1DM, as well as in children referred for treatment of pediatric feeding problems. Additionally, the BPFAS has allowed researchers to delineate patterns of challenging mealtime behavior observed in these populations, better guiding intervention for these children. Also, the BPFAS can be administered and scored quickly and thus has practical uses in a clinical setting. It can allow health professionals to monitor the presence of feeding difficulties in specific populations of children at-risk for nutritional deficiency, facilitating more prompt intervention. The use of the BPFAS as a proxy for observed mealtime behavior is supported by the research of Piazza-Waggoner and colleagues who found that parental responses on the BPFAS are a reliable report of actual child mealtime behavior (Piazza-Waggoner et al. 2008).

215.3.2.2 Children's Eating Behavior Inventory (CEBI)

The CEBI (Archer et al. 1991) was designed to evaluate the presence of eating and mealtime behavior problems in children with a variety of medical and developmental disorders. The authors created the CEBI due to the dearth of measures available to assess mealtime behavior problems in young children. The authors intended to create an objective measure that could screen not only for the frequency and severity of mealtime problems, as with the BPFAS, but also evaluate the level of caregiver stress related to mealtime behavior.

The CEBI was created from items generated by specialists who worked with children with eating and mealtime behavior problems, as well as literature regarding the assessment and treatment of feeding problems. The inventory was originally a 71-item questionnaire, since reduced to 40 items. Twenty-eight items relate to food preference, motor skills, and mealtime behavior in young children, while 12 items evaluate caregiver emotion and interactions related to mealtime behavior.

As with the BPFAS, a caregiver indicates how often a child engages in a particular eating behavior or how often the caregiver experiences a particular emotion at mealtimes, using a five-point Likert scale with anchors of never, seldom, sometimes, often, and always. Items are phrased both positively and negatively, and some items are transformed such that higher scores represent more problematic mealtime behavior. Responses to the Likert scale items are summed to create a total eating problem score.

Similar to the BPFAS, a total problem score provides information on the respondent's perception of their child's behavior as problematic. Caregivers are asked to indicate if they consider a particular child behavior or parental strategy to be a problem, indicating "Yes" or "No." Items to which a caregiver responded "Yes" are summed to create a total problem score.

In the original validation of the measure, children referred to a clinic for pediatric feeding problems or identified as "at risk" for feeding problems were compared to children not referred to clinics and otherwise considered to be healthy. Cronbach's alpha was used to assess the internal consistency of the measure. In the combined sample, alpha was assessed for four subgroups (two parents with

two or more children, two parents with one child, one parent with two or more children, and one parent with one child). Alphas ranged from .71 to .76 for all participants with the exception of families with one parent and multiple children (.58). Test–retest reliability was assessed over a 4–6-week period, revealing reliability coefficients of .87 for the total problem score and .84 for the percentage of items perceived by caregivers as problematic. With regard to construct validity, both the total eating problem score of the CEBI and the proportion of items perceived as a problem were found to discriminate between children referred to a clinic for treatment of, or at risk for, feeding difficulties and children not referred.

The CEBI has been utilized to evaluate the presence of mealtime behavior problems in children with autism. In a series of studies assessing the nature and prevalence of feeding problems in children with autism, Schreck and Williams utilized the CEBI. The authors found that children with autism presented with significant levels of mealtime behavior problems, including food refusal, specific food preferences, preference for specific utensils, and preference for foods of pureed texture over foods of advanced texture (Schreck et al. 2004). In a follow-up study, further evaluating the nature of mealtime behavior problems in children with autism, the authors replicated their findings that children with autism presented with limited oral intake, a limited variety of foods eaten, and preference for specific utensils or foods (Schreck and Williams 2006).

The CEBI has also been used to evaluate outcomes from an intensive treatment program for children presenting with pediatric feeding disorders (Greer et al. 2008). The authors found that for children admitted to a comprehensive and interdisciplinary intervention program, the severity of mealtime behavior as measured by the CEBI predicted higher levels of caregiver stress upon admission. As well, the authors reported a decrease in CEBI total problem score as well as perception of problems score from admission to discharge, suggesting the effectiveness of the intervention in decreasing mealtime behavior problems. Further study including a comparison group is warranted.

The CEBI has demonstrated utility as a tool for use in research and clinical practice. The validation studies for the CEBI are somewhat more limited than the BPFAS, and some researchers have used a 19-item version of the CEBI (CEBI-R; Archer and Streiner 1994). Further research is warranted to examine the psychometric properties of the brief version of this measure. The authors suggest the possibility of determining a specific score that can indicate the presence or absence of a significant feeding difficulty, which may support the clinical utility of the measure upon further validation.

215.3.2.3 Screening Tool of Feeding Problems (STEP)

The STEP (Matson and Kuhn 2001) was constructed to assist in the early identification and subsequent treatment of feeding problems observed specifically in individuals with mental retardation. Twenty-three items were initially generated from the literature on feeding difficulties in individuals with mental retardation (Table 215.6). Items were created to assess mealtime behavior problems related to aspiration risk, food selectivity, feeding skills, disruptive mealtime behavior, and nutrition-related feeding problems.

In the initial validation of the measure, the inventory was completed by caregivers in a residential facility. As with the BPFAS and CEBI, raters are asked to rate the frequency of the behavior observed as well as the severity of the behavior. The STEP, however, utilizes a three-point Likert scale. With regard to the frequency of behavioral difficulties, a rating of 0 indicates that the behavior never occurs, a rating of 1 indicates occurrence between one and ten times over the past month, and a rating of 2 indicates occurrence of more than ten times over the past month. If the response is 1 or 2, a follow-up question requires the responder to rate the severity of the behavior on a scale of 0 to 3.

Psychometric analysis of the measure was conducted in two studies. A factor analysis in the initial validation study revealed an eight-factor structure, with seven interpretable factors. Reliability

Table 215.6 Sample items from the Screening Tool of Feeding Problems (Adapted by permission from Matson and Kuhn (2001). For more information, please contact the author: johnmatson@aol.com)

Ability to chew	Spits out food
Selective by type	Rumination
Steal food at meals	Selective by feeder
Special equipment	Selective by texture

This table depicts sample items from the STEP. Items are rated on a three-point Likert scale

data was strong for the full measure and variable for each of the subscales (Matson and Kuhn 2001). More specifically, internal consistency for the full measure was modest, with Cronbach's alpha equal to.68. Alpha for the individual scales was variable, ranging from.19 to.70. Test–retest reliability over three weeks was.72 for the full scale and ranged from.26 to.79 for each of the subscales. Interrater reliability was.71 for the full scale and ranged from.55 to.81 for individual scales. A second validation study conducted in 2002 lent preliminary support to the validity of the STEP as a tool to facilitate diagnosis of two specific feeding disorders, rumination and pica (Kuhn and Matson 2002).

The STEP has not been as widely utilized as other measures of mealtime behavior problems. The authors indicate that although some of the psychometric data is modest (e.g., internal consistency and interrater reliability of individual scales), the data for the full scale is strong. Further validation and possible changes to the structure of the scale may elucidate the psychometric stability of the measure. Ongoing study is necessary to determine the clinical utility of this measure as well.

215.3.2.4 Brief Autism Mealtime Behavior Inventory (BAMBI)

The BAMBI (Lukens and Linscheid 2008) was initially designed as a 20-item scale to evaluate the nature of mealtime behavior problems in children with autism. The initial pool of items was generated from the literature describing and evaluating interventions for pediatric feeding problems in children with autism, and the measure was subjected to preliminary psychometric analyses in a pilot study with 50 participants (Lukens 2002). As with the BPFAS, both positively and negatively worded items were included, and items were phrased such that the caregiver is asked to indicate how often his or her child engages in a particular eating behavior. The inventory employs a Likert scale, with responses ranging from 1 to 5, for reporting the frequency of behaviors. A total frequency score is derived from the sum of the items (including the reversed scores), with higher scores representing more problematic mealtime behavior. Preliminary psychometric analyses conducted in that pilot study revealed a reliability coefficient of.61 for the full scale. The scale as initially developed was comprised of a Limited Variety factor, a Food Refusal factor, as well as a number of items that did not load on either factor.

In a validation study for the measure, an additional item was added to create a potential third factor (Lukens and Linscheid 2008). Prior to conducting further reliability and validity analyses, the 21-item BAMBI was examined at the item level, and retention and deletion of items occurred in accordance with examination of item variances, item distributions, and item–scale and inter-item correlations. The resultant 18-item measure (Table 215.7) was subjected to factor analysis, and a three-factor model was selected as the most plausible. Examination of the factor structure suggested that eight items were related to eating a limited variety of foods, five items were suggestive of food refusal and disruptive mealtime behavior, and five items loaded on a third factor and included behaviors that occurred at mealtime which are related to characteristics associated with autism.

Table 215.7 Sample items from the Brief Autism Mealtime Behavior Inventory (Adapted with permission from Lukens and Linscheid (2008). For more information, please contact the author: lukens@email.chop.edu)

	Never	Seldom	Occasionally	Often	Almost
	Every meal				
My child cries or screams during mealtimes	1	2	3	4	5
My child is aggressive during mealtimes	1	2	3	4	5
My child is willing to try new foods	1	2	3	4	5
My child prefers the same foods at each meal	1	2	3	4	5
My child accepts or prefers a variety of foods	1	2	3	4	5
My child prefers only sweet foods	1	2	3	4	5

This table contains sample items from the BAMBI

Evaluation of the internal consistency of the 18-item BAMBI revealed an alpha coefficient of.88 for the full scale. An alpha coefficient of.87 was found for the Limited Variety factor,.76 for the Food Refusal factor, and.63 for the Features of Autism factor. Temporal stability of the measure was supported by a test–retest reliability coefficient over a 7-month period of.87. High interrater reliability was observed as well.

Criterion-related validity of the BAMBI was confirmed by examining correlations between the BAMBI total frequency score and scores on the BPFAS, and positive and significant correlations were found. As expected, these correlations were high but not perfect, given that the BAMBI was not only expected to assess mealtime behavior problems but also to tap into slightly different subdomains of feeding problems than did previously existing measures. Correlations between individual factor scores and external criterion measures supported the construct validity of the individual factors of the BAMBI. For example, the Limited Variety factor was negatively associated with servings of meats, fruits, and vegetables, as assessed by a food frequency questionnaire. The Features of Autism factor was strongly and positively correlated with subscales of the Gilliam Autism Rating Scale, suggesting that this factor does in fact tap into DSM IV characteristics and associated features of autism.

Significant correlations among the factors of the BAMBI evidenced the convergent validity of the measure. In further support of construct validity, the BAMBI total frequency score and total score for each factor successfully discriminated between a group of children with autism and a group of typically developing children, with children in the autism group obtaining higher scores than children in the typically developing group.

Given these results, the BAMBI shows promise as a measure of mealtime behavior problems in children with autism. However, further validation of this measure is necessary before it can be used as a clinical tool. To further confirm the validity of the BAMBI, alternative methods for evaluating mealtime behavior, such as direct observation, should be examined in relation to BAMBI scores. Additionally, discriminative validity should be considered. In the validation study, the BAMBI was found to be important in discriminating between children with autism and typically developing children. The next logical step is to evaluate the ability of the BAMBI to differentiate between children with feeding problems (i.e., clinic-referred) and children without feeding problems (i.e., non-clinic-referred). Finally, cross validation and replication on a larger, independent sample is necessary to confirm the factor structure of the BAMBI.

215.4 Concluding Comments

This review provides information on some of the most commonly utilized assessment tools in the behavioral assessment of pediatric feeding problems. These tools can be employed in both research and clinical practice, and the advantages and disadvantages of each have been presented. Researchers

and clinicians are advised to carefully select appropriate measures, and the purpose of the assessment should guide the choice of measurement methods and tools. For example, it is recommended that practitioners and researchers utilize a tool such as the BAMBI when working with children with autism or the STEP when assessing the mealtime behavior of individuals with mental retardation.

Researchers are encouraged to continue examining the psychometric properties of these measures, as further examination of the nature and prevalence of feeding problems is warranted. Many of the studies described above offer conflicting findings, depending on the type of measures used. For example, when using a behavioral coding system, researchers did not find significant differences in the mealtime behavior of children with cystic fibrosis as compared to children without cystic fibrosis. However, research using caregiver-report measures suggests that children with cystic fibrosis demonstrate a higher frequency of mealtime behavior problems as compared to children without cystic fibrosis. In contrast, there is preliminary evidence that data obtained via observational coding systems correlate with those collected by caregiver-report inventories (Sanders et al. 1993; Piazza-Waggoner et al. 2008). As such, ongoing study examining the validity of these measures as well as the correlation among measures of mealtime behavior difficulties in young children will be beneficial in enhancing these measures for use in research and practice.

Summary Points

- Pediatric feeding disorders are indicated if a child's maladaptive eating behavior results in insufficient weight gain or significant nutritional deficits or if a child demonstrates severely disruptive behavior at mealtime.
- The maintenance of maladaptive mealtime behaviors by environmental factors necessitates a behavioral approach to their assessment and treatment, and the effectiveness of the evaluation and treatment of pediatric feeding problems from a behavioral perspective has been well documented.
- The most common methods for evaluating mealtime behavior include caregiver interviews, observational coding systems, and standardized caregiver self-report measures.
- There are a number of behavioral observational coding systems and caregiver-report inventories that have demonstrated adequate psychometric properties for use in research.
- Further research is necessary to determine the clinical utility of these measures.

Key Terms and Definitions

Pediatric feeding disorders: a class of disorders in which a child's mealtime behavior interferes with the maintenance of adequate weight gain, linear growth, and/or nutritional stability.
Behavioral assessment: a systematic method for evaluating, understanding, and reporting behavior using reliable and valid instruments that involves hypothesis testing, problem-solving, and drawing of conclusions regarding the relationship between behavior and environmental contingencies.
Observational coding system: a method of behavioral assessment in which behavior is observed and recorded according to a pre-established standard and is assumed to be similar to what would typically occur in a child's daily life.
Caregiver self-report inventory: a method of behavioral assessment in which a primary caregiver is asked to respond to questions about a child's behavior.
Reliability: consistency in measurement.
Validity: the degree to which an inventory measures what it is intended to measure.

References

Archer LA, Streiner DL. The revised Children's Eating Behavior Inventory: Further psychometric properties; 1994, unpublished manuscript.

Archer LA, Rosenbaum PL, Streiner DL. J Pediatr Psychol. 1991;16:629–42.

Babbitt RI, Coe DA, Cataldo MF, Kelly KJ, Stackhouse C, Perman JA. J Dev Behav Pediatr. 1994;15:278–91.

Borowitz D, Baker R, Stallings V. J Pediatr Gastroenterol Nutr. 2002;35:246–59.

Byars KC, Burklow KA, Ferguson K, O'Flaherty T, Santoro K, Kaul A. J Pediatr Gastroenterol Nutr. 2003;37:473–80.

Chatoor I, Getson P, MenvielleE, Brasseaux C, O'Donnell R, Rivera Y, Mraznek D. Infant Ment Health J. 1997;18:76–91.

Chung K, Kang S. Pediatric feeding disorders. In: Fischer JE, O'Donohue WT, editors. Practitioner's guide to evidence-based psychotherapy. New York: Springer; 2006. pp. 514–23.

Crist W, Napier-Phillips A. J Dev Behav Pediatr. 2001;22:279–86.

Crist W, McDonnell P, Beck M, Gillespie CT. J Dev Behav Pediatr. 1994;15:157–61.

Fischer E, Silverman A. Semin Speech Lang. 2007;28:223–31.

Girolami PA, Scotti JR. Educ Training Ment Ret. 2001;36:207–23.

Greer AJ, Gulotta CS, Masler EA, Laud RB. J Pediatr Psychol. 2008;33:612–20.

Hayden LC, Schiller M, Dickstein S, Seifer R, Sameroff AJ, Miller I, Keitner G, Rasmussen S. J Fam Psychol. 1998;12:7–22.

Kedesdy JH, Budd KS. Childhood feeding disorders: Biobehavioral assessment and intervention. Baltimore, MD: Paul H Brookes Publishing; 1998.

Kerwin ME. J Pediatr Psychol. 1999;24:193–214.

Kuhn DE, Matson JL. J Intellect Dev Disabil. 2002;27:161–7.

Lewinsohn PM, Holm-Denoma JM, Gau JM, Joiner TE, Striegel-Moore R, Bear P, Lamoureux B. Int J Eat Disord. 2005;38:208–19.

Linscheid TR. Behav Modif. 2006;30:6–23.

Linscheid TR, Budd KS, Rasnake LK. Pediatric feeding problems. In: Roberts MC, editor. Handbook of pediatric psychology, 3rd ed. New York: Guilford Press; 2003. pp. 481–98.

Lukens CT. Assessing eating and mealtime behavior problems in children with autism. Unpublished master's thesis. Columbus, OH: The Ohio State University; 2002.

Lukens CT, Linscheid TR. J Autism Dev Disord. 2008;38:342–52.

Martins Y, Young RL, Robson DC. J Autism Dev Disord. 2008;38:1878–87.

Mash EJ, Terdal LG. Assessment of child and family disturbance: a behavioral-systems approach. In Mash EJ, Terdal LG, editors. Assessment of childhood disorders. 3rd ed. New York: Guilford Press; 1997. pp. 3–68.

Matson JL, Kuhn DE. Res Dev Disabil. 2001;22:165–72.

Mitchell MJ, Powers SW, Byars KC, Dickstein S, Stark LJ. J Dev Behav Pediatr. 2004;25:335–46.

Munk DD, Repp AC. J Appl Behav Anal. 1994;27:241–50.

Patton SR, Dolan LM, Powers SW. Diabetes Care. 2006a;29:1002.

Patton SR, Dolan LM, Powers SW. J Dev Behav Pediatr. 2006b;27:202–8.

Patton SR, Dolan LM, Mitchell MJ, Byars KC, Standiford D, Powers SW. Pediatr Diabetes. 2004;5:190–8.

Piazza CC, Fisher WW, Brown KA, Shore BA, Patel MR, Katz RM, Sevin BM, Gulotta CS, Blakely-Smith A. J Appl Behav Anal. 2003;36:187–204.

Piazza-Waggoner C, Driscoll KA, Gilman DK, Powers SW. Child Health Care. 2008;37:38–48.

Powers SW, Patton S, Byars KC, Mitchell MJ, Jelalian E, Mulvihill M, Hovell MF, Stark LJ. Pediatrics. 2002;109:75–80.

Powers SW, Byars KC, Mitchell MJ, Patton SR, Schindler T, Zeller MH. Child Health Care. 2003;32:297–311.

Powers SW, Mitchell MJ, Patton SR, Byars KC, Jelalian E, Mulvihill MM, Hovell MF, Stark LJ. J Cyst Fibros. 2005;4:175–82.

Sanders MR, Patel RK, LeGrice B, Shepherd RW. Health Psychol. 1993;12:64–73.

Sanders MR, Turner KMT, Wall CR, Waugh LM, Tully LA. J Pediatr Psychol. 1997;22:881–900.

Schreck KA, Williams K. Res Dev Disabil. 2006;27:353–63.

Schreck KA, Williams K, Smith AF. J Autism Dev Disord. 2004;34:433–38.

Stark LJ, Powers SW, Jelalian E, Rape RN, Miller DL. J Pediatr Psychol. 1994;19:751–68.

Stark LJ, Jelalian E, Powers SW, Mulvihill MM, Opipari LC, Bowen A, Harwood I, Passero MA, Lapey A, Light M, Hovell MF. J Pediatr. 2000;136:195–200.

Stark LJ, Jelalian E, Janicke DM, Opipari LC, Powers SW, Mulvihill MM, Hovell MF. Health Psychol. 2005;24:274–80.

Chapter 216
Use of the International Personality Disorder Examination (IPDE) and the Millon Clinical Multiaxial Inventory (MCMI) to Assess Personality Disorders in Eating Disorders

Izaskun Marañon and Iratxe Gonzalez

Abbreviations

AN	Anorexia Nervosa
BMI	Body Mass Index
BN	Bulimia Nervosa
BR	Base Rate
BSI	Borderline Syndrome Index
CCG	Clinical Control Group
DSM	Diagnostic and Statistical Manual of Mental Disorders
ED	Eating Disorder
ICD	International Classification of Disorders
IPDE	International Personality Disorder Examination
MCMI-II	Millon Clinical Multiaxial Inventory-II
NCG	Normative Control Group
NPV	Negative Predictive Value
PD	Personality Disorder
PDE	Personality Disorders Examination
PDQ-R	Personality Diagnostic Questionnaire- Revised
PPV	Positive Predictive Value
SCID-II	Structured Clinical Interview for DSM-IV Axis II Personality Disorders
SEN	Sensitivity
SPE	Specificity

216.1 Introduction

The relation between personality characteristics and eating disorders (ED) has been the main area of attention in many pieces of research. The personality of individuals diagnosed with anorexia nervosa (AN) has been described as obsessive–compulsive, introverted, socially insecure, and dependent,

I. Marañon (✉)
Navarra Health Service (Osasunbidea), Itsasargi 11-3, 20280 Hondarribia, Spain
e-mail: izasmara@hotmail.com

whereas the personality of patients with bulimia nervosa (BN) has been associated with great impulsivity or low self-esteem. However, this chapter is not dedicated to analyzing the personality traits of patients diagnosed with EDs. The objective is to show the principal instruments that can evaluate personality disorders (PD) in addition to analyzing comorbidity of Axis II diagnostics and eating disorders.

The comorbidity of ED and PD has been studied since the incorporation of the criteria for PDs on Axis II in the Diagnostic and Statistical Manual of Mental Disorders (DSM) (Matsunaga et al. 1998). The development of structured diagnostic interviews, such as the International Personality Disorder Examination (IPDE; Loranger 1995) or Structured Clinical Interview for DSM-IV Axis II Personality Disorders (SCID-II; Spitzer et al. 1987), as well as self-report questionnaires, such as the Millon Clinical Multiaxial Inventory-II (MCMI-II; Millon 1987), has been important for the study of this comorbidity.

The esthetics of beauty–thinness–youth (society is more critical than ever of obesity and aging) has become associated with attractiveness and success in popular society. Bearing this in mind, it is not surprising that alterations in eating habits have nowadays become a significant problem, especially among young people and teenage girls. The prevalence of these clinical disorders ranges from 0.2% to 0.8% of the general population. However, in young girls these rates are higher: between 1% and 2% in the case of AN, and between 2% and 3% in the case of BN. In addition, these disorders are ten times more frequent in women than in men (cited in Echeburúa and Marañon 2001).

Eating disorders are characterized by serious alterations in eating habits in patients. Specifically, the main feature of AN is the refusal to maintain body weight in the lower normal levels (BMI > 17.5, according to the criteria of the World Health Organization) and can exist in the form of drastic diets and excessive physical exercise (restrictive anorexia) as well as binging and purging (compulsive/purging anorexia). BN is characterized by constant binging and use of inappropriate compensatory methods to prevent weight gain such as vomiting or misuse of laxatives and diuretics (purging bulimia) or, in other cases, fasting and excessive exercise (bulimia without purging). Finally, there are other unspecified EDs such as compulsive overconsumption or certain types of morbid obesity.

Furthermore, PDs reflect inflexible behavior patterns that are not adaptive. These patients also show problems in learning effective strategies for coping with daily difficulties. PDs also generate interpersonal conflicts and lead to severe constraints (social and work) in daily life, as well as an increase in subjective discomfort. PDs, as opposed to mental disorders, are stable and reflect a temporary deterioration of the overall person.

According to the DSM-IV-R (American Psychiatric Association 2000), there are ten personality disorders, grouped into three major types (see Tables 216.1, 216.2, and 216.3).

The lack of definition of these disorders, the lack of homogeneity in the populations studied, and the absence thus far of adequate evaluation tools explain the absence of reliable epidemiological data (cited in Echeburúa and Marañon 2001). The frequency, however, is high. People suffering from such disorders can be 6–12% of the general population and 20–40% of patients seen in outpatient psychiatric practices with a slight predominance of women. Specific disorders with a higher prevalence are those of borderline, dependence, avoidance (women are predominant in the first three), and schizotypal type (the latter more common in men) (Table 216.4).

The frequent comorbidity between PDs and Axis I disorders may be due to alteration of personality acting as a predisposing factor of mental disorders. It could also be due to the fact that alteration of personality is a residual sequel of the mental disorder or, lastly, due to the fact that eating and personality disorders can appear independently no matter if one or the other previously exists (Medina and Moreno 1998). In any case, personality disorders are often associated with behavior problems that are very important in everyday medical practice (Dowson and Grounds 1995).

Table 216.1 DSM-IV-TR: Cluster A. Odd or eccentric disorders

Diagnostic	Main features	Common factors
Paranoid disorder	Irrational suspicions and mistrust of others. Hypersensitivity. Constricted emotions	Independent
Schizoid disorder	Lack of interest in social relationships. Emotionally cold. Failure to recognize other people's emotions and feelings	Introvert
Schizotypal disorder	Oddities of thinking, perceiving, communicating and behavior without meeting the criteria for schizophrenia	Badly socialized Emotionally unstable

This table shows the three cluster A personality disorders as defined by the DSM-IV-TR, their main features and characteristics common to all

Table 216.2 DSM-IV-TR: Cluster B. Dramatic, emotional, or erratic disorders

Diagnostic	Main features	Common factors
Antisocial disorder	Continuous and chronic antisocial behavior. Aggressiveness Documented history of a conduct disorder before the age of 15	Dependent
Borderline disorder	Instability in relationships, self-image, identity, and behavior	Extrovert
Histrionic disorder	Pervasive attention-seeking behavior including exaggerated emotions and theatricality. Egocentrism and manipulation	Badly socialized
Narcissistic disorder	Grandiosity. Fantasy of unlimited success. Need for admiration. Lack of empathy	Emotionally unstable

This table shows the three cluster B personality disorders as defined by the DSM-IV-TR, their main features and characteristics common to all

Table 216.3 DSM-IV-TR: Cluster C. Anxious or fearful disorders

Diagnostic	Main features	Common factors
Avoidant disorder	Extreme sensitivity to negative evaluation. Fear of being ridiculed or humiliated. Social inhibition. Low self-esteem	Dependent
Dependent disorder	Turn their decisions and responsibilities over to others. Passivity and dependency of others. Lack of self-confidence	Introvert Badly socialized
Obsessive–compulsive disorder	Perfectionism. Rigidity. Hesitancy. Excessively devoted to work. Find it difficult to express emotions	Emotionally unstable

This table shows the three cluster C personality disorders as defined by the DSM-IV-TR, their main features and characteristics common to all

Table 216.4 Prevalence rates depending on the type of personality disorder

Type	Personality disorders	General population (%)	Clinical samples (%)
A	Paranoid PD	0.5–2.5	4.2–30
Odd and eccentric	Schizoid PD	0.5–4.5	1.4–16.7
	Schizotypal PD	3–5	0.6–20
B	Antisocial PD	1–3	3–41
Immature	Borderline PD	2–3	9.3–40
	Histrionic PD	2–3	1–15
	Narcissistic PD	<1	2–20
C	Avoidant PD	0.5–1	10
Fearful	Dependent PD	15	1.4–33
	Obsessive-compulsive PD	1	3–10

This table shows the prevalence of different personality disorders in the general population and in clinical samples

216.2 Evaluation Tools

This section is devoted to analyzing PD assessment instruments. In this case, however, due to the great number of instruments, we will only analyze those instruments that assess all PDs described in the current psychopathological classifications, whether these are interviews or self-report questionnaires.

216.2.1 Interviews

For the assessment of PDs, interview problems are the same as in all other clinical interviews, but in this case, they appear to be of greater importance. The clinician may obtain a first impression of the patient and then steer the interview toward a point that may not be essential. The clinician can also forget that social and environmental circumstances are the cause of the behavior of the suspected patients, and that this is the sole contributor to the behavior of their personality traits. The possible distortion of the information provided by the patients must also be taken into account.

Notwithstanding the above, the assessment of PD interviews is necessary because they allow direct observation of the patient. This observation is considered necessary for the diagnosis of PDs, but not for other mental disorders which correspond to Axis I DSM-IV-TR (Zimmerman et al 2005).

The two most commonly used interviews to assess personality disorders are discussed below.

216.2.1.1 International Personality Disorder Examination (IPDE)

The International Personality Disorder Examination (IPDE) (Loranger 1995) is a semi-structured clinical interview developed from the Personality Disorders Examination (PDE; Loranger 1988). The aim of the IPDE is to systematically evaluate the presence or absence of the PD criteria described in the current classifications. This is the reason why it has been carried out in two forms, one for the ICD-10 personality disorder criteria and the other for the DSM-IV personality disorder criteria.

The IPDE is developed in a way that aims to provide an optimum balance between a natural and spontaneous clinical interview and standardization and objectivity requirements. The questions are asked in a natural and comfortable sequence by the clinician according to six thematic headings: work, self, interpersonal relationships, feelings, reality testing, and impulse control.

A self-administered IPDE screening questionnaire is available. In this screening test, the items have a true–false answer format. The IPDE screening questionnaire in the DSM-IV form has 77 items. The IPDE screening questionnaire in the ICD-10 form has 59 items. The screening questionnaire assists the interviewer in quick identification of patients with a specific PD. This questionnaire has no diagnostic value and is used to identify those who should have the interview. It can also be used to identify specific disorders and, if necessary, the corresponding part of the interview can be carried out.

The different sections of the interview begin with open questions that offer the subject the possibility to speak about the topic as much as he or she wants, and allow the clinician to establish a base on which to judge the clinical meaning of the answers to the specific questions that follow the open ones. The IPDE interview DSM-IV form has 92 questions and 7 criteria that the interviewer must fulfill once the interview is finished. The ICD-10 form has 64 questions and 3 criteria to be completed by the interviewer.

The IPDE requires a behavior or trait to be present at least 5 years before it is considered a manifestation of the personality. This conservative and somewhat arbitrary convention is intended to

reflect the relatively enduring nature of personality traits and to avoid confusing them with transient or situational phenomena and episodic abnormalities of mental state behavior. The IPDE also requires that at least one criteria of a disorder be fulfilled before age 25, before that particular disorder can be diagnosed.

216.2.1.2 Structured Clinical Interview for DSM-IV Axis II Personality Disorders (SCID-II)

Like the IPDE, the Structured Clinical Interview for DSM-IV Axis II Personality Disorders (SCID-II) (Spitzer et al 1987; First et al 1997) is a semi-structured clinical interview. SCID-II covers all the criteria for the 11 Axis II diagnoses of DSM-IV (including the non-specified personality disorder), the criteria for depressive personality disorder and passive–aggressive personality disorder (both included in appendix B of DSM-IV)

The interview starts with some open questions that assess personality characteristics. It then proceeds to evaluate each of the ten PDs and the two specific Appendix categories in the following order: avoidant, dependent, obsessive–compulsive, passive–aggressive, depressive, paranoid, schizotypal, schizoid, histrionic, narcissistic, borderline, and antisocial PD.

We can give a diagnosis of a non-specified PD in cases where the characteristics of the PD do not meet the full criteria for any specific PD.

The SCID-II uses a four-point scale to rate the intensity of the characteristics examined. It is recommended that the assessor ask as many additional questions for clarification as required. If necessary, the interviewer can use other sources of information in addition to the subject being interviewed.

As a selection or screening tool, the SCID-II has a self-administered questionnaire of 119 items with a response format of yes–no, which corresponds to the questions in the interview. This questionnaire is then used to conduct the interview. Only those questions answered affirmatively in the questionnaire are actually used in the interview stage.

Data on the reliability and validity of the SCID-II is heterogeneous. The kappa index for test–retest reliability, for example, varies from 0.24 to 0.87 depending on the sample and the disorder studied (cited in First et al. 1997).

216.2.2 Self-Report Questionnaires

In the case of self-report questionnaires that evaluate PDs, in addition to the biases that affect the questionnaires in general, it should be noted that this type of tool exaggerates the patient's answers. This is due to the interference of situational factors when answering, as well as the acquiescence bias and a tendency to exaggerate symptoms when it is oneself who describes them.

216.2.2.1 Millon Clinical Multiaxial Inventory (MCMI)

The MCMI-II (Millon 1987) is a self-administered questionnaire consisting of 175 items with a true–false response format. It was built around Millon's personality theory. Each of its scales was established as an operational measure of a syndrome derived from a theory of personality and psychopathology. This theory is based on diagnostic categories, and suggests ten basic styles of personality functioning based on a 5×2 matrix. The two dimensions of the matrix represent the patient's primary source of getting positive or negative reinforcement (retracted individuals, discordant

personalities, dependent, independent and ambivalent) and the basic pattern of instrumental conduct or coping that the patient uses to increase rewards and decrease pain (active and passive pattern).

As far as personality is concerned, the MCMI-III contains 11 moderate personality disorder scales: Schizoid, Avoidant, Depressive, Dependent, Histrionic, Narcissistic, Antisocial, Sadistic (Aggressive), Compulsive, Negativistic (Passive–aggressive), and Masochistic (Self-defeting). It also has three severe personality pathology scales: Schizotypal, Borderline, and Paranoid.

The MCMI-III includes ten symptom scales. Unlike PDs (Axis II), the clinical syndromes of Axis I are best explained as extensions or distortions of the personality patterns that are often relatively brief and transitory. Although each syndrome may occur with all patterns of personality, some syndromes occur more frequently with certain PDs. Because syndromes of Axis I and Axis II patterns can be combined, a model that clearly explains these interrelationships is needed. This is the reason why the MCMI-III includes ten scales, seven of which are moderate syndrome scales: Anxiety, Somatoform, Manic, Dysthymia, Alcohol Dependence, Drug Dependence, Post-Traumatic Stress Disorder; and three severe syndrome scales: Thought Disorder, Major Depression, and Delusional Disorder.

In addition to being created from a theory, the MCMI-III reflects the diagnostic criteria of DSM-IV. In fact, its scales are coordinated with the DSM and its categories.

The first version of MCMI dates from 1977, but since its creation there have been numerous changes to correct the tendency to distort responses, and incorporate new concepts and theoretical aspects of the new versions of the DSM. The MCMI-II was published in 1987 and the MCMI-III in 1994 (Millon 1977, 1987; Millon and Davis 1996).

In the original version of the MCMI-III, internal consistency indices were higher than 0.80 for all scales.

216.3 Review of Comorbidity Between Eating Disorders and Personality Disorders

Subsequently, we separately analyze comorbidity between eating disorders in general, anorexia nervosa, bulimia nervosa, eating disorders not otherwise specified, and personality disorders.

216.3.1 Eating Disorders and Personality Disorders

Gartner et al. (1989) presented the first article of reference related to this topic. The sample consisted of 35 inpatients diagnosed with restricting AN (6), BN (8), or AN and BN (21). The main results were that 57% of the patients met the criteria for at least one PD. Borderline, self-defeating, and avoidant were the most frequently assigned PDs, and no differences were found in the distribution of diagnoses between patients with different ED diagnoses.

Wonderlich et al. (1990) carried out more precise research with 46 eating disorder patients. In total, 72% of the sample met the criteria for at least one PD. More precisely, obsessive personality was more common in AN restrictive type, and borderline and histrionic personality in bulimia.

Kennedy et al. (1990) carried out a study with 44 ED patients (19 with AN, 16 with BN, and 9 with a combination of both disorders). MCMI and BSI were administered both before and after treatment to measure PDs. Before treatment, 93% of the patients met criteria for at least one PD and after treatment, that percentage decreased to seventy-nine percent. When the PD was measured with the

MCMI, the three most frequent PDs at admission were borderline (79.5%), dependent (75%), and passive aggressive (70.5%). Dependent and passive aggressive disorders remained most prevalent at discharge (43.2% and 40.9%, respectively) while the frequency of subjects who met borderline criteria was 31.8% at the time of discharge. With regard to the BSI, 75% subjects met borderline criteria on admission, compared to 41% at discharge.

Norman et al. (1993), with a sample of 87 ED patients (17 anorexics, 58 bulimics, and 12 who met criteria for both bulimia and anorexia), found that 84% were diagnosed as having a PD. The different ED groups did not differ significantly in terms of the overall prevalence rate of PDs. The MCMI (BR > 84) was used to determine the prevalence and profile of PDs.

In research conducted by Grilo et al. (1996), with 136 hospitalized patients diagnosed with various EDs, 84% had one or more PDs. Among these, the most frequent were borderline (71%), avoidance (19.4%), and dependent (12.9%) PDs.

According to a study by Matsunaga et al. (1998) with 108 patients with different EDs, 51% of the sample suffered from PDs, especially from groups B (antisocial and borderline, in the case of bulimia) and C (without clear predominance of one or the other, in the case of anorexia and bulimia).

In the study by Matsunaga et al. (2000), focusing on patients who had recovered from an ED and who had not displayed any symptoms during the previous year, 26% of a sample of 54 patients met criteria for the diagnosis of at least one PD. This percentage is lower than the percentage found in other studies with patients having AN and BN who were still in treatment. Personality disorders were highly variable, but disorders in Group C (obsessive, dependent, and avoidant) were more common than Group B (borderline).

In a study with a Spanish sample in which the structured interview SCID-II was used, Diaz-Marsá et al. (2000) found that 61.8% of patients with an ED met criteria for a PD, while only 5% of the control sample met the criteria.

Inceoglu et al. (2000) evaluated a sample of patients diagnosed with EDs who were attending a day center using the questionnaire PDQ-R and found a comorbidity rate of 49.2%. Curiously, and unlike other studies, the most prevalent disorder in their sample was the paranoid PD (35.4%), followed by borderline personality disorder (33.9%), then dependent (26.2), histrionic (23.1%), and avoidant (23.1%).

Godt (2002) conducted a study with 176 women attending outpatient treatment and submitting an ED. He used the SCID-II to assess PDs and found that one-third of the sample (33%) had at least one PD. The most common disorders were those in group C (26.1%), followed by those in group B (9.7%) and A (3.4%). The most common PDs were avoidant (18.8%), dependent (8.5%), borderline (5.7%), and histrionic PDs (5.1%).

Karwautz et al. (2002), in their study of 45 patients with an ED, used the version of IPDE adapted to ICD-10. The most common PDs were anancastic (22.7% versus 4.7%), anxious (20.5% versus 2.3%), and dependent (13.6% versus 0%).

In studies that compare a sample of patients with ED with a psychiatric control group, it appears that the former are more often diagnosed with at least one PD (Grilo et al. 1996; Striegel-Moore et al. 1999). The same is true in studies that compare the comorbidity with PDs in samples of EDs with control samples of the general population (Herpertz-Dahlmann et al. 2001). Karwautz et al. (2002), in their study of 45 patients with an ED and a control sample of 45 of the patients' sisters who did not present an ED, found that 54% of the patients showed at least one PD, while in only 7% of the patients' sisters was it present.

Other investigations have focused on comorbidity according to gender. Thus, according to the work of Striegel-Moore et al. (1999) with a sample of 161 war veterans (98 men and 63 women) suffering from EDs, 49% of the women and 18% of the men had some form of PD, so this comorbidity was significantly more frequent in women than in men. However, as the average age of the sample

(men: 53.5 years, women 35.3 years) was higher than that normally found in the clinic, this data cannot be used to make generalizations.

In general, when patients are hospitalized, comorbidity rates are higher – ranging from 69% to 74% of the total – than when they are undergoing outpatient treatment (Wonderlich et al. 1990; Braun et al. 1994; Kennedy et al. 1995).

Recent studies (Martín et al. 2009; Vrabel et al. 2010; Zanarini et al. 2009) are longitudinal studies that examine comorbidity rates of PDs in patients with ED before and after treatment. In general, there is a decline in these rates.

216.3.2　Anorexia Nervosa and Personality Disorders

Although some authors suggest that PDs are relatively uncommon in AN (Pope and Hudson 1989; Herzog et al. 1992), it is common to find a relatively high comorbidity rate between both PDs and ANs.

Norman et al. (1993) found that 77.8% of patients with AN met the criteria for at least one PD diagnosis. The most common PDs in this sample were avoidant (47.1%), dependent (41.2%), schizoid (35.3%), and borderline (35.3%).

Wiederman and Pryor (1997), in their study of 165 women with an ED (27 with restrictive AN, 33 with purging AN, and 105 with purging BN), in which the PDs were assessed by MCMI-II, found that the more common PDs in patients with restrictive AN were dependent (77.8%), compulsive (66.7%), self-defeating (63%), and avoidant (59.3%). In patients with purging AN, however, the most common PDs were avoidant (51.5%), self-defeating (51.5%), dependent (48.5%), passive aggressive (45.5%), and compulsive (42.4%). Patients with restrictive anorexia had more PDs than patients with purging AN (77.8% versus 48.5%). Furthermore, patients with AN (66.7% of restrictive and 42.4% of purging) more often had a compulsive PD than patients with bulimia (22.9%).

In the study by Diaz-Marsá et al. (2000), 50% of patients with restrictive AN and 71.4% of patients with purging AN met criteria for at least one PD measured by the SCID-II. Furthermore, 15% of patients with restrictive AN and 21.3% of patients with purging AN had more than one PD. In this study, the most common PDs in patients with restrictive AN were avoidant (25%), obsessive–compulsive (20%), borderline (10%), paranoid (10%), and dependent (5%); and the most common PDs in patients with purging AN were borderline (35.7%), histrionic (28.6%), obsessive–compulsive (21.4%), passive–aggressive (14.3%), dependent (7.1%), avoidant (7.1%), and narcissistic (7.1%).

Inceoglu et al. (2000) found a comorbidity rate of PDs in AN of 45.2%.

Martin et al. (2001), in a sample of 31 individuals (11 with restrictive AN, 9 with purging BN, and 11 controls), found that 54% of patients with AN exceeded the cut-off point of 85 on the MCMI-II on at least one personality scale, whereas 73% of these patients exceeded the cut-off point of 75. With regard to patients with BN, those with AN showed statistically significantly higher scores on the schizoid ($\overline{X}$ = 93.27 versus $\overline{X}$ = 72.11, $p < 0.05$) and phobic scales ($\overline{X}$ = 77.27 versus $\overline{X}$ = 54.33, $p < 0.05$). With respect to the control group, there were statistical differences in nearly all the average ratings, though these did not exceed the pathological cut-off.

In the study by Godt (2002), 20.8% of patients with AN had at least one PD. The most common was avoidant PD (10.4%), followed by dependent PD (4.2%) and borderline PD (4.2%).

As seen in previous studies, PDs are not uniform in AN. However, in general, we can say that the higher comorbidity of restrictive AN occurs with PDs of group C, especially with obsessive and avoidant PD (between 25% and 35% of cases) (Gartner et al. 1989; Gillberg et al. 1995; Thornton and Russell 1997). By contrast, 40% of people with purging AN have comorbidity with borderline

PD (Piran et al. 1988; Fahy and Eisler 1993; Garner and Sackeyfio 1993). In fact, in these cases, there are related problems of impulse control such as self-mutilation, suicide attempts, robberies, etc.

In anorexic patients who were treated successfully a lower morbidity rate is diagnosed. Thus, according to the above quoted study of Matsunaga et al. (2000), only 20% of patients having recovered from AN met criteria for diagnosis of at least one PD.

216.3.3 Bulimia Nervosa and Personality Disorders

According to Bulik et al. (1995) and Levin and Hyler (1986), 63% of bulimic patients have a PD, in particular the borderline disorder, as well as any other from group C (avoidant, obsessive, or dependent) or from group A (paranoid, schizoid, or schizotypal). A revision study (Dolan et al. 1994) pointed to the existence of a comorbidity rate from 24% to 44% between bulimia and borderline personality.

However, comorbidity rates between BN and PDs differ depending on the study; that is, they depend on the diagnostic criteria, the samples, and the diagnostic tools used.

Levin and Hyler (1986), in their study of 24 women with BN who had an appropriate weight and with no other Axis I disorder, assessed PDs by the PDQ and by a personal interview. They found that 62.5% met criteria for at least one PD. The most common PDs in their sample were histrionic PD (37.5%) and borderline PD (25%).

Pendleton et al. (1991) compared, using the MCMI, 37 women with BN with 32 women with other psychiatric disorders and with 30 women from the general population who did not present any psychiatric disorder. The patients with BN presented more avoidant and dependent PDs than patients in the clinical control group. They also presented more schizoid, avoidant, dependent, narcissistic, compulsive, passive aggressive, schizotypal, and borderline personality disorders than women from the normative control group.

Norman et al. (1993) found that 84.5% of patients with BN met the criteria for at least one PD diagnosis. The most common PD in this sample were passive–aggressive (44.8%), dependent (41.4%), histrionic (34.5%), and borderline (25%). Subjects with bulimia had a significantly lower rate of schizoid, avoidant, and schizotypal PDs than the subjects with anorexia or than the subjects with both anorexia and bulimia. Similarly, the bulimics had a significantly lower frequency of Cluster A diagnosis than the other two groups.

Wiederman and Pryor (1997) found that the most common PDs in patients with BN were self-defeating (68.6%), dependent (59%), avoidant (55.2%), and passive–aggressive (42.4%). Furthermore, they noted that patients with BN presented more histrionic PDs (47.6%) than patients with AN (14.8% of the restrictive and 27.3% of the purging). Also, patients with BN presented more antisocial PDs (20% versus 3.7%) and passive–aggressive (52.4% versus 25.9%) than patients with restrictive AN.

In the study by Diaz-Marsá et al. (2000), 66.7% of patients with BN met criteria for a PD and 37.8% of patients had more than one of these criteria. The most common PDs in BN were borderline (33.3%), dependent (23.8%), avoidant (19%), passive–aggressive (14.3%), obsessive–compulsive (14.3%), schizoid (9.5%), and paranoid (4.8%) PD.

Inceoglu et al. (2000) found a comorbidity rate of PDs in BN of 44.1%.

Martin et al. (2001) found that 22% of patients with BN exceeded the cut-off point of 85 on the MCMI-II on at least one personality scale, while 77.8% of these patients exceeded the cut-off of 75. With respect to patients with AN, those with BN showed statistically significant higher scores on the histrionic scale (77.33 versus 45.90). With respect to the control group there were statistical differences in practically all the average ratings, though these did not exceed the pathological cut-off.

Del Rio et al. (2002) evaluated 33 patients with purging BN using the MCMI-II. Of these, 81% had at least one personality disorder according to the questionnaire (RB > 75), and the most common PDs in this sample were avoidant (39.39%), histrionic (39.39%), and self-defeating PDs (39.39%), followed by passive–aggressive (36.36%) and schizoid (30.30%) PDs.

In the study by Godt (2002), 31% of patients with BN had at least one PD. The most common was avoidant PD (18.5%), followed by dependent (13, 6%), histrionic (7.4%), and borderline (6.2%) PDs.

Comorbidity of BN also varies according to sex. Thus, in men with BN there is a higher rate of homosexuality and perfectionism and susceptibility features appear more often (Herzog et al. 1984; Schneider and Agras 1987). In women with BN, in contrast, weight concerns and an obsession with thinness dominated (Joiner et al. 2000).

Finally, as in people with AN, patients with BN who were treated successfully were diagnosed with a lower comorbidity. Thus, according to the study quoted above by Matsunaga et al. (2000), 21% of patients who recovered from bulimia met the criteria for a diagnosis of at least one PD.

216.3.4 Eating Disorders Not Otherwise Specified and Personality Disorders

Morbid obesity has been studied from this perspective. According to Black et al. (1992), 72% of individuals are also affected by PDs (50% more than one). As regards the actual type of deterioration, in general there is some relationship between the behavioral characteristics of borderline personality (impulsivity, self-defeating behaviors, etc.) and morbid obesity, at least in women (Sansone et al. 1996).

However, in other studies on obesity the data is more variable. Thus, disorders submitted by the sample from the study of Black et al. (1992) are diverse (histrionic, borderline, passive–aggressive), without a clear predominance of one over the other. By contrast, the study by Grana et al. (1989) concerning morbid obesity showed that the most prevalent PDs were others, specifically avoidant, antisocial, and obsessive personality. In the study by Guisado et al. (2001), the most prevalent PDs were paranoid, anancastic, schizoid, and anxious.

In conclusion, the prevalence rate of PDs in obese individuals is very high, but very variable too, depending on the methodology and the type of sample used in the studies. However, we cannot establish a clear association between a specific type of disorder and morbid obesity. Conversely, when there is an association between morbid obesity and compulsive overeating, the results are clearer. According to Yanovski et al. (1993), 16% of the obese sample presents PDs, but this rate rises to 35% in the obese who binge. In the latter case, the PDs most frequently involved are borderline (14%) and avoidant (9%).

Finally, it should be noted that in the study by Godt (2002), 36.2% of patients with a non-specified eating disorder had at least one PD. The most common was avoidant PD (27.7%), followed by borderline PD (6.4%).

216.3.5 Personality Disorders and Eating Disorders

When studies focus on PDs and, as a result, on the comorbidity with Axis I disorders, EDs correlate with group B personality disorders (Modestin et al. 1997).

More specifically, borderline PD has a higher rate of comorbidity with BN (it can range from 2% to 47%) than with the rest of the Axis I disorder (Wonderlich 1995). This broad range is related to

the methodological problems of studies (e.g., inexact diagnoses and lack of control groups) and, above all, to some overlap of diagnostic criteria that are common in the borderline disorder (e.g., criterion 4: binging, which is the result of impulsivity) and BN. This overlap in criteria poses a risk of overdiagnosis of borderline PD in subjects with bulimia. In fact, there is usually a decline in the rate of borderline PDs after short-term treatment focused on bulimia symptoms.

The comorbidity of borderline PD may be mediated by the sex of the patients. Specifically, impulsivity (typical of this disorder) is expressed in males as alcohol or drug abuse (men: 63.3–81.9%; women: 38.1–59.1%) and in women in the form of binge eating or unspecified problems (men: 10.8–13.6%; women: 29.5–30.4%) (Zanarini et al. 1998; Zlotnick et al. 2002).

With regard to the comorbidity between BN and borderline disorder, a point of interest is the possible existence of sexual abuse in childhood. In several previous studies it has been indicated that a history of sexual abuse is three times more common in patients with BN than in normal people (Garfinkel et al. 1995) and patients with restrictive AN (Coovert et al. 1989). More recently, however, it has been indicated that bulimics with a previous history of sexual abuse have a more severe clinical picture and a higher rate of comorbidity with the borderline disorder (Claridge et al. 1998).

It should be noted that, in the study conducted by Marino and Zanarini (2001), 33% of patients with borderline PD met criteria for an ED not otherwise specified. Of these patients, 20% had restrictive patterns without weight loss, 37% purges without binging, 37% a pattern of binging without purging, and the remaining 33% had weight loss without menstruation.

216.3.6 Research

The data of comorbidity between EDs and PDs outlined in various studies do not correspond. The discrepancies obtained correspond to various reasons: the type of samples (outpatients or hospitalized patients), the sex and age of the patients, the degree of evolution of the disorder (in an acute period, in a situation of chronic phase or in remission), the diagnostic tools used to assess personality disorders (self-report questionnaires or interviews) and the differences between the diagnostic criteria. An important methodological limitation is the absence of clinical control groups (patients with mental disorders other than anorexia or bulimia) and normal subjects (subjects from the normal population). This means that one should exercise a degree of caution as regards the conclusions reached.

We therefore consider it important now to bring to attention the study from the doctoral thesis of the first author of this chapter (Marañon et al. 2007a, b). This study forms part of a large investigation whose purpose is to measure the comorbidity between PDs and EDs, assessed by the MCMI-II and the IPDE. The main contribution of this study to provide better knowledge of comorbidity between PDs and ED is related to the specific method used. What this means is that, apart from the ED group, there were clinical and normative control groups. The aim of this procedure was to discover whether the frequency and profile of PDs among EDs were different from the normal population and from non-ED patients seeking treatment for another Axis I mental disorder.

According to the results in previous studies of PDs in patients with EDs, this study found that the prevalence rates of comorbidity were high both in IPDE (54.8%) and MCMI-II (77.4%) (see Table 216.5). As expected in previous studies, the highest rates of PD in patients with ED were obtained with the MCMI-II. The correspondence between the IPDE and the MCMI-II in diagnosing personality disorders in patients with eating disorders is very low. The MCMI-II tends to overdiagnose specific PDs and, as a result, it is not a good assessment measure for obtaining PD diagnosis. This finding is consistent with that of Kennedy et al. (1995) using the SCID-II and the MCMI-II to

Table 216.5 Key features of International Personality Disorder Examination

1. IPDE is a semi-structured interview
2. IPDE has two versions that the interviewer can choose: one for the ICD-10 personality disorder criteria and the other for the DSM-IV personality disorder criteria
3. It consists of a self-screening questionnaire whose answers are either true or false
4. The screening questionnaire has no diagnostic value but can be used to select which part of the interview will be carried out
5. The whole interview can be used or it can also be used to identify specific disorders that have given positive in the self-administered questionnaire
6. The patient is asked to answer the questions taking into account how he or she usually is or acts. He or she is also asked to tell us if he or she has experienced a permanent change in his or her way of acting
7. The questions are organized under the following headings: work, self, interpersonal relationships, feelings, reality testing, and impulse control
8. The various sections of the interview begin with open questions that allow the patient to answer with as much information as desired and the interviewer to situate the context for understanding the subsequent responses to specific questions
9. The clinician assesses the responses with a score of 0 if the evaluated behavior is absent, with a score of 1 if the behavior is increased and with a score of 2 if the behavior meets diagnostic criteria or reaches pathological levels
10. IPDE can be administered to subjects aged over 18
11. To implement reliable results the interviewer needs to be trained
12. Qualified interviewers administer IPDE in about 45–60 min. Those who are not trained require more than 90 min

In this table the major features of IPDE are listed, as well as the steps and requirements for administration and correction

assess PDs in patients with EDs. On the other hand, as Wetzler and Dubro (1990) observed in their study, the MCMI-II detects the subjects who may have a possible PD. Therefore, we can conclude that the MCMI-II does not replace a diagnostic interview. The MCMI-II can be used as a screening tool, but not as a personality disorder diagnostic instrument. The high negative predictive value indicates that the MCMI-II performs well in indicating when the disorder was not present during IPDE. In contrast, if the MCMI-II obtained a PD diagnosis, it would probably be a false positive.

It would be possible to say that PD measurement with the MCMI-II is a statistic artifact. It can be understood clearly if we consider that 58% of subjects with at least one PD according to the MCMI-II, have more than four PDs altogether. Another piece of evidence for the above affirmation is that 32% of the AN patients have a schizoid PD assessed with the MCMI-II and not one of the same patients has the same diagnosis measured with the IPDE. In any case these results might also reflect problems in the PD diagnostic criteria, or they could be due to genuine high PD base rates (and comorbidity rates) in ED patients. For the interpretation of these differing results between the IPDE and the MCMI-II, the validity of the PD construct has been taken into account. We cannot forget that the ambiguity of the PD definition could be one of the reasons for the lack of correspondence between instruments.

Taking the above into account, and therefore considering the data from personality disorders obtained by IPDE, the most relevant conclusion of this study was that more than half of subjects with ED (55%) met DSM-IV-TR diagnostic criteria for at least one PD, compared to 22% of the non-ED patients and 9% of the normative control group (See Table 216.6). The main contribution of this study, consequently, is to have proven that this high rate of comorbidity with PDs is specific in EDs and much higher than in other Axis I mental disorders. This finding is consistent with those of previous reports using structured interviews to assess PDs in EDs (Gartner et al. 1989; Matsunaga et al. 1998). It is also consistent with those using only one of the control groups we used (Díaz-Marsá et al. 2000; Grilo et al. 1996; Herpertz-Dahlmann et al. 2001). This fact is a challenge for clinical practices because the presence of a PD in a patient with AN or BN complicates treatment, and the prognosis of the ED becomes poorer.

Table 216.6 Key features of Millon Clinical Multiaxial Inventory

1. MCMI is a self-administered questionnaire
2. The subject must answer 175 questions in a true–false answer format
3. Before beginning to answer the questionnaire the clinician should make sure that the subject has understood the instructions
4. Once the questionnaire is answered, correction can be done manually (with template correction) via Internet or using a local software
5. It should be taken into account whether the subject is a person of the general population, if he or she is an adult undergoing psychiatric treatment in a hospital, or if he/she is an adult undergoing psychiatric outpatient treatment
6. While correcting, the sex of the subject must be specified
7. MCMI can be administered to subjects aged over 18 with a reading level equivalent to 8 years of schooling
8. The subjects typically need about 25–30 min to answer all questions
9. Those whose scales give a score greater than 84 BR are considered pathological

In this table the main characteristics of MCMI are listed, as well as the steps and requirements for administration and correction

216.4 Application to Other Areas of Health and Disease

Beyond the different data found in the published studies, EDs are disorders which are rarely found in a psychopathologically pure state: they are often found with Axis II clinical disorders. The presence of a PD with an ED complicates the clinical picture. Specifically, it makes the early detection of the problem more difficult, as well as making the treatment difficult. It also hinders therapeutic prognosis (cited in Echeburúa and Marañón 2001); in fact, patients with AN and BN who are affected by a PD have a greater incidence of binging, vomiting, symptoms of anxiety and depression, and excessive alcohol consumption, as well as greater difficulties in social integration and an increased frequency of suicide attempts (Gartner et al. 1989; Wonderlich et al. 1990; Braun et al. 1994; Steiger and Stotland 1996; Kozyk et al. 1998; Matsunaga et al. 1998). This fact should be taken into account when planning treatment. To do so, the design of intervention programs that consider personality aspects would be useful, just as the development of specific therapeutic programs for EDs comorbid with PDs is a challenge for clinical research (Palmer et al. 2003).

On the other hand, it seems that the MCMI is not a good diagnostic tool to diagnose PDs in EDs. Therefore, to obtain a reliable diagnosis to determine whether a patient has a PD or not, we recommend evaluation using a clinical interview. In addition, using an interview will allow us to obtain valuable information in order to design specific treatment for a patient, as it will allow us to discover the patient's strong points and his or her weaknesses. However, MCMI may function best as a screening tool and more conservative clinical norms/cut-offs could help correct overdiagnosis problems.

216.5 Conclusion

In this chapter, according to the diagnostic philosophy contained within DSM-IV-TR, PDs have been considered in a categorical way, that is, as discrete entities of abnormal behavior patterns. However, although DSM-IV-TR approaches clinical diagnoses from a categorical perspective, there is increasing empirical research approaching the clinical assessment of PDs from a dimensional perspective (Segal and Coolidge 1998), since one of the most perplexing difficulties in this clinical field is the definition and measurement of personality dysfunction (Sansone et al. 2005). This point needs to be researched further.

In general, the comorbidity of EDs and PDs is very high: it can range from 20% to 80%. When considering PDs by type (A, B, and C), we found that the most prevalent PDs in AN are those from

Table 216.7 Agreement between IPDE and MCMI-II personality disorders

DIAGNOSTIC	IPDE positive (%)	MCMI positive (%)	Agreement (%)	KAPPA	SEN (%)	SPE (%)	PPV (%)	NPV (%)
Cluster A	1.2	32.1	66.66	−0.023	0	67.46	0	98.24
Paranoid	1.2	9.5	89.28	−0.022	0	90.36	0	98.69
Schizoid	0	21.4	78.57	–	–	78.57	0	100
Schizotypal	0	4.8	95.23	–	–	95.23	0	100
Cluster B	20.2	33.3	67.85	0.198	52.94	71.64	32.14	85.71
Antisocial	0	13.1	86.90	–	–	86.90	0	100
Borderline	19	8.3	79.76	0.164	18.75	94.11	42.85	83.11
Histrionic	2.4	25	77.38	0.136*	100	76.82	9.52	100
Narcissistic	1.2	11.9	86.90	−0.022	0	87.79	0	98.64
Cluster C	31	28.6	66.66	0.203	42.30	77.58	45.83	75
Avoidant	16.7	14.3	85.71	0.455**	50	92.85	58.33	90.27
Dependent	2.4	11.9	88.09	0.132	50	89.02	10	98.64
Obsessive–compulsive	22.6	11.9	70.23	−0.021	10.52	87.69	20	77.02
Any disorder	54.8	77.4	79.76	0.322	91.30	39.47	64.61	78.94

The frequency of the 12 personality disorders and three clusters, the agreement percentage between the IPDE and the MCMI-II, values for Kappa, sensitivity (SEN), specificity (SPE), positive predictive value (PPV), and negative predictive value (NPV) are presented in this table. Correspondence between the two measures was only marginal. In most of the personality scales the kappa value was around 0, so correspondence between the two measures was only at chance level. Sensitivity refers to the likelihood that the MCMI-II will be positive when there is a diagnostic present according to the IPDE. Specificity refers to the likelihood that the MCMI-II will be negative when the IPDE is negative for a particular diagnosis. Positive predictive value is the probability that the IPDE will be positive when the MCMI-II is positive. Negative predictive value is the probability that the IPDE will be negative when this disorder is absent according to the MCMI-II

* $p < .05$

** $p < .01$

Table 216.8 Frequency of personality disorders in all sample

Personality disorders	ED n = 84		CCG n = 23		NCG n = 23		
	n	%	n	%	N	%	X^2
Paranoid	1	1.2	0	0	0	0	0.552
Schizoid	0	0	0	0	0	0	–
Schizotypal	0	0	0	0	0	0	–
Histrionic	2	2.4	1	4.3	0	0	0.970
Antisocial	0	0	0	0	0	0	–
Narcissistic	1	1.2	1	4.3	0	0	1.625
Borderline	16	19	2	8.7	0	0	6.113*
Obsessive–compulsive	19	22.6	1	4.3	2	8.7	5.633
Dependent	2	2.4	0	0	0	0	1.112
Avoidant	14	16.7	2	8.7	0	0	4.985
Non-specified	10	11.9	0	0	0	0	5.933*
TOTAL[a]	46	54.8	5	21.7	2	8.7	20.058**

This table shows the number of patients who present a type of PD as well as a percentage. When all the subjects with an ED were considered together, obsessive–compulsive PD (22.6%) was most commonly found, followed by borderline PD (19%), avoidant PD (16.7%), and not-otherwise-specified PD (11.9%). No diagnoses of schizoid, schizotypal or antisocial PD were made in this sample. The most frequently diagnosed PDs in the clinical control group were borderline (8.7%) and avoidant (8.7%). Finally, in the normative control group there were only two subjects (8.7%) with an obsessive–compulsive PD. When the three groups were compared, the patients with EDs were more frequently diagnosed with a borderline PD ($X^2_2 = 6.11$, $p < .05$) and with a not otherwise specified PD ($X^2_2 = 5.93$, $p < .05$) than the subjects belonging to the two control groups. The overall prevalence rate for at least one PD was 54.8% for the ED sample. In contrast, 21.7% of the clinical control sample and 8.7% of the normative control group showed at least one personality disorder. The differences found between the three groups were statistically significant ($X^2_2 = 20.06$, $p < .001$). PDs were more frequently diagnosed in patients with EDs than in the women of the two control groups
ED eating disorder, CCG = clinical control group, *NCG* normative control group
[a]The total number of people affected by PD is inferior to the total sum of disorders because there are patients who present more than one PD
*$p < .05$
**$p < .001$

type C. These results are consistent with other studies (Norman et al. 1993; Matsunaga et al. 1998, 2000; Díaz-Marsá et al. 2000; Godt 2002; Marañon et al. 2007a). In the case of BN, in most studies (Norman et al. 1993; Matsunaga et al. 2000; Godt 2002) the most prevalent PDs are those from type B (especially borderline personality disorder). However, in our study (Marañon et al. 2007a), PDs from types B and C are equally common.

In the future, the symptoms related to the presence of PDs in ED patients should be analyzed. This knowledge is necessary to create and to implement differentiated intervention programs that examine the differences between eating disorder patients with or without PDs.

Finally, it seems that it is better to use an interview to diagnose PDs. The MCMI-II overdiagnoses specific PDs and as a result it is not a valid tool for clinical diagnostics.

Summary Points

- Eating disorders (anorexia nervosa and bulimia nervosa) have become a significant public health problem.
- Eating disorders are characterized by serious alterations in eating habits. There is a refusal to gain weight above the lower normal levels.
- Personality disorders reflect inflexible behavior patterns, stable over time, which are not adaptive.

- Eating disorders are rarely found in a pure state: they are often found with personality disorders. In this case, we say that there is comorbidity between the two of them.
- The comorbidity between eating disorders and personality disorders can range from 20% to 80% depend on the study.
- There are different assessment instruments to diagnose personality disorders. Some are interviews (e.g., IPDE) and some self-administered questionnaires (e.g., MCMI).
- The prevalence rate of personality disorders in eating disorder patients differs depending on the diagnostic instrument used to diagnose personality disorders.
- The MCMI is easy and quick to administer but overdiagnoses personality disorders, making false-positive diagnostics.
- The IPDE interview requires a trained interviewer and the administration time is greater, but the diagnostics are more reliable.
- Knowing whether a patient with an eating disorder has a personality disorder or not is important, because comorbidity influences behavior (increases in binging, purging and dietary restrictions) and complicates the treatment.

Key Terms and Definitions

IPDE: The *International Personality Disorder Examination* (IPDE; Loranger 1995) is a semi-structured clinical interview outgrowth of Personality Disorders Examination (PDE; Loranger 1988). IPDEs aim is to evaluate systematically the presence or absence of the personality disorder criteria described in the current classifications. This is why it has been carried out in two modules: one for ICD-10 personality disorder criteria and the other for the DSM-IV personality disorder criteria.

MCMI: The MCMI-II is a 175-item, true–false, self-report questionnaire. It contains eight basic personality scales: Schizoid (1), Avoidant (2), Dependent (3), Histrionic (4), Narcissistic (5), Antisocial (6A), Aggressive–Sadistic (6B), Compulsive (7A), Passive–aggressive (7B) and Self-Defeating (8). In addition to the basic personality patterns, there are three pathological personality scales: Schizotypal (S), Borderline (B) and Paranoid (P). According to the conservative criteria of Weltzler (1990), a base rate score above 84 is considered to be significant.

Eating Disorders: Eating disorders are characterized by serious alterations in eating habits in the patients. Specifically, the main feature of anorexia nervosa is the refusal to maintain body weight in the lower normal levels and can exist in the form of drastic diets and excessive physical exercise as well as binging and purging. Bulimia nervosa is characterized by constant binging and use of inappropriate compensatory methods to prevent weight gain such as vomiting or misuse of laxatives and diuretics or, in other cases, fasting and excessive exercise. Finally, there are other unspecified eating disorders such as compulsive overconsumption or certain types of morbid obesity.

Personality Disorders: Personality disorders reflect inflexible behavior patterns which are not adaptive. Patients with these disorders show problems in learning effective strategies for coping with daily difficulties. Personality disorders generate interpersonal conflicts and lead to severe constraints (social and work) in daily life, as well as an increase in subjective discomfort. Personality disorders, as opposed to mental disorders, are stable and reflect a temporary deterioration of the overall person.

According to the DSM-IV-R (American Psychiatric Association 2000), there are ten personality disorders.

Comorbidity: Presence of more than one disorder at the same time in the same person. Co-occurrence and simultaneous presence of more than one disorder in the same person.

References

American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 4th ed. revised. Washington, DC: APA; 2000.

Black DW, Goldstein RB, Mason EE. Am J Psychiatr. 1992;149:227–34.

Braun DL, Sunday SR. Psychol Med. 1994;24:859–67.

Bulik C, Sullivan P, Joyce P, Carter F. J Nerv Ment Dis. 1995;183:593–8.

Claridge G, Davis C, Bellhouse M, Simone K. Pers Individ Dif. 1998;25:339–51.

Coovert DL, Kinder BN, Thompson JK. Clin Psychol. 1989;9:169–80.

Del Río C, Torres I, Borda M. Int J Clin Health Psychol. 2002;2:425–38.

Díaz-Marsá M, Carrasco JL, Sáiz J. J Pers Disord. 2000;14:352–9.

Dolan B, Evans C, Norton K. J Pers Disord. 1994;8:17–27.

Dowson JH, Grounds AT. Personality disorders: recognition and clinical management. Cambridge: Cambridge University Press; 1995.

Echeburúa E, Marañon I. Psicol Conductual. 2001;9:513–25.

Fahy T, Eisler I. Br J Psychiatr. 1993;162:193–7.

First MB, Gibbon M, Spitzer RL, Williams JBW, Smith L. Structured Clinical Interview for DSM-IV Axis II Personality Disorders (SCID-II). Washington, DC: American Psychiatric Press; 1997.

Garfinkel PE, Lin E, Goering P, Spegg C, Goldbloom DS, Kennedy S, Kaplan AS, Woodside DB. Am J Psychiatr. 1995;148:831–43.

Garner, DM, Sackeyfio, AH. In: Bellack AS, Hersen M, editor. Handbook of behavior therapy in the psychiatric setting. New York: Plenum; 1993. pp. 477–98.

Gartner AF, Marcus RN, Halmi K, Loranger AW. Am J Psychiatr. 1989;146:1585–91.

Gillberg G, Rastam M, Gillberg C. Compr Psychiatr. 1995;36:61–9.

Godt K. Eur Eat Disord Rev. 2002;10:102–9.

Grana AS, Coolidge FL, Merwin MM. J Clin Psychol. 1989;45:762–5.

Grilo CM, Levy KN, Becker DF, Edell WS, McGlashan TH. Psychiatr Serv. 1996;47:426–9.

Guisado JA, Vaz FJ, Rubio MA, López-Ibor JJ Psiquiatr Biol. 2001 8:9–10.

Herpertz-Dahlmann B, Müller B, Herpertz S, Heussen N. J Child Psychol Psychiatr. 2001;42:603–12.

Herzog DB, Keller MB, Sacks NR, Yeh CJ, Lavori PW. J Am Acad Child Adolesc Psychiatr. 1992;31:810–8.

Herzog DB, Norman DK, Gordon C, Chevron E. Am J Psychiatr. 1984;141:989–90.

Inceoglu I, Franzen U, Backmund H, Gerlinghoff M. Eur Eat Disord Rev. 2000;8:67–72.

Joiner ET, Katz J, Heatherton TF. Int J Eat Disord. 2000;27:191–7.

Karwautz A, Rabe-Hesketh S, Collier DA, Treasure JL. Eur Eat Disord Rev. 2002;10:255–70.

Kennedy SH, Katz R, Rockert W, Mendlowitz S, Ralevski E, Clewes J. J Nerv Ment Dis. 1995;183:358–64.

Kennedy SH, McVey G, Katz R. J Psychiatr Res. 1990;24:259–69.

Kozyk JC, Touyz SW, Beumont J. Int J Eat Disord. 1998;24:95–9.

Levin AP, Hyler SE. Compr Psychiatr. 1986;27:47–53.

Loranger AW. Personality Disorder Examination (PDE Manual). Yonkers, NY: DV Communications; 1988.

Loranger AW. International Personality Disorder Examination (IPDE). Geneva: World Health Organization; 1995.

Marañon I, Echeburúa E, Grijalvo J. Int J Clin Health Psychol. 2007a;7:283–93.

Marañon I, Grijalvo J, Echeburúa E. Int J Clin Health Psychol. 2007b;7:587–94.

Marino MF, Zanarini MC. Int J Eat Disord. 2001;29:349–53.

Martín FM, Motos A, Del Águila E. Rev Psiquiatr Psicol Nino Adolescente. 2001;1:2–8.

Martín FM, Cangas AJ, Pozo EM, Martínez M, López M. Psicothema. 2009;21:33–8.

Matsunaga H, Kaye WH, McConaha C, Plotnicov K, Pollice C, Rao R. Int J Eat Disord. 2000;27:353–7.

Matsunaga H, Kiriike N, Nagata T, Yamagami S. Int J Eat Disord. 1998;23:399–408.

Medina A, Moreno MJ. Los trastornos de la personalidad. Un estudio médico-filosófico. Cordoba: Nanuk; 1998.

Millon T. Millon Clinical Multiaxial Inventory manual. Minneapolis, MN: National Computer Systems; 1977.

Millon T. Millon Clinical Multiaxial Inventory-II (MCMI-II). Minneapolis, MN: National Computer Systems; 1987.

Millon T. Millon Clinical Multiaxial Inventory-III (MCMI-III). Minneapolis. MN: National Computer Systems; 1994.

Millon T, Davis RD. Disorders of personality: DSM-IV and beyond. 2nd ed. New York: Wiley; 1996.

Modestin J, Oberson B, Erni T. Acta Psychiatr Scand. 1997;96:424–30.

Norman D, Blais MA, Herzog D. J Pers Disord. 1993;7:1–9.

Palmer RL, Birchall H, Damani S, Gatward N, McGrain, Parker L. Int J Eat Disord. 2003;33:281–6.

Pendleton L, Tisdale M, Marler M. Compr Psychiatr. 1991;32:516–20.

Piran N, Lerner P, Garfinkel PE, Kennedy SH, Brouilette C. Int J Eat Disord. 1988;5:589–99.

Pope HG, Hudson JI. Int J Eat Disord. 1989;8:1–9.

Sansone R, Levitt JL, Sansone LA. Eat Disord: J Treat Prev. 2005;13:7–21.

Sansone RA, Sansone LA, Morris DW. Am J Psychiatr. 1996;153:117–18.

Segal, DL, Coolidge, FL. In: Edelstein B, editor. Clinical geropsychology. Comprehensive Clinical Psychology, vol. 7. Amsterdam: Elsevier; 1998. pp. 267–89.

Schneider JA, Agras WS. Int J Eat Disord. 1987;6:235–42.

Spitzer RL, Williams JB, Gibbon M. The Structured Clinical Interview for DSM-III-R Personality Disorders. Biometric research. New York: New York State Psychiatric Institute; 1987.

Steiger H, Stotland S. Int J Eat Disord. 1996;20:141–61.

Striegel-Moore RH, Garvin V, Dohm FA, Rosenheck RA. Int J Eat Disord. 1999;25:405–14.

Thornton C, Russell J. Int J Eat Disord. 1997;21:83–7.

Vrabel KR, Rø Ø, Martinsen EW, Hoffart A, RosenvingeJH Int J Eat Disord. 2010;43:22–8.

Wetzler S. J Pers Assess. 1990;55:445–64.

Wetzler S, Dubro A. J Nerv Ment Dis. 1990;178:261–3

Wiederman MW, Pryor TL J Pers Assess. 1997;69:508–16.

Wonderlich SA, Swift WJ, Slotnick HB, Goodman S. Int J Eat Disord. 1990;9:607–16.

Wonderlich, SA. In: Brownell KD, Fairburn CG, editors. Eating disorders and obesity: a comprehensive handbook. New York: Guilford Press; 1995.

World Health Organization. The ICD-10 Classification of Mental and Behavioral Disorders. Geneva, Switzerland: World Health Organization; 1992.

Yanovski SZ, Nelson JE, Dubbert BK, Spitzer RL. Am J Psychiatr. 1993;150:1472–9.

Zanarini MC, Frankenburg FR, Dubo ED, Sickel AE, Trikha A, Levin A, Reynods V. Am J Psychiatr. 1998;155:1733–9.

Zanarini MC, Reichman CA, Frankenburg FR, Reich DB, Fitzmaurice G. Int J Eat Disord. 2009;43(4):226–32.

Zimmerman M, Rothschild L, Chelminski I. Am J Psychiatr. 2005;162:1911–18.

Zlotnick C, Rothschild L, Zimmerman M. J Pers Disord. 2002;16:277–82.

Chapter 217
The Assessment of Bulimic Symptomatology: Factorial Structure and Measurement Invariance of the Bulimic Investigatory Test, Edinburgh Across Gender and Age

Eduardo Fonseca-Pedrero, Susana Sierra-Baigrie, Mercedes Paíno,
and Serafín Lemos-Giráldez, José Muñiz

Abbreviations

APA	American Psychiatric Association
BITE	Bulimic Investigatory Test, Edinburgh
BULIT	Bulimia Test
CAT	Computerized Adaptive Testing
CFA	Confirmatory Factor Analysis
DSM	Diagnostic and Statistical Manual of Mental Disorders
EAT-40	Eating Attitudes Test-40
EDDS	Eating Diagnostic Disorder Scale
EDE-Q	Eating Disorder Examination
EDI-2	Eating Disorder Inventory-2
IRT	Item Response Theory
MI	Measurement Invariance
Q-EDD	Questionnaire for Eating Disorder Diagnoses

217.1 Introduction

Since Russell first described in 1979 what we now know as bulimia nervosa and its subsequent inclusion in the DSM-III (American Psychiatric Association [APA] 1980) as a distinct eating disorder category, characterized by recurrent binge-eating episodes accompanied by inappropriate compensatory methods, many changes have taken place regarding its diagnostic criteria, psychological and pharmacological treatment, and the construction of new assessment instruments. The key facts of the DSM can be seen in Table 217.1.

According to the DSM-IV-TR (APA 2000), the main diagnostic features of bulimia nervosa are the presence of binge eating and maladaptive compensatory methods along with an excessive influence of body shape and weight on self-evaluation. For an individual to receive a bulimia diagnosis, these binge-eating episodes and compensatory methods must occur at least twice a week for a minimum

E. Fonseca-Pedrero (✉)
Department of Psychology, University of Oviedo, Centro de Investigación
Biomédica en Red de Salud Mental, CIBERSAM, Plaza Feijoo, s/n, Oviedo, 33003, Spain
e-mail: efonseca@cop.es

Table 217.1 Key features of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM)

- It is a categorical system for the classification of mental disorders according to certain established criteria.
- The first edition of the DSM was published in 1952; the latest edition is the DSM-IV-TR (2000) and currently experts are working on the DSM-V.
- It allows proper communication among researchers and clinicians regarding the diagnosis, study, and treatment of different mental disorders.
- It is a useful tool for educational, research, and clinical purposes and it is used by clinicians and researchers throughout the world.
- The terms and codes used in the DSM for classification of disorders are compatible with those provided by the International Statistical Classification of Diseases and Related health Problems (ICD-10) developed by the World Health Organization.

This table summarizes the main features of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM)

of 3 months. The compensatory method employed by 80–90% of bulimics presenting themselves for treatment is self-induced vomiting (APA 2000). After vomiting, the person feels relieved as there is a reduction in physical discomfort and fear of gaining weight. Other compensatory methods employed by bulimic patients include: excessive exercise, use of diet pills, water pills, laxatives, diuretics or enemas, dieting, and ruminatory behavior (APA 2000), all of which have the potential to seriously harm the person's well-being. Bulimia nervosa is associated with significant distress, role impairment, and medical and psychological consequences whichthat severely affect the individual's quality of life. Several comorbid conditions have been shown to be present in bulimia nervosa patients such as depression, anxiety, personality disorders, obsessive–compulsive symptoms, substance abuse, and impulse control problems among others (Albert et al. 2001; APA 2000; Duncan et al. 2006; Echeburúa and Marañón 2001; Stice et al. 2004). Therefore, as bulimia nervosa represents an important public-health concern, finding ways of early detection of at-risk individuals is vital for the prevention of the disorder and its devastating consequences.

Epidemiological data place lifetime prevalence of bulimia nervosa in the range 1–3% (APA 2000), although given the secretive nature of bingeing and purging, and that many individuals with bulimia do not seek help, many cases may go undetected (Hoek et al. 2003). There is a clear gender difference in the prevalence rates of bulimia, with 90% of the cases being female (APA 2000). In addition, research shows that the percentage of individuals with subclinical forms of the disorder, that is, individuals suffering from bulimic symptoms associated with great distress but that may not meet the diagnostic criteria for bulimia nervosa, is fairly high (Chamay-Weber et al. 2005).

It should be mentioned that bulimic symptomatology is not restricted to individuals with eating disorders, but rather studies have shown that bulimic symptoms are also present in the general population (Pinheiro et al. 2008; Rodríguez et al. 2001; Sierra-Baigrie et al. 2009). For example, recent research studies have found that binge eating is present in nonclinical adolescent populations (Rodríguez et al. 2001; Sierra-Baigrie et al. 2009) as well as the use of inappropriate compensatory methods such as self-induced vomiting, laxative misuse, or excessive exercising (Pinheiro et al. 2008).

There is no doubt that adolescence is a period of particular interest for the study of bulimic symptomatology given the numerous psychological, physical, social, and cognitive changes that take place and that can be a source of stress in some individuals (Stice et al. 1998b). On the other hand, epidemiological data show that bulimia nervosa usually begins during late adolescence and/or early adulthood (APA 2000); hence, it is especially interesting to explore the variables associated to the development of maladaptive eating-related behaviors in nonclinical young adolescents.

Thus, bulimic symptomatology is present in a wide range of individuals and may be distributed along a continuum of severity, which goes from the absence of bulimic symptoms to full-blown bulimia nervosa in its extreme (Stice et al. 1998a). In this sense, according to the vulnerability-stress

Table 217.2 Key features of the vulnerability-stress model

- This model, also known as the diathesis-stress model, considers that for an individual to develop a psychological disorder, the conjunction of two factors, vulnerability and stress, must take place to a greater or lesser degree.
- The concept of vulnerability makes reference to certain biological traits mainly of a genetic origin, although not necessarily, which confer a certain predisposition toward a psychological disorder.
- Diathesis is considered a continuous variable that can be expressed with different degrees of intensity and that is in constant interaction with environmental factors.
- The probability of an individual developing a disorder depends on where he or she stands in the vulnerability continuum. Individuals situated at the extreme end present a greater vulnerability toward the development of a psychological disorder; individuals in the middle of the continuum may present subclinical or attenuated symptoms of the disorder.
- The relationship between vulnerability and stress is inversely proportional, that is, individuals with a high vulnerability toward a psychological disorder would require a lesser degree of stress to transit into a severe form of the disorder and those with a reduced level of vulnerability would require a greater degree of stress to develop the disorder.

This table shows the key features of the vulnerability-stress model. This model is possibly one of the most accepted models for the explanation and comprehension of the etiology of many psychological disorders. Its extensive use in clinical and research fields is due to the fact that it offers an easy explanation for the complex interactions occurring among genetic and environmental factors.
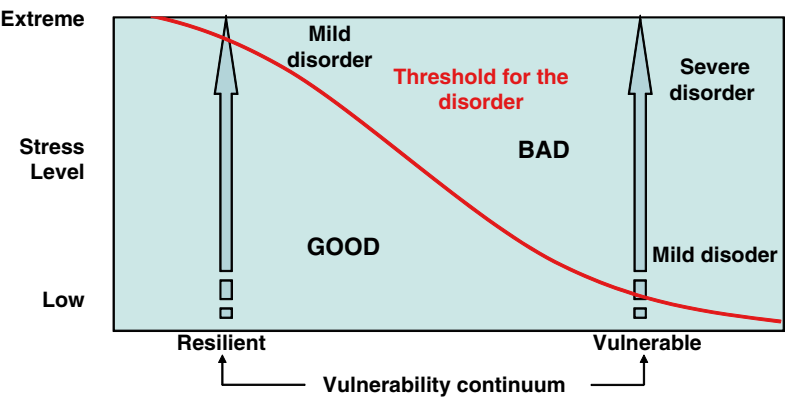

Fig. 217.1 Vulnerability–stress model for psychological disorders. In this figure, a representation of the vulnerability-stress model is shown. As can be observed, if an individual stands at the extreme end of the resilience-vulnerability continuum, a lesser degree of stress is required to surpass the threshold and transit toward a more severe form of a given psychological disorder

models, the probability of transiting toward a psychological disorder, in this case bulimia nervosa, would be determined by the interaction between the individual's predisposition and environmental factors (see Table 217.2 for key features of the vulnerability-stress model).

As can be seen in Fig. 217.1, the relationship between both concepts is inversely proportional. An individual who is closer to the normality end of the continuum would require the conjunction of greater stressful events to surpass the threshold; however, a person who is closer to the maladaptive end would require a lesser amount of stress to surpass the threshold and develop a disorder.

Therefore, the study of the presence of bulimic symptomatology in nonclinical populations, such as adolescents who have not yet developed a full-blown eating disorder, is important to further our understanding of this phenomenon and improve our assessment methods in order to detect individuals at high risk for bulimia nervosa and prevent them from developing this disorder.

217.2 Measurement Instruments for the Assessment of Bulimic Symptomatology

The field of psychological assessment of eating disorders, and in particular of bulimic symptomatology, has advanced considerably in the last few years. Table 217.3 shows some of the most widely used instruments for the assessment of eating disorders. In this regard, in the scientific literature, we can find numerous self-reports developed for the assessment of behaviors, symptomatology, and beliefs related to bulimia nervosa. There is no doubt that the assessment of bulimic symptomatology only makes sense if the measurement instruments employed are capable of measuring the construct with all psychometric guarantees. There is no use utilizing self-reports if their psychometric properties have not been exhaustively analyzed since the conclusions and decisions based on the participants' scores on these may be completely wrong or unfounded (Zumbo 2007).

More specifically, for the assessment of bulimic symptomatology we find the Bulimia Test (BULIT) (Smith and Thelen 1984), and the Bulimic Investigatory Test, Edinburgh (BITE) (Henderson and Freeman 1987), although it is true that other self-reports such as the Eating Disorder Inventory-2 (EDI-2) (Garner 1991) assess both bulimic and anorexic symptoms. The EDI-2 (Garner 1991) is a self-report, composed of 64 items in a six-point Likert-type format, which focuses on the description and precise measurement of several behavioral and psychological traits that are common in two eating disorders, bulimia and anorexia nervosa, as well as the severity of the clinically relevant symptomatology. The Eating Disorder Inventory-2 EDI-2 may be utilized as a screening device, outcome measure, or part of typological research but cannot be used for diagnostic purposes. This instrument presents adequate psychometric properties in reference to its internal consistency; test–retest reliability; and content, concurrent, and construct validity (Garner 1991; McCarthy et al. 2002; Miller et al. 2009; Tasca et al. 2003).

For its part, the Bulimia Test (BULIT) (Smith and Thelen 1984), or its revised version the BULIT-R (Thelen et al. 1996), is a self-report which was developed with the aim of solving some of the shortcomings detected in the field of bulimia nervosa assessment. The BULIT is composed of 32 items in a five-point Likert response format (plus four items to obtain information regarding laxative

Table 217.3 Main self-reports used in the assessment of eating disorders

Measurement instruments	Abbreviation	Number of items	Response format	Reference
Eating Attitudes Test	EAT-40	40	Likert 6	Garner and Garfinkel (1979)
Eating Disorder Inventory-2	EDI-2	64	Likert 7	Garner (1991)
Eating Disorder Examination-Questionnaire	EDE-Q	33	Likert 7	Fairburn and Beglin (1994)
Questionnaire for Eating Disorder Diagnoses	Q-EDD	50	Likert 7	Mintz (1997)
Eating Diagnostic Disorder Scale	EDDS	22	Likert and Yes/No	Stice et al. (2000)
Bulimia Test	BULIT	36	Likert 5	Smith and Thelen (1984)
The Bulimic Investigatory Test, Edinburgh	BITE	33	Yes/No and Likert	Henderson and Freeman (1987)

In this table we can see some of the most commonly utilized self-reports for the assessment of eating disorders